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Diagnostic features, management, and prognosis of Type 2 myocardial infarction: A systematic review and metaanalysis.

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Title Page

Manuscript Title

Diagnostic features, management, and prognosis of Type 2 myocardial infarction: A systematic review and meta-analysis.

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Abstract

Importance

Distinguishing type 2 (T2MI) from type 1 myocardial infarction (T1MI) in clinical practice can be difficult, and the management and prognosis for T2MI remain uncertain.

Objective

To compare precipitating factors, risk factors, investigations, management, and outcomes for T2MI and T1MI.

Data Sources

MEDLINE and EMBASE databases as well as reference list of recent articles were searched January 2009 to December 2020 for term "type 2 myocardial infarction".

Study Selection

Studies were included if they analysed if universal definition of MI was used and reported quantitative data on at least one variable of interest.

Data Extraction and Synthesis

Data was pooled using random-effect meta-analysis. Risk of bias was assessed using Newcastle-Ottawa Quality Assessment Form. Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA) guidelines were followed. All review stages were conducted by two reviewers.

Main Outcomes and Measures

Risk factors, presenting symptoms, cardiac investigations such as troponin and angiogram, management, and outcomes such as mortality.

Results

41 cohort studies comprising 116,565 T1MI and 15,258 T2MI patients were included. Compared to T1MI, T2MI patients were: more likely to have pre-existing chronic kidney disease (OR 1.89; 95%CI 1.59-2.25) and chronic heart failure (OR 2.34; 95%CI 1.87-2.93), less likely to present with typical cardiac symptoms of chest pain (OR 0.19; 95%CI 0.15-0.26) and more likely to present with dyspnoea (OR 2.83; 95%CI 1.96-4.08); more likely to demonstrate non-specific ST-T wave changes on electrocardiography (OR 2.62; 95%CI 1.81-3.79) and less likely to show ST elevation (OR 0.22; 95%CI 0.18-0.28); less likely to undergo coronary angiography (OR 0.09; 95%CI 0.06-0.12) and percutaneous coronary intervention (OR 0.06; 95%CI 0.04-0.10) or receive cardioprotective medications, such as statins (OR 0.25; 95%CI 0.17-0.36) and beta-blockers (OR 0.46; 95%CI 0.34-0.62). T2MI had more risk of all cause one-year mortality (OR 2.94; 95%CI 2.07-4.17), with no differences in cardiovascular deaths (OR 1.17; 95%CI 0.70-1.97).

Conclusion and Relevance

This review has identified clinical, management and survival differences between T2MI and T1MI with greater precision and scope than previously reported. Differential use of coronary

> revascularisation and cardioprotective medications highlight ongoing uncertainty of their utility in T2MI compared to T1MI.

Strength and Limitations

- Inclusion of all contemporary cohort studies in the troponin era
- Large patient population of T2MI and T1MI patients analysed allowing high level of precision
- inc ically sig. mortality due ι. Wide array of clinically significant variables assessed providing a comprehensive analysis •
- Analysis of crude mortality due to individual patient data not available •

Introduction

The clinical definition of myocardial infarction has evolved over time (Table S1). The 2007 Universal Definition of Myocardial Infarction included a subset of MI that was secondary to aetiologies unrelated to underlying occlusive coronary artery disease (1). In 2012, the Third Universal Definition of Myocardial Infarction Consensus Document (2) gave rise to the aetiological distinction between T1MI, defined as MI due to plaque erosion and/or rupture, and T2MI, defined as MI caused by increased oxygen demand or decreased blood supply, in the absence of acute plaque rupture or coronary thrombosis. More recently, in 2018, the Fourth Universal definition of MI updated concepts of T2MI regarding specific situations associated with oxygen demand and supply imbalance and the relevance of the presence or absence of underlying coronary artery disease to therapy and prognosis (3).

In clinical practice, distinguishing T2MI from T1MI based on clinical presentation, electrocardiograph (ECG) features and cardiac troponin (cTn) values can be difficult. In the absence of randomised controlled trials that have evaluated different investigational and therapeutic interventions in patients with T2MI, there is uncertainty around the appropriate management of such patients, particularly those with known or suspected coronary artery disease. Past reviews have assessed one or more attributes of T2MI in comparison to T1MI (4-8) but, to our knowledge, none have undertaken a comprehensive analysis of symptoms, physical signs, investigation results, management regimens and clinical outcomes of T2MI versus T1MI.

We undertook a systematic review of observational studies with the aims of identifying diagnostic and investigational findings which can assist clinicians to better distinguish T2MI from T1MI, different management strategies in T2MI compared to T1MI and differences in clinical outcomes between T2MI and T1MI.

Methods

Study design

The review was undertaken in accordance with recommendations of the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (9). Our review was registered on PROSPERO prior to commencement (Registration number: CRD42021237746). MEDLINE and EMBASE databases were searched for all studies published between January 1st, 2009, and December 31st, 2020, using search terms to identify all studies related to T2MI (Tables S2, S3). Reference lists of all relevant articles were also assessed to identify additional relevant studies. The study PRISMA flowchart is shown in Figure 1.

Studies were selected if they compared patient populations with T2MI and T1MI, used a universal definition of MI and included at least one variable of interest. Studies were excluded if no full text was available or less than 200 participants. Initial screening of titles and abstracts for eligible studies was performed independently by two authors (MK, KW), as was full text review for inclusion, with any differences in review settled by consensus agreement.

Data collection and synthesis

Data pertaining to all variables of interest were collected from all included studies using a standardised proforma by one author (MK) and independently reviewed by the second author (KW). These variables comprised: study dates, design, sample size, definition used to define T2MI and T1MI, patient demographics, pre-existing medical conditions, precipitating factors, clinical symptoms, ECG findings, laboratory values, echocardiographic results, any clinical interventions or medical treatments administered, and clinical outcomes observed.

Data on variables reported as, or able to be converted to, raw numbers, were pooled from all studies and subject to comparative meta-analysis using Review Manager (RevMan, Computer program. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For each variable, the weighted odds ratio (OR) comparing T2MI to T1MI, and its 95% confidence interval (CI), was calculated using the random effects method in anticipation of study heterogeneity of at least moderate degree (I² statistic of heterogeneity >50%) (10). In addition to the weighted OR, we also report the crude, unweighted total event rates for each variable subject to meta-analysis in order to provide a more clinically meaningful estimate of the prevalence of these events in each patient group in view of the large sample sizes. Studies reporting mean or median values only are also reproduced as reported in the original study.

Risk of bias within each study was assessed using the Newcastle-Ottawa quality assessment tool for cohort studies (11, 12), with scores 7-8 denoting good quality studies, 4-6 fair quality, and 0-3 poor quality.

Patient and Public Involvement

No patient involved.

Results

 A total of 41 studies were included for analysis (13-53) and their characteristics are summarised in the online supplement, Table S4. They comprised a total of 131,823 participants of whom 116,565 participants (88%) were identified as T1MI and 15,258 (12%) as T2MI.

The 2007 definition (1) was used in 8 (19%) studies (15-17, 28, 30, 44, 45, 52), the 2012 definition (2) was used in 25 (61%) studies (13, 18, 20-22, 24-27, 31-36, 38, 40, 41, 43, 46-49, 51, 53), and the 2018 definition (3) was used 8 (19%) studies (14, 19, 23, 29, 37, 39, 42, 50). Of the 41 studies, 18 (44%) were prospective (15-17, 19, 20, 23, 30, 34, 35, 37, 38, 44, 45, 47-49, 51, 52) and 23 (56%) were retrospective (13, 14, 18, 21, 22, 24-29, 31-33, 36, 39-43, 47, 50, 53).

Risk of bias assessment

Of the 41 studies, 32 (78%) were assessed as good quality (13, 15-20, 23, 24, 28-36, 38-47, 49, 53), 6 (15%) as fair quality (14, 25-27, 50), and 3 (7%) as poor quality (21, 37, 48), as summarised in online supplement, Table S5. Selection bias resulting in unrepresentative cohorts such as admission criteria to coronary care units or entry criteria into MI registries favouring T1MI (14, 21, 25-27, 37, 48, 50), absence of independent adjudication of MI type as T1MI or T2MI (37, 39, 48), non-comparability of T1MI and T2MI cohorts (21, 25, 26, 48), poorly specified outcome measures (37, 39, 48) and short follow-up period resulting in few events (14, 21, 25, 37) comprised most forms of bias.

Participant characteristics

Patients with T1MI had a median age range of 60-82 years in the included studies that did not select a specific age population, compared to a median age range of 62-79 years in patients with T2MI. The sex distribution was also similar, with 59.8% and 54% of patients with T1MI and T2MI being male respectively.

Regarding pre-existing medical conditions (Table 1), T2MI patients compared to T1MI patients were more likely to have chronic kidney disease (26.9% vs 19.3%; OR 1.89; 95%CI 1.59-2.25), chronic heart failure (19% vs 8.1%; OR 2.34; 95%CI 1.87-2.93), atrial fibrillation (22.9% vs 6.1%; OR 3.02; 95%CI 2.29-3.99), and hypertension (66.8% vs 61.3%; OR 1.22; 95%CI 1.05-1.43). Patients with T2MI were less likely to have dyslipidaemia (43.4% vs 45.9%; OR 0.74; 95%CI 0.58-0.94) and smoking history (37.2% vs 53.9%; OR 0.61; 95%CI 0.50-0.74). There was no difference in the prevalence of type 2 diabetes mellitus or ischaemic heart disease between the two groups.

Precipitating factors

Less than half of the studies (n=18; 44%) included data on precipitating factors associated with T2MI (13, 15, 16, 18, 20, 22-25, 28, 32, 33, 36, 41, 45, 46, 51, 52). Data on each precipitating factor was not constantly available across the studies, for example only 18 studies representing 45% of T2MI patients assessed for presence of arrythmia

The most common precipitant was sepsis (35.9%), followed by arrythmia (29.8%), and heart failure 28.6% (Table S6), with non-cardiac surgery being deemed a cause in 12.2% of cases where data for this variable were collected.

Presenting clinical features

As summarised in Table S7, compared to T1MI patients, T2MI patients were less likely to present with typical cardiac symptoms of chest pain (59.2% vs 87.7%; OR 0.19; 95%CI 0.15-0.26) or discomfort in the arm or shoulder (8.5% vs 35%; OR 0.18; 95%CI 0.11-0.3). In contrast, T2MI patients were more likely to present with dyspnoea (27.6% vs 9.9%; OR 2.83; 95%CI 1.96-4.08).

Investigations

With regards to ECG findings on presentation (Table S8), ST elevation (13.4% vs 42.1%; OR 0.22; 95%CI 0.18-0.28) and pathological Q waves (6.7% vs 20.8%; OR 0.38; 95%CI 0.20-0.71) were less likely to be observed in T2MI than in T1MI. In contrast, non-specific ST-T wave changes (24.7% vs 10.8%; OR 2.62; 95%CI 1.81-3.79), and atrial arrythmias (27% vs 10.2%; OR 3.70; 95%CI 2.87-4.77) were more common among T2MI than T1MI patients. No differences between groups were seen in the frequency of ST depression or T wave inversion.

Cardiac troponin results were reported in 27 studies (Table S8), with 19 reporting cTnl (13, 18-20, 26, 28, 30, 33, 35, 36, 38-40, 44-47, 49, 51), 6 reporting cTnT (15, 16, 31, 32, 42, 43), one reporting both (21) and one not specifying the assay used (24). Only two of the 27 studies reporting troponin failed to state the upper limit of normal (ULN) of the assay used (24, 32). The troponin assays, and therefore units and reference ranges, varied between the studies, preventing direct comparison of troponin values. As a result, troponin values were converted to a multiple of the upper limit of normal for each assay to allow direct comparison. For peak troponin, patients with T1MI had a

higher and wider range of 5-1702 times the ULN compared to patients with T2MI with a range of 2.8-447 times the ULN. Studies yielded mixed results as to whether the magnitude of change (or delta) in serial cardiac troponin assays was more predictive of T2MI or T1MI compared to absolute values of peak levels (34). Lowering the diagnostic threshold for troponin with the advent of more sensitive troponin assays preferentially increased the numbers of patients identified with T2MI by up to 50% (37), with more recent studies showing the incidence of T2MI equalling or exceeding that of T1MI (16, 34, 37).

Echocardiography was less frequently performed among T2MI than T1MI patients (47.9% vs 55.5%; OR 0.44; 95%CI 0.20-0.96) and when reported (Table S8), there was no difference in the prevalence of regional wall motion abnormalities or the level of left ventricular (LV) function, with median LV ejection fraction being 42.3%-55% in T1MI patients and 40%-56% in T2MI patients.

Coronary angiography was also less frequently performed among T2MI than in T1MI patients (34.4% vs 83.4%; OR 0.09; 95%CI 0.06-0.12, Table S8). When performed, T2MI patients were less likely to demonstrate obstructive coronary artery disease (34% vs 44.9%; OR 0.16; 95%CI 0.05-0.54), with obstruction variously defined as 50%-70% occlusion of one or more vessels.

Management

T2MI patients, compared to T1MI patients, were significantly less likely to receive conventional cardioprotective medications (Table 2), comprising beta blockers (61.6% vs 78.2%; OR 0.46; 95%CI 0.34-0.62), anti-platelet agents (57.4% vs 87.3%; OR 0.24; 95%CI 0.17-0.36) and statins (55.3% vs 87.2%; OR 0.25; 95%CI 0.17-0.36). Of note, T2MI patients were more likely to receive diuretics (46.5% vs 18.8%; OR 1.99; 95%CI 1.56-2.53) or anti-coagulants (26.1% vs 21.3%; OR 1.90; 95%CI 1.17-3.10).

Percutaneous coronary intervention (PCI) (20% vs 75.1%; OR 0.06; 95%CI 0.04-0.10) and coronary artery bypass surgery (2.4% vs 6.1%; OR 0.23; 95%CI 0.12-0.42) were also significantly less likely to be performed in T2MI patients than T1MI patients.

Prognosis

T2MI patients had significantly increased risk of all-cause death compared to patients with T1MI in both short- and long-term follow-up (Table 3). Specifically, compared to T1MI patients, T2MI demonstrated increased all-cause mortality in-hospital (12.5% vs 5.8%; OR 1.94; 95%CI 1.35-2.79, Figure S44), at one-year (20.6% vs 8.8%; OR 2.94; 95%CI 2.07-4.17, Figure 1) and at 5 to 10 years, (53.7% vs 28.5%, OR 3.24; 95%CI 2.73-3.84, Figure 2). In contrast, there were no differences between T2MI and T1MI patients in the risk of cardiovascular related in-hospital mortality (6% vs 3.8%; OR 1.17; 95%CI 0.70-1.97) or short-term mortality at 120-180 days (23.0% vs 12.5%; OR 1.34; 95%CI 0.63-2.85).

Discussion

Up to three quarters of all myocardial infarctions in routine care can be T2MI (34, 35), the management of which is different to that for T1MI. Distinguishing T2MI from T1MI on clinical criteria is often challenging, the management strategies used by clinicians in real-world practice for T2MI often vary, and the clinical outcomes of T2MI compared to T1MI, particularly over the long term,

have been uncertain. This comprehensive review of contemporary studies provides information that helps characterise these two groups of patients according to multiple variables and may assist in clinical decision-making and prognostication.

In this review, T2MI patients were older with more medical comorbidities than T1MI patients, as noted in a recent meta-analysis (6). Our review highlighted the much higher incidence of pre-existing generalised vascular disease, atrial fibrillation, renal impairment, and heart failure among T2MI patients.

Sepsis (10, 17, 28) and anaemia (52) ranked highly as triggers, together with other acute cardiac events such as valve dysfunction or arrhythmias. In one study, a more favourable prognosis in T2MI was seen when the principal trigger was arrhythmia, in comparison with non-cardiac surgery, hypotension, anaemia or hypoxia (30). In another study, only shock syndromes were triggers portending a worse prognosis compared to all other triggers (33). In our analysis, non-cardiac surgery as a trigger of T2MI was less frequent than reported by other investigators (27) whereby peri-operative stressors including blood loss, anaesthesia induced hypotension and wound infections cause imbalance in myocardial contractility, oxygen demand and blood flow (54).

Analysis of cTn levels showed uniformly higher values in T1MI than T2MI which accord with one review (5) reporting cTn values 30% to 94% higher in patients with T1MI, and which other investigators regard as being highly specific diagnostic markers for T1MI (54).

Coronary angiography and revascularisation were both performed much less frequently in T2MI than in T1MI patients. Treating physicians may perceive invasive strategies as being contraindicated or potentially harmful in the presence of various co-morbidities more commonly seen in T2MI and which are associated with competing mortality risk. In our pooled data, only 1 in 3 T2MI patients who underwent angiography demonstrated obstructive coronary artery disease, although this figure may be an underestimate due to selection bias whereby younger, less multi-morbid patients preferentially underwent angiography. In contrast, in the CASABLANCA cohort study where all consecutive patients with incident T2MI underwent angiography, 47.7% demonstrated ≥70% stenosis in at least 2 major coronary arteries (55). These conflicting findings question whether patients presenting with T2MI would benefit from routine use of invasive strategies that define coronary anatomy and, if plaque rupture or critical stenoses are seen, prompt revascularisation, with resultant improvement in patient outcomes. In one study (19), angiography unmasked acute plaque rupture in 29% of patients classified as T2MI. In another study, among 11.4% of 236 patients with T2MI who underwent revascularisation, the odds of all-cause death were reduced by 67% compared to the remaining 88.6% who were not revascularized (24). In contrast, in a third more rigorous study comparing T2MI versus T1MI patients following PCI within 24 hours of symptom onset, and adjusting results using multivariate logistic regression analysis and inverted probability weighting, (15) inhospital mortality was lower in patients with T1MI and receiving PCI (OR 0.47; 95% CI 0.40–0.55; p < 10000.001), but not in those with T2MI receiving PCI (OR 1.09; 95% CI 0.62–1.94; p = 0.763). However, all these studies are observational, so completion of randomised trials, such as the Appropriateness of Coronary investigation in myocardial injury and Type 2 myocardial infarction (ACT-2) trial which is currently in recruitment (54), will hopefully provide a more definitive answer.

The lower use of cardioprotective agents in T2MI patients remains unexplained, reflecting either uncertainty around their cardioprotective utility in T2MI, or concerns about the potential for adverse interactions with other drugs or diseases commonly seen in multi-morbid T2MI patients. The higher use of diuretics in the T2MI population likely reflects the higher prevalence of heart failure and hypertension.

An important finding is the much higher all-cause in-hospital and one-year mortality in T2MI compared to T1MI patients, which is similar to the two-fold greater mortality rate in T2MI noted in a recent systematic review of 9 studies (8). In our review, this excess mortality was not driven by an excess of cardiovascular deaths, and likely reflects the competing risks of older age and multiple co-morbidities, rather than underlying multi-vessel obstructive coronary artery disease which was seen in 30-50% of T2MI patients (27, 32). Studies yielded mixed results as to whether coronary artery disease is an independent predictor of T2MI (21, 43), while others question the angiographic distinction between T2MI and T1MI. For example, in a study of 450 consecutive patients with MI who all underwent coronary angiography within 24 hours of symptom onset, 145 (32.2%) patients had 'true' T1MI (acute atherothrombosis and no systemic triggers), 114 (25.3%) had 'true' T2MI (no atherothrombosis and systemic triggers), 61 (13.6%) patients had neither, and 130 (28.9%) patients had both, suggesting a discordance of angiographic and clinical definitions of MI type in 42.5% of patients (41).

Our review has several limitations. First, in the absence of individual patient data from all included studies, we were unable to perform multivariate regression analysis in identifying weighted predictors of diagnosis, management, or prognosis of T2MI. Second, we did not perform separate analyses of cohort studies that used different versions of the Universal Definition of MI or used different troponin thresholds to define MI, which may impact management and prognosis. The only study which compared T2MI cohorts as defined by the 2007 and the 2012 versions revealed a lower frequency of co-morbidities and less use of cardioprotective medications in the 2012 cohort, likely due to less severe MIs as a result of using more sensitive troponin assays (23). Third, we did not collect haemodynamic variables in analysing clinical presentations as these were very inconsistently reported. Fourth, our mortality meta-analyses relied on crude mortality rates reported in each study, with 56% of studies (15-20, 23-29, 31, 32, 35, 36, 38, 41-43, 46, 47) also undertaking multivariate regression and/or competing risk analyses and reporting adjusted mortality rates which, for the T2MI cohorts in general, tended to be lower, and the differences in rates compared to those of T1MI were of smaller magnitude. Fifth, we did not analyse 30-day readmission rates as these were reported in only three studies (13, 14, 24). Sixth, we did not perform sensitivity analyses comparing results of prospective versus retrospective studies, as neither group demonstrated less or more risk of bias than the other, or compare results of good quality studies against fair/poor quality studies as the latter comprised only 16.7% (22,001/131,823) of all patients. Finally, we did not attempt subanalyses based on risk stratification using validated risk scores or seek to identify predictive models for mortality, as such analyses were reported in only two studies (27, 41).

The strengths of this review are the inclusion of all contemporary cohort studies in the troponin era, analysis of a broader range of variables than those of previous studies, and the more precise discernment of clinically meaningful differences between the two MI populations in patient characteristics, patterns of care and outcomes.

Our findings help to inform clinical diagnosis and management, hospital coding and epidemiological trending, quality of care indicators and inter-hospital benchmarking of performance relating to the care of patients with a diagnosis of T2MI.

Conclusion

This review has identified differences between T2MI and T1MI patients in presenting clinical features, investigation and management profiles, and clinical outcomes with greater scope and precision than previously reported. These findings may assist clinicians to better recognise T2MI and advise patients about its sequelae. The review has also helped define persisting gaps in our understanding of the utility and prognostic effects of invasive investigations, revascularization strategies and cardioprotective medications in T2MI patients that can only be remedied by conducting more randomised trials that enrol such patients.

Tables

Table 1. Pre-	existing me	dical con	ditions i	n patients v	with T2M	l versus	T1MI.
		т2МІ					
Pre-existing medical condition	Number of patients with the specified condition	Total number of patients	%	Number of patients with the specified condition	Total number of patients	%	Odds ratio* (95% CI)
CAD	3915	11706	33.4%	27538	110213	25.0%	1.13 [0.96, 1.32]
Type 2 DM	3420	13560	25.2%	27169	110833	24.5%	0.98 [0.86, 1.10]
HTN	8296	12424	66.8%	64648	105505	61.3%	1.22 [1.05, 1.43]
Dyslipidaemia	4626	10652	43.4%	40099	87366	45.9%	0.74 [0.58, 0.94]
Smoker	4213	11332	37.2%	49796	92377	53.9%	0.61 [0.50, 0.74]
Obesity	1225	3672	33.4%	30963	56970	54.3%	0.63 [0.46, 0.87]
Renal failure	2002	7443	26.9%	15969	82882	19.3%	1.89 [1.59, 2.25]
Heart failure	1949	10276	19.0%	7471	91700	8.1%	2.34 [1.87, 2.93]
PVD	584	5856	10.0%	2066	41280	5.0%	1.33 [1.05, 1.69]
CVD	1164	9941	11.7%	7669	105310	7.3%	1.48 [1.30, 1.69]
Atrial fibrillation	836	3645	22.9%	1220	19843	6.1%	3.02 [2.29, 3.99]
COPD	800	5018	15.9%	823	48375	1.7%	1.94 [1.22, 3.08]
Illicit drug Use	46	204	22.5%	8	220	3.6%	8.15 [1.03, 64.46]

*Comparing T2MI with T1MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: CAD- coronary heart disease, DM- diabetes mellitus, HTN- hypertension, BMI- body mass index, PVD- peripheral vascular disease, CVD- cerebrovascular disease, COPD- chronic obstructive pulmonary disease

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Table 2. Medical management and invasive interventions in patients with T2MI versus T1MI.

		T2MI			T1MI				
Intervention	No. patients receiving intervent ion	Total numbe r of % patient s		No. patients receiving intervention	Total number of patients	%	Odds ratio* (95% CI)		
Medication		•	-	•					
Beta blockers	6113	9926	61.6%	78733	100645	78.2%	0.46 [0.34, 0.62]		
ACEI / ARB	4692	9245	50.8%	69684	99281	70.2%	0.52 [0.41, 0.66]		
Anti-platelets	5742	10002	57.4%	88612	101492	87.3%	0.24 [0.17, 0.36]		
Anti-coagulants	1738	6658	26.1%	17048	79903	21.3%	1.90 [1.17, 3.10]		
Anti-anginal agents	2322	3594	64.6%	55149	60256	91.5%	0.51 [0.26, 1.00]		
Diuretics	2042	4388	46.5%	11877	63267	18.8%	1.99 [1.56, 2.53]		
Statins	4344	7858	55.3%	71915	82430	87.2%	0.25 [0.17, 0.36]		
Invasive									
PCI	2267	11339	20.0%	78009	103913	75.1%	0.06 [0.04, 0.10]		
CABG	117	4854	2.4%	4010	66219	6.1%	0.23 [0.12, 0.42]		

*Comparing T2MI with T1MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: ACEI- Angiotensin converting enzyme inhibitors, ARB- Angiotensin receptor blockers; CI=confidence interval; T2MI=type 2 myocardial infarction; T1MI=type 1 myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft

		T2MI					
Outcomes	No. patients with outcome	Total number of patients	%	No. patients with outcome	Total number of patients	%	Odds rat (95% C
CV in-hospital mortality	212	3512	6.0%	891	23736	3.8%	1.17 [0.70,
All-cause in- hospital mortality	667	5321	12.5%	1508	25997	5.8%	1.94 [1.35,
Short-term all- cause mortality	204	887	23.0%	250	1998	12.5%	1.34 [0.63
1-year all-cause mortality	979	4743	20.6%	3660	41691	8.8%	2.94 [2.07
2-year all-cause mortality	246	926	26.6%	428	2587	16.5%	1.63 [1.11
3-year all-cause mortality	193	525	36.8%	710	4305	16.5%	2.00 [1.07
Long-term all- cause mortality	1453	2708	53.7%	1320	4633	28.5%	3.24 [2.73
effects meta-anal Abbreviations: CV	ysis '- Cardiovaso	cular, MACE- I	Major adve	rse cardiova	scular event		
effects meta-anal Abbreviations: CV	ysis '- Cardiovaso	cular, MACE- I	Major adve	rse cardiova	scular event		
effects meta-anal Abbreviations: CV	ysis '- Cardiovaso	cular, MACE- I	Major adve	rse cardiova	scular event	s; T2MI=ty	
*Comparing T1MI effects meta-anal Abbreviations: CV infarction; T1MI=t	ysis '- Cardiovaso	cular, MACE- I	Major adve	rse cardiova	scular event	s; T2MI=ty	
effects meta-anal Abbreviations: CV	ysis '- Cardiovaso	cular, MACE- I	Major adve	rse cardiova	scular event	s; T2MI=ty	
effects meta-anal Abbreviations: CV	ysis '- Cardiovaso	cular, MACE- I	Major adve	rse cardiova	scular event	s; T2MI=ty	
effects meta-anal Abbreviations: CV	ysis '- Cardiovaso	cular, MACE- I	Major adve	rse cardiova	scular event	s; T2MI=ty	
effects meta-anal Abbreviations: CV	ysis '- Cardiovaso	cular, MACE- I	Major adve	rse cardiova	scular event	s; T2MI=ty	
effects meta-anal Abbreviations: CV	ysis '- Cardiovaso	cular, MACE- I	Major adve	rse cardiova	scular event	s; T2MI=ty	

Contribution Statement

All authors contribute equally to the research proposal, data acquisition and analysis, as well as, the manuscript preparation.

Competing Interests

The authors declare there are no conflict of interest with respect the article.

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Data Sharing Statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Ethic Approval Statement

No ethics approval was sought for this research project as no patient data was used.

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	T2M		T1N			Odds Ratio			
Study or Subgroup			Events		Weight	M-H, Random, 95%		T M-H, Rand	om, 95% CI
Arora 2018	89	264	96	775	11.8%	3.60 [2.58, 5.0	12]	ebr	-
Baron 2015	347	1403	2361	17488	12.9%	2.11 [1.85, 2.3	9]	uary	•
Chapman 2020	258	1121	720	4981	12.8%	1.77 [1.51, 2.0	18]	202	•
El haddad 2012	84	295	28	512		6.88 [4.36, 10.8	[7]		
Furie 2019	80	206	93	349	11.5%	1.75 [1.21, 2.5	[2]	lowr	-
Lopez Cuenca 2016	27	117	102	707	10.6%	1.78 [1.10, 2.8	[7]	nloac	
Radovanovic 2017	14	1091		13828	9.9%	1.52 [0.87, 2.6	ן טי ודי	ded t	
Saaby 2014 Stein 2014	65 15	119	25	360	10.0%	16.13 [9.37, 27.7	/] 61	from	
Stein 2014	15	127	118	2691	9.8%	2.92 [1.65, 5.1	oj .	http	-
Total (95% CI)		4743		41691	100.0%	2.94 [2.07, 4.1]	71	://b	•
						210 1 [2101]	41	3	•
Total events	979		3660			2101 [2101]	'I	February 2022. Downloaded from http://bmjope	Ŧ
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Total events	0.24; Chř	= 96.2	9, df = 8 (0.01	ë 	
Total events Heterogeneity: Tau ² = Test for overall effect:	0.24; Chř Z = 6.03 (= 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); I² =	92%	0.01 . F	D.1 1 Svours T1MI	Favours T2MI
Total events Heterogeneity: Tau ² =	0.24; Chř Z = 6.03 (= 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); I² =	92%	0.01 F	3 0.1 1 Sours T1MI	Favours T2MI
Total events Heterogeneity: Tau ² = Test for overall effect:	0.24; Chř Z = 6.03 (= 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); I² =	92%	0.01 . Finatients co	a 0.1 1 Syours T1MI	Favours T2MI
Total events Heterogeneity: Tau ² = Test for overall effect:	0.24; Chř Z = 6.03 (= 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); I² =	92%	0.01 . Fi	popared to T	Favours T2MI
Total events Heterogeneity: Tau ² = Test for overall effect:	0.24; Chř Z = 6.03 (= 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); I² =	92%	0.01 . Fi	popared to T	Favours T2MI
Total events Heterogeneity: Tau ² = Test for overall effect:	0.24; Chř Z = 6.03 (= 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); I² =	92%	0.01 . Fi	popared to T	Favours T2MI
Total events Heterogeneity: Tau ² = Test for overall effect:	0.24; Chř Z = 6.03 (= 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); I² =	92%	0.01 . Finatients co	poppared to T	Favours T2MI
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Total events Heterogeneity: Tau ² = Test for overall effect:	0.24; Chř Z = 6.03 (= 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); I² =	92%	0.01 . Finatients co	poppared to T	Favours T2MI
Total events Heterogeneity: Tau ² = Test for overall effect:	0.24; Chř Z = 6.03 (= 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); I² =	92%	0.01 . Finatients co	popared to T	Favours T2MI

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— —									Odds Ratio
		T2M		T1M			Odds Ratio		
-	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	-	M-H, Random, 95% CI
	Chapman 2018	268	429	430		28.3%	2.87 [2.28, 3.61]		
	Raphael 2020	766	1054	638			3.03 [2.55, 3.60]	uary	
	Singh 2020	419	1225	252	2097	35.5%	3.81 [3.19, 4.54]		
	Total (95% CI)		2708		4633	100.0%	3.24 [2.73, 3.84]		
	Total events	1453		1320					
	Heterogeneity: Tau ² =	0.01; Chř	= 4.84	, df = 2 (F	e 0.09	3); I² = 599	6		
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			i meta-	analysis c	of the ri	sk long-tei	rm mortality of T2MI pati		mpared to T1MI patients.
				analysis c	of the ri	<u>sk long-te</u>	rm mortality of T2MI pati		

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Table	S1. Evolving definitions of Type 2 Myocardial Infarction.
Year	Universal Definition of Type 2 Myocardial Infarction
2007	Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrythmias,
	hypotension or hypertension
2012	Instances of myocardial injury with necrosis where a condition other than coronary artery disease contributes to an imbalance between myocardial oxygen supply and/or demand e.g. coronary artery spasm, coronary embolism, anaemia, arrythmias, hypotension or hypertension
2018	 Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following: Symptoms of acute myocardial ischaemia New ischaemic ECG changes Development of pathological Q waves Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology

 Table S1. MEDLINE search strategy.

 (type 2 adj3 myocard*) OR (type-2 adj3 myocard*) OR (type II adj3 myocard*) OR (type-II adj3 myocard*) OR (type 2 adj3 MI) OR (type-2 adj3 MI) OR T2MI OR (supply demand adj3 myocard*)

Table S2. EMBASE search strategy.

('type 2' NEXT/3 myocard*) OR ('type-2' NEXT/3 myocard*) OR ('type ii' NEXT/3 myocard*) OR ('type-ii' NEXT/3 myocard*) OR ('type 2' NEXT/3 mi) OR ('type-2' NEXT/3 mi) OR ('t2mi') OR ('supply demand' NEXT/3 myocard*)

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Table S4. St	-		STICS.				Voriak	17		
Author,	Patie	ents	Design	Definition	Pre-existing		Variak Investigatio	Tropenin	Manageme	
Year	T1MI	T2MI	Design	of MI	conditions	Symptoms	ns	Values	nt	Progn
Arora, 2018 (1)	775	264	Retrospective	2012	x		X	* 2022.	x	x
Balanescu, 2020 (2)	152	49	Retrospective	2018		x	x	Down	x	
Baron, 2015 (3)	17488	1403	Prospective	2007	x	x	x	oaded	x	x
Baron, 2016 (4)	40501	1313	Prospective	2007	x	x	x	from h	x	
Bonaca, 2012 (5)	359	42	Prospective	2007				ttp://br		
Cediel, 2017 (6)	376	194	Retrospective	2012	x	x	x	njopen		x
Chapman, 2018 (7)	1171	429	Prospective	2012	x	101	x	.bmj.co	x	x
Chapman, 2020 (8)	4981	1121	Prospective	2018	x	x	x	m/on		x
Consuegra- Sanchaz, 2018 (9)	125	75	Retrospective	2012	х	x	x	Downloaded from http://brnjopen.bmj.com/on June 21, 2		
El-Haddad, 2012 (10)	512	295	Retrospective	2012			,	2024 by		х
Etaher, 2020 (11)	97	121	Prospective	2018	x		x	/ guest.	x	
Furie, 2019 (12)	349	206	Retrospective	2012	x	х	х		x	х
Guimaraes, 2018 (13)	847	76	Retrospective	2012	x		х	Protected by copyright	x	х

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Hawatmeh, 2020 (14)	664	281	Retrospective	2012	х		х	1-055755 o	x	
Higuchi, 2019 (15)	12023	491	Retrospective	2012	х		Х	on 17 F	х	x
Javed, 2009 (16)	143	64	Retrospective	2007	х		Х	r February		x
Kadesjo, 2019 (17)	1111	251	Retrospective	2018	х			2022.	x	x
Lambrecht, 2018 (18)	360	119	Prospective	2007	х		х	Down		x
Landes, 2016 (19)	107	107	Retrospective	2012	х	х	х	oaded		
Lopez- Cuenca, 2016 (20)	707	117	Retrospective	2012	x	х	х	2022. Downloaded from http://bmjopen.bmj.com/on June	x	x
Meigher, 2016 (21)	340	452	Retrospective	2012	x	х	х	toľXd//		x
Nestelberg er, 2017 (22)	684	128	Prospective	2012	х	10	х	oen.bmj.co	x	x
Neumann, 2017 (23)	188	99	Prospective	2012	х	1	х	om/Xou		x
Paiva, 2015 (24)	764	236	Retrospective	2012	х		x	June 2		x
Pandey, 2020 (25)	97	103	Prospective	2018	х			1, 202		
Putot, 2018 (26)	2036	847	Prospective	2012	х		х	4 b <u>¥</u> gu		x
Putot, 2019 (27)	365	254	Retrospective	2018	х		Х	21, 2024 by gluest. Protected by copyright		x
Putot, 2020 (28)	3710	862	Retrospective	2012	х		х	otecte		x
Radovanovi c, 2017 (29)	13828	1091	Retrospective	2012	х		х	d by c	x	x

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Raphael, 2020 (30)	1365	1054	Retrospective	2018	х		Х	5755 oi	х	>
Reed, 2017 (31)	88	162	Retrospective	2012			x	n 17 Fe	x	
Saaby 2013 (32)	397	144	Prospective	2007	х		x	17 February		
Saaby, 2014 (33)	360	119	Prospective	2007	х		x	20 <u>2</u> 2.	x	>
Sandoval, 2014 (34)	66	190	Retrospective	2012	х	x	x	Down		>
Sandoval, 2017 (35)	77	140	Prospective	2012	х	x	x	2022. Downloaded from http://bmjogen.bmj.com/ on June	x	>
Sato, 2020 (36)	2834	155	Prospective	2012	x		x	from h	x	>
Shah, 2015 (37)	1171	429	Prospective	2012	x	x	x	ttp://br	x	>
Singh, 2020 (38)	2097	1225	Retrospective	2018	x		х	njopen Xen	x	>
Smilowitz, 2018 (39)	137	146	Prospective	2012	х	x	х	.bmj.cc	x	>
Stein, 2014 (40)	2691	127	Prospective	2007	х	x	x	m/ on	x	>
Truong, 2020 (41)	275	175	Retrospective	2012	х	Х	X	June 2	Х	>
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Table S5. Ris	k of bias ass	essment					omjopen-2021-055755		
		Se	lection		Comparability		Outcome		
Author, Year	Representa tive of Exposed Cohort	Selection of Non- exposed	Ascertainme nt of Exposure	Outcome was not present at start	Comparability of Cohorts	Assessment	17 February Follow-upp Length	Adequacy of Follow- Up	Summary
Arora, 2018 (1)	х	x	x	x	x	x	2022. x	x	8 (good quality
Balanescu, 2020 (2)	0	x	x	x	x	x	0 vnloaded x	x	6 (fair quality)
Baron, 2015 (3)	x	x	x	x	x	x		x	8 (good quality
Baron, 2016 (4)	x	x	x	x	x	x	from http://bm x x	x	8 (good quality
Bonaca, 2012 (5)	x	x	х	x	x	x	p://bm x	x	8 (good quality
Cediel, 2017 (6)	х	x	х	x	x	x	x x	x	8 (good quality
Chapman, 2018 (7)	x	x	х	x	x	x	x x x	x	8 (good quality
Chapman, 2020 (8)	x	x	х	х	х	x	<u></u> ζ	x	8 (good quality
Consuegra- Sanchaz, 2018 (9)	0	0	х	x	0	x	une 21, 21	0	3 (poor quality
El-Haddad, 2012 (10)	x	x	х	x	x	0	024 by	0	5 (fair quality)
Etaher, 2020 (11)	х	x	х	x	x	x	guest. x	x	8 (good quality
Furie, 2019 (12)	х	x	х	x	x	x	Protected by copyright.	x	8 (good quality
Guimaraes, 2018 (13)	0	0	х	х	0	x	0 b	x	4 (fair quality)

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Hawatmeh, 2020 (14)	0	0	x	x	0	x	x o	0	4 (fair qual
Higuchi, 2019 (15)	0	0	x	x	x	x	ת ד X ד X	1	5 (fair qual
Javed, 2009 (16)	х	x	x	x	x	x	ebruary x x	x	8 (good qua
Kadesjo, 2019 (17)	х	x	×	x	x	x	x x		8 (good qua
Lambrecht, 2018 (18)	х	x	x	x	x	x	x	x	8 (good qua
Landes, 2016 (19)	х	x	x	x	x	x	vaded x	x	8 (good qua
Lopez- Cuenca, 2016 (20)	х	x	x	ex.	x	x	x nup:	x	8 (good qua
Meigher, 2016 (21)	х	x	x	x	x	x	x ao[ua/v	x	8 (good qua
Nestelberger , 2017 (22)	х	x	x	x	x	x	x x	x	8 (good qua
Neumann, 2017 (23)	х	x	x	x	x	x	y.com/ x	x	8 (good qua
Paiva, 2015 (24)	х	x	x	x	x	x	x	x	8 (good qua
Pandey, 2020 (25)	0	0	x	0	x	0	e z1, z 0	0	2 (poor qua
Putot, 2018 (26)	х	x	x	x	x	x	x	x	8 (good qua
Putot, 2019 (27)	х	x	x	x	x	0	y gues	x	7 (good qua
Putot, 2020 (28)	х	x	x	x	x	x	. Prote х	x	8 (good qua
Radovanovic, 2017 (29)	х	x	x	x	x	х	x cted by	x	8 (good qua

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Raphael, 2020 (30)	x	x	x	x	x	x	55755 o x	x	8 (good qualit
Reed, 2017 (31)	х	x	x	x	x	x	ر ر		8 (good qualit
Saaby 2013 (32)	х	x	x	x	x	x	17 February x x x	x	8 (good qualit
Saaby, 2014 (33)	х	x	×	x	x	x	x x	x	8 (good quali
Sandoval, 2014 (34)	х	x	x	x	x	x		x	8 (good qualit
Sandoval, 2017 (35)	х	х	x	x	x	x	x Downloaded	x	8 (good quali
Sato, 2020 (36)	0	0	0	x	0	0	x x	x	2 (poor qualit
Shah, 2015 (37)	х	x	x	x	x	x	from http://br	x	8 (good qualit
Singh, 2020 (38)	0	0	x	x	x	x	x x	x	6 (fair quality
Smilowitz, 2018 (39)	х	х	0	x	x	x	njopen.bmj.cc x x x	x	7 (good qualit
Stein, 2014 (40)	х	х	0	x	x	x	x x	x	7 (good qualit
Truong, 2020 (41)	х	x	x	x	x	x	June 2	x	8 (good qualit
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Precipitating Factor	Events	Patients	%	
Sepsis	1116	3110	35.9	
Arrhythmia	2047	6868	29.8	
Heart failure	958	3346	28.69	
Valvular abnormality	351	1301	27.0	
Anaemia	1692	6281	26.99	
Respiratory failure	762	4424	17.29	
Non-cardiac surgery	103	841	12.29	
Infection	361	3412	10.69	
Shock/hypotension	291	3006	9.7%	
Hypertension	321	3620	8.9%	
Pulmonary oedema	33	380	8.7%	
Chronic obstructive pulmonary disease	137	1661	8.2%	
Bradycardia	35	484	7.2%	
Renal failure	133	1956	6.8%	
Stroke	68	1731	3.9%	
Coronary spasm	36	1048	3.4%	
Bleeding	53	1834	2.9%	
Coronary endothetial dysfunction	1	592	0.2%	

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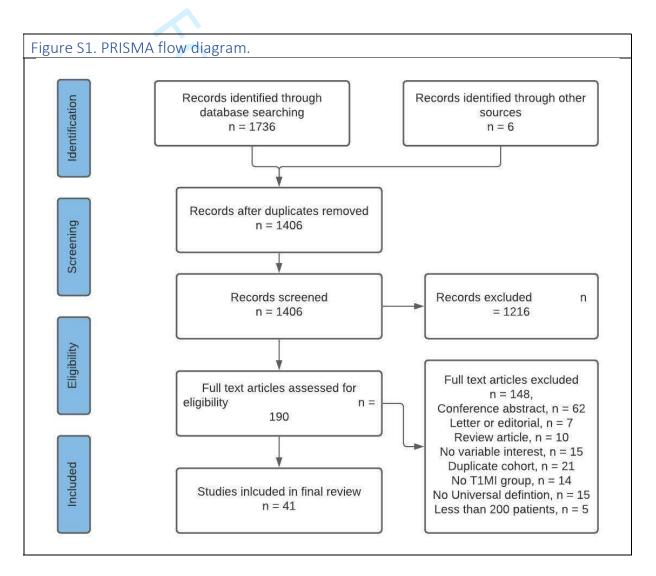
		T2MI			T1MI		
Presenting Symptom	No. patients with presenting symptom	Total number of patients	%	No. patients with presenting symptom	Total number of patients	%	Odds ratio * [95% Cl]
Chest pain	4344	7335	59.2%	73103	83371	87.7%	0.19 [0.15, 0.26]
Dyspnoea	1681	6080	27.6%	8154	82617	9.9%	2.83 [1.96, 4.08]
Arm or shoulder discomfort	28	330	8.5%	50	143	35.0%	0.18 [0.11, 0.30]
Jaw or neck discomfort	6	140	4.3%	12	77	15.6%	0.24 [0.09, 0.68]
Epigastric discomfort	8	140	5.7%	8	77	10.4%	0.52 [0.19, 1.45]
Nausea or vomiting	46	330	13.9%	39	143	27.3%	0.46 [0.28, 0.74]
Fatigue	5	140	3.6%	5	77	6.5%	0.53 [0.15, 1.90]
Diaphoresis	16	140	11.4%	16	77	20.8%	0.49 [0.23, 1.05]
Other nonspecific symptoms	1252	2932	42.7%	4096	58884	7.0%	4.19 [0.72, 24.39]
Collapse / syncope	99	2125	4.7%	157	7152	2.2%	2.10 [1.05, 4.18]

*Comparing T2MI with T1MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: URL- upper reference limit; STEMI- ST elevation myocardial infarction; NSTEMI- Non- ST elevation myocardial infarction; MI- Myocardial infarction; cTn- cardiac troponin; T1MI- Type 1 myocardial infarction; T2MI- Type 2 myocardial infarction; ECG- electrocardiogram; CAD- coronary artery disease; PCI- percutaneous coronary intervention; CABG- coronary artery bypass graft; IHD- ischaemic heart disease; MACE- Major adverse cardiovascular events; CI-confidence interval

		T2MI			T1MI		
Variable	No. patients with nominate d diagnostic findings	Total no. patient s	%	No. patients with nominate d diagnostic findings	Total no of patient s	%	Odds ratio (95% CI)
ECG	0						
ST elevation	1265	9417	13.4%	42726	101584	42.1%	0.22 [0.18, 0.
ST depression or T wave Inversion	2174	6314	34.4%	14938	68530	21.8%	1.38 [0.94, 2.
Pathological Q Waves	30	447	6.7%	177	850	20.8%	0.38 [0.20, 0.
Non-specific ST-T wave changes	146	592	24.7%	45	417	10.8%	2.62 [1.81, 3.
Left bundle branch block	338	3330	10.2%	3045	60031	5.1%	1.72 [1.40, 2.
Atrial fibrillation/flutter	448	1660	27.0%	1871	18272	10.2%	3.70 [2.87, 4.
Echocardiograph							
Echocardiogram performed	648	1353	47.9%	1571	2830	55.5%	0.44 [0.20, 0.
Presence of RWMA	97	286	33.9%	101	214	47.2%	0.48 [0.06, 3.
Angiogram							
Angiogram performed	3686	10721	34.4%	56242	67432	83.4%	0.09 [0.06, 0.
Obstructive coronary artery disease present	1246	3663	34.0%	19923	44404	44.9%	0.16 [0.05, 0.
Multivessel disease present	593	2147	27.6%	11839	41715	28.4%	0.40 [0.19, 0.
*Comparing T2MI with effects meta-analysis RWMA=regional wall m							

Table S9. Troponin mea	surements.									
Troponin Measurement Number of Studies T1MI (min-max) T2MI (min-max)										
Baseline cTn (xULN)	12	0.14-190	0.1-8.2							
6h cTn (xULN)	4	13.2-142	4.25-11							
Peak cTn (xULN)	21	5.1-1703	2.8-447							
Abbreviations: xULN= times	s upper limit normal		1							



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	T2M	I.	T1N	41		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95
Arora 2018	56	264	209	775	3.6%	0.73 [0.52, 1.02]		-
Baron 2015	563	1403	5316	17488	4.2%	1.53 [1.37, 1.72]		-
Bonaca 2012	380	1313	9998	40501	4.1%	1.24 [1.10, 1.40]		-
Cediel 2017	41	194	120	376	3.3%	0.57 [0.38, 0.86]		
Chapman 2018	191	429	497	1171	3.9%	1.09 [0.87, 1.36]		+
Chapman 2020	454	1121	1519	4981	4.1%	1.55 [1.36, 1.77]		-
Conseugra Sanchez 2018	30	75	69	125		0.54 [0.30, 0.97]		
Etaher 2020	95	171	63	97	2.9%	0.67 [0.40, 1.13]		-+
Furie 2019	119	206	220	349	3.5%	0.80 [0.56, 1.14]		-
Guimares 2018	37	76	416	847	3.1%	0.98 [0.61, 1.57]		+
Hawatmeh 2020	127	281	387	664	3.7%	0.59 [0.45, 0.78]		+
Higuchi 2019	65	491	1120	12023	3.8%	1.49 [1.14, 1.94]		-
Kadesjo 2019	48	251	48	1111	3.2%	5.24 [3.42, 8.03]		-
Landes 2016	68	107	50	107	2.8%	1.99 [1.15, 3.43]		
Lopez Cuenca 2016	19	117	101	707	2.8%	1.16 [0.68, 1.99]		
Meigher 2016	59	452	51	340	3.3%	0.85 [0.57, 1.27]		-+
Nestelberger 2020	0	128	283	684	0.3%	0.01 [0.00, 0.09]	+	-
Neumann 2017	14	99	55	188	2.5%	0.40 [0.21, 0.76]		
Pandey 2020	47	103	47	97	2.8%	0.89 [0.51, 1.56]		-
Putot 2018	291	847	407	2036	4.0%	2.09 [1.75, 2.50]		
Putot 2020	319	862	853	3710	4.1%	1.97 [1.68, 2.30]		+
Radovanovic 2017	401	1091	3817	13828	4.1%	1.52 [1.34, 1.73]		-
Saaby 2013	39	144	96	397	3.2%	1.16 [0.75, 1.80]		+-
Saaby 2014	26	119	71	360	2.9%	1.14 [0.69, 1.89]		+
Sandoval 2014	27	190	20	66	2.4%	0.38 [0.20, 0.74]		
Sandoval 2017	24	140	24	77	2.4%	0.46 [0.24, 0.88]		
Sato 2020	18	155	350	2834	3.0%	0.93 [0.56, 1.54]		+
Shah 2015	191	429	497	1171	3.9%	1.09 [0.87, 1.36]		+
Smilowitz 2018	28	146	26	137	2.6%	1.01 [0.56, 1.83]		+
Stein 2014	56	127	756	2691	3.5%	2.02 [1.41, 2.89]		
Troung 2020	82	175	52	275	3.2%	3.78 [2.48, 5.77]		
Total (95% CI)		11706		110213	100.0%	1.13 [0.96, 1.32]		•
Total events	3915		27538					
Heterogeneity: Tau ² = 0.15;	Chi ² = 291	.95, df =	= 30 (P < 0	0.00001)	; l ² = 90%		0.01	0.1 1
Test for overall effect: Z = 1.	.47 (P = 0.1	14)					0.01	0.1 T T1MI T2MI

Study or Subgroup Arora 2018 Baron 2015	T2M		7.48		lellitus		011.0.0
Arora 2018 Baron 2015			T1M Events		Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% Cl
Baron 2015	Events 110	264	371	775	3.3%	0.78 [0.59, 1.03]	m-n, Kandoni, 55% Cr
	376	1403	3882	17488	3.8%	1.28 [1.13, 1.45]	
Baron 2016	306	1313	9395	40501	3.8%	1.01 [0.88, 1.15]	Ļ
Cediel 2017	73	194	132	376	2.9%	1.12 [0.78, 1.60]	
Chapman 2018	93	429	185	1171	3.3%	1.48 [1.12, 1.95]	-
Chapman 2020	147	1121	802	4981	3.6%	0.79 [0.65, 0.95]	-
Conseugra Sanchez 2018	29	75	59	125	2.1%	0.71 [0.39, 1.26]	-+
Etaher 2020	64	171	36	97	2.3%	1.01 [0.61, 1.70]	+
Furie 2019	100	206	199	349	3.0%	0.71 [0.50, 1.00]	-
Guimares 2018	27	76	419	847	2.4%	0.56 [0.35, 0.92]	
Hawatmeh 2020	101	281	303	664	3.2%	0.67 [0.50, 0.89]	
Higuchi 2019	148	491	3745	12023	3.6%	0.95 [0.78, 1.16]	t
Javed 2009	24	64	61	143	2.0%	0.81 [0.44, 1.48]	-
Kadesjo 2019	56	251	213	1111	3.1%	1.21 [0.87, 1.69]	T-
Lambrecht 2018	28	119	46	360	2.3%	2.10 [1.24, 3.55]	
Landes 2016	54	107	54	107	2.3%	1.00 [0.59, 1.71]	I
Lopez Cuenca 2016	52 122	117 452	336 126	707	2.8% 3.2%	0.88 [0.60, 1.31]	
Meigher 2016	26	128	120	340 684	2.5%	0.63 [0.46, 0.85]	-
Nestelberger 2020 Neumann 2017	12	99	42	188	1.8%	0.71 [0.45, 1.13] 0.48 [0.24, 0.96]	
Pandey 2020	47	103	44	97	2.2%	1.01 [0.58, 1.76]	
Putot 2018	264	847	504	2036	3.6%	1.38 [1.15, 1.64]	-
Putot 2019	99	254	138	365	3.1%	1.05 [0.76, 1.46]	+
Radovanovic 2017	286	1091	2766	13828	3.7%	1.42 [1.23, 1.64]	-
Raphael 2020	150	1054	313	1365	3.5%	0.56 [0.45, 0.69]	-
Saaby 2013	40	144	52	397	2.5%	2.55 [1.60, 4.07]	-
Saaby 2014	28	119	46	360	2.3%	2.10 [1.24, 3.55]	
Sandoval 2014	57	190	21	66	2.0%	0.92 [0.50, 1.68]	-
Sandoval 2017	43	140	32	77	2.1%	0.62 [0.35, 1.11]	+
Sato 2020	40	155	1015	2834	2.9%	0.62 [0.43, 0.90]	-
Shah 2015	93	429	185	1171	3.3%	1.48 [1.12, 1.95]	-
Singh 2020	165	1225	405	2097	3.6%	0.65 [0.53, 0.79]	<u> </u>
Smilowitz 2018	58	146	61	137	2.5%	0.82 [0.51, 1.32]	- -
Stein 2014	61	127	945	2691	3.0%	1.71 [1.19, 2.44]	
Troung 2020	41	175	56	275	2.6%	1.20 [0.76, 1.89]	E E
Total (95% CI)		13560		110833	100.0%	0.98 [0.86, 1.10]	4
Total events	3420		27169				
Heterogeneity: Tau ² = 0.10;	Chi ² = 208	.56, df =		0.00001);	l ² = 84%	I	
Test for overall effect: Z = 0.	39 (P = 0.7	70)					0.01 0.1 1 10 T1MI T2MI

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	T2M	í.	T1N	11		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events		Weight	M-H, Random, 95% CI		M-H, Random, 95%
Arora 2018	225	264	642	775	3.1%	1.20 [0.81, 1.76]		
Baron 2015	760	1403	8866	17488	3.7%	1.15 [1.03, 1.28]		E E
Baron 2016	962	1313	26334	40501	3.7%	1.47 [1.30, 1.67]		-
Cediel 2017	153	194	270	376	3.0%	1.47 [0.97, 2.21]		⊢
Chapman 2018	254	429	533	1171	3.5%	1.74 [1.39, 2.17]		+
Conseugra Sanchez 2018	54	75	91	125	2.3%	0.96 [0.51, 1.82]		-
Etaher 2020	128	171	56	97	2.6%	2.18 [1.28, 3.71]		_ - −
Furie 2019	159	206	265	349	3.0%	1.07 [0.71, 1.61]		+
Guimares 2018	60	76	688	847	2.5%	0.87 [0.49, 1.54]		-
Hawatmeh 2020	242	281	583	664	3.0%	0.86 [0.57, 1.30]		-
Higuchi 2019	311	491	7064	12023	3.6%	1.21 [1.01, 1.46]		+
Javed 2009	53	64	126	143	1.8%	0.65 [0.29, 1.48]		-+
Lambrecht 2018	66	119	193	360	3.0%	1.08 [0.71, 1.63]		+
Landes 2016	87	107	82	107	2.2%	1.33 [0.68, 2.57]		
Lopez Cuenca 2016	103	117	522	707	2.5%	2.61 [1.46, 4.67]		
Meigher 2016	289	452	224	340	3.3%	0.92 [0.68, 1.23]		+
Nestelberger 2020	92	128	521	684	3.0%	0.80 [0.52, 1.22]		-
Neumann 2017	77	99	154	188	2.4%	0.77 [0.42, 1.41]		-
Paiva 2015	192	236	580	764	3.1%	1.38 [0.96, 2.00]		
Pandey 2020	68	103	68	97	2.4%	0.83 [0.46, 1.50]		-
Putot 2018	683	847	1140	2036	3.6%	3.27 [2.70, 3.96]		
Putot 2019	211	254	279	365	3.0%	1.51 [1.01, 2.27]		L
Radovanovic 2017	802	1091	8504	13828	3.7%	1.74 [1.51, 2.00]		-
Raphael 2020	716	1054	966	1365	3.6%	0.87 [0.74, 1.04]		1
Saaby 2013	81	144	215	397	3.1%			1
Saaby 2013 Saaby 2014	66	119	193	360	3.0%	1.09 [0.74, 1.60] 1.08 [0.71, 1.63]		1
Sandoval 2014	125	190	49	66	2.3%			
Sandoval 2014 Sandoval 2017					2.2%	0.67 [0.36, 1.25]		
	104	140 155	62	77	3.2%	0.70 [0.35, 1.38]		1
Sato 2020	103		1885	2834		1.00 [0.71, 1.40]		_
Shah 2015 Singh 2020	254	429	533	1171	3.5%	1.74 [1.39, 2.17]		
Singh 2020	419	1225	970	2097	3.7%	0.60 [0.52, 0.70]		
Smilowitz 2018	128	146	118	137	2.2%	1.15 [0.57, 2.29]		
Stein 2014	108	127	1631	2691	2.7%	3.69 [2.25, 6.05]		
Troung 2020	161	175	241	275	2.3%	1.62 [0.84, 3.12]		
Total (95% CI)		12424		105505	100.0%	1.22 [1.05, 1.43]		+
Total events	8296		64648					.
Heterogeneity: Tau ² = 0.16;			= 33 (P <	0.00001);	$l^2 = 90\%$		0.01	0.1 1
Test for overall effect: Z = 2	.52 (P = 0.0	01)					0.01	T1MI T2MI

Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl M-H, Random, 95% Cl Arora 2016 548 131 14893 40501 3.5% 1.23 [1.10, 1.38] Chapman 2018 177 429 539 1171 3.4% 0.82 [0.66, 1.03] Conseugra Sanchez 2018 38 75 66 125 2.9% 0.92 [0.52, 1.63] Etaher 2020 89 171 48 97 3.1% 1.11 [0.67, 1.82] Fuire 2019 121 206 2.18 349 3.3% 0.86 [0.60, 1.22] Guimares 2018 58 76 625 847 3.0% 1.14 [0.66, 1.96] Hawatmeh 2020 205 281 505 664 3.3% 0.85 [0.63, 0.92] Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Landes 2016 62 107 69 107 2.9% 1.81 [0.99, 3.28] Lopez Cuenca 2016 89 117
Baron 2016 548 1313 14893 40501 3.5% 1.23 [1.10, 1.38] Chapman 2018 177 429 539 1171 3.4% 0.82 [0.66, 1.03] Conseugra Sanchez 2018 38 75 66 125 2.9% 0.92 [0.52, 1.63] Etaher 2020 89 171 48 97 3.3% 0.86 [0.60, 1.22] Guimares 2018 58 76 625 847 3.0% 1.11 [0.67, 1.82] Hawatmeh 2020 205 281 505 664 3.3% 0.86 [0.60, 1.22] Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Lambrecht 2018 48 119 137 360 3.2% 1.10 [0.72, 1.68] Landes 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Meigher 2016 194 452 180 340 3.4% 0.62 [0.61, 1.10] Parka 2015 125 236 442 764 3.4%
$\begin{array}{c c c c c c c c c c c c c c c c c c c $
$\begin{array}{c} \mbox{Conseugra Sanchez 2018} & 38 & 75 & 66 & 125 & 2.9\% & 0.92 [0.52, 1.63] \\ \mbox{Etaher 2020} & 89 & 171 & 48 & 97 & 3.1\% & 1.11 [0.67, 1.62] \\ \mbox{Furie 2019} & 121 & 206 & 218 & 349 & 3.3\% & 0.86 [0.60, 1.22] \\ \mbox{Guimares 2018} & 58 & 76 & 625 & 847 & 3.0\% & 1.14 [0.66, 1.98] \\ \mbox{Hawatneh 2020} & 205 & 281 & 505 & 664 & 3.3\% & 0.85 [0.62, 1.17] \\ \mbox{Higher 2019} & 174 & 491 & 5044 & 12023 & 3.5\% & 0.76 [0.63, 0.92] \\ \mbox{Javed 2009} & 34 & 64 & 113 & 143 & 2.8\% & 0.30 [0.16, 0.57] \\ \mbox{Lambrecht 2018} & 48 & 119 & 137 & 360 & 3.2\% & 1.10 [0.72, 1.68] \\ \mbox{Lambrecht 2016} & 82 & 107 & 69 & 107 & 2.9\% & 1.81 [0.99, 3.28] \\ \mbox{Lopez Cuenca 2016} & 89 & 117 & 530 & 707 & 3.1\% & 1.06 [0.67, 1.68] \\ \mbox{Meigher 2016} & 194 & 452 & 180 & 340 & 3.4\% & 0.67 [0.50, 0.89] \\ \mbox{Nestelberger 2020} & 46 & 128 & 440 & 684 & 3.2\% & 0.31 [0.21, 0.46] \\ \mbox{Paiva 2015} & 125 & 236 & 442 & 764 & 3.4\% & 0.82 [0.61, 1.10] \\ \mbox{Paiva 2015} & 125 & 236 & 442 & 764 & 3.4\% & 0.82 [0.61, 1.10] \\ \mbox{Paiva 2015} & 125 & 236 & 442 & 764 & 3.4\% & 0.88 [0.58, 1.51] \\ \mbox{Radovanovic 2017} & 631 & 1091 & 8076 & 13828 & 3.5\% & 0.98 [0.86, 1.11] \\ \mbox{Puto 2019} & 169 & 254 & 259 & 365 & 3.3\% & 0.81 [0.58, 1.15] \\ \mbox{Radovanovic 2017} & 631 & 1091 & 8076 & 13828 & 3.5\% & 0.98 [0.86, 1.11] \\ \mbox{Radovanovic 2017} & 61 & 140 & 50 & 77 & 2.9\% & 0.42 [0.23, 0.73] \\ \mbox{Sandoval 2014} & 48 & 119 & 137 & 360 & 3.2\% & 1.10 [0.72, 1.68] \\ \mbox{Sandoval 2014} & 48 & 119 & 137 & 360 & 3.2\% & 1.08 [0.73, 1.59] \\ \mbox{Sandoval 2014} & 48 & 119 & 137 & 366 & 3.2\% & 0.44 [0.23, 0.73] \\ \mbox{Sandoval 2017} & 61 & 140 & 50 & 77 & 2.9\% & 0.42 [0.23, 0.74] \\ \mbox{Sandoval 2014} & 48 & 119 & 137 & 3.0\% & 0.92 [0.55, 1.54] \\ \mbox{Sandoval 2014} & 428 & 190 & 36 & 66 & 2.9\% & 0.41 [0.23, 0.73] \\ \mbox{Sandoval 2014} & 426 & 40099 \\ \mbox{Heterogeneity: Tau^2 = 0.42; Chi^2 = 703.94, df = 30 (P < 0.00001); l^2 = 96\% \\ \mbox{Total (effect: Z = 2.50 (P = 0.01) \\ \mbox{Total events} & 4626 & 40099 \\ \mbo$
Etaher 2020 89 171 48 97 3.1% 1.11 [0.67, 1.82] Furie 2019 121 206 218 349 3.3% 0.86 [0.60, 1.22] Guimares 2018 58 76 625 847 3.0% 1.14 [0.66, 1.98] Hawatmeh 2020 205 281 505 664 3.3% 0.86 [0.62, 1.17] Higuchi 2019 174 491 5044 12023 3.5% 0.76 [0.63, 0.92] Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Lambrecht 2018 48 119 137 360 3.2% 1.10 [0.72, 1.68] Landes 2016 82 107 69 107 2.9% 0.81 [0.29, 0.89] Neestelberger 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Meigher 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] Paiva 2015 125 236 3.5%
Furite 2019 121 206 218 349 3.3% 0.86 0.060 1.22 Guimares 2018 58 76 625 847 3.0% 1.14 [0.66, 1.98] Hawatmeh 2020 205 281 505 664 3.3% 0.86 [0.62, 1.17] Higuchi 2019 174 491 5044 12023 3.5% 0.76 [0.63, 0.92] Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Lambrecht 2016 82 107 69 107 2.9% 1.81 [0.99, 3.28] Lopez Cuenca 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Meigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89]
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Hawatmeh 2020 205 281 505 664 3.3% 0.85 [0.62, 1.17] Higuchi 2019 174 491 5044 12023 3.5% 0.76 [0.63, 0.92] Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Lambrecht 2018 48 119 137 360 3.2% 1.10 [0.72, 1.68] Landes 2016 82 107 69 107 2.9% 1.81 [0.99, 3.28] Lopez Cuenca 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Meigher 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] Paixa 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] Paixa 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] Paixa 2015 125 236 442 764 3.4% 0.82 [0.68, 1.11] Radovanovic 2017 631 1091 8076 13828
Higuchi 2019 174 491 5044 12023 3.5% 0.76 [0.63, 0.92] Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Lambrecht 2018 48 119 137 360 3.2% 1.10 [0.99, 3.28] Lopez Cuenca 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Meigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89]
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Lambrecht 2018 48 119 137 360 3.2% 1.10 [0.72, 1.68] Landes 2016 82 107 69 107 2.9% 1.81 [0.99, 3.28] Lopez Cuenca 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Meigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89] Nestelberger 2020 46 128 440 684 3.2% 0.31 [0.21, 0.46] Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] Pandey 2020 38 103 51 97 3.0% 0.53 [0.30, 0.93] Putot 2018 419 847 919 2036 3.5% 1.19 [1.01, 1.40] Putot 2018 419 847 919 2036 3.5% 0.81 [0.58, 1.15] Radovanovic 2017 631 1091 8076 13828 3.5% 0.98 [0.86, 1.11] Raphael 2020 359 1054 790 1365 3.5% 0.38 [0.32, 0.44] Saaby 2013 60 144 158 397 3.2% 1.08 [0.73, 1.59] Saaby 2014 48 119 137 360 3.2% 1.10 [0.72, 1.68] Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sandoval 2017 61 40 50 77 2.9% 0.42 [0.23, 0.74] Stato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56] Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63] Total (95% CI) 10652 87366 100.0% 0.74 [0.58, 0.94] Total events 4626 40099 Heterogeneity: Tau ² = 0.42; Chi ² = 703.94, df = 30 (P < 0.00001); I ² = 96% Test for overall effect: Z = 2.50 (P = 0.01) T11
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Meigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89] Nestelberger 2020 46 128 440 684 3.2% 0.31 [0.21, 0.46]
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Radovanovic 2017 631 1091 8076 13828 3.5% 0.98 [0.86, 1.11] Raphael 2020 359 1054 790 1365 3.5% 0.38 [0.32, 0.44] Saaby 2013 60 144 158 397 3.2% 1.08 [0.73, 1.59] Saaby 2014 48 119 137 360 3.2% 1.10 [0.72, 1.68] Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56] * Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] * Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] * Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63] Total (95% CI) 10652 873
Raphael 2020 359 1054 790 1365 3.5% 0.38 $[0.32, 0.44]$ Saaby 2013 60 144 158 397 3.2% 1.08 $[0.73, 1.59]$ Saaby 2014 48 119 137 360 3.2% 1.10 $[0.72, 1.68]$ Sandoval 2014 63 190 36 66 2.9% 0.41 $[0.23, 0.74]$ Sandoval 2017 61 140 50 77 2.9% 0.42 $[0.23, 0.74]$ Sato 2020 95 155 1435 2834 3.3% 1.54 $[1.11, 2.15]$ Shah 2015 117 429 539 1171 3.4% 0.44 $[0.35, 0.56]$ -66 Singh 2020 172 1225 1229 2097 3.5% 0.12 $[0.10, 0.14]$ -66 Smilowitz 2018 102 146 98 137 3.0% 0.92 $[0.55, 1.54]$ 10652 87366 100.0% 0.74 $[0.58, 0.94]$ 0.01 0.1
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Saaby 2014 48 119 137 360 3.2% 1.10 [0.72, 1.68] Sandoval 2014 63 190 36 66 2.9% 0.41 [0.23, 0.73] Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56] Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63] Total (95% CI) 10652 87366 100.0% 0.74 [0.58, 0.94] Total events 4626 40099 0.01 0.11 Heterogeneity: Tau ² = 0.42; Chi ² = 703.94, df = 30 (P < 0.00001); l ² = 96% 0.01 0.1 Test for overall effect: Z = 2.50 (P = 0.01) T11 T11
Sandoval 2014 63 190 36 66 2.9% 0.41 [0.23, 0.73] Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56]
Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56]
Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56] - Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] - Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] - Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63] Total (95% CI) 10652 87366 100.0% 0.74 [0.58, 0.94] Total events 4626 40099
Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56] - Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] - Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63] Total (95% CI) 10652 87366 100.0% 0.74 [0.58, 0.94] Total events 4626 40099 Heterogeneity: Tau ² = 0.42; Chi ² = 703.94, df = 30 (P < 0.00001); I ² = 96% 0.01 0.1 Test for overall effect: Z = 2.50 (P = 0.01) T1
Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63] Total (95% CI) 10652 87366 100.0% 0.74 [0.58, 0.94] Total events 4626 40099 Heterogeneity: Tau ² = 0.42; Chi ² = 703.94, df = 30 (P < 0.00001); l ² = 96% 0.01 0.1 Test for overall effect: Z = 2.50 (P = 0.01) T11
Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63] Total (95% CI) 10652 87366 100.0% 0.74 [0.58, 0.94] Total events 4626 40099 Heterogeneity: Tau ² = 0.42; Chi ² = 703.94, df = 30 (P < 0.00001); l ² = 96% 0.01 0.1 Test for overall effect: Z = 2.50 (P = 0.01) T11
Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63] Total (95% CI) 10652 87366 100.0% 0.74 [0.58, 0.94] Total events 4626 40099 Heterogeneity: Tau ² = 0.42; Chi ² = 703.94, df = 30 (P < 0.00001); l ² = 96% 0.01 0.1 Test for overall effect: Z = 2.50 (P = 0.01) T11
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	T2M	1	T1N	11		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95%
Arora 2018	80	264	327	775	3.6%	0.60 [0.44, 0.80]		-
Baron 2015	765	1403	10248	17488	3.9%	0.85 [0.76, 0.94]		-
Baron 2016	771	1313	24754	40501	3.9%	0.90 [0.81, 1.01]		
Cediel 2017	62	194	218	376	3.5%	0.34 [0.24, 0.49]		-
Chapman 2018	62	429	380	1171	3.6%	0.35 [0.26, 0.47]		+
Conseugra Sanchez 2018	10	75	27	125	2.4%	0.56 [0.25, 1.23]		+
Etaher 2020	21	171	30	97	2.8%	0.31 [0.17, 0.59]		
Furie 2019	73	206	133	349	3.5%	0.89 [0.62, 1.28]		-
Guimares 2018	36	76	304	847	3.2%	1.61 [1.00, 2.58]		-
Hawatmeh 2020	88	281	272	664	3.6%	0.66 [0.49, 0.88]		-
Javed 2009	30	64	66	143	2.9%	1.03 [0.57, 1.86]		+
Lambrecht 2018	91	119	284	360	3.1%	0.87 [0.53, 1.42]		-+
Landes 2016	44	107	41	107	3.0%	1.12 [0.65, 1.94]		+
Lopez Cuenca 2016	23	117	232	707	3.2%	0.50 [0.31, 0.81]		-
Meigher 2016	172	452	129	340	3.6%	1.00 [0.75, 1.34]		+
Nestelberger 2020	21	128	181	684	3.1%	0.55 [0.33, 0.90]		
Neumann 2017	17	99	52	188	2.8%	0.54 [0.29, 1.00]		-
Pandey 2020	13	103	16	97	2.4%	0.73 [0.33, 1.61]		-+
Putot 2018	280	847	1271	2036	3.8%	0.30 [0.25, 0.35]		
Putot 2019	101	254	243	365	3.5%	0.33 [0.24, 0.46]		-
Radovanovic 2017	340	1091	5697	13828	3.9%	0.65 [0.57, 0.74]		+
Raphael 2020	462	1054	907	1365	3.8%	0.39 [0.33, 0.47]		-
Saaby 2013	35	144	129	397	3.3%	0.67 [0.43, 1.03]		-
Saaby 2014	91	119	284	360	3.1%	0.87 [0.53, 1.42]		-
Sandoval 2017	52	140	23	77	2.9%	1.39 [0.76, 2.52]		
Sato 2020	51	155	921	2834	3.5%	1.02 [0.72, 1.44]		+
Shah 2015	62	429	380	1171	3.6%	0.35 [0.26, 0.47]		+
Singh 2020	244	1225	1063	2097	3.8%	0.24 [0.21, 0.29]		•
Smilowitz 2018	96	146	89	137	3.2%	1.04 [0.63, 1.69]		+
Stein 2014	20	127	1095	2691	3.2%	0.27 [0.17, 0.44]		
Total (95% CI)		11332		92377	100.0%	0.61 [0.50, 0.74]		•
Total events	4213		49796					
Heterogeneity: Tau ² = 0.25;	Chi ² = 430	.67, df =	= 29 (P <	0.00001); I ² = 93%		0.01	0.1 1 1
Test for overall effect: Z = 5							0.01	0.1 1 1 T1MI T2MI

Figure S7	Forest Plot.	Obesity.
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	T2M	1	T1N	41		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Baron 2016	824	1313	27283	40501	21.6%	0.82 [0.73, 0.91]	
Javed 2009	14	64	54	143	11.0%	0.46 [0.23, 0.91]	
Pandey 2020	22	103	22	97	11.2%	0.93 [0.47, 1.81]	
Putot 2018	91	847	423	2036	19.7%	0.46 [0.36, 0.58]	-
Putot 2019	27	254	97	365	15.2%	0.33 [0.21, 0.52]	
Radovanovic 2017	247	1091	3084	13828	21.2%	1.02 [0.88, 1.18]	•
Total (95% CI)		3672		56970	100.0%	0.63 [0.46, 0.87]	•
Total events	1225		30963				25 25 25
Heterogeneity: Tau ² =	0.12; Chi ²	= 47.7.	2, df = 5 (P < 0.00	0001); l ² =	90%	0.01 0.1 1 10 10
Test for overall effect:	Z = 2.80 (P = 0.0	05)				0.01 0.1 1 10 10 T1MI T2MI

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Figure S8.	Forest Plot.	Chronic	Kidney Disease.
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	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Arora 2018	66	264	130	775	6.1%	1.65 [1.18, 2.32]	-
Baron 2015	624	1403	4669	17488	7.7%	2.20 [1.97, 2.46]	
Baron 2016	355	1313	8056	40501	7.6%	1.49 [1.32, 1.69]	×
Cediel 2017	51	194	42	376	5.2%	2.84 [1.80, 4.46]	
Etaher 2020	83	171	15	97	3.9%	5.16 [2.75, 9.65]	
Furie 2019	74	206	99	349	5.9%	1.42 [0.98, 2.04]	
Javed 2009	33	64	43	143	4.0%	2.48 [1.35, 4.54]	
Landes 2016	29	107	17	107	3.6%	1.97 [1.01, 3.85]	
Meigher 2016	86	452	54	340	5.8%	1.24 [0.86, 1.81]	+ −
Putot 2018	122	847	113	2036	6.6%	2.86 [2.19, 3.75]	
Putot 2019	55	254	45	365	5.3%	1.97 [1.28, 3.03]	
Radovanovic 2017	158	1091	982	13828	7.3%	2.22 [1.85, 2.65]	-
Saaby 2013	20	144	23	397	3.9%	2.62 [1.39, 4.94]	
Sandoval 2014	49	190	9	66	3.1%	2.20 [1.01, 4.78]	
Sandoval 2017	20	140	13	77	3.2%	0.82 [0.38, 1.76]	
Sato 2020	68	155	1261	2834	6.2%	0.97 [0.70, 1.35]	+
Smilowitz 2018	41	146	41	137	4.7%	0.91 [0.55, 1.53]	-
Stein 2014	45	127	328	2691	5.7%	3.95 [2.70, 5.79]	
Troung 2020	23	175	29	275	4.2%	1.28 [0.72, 2.30]	· -
Total (95% CI)		7443		82882	100.0%	1.89 [1.59, 2.25]	•
Total events	2002		15969				
Heterogeneity: Tau ² =	0.10; Chi ²	= 100.1	16, df = 1	8 (P < 0	.00001); P	= 82%	
Test for overall effect:					,1		0.01 0.1 1 10 T1MI T2MI

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Study or Subgroup Baron 2015 Baron 2016	Events			11		Odds Ratio	0	dds Ratio
		Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Ra	andom, 95% Cl
Baron 2016	288	1403	1854	17488	4.9%	2.18 [1.90, 2.50]		-
	151	1313	3035	40501	4.9%	1.60 [1.35, 1.91]		-
Cediel 2017	31	194	15	376	3.5%	4.58 [2.40, 8.71]		I
Chapman 2020	292	1121	792	4981	4.9%	1.86 [1.60, 2.17]		-
taher 2020	42	171	5	97	2.6%	5.99 [2.28, 15.72]		
urie 2019	66	206	96	349	4.4%	1.24 [0.85, 1.81]		<u>+</u> -
lawatmeh 2020	79	281	119	664	4.5%	1.79 [1.29, 2.48]		-
(adesjo 2019	40	251	91	1111	4.3%	2.12 [1.42, 3.17]		-
ambrecht 2018	26	119	32	360	3.8%	2.87 [1.63, 5.05]		
andes 2016	21	107	17	107	3.3%	1.29 [0.64, 2.61]		+-
opez Cuenca 2016	21	117	42	707	3.8%	3.46 [1.97, 6.10]		
Aeigher 2016	118	452	54	340	4.4%	1.87 [1.31, 2.68]		-
leumann 2017	25	99	36	188	3.7%	1.43 [0.80, 2.55]		+-
Putot 2018	231	847	71	2036	4.6%	10.38 [7.84, 13.75]		-
Putot 2019	78	254	36	365	4.2%	4.05 [2.62, 6.26]		
Radovanovic 2017	74	1091	290	13828	4.7%	3.40 [2.61, 4.42]		-
Raphael 2020	86	1054	26	1365	4.2%	4.58 [2.93, 7.15]		
Saaby 2013	34	144	45	397	4.0%	2.42 [1.48, 3.96]		
Saaby 2014	26	119	32	360	3.8%	2.87 [1.63, 5.05]		I
Sandoval 2014	46	190	7	66	2.9%	2.69 [1.15, 6.31]		
Sandoval 2017	40	140	10	77	3.2%	2.68 [1.25, 5.72]		
Sato 2020	13	155	433	2834	3.7%	0.51 [0.29, 0.90]	-	
Smilowitz 2018	75	146	61	137	4.1%	1.32 [0.82, 2.10]		†
Stein 2014	33	127	248	2691	4.3%	3.46 [2.28, 5.25]		-
roung 2020	13	175	24	275	3.3%	0.84 [0.42, 1.70]		+
otal (95% CI)		10276		91700	100.0%	2.34 [1.87, 2.93]		•
otal events	1949		7471					

	T2M		T1N	11		0	dds Ratio			Odds Ratio		
Study or Subgroup					Weight		Random, 95%	CI	M-I	H, Random, 95		
Arora 2018	46	264	111	775	6.3%		1.26 [0.87, 1.8					_
Cediel 2017	21	194	52	376	5.4%		0.76 [0.44, 1.3	-		-+		
Chapman 2018	29	429	85	1171	5.9%		0.93 [0.60, 1.4	-		-		
Furie 2019	28	206	56	349	5.6%		0.82 [0.50, 1.3					
Hawatmeh 2020	28	281	89	664	5.9%		0.72 [0.46, 1.1					
Higuchi 2019	8	491		12023	4.4%		1.08 [0.53, 2.2			-		
Lambrecht 2018	17	119	20	360	4.6%		2.83 [1.43, 5.6	-			-	
Lopez Cuenca 2016	11	117	57	707	4.6%		1.18 [0.60, 2.3			_ _		
Nestelberger 2020	2	128	72	684	2.0%		0.13 [0.03, 0.5			<u> </u>		
Putot 2018	110	847	138	2036	6.8%		2.05 [1.58, 2.6	-				
Putot 2019	55	254	54	365	6.0%		1.59 [1.05, 2.4	-				
Radovanovic 2017		1091		13828	7.0%		2.11 [1.70, 2.6			-		
Saaby 2013	18	144	21	397	4.7%		2.56 [1.32, 4.9					
Saaby 2014	17	119	20	360	4.6%		2.83 [1.43, 5.6	-			-	
Sandoval 2017	3	140	5	77	1.9%		0.32 [0.07, 1.3					
Sato 2020	14	155	121	2834	5.1%		2.23 [1.25, 3.9					
Shah 2015	29	429	82	1171	5.9%		0.96 [0.62, 1.4			-		
Smilowitz 2018	11	146	13	137	3.8%		0.78 [0.34, 1.8					
Stein 2014	22	127	229	2691	5.7%		2.25 [1.40, 3.6	-				
Troung 2020	12	175	9	275	3.6%		2.18 [0.90, 5.2					
Total (95% CI)		5856		41280	100.0%		1.33 [1.05, 1.6	91		•		
Total events	584		2066							ľ		
Heterogeneity: Tau ² =		= 81.8		(P < 0)	10001)· I ² :	= 77%		⊢				_
Test for overall effect:								0.0	1 0.1	1 T1MI T2MI	10	1

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	T2M		T1N	11		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	1	M-H, Random, 95% C
Baron 2015	195	1403	1609	17488	7.1%	1.59 [1.36, 1.87]		-
Baron 2016	99	1313	2696	40501	6.6%	1.14 [0.93, 1.41]		+
Cediel 2017	29	194	38	376	3.6%	1.56 [0.93, 2.62]		
Chapman 2018	48	429	92	1171	4.9%	1.48 [1.02, 2.13]		⊢
Chapman 2020	135	1121	368	4981	6.6%	1.72 [1.39, 2.11]		-
Etaher 2020	28	171	10	97	2.2%	1.70 [0.79, 3.68]		+
Furie 2019	42	206	98	349	4.5%	0.66 [0.43, 0.99]		-
awatmeh 2020	24	281	64	664	3.8%	0.88 [0.54, 1.43]		+
liguchi 2019	35	491	748	12023	5.1%	1.16 [0.81, 1.64]		+
kadesjo 2019	19	251	71	1111	3.5%	1.20 [0.71, 2.03]		+-
ambrecht 2018	24	119	43	360	3.4%	1.86 [1.08, 3.23]		
opez Cuenca 2016	20	117	81	707	3.5%	1.59 [0.93, 2.72]		
lestelberger 2020	5	128	52	684	1.6%	0.49 [0.19, 1.26]		+
Paiva 2015	29	236	59	764	4.0%	1.67 [1.05, 2.68]		-
Putot 2018	122	847	127	2036	6.0%	2.53 [1.94, 3.29]		-
Putot 2019	50	254	40	365	4.1%	1.99 [1.27, 3.13]		
Radovanovic 2017	84	1091	774	13828	6.4%	1.41 [1.11, 1.78]		-
Saaby 2013	31	144	54	397	3.8%	1.74 [1.07, 2.84]		⊢ •−
Saaby 2014	24	119	43	360	3.4%	1.86 [1.08, 3.23]		
Sandoval 2017	18	140	3	77	1.0%	3.64 [1.04, 12.78]		
Sato 2020	17	155	276	2834	3.6%	1.14 [0.68, 1.92]		+
Shah 2015	48	429	92	1171	4.9%	1.48 [1.02, 2.13]		 +-
Stein 2014	22	127	215	2691	3.9%	2.41 [1.49, 3.90]		-
roung 2020	16	175	16	275	2.4%	1.63 [0.79, 3.35]		<u>†</u>
otal (95% CI)		9941		105310	100.0%	1.48 [1.30, 1.69]		•
fotal events	1164		7669					
leterogeneity: Tau ² = est for overall effect:				(P < 0.00	001); I ² = 6	3%	0.01 (D.1 1 10 T1MI T2MI

	T2M	1	T1M	1		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-ł	l, Random, 95% Cl
Javed 2009	17	64	2	143	46.0%	25.50 [5.68, 114.50]		
Sandoval 2017	29	140	6	77	54.0%	3.09 [1.22, 7.82]		
Total (95% CI)		204		220	100.0%	8.15 [1.03, 64.46]		
Total events	46		8					

Cediel 2017 Etaher 2020	ents 67	Total	Events	Total						
Etaher 2020	67			Total	Weight	M-H, Random, 95% CI		M-H, Rando	m,95% (CI
		194	37	376	8.8%	4.83 [3.08, 7.58]			_	
	42	171	5	97	4.8%	5.99 [2.28, 15.72]		I		_
Furie 2019	42	206	68	349	8.9%	1.06 [0.69, 1.63]		-	-	
Hawatmeh 2020	48	281	54	664	9.0%	2.33 [1.53, 3.53]			-	
Lambrecht 2018	25	119	32	360	7.7%	2.73 [1.54, 4.83]				
Lopez Cuenca 2016	51	117	103	707	9.0%	4.53 [2.97, 6.90]			-	
Neumann 2017	34	99	20	188	7.2%	4.39 [2.36, 8.19]			_	
Paiva 2015	72	236	117	764	9.7%	2.43 [1.73, 3.41]			-	
Putot 2018	235	847	160	2036	10.6%	4.50 [3.61, 5.61]				
Radovanovic 2017	170	1091	567	13828	10.8%	4.32 [3.59, 5.19]				
Saaby 2013	34	144	50	397	8.4%	2.15 [1.32, 3.49]			-	
Sandoval 2017	16	140	7	77	5.0%	1.29 [0.51, 3.29]		-+	-	
Total (95% CI)		3645		19843	100.0%	3.02 [2.29, 3.99]			٠	
Total events	836		1220							
Heterogeneity: Tau ² = 0.18;	Chi ²	= 62.33	3, df = 11	(P < 0.0)0001); l² =	= 82%			1	
Test for overall effect: Z = 7	.83 (F	P < 0.00	0001)				0.01	0.1 1 T1MI		0 10

	T2M	I	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95%
Balanescu 2020	8	49	67	152	4.5%	0.25 [0.11, 0.56]	
Baron 2015	870	1403	14830	17488	7.2%	0.29 [0.26, 0.33]	•
Baron 2016	899	1313	35883	40501	7.2%	0.28 [0.25, 0.32]	-
Cediel 2017	42	194	337	376	6.1%	0.03 [0.02, 0.05]	-
Chapman 2020	749	1121	4061	4981	7.2%	0.46 [0.40, 0.53]	-
Conseugra Sanchez 2018	62	75	102	125	4.8%	1.08 [0.51, 2.28]	
Furie 2019	88	206	258	349	6.5%	0.26 [0.18, 0.38]	-
Landes 2016	65	107	103	107	3.6%	0.06 [0.02, 0.18]	
Lopez Cuenca 2016	87	117	618	707	6.1%	0.42 [0.26, 0.67]	
Meigher 2016	41	452	201	340	6.4%	0.07 [0.05, 0.10]	-
Radovanovic 2017	853	1091	12846	13828	7.1%	0.27 [0.23, 0.32]	-
Sandoval 2014	65	190	56	66	4.9%	0.09 [0.04, 0.19]	
Sandoval 2017	22	140	38	77	5.3%	0.19 [0.10, 0.36]	
Shah 2015	217	429	1041	1171	6.9%	0.13 [0.10, 0.17]	-
Smilowitz 2018	46	146	128	137	4.8%	0.03 [0.02, 0.07]	I
Stein 2014	69	127	2274	2691	6.5%	0.22 [0.15, 0.31]	-
Troung 2020	161	175	260	275	4.8%	0.66 [0.31, 1.41]	-+
Total (95% CI)		7335		83371	100.0%	0.19 [0.15, 0.26]	•
Total events	4344		73103				
Heterogeneity: Tau ² = 0.29;	Chi ² = 280).74, df	= 16 (P <	0.0000	1); l ² = 94°	%	0.01 0.1 1 1
Test for overall effect: Z = 1	1.30 (P < 0	0.00001)				0.01 0.1 1 1 T1MI T2MI

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	T2M	1	T1N	11		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95%	CI
Baron 2015	269	870	1224	17488	8.5%	5.95 [5.09, 6.94]		
Baron 2016	195	1313	1774	40501	8.4%	3.81 [3.25, 4.47]	-	
Cediel 2017	90	194	37	376	7.6%	7.93 [5.10, 12.33]		
Chapman 2020	116	1121	171	4981	8.3%	3.25 [2.54, 4.15]	-	
Furie 2019	122	206	178	349	8.0%	1.40 [0.98, 1.98]	-	
Landes 2016	78	107	38	107	7.1%	4.88 [2.73, 8.74]	-	
Lopez Cuenca 2016	22	117	38	707	7.1%	4.08 [2.31, 7.19]		
Radovanovic 2017	482	1091	4425	13828	8.5%	1.68 [1.48, 1.91]	-	
Sandoval 2014	112	190	35	66	7.1%	1.27 [0.72, 2.23]	+-	
Sandoval 2017	72	140	40	77	7.2%	0.98 [0.56, 1.71]		
Shah 2015	80	429	45	1171	7.8%	5.74 [3.91, 8.42]	-	
Stein 2014	15	127	105	2691	7.1%	3.30 [1.86, 5.85]	-	
Troung 2020	28	175	44	275	7.3%	1.00 [0.60, 1.68]	+	
Total (95% CI)		6080		82617	100.0%	2.83 [1.96, 4.08]	•	
Total events	1681		8154					
Heterogeneity: Tau ² =	0.41; Chi ²	= 266.3	38, df = 1	2 (P < 0	.00001); P	2 = 95%	0.01 0.1 1 1	10
Test for overall effect:	Z = 5.55 (P < 0.0	0001)				T1MI T2MI	10

	T2M	I	T1M	1		Odds Ratio	0	dds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Ra	andom, 95% Cl
Sandoval 2014	13	190	20	66	45.6%	0.17 [0.08, 0.36]		
Sandoval 2017	15	140	30	77	54.4%	0.19 [0.09, 0.38]		1
Total (95% CI)		330		143	100.0%	0.18 [0.11, 0.30]	+	
Total events	28		50					
Heterogeneity: Tau ² =	0.00; Chi ²	= 0.04	df = 1 (F	= 0.84); l ² = 0%		0.01 0.1	1 10 10
Test for overall effect:	Z = 6.49 (P < 0.0	0001)				77.55 C	1 10 10 1MI T2MI

	T2M	T2MI				Odds Ratio	Od	Ids Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Ra	ndom, 95% CI	
Sandoval 2017	6	140	12	77	100.0%	0.24 [0.09, 0.68]	-		
Total (95% CI)		140		77	100.0%	0.24 [0.09, 0.68]	-	-	
Total events	6		12						

			T1M	4		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	
Sandoval 2017	8	140	8	77	100.0%	0.52 [0.19, 1.45]		
Total (95% CI)		140		77	100.0%	0.52 [0.19, 1.45]	-	
Total events	8		8					

Figure S19. Forest F	lot. Nausea /	Vomiting.
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	T2M	1	T1M	I.		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI	
Sandoval 2014	21	190	14	66	42.8%	0.46 [0.22, 0.97]			
Sandoval 2017	25	140	25	77	57.2%	0.45 [0.24, 0.86]			
Total (95% CI)		330		143	100.0%	0.46 [0.28, 0.74]		•	
Total events	46		39						
Heterogeneity: Tau ² =	0.00; Chi ²	= 0.00,	df = 1 (F	= 0.97); l² = 0%		0.01	0.1 1 10	100
Test for overall effect:	Z = 3.16 (P = 0.0	02)				0.01	T1MI T2MI	100

	T2M	1	T1M	1		Odds Ratio		Oc	Ids Ratio	2	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Ra	ndom, 9	5% CI	
Sandoval 2017	5	140	5	77	100.0%	0.53 [0.15, 1.90]		-	-		
Total (95% CI)		140		77	100.0%	0.53 [0.15, 1.90]		-			
Total events	5		5								
Heterogeneity: Not ap	plicable						0.01	0.1	-	10	100
Test for overall effect:	Z = 0.97 (P = 0.3	3)				0.01		MI T2M	10	10

	T2M	1	T1M	1		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% (
Sandoval 2017	16	140	16	77	100.0%	0.49 [0.23, 1.05]		
Total (95% CI)		140		77	100.0%	0.49 [0.23, 1.05]	•	
Total events	16		16					

	T2M	1	T1N	41		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rand	om, 95% CI	
Baron 2015	264	1403	1434	17488	25.4%	2.59 [2.25, 3.00]				
Baron 2016	899	1313	2506	40501	25.5%	32.92 [29.11, 37.24]				
Lopez Cuenca 2016	8	117	51	707	24.3%	0.94 [0.44, 2.04]		_	-	
Neumann 2017	81	99	105	188	24.8%	3.56 [1.98, 6.39]			-	
Total (95% CI)		2932		58884	100.0%	4.19 [0.72, 24.39]		-	-	
Total events	1252		4096							
Heterogeneity: Tau ² =	3.17; Chi ²	= 760.	73. df = 3	(P < 0.0	00001); l ²	= 100%	—		<u> </u>	
Heterogeneity: Tau ² = Test for overall effect:				(P < 0.0	00001); l² :	= 100%	0.01	0.1 T1MI	1 10 T2MI	1

	T2M	1	T1M	1		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95%	CI
Cediel 2017	15	194	5	376	17.2%	6.22 [2.22, 17.38]	-	12
Chapman 2020	38	1121	102	4981	25.6%	1.68 [1.15, 2.45]	-	
Furie 2019	12	206	24	349	21.4%	0.84 [0.41, 1.71]		
Shah 2015	31	429	21	1171	23.4%	4.27 [2.42, 7.51]		
Troung 2020	3	175	5	275	12.5%	0.94 [0.22, 3.99]	10 6	
Total (95% CI)		2125		7152	100.0%	2.10 [1.05, 4.18]	•	
Total events	99		157					
Heterogeneity: Tau ² =	0.45; Chi ²	= 19.1	2, df = 4 (P = 0.0	007); l ² =	79%		-
Test for overall effect:	Z = 2.10 (P = 0.0	4)				0.01 0.1 1 1 T1ML T2ML	10 10

Figure S24. For	est Plot	:. ST E	Elevati	on.				
	T2M	1	T1I	IN		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	om, 95% Cl
Baron 2015	136	1403	5544	17488	7.8%	0.23 [0.19, 0.28]		
Baron 2016	173	1313	14824	40501	7.9%	0.26 [0.22, 0.31]		
Cediel 2017	5	194	92	376	3.4%	0.08 [0.03, 0.20]		
Chapman 2020	36	1121	870	4981	6.9%	0.16 [0.11, 0.22]	-	
Furie 2019	4	206	18	349	2.7%	0.36 [0.12, 1.09]		
Higuchi 2019	288	491	8917	12023	7.8%	0.49 [0.41, 0.59]	+	
Landes 2016	11	107	11	107	3.5%	1.00 [0.41, 2.42]	_	—
Lopez Cuenca 2016	1	117	225	707	1.1%	0.02 [0.00, 0.13]	←	
Nestelberger 2020	4	128	115	684	3.0%	0.16 [0.06, 0.44]		
Paiva 2015	35	236	417	764	6.6%	0.14 [0.10, 0.21]	-	
Putot 2019	28	254	136	365	6.1%	0.21 [0.13, 0.33]	-	
Putot 2020	207	862	1929	3710	7.8%	0.29 [0.25, 0.35]		
Radovanovic 2017	213	1091	7436	13828	7.9%	0.21 [0.18, 0.24]		
Raphael 2020	23	1054	198	1365	6.2%	0.13 [0.08, 0.20]	-	
Saaby 2013	5	144	130	397	3.4%	0.07 [0.03, 0.18]		
Sandoval 2017	31	140	24	77	4.9%	0.63 [0.34, 1.17]	_	-
Shah 2015	40	429	427	1171	6.8%	0.18 [0.13, 0.25]	-	
Stein 2014	25	127	1413	2691	6.2%	0.22 [0.14, 0.35]	-	
Total (95% CI)		9417		101584	100.0%	0.22 [0.18, 0.28]	•	
Total events	1265		42726					
Heterogeneity: Tau ² =	0.15; Chi ²	= 131.1	14. df = 1	7 (P < 0.0	00001); l ² =	= 87%		<u> </u>
Test for overall effect:							0.01 0.1 T1MI	10 T2MI

Figure S25. Fores	t Plot	. ST [Depre	ession	OFIV	Nave I	nversion.						
		T2MI		T1M	-		Odds Ratio				dds R		
Study or Subgroup	Ev	11110-0010					M-H, Random, 9			M-H, R	landor	m, 95	%0
Arora 2018		120	264	369	775	7.1%	0.92 [0.69,	-			1.	_	
Baron 2015 Baron 2016			1403 1313		17488 40501	7.3% 7.3%	1.59 [1.41, 1.31 [1.15,						
Cediel 2017		16	194	94	376	6.4%	0.27 [0.15,			_	_ [
Chapman 2020			1121	865	4981	7.3%	1.57 [1.35.					•	
Conseugra Sanchez 201	18	7	75	43	125	5.4%	0.20 [0.08,				-		
Hawatmeh 2020		223	281	86	664	6.9%	25.84 [17.90,	37.30]					
Landes 2016		71	107	75	107	6.3%	0.84 [0.47,	1.50]			-		
Lopez Cuenca 2016		35	117	152	707	6.8%	1.56 [1.01,				Ŀ	_	
Meigher 2016		68	452	61	340	6.9%	0.81 [0.55,						
Nestelberger 2020		33	128	234	684	6.8%	0.67 [0.44,	-					_
Saaby 2013 Sandoval 2017		139 74	144 140	267 40	397 77	5.2% 6.4%	13.54 [5.41, 3 1.04 [0.59,				_	_	
Shah 2015		249	429	332	1171	7.2%	3.50 [2.78,	-				-	
Smilowitz 2018		85	146	89	137	6.6%	0.75 [0.46,	-			-+		
Total (95% CI)			6314		68530	100.0%	1.38 [0.94,	2.02]			- 19		
Total events		2174		14938									
Unterpagements: Tauz 0									1				
Test for overall effect: Z	= 1.64 (P = 0.1	10)		0.00001	l); l ² = 97	%		0.01	0.1 T	1 1111 1	Г2МІ	
Test for overall effect: Z Figure S26. Fores	= 1.64 (I t Plot T2MI	P = 0.1	Vaves T1	MI	6	0	dds Ratio				3-	Г2МІ	1
COLOR DO DI COLOR DO DE COLOR D	t Plot T2MI Events	P = 0.1 . Q V Total	Vaves T1 Events	MI s Total	Weigh	O t M-H,I	dds Ratio Random, 95% Cl			Т	atio		1
Test for overall effect: Z Figure S26. Fores Study or Subgroup I Lopez Cuenca 2016	t Plot. T2MI Events 12	P = 0.1 . Q V <u>Total</u> 117	Vaves T1 Events 156	MI s Total 5 707	Weigh 48.4%	0 t M-H,1 6	dds Ratio Random, 95% Cl 0.40 [0.22, 0.75]			T Odds Ra	atio		1
Test for overall effect: Z Figure S26. Fores Study or Subgroup I Lopez Cuenca 2016 Sandoval 2014	= 1.64 (I t Plot T2MI Events 12 2	P = 0.1 . Q V <u>Total</u> 117 190	Vaves T1 Events 156	MI s Total 6 707 6 66	Weigh 48.4% 12.8%	0 t <u>M-H,1</u> 6 6	dds Ratio Random, 95% Cl 0.40 [0.22, 0.75] 0.11 [0.02, 0.54]			T Odds Ra	atio		1
Test for overall effect: Z Figure S26. Fores Study or Subgroup	t Plot. T2MI Events 12	P = 0.1 . Q V <u>Total</u> 117	Vaves T1 Events 156	MI s Total 6 707 6 66	Weigh 48.4%	0 t <u>M-H,1</u> 6 6	dds Ratio Random, 95% Cl 0.40 [0.22, 0.75]			T Odds Ra	atio		1
Test for overall effect: Z Figure S26. Fores Study or Subgroup I Lopez Cuenca 2016 Sandoval 2014 Sandoval 2017	= 1.64 (I t Plot T2MI Events 12 2	P = 0.1 . Q V <u>Total</u> 117 190	Vaves T1 Events 156	MI s Total 5 707 5 66 5 77	Weigh 48.4% 12.8%	O t M-H, I 6 6	dds Ratio Random, 95% Cl 0.40 [0.22, 0.75] 0.11 [0.02, 0.54]			T Odds Ra	atio		1
Test for overall effect: Z Figure S26. Fores Study or Subgroup I Lopez Cuenca 2016 Sandoval 2014	= 1.64 (I t Plot T2MI Events 12 2	P = 0.1 . Q V <u>Total</u> 117 190 140	Vaves T1 Events 156	MI s Total 5 707 5 66 5 77 850	Weigh 48.4% 12.8% 38.8%	O t M-H, I 6 6	dds Ratio Random, 95% Cl 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15]			T Odds Ra	atio		1
Test for overall effect: Z Figure S26. Fores Study or Subgroup I Lopez Cuenca 2016 Sandoval 2014 Sandoval 2017 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1	= 1.64 (I <u>t Plot</u> <u>T2MI</u> <u>Events</u> 12 2 16 30 11; Chi ²	P = 0.1 . Q V <u>Total</u> 117 190 140 447 = 3.09	Vaves T1 Event: 156 (15 , df = 2	MI s Total 5 707 5 66 5 77 850 7	Weigh 48.4% 12.8% 38.8% 100.0%	O t M-H,1 6 6 6	dds Ratio Random, 95% Cl 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15]	0.01	<u>M-H,</u>	T Odds Ra	atio 1, 95% (CI	
Test for overall effect: Z Figure S26. Fores Study or Subgroup I opez Cuenca 2016 Sandoval 2014 Sandoval 2017 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1	= 1.64 (I <u>t Plot</u> <u>T2MI</u> <u>Events</u> 12 2 16 30 11; Chi ²	P = 0.1 . Q V <u>Total</u> 117 190 140 447 = 3.09	Vaves T1 Event: 156 (15 , df = 2	MI s Total 5 707 5 66 5 77 850 7	Weigh 48.4% 12.8% 38.8% 100.0%	O t M-H,1 6 6 6	dds Ratio Random, 95% Cl 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15]	0.01	<u>M-H,</u>	T Odds Ra	atio 1, 95% (
Test for overall effect: Z Figure S26. Fores Study or Subgroup I opez Cuenca 2016 Sandoval 2014 Sandoval 2017 Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.1	= 1.64 (I <u>t Plot</u> <u>T2MI</u> <u>Events</u> 12 2 16 30 11; Chi ²	P = 0.1 . Q V <u>Total</u> 117 190 140 447 = 3.09	Vaves T1 Event: 156 (15 , df = 2	MI s Total 5 707 5 66 5 77 850 7	Weigh 48.4% 12.8% 38.8% 100.0%	O t M-H,1 6 6 6	dds Ratio Random, 95% Cl 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15]	0.01	<u>M-H,</u>	Odds Ra Random	atio 1, 95% (CI	
Test for overall effect: Z Figure S26. Fores Study or Subgroup II opez Cuenca 2016 Sandoval 2014 Sandoval 2017 Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 0. Fest for overall effect: Z =	= 1.64 (I <u>t Plot</u> <u>T2MI</u> <u>Events</u> 12 2 16 30 11; Chi ² = 3.03 (F	P = 0.1 . Q V <u>Total</u> 117 190 140 447 = 3.09 P = 0.0	Vaves T1 Event: 156 (15 (15 (15 (15 (15)(15)	MI s Total 5 707 5 66 5 77 850 7 (P = 0.21	Weigh 48.4% 12.8% 38.8% 100.0%	O t <u>M-H,1</u> 6 6 6 5%	dds Ratio Random, 95% Cl 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15]	0.01	<u>M-H,</u>	Odds Ra Random	atio 1, 95% (CI	
Test for overall effect: Z Figure S26. Fores Study or Subgroup II Lopez Cuenca 2016 Sandoval 2014 Sandoval 2017 Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 0. Test for overall effect: Z = Figure S27. Fores	= 1.64 (1 t Plot T2MI Events 12 2 16 30 11; Chi ² = 3.03 (F t Plot T2M	P = 0.1 . Q V <u>Total</u> 117 190 140 447 = 3.09 P = 0.0 . Nor	Vaves T1 Event: 156 (15 (15 (15 (15 (15 (15)) (15) (15)) (15)) (15)) (15)) (15))(15))	MI s Total 5 707 5 66 5 77 850 7 (P = 0.21 Cific S	Weigh 48.4% 12.8% 38.8% 100.0%); I ² = 3 T Chal	0 t <u>M-H,1</u> 6 6 5% nges.	dds Ratio Random, 95% Cl 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15] 0.38 [0.20, 0.71]	0.01	<u>M-H,</u>	Odds Ra Random	atio 1,95% (1 2MI atio	0	1
Test for overall effect: Z Figure S26. Fores Study or Subgroup II opez Cuenca 2016 Sandoval 2014 Sandoval 2017 Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 0. Fest for overall effect: Z = Figure S27. Fores Study or Subgroup	= 1.64 (1 t Plot T2MI Events 12 2 16 30 11; Chi ² = 3.03 (F t Plot T2M Events	P = 0.1 . Q V <u>Total</u> 117 190 140 447 = 3.09, P = 0.0 . Nor I <u>Total</u>	Vaves T1 Event: 156 (15 (15 (15 (15 (15 (15)) (15) (15)) (15) (15)) (15)) (15)) (15)) (15))(15))	MI <u>s Total</u> <u>5 707</u> <u>8 66</u> <u>5 77</u> <u>850</u> <u>7</u> (P = 0.21 <u>101</u> <u>cific S</u>	Weigh 48.4% 12.8% 38.8% 100.0% 1); I ² = 3 T Chal	O t <u>M-H,</u> 6 6 6 5% nges.	dds Ratio Random, 95% Cl 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15] 0.38 [0.20, 0.71] 0.38 [0.20, 0.71]	0.01	<u>M-H,</u>	Odds Ra Random	atio 1,95% (1 2MI atio	0	
Test for overall effect: Z Figure S26. Fores Study or Subgroup I opez Cuenca 2016 Sandoval 2014 Sandoval 2017 Total (95% CI) Total events Heterogeneity: Tau ² = 0. Fest for overall effect: Z = Figure S27. Fores Study or Subgroup Meigher 2016	= 1.64 (1 <u>t Plot</u> <u>T2MI</u> <u>Events</u> <u>12</u> <u>2</u> <u>16</u> <u>30</u> <u>11; Chi² = 3.03 (F <u>t Plot</u> <u>T2M</u> <u>Events</u> <u>90</u></u>	P = 0.1 . Q V <u>Total</u> 117 190 140 447 = 3.09 P = 0.0 . Nor I <u>Total</u> 452	Vaves T11 Event: 156 (15 (15 (15 (15 (15 (15 (15)) (15) (15)) (15) (15)) (15)) (15))(15))	MI <u>s Total</u> <u>5 707</u> <u>8 66</u> <u>5 77</u> <u>850</u> <u>7</u> (P = 0.21 <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>101</u> <u>1</u>	Weigh 48.49 12.89 38.89 100.09 (); I ² = 3 T Chal	O t M-H,1 6 6 6 5% nges.	dds Ratio <u>Random, 95% C1</u> 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15] 0.38 [0.20, 0.71] 0.38 [0.20, 0.71] Odds Ratio <u>Random, 95% C1</u> 2.88 [1.83, 4.55]	0.01	<u>M-H,</u>	Odds Ra Random	atio 1,95% (1 2MI atio	0	
Test for overall effect: Z Figure S26. Fores Study or Subgroup I opez Cuenca 2016 Sandoval 2014 Sandoval 2017 Total (95% CI) Total events Heterogeneity: Tau ² = 0. Fest for overall effect: Z = Figure S27. Fores Study or Subgroup Meigher 2016	= 1.64 (1 t Plot T2MI Events 12 2 16 30 11; Chi ² = 3.03 (F t Plot T2M Events	P = 0.1 . Q V <u>Total</u> 117 190 140 447 = 3.09, P = 0.0 . Nor I <u>Total</u>	Vaves T11 Event: 156 (15 (15 (15 (15 (15 (15 (15)) (15) (15)) (15) (15)) (15)) (15))(15))	MI <u>s Total</u> <u>5 707</u> <u>8 66</u> <u>5 77</u> <u>850</u> <u>7</u> (P = 0.21 <u>101</u> <u>cific S</u>	Weigh 48.49 12.89 38.89 100.09 (); I ² = 3 T Chal	O t M-H,1 6 6 6 5% nges.	dds Ratio Random, 95% Cl 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15] 0.38 [0.20, 0.71] 0.38 [0.20, 0.71]	0.01	<u>M-H,</u>	Odds Ra Random	atio 1,95% (1 2MI atio	0	
Test for overall effect: Z Figure S26. Fores Study or Subgroup II Lopez Cuenca 2016 Sandoval 2014 Sandoval 2017 Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 0. Fest for overall effect: Z = Figure S27. Fores	= 1.64 (1 <u>t Plot</u> <u>T2MI</u> <u>Events</u> <u>12</u> <u>2</u> <u>16</u> <u>30</u> <u>11; Chi² = 3.03 (F <u>t Plot</u> <u>T2M</u> <u>Events</u> <u>90</u></u>	P = 0.1 . Q V <u>Total</u> 117 190 140 447 = 3.09 P = 0.0 . Nor I <u>Total</u> 452	Vaves T11 Event: 156 (15 (15 (15 (15 (15 (15)(15)	MI <u>s Total</u> <u>5 707</u> <u>8 66</u> <u>5 77</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>857</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>850</u> <u>7</u> <u>7</u> <u>7</u> <u>7</u> <u>7</u> <u>7</u> <u>7</u> <u>7</u>	Weigh 48.49 12.89 38.89 100.09 (); I ² = 3 T Chal	O t M-H, 6 6 6 5% 5% nges. 0 ht M-H, %	dds Ratio <u>Random, 95% C1</u> 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15] 0.38 [0.20, 0.71] 0.38 [0.20, 0.71] Odds Ratio <u>Random, 95% C1</u> 2.88 [1.83, 4.55]	0.01	<u>M-H,</u>	Odds Ra Random	atio 1,95% (1 2MI atio	0	
Test for overall effect: Z Figure S26. Fores Study or Subgroup II opez Cuenca 2016 Sandoval 2014 Sandoval 2017 Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 0. Fest for overall effect: Z = Figure S27. Fores Study or Subgroup Meigher 2016 Sandoval 2017	= 1.64 (1 <u>t Plot</u> <u>T2MI</u> <u>Events</u> 12 2 16 30 11; Chi ² = 3.03 (F <u>t Plot</u> <u>T2M</u> <u>Events</u> 90 56 146	P = 0.1 . Q V <u>Total</u> 117 190 140 447 = 3.09, P = 0.0 . Nor I <u>Total</u> 452 140 592	Vaves T11 Event: 156 (15 (15 (15 (15 (15 (15 (15) (15) (MI <u>s Total</u> 5 707 5 66 5 77 850 7 (P = 0.21 Cific S (MI ts Tota 7 340 8 77 417 5	Weigh 48.49 12.89 38.89 100.09 (); I ² = 30 F Chal 65.44 34.66 34.66 100.09	O t M-H,1 6 6 6 5% 5% nges. C t M-H, %	dds Ratio <u>Random, 95% C1</u> 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15] 0.38 [0.20, 0.71] 0.38 [0.20, 0.71] Ddds Ratio <u>Random, 95% C1</u> 2.88 [1.83, 4.55] 2.19 [1.17, 4.09]	0.01	<u>M-H,</u>	Odds Ra Random	atio 1,95% (1 2MI atio	0	

Study or Subgroup	T2M Events		T1M Events	Since and the	Weight	Odds Ratio M-H, Random, 95% Cl		Odds R M-H, Randor	Contract Contract	
Lopez Cuenca 2016	12	117	156	707	48.4%	0.40 [0.22, 0.75]			1100/001	
Sandoval 2014	2	190	6	66	12.8%	0.11 [0.02, 0.54]	-			
Sandoval 2017	16	140	15	77	38.8%	0.53 [0.25, 1.15]				
Total (95% CI)		447		850	100.0%	0.38 [0.20, 0.71]		•		
Total events	30		177							
			1.00	= 0.21): 1 ² = 359		0.01	01 1		_

	T2M	1	T1M	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Meigher 2016	90	452	27	340	65.4%	2.88 [1.83, 4.55]	
Sandoval 2017	56	140	18	77	34.6%	2.19 [1.17, 4.09]	
Total (95% CI)		592		417	100.0%	2.62 [1.81, 3.79]	•
Total events	146		45				

Baron 2016 95 1313 1791 40501 30.5% 1.69 [1.36, 2.09] Cediel 2017 40 194 72 376 15.3% 1.10 [0.71, 1.69] Lopez Cuenca 2016 10 117 35 707 6.9% 1.79 [0.86, 3.73] Nestelberger 2020 9 128 34 684 6.5% 1.45 [0.68, 3.09] Troung 2020 21 175 11 275 6.5% 3.27 [1.54, 6.97] Total (95% CI) 3330 60031 100.0% 1.72 [1.40, 2.12] ♦		T2M	1	T1N	11		Odds Ratio	Odds Ratio
Baron 2016 95 1313 1791 40501 30.5% 1.69 [1.36, 2.09] Cediel 2017 40 194 72 376 15.3% 1.10 [0.71, 1.69] Lopez Cuenca 2016 10 117 35 707 6.9% 1.79 [0.86, 3.73] Nestelberger 2020 9 128 34 684 6.5% 1.45 [0.68, 3.09] Troung 2020 21 175 11 275 6.5% 3.27 [1.54, 6.97] Total (95% CI) 3330 60031 100.0% 1.72 [1.40, 2.12] Image: constant constan	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cediel 2017 40 194 72 376 15.3% 1.10 [0.71, 1.69] Lopez Cuenca 2016 10 117 35 707 6.9% 1.79 [0.86, 3.73] Nestelberger 2020 9 128 34 684 6.5% 1.45 [0.68, 3.09] Troung 2020 21 175 11 275 6.5% 3.27 [1.54, 6.97] Total (95% CI) 3330 60031 100.0% 1.72 [1.40, 2.12] Image: constraint of the second sec	Baron 2015	163	1403	1102	17488	34.3%	1.95 [1.64, 2.33]	
Lopez Cuenca 2016 10 117 35 707 6.9% 1.79 [0.86, 3.73] Nestelberger 2020 9 128 34 684 6.5% 1.45 [0.68, 3.09] Troung 2020 21 175 11 275 6.5% 3.27 [1.54, 6.97] Total (95% CI) 3330 60031 100.0% 1.72 [1.40, 2.12] Image: constraint of the second se	Baron 2016	95	1313	1791	40501	30.5%	1.69 [1.36, 2.09]	-
Nestelberger 2020 9 128 34 684 6.5% 1.45 [0.68, 3.09] Troung 2020 21 175 11 275 6.5% 3.27 [1.54, 6.97] Total (95% CI) 3330 60031 100.0% 1.72 [1.40, 2.12] ♦	Cediel 2017	40	194	72	376	15.3%	1.10 [0.71, 1.69]	
Troung 2020 21 175 11 275 6.5% 3.27 [1.54, 6.97] Total (95% CI) 3330 60031 100.0% 1.72 [1.40, 2.12] ♦	Lopez Cuenca 2016	10	117	35	707	6.9%	1.79 [0.86, 3.73]	
Total (95% CI) 3330 60031 100.0% 1.72 [1.40, 2.12]	Nestelberger 2020	9	128	34	684	6.5%	1.45 [0.68, 3.09]	
	Troung 2020	21	175	11	275	6.5%	3.27 [1.54, 6.97]	
Total events 338 3045	Total (95% CI)		3330		60031	100.0%	1.72 [1.40, 2.12]	•
	Total events	338		3045				2

Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI Baron 2015 394 1403 1819 17488 75.7% 3.36 [2.97, 3.82] Image: Comparison of the state		T2M	I	T1N	11		Odds Ratio			Odds Ratio	
Lopez Cuenca 2016 32 117 49 707 20.3% 5.06 [3.07, 8.33] Sandoval 2017 22 140 3 77 4.0% 4.60 [1.33, 15.90] Total (95% CI) 1660 18272 100.0% 3.70 [2.87, 4.77] Total events 448 1871 Heterogeneity: Tau ² = 0.02; Chi ² = 2.61, df = 2 (P = 0.27); l ² = 23% Test for overall effect: Z = 10.07 (P < 0.00001) T1MI T2MI	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C		М-Н,	Random, 95%	6CI
Sandoval 2017 22 140 3 77 4.0% 4.60 [1.33, 15.90] Total (95% CI) 1660 18272 100.0% 3.70 [2.87, 4.77] Total events 448 1871 Heterogeneity: Tau ² = 0.02; Chi ² = 2.61, df = 2 (P = 0.27); l ² = 23% Test for overall effect: Z = 10.07 (P < 0.00001) T1MI T2MI		394	1403	1819	17488	75.7%	3.36 [2.97, 3.82]				
Total (95% CI) 1660 18272 100.0% 3.70 [2.87, 4.77] Total events 448 1871 Heterogeneity: Tau ² = 0.02; Chi ² = 2.61, df = 2 (P = 0.27); l ² = 23% Test for overall effect: Z = 10.07 (P < 0.00001) T1MI T2MI	Lopez Cuenca 2016	32	117	49	707	20.3%	5.06 [3.07, 8.33]			-	-
Total events 448 1871 Heterogeneity: Tau ² = 0.02; Chi ² = 2.61, df = 2 (P = 0.27); l ² = 23% Test for overall effect: Z = 10.07 (P < 0.00001) T1MI T2MI	Sandoval 2017	22	140	3	77	4.0%	4.60 [1.33, 15.90]	l			
Heterogeneity: Tau ² = 0.02; Chi ² = 2.61, df = 2 (P = 0.27); I ² = 23% Test for overall effect: Z = 10.07 (P < 0.00001)	Fotal (95% CI)		1660		18272	100.0%	3.70 [2.87, 4.77]			•	
Test for overall effect: Z = 10.07 (P < 0.00001)	Total events	448		1871							
T1MI T2MI) = 0.27)	; l² = 23%		0.01	0 1		10
	Test for overall effect:	Z = 10.07	(P < 0.	00001)				0.01	0.1	T1MI T2MI	10

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Total events 3686 56242 Heterogeneity: Tau ² = 0.69; Chi ² = 738.32, df = 27 (P < 0.00001); I ² = 96% 0.01 0.1 1	Total events 3686 56242 Heterogeneity: Tau ² = 0.69; Chi ² = 738.32, df = 27 (P < 0.00001); I ² = 96% Dest for overall effect: 7 = 14 61 (P < 0.00001)									
Heterogeneity: Tau ² = 0.69; Chi ² = 738.32, df = 27 (P < 0.00001); l ² = 96%	Heterogeneity: Tau ² = 0.69; Chi ² = 738.32, df = 27 (P < 0.00001); I ² = 96% 0.01 0.1 1 1	Fotal (95% CI)		10721		67432	100.0%	0.09 [0.06, 0.12]	•	
Test for overall effect: 7 = 14 61 (P < 0.00001) 0.01 0.1 1	Test for overall effect: 7 = 14 61 (P < 0.00001) U.U1 U.1 1	Total events	3686		56242					
Test for overall effect: 7 = 14 61 (P < 0.00001) U.U.1 1	Test for overall effect: 7 = 14.61 (P < 0.00001) U.U1 U.1 1	Heterogeneity: Tau ² = 0.69	: Chi ² = 738	.32, df =	= 27 (P <	0.00001); l ² = 96%	6		1 10
		-					//			
		Test for overall effect: Z = 1	14.61 (P < 0	.00001)				0		I T2MI

	T2M	1	T1N	11		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H	,Rando	m, 95°	%0
Baron 2016	533	1313	17456	40501	9.6%	0.90 [0.81, 1.01]				
Conseugra Sanchez 2018	4	75	82	125	9.0%	0.03 [0.01, 0.09]		- 1		
Furie 2019	7	206	166	349	9.3%	0.04 [0.02, 0.08]	_	- 1		
Javed 2009	25	64	111	143	9.4%	0.18 [0.10, 0.35]	_	-		
Lopez Cuenca 2016	78	117	64	707	9.5%	20.09 [12.66, 31.90]		- 1		
Putot 2019	238	254	346	365	9.3%	0.82 [0.41, 1.62]		-	-	
Raphael 2020	162	1054	1058	1365	9.6%	0.05 [0.04, 0.07]	-	- 1		
Saaby 2014	15	119	236	360	9.4%	0.08 [0.04, 0.14]		- 1		
Sandoval 2017	7	140	42	77	9.2%	0.04 [0.02, 0.11]		- 1		
Smilowitz 2018	14	146	87	137	9.4%	0.06 [0.03, 0.12]	_	- 1		
Troung 2020	163	175	275	275	6.3%	0.02 [0.00, 0.40]	←	-		
Total (95% CI)		3663		44404	100.0%	0.16 [0.05, 0.54]				
Total events	1246		19923					- 1		
Heterogeneity: Tau ² = 4.01;	Chi ² = 989	.87, df	= 10 (P <	0.0000	1); l ² = 99 ⁶	%				-
Test for overall effect: Z = 2	.95 (P = 0.	003)					0.01 0.1	T1MI	T2MI	10

	T2M	1	T1N	11		Odds Ratio		Odds	s Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	}	M-H, Rand	lom, 95%	CI	
Baron 2016	381	1313	11340	40501	22.4%	1.05 [0.93, 1.19]			•		
Putot 2019	59	254	150	365	21.4%	0.43 [0.30, 0.62]		+			
Saaby 2014	11	119	115	360	19.0%	0.22 [0.11, 0.42]					
Sandoval 2017	1	140	15	77	8.1%	0.03 [0.00, 0.23]	+				
Smilowitz 2018	1	146	24	137	8.3%	0.03 [0.00, 0.24]	+ -				
Troung 2020	140	175	195	275	20.7%	1.64 [1.04, 2.58]			.		
Total (95% CI)		2147		41715	100.0%	0.40 [0.19, 0.82]		•			
Total events	593		11839								
Heterogeneity: Tau ² =	0.62; Chi ²	= 68.9	8, df = 5 (P < 0.00	0001); I ² =	93%	0.01	0.1	1	1	400
Test for overall effect:	Z = 2.48 (P = 0.0	1)	8 925808	9609153947		0.01	0.1 T1MI	T2MI	10	100
Figure S33. Fore	est Plot.	. Echo	ocardio	ogram	n Perfo	rmed.					
	T2MI	1	T1M	6		Odds Ratio		Odds I	Datio		

	T2M	1	T1M	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cediel 2017	79	194	359	376	14.1%	0.03 [0.02, 0.06]	-
Furie 2019	103	206	195	349	14.7%	0.79 [0.56, 1.12]	
Lambrecht 2018	54	119	180	360	14.6%	0.83 [0.55, 1.26]	-
Saaby 2014	91	119	321	360	14.2%	0.39 [0.23, 0.68]	
Sandoval 2017	72	140	62	77	13.7%	0.26 [0.13, 0.49]	
Shah 2015	122	429	340	1171	15.0%	0.97 [0.76, 1.24]	+
Smilowitz 2018	127	146	114	137	13.7%	1.35 [0.70, 2.60]	
Total (95% CI)		1353		2830	100.0%	0.44 [0.20, 0.96]	•
Total events	648		1571				

Figure S34. Fore	est Plot	. Reg	ional V	Vall N	Notion	Abnormalities.			
	T2M	1	T1M	1		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% Cl	
Sandoval 2017	22	140	41	77	49.5%	0.16 [0.09, 0.31]			
Smilowitz 2018	75	146	60	137	50.5%	1.36 [0.85, 2.17]		-	
Total (95% CI)		286		214	100.0%	0.48 [0.06, 3.78]			
Total events	97		101						
Heterogeneity: Tau ² =	2.15; Chi ²	= 27.3	9, df = 1 (P < 0.0	0001); l ² =	96%	0.01	0.1 1 10	100
Test for overall effect:	Z = 0.70 (P = 0.4	B)				0.01	T1MI T2MI	100

Figure S35. Fore	est Plot. Bet	a-Blockers.	
	T2MI	T1MI	

	T2M	1	T1N	41		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rando	m, 95% CI	
Arora 2018	165	264	645	775	4.5%	0.34 [0.25, 0.46]		-		
Balanescu 2020	30	49	127	152	3.7%	0.31 [0.15, 0.64]				
Baron 2015	1146	1403	15302	17488	4.6%	0.64 [0.55, 0.73]		-		
Baron 2016	1123	1313	36410	40501	4.6%	0.66 [0.57, 0.78]		-		
Chapman 2018	126	429	651	1171	4.5%	0.33 [0.26, 0.42]		-		
Etaher 2020	83	171	68	97	4.1%	0.40 [0.24, 0.68]				
Furie 2019	141	206	247	349	4.4%	0.90 [0.62, 1.30]		- +		
Hawatmeh 2020	165	281	551	664	4.5%	0.29 [0.21, 0.40]		-		
Higuchi 2019	236	491	6786	12023	4.6%	0.71 [0.60, 0.86]		-		
Kadesjo 2019	169	251	946	1111	4.5%	0.36 [0.26, 0.49]		-		
Lopez Cuenca 2016	86	117	614	707	4.2%	0.42 [0.26, 0.67]				
Nestelberger 2020	72	128	548	684	4.3%	0.32 [0.21, 0.47]				
Radovanovic 2017	595	1091	7396	13828	4.6%	1.04 [0.92, 1.18]		ł		
Raphael 2020	766	1054	1215	1365	4.6%	0.33 [0.26, 0.41]		-		
Reed 2017	75	162	41	88	4.1%	0.99 [0.59, 1.66]		-+	-	
Saaby 2014	44	119	208	360	4.3%	0.43 [0.28, 0.66]				
Sandoval 2017	81	140	53	77	4.0%	0.62 [0.35, 1.12]		+		
Sato 2020	53	155	1838	2834	4.4%	0.28 [0.20, 0.40]		-		
Shah 2015	124	429	660	1171	4.5%	0.31 [0.25, 0.40]		-		
Singh 2020	513	1225	1878	2097	4.6%	0.08 [0.07, 0.10]		*		
Smilowitz 2018	70	146	78	137	4.2%	0.70 [0.44, 1.11]				
Stein 2014	91	127	2234	2691	4.3%	0.52 [0.35, 0.77]				
Troung 2020	159	175	237	275	3.9%	1.59 [0.86, 2.96]		t	-	
Total (95% CI)		9926		100645	100.0%	0.46 [0.34, 0.62]		•		
Total events	6113		78733							
Heterogeneity: Tau ² =	0.51; Chi ²	= 663.	71, df = 2	2 (P < 0.0	00001); l ² =	= 97%		0.1 1	10	1
Test for overall effect:							0.01	0.1 1 T1MI		1(

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	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup					Weight	M-H, Random, 95% CI	
Baron 2015		1403		17488		0.59 [0.52, 0.66]	•
Baron 2016	945	1313	30781	40501	5.8%	0.81 [0.72, 0.92]	-
Chapman 2018	156	429	724	1171	5.6%	0.35 [0.28, 0.44]	-
Etaher 2020	57	171	49	97	4.6%	0.49 [0.29, 0.82]	
Hawatmeh 2020	99	281	325	664	5.4%	0.57 [0.43, 0.76]	-
Higuchi 2019	254	491	7531	12023	5.7%	0.64 [0.53, 0.77]	-
Kadesjo 2019	118	251	725	1111	5.4%	0.47 [0.36, 0.62]	
Lopez Cuenca 2016	53	117	438	707	5.0%	0.51 [0.34, 0.75]	
Nestelberger 2020	70	128	546	684	5.0%	0.31 [0.21, 0.45]	
Radovanovic 2017	566	1091	7448	13828		0.92 [0.82, 1.04]	•
Raphael 2020	571	1054	976	1365	5.7%	0.47 [0.40, 0.56]	•
Saaby 2014	38		154	360	4.9%	0.63 [0.40, 0.97]	
Sandoval 2017	43		39	77	4.3%	0.43 [0.24, 0.77]	
Sato 2020	93		2103		5.3%	0.52 [0.37, 0.73]	-
Shah 2015	135	429	735		5.6%	0.27 [0.22, 0.34]	-
Singh 2020		1225	1269		5.7%	0.19 [0.16, 0.22]	- I
Smilowitz 2018	62		63	137	4.7%	0.87 [0.54, 1.39]	-+
Stein 2014	88		2126		5.1%	0.60 [0.41, 0.88]	
Troung 2020	147	175	221	275	4.6%	1.28 [0.78, 2.12]	+
Total (95% CI)		9245		99281	100.0%	0.52 [0.41, 0.66]	•
Total events	4692		69684				
Heterogeneity: Tau ² =				8 (P < 0	.00001); P	2 = 95%	0.01 0.1 1 10
Test for overall effect:	Z = 5.52 (P < 0.0	0001)		_		T1MI T2MI

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	T2M		T1N	41		Odds Ratio	Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	lom, 95%	6CI
Arora 2018	154	264	637	775	4.4%	0.30 [0.22, 0.41]	-		
Balanescu 2020	25	49	128	152	3.9%	0.20 [0.10, 0.40]			
Baron 2015	655	1403	14235	17488	4.5%	0.20 [0.18, 0.22]			
Baron 2016	722	1313	34021	40501	4.5%	0.23 [0.21, 0.26]			
Chapman 2018	284	429	896	1171	4.4%	0.60 [0.47, 0.77]	+		
Etaher 2020	92	171	85	97	3.9%	0.16 [0.08, 0.32]			
Furie 2019	163	206	335	349	4.0%	0.16 [0.08, 0.30]			
Guimares 2018	74	76	839	847	2.6%	0.35 [0.07, 1.69]	-	⊢	
lawatmeh 2020	156	281	594	664	4.3%	0.15 [0.10, 0.21]			
liguchi 2019	442	491	11662	12023	4.4%	0.28 [0.20, 0.38]	-		
Kadesjo 2019	101	251	918	1111	4.4%	0.14 [0.11, 0.19]	+		
opez Cuenca 2016	72	117	64	707	4.2%	16.07 [10.22, 25.27]			
Vestelberger 2020	36	128	619	684	4.2%	0.04 [0.03, 0.07]			
Radovanovic 2017	983	1091	13772	13828	4.3%	0.04 [0.03, 0.05]	-		
Raphael 2020	648	1054	1114	1365	4.4%	0.36 [0.30, 0.43]	+		
Reed 2017	63	162	28	88	4.1%	1.36 [0.79, 2.36]	-	!-	
Saaby 2014	56	119	269	360	4.2%	0.30 [0.20, 0.46]	-		
Sandoval 2017	64	140	66	77	3.9%	0.14 [0.07, 0.29]			
Sato 2020	70	155	2562	2834	4.3%	0.09 [0.06, 0.12]	-		
Shah 2015	166	429	910	1171	4.4%	0.18 [0.14, 0.23]	-		
Singh 2020	416	1225	1945	2097	4.4%	0.04 [0.03, 0.05]	+		
Smilowitz 2018	31	146	58	137	4.1%	0.37 [0.22, 0.62]	_		
Stein 2014	109	127	2610	2691	4.1%	0.19 [0.11, 0.32]	_		
Froung 2020	160	175	245	275	4.0%	1.31 [0.68, 2.50]	-	-	
Fotal (95% CI)		10002		101492	100.0%	0.24 [0.17, 0.36]	•		
Fotal events	5742		88612						
Heterogeneity: Tau ² =	0.86; Chi ²	= 1006.	15, df = 2	3 (P < 0.0	00001); l²	= 98%	0.01 0.1		10
Test for overall effect:	Z = 7.21 (F	P < 0.00	001)					T2MI	10

	Figure S38.	Forest Pl	ot. Ant	icoagu	lants.
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Figure 538. Fore	SUPIOL	Anti	coagu	iants.					
	T2M	1	T1N	11		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M	H, Random, 95% Cl	
Baron 2015	219	1403	1294	17488	9.1%	2.31 [1.98, 2.70]		-	
Baron 2016	236	1313	3240	40501	9.1%	2.52 [2.18, 2.91]		•	
Chapman 2018	44	429	33	1171	8.5%	3.94 [2.47, 6.28]		-	
Furie 2019	24	206	42	349	8.3%	0.96 [0.57, 1.64]		-	
Lopez Cuenca 2016	44	117	89	707	8.6%	4.19 [2.71, 6.47]			
Radovanovic 2017	801	1091	11774	13828	9.1%	0.48 [0.42, 0.56]		•	
Raphael 2020	239	1054	167	1365	9.0%	2.10 [1.69, 2.61]		-	
Sandoval 2017	20	140	3	77	5.7%	4.11 [1.18, 14.31]			
Sato 2020	24	155	327	2834	8.5%	1.40 [0.90, 2.20]		† •−	
Shah 2015	52	429	35	1171	8.6%	4.48 [2.87, 6.98]		-	
Smilowitz 2018	11	146	11	137	7.1%	0.93 [0.39, 2.23]		-	
Troung 2020	24	175	33	275	8.2%	1.17 [0.66, 2.05]		+	
Total (95% CI)		6658		79903	100.0%	1.90 [1.17, 3.10]		•	
Total events	1738		17048						
Heterogeneity: Tau ² =	0.67; Chi ²	= 401.1	15, df = 1	1 (P < 0	.00001); P	2 = 97%	0.01 0.	1 1 10	10
Test for overall effect:	Z = 2.59 (P = 0.0	10)				0.01 0.	T1MI T2MI	10

Baron 2015 1041 1403 16194 17488 17.5% 0.23 [0.20, 0.26] Image: Comparison of the comp		Ratio	Odds R		Odds Ratio		H	T1M	1	T2M	
Baron 2016 1050 1313 38476 40501 17.5% 0.21 [0.18, 0.24] Chapman 2018 77 429 143 1171 17.0% 1.57 [1.16, 2.13] Nestelberger 2020 13 128 168 684 15.5% 0.35 [0.19, 0.63] Smilowitz 2018 86 146 101 137 16.0% 0.51 [0.31, 0.85]	CI	om, 95% CI	M-H, Random	5%CI	M-H, Random, 95% C	Weight	Total	Events	Total	Events	Study or Subgroup
Chapman 2018 77 429 143 1171 17.0% 1.57 [1.16, 2.13] Nestelberger 2020 13 128 168 684 15.5% 0.35 [0.19, 0.63] Smilowitz 2018 86 146 101 137 16.0% 0.51 [0.31, 0.85]				0.26]	0.23 [0.20, 0.26	17.5%	17488	16194	1403	1041	Baron 2015
Chapman 2018 77 429 143 1171 17.0% 1.57 [1.16, 2.13] Nestelberger 2020 13 128 168 684 15.5% 0.35 [0.19, 0.63] Smilowitz 2018 86 146 101 137 16.0% 0.51 [0.31, 0.85]				0.24]	0.21 [0.18, 0.24	17.5%	40501	38476	1313	1050	Baron 2016
Smilowitz 2018 86 146 101 137 16.0% 0.51 [0.31, 0.85]		-	12.5	2.13]	1.57 [1.16, 2.13	17.0%	1171	143	429	77	Chapman 2018
			(0.63]	0.35 [0.19, 0.63	15.5%	684	168	128	13	Nestelberger 2020
Troung 2020 55 175 67 275 16.5% 1.42 [0.93, 2.17]			2 1 - 1	0.85]	0.51 [0.31, 0.85	16.0%	137	101	146	86	Smilowitz 2018
		-	-	2.17]	1.42 [0.93, 2.17	16.5%	275	67	175	55	Troung 2020
Total (95% CI) 3594 60256 100.0% 0.51 [0.26, 1.00]			•	1.00]	0.51 [0.26, 1.00	100.0%	60256		3594		Total (95% CI)
Total events 2322 55149								55149		2322	Total events

	T2M		T1N	11		Odds Ratio		Odds Ratio	
Study or Subgroup					Weight		м	-H, Random, 95%	CI
Baron 2015		1403		17488		2.11 [1.89, 2.36]			
Baron 2016	315	1313	4860	40501	21.6%	2.31 [2.03, 2.64]			
Etaher 2020	53	171	9	97	7.1%	4.39 [2.06, 9.38]			-
Lopez Cuenca 2016	70	117	230	707	14.1%	3.09 [2.07, 4.62]		-	
Raphael 2020	831	1054	990	1365	20.2%	1.41 [1.17, 1.71]		=	
Sato 2020	0	155	23	2834	0.7%	0.38 [0.02, 6.36]			
Troung 2020	67	175	99	275	14.4%	1.10 [0.75, 1.63]		+	
Total (95% CI)		4388		63267	100.0%	1.99 [1.56, 2.53]		•	
Total events	2042		11877						
Test for overall effect:	Z = 5.56 (I	P < 0.0	0001)				0.01 0	.1 1 T1MI T2MI	10

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Study or subgroup Events Total Weight M-H, Random, 95% Cl M-H, Random, 95% Cl Avora 2018 153 264 646 775 6.0% 0.28 [0.20, 0.37] Jatanescu 2020 29 49 131 152 5.1% 0.23 [0.11, 0.48] - Jaron 2015 926 403 15040 17488 6.3% 0.32 [0.28, 0.38] - Jaron 2016 972 1313 372.61 40501 6.3% 0.25 [0.21, 0.48] - Chapman 2018 204 429 872 1171 6.1% 0.31 [0.25, 0.39] + Unie 2019 125 206 260 349 5.9% 0.38 [0.26, 0.56] + Jawatmeh 2020 141 281 578 664 6.9% 0.15 [0.11, 0.21] + Jupchi2019 298 491 923 1203 6.2% 0.20 [0.16, 0.24] - Jopez Cuenca 2016 92 117 648 707 5.6% 0.20 [0.16, 0.24]	Arrora 2018 153 264 646 775 6.0% 0.28 [0.20, 0.37] Balanescu 2020 29 49 131 152 5.1% 0.23 [0.11, 0.48] Baron 2015 926 1403 15040 17488 6.3% 0.32 [0.28, 0.36] Chapman 2016 972 1313 37261 40501 6.3% 0.25 [0.22, 0.28] Chapman 2018 204 429 872 1171 6.1% 0.31 [0.25, 0.39]		T2M		T1M		100 10 100	Odds Ratio	Odds Ratio
Balanescu 2020 29 49 131 152 5.1% 0.23 [0.11, 0.48] Baron 2015 926 1403 15040 17488 6.3% 0.32 [0.28, 0.36] Baron 2016 972 1313 37261 40501 6.3% 0.25 [0.22, 0.28] Chapman 2018 204 429 872 1171 6.1% 0.31 [0.25, 0.39] - Etaher 2020 95 171 81 97 5.4% 0.25 [0.13, 0.46] - Furie 2019 125 206 280 349 5.9% 0.38 [0.26, 0.56] - Hawatmeh 2020 141 281 578 664 6.0% 0.15 [0.11, 0.21] - Higuchi 2019 298 491 9238 12023 6.2% 0.47 [0.39, 0.56] - Lopez Cuenca 2016 92 117 648 707 5.6% 0.34 [0.20, 0.56] - Raphael 2020 570 1054 1167 1365 6.2% 0.20 [0.16, 0.24] - Sato 2020 112 155 2303 2834 5.9%	Balanescu 2020 29 49 131 152 5.1% 0.23 [0.11, 0.48] Baron 2015 926 1403 15040 17488 6.3% 0.32 [0.28, 0.36] Baron 2016 972 1313 37261 40501 6.3% 0.25 [0.22, 0.28] Chapman 2018 204 429 872 1171 6.1% 0.31 [0.25, 0.39] - Chapman 2018 204 429 872 1171 6.1% 0.31 [0.26, 0.56] - Urie 2019 125 206 280 349 5.9% 0.38 [0.26, 0.56] - tawatmeh 2020 141 281 578 664 6.0% 0.15 [0.11, 0.21] - tawatmeh 2020 141 281 578 664 6.0% 0.47 [0.39, 0.56] - tawatmeh 2020 141 281 578 664 5.8% 0.06 [0.04, 0.09] - kadesio 2019 92 251 883 111 6.1% 0.34 [0.20, 0.56] - kadesio 2020 570 1054 1167 1365 6.2% 0	Study or Subgroup						M-H, Random, 95% CI	
Baron 2015 926 1403 15040 17488 6.3% 0.32 [0.28, 0.36] Baron 2016 972 1313 37261 40501 6.3% 0.25 [0.22, 0.28] Chapman 2018 204 429 872 1171 6.1% 0.31 [0.25, 0.39] Etaher 2020 95 171 81 97 5.4% 0.25 [0.13, 0.46] Furie 2019 125 206 280 349 5.9% 0.38 [0.26, 0.56] Hawatmeh 2020 141 281 578 664 6.0% 0.15 [0.11, 0.21] Higuchi 2019 298 491 9238 12023 6.2% 0.47 [0.39, 0.56] Cadesjo 2019 92 251 883 1111 6.1% 0.15 [0.11, 0.20] Lopez Cuenca 2016 92 117 648 707 5.6% 0.34 [0.20, 0.56] Raphael 2020 39 128 606 684 5.8% 0.06 [0.04, 0.09] Raphael 2020 570 1054 1167 1365 6.2% 0.20 [0.16, 0.24] Sato 2020 112 155 2303 2834 5.9% 0.60 [0.42, 0.86] Froung 2020 158 175 241 275 5.4% 1.31 [0.71, 2.43] Fotal (95% CI) 7858 82430 100.0% 0.25 [0.17, 0.36] Fotal events 4344 71915 Heterogeneity: Tau ² = 0.57; Ch ² = 583.06, df = 16 (P < 0.00001); l ² = 97%	Baron 2015 926 1403 15040 17488 6.3% 0.32 [0.28, 0.36] Baron 2016 972 1313 37261 40501 6.3% 0.25 [0.22, 0.28] Chapman 2018 204 429 872 1171 6.1% 0.31 [0.25, 0.39] taher 2020 95 171 81 97 5.4% 0.25 [0.13, 0.46] urie 2019 125 206 280 349 5.9% 0.38 [0.26, 0.56] tawatmeh 2020 141 281 578 664 6.0% 0.15 [0.11, 0.21] tawatmeh 2020 141 281 578 664 6.0% 0.47 [0.39, 0.56] (adesjo 2019 92 251 883 1111 6.1% 0.15 [0.11, 0.20] opez Cuenca 2016 92 117 648 707 5.6% 0.34 [0.20, 0.56] (asphael 2020 39 128 606 684 5.8% 0.06 [0.04, 0.09] (bestelberger 2020 39 128 606 684 5.8% 0.06 [0.42, 0.86] (asphael 2020 112 155 2303 2834 5.9% 0.60 [0.42, 0.86] (asphael 2020 112 155 2303 2834 5.9% 0.60 [0.42, 0.86] (bingh 2020 255 1225 1840 2097 6.2% 0.04 [0.30, 0.04] (cound 205 125 125 1840 2097 6.2% 0.04 [0.30, 0.04] (cound 205 125 125 1840 2097 6.2% 0.04 [0.30, 0.04] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 241 275 5.4% 1.31 [0.71, 2.43] (cound 205 158 175 245 205 200001); 1 ² = 97%								
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U.UT U.T T 10	0.01 0.1 1 10		4344		71915				
		Heterogeneity: Tau ² =	0.57; Chi ²	= 583.	06, df = 1	6 (P < 0	.00001); l ²	² = 97%	
		fest for overall effect:	Z = 7.30 (F	P < 0.0	0001)				

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	T2M	1	T1M	II		Odds Ratio		Odds	s Ratio
Study or Subgroup	Events	Total	Events		Weight	M-H, Random, 95% (1	M-H, Rand	lom, 95% Cl
Arora 2018	32	264	363	775	4.7%	0.16 [0.11, 0.23]	-	
Balanescu 2020	0	0	0	0		Not estimabl	e		
Baron 2015	175	1403	10598	17488	4.9%	0.09 [0.08, 0.11]	-	
Baron 2016	723	1313	34264	40501	4.9%	0.22 [0.20, 0.25			
Chapman 2020	17	1121	2021	4981	4.6%	0.02 [0.01, 0.04	1 -	-	
Etaher 2020	7	171	12	97	4.0%	0.30 [0.11, 0.80]		
Furie 2019	3	206	128	349	3.6%	0.03 [0.01, 0.08] ← •		
Guimares 2018	27	76	440	847	4.6%	0.51 [0.31, 0.83]		
Higuchi 2019	258	491	9206	12023	4.9%	0.34 [0.28, 0.41]	-	
Landes 2016	14	107	85	107	4.3%	0.04 [0.02, 0.08] —	-	
Lopez Cuenca 2016	11	117	486	707	4.4%	0.05 [0.02, 0.09] –	-	
Nestelberger 2020	1	128	457	684	2.4%	0.00 [0.00, 0.03] ←		
Neumann 2017	0	99	126	188	1.6%	0.00 [0.00, 0.04	-	_	
Paiva 2015	27	236	507	764	4.7%	0.07 [0.04, 0.10]	-	
Putot 2018	103	847	1519	2036	4.9%	0.05 [0.04, 0.06]	+	
Putot 2019	29	254	235	365	4.7%	0.07 [0.05, 0.11	-	-	
Radovanovic 2017	557	1091	11684	13828	4.9%	0.19 [0.17, 0.22			
Raphael 2020	77	1054	791	1365		0.06 [0.04, 0.07		+	
Saaby 2014	4	119	194	360	3.9%	0.03 [0.01, 0.08	-		
Sandoval 2017	1	140	34	77	2.4%	0.01 [0.00, 0.07	•		
Shah 2015	1	429	564	1171	2.4%	0.00 [0.00, 0.02	-		
Singh 2020	27	1225	1786	2097	4.7%	0.00 [0.00, 0.01			
Smilowitz 2018	8	146	53	137	4.2%	0.09 [0.04, 0.20			
Stein 2014	64	127	2199	2691	4.8%	0.23 [0.16, 0.33	-		
Troung 2020	101	175	257	275	4.5%	0.10 [0.05, 0.17	1	-	
Total (95% CI)		11339		103913	100.0%	0.06 [0.04, 0.10]	•	
Total events	2267		78009						I .
Heterogeneity: Tau ² =				(P < 0.00	0001); l² =	98%	0.01	0.1	1 10
Test for overall effect:	Z = 12.56	(P < 0.0	0001)				0.01	T1MI	T2MI

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Arora 2018	4	264	91	775	9.2%	0.12 [0.04, 0.32]	
Baron 2015	15	1403	909	17488	11.3%	0.20 [0.12, 0.33]	la tradition of
Baron 2016	68	1313	2673	40501	12.1%	0.77 [0.60, 0.99]	
Etaher 2020	8	171	15	97	9.7%	0.27 [0.11, 0.66]	
Furie 2019	0	206	16	349	3.4%	0.05 [0.00, 0.82]	· · ·
Guimares 2018	7	76	73	847	10.1%	1.08 [0.48, 2.43]	
Landes 2016	8	107	33	107	10.0%	0.18 [0.08, 0.42]	10 10 10 10 10 10 10 10 10 10 10 10 10 1
Lopez Cuenca 2016	0	117	28	707	3.4%	0.10 [0.01, 1.67]	· - +
Nestelberger 2020	0	128	59	684	3.4%	0.04 [0.00, 0.67]	<u>← • • • • • • • • • • • • • • • • • • •</u>
Putot 2019	4	254	29	365	9.0%	0.19 [0.06, 0.53]	200 - 200 - 200 - 200 - 200 - 200 - 200 - 200 - 200 - 200 - 200 - 200 - 200 - 200 - 200 - 200 - 200 - 200 - 200
Saaby 2014	0	119	9	360	3.3%	0.15 [0.01, 2.68]	• • • • •
Sandoval 2017	0	140	3	77	3.1%	0.08 [0.00, 1.49]	•
Shah 2015	3	429	56	1171	8.5%	0.14 [0.04, 0.45]	
Stein 2014	0	127	16	2691	3.4%	0.64 [0.04, 10.66]	
Total (95% CI)		4854		66219	100.0%	0.23 [0.12, 0.42]	•
Total events	117		4010				

Figure S44. All ca	ause In-	hosp	ital mo	ortalit	y. T2M	compared to T1	MI.
	T2M		T1M	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Furie 2019	21	206	33	349	7.1%	1.09 [0.61, 1.93]	+-
Higuchi 2019	54	491	769	12023	8.2%	1.81 [1.35, 2.42]	-
Javed 2009	9	64	15	143	5.7%	1.40 [0.58, 3.38]	- -
Lopez Cuenca 2016	6	117	41	707	5.7%	0.88 [0.36, 2.12]	_ _
Meigher 2016	54	452	37	340	7.6%	1.11 [0.71, 1.73]	+-
Paiva 2015	23	236	66	764	7.4%	1.14 [0.69, 1.88]	+-
Putot 2018	133	847	125	2036	8.3%	2.85 [2.20, 3.69]	-
Putot 2019	38	254	24	365	7.2%	2.50 [1.46, 4.28]	
Putot 2020	95	862	186	3710	8.3%	2.35 [1.81, 3.04]	-
Saaby 2014	29	119	10	360	6.3%	11.28 [5.30, 24.00]	
Singh 2020	160	1225	42	2097	8.0%	7.35 [5.19, 10.41]	-
Smilowitz 2018	17	146	18	137	6.5%	0.87 [0.43, 1.77]	-+-
Stein 2014	15	127	113	2691	7.1%	3.06 [1.73, 5.41]	
Troung 2020	13	175	29	275	6.6%	0.68 [0.34, 1.35]	
Total (95% CI)		5321		25997	100.0%	1.94 [1.35, 2.79]	◆
Total events	667		1508				
Heterogeneity: Tau ² =	0.40; Chř	= 115.	87, df = 1	3 (P < 0	.00001): P	²= 89%	
Test for overall effect: 2							0.01 0.1 1 10
							Favours T1MI Favours T2N

	T2M	1	T1M	1		Odds Ratio	0
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, R
Nestelberger 2020	1	128	42	684	10.4%	0.12 [0.02, 0.88]	
Sandoval 2014	51	190	15	66	29.6%	1.25 [0.65, 2.41]	
Sandoval 2017	18	140	6	77	23.4%	1.75 [0.66, 4.60]	
Shah 2015	134	429	187	1171	36.7%	2.39 [1.85, 3.09]	
Total (95% CI)		887		1998	100.0%	1.34 [0.63, 2.85]	
Total events	204		250				
Heterogeneity: Tau ² =	0.38; Ch ř	= 12.1	1, df = 3 (P = 0.0	107); I ² = 7	5%	
Test for overall effect:	Z = 0.77 (I	P = 0.4	4)	-			0.01 0.1 Favours T
							avours i

Figure S47. Two-year	r all-caus	se moi	rtality. T	2MI c	ompared	to T1MI.	
	T2M	1	T1M	I		Odds Ratio	(
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, I
Cediel 2017	77	194	74	376	19.0%	2.69 [1.83, 3.94]	
Guimares 2018	19	76	156	847	15.9%	1.48 [0.85, 2.55]	
Neumann 2017	14	99	18	188	12.5%	1.56 [0.74, 3.28]	
Paiva 2015	62	236	92	764	19.3%	2.60 [1.81, 3.74]	
Smilowitz 2018	45	146	41	137	16.6%	1.04 [0.63, 1.73]	
Troung 2020	29	175	47	275	16.6%	0.96 [0.58, 1.60]	
Total (95% CI)		926		2587	100.0%	1.63 [1.11, 2.41]	
Total events	246		428				
Heterogeneity: Tau ² = 1	0.17; Chř	= 19.1	0, df = 5 (P = 0.0	102); I ^z = 7	4%	0.01 0.1
Test for overall effect: 2	Z = 2.48 (I	P = 0.0	1)				Favours 1

	T2M	1	T1M	1		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-
Kadesjo 2019	101	251	259	1111	36.0%	2.21 [1.66, 2.95]	
Lambrecht 2018	74	119	114	360	32.9%	3.55 [2.30, 5.47]	
Sato 2020	18	155	337	2834	31.1%	0.97 [0.59, 1.61]	
Total (95% CI)		525		4305	100.0%	2.00 [1.07, 3.76]	
Total events	193		710				

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PRISMA 2020 Checklist

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1 2 PRIS	SMA 2	020 Checklist	
3 4 Section and 5 Topic	ltem #	Checklist item	Location where item is reported
6 TITLE		9 9	
7 Title	1	Identify the report as a systematic review.	1
8 ABSTRACT	-	e 0 0	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
	1	۲ ۲	
12 Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
13 Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
¹⁴ METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
¹⁰ Information ¹⁷ sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to dentify studies. Specify the date when each source was last searched or consulted.	4
19 Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supp
20 Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reverse screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
22 Data collection 23 process 24	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
25 Data items 26	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each autcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
27 28	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
29 Study risk of bias30 assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how may reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5
³ Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5
32 33 Synthesis 34 methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5
34 35 36	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5
37	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5
38 39	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5
40	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysie, meta-regression).	5
41	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
42 43 Reporting bias 43 assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5
44 45 Certainty	15	Describe any methods used topassess/centainty (ortopr/fidenjce) in the body of evidence/for are butsomerni	N/A

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PRISMA 2020 Checklist

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	SMA 2	020 Checklist	
PRIS			
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RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the real method in the review, ideally using a flow diagram.	5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5
Study characteristics	17	Cite each included study and present its characteristics.	Supp
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supp
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effed estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supp
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supp
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Supp
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Supp
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	7
	23b	Discuss any limitations of the evidence included in the review.	9
	23c	Discuss any limitations of the review processes used.	9
	23d	Discuss implications of the results for practice, policy, and future research.	9
OTHER INFORMA	1	4 4 8	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A





10.1136/bmj.n71

PRISMA 2020 Checklist

For more information, visit: http://www.prisma-statement.org/

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Diagnostic features, management, and prognosis of Type 2 myocardial infarction compared to Type 1 myocardial infarction: A systematic review and meta-analysis.

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Title Page

Manuscript Title

Diagnostic features, management, and prognosis of Type 2 myocardial infarction compared to Type 1 myocardial infarction: A systematic review and meta-analysis.

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Abstract

Importance

Distinguishing type 2 (T2MI) from type 1 myocardial infarction (T1MI) in clinical practice can be difficult, and the management and prognosis for T2MI remain uncertain.

Objective

To compare precipitating factors, risk factors, investigations, management, and outcomes for T2MI and T1MI.

Data Sources

MEDLINE and EMBASE databases as well as reference list of recent articles were searched January 2009 to December 2020 for term "type 2 myocardial infarction".

Study Selection

Studies were included if they analysed if universal definition of MI was used and reported quantitative data on at least one variable of interest.

Data Extraction and Synthesis

Data was pooled using random-effect meta-analysis. Risk of bias was assessed using Newcastle-Ottawa Quality Assessment Form. Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA) guidelines were followed. All review stages were conducted by two reviewers.

Main Outcomes and Measures

Risk factors, presenting symptoms, cardiac investigations such as troponin and angiogram, management, and outcomes such as mortality.

Results

41 cohort studies comprising 116,565 T1MI and 15,258 T2MI patients were included. Compared to T1MI, T2MI patients were: more likely to have pre-existing chronic kidney disease (OR 1.89; 95%CI 1.59-2.25) and chronic heart failure (OR 2.34; 95%CI 1.87-2.93), less likely to present with typical cardiac symptoms of chest pain (OR 0.19; 95%CI 0.15-0.26) and more likely to present with dyspnoea (OR 2.83; 95%CI 1.96-4.08); more likely to demonstrate non-specific ST-T wave changes on electrocardiography (OR 2.62; 95%CI 1.81-3.79) and less likely to show ST elevation (OR 0.22; 95%CI 0.18-0.28); less likely to undergo coronary angiography (OR 0.09; 95%CI 0.06-0.12) and percutaneous coronary intervention (OR 0.06; 95%CI 0.04-0.10) or receive cardioprotective medications, such as statins (OR 0.25; 95%CI 0.17-0.36) and beta-blockers (OR 0.46; 95%CI 0.34-0.62). T2MI had more risk of all cause one-year mortality (OR 2.94; 95%CI 2.07-4.17), with no differences in cardiovascular deaths (OR 1.17; 95%CI 0.70-1.97).

Conclusion and Relevance

This review has identified clinical, management and survival differences between T2MI and T1MI with greater precision and scope than previously reported. Differential use of coronary

revascularisation and cardioprotective medications highlight ongoing uncertainty of their utility in T2MI compared to T1MI.

Strength and Limitations

- Inclusion of all contemporary cohort studies in the troponin era
- Large patient population of T2MI and T1MI patients analysed allowing high level of precision
- rcally s_{ιδ} mortality only . Wide array of clinically significant variables assessed providing a comprehensive analysis •
- Analysis of crude mortality only was possible due to lack of individual patient data •

Introduction

The clinical definition of myocardial infarction has evolved over time. The 2007 Universal Definition of Myocardial Infarction included a subset of MI that was secondary to aetiologies unrelated to underlying occlusive coronary artery disease (1). In 2012, the Third Universal Definition of Myocardial Infarction Consensus Document (2) gave rise to the aetiological distinction between T1MI, defined as MI due to plaque erosion and/or rupture, and T2MI, defined as MI caused by increased oxygen demand or decreased blood supply, in the absence of acute plaque rupture or coronary thrombosis. More recently, in 2018, the Fourth Universal definition of MI updated concepts of T2MI regarding specific situations associated with oxygen demand and supply imbalance and the relevance of the presence or absence of underlying coronary artery disease to therapy and prognosis (3). (see on-line supplement Table S1 for more detail)

In clinical practice, distinguishing T2MI from T1MI based on clinical presentation, electrocardiograph (ECG) features and cardiac troponin (cTn) values can be difficult. In the absence of randomised controlled trials that have evaluated different investigational and therapeutic interventions in patients with T2MI, uncertainty remains around the appropriate management of such patients, particularly those with known or suspected coronary artery disease. Past reviews have assessed one or more attributes of T2MI in comparison to T1MI (4-8) but, to our knowledge, none have undertaken a comprehensive analysis of symptoms, physical signs, investigation results, management regimens and clinical outcomes, both short and long term, of T2MI versus T1MI.

We undertook a systematic review of observational studies with the aims of identifying diagnostic and investigational findings which can assist clinicians to better distinguish T2MI from T1MI, and compare T2MI with T1MI in defining differences in management strategies and clinical outcomes.

Methods

Study design

The review was undertaken in accordance with recommendations of the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (9). Our review was registered on PROSPERO prior to commencement (Registration number: CRD42021237746). MEDLINE and EMBASE databases were searched for all studies published between January 1st, 2009, and December 31st, 2020, using search terms to identify all studies related to T2MI (see Table S2). Reference lists of all relevant articles were also assessed to identify additional relevant studies. The study PRISMA flowchart is shown in Figure S1.

Studies were included if they: 1) compared patient populations with T2MI and T1MI, 2) used a universal definition of MI, 3) included at least one variable of interest, 4) were available as full text in English and 5) were either a randomised control trial or comparative observational study. Studies were excluded if : 1) no full text was available, 2) duplicate data was utilised or 3) less than 200 participants in total were included. Initial screening of titles and abstracts for eligible studies was performed independently by two authors (MK, KW), as was full text review for inclusion, with any differences in review settled by consensus agreement.

Data collection and synthesis

Data pertaining to all variables of interest were collected from all included studies using a standardised proforma by one author (MK) and independently reviewed by the second author (KW). These variables comprised: study dates, design, sample size, definition used to define T2MI and T1MI, patient demographics, pre-existing medical conditions, precipitating factors, clinical symptoms, ECG findings, laboratory values, echocardiographic results, any clinical interventions or medical treatments administered, and clinical outcomes observed.

Data on variables reported as, or able to be converted to, raw numbers, were pooled from all studies and subject to comparative meta-analysis using Review Manager (RevMan, Computer program. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For each variable, the weighted odds ratio (OR) comparing T2MI to T1MI, and its 95% confidence interval (CI), was calculated using the random effects method. As specified in the registered study protocol, the random effects method was used in anticipation of study heterogeneity of at least moderate degree (l² statistic of heterogeneity >50%) (10). In addition to the weighted OR, we also report the crude, unweighted total event rates for each variable subject to meta-analysis in order to provide a more clinically meaningful estimate of the prevalence of these events in each patient group in view of the large sample sizes. Studies reporting mean or median values only were reproduced as reported in the original study.

Risk of bias within each study was assessed using the Newcastle-Ottawa quality assessment tool for cohort studies (11, 12), with scores 7-8 denoting good quality studies, 4-6 fair quality, and 0-3 poor quality.

Patient and Public Involvement

We did not seek patient or public comment in designing the study.

Results

A total of 41 studies were included for analysis (13-53) and their characteristics are summarised in Table S3. They comprised a total of 131,823 participants of whom 116,565 participants (88%) were classified as T1MI and 15,258 (12%) as T2MI. In the following text, we report key findings; more information and forest plots for each analysis involving more than one study and more than 100 total cases can be found in the on-line supplement, Figures S2-S43.

The 2007 definition (1) was used in 8 (19%) studies (15-17, 28, 30, 44, 45, 52), the 2012 definition (2) in 25 (61%) studies (13, 18, 20-22, 24-27, 31-36, 38, 40, 41, 43, 46-49, 51, 53), and the 2018 definition (3) in 8 (19%) studies (14, 19, 23, 29, 37, 39, 42, 50). Of the 41 studies, 18 (44%) were prospective (15-17, 19, 20, 23, 30, 34, 35, 37, 38, 44, 45, 47-49, 51, 52) and 23 (56%) were retrospective (13, 14, 18, 21, 22, 24-29, 31-33, 36, 39-43, 47, 50, 53).

Risk of bias assessment

Of the 41 studies, 32 (78%) were assessed as good quality (13, 15-20, 23, 24, 28-36, 38-47, 49, 53), 6 (15%) as fair quality (14, 25-27, 50), and 3 (7%) as poor quality (21, 37, 48), as summarised in Table S4. Selection bias resulting in unrepresentative cohorts such as admission criteria to coronary care units or entry criteria into MI registries favouring T1MI (14, 21, 25-27, 37, 48, 50), absence of independent adjudication of MI type as T1MI or T2MI (37, 39, 48), non-comparability of T1MI and

T2MI cohorts (21, 25, 26, 48), poorly specified outcome measures (37, 39, 48) and short follow-up period resulting in few events (14, 21, 25, 37) comprised most forms of bias.

Participant characteristics

Patients with T1MI had a median age range of 60-82 years in the included studies that did not select a specific age population, compared to a median age range of 62-79 years in patients with T2MI. The sex distribution was also similar, with 59.8% and 54% of patients with T1MI and T2MI being male respectively.

Regarding pre-existing medical conditions (Table 1), T2MI patients compared to T1MI patients were more likely to have chronic kidney disease (26.9% vs 19.3%; OR 1.89; 95%CI 1.59-2.25), chronic heart failure (19% vs 8.1%; OR 2.34; 95%CI 1.87-2.93), atrial fibrillation (22.9% vs 6.1%; OR 3.02; 95%CI 2.29-3.99), and hypertension (66.8% vs 61.3%; OR 1.22; 95%CI 1.05-1.43). Patients with T2MI were less likely to have dyslipidaemia (43.4% vs 45.9%; OR 0.74; 95%CI 0.58-0.94) and smoking history (37.2% vs 53.9%; OR 0.61; 95%CI 0.50-0.74). There was no difference in the prevalence of type 2 diabetes mellitus or ischaemic heart disease between the two groups.

Precipitating factors

Less than half of the studies (n=18; 44%) included data on precipitating factors associated with T2MI (13, 15, 16, 18, 20, 22-25, 28, 32, 33, 36, 41, 45, 46, 51, 52). Data on each precipitating factor was not consistently available across the studies, for example only 18 studies representing 45% of T2MI patients assessed presence of arrythmia

The most common precipitant was sepsis (35.9%), followed by arrythmia (29.8%), and heart failure 28.6% (Table S5), with non-cardiac surgery being deemed a cause in 12.2% of cases where data for this variable were collected.

Presenting clinical features

As summarised in Table S6, compared to T1MI patients, T2MI patients were less likely to present with typical cardiac symptoms of chest pain (59.2% vs 87.7%; OR 0.19; 95%CI 0.15-0.26) or discomfort in the arm or shoulder (8.5% vs 35%; OR 0.18; 95%CI 0.11-0.3), but more likely to present with dyspnoea (27.6% vs 9.9%; OR 2.83; 95%CI 1.96-4.08).

Investigations

ECG findings on presentation (Table S7) such as ST elevation (13.4% vs 42.1%; OR 0.22; 95%CI 0.18-0.28) and pathological Q waves (6.7% vs 20.8%; OR 0.38; 95%CI 0.20-0.71) were less evident in T2MI than in T1MI. In contrast, non-specific ST-T wave changes (24.7% vs 10.8%; OR 2.62; 95%CI 1.81-3.79), and atrial arrythmias (27% vs 10.2%; OR 3.70; 95%CI 2.87-4.77) were more common among T2MI. No differences between groups were seen in the frequency of ST depression or T wave inversion.

Among the 41 studies, five studies (12%) reported the use of high-sensitivity cardiac troponin (cTn) assays, 22 (54%) reported sensitive assays, and 14 (34%) did not specify what generation assay was used (Table S3b). The results of troponin assays were reported in 27 (66%) studies, specific to cTnI assays in 19 studies, cTnT in 6, both assays in one, while another did not specify the assay used. Only

two of these studies reporting troponin failed to state the upper limit of normal (ULN) of the assay used (24, 32). The troponin assays, and therefore units and reference ranges, varied between the studies, preventing direct comparison of troponin values. As a result, we converted troponin values to a multiple of the upper limit of normal for each assay to allow direct comparison (Table S8). For peak troponin, patients with T1MI had a higher and wider range of between 5 and 1702 times the ULN compared to patients with T2MI with a range of 2.8-447 times the ULN. Studies yielded mixed results as to whether the magnitude of change (or delta) in serial cardiac troponin assays was more predictive of T2MI or T1MI compared to absolute values of peak levels (34). Lowering the diagnostic threshold for troponin with the advent of more sensitive assays has increased the numbers of patients identified with T2MI by up to 50% (37), with more recent studies showing the incidence of T2MI equalling or exceeding that of T1MI (16, 34, 37).

Echocardiography was less frequently performed among T2MI than T1MI patients (47.9% vs 55.5%; OR 0.44; 95%CI 0.20-0.96) and when reported (Table S7), there was no difference in the prevalence of regional wall motion abnormalities or the level of left ventricular (LV) function, with reported median LV ejection fraction being 42.3%-55% in T1MI patients and 40%-56% in T2MI patients.

Coronary angiography was also less frequently performed among T2MI than in T1MI patients (34.4% vs 83.4%; OR 0.09; 95%CI 0.06-0.12, Table S7). When performed, T2MI patients were less likely to demonstrate obstructive coronary artery disease (34% vs 44.9%; OR 0.16; 95%CI 0.05-0.54), with obstruction variously defined as 50%-70% occlusion of one or more vessels.

Management

T2MI patients, compared to T1MI patients, were significantly less likely to receive conventional cardioprotective medications (Table 2), comprising beta-blockers (61.6% vs 78.2%; OR 0.46; 95%CI 0.34-0.62), anti-platelet agents (57.4% vs 87.3%; OR 0.24; 95%CI 0.17-0.36) and statins (55.3% vs 87.2%; OR 0.25; 95%CI 0.17-0.36). Of note, T2MI patients were more likely to receive diuretics (46.5% vs 18.8%; OR 1.99; 95%CI 1.56-2.53) or anti-coagulants (26.1% vs 21.3%; OR 1.90; 95%CI 1.17-3.10).

Percutaneous coronary intervention (PCI) (20% vs 75.1%; OR 0.06; 95%CI 0.04-0.10) and coronary artery bypass surgery (2.4% vs 6.1%; OR 0.23; 95%CI 0.12-0.42) were also significantly less likely to be performed in T2MI patients than T1MI patients.

Prognosis

T2MI patients had significantly increased risk of all-cause death compared to patients with T1MI in both short- and long-term follow-up (Table 3). Specifically, compared to T1MI patients, T2MI demonstrated increased all-cause mortality in-hospital (12.5% vs 5.8%; OR 1.94; 95%CI 1.35-2.79, Figure S44), at one-year (20.6% vs 8.8%; OR 2.94; 95%CI 2.07-4.17, Figure 1) and at 5 to 10 years, (53.7% vs 28.5%, OR 3.24; 95%CI 2.73-3.84, Figure 2). In contrast, there were no differences between T2MI and T1MI patients in the risk of cardiovascular related in-hospital mortality (6% vs 3.8%; OR 1.17; 95%CI 0.70-1.97) or short-term mortality at 120-180 days (23.0% vs 12.5%; OR 1.34; 95%CI 0.63-2.85).

Discussion

To our knowledge, this is the most comprehensive systematic review and meta-analysis of contemporary studies comparing T2MI with T1MI in the troponin era, comprising 131,000 patients from 41 cohort studies across 14 countries, and which used formal definitions of T2MI and T1MI. Up to three quarters of all myocardial infarctions in routine care can be T2MI (34, 35), and distinguishing T2MI from T1MI on clinical criteria is often challenging. The management strategies used by clinicians in real-world practice for T2MI often vary, and the clinical outcomes of T2MI compared to T1MI, particularly over the long term, have been uncertain. This review provides information that helps characterise these two groups of patients according to multiple variables and which may assist in clinical decision-making and prognostication.

In this review, T2MI patients demonstrated more medical comorbidities than T1MI patients, as noted in a recent meta-analysis (6). Our review highlighted the much higher incidence of pre-existing generalised vascular disease, atrial fibrillation, renal impairment, and heart failure among T2MI patients.

Sepsis (10, 17, 28) and anaemia (52) ranked highly as triggers, together with other acute cardiac events such as valve dysfunction or arrhythmias. In one study, a more favourable prognosis in T2MI was seen when the principal trigger was arrhythmia compared to non-cardiac surgery, hypotension, anaemia or hypoxia (30). In another study, shock syndromes were triggers portending a worse prognosis compared to all other triggers (33). In our analysis, non-cardiac surgery as a trigger was less frequent than reported by other investigators (27) whereby peri-operative stressors including blood loss, anaesthesia induced hypotension and wound infections cause imbalance in myocardial contractility, oxygen demand and blood flow (54).

Analysis of cTn levels showed uniformly higher values in T1MI than T2MI which accord with one review (5) reporting cTn values 30% to 94% higher in patients with T1MI, and which other investigators regard as being highly specific diagnostic markers for T1MI (54).

Coronary angiography and revascularisation were both performed much less frequently in T2MI than in T1MI patients. Treating physicians may perceive invasive strategies as being contraindicated or potentially harmful in the presence of various co-morbidities more commonly seen in T2MI and associated with competing mortality risk. In our pooled data, only one in three T2MI patients who underwent angiography demonstrated obstructive coronary artery disease, although this figure may be an underestimate due to selection bias whereby younger, less multi-morbid patients preferentially underwent angiography. In the CASABLANCA cohort study, which enrolled patients with high likelihood of coronary or peripheral artery disease and subjected them to peripheral or coronary angiography, of all those who subsequently suffered incident T2MI, almost half (47.7%) demonstrated ≥70% stenosis in at least 2 major coronary arteries (55). These conflicting findings question whether patients presenting with T2MI would benefit from routine use of invasive strategies that define coronary anatomy and, if plaque rupture or critical stenoses are seen, prompt revascularisation, with resultant improvement in patient outcomes. In one study (19), angiography unmasked acute plaque rupture in 29% of patients classified as T2MI. In another study, among 27 of 236 patients with T2MI who underwent revascularisation, the odds of all-cause death were reduced by 67% compared to the remaining 209 non-revascularised patients (24). In contrast, in a third more

rigorous study comparing T2MI versus T1MI patients who received or did not receive PCI within 24 hours of symptom onset, after adjusting results using multivariate logistic regression analysis and inverted probability weighting,(15) in-hospital mortality was lower in those with T1MI receiving PCI (OR 0.47; 95% CI 0.40–0.55; p < 0.001), but not in those with T2MI receiving PCI (OR 1.09; 95% CI 0.62–1.94; p = 0.763). However, all these studies are observational, so completion of randomised trials, such as the Appropriateness of Coronary investigation in myocardial injury and Type 2 myocardial infarction (ACT-2) trial, which is currently in recruitment (54), will hopefully provide a more definitive answer.

Given that a third of T2MI patients had pre-existing coronary artery disease and most of the remainder had one or more cardiovascular risk factors, the relative underuse of cardioprotective medications is perplexing. It may reflect either clinician uncertainty around their cardioprotective utility in T2MI, or concerns about the potential for adverse interactions with other drugs or diseases commonly seen in multi-morbid T2MI patients. The higher use of diuretics in the T2MI population likely reflects the higher prevalence of heart failure and hypertension. Recognizing the heterogeneous mechanisms or conditions leading to T2MI, a phenotype specific-approach to the design of future trials will be useful in identifying effective therapies.

An important finding is the much higher all-cause in-hospital and one-year mortality in T2MI compared to T1MI patients, similar to the two-fold greater mortality rate in T2MI noted in a recent systematic review of 9 studies (8). In our review, this excess mortality was not driven by an excess of cardiovascular deaths, and likely reflects the competing risks of multiple co-morbidities, rather than underlying obstructive coronary artery disease which was seen in 30-50% of T2MI patients (27, 32). Studies yielded mixed results as to whether coronary artery disease is an independent predictor of T2MI (21, 43), while others question the angiographic distinction between T2MI and T1MI. For example, in a study of 450 consecutive patients with MI who all underwent coronary angiography within 24 hours of symptom onset, 145 (32.2%) patients had 'true' T1MI (acute atherothrombosis and no systemic triggers), 114 (25.3%) had 'true' T2MI (no atherothrombosis and systemic triggers), 61 (13.6%) patients had neither, and 130 (28.9%) patients had both (41). This yields a discordance of angiographic and clinical definitions of MI type in 42.5% of patients.

Our review has several limitations. First, in the absence of individual patient data from all included studies, we could not perform multivariate regression analysis in identifying weighted predictors of diagnosis, management, or prognosis of T2MI. Second, we did not perform separate analyses of studies according to each version of the Universal Definition of MI or to different troponin thresholds to define MI, which may impact management and prognosis. However, potential misclassification bias was addressed in a recent study which showed little change in MI classification as type 1 or 2 in the same cohort of emergency admissions to whom the 3rd and 4th universal definitions were applied.(56) In another study which compared separate T2MI cohorts, as defined by the 2007 and the 2012 definitions, co-morbidities and use of cardioprotective medications were less frequent in the 2012 cohort, likely due to less severe MIs being included as a result of using more sensitive troponin assays (23). Third, we did not collect haemodynamic variables or other physiological measures such as haemoglobin levels and glomerular filtration rate in analysing clinical presentations as these were very inconsistently reported. Fourth, our mortality meta-analyses relied on crude mortality rates reported in each study, with 56% of studies (15-20, 23-29, 31, 32, 35, 36,

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38, 41-43, 46, 47) also undertaking multivariate regression and/or competing risk analyses and reporting adjusted mortality rates. For the T2MI cohorts in general, these rates tended to be lower and the differences in rates compared to those of T1MI were of smaller magnitude. Fifth, we did not analyse 30-day readmission rates as these were reported in only three studies (13, 14, 24). Sixth, we did not perform sensitivity analyses comparing results of prospective versus retrospective studies, as neither group demonstrated less or more risk of bias than the other, or compare results of good quality studies against fair/poor quality studies as the latter comprised only 16.7% (22,001/131,823) of all patients. Finally, we did not attempt sub-analyses based on risk stratification using validated risk scores or seek to identify predictive models for mortality, as such analyses were reported in only two studies (27, 41).

The strengths of this review are the inclusion of all contemporary cohort studies in the troponin era that employed formal definitions of T2MI, analysis of a broader range of variables than those of previous studies, and the more precise discernment of clinically meaningful differences between the two MI populations in patient characteristics, clinical presentation, patterns of care and outcomes. We are aware of a large US cohort study published since completion of our review (57) which compared T1MI with T2MI patients, but was limited by misclassification bias (relying on administrative hospital discharge data containing an International Classification of Diseases-10th Revision code specific for type 2 MI, rather than a registry or chart diagnosis based on a formal MI definition), short study period of 3 months in late 2017, and inability to analyse clinical features, investigation results, medication use, coronary anatomy, and post-discharge mortality due to their omission in the datasets.

Conclusion

This review has identified differences between T2MI and T1MI patients in presenting clinical features, investigation and management profiles, and clinical outcomes. These findings may assist clinicians to better recognise T2MI and advise patients about its sequelae, and inform hospital coding and epidemiological trending, quality of care indicators and inter-hospital benchmarking of performance relating to the care of patients with T2MI.

The review has also defined persisting gaps in our understanding of the utility and prognostic effects of invasive investigations, revascularization strategies and cardioprotective medications in T2MI patients that warrant more randomised trials that enrol such patients.

Tables

		T2MI			T1MI		
Pre-existing medical condition	Number of patients with the specified condition	Total number of patients	%	Number of patients with the specified condition	Total number of patients	%	Odds ratio* (95% CI)
CAD	3915	11706	33.4%	27538	110213	25.0%	1.13 [0.96, 1.32
Type 2 DM	3420	13560	25.2%	27169	110833	24.5%	0.98 [0.86, 1.10
HTN	8296	12424	66.8%	64648	105505	61.3%	1.22 [1.05, 1.43
Dyslipidaemia	4626	10652	43.4%	40099	87366	45.9%	0.74 [0.58, 0.9 [,]
Smoker	4213	11332	37.2%	49796	92377	53.9%	0.61 [0.50, 0.74
Obesity	1225	3672	33.4%	30963	56970	54.3%	0.63 [0.46, 0.8
Renal failure	2002	7443	26.9%	15969	82882	19.3%	1.89 [1.59, 2.2
Heart failure	1949	10276	19.0%	7471	91700	8.1%	2.34 [1.87, 2.9
PVD	584	5856	10.0%	2066	41280	5.0%	1.33 [1.05, 1.6
CVD	1164	9941	11.7%	7669	105310	7.3%	1.48 [1.30, 1.6
Atrial fibrillation	836	3645	22.9%	1220	19843	6.1%	3.02 [2.29, 3.9
COPD	800	5018	15.9%	823	48375	1.7%	1.94 [1.22, 3.0
Illicit drug Use	46	204	22.5%	8	220	3.6%	8.15 [1.03, 64.46]

*Comparing T2MI with T1MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: CAD= coronary heart disease, DM= diabetes mellitus, HTN= hypertension, BMI= body mass index, PVD= peripheral vascular disease, CVD= cerebrovascular disease, COPD= chronic obstructive pulmonary disease

Table 2. Pharmacological management and invasive interventions in patients with	
T2MI versus T1MI.	

		T2MI			T1MI		
Intervention	No. patients receiving intervent ion	Total numbe r of patient s	%	No. patients receiving intervention	Total number of patients	%	Odds ratio* (95% Cl)
Medication		1		I			
Beta blockers	6113	9926	61.6%	78733	100645	78.2%	0.46 [0.34, 0.62]
ACEI / ARB	4692	9245	50.8%	69684	99281	70.2%	0.52 [0.41, 0.66]
Anti-platelets	5742	10002	57.4%	88612	101492	87.3%	0.24 [0.17, 0.36]
Anti-coagulants	1738	6658	26.1%	17048	79903	21.3%	1.90 [1.17, 3.10]
Anti-anginal agents	2322	3594	64.6%	55149	60256	91.5%	0.51 [0.26, 1.00]
Diuretics	2042	4388	46.5%	11877	63267	18.8%	1.99 [1.56, 2.53]
Statins	4344	7858	55.3%	71915	82430	87.2%	0.25 [0.17, 0.36]
Invasive							
PCI	2267	11339	20.0%	78009	103913	75.1%	0.06 [0.04, 0.10]
CABG	117	4854	2.4%	4010	66219	6.1%	0.23 [0.12, 0.42]

*Comparing T2MI with T1MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: ACEI= Angiotensin converting enzyme inhibitors, ARB= Angiotensin receptor blockers; CI=confidence interval; T2MI=type 2 myocardial infarction; T1MI=type 1 myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft

		T2MI			T1MI			
Outcomes	No. patients with outcome	Total number of patients	%	No. patients with outcome	Total number of patients	%	Odds ratio* (95% Cl)	
CV in-hospital mortality	212	3512	6.0%	891	23736	3.8%	1.17 [0.70, 1.97]	
All-cause in- hospital mortality	667	5321	12.5%	1508	25997	5.8%	1.94 [1.35, 2.79]	
Short-term all- cause mortality	204	887	23.0%	250	1998	12.5%	1.34 [0.63, 2.85]	
1-year all-cause mortality	979	4743	20.6%	3660	41691	8.8%	2.94 [2.07, 4.17]	
2-year all-cause mortality	246	926	26.6%	428	2587	16.5%	1.63 [1.11, 2.41]	
3-year all-cause mortality	193	525	36.8%	710	4305	16.5%	2.00 [1.07, 3.76]	
Long-term all- cause mortality	1453	2708	53.7%	1320	4633	28.5%	3.24 [2.73, 3.84]	

*Comparing T1MI with T2MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: CV= Cardiovascular, MACE= Major adverse cardiovascular events; T2MI=type 2 myocardial infarction; T1MI=type 1 myocardial infarction; CI=confidence interval

Figures

 Figure 1. Forest plot of one-year all-cause mortality of T2MI patients compared to T1MI patients.

Figure 2. Forest plot of long-term all-cause mortality of T2MI patients compared to T1MI patients.

Figure S1. PRISMA flow diagram.

Figure S2. Forest Plot. Presence of Ischaemic Heart Disease.

Figure S3. Forest Plot. Presence of Type 2 Diabetes Mellitus.

Figure S4. Forest Plot. Presence of Hypertension.

Figure S5. Forest Plot. Presence of Dyslipidaemia.

Figure S6. Forest Plot. Smoking Status.

Figure S7. Forest Plot. Obesity Status.

Figure S8. Forest Plot. Presence of Chronic Kidney Disease.

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3 4	Figure S9. Forest Plot. Presence of Heart Failure.
5	Figure S10. Forest Plot. Presence of Peripheral Vascular Disease.
7	Figure S11. Forest Plot. Presence of Cerebrovascular Disease.
8 9	Figure S12. Forest Plot. Presence of Illicit Drug Use.
10 11	Figure S13. Forest Plot. Presence of Atrial Fibrillation.
12 13	Figure S14. Forest Plot. Chest Pain as Presenting Feature.
14 15	Figure S15. Forest Plot. Dyspnoea as Presenting Feature.
16 17	Figure S16. Forest Plot. Arm / Shoulder Discomfort as Presenting Feature.
18 19	Figure S17. Forest Plot. Nausea / Vomiting as Presenting Feature.
20 21	Figure S18. Forest Plot. Non-specific Symptoms as Presenting Features.
22	Figure S19. Forest Plot. Collapse / Syncope as Presenting Features.
23 24	Figure S20. Forest Plot. ST Elevation on ECG.
25 26	Figure S21. Forest Plot. ST Depression or T Wave Inversion on ECG.
27 28	Figure S22. Forest Plot. Q Waves on ECG.
29 30	Figure S23. Forest Plot. Non-specific ST Changes on ECG.
31 32	Figure S24. Forest Plot. Left Bundle Branch Block on ECG.
33 34	Figure S25. Forest Plot. Atrial Fibrillation on ECG.
35 36	Figure S26. Forest Plot. Coronary Angiogram Performed.
37 38	Figure S27. Forest Plot. Obstructive Coronary Artery Disease on Coronary Angiogram.
39	Figure S28. Forest Plot. Multivessel Disease on Coronary Angiogram.
40 41	Figure S29. Forest Plot. Echocardiogram Performed.
42 43	Figure S30. Forest Plot. Regional Wall Motion Abnormalities on Echocardiogram.
44 45	Figure S31. Forest Plot. Beta-Blockers Prescribed.
46 47	Figure S32. Forest Plot. ACEi/ARB Prescribed.
48 49	Figure S33. Forest Plot. Antiplatelets Prescribed.
50 51	Figure S34. Forest Plot. Anticoagulants Prescribed.
52 53	Figure S35. Forest Plot. Antianginal Drugs Prescribed.
54	Figure S36. Forest Plot. Diuretics Prescribed.
55 56	Figure S37. Forest Plot. Statins Prescribed.
57 58	Figure S38. Forest Plot. Percutaneous Coronary Intervention Performed.
59 60	Figure S37. Forest Plot. Statins Prescribed.

Figure S38. Forest Plot. Percutaneous Coronary Intervention Performed.

Contribution Statement

All authors (KW, MK, IS) contributed to the conception of the work. MK and KW performed the acquisition and analysis of the data. KW and IS were responsible for the interpretation of data. All authors (MK, KW, IS) were responsible for drafting manuscript and final approval of the version to be published. All authors (KW, MK, IS) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing Interests

The authors declare there are no conflict of interest with respect the article.

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	T2M		T1N	11		Odds Ratio		Odds Ratio
Study or Subgrou	b Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI
Arora 2018	89	264	96	775	11.8%	3.60 [2.58, 5.02]	гер	
Baron 2015	347	1403	2361	17488	12.9%	2.11 [1.85, 2.39]	ruar	•
Chapman 2020	258	1121	720	4981	12.8%	1.77 [1.51, 2.08]	ע בנ	-
El haddad 2012	84	295	28	512	10.8%	6.88 [4.36, 10.87]	122.	5 —
Furie 2019	80	206	93	349	11.5%	1.75 [1.21, 2.52]		
Lopez Cuenca 201	6 27	117	102	707	10.6%	1.78 [1.10, 2.87]	VIIIO	
Radovanovic 2017	14	1091	117	13828	9.9%	1.52 [0.87, 2.66]	auer	
Saaby 2014	65	119	25	360	10.0%	16.13 [9.37, 27.77]		
Stein 2014	15	127	118	2691	9.8%	2.92 [1.65, 5.16]		
010111 2014								
Total (95% CI)		4743		41691	100.0%	2.94 [2.07, 4.17]	.//011	•
	979	4743	3660	41691	100.0%	2.94 [2.07, 4.17]	רפטועמוץ בטבב. הסאוווסמספס ווסוח חווף://סוחוסספ	
Total (95% CI) Total events Heterogeneity: Tau	² = 0.24; Chr	e 96.2	9, df = 8 (1	
Total (95% CI) Total events	² = 0.24; Chr	e 96.2	9, df = 8 (0.01	
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Total (95% CI) Total events Heterogeneity: Tau Test for overall effe	² = 0.24; Chř ct: Z = 6.03 (² = 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); l²=	92%	0.01 Fa	0.1 1 10 10 vours T1MI Favours T2MI
Total (95% CI) Total events Heterogeneity: Tau Test for overall effe	² = 0.24; Chř ct: Z = 6.03 (² = 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); l²=	92%	0.01 Fa	0.1 1 10 10 vours T1MI Favours T2MI
Total (95% CI) Total events Heterogeneity: Tau Test for overall effe	² = 0.24; Chř ct: Z = 6.03 (² = 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); l²=	92%	0.01 Fents co	0.1 1 10 10 vours T1MI Favours T2MI npared to T1MI patients.
Total (95% CI) Total events Heterogeneity: Tau Test for overall effe	² = 0.24; Chř ct: Z = 6.03 (² = 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); l²=	92%	0.01 Fents co	0.1 1 10 10 vours T1MI Favours T2MI
Total (95% CI) Total events Heterogeneity: Tau Test for overall effe	² = 0.24; Chř ct: Z = 6.03 (² = 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); l²=	92%	0.01 Fents co	0.1 1 10 10 vours T1MI Favours T2MI npared to T1MI patients.
Total (95% CI) Total events Heterogeneity: Tau Test for overall effe	² = 0.24; Chř ct: Z = 6.03 (² = 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); l²=	92%	0.01 Fants cot	0.1 1 10 10 vours T1MI Favours T2MI
Total (95% CI) Total events Heterogeneity: Tau Test for overall effe	² = 0.24; Chř ct: Z = 6.03 (² = 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); l²=	92%	0.01 Faile 21, 2024 by guest.	0.1 1 10 10 vours T1MI Favours T2MI npared to T1MI patients.
Total (95% CI) Total events Heterogeneity: Tau Test for overall effe	² = 0.24; Chř ct: Z = 6.03 (² = 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); l²=	92%	0.01 Faile 21, 2024 by guest.	0.1 1 10 10 vours T1MI Favours T2MI npared to T1MI patients.
Total (95% CI) Total events Heterogeneity: Tau Test for overall effe	² = 0.24; Chř ct: Z = 6.03 (² = 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); l²=	92%	0.01 Faile 21, 2024 by guest.	0.1 1 10 10 vours T1MI Favours T2MI npared to T1MI patients.
Total (95% CI) Total events Heterogeneity: Tau Test for overall effe	² = 0.24; Chř ct: Z = 6.03 (² = 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); l²=	92%	0.01 Faile 21, 2024 by guest.	0.1 1 10 10 vours T1MI Favours T2MI npared to T1MI patients.
Total (95% CI) Total events Heterogeneity: Tau Test for overall effe	² = 0.24; Chř ct: Z = 6.03 (² = 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); l²=	92%	0.01 Faile 21, 2024 by guest.	0.1 1 10 10 vours T1MI Favours T2MI npared to T1MI patients.
Total (95% CI) Total events Heterogeneity: Tau Test for overall effe	² = 0.24; Chř ct: Z = 6.03 (² = 96.2 P < 0.0	9, df = 8 (0001)	(P < 0.0(0001); l²=	92%	0.01 Fants cot	0.1 1 10 10 vours T1MI Favours T2MI npared to T1MI patients.

3 4

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Total (95% Cl) 2708 4633 100.0% 3.24 [2.73, 3.84] Total of the result of meta-analysis of the risk long-term mortality of T2MI patients. 0.011 1 100						BMJ Ope	n	_	omjopen-2021-055	
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI Chapman 2018 268 429 430 1171 28.3% 2.87 [2.28, 3.61] P Raphael 2020 766 1054 638 1365 36.2% 3.03 [2.55, 3.60] P P Singh 2020 419 1225 252 2097 35.5% 3.81 [3.19, 4.54] P P Total (95% CI) 2708 4633 100.0% 3.24 [2.73, 3.84] P P Total events 1453 1320 Image: Singh 20.00 Image: Singh 20.00 Image: Singh 20.01 Image: Singh									021-055	
Chapman 2018 268 429 430 1171 28.3% 2.87 [2.28, 3.61] F Raphael 2020 766 1054 638 1365 36.2% 3.03 [2.55, 3.60] F Singh 2020 419 1225 252 2097 35.5% 3.81 [3.19, 4.54] F Total (95% CI) 2708 4633 100.0% 3.24 [2.73, 3.84] F Total events 1453 1320 1320 F 59% Heterogeneity: Tau ² = 0.01; Ch ² = 4.84, df = 2 (P = 0.09); I ² = 59% 0.01 0.01 100 rest for overall effect: Z = 13.42 (P < 0.00001) Favours T2MI Favours T2MI igure 2. Forest plot of the result of meta-analysis of the risk long-term mortality of T2MI patients compared to T1MI patients.										
Total (95% CI)27084633100.0% 3.24 [2.73, 3.84]Total events14531320Heterogeneity: Tau ² = 0.01; Chi ² = 4.84, df = 2 (P = 0.09); I ² = 59% $0.01 = 0.1 = 1 = 0.01 $									<mark>⇒M-H, Random, 95%</mark>	CI
Total (95% CI)27084633100.0% 3.24 [2.73, 3.84]Total events14531320Heterogeneity: Tau ² = 0.01; Chi ² = 4.84, df = 2 (P = 0.09); I ² = 59% $0.01 = 0.1 = 1$ Test for overall effect: Z = 13.42 (P < 0.00001)	-									
Total (95% CI)27084633100.0% 3.24 [2.73, 3.84]Total events14531320Heterogeneity: Tau ² = 0.01; Chi ² = 4.84, df = 2 (P = 0.09); I ² = 59% $0.01 = 0.1 = 1$ Test for overall effect: Z = 13.42 (P < 0.00001)	•									
Total (95% CI)27084633100.0% 3.24 [2.73, 3.84]Total events14531320Heterogeneity: Tau ² = 0.01; Chr ² = 4.84, df = 2 (P = 0.09); I ² = 59% $0.01 = 0.1 = 1 = 10 = 100$ Test for overall effect: Z = 13.42 (P < 0.00001)	Singh 2020	419 1	1225	252	2097	35.5%	3.81 [3.19, 4.54]		2022	
igure 2. Forest plot of the result of meta-analysis of the risk long-term mortality of T2MI patients compared to T1MI patients.	Total (95% CI)	2	2708		4633	100.0%	3.24 [2.73, 3.84]			
gure 2. Forest plot of the result of meta-analysis of the risk long-term mortality of T2MI patients compared to T1MI patients.		1453		1320			•		nlo	
gure 2. Forest plot of the result of meta-analysis of the risk long-term mortality of T2MI patients compared to T1MI patients.			4.84, c		= 0.09)); l² = 59%				
gure 2. Forest plot of the result of meta-analysis of the risk long-term mortality of T2MI patients compared to T1MI patients.			-					0.01		
				,				r.		1201
	gure 2 Forest plot of th	ne result of n	meta-ar	nalysis o	f the riv	sk long-ter	m mortality of T2MI nat	ents c	#mnared to T1MI natie	nts
									7	

Table S	S1. Evolving definitions of Type 2 Myocardial Infarction.
Year	Universal Definition of Type 2 Myocardial Infarction
2007	Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrythmias, hypotension or hypertension
2012	Instances of myocardial injury with necrosis where a condition other than coronary artery disease contributes to an imbalance between myocardial oxygen supply and/or demand e.g. coronary artery spasm, coronary embolism, anaemia, arrythmias, hypotension or hypertension
2018	 Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following: Symptoms of acute myocardial ischaemia New ischaemic ECG changes Development of pathological Q waves Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology

Table S2. Search	n strategy.
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MEDLINE: (type 2 adj3 myocard*) OR (type-2 adj3 myocard*) OR (type II adj3 myocard*) OR (type-II adj3 myocard*) OR (type 2 adj3 MI) OR (type-2 adj3 MI) OR T2MI OR (supply demand adj3 myocard*)

EMBASE: ('type 2' NEXT/3 myocard*) OR ('type-2' NEXT/3 myocard*) OR ('type ii' NEXT/3 myocard*) OR ('type-ii' NEXT/3 myocard*) OR ('type 2' NEXT/3 mi) OR ('type-2' NEXT/3 mi) OR ('t2mi') OR ('supply demand' NEXT/3 myocard*)

tics ents T2MI 264 49 1403 1313 42 194 429 1121 75 295 121 206	Design Retrospective Retrospective Prospective Prospective Prospective Retrospective Prospective Retrospective Retrospective Retrospective	Definition of MI 2012 2018 2007 2007 2007 2012 2012 2018 2012 2012	Geographic location USA USA Sweden Sweden Sweden Multinational Spain UK UK Spain UK	Screening B Screening B Screening B Screening B Screening B S Screening B S S S S S S S S S S S S S S S S S S	Troponin Assay cTnl N/A hs-cTnT hs-cTnT N/A cTnl cTnl cTnl cTnl cTnl ns-cTnT N/A
ents T2MI 264 49 1403 1313 42 194 429 1121 75 295 121	Retrospective Retrospective Prospective Prospective Prospective Retrospective Prospective Retrospective Retrospective	of MI 2012 2018 2007 2007 2007 2012 2012 2012 2018 2012 2012	location USA USA Sweden Sweden Multinational Spain UK UK Spain	Screening Screen	Assay cTnl N/A hs-cTnT hs-cTnT N/A cTnl cTnl cTnl cTnl hs-cTnT
ents T2MI 264 49 1403 1313 42 194 429 1121 75 295 121	Retrospective Retrospective Prospective Prospective Prospective Retrospective Prospective Retrospective Retrospective	of MI 2012 2018 2007 2007 2007 2012 2012 2012 2018 2012 2012	location USA USA Sweden Sweden Multinational Spain UK UK Spain	Screening Screen	Assay cTnl N/A hs-cTnT hs-cTnT N/A cTnl cTnl cTnl cTnl hs-cTnT
ents T2MI 264 49 1403 1313 42 194 429 1121 75 295 121	Retrospective Retrospective Prospective Prospective Prospective Retrospective Prospective Retrospective Retrospective	of MI 2012 2018 2007 2007 2007 2012 2012 2012 2018 2012 2012	location USA USA Sweden Sweden Multinational Spain UK UK Spain	Screening Screen	Assay cTnl N/A hs-cTnT hs-cTnT N/A cTnl cTnl cTnl cTnl hs-cTnT
ents T2MI 264 49 1403 1313 42 194 429 1121 75 295 121	Retrospective Retrospective Prospective Prospective Prospective Retrospective Prospective Retrospective Retrospective	of MI 2012 2018 2007 2007 2007 2012 2012 2012 2018 2012 2012	location USA USA Sweden Sweden Multinational Spain UK UK Spain	Screening Screen	Assay cTnl N/A hs-cTnT hs-cTnT N/A cTnl cTnl cTnl cTnl hs-cTnT
ents T2MI 264 49 1403 1313 42 194 429 1121 75 295 121	Retrospective Retrospective Prospective Prospective Prospective Retrospective Prospective Retrospective Retrospective	of MI 2012 2018 2007 2007 2007 2012 2012 2012 2018 2012 2012	location USA USA Sweden Sweden Multinational Spain UK UK Spain	Screening Screening NSTEMI patient AMI patient AMI patient AMI patient AMI patient AMI patient ED patients with at lease 1 troponin ED with elevated t Suspected A ED patients with at lease 1 troponin	Assay cTnl N/A hs-cTnT hs-cTnT N/A cTnl cTnl cTnl cTnl hs-cTnT
264 49 1403 1313 42 194 429 1121 75 295 121	Retrospective Retrospective Prospective Prospective Prospective Retrospective Prospective Retrospective Retrospective	2012 2018 2007 2007 2007 2012 2012 2012 2018 2012 2012	USA USA Sweden Sweden Multinational Spain UK UK Spain	NSTEMI patients AMI patients AMI patients AMI patients AMI patients AMI patients TRITON TIMI 38 Trial ED patients with at lease 1 troponin Suspected Aes ED patients with at lease 1 troponin Suspected Aes ED patients with at lease 1 troponin	cTnl N/A hs-cTnT hs-cTnT N/A cTnl cTnl cTnl cTnl hs-cTnT
264 49 1403 1313 42 194 429 1121 75 295 121	RetrospectiveProspectiveProspectiveProspectiveRetrospectiveProspectiveProspectiveRetrospectiveRetrospectiveRetrospectiveRetrospective	2018 2007 2007 2012 2012 2012 2018 2012 2012 2012	USA Sweden Sweden Multinational Spain UK UK Spain	AMI patients AMI patients AMI patients AMI patients TRITON TIMI 38 Trial ED patients with at lease 1 troponin ED with elevated troponin Suspected Aes ED patients with at lease 1 troponin	N/A hs-cTnT hs-cTnT N/A cTnI cTnI cTnI cTnI hs-cTnT
49 1403 1313 42 194 429 1121 75 295 121	RetrospectiveProspectiveProspectiveProspectiveRetrospectiveProspectiveProspectiveRetrospectiveRetrospectiveRetrospectiveRetrospective	2018 2007 2007 2012 2012 2012 2018 2012 2012 2012	USA Sweden Sweden Multinational Spain UK UK Spain	AMI patients AMI patients AMI patients AMI patients TRITON TIMI 38 Trial ED patients with at lease 1 troponin ED with elevated troponin Suspected Aes ED patients with at lease 1 troponin	N/A hs-cTnT hs-cTnT N/A cTnI cTnI cTnI cTnI hs-cTnT
1403 1313 42 194 429 1121 75 295 121	Prospective Prospective Prospective Prospective Prospective Prospective Retrospective Retrospective	2007 2007 2012 2012 2012 2018 2012 2012 2012	Sweden Sweden Multinational Spain UK UK Spain	AMI patients AMI patients TRITON TIMI 38 TRITON TIMI 38 Trial ED patients with at lease 1 troponin ED with elevated troponin Suspected Aes ED patients with at lease 1 troponin	hs-cTnT hs-cTnT N/A cTnI cTnI cTnI cTnI hs-cTnT
1313 42 194 429 1121 75 295 121	Prospective Prospective Retrospective Prospective Prospective Retrospective Retrospective	2007 2007 2012 2012 2018 2018 2012 2012	Sweden Multinational Spain UK UK Spain	AMI patients TRITON TIMI 38 Trial ED patients with at lease 1 troponin ED with elevated tepponin Suspected Aes ED patients with at lease 1 troponin	hs-cTnT N/A cTnl cTnl cTnl cTnl hs-cTnT
42 194 429 1121 75 295 121	Prospective Retrospective Prospective Prospective Retrospective Retrospective	2007 2012 2012 2018 2018 2012 2012	Multinational Spain UK UK Spain	TRITON TIMI 38 ED patients with at lease 1 troponin ED with elevated troponin Suspected Aes ED patients with at lease 1 troponin	N/A cTnl cTnl cTnl cTnl hs-cTnT
429 1121 75 295 121	Retrospective Prospective Prospective Retrospective Retrospective	2012 2018 2012 2012	UK UK Spain	ED patients with at lease 1 troponin ED with elevated tepponin Suspected Aes ED patients with at lease 1 troponin	cTnl cTnl cTnl cTnl hs-cTnT
1121 75 295 121	Prospective Prospective Retrospective Retrospective	2018 2012 2012	UK UK Spain	Suspected A S ED patients with at lease 1 troponin	cTnl cTnl hs-cTnT
75 295 121	Retrospective Retrospective	2012 2012	Spain	ED patients with at lease 1 troponin	cTnI hs-cTnT
295 121	Retrospective	2012		ੂ ਹੋ .	hs-cTnT
121	•		USA	Patients with elevated troponin	
	Prospective				
206		2018	Australia	Patients with elevated troponin	N/A
	Retrospective	2012	Israel	NSTEMI on general ward	Unknowr
76	Retrospective	2012	Multinational	ACS during TRACE trial	N/A
281	Retrospective	2012	USA	NSTEMI patients	cTnl
491	Retrospective	2012	Tokyo	Admitted to CU	N/A
64	Retrospective	2007	USA	Patients with elevated troponin	cTnl
251	Retrospective	2018	Sweden	MI, Registry	N/A
119	Prospective	2007	Denmark	Hospitalised patients with troponin measuredဖြို	cTnl
107	Retrospective	2012	Israel	Diagnosed with T2Mb nd T1MI	cTnT
117	Retrospective	2012	Spain	Diagnosed with T2MB nd T1MI	hs-cTnT
452	Retrospective	2012	Germany	ED patients with elevated troponin	cTnl
128	Prospective	2012	Multinational	ED patients with MI	N/A
	64 251 119 107 117 452	64Retrospective251Retrospective119Prospective107Retrospective117Retrospective452Retrospective	64Retrospective2007251Retrospective2018119Prospective2007107Retrospective2012117Retrospective2012452Retrospective2012	64Retrospective2007USA251Retrospective2018Sweden119Prospective2007Denmark107Retrospective2012Israel117Retrospective2012Spain452Retrospective2012Germany	64Retrospective2007USAPatients with elevated troponin251Retrospective2018SwedenMI, Registry119Prospective2007DenmarkHospitalised patients with troponin measured107Retrospective2012IsraelDiagnosed with T2MG and T1MI117Retrospective2012SpainDiagnosed with T2MG and T1MI452Retrospective2012GermanyED patients with elevated troponin

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Neumann, 2017 (23)	188	99	Prospective	2012	Germany	ED patients with suspected MI	hs-cTnl
Paiva, 2015 (24)	764	236	Retrospective	2012	Portugal	Admitted to CCU with MI	cTnl
Pandey, 2020 (25)	97	103	Prospective	2018	USA	MI 🗎	N/A
Putot, 2018 (26)	2036	847	Prospective	2012	France	ED or cardiology ward with elevated troponin 걸	cTnl
Putot, 2019 (27)	365	254	Retrospective	2018	France	Hospitalised patients with CAD	cTnl
Putot, 2020 (28)	3710	862	Retrospective	2012	France	Hospitalised patient&with MI	cTnl
Radovanovic, 2017 (29)	13828	1091	Retrospective	2012	Switzerland	Diagnosed Al	N/A
Raphael, 2020 (30)	1365	1054	Retrospective	2018	USA	Raised troponsin	cTnT
Reed, 2017 (31)	88	162	Retrospective	2012	USA	Underwent vasculaesurgery procedure	cTnT
Saaby 2013 (32)	397	144	Prospective	2007	Denmark	Troponin meas dred	cTnl
Saaby, 2014 (33)	360	119	Prospective	2007	Denmark	Elevated troponin	cTnl
Sandoval, 2014 (34)	66	190	Retrospective	2012	USA	ED patients with tropon measured	cTnl
Sandoval, 2017 (35)	77	140	Prospective	2012	USA	ED patients with troporm measured	cTnl
Sato, 2020 (36)	2834	155	Prospective	2012	Japan	Hospitalised patien Ewith MI	N/A
Shah, 2015 (37)	1171	429	Prospective	2012	UK	Admitted with elevated troponin	cTnl
Singh, 2020 (38)	2097	1225	Retrospective	2018	USA	Age <50, MI or raise	N/A
Smilowitz, 2018 (39)	137	146	Prospective	2012	USA	Admitted with raised troponin	cTnl
Stein, 2014 (40)	2691	127	Prospective	2007	Israel	Admitted to cardiology	N/A
Truong, 2020 (41)	275	175	Retrospective	2012	Russia	MI, undergoing angiogram	N/A
						ocardial infarction; MI = र्फ्सुocardial infarc ary care unit; CAD = corom्र्र् artery disea	
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Author, Year	Pati	ents	Variables S						
	T1MI	T2MI	Pre-existing conditions	Symptoms	Investigation s	Troponin Values	ាវManagement	Prognosis	
Arora, 2018 (1)	775	264	X		X	X	Februa	X	
Balanescu, 2020 (2)	152	49		Х	Х		μζ X		
Baron, 2015 (3)	17488	1403	X	Х	Х	Х	202 X	Х	
Baron, 2016 (4)	40501	1313	X	Х	Х	Х	N X		
Bonaca, 2012 (5)	359	42							
Cediel, 2017 (6)	376	194	Х	Х	Х	Х	nlc	Х	
Chapman, 2018 (7)	1171	429	Х		Х	Х	ded X	Х	
Chapman, 2020 (8)	4981	1121	X	Х	Х	Х	d f	X	
Consuegra-Sanchaz, 2018 (9)	125	75	X	Х	Х	Х	from		
El-Haddad, 2012 (10)	512	295					htt	X	
Etaher, 2020 (11)	97	121	X	6	Х		X		
Furie, 2019 (12)	349	206	Х	X	Х	Х	<u>3</u> . X	X	
Guimaraes, 2018 (13)	847	76	X	CI.	• X		₩ K	X	
Hawatmeh, 2020 (14)	664	281	Х		Х	Х	b X		
Higuchi, 2019 (15)	12023	491	Х		X		<u>, X</u>	X	
Javed, 2009 (16)	143	64	Х		X	Х		Х	
Kadesjo, 2019 (17)	1111	251	Х				⊇ X	Х	
Lambrecht, 2018 (18)	360	119	Х		Х	Х	ے ب	Х	
Landes, 2016 (19)	107	107	Х	Х	Х	X	ne		
Lopez-Cuenca, 2016 (20)	707	117	Х	Х	Х	Х	Р <u>1,</u> Х	Х	
Meigher, 2016 (21)	340	452	Х	Х	Х	Х	202	X	
Nestelberger, 2017 (22)	684	128	Х		Х		24 X	X	
Neumann, 2017 (23)	188	99	Х		Х	Х	D K	X	
Paiva, 2015 (24)	764	236	X		Х	Х	lues	Х	
Pandey, 2020 (25)	97	103	Х				- ;: - D		
Putot, 2018 (26)	2036	847	Х		Х	Х		X	
Putot, 2019 (27)	365	254	Х		Х	Х	rotected	X	
Putot, 2020 (28)	3710	862	Х		Х	Х	р Б	X	
Radovanovic, 2017 (29)	13828	1091	Х		Х		by copyright.	X	

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Raphael, 2020 (30)	1365	1054	Х		Х	X	1-055758	Х	>
Reed, 2017 (31)	88	162			Х	Х	0	Х	
Saaby 2013 (32)	397	144	Х		Х	Х	n 17		
Saaby, 2014 (33)	360	119	Х		Х	Х	February	Х	X
Sandoval, 2014 (34)	66	190	Х	X	Х	Х	bru		X
Sandoval, 2017 (35)	77	140	Х	Х	Х	Х	ary	Х	X
Sato, 2020 (36)	2834	155	Х		Х		202	Х	×
Shah, 2015 (37)	1171	429	Х	Х	Х	Х	22.	Х	X
Singh, 2020 (38)	2097	1225	Х		Х		Dov	Х	×
Smilowitz, 2018 (39)	137	146	Х	Х	Х	Х	Vnlo	Х	X
Stein, 2014 (40)	2691	127	Х	Х	Х		wnløaded	Х	×
Truong, 2020 (41)	275	175	Х	Х	Х		-	Х	X
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Table S4. Risk of bia	s assessment				omjopen-2021-055755	
			Outcome		on	
Author, Year	Representative of Exposed Cohort	Selection of Non-exposed	Assessment	Follow-up Length	Adequacy of follow- Up 딸	Summary
Arora, 2018 (1)	х	х	х	х	x ₹	8 (good quality)
Balanescu, 2020 (2)	0	х	х	0	x 20222.	6 (fair quality)
Baron, 2015 (3)	x	х	х	Х	x <u>N</u>	8 (good quality)
Baron, 2016 (4)	х	х	Х	Х	x §	8 (good quality)
Bonaca, 2012 (5)	x	X	х	Х	x nlo	8 (good quality)
Cediel, 2017 (6)	х	x	х	х	x	8 (good quality)
Chapman, 2018 (7)	х	x	х	х	x đ	8 (good quality)
Chapman, 2020 (8)	х	x	x	х	x d from	8 (good quality)
Consuegra-Sanchaz, 2018 (9)	0	0	x	0	0	3 (poor quality)
El-Haddad, 2012 (10)	х	х	0	0	0 🧕	5 (fair quality)
Etaher, 2020 (11)	х	х	x	x	x	8 (good quality)
Furie, 2019 (12)	х	х	x	x	x ⁿ .b	8 (good quality)
Guimaraes, 2018 (13)	0	0	x	0	x con	4 (fair quality)
Hawatmeh, 2020 (14)	0	0	x	x	0 J	4 (fair quality)
Higuchi, 2019 (15)	0	0	х	х	xne	5 (fair quality)
Javed, 2009 (16)	х	х	х	Х	x 21	8 (good quality)
Kadesjo, 2019 (17)	х	х	х	х	× 2024	8 (good quality)
Lambrecht, 2018 (18)	x	х	х	х	x Þ	8 (good quality)
Landes, 2016 (19)	х	х	х	Х	guest.	8 (good quality)
Lopez-Cuenca, 2016 (20)	x	x	х	х	st. Profected	8 (good quality)
Meigher, 2016 (21)	х	х	х	х	x ct	8 (good quality)
Nestelberger, 2017 (22)	x	х	х	Х	ed by copyright.	8 (good quality)

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						omjopen-2021-055755 on 17 × × 0	
	Noursen 2017 (22)					055	
	Neumann, 2017 (23)	X	x	X	x	X 57	8 (good quality)
	Paiva, 2015 (24)	x 0	x 0	x 0	x 0	xg	8 (good quality)
	Pandey, 2020 (25)						2 (poor quality)
	Putot, 2018 (26)	X	x	X	x	x Febru	8 (good quality)
	Putot, 2019 (27)	X	X	0	x		7 (good quality)
	Putot, 2020 (28)	x	x	Х	x	x x	8 (good quality)
	Radovanovic, 2017 (29)	x	x	х	х	2022. ×	8 (good quality)
	Raphael, 2020 (30)	x	x	Х	x	x Q	8 (good quality)
	Reed, 2017 (31)	x	X	х	x	x nl	8 (good quality)
	Saaby 2013 (32)	х	x	х	x	bad x	8 (good quality)
	Saaby, 2014 (33)	х	X	х	x	хÖ	8 (good quality)
	Sandoval, 2014 (34)	х	x	х	x	x	8 (good quality)
	Sandoval, 2017 (35)	х	x	x	х	X t	8 (good quality)
	Sato, 2020 (36)	0	0	0	х	x p	2 (poor quality)
	Shah, 2015 (37)	х	х	х	х	x b	8 (good quality)
	Singh, 2020 (38)	0	0	x	x	x g	6 (fair quality)
	Smilowitz, 2018 (39)	х	x	х	x	x <u>P</u>	7 (good quality)
	Stein, 2014 (40)	х	x	х	x	x <u>j</u>	7 (good quality)
	Truong, 2020 (41)	х	х	х	x	x 8	8 (good quality)
						com/ on June 21, 2024 by guest. Protected by copyright.	
		For	peer review only - h	ttp://bmjopen.bmj.o	com/site/about/guide	lines.xhtml	

Precipitating Factor	Events	Patients	%
Sepsis	1116	3110	35.9%
Arrhythmia	2047	6868	29.8%
Heart failure	958	3346	28.6%
Valvular abnormality	351	1301	27.0%
Anaemia	1692	6281	26.9%
Respiratory failure	762	4424	17.2%
Non-cardiac surgery	103	841	12.2%
Infection	361	3412	10.6%
Shock/hypotension	291	3006	9.7%
Hypertension	321	3620	8.9%
Pulmonary oedema	33	380	8.7%
Chronic obstructive pulmonary disease	137	1661	8.2%
Bradycardia	35	484	7.2%
Renal failure	133	1956	6.8%
Stroke	68	1731	3.9%
Coronary spasm	36	1048	3.4%
Bleeding	53	1834	2.9%
Coronary endothelial dysfunction	1	592	0.2%

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		T2MI			T1MI		
Presenting Symptom	No. patients with presenting symptom	Total number of patients	%	No. patients with presenting symptom	Total number of patients	%	Odds ratio [95% Cl]
Chest pain	4344	7335	59.2%	73103	83371	87.7%	0.19 [0.15, 0.2
Dyspnoea	1681	6080	27.6%	8154	82617	9.9%	2.83 [1.96, 4.08
Arm or shoulder discomfort	28	330	8.5%	50	143	35.0%	0.18 [0.11, 0.3
Jaw or neck discomfort	6	140	4.3%	12	77	15.6%	0.24 [0.09, 0.68
Epigastric discomfort	8	140	5.7%	8	77	10.4%	0.52 [0.19, 1.4
Nausea or vomiting	46	330	13.9%	39	143	27.3%	0.46 [0.28, 0.74
Fatigue	5	140	3.6%	5	77	6.5%	0.53 [0.15, 1.90
Diaphoresis	16	140	11.4%	16	77	20.8%	0.49 [0.23, 1.05
Other nonspecific symptoms	1252	2932	42.7%	4096	58884	7.0%	4.19 [0.72, 24.3
Collapse / syncope	99	2125	4.7%	157	7152	2.2%	2.10 [1.05, 4.1

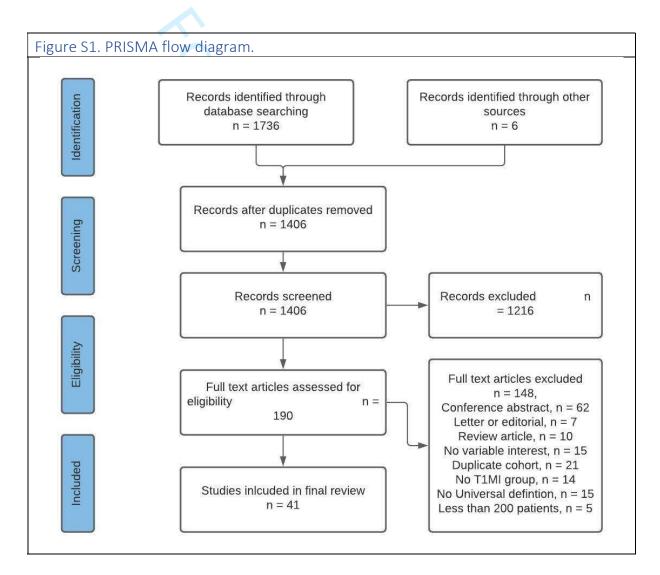
*Comparing T2MI with T1MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: URL- upper reference limit; STEMI- ST elevation myocardial infarction; NSTEMI- Non- ST elevation myocardial infarction; MI- Myocardial infarction; cTn- cardiac troponin; T1MI- Type 1 myocardial infarction; T2MI- Type 2 myocardial infarction; ECG- electrocardiogram; CAD- coronary artery disease; PCI- percutaneous coronary intervention; CABG- coronary artery bypass graft; IHD- ischaemic heart disease; MACE- Major adverse cardiovascular events; CI-confidence interval

		T2MI			T1MI		Odds ratio* (95% CI)
Variable	No. patients with nominated diagnostic findings	Total no. patients	%	No. patients with nominated diagnostic findings	Total no of patients	%	
ECG							
ST elevation	1265	9417	13.4%	42726	101584	42.1%	0.22 [0.18, 0.28
ST depression or T wave Inversion	2174	6314	34.4%	14938	68530	21.8%	1.38 [0.94, 2.02
Pathological Q Waves	30	447	6.7%	177	850	20.8%	0.38 [0.20, 0.71
Non-specific ST-T wave changes	146	592	24.7%	45	417	10.8%	2.62 [1.81, 3.79
Left bundle branch block	338	3330	10.2%	3045	60031	5.1%	1.72 [1.40, 2.12
Atrial fibrillation/flutter	448	1660 🧹	27.0%	1871	18272	10.2%	3.70 [2.87, 4.77
Echocardiograph							
Echocardiogram performed	648	1353	47.9%	1571	2830	55.5%	0.44 [0.20, 0.96
Presence of RWMA	97	286	33.9%	101	214	47.2%	0.48 [0.06, 3.78
Angiogram							
Angiogram performed	3686	10721	34.4%	56242	67432	83.4%	0.09 [0.06, 0.12
Obstructive coronary artery disease present	1246	3663	34.0%	19923	44404	44.9%	0.16 [0.05, 0.54
Multivessel disease present	593	2147	27.6%	11839	41715	28.4%	0.40 [0.19, 0.82
*Comparing T2MI with meta-analysis ECG=electrocardiograpl myocardial infarction; T	n; RWMA=regio	onal wall m	otion abn	-			-

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Table S8. Troponin mea	surements.		
Troponin Measurement	Number of Studies	T1MI (min-max)	T2MI (min-max)
Baseline cTn (xULN)	12	0.14-190	0.1-8.2
6h cTn (xULN)	4	13.2-142	4.25-11
Peak cTn (xULN)	21	5.1-1703	2.8-447
Abbreviations: xULN= times	s upper limit normal		I



Arora 2018 56 264 209 775 3.6% 0.73 [0.52, 1.02] Baron 2015 563 1403 5316 17488 4.2% 1.53 [1.37, 1.72] Bonaca 2012 380 1313 9998 40501 4.1% 1.24 [1.10, 1.40] Cediel 2017 41 194 120 376 3.3% 0.57 [0.38, 0.86] Chapman 2020 454 1121 1519 4981 4.1% 1.55 [1.36, 1.77] Conseugra Sanchez 2018 30 75 69 125 2.7% 0.54 [0.30, 0.97] Etaher 2020 95 171 63 97 2.9% 0.67 [0.40, 1.13] Guimares 2018 37 76 416 847 3.1% 0.98 [0.61, 1.57] Hawatmeh 2020 127 281 387 664 3.7% 0.59 [0.45, 0.78] Higuchi 2019 45 491 1120 12023 3.8% 1.49 [1.41, 1.94] Kadesjo 2019 48 251 48 1111 3.2% 5.24 [3.42, 8.03] Landes 2016 68 107 50	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
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Heterogeneity: Tau ² = 0.15; Chi ² = 291.95, df = 30 (P < 0.00001); l ² = 90%	0.15: Cbi2 = 291.95. df = 30 (P < 0.00001): 12 = 90%
Test for suprol offset: 7 = 1.47 (D = 0.14)	
	Z = 1.47 (P = 0.14) T1MI T2N

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Test for overall effect: 7 = 0.39 (P = 0.70) 0.01 0.1 1 10	Test for overall effect: 7 = 0.39 (P = 0.70) 0.01 0.1 1								
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		Test for overall effect: $Z = 0$.	.39 (P = 0.	70)					

	T2M	II	T1N			Odds Ratio	Odd	s R
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% CI	M-H, Rand	lon
Arora 2018 Baron 2015	225 760	264 1403	642 8866	775	3.1%	1.20 [0.81, 1.76]	1	Ľ
Baron 2015 Baron 2016	962	1403	26334	17488 40501	3.7% 3.7%	1.15 [1.03, 1.28] 1.47 [1.30, 1.67]		ſ.
Cediel 2017	153	194	20004	376	3.0%	1.47 [0.97, 2.21]		┝
Chapman 2018	254	429	533	1171	3.5%	1.74 [1.39, 2.17]		-
Conseugra Sanchez 2018	54	75	91	125	2.3%	0.96 [0.51, 1.82]	-	╋
Etaher 2020	128	171	56	97	2.6%	2.18 [1.28, 3.71]		1-
Furie 2019	159	206	265	349	3.0%	1.07 [0.71, 1.61]	-	t
Guimares 2018	60	76	688	847	2.5%	0.87 [0.49, 1.54]	_	Γ
Hawatmeh 2020 Higuchi 2019	242 311	281 491	583 7064	664 12023	3.0%	0.86 [0.57, 1.30] 1.21 [1.01, 1.46]		l
Javed 2009	53	64	126	143	1.8%	0.65 [0.29, 1.48]		Ļ
Lambrecht 2018	66	119	193	360	3.0%	1.08 [0.71, 1.63]	-	┢
Landes 2016	87	107	82	107	2.2%	1.33 [0.68, 2.57]	-	┢╸
Lopez Cuenca 2016	103	117	522	707	2.5%	2.61 [1.46, 4.67]		ŀ
Meigher 2016	289	452	224	340	3.3%	0.92 [0.68, 1.23]	-	t
Nestelberger 2020	92	128	521	684	3.0%	0.80 [0.52, 1.22]	_	Ĺ
Neumann 2017 Paiva 2015	77 192	99 236	154 580	188 764	2.4% 3.1%	0.77 [0.42, 1.41] 1.38 [0.96, 2.00]		L
Pandey 2020	68	103	68	97	2.4%	0.83 [0.46, 1.50]	_	┡
Putot 2018	683	847	1140	2036	3.6%	3.27 [2.70, 3.96]		L
Putot 2019	211	254	279	365	3.0%	1.51 [1.01, 2.27]		ŀ
Radovanovic 2017	802	1091	8504	13828	3.7%	1.74 [1.51, 2.00]		Ŀ
Raphael 2020	716	1054	966	1365	3.6%	0.87 [0.74, 1.04]		1
Saaby 2013	81	144	215	397	3.1%	1.09 [0.74, 1.60]		
Saaby 2014 Sandoval 2014	66 125	119 190	193 49	360	3.0%	1.08 [0.71, 1.63] 0.67 [0.36, 1.25]	_	t.
Sandoval 2017	104	140	62	77	2.2%	0.70 [0.35, 1.38]		Ŧ
Sato 2020	103	155	1885	2834	3.2%	1.00 [0.71, 1.40]	-	┢
Shah 2015	254	429	533	1171	3.5%	1.74 [1.39, 2.17]		ŀ
Singh 2020	419	1225	970	2097	3.7%	0.60 [0.52, 0.70]	*	L
Smilowitz 2018	128	146	118	137		1.15 [0.57, 2.29]	-	t
Stein 2014	108	127	1631	2691	2.7%	3.69 [2.25, 6.05]		L
	161	175	241	275	2.3%	1.62 [0.84, 3.12]		Г
Troung 2020		12424	64648	105505	100.0%	1.22 [1.05, 1.43]		Þ
Total (95% CI)	0000	37 df -		0.00001)	: l ² = 90%			L
	8296 5; Chi ² = 318						0.01 0.1	1
Total (95% CI) Total events	6; Chi ² = 318						0.01 0.1 T1M	1

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Arora 2018 131 264 441 775 3.4% 0.75 [0.56, 0.99] - Baron 2016 548 1313 14893 40501 3.5% 1.23 [1.10, 1.38] Chapman 2018 177 429 539 1171 3.4% 0.82 [0.66, 1.03] Conseugra Sanchez 2018 38 75 66 125 2.9% 0.92 [0.52, 1.63] - Furie 2019 121 206 218 349 3.3% 0.86 [0.60, 1.22] - Guimares 2018 58 76 625 847 3.0% 0.85 [0.62, 1.17] - Hawatmeh 2020 205 281 505 664 3.3% 0.85 [0.62, 1.17] - Hawatmeh 2020 205 201 504 12023 3.5% 0.76 [0.63, 0.92] - Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] - Landes 2016 82 107 69 107 2.9% 1.81 [0.99, 3.28] - Nestelberger 2016 194 452 180 340 3.4% <th></th> <th>T2M</th> <th>1</th> <th>T1N</th> <th>11</th> <th></th> <th>Odds Ratio</th> <th></th> <th>Odds Ratio</th>		T2M	1	T1N	11		Odds Ratio		Odds Ratio
Baron 2016 548 1313 14893 40501 3.5% 1.23 [1.10, 1.38] Chapman 2018 177 429 539 1171 3.4% 0.82 [0.66, 1.03] Conseugra Sanchez 2018 38 75 66 125 2.9% 0.82 [0.62, 1.63] Furie 2019 121 206 218 349 3.3% 0.86 [0.62, 1.17] Guimares 2018 58 76 625 847 3.0% 1.14 [0.66, 1.98] Hawatmeh 2020 205 281 505 6644 3.3% 0.86 [0.62, 1.17] 141 Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Lambrecht 2018 48 119 137 360 3.2% 1.10 [0.72, 1.68] Landes 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Meigher 2016 194 452 180 3.4% <	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95%
Chapman 2018 177 429 539 1171 3.4% 0.82 [0.66, 1.03] Conseugra Sanchez 2018 36 75 66 125 2.9% 0.92 [0.52, 1.63] - Etaher 2020 89 171 48 97 3.1% 1.11 [0.60, 1.22] - Guimares 2018 58 76 625 847 3.0% 1.14 [0.66, 1.98] Hawatmeh 2020 205 281 505 664 3.3% 0.85 [0.62, 1.17] Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Lambrecht 2018 48 119 137 360 3.2% 1.10 [0.72, 1.68] Landes 2016 82 107 69 107 2.9% 1.81 [0.99, 3.28] Lopez Cuenca 2016 89 117 530 707 3.1% 0.67 [0.50, 0.89] - Neigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89] - Neumann 2017 40	Arora 2018	131	264	441	775	3.4%	0.75 [0.56, 0.99]		-
Conseugra Sanchez 2018 38 75 66 125 2.9% 0.92 [0.52, 1.63] Etaher 2020 89 171 48 97 3.1% 1.11 [0.67, 1.82] Furie 2019 121 206 218 349 3.3% 0.86 [0.60, 1.22] Guimares 2018 58 76 6625 847 3.0% 1.14 [0.66, 1.98] Hawatmeh 2020 205 281 505 664 3.3% 0.85 [0.62, 1.17] Higuchi 2019 174 491 5044 12023 3.5% 0.76 [0.63, 0.92] Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Landbes 2016 82 107 69 107 2.9% 1.81 [0.99, 3.28] Landes 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Meigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89] Paiva 2015 125 236 442 764 3.4%	Baron 2016	548	1313	14893	40501	3.5%	1.23 [1.10, 1.38]		-
Etaher 2020 89 171 48 97 3.1% 1.11 [0.67, 1.82] Furie 2019 121 206 218 349 3.3% 0.86 [0.60, 1.22] Guimares 2018 58 76 625 847 3.0% 1.14 [0.66, 1.98] Hawatmeh 2020 205 281 505 664 3.3% 0.85 [0.62, 1.17] Higuchi 2019 174 491 5044 12023 3.5% 0.76 [0.63, 0.92] Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Landes 2016 82 107 69 107 2.9% 1.81 [0.99, 3.28] Lopez Cuenca 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Weigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89] Neumann 2017 40 99 108 188 3.1% 0.50 [0.31, 0.82] Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] - Paiva 2015 125 236	Chapman 2018	177	429	539	1171	3.4%	0.82 [0.66, 1.03]		-
Furie 2019 121 206 218 349 3.3% 0.86 [0.60, 1.22] Guimares 2018 58 76 625 847 3.0% 1.14 [0.66, 1.98] Hawatmeh 2020 205 281 505 664 3.3% 0.85 [0.62, 1.17] Higuchi 2019 174 491 5044 12023 3.5% 0.76 [0.63, 0.92] Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Javed 2016 82 107 69 107 2.9% 1.81 [0.99, 3.28] Landes 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Weigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89] - Vestelberger 2020 46 128 440 684 3.2% 0.31 [0.1, 1.08] - Paiva 2015 125 236 442 764 3.4%	Conseugra Sanchez 2018	38	75	66	125	2.9%	0.92 [0.52, 1.63]		-
Suimares 2018 58 76 625 847 3.0% 1.14 [0.66, 1.98] Hawatmeh 2020 205 281 505 664 3.3% 0.85 [0.62, 1.17] Higuchi 2019 174 491 5044 12023 3.5% 0.76 [0.63, 0.92] Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Lambrecht 2018 48 119 137 360 3.2% 1.10 [0.72, 1.68] Landes 2016 82 107 69 107 2.9% 1.81 [0.99, 3.28] Lopez Cuenca 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Meigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89] Vestelberger 2020 46 128 440 684 3.2% 0.31 [0.21, 0.46] Paiva 2015 125 236 442 764 3.4% 0.62 [0.61, 1.10] Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.14] Paiva 2018 419 847 919	Etaher 2020	89	171	48	97	3.1%	1.11 [0.67, 1.82]		+
Hawatmeh 2020 205 281 505 664 3.3% 0.85 [0.62, 1.17] Higuchi 2019 174 491 5044 12023 3.5% 0.76 [0.63, 0.92] Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Lambrecht 2018 48 119 137 360 3.2% 1.10 [0.99, 3.28] Lopez Cuenca 2016 89 117 530 707 3.1% 1.06 [0.67, 1.66] Meigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89] ¬ Nestelberger 2020 46 128 440 684 3.2% 0.31 [0.21, 0.46] ¬ Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] ¬ Paiva 2015 125 236 442 764 3.4% 0.81 [0.58, 1.15] ¬ Paidey 2020 38 103 51 97 3.0% 0.53 [0.30, 0.93] ¬ Putot 2018	Furie 2019	121	206	218	349	3.3%	0.86 [0.60, 1.22]		-+
Higuchi 2019 174 491 5044 12023 3.5% 0.76 [0.63, 0.92] Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Lambrecht 2018 48 119 137 360 3.2% 1.10 [0.72, 1.68] Landes 2016 82 107 69 107 2.9% 1.81 [0.99, 3.28] Lopez Cuenca 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Meigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89] - Nestelberger 2020 46 128 440 684 3.2% 0.31 [0.21, 0.46] - Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] - Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] - Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] - Paivot 2018	Guimares 2018	58	76	625	847	3.0%	1.14 [0.66, 1.98]		+
Javed 2009 34 64 113 143 2.8% 0.30 [0.16, 0.57] Lambrecht 2018 48 119 137 360 3.2% 1.10 [0.72, 1.68] Landes 2016 82 107 69 107 2.9% 1.81 [0.99, 3.28] Lopez Cuenca 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Weigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89] Neumann 2017 40 99 108 188 3.1% 0.50 [0.31, 0.82] Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] Pandey 2020 38 103 51 97 3.0% 0.53 [0.30, 0.93] Putot 2018 419 847 919 2036 3.5% 1.19 [1.01, 1.40] Putot 2019 169 254 259 365 3.3% 0.81 [0.58, 1.15] Radovanovic 2017 631 1091 8076 13828 3.5%	Hawatmeh 2020	205	281	505	664	3.3%	0.85 [0.62, 1.17]		-+
Lambrecht 2018 48 119 137 360 3.2% 1.10 [0.72, 1.68] Landes 2016 82 107 69 107 2.9% 1.81 [0.99, 3.28] Lopez Cuenca 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Meigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89] - Nestelberger 2020 46 128 440 684 3.2% 0.31 [0.21, 0.46] - Paiva 2015 125 236 442 764 3.4% 0.62 [0.61, 1.10] - Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] - Pandey 2020 38 103 51 97 3.0% 0.53 [0.30, 0.93] - Putot 2018 419 847 919 2036 3.5% 1.19 [1.01, 1.40] Putot 2019 169 254 259 365 3.3% 0.81 [0.58, 1.15] - Radovanovic 2017 631 1091 8076 13828 3.5% 0.98 [0.86, 1.11]	Higuchi 2019	174	491	5044	12023	3.5%	0.76 [0.63, 0.92]		-
Landes 2016 82 107 69 107 2.9% 1.81 [0.99, 3.28] Lopez Cuenca 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Meigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89] - Nestelberger 2020 46 128 440 684 3.2% 0.31 [0.21, 0.46] - Neumann 2017 40 99 108 188 3.1% 0.50 [0.31, 0.82] - Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] - Pandey 2020 38 103 51 97 3.0% 0.53 [0.30, 0.93] - Putot 2018 419 847 919 2036 3.5% 1.19 [1.01, 1.40] Putot 2019 169 254 259 365 3.3% 0.81 [0.58, 1.15] - Radovanovic 2017 631 1091 8076 13828 3.5% 0.98 [0.86, 1.11] Saaby 2	Javed 2009	34	64	113	143	2.8%	0.30 [0.16, 0.57]		
Lopez Cuenca 2016 89 117 530 707 3.1% 1.06 [0.67, 1.68] Meigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89]	Lambrecht 2018	48	119	137	360	3.2%	1.10 [0.72, 1.68]		+
Meigher 2016 194 452 180 340 3.4% 0.67 [0.50, 0.89] Nestelberger 2020 46 128 440 684 3.2% 0.31 [0.21, 0.46] Neumann 2017 40 99 108 188 3.1% 0.50 [0.31, 0.82] Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] Pandey 2020 38 103 51 97 3.0% 0.53 [0.30, 0.93] - Putot 2018 419 847 919 2036 3.5% 1.19 [1.01, 1.40] Putot 2019 169 254 259 365 3.3% 0.81 [0.58, 1.15] - Radovanovic 2017 631 1091 8076 13828 3.5% 0.98 [0.86, 1.11] Raphael 2020 359 1054 790 1365 3.5% 0.38 [0.32, 0.44] - Saaby 2013 60 144 158 397	Landes 2016	82	107	69	107	2.9%	1.81 [0.99, 3.28]		-
Nestelberger 2020 46 128 440 684 3.2% 0.31 [0.21, 0.46] Neumann 2017 40 99 108 188 3.1% 0.50 [0.31, 0.82] Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] Pandey 2020 38 103 51 97 3.0% 0.53 [0.30, 0.93] - Putot 2018 419 847 919 2036 3.5% 1.19 [1.01, 1.40] - Putot 2019 169 254 259 365 3.3% 0.81 [0.58, 1.15] - Radovanovic 2017 631 1091 8076 13828 3.5% 0.98 [0.86, 1.11] Raphael 2020 359 1054 790 1365 3.5% 0.38 [0.32, 0.44] - Saaby 2013 60 144 158 397 3.2% 1.08 [0.73, 1.59] - Saaby 2014 48 119 137 360 3.2% 1.10 [0.72, 1.68] - Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] -	Lopez Cuenca 2016	89	117	530	707	3.1%	1.06 [0.67, 1.68]		+
Neumann 2017 40 99 108 188 3.1% 0.50 [0.31, 0.82] Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] Pandey 2020 38 103 51 97 3.0% 0.53 [0.30, 0.93] - Putot 2018 419 847 919 2036 3.5% 1.19 [1.01, 1.40] Putot 2019 169 254 259 365 3.3% 0.81 [0.58, 1.15] Radovanovic 2017 631 1091 8076 13828 3.5% 0.98 [0.86, 1.11] Raphael 2020 359 1054 790 1365 3.5% 0.38 [0.32, 0.44] - Saaby 2013 60 144 158 397 3.2% 1.08 [0.73, 1.59] - Saaby 2014 48 119 137 360 3.2% 1.10 [0.72, 1.68] - Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] - Sato 2020 95	Meigher 2016	194	452	180	340	3.4%	0.67 [0.50, 0.89]		-
Paiva 2015 125 236 442 764 3.4% 0.82 [0.61, 1.10] Pandey 2020 38 103 51 97 3.0% 0.53 [0.30, 0.93] - Putot 2018 419 847 919 2036 3.5% 1.19 [1.01, 1.40] Putot 2019 169 254 259 365 3.3% 0.81 [0.58, 1.15] Radovanovic 2017 631 1091 8076 13828 3.5% 0.98 [0.86, 1.11] Raphael 2020 359 1054 790 1365 3.5% 0.38 [0.32, 0.44] Saaby 2013 60 144 158 397 3.2% 1.08 [0.73, 1.59] Saaby 2014 48 119 137 360 3.2% 1.10 [0.72, 1.68] Sandoval 2014 63 190 36 66 2.9% 0.41 [0.23, 0.73] Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539	Nestelberger 2020	46	128	440	684	3.2%	0.31 [0.21, 0.46]		
Pandey 2020 38 103 51 97 3.0% 0.53 [0.30, 0.93] Putot 2018 419 847 919 2036 3.5% 1.19 [1.01, 1.40] Putot 2019 169 254 259 365 3.3% 0.81 [0.58, 1.15] Radovanovic 2017 631 1091 8076 13828 3.5% 0.98 [0.86, 1.11] Raphael 2020 359 1054 790 1365 3.5% 0.38 [0.32, 0.44] Saaby 2013 60 144 158 397 3.2% 1.08 [0.73, 1.59] Saaby 2014 48 119 137 360 3.2% 1.10 [0.72, 1.68] Sandoval 2014 63 190 36 66 2.9% 0.41 [0.23, 0.73] Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% <t< td=""><td>Neumann 2017</td><td>40</td><td>99</td><td>108</td><td>188</td><td>3.1%</td><td>0.50 [0.31, 0.82]</td><td></td><td></td></t<>	Neumann 2017	40	99	108	188	3.1%	0.50 [0.31, 0.82]		
Putot 2018 419 847 919 2036 3.5% 1.19 [1.01, 1.40] Putot 2019 169 254 259 365 3.3% 0.81 [0.58, 1.15] Radovanovic 2017 631 1091 8076 13828 3.5% 0.98 [0.86, 1.11] Raphael 2020 359 1054 790 1365 3.5% 0.38 [0.32, 0.44] Saaby 2013 60 144 158 397 3.2% 1.08 [0.73, 1.59] Saaby 2014 48 119 137 360 3.2% 1.10 [0.72, 1.68] Sandoval 2014 63 190 36 66 2.9% 0.41 [0.23, 0.73] Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56] = Singh 2020 172 1225 1229 2097	Paiva 2015	125	236	442	764	3.4%	0.82 [0.61, 1.10]		-
Putot 2019 169 254 259 365 3.3% 0.81 [0.58, 1.15] Radovanovic 2017 631 1091 8076 13828 3.5% 0.98 [0.86, 1.11] Raphael 2020 359 1054 790 1365 3.5% 0.38 [0.32, 0.44] Saaby 2013 60 144 158 397 3.2% 1.08 [0.73, 1.59] Saaby 2014 48 119 137 360 3.2% 1.10 [0.72, 1.68] Sandoval 2014 63 190 36 66 2.9% 0.41 [0.23, 0.73] Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56] = Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] = Smilowitz 2018 102 146 98	Pandey 2020	38	103	51	97	3.0%	0.53 [0.30, 0.93]		
Radovanovic 2017 631 1091 8076 13828 3.5% 0.98 [0.86, 1.11] Raphael 2020 359 1054 790 1365 3.5% 0.38 [0.32, 0.44] Saaby 2013 60 144 158 397 3.2% 1.08 [0.73, 1.59] Saaby 2014 48 119 137 360 3.2% 1.10 [0.72, 1.68] Sandoval 2014 63 190 36 66 2.9% 0.41 [0.23, 0.73] Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56] = Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] = Smilowitz 2018 102 146 98 137 3.0%	Putot 2018	419	847	919	2036	3.5%	1.19 [1.01, 1.40]		-
Raphael 2020 359 1054 790 1365 3.5% 0.38 [0.32, 0.44] Saaby 2013 60 144 158 397 3.2% 1.08 [0.73, 1.59] Saaby 2014 48 119 137 360 3.2% 1.10 [0.72, 1.68] Sandoval 2014 63 190 36 66 2.9% 0.41 [0.23, 0.73] Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56] * Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] * Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.73, 1.63] Stein 2014 93 127 1924 2691 3.2% <	Putot 2019	169	254	259	365	3.3%	0.81 [0.58, 1.15]		-
Saaby 2013 60 144 158 397 3.2% 1.08 [0.73, 1.59] Saaby 2014 48 119 137 360 3.2% 1.10 [0.72, 1.68] Sandoval 2014 63 190 36 66 2.9% 0.41 [0.23, 0.73] Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56] Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63]	Radovanovic 2017	631	1091	8076	13828	3.5%	0.98 [0.86, 1.11]		+ t
Saaby 2014 48 119 137 360 3.2% 1.10 [0.72, 1.68] Sandoval 2014 63 190 36 66 2.9% 0.41 [0.23, 0.73]	Raphael 2020	359	1054	790	1365	3.5%	0.38 [0.32, 0.44]		-
Sandoval 2014 63 190 36 66 2.9% 0.41 [0.23, 0.73] Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56] Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63]	Saaby 2013	60	144	158	397	3.2%	1.08 [0.73, 1.59]		+
Sandoval 2017 61 140 50 77 2.9% 0.42 [0.23, 0.74] Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56] • Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] • Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] • Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63]	Saaby 2014	48	119	137	360	3.2%	1.10 [0.72, 1.68]		+
Sato 2020 95 155 1435 2834 3.3% 1.54 [1.11, 2.15] Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56] + Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] + Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] - Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63]	Sandoval 2014	63	190	36	66	2.9%	0.41 [0.23, 0.73]		
Shah 2015 117 429 539 1171 3.4% 0.44 [0.35, 0.56] + Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] + Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] + Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63] +	Sandoval 2017	61	140	50	77	2.9%	0.42 [0.23, 0.74]		
Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] - Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63] -	Sato 2020	95	155	1435	2834	3.3%	1.54 [1.11, 2.15]		
Singh 2020 172 1225 1229 2097 3.5% 0.12 [0.10, 0.14] Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63]	Shah 2015	117	429	539	1171	3.4%	0.44 [0.35, 0.56]		+
Smilowitz 2018 102 146 98 137 3.0% 0.92 [0.55, 1.54] - Stein 2014 93 127 1924 2691 3.2% 1.09 [0.73, 1.63] -	Singh 2020	172	1225	1229	2097	3.5%			-
	Smilowitz 2018	102	146	98			0.92 [0.55, 1.54]		-
Total (05% C1) 40652 97266 400.0% 0.74 (0.5% 0.04)	Stein 2014	93	127	1924	2691	3.2%	1.09 [0.73, 1.63]		+
1005Z 07500 100.0% 0.14 [0.50, 0.54]	Total (95% CI)		10652		87366	100.0%	0.74 [0.58, 0.94]		•
Total events 4626 40099	Total events	4626		40099					
Heterogeneity: Tau ² = 0.42; Chi ² = 703.94, df = 30 (P < 0.00001); l ² = 96%	Heterogeneity: Tau ² = 0.42; (Chi ² = 703	.94, df =	= 30 (P <	0.00001); I ² = 96%	6	0.01	01

Figure S6. Forest Pl									
	T2M	-	T1N			Odds Ratio		Odds F	
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% CI		M-H, Rando	m, 95%
Arora 2018	80	264	327	775	3.6%	0.60 [0.44, 0.80]			
Baron 2015	765	1403		17488	3.9%	0.85 [0.76, 0.94]		- 1	
Baron 2016	771	1313	24754		3.9%	0.90 [0.81, 1.01]		1	
Cediel 2017	62	194	218	376	3.5%	0.34 [0.24, 0.49]		-	
Chapman 2018	62	429	380	1171	3.6%	0.35 [0.26, 0.47]		-	
Conseugra Sanchez 2018	10	75	27	125	2.4%	0.56 [0.25, 1.23]		+	
Etaher 2020	21	171	30	97	2.8%	0.31 [0.17, 0.59]			
Furie 2019	73	206	133	349	3.5%	0.89 [0.62, 1.28]		- +	
Guimares 2018	36	76	304	847	3.2%	1.61 [1.00, 2.58]		F	-
Hawatmeh 2020	88	281	272	664	3.6%	0.66 [0.49, 0.88]		-	
Javed 2009	30	64	66	143	2.9%	1.03 [0.57, 1.86]		-+	_
Lambrecht 2018	91	119	284	360	3.1%	0.87 [0.53, 1.42]		-+	-
Landes 2016	44	107	41	107	3.0%	1.12 [0.65, 1.94]		+	_
Lopez Cuenca 2016	23	117	232	707	3.2%	0.50 [0.31, 0.81]			
Meigher 2016	172	452	129	340	3.6%	1.00 [0.75, 1.34]		+	
Nestelberger 2020	21	128	181	684	3.1%	0.55 [0.33, 0.90]			
Neumann 2017	17	99	52	188	2.8%	0.54 [0.29, 1.00]			
Pandey 2020	13	103	16	97	2.4%	0.73 [0.33, 1.61]		-+	-
Putot 2018	280	847	1271	2036	3.8%	0.30 [0.25, 0.35]		-	
Putot 2019	101	254	243	365	3.5%	0.33 [0.24, 0.46]			
Radovanovic 2017	340	1091	5697	13828	3.9%	0.65 [0.57, 0.74]		•	
Raphael 2020	462	1054	907	1365	3.8%	0.39 [0.33, 0.47]		-	
Saaby 2013	35	144	129	397	3.3%	0.67 [0.43, 1.03]			
Saaby 2014	91	119	284	360	3.1%	0.87 [0.53, 1.42]		-+	-
Sandoval 2017	52	140	23	77	2.9%	1.39 [0.76, 2.52]		+	_
Sato 2020	51	155	921	2834	3.5%	1.02 [0.72, 1.44]		+	-
Shah 2015	62	429	380	1171	3.6%	0.35 [0.26, 0.47]		-	
Singh 2020	244	1225	1063	2097	3.8%	0.24 [0.21, 0.29]		•	
Smilowitz 2018	96	146	89	137	3.2%	1.04 [0.63, 1.69]		+	-
Stein 2014	20	127	1095	2691	3.2%	0.27 [0.17, 0.44]			
Total (95% CI)		11332		92377	100.0%	0.61 [0.50, 0.74]		•	
Total events	4213		49796						
Heterogeneity: Tau ² = 0.25;		.67. df =		0.00001); ² = 93%			<u> </u>	
Test for overall effect: Z = 5			1.				0.01	0.1 1 T1MI	

	T2M	1	T1N	11		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	
Baron 2016	824	1313	27283	40501	21.6%	0.82 [0.73, 0.91]		
Javed 2009	14	64	54	143	11.0%	0.46 [0.23, 0.91]		
Pandey 2020	22	103	22	97	11.2%	0.93 [0.47, 1.81]		
Putot 2018	91	847	423	2036	19.7%	0.46 [0.36, 0.58]	-	
Putot 2019	27	254	97	365	15.2%	0.33 [0.21, 0.52]		
Radovanovic 2017	247	1091	3084	13828	21.2%	1.02 [0.88, 1.18]	- 1	
Total (95% CI)		3672		56970	100.0%	0.63 [0.46, 0.87]	•	
Total events	1225		30963				10 AN 10 AN	

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	T2M	1	T1N	11		Odds Ratio		Odds Ratio	
Study or Subgroup			Events		Weight	M-H, Random, 95% CI	M-	H, Random, 95% Cl	
Arora 2018	66	264	130	775	6.1%	1.65 [1.18, 2.32])	-	
Baron 2015	624	1403	4669	17488	7.7%	2.20 [1.97, 2.46]		•	
Baron 2016	355	1313	8056	40501	7.6%	1.49 [1.32, 1.69]			
Cediel 2017	51	194	42	376	5.2%	2.84 [1.80, 4.46]			
Etaher 2020	83	171	15	97	3.9%	5.16 [2.75, 9.65]			
Furie 2019	74	206	99	349	5.9%	1.42 [0.98, 2.04]		-	
Javed 2009	33	64	43	143	4.0%	2.48 [1.35, 4.54]			
Landes 2016	29	107	17	107	3.6%	1.97 [1.01, 3.85]			
Meigher 2016	86	452	54	340	5.8%	1.24 [0.86, 1.81]		+	
Putot 2018	122	847	113	2036	6.6%	2.86 [2.19, 3.75]		-	
Putot 2019	55	254	45	365	5.3%	1.97 [1.28, 3.03]			
Radovanovic 2017	158	1091	982	13828	7.3%	2.22 [1.85, 2.65]		*	
Saaby 2013	20	144	23	397	3.9%	2.62 [1.39, 4.94]			
Sandoval 2014	49	190	9	66	3.1%	2.20 [1.01, 4.78]		—	
Sandoval 2017	20	140	13	77	3.2%	0.82 [0.38, 1.76]			
Sato 2020	68	155	1261	2834	6.2%	0.97 [0.70, 1.35]		+	
Smilowitz 2018	41	146	41	137	4.7%	0.91 [0.55, 1.53]		+	
Stein 2014	45	127	328	2691	5.7%	3.95 [2.70, 5.79]			
Troung 2020	23	175	29	275	4.2%	1.28 [0.72, 2.30]		+	
Total (95% CI)		7443		82882	100.0%	1.89 [1.59, 2.25]		•	
Total events	2002		15969						
Heterogeneity: Tau ² =				8 (P < 0	.00001); P	2 = 82%	0.01 0.	1 1 10	
Test for overall effect:	Z = 7.15 (P < 0.0	0001)				0.01 0.	T1MI T2MI	

	T2M		T1N	11		Odds Ratio	Odds Ratio
tudy or Subgroup					Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Baron 2015	288	1403		17488	4.9%	2.18 [1.90, 2.50]	
aron 2016	151	1313	3035	40501	4.9%	1.60 [1.35, 1.91]	-
ediel 2017	31	194	15	376	3.5%	4.58 [2.40, 8.71]	
hapman 2020	292	1121	792	4981	4.9%	1.86 [1.60, 2.17]	-
taher 2020	42	171	5	97	2.6%	5.99 [2.28, 15.72]	
urie 2019	66	206	96	349	4.4%	1.24 [0.85, 1.81]	+-
lawatmeh 2020	79	281	119	664	4.5%	1.79 [1.29, 2.48]	-
adesjo 2019	40	251	91	1111	4.3%	2.12 [1.42, 3.17]	-
ambrecht 2018	26	119	32	360	3.8%	2.87 [1.63, 5.05]	 -
andes 2016	21	107	17	107		1.29 [0.64, 2.61]	- -
opez Cuenca 2016	21	117	42	707	3.8%	3.46 [1.97, 6.10]	
Neigher 2016	118	452	54	340	4.4%	1.87 [1.31, 2.68]	-
leumann 2017	25	99	36	188	3.7%	1.43 [0.80, 2.55]	+
Putot 2018	231	847	71	2036	4.6%	10.38 [7.84, 13.75]	
Putot 2019	78	254	36	365	4.2%	4.05 [2.62, 6.26]	
Radovanovic 2017	74	1091		13828		3.40 [2.61, 4.42]	-
Raphael 2020	86	1054	26	1365		4.58 [2.93, 7.15]	
aaby 2013	34	144	45	397		2.42 [1.48, 3.96]	
aaby 2014	26	119	32	360	3.8%	2.87 [1.63, 5.05]	
andoval 2014	46	190	7	66	2.9%	2.69 [1.15, 6.31]	
andoval 2017	40	140	10	77		2.68 [1.25, 5.72]	
ato 2020	13	155	433	2834		0.51 [0.29, 0.90]	
Smilowitz 2018	75	146	61	137		1.32 [0.82, 2.10]	+
stein 2014	33	127	248		4.3%	3.46 [2.28, 5.25]	-
roung 2020	13	175	24	275	3.3%	0.84 [0.42, 1.70]	+
otal (95% CI)		10276		91700	100.0%	2.34 [1.87, 2.93]	•
otal events	1949		7471				
leterogeneity: Tau ² =	0.26; Chi ²	= 232.8	3, df = 24	(P < 0.0	00001); l ²	= 90%	0.01 0.1 1 10
est for overall effect:							0.01 0.1 1 10 T1MI T2MI
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	T2M	1	T1M	11		Odds Rati	0			Odds Ratio		
Study or Subgroup			Events		Weight					Random, 95		
Arora 2018	46	264	111	775	6.3%	1.26 [0.8				-		_
Cediel 2017	21	194	52	376	5.4%	0.76 [0.4				-+		
Chapman 2018	29	429	85	1171	5.9%	0.93 [0.6				+		
Furie 2019	28	206	56	349	5.6%	0.82 [0.5				-		
Hawatmeh 2020	28	281	89	664	5.9%	0.72 [0.4	6, 1, 12]					
Higuchi 2019	8	491	182	12023	4.4%	1.08 [0.5				+-		
Lambrecht 2018	17	119	20	360	4.6%	2.83 [1.4	3, 5.61]					
Lopez Cuenca 2016	11	117	57	707	4.6%	1.18 [0.6	0, 2.33]			- - -		
Nestelberger 2020	2	128	72	684	2.0%	0.13 [0.0		-	-	-1		
Putot 2018	110	847	138	2036	6.8%	2.05 [1.5	8, 2.67]					
Putot 2019	55	254	54	365	6.0%	1.59 [1.0	5, 2.41]			⊢ ⊷		
Radovanovic 2017	103	1091	650	13828	7.0%	2.11 [1.7	0, 2.63]			-		
Saaby 2013	18	144	21	397	4.7%	2.56 [1.3	2, 4.95]					
Saaby 2014	17	119	20	360	4.6%	2.83 [1.4	3, 5.61]			- I		
Sandoval 2017	3	140	5	77	1.9%	0.32 [0.0	7, 1.36]			-+		
Sato 2020	14	155	121	2834	5.1%	2.23 [1.2	5, 3.97]					
Shah 2015	29	429	82	1171	5.9%	0.96 [0.6	2, 1.49]			+		
Smilowitz 2018	11	146	13	137	3.8%	0.78 [0.3	4, 1.80]					
Stein 2014	22	127	229	2691	5.7%	2.25 [1.4	0, 3.64]					
Froung 2020	12	175	9	275	3.6%	2.18 [0.9	0, 5.28]			-		
Total (95% CI)		5856		41280	100.0%	1.33 [1.0	5, 1.69]			•		
Total events	584		2066									
Heterogeneity: Tau ² =	0.20; Chi ²	= 81.80), df = 19	(P < 0.0	00001); l ²	= 77%		0.01	0.1	-	10	
Test for overall effect:	Z = 2.36 (P = 0.0	2)					0.01		T1MI T2MI	10	

	T2M	1	T1N	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Baron 2015	195	1403	1609	17488	7.1%	1.59 [1.36, 1.87]	-
Baron 2016	99	1313	2696	40501	6.6%	1.14 [0.93, 1.41]	+
Cediel 2017	29	194	38	376	3.6%	1.56 [0.93, 2.62]	
Chapman 2018	48	429	92	1171	4.9%	1.48 [1.02, 2.13]	
Chapman 2020	135	1121	368	4981	6.6%	1.72 [1.39, 2.11]	-
Etaher 2020	28	171	10	97	2.2%	1.70 [0.79, 3.68]	
Furie 2019	42	206	98	349	4.5%	0.66 [0.43, 0.99]	-
Hawatmeh 2020	24	281	64	664	3.8%	0.88 [0.54, 1.43]	-+
Higuchi 2019	35	491	748	12023	5.1%	1.16 [0.81, 1.64]	+
Kadesjo 2019	19	251	71	1111	3.5%	1.20 [0.71, 2.03]	
Lambrecht 2018	24	119	43	360	3.4%	1.86 [1.08, 3.23]	
Lopez Cuenca 2016	20	117	81	707	3.5%	1.59 [0.93, 2.72]	
Nestelberger 2020	5	128	52	684	1.6%	0.49 [0.19, 1.26]	+
Paiva 2015	29	236	59	764	4.0%	1.67 [1.05, 2.68]	
Putot 2018	122	847	127	2036	6.0%	2.53 [1.94, 3.29]	+
Putot 2019	50	254	40	365	4.1%	1.99 [1.27, 3.13]	
Radovanovic 2017	84	1091	774	13828	6.4%	1.41 [1.11, 1.78]	· ·
Saaby 2013	31	144	54	397	3.8%	1.74 [1.07, 2.84]	
Saaby 2014	24	119	43	360	3.4%	1.86 [1.08, 3.23]	
Sandoval 2017	18	140	3	77	1.0%	3.64 [1.04, 12.78]	
Sato 2020	17	155	276	2834	3.6%	1.14 [0.68, 1.92]	+
Shah 2015	48	429	92	1171	4.9%	1.48 [1.02, 2.13]	
Stein 2014	22	127	215	2691	3.9%	2.41 [1.49, 3.90]	-
Troung 2020	16	175	16	275	2.4%	1.63 [0.79, 3.35]	+
Total (95% CI)		9941		105310	100.0%	1.48 [1.30, 1.69]	•
Total events	1164		7669				
Heterogeneity: Tau ² =	0.06; Chi ²	= 62.7	7, df = 23	(P < 0.00	01); I ² = 6	3%	0.01 0.1 1 10
Test for overall effect:							0.01 0.1 1 10 T1MI T2MI

Study or Subgroup	T2MI		T1MI			Odds Ratio	Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Javed 2009	17	64	2	143	46.0%	25.50 [5.68, 114.50]	
Sandoval 2017	29	140	6	77	54.0%	3.09 [1.22, 7.82]	
Fotal (95% CI)		204		220	100.0%	8.15 [1.03, 64.46]	-
Fotal events	46		8				

	T2M		T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cediel 2017	67	194	37	376	8.8%	4.83 [3.08, 7.58]	
Etaher 2020	42	171	5	97	4.8%	5.99 [2.28, 15.72]	
Furie 2019	42	206	68	349	8.9%	1.06 [0.69, 1.63]	+
Hawatmeh 2020	48	281	54	664	9.0%	2.33 [1.53, 3.53]	-
Lambrecht 2018	25	119	32	360	7.7%	2.73 [1.54, 4.83]	
Lopez Cuenca 2016	51	117	103	707	9.0%	4.53 [2.97, 6.90]	
Neumann 2017	34	99	20	188	7.2%	4.39 [2.36, 8.19]	
Paiva 2015	72	236	117	764	9.7%	2.43 [1.73, 3.41]	-
Putot 2018	235	847	160	2036	10.6%	4.50 [3.61, 5.61]	
Radovanovic 2017	170	1091	567	13828	10.8%	4.32 [3.59, 5.19]	
Saaby 2013	34	144	50	397	8.4%	2.15 [1.32, 3.49]	
Sandoval 2017	16	140	7	77	5.0%	1.29 [0.51, 3.29]	
Total (95% CI)		3645		19843	100.0%	3.02 [2.29, 3.99]	•
Total events	836		1220				
Heterogeneity: Tau ² = Test for overall effect:				(P < 0.0	00001); l² :	= 82%	0.01 0.1 1 10 T1MI T2MI

	T2M		T1N			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95%
Balanescu 2020	8	49	67	152	4.5%	0.25 [0.11, 0.56]	
Baron 2015	870	1403	14830	17488	7.2%	0.29 [0.26, 0.33]	-
Baron 2016	899	1313	35883	40501	7.2%	0.28 [0.25, 0.32]	-
Cediel 2017	42	194	337	376	6.1%	0.03 [0.02, 0.05]	-
Chapman 2020	749	1121	4061	4981	7.2%	0.46 [0.40, 0.53]	-
Conseugra Sanchez 2018	62	75	102	125	4.8%	1.08 [0.51, 2.28]	-+
Furie 2019	88	206	258	349	6.5%	0.26 [0.18, 0.38]	-
Landes 2016	65	107	103	107	3.6%	0.06 [0.02, 0.18]	
Lopez Cuenca 2016	87	117	618	707	6.1%	0.42 [0.26, 0.67]	
Meigher 2016	41	452	201	340	6.4%	0.07 [0.05, 0.10]	-
Radovanovic 2017	853	1091	12846	13828	7.1%	0.27 [0.23, 0.32]	-
Sandoval 2014	65	190	56	66	4.9%	0.09 [0.04, 0.19]	
Sandoval 2017	22	140	38	77	5.3%	0.19 [0.10, 0.36]	
Shah 2015	217	429	1041	1171	6.9%	0.13 [0.10, 0.17]	-
Smilowitz 2018	46	146	128	137	4.8%	0.03 [0.02, 0.07]	I
Stein 2014	69	127	2274	2691	6.5%	0.22 [0.15, 0.31]	-
Troung 2020	161	175	260	275	4.8%	0.66 [0.31, 1.41]	
Total (95% CI)		7335		83371	100.0%	0.19 [0.15, 0.26]	•
Total events	4344		73103				
Heterogeneity: Tau ² = 0.29;	Chi ² = 280).74, df	= 16 (P <	0.0000	1); I ² = 94	%	0.01 0.1 1

	T2M	í.	T1N	1		Odds Ratio	Odds Ratio
Study or Subgroup		-	Events		Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Baron 2015	269	870		17488		5.95 [5.09, 6.94]	
Baron 2016	195	1313	1774	40501	8.4%	3.81 [3.25, 4.47]	•
Cediel 2017	90	194	37	376	7.6%	7.93 [5.10, 12.33]	
Chapman 2020	116	1121	171	4981	8.3%	3.25 [2.54, 4.15]	
Furie 2019	122	206	178	349	8.0%	1.40 [0.98, 1.98]	-
Landes 2016	78	107	38	107	7.1%	4.88 [2.73, 8.74]	· · · ·
Lopez Cuenca 2016	22	117	38	707	7.1%	4.08 [2.31, 7.19]	· · · ·
Radovanovic 2017	482	1091	4425	13828	8.5%	1.68 [1.48, 1.91]	
Sandoval 2014	112	190	35	66	7.1%	1.27 [0.72, 2.23]	+ -
Sandoval 2017	72	140	40	77	7.2%	0.98 [0.56, 1.71]	
Shah 2015	80	429	45	1171	7.8%	5.74 [3.91, 8.42]	-
Stein 2014	15	127	105	2691	7.1%	3.30 [1.86, 5.85]	
Troung 2020	28	175	44	275	7.3%	1.00 [0.60, 1.68]	+
Total (95% CI)		6080		82617	100.0%	2.83 [1.96, 4.08]	•
Total events	1681		8154				
Heterogeneity: Tau ² =	0.41; Chi ²	= 266.3	38, df = 1	2 (P < 0	.00001); I	² = 95%	0.01 0.1 1 10
Test for overall effect:	Z = 5.55 (P < 0.0	0001)				T1MI T2MI
Figure S16. Fore	est Plot.	. Arm	/ Sho	ulder	Discon	nfort as Presenting	g Feature.
	T2M		T1M			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Sandoval 2014	13	190	20	66	45.6%	0.17 [0.08, 0.36]	
Sandoval 2017	15	140	30	77	54.4%	0.19 [0.09, 0.38]	
		0.00			100.00	0.40.50.44.0.203	
Total (95% CI)		330		143	100.0%	0.18 [0.11, 0.30]	

	T2M	I	T1M	1		Odds Ratio	Odd	s Ratio
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Random, 95% Cl	M-H, Ran	dom, 95% Cl
Sandoval 2014	13	190	20	66	45.6%	0.17 [0.08, 0.36]		8.8
Sandoval 2017	15	140	30	77	54.4%	0.19 [0.09, 0.38]		
Total (95% CI)		330		143	100.0%	0.18 [0.11, 0.30]	•	
Total events	28		50					
Heterogeneity: Tau ² =	0.00; Chi ²	= 0.04	df = 1 (F	= 0.84); l ² = 0%	ţ	0.01 0.1	1 10
Test for overall effect:	Z = 6.49 (P < 0.0	0001)			,	D.01 0.1 T1M	1 10 I T2MI

	T2M	1	T1M			Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	
Sandoval 2014	21	190	14	66	42.8%	0.46 [0.22, 0.97]		
Sandoval 2017	25	140	25	77	57.2%	0.45 [0.24, 0.86]		
Total (95% CI)		330		143	100.0%	0.46 [0.28, 0.74]	•	
Total events	46		39					

	T2M	1	T1N	11		Odds Ratio		Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 9	5% CI	
Baron 2015	264	1403	1434	17488	25.4%	2.59 [2.25, 3.00]				
Baron 2016	899	1313	2506	40501	25.5%	32.92 [29.11, 37.24]				
Lopez Cuenca 2016	8	117	51	707	24.3%	0.94 [0.44, 2.04]				
Neumann 2017	81	99	105	188	24.8%	3.56 [1.98, 6.39]			-	
Total (95% CI)		2932		58884	100.0%	4.19 [0.72, 24.39]				-
Total events	1252		4096							
Heterogeneity: Tau ² =	3.17; Chi ²	= 760.	73, df = 3	(P < 0.0	00001); l ² :	= 100%			+	4.04
Test for overall effect:	Z = 1.59 (P = 0.1	1)				0.01	0.1 1 T1MI T2M	10	100

	T2M	1	T1M	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Cediel 2017	15	194	5	376	17.2%	6.22 [2.22, 17.38]	
Chapman 2020	38	1121	102	4981	25.6%	1.68 [1.15, 2.45]	
Furie 2019	12	206	24	349	21.4%	0.84 [0.41, 1.71]	
Shah 2015	31	429	21	1171	23.4%	4.27 [2.42, 7.51]	
Troung 2020	3	175	5	275	12.5%	0.94 [0.22, 3.99]	10
Total (95% CI)		2125		7152	100.0%	2.10 [1.05, 4.18]	•
Total events	99		157				

Heterogeneity: Tau ² = Test for overall effect:				(P < 0.0	0001); l² =	= 100%	0.01	0.1 T1MI	1 10 T2MI	
								1 HVII	1211	
Figure S19. Fore	est Plot	. Coll	apse /	Synco	ope as	Presenting Featu	ires.			
Study or Subgroup	T2N Events		T1M Events		Weight	Odds Ratio M-H, Random, 95% CI		Odds M-H, Rando		
Cediel 2017	15	194	5	376	17.2%	6.22 [2.22, 17.38]			_	
Chapman 2020	38	1121	102	4981	25.6%	1.68 [1.15, 2.45]		-	-	
Furie 2019	12	206	24	349	21.4%	0.84 [0.41, 1.71]			-	
Shah 2015	31	429	21		23.4%	4.27 [2.42, 7.51]				
Troung 2020	3	175	5	275	12.5%	0.94 [0.22, 3.99]				
Total (95% CI)		2125		7152	100.0%	2.10 [1.05, 4.18]		-	•	
Total events	99		157			1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1				
Heterogeneity: Tau ² =	0.45; Chi	= 19.1	2. df = 4 (P = 0.00	007); l ² = 7	79%	-		1	100
Test for overall effect:				105X74			0.01	0.1 1 T1MI	10 T2MI	1
с. с. с. с		ст г	a		FCC					
Figure S20. Fore					ECG.	Odds Ratio		bbO	s Ratio	
	est Plot T2M Events	l	T1N	11		Odds Ratio M-H, Random, 95% C	1		s Ratio dom, 95% (
Figure S20. Fore Study or Subgroup Baron 2015	T2M Events	l	T1N	11	Weight	M-H, Random, 95% C			s Ratio dom,95% (CI
Study or Subgroup	T2M Events 136	Total	T1N Events	1I Total	Weight 7.8%	M-H, Random, 95% C 0.23 [0.19, 0.28]			CI
Study or Subgroup Baron 2015	T2M Events 136	Total 1403	T1N Events 5544	11 <u>Total</u> 17488	Weight 7.8% 7.9%	M-H, Random, 95% C]]			
Study or Subgroup Baron 2015 Baron 2016	T2M Events 136 173 5	Total 1403 1313	T1N Events 5544 14824	Total 17488 40501	Weight 7.8% 7.9% 3.4%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31]]]			
Study or Subgroup Baron 2015 Baron 2016 Cediel 2017	T2M Events 136 173 5	Total 1403 1313 194	T1N Events 5544 14824 92	11 17488 40501 376	Weight 7.8% 7.9% 3.4% 6.9%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31 0.08 [0.03, 0.20]]]]			21
Study or Subgroup Baron 2015 Baron 2016 Cediel 2017 Chapman 2020	T2M Events 136 173 5 36	Total 1403 1313 194 1121	T1N Events 5544 14824 92 870	II 17488 40501 376 4981	Weight 7.8% 7.9% 3.4% 6.9% 2.7%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31 0.08 [0.03, 0.20 0.16 [0.11, 0.22]]]]			
Study or Subgroup Baron 2015 Baron 2016 Cediel 2017 Chapman 2020 Furie 2019	T2M Events 136 173 5 36 4	Total 1403 1313 194 1121 206	T1N Events 5544 14824 92 870 18	II 17488 40501 376 4981 349	Weight 7.8% 7.9% 3.4% 6.9% 2.7% 7.8%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31 0.08 [0.03, 0.20 0.16 [0.11, 0.22 0.36 [0.12, 1.09]]]]]			21
Study or Subgroup Baron 2015 Baron 2016 Cediel 2017 Chapman 2020 Furie 2019 Higuchi 2019	T2M Events 136 173 5 36 4 288	Total 1403 1313 194 1121 206 491	T1N Events 5544 14824 92 870 18 8917	Total 17488 40501 376 4981 349 12023	Weight 7.8% 7.9% 3.4% 6.9% 2.7% 7.8% 3.5%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31 0.08 [0.03, 0.20 0.16 [0.11, 0.22 0.36 [0.12, 1.09 0.49 [0.41, 0.59]]]]]]			21
Study or Subgroup Baron 2015 Baron 2016 Cediel 2017 Chapman 2020 Furie 2019 Higuchi 2019 Landes 2016 Lopez Cuenca 2016 Nestelberger 2020	T2M Events 136 173 5 36 4 288 11 1 4	Total 1403 1313 194 1121 206 491 107 117 128	T1N Events 5544 14824 92 870 18 8917 11 225 115	II Total 17488 40501 376 4981 349 12023 107 707 684	Weight 7.8% 7.9% 3.4% 6.9% 2.7% 7.8% 3.5% 1.1% 3.0%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31 0.08 [0.03, 0.20 0.16 [0.11, 0.22 0.36 [0.12, 1.09 0.49 [0.41, 0.59 1.00 [0.41, 2.42 0.02 [0.00, 0.13 0.16 [0.06, 0.44]]]]] ←			21
Study or Subgroup Baron 2015 Baron 2016 Cediel 2017 Chapman 2020 Furie 2019 Higuchi 2019 Landes 2016 Lopez Cuenca 2016 Nestelberger 2020 Paiva 2015	T2M Events 136 173 5 36 4 288 11 1 4 35	Total 1403 1313 194 1121 206 491 107 117 128 236	T1N Events 5544 14824 92 870 18 8917 11 225 115 417	II Total 17488 40501 376 4981 349 12023 107 707 684 764	Weight 7.8% 7.9% 3.4% 6.9% 2.7% 7.8% 3.5% 1.1% 3.0% 6.6%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31 0.08 [0.03, 0.20 0.16 [0.11, 0.22 0.36 [0.12, 1.09 0.49 [0.41, 0.59 1.00 [0.41, 2.42 0.02 [0.00, 0.13 0.16 [0.06, 0.44 0.14 [0.10, 0.21]]]]] ↓ ↓			21
Study or Subgroup Baron 2015 Baron 2016 Cediel 2017 Chapman 2020 Furie 2019 Higuchi 2019 Landes 2016 Lopez Cuenca 2016 Nestelberger 2020 Paiva 2015 Putot 2019	T2M Events 136 173 5 36 4 288 11 1 4 35 28	Total 1403 1313 194 1121 206 491 107 117 128 236 254	T1N Events 5544 14824 92 870 18 8917 11 225 115 417 136	II <u>Total</u> 17488 40501 376 4981 349 12023 107 707 684 764 365	Weight 7.8% 7.9% 3.4% 6.9% 2.7% 7.8% 3.5% 1.1% 3.0% 6.6% 6.1%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31 0.08 [0.03, 0.20 0.16 [0.11, 0.22 0.36 [0.12, 1.09 0.49 [0.41, 0.59 1.00 [0.41, 2.42 0.02 [0.00, 0.13 0.16 [0.06, 0.44 0.14 [0.10, 0.21 0.21 [0.13, 0.33]]]]] ↓ ↓]] ↓			21
Study or Subgroup Baron 2015 Baron 2016 Cediel 2017 Chapman 2020 Furie 2019 Higuchi 2019 Landes 2016 Lopez Cuenca 2016 Nestelberger 2020 Paiva 2015 Putot 2019 Putot 2020	T2MI Events 136 173 5 36 4 288 11 1 4 35 28 207	Total 1403 1313 194 1121 206 491 107 117 128 236 254 862	T1N Events 5544 14824 92 870 18 8917 11 225 115 417 136 1929	II Total 17488 40501 376 4981 349 12023 107 707 684 764 365 3710	Weight 7.8% 7.9% 3.4% 6.9% 2.7% 7.8% 3.5% 1.1% 3.0% 6.6% 6.1% 7.8%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31 0.08 [0.03, 0.20 0.16 [0.11, 0.22 0.36 [0.12, 1.09 0.49 [0.41, 0.59 1.00 [0.41, 2.42 0.02 [0.00, 0.13 0.16 [0.06, 0.44 0.14 [0.10, 0.21 0.21 [0.13, 0.33 0.29 [0.25, 0.35]]]]] ↓ ↓ ↓			
Study or Subgroup Baron 2015 Baron 2016 Cediel 2017 Chapman 2020 Furie 2019 Higuchi 2019 Landes 2016 Lopez Cuenca 2016 Nestelberger 2020 Paiva 2015 Putot 2019 Putot 2020 Radovanovic 2017	T2MI Events 136 173 5 36 4 288 11 1 4 35 28 207 213	Total 1403 1313 194 1121 206 491 107 117 128 236 254 862 1091	T1N Events 5544 14824 92 870 18 8917 11 225 115 417 136 1929 7436	II Total 17488 40501 376 4981 349 12023 107 707 684 764 365 3710 13828	Weight 7.8% 7.9% 3.4% 6.9% 2.7% 7.8% 3.5% 1.1% 3.0% 6.6% 6.1% 7.8% 7.9%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31 0.08 [0.03, 0.20 0.16 [0.11, 0.22 0.36 [0.12, 1.09 0.49 [0.41, 0.59 1.00 [0.41, 2.42 0.02 [0.00, 0.13 0.16 [0.06, 0.44 0.14 [0.10, 0.21 0.21 [0.13, 0.33 0.29 [0.25, 0.35 0.21 [0.18, 0.24]]]]] ↓ ↓ ↓			
Study or Subgroup Baron 2015 Baron 2016 Cediel 2017 Chapman 2020 Furie 2019 Higuchi 2019 Landes 2016 Lopez Cuenca 2016 Nestelberger 2020 Paiva 2015 Putot 2019 Putot 2020 Radovanovic 2017 Raphael 2020	T2MI Events 136 173 5 36 4 288 11 1 4 35 28 207 213 23	Total 1403 1313 194 1121 206 491 107 117 128 236 254 862 1091 1054	T1N Events 5544 14824 92 870 18 8917 11 225 115 417 136 1929 7436 198	II 17488 40501 376 4981 349 12023 107 707 684 764 365 3710 13828 1365	Weight 7.8% 7.9% 3.4% 6.9% 2.7% 7.8% 3.5% 1.1% 3.0% 6.6% 6.1% 7.8% 7.9% 6.2%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31 0.08 [0.03, 0.20 0.16 [0.11, 0.22 0.36 [0.12, 1.09 0.49 [0.41, 0.59 1.00 [0.41, 2.42 0.02 [0.00, 0.13 0.16 [0.06, 0.44 0.14 [0.10, 0.21 0.21 [0.13, 0.33 0.29 [0.25, 0.35 0.21 [0.18, 0.24 0.13 [0.08, 0.20]]]]] ↓ ↓ ↓]]]			21
Study or Subgroup Baron 2015 Baron 2016 Cediel 2017 Chapman 2020 Furie 2019 Higuchi 2019 Landes 2016 Lopez Cuenca 2016 Nestelberger 2020 Paiva 2015 Putot 2019 Putot 2020 Radovanovic 2017 Raphael 2020 Saaby 2013	T2MI Events 136 173 5 36 4 288 11 1 4 35 28 207 213 23 5	Total 1403 1313 194 1121 206 491 107 117 128 236 254 862 1091 1054 144	T1N Events 5544 14824 92 870 18 8917 11 225 115 417 136 1929 7436 198 130	II Total 17488 40501 376 4981 349 12023 107 707 684 764 365 3710 13828 1365 397	Weight 7.8% 7.9% 3.4% 6.9% 2.7% 7.8% 3.5% 1.1% 3.0% 6.6% 6.1% 7.8% 7.9% 6.2% 3.4%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31 0.08 [0.03, 0.20 0.16 [0.11, 0.22 0.36 [0.12, 1.09 0.49 [0.41, 0.59 1.00 [0.41, 2.42 0.02 [0.00, 0.13 0.16 [0.06, 0.44 0.14 [0.10, 0.21 0.21 [0.13, 0.33 0.29 [0.25, 0.35 0.21 [0.18, 0.24 0.13 [0.08, 0.20 0.07 [0.03, 0.18]]]]] ↓ ↓]]]]]]]]]]			21
Study or Subgroup Baron 2015 Baron 2016 Cediel 2017 Chapman 2020 Furie 2019 Higuchi 2019 Landes 2016 Lopez Cuenca 2016 Nestelberger 2020 Paiva 2015 Putot 2019 Putot 2020 Radovanovic 2017 Raphael 2020 Saaby 2013 Sandoval 2017	T2MI Events 136 173 5 36 4 288 11 1 4 35 28 207 213 23 5 31	Total 1403 1313 194 1121 206 491 107 117 128 236 254 862 1091 1054 144 140	T1N Events 5544 14824 92 870 18 8917 11 225 115 417 136 1929 7436 198 130 24	II Total 17488 40501 376 4981 349 12023 107 707 684 764 365 3710 13828 1365 397 77	Weight 7.8% 7.9% 3.4% 6.9% 2.7% 7.8% 3.5% 1.1% 3.0% 6.6% 6.1% 7.8% 7.9% 6.2% 3.4% 4.9%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31 0.08 [0.03, 0.20 0.16 [0.11, 0.22 0.36 [0.12, 1.09 0.49 [0.41, 0.59 1.00 [0.41, 2.42 0.02 [0.00, 0.13 0.16 [0.06, 0.44 0.14 [0.10, 0.21 0.21 [0.13, 0.33 0.29 [0.25, 0.35 0.21 [0.18, 0.24 0.13 [0.08, 0.20 0.07 [0.03, 0.18 0.63 [0.34, 1.17	□ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □			21
Study or Subgroup Baron 2015 Baron 2016 Cediel 2017 Chapman 2020 Furie 2019 Higuchi 2019 Landes 2016 Lopez Cuenca 2016 Nestelberger 2020 Paiva 2015 Putot 2019 Putot 2020 Radovanovic 2017 Raphael 2020 Saaby 2013	T2MI Events 136 173 5 36 4 288 11 1 4 35 28 207 213 23 5	Total 1403 1313 194 1121 206 491 107 117 128 236 254 862 1091 1054 144	T1N Events 5544 14824 92 870 18 8917 11 225 115 417 136 1929 7436 198 130	II Total 17488 40501 376 4981 349 12023 107 707 684 764 365 3710 13828 1365 397	Weight 7.8% 7.9% 3.4% 6.9% 2.7% 7.8% 3.5% 1.1% 3.0% 6.6% 6.1% 7.8% 7.9% 6.2% 3.4% 4.9% 6.8%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31 0.08 [0.03, 0.20 0.16 [0.11, 0.22 0.36 [0.12, 1.09 0.49 [0.41, 0.59 1.00 [0.41, 2.42 0.02 [0.00, 0.13 0.16 [0.06, 0.44 0.14 [0.10, 0.21 0.21 [0.13, 0.33 0.29 [0.25, 0.35 0.21 [0.18, 0.24 0.13 [0.08, 0.20 0.07 [0.03, 0.18 0.63 [0.34, 1.17	D D D D D D D D D D D D D D			21
Study or Subgroup Baron 2015 Baron 2016 Cediel 2017 Chapman 2020 Furie 2019 Higuchi 2019 Landes 2016 Lopez Cuenca 2016 Nestelberger 2020 Paiva 2015 Putot 2019 Putot 2020 Radovanovic 2017 Raphael 2020 Saaby 2013 Sandoval 2017 Shah 2015 Stein 2014	T2MI Events 136 173 5 36 4 288 11 1 4 35 28 207 213 23 5 31 40	Total 1403 1313 194 1121 206 491 107 117 128 236 254 862 1091 1054 144 140 429 127	T1N Events 5544 14824 92 870 18 8917 11 225 115 417 136 1929 7436 198 130 24 427 1413	II Total 17488 40501 376 4981 349 12023 107 707 684 764 365 3710 13828 1365 397 77 1171 2691	Weight 7.8% 7.9% 3.4% 6.9% 2.7% 7.8% 3.5% 1.1% 3.0% 6.6% 6.1% 7.8% 7.9% 6.2% 3.4% 4.9% 6.8% 6.2%	M-H, Random, 95% C 0.23 [0.19, 0.28 0.26 [0.22, 0.31 0.08 [0.03, 0.20 0.16 [0.11, 0.22 0.36 [0.12, 1.09 0.49 [0.41, 0.59 1.00 [0.41, 2.42 0.02 [0.00, 0.13 0.16 [0.06, 0.44 0.14 [0.10, 0.21 0.21 [0.13, 0.33 0.29 [0.25, 0.35 0.21 [0.18, 0.24 0.13 [0.08, 0.20 0.07 [0.03, 0.18 0.63 [0.34, 1.17 0.18 [0.13, 0.25 0.22 [0.14, 0.35	D D D D D D D D D D D D D D D D D D D			
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T2MI T1MI Odds Ratio Odds Ratio Arora 2016 120 244 369 775 7.1% 0.92 (0.68, 1.21) Baron 2015 446 1403 3970 17486 7.3% 1.59 [141, 1.79] Baron 2016 330 1313 6261 40501 7.3% 1.51 [141, 1.79] Baron 2016 330 1313 6261 40501 7.3% 1.51 [141, 1.79] Cediel 2017 16 149 44 376 6.4% 0.27 [0.16, 0.47] Chapman 2020 278 1121 865 4981 7.3% 1.57 [1.35, 1.83] Conseugra Sanchez 2016 71 107 75 107 6.3% 0.26 [0.08, 1.61] Lopez Cuenca 2016 35 117 152 707 6.8% 0.51 [0.41, 1.02] Saaby 2013 139 144 267 397 5.2% 13.54 [5.41, 3.3.4] Saaby 2015 249 429 332 117 7.2% 3.50 [
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T2MI T1MI Odds Ratio Odds Ratio Arora 2016 120 244 369 775 7.1% 0.92 (0.68, 1.21) Baron 2015 446 1403 3970 17486 7.3% 1.59 [141, 1.79] Baron 2016 330 1313 6261 40501 7.3% 1.51 [141, 1.79] Baron 2016 330 1313 6261 40501 7.3% 1.51 [141, 1.79] Cediel 2017 16 149 44 376 6.4% 0.27 [0.16, 0.47] Chapman 2020 278 1121 865 4981 7.3% 1.57 [1.35, 1.83] Conseugra Sanchez 2016 71 107 75 107 6.3% 0.26 [0.08, 1.61] Lopez Cuenca 2016 35 117 152 707 6.8% 0.51 [0.41, 1.02] Saaby 2013 139 144 267 397 5.2% 13.54 [5.41, 3.3.4] Saaby 2015 249 429 332 117 7.2% 3.50 [
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$\begin{array}{c} \mbox{Conseugra Sanchez 2018} & 7 & 75 & 43 & 125 & 5.4\% & 0.20 [0.08, 0.46] \\ \mbox{Hawatmeh 2020} & 223 & 281 & 86 & 664 & 6.9\% & 25.84 [17:90, 37.30] \\ \mbox{Landes 2016} & 71 & 107 & 75 & 107 & 6.3\% & 0.84 [0.47, 1.50] \\ \mbox{Londes 2016} & 35 & 117 & 152 & 707 & 6.8\% & 0.56 [1.01, 2.41] \\ \mbox{Meigher 2016} & 68 & 452 & 61 & 340 & 6.9\% & 0.81 [0.55, 1.18] \\ \mbox{Nestelberger 2020} & 33 & 128 & 234 & 684 & 6.8\% & 0.67 [0.44, 1.02] \\ \mbox{Sandoval 2017} & 74 & 140 & 40 & 77 & 6.4\% & 1.04 [0.59, 1.81] \\ \mbox{Sandoval 2017} & 74 & 140 & 40 & 77 & 6.4\% & 1.04 [0.59, 1.81] \\ \mbox{Sandoval 2017} & 74 & 140 & 40 & 77 & 6.4\% & 1.04 [0.59, 1.81] \\ \mbox{Sandoval 2017} & 74 & 140 & 40 & 77 & 6.4\% & 0.75 [0.46, 1.22] \\ \mbox{Total (95% CI)} & 6314 & 68530 & 100.0\% & 1.38 [0.94, 2.02] \\ \mbox{Total events} & 2.174 & 14938 \\ \mbox{Heterogeneity: Tau" = 0.52; Ch" = 416.57, df = 14 (P < 0.00001); P = 97\% \\ \mbox{Levents} & 1.64 (P = 0.10) \\ \mbox{Total events} & 2.174 & 14938 \\ \mbox{Heterogeneity: Tau" = 0.52; Ch" = 416.57, df = 14 (P < 0.00001); P = 97\% \\ \mbox{Lopez Cuenca 2016} & 12 & 117 & 156 & 707 & 48.4\% & 0.40 [0.22, 0.75] \\ \mbox{Lopez Cuenca 2016} & 12 & 117 & 156 & 707 & 48.4\% & 0.40 [0.22, 0.75] \\ \mbox{Sandoval 2017} & 16 & 140 & 15 & 77 & 38.8\% & 0.53 [0.25, 1.15] \\ \mbox{Total events} & 30 & 177 \\ \mbox{Heterogeneity: Tau" = 0.11; Ch" = 3.09, df = 2 (P = 0.21); P = 35\% \\ \mbox{Total events} & 30 & 177 \\ \mbox{Heterogeneity: Tau" = 0.11; Ch" = 3.09, df = 2 (P = 0.21); P = 35\% \\ \mbox{Total events} & 30 & 177 \\ \mbox{Heterogeneity: Tau" = 0.11; Ch" = 3.09, df = 2 (P = 0.21); P = 35\% \\ \mbox{Total events} & 30 & 177 \\ \mbox{Heterogeneity: Tau" = 0.11; Ch" = 3.09, df = 2 (P = 0.21); P = 35\% \\ \mbox{Total events} & 30 & 177 \\ \mbox{Heterogeneity: Tau" = 0.00; Ch" = 0.49, df = 1 (P = 0.48); P = 0\% \\ \mbox{Meigher 2016} & 90 & 452 & 27 & 340 & 65.4\% & 2.86 [1.83, 4.55] \\ \mbox{Sandoval 2017} & 56 & 140 & 18 & 77 & 34.6\% & 2.19 [1.17, 4.09] \\ \mbox{Meigher 2016} & 90 & 452 & 27 & 340 & 65.4\% & 2.48 [1$						376		0.27 [0.15	0.47]		-	
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Test for overall ellect. 2 = 3.03 (P = 0.002) TIMI T2MI Figure S23. Forest Plot. Non-specific ST Changes on ECG. TIMI T1MI Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Meigher 2016 90 452 27 340 65.4% 2.88 [1.83, 4.55] Image: Colspan="2">Sandoval 2017 Total (95% CI) 592 417 100.0% 2.62 [1.81, 3.79] Total (95% CI) 592 417 100.0% 2.62 [1.81, 3.79] Total events 146 45 Heterogeneity: Tau ² = 0.00; Chi ² = 0.49, df = 1 (P = 0.48); l ² = 0% 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 <th colsp<="" td=""><td>Total events Heterogeneity: Tau² = 0 Test for overall effect: Z Figure S22. Fores <u>Study or Subgroup</u> Lopez Cuenca 2016 Sandoval 2014 Sandoval 2017 Total (95% CI)</td><td>52; Chi² = 1.64 (F st Plot. T2MI Events 12 2 16</td><td>2174 = 416. P = 0.1 Q V Total 117 190 140</td><td>1 57, df = 1 0) /aves T1M Events 156 6 15</td><td>4938 I4 (P < I On EC I Total 707 66 77</td><td>0.00001) CG. Weight 48.4% 12.8% 38.8%</td><td>); I² = 97</td><td>% dds Ratio <u>Random, 95% CI</u> 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15]</td><td></td><td>Odds</td><td>T1Mi Ratio</td></th>	<td>Total events Heterogeneity: Tau² = 0 Test for overall effect: Z Figure S22. Fores <u>Study or Subgroup</u> Lopez Cuenca 2016 Sandoval 2014 Sandoval 2017 Total (95% CI)</td> <td>52; Chi² = 1.64 (F st Plot. T2MI Events 12 2 16</td> <td>2174 = 416. P = 0.1 Q V Total 117 190 140</td> <td>1 57, df = 1 0) /aves T1M Events 156 6 15</td> <td>4938 I4 (P < I On EC I Total 707 66 77</td> <td>0.00001) CG. Weight 48.4% 12.8% 38.8%</td> <td>); I² = 97</td> <td>% dds Ratio <u>Random, 95% CI</u> 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15]</td> <td></td> <td>Odds</td> <td>T1Mi Ratio</td>	Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z Figure S22. Fores <u>Study or Subgroup</u> Lopez Cuenca 2016 Sandoval 2014 Sandoval 2017 Total (95% CI)	52; Chi ² = 1.64 (F st Plot. T2MI Events 12 2 16	2174 = 416. P = 0.1 Q V Total 117 190 140	1 57, df = 1 0) /aves T1M Events 156 6 15	4938 I4 (P < I On EC I Total 707 66 77	0.00001) CG. Weight 48.4% 12.8% 38.8%); I ² = 97	% dds Ratio <u>Random, 95% CI</u> 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15]		Odds	T1Mi Ratio
T2MI T1MI Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random	Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z Figure S22. Fores <u>Study or Subgroup</u> Lopez Cuenca 2016 Sandoval 2014 Sandoval 2017 Total (95% CI) Total events	52; Chi ² = = 1.64 (F st Plot. T2MI Events 12 2 16 30	2174 = 416. P = 0.1 Q V Total 117 190 140 447	1 57, df = 1 0) Vaves T1M Events 156 6 15	4938 I4 (P < 1 on EC I Total 707 66 77 850	0.00001) CG. Weight 48.4% 12.8% 38.8% 100.0%); I ^z = 97 0 : <u>M-H,</u>	% dds Ratio <u>Random, 95% CI</u> 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15]		Odds	T1M	
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Sandoval 2017 56 140 18 77 34.6% 2.19 [1.17, 4.09] Total (95% CI) 592 417 100.0% 2.62 [1.81, 3.79] Total events 146 45 Heterogeneity: Tau ² = 0.00; Chi ² = 0.49, df = 1 (P = 0.48); l ² = 0% 0.01 0.1	Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z Figure S22. Fores Study or Subgroup Lopez Cuenca 2016 Sandoval 2014 Sandoval 2017 Total (95% CI) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z Figure S23. Fores	52; Chi ² = = 1.64 (F st Plot. T2MI Events 12 2 16 30 11; Chi ² = = 3.03 (P st Plot. T2MI	2174 = 416. P = 0.1 117 190 140 447 = 3.09, = 0.0	1 57, df = 1 0) /aves T1M Events 156 6 15 157 df = 2 (F 02)	4938 14 (P < 1 0 n EC 1 707 66 77 850 P = 0.21 ific ST	0.00001) CG. <u>Weight</u> 48.4% 12.8% 38.8% 100.0%); I ² = 35); I ² = 97 0 : M-H, ; ; ; ; ; ; ; ; ; ; ;	% dds Ratio <u>Random, 95% CI</u> 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15] 0.38 [0.20, 0.71] 0.38 [0.20, 0.71] n ECG.		Odds M-H, Rand 0.1 0.1 T1MI	T1MI Ratio om, 95	
Total (95% CI) 592 417 100.0% 2.62 [1.81, 3.79] Total events 146 45 Heterogeneity: Tau ² = 0.00; Chi ² = 0.49, df = 1 (P = 0.48); l ² = 0% 0.01 0.1	Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z Figure S22. Fores Study or Subgroup Lopez Cuenca 2016 Sandoval 2014 Sandoval 2017 Total (95% CI) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z Figure S23. Fores Study or Subgroup	52; Chi ² = = 1.64 (F st Plot. T2MI Events 12 2 16 30 11; Chi ² = = 3.03 (P st Plot. T2MI Events	2174 = 416. P = 0.1 117 190 140 447 = 3.09, = 0.0 Nor	1 57, df = 1 0) Vaves T1M Events 156 6 15 157 df = 2 (F 02) D-SPEC T11 Events	4938 14 (P < 1 0 n EC 1 707 66 77 850 P = 0.21 ific ST All Total	0.00001) CG. <u>Weight</u> 48.4% 12.8% 38.8% 100.0%); I ² = 35); I ² = 97	% dds Ratio <u>Random, 95% CI</u> 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15] 0.38 [0.20, 0.71] 0.38 [0.20, 0.71] <u>n ECG.</u> Ddds Ratio <u>Random, 95% CI</u>	0.01	Odds M-H, Rand 0.1 0.1 T1MI	T1MI Ratio om, 95	
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Total events 146 45 Heterogeneity: Tau ² = 0.00; Chi ² = 0.49, df = 1 (P = 0.48); l ² = 0%	Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z Figure S22. Fores <u>Study or Subgroup</u> Lopez Cuenca 2016 Sandoval 2014 Sandoval 2017 Total (95% CI) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z Figure S23. Fores <u>Study or Subgroup</u> Meigher 2016	52; Chi ² = = 1.64 (F st Plot. T2MI Events 12 2 16 30 11; Chi ² = = 3.03 (P st Plot. T2MI Events 90	2174 = 416. P = 0.1 Q V Total 117 190 140 447 = 3.09, = 0.0 Nor I Total 452	1 57, df = 1 0) Vaves T1M Events 156 6 15 177 df = 2 (F 02) 0-Spec T1M Events 27	4938 14 (P < 1 0 n EC 1 707 66 77 850 P = 0.21 ific ST All 340	0.00001) CG. <u>Weight</u> 48.4% 12.8% 38.8% 100.0%); I ² = 35 <u>C Char</u> <u>Weigh</u> 65.4%); I ² = 97	% dds Ratio <u>Random, 95% Cl</u> 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15] 0.38 [0.20, 0.71] 0.38 [0.20, 0.71] n ECG. Ddds Ratio <u>Random, 95% Cl</u> 2.88 [1.83, 4.55]	0.01	Odds M-H, Rand 0.1 0.1 T1MI	Ratio om, 95	
Test for overall effect: 7 = 5 12 (P < 0.00001) 0.01 1	Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z Figure S22. Fores Study or Subgroup Lopez Cuenca 2016 Sandoval 2014 Sandoval 2017 Total (95% CI) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z Figure S23. Fores Study or Subgroup Meigher 2016 Sandoval 2017	52; Chi ² = = 1.64 (F st Plot. T2MI Events 12 2 16 30 11; Chi ² = = 3.03 (P st Plot. T2MI Events 90	2174 = 416. P = 0.1 117 190 140 447 = 3.09, = 0.0 Nor <u>Total</u> 447 447	1 57, df = 1 0) /aves T1M Events 156 6 15 157 (df = 2 (F 02) -spec T11 Events 27 18	4938 14 (P < 1 0 n EC 1 Total 707 66 77 850 P = 0.21 ific ST 41 340 77	0.00001) CG. <u>Weight</u> 48.4% 12.8% 38.8% 100.0%); I ² = 35 <u>C Char</u> 65.4% 34.6%); I ² = 97	% dds Ratio <u>Random, 95% CI</u> 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15] 0.38 [0.20, 0.71] 0.38 [0.20, 0.71] n ECG. Ddds Ratio <u>Random, 95% CI</u> 2.88 [1.83, 4.55] 2.19 [1.17, 4.09]	0.01	Odds M-H, Rand 0.1 0.1 T1MI	Ratio om, 95	
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	Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z Figure S22. Fores <u>Study or Subgroup</u> Lopez Cuenca 2016 Sandoval 2014 Sandoval 2017 Total (95% CI) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z Figure S23. Fores <u>Study or Subgroup</u> Meigher 2016 Sandoval 2017 Total (95% CI) Total events Heterogeneity: Tau ² = 0	52; Chi ² = = 1.64 (F st Plot. T2MI Events 12 2 16 30 11; Chi ² = = 3.03 (P st Plot. T2MI Events 90 56 146 .00; Chi ²	2174 = 416. 2 = 0.1 117 190 140 447 = 3.09, = 0.0 Nor 1 Total 452 140 592 = 0.4§	1 57, df = 1 0) Vaves T1M Events 156 6 15 177 df = 2 (F 02) 0-SPEC T1M Events 27 18 45 9, df = 1 (4938 14 (P < 1 0 n EC 1 Total 707 66 77 850 P = 0.21 ific ST Al 340 77 417	0.00001) CG. Weight 48.4% 12.8% 38.8% 100.0%); I ² = 35 C Char 65.4% 34.6% 100.0%); I ² = 97 O : M-H, ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ;	% dds Ratio <u>Random, 95% CI</u> 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15] 0.38 [0.20, 0.71] 0.38 [0.20, 0.71] n ECG. Ddds Ratio <u>Random, 95% CI</u> 2.88 [1.83, 4.55] 2.19 [1.17, 4.09]	0.01	Odds M-H, Rand	Ratio om, 95	
	Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z Figure S22. Fores <u>Study or Subgroup</u> Lopez Cuenca 2016 Sandoval 2014 Sandoval 2017 Total (95% CI) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z Figure S23. Fores <u>Study or Subgroup</u> Meigher 2016 Sandoval 2017 Total (95% CI) Total events Heterogeneity: Tau ² = 0	52; Chi ² = = 1.64 (F st Plot. T2MI Events 12 2 16 30 11; Chi ² = = 3.03 (P st Plot. T2MI Events 90 56 146 .00; Chi ²	2174 = 416. 2 = 0.1 117 190 140 447 = 3.09, = 0.0 Nor 1 Total 452 140 592 = 0.4§	1 57, df = 1 0) Vaves T1M Events 156 6 15 177 df = 2 (F 02) 0-SPEC T1M Events 27 18 45 9, df = 1 (4938 14 (P < 1 0 n EC 1 Total 707 66 77 850 P = 0.21 ific ST Al 340 77 417	0.00001) CG. Weight 48.4% 12.8% 38.8% 100.0%); I ² = 35 C Char 65.4% 34.6% 100.0%); I ² = 97 O : M-H, ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ;	% dds Ratio <u>Random, 95% CI</u> 0.40 [0.22, 0.75] 0.11 [0.02, 0.54] 0.53 [0.25, 1.15] 0.38 [0.20, 0.71] 0.38 [0.20, 0.71] n ECG. Ddds Ratio <u>Random, 95% CI</u> 2.88 [1.83, 4.55] 2.19 [1.17, 4.09]	0.01	Odds M-H, Rand 0.1 0.1 0.1 0.1	Ratio om, 95	

	T2M	1	T1M	I		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rando	om, 95% Cl	
Lopez Cuenca 2016	12	117	156	707	48.4%	0.40 [0.22, 0.75]				
Sandoval 2014	2	190	6	66	12.8%	0.11 [0.02, 0.54]	-			
Sandoval 2017	16	140	15	77	38.8%	0.53 [0.25, 1.15]			5	
Total (95% CI)		447		850	100.0%	0.38 [0.20, 0.71]		•		
Total events	30		177							
Total events Heterogeneity: Tau ² =		= 3.09	10000	= 0.21	1- 12 = 359	6	0.01	01 1		3

	T2M	I	T1M	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Meigher 2016	90	452	27	340	65.4%	2.88 [1.83, 4.55]	
Sandoval 2017	56	140	18	77	34.6%	2.19 [1.17, 4.09]	
Total (95% CI)		592		417	100.0%	2.62 [1.81, 3.79]	•
Total events	146		45				

	T2M	1	T1N	41		Odds Ratio	Odds	s Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	lom, 95% Cl
Baron 2015	163	1403	1102	17488	34.3%	1.95 [1.64, 2.33]		
Baron 2016	95	1313	1791	40501	30.5%	1.69 [1.36, 2.09]		-
Cediel 2017	40	194	72	376	15.3%	1.10 [0.71, 1.69]	3	• -
Lopez Cuenca 2016	10	117	35	707	6.9%	1.79 [0.86, 3.73]	10	
Nestelberger 2020	9	128	34	684	6.5%	1.45 [0.68, 3.09]	5	-
Troung 2020	21	175	11	275	6.5%	3.27 [1.54, 6.97]		1
Total (95% CI)		3330		60031	100.0%	1.72 [1.40, 2.12]		•
Total events	338		3045					- 22
Heterogeneity: Tau ² =	0.03: Chi ²	= 8.96	df = 5 (F	P = 0.11	$ ^2 = 44\%$		0.01 0.1	1 10 1

	C							
Figure S25. Fore	est Plot. At	rial Fibr	illatio	n on EC	G.			
	T2MI	T1I	IIV		Odds Ratio		Odds Ratio	
Study or Subgroup	Events To	tal Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI	
Baron 2015	394 14	03 1819	17488	75.7%	3.36 [2.97, 3.82]			
Lopez Cuenca 2016		17 49			5.06 [3.07, 8.33]			
Sandoval 2017	22 1	40 3	77	4.0%	4.60 [1.33, 15.90]			
Total (95% CI)	160	60	18272	100.0%	3.70 [2.87, 4.77]		•	
Total events	448	1871						
Heterogeneity: Tau ² =			P = 0.27)); I² = 23%		0.01	0,1 1 10	1
Test for overall effect:	Z = 10.07 (P <	0.00001)				0.01	T1MI T2MI	

T2MI T1MI Odds Ratio Odds Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI	Study or Subgroup Events Total Events Total Weight M-H, Random, 95% C1 M A M A M A	T2MI T1MI Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random								
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T2MI T1MI Odds Ratio Odds Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95%	T2MI T1MI Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random,	T2MI T1MI Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random								
T2MI T1MI Odds Ratio Odds Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95%	T2MI T1MI Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random,	T2MI T1MI Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random	Figure S26 Forest F	Plot Cou	Conari	V Angi	ogran	 Perfor	rmed	
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl M A M A M A <	Study or Subgroup Events Total Events Total Weight M-H, Random, 95% C1 M C10 M C1 M C1	Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl M-H, Random, 95% Cl Arora 2018 68 264 609 775 3.8% 0.09 [0.07, 0.13] - Balanescu 2020 9 9 99 152 3.2% 0.12 [0.05, 0.27] - Cediel 2017 11 194 278 376 3.4% 0.02 [0.01, 0.04] + Conseugra Sanchez 2018 12 75 91 125 3.3% 0.07 [0.03, 0.15] - Furie 2019 22 206 190 3.49 3.7% 0.10 [0.60, 0.16] + Guimares 2018 56 76 711 847 3.6% 0.54 [0.31, 0.92] + Higuchi 2019 427 491 11406 12023 3.9% 0.08 [0.27, 0.46] + Javed 2009 32 64 124 143 3.4% 0.51 [0.80, 0.30] + Javed 2019 425 1140 613 3.7%				, 0	0			bbO
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Troung 2020 175 175 275 275 Not estimable Total (95% CI) 10721 67432 100.0% 0.09 [0.06, 0.12] ♦ Total events 3686 56242 • • • • Heterogeneity: Tau ² = 0.69; Chi ² = 738.32, df = 27 (P < 0.00001); I ² = 96% • • • • Test for overall effect: Z = 14.61 (P < 0.00001)	Troung 2020 175 175 275 275 Not estimable Total (95% CI) 10721 67432 100.0% 0.09 [0.06, 0.12] ♦ Total events 3686 56242 • • • • Heterogeneity: Tau ² = 0.69; Chi ² = 738.32, df = 27 (P < 0.00001); I ² = 96% • • • • Test for overall effect: Z = 14.61 (P < 0.00001)	Troung 2020 175 175 275 275 Not estimable Total (95% CI) 10721 67432 100.0% 0.09 [0.06, 0.12] ♦ Total events 3686 56242 • • • • Heterogeneity: Tau ² = 0.69; Chi ² = 738.32, df = 27 (P < 0.00001); I ² = 96% • • • • Test for overall effect: Z = 14.61 (P < 0.00001)						3.4%	0.03 [0.02, 0.06]	
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Heterogeneity: Tau ² = 0.69; Chi ² = 738.32, df = 27 (P < 0.00001); l ² = 96% Test for overall effect: Z = 14.61 (P < 0.00001) T1MI	Heterogeneity: Tau ² = 0.69; Chi ² = 738.32, df = 27 (P < 0.00001); I ² = 96% Test for overall effect: Z = 14.61 (P < 0.00001) T1MI	Heterogeneity: Tau ² = 0.69; Chi ² = 738.32, df = 27 (P < 0.00001); I ² = 96% Test for overall effect: Z = 14.61 (P < 0.00001) T1MI			10721	50040	67432	100.0%	0.09 [0.06, 0.12]	•
Test for overall effect: Z = 14.61 (P < 0.00001)	Test for overall effect: Z = 14.61 (P < 0.00001)	Test for overall effect: Z = 14.61 (P < 0.00001)			.32. df =		0.00001): ² = 96%		L

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	T2M	1	T1N	11		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rando	om, 95% C
Baron 2016	533	1313	17456	40501	9.6%	0.90 [0.81, 1.01]		
Conseugra Sanchez 2018	4	75	82	125	9.0%	0.03 [0.01, 0.09]		
Furie 2019	7	206	166	349	9.3%	0.04 [0.02, 0.08]		
Javed 2009	25	64	111	143	9.4%	0.18 [0.10, 0.35]		
Lopez Cuenca 2016	78	117	64	707	9.5%	20.09 [12.66, 31.90]		
Putot 2019	238	254	346	365	9.3%	0.82 [0.41, 1.62]		_
Raphael 2020	162	1054	1058	1365	9.6%	0.05 [0.04, 0.07]	-	
Saaby 2014	15	119	236	360	9.4%	0.08 [0.04, 0.14]		
Sandoval 2017	7	140	42	77	9.2%	0.04 [0.02, 0.11]		
Smilowitz 2018	14	146	87	137	9.4%	0.06 [0.03, 0.12]		
Troung 2020	163	175	275	275	6.3%	0.02 [0.00, 0.40]	·	
Total (95% CI)		3663		44404	100.0%	0.16 [0.05, 0.54]	-	
Total events	1246		19923					
Heterogeneity: Tau ² = 4.01; (Chi ² = 989	9.87, df	= 10 (P <	0.0000	1); l ² = 999	%		10
Test for overall effect: Z = 2.9	95 (P = 0.	003)					0.01 0.1 1 T1MI	10 T2MI

	T2M	1	T1N	41		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	om, 95% Cl
Baron 2016	381	1313	11340	40501	22.4%	1.05 [0.93, 1.19]		
Putot 2019	59	254	150	365	21.4%	0.43 [0.30, 0.62]	-	
Saaby 2014	11	119	115	360	19.0%	0.22 [0.11, 0.42]		
Sandoval 2017	1	140	15	77	8.1%	0.03 [0.00, 0.23]	< <u>-</u> →	
Smilowitz 2018	1	146	24	137	8.3%	0.03 [0.00, 0.24]	←	
Troung 2020	140	175	195	275	20.7%	1.64 [1.04, 2.58]		.
Total (95% CI)		2147		41715	100.0%	0.40 [0.19, 0.82]	•	
Total events	593		11839					

	T2M	1	T1M	L		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Cediel 2017	79	194	359	376	14.1%	0.03 [0.02, 0.06]	-
Furie 2019	103	206	195	349	14.7%	0.79 [0.56, 1.12]	-=+
Lambrecht 2018	54	119	180	360	14.6%	0.83 [0.55, 1.26]	-
Saaby 2014	91	119	321	360	14.2%	0.39 [0.23, 0.68]	
Sandoval 2017	72	140	62	77	13.7%	0.26 [0.13, 0.49]	
Shah 2015	122	429	340	1171	15.0%	0.97 [0.76, 1.24]	+
Smilowitz 2018	127	146	114	137	13.7%	1.35 [0.70, 2.60]	
Total (95% CI)		1353		2830	100.0%	0.44 [0.20, 0.96]	•
			1571				

	T2M	1	T1M	1		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
Sandoval 2017	22	140	41	77	49.5%	0.16 [0.09, 0.31]	-	
Smilowitz 2018	75	146	60	137	50.5%	1.36 [0.85, 2.17]	•	
Total (95% CI)		286		214	100.0%	0.48 [0.06, 3.78]		
Total events	97		101					

	T2M	1	T1	II		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% (
Arora 2018	165	264	645	775	4.5%	0.34 [0.25, 0.46]	-
Balanescu 2020	30	49	127	152	3.7%	0.31 [0.15, 0.64]	
Baron 2015	1146	1403	15302	17488	4.6%	0.64 [0.55, 0.73]	-
Baron 2016	1123	1313	36410	40501	4.6%	0.66 [0.57, 0.78]	-
Chapman 2018	126	429	651	1171	4.5%	0.33 [0.26, 0.42]	-
Etaher 2020	83	171	68	97	4.1%	0.40 [0.24, 0.68]	
Furie 2019	141	206	247	349	4.4%	0.90 [0.62, 1.30]	-+
Hawatmeh 2020	165	281	551	664	4.5%	0.29 [0.21, 0.40]	-
Higuchi 2019	236	491	6786	12023	4.6%	0.71 [0.60, 0.86]	-
Kadesjo 2019	169	251	946	1111	4.5%	0.36 [0.26, 0.49]	-
Lopez Cuenca 2016	86	117	614	707	4.2%	0.42 [0.26, 0.67]	
Nestelberger 2020	72	128	548	684	4.3%	0.32 [0.21, 0.47]	-
Radovanovic 2017	595	1091	7396	13828	4.6%	1.04 [0.92, 1.18]	ł
Raphael 2020	766	1054	1215	1365	4.6%	0.33 [0.26, 0.41]	-
Reed 2017	75	162	41	88	4.1%	0.99 [0.59, 1.66]	-+
Saaby 2014	44	119	208	360	4.3%	0.43 [0.28, 0.66]	
Sandoval 2017	81	140	53	77	4.0%	0.62 [0.35, 1.12]	
Sato 2020	53	155	1838	2834	4.4%	0.28 [0.20, 0.40]	-
Shah 2015	124	429	660	1171	4.5%	0.31 [0.25, 0.40]	-
Singh 2020	513	1225	1878	2097	4.6%	0.08 [0.07, 0.10]	-
Smilowitz 2018	70	146	78	137	4.2%	0.70 [0.44, 1.11]	
Stein 2014	91	127	2234	2691	4.3%	0.52 [0.35, 0.77]	-
Troung 2020	159	175	237	275	3.9%	1.59 [0.86, 2.96]	†
Total (95% CI)		9926		100645	100.0%	0.46 [0.34, 0.62]	•
Total events	6113		78733				

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	T2M		T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup					Weight	M-H, Random, 95% CI	
Baron 2015		1403		17488	5.8%	0.59 [0.52, 0.66]	
Baron 2016	945	1313	30781	40501	5.8%	0.81 [0.72, 0.92]	
Chapman 2018	156	429	724	1171	5.6%	0.35 [0.28, 0.44]	
Etaher 2020	57	171	49	97	4.6%	0.49 [0.29, 0.82]	
Hawatmeh 2020	99	281	325	664	5.4%	0.57 [0.43, 0.76]	-
Higuchi 2019	254	491	7531	12023	5.7%	0.64 [0.53, 0.77]	
Kadesjo 2019	118	251	725	1111	5.4%	0.47 [0.36, 0.62]	
Lopez Cuenca 2016	53	117	438	707	5.0%	0.51 [0.34, 0.75]	
Nestelberger 2020	70	128	546	684	5.0%	0.31 [0.21, 0.45]	
Radovanovic 2017	566	1091	7448	13828	5.8%	0.92 [0.82, 1.04]	
Raphael 2020	571	1054	976	1365	5.7%	0.47 [0.40, 0.56]	•
Saaby 2014	38	119	154	360	4.9%	0.63 [0.40, 0.97]	
Sandoval 2017	43	140	39	77	4.3%	0.43 [0.24, 0.77]	
Sato 2020	93	155	2103	2834	5.3%	0.52 [0.37, 0.73]	-
Shah 2015	135	429	735	1171	5.6%	0.27 [0.22, 0.34]	
Singh 2020		1225	1269	2097	5.7%	0.19 [0.16, 0.22]	
Smilowitz 2018	62	146	63	137	4.7%	0.87 [0.54, 1.39]	
Stein 2014	88	127	2126	2691	5.1%	0.60 [0.41, 0.88]	
Troung 2020	147	175	221	275	4.6%	1.28 [0.78, 2.12]	+
Total (95% CI)		9245		99281	100.0%	0.52 [0.41, 0.66]	•
Total events	4692		69684				
Heterogeneity: Tau ² =	0.24; Chi ²	= 363.	88, df = 1	8 (P < 0	.00001); P	² = 95%	0.01 0.1 1 10
Test for overall effect:	Z = 5.52 (P < 0.0	0001)				T1ML T2ML

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	T2M	1	T1N	11		Odds Ratio	Odds F	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rando	m, 95% Cl
Arora 2018	154	264	637	775	4.4%	0.30 [0.22, 0.41]	+	
Balanescu 2020	25	49	128	152	3.9%	0.20 [0.10, 0.40]		
Baron 2015	655	1403	14235	17488	4.5%	0.20 [0.18, 0.22]		
Baron 2016	722	1313	34021	40501	4.5%	0.23 [0.21, 0.26]	•	
Chapman 2018	284	429	896	1171	4.4%	0.60 [0.47, 0.77]	+	
Etaher 2020	92	171	85	97	3.9%	0.16 [0.08, 0.32]		
Furie 2019	163	206	335	349	4.0%	0.16 [0.08, 0.30]		
Guimares 2018	74	76	839	847	2.6%	0.35 [0.07, 1.69]		-
Hawatmeh 2020	156	281	594	664	4.3%	0.15 [0.10, 0.21]	-	
Higuchi 2019	442	491	11662	12023	4.4%	0.28 [0.20, 0.38]	-	
Kadesjo 2019	101	251	918	1111	4.4%	0.14 [0.11, 0.19]	+	
Lopez Cuenca 2016	72	117	64	707	4.2%	16.07 [10.22, 25.27]		_
Nestelberger 2020	36	128	619	684	4.2%	0.04 [0.03, 0.07]	-	
Radovanovic 2017	983	1091	13772	13828	4.3%	0.04 [0.03, 0.05]	-	
Raphael 2020	648	1054	1114	1365	4.4%	0.36 [0.30, 0.43]	+	
Reed 2017	63	162	28	88	4.1%	1.36 [0.79, 2.36]	+	-
Saaby 2014	56	119	269	360	4.2%	0.30 [0.20, 0.46]		
Sandoval 2017	64	140	66	77	3.9%	0.14 [0.07, 0.29]		
Sato 2020	70	155	2562	2834	4.3%	0.09 [0.06, 0.12]	-	
Shah 2015	166	429	910	1171	4.4%	0.18 [0.14, 0.23]	-	
Singh 2020	416	1225	1945	2097	4.4%	0.04 [0.03, 0.05]	+	
Smilowitz 2018	31	146	58	137	4.1%	0.37 [0.22, 0.62]		
Stein 2014	109	127	2610	2691	4.1%	0.19 [0.11, 0.32]		
Troung 2020	160	175	245	275	4.0%	1.31 [0.68, 2.50]	1	_
Total (95% CI)		10002		101492	100.0%	0.24 [0.17, 0.36]	•	
Total events	5742		88612					
Heterogeneity: Tau ² =	0.86; Chi ²	= 1006.	15. df = 2	3 (P < 0.0	00001); l ²	= 98%	0.01 0.1 1	10

	T2M	1	T1N	41		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% Cl
Baron 2015	219	1403	1294	17488	9.1%	2.31 [1.98, 2.70]		
Baron 2016	236	1313	3240	40501	9.1%	2.52 [2.18, 2.91]		•
Chapman 2018	44	429	33	1171	8.5%	3.94 [2.47, 6.28]		
Furie 2019	24	206	42	349	8.3%	0.96 [0.57, 1.64]		+
Lopez Cuenca 2016	44	117	89	707	8.6%	4.19 [2.71, 6.47]		-
Radovanovic 2017	801	1091	11774	13828	9.1%	0.48 [0.42, 0.56]		•
Raphael 2020	239	1054	167	1365	9.0%	2.10 [1.69, 2.61]		-
Sandoval 2017	20	140	3	77	5.7%	4.11 [1.18, 14.31]		
Sato 2020	24	155	327	2834	8.5%	1.40 [0.90, 2.20]		+-
Shah 2015	52	429	35	1171	8.6%	4.48 [2.87, 6.98]		
Smilowitz 2018	11	146	11	137	7.1%	0.93 [0.39, 2.23]		-
Troung 2020	24	175	33	275	8.2%	1.17 [0.66, 2.05]		+
Total (95% CI)		6658		79903	100.0%	1.90 [1.17, 3.10]		◆
Total events	1738		17048					
Heterogeneity: Tau ² =	0.67; Chi ²	= 401.	15, df = 1	1 (P < 0)	.00001); l ²	² = 97%	0.01	0.1 1 10

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Baron 2015 1041 1403 16194 17488 17.5% 0.23 [0.20, 0.26] Baron 2016 1050 1313 38476 40501 17.5% 0.21 [0.18, 0.24]	M-H, Random, 95% Cl
Baron 2016 1050 1313 38476 40501 17.5% 0.21 [0.18, 0.24]	
Chapman 2018 77 429 143 1171 17.0% 1.57 [1.16.2.13]	
	-
Nestelberger 2020 13 128 168 684 15.5% 0.35 [0.19, 0.63]	
Smilowitz 2018 86 146 101 137 16.0% 0.51 [0.31, 0.85]	2
Troung 2020 55 175 67 275 16.5% 1.42 [0.93, 2.17]	-
Total (95% CI) 3594 60256 100.0% 0.51 [0.26, 1.00]	•
Total events 2322 55149	5-539

	T2M		T1N	11		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI	
Baron 2015	706	1403	5666	17488	22.0%	2.11 [1.89, 2.36]			
Baron 2016	315	1313	4860	40501	21.6%	2.31 [2.03, 2.64]			
Etaher 2020	53	171	9	97	7.1%	4.39 [2.06, 9.38]			
Lopez Cuenca 2016	70	117	230	707	14.1%	3.09 [2.07, 4.62]		-	
Raphael 2020	831					1.41 [1.17, 1.71]		-	
Sato 2020	0	155		2834	0.7%	0.38 [0.02, 6.36]			
Troung 2020	67	175	99	275	14.4%	1.10 [0.75, 1.63]		1	
Fotal (95% CI)		4388		63267	100.0%	1.99 [1.56, 2.53]		•	
Total events	2042		11877						
Heterogeneity: Tau ² =				P < 0.00	0001); l² =	84%	0.01	0.1 1 10	
Test for overall effect:	Z = 5.56 (P < 0.0	0001)					T1MI T2MI	

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	T2M	1	T1N	11		Odds Ratio	Odds R	atio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Randon	n, 95% CI
Arora 2018	153	264	646	775	6.0%	0.28 [0.20, 0.37]	-	
Balanescu 2020	29	49	131	152	5.1%	0.23 [0.11, 0.48]		
Baron 2015	926	1403	15040	17488	6.3%	0.32 [0.28, 0.36]	-	
Baron 2016	972	1313	37261	40501	6.3%	0.25 [0.22, 0.28]		
Chapman 2018	204	429	872	1171	6.1%	0.31 [0.25, 0.39]	+	
Etaher 2020	95	171	81	97	5.4%	0.25 [0.13, 0.46]		
Furie 2019	125	206	280	349	5.9%	0.38 [0.26, 0.56]	-	
Hawatmeh 2020	141	281	578	664	6.0%	0.15 [0.11, 0.21]	+	
Higuchi 2019	298	491	9238	12023	6.2%	0.47 [0.39, 0.56]	-	
Kadesjo 2019	92	251	883	1111	6.1%	0.15 [0.11, 0.20]		
Lopez Cuenca 2016	92	117	648	707	5.6%	0.34 [0.20, 0.56]		
Nestelberger 2020	39	128	606	684	5.8%	0.06 [0.04, 0.09]	-	
Raphael 2020	570	1054	1167	1365	6.2%	0.20 [0.16, 0.24]	-	
Sato 2020	112	155	2303	2834	5.9%	0.60 [0.42, 0.86]	-	
Singh 2020	255	1225	1840	2097	6.2%	0.04 [0.03, 0.04]	*	
Smilowitz 2018	83	146	100	137	5.7%	0.49 [0.30, 0.80]		
Troung 2020	158	175	241	275	5.4%	1.31 [0.71, 2.43]	+	_
Total (95% CI)		7858		82430	100.0%	0.25 [0.17, 0.36]	•	
Total events	4344		71915					
Heterogeneity: Tau ² =	0.57; Chi ²	= 583.0	06, df = 1	6 (P < 0	.00001); l ²	² = 97%	0.01 0.1 1	10

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	T2M		T1M	1		Odds Ratio		Odds	Ratio
tudy or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl		M-H, Rand	
rora 2018	32	264	363	775	4.7%	0.16 [0.11, 0.23]		+	
alanescu 2020	0	0	0	0		Not estimable			
aron 2015	175	1403	10598	17488	4.9%	0.09 [0.08, 0.11]		-	
aron 2016	723	1313	34264	40501	4.9%	0.22 [0.20, 0.25]		•	
hapman 2020	17	1121	2021	4981	4.6%	0.02 [0.01, 0.04]	-	-	
taher 2020	7	171	12	97	4.0%	0.30 [0.11, 0.80]			
urie 2019	3	206	128	349	3.6%	0.03 [0.01, 0.08]	+	_	
Suimares 2018	27	76	440	847	4.6%	0.51 [0.31, 0.83]			
liguchi 2019	258	491	9206	12023	4.9%	0.34 [0.28, 0.41]		-	
andes 2016	14	107	85	107		0.04 [0.02, 0.08]	_	- 1	
opez Cuenca 2016	11	117	486	707		0.05 [0.02, 0.09]	-	-	
lestelberger 2020	1	128	457	684	2.4%	0.00 [0.00, 0.03]	←		
leumann 2017	0	99	126	188	1.6%	0.00 [0.00, 0.04]		-	
aiva 2015	27	236	507	764		0.07 [0.04, 0.10]		-	
Putot 2018	103	847	1519	2036	4.9%	0.05 [0.04, 0.06]		+	
Putot 2019	29	254	235	365		0.07 [0.05, 0.11]			
adovanovic 2017	557	1091	11684	13828		0.19 [0.17, 0.22]			
aphael 2020	77	1054	791	1365		0.06 [0.04, 0.07]		+	
aaby 2014	4	119	194	360	3.9%	0.03 [0.01, 0.08]	_	_	
andoval 2017	1	140	34	77	2.4%	0.01 [0.00, 0.07]	+	_	
hah 2015	1	429	564	1171	2.4%	0.00 [0.00, 0.02]	1.00		
ingh 2020	27	1225	1786	2097	4.7%	0.00 [0.00, 0.01]			
milowitz 2018	8	146	53	137		0.09 [0.04, 0.20]			
tein 2014	64	127	2199	2691	4.8%	0.23 [0.16, 0.33]		-	
roung 2020	101	175	257	275	4.5%	0.10 [0.05, 0.17]		+	
otal (95% CI)		11339		103913	100.0%	0.06 [0.04, 0.10]		•	
otal events	2267		78009						
leterogeneity: Tau ² =	0.99; Chi ² :	= 982.8		(P < 0.0)	0001); l ² = 9	8%	0.01	0.1 1	1 10
est for overall effect:							0.01		T2MI
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	T2M	1	T1N	41		Odds Ratio	Odds R	atio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random	n, 95% Cl
Arora 2018	4	264	91	775	9.2%	0.12 [0.04, 0.32]		
Baron 2015	15	1403	909	17488	11.3%	0.20 [0.12, 0.33]	A Ter State	
Baron 2016	68	1313	2673	40501	12.1%	0.77 [0.60, 0.99]	-	
Etaher 2020	8	171	15	97	9.7%	0.27 [0.11, 0.66]	- (*)	
Furie 2019	0	206	16	349	3.4%	0.05 [0.00, 0.82]		
Guimares 2018	7	76	73	847	10.1%	1.08 [0.48, 2.43]		-82
Landes 2016	8	107	33	107	10.0%	0.18 [0.08, 0.42]	8. 3 8	
Lopez Cuenca 2016	0	117	28	707	3.4%	0.10 [0.01, 1.67]	· · · · · · · · · · · · · · · · · · ·	
Nestelberger 2020	0	128	59	684	3.4%	0.04 [0.00, 0.67]	· · · ·	
Putot 2019	4	254	29	365	9.0%	0.19 [0.06, 0.53]		
Saaby 2014	0	119	9	360	3.3%	0.15 [0.01, 2.68]	· · · ·	-0
Sandoval 2017	0	140	3	77	3.1%	0.08 [0.00, 1.49]	· · · · · ·	
Shah 2015	3	429	56	1171	8.5%	0.14 [0.04, 0.45]		
Stein 2014	0	127	16	2691	3.4%	0.64 [0.04, 10.66]	-	
Total (95% CI)		4854		66219	100.0%	0.23 [0.12, 0.42]	•	
Total events	117		4010					

Figure S40. All ca	ause In-	hosp	ital mo	ortalit	y. T2M	compared to T1	MI.
	T2M		T1M	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Furie 2019	21	206	33	349	7.1%	1.09 [0.61, 1.93]	+
Higuchi 2019	54	491	769	12023	8.2%	1.81 [1.35, 2.42]	-
Javed 2009	9	64	15	143	5.7%	1.40 [0.58, 3.38]	- -
Lopez Cuenca 2016	6	117	41	707	5.7%	0.88 [0.36, 2.12]	
Meigher 2016	54	452	37	340	7.6%	1.11 [0.71, 1.73]	+-
Paiva 2015	23	236	66	764	7.4%	1.14 [0.69, 1.88]	+-
Putot 2018	133	847	125	2036	8.3%	2.85 [2.20, 3.69]	-
Putot 2019	38	254	24	365	7.2%	2.50 [1.46, 4.28]	
Putot 2020	95	862	186	3710	8.3%	2.35 [1.81, 3.04]	-
Saaby 2014	29	119	10	360	6.3%	11.28 [5.30, 24.00]	
Singh 2020	160	1225	42	2097	8.0%	7.35 [5.19, 10.41]	
Smilowitz 2018	17	146	18	137	6.5%	0.87 [0.43, 1.77]	-+-
Stein 2014	15	127	113	2691	7.1%	3.06 [1.73, 5.41]	
Troung 2020	13	175	29	275	6.6%	0.68 [0.34, 1.35]	-+
Total (95% CI)		5321		25997	100.0%	1.94 [1.35, 2.79]	•
Total events	667		1508				
Heterogeneity: Tau ² =	0.40; Chř	= 115.0	87, df = 1	3 (P < 0	.00001); P	²= 89%	
Test for overall effect: 2	Z = 3.58 (I	P = 0.0	003)				0.01 0.1 1 10 Favours T1MI Favours T2M

	T2M		T1M	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Nestelberger 2020	1	128	42	684	10.4%	0.12[0.02, 0.88]	
Sandoval 2014	51	190	15	66	29.6%	1.25 [0.65, 2.41]	
Sandoval 2017	18	140	6	77	23.4%	1.75 [0.66, 4.60]	+
Shah 2015	134	429	187	1171	36.7%	2.39 [1.85, 3.09]	
Total (95% CI)		887		1998	100.0%	1.34 [0.63, 2.85]	•
Total events	204		250				
Heterogeneity: Tau ² = 1	0.38; Chř	= 12.1	1. df = 3 (P = 0.0	007); I ² = 7	5%	
Test for overall effect: 2	Z = 0.77 (F	P = 0.4	4)				0.01 0.1 1 10 Favours T1MI Favours T2M

	T2M	1	T1M	1		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
Cediel 2017	77	194	74	376	19.0%	2.69 [1.83, 3.94]	-	
Guimares 2018	19	76	156	847	15.9%	1.48 [0.85, 2.55]		
Neumann 2017	14	99	18	188	12.5%	1.56 [0.74, 3.28]		
Paiva 2015	62	236	92	764	19.3%	2.60 [1.81, 3.74]	-	
Smilowitz 2018	45	146	41	137	16.6%	1.04 [0.63, 1.73]	+	
Troung 2020	29	175	47	275	16.6%	0.96 [0.58, 1.60]	+	
Total (95% CI)		926		2587	100.0%	1.63 [1.11, 2.41]	•	
Total events	246		428					
Heterogeneity: Tau ² =	0.17; Chr	= 19.1	D, df = 5 (P = 0.0)02); I ² = 7	4%		
Test for overall effect:	Z = 2.48 (I	P = 0.0	1)				0.01 0.1 1 10 1 Favours T1MI Favours T2MI	

	T2M	1	T1M			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
<adesjo 2019<="" td=""><td>101</td><td>251</td><td>259</td><td>1111</td><td>36.0%</td><td>2.21 [1.66, 2.95]</td><td>-</td></adesjo>	101	251	259	1111	36.0%	2.21 [1.66, 2.95]	-
ambrecht 2018	74	119	114	360	32.9%	3.55 [2.30, 5.47]	
Sato 2020	18	155	337	2834	31.1%	0.97 [0.59, 1.61]	+
Total (95% CI)		525		4305	100.0%	2.00 [1.07, 3.76]	•
Fotal events	193		710				

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PRISMA 2020 Checklist

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1 2 PRIS	SMA 2	020 Checklist	
3 4 Section and 5 Topic	ltem #	Checklist item	Location where item is reported
6 TITLE		9 9	
7 Title	1	Identify the report as a systematic review.	1
8 ABSTRACT	-	e 0 0	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
	1	۲ ۲	
12 Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
13 Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
¹⁴ METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
¹⁰ Information ¹⁷ sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to dentify studies. Specify the date when each source was last searched or consulted.	4
19 Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supp
20 Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reverse screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
22 Data collection 23 process 24	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
25 Data items 26	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each autcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
27 28	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
29 Study risk of bias30 assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how may reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5
³ Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5
32 33 Synthesis 34 methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5
34 35 36	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5
37	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5
38 39	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5
40	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysie, meta-regression).	5
41	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
42 43 Reporting bias 43 assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5
44 45 Certainty	15	Describe any methods used topassess/centainty (ortopr/fidenjce) in the body of evidence/for are butsomerni	N/A

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PRISMA 2020 Checklist

		BMJ Open	Page 62 c
	SMA 2	020 Checklist	
PRIS			
Section and	ltem		Location
Topic	#	Checklist item 57	where iten is reported
assessment		01 01	
RESULTS	<u> </u>		
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the real mathematical sector of studies included in the review, ideally using a flow diagram.	5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5
Study characteristics	17	Cite each included study and present its characteristics.	Supp
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supp
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effed estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supp
Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supp
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Supp
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Supp
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	7
	23b	Discuss any limitations of the evidence included in the review.	9
	23c	Discuss any limitations of the review processes used.	9
	23d	Discuss implications of the results for practice, policy, and future research.	9
OTHER INFORMA	TION	4 	
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A





10.1136/bmj.n71

PRISMA 2020 Checklist

For more information, visit: http://www.prisma-statement.org/

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Diagnostic features, management, and prognosis of Type 2 myocardial infarction compared to Type 1 myocardial infarction: A systematic review and meta-analysis.

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Secondary Subject Heading:	Cardiovascular medicine, Diagnostics			
Keywords:	Coronary heart disease < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY			





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Title Page

Manuscript Title

Diagnostic features, management, and prognosis of Type 2 myocardial infarction compared to Type 1 myocardial infarction: A systematic review and meta-analysis.

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Manuscript Word Count

Abstract

Importance

Distinguishing type 2 (T2MI) from type 1 myocardial infarction (T1MI) in clinical practice can be difficult, and the management and prognosis for T2MI remain uncertain.

Objective

To compare precipitating factors, risk factors, investigations, management, and outcomes for T2MI and T1MI.

Data Sources

MEDLINE and EMBASE databases as well as reference list of recent articles were searched January 2009 to December 2020 for term "type 2 myocardial infarction".

Study Selection

Studies were included if they analysed if universal definition of MI was used and reported quantitative data on at least one variable of interest.

Data Extraction and Synthesis

Data was pooled using random-effect meta-analysis. Risk of bias was assessed using Newcastle-Ottawa Quality Assessment Form. Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA) guidelines were followed. All review stages were conducted by two reviewers.

Main Outcomes and Measures

Risk factors, presenting symptoms, cardiac investigations such as troponin and angiogram, management, and outcomes such as mortality.

Results

40 cohort studies comprising 98,930 T1MI and 13,803 T2MI patients were included. Compared to T1MI, T2MI patients were: more likely to have pre-existing chronic kidney (OR 1.87; 95%CI 1.53-2.28) and chronic heart failure (OR 2.35; 95%CI 1.82-3.03), less likely to present with typical cardiac symptoms of chest pain (OR 0.19; 95%CI 0.13-0.26) and more likely to present with dyspnoea (OR 2.64; 95%CI 1.86-3.74); more likely to demonstrate non-specific ST-T wave changes on electrocardiography (OR 2.62; 95%CI 1.81-3.79) and less likely to show ST elevation (OR 0.22; 95%CI 0.17-0.28); less likely to undergo coronary angiography (OR 0.09; 95%CI 0.06-0.12) and percutaneous coronary intervention (OR 0.09; 95%CI 0.06-0.12) or receive cardioprotective medications, such as statins (OR 0.25; 95%CI 0.16-0.38) and beta-blockers (OR 0.45; 95%CI 0.33-0.63). T2MI had more risk of all cause one-year mortality (OR 3.11; 95%CI 1.91-5.08), with no differences in short-term mortality (OR 1.34; 95%CI 0.63-2.85).

Conclusion and Relevance

This review has identified clinical, management and survival differences between T2MI and T1MI with greater precision and scope than previously reported. Differential use of coronary

revascularisation and cardioprotective medications highlight ongoing uncertainty of their utility in T2MI compared to T1MI.

Strength and Limitations

- Inclusion of all contemporary cohort studies in the troponin era
- Large patient population of T2MI and T1MI patients analysed allowing high level of precision
- rcally s_{ιδ} mortality only . Wide array of clinically significant variables assessed providing a comprehensive analysis •
- Analysis of crude mortality only was possible due to lack of individual patient data •

Introduction

The clinical definition of myocardial infarction has evolved over time. The 2007 Universal Definition of Myocardial Infarction included a subset of MI that was secondary to aetiologies unrelated to underlying occlusive coronary artery disease (1). In 2012, the Third Universal Definition of Myocardial Infarction Consensus Document (2) gave rise to the aetiological distinction between T1MI, defined as MI due to plaque erosion and/or rupture, and T2MI, defined as MI caused by increased oxygen demand or decreased blood supply, in the absence of acute plaque rupture or coronary thrombosis. More recently, in 2018, the Fourth Universal definition of MI updated concepts of T2MI regarding specific situations associated with oxygen demand and supply imbalance and the relevance of the presence or absence of underlying coronary artery disease to therapy and prognosis (3). (see on-line supplement Table S1 for more detail)

In clinical practice, distinguishing T2MI from T1MI based on clinical presentation, electrocardiograph (ECG) features and cardiac troponin (cTn) values can be difficult. In the absence of randomised controlled trials that have evaluated different investigational and therapeutic interventions in patients with T2MI, uncertainty remains around the appropriate management of such patients, particularly those with known or suspected coronary artery disease. Past reviews have assessed one or more attributes of T2MI in comparison to T1MI (4-8) but, to our knowledge, none have undertaken a comprehensive analysis of symptoms, physical signs, investigation results, management regimens and clinical outcomes, both short and long term, of T2MI versus T1MI.

We undertook a systematic review of observational studies with the aims of identifying diagnostic and investigational findings which can assist clinicians to better distinguish T2MI from T1MI, and compare T2MI with T1MI in defining differences in management strategies and clinical outcomes.

Methods

Study design

The review was undertaken in accordance with recommendations of the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (9). Our review was registered on PROSPERO prior to commencement (Registration number: CRD42021237746). MEDLINE and EMBASE databases were searched for all studies published between January 1st, 2009, and December 31st, 2020, using search terms to identify all studies related to T2MI (see Table S2). Reference lists of all relevant articles were also assessed to identify additional relevant studies. The study PRISMA flowchart is shown in Figure S1. January 2009 was chosen as the start date for the literature search in order to restrict our analyses to contemporary studies in the troponin era that employed formal definitions of T2MI which were only devised from 2007 onwards.

Studies were included if they: 1) compared patient populations with T2MI and T1MI, 2) used a universal definition of MI, 3) included at least one variable of interest, 4) were available as full text in English and 5) were either a randomised control trial or comparative observational study. Studies were excluded if: 1) no full text was available, 2) duplicate data was utilised or 3) less than 200 participants in total were included. Initial screening of titles and abstracts for eligible studies was

performed independently by two authors (MK, KW), as was full text review for inclusion, with any differences in review settled by consensus agreement.

Data collection and synthesis

 Data pertaining to all variables of interest were collected from all included studies using a standardised proforma by one author (MK) and independently reviewed by the second author (KW). These variables comprised: study dates, design, sample size, definition used to define T2MI and T1MI, patient demographics, pre-existing medical conditions, precipitating factors, clinical symptoms, ECG findings, laboratory values, echocardiographic results, any clinical interventions or medical treatments administered, and clinical outcomes observed.

Data on variables reported as, or able to be converted to, raw numbers, were pooled from all studies and subject to comparative meta-analysis using Review Manager (RevMan, Computer program. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For each variable, the odds ratio (OR) comparing T2MI to T1MI, and its 95% confidence interval (CI), was calculated and weighted using the random effects method. As specified in the registered study protocol, the random effects method was used in anticipation of study heterogeneity of at least moderate degree (I² statistic of heterogeneity >50%) (10). In addition to the weighted OR, we also report the crude total event rates for each variable subject to meta-analysis in order to provide a more clinically meaningful estimate of the prevalence of these events in each patient group in view of the large sample sizes. Studies reporting mean or median values only were reproduced as reported in the original study.

Risk of bias within each study was assessed using the Newcastle-Ottawa quality assessment tool for cohort studies (11, 12), with scores 7-8 denoting good quality studies, 4-6 fair quality, and 0-3 poor quality.

Patient and Public Involvement

We did not seek patient or public comment in designing the study.

Results

A total of 40 studies were included for analysis (13-52) and their characteristics are summarised in Table S3. They comprised a total of 127,620 participants of whom 98,930 participants (77.5%) were classified as T1MI and 13,803 (10.8%) as T2MI. In the following text, we report key findings; more information and forest plots for each analysis involving more than one study and more than 100 total cases can be found in the on-line supplement, Figures S2-S44.

The 2007 definition (1) was used in 7 (17.5%) studies (15, 16, 27, 29, 43, 44, 51, 53), the 2012 definition (2) in 25 (62.5%) studies (13, 17, 19-21, 23-26, 30-35, 37, 39, 40, 42, 45-48, 50, 52), and the 2018 definition (3) in 8 (20%) studies (14, 18, 22, 28, 36, 38, 41, 49). Of the 40 studies, 17 (42.5%) were prospective (15, 16, 18, 19, 22, 29, 33, 34, 36, 37, 43, 44, 46-48, 50, 51, 53) and 23 (57.5%) were retrospective (13, 14, 17, 20, 21, 23-28, 30-32, 35, 38-42, 46, 49, 52).

Risk of bias assessment

Of the 40 studies, 31 (77.5%) were assessed as good quality (13, 15-19, 22, 23, 27-35, 37-46, 48, 52, 53), 6 (15%) as fair quality (14, 24-26, 49), and 3 (7.5%) as poor quality (20, 36, 47), as summarised in Table S4. Selection bias resulting in unrepresentative cohorts such as admission criteria to coronary care units or entry criteria into MI registries favouring T1MI (14, 20, 24-26, 36, 47, 49), absence of independent adjudication of MI type as T1MI or T2MI (36, 38, 47), non-comparability of T1MI and T2MI cohorts (20, 24, 25, 47), poorly specified outcome measures (36, 38, 47) and short follow-up period resulting in few events (14, 20, 24, 36) comprised most forms of bias.

Participant characteristics

Patients with T1MI had a median age range of 60-82 years in the included studies that did not select a specific age population, compared to a median age range of 62-81 years in patients with T2MI. The sex distribution was also similar, with 58.4% and 53% of patients with T1MI and T2MI being male respectively.

Regarding pre-existing medical conditions (Table 1), T2MI patients compared to T1MI patients were more likely to have chronic kidney disease (22.8% vs 17.3%; OR 1.87; 95%CI 1.53-2.28), chronic heart failure (13.1% vs 7.6%; OR 2.35; 95%CI 1.82-3.03), atrial fibrillation (22.9% vs 6.1%; OR 3.02; 95%CI 2.29-3.99), and hypertension (66.4% vs 63.4%; OR 1.22; 95%CI 1.03-1.45). Patients with T2MI were less likely to have dyslipidaemia (43.4% vs 45.9%; OR 0.74; 95%CI 0.58-0.94) and smoking history (34.7% vs 52.8%; OR 0.6; 95%CI 0.49-0.73). There was no difference in the prevalence of type 2 diabetes mellitus or ischaemic heart disease between the two groups.

Precipitating factors

Less than half of the studies (n=17; 43%) included data on precipitating factors associated with T2MI (13, 15, 17, 19, 21-24, 27, 31, 32, 35, 40, 44, 45, 50, 51, 53). Data on each precipitating factor was not consistently available across the studies, for example only 17 studies representing 45% of T2MI patients assessed presence of arrythmia

The most common precipitants were sepsis (35.9%) and heart failure (35.9%, followed by arrythmia (29.8%) (Table S5), with non-cardiac surgery being deemed a cause in 12.2% of cases where data for this variable were collected.

Presenting clinical features

As summarised in Table S6, compared to T1MI patients, T2MI patients were less likely to present with typical cardiac symptoms of chest pain (58.6% vs 88.4%; OR 0.19; 95%CI 0.13-0.26) or discomfort in the arm or shoulder (8.5% vs 35%; OR 0.18; 95%CI 0.11-0.3), but more likely to present with dyspnoea (27.1% vs 10.6%; OR 2.64; 95%CI 1.86-3.74).

Investigations

ECG findings on presentation (Table S7) such as ST elevation (14.1% vs 44.2%; OR 0.22; 95%CI 0.17-0.28) and pathological Q waves (6.7% vs 20.8%; OR 0.38; 95%CI 0.20-0.71) were less evident in T2MI than in T1MI. In contrast, non-specific ST-T wave changes (24.7% vs 10.8%; OR 2.62; 95%CI 1.81-3.79), and atrial arrythmias (21% vs 6.6%; OR 4.99; 95%CI 3.14-7.93) were more common among T2MI. No differences between groups were seen in the frequency of ST depression or T wave inversion. Among the 40 studies, four studies (10%) reported the use of high-sensitivity cardiac troponin (cTn) assays, 21 (53%) reported sensitive assays, and 14 (35%) did not specify what generation assay was used (Table S3b). The results of troponin assays were reported in 26 (65%) studies, specific to cTnI assays in 19 studies, cTnT in 5, both assays in one, while another did not specify the assay used. Only two of these studies reporting troponin failed to state the upper limit of normal (ULN) of the assay used (23, 31). The troponin assays, and therefore units and reference ranges, varied between the studies, preventing direct comparison of troponin values. As a result, we converted troponin values to a multiple of the upper limit of normal for each assay to allow direct comparison (Table S8). For peak troponin, patients with T1MI had a higher and wider range of between 5 and 1702 times the ULN compared to patients with T2MI with a range of 2.8-447 times the ULN. Studies yielded mixed results as to whether the magnitude of change (or delta) in serial cardiac troponin assays was more predictive of T2MI or T1MI compared to absolute values of peak levels (33). Lowering the diagnostic threshold for troponin with the advent of more sensitive assays has increased the numbers of patients identified with T2MI by up to 50% (36), with more recent studies showing the incidence of T2MI equalling or exceeding that of T1MI (15, 33, 36).

Echocardiography was less frequently performed among T2MI than T1MI patients (47.9% vs 55.5%; OR 0.44; 95%CI 0.20-0.96) and when reported (Table S7), there was no difference in the prevalence of regional wall motion abnormalities or the level of left ventricular (LV) function, with reported median LV ejection fraction being 42.3%-55% in T1MI patients and 40%-56% in T2MI patients.

Coronary angiography was also less frequently performed among T2MI than in T1MI patients (34.1% vs 85.5%; OR 0.09; 95%CI 0.06-0.12, Table S7). When performed, T2MI patients were less likely to demonstrate obstructive coronary artery disease (34% vs 44.9%; OR 0.16; 95%CI 0.05-0.54), with obstruction variously defined as 50%-70% occlusion of one or more vessels.

Management

 T2MI patients, compared to T1MI patients, were significantly less likely to receive conventional cardioprotective medications (Table 2), comprising beta-blockers (58.3% vs 76.3%; OR 0.45; 95%CI 0.33-0.63), anti-platelet agents (70.8% vs 88.5%; OR 0.24; 95%CI 0.16-0.38) and statins (52.9% vs 87.6%; OR 0.25; 95%CI 0.16-0.38). Of note, T2MI patients were more likely to receive diuretics (44.8% vs 13.6%; OR 1.98; 95%CI 1.37-2.86) or anti-coagulants (28.9% vs 25.2%; OR 1.87; 95%CI 1.06-3.30).

Percutaneous coronary intervention (PCI) (21.1% vs 78%; OR 0.06; 95%CI 0.04-0.10) and coronary artery bypass surgery (2.9% vs 6.4%; OR 0.23; 95%CI 0.12-0.45) were also significantly less likely to be performed in T2MI patients than T1MI patients.

Prognosis

T2MI patients had significantly increased risk of all-cause death compared to patients with T1MI in both short- and long-term follow-up (Table 3). Specifically, compared to T1MI patients, T2MI demonstrated increased all-cause mortality in-hospital (12.5% vs 5.8%; OR 1.94; 95%CI 1.35-2.79, Figure S40), at one-year (18.9% vs 5.4%; OR 3.11; 95%CI 1.91-5.08, Figure 1) and at 5 to 10 years, (53.7% vs 28.5%, OR 3.24; 95%CI 2.73-3.84, Figure 2). In contrast, there were no differences

between T2MI and T1MI patients in the risk of short-term mortality at 120-180 days (23.0% vs 12.5%; OR 1.34; 95%CI 0.63-2.85).

Discussion

To our knowledge, this is the most comprehensive systematic review and meta-analysis of contemporary studies comparing T2MI with T1MI in the troponin era, comprising 127,620 patients from 40 cohort studies across 14 countries, and which used formal definitions of T2MI and T1MI. Up to three quarters of all myocardial infarctions in routine care can be T2MI (33, 34), and distinguishing T2MI from T1MI on clinical criteria is often challenging. The management strategies used by clinicians in real-world practice for T2MI often vary, and the clinical outcomes of T2MI compared to T1MI, particularly over the long term, have been uncertain. This review provides information that helps characterise these two groups of patients according to multiple variables and which may assist in clinical decision-making and prognostication.

In this review, T2MI patients demonstrated more medical comorbidities than T1MI patients, as noted in a recent meta-analysis (6). Our review highlighted the much higher incidence of pre-existing generalised vascular disease, atrial fibrillation, renal impairment, and heart failure among T2MI patients.

Sepsis (10, 16, 27) and anaemia (51) ranked highly as triggers, together with other acute cardiac events such as valve dysfunction or arrhythmias. In one study, a more favourable prognosis in T2MI was seen when the principal trigger was arrhythmia compared to non-cardiac surgery, hypotension, anaemia or hypoxia (29). In another study, shock syndromes were triggers portending a worse prognosis compared to all other triggers (32). In our analysis, non-cardiac surgery as a trigger was less frequent than reported by other investigators (26) whereby peri-operative stressors including blood loss, anaesthesia induced hypotension and wound infections cause imbalance in myocardial contractility, oxygen demand and blood flow (54).

Analysis of cTn levels showed uniformly higher values in T1MI than T2MI which accord with one review (5) reporting cTn values 30% to 94% higher in patients with T1MI, and which other investigators regard as being highly specific diagnostic markers for T1MI (54).

Coronary angiography and revascularisation were both performed much less frequently in T2MI than in T1MI patients. Treating physicians may perceive invasive strategies as being contraindicated or potentially harmful in the presence of various co-morbidities more commonly seen in T2MI and associated with competing mortality risk. In our pooled data, only one in three T2MI patients who underwent angiography demonstrated obstructive coronary artery disease, although this figure may be an underestimate due to selection bias whereby younger, less multi-morbid patients preferentially underwent angiography. In the CASABLANCA cohort study, which enrolled patients with high likelihood of coronary or peripheral artery disease and subjected them to peripheral or coronary angiography, of all those who subsequently suffered incident T2MI, almost half (47.7%) demonstrated ≥70% stenosis in at least 2 major coronary arteries (55). These conflicting findings question whether patients presenting with T2MI would benefit from routine use of invasive strategies that define coronary anatomy and, if plaque rupture or critical stenoses are seen, prompt revascularisation, with resultant improvement in patient outcomes. In one study (18), angiography

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unmasked acute plaque rupture in 29% of patients classified as T2MI. In another study, among 27 of 236 patients with T2MI who underwent revascularisation, the odds of all-cause death were reduced by 67% compared to the remaining 209 non-revascularised patients (23). In contrast, in a third more rigorous study comparing T2MI versus T1MI patients who received or did not receive PCI within 24 hours of symptom onset, after adjusting results using multivariate logistic regression analysis and inverted probability weighting,(15) in-hospital mortality was lower in those with T1MI receiving PCI (OR 0.47; 95% CI 0.40–0.55; p < 0.001), but not in those with T2MI receiving PCI (OR 1.09; 95% CI 0.62–1.94; p = 0.763). However, all these studies are observational, so completion of randomised trials, such as the Appropriateness of Coronary investigation in myocardial injury and Type 2 myocardial infarction (ACT-2) trial, which is currently in recruitment (54), will hopefully provide a more definitive answer.

Given that a third of T2MI patients had pre-existing coronary artery disease and most of the remainder had one or more cardiovascular risk factors, the relative underuse of cardioprotective medications is perplexing. It may reflect either clinician uncertainty around their cardioprotective utility in T2MI, or concerns about the potential for adverse interactions with other drugs or diseases commonly seen in multi-morbid T2MI patients. The higher use of diuretics in the T2MI population likely reflects the higher prevalence of heart failure and hypertension. Recognizing the heterogeneous mechanisms or conditions leading to T2MI, a phenotype specific-approach to the design of future trials will be useful in identifying effective therapies.

An important finding is the much higher all-cause in-hospital and one-year mortality in T2MI compared to T1MI patients, similar to the two-fold greater mortality rate in T2MI noted in a recent systematic review of 9 studies (8). In our review, this excess mortality was not driven by an excess of cardiovascular deaths, and likely reflects the competing risks of multiple co-morbidities, rather than underlying obstructive coronary artery disease which was seen in 30-50% of T2MI patients (26, 31). Studies yielded mixed results as to whether coronary artery disease is an independent predictor of T2MI (20, 42), while others question the angiographic distinction between T2MI and T1MI. For example, in a study of 450 consecutive patients with MI who all underwent coronary angiography within 24 hours of symptom onset, 145 (32.2%) patients had 'true' T1MI (acute atherothrombosis and no systemic triggers), 114 (25.3%) had 'true' T2MI (no atherothrombosis and systemic triggers), 61 (13.6%) patients had neither, and 130 (28.9%) patients had both (41). This yields a discordance of angiographic and clinical definitions of MI type in 42.5% of patients.

Our review has several limitations. First, in the absence of individual patient data from all included studies, we could not perform multivariate regression analysis in identifying independentpredictors of diagnosis, management, or prognosis of T2MI. Second, we did not perform separate analyses of studies according to each version of the Universal Definition of MI or to different troponin thresholds to define MI, which may impact management and prognosis. However, potential misclassification bias was addressed in a recent study which showed little change in MI classification as type 1 or 2 in the same cohort of emergency admissions to whom the 3rd and 4th universal definitions were applied(55). In another study which compared separate T2MI cohorts, as defined by the 2007 and the 2012 definitions, co-morbidities and use of cardioprotective medications were less frequent in the 2012 cohort, likely due to less severe MIs being included as a result of using more sensitive troponin assays (22). Third, we did not collect haemodynamic variables or other

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 physiological measures such as haemoglobin levels and glomerular filtration rate in analysing clinical presentations as these were very inconsistently reported. Fourth, our mortality meta-analyses relied on crude mortality rates reported in each study, with 55% of studies (15-19, 22-28, 30, 31, 34, 35, 37, 40-42, 45, 46, 53) also undertaking multivariate regression and/or competing risk analyses and reporting adjusted mortality rates. For the T2MI cohorts in general, these rates tended to be lower and the differences in rates compared to those of T1MI were of smaller magnitude. Fifth, we did not analyse 30-day readmission rates as these were reported in only three studies (13, 14, 23). Sixth, we did not perform sensitivity analyses comparing results of prospective versus retrospective studies, as neither group demonstrated less or more risk of bias than the other, or compare results of good quality studies against fair/poor quality studies as the latter comprised only 16.7% of all patients. Finally, we did not attempt sub-analyses based on risk stratification using validated risk scores or seek to identify predictive models for mortality, as such analyses were reported in only two studies (26, 40).

The strengths of this review are the inclusion of all contemporary cohort studies in the troponin era that employed formal definitions of T2MI, analysis of a broader range of variables than those of previous studies, and the more precise discernment of clinically meaningful differences between the two MI populations in patient characteristics, clinical presentation, patterns of care and outcomes. As studies originated from several different jurisdictions, we believe our findings are generalisable to different healthcare systems, although absolute values for some measures did vary between countries. We are aware of a large US cohort study published since completion of our review (56) which compared T1MI with T2MI patients, but was limited by misclassification bias (relying on administrative hospital discharge data containing an International Classification of Diseases-10th Revision code specific for type 2 MI, rather than a registry or chart diagnosis based on a formal MI definition), short study period of 3 months in late 2017, and inability to analyse clinical features, investigation results, medication use, coronary anatomy, and post-discharge mortality due to their omission in the datasets.

Conclusion

This review has identified differences between T2MI and T1MI patients in presenting clinical features, investigation and management profiles, and clinical outcomes. These findings may assist clinicians to better recognise T2MI and advise patients about its sequelae, and inform hospital coding and epidemiological trending, quality of care indicators and inter-hospital benchmarking of performance relating to the care of patients with T2MI.

The review has also defined persisting gaps in our understanding of the utility and prognostic effects of invasive investigations, revascularization strategies and cardioprotective medications in T2MI patients that warrant more randomised trials that enrol such patients.

Tables

	Τ2ΜΙ			T1MI			
Pre-existing medical condition	Number of patients with the specified condition	Total number of patients	%	Number of patients with the specified condition	Total number of patients	%	Odds ratio* (95% CI)
CAD	3352	10303	32.5%	22222	92725	24%	1.1 [0.93, 1.31]
Type 2 DM	3044	12157	25%	23287	93345	24.9%	0.97 [0.85, 1.10
HTN	7536	11021	66.4%	55782	88017	63.4%	1.22 [1.03, 1.45
Dyslipidaemia	4626	10652	43.4%	40099	87366	45.9%	0.74 [0.58, 0.94
Smoker	3448	9929	34.7%	39548	74889	52.8%	0.60 [0.49, 0.73
Obesity	1225	3672	33.4%	30963	56970	54.3%	0.63 [0.46, 0.87
Renal failure	1378	6040	22.8%	11300	65394	17.3%	1.87 [1.53, 2.28
Heart failure	1661	8873	13.1%	5617	74212	7.6%	2.35 [1.82, 3.03
PVD	584	5856	10.0%	2066	41280	5.0%	1.33 [1.05, 1.69
CVD	969	8538	11.3%	6060	87822	6.9%	1.47 [1.27, 1.72
Atrial fibrillation	836	3645	22.9%	1220	19843	6.1%	3.02 [2.29, 3.99
COPD	800	5018	15.9%	823	48375	1.7%	1.94 [1.22, 3.08
Illicit drug Use	46	204	22.5%	8	220	3.6%	8.15 [1.03 <i>,</i> 64.46]

*Comparing T2MI with T1MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: CAD= coronary heart disease, DM= diabetes mellitus, HTN= hypertension, BMI= body mass index, PVD= peripheral vascular disease, CVD= cerebrovascular disease, COPD= chronic obstructive pulmonary disease

Table 2. Pharmacological management and invasive interventions in patients with	
T2MI versus T1MI.	

	T2MI				T1MI		
Intervention	No. patients receiving intervent ion	Total number of patients	%	No. patients receiving intervention	Total number of patients	%	Odds ratio* (95% CI)
Medication							
Beta blockers	4967	8523	58.3%	63431	83157	76.3%	0.45 [0.33, 0.63]
ACEI / ARB	3766	7842	48%	56253	81793	68.8%	0.52 [0.40, 0.67]
Anti-platelets	5087	8599	70.8%	74377	84004	88.5%	0.25 [0.16, 0.38]
Anti-coagulants	1519	5255	28.9%	15754	62415	25.2%	1.87 [1.06, 3.30]
Anti-anginal agents	1281	2191	58.5%	38955	42768	91.1%	0.61 [0.21, 1.74]
Diuretics	1336	2985	44.8%	6211	45779	13.6%	1.98 [1.37, 2.86]
Statins	3418	6455	52.9%	56875	64942	87.6%	0.25 [0.16, 0.38]
Invasive				·			
PCI	2092	9936	21.1%	67411	86425	78%	0.06 [0.04, 0.10]
CABG	102	3451	2.9%	3101	48731	6.4%	0.23 [0.12, 0.45]

*Comparing T2MI with T1MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: ACEI= Angiotensin converting enzyme inhibitors, ARB= Angiotensin receptor blockers; CI=confidence interval; T2MI=type 2 myocardial infarction; T1MI=type 1 myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft

Outcomes	T2MI				T1MI		
	No. patients with outcome	Total number of patients	%	No. patients with outcome	Total number of patients	%	Odds ratio* (95% CI)
CV in-hospital mortality	184	2109	8.7%	331	6248	5.3%	1.61 [1.17, 2.22
All-cause in- hospital mortality	667	5321	12.5%	1508	25997	5.8%	1.94 [1.35, 2.79
Short-term all- cause mortality	204	887	23.0%	250	1998	12.5%	1.34 [0.63, 2.85]
1-year all-cause mortality	632	3340	18.9%	1299	24203	5.4%	3.11 [1.91, 5.08]
2-year all-cause mortality	246	926	26.6%	428	2587	16.5%	1.63 [1.11, 2.41]
3-year all-cause mortality	193	525	36.8%	710	4305	16.5%	2.00 [1.07, 3.76]
Long-term all- cause mortality	1453	2708	53.7%	1320	4633	28.5%	3.24 [2.73, 3.84]

*Comparing T1MI with T2MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: CV= Cardiovascular, MACE= Major adverse cardiovascular events; T2MI=type 2 myocardial infarction; T1MI=type 1 myocardial infarction; CI=confidence interval

Figures

 Figure 1. Forest plot of one-year all-cause mortality of T2MI patients compared to T1MI patients.

Figure 2. Forest plot of long-term all-cause mortality of T2MI patients compared to T1MI patients.

Figure S1. PRISMA flow diagram.

Figure S2. Forest Plot. Presence of Ischaemic Heart Disease.

Figure S3. Forest Plot. Presence of Type 2 Diabetes Mellitus.

Figure S4. Forest Plot. Presence of Hypertension.

Figure S5. Forest Plot. Presence of Dyslipidaemia.

Figure S6. Forest Plot. Smoking Status.

Figure S7. Forest Plot. Obesity Status.

Figure S8. Forest Plot. Presence of Chronic Kidney Disease.

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3 4	Figure S9. Forest Plot. Presence of Heart Failure.
5	Figure S10. Forest Plot. Presence of Peripheral Vascular Disease.
7	Figure S11. Forest Plot. Presence of Cerebrovascular Disease.
8 9	Figure S12. Forest Plot. Presence of Illicit Drug Use.
10 11	Figure S13. Forest Plot. Presence of Atrial Fibrillation.
12 13	Figure S14. Forest Plot. Chest Pain as Presenting Feature.
14 15	Figure S15. Forest Plot. Dyspnoea as Presenting Feature.
16 17	Figure S16. Forest Plot. Arm / Shoulder Discomfort as Presenting Feature.
18 19	Figure S17. Forest Plot. Nausea / Vomiting as Presenting Feature.
20	Figure S18. Forest Plot. Non-specific Symptoms as Presenting Features.
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23 24	Figure S20. Forest Plot. ST Elevation on ECG.
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29 30	Figure S23. Forest Plot. Non-specific ST Changes on ECG.
31 32	Figure S24. Forest Plot. Left Bundle Branch Block on ECG.
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35 36	Figure S26. Forest Plot. Coronary Angiogram Performed.
37	Figure S27. Forest Plot. Obstructive Coronary Artery Disease on Coronary Angiogram.
38 39	Figure S28. Forest Plot. Multivessel Disease on Coronary Angiogram.
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44 45	Figure S31. Forest Plot. Beta-Blockers Prescribed.
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50 51	Figure S34. Forest Plot. Anticoagulants Prescribed.
52 53	Figure S35. Forest Plot. Antianginal Drugs Prescribed.
54	Figure S36. Forest Plot. Diuretics Prescribed.
55 56	Figure S37. Forest Plot. Statins Prescribed.
57 58	Figure S38. Forest Plot. Percutaneous Coronary Intervention Performed.
59 60	Figure S39. Forest Plot. Coronary Artery Bypass Graft Performed.

Figure S40. Forest Plot. All cause In-hospital mortality. T2MI compared to T1MI.
Figure S41. Forest Plot. Short-term all-cause mortality. T2MI compared to T1MI.
Figure S42. Forest Plot. Two-year all-cause mortality. T2MI compared to T1MI.
Figure S43. Forest Plot. Three-year all-cause mortality. T2MI compared to T1MI.
Figure S44. Forest Plot. CVS In-hospital mortality. T2MI compared to T1MI.

Contribution Statement

All authors (KW, MK, IS) contributed to the conception of the work. MK and KW performed the acquisition and analysis of the data. KW and IS were responsible for the interpretation of data. All authors (MK, KW, IS) were responsible for drafting manuscript and final approval of the version to be published. All authors (KW, MK, IS) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing Interests

The authors declare there are no conflict of interest with respect the article.

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					BMJ Op	en	jopen-
							omjopen-2021-055 Odds Ratio
	T2M	I	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% C
Arora 2018	89	264	96	775	13.1%	3.60 [2.58, 5.02]	7 Fe
Chapman 2020	258	1121	720	4981	13.7%	1.77 [1.51, 2.08]	ibru:
El haddad 2012	84	295	28	512	12.4%	6.88 [4.36, 10.87]	
Furie 2019	80	206	93	349	12.9%	1.75 [1.21, 2.52]	
Lopez Cuenca 2016	27	117	102	707	12.3%	1.78 [1.10, 2.87]	
Radovanovic 2017	14	1091	117	13828	11.8%	1.52 [0.87, 2.66]	
Saaby 2014	65	119	25	360	11.9%	16.13 [9.37, 27.77]	oad –
Stein 2014	15	127	118	2691	11.7%	2.92 [1.65, 5.16]	
				24202	100.0%	2 44 54 04 5 001	m
Total (95% CI)		3340		24203	100.0%	3.11 [1.91, 5.08]	i i ▼
Total (95% CI) Total events Heterogeneity: Tau ² =		= 94.64	-				February 2022. Downloaded from http://brrjope
Total events Heterogeneity: Tau ² = Test for overall effect:	0.45; Chi ² Z = 4.55 (= 94.6 P < 0.0	4, df = 7 (0001)	P < 0.00	0001); I² =	93%	0.01 0.1 1 10 Favours T1MI Favours 1
Total events Heterogeneity: Tau ² = Test for overall effect:	0.45; Chi ² Z = 4.55 (= 94.6 P < 0.0	4, df = 7 (0001)	P < 0.00	0001); I² =	93%	0.01 8 0.1 1 10
Total events Heterogeneity: Tau ² = Test for overall effect:	0.45; Chi ² Z = 4.55 (= 94.6 P < 0.0	4, df = 7 (0001)	P < 0.00	0001); I² =	93%	0.01 0.1 1 10 Fayours T1MI Favours 1 ients compared to T1MI patier
Total events Heterogeneity: Tau ² = Test for overall effect:	0.45; Chi ² Z = 4.55 (= 94.6 P < 0.0	4, df = 7 (0001)	P < 0.00	0001); I² =	93%	0.01 0.1 1 10 Fayours T1MI Favours 1 ents compared to T1MI patier
Total events Heterogeneity: Tau ² = Test for overall effect:	0.45; Chi ² Z = 4.55 (= 94.6 P < 0.0	4, df = 7 (0001)	P < 0.00	0001); I² =	93%	0.01 0.1 1 10 Favours T1MI Favours T ents compared to T1MI patier
Total events Heterogeneity: Tau ² = Test for overall effect:	0.45; Chi ² Z = 4.55 (= 94.6 P < 0.0	4, df = 7 (0001)	P < 0.00	0001); I² =	93%	0.01 0.1 1 10 Favours T1MI Favours T ents compared to T1MI patier
Total events Heterogeneity: Tau ² = Test for overall effect:	0.45; Chi ² Z = 4.55 (= 94.6 P < 0.0	4, df = 7 (0001)	P < 0.00	0001); I² =	93%	0.01 0.1 1 10 Favours T1MI Favours T ents compared to T1MI patier
Total events Heterogeneity: Tau ² = Test for overall effect:	0.45; Chi ² Z = 4.55 (= 94.6 P < 0.0	4, df = 7 (0001)	P < 0.00	0001); I² =	93%	0.01 9 0.1 1 10 Favours T1MI Favours ents compared to T1MI patier
Total events Heterogeneity: Tau ² = Test for overall effect:	0.45; Chi ² Z = 4.55 (= 94.6 P < 0.0	4, df = 7 (0001)	P < 0.00	0001); I² =	93%	0.01 9 0.1 1 10 Favours T1MI Favours ents compared to T1MI patier
Total events Heterogeneity: Tau ² = Test for overall effect:	0.45; Chi ² Z = 4.55 (= 94.6 P < 0.0	4, df = 7 (0001)	P < 0.00	0001); I² =	93%	0.01 9 0.1 1 10 Favours T1MI Favours T ients compared to T1MI patier
Total events Heterogeneity: Tau ² = Test for overall effect:	0.45; Chi ² Z = 4.55 (= 94.6 P < 0.0	4, df = 7 (0001)	P < 0.00	0001); I² =	93%	0.01 9 0.1 1 10 Favours T1MI Favours T ients compared to T1MI patier
Total events Heterogeneity: Tau ² = Test for overall effect:	0.45; Chi ² Z = 4.55 (= 94.6 P < 0.0	4, df = 7 (0001)	P < 0.00	0001); I² =	93%	0.01 9 0.1 1 10 Favours T1MI Favours T ients compared to T1MI patier
Total events Heterogeneity: Tau ² = Test for overall effect:	0.45; Chi ² Z = 4.55 (= 94.6 P < 0.0	4, df = 7 (0001)	P < 0.00	0001); I² =	93%	0.01 9 0.1 1 10 Favours T1MI Favours T ients compared to T1MI patier
Total events Heterogeneity: Tau ² = Test for overall effect:	0.45; Chi ² Z = 4.55 (= 94.6 P < 0.0	4, df = 7 (0001)	P < 0.00	0001); I² =	93%	0.01 9 0.1 1 10 Favours T1MI Favours ents compared to T1MI patier

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	T2M		T1M			Odds Ratio		755 on Odds Ratio	
Study or Subgroup	Events				Weight	M-H, Random, 95% (<u>1 M-H, Random, 95% Cl</u>	
Chapman 2018	268	429	430	1171	28.3%	2.87 [2.28, 3.61]	ebru 1	
Raphael 2020	766	1054	638	1365	36.2%	3.03 [2.55, 3.60		ary X	
Singh 2020	419	1225	252	2097	35.5%	3.81 [3.19, 4.54	1	February 2022	
Total (95% CI)		2708		4633	100.0%	3.24 [2.73, 3.84]			
Total events	1453		1320					Downloa	
Heterogeneity: Tau ² =	0.01; Chř	= 4.84,	df = 2 (P	= 0.09)); l² = 59%		0.01		ᆟ
Test for overall effect:	Z = 13.42	(P < 0.0	00001)				0.01 F	≌ 0.1 1 10 1 SavoursT1MI Favours T2MI	00
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gure 2. Forest plot of th	ne result o	f meta-	analysis o	of the ri	sk long-ter	m mortality of T2MI pa		ampared to T1MI patients.	
gure 2. Forest plot of th	<u>ne result o</u>	f meta-	analysis o	f the ri	sk long-ter	m mortality of T2MI pa	<u>y</u>	http: mippen.bmj.com/ on June 21, 2024 by guest.	

Table	S1. Evolving definitions of Type 2 Myocardial Infarction.
Year	Universal Definition of Type 2 Myocardial Infarction
2007	Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrythmias, hypotension or hypertension
2012	Instances of myocardial injury with necrosis where a condition other than coronary artery disease contributes to an imbalance between myocardial oxygen supply and/or demand e.g. coronary artery spasm, coronary embolism, anaemia, arrythmias, hypotension or hypertension
2018	 Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following: Symptoms of acute myocardial ischaemia New ischaemic ECG changes Development of pathological Q waves Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology

Table S2. Search	strategy.
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MEDLINE: (type 2 adj3 myocard*) OR (type-2 adj3 myocard*) OR (type II adj3 myocard*) OR (type-II adj3 myocard*) OR (type 2 adj3 MI) OR (type-2 adj3 MI) OR T2MI OR (supply demand adj3 myocard*)

EMBASE: ('type 2' NEXT/3 myocard*) OR ('type-2' NEXT/3 myocard*) OR ('type ii' NEXT/3 myocard*) OR ('type-ii' NEXT/3 myocard*) OR ('type 2' NEXT/3 mi) OR ('type-2' NEXT/3 mi) OR ('t2mi') OR ('supply demand' NEXT/3 myocard*)

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Table S3a. Study ch	aracteris	stics				0 1	
Author, Year	Pati	ents	Design	Definition	Geographic	Screening &	Troponir
Autior, real	T1MI	T2MI	Design	of MI	location		Assay
Arora, 2018 (1)	775	264	Retrospective	2012	USA	NSTEMI patie	cTnl
Balanescu, 2020 (2)	152	49	Retrospective	2018	USA	AMI patient	N/A
Baron, 2016 (3)	40501	1313	Prospective	2007	Sweden	AMI patients	hs-cTnT
Bonaca, 2012 (4)	359	42	Prospective	2007	Multinational	TRITON TIMI 38 trial	N/A
Cediel, 2017 (5)	376	194	Retrospective	2012	Spain	ED patients with at leas 1 troponin	cTnl
Chapman, 2018 (6)	1171	429	Prospective	2012	UK	ED with elevated to ponin	cTnl
Chapman, 2020 (7)	4981	1121	Prospective	2018	UK	Suspected A	cTnl
Consuegra-Sanchaz, 2018 (8)	125	75	Retrospective	2012	Spain	ED patients with at least 1 troponin	cTnl hs-cTnT
El-Haddad, 2012 (9)	512	295	Retrospective	2012	USA	Patients with elevate troponin	N/A
Etaher, 2020 (10)	97	121	Prospective	2018	Australia	Patients with elevated troponin	N/A
Furie, 2019 (11)	349	206	Retrospective	2012	Israel	NSTEMI on genera ward	Unknowr
Guimaraes, 2018 (12)	847	76	Retrospective	2012	Multinational	ACS during TRACE trial	N/A
Hawatmeh, 2020 (13)	664	281	Retrospective	2012	USA	NSTEMI patiegts	cTnl
Higuchi, 2019 (14)	12023	491	Retrospective	2012	Tokyo	Admitted to C 🔁 U	N/A
Javed, 2009 (15)	143	64	Retrospective	2007	USA	Patients with elevate troponin	cTnl
Kadesjo, 2019 (16)	1111	251	Retrospective	2018	Sweden	MI, Registry	N/A
Lambrecht, 2018 (17)	360	119	Prospective	2007	Denmark	Hospitalised patients with troponin measured $\frac{4}{\sigma}$	cTnl
Landes, 2016 (18)	107	107	Retrospective	2012	Israel	Diagnosed with T2Mb and T1MI	cTnT
Lopez-Cuenca, 2016 (19)	707	117	Retrospective	2012	Spain	Diagnosed with T2MF and T1MI	hs-cTnT
Meigher, 2016 (20)	340	452	Retrospective	2012	Germany	ED patients with elevat add troponin	cTnl
Nestelberger, 2017 (21)	684	128	Prospective	2012	Multinational	ED patients with MI	N/A
Neumann, 2017 (22)	188	99	Prospective	2012	Germany	ED patients with suspected MI	hs-cTnl

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Paiva, 2015 (23)	764	236	Retrospective	2012	Portugal	Admitted to CCU with MI	cTnl
Pandey, 2020 (24)	97	103	Prospective	2018	USA	MI o	N/A
Putot, 2018 (25)	2036	847	Prospective	2012	France	ED or cardiology ward with elevated troponin 고	cTnl
Putot, 2019 (26)	365	254	Retrospective	2018	France	Hospitalised patients with CAD	cTnl
Putot, 2020 (27)	3710	862	Retrospective	2012	France	Hospitalised patient with MI	cTnl
Radovanovic, 2017 (28)	13828	1091	Retrospective	2012	Switzerland	Diagnosed Ala	N/A
Raphael, 2020 (29)	1365	1054	Retrospective	2018	USA	Raised tropor	cTnT
Reed, 2017 (30)	88	162	Retrospective	2012	USA	Underwent vasculassurgery procedure	cTnT
Saaby 2013 (31)	397	144	Prospective	2007	Denmark	Troponin meas	cTnl
Saaby, 2014 (32)	360	119	Prospective	2007	Denmark	Elevated tropandin	cTnl
Sandoval, 2014 (33)	66	190	Retrospective	2012	USA	ED patients with troponin measured	cTnl
Sandoval, 2017 (34)	77	140	Prospective	2012	USA	ED patients with tropont measured	cTnl
Sato, 2020 (35)	2834	155	Prospective	2012	Japan	Hospitalised patien gwith MI	N/A
Shah, 2015 (36)	1171	429	Prospective	2012	UK	Admitted with elevat 🛃 troponin	cTnl
Singh, 2020 (37)	2097	1225	Retrospective	2018	USA	Age <50, MI or raise troponin	N/A
Smilowitz, 2018 (38)	137	146	Prospective	2012	USA	Admitted with raise	cTnl
Stein, 2014 (39)	2691	127	Prospective	2007	Israel	Admitted to card Blogy	N/A
Truong, 2020 (40)	275	175	Retrospective	2012	Russia	MI, undergoing angiogram	N/A
•	-			•	•	ocardial infarction; MI = m੍ਰੈyocardial infar ary care unit; CAD = coroਸ਼੍ਰਿry artery disea	-

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Table S3b. Study character			1					
Author, Year		ents				riables	on .	-
	T1MI	T2MI	Pre-existing	Symptoms	Investigation	Troponin	לאΩnagement די	Prognos
Arora 2018 (1)	775	264	conditions		s X	Values	Februa X	Х
Arora, 2018 (1)	152	49	X	X	X	Х		X
Balanescu, 2020 (2)		1313	X	X	X	Х		
Baron, 2016 (3)	40501	1	×	×	×		20 X	
Bonaca, 2012 (4)	359	42		Y	N N	~	Dow	V
Cediel, 2017 (5)	376	194	X	Х	X	X	× c	X
Chapman, 2018 (6)	1171	429	X		X	X	nlo X	X
Chapman, 2020 (7)	4981	1121	X	X	X	X	aded	Х
Consuegra-Sanchaz, 2018 (8)	125	75	X	Х	Х	Х	from	
El-Haddad, 2012 (9)	512	295					3	Х
Etaher, 2020 (10)	97	121	x		X		http X	
Furie, 2019 (11)	349	206	x	X	Х	Х	X	Х
Guimaraes, 2018 (12)	847	76	Х		Х		mjøpe X .b X	Х
Hawatmeh, 2020 (13)	664	281	X		X	Х	pe x	
Higuchi, 2019 (14)	12023	491	Х		X			Х
Javed, 2009 (15)	143	64	X		X	Х	mj.o	Х
Kadesjo, 2019 (16)	1111	251	X				р <mark>о</mark> й Х	Х
Lambrecht, 2018 (17)	360	119	X		Х	X	on	Х
Landes, 2016 (18)	107	107	X	Х	Х	X	June X	
Lopez-Cuenca, 2016 (19)	707	117	X	X	Х	X		Х
Meigher, 2016 (20)	340	452	X	Х	Х	X	21,	Х
Nestelberger, 2017 (21)	684	128	X		Х		2024	Х
Neumann, 2017 (22)	188	99	X		Х	Х	4	Х
Paiva, 2015 (23)	764	236	Х		Х	Х	by gr	Х
Pandey, 2020 (24)	97	103	Х				lues	
Putot, 2018 (25)	2036	847	Х		Х	Х		Х
Putot, 2019 (26)	365	254	Х		Х	Х	rote	Х
Putot, 2020 (27)	3710	862	Х		Х	Х	ecte	Х
Radovanovic, 2017 (28)	13828	1091	X		Х		rotected by copyright.	Х
Raphael, 2020 (29)	1365	1054	Х		х	Х	α X	Х

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Deed 2017 (20)	00	102			V	V	21-05575	V	1
Reed, 2017 (30)	88	162			X	X	01	Х	
Saaby 2013 (31)	397	144	X		X	X	<u> </u>		
Saaby, 2014 (32)	360	119	Х		X	X		Х	
Sandoval, 2014 (33)	66	190	Х	X	Х	X	' February		2
Sandoval, 2017 (34)	77	140	Х	Х	Х	Х		Х	2
Sato, 2020 (35)	2834	155	Х		Х		ary	Х	
Shah, 2015 (36)	1171	429	Х	Х	Х	Х	2022.	Х	
Singh, 2020 (37)	2097	1225	Х		Х			Х	
Smilowitz, 2018 (38)	137	146	Х	X	Х	Х	Downloaded	Х	
Stein, 2014 (39)	2691	127	Х	X	Х		Vnle	Х	
Truong, 2020 (40)	275	175	Х	X	Х		bad	Х	
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Table S4. Risk of bia	is assessment					
Author, Year	Representative of Exposed Cohort	Selection of Non-exposed	Outcome Assessment	Follow-up Length	음 Adequacy of 뷰ollow- Up 딸	Summary
Arora, 2018 (1)	х	х	х	х	x Ÿ	8 (good quality)
Balanescu, 2020 (2)	0	х	х	0	x 20222.	6 (fair quality)
Baron, 2016 (3)	x	х	x	х	^	8 (good quality)
Bonaca, 2012 (4)	x	х	x	х	xş	8 (good quality)
Cediel, 2017 (5)	x	X	х	х	x nlo	8 (good quality)
Chapman, 2018 (6)	х	x	х	х	x de	8 (good quality)
Chapman, 2020 (7)	х	x	х	х	X ^Q	8 (good quality)
Consuegra-Sanchaz, 2018 (8)	0	0	x	0	x from htt	3 (poor quality)
El-Haddad, 2012 (9)	х	х	0	0	0	5 (fair quality)
Etaher, 2020 (10)	х	х	x	х	x <u>B</u>	8 (good quality)
Furie, 2019 (11)	х	Х	х	×	x pp	8 (good quality)
Guimaraes, 2018 (12)	0	0	x	0	x mj.	4 (fair quality)
Hawatmeh, 2020 (13)	0	0	x	x	0 / 01	4 (fair quality)
Higuchi, 2019 (14)	0	0	х	x	x L	5 (fair quality)
Javed, 2009 (15)	х	х	х	x	une x	8 (good quality)
Kadesjo, 2019 (16)	x	х	х	х	x 1	8 (good quality)
Lambrecht, 2018 (17)	x	х	x	х	2024 ×	8 (good quality)
Landes, 2016 (18)	х	х	х	х	x y gu	8 (good quality)
Lopez-Cuenca, 2016 (19)	х	х	x	х	guest. I	8 (good quality)
Meigher, 2016 (20)	x	х	х	х	x rot	8 (good quality)
Nestelberger, 2017 (21)	x	x	x	х	x x	8 (good quality)
, Neumann, 2017 (22)	х	х	х	x	by copyright.	8 (good quality)

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Palva, 2015 (23) x						021-	
Putot, 2018 (25)xxx <th>Paiva, 2015 (23)</th> <th>X</th> <th>X</th> <th>×</th> <th>x</th> <th>0557?</th> <th>8 (good qua</th>	Paiva, 2015 (23)	X	X	×	x	0557?	8 (good qua
Putot, 2018 (25)xxx <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>							
Putot, 2019 (26)xxx0xx7 (good quadra duadra duadr							
Reed, 2017 (30) x							
Reed, 2017 (30) x						x e	
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Reed, 2017 (30) x		x	х	x	x	x ≺ ≥	8 (good qua
Reed, 2017 (30) x		x	x	x	x	x 22	8 (good qua
Saaby 2013 (31)xxx						x 7	
Saaby, 2014 (32) x						x 5	
Sandoval, 2014 (33) x	-						
Sandoval, 2017 (34) x						x d	
Sato, 2020 (35) 0 0 0 x x 2 (poor quality of qualit							
Shah, 2015 (36) x x x x x x x 8 (good quadratic	,						
Singh, 2020 (37) 0 0 x x x g 6 (fair qua Gair qua Stein, 2018 (38) Smilowitz, 2018 (38) x x x x x x 7 (good qua 7 (good qua 7 (good qua Truong, 2020 (40) x x x x x x 3							
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Precipitating Factor	Events	Patients	%
Sepsis	1116	3110	35.9%
Heart failure	698	1943	35.9%
Arrhythmia	1716	5465	31.4%
Anaemia	1506	4878	30.9%
Valvular abnormality	351	1301	27.0%
Respiratory failure	743	3021	24.6%
Chronic obstructive pulmonary disease	59	258	22.9%
Stroke	44	328	13.4%
Hypertension	291	2217	13.1%
Non-cardiac surgery	103	841	12.2%
Shock/hypotension	291	3006	9.7%
Renal failure	51	553	9.2%
Pulmonary oedema	33	380	8.7%
Bradycardia	35	484	7.2%
Infection	115	2009	5.7%
Coronary spasm	36	1048	3.4%
Bleeding	53	1834	2.9%
Coronary endothelial dysfunction		592	0.2%

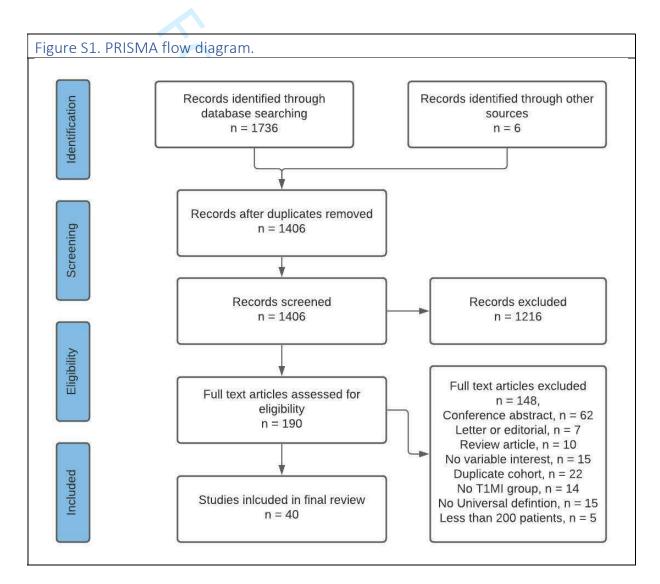
		T2MI					
Presenting Symptom	No. patients with presenting symptom	Total number of patients	%	No. patients with presenting symptom	Total number of patients	%	Odds ratio * [95% Cl]
Chest pain	3474	5932	58.6%	58273	65883	88.4%	0.19 [0.13, 0.20
Dyspnoea	1412	5210	27.1%	6930	65129	10.6%	2.64 [1.86, 3.74
Arm or shoulder discomfort	28	330	8.5%	50	143	35.0%	0.18 [0.11, 0.30
Jaw or neck discomfort	6	140	4.3%	12	77	15.6%	0.24 [0.09, 0.68
Epigastric discomfort	8	140	5.7%	8	77	10.4%	0.52 [0.19, 1.4
Nausea or vomiting	46	330	13.9%	39	143	27.3%	0.46 [0.28, 0.74
Fatigue	5	140	3.6%	5	77	6.5%	0.53 [0.15, 1.9
Diaphoresis	16	140	11.4%	16	77	20.8%	0.49 [0.23, 1.0
Other nonspecific symptoms	988	1529	64.6%	2662	41396	6.4%	4.9 [0.48, 50.3
Collapse / syncope	99	2125	4.7%	157	7152	2.2%	2.10 [1.05, 4.1

*Comparing T2MI with T1MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: URL- upper reference limit; STEMI- ST elevation myocardial infarction; NSTEMI- Non- ST elevation myocardial infarction; MI- Myocardial infarction; cTn- cardiac troponin; T1MI- Type 1 myocardial infarction; T2MI- Type 2 myocardial infarction; ECG- electrocardiogram; CAD- coronary artery disease; PCI-percutaneous coronary intervention; CABG- coronary artery bypass graft; IHD- ischaemic heart disease; MACE- Major adverse cardiovascular events; CI-confidence interval

		T2MI			Odds ratio* (95% CI)		
Variable	No. patients with nominated diagnostic findings	Total no. patients	%	No. patients with nominated diagnostic findings	Total no of patients	%	
ECG							
ST elevation	1129	8014	14.1%	37182	84096	44.2%	0.22 [0.17, 0.28
ST depression or T wave Inversion	1728	4911	35.2%	10968	51042	21.5%	1.36 [0.85, 2.17
Pathological Q Waves	30	447	6.7%	177	850	20.8%	0.38 [0.20, 0.71
Non-specific ST-T wave changes	146	592	24.7%	45	417	10.8%	2.62 [1.81, 3.79
Left bundle branch block	175	1927	9.1%	1943	42543	4.6%	1.62 [1.21, 2.17
Atrial fibrillation/flutter	54	257	21%	52	784	6.6%	4.99 [3.14, 7.93
Echocardiograph							
Echocardiogram performed	648	1353	47.9%	1571	2830	55.5%	0.44 [0.20, 0.96
Presence of RWMA	97	286	33.9%	101	214	47.2%	0.48 [0.06, 3.78
Angiogram							
Angiogram performed	3182	9318	34.1%	42724	49944	85.5%	0.09 [0.06, 0.12
Obstructive coronary artery disease present	1246	3663	34.0%	19923	44404	44.9%	0.16 [0.05, 0.54
Multivessel disease present	593	2147	27.6%	11839	41715	28.4%	0.40 [0.19, 0.82
*Comparing T2MI with meta-analysis ECG=electrocardiograp myocardial infarction; T	h; RWMA=regio	onal wall m	otion abn	C		0 0	C

Table S8. Troponin measurements.									
Troponin Measurement	Number of Studies	T1MI (min-max)	T2MI (min-max)						
Baseline cTn (xULN)	12	0.14-190	0.1-8.2						
6h cTn (xULN)	4	13.2-142	4.25-11						
Peak cTn (xULN)	20	5.1-1703	2.8-447						
Abbreviations: xULN= times	s upper limit normal		1						



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igure S2. Forest Plo	ot. Pres	sence	e of Isc	chaen	nic Hea	rt Disease.	
Study or Subgroup	T2M Events		T1N Events		Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H. Random, 95% CI
Arora 2018	56	264	209	775	3.7%	0.73 [0.52, 1.02]	
Bonaca 2012	380	1313		40501	4.2%	1.24 [1.10, 1.40]	
Cediel 2017 Chapman 2018	41 191	194 429	120 497	376 1171	3.5%	0.57 [0.38, 0.86] 1.09 [0.87, 1.36]	
Chapman 2020	454	1121	1519	4981	4.2%	1.55 [1.36, 1.77]	
Conseugra Sanchez 2018	30	75	69	125	2.9%	0.54 [0.30, 0.97]	
Etaher 2020	95	171	63	97	3.1%	0.67 [0.40, 1.13]	
Furie 2019	119	206	220	349	3.6% 3.2%	0.80 [0.56, 1.14]	
Guimares 2018 Hawatmeh 2020	37 127	76 281	416 387	847 664	3.2%	0.98 [0.61, 1.57] 0.59 [0.45, 0.78]	
Higuchi 2019	65	491	1120		3.9%	1.49 [1.14, 1.94]	
Kadesjo 2019	48	251	48	1111	3.4%	5.24 [3.42, 8.03]	
Landes 2016	68	107	50	107	3.0%	1.99 [1.15, 3.43]	
Lopez Cuenca 2016	19	117	101	707	3.0%	1.16 [0.68, 1.99]	
Meigher 2016 Nestelberger 2020	59 0	452 128	51 283	340 684	3.5% 0.3%	0.85 [0.57, 1.27] 0.01 [0.00, 0.09]	
Neumann 2017	14	99	55	188	2.7%	0.40 [0.21, 0.76]	
Pandey 2020	47	103	47	97	3.0%	0.89 [0.51, 1.56]	
Putot 2018	291	847	407	2036	4.1%	2.09 [1.75, 2.50]	
Putot 2020	319	862	853	3710	4.1%	1.97 [1.68, 2.30]	
Radovanovic 2017 Saaby 2013	401 39	1091 144	3817	13828 397	4.2%	1.52 [1.34, 1.73] 1.16 [0.75, 1.80]	
Saaby 2013	26	119	71	360	3.1%	1.14 [0.69, 1.89]	
Sandoval 2014	27	190	20	66	2.6%	0.38 [0.20, 0.74]	
Sandoval 2017	24	140	24	77	2.6%	0.46 [0.24, 0.88]	
Sato 2020	18	155	350	2834	3.1%	0.93 [0.56, 1.54]	
Shah 2015 Smilowitz 2018	191 28	429 146	497 26	1171 137	4.0% 2.8%	1.09 [0.87, 1.36] 1.01 [0.56, 1.83]	
Stein 2014	56	127	756	2691	3.6%	2.02 [1.41, 2.89]	
Troung 2020	82	175	52	275	3.4%	3.78 [2.48, 5.77]	-
Total (95% CI)		10303	22222	92725	100.0%	1.10 [0.93, 1.31]	•
Total events Heterogeneity: Tau ² = 0.18;	3352 Chi ² = 287	89 df =	22222 = 29 (P <	0 00001): 12 = 90%		0.01 0.1 1 10
Test for overall effect: Z = 1.			20 (1 4	0.00001	, i = 30 %		0.01 0.1 1 10 Favours T1MI Favours T2MI

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Arora 2018	110	264	371	775	3.4%	0.78 [0.59, 1.03]	-
Baron 2016	306	1313	9395	40501	3.9%	1.01 [0.88, 1.15]	ł
Cediel 2017	73	194	132	376	3.1%	1.12 [0.78, 1.60]	+
Chapman 2018	93	429	185	1171	3.4%	1.48 [1.12, 1.95]	+
Chapman 2020	147	1121	802	4981	3.7%	0.79 [0.65, 0.95]	-
Conseugra Sanchez 2018	29	75	59	125	2.2%	0.71 [0.39, 1.26]	-+
Etaher 2020	64	171	36	97	2.4%	1.01 [0.61, 1.70]	+
Furie 2019	100	206	199	349	3.1%	0.71 [0.50, 1.00]	
Guimares 2018	27	76	419	847	2.5%	0.56 [0.35, 0.92]	
lawatmeh 2020	101	281	303	664	3.3%	0.67 [0.50, 0.89]	-
liguchi 2019	148	491		12023	3.7%	0.95 [0.78, 1.16]	+
Javed 2009	24	64	61	143	2.1%	0.81 [0.44, 1.48]	-+
Kadesjo 2019	56	251	213	1111	3.2%	1.21 [0.87, 1.69]	<u>+</u>
ambrecht 2018	28	119	46	360	2.4%	2.10 [1.24, 3.55]	
andes 2016	54	107	54	107	2.4%	1.00 [0.59, 1.71]	+
opez Cuenca 2016	52	117	336	707	2.9%	0.88 [0.60, 1.31]	+
Meigher 2016	122	452	126	340	3.3%	0.63 [0.46, 0.85]	
Vestelberger 2020	26	128	180	684	2.6%	0.71 [0.45, 1.13]	
Veumann 2017	12	99	42	188	1.9%	0.48 [0.24, 0.96]	
Pandey 2020	47	103	44	97	2.3%	1.01 [0.58, 1.76]	
Putot 2018	264	847	504	2036	3.7%	1.38 [1.15, 1.64]	+
Putot 2019	99	254	138	365	3.2%	1.05 [0.76, 1.46]	+
Radovanovic 2017	286	1091		13828	3.8%	1.42 [1.23, 1.64]	-
Raphael 2020	150	1054	313	1365	3.6%	0.56 [0.45, 0.69]	-
Saaby 2013	40	144	52	397	2.6%	2.55 [1.60, 4.07]	
Saaby 2014	28	119	46	360	2.4%	2.10 [1.24, 3.55]	
Sandoval 2014	57	190	21	66	2.1%	0.92 [0.50, 1.68]	
Sandoval 2017	43	140	32	77	2.2%	0.62 [0.35, 1.11]	-+
Sato 2020	40	155	1015	2834	3.0%	0.62 [0.43, 0.90]	
Shah 2015	93	429	185	1171	3.4%	1.48 [1.12, 1.95]	-
Singh 2020	165	1225	405	2097	3.7%	0.65 [0.53, 0.79]	+
Smilowitz 2018	58	146	61	137	2.6%	0.82 [0.51, 1.32]	-
Stein 2014	61	127	945	2691	3.1%	1.71 [1.19, 2.44]	
Froung 2020	41	175	56	275	2.7%	1.20 [0.76, 1.89]	+
Fotal (95% CI)		12157		93345	100.0%	0.97 [0.85, 1.10]	
Total events	3044		23287				1
Heterogeneity: Tau ² = 0.11;		46 df -		0 00001): 12 = 839	6	
Test for overall effect: Z = 0.			0011	0.00001), 1 = 007	•	0.01 0.1 1 10 Favours T1MI Favours T2

gure S4. Forest Plo	T2M		T1N			Odds Ratio	Odds Ratio
Study or Subgroup	Events	-	Events		Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Arora 2018	225	264	642	775	3.2%	1.20 [0.81, 1.76]	
Baron 2016	962	1313		40501	3.7%	1.47 [1.30, 1.67]	-
Cediel 2017	153	194	270	376	3.1%	1.47 [0.97, 2.21]	-
Chapman 2018	254	429	533	1171	3.6%	1.74 [1.39, 2.17]	+
Conseugra Sanchez 2018	54	75	91	125	2.5%	0.96 [0.51, 1.82]	
Etaher 2020	128	171	56	97	2.8%	2.18 [1.28, 3.71]	
Furie 2019	159	206	265	349	3.1%	1.07 [0.71, 1.61]	+
Guimares 2018	60	76	688	847	2.6%	0.87 [0.49, 1.54]	-+
Hawatmeh 2020	242	281	583	664	3.1%	0.86 [0.57, 1.30]	-+
Higuchi 2019	311	491	7064	12023	3.6%	1.21 [1.01, 1.46]	
Javed 2009	53	64	126	143	2.0%	0.65 [0.29, 1.48]	-++
Lambrecht 2018	66	119	193	360	3.1%	1.08 [0.71, 1.63]	+
Landes 2016	87	107	82	107	2.4%	1.33 [0.68, 2.57]	
Lopez Cuenca 2016	103	117	522	707	2.6%	2.61 [1.46, 4.67]	—
Weigher 2016	289	452	224	340	3.4%	0.92 [0.68, 1.23]	1
Nestelberger 2020	92	128	521	684	3.1%	0.80 [0.52, 1.22]	7
Neumann 2017	77	99	154	188	2.6%	0.77 [0.42, 1.41]	
Paiva 2015	192	236	580	764	3.2%	1.38 [0.96, 2.00]	
Pandey 2020	68	103	68	97	2.6%	0.83 [0.46, 1.50]	
Putot 2018	683	847	1140	2036	3.6%	3.27 [2.70, 3.96]	
Putot 2019	211	254	279	365	3.1%	1.51 [1.01, 2.27]	
Radovanovic 2017	802 716	1091 1054	8504 966	13828	3.7%	1.74 [1.51, 2.00]	1-
Raphael 2020	81	1054	215	1365 397	3.7% 3.2%	0.87 [0.74, 1.04]	1
Saaby 2013 Saaby 2014	66	119	193	360	3.1%	1.09 [0.74, 1.60] 1.08 [0.71, 1.63]	1
Sandoval 2014	125	190	49	66	2.5%	0.67 [0.36, 1.25]	-+
Sandoval 2017	104	140	62	77	2.4%	0.70 [0.35, 1.38]	-+
Sato 2020	103	155	1885	2834	3.3%	1.00 [0.71, 1.40]	+
Shah 2015	254	429	533	1171	3.6%	1.74 [1.39, 2.17]	-
Singh 2020	419	1225	970	2097	3.7%	0.60 [0.52, 0.70]	-
Smilowitz 2018	128	146	118	137	2.3%	1.15 [0.57, 2.29]	_ _
Stein 2014	108	127	1631	2691	2.9%	3.69 [2.25, 6.05]	· · · ·
Troung 2020	161	175	241	275	2.4%	1.62 [0.84, 3.12]	
Total (95% CI)		11021		88017	100.0%	1.22 [1.03, 1.45]	+
Total events	7536		55782				ľ
Heterogeneity: Tau ² = 0.20;	Chi ² = 315	.20, df =	= 32 (P <	0.00001); l ² = 90%		0.01 0.1 1 10
Test for overall effect: Z = 2.		-					0.01 0.1 1 10 Favours T1MI Favours T2N
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	T2M	i i	T1N	11		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95%
Arora 2018	131	264	441	775	3.4%	0.75 [0.56, 0.99]		-
Baron 2016	548	1313	14893	40501	3.5%	1.23 [1.10, 1.38]		-
Chapman 2018	177	429	539	1171	3.4%	0.82 [0.66, 1.03]		-
Conseugra Sanchez 2018	38	75	66	125	2.9%	0.92 [0.52, 1.63]		-
Etaher 2020	89	171	48	97	3.1%	1.11 [0.67, 1.82]		+
Furie 2019	121	206	218	349	3.3%	0.86 [0.60, 1.22]		-+
Guimares 2018	58	76	625	847	3.0%	1.14 [0.66, 1.98]		+-
Hawatmeh 2020	205	281	505	664	3.3%	0.85 [0.62, 1.17]		-
Higuchi 2019	174	491	5044	12023	3.5%	0.76 [0.63, 0.92]		-
Javed 2009	34	64	113	143	2.8%	0.30 [0.16, 0.57]		
Lambrecht 2018	48	119	137	360	3.2%	1.10 [0.72, 1.68]		+
Landes 2016	82	107	69	107	2.9%	1.81 [0.99, 3.28]		-
Lopez Cuenca 2016	89	117	530	707	3.1%	1.06 [0.67, 1.68]		+
Meigher 2016	194	452	180	340	3.4%	0.67 [0.50, 0.89]		-
Nestelberger 2020	46	128	440	684	3.2%	0.31 [0.21, 0.46]		-
Neumann 2017	40	99	108	188	3.1%	0.50 [0.31, 0.82]		
Paiva 2015	125	236	442	764	3.4%	0.82 [0.61, 1.10]		-+
Pandey 2020	38	103	51	97	3.0%	0.53 [0.30, 0.93]		
Putot 2018	419	847	919	2036	3.5%	1.19 [1.01, 1.40]		-
Putot 2019	169	254	259	365	3.3%	0.81 [0.58, 1.15]		-
Radovanovic 2017	631	1091	8076	13828	3.5%	0.98 [0.86, 1.11]		t
Raphael 2020	359	1054	790	1365	3.5%	0.38 [0.32, 0.44]		-
Saaby 2013	60	144	158	397	3.2%	1.08 [0.73, 1.59]		+
Saaby 2014	48	119	137	360	3.2%	1.10 [0.72, 1.68]		+
Sandoval 2014	63	190	36	66	2.9%	0.41 [0.23, 0.73]		
Sandoval 2017	61	140	50	77	2.9%	0.42 [0.23, 0.74]		
Sato 2020	95	155	1435	2834	3.3%	1.54 [1.11, 2.15]		
Shah 2015	117	429	539	1171	3.4%	0.44 [0.35, 0.56]		+
Singh 2020	172	1225	1229	2097	3.5%	0.12 [0.10, 0.14]		-
Smilowitz 2018	102	146	98	137	3.0%	0.92 [0.55, 1.54]		+
Stein 2014	93	127	1924	2691	3.2%	1.09 [0.73, 1.63]		+
Total (95% CI)		10652		87366	100.0%	0.74 [0.58, 0.94]		•
Total events	4626		40099					
Heterogeneity: Tau ² = 0.42;	Chi ² = 703	.94, df =	= 30 (P <	0.00001); I ² = 96%		0.01	0.1 1 1
Test for overall effect: Z = 2	.50 (P = 0.0	01)					0.01	T1MI T2MI

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
vrora 2018	80	264	327	775	3.7%	0.60 [0.44, 0.80]	-
Baron 2016	771	1313	24754	40501	4.0%	0.90 [0.81, 1.01]	-
Cediel 2017	62	194	218	376	3.6%	0.34 [0.24, 0.49]	-
Chapman 2018	62	429	380	1171	3.8%	0.35 [0.26, 0.47]	
Conseugra Sanchez 2018	10	75	27	125	2.5%	0.56 [0.25, 1.23]	
taher 2020	21	171	30	97	2.9%	0.31 [0.17, 0.59]	
urie 2019	73	206	133	349	3.6%	0.89 [0.62, 1.28]	-+
Guimares 2018	36	76	304	847	3.3%	1.61 [1.00, 2.58]	
lawatmeh 2020	88	281	272	664	3.8%	0.66 [0.49, 0.88]	-
aved 2009	30	64	66	143	3.0%	1.03 [0.57, 1.86]	+
ambrecht 2018	91	119	284	360	3.3%	0.87 [0.53, 1.42]	
andes 2016	44	107	41	107	3.1%	1.12 [0.65, 1.94]	+-
opez Cuenca 2016	23	117	232	707	3.3%	0.50 [0.31, 0.81]	
Meigher 2016	172	452	129	340	3.8%	1.00 [0.75, 1.34]	+
lestelberger 2020	21	128	181	684	3.3%	0.55 [0.33, 0.90]	
eumann 2017	17	99	52	188	3.0%	0.54 [0.29, 1.00]	
Pandey 2020	13	103	16	97	2.5%	0.73 [0.33, 1.61]	-+
Putot 2018	280	847	1271	2036	4.0%	0.30 [0.25, 0.35]	+
Putot 2019	101	254	243	365	3.7%	0.33 [0.24, 0.46]	
Radovanovic 2017	340	1091	5697	13828	4.0%	0.65 [0.57, 0.74]	*
Raphael 2020	462	1054	907	1365	4.0%	0.39 [0.33, 0.47]	•
Saaby 2013	35	144	129	397	3.4%	0.67 [0.43, 1.03]	
Saaby 2014	91	119	284	360	3.3%	0.87 [0.53, 1.42]	-+
Sandoval 2017	52	140	23	77	3.0%	1.39 [0.76, 2.52]	+
Sato 2020	51	155	921	2834	3.7%	1.02 [0.72, 1.44]	+
Shah 2015	62	429	380	1171	3.8%	0.35 [0.26, 0.47]	
Singh 2020	244	1225	1063	2097	4.0%	0.24 [0.21, 0.29]	-
Smilowitz 2018	96	146	89	137	3.3%	1.04 [0.63, 1.69]	+
Stein 2014	20	127	1095	2691	3.3%	0.27 [0.17, 0.44]	
fotal (95% CI)		9929		74889	100.0%	0.60 [0.49, 0.73]	•
otal events	3448		39548				
leterogeneity: Tau ² = 0.26		1.27, df		0.0000	1); l ² = 93 ⁶	% H	.01 0.1 1 10

	T2M	1	T1N	11		Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random	,95% CI	
Baron 2016	824	1313	27283	40501	21.6%	0.82 [0.73, 0.91]				
Javed 2009	14	64	54	143	11.0%	0.46 [0.23, 0.91]				
Pandey 2020	22	103	22	97	11.2%	0.93 [0.47, 1.81]				
Putot 2018	91	847	423	2036	19.7%	0.46 [0.36, 0.58]		-		
Putot 2019	27	254	97	365	15.2%	0.33 [0.21, 0.52]				
Radovanovic 2017	247	1091	3084	13828	21.2%	1.02 [0.88, 1.18]		•		
Total (95% CI)		3672		56970	100.0%	0.63 [0.46, 0.87]		٠		
	1225		30963							

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	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Arora 2018	66	264	130	775	6.5%	1.65 [1.18, 2.32]	-
Baron 2016	355	1313	8056	40501	7.7%	1.49 [1.32, 1.69]	•
Cediel 2017	51	194	42	376	5.6%	2.84 [1.80, 4.46]	
Etaher 2020	83	171	15	97	4.4%	5.16 [2.75, 9.65]	
Furie 2019	74	206	99	349	6.3%	1.42 [0.98, 2.04]	-
Javed 2009	33	64	43	143	4.6%	2.48 [1.35, 4.54]	
Landes 2016	29	107	17	107	4.2%	1.97 [1.01, 3.85]	-
Meigher 2016	86	452	54	340	6.2%	1.24 [0.86, 1.81]	
Putot 2018	122	847	113	2036	6.9%	2.86 [2.19, 3.75]	-
Putot 2019	55	254	45	365	5.8%	1.97 [1.28, 3.03]	-
Radovanovic 2017	158	1091	982	13828	7.5%	2.22 [1.85, 2.65]	-
Saaby 2013	20	144	23	397	4.4%	2.62 [1.39, 4.94]	
Sandoval 2014	49	190	9	66	3.6%	2.20 [1.01, 4.78]	
Sandoval 2017	20	140	13	77	3.7%	0.82 [0.38, 1.76]	
Sato 2020	68	155	1261	2834	6.6%	0.97 [0.70, 1.35]	+
Smilowitz 2018	41	146	41	137	5.2%	0.91 [0.55, 1.53]	-+
Stein 2014	45	127	328	2691	6.2%	3.95 [2.70, 5.79]	
Troung 2020	23	175	29	275	4.7%	1.28 [0.72, 2.30]	
Total (95% CI)		6040		65394	100.0%	1.87 [1.53, 2.28]	•
Total events	1378		11300				

	T2M	I.	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup					Weight		M-H, Random, 95% CI
Baron 2016	151	1313		40501	4.9%	1.60 [1.35, 1.91]	-
Cediel 2017	31	194	15	376	3.8%	4.58 [2.40, 8.71]	
Chapman 2020		1121	792	4981	4.9%	1.86 [1.60, 2.17]	
Etaher 2020	42	171	5	97	2.9%	5.99 [2.28, 15.72]	
Furie 2019	66	206	96	349	4.5%	1.24 [0.85, 1.81]	I •-
lawatmeh 2020	79	281	119	664	4.6%	1.79 [1.29, 2.48]	-
Kadesjo 2019	40	251	91	1111	4.5%	2.12 [1.42, 3.17]	
ambrecht 2018	26	119	32	360		2.87 [1.63, 5.05]	_
andes 2016	21	107	17	107	3.6%	1.29 [0.64, 2.61]	_ _
opez Cuenca 2016	21	117	42	707	4.0%	3.46 [1.97, 6.10]	
Meigher 2016	118	452	54	340	4.6%	1.87 [1.31, 2.68]	-
-							
Neumann 2017	25	99	36	188	4.0%	1.43 [0.80, 2.55]	_
Putot 2018	231	847	71	2036	4.7%	10.38 [7.84, 13.75]	
Putot 2019	78	254	36	365		4.05 [2.62, 6.26]	
Radovanovic 2017	74	1091		13828	4.8%	3.40 [2.61, 4.42]	-
Raphael 2020	86	1054	26	1365		4.58 [2.93, 7.15]	
Saaby 2013	34	144	45	397	4.2%	2.42 [1.48, 3.96]	
Saaby 2014	26	119	32	360	4.0%	2.87 [1.63, 5.05]	
Sandoval 2014	46	190	7	66	3.2%	2.69 [1.15, 6.31]	
Sandoval 2017	40	140	10	77	3.5%	2.68 [1.25, 5.72]	
Sato 2020	13	155	433			0.51 [0.29, 0.90]	
Smilowitz 2018	75	146	61	137	4.3%	1.32 [0.82, 2.10]	† •-
Stein 2014	33	127	248	2691	4.4%	3.46 [2.28, 5.25]	
Froung 2020	13	175	24	275	3.6%	0.84 [0.42, 1.70]	
Fotal (95% CI)		8873		74212	100.0%	2.35 [1.82, 3.03]	•
Total events	1661		5617				
Heterogeneity: Tau ² =	0.33; Chi ²	= 232.	52, df = 2	3 (P < 0	.00001); F	² = 90%	1 0.1 1 10
Test for overall effect:	Z = 6.60 (P < 0.0	0001)				Irs [experimental] Favours [control

	T2M		T1N			Odds Ratio		Odds Ratio	
tudy or Subgroup			Events			M-H, Random, 95% C		M-H, Random, 95% Cl	
rora 2018	46	264	111	775	6.3%	1.26 [0.87, 1.84]			
ediel 2017	21	194	52	376	5.4%	0.76 [0.44, 1.30]		T	
hapman 2018 jurie 2019	29 28	429 206	85 56	1171 349	5.9%	0.93 [0.60, 1.43]		1	
lawatmeh 2020	28	200	89	664	5.6% 5.9%	0.82 [0.50, 1.34] 0.72 [0.46, 1.12]		-	
liguchi 2019	20	491		12023	4.4%	1.08 [0.53, 2.20]			
ambrecht 2018	17	119	20	360	4.6%	2.83 [1.43, 5.61]			
opez Cuenca 2016	11	117	57	707	4.6%	1.18 [0.60, 2.33]		_ _	
lestelberger 2020	2	128	72	684	2.0%	0.13 [0.03, 0.56]		<u> </u>	
utot 2018	110	847	138	2036	6.8%	2.05 [1.58, 2.67]		-	
utot 2019	55	254	54	365	6.0%	1.59 [1.05, 2.41]		⊢	
adovanovic 2017	103	1091	650	13828	7.0%	2.11 [1.70, 2.63]		+	
aaby 2013	18	144	21	397	4.7%	2.56 [1.32, 4.95]			
aaby 2014	17	119	20	360	4.6%	2.83 [1.43, 5.61]			
andoval 2017	3	140	5	77	1.9%	0.32 [0.07, 1.36]	1	+	
ato 2020	14	155	121	2834	5.1%	2.23 [1.25, 3.97]			
hah 2015	29	429	82	1171	5.9%	0.96 [0.62, 1.49]		+	
milowitz 2018	11	146	13	137	3.8%	0.78 [0.34, 1.80]			
tein 2014	22	127	229	2691	5.7%	2.25 [1.40, 3.64]			
roung 2020	12	175	9	275	3.6%	2.18 [0.90, 5.28]			
otal (95% CI)		5856		41280	100.0%	1.33 [1.05, 1.69]		•	
otal events			20000						
OBLEVENS	584		2000						
	584 0.20: Chi ²	= 81.8	2066 D. df = 19	(P < 0.0	00001); l ² :	= 77%	L		
leterogeneity: Tau ² = 1 est for overall effect: 2	0.20; Chi ²		D, df = 19	(P < 0.0	00001); l² :	= 77%	0.01 (0.1 1 10 T1MI T2MI	1
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ²	= 77%	0.01 (0.1 1 10 T1MI T2MI	1
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01 (1
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0)0001); l ²	= 77%	0.01 (1
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01 (1
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ^z	= 77%	0.01 (1
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ²	= 77%	0.01 (1
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01 (1
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01 (1
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ²	= 77%	0.01 (1
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01		7
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01		1
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ²	= 77%	0.01		
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01		
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01		
eterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01		
eterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01		
eterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01		
eterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01		
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01		
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01		
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01		
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01		
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01		
leterogeneity: Tau ² =	0.20; Chi ²		D, df = 19	(P < 0.0	00001); I ² :	= 77%	0.01		

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Baron 2016	99	1313	2696	40501	6.7%	1.14 [0.93, 1.41]	· +
Cediel 2017	29	194	38	376	4.0%	1.56 [0.93, 2.62]	
Chapman 2018	48	429	92	1171	5.2%	1.48 [1.02, 2.13]	
Chapman 2020	135	1121	368	4981	6.7%	1.72 [1.39, 2.11]	+
Etaher 2020	28	171	10	97	2.5%	1.70 [0.79, 3.68]	· +
Furie 2019	42	206	98	349	4.9%	0.66 [0.43, 0.99]	
Hawatmeh 2020	24	281	64	664	4.2%	0.88 [0.54, 1.43]	· − +
Higuchi 2019	35	491	748	12023	5.4%	1.16 [0.81, 1.64]	i +
Kadesjo 2019	19	251	71	1111	3.9%	1.20 [0.71, 2.03]	+ −
Lambrecht 2018	24	119	43	360	3.7%	1.86 [1.08, 3.23]	
Lopez Cuenca 2016	20	117	81	707	3.9%	1.59 [0.93, 2.72]	
Nestelberger 2020	5	128	52	684	1.9%	0.49 [0.19, 1.26]	·
Paiva 2015	29	236	59	764	4.3%	1.67 [1.05, 2.68]	
Putot 2018	122	847	127	2036	6.2%	2.53 [1.94, 3.29]	
Putot 2019	50	254	40	365	4.5%	1.99 [1.27, 3.13]	→
Radovanovic 2017	84	1091	774	13828	6.5%	1.41 [1.11, 1.78]	· · · ·
Saaby 2013	31	144	54	397	4.2%	1.74 [1.07, 2.84]	
Saaby 2014	24	119	43	360	3.7%	1.86 [1.08, 3.23]	
Sandoval 2017	18	140	3	77	1.2%	3.64 [1.04, 12.78]	· · · ·
Sato 2020	17	155	276	2834	4.0%	1.14 [0.68, 1.92]	
Shah 2015	48	429	92	1171	5.2%	1.48 [1.02, 2.13]	 - -
Stein 2014	22	127	215	2691	4.3%	2.41 [1.49, 3.90]	
Troung 2020	16	175	16	275	2.7%	1.63 [0.79, 3.35]	
Total (95% CI)		8538		87822	100.0%	1.47 [1.27, 1.71]	i ♦
Total events	969		6060				
Heterogeneity: Tau ² =	0.07; Chi ²	= 62.13	, df = 22	(P < 0.0	001); l ² =	65%	0.01 0.1 1 10

	T2M	1	T1M	1		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M	-H, Random, 95% CI
Javed 2009	17	64	2	143	46.0%	25.50 [5.68, 114.50]		
Sandoval 2017	29	140	6	77	54.0%	3.09 [1.22, 7.82]		
Total (95% CI)		204		220	100.0%	8.15 [1.03, 64.46]		
Total events	46		8					
Heterogeneity: Tau ² =	1.83; Chi ²	= 5.52	df = 1 (F	= 0.02); 1 ² = 829	6	0.01 0	
Test for overall effect:	Z = 1.99 (P = 0.0	5)		Mari Alexio		0.01 0	.1 1 10 T1MI T2MI

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	T2M		T1N	11		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M	-H, Random, 95% Cl
Cediel 2017	67	194	37	376	8.8%	4.83 [3.08, 7.58]		
Etaher 2020	42	171	5	97	4.8%	5.99 [2.28, 15.72]		
Furie 2019	42	206	68	349	8.9%	1.06 [0.69, 1.63]		+
Hawatmeh 2020	48	281	54	664	9.0%	2.33 [1.53, 3.53]		-
Lambrecht 2018	25	119	32	360	7.7%	2.73 [1.54, 4.83]		
Lopez Cuenca 2016	51	117	103	707	9.0%	4.53 [2.97, 6.90]		
Neumann 2017	34	99	20	188	7.2%	4.39 [2.36, 8.19]		
Paiva 2015	72	236	117	764	9.7%	2.43 [1.73, 3.41]		-
Putot 2018	235	847	160	2036	10.6%	4.50 [3.61, 5.61]		*
Radovanovic 2017	170	1091	567	13828	10.8%	4.32 [3.59, 5.19]		
Saaby 2013	34	144	50	397	8.4%	2.15 [1.32, 3.49]		
Sandoval 2017	16	140	7	77	5.0%	1.29 [0.51, 3.29]		
Total (95% CI)		3645		19843	100.0%	3.02 [2.29, 3.99]		•
Total events	836		1220					
Heterogeneity: Tau ² =	0.18; Chi ²	= 62.33	3, df = 11	(P < 0.0	00001); I ² :	= 82%		
Test for overall effect:	Z = 7.83 (P < 0.0	0001)				0.01 0	.1 1 10 T1MI T2MI

	T2M	1	T1N	11		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95	%CI
Balanescu 2020	8	49	67	152	5.2%	0.25 [0.11, 0.56]		
Baron 2016	899	1313	35883	40501	7.4%	0.28 [0.25, 0.32]	-	
Cediel 2017	42	194	337	376	6.5%	0.03 [0.02, 0.05]		
Chapman 2020	749	1121	4061	4981	7.4%	0.46 [0.40, 0.53]	-	
Conseugra Sanchez 2018	62	75	102	125	5.5%	1.08 [0.51, 2.28]		
Furie 2019	88	206	258	349	6.9%	0.26 [0.18, 0.38]	-	
Landes 2016	65	107	103	107	4.3%	0.06 [0.02, 0.18]		
Lopez Cuenca 2016	87	117	618	707	6.5%	0.42 [0.26, 0.67]		
Meigher 2016	41	452	201	340	6.8%	0.07 [0.05, 0.10]	-	
Radovanovic 2017	853	1091	12846	13828	7.3%	0.27 [0.23, 0.32]	-	
Sandoval 2014	65	190	56	66	5.5%	0.09 [0.04, 0.19]		
Sandoval 2017	22	140	38	77	5.9%	0.19 [0.10, 0.36]		
Shah 2015	217	429	1041	1171	7.1%	0.13 [0.10, 0.17]	-	
Smilowitz 2018	46	146	128	137	5.4%	0.03 [0.02, 0.07]		
Stein 2014	69	127	2274	2691	6.9%	0.22 [0.15, 0.31]	-	
Troung 2020	161	175	260	275	5.4%	0.66 [0.31, 1.41]		
Total (95% CI)		5932		65883	100.0%	0.19 [0.13, 0.26]	•	
Total events	3474		58273					
Heterogeneity: Tau ² = 0.40;	Chi ² = 278	3.78, df	= 15 (P <	< 0.0000	1); I ² = 95 ⁶	%	0.01 0.1 1	10

	T2M	1	T1N	11		Odds Ratio	Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95	5%CI	
Baron 2016	195	1313	1774	40501	9.4%	3.81 [3.25, 4.47	ŋ .		
Cediel 2017	90	194	37	376	8.3%	7.93 [5.10, 12.33	1		
Chapman 2020	116	1121	171	4981	9.2%	3.25 [2.54, 4.15] –	-	
Furie 2019	122	206	178	349	8.8%	1.40 [0.98, 1.98	1		
Landes 2016	78	107	38	107	7.6%	4.88 [2.73, 8.74	.] –	•	
Lopez Cuenca 2016	22	117	38	707	7.7%	4.08 [2.31, 7.19	a –	-	
Radovanovic 2017	482	1091	4425	13828	9.5%	1.68 [1.48, 1.91] –		
Sandoval 2014	112	190	35	66	7.7%	1.27 [0.72, 2.23	ij +-		
Sandoval 2017	72	140	40	77	7.7%	0.98 [0.56, 1.71	1 +		
Shah 2015	80	429	45	1171	8.6%	5.74 [3.91, 8.42	1]	-	
Stein 2014	15	127	105	2691	7.6%	3.30 [1.86, 5.85	j —	—	
Troung 2020	28	175	44	275	7.9%	1.00 [0.60, 1.68	a 🕇		
Total (95% CI)		5210		65129	100.0%	2.64 [1.86, 3.74	a 🖌 🔶		
Total events	1412		6930						
Heterogeneity: Tau ² = (1 (P < 0.	.00001); l²	= 93%	0.01 0.1 1	10	
Test for overall effect: 2	Z = 5.46 (P < 0.0	0001)				Favours [experimental] Favo	urs [contr	

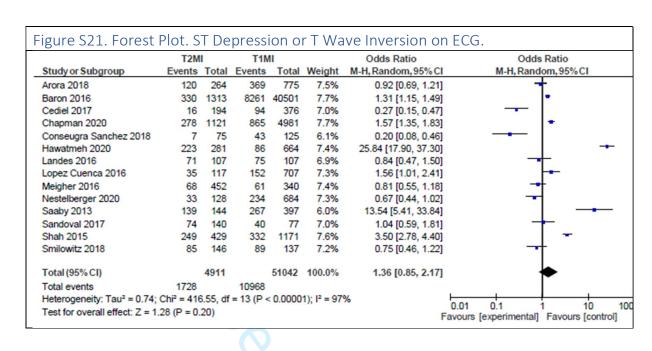
	T2M	I	T1M			Odds Ratio	Odd	Is Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Ran	dom, 95% Cl
Sandoval 2014	13	190	20	66	45.6%	0.17 [0.08, 0.36]		8.6
Sandoval 2017	15	140	30	77	54.4%	0.19 [0.09, 0.38]		
Total (95% CI)		330		143	100.0%	0.18 [0.11, 0.30]	+	
Total events	28		50					
Heterogeneity: Tau ² =	0.00; Chi ²	= 0.04,	df = 1 (P	= 0.84); l ² = 0%		0.01 0.1	1 10 1
Test for overall effect:	Z = 6.49 (I	P < 0.0	0001)				0.01 0.1 T1N	10 CT

	T2M	I	T1M			Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	
Sandoval 2014	21	190	14	66	42.8%	0.46 [0.22, 0.97]		
Sandoval 2017	25	140	25	77	57.2%	0.45 [0.24, 0.86]		
Total (95% CI)		330		143	100.0%	0.46 [0.28, 0.74]	•	
Total events	46		39					

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% CI
Baron 2016	899	1313	2506	40501	34.0%	32.92 [29.11, 37.24]	
Lopez Cuenca 2016	8	117	51	707	32.8%	0.94 [0.44, 2.04]	i —
Neumann 2017	81	99	105	188	33.3%	3.56 [1.98, 6.39]	
Total (95% CI)		1529		41396	100.0%	4.90 [0.48, 50.33]	
Total events	988		2662				

	T2M	1	T1M	1		Odds Ratio		Odd	s Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	1	M-H, Ran	dom, 95% Cl	
Cediel 2017	15	194	5	376	17.2%	6.22 [2.22, 17.38]				
Chapman 2020	38	1121	102	4981	25.6%	1.68 [1.15, 2.45]			-	
Furie 2019	12	206	24	349	21.4%	0.84 [0.41, 1.71]			-	
Shah 2015	31	429	21	1171	23.4%	4.27 [2.42, 7.51]				
Froung 2020	3	175	5	275	12.5%	0.94 [0.22, 3.99]		10 	-	
Fotal (95% CI)		2125		7152	100.0%	2.10 [1.05, 4.18]			•	
Total events	99		157							
Heterogeneity: Tau ² =	O AE Chie	- 10 1	2 df - 4/	D - 0.0	0071-12-	709/	<u> </u>	22	10 AL	

	T2M	1	T1N	11		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
Baron 2016	173	1313	14824	40501	8.3%	0.26 [0.22, 0.31]	-	
Cediel 2017	5	194	92	376	3.9%	0.08 [0.03, 0.20]		
Chapman 2020	36	1121	870	4981	7.4%	0.16 [0.11, 0.22]	-	
Furie 2019	4	206	18	349	3.2%	0.36 [0.12, 1.09]		
Higuchi 2019	288	491	8917	12023	8.2%	0.49 [0.41, 0.59]	+	
Landes 2016	11	107	11	107	4.1%	1.00 [0.41, 2.42]	_ _	
Lopez Cuenca 2016	1	117	225	707	1.3%	0.02 [0.00, 0.13]	·	
Nestelberger 2020	4	128	115	684	3.5%	0.16 [0.06, 0.44]		
Paiva 2015	35	236	417	764	7.1%	0.14 [0.10, 0.21]	-	
Putot 2019	28	254	136	365	6.7%	0.21 [0.13, 0.33]	-	
Putot 2020	207	862	1929	3710	8.2%	0.29 [0.25, 0.35]	* I	
Radovanovic 2017	213	1091	7436	13828	8.3%	0.21 [0.18, 0.24]	•	
Raphael 2020	23	1054	198	1365	6.7%	0.13 [0.08, 0.20]	-	
Saaby 2013	5	144	130	397	3.9%	0.07 [0.03, 0.18]		
Sandoval 2017	31	140	24	77	5.5%	0.63 [0.34, 1.17]		
Shah 2015	40	429	427	1171	7.3%	0.18 [0.13, 0.25]	-	
Stein 2014	25	127	1413	2691	6.7%	0.22 [0.14, 0.35]	-	
Total (95% CI)		8014		84096	100.0%	0.22 [0.17, 0.28]	◆	
Total events	1129		37182					
Heterogeneity: Tau ² =	0.18: Chi ²	= 130.4	47. df = 1	6 (P < 0	.00001); I ²	* = 88%	0.01 0.1 1 10	_



	T2M	1	T1M	1		Odds Ratio		Odds Rati	0
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-	H, Random, 9	5% CI
Lopez Cuenca 2016	12	117	156	707	48.4%	0.40 [0.22, 0.75]			
Sandoval 2014	2	190	6	66	12.8%	0.11 [0.02, 0.54]			
Sandoval 2017	16	140	15	77	38.8%	0.53 [0.25, 1.15]		3 -8 -	
Total (95% CI)		447		850	100.0%	0.38 [0.20, 0.71]		•	
Total events	30		177						
Heterogeneity: Tau ² =	0.11; Chi ²	= 3.09	df = 2(F	= 0.21); I ² = 35%	6	0.01 0.1		1

	T2M	1	T1M	1		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H	H, Random, 95% Cl
Meigher 2016	90	452	27	340	65.4%	2.88 [1.83, 4.55]		
Sandoval 2017	56	140	18	77	34.6%	2.19 [1.17, 4.09]		
Total (95% CI)		592		417	100.0%	2.62 [1.81, 3.79]		•
Total events	146		45					

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Baron 2016	95	1313	1791	40501	40.5%	1.69 [1.36, 2.09]	-
Cediel 2017	40	194	72	376	24.2%	1.10 [0.71, 1.69]	+
Lopez Cuenca 2016	10	117	35	707	12.2%	1.79 [0.86, 3.73]	+-
Nestelberger 2020	9	128	34	684	11.5%	1.45 [0.68, 3.09]	- +
Troung 2020	21	175	11	275	11.6%	3.27 [1.54, 6.97]	
Total (95% CI)		1927		42543	100.0%	1.62 [1.21, 2.17]	◆
Total events	175		1943				
Heterogeneity: Tau ² = (0.04: Chi ²	= 6.75	df = 4 (F)	P = 0.15	$ ^2 = 41\%$		0.01 0.1 1 10

	T2MI	T1M	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events Tot	tal Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Lopez Cuenca 2016		17 49	707	86.1%	5.06 [3.07, 8.33]	
Sandoval 2017	22 14	40 3	77	13.9%	4.60 [1.33, 15.90]	
Total (95% CI)	2	57	784	100.0%	4.99 [3.14, 7.93]	•
Total events	54	52				
Heterogeneity: Tau ² =	0.00; Chi ² = 0.	02, df = 1 (P	9 = 0.89); l ² = 0%		0.01 0.1 1 10
Test for overall effect:	Z = 6.80 (P < 6	0.00001)			F	avours [experimental] Favours [con

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	T2M	1	T1N	11		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	om, 95% CI
Arora 2018	68	264	609	775	4.0%	0.09 [0.07, 0.13]	-	
Balanescu 2020	9	49	99	152	3.4%	0.12 [0.05, 0.27]		
Cediel 2017	11	194	278	376	3.6%	0.02 [0.01, 0.04]		
Chapman 2020	112	1121	2928	4981	4.0%	0.08 [0.06, 0.10]	+	
Conseugra Sanchez 2018	12	75	91	125	3.5%	0.07 [0.03, 0.15]		
Etaher 2020	25	171	41	97	3.7%	0.23 [0.13, 0.42]		
Furie 2019	22	206	190	349	3.8%	0.10 [0.06, 0.16]	_	
Guimares 2018	56	76	711	847	3.8%	0.54 [0.31, 0.92]		
Higuchi 2019	427	491	11406	12023	4.0%	0.36 [0.27, 0.48]	-	
Javed 2009	32	64	124	143	3.6%	0.15 [0.08, 0.30]		
Lambrecht 2018	28	119	268	360	3.8%	0.11 [0.07, 0.17]		
Lopez Cuenca 2016	46	117	622	707	3.9%	0.09 [0.06, 0.14]		
Nestelberger 2020	23	128	582	684	3.8%	0.04 [0.02, 0.06]		
Neumann 2017	38	99	163	188	3.7%	0.10 [0.05, 0.17]		
Paiva 2015	121	236	619	764	4.0%	0.25 [0.18, 0.34]	-	
Putot 2018	325	847	2036	2036	1.2%	0.00 [0.00, 0.00]	•	
Putot 2019	105	254	351	365	3.7%	0.03 [0.02, 0.05]		
Radovanovic 2017	660	1091	12067	13828	4.1%	0.22 [0.20, 0.25]		
Raphael 2020	402	1054	1200	1365	4.0%	0.08 [0.07, 0.10]	-	
Reed 2017	16	146	49	137	3.7%	0.22 [0.12, 0.41]		
Saaby 2014	28	119	268	360	3.8%	0.11 [0.07, 0.17]		
Sandoval 2017	13	140	46	77	3.5%	0.07 [0.03, 0.14]	_	
Sato 2020	63	155	2485	2834	4.0%	0.10 [0.07, 0.14]		
Shah 2015	31	429	744	1171	3.9%	0.04 [0.03, 0.07]	-	
Singh 2020	269	1225	1971	2097	4.0%	0.02 [0.01, 0.02]	-	
Smilowitz 2018	19	146	114	137	3.6%	0.03 [0.02, 0.06]		
Stein 2014	46	127	2387	2691	3.9%	0.07 [0.05, 0.11]		
Troung 2020	175	175	275	275		Not estimable		
Total (95% CI)		9318		49944	100.0%	0.09 [0.06, 0.12]	+	
Total events	3182		42724					
Heterogeneity: Tau ² = 0.85;	Chi ² = 698	8.89, df	= 26 (P <	0.0000	1); I ² = 969	6	0.01 0.1	1 10

	T2M	I	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95%
Baron 2016	533	1313	17456	40501	9.6%	0.90 [0.81, 1.01]	
Conseugra Sanchez 2018	4	75	82	125	9.0%	0.03 [0.01, 0.09]	
Furie 2019	7	206	166	349	9.3%	0.04 [0.02, 0.08]	
Javed 2009	25	64	111	143	9.4%	0.18 [0.10, 0.35]	
Lopez Cuenca 2016	78	117	64	707	9.5%	20.09 [12.66, 31.90]	
Putot 2019	238	254	346	365	9.3%	0.82 [0.41, 1.62]	
Raphael 2020	162	1054	1058	1365	9.6%	0.05 [0.04, 0.07]	-
Saaby 2014	15	119	236	360	9.4%	0.08 [0.04, 0.14]	
Sandoval 2017	7	140	42	77	9.2%	0.04 [0.02, 0.11]	_ _
Smilowitz 2018	14	146	87	137	9.4%	0.06 [0.03, 0.12]	
Troung 2020	163	175	275	275	6.3%	0.02 [0.00, 0.40]	·
Total (95% CI)		3663		44404	100.0%	0.16 [0.05, 0.54]	-
Total events	1246		19923				
Heterogeneity: Tau ² = 4.01;	Chi ² = 989	9.87, df	= 10 (P <	0.0000	1); l ² = 99 ⁶	%	0.01 0.1 1

	T2M	1	T1N	11		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	om, 95% Cl
Baron 2016	381	1313	11340	40501	22.4%	1.05 [0.93, 1.19]		
Putot 2019	59	254	150	365	21.4%	0.43 [0.30, 0.62]	-	
Saaby 2014	11	119	115	360	19.0%	0.22 [0.11, 0.42]		
Sandoval 2017	1	140	15	77	8.1%	0.03 [0.00, 0.23]	< <u>-</u> -	
Smilowitz 2018	1	146	24	137	8.3%	0.03 [0.00, 0.24]	← ∎	
Troung 2020	140	175	195	275	20.7%	1.64 [1.04, 2.58]		.
Total (95% CI)		2147		41715	100.0%	0.40 [0.19, 0.82]	•	
			11839					

Daron 2010	301	1313	11340	4030	22.470	1.05 [0.95, 1.19	1
Putot 2019	59	254	150	365	5 21.4%	0.43 [0.30, 0.62	9 -
Saaby 2014	11	119	115	360	19.0%	0.22 [0.11, 0.42	g
Sandoval 2017	1	140	15	77	8.1%	0.03 [0.00, 0.23	s] ••••
Smilowitz 2018	1	146	24	137	8.3%	0.03 [0.00, 0.24	ı] ← ∎ − − [
Troung 2020	140	175	195	275	5 20.7%	1.64 [1.04, 2.58	1
Total (95% CI)		2147		41715	100.0%	0.40 [0.19, 0.82	1 🔶
Total events	593		11839				
Heterogeneity: Tau ² =	= 0.62; Chi ²	= 68.9	8, df = 5 ((P < 0.0	00001); I ² =	= 93%	0.01 0.1 1 10
Test for overall effect	: Z = 2.48 (P = 0.0	1)				T1MI T2MI
							1 100 1200
Figure S29. Fore	est Plot	. Ech	ocardi	ograr	n Perfo	ormed.	
0	T2M		T1M	-		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cediel 2017	79	194	359	376	14.1%	0.03 [0.02, 0.06]	
Furie 2019	103	206	195	349	14.7%	0.79 [0.56, 1.12]	
Lambrecht 2018	54	119	180	360	14.6%	0.83 [0.55, 1.26]	-
Saaby 2014	91	119	321	360	14.2%	0.39 [0.23, 0.68]	
Sandoval 2017	72	140	62	77	13.7%	0.26 [0.13, 0.49]	
Shah 2015	122	429	340	1171	15.0%	0.97 [0.76, 1.24]	+
Smilowitz 2018	127	146	114	137	13.7%	1.35 [0.70, 2.60]	
Total (95% CI)		1353		2830	100.0%	0.44 [0.20, 0.96]	•
Total events	648		1571				
Heterogeneity: Tau ² =	1.07; Chi ²	= 138.1	14, df = 6	(P < 0.	00001); l ²	= 96%	0.01 0.1 1 10
Test for overall effect:	Z = 2.05 (F	P = 0.04	4)				T1MI T2MI
						4	
Figure S30. Fore	est Plot	. Reg	ional V	Vall N	Notion	Abnormalities or	n Echocardiogram.
	T2M	I	T1M	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Sandoval 2017	22	140	41	77	49.5%	0.16 [0.09, 0.31]	
Smilowitz 2018	75	146	60	137	50.5%	1.36 [0.85, 2.17]	•
Total (95% CI)		286		214	100.0%	0.48 [0.06, 3.78]	
Total events	97		101				
Heterogeneity: Tau ² =		= 27.3			0001)- 12 =	96%	

	T2M	1	T1M	1		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	
Sandoval 2017	22	140	41	77	49.5%	0.16 [0.09, 0.31]	-	
Smilowitz 2018	75	146	60	137	50.5%	1.36 [0.85, 2.17]	-	
Total (95% CI)		286		214	100.0%	0.48 [0.06, 3.78]		
Total events	97		101					

	T2M	1	T1N	11		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
Arora 2018	165	264	645	775	4.7%	0.34 [0.25, 0.46]	-	
Balanescu 2020	30	49	127	152	3.9%	0.31 [0.15, 0.64]		
Baron 2016	1123	1313	36410	40501	4.8%	0.66 [0.57, 0.78]	-	
Chapman 2018	126	429	651	1171	4.7%	0.33 [0.26, 0.42]	-	
Etaher 2020	83	171	68	97	4.3%	0.40 [0.24, 0.68]		
Furie 2019	141	206	247	349	4.6%	0.90 [0.62, 1.30]	-+	
Hawatmeh 2020	165	281	551	664	4.7%	0.29 [0.21, 0.40]	-	
Higuchi 2019	236	491	6786	12023	4.8%	0.71 [0.60, 0.86]	+	
Kadesjo 2019	169	251	946	1111	4.7%	0.36 [0.26, 0.49]	-	
Lopez Cuenca 2016	86	117	614	707	4.4%	0.42 [0.26, 0.67]		
Nestelberger 2020	72	128	548	684	4.5%	0.32 [0.21, 0.47]	-	
Radovanovic 2017	595	1091	7396	13828	4.8%	1.04 [0.92, 1.18]	t	
Raphael 2020	766	1054	1215	1365	4.8%	0.33 [0.26, 0.41]	-	
Reed 2017	75	162	41	88	4.3%	0.99 [0.59, 1.66]		
Saaby 2014	44	119	208	360	4.5%	0.43 [0.28, 0.66]		
Sandoval 2017	81	140	53	77	4.2%	0.62 [0.35, 1.12]		
Sato 2020	53	155	1838	2834	4.6%	0.28 [0.20, 0.40]	-	
Shah 2015	124	429	660	1171	4.7%	0.31 [0.25, 0.40]	-	
Singh 2020	513	1225	1878	2097	4.8%	0.08 [0.07, 0.10]	+	
Smilowitz 2018	70	146	78	137	4.4%	0.70 [0.44, 1.11]		
Stein 2014	91	127	2234	2691	4.5%	0.52 [0.35, 0.77]		
Troung 2020	159	175	237	275	4.1%	1.59 [0.86, 2.96]		
Total (95% CI)		8523		83157	100.0%	0.45 [0.33, 0.63]	◆	
Total events	4967		63431					
Heterogeneity: Tau ² =	0.58; Chi ²	= 647.0	37, df = 2	1 (P < 0	.00001); l ²	= 97%	0.01 0.1 1 10	_
Test for overall effect:	Z = 4.73 (F	P < 0.0	0001)			F	avours [experimental] Favours [cor	ntro

	T2MI		T1MI		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Baron 2016	945	1313	30781	40501	6.0%	0.81 [0.72, 0.92]	-
Chapman 2018	156	429	724	1171	5.9%	0.35 [0.28, 0.44]	-
Etaher 2020	57	171	49	97	5.0%	0.49 [0.29, 0.82]	
Hawatmeh 2020	99	281	325	664	5.7%	0.57 [0.43, 0.76]	+
Higuchi 2019	254	491	7531	12023	6.0%	0.64 [0.53, 0.77]	-
Kadesjo 2019	118	251	725	1111	5.7%	0.47 [0.36, 0.62]	-
Lopez Cuenca 2016	53	117	438	707	5.4%	0.51 [0.34, 0.75]	-
Nestelberger 2020	70	128	546	684	5.4%	0.31 [0.21, 0.45]	-
Radovanovic 2017	566	1091	7448	13828	6.0%	0.92 [0.82, 1.04]	
Raphael 2020	571	1054	976	1365	6.0%	0.47 [0.40, 0.56]	-
Saaby 2014	38	119	154	360	5.2%	0.63 [0.40, 0.97]	
Sandoval 2017	43	140	39	77	4.7%	0.43 [0.24, 0.77]	
Sato 2020	93	155	2103	2834	5.6%	0.52 [0.37, 0.73]	-
Shah 2015	135	429	735	1171	5.8%	0.27 [0.22, 0.34]	-
Singh 2020	271	1225	1269	2097	6.0%	0.19 [0.16, 0.22]	•
Smilowitz 2018	62	146	63	137	5.1%	0.87 [0.54, 1.39]	-
Stein 2014	88	127	2126	2691	5.4%	0.60 [0.41, 0.88]	-
Troung 2020	147	175	221	275	5.0%	1.28 [0.78, 2.12]	+
Total (95% CI)		7842		81793	100.0%	0.52 [0.40, 0.67]	◆
Total events	3766		56253				

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	T2M	I .	T1N	11		Odds Ratio		Odds	s Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95%	%CI	M-H, Rand	lom, 95%	6CI
Arora 2018	154	264	637	775	4.5%	0.30 [0.22, 0).41]			
Balanescu 2020	25	49	128	152	4.1%	0.20 [0.10, 0	0.40]		1	
Baron 2016	722	1313	34021	40501	4.6%	0.23 [0.21, 0	0.26]		1	
Chapman 2018	284	429	896	1171	4.6%	0.60 [0.47, 0).77]	+	1	
Etaher 2020	92	171	85	97	4.2%	0.16 [0.08, 0	.32]		1	
Furie 2019	163	206	335	349	4.2%	0.16 [0.08, 0	0.30]		1	
Guimares 2018	74	76	839	847	2.9%	0.35 [0.07, 1	.69]		t i	
Hawatmeh 2020	156	281	594	664	4.5%	0.15 [0.10, 0	0.21]		1	
Higuchi 2019	442	491	11662	12023	4.5%	0.28 [0.20, 0	.38]		1	
Kadesjo 2019	101	251	918	1111	4.5%	0.14 [0.11, 0	0.19]	-	1	
Lopez Cuenca 2016	72	117	64	707	4.4%	16.07 [10.22, 25	5.27]		1	
Nestelberger 2020	36	128	619	684	4.4%	0.04 [0.03, 0	.07] -	-	1	
Radovanovic 2017	983	1091	13772	13828	4.5%	0.04 [0.03, 0	0.05] -	-	1	
Raphael 2020	648	1054	1114	1365	4.6%	0.36 [0.30, 0	.43]	-	1	
Reed 2017	63	162	28	88	4.3%	1.36 [0.79, 2	2.36]	-	•••	
Saaby 2014	56	119	269	360	4.4%	0.30 [0.20, 0	0.46]	_	1	
Sandoval 2017	64	140	66	77	4.1%	0.14 [0.07, 0	.29]	_	1	
Sato 2020	70	155	2562	2834	4.5%	0.09 [0.06, 0	0.12]	-	1	
Shah 2015	166	429	910	1171	4.6%	0.18 [0.14, 0).23]	-	1	
Singh 2020	416	1225	1945	2097	4.6%	0.04 [0.03, 0	0.05]	-	1	
Smilowitz 2018	31	146	58	137	4.3%	0.37 [0.22, 0	0.62]		1	
Stein 2014	109	127	2610	2691	4.3%	0.19 [0.11, 0	.32]		1	
Troung 2020	160	175	245	275	4.2%	1.31 [0.68, 2	2.50]	-	<u>†</u>	
Total (95% CI)		8599		84004	100.0%	0.25 [0.16, 0	.38]	•		
Total events	5087		74377						1	
Heterogeneity: Tau ² =	1.12; Chi ²	= 1005	.85, df =	22 (P <	0.00001);	l ² = 98%	0.01	0.1	-	10
Test for overall effect:	Z = 6.16 (P < 0.0	0001)					[experimental]	Favou	

	T2M	1	T1N	41		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	I M-H, Random, 95% CI
Baron 2016	236	1313	3240	40501	9.9%	2.52 [2.18, 2.91	1
Chapman 2018	44	429	33	1171	9.3%	3.94 [2.47, 6.28	1 –
Furie 2019	24	206	42	349	9.1%	0.96 [0.57, 1.64	i +
Lopez Cuenca 2016	44	117	89	707	9.4%	4.19 [2.71, 6.47	1
Radovanovic 2017	801	1091	11774	13828	9.9%	0.48 [0.42, 0.56	•
Raphael 2020	239	1054	167	1365	9.8%	2.10 [1.69, 2.61	1 +
Sandoval 2017	20	140	3	77	6.7%	4.11 [1.18, 14.31	ı —
Sato 2020	24	155	327	2834	9.4%	1.40 [0.90, 2.20	1 +
Shah 2015	52	429	35	1171	9.4%	4.48 [2.87, 6.98	1 –
Smilowitz 2018	11	146	11	137	8.1%	0.93 [0.39, 2.23	
Troung 2020	24	175	33	275	9.1%	1.17 [0.66, 2.05	1 +
Total (95% CI)		5255		62415	100.0%	1.87 [1.06, 3.30	•
Total events	1519		15754				

	T2M	I	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	I M-H, Random, 95% CI
Baron 2016	1050	1313	38476	40501	20.6%	0.21 [0.18, 0.24	
Chapman 2018	77	429	143	1171	20.3%	1.57 [1.16, 2.13	1 +
Nestelberger 2020	13	128	168	684	19.4%	0.35 [0.19, 0.63	
Smilowitz 2018	86	146	101	137	19.7%	0.51 [0.31, 0.85	_ _ _
Troung 2020	55	175	67	275	20.0%	1.42 [0.93, 2.17	ı † ∙-
Total (95% CI)		2191		42768	100.0%	0.61 [0.21, 1.74	-
Total events	1281		38955				
Heterogeneity: Tau ² =	1 39. Chi2	= 199 (h = 4	(P<00	10001)-12	= 98%	

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	I M-H, Random, 95% CI
Baron 2016	315	1313	4860	40501	24.2%	2.31 [2.03, 2.64]] •
Etaher 2020	53	171	9	97	12.1%	4.39 [2.06, 9.38]	1
Lopez Cuenca 2016	70	117	230	707	19.2%	3.09 [2.07, 4.62]]
Raphael 2020	831	1054	990	1365	23.4%	1.41 [1.17, 1.71]] –
Sato 2020	0	155	23	2834	1.6%	0.38 [0.02, 6.36]	· · · ·
Troung 2020	67	175	99	275	19.4%	1.10 [0.75, 1.63	1 +
Total (95% CI)		2985		45779	100.0%	1.98 [1.37, 2.86]	1 ♦
Total events	1336		6211				
Heterogeneity: Tau ² =	0.14; Chi ²	= 36.7	9, df = 5 (P < 0.00	0001); l ² =	86%	0.01 0.1 1 10
Test for overall effect:	Z = 3.64 (P = 0.0	003)				Favours [experimental] Favours [cont
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	T2M	1	T1N	41		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Arora 2018	153	264	646	775	6.4%	0.28 [0.20, 0.37]	-
Balanescu 2020	29	49	131	152	5.5%	0.23 [0.11, 0.48]	
Baron 2016	972	1313	37261	40501	6.6%	0.25 [0.22, 0.28]	-
Chapman 2018	204	429	872	1171	6.5%	0.31 [0.25, 0.39]	+
Etaher 2020	95	171	81	97	5.8%	0.25 [0.13, 0.46]	
Furie 2019	125	206	280	349	6.3%	0.38 [0.26, 0.56]	-
Hawatmeh 2020	141	281	578	664	6.4%	0.15 [0.11, 0.21]	-
Higuchi 2019	298	491	9238	12023	6.5%	0.47 [0.39, 0.56]	-
Kadesjo 2019	92	251	883	1111	6.4%	0.15 [0.11, 0.20]	-
Lopez Cuenca 2016	92	117	648	707	6.0%	0.34 [0.20, 0.56]	
Nestelberger 2020	39	128	606	684	6.2%	0.06 [0.04, 0.09]	
Raphael 2020	570	1054	1167	1365	6.5%	0.20 [0.16, 0.24]	+
Sato 2020	112	155	2303	2834	6.3%	0.60 [0.42, 0.86]	
Singh 2020	255	1225	1840	2097	6.5%	0.04 [0.03, 0.04]	-
Smilowitz 2018	83	146	100	137	6.1%	0.49 [0.30, 0.80]	
Troung 2020	158	175	241	275	5.8%	1.31 [0.71, 2.43]	+
Total (95% CI)		6455		64942	100.0%	0.25 [0.16, 0.38]	◆
Total events	3418		56875				

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	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Arora 2018	32	264	363	775	4.9%	0.16 [0.11, 0.23]	-
Balanescu 2020	0	0	0	0		Not estimable	
Baron 2016	723	1313	34264	40501	5.1%	0.22 [0.20, 0.25]	• •
Chapman 2020	17	1121	2021	4981	4.8%	0.02 [0.01, 0.04]	
Etaher 2020	7	171	12	97	4.2%	0.30 [0.11, 0.80]	
Furie 2019	3	206	128	349	3.9%	0.03 [0.01, 0.08]	<u>←</u>
Guimares 2018	27	76	440	847	4.8%	0.51 [0.31, 0.83]	
Higuchi 2019	258	491	9206	12023	5.0%	0.34 [0.28, 0.41]	-
Landes 2016	14	107	85	107	4.5%	0.04 [0.02, 0.08]	
Lopez Cuenca 2016	11	117	486	707	4.7%	0.05 [0.02, 0.09]	
Nestelberger 2020	1	128	457	684	2.7%	0.00 [0.00, 0.03]	←
Neumann 2017	0	99	126	188	1.9%	0.00 [0.00, 0.04]	←
Paiva 2015	27	236	507	764	4.9%	0.07 [0.04, 0.10]	-
Putot 2018	103	847	1519	2036	5.0%	0.05 [0.04, 0.06]	
Putot 2019	29	254	235	365	4.9%	0.07 [0.05, 0.11]	
Radovanovic 2017	557	1091	11684	13828	5.1%	0.19 [0.17, 0.22]	-
Raphael 2020	77	1054	791	1365	5.0%	0.06 [0.04, 0.07]	-
Saaby 2014	4	119	194	360	4.1%	0.03 [0.01, 0.08]	
Sandoval 2017	1	140	34	77	2.7%	0.01 [0.00, 0.07]	←
Shah 2015	1	429	564	1171	2.7%	0.00 [0.00, 0.02]	←
Singh 2020	27	1225	1786	2097	4.9%	0.00 [0.00, 0.01]	•
Smilowitz 2018	8	146	53	137	4.5%	0.09 [0.04, 0.20]	
Stein 2014	64	127	2199	2691	4.9%	0.23 [0.16, 0.33]	-
Troung 2020	101	175	257	275	4.7%	0.10 [0.05, 0.17]	-
Total (95% CI)		9936		86425	100.0%	0.06 [0.04, 0.10]	•
Total events	2092		67411				
Heterogeneity: Tau ² =	1.17; Chi ²	= 976.	84, df = 2	2 (P < 0	.00001); I	= 98%	0.01 0.1 1 10

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Study or Subgroup	Events		Events		Weight	M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Arora 2018	4	264	91	775	10.3%	0.12 [0.04, 0.32]	[
Baron 2016	68	1313	2673	40501	13.5%	0.77 [0.60, 0.99]	
Etaher 2020	8	171	15	97	10.9%	0.27 [0.11, 0.66]	
Furie 2019	0	206	16	349	3.9%	0.05 [0.00, 0.82]	·
Guimares 2018	7	76	73	847	11.3%	1.08 [0.48, 2.43]	
Landes 2016	8	107	33	107	11.3%	0.18 [0.08, 0.42]	
Lopez Cuenca 2016	0	117	28	707	3.9%	0.10 [0.01, 1.67]	· · · · · · · · · · · · · · · · · · ·
Nestelberger 2020	0	128	59	684	3.9%	0.04 [0.00, 0.67]	← ■
Putot 2019	4	254	29	365	10.1%	0.19 [0.06, 0.53]	
Saaby 2014	0	119	9	360	3.8%	0.15 [0.01, 2.68]	· · · · ·
Sandoval 2017	0	140	3	77	3.6%	0.08 [0.00, 1.49]	· · · · · · · · · · · · · · · · · · ·
Shah 2015	3	429	56	1171	9.6%	0.14 [0.04, 0.45]	
Stein 2014	0	127	16	2691	3.9%	0.64 [0.04, 10.66]	
Total (95% CI)		3451		48731	100.0%	0.23 [0.12, 0.45]	•
Total events	102		3101				-

	T2M		T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% C
Furie 2019	21	206	33	349	7.1%	1.09 [0.61, 1.93]	+
Higuchi 2019	54	491	769	12023	8.2%	1.81 [1.35, 2.42]	-
Javed 2009	9	64	15	143	5.7%	1.40 [0.58, 3.38]	- -
Lopez Cuenca 2016	6	117	41	707	5.7%	0.88 [0.36, 2.12]	
Meigher 2016	54	452	37	340	7.6%	1.11 [0.71, 1.73]	+-
Paiva 2015	23	236	66	764	7.4%	1.14 [0.69, 1.88]	+-
Putot 2018	133	847	125	2036	8.3%	2.85 [2.20, 3.69]	-
Putot 2019	38	254	24	365	7.2%	2.50 [1.46, 4.28]	
Putot 2020	95	862	186	3710	8.3%	2.35 [1.81, 3.04]	-
Saaby 2014	29	119	10	360	6.3%	11.28 [5.30, 24.00]	
Singh 2020	160	1225	42	2097	8.0%	7.35 [5.19, 10.41]	-
Smilowitz 2018	17	146	18	137	6.5%	0.87 [0.43, 1.77]	
Stein 2014	15	127	113	2691	7.1%	3.06 [1.73, 5.41]	
Troung 2020	13	175	29	275	6.6%	0.68 [0.34, 1.35]	-+
Total (95% CI)		5321		25997	100.0%	1.94 [1.35, 2.79]	•
Total events	667		1508				
Heterogeneity: Tau ² =	0.40; Chř	= 115.3	87, df = 1	3 (P < 0	.00001); P	²= 89%	
Test for overall effect: 1							0.01 0.1 1 10 Favours T1MI Favours T

	T2M	1	T1M	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Nestelberger 2020	1	128	42	684	10.4%	0.12[0.02, 0.88]	
Sandoval 2014	51	190	15	66	29.6%	1.25 [0.65, 2.41]	
Sandoval 2017	18	140	6	77	23.4%	1.75 [0.66, 4.60]	+
Shah 2015	134	429	187	1171	36.7%	2.39 [1.85, 3.09]	
Total (95% CI)		887		1998	100.0%	1.34 [0.63, 2.85]	•
	204		250				

	T2M	1	T1M	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cediel 2017	77	194	74	376	19.0%	2.69 [1.83, 3.94]	
Guimares 2018	19	76	156	847	15.9%	1.48 [0.85, 2.55]	+
Neumann 2017	14	99	18	188	12.5%	1.56 [0.74, 3.28]	+
Paiva 2015	62	236	92	764	19.3%	2.60 [1.81, 3.74]	-
Smilowitz 2018	45	146	41	137	16.6%	1.04 [0.63, 1.73]	+
Troung 2020	29	175	47	275	16.6%	0.96 [0.58, 1.60]	+
Total (95% CI)		926		2587	100.0%	1.63 [1.11, 2.41]	•
Total events	246		428				

	T2M	Í.	T1M	I		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
<adesjo 2019<="" td=""><td>101</td><td>251</td><td>259</td><td>1111</td><td>36.0%</td><td>2.21 [1.66, 2.95]</td><td>-</td></adesjo>	101	251	259	1111	36.0%	2.21 [1.66, 2.95]	-
ambrecht 2018	74	119	114	360	32.9%	3.55 [2.30, 5.47]	-
Sato 2020	18	155	337	2834	31.1%	0.97 [0.59, 1.61]	+
Total (95% CI)		525		4305	100.0%	2.00 [1.07, 3.76]	•
Fotal events	193		710				

	T2M	1	T1M	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Putot 2018	79	847	114	2036	37.0%	1.73 [1.29, 2.34]	+
Putot 2019	24	254	23	365	18.9%	1.55 [0.86, 2.82]	+
Putot 2020	78	862	186	3710	38.9%	1.88 [1.43, 2.48]	
Smilowitz 2018	3	146	8	137	5.1%	0.34 [0.09, 1.30]	
Total (95% CI)		2109		6248	100.0%	1.61 [1.17, 2.22]	◆
Total events	184		331				

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PRISMA 2020 Checklist

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DRIS	MA 2	020 Checklist	njoper	
			1-2021	
Section and Topic	ltem #	Checklist item	1-055755	Location where item is reported
TITLE			0 0	
Title	1	Identify the report as a systematic review.	17	1
ABSTRACT			тер	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	rua	3
INTRODUCTION			Y 2	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	022	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	<u>D</u>	4
METHODS				
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.		4
, Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to date when each source was last searched or consulted.	dentify studies. Specify the	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	ă	Supp
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many rev and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in		4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of a process.		4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results analyses).		4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, fundi assumptions made about any missing or unclear information.	ອ ຫຼັ sources). Describe any ິ	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how ma study and whether they worked independently, and if applicable, details of automation tools used in the process.	E by reviewers assessed each	5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentati	gn of results.	5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study inter comparing against the planned groups for each synthesis (item #5)).	ष्ट्रि vention characteristics and ज	5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing sumn conversions.	ୁ ୱ୍ୱିry statistics, or data ଞ୍ଚ	5
7	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.		5
8	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was per model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.		5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analys	o. i g , meta-regression).	5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biase	ው አምር ት	5
Certainty	15	Describe any methods used to assess centainty (or confidence) in the body of evidence for a butcontem	, , , , , , , , , , , , , , , , , , , 	N/A

PRISMA 2020 Checklist

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PRIS	MA 2	020 Checklist	
Section and Topic	ltem #	Checklist item	Location where item is reported
assessment		O N	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5
1	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were executed.	5
2 Study characteristics	17	Cite each included study and present its characteristics.	Supp
4 Risk of bias in 5 studies	18	Present assessments of risk of bias for each included study.	Supp
6 Results of 7 individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supp
Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supp
9 syntheses 0	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Supp
1	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Supp
2 3	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
4 Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
5 Certainty of 6 evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION		O	
⁸ Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	7
9	23b	Discuss any limitations of the evidence included in the review.	9
1	23c	Discuss any limitations of the review processes used.	9
2	23d	Discuss implications of the results for practice, policy, and future research.	9
OTHER INFORMA	TION		
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
5 protocol 6	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
7	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
8 Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
<pre>9 Competing 9 interests</pre>	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

46 From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:



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Title Page

Manuscript Title

Diagnostic features, management, and prognosis of Type 2 myocardial infarction compared to Type 1 myocardial infarction: A systematic review and meta-analysis.

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Abstract

Importance

Distinguishing type 2 (T2MI) from type 1 myocardial infarction (T1MI) in clinical practice can be difficult, and the management and prognosis for T2MI remain uncertain.

Objective

To compare precipitating factors, risk factors, investigations, management, and outcomes for T2MI and T1MI.

Data Sources

MEDLINE and EMBASE databases as well as reference list of recent articles were searched January 2009 to December 2020 for term "type 2 myocardial infarction".

Study Selection

Studies were included if they analysed if universal definition of MI was used and reported quantitative data on at least one variable of interest.

Data Extraction and Synthesis

Data was pooled using random-effect meta-analysis. Risk of bias was assessed using Newcastle-Ottawa Quality Assessment Form. Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA) guidelines were followed. All review stages were conducted by two reviewers.

Main Outcomes and Measures

Risk factors, presenting symptoms, cardiac investigations such as troponin and angiogram, management, and outcomes such as mortality.

Results

40 cohort studies comprising 98,930 T1MI and 13,803 T2MI patients were included. Compared to T1MI, T2MI patients were: more likely to have pre-existing chronic kidney (OR 1.87; 95%CI 1.53-2.28) and chronic heart failure (OR 2.35; 95%CI 1.82-3.03), less likely to present with typical cardiac symptoms of chest pain (OR 0.19; 95%CI 0.13-0.26) and more likely to present with dyspnoea (OR 2.64; 95%CI 1.86-3.74); more likely to demonstrate non-specific ST-T wave changes on electrocardiography (OR 2.62; 95%CI 1.81-3.79) and less likely to show ST elevation (OR 0.22; 95%CI 0.17-0.28); less likely to undergo coronary angiography (OR 0.09; 95%CI 0.06-0.12) and percutaneous coronary intervention (OR 0.09; 95%CI 0.06-0.12) or receive cardioprotective medications, such as statins (OR 0.25; 95%CI 0.16-0.38) and beta-blockers (OR 0.45; 95%CI 0.33-0.63). T2MI had more risk of all cause one-year mortality (OR 3.11; 95%CI 1.91-5.08), with no differences in short-term mortality (OR 1.34; 95%CI 0.63-2.85).

Conclusion and Relevance

This review has identified clinical, management and survival differences between T2MI and T1MI with greater precision and scope than previously reported. Differential use of coronary

> revascularisation and cardioprotective medications highlight ongoing uncertainty of their utility in T2MI compared to T1MI.

Strength and Limitations

- Inclusion of all contemporary cohort studies in the troponin era
- Large patient population of T2MI and T1MI patients analysed allowing high level of precision
- rcally s_{ιδ} mortality only . Wide array of clinically significant variables assessed providing a comprehensive analysis •
- Analysis of crude mortality only was possible due to lack of individual patient data •

Introduction

The clinical definition of myocardial infarction has evolved over time. The 2007 Universal Definition of Myocardial Infarction included a subset of MI that was secondary to aetiologies unrelated to underlying occlusive coronary artery disease (1). In 2012, the Third Universal Definition of Myocardial Infarction Consensus Document (2) gave rise to the aetiological distinction between T1MI, defined as MI due to plaque erosion and/or rupture, and T2MI, defined as MI caused by increased oxygen demand or decreased blood supply, in the absence of acute plaque rupture or coronary thrombosis. More recently, in 2018, the Fourth Universal definition of MI updated concepts of T2MI regarding specific situations associated with oxygen demand and supply imbalance and the relevance of the presence or absence of underlying coronary artery disease to therapy and prognosis (3). (see on-line supplement Table S1 for more detail)

In clinical practice, distinguishing T2MI from T1MI based on clinical presentation, electrocardiograph (ECG) features and cardiac troponin (cTn) values can be difficult. In the absence of randomised controlled trials that have evaluated different investigational and therapeutic interventions in patients with T2MI, uncertainty remains around the appropriate management of such patients, particularly those with known or suspected coronary artery disease. Past reviews have assessed one or more attributes of T2MI in comparison to T1MI (4-8) but, to our knowledge, none have undertaken a comprehensive analysis of symptoms, physical signs, investigation results, management regimens and clinical outcomes, both short and long term, of T2MI versus T1MI.

We undertook a systematic review of observational studies with the aims of identifying diagnostic and investigational findings which can assist clinicians to better distinguish T2MI from T1MI, and compare T2MI with T1MI in defining differences in management strategies and clinical outcomes.

Methods

Study design

The review was undertaken in accordance with recommendations of the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (9). Our review was registered on PROSPERO prior to commencement (Registration number: CRD42021237746). MEDLINE and EMBASE databases were searched for all studies published between January 1st, 2009, and December 31st, 2020, using search terms to identify all studies related to T2MI (see Table S2). Reference lists of all relevant articles were also assessed to identify additional relevant studies. The study PRISMA flowchart is shown in Figure S1. January 2009 was chosen as the start date for the literature search in order to restrict our analyses to contemporary studies in the troponin era that employed formal definitions of T2MI which were only devised from 2007 onwards.

Studies were included if they: 1) compared patient populations with T2MI and T1MI, 2) used a universal definition of MI, 3) included at least one variable of interest, 4) were available as full text in English and 5) were either a randomised control trial or comparative observational study. Studies were excluded if: 1) no full text was available, 2) duplicate data was utilised or 3) less than 200 participants in total were included. Initial screening of titles and abstracts for eligible studies was

performed independently by two authors (MK, KW), as was full text review for inclusion, with any differences in review settled by consensus agreement.

Data collection and synthesis

Data pertaining to all variables of interest were collected from all included studies using a standardised proforma by one author (MK) and independently reviewed by the second author (KW). These variables comprised: study dates, design, sample size, definition used to define T2MI and T1MI, patient demographics, pre-existing medical conditions, precipitating factors, clinical symptoms, ECG findings, laboratory values, echocardiographic results, any clinical interventions or medical treatments administered, and clinical outcomes observed.

Data on variables reported as, or able to be converted to, raw numbers, were pooled from all studies and subject to comparative meta-analysis using Review Manager (RevMan, Computer program. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For each variable, the odds ratio (OR) comparing T2MI to T1MI, and its 95% confidence interval (CI), was calculated and weighted using the random effects method. As specified in the registered study protocol, the random effects method was used in anticipation of study heterogeneity of at least moderate degree (I² statistic of heterogeneity >50%) (10). In addition to the weighted OR, we also report the crude total event rates for each variable subject to meta-analysis in order to provide a more clinically meaningful estimate of the prevalence of these events in each patient group in view of the large sample sizes. Studies reporting mean or median values only were reproduced as reported in the original study.

Risk of bias within each study was assessed using the Newcastle-Ottawa quality assessment tool for cohort studies (11, 12), with scores 7-8 denoting good quality studies, 4-6 fair quality, and 0-3 poor quality. Publication bias was assessed using funnel plots.

Patient and Public Involvement

We did not seek patient or public comment in designing the study.

Results

A total of 40 studies were included for analysis (13-52) and their characteristics are summarised in Table S3. They comprised a total of 127,620 participants of whom 98,930 participants (77.5%) were classified as T1MI and 13,803 (10.8%) as T2MI. In the following text, we report key findings; more information and forest plots for each analysis involving more than one study and more than 100 total cases can be found in the on-line supplement, Figures S2-S44.

The 2007 definition (1) was used in 7 (17.5%) studies (15, 16, 27, 29, 43, 44, 51, 52), the 2012 definition (2) in 25 (62.5%) studies (13, 17, 19-21, 23-26, 30-35, 37, 39, 40, 42, 45-48, 50, 51), and the 2018 definition (3) in 8 (20%) studies (14, 18, 22, 28, 36, 38, 41, 49). Of the 40 studies, 17 (42.5%) were prospective (15, 16, 18, 19, 22, 29, 33, 34, 36, 37, 43, 44, 46-48, 5052) and 23 (57.5%) were retrospective (13, 14, 17, 20, 21, 23-28, 30-32, 35, 38-42, 46, 49, 52).

Risk of bias assessment

Of the 40 studies, 31 (77.5%) were assessed as good quality (13, 15-19, 22, 23, 27-35, 37-46, 48, 50-52), 6 (15%) as fair quality (14, 24-26, 49), and 3 (7.5%) as poor quality (20, 36, 47), as summarised in Table S4. Selection bias resulting in unrepresentative cohorts such as admission criteria to coronary care units or entry criteria into MI registries favouring T1MI (14, 20, 24-26, 36, 47, 49), absence of independent adjudication of MI type as T1MI or T2MI (36, 38, 47), non-comparability of T1MI and T2MI cohorts (20, 24, 25, 47), poorly specified outcome measures (36, 38, 47) and short follow-up period resulting in few events (14, 20, 24, 36) comprised most forms of bias.

Funnel plots for in-hospital and 1-year all-cause mortality showed no asymmetry (on-line supplement, Figures S45, S46). Funnel plots for all other analyses showed similar results (available on request).

Participant characteristics

Patients with T1MI had a median age range of 60-82 years in the included studies that did not select a specific age population, compared to a median age range of 62-81 years in patients with T2MI. The sex distribution was also similar, with 58.4% and 53% of patients with T1MI and T2MI being male respectively.

Regarding pre-existing medical conditions (Table 1), T2MI patients compared to T1MI patients were more likely to have chronic kidney disease (22.8% vs 17.3%; OR 1.87; 95%CI 1.53-2.28), chronic heart failure (13.1% vs 7.6%; OR 2.35; 95%CI 1.82-3.03), atrial fibrillation (22.9% vs 6.1%; OR 3.02; 95%CI 2.29-3.99), and hypertension (66.4% vs 63.4%; OR 1.22; 95%CI 1.03-1.45). Patients with T2MI were less likely to have dyslipidaemia (43.4% vs 45.9%; OR 0.74; 95%CI 0.58-0.94) and smoking history (34.7% vs 52.8%; OR 0.6; 95%CI 0.49-0.73). There was no difference in the prevalence of type 2 diabetes mellitus or ischaemic heart disease between the two groups.

Precipitating factors

Less than half of the studies (n=17; 43%) included data on precipitating factors associated with T2MI (13, 15, 17, 19, 21-24, 27, 31, 32, 35, 40, 44, 45, 50, 51, 52). Data on each precipitating factor was not consistently available across the studies, for example only 17 studies representing 45% of T2MI patients assessed presence of arrythmia

The most common precipitants were sepsis (35.9%) and heart failure (35.9%, followed by arrythmia (29.8%) (Table S5), with non-cardiac surgery being deemed a cause in 12.2% of cases where data for this variable were collected.

Presenting clinical features

As summarised in Table S6, compared to T1MI patients, T2MI patients were less likely to present with typical cardiac symptoms of chest pain (58.6% vs 88.4%; OR 0.19; 95%CI 0.13-0.26) or discomfort in the arm or shoulder (8.5% vs 35%; OR 0.18; 95%CI 0.11-0.3), but more likely to present with dyspnoea (27.1% vs 10.6%; OR 2.64; 95%CI 1.86-3.74).

Investigations

ECG findings on presentation (Table S7) such as ST elevation (14.1% vs 44.2%; OR 0.22; 95%CI 0.17-0.28) and pathological Q waves (6.7% vs 20.8%; OR 0.38; 95%CI 0.20-0.71) were less evident in T2MI

than in T1MI. In contrast, non-specific ST-T wave changes (24.7% vs 10.8%; OR 2.62; 95%CI 1.81-3.79), and atrial arrythmias (21% vs 6.6%; OR 4.99; 95%CI 3.14-7.93) were more common among T2MI. No differences between groups were seen in the frequency of ST depression or T wave inversion.

Among the 40 studies, four studies (10%) reported the use of high-sensitivity cardiac troponin (cTn) assays, 21 (53%) reported sensitive assays, and 14 (35%) did not specify what generation assay was used (Table S3b). The results of troponin assays were reported in 26 (65%) studies, specific to cTnI assays in 19 studies, cTnT in 5, both assays in one, while another did not specify the assay used. Only two of these studies reporting troponin failed to state the upper limit of normal (ULN) of the assay used (23, 31). The troponin assays, and therefore units and reference ranges, varied between the studies, preventing direct comparison of troponin values. As a result, we converted troponin values to a multiple of the upper limit of normal for each assay to allow direct comparison (Table S8). For peak troponin, patients with T1MI had a higher and wider range of between 5 and 1702 times the ULN compared to patients with T2MI with a range of 2.8-447 times the ULN. Studies yielded mixed results as to whether the magnitude of change (or delta) in serial cardiac troponin assays was more predictive of T2MI or T1MI compared to absolute values of peak levels (33). Lowering the diagnostic threshold for troponin with the advent of more sensitive assays has increased the numbers of patients identified with T2MI by up to 50% (36), with more recent studies showing the incidence of T2MI equalling or exceeding that of T1MI (15, 33, 36).

Echocardiography was less frequently performed among T2MI than T1MI patients (47.9% vs 55.5%; OR 0.44; 95%CI 0.20-0.96) and when reported (Table S7), there was no difference in the prevalence of regional wall motion abnormalities or the level of left ventricular (LV) function, with reported median LV ejection fraction being 42.3%-55% in T1MI patients and 40%-56% in T2MI patients.

Coronary angiography was also less frequently performed among T2MI than in T1MI patients (34.1% vs 85.5%; OR 0.09; 95%CI 0.06-0.12, Table S7). When performed, T2MI patients were less likely to demonstrate obstructive coronary artery disease (34% vs 44.9%; OR 0.16; 95%CI 0.05-0.54), with obstruction variously defined as 50%-70% occlusion of one or more vessels.

Management

T2MI patients, compared to T1MI patients, were significantly less likely to receive conventional cardioprotective medications (Table 2), comprising beta-blockers (58.3% vs 76.3%; OR 0.45; 95%CI 0.33-0.63), anti-platelet agents (70.8% vs 88.5%; OR 0.24; 95%CI 0.16-0.38) and statins (52.9% vs 87.6%; OR 0.25; 95%CI 0.16-0.38). Of note, T2MI patients were more likely to receive diuretics (44.8% vs 13.6%; OR 1.98; 95%CI 1.37-2.86) or anti-coagulants (28.9% vs 25.2%; OR 1.87; 95%CI 1.06-3.30).

Percutaneous coronary intervention (PCI) (21.1% vs 78%; OR 0.06; 95%CI 0.04-0.10) and coronary artery bypass surgery (2.9% vs 6.4%; OR 0.23; 95%CI 0.12-0.45) were also significantly less likely to be performed in T2MI patients than T1MI patients.

Prognosis

T2MI patients had significantly increased risk of all-cause death compared to patients with T1MI in both short- and long-term follow-up (Table 3). Specifically, compared to T1MI patients, T2MI

demonstrated increased all-cause mortality in-hospital (12.5% vs 5.8%; OR 1.94; 95%Cl 1.35-2.79, Figure S40), at one-year (18.9% vs 5.4%; OR 3.11; 95%Cl 1.91-5.08, Figure 1) and at 5 to 10 years, (53.7% vs 28.5%, OR 3.24; 95%Cl 2.73-3.84, Figure 2). In contrast, there were no differences between T2MI and T1MI patients in the risk of short-term mortality at 120-180 days (23.0% vs 12.5%; OR 1.34; 95%Cl 0.63-2.85).

Discussion

To our knowledge, this is the most comprehensive systematic review and meta-analysis of contemporary studies comparing T2MI with T1MI in the troponin era, comprising 127,620 patients from 40 cohort studies across 14 countries, and which used formal definitions of T2MI and T1MI. Up to three quarters of all myocardial infarctions in routine care can be T2MI (33, 34), and distinguishing T2MI from T1MI on clinical criteria is often challenging. The management strategies used by clinicians in real-world practice for T2MI often vary, and the clinical outcomes of T2MI compared to T1MI, particularly over the long term, have been uncertain. This review provides information that helps characterise these two groups of patients according to multiple variables and which may assist in clinical decision-making and prognostication.

In this review, T2MI patients demonstrated more medical comorbidities than T1MI patients, as noted in a recent meta-analysis (6). Our review highlighted the much higher incidence of pre-existing generalised vascular disease, atrial fibrillation, renal impairment, and heart failure among T2MI patients.

Sepsis (10, 16, 27) and anaemia (51) ranked highly as triggers, together with other acute cardiac events such as valve dysfunction or arrhythmias. In one study, a more favourable prognosis in T2MI was seen when the principal trigger was arrhythmia compared to non-cardiac surgery, hypotension, anaemia or hypoxia (29). In another study, shock syndromes were triggers portending a worse prognosis compared to all other triggers (32). In our analysis, non-cardiac surgery as a trigger was less frequent than reported by other investigators (26) whereby peri-operative stressors including blood loss, anaesthesia induced hypotension and wound infections cause imbalance in myocardial contractility, oxygen demand and blood flow (53).

Analysis of cTn levels showed uniformly higher values in T1MI than T2MI which accord with one review (5) reporting cTn values 30% to 94% higher in patients with T1MI, and which other investigators regard as being highly specific diagnostic markers for T1MI (53).

Coronary angiography and revascularisation were both performed much less frequently in T2MI than in T1MI patients. Treating physicians may perceive invasive strategies as being contraindicated or potentially harmful in the presence of various co-morbidities more commonly seen in T2MI and associated with competing mortality risk. In our pooled data, only one in three T2MI patients who underwent angiography demonstrated obstructive coronary artery disease, although this figure may be an underestimate due to selection bias whereby younger, less multi-morbid patients preferentially underwent angiography. In the CASABLANCA cohort study, which enrolled patients with high likelihood of coronary or peripheral artery disease and subjected them to peripheral or coronary angiography, of all those who subsequently suffered incident T2MI, almost half (47.7%) demonstrated ≥70% stenosis in at least 2 major coronary arteries (54). These conflicting findings **BMJ** Open

question whether patients presenting with T2MI would benefit from routine use of invasive strategies that define coronary anatomy and, if plaque rupture or critical stenoses are seen, prompt revascularisation, with resultant improvement in patient outcomes. In one study (18), angiography unmasked acute plaque rupture in 29% of patients classified as T2MI. In another study, among 27 of 236 patients with T2MI who underwent revascularisation, the odds of all-cause death were reduced by 67% compared to the remaining 209 non-revascularised patients (23). In contrast, in a third more rigorous study comparing T2MI versus T1MI patients who received or did not receive PCI within 24 hours of symptom onset, after adjusting results using multivariate logistic regression analysis and inverted probability weighting (15), in-hospital mortality was lower in those with T1MI receiving PCI (OR 0.47; 95% CI 0.40–0.55; p < 0.001), but not in those with T2MI receiving PCI (OR 1.09; 95% CI 0.62–1.94; p = 0.763). However, all these studies are observational, so completion of randomised trials, such as the Appropriateness of Coronary investigation in myocardial injury and Type 2 myocardial infarction (ACT-2) trial, which is currently in recruitment (55), will hopefully provide a more definitive answer.

Given that a third of T2MI patients had pre-existing coronary artery disease and most of the remainder had one or more cardiovascular risk factors, the relative underuse of cardioprotective medications is perplexing. It may reflect either clinician uncertainty around their cardioprotective utility in T2MI, or concerns about the potential for adverse interactions with other drugs or diseases commonly seen in multi-morbid T2MI patients. The higher use of diuretics in the T2MI population likely reflects the higher prevalence of heart failure and hypertension. Recognizing the heterogeneous mechanisms or conditions leading to T2MI, a phenotype specific-approach to the design of future trials will be useful in identifying effective therapies.

An important finding is the much higher all-cause in-hospital and one-year mortality in T2MI compared to T1MI patients, similar to the two-fold greater mortality rate in T2MI noted in a recent systematic review of 9 studies (8). In our review, this excess mortality was not driven by an excess of cardiovascular deaths, and likely reflects the competing risks of multiple co-morbidities, rather than underlying obstructive coronary artery disease which was seen in 30-50% of T2MI patients (26, 31). Studies yielded mixed results as to whether coronary artery disease is an independent predictor of T2MI (20, 42), while others question the angiographic distinction between T2MI and T1MI. For example, in a study of 450 consecutive patients with MI who all underwent coronary angiography within 24 hours of symptom onset, 145 (32.2%) patients had 'true' T1MI (acute atherothrombosis and no systemic triggers), 114 (25.3%) had 'true' T2MI (no atherothrombosis and systemic triggers), 61 (13.6%) patients had neither, and 130 (28.9%) patients had both (41). This yields a discordance of angiographic and clinical definitions of MI type in 42.5% of patients.

Our review has several limitations. First, in the absence of individual patient data from all included studies, we could not perform multivariate regression analysis in identifying independent predictors of diagnosis, management, or prognosis of T2MI. Second, we did not perform separate analyses of studies according to each version of the Universal Definition of MI or to different troponin thresholds to define MI, which may impact management and prognosis. However, potential misclassification bias was addressed in a recent study which showed little change in MI classification as type 1 or 2 in the same cohort of emergency admissions to whom the 3rd and 4th universal definitions were applied (56). In another study which compared separate T2MI cohorts, as defined

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by the 2007 and the 2012 definitions, co-morbidities and use of cardioprotective medications were less frequent in the 2012 cohort, likely due to less severe MIs being included as a result of using more sensitive troponin assays (22). Third, we did not collect haemodynamic variables or other physiological measures such as haemoglobin levels and glomerular filtration rate in analysing clinical presentations as these were very inconsistently reported. Fourth, our mortality meta-analyses relied on crude mortality rates reported in each study, with 55% of studies (15-19, 22-28, 30, 31, 34, 35, 37, 40-42, 45, 46, 52) also undertaking multivariate regression and/or competing risk analyses and reporting adjusted mortality rates. For the T2MI cohorts in general, these rates tended to be lower and the differences in rates compared to those of T1MI were of smaller magnitude. Similarly, we did not attempt sub-analyses based on risk stratification using validated risk scores or seek to identify predictive models for mortality, as such analyses were reported in only two studies (26, 40). Fifth, we did not analyse 30-day readmission rates as these were reported in only three studies (13, 14, 23). Sixth, we did not perform sensitivity analyses comparing results of prospective versus retrospective studies, as neither group demonstrated less or more risk of bias than the other, or compared results of good quality studies against fair/poor quality studies as the latter comprised only 17% of all patients. Seventh, as we searched only two databases and did not include grey literature, relevant studies may have been missed, although in a recent analysis searching MEDLINE and EMBASE combined yielded 93% of relevant studies, with Google Scholar, despite requiring much more time and effort, only yielded another 3% (57). Eighth, while publication bias is possible, all funnel plots performed for every analysis showed no asymmetry. Finally, we did not perform subgroup analyses or meta-regression in assessing between-study heterogeneity, as study parameters (such as study design and analytic methods) were often ill-defined and widely variable across this large number of real-world observational studies (58).

The strengths of this review are the inclusion of all contemporary cohort studies in the troponin era that employed formal definitions of T2MI, analysis of a broader range of variables than those of previous studies, and the more precise discernment of clinically meaningful differences between the two MI populations in patient characteristics, clinical presentation, patterns of care and outcomes. As studies originated from several different jurisdictions, we believe our findings are generalisable to different healthcare systems, although absolute values for some measures did vary between countries. We are aware of a large US cohort study published since completion of our review (59) which compared T1MI with T2MI patients, but was limited by misclassification bias (relying on administrative hospital discharge data containing an International Classification of Diseases-10th Revision code specific for type 2 MI, rather than a registry or chart diagnosis based on a formal MI definition), short study period of 3 months in late 2017, and inability to analyse clinical features, investigation results, medication use, coronary anatomy, and post-discharge mortality due to their omission in the datasets.

Conclusion

This review has identified differences between T2MI and T1MI patients in presenting clinical features, investigation and management profiles, and clinical outcomes. These findings may assist clinicians to better recognise T2MI and advise patients about its sequelae, and inform hospital coding and epidemiological trending, quality of care indicators and inter-hospital benchmarking of performance relating to the care of patients with T2MI.

The review has also defined persisting gaps in our understanding of the utility and prognostic effects of invasive investigations, revascularization strategies and cardioprotective medications in T2MI patients that warrant more randomised trials that enrol such patients.

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Tables

		T2MI			T1MI		
Pre-existing medical condition	Number of patients with the specified condition	Total number of patients	%	Number of patients with the specified condition	Total number of patients	%	Odds ratio* (95% Cl)
CAD	3352	10303	32.5%	22222	92725	24%	1.1 [0.93, 1.31]
Type 2 DM	3044	12157	25%	23287	93345	24.9%	0.97 [0.85, 1.10
HTN	7536	11021	66.4%	55782	88017	63.4%	1.22 [1.03, 1.45
Dyslipidaemia	4626	10652	43.4%	40099	87366	45.9%	0.74 [0.58, 0.94
Smoker	3448	9929	34.7%	39548	74889	52.8%	0.60 [0.49, 0.73
Obesity	1225	3672	33.4%	30963	56970	54.3%	0.63 [0.46, 0.8]
Renal failure	1378	6040	22.8%	11300	65394	17.3%	1.87 [1.53, 2.28
Heart failure	1661	8873	13.1%	5617	74212	7.6%	2.35 [1.82, 3.03
PVD	584	5856	10.0%	2066	41280	5.0%	1.33 [1.05, 1.6
CVD	969	8538	11.3%	6060	87822	6.9%	1.47 [1.27, 1.7]
Atrial fibrillation	836	3645	22.9%	1220	19843	6.1%	3.02 [2.29, 3.9
COPD	800	5018	15.9%	823	48375	1.7%	1.94 [1.22, 3.0
Illicit drug Use	46	204	22.5%	8	220	3.6%	8.15 [1.03, 64.46]

*Comparing T2MI with T1MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: CAD= coronary heart disease, DM= diabetes mellitus, HTN= hypertension, BMI= body mass index, PVD= peripheral vascular disease, CVD= cerebrovascular disease, COPD= chronic obstructive pulmonary disease

Table 2. Pharmacological management and invasive interventions in patients with T2MI versus T1MI.

		T2MI			T1MI		
Intervention	No. patients receiving intervent ion	Total number of patients	%	No. patients receiving intervention	Total number of patients	%	Odds ratio* (95% Cl)
Medication							
Beta blockers	4967	8523	58.3%	63431	83157	76.3%	0.45 [0.33, 0.63]
ACEI / ARB	3766	7842	48%	56253	81793	68.8%	0.52 [0.40, 0.67]
Anti-platelets	5087	8599	70.8%	74377	84004	88.5%	0.25 [0.16, 0.38]
Anti-coagulants	1519	5255	28.9%	15754	62415	25.2%	1.87 [1.06, 3.30]
Anti-anginal agents	1281	2191	58.5%	38955	42768	91.1%	0.61 [0.21, 1.74]
Diuretics	1336	2985	44.8%	6211	45779	13.6%	1.98 [1.37, 2.86]
Statins	3418	6455	52.9%	56875	64942	87.6%	0.25 [0.16, 0.38]
Invasive							
PCI	2092	9936	21.1%	67411	86425	78%	0.06 [0.04, 0.10]
CABG	102	3451	2.9%	3101	48731	6.4%	0.23 [0.12, 0.45]
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*Comparing T2MI with T1MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: ACEI= Angiotensin converting enzyme inhibitors, ARB= Angiotensin receptor blockers; CI=confidence interval; T2MI=type 2 myocardial infarction; T1MI=type 1 myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft

		T2MI			T1MI		
Outcomes	No. patients with outcome	Total number of patients	%	No. patients with outcome	Total number of patients	%	Odds ratio [*] (95% Cl)
CV in-hospital mortality	184	2109	8.7%	331	6248	5.3%	1.61 [1.17, 2.2
All-cause in- hospital mortality	667	5321	12.5%	1508	25997	5.8%	1.94 [1.35, 2.7
Short-term all- cause mortality	204	887	23.0%	250	1998	12.5%	1.34 [0.63, 2.8
1-year all-cause mortality	632	3340	18.9%	1299	24203	5.4%	3.11 [1.91, 5.0
2-year all-cause mortality	246	926	26.6%	428	2587	16.5%	1.63 [1.11, 2.4
3-year all-cause mortality	193	525	36.8%	710	4305	16.5%	2.00 [1.07, 3.7
Long-term all- cause mortality	1453	2708	53.7%	1320	4633	28.5%	3.24 [2.73, 3.8

*Comparing T1MI with T2MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: CV= Cardiovascular, MACE= Major adverse cardiovascular events; T2MI=type 2 myocardial infarction; T1MI=type 1 myocardial infarction; CI=confidence interval

Figures

Figure 1. Forest plot of one-year all-cause mortality of T2MI patients compared to T1MI patients.

Figure 2. Forest plot of long-term all-cause mortality of T2MI patients compared to T1MI patients.

Figure S1. PRISMA flow diagram.

Figure S2. Forest Plot. Presence of Ischaemic Heart Disease.

Figure S3. Forest Plot. Presence of Type 2 Diabetes Mellitus.

Figure S4. Forest Plot. Presence of Hypertension.

Figure S5. Forest Plot. Presence of Dyslipidaemia.

Figure S6. Forest Plot. Smoking Status.

Figure S7. Forest Plot. Obesity Status.

Figure S8. Forest Plot. Presence of Chronic Kidney Disease.

Figure S9. Forest Plot. Presence of Heart Failure.

Figure S12. Forest Plot. Presence of Illicit Drug Use.

Figure S13. Forest Plot. Presence of Atrial Fibrillation.

Figure S14. Forest Plot. Chest Pain as Presenting Feature.

Figure S15. Forest Plot. Dyspnoea as Presenting Feature.

Figure S20. Forest Plot. ST Elevation on ECG.

Figure S22. Forest Plot. Q Waves on ECG.

Figure S16. Forest Plot. Arm / Shoulder Discomfort as Presenting Feature.

Figure S18. Forest Plot. Non-specific Symptoms as Presenting Features.

Figure S17. Forest Plot. Nausea / Vomiting as Presenting Feature.

Figure S19. Forest Plot. Collapse / Syncope as Presenting Features.

Figure S21. Forest Plot. ST Depression or T Wave Inversion on ECG.

Figure S23. Forest Plot. Non-specific ST Changes on ECG.

Figure S24. Forest Plot. Left Bundle Branch Block on ECG.

Figure S26. Forest Plot. Coronary Angiogram Performed.

Figure S28. Forest Plot. Multivessel Disease on Coronary Angiogram.

Figure S38. Forest Plot. Percutaneous Coronary Intervention Performed.

Figure S39. Forest Plot. Coronary Artery Bypass Graft Performed.

Figure S27. Forest Plot. Obstructive Coronary Artery Disease on Coronary Angiogram.

Figure S30. Forest Plot. Regional Wall Motion Abnormalities on Echocardiogram.

Figure S25. Forest Plot. Atrial Fibrillation on ECG.

Figure S29. Forest Plot. Echocardiogram Performed.

Figure S31. Forest Plot. Beta-Blockers Prescribed.

Figure S33. Forest Plot. Antiplatelets Prescribed.

Figure S34. Forest Plot. Anticoagulants Prescribed.

Figure S35. Forest Plot. Antianginal Drugs Prescribed.

Figure S32. Forest Plot. ACEi/ARB Prescribed.

Figure S36. Forest Plot. Diuretics Prescribed.

Figure S37. Forest Plot. Statins Prescribed.

Figure S10. Forest Plot. Presence of Peripheral Vascular Disease.

Figure S11. Forest Plot. Presence of Cerebrovascular Disease.

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59 60 Figure S40. Forest Plot. All cause In-hospital mortality. T2MI compared to T1MI.
Figure S41. Forest Plot. Short-term all-cause mortality. T2MI compared to T1MI.
Figure S42. Forest Plot. Two-year all-cause mortality. T2MI compared to T1MI.
Figure S43. Forest Plot. Three-year all-cause mortality. T2MI compared to T1MI.
Figure S44. Forest Plot. CVS In-hospital mortality. T2MI compared to T1MI.
Figure S45. Funnel Plot. All-cause In-hospital mortality. T2MI compared to T1MI.
Figure S46. Funnel Plot. One-year All-cause mortality. T2MI compared to T1MI.

Contribution Statement

All authors (KW, MK, IS) contributed to the conception of the work. MK and KW performed the acquisition and analysis of the data. KW and IS were responsible for the interpretation of data. All authors (MK, KW, IS) were responsible for drafting manuscript and final approval of the version to be published. All authors (KW, MK, IS) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing Interests

The authors declare there are no conflict of interest with respect the article.

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Ethic Approval Statement

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					BMJ Op	ben	omjopen-2021-055
	T2M	I	T1N	11		Odds Ratio	755 Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Arora 2018	89	264	96	775	13.1%	3.60 [2.58, 5.02]	
Chapman 2020	258	1121	720	4981	13.7%	1.77 [1.51, 2.08]	bru:
El haddad 2012	84	295	28	512	12.4%	6.88 [4.36, 10.87]	
Furie 2019	80	206	93	349	12.9%	1.75 [1.21, 2.52]	
Lopez Cuenca 2016	27	117	102	707	12.3%	1.78 [1.10, 2.87]	
Radovanovic 2017	14	1091	117	13828	11.8%	1.52 [0.87, 2.66]	
Saaby 2014	65	119	25	360	11.9%	16.13 [9.37, 27.77]	oade
Stein 2014	15	127	118	2691	11.7%	2.92 [1.65, 5.16]	ed fro
Total (95% CI)		3340		24203	100.0%	3.11 [1.91, 5.08]	February 2022. Downloaded from http://b
Total events	632		1299				p://b
Test for overall effect:				of the r	isk one-ye	ear mortality of T2MI pati	Fayours T1MI Favours T2MI ients compared to T1MI patients.
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<u></u>								Odds Ratio
	T2M	1	T1M	I		Odds Ratio		Odds Ratio
Study or Subgrou	up Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% Cl
Chapman 2018	268		430		28.3%	2.87 [2.28, 3.61]		
Raphael 2020	766	1054	638	1365	36.2%	3.03 [2.55, 3.60]	ualy	
Singh 2020	419	1225	252	2097	35.5%	3.81 [3.19, 4.54]	2022	
Total (95% CI)		2708		4633	100.0%	3.24 [2.73, 3.84]		
Total events	1453		1320					
Heterogeneity: Ta	ur = 0.01; Chr	² = 4.84,	df = 2 (F	P = 0.09)); l² = 599	6		
Test for overall eff	-						0.01	0.1 1 10 10 avoursT1MI FavoursT2MI
Figure 2. Forest plot	of the result o	f meta-	analysis c	of the ri	sk long-tei	rm mortality of T2MI pati		mpared to T1MI patients.
Figure 2. Forest plot	<u>of the result o</u>	<u>f meta-</u>	analysis c	of the ri	<u>sk long-te</u>	rm mortality of T2MI pati		

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Table S	51. Evolving definitions of Type 2 Myocardial Infarction.
Year	Universal Definition of Type 2 Myocardial Infarction
2007	Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrythmias, hypotension or hypertension
2012	Instances of myocardial injury with necrosis where a condition other than coronary artery disease contributes to an imbalance between myocardial oxygen supply and/or demand e.g. coronary artery spasm, coronary embolism, anaemia, arrythmias, hypotension or hypertension
2018	 Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following: Symptoms of acute myocardial ischaemia New ischaemic ECG changes Development of pathological Q waves Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology

Table	S2.	Search	strategy.
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MEDLINE: (type 2 adj3 myocard*) OR (type-2 adj3 myocard*) OR (type II adj3 myocard*) OR (type-II adj3 myocard*) OR (type 2 adj3 MI) OR (type-2 adj3 MI) OR T2MI OR (supply demand adj3 myocard*)

EMBASE: ('type 2' NEXT/3 myocard*) OR ('type-2' NEXT/3 myocard*) OR ('type ii' NEXT/3 myocard*) OR ('type-ii' NEXT/3 myocard*) OR ('type 2' NEXT/3 mi) OR ('type-2' NEXT/3 mi) OR ('t2mi') OR ('supply demand' NEXT/3 myocard*)

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Table S3a. Study ch	aracteris	stics				0 n 1	
Author, Year	Patients		Design	Definition	Geographic	្រុ Screening ម្នី	Troponin
Addior, rear	T1MI	T2MI	Design	of MI	location	a	Assay
Arora, 2018 (1)	775	264	Retrospective	2012	USA	NSTEMI patients	cTnl
Balanescu, 2020 (2)	152	49	Retrospective	2018	USA	AMI patient	N/A
Baron, 2016 (3)	40501	1313	Prospective	2007	Sweden	AMI patients	hs-cTnT
Bonaca, 2012 (4)	359	42	Prospective	2007	Multinational	TRITON TIMI 38 grial	N/A
Cediel, 2017 (5)	376	194	Retrospective	2012	Spain	ED patients with at lea 🐺 1 troponin	cTnl
Chapman, 2018 (6)	1171	429	Prospective	2012	UK	ED with elevated topponin	cTnl
Chapman, 2020 (7)	4981	1121	Prospective	2018	UK	Suspected AS	cTnl
Consuegra-Sanchaz, 2018 (8)	125	75	Retrospective	2012	Spain	ED patients with at least 1 troponin	cTnl hs-cTn ⁻
El-Haddad, 2012 (9)	512	295	Retrospective	2012	USA	Patients with elevate troponin	N/A
Etaher, 2020 (10)	97	121	Prospective	2018	Australia	Patients with elevated troponin	N/A
Furie, 2019 (11)	349	206	Retrospective	2012	Israel	NSTEMI on generad ward	Unknow
Guimaraes, 2018 (12)	847	76	Retrospective	2012	Multinational	ACS during TRACER trial	N/A
Hawatmeh, 2020 (13)	664	281	Retrospective	2012	USA	NSTEMI patiegts	cTnl
Higuchi, 2019 (14)	12023	491	Retrospective	2012	Tokyo	Admitted to CEU	N/A
Javed, 2009 (15)	143	64	Retrospective	2007	USA	Patients with elevate troponin	cTnl
Kadesjo, 2019 (16)	1111	251	Retrospective	2018	Sweden	MI, Registry	N/A
Lambrecht, 2018 (17)	360	119	Prospective	2007	Denmark	Hospitalised patients with troponin measured $\frac{4}{\sigma}$	cTnl
Landes, 2016 (18)	107	107	Retrospective	2012	Israel	Diagnosed with T2Mkand T1MI	cTnT
Lopez-Cuenca, 2016 (19)	707	117	Retrospective	2012	Spain	Diagnosed with T2MF and T1MI	hs-cTn
Meigher, 2016 (20)	340	452	Retrospective	2012	Germany	ED patients with eleva add troponin	cTnl
Nestelberger, 2017 (21)	684	128	Prospective	2012	Multinational	ED patients wit	N/A
Neumann, 2017 (22)	188	99	Prospective	2012	Germany	ED patients with suspected MI	hs-cTn

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Paiva, 2015 (23)	764	236	Retrospective	2012	Portugal	Admitted to CCU with MI	cTnl
Pandey, 2020 (24)	97	103	Prospective	2018	USA	MI o	N/A
Putot, 2018 (25)	2036	847	Prospective	2012	France	ED or cardiology ward with elevated	cTnl
Putot, 2019 (26)	365	254	Retrospective	2018	France	Hospitalised patients with CAD	cTnl
Putot, 2020 (27)	3710	862	Retrospective	2012	France	Hospitalised patient with MI	cTnl
Radovanovic, 2017 (28)	13828	1091	Retrospective	2012	Switzerland	Diagnosed A	N/A
Raphael, 2020 (29)	1365	1054	Retrospective	2018	USA	Raised tropor	cTnT
Reed, 2017 (30)	88	162	Retrospective	2012	USA	Underwent vascula procedure	cTnT
Saaby 2013 (31)	397	144	Prospective	2007	Denmark	Troponin meas	cTnl
Saaby, 2014 (32)	360	119	Prospective	2007	Denmark	Elevated tropadin	cTnl
Sandoval, 2014 (33)	66	190	Retrospective	2012	USA	ED patients with troponin measured	cTnl
Sandoval, 2017 (34)	77	140	Prospective	2012	USA	ED patients with tropon measured	cTnl
Sato, 2020 (35)	2834	155	Prospective	2012	Japan	Hospitalised patien gwith MI	N/A
Shah, 2015 (36)	1171	429	Prospective	2012	UK	Admitted with elevat 🛃 troponin	cTnl
Singh, 2020 (37)	2097	1225	Retrospective	2018	USA	Age <50, MI or raise troponin	N/A
Smilowitz, 2018 (38)	137	146	Prospective	2012	USA	Admitted with raise	cTnl
Stein, 2014 (39)	2691	127	Prospective	2007	Israel	Admitted to card blogy	N/A
	275	175	Retrospective	2012	Russia	MI, undergoing angiogram	N/A



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Table S3b. Study characteriAuthor, YearArora, 2018 (1)Balanescu, 2020 (2)Baron, 2016 (3)	Patie T1MI 775	ents T2MI					omjopen-2021-05\$755					
Author, Year Arora, 2018 (1) Balanescu, 2020 (2) Baron, 2016 (3)	Patie T1MI 775						5575					
Author, Year Arora, 2018 (1) Balanescu, 2020 (2) Baron, 2016 (3)	Patie T1MI 775						<u>~</u>					
Arora, 2018 (1) Balanescu, 2020 (2) Baron, 2016 (3)	T1MI 775		D	Patients Variables 9								
Balanescu, 2020 (2) Baron, 2016 (3)	775		Pre-existing	Symptoms	Investigation	Troponin	 ⊐Management	Progn				
Balanescu, 2020 (2) Baron, 2016 (3)			conditions		s	Values	Г e					
Balanescu, 2020 (2) Baron, 2016 (3)		264	X		Х	Х	Februa X	X				
	152	49		Х	Х		-Σ X					
	40501	1313	X	Х	Х	Х	20 X					
Bonaca, 2012 (4)	359	42										
Cediel, 2017 (5)	376	194	X	Х	Х	Х	D o w	X				
Chapman, 2018 (6)	1171	429	X		Х	Х	nlo X	X				
Chapman, 2020 (7)	4981	1121	Х	Х	Х	Х	nloaded from	X				
Consuegra-Sanchaz, 2018 (8)	125	75	X	Х	Х	Х	d f					
El-Haddad, 2012 (9)	512	295						X				
Etaher, 2020 (10)	97	121	x		Х		<u>∃</u> X					
Furie, 2019 (11)	349	206	X	X	Х	Х	<u>р://</u> Х	Х				
Guimaraes, 2018 (12)	847	76	X	6	Х		ji x	Х				
Hawatmeh, 2020 (13)	664	281	X	C	• X	Х	ope X .b X					
Higuchi, 2019 (14)	12023	491	X		Х		b X	Х				
Javed, 2009 (15)	143	64	X	-	Х	Х	mj.o	X				
Kadesjo, 2019 (16)	1111	251	X				Y X	Х				
Lambrecht, 2018 (17)	360	119	X		X	X	or	X				
Landes, 2016 (18)	107	107	X	Х	Х	Х	י רו					
Lopez-Cuenca, 2016 (19)	707	117	X	Х	Х	Х	ne X	X				
Meigher, 2016 (20)	340	452	X	Х	Х	Х	21,	X				
Nestelberger, 2017 (21)	684	128	X		Х		2024	X				
Neumann, 2017 (22)	188	99	X		Х	Х	4	X				
Paiva, 2015 (23)	764	236	X		Х	Х	by gu	Х				
Pandey, 2020 (24)	97	103	Х				luest.					
Putot, 2018 (25)	2036	847	Х		Х	Х	D	Х				
Putot, 2019 (26)	365	254	Х		Х	Х	rote	X				
Putot, 2020 (27)	3710	862	Х		Х	Х	ecte	X				
Radovanovic, 2017 (28)	13828	1091	X		Х		а X	X				
Raphael, 2020 (29)	1365	1054	Х		Х	Х	rotected by copyright.	Х				

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Reed, 2017 (30)	88	162			Х	Х	1-055758	Х	
Saaby 2013 (31)	397	144	Х		Х	Х	5 01		
Saaby, 2014 (32)	360	119	Х		Х	X		Х	X
Sandoval, 2014 (33)	66	190	Х	Х	Х	Х			X
Sandoval, 2017 (34)	77	140	Х	Х	Х	Х	February	Х	X
Sato, 2020 (35)	2834	155	Х		Х			Х	X
Shah, 2015 (36)	1171	429	Х	Х	Х	Х	20	Х	X
Singh, 2020 (37)	2097	1225	Х		Х		22.	Х	X
Smilowitz, 2018 (38)	137	146	Х	X	Х	Х	Doy	Х	X
Stein, 2014 (39)	2691	127	Х	X	Х		vnle	Х	X
Truong, 2020 (40)	275	175	Х	Х	Х		wnloaded	Х	X
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Table S4. Risk of bia	s assessment					
Author, Year	Representative of Exposed Cohort	Selection of Non-exposed	Outcome Assessment	Follow-up Length	음 Adequacy of Follow- Up 딸	Summary
Arora, 2018 (1)	х	х	x	x	x Ÿ	8 (good quality
Balanescu, 2020 (2)	0	х	x	0	x 2022. x x	6 (fair quality)
Baron, 2016 (3)	x	х	x	x		8 (good quality
Bonaca, 2012 (4)	x	х	x	x	x ş	8 (good quality
Cediel, 2017 (5)	x	X X	x	x	x nlc	8 (good quality
Chapman, 2018 (6)	х	x	х	x	nloade x x	8 (good quality
Chapman, 2020 (7)	х	x	x	x	X ^d	8 (good quality
Consuegra-Sanchaz, 2018 (8)	0	0	x	0	x from htt	3 (poor quality
El-Haddad, 2012 (9)	х	х	0	0	0	5 (fair quality)
Etaher, 2020 (10)	х	х	x	x	x <u>s</u>	8 (good quality
Furie, 2019 (11)	х	х	x	×	x b	8 (good quality
Guimaraes, 2018 (12)	0	0	x	0	x mj.	4 (fair quality)
Hawatmeh, 2020 (13)	0	0	x	x	0 /00	4 (fair quality)
Higuchi, 2019 (14)	0	0	x	x	x L	5 (fair quality)
Javed, 2009 (15)	х	х	x	x	x ne	8 (good quality
Kadesjo, 2019 (16)	х	х	x	х	x 21	8 (good quality
Lambrecht, 2018 (17)	х	х	x	x	2024 x	8 (good quality
Landes, 2016 (18)	х	х	x	х	x م م	8 (good quality
Lopez-Cuenca, 2016 (19)	х	x	x	x	guest. F	8 (good quality
Meigher, 2016 (20)	х	х	x	x	x rot	8 (good quality
Nestelberger, 2017 (21)	x	x	x	x	ected x	8 (good quality
Neumann, 2017 (22)	х	х	x	x	by copyright.	8 (good quality

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Paiva, 2015 (23)	х	x	х	х	x 75	8 (good quality)
Pandey, 2020 (24)	0	0	0	0	0 o	2 (poor quality)
Putot, 2018 (25)	х	х	х	х	X -1	8 (good quality)
Putot, 2019 (26)	х	х	0	х	x Ţ	7 (good quality)
Putot, 2020 (27)	х	х	х	х	x	8 (good quality)
Radovanovic, 2017 (28)	x	x	х	х	r February 2022. x x x x x x x	8 (good quality)
Raphael, 2020 (29)	x	х	х	х	x .22	8 (good quality)
Reed, 2017 (30)	х	х	х	х	хQ	8 (good quality)
Saaby 2013 (31)	х	x	х	х	x n	8 (good quality)
Saaby, 2014 (32)	х	x	х	х	x a	8 (good quality)
Sandoval, 2014 (33)	х	x	х	х	x Downloaded x ded	8 (good quality)
Sandoval, 2017 (34)	х	x	Х	х	fron x	8 (good quality)
Sato, 2020 (35)	0	0	0	х	X T	2 (poor quality)
Shah, 2015 (36)	х	х	х	х	x	8 (good quality)
Singh, 2020 (37)	0	0	х	х	x br	6 (fair quality)
Smilowitz, 2018 (38)	х	х	x	х	x en .t	7 (good quality)
Stein, 2014 (39)	х	х	x	х	x n	7 (good quality)
Truong, 2020 (40)	х	х	х	х		8 (good quality)
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		%
1116	3110	35.9%
698	1943	35.9%
1716	5465	31.4%
1506	4878	30.9%
351	1301	27.0%
743	3021	24.6%
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44	328	13.4%
291	2217	13.19
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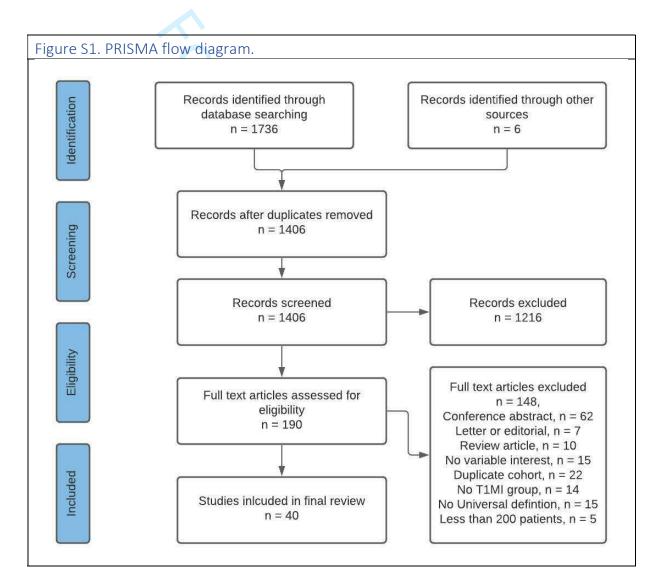
		T2MI					
Presenting Symptom	No. patients with presenting symptom	Total number of patients	%	No. patients with presenting symptom	Total number of patients	%	Odds ratio * [95% Cl]
Chest pain	3474	5932	58.6%	58273	65883	88.4%	0.19 [0.13, 0.26]
Dyspnoea	1412	5210	27.1%	6930	65129	10.6%	2.64 [1.86, 3.74]
Arm or shoulder discomfort	28	330	8.5%	50	143	35.0%	0.18 [0.11, 0.30]
Jaw or neck discomfort	6	140	4.3%	12	77	15.6%	0.24 [0.09, 0.68]
Epigastric discomfort	8	140	5.7%	8	77	10.4%	0.52 [0.19, 1.45]
Nausea or vomiting	46	330	13.9%	39	143	27.3%	0.46 [0.28, 0.74]
Fatigue	5	140	3.6%	5	77	6.5%	0.53 [0.15, 1.90]
Diaphoresis	16	140	11.4%	16	77	20.8%	0.49 [0.23, 1.05]
Other nonspecific symptoms	988	1529	64.6%	2662	41396	6.4%	4.9 [0.48, 50.33]
Collapse / syncope	99	2125	4.7%	157	7152	2.2%	2.10 [1.05, 4.18]

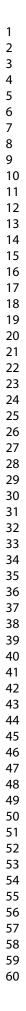
*Comparing T2MI with T1MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis

Abbreviations: URL- upper reference limit; STEMI- ST elevation myocardial infarction; NSTEMI- Non- ST elevation myocardial infarction; MI- Myocardial infarction; cTn- cardiac troponin; T1MI- Type 1 myocardial infarction; T2MI- Type 2 myocardial infarction; ECG- electrocardiogram; CAD- coronary artery disease; PCI-percutaneous coronary intervention; CABG- coronary artery bypass graft; IHD- ischaemic heart disease; MACE- Major adverse cardiovascular events; CI-confidence interval

		T2MI			Odds ratio* (95% CI)		
Variable	No. patients with nominated diagnostic findings	Total no. patients	%	No. patients with nominated diagnostic findings	Total no of patients	%	
ECG							
ST elevation	1129	8014	14.1%	37182	84096	44.2%	0.22 [0.17, 0.2
ST depression or T wave Inversion	1728	4911	35.2%	10968	51042	21.5%	1.36 [0.85, 2.1
Pathological Q Waves	30	447	6.7%	177	850	20.8%	0.38 [0.20, 0.7
Non-specific ST-T wave changes	146	592	24.7%	45	417	10.8%	2.62 [1.81, 3.7
Left bundle branch block	175	1927	9.1%	1943	42543	4.6%	1.62 [1.21, 2.1
Atrial fibrillation/flutter	54	257	21%	52	784	6.6%	4.99 [3.14, 7.9
Echocardiograph							
Echocardiogram performed	648	1353	47.9%	1571	2830	55.5%	0.44 [0.20, 0.9
Presence of RWMA	97	286	33.9%	101	214	47.2%	0.48 [0.06, 3.7
Angiogram							
Angiogram performed	3182	9318	34.1%	42724	49944	85.5%	0.09 [0.06, 0.1
Obstructive coronary artery disease present	1246	3663	34.0%	19923	44404	44.9%	0.16 [0.05, 0.5
Multivessel disease present	593	2147	27.6%	11839	41715	28.4%	0.40 [0.19, 0.8
*Comparing T2MI with meta-analysis ECG=electrocardiograp myocardial infarction; T	h; RWMA=regio	onal wall m	otion abn	-	·		-

Table S8. Troponin measurements.								
Troponin Measurement	Number of Studies	T1MI (min-max)	T2MI (min-max)					
Baseline cTn (xULN)	12	0.14-190	0.1-8.2					
6h cTn (xULN)	4	13.2-142	4.25-11					
Peak cTn (xULN)	20	5.1-1703	2.8-447					
Abbreviations: xULN= times	s upper limit normal		1					





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	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Arora 2018	56	264	209	775	3.7%	0.73 [0.52, 1.02]	-
Bonaca 2012	380	1313	9998	40501	4.2%	1.24 [1.10, 1.40]	-
Cediel 2017	41	194	120	376	3.5%	0.57 [0.38, 0.86]	
Chapman 2018	191	429	497	1171	4.0%	1.09 [0.87, 1.36]	+
Chapman 2020	454	1121	1519	4981	4.2%	1.55 [1.36, 1.77]	•
Conseugra Sanchez 2018	30	75	69	125	2.9%	0.54 [0.30, 0.97]	
Etaher 2020	95	171	63	97	3.1%	0.67 [0.40, 1.13]	
Furie 2019	119	206	220	349	3.6%	0.80 [0.56, 1.14]	
Guimares 2018	37	76	416	847	3.2%	0.98 [0.61, 1.57]	+
Hawatmeh 2020	127	281	387	664	3.8%	0.59 [0.45, 0.78]	-
Higuchi 2019	65	491	1120	12023	3.9%	1.49 [1.14, 1.94]	-
Kadesjo 2019	48	251	48	1111	3.4%	5.24 [3.42, 8.03]	-
Landes 2016	68	107	50	107	3.0%	1.99 [1.15, 3.43]	
Lopez Cuenca 2016	19	117	101	707	3.0%	1.16 [0.68, 1.99]	
Meigher 2016	59	452	51	340	3.5%	0.85 [0.57, 1.27]	-
Nestelberger 2020	0	128	283	684	0.3%	0.01 [0.00, 0.09]	←
Neumann 2017	14	99	55	188	2.7%	0.40 [0.21, 0.76]	
Pandey 2020	47	103	47	97	3.0%	0.89 [0.51, 1.56]	-
Putot 2018	291	847	407	2036	4.1%	2.09 [1.75, 2.50]	-
Putot 2020	319	862	853	3710	4.1%	1.97 [1.68, 2.30]	-
Radovanovic 2017	401	1091	3817	13828	4.2%	1.52 [1.34, 1.73]	•
Saaby 2013	39	144	96	397	3.4%	1.16 [0.75, 1.80]	+
Saaby 2014	26	119	71	360	3.1%	1.14 [0.69, 1.89]	+
Sandoval 2014	27	190	20	66	2.6%	0.38 [0.20, 0.74]	
Sandoval 2017	24	140	24	77	2.6%	0.46 [0.24, 0.88]	
Sato 2020	18	155	350	2834	3.1%	0.93 [0.56, 1.54]	-
Shah 2015	191	429	497	1171	4.0%	1.09 [0.87, 1.36]	t t
Smilowitz 2018	28	146	26	137	2.8%	1.01 [0.56, 1.83]	+
Stein 2014	56	127	756	2691	3.6%	2.02 [1.41, 2.89]	-
Troung 2020	82	175	52	275	3.4%	3.78 [2.48, 5.77]	-
Total (95% CI)		10303		92725	100.0%	1.10 [0.93, 1.31]	•
Total events	3352		22222				
Heterogeneity: Tau ² = 0.18;	Chi ² = 287	.89, df =	= 29 (P <	0.00001); I ² = 90%		0.01 0.1 1 10
Test for overall effect: Z = 1.							Favours T1MI Favours T2

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Arora 2018	110	264	371	775	3.4%	0.78 [0.59, 1.03]	-
Baron 2016	306	1313	9395	40501	3.9%	1.01 [0.88, 1.15]	+
Cediel 2017	73	194	132	376	3.1%	1.12 [0.78, 1.60]	+
Chapman 2018	93	429	185	1171	3.4%	1.48 [1.12, 1.95]	+
Chapman 2020	147	1121	802	4981	3.7%	0.79 [0.65, 0.95]	-
Conseugra Sanchez 2018	29	75	59	125	2.2%	0.71 [0.39, 1.26]	+
Etaher 2020	64	171	36	97	2.4%	1.01 [0.61, 1.70]	+
Furie 2019	100	206	199	349	3.1%	0.71 [0.50, 1.00]	
Guimares 2018	27	76	419	847	2.5%	0.56 [0.35, 0.92]	
Hawatmeh 2020	101	281	303	664	3.3%	0.67 [0.50, 0.89]	-
Higuchi 2019	148	491	3745	12023	3.7%	0.95 [0.78, 1.16]	+
Javed 2009	24	64	61	143	2.1%	0.81 [0.44, 1.48]	
Kadesjo 2019	56	251	213	1111	3.2%	1.21 [0.87, 1.69]	+
Lambrecht 2018	28	119	46	360	2.4%	2.10 [1.24, 3.55]	
Landes 2016	54	107	54	107	2.4%	1.00 [0.59, 1.71]	+
Lopez Cuenca 2016	52	117	336	707	2.9%	0.88 [0.60, 1.31]	+
Meigher 2016	122	452	126	340	3.3%	0.63 [0.46, 0.85]	-
Nestelberger 2020	26	128	180	684	2.6%	0.71 [0.45, 1.13]	
Neumann 2017	12	99	42	188	1.9%	0.48 [0.24, 0.96]	
Pandey 2020	47	103	44	97	2.3%	1.01 [0.58, 1.76]	+
Putot 2018	264	847	504	2036	3.7%	1.38 [1.15, 1.64]	+
Putot 2019	99	254	138	365	3.2%	1.05 [0.76, 1.46]	+
Radovanovic 2017	286	1091	2766	13828	3.8%	1.42 [1.23, 1.64]	-
Raphael 2020	150	1054	313	1365	3.6%	0.56 [0.45, 0.69]	-
Saaby 2013	40	144	52	397	2.6%	2.55 [1.60, 4.07]	
Saaby 2014	28	119	46	360	2.4%	2.10 [1.24, 3.55]	
Sandoval 2014	57	190	21	66	2.1%	0.92 [0.50, 1.68]	-
Sandoval 2017	43	140	32	77	2.2%	0.62 [0.35, 1.11]	
Sato 2020	40	155	1015	2834	3.0%	0.62 [0.43, 0.90]	
Shah 2015	93	429	185	1171	3.4%	1.48 [1.12, 1.95]	-
Singh 2020	165	1225	405	2097	3.7%	0.65 [0.53, 0.79]	+
Smilowitz 2018	58	146	61	137	2.6%	0.82 [0.51, 1.32]	-+
Stein 2014	61	127	945	2691	3.1%	1.71 [1.19, 2.44]	
Troung 2020	41	175	56	275	2.7%	1.20 [0.76, 1.89]	T
Total (95% CI)		12157		93345	100.0%	0.97 [0.85, 1.10]	•
Total events	3044		23287				
Heterogeneity: Tau ² = 0.11;	Chi ² = 193	.46, df =	= 33 (P <	0.00001); l ² = 83%	6	0.01 0.1 1 10
Test for overall effect: Z = 0.	53 (P = 0.	59)					0.01 0.1 1 10 Favours T1MI Favours T2M

Study or Subgroup Events Total Events Total Weight M-H, Random, 95% C1 Arora 2018 225 264 642 775 3.2% 1.20 [0.81, 1.76] Baron 2016 962 1313 26334 40501 3.7% 1.47 [0.97, 2.21] Chapman 2018 254 429 533 1171 3.6% 1.74 [1.39, 2.17] Conseugra Sanchez 2018 54 75 91 125 2.5% 0.96 [0.51, 1.82] Etaher 2020 128 171 56 97 2.8% 2.18 [0.49, 1.54] Guimares 2018 60 76 688 847 2.6% 0.87 [0.49, 1.54] Hawatmeh 2020 242 281 583 664 3.1% 0.065 [0.29, 1.48] Javed 2009 53 64 126 143 2.0% 0.65 [0.29, 1.48] Landes 2016 87 107 82 107 2.4% 2.68 [1.46, 4.67] Meigher 2016 289 452 224 340	Odds Ratio	Odds Ratio		11	T1N		T2M	
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Higuchi 2019 311 491 7064 12023 3.6% 1.21 [1.01, 1.46] Javed 2009 53 64 126 143 2.0% 0.65 [0.29, 1.48] Lambrecht 2018 66 119 193 360 3.1% 1.08 [0.71, 1.63] Lopez Cuenca 2016 103 117 522 707 2.6% 2.61 [1.46, 4.67] Weigher 2016 289 452 224 340 0.92 [0.68, 1.23] Nestelberger 2020 92 128 521 684 3.1% 0.80 [0.52, 1.22] Neumann 2017 77 99 154 188 2.6% 0.77 [0.42, 1.41] Paiva 2015 192 236 580 764 3.2% 1.38 [0.96, 2.00] Pandey 2020 68 103 68 97 2.6% 0.83 [0.46, 1.50] Putot 2018 683 847 1140 2036 3.6% 3.27 [2.70, 3.96] Putot 2019 211 254 279 365 3.1% 1.51 [1.01, 2.27] Radovanovic 2017 802 1091 8504 13828 3.7% </td <td>54]</td> <td>0.87 [0.49, 1.54]</td> <td>2.6%</td> <td>847</td> <td>688</td> <td>76</td> <td>60</td> <td>Guimares 2018</td>	54]	0.87 [0.49, 1.54]	2.6%	847	688	76	60	Guimares 2018
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Fotal events 7536 55782 Heterogeneity: Tau ² = 0.20; Chi ² = 315.20, df = 32 (P < 0.00001); I ² = 90% 0.01 Set for overall effect: 7 = 2 31 (P = 0.02) 0.01								-
Heterogeneity: Tau ² = 0.20; Chi ² = 315.20, df = 32 (P < 0.00001); l ² = 90%	45]	1.22 [1.03, 1.45]	100.0%	88017		11021		
Cect for overall effect: 7 = 2 31 (P = 0.02)		L	12 - 009/	0.00004		20 df -		
Fest for overall effect. $2 = 2.51 (F = 0.02)$	0.01 0.1 1 10	0.0), 1- = 90%	0.00001	52 (P <			
	Favours T1MI Favours T2M					12)	.51 (F = 0.0	rescript overall effect. 2 = 2.

igure S5. Forest Plo								
	T2M		T1N			Odds Ratio		Odds Ratio
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% CI		M-H, Random, 95%
Arora 2018	131	264	441	775	3.4%	0.75 [0.56, 0.99]		٦
Baron 2016	548	1313	14893		3.5%	1.23 [1.10, 1.38]		
Chapman 2018	177 38	429 75	539 66	1171 125	3.4% 2.9%	0.82 [0.66, 1.03]		1
Conseugra Sanchez 2018 Etaher 2020	89	171	48	97	3.1%	0.92 [0.52, 1.63] 1.11 [0.67, 1.82]		1
Furie 2019	121	206	218	349	3.3%	0.86 [0.60, 1.22]		-
Guimares 2018	58	76	625	847	3.0%	1.14 [0.66, 1.98]		+
lawatmeh 2020	205	281	505	664	3.3%	0.85 [0.62, 1.17]		-
liguchi 2019	174	491	5044	12023	3.5%	0.76 [0.63, 0.92]		-
aved 2009	34	64	113	143	2.8%	0.30 [0.16, 0.57]		
ambrecht 2018	48	119	137	360	3.2%	1.10 [0.72, 1.68]		+
andes 2016	82	107	69	107	2.9%	1.81 [0.99, 3.28]		-
opez Cuenca 2016	89	117	530	707	3.1%	1.06 [0.67, 1.68]		+
Neigher 2016	194	452	180	340	3.4%	0.67 [0.50, 0.89]		_ _
lestelberger 2020	46	128	440	684	3.2%	0.31 [0.21, 0.46]		-
Veumann 2017	40	99	108	188	3.1%	0.50 [0.31, 0.82]		
Paiva 2015	125	236	442	764	3.4%	0.82 [0.61, 1.10]		
Pandey 2020	38	103	51	97	3.0%	0.53 [0.30, 0.93]		-1
Putot 2018	419	847 254	919 259	2036 365	3.5%	1.19 [1.01, 1.40]		1
Putot 2019 Radovanovic 2017	169 631	1091	259	13828	3.3% 3.5%	0.81 [0.58, 1.15]		1
Raphael 2020	359	1054	790	1365	3.5%	0.98 [0.86, 1.11] 0.38 [0.32, 0.44]		- 1
Saaby 2013	60	144	158	397	3.2%	1.08 [0.73, 1.59]		+
Saaby 2014	48	119	137	360	3.2%	1.10 [0.72, 1.68]		+
Sandoval 2014	63	190	36	66	2.9%	0.41 [0.23, 0.73]		
Sandoval 2017	61	140	50	77	2.9%	0.42 [0.23, 0.74]		
Sato 2020	95	155	1435	2834	3.3%	1.54 [1.11, 2.15]		
Shah 2015	117	429	539	1171	3.4%	0.44 [0.35, 0.56]		+
Singh 2020	172	1225	1229	2097	3.5%	0.12 [0.10, 0.14]		-
Smilowitz 2018	102	146	98	137	3.0%	0.92 [0.55, 1.54]		+
Stein 2014	93	127	1924	2691	3.2%	1.09 [0.73, 1.63]		+
fotal (95% CI)		10652		87366	100.0%	0.74 [0.58, 0.94]		•
	4626		40099					.
			= 30 (P <	0.00001); I ² = 96%	6	0.01	
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.42; Fest for overall effect: Z = 2.	4626 Chi ² = 703	10652 .94, df =	40099	87366	100.0%	0.74 [0.58, 0.94]	0.01	0.1 1 T1MI T2M

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% CI
Arora 2018	80	264	327	775	3.7%	0.60 [0.44, 0.80]	· -
Baron 2016	771	1313	24754	40501	4.0%	0.90 [0.81, 1.01]	i •
Cediel 2017	62	194	218	376	3.6%	0.34 [0.24, 0.49]	-
Chapman 2018	62	429	380	1171	3.8%	0.35 [0.26, 0.47]	
Conseugra Sanchez 2018	10	75	27	125	2.5%	0.56 [0.25, 1.23]	
Etaher 2020	21	171	30	97	2.9%	0.31 [0.17, 0.59]	
Furie 2019	73	206	133	349	3.6%	0.89 [0.62, 1.28]	i 4
Guimares 2018	36	76	304	847	3.3%	1.61 [1.00, 2.58]	
Hawatmeh 2020	88	281	272	664	3.8%	0.66 [0.49, 0.88]	
Javed 2009	30	64	66	143	3.0%	1.03 [0.57, 1.86]	
Lambrecht 2018	91	119	284	360	3.3%	0.87 [0.53, 1.42]	· -+
Landes 2016	44	107	41	107	3.1%	1.12 [0.65, 1.94]	i +−
Lopez Cuenca 2016	23	117	232	707	3.3%	0.50 [0.31, 0.81]	
Meigher 2016	172	452	129	340	3.8%	1.00 [0.75, 1.34]	i +
Nestelberger 2020	21	128	181	684	3.3%	0.55 [0.33, 0.90]	
Neumann 2017	17	99	52	188	3.0%	0.54 [0.29, 1.00]	
Pandey 2020	13	103	16	97	2.5%	0.73 [0.33, 1.61]	
Putot 2018	280	847	1271	2036	4.0%	0.30 [0.25, 0.35]	+
Putot 2019	101	254	243	365	3.7%	0.33 [0.24, 0.46]	
Radovanovic 2017	340	1091	5697	13828	4.0%	0.65 [0.57, 0.74]	+
Raphael 2020	462	1054	907	1365	4.0%	0.39 [0.33, 0.47]	•
Saaby 2013	35	144	129	397	3.4%	0.67 [0.43, 1.03]	
Saaby 2014	91	119	284	360	3.3%	0.87 [0.53, 1.42]	· -+
Sandoval 2017	52	140	23	77	3.0%	1.39 [0.76, 2.52]	↓ ↓
Sato 2020	51	155	921	2834	3.7%	1.02 [0.72, 1.44]	i +
Shah 2015	62	429	380	1171	3.8%	0.35 [0.26, 0.47]	
Singh 2020	244	1225	1063	2097	4.0%	0.24 [0.21, 0.29]	
Smilowitz 2018	96	146	89	137	3.3%	1.04 [0.63, 1.69]	i +
Stein 2014	20	127	1095	2691	3.3%	0.27 [0.17, 0.44]	
Total (95% CI)		9929		74889	100.0%	0.60 [0.49, 0.73]	· ◆
Total events	3448		39548				
Heterogeneity: Tau ² = 0.26 Test for overall effect: Z = 4				0.0000	1); l² = 939		0.01 0.1 1 10 Favours [experimental] Favours [control

	T2M	1	T1N	41		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Baron 2016	824	1313	27283	40501	21.6%	0.82 [0.73, 0.91]	
Javed 2009	14	64	54	143	11.0%	0.46 [0.23, 0.91]	
Pandey 2020	22	103	22	97	11.2%	0.93 [0.47, 1.81]	
Putot 2018	91	847	423	2036	19.7%	0.46 [0.36, 0.58]	-
Putot 2019	27	254	97	365	15.2%	0.33 [0.21, 0.52]	
Radovanovic 2017	247	1091	3084	13828	21.2%	1.02 [0.88, 1.18]	•
Total (95% CI)		3672		56970	100.0%	0.63 [0.46, 0.87]	•
Total events	1225		30963				26 05 26

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Arora 2018	66	264	130	775	6.5%	1.65 [1.18, 2.32]	-
Baron 2016	355	1313	8056	40501	7.7%	1.49 [1.32, 1.69]	-
Cediel 2017	51	194	42	376	5.6%	2.84 [1.80, 4.46]	 -
Etaher 2020	83	171	15	97	4.4%	5.16 [2.75, 9.65]	_ −
Furie 2019	74	206	99	349	6.3%	1.42 [0.98, 2.04]	
Javed 2009	33	64	43	143	4.6%	2.48 [1.35, 4.54]	
Landes 2016	29	107	17	107	4.2%	1.97 [1.01, 3.85]	-
Meigher 2016	86	452	54	340	6.2%	1.24 [0.86, 1.81]	↓ -
Putot 2018	122	847	113	2036	6.9%	2.86 [2.19, 3.75]	-
Putot 2019	55	254	45	365	5.8%	1.97 [1.28, 3.03]	
Radovanovic 2017	158	1091	982	13828	7.5%	2.22 [1.85, 2.65]	-
Saaby 2013	20	144	23	397	4.4%	2.62 [1.39, 4.94]	
Sandoval 2014	49	190	9	66	3.6%	2.20 [1.01, 4.78]	
Sandoval 2017	20	140	13	77	3.7%	0.82 [0.38, 1.76]	-+-
Sato 2020	68	155	1261	2834	6.6%	0.97 [0.70, 1.35]	+
Smilowitz 2018	41	146	41	137	5.2%	0.91 [0.55, 1.53]	-
Stein 2014	45	127	328	2691	6.2%	3.95 [2.70, 5.79]	
Troung 2020	23	175	29	275	4.7%	1.28 [0.72, 2.30]	+ -
Total (95% CI)		6040		65394	100.0%	1.87 [1.53, 2.28]	•
Total events	1378		11300				

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	T2M	1	T1N	11		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% CI	
Baron 2016	151	1313	3035	40501	4.9%	1.60 [1.35, 1.91]	· · · · ·	
Cediel 2017	31	194	15	376	3.8%	4.58 [2.40, 8.71		
Chapman 2020	292	1121	792	4981	4.9%	1.86 [1.60, 2.17	· · · ·	
Etaher 2020	42	171	5	97	2.9%	5.99 [2.28, 15.72		
Furie 2019	66	206	96	349	4.5%	1.24 [0.85, 1.81	1 +	
Hawatmeh 2020	79	281	119	664	4.6%	1.79 [1.29, 2.48	· -	
Kadesjo 2019	40	251	91	1111	4.5%	2.12 [1.42, 3.17]	I −	
Lambrecht 2018	26	119	32	360	4.0%	2.87 [1.63, 5.05	I	
Landes 2016	21	107	17	107	3.6%	1.29 [0.64, 2.61]	ı ∔	
Lopez Cuenca 2016	21	117	42	707	4.0%	3.46 [1.97, 6.10]		
Meigher 2016	118	452	54	340	4.6%	1.87 [1.31, 2.68	I −	
Neumann 2017	25	99	36	188	4.0%	1.43 [0.80, 2.55	1 +	
Putot 2018	231	847	71	2036	4.7%	10.38 [7.84, 13.75	· · ·	
Putot 2019	78	254	36	365	4.4%	4.05 [2.62, 6.26]	· · ·	
Radovanovic 2017	74	1091	290	13828	4.8%	3.40 [2.61, 4.42	I -	
Raphael 2020	86	1054	26	1365	4.4%	4.58 [2.93, 7.15	· · ·	
Saaby 2013	34	144	45	397	4.2%	2.42 [1.48, 3.96	· · ·	
Saaby 2014	26	119	32	360	4.0%	2.87 [1.63, 5.05	I —	
Sandoval 2014	46	190	7	66	3.2%	2.69 [1.15, 6.31		
Sandoval 2017	40	140	10	77	3.5%	2.68 [1.25, 5.72		
Sato 2020	13	155	433	2834	4.0%	0.51 [0.29, 0.90	·	
Smilowitz 2018	75	146	61	137	4.3%	1.32 [0.82, 2.10	1 +	
Stein 2014	33	127	248	2691	4.4%	3.46 [2.28, 5.25		
Troung 2020	13	175	24	275	3.6%	0.84 [0.42, 1.70	· -+	
Total (95% CI)		8873		74212	100.0%	2.35 [1.82, 3.03]	∣ ♦	
Total events	1661		5617					

	T2M	I	T1M	11		Odds Ratio	Odds Ratio
Study or Subgroup			Events		Weight	M-H, Random, 95% Cl	
Arora 2018	46	264	111	775		1.26 [0.87, 1.84]	
Cediel 2017	21	194	52	376	5.4%	0.76 [0.44, 1.30]	
Chapman 2018	29	429	85	1171		0.93 [0.60, 1.43]	
Furie 2019	28	206	56	349		0.82 [0.50, 1.34]	
lawatmeh 2020	28	281	89	664	5.9%	0.72 [0.46, 1.12]	
liguchi 2019	8	491	182	12023		1.08 [0.53, 2.20]	
ambrecht 2018	17	119	20	360		2.83 [1.43, 5.61]	
opez Cuenca 2016	11	117	57	707		1.18 [0.60, 2.33]	
Vestelberger 2020	2	128	72	684		0.13 [0.03, 0.56]	
Putot 2018	110	847	138	2036		2.05 [1.58, 2.67]	
Putot 2019	55	254	54	365		1.59 [1.05, 2.41]	
Radovanovic 2017		1091		13828		2.11 [1.70, 2.63]	
Saaby 2013	18	144	21	397		2.56 [1.32, 4.95]	
Saaby 2014	17	119	20	360		2.83 [1.43, 5.61]	
Sandoval 2017	3	140	5	77		0.32 [0.07, 1.36]	
Sato 2020	14	155	121	2834		2.23 [1.25, 3.97]	
Shah 2015	29	429	82	1171		0.96 [0.62, 1.49]	
Smilowitz 2018	11	146	13	137		0.78 [0.34, 1.80]	
Stein 2014	22	127	229	2691		2.25 [1.40, 3.64]	
Froung 2020	12	175	9	2051		2.18 [0.90, 5.28]	
roung 2020	12	115	5	215	5.076	2.10 [0.00, 0.20]	
Fotal (95% CI)		5856		41280	100.0%	1.33 [1.05, 1.69]	●
Fotal events	584		2066				
Heterogeneity: Tau ² = (0.20; Chi ²	= 81.8	0, df = 19	(P < 0.0	00001); l² :	= 77%	0.01 0.1 1 10
Fest for overall effect: 2	Z = 2.36 (P = 0.0	2)				T1MI T2MI

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	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Baron 2016	99	1313	2696	40501	6.7%	1.14 [0.93, 1.41]	
Cediel 2017	29	194	38	376	4.0%	1.56 [0.93, 2.62]	
Chapman 2018	48	429	92	1171	5.2%	1.48 [1.02, 2.13]	
Chapman 2020	135	1121	368	4981	6.7%	1.72 [1.39, 2.11]	+
Etaher 2020	28	171	10	97	2.5%	1.70 [0.79, 3.68]	
Furie 2019	42	206	98	349	4.9%	0.66 [0.43, 0.99]	
Hawatmeh 2020	24	281	64	664	4.2%	0.88 [0.54, 1.43]	-+
Higuchi 2019	35	491	748	12023	5.4%	1.16 [0.81, 1.64]	+
Kadesjo 2019	19	251	71	1111	3.9%	1.20 [0.71, 2.03]	+
Lambrecht 2018	24	119	43	360	3.7%	1.86 [1.08, 3.23]	
Lopez Cuenca 2016	20	117	81	707	3.9%	1.59 [0.93, 2.72]	
Nestelberger 2020	5	128	52	684	1.9%	0.49 [0.19, 1.26]	
Paiva 2015	29	236	59	764	4.3%	1.67 [1.05, 2.68]	
Putot 2018	122	847	127	2036	6.2%	2.53 [1.94, 3.29]	
Putot 2019	50	254	40	365	4.5%	1.99 [1.27, 3.13]	
Radovanovic 2017	84	1091	774	13828	6.5%	1.41 [1.11, 1.78]	-
Saaby 2013	31	144	54	397	4.2%	1.74 [1.07, 2.84]	
Saaby 2014	24	119	43	360	3.7%	1.86 [1.08, 3.23]	
Sandoval 2017	18	140	3	77	1.2%	3.64 [1.04, 12.78]	
Sato 2020	17	155	276	2834	4.0%	1.14 [0.68, 1.92]	+
Shah 2015	48	429	92	1171	5.2%	1.48 [1.02, 2.13]	
Stein 2014	22	127	215	2691	4.3%	2.41 [1.49, 3.90]	-
Troung 2020	16	175	16	275	2.7%	1.63 [0.79, 3.35]	
Total (95% CI)		8538		87822	100.0%	1.47 [1.27, 1.71]	•
Total events	969		6060				
Heterogeneity: Tau ² =	0.07; Chi ²	= 62.13	3, df = 22	(P < 0.0	0001); l ² =	65%	0.01 0.1 1 10

T2M	1	T1M	1		Odds Ratio	Odds Ratio	
Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95%	%CI
17	64	2	143	46.0%	25.50 [5.68, 114.50]		-
29	140	6	77	54.0%	3.09 [1.22, 7.82]	-8-	
	204		220	100.0%	8.15 [1.03, 64.46]		
46		8					
1.83; Chi ²	= 5.52,	df = 1 (F	= 0.02	2); 12 = 829	6	0.01 0.1 1	10
	Events 17 29 46	17 64 29 140 204 46	Events Total Events 17 64 2 29 140 6 204 46 8	Events Total Events Total 17 64 2 143 29 140 6 77 204 220 46 8	Events Total Events Total Weight 17 64 2 143 46.0% 29 140 6 77 54.0% 204 220 100.0% 46 8	Events Total Events Total Weight M-H, Random, 95% CI 17 64 2 143 46.0% 25.50 [5.68, 114.50] 29 140 6 77 54.0% 3.09 [1.22, 7.82] 204 220 100.0% 8.15 [1.03, 64.46]	Events Total Events Total Weight M-H, Random, 95% Cl M-H, Random, 95% 17 64 2 143 46.0% 25.50 [5.68, 114.50] 140 150 140 140 140 140 <t< td=""></t<>

	T2M		T1N	11		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95	%CI
Cediel 2017	67	194	37	376	8.8%	4.83 [3.08, 7.58]			-
Etaher 2020	42	171	5	97	4.8%	5.99 [2.28, 15.72]		-	•
Furie 2019	42	206	68	349	8.9%	1.06 [0.69, 1.63]		+	
Hawatmeh 2020	48	281	54	664	9.0%	2.33 [1.53, 3.53]		-	
Lambrecht 2018	25	119	32	360	7.7%	2.73 [1.54, 4.83]			
Lopez Cuenca 2016	51	117	103	707	9.0%	4.53 [2.97, 6.90]		-	-
Neumann 2017	34	99	20	188	7.2%	4.39 [2.36, 8.19]		¬	_
Paiva 2015	72	236	117	764	9.7%	2.43 [1.73, 3.41]			
Putot 2018	235	847	160	2036	10.6%	4.50 [3.61, 5.61]			-
Radovanovic 2017	170	1091	567	13828	10.8%	4.32 [3.59, 5.19]			
Saaby 2013	34	144	50	397	8.4%	2.15 [1.32, 3.49]			
Sandoval 2017	16	140	7	77	5.0%	1.29 [0.51, 3.29]			
Total (95% CI)		3645		19843	100.0%	3.02 [2.29, 3.99]		•	
Total events	836		1220						
Heterogeneity: Tau ² =	0.18; Chi ²	= 62.33	3, df = 11	(P < 0.0	00001); l ² :	= 82%	0.01		10
Test for overall effect:				(1 < 0.0	,0001),1	0276	0.01	0.1 1 T1MI T2MI	10

Figure S13. Forest								Odds Datis
Study or Subgroup E	T2MI vents	Total E	T1MI vents		Weight	Odds Ratio M-H, Random, 95% 0		Odds Ratio M-H, Random, 95%
Cediel 2017	67	194	37	376	8.8%	4.83 [3.08, 7.58		-
Etaher 2020	42	171	5	97	4.8%	5.99 [2.28, 15.72		
Furie 2019	42	206	68	349	8.9%	1.06 [0.69, 1.63	-	+
Hawatmeh 2020	48	281	54	664	9.0%	2.33 [1.53, 3.53		-
Lambrecht 2018	25	119	32	360	7.7%	2.73 [1.54, 4.83	-	
Lopez Cuenca 2016	51	117	103	707	9.0%	4.53 [2.97, 6.90	-	
Neumann 2017 Paiva 2015	34 72	99 236	20 117	188 764	7.2% 9.7%	4.39 [2.36, 8.19 2.43 [1.73, 3.4	-	
Putot 2018	235	236 847	160	2036	9.7%		-	- T-
Radovanovic 2017		1091		13828	10.8%	4.50 [3.61, 5.64 4.32 [3.59, 5.19		
Saaby 2013	34	144	50	397	8.4%	2.15 [1.32, 3.49	-	
Sandoval 2017	16	140	7	77	5.0%	1.29 [0.51, 3.29	-	-+
Total/05% CD		2645		0043	100 00/	2 0 2 1 2 2 0 2 0 0	1	
Total (95% CI)	820	3645		19843	100.0%	3.02 [2.29, 3.99	1	•
Total events Heterogeneity: Tau ² = 0.1	836 8: Chiž	= 62.33	1220 ff = 11 (P-00	00011-12	= 82%	—	
Test for overall effect: Z =				1 - 0.0	0001), 1	- 0276	0.01	0.1 1 1 T1MI T2MI
Figure S14 Forest	Plot	Chest	Pain	as Pr	resenti	ng Feature		
Figure S14. Forest					esenti	<u> </u>		
0	Т	2MI	T11	IN		Odds Ratio		Odds Ratio
Study or Subgroup	Т	2MI its Total	T1I Events	MI Total	Weight	Odds Ratio M-H, Random, 95% Cl		Odds Ratio
	T Ever	2MI	T1I Events 67	MI Total	Weight 5.2%	Odds Ratio		
Study or Subgroup Balanescu 2020 Baron 2016 Cediel 2017	T Even	2MI ats Total 8 49 99 1313 42 194	T11 Events 67 35883 337	MI 152 40501 376	Weight 5.2% 7.4% 6.5%	Odds Ratio M-H, Random, 95% Cl 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05]		
Study or Subgroup Balanescu 2020 Baron 2016 Cediel 2017 Chapman 2020	T Even 8 7	2MI ats Total 8 49 99 1313 42 194 49 1121	T11 Events 67 35883 337 4061	MI 152 40501 376 4981	Weight 5.2% 7.4% 6.5% 7.4%	Odds Ratio M-H, Random, 95% Cl 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05] 0.46 [0.40, 0.53]	-	
Study or Subgroup Balanescu 2020 Baron 2016 Cediel 2017 Chapman 2020 Conseugra Sanchez 2018	T Ever 8	2MI 8 49 99 1313 42 194 49 1121 62 75	T11 Events 67 35883 337 4061 102	MI 152 40501 376 4981 125	Weight 5.2% 7.4% 6.5% 7.4% 5.5%	Odds Ratio M-H, Random, 95% Cl 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05] 0.46 [0.40, 0.53] 1.08 [0.51, 2.28]		
Study or Subgroup Balanescu 2020 Baron 2016 Cediel 2017 Chapman 2020	T Ever 8	2MI ats Total 8 49 99 1313 42 194 49 1121	T11 Events 67 35883 337 4061	MI 152 40501 376 4981 125 349	Weight 5.2% 7.4% 6.5% 7.4% 5.5% 6.9%	Odds Ratio M-H, Random, 95% Cl 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05] 0.46 [0.40, 0.53]		
Study or Subgroup Balanescu 2020 Baron 2016 Cediel 2017 Chapman 2020 Conseugra Sanchez 2018 Furie 2019	T Ever 8	2MI 1ts Total 8 49 99 1313 42 194 49 1121 62 75 88 206 65 107 87 117	T11 Events 67 35883 337 4061 102 258	MI Total 152 40501 376 4981 125 349 107	Weight 5.2% 7.4% 6.5% 7.4% 5.5% 6.9% 4.3% 6.5%	Odds Ratio M-H, Random, 95% CI 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05] 0.46 [0.40, 0.53] 1.08 [0.51, 2.28] 0.26 [0.18, 0.38] 0.06 [0.02, 0.18] 0.42 [0.26, 0.67]		
Study or Subgroup Balanescu 2020 Baron 2016 Cediel 2017 Chapman 2020 Conseugra Sanchez 2018 Furie 2019 Landes 2016 Lopez Cuenca 2016 Meigher 2016	T Ever 8	2MI 1ts Total 8 49 99 1313 42 194 49 1121 62 75 88 206 65 107 87 117 41 452	T11 Events 67 35883 337 4061 102 258 103 618 201	MI Total 152 40501 376 4981 125 349 107 707 340	Weight 5.2% 7.4% 6.5% 7.4% 5.5% 6.9% 4.3% 6.5% 6.8%	Odds Ratio M-H, Random, 95% CI 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05] 0.46 [0.40, 0.53] 1.08 [0.51, 2.28] 0.26 [0.18, 0.38] 0.06 [0.02, 0.18] 0.42 [0.26, 0.67] 0.07 [0.05, 0.10]	-	
Study or Subgroup Balanescu 2020 Baron 2016 Cediel 2017 Chapman 2020 Conseugra Sanchez 2018 Furie 2019 Landes 2016 Lopez Cuenca 2016 Meigher 2016 Radovanovic 2017	T Ever 8 7	2MI 8 49 99 1313 42 194 49 1121 62 75 88 206 65 107 87 117 41 452 53 1091	T11 Events 67 35883 337 4061 102 258 103 618 201 12846	MI Total 152 40501 376 4981 125 349 107 707 340 13828	Weight 5.2% 7.4% 6.5% 6.5% 6.9% 4.3% 6.5% 6.8% 7.3%	Odds Ratio M-H, Random, 95% CI 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05] 0.46 [0.40, 0.53] 1.08 [0.51, 2.28] 0.26 [0.18, 0.38] 0.06 [0.02, 0.18] 0.42 [0.26, 0.67] 0.07 [0.05, 0.10] 0.27 [0.23, 0.32]		
Study or Subgroup Balanescu 2020 Baron 2016 Cediel 2017 Chapman 2020 Conseugra Sanchez 2018 Furie 2019 Landes 2016 Lopez Cuenca 2016 Meigher 2016 Radovanovic 2017 Sandoval 2014	T Ever 8 7	2MI 8 49 99 1313 42 194 49 1121 62 75 88 206 65 107 87 117 41 452 53 1091 65 190	T11 Events 67 35883 337 4061 102 258 103 618 201 12846 56	MI Total 152 40501 376 4981 125 349 107 707 340 13828 66	Weight 5.2% 7.4% 6.5% 6.5% 6.9% 4.3% 6.5% 6.8% 7.3% 5.5%	Odds Ratio M-H, Random, 95% CI 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05] 0.46 [0.40, 0.53] 1.08 [0.51, 2.28] 0.26 [0.18, 0.38] 0.06 [0.02, 0.18] 0.42 [0.26, 0.67] 0.07 [0.05, 0.10] 0.27 [0.23, 0.32] 0.09 [0.04, 0.19]		
Study or Subgroup Balanescu 2020 Baron 2016 Cediel 2017 Chapman 2020 Conseugra Sanchez 2018 Furie 2019 Landes 2016 Lopez Cuenca 2016 Meigher 2016 Radovanovic 2017	T Ever 8 7	2MI 8 49 99 1313 42 194 49 1121 62 75 88 206 65 107 87 117 41 452 53 1091	T11 Events 67 35883 337 4061 102 258 103 618 201 12846	MI <u>Total</u> 152 40501 376 4981 125 349 107 707 340 13828 66 77	Weight 5.2% 7.4% 6.5% 6.5% 6.9% 4.3% 6.5% 6.8% 7.3% 5.5% 5.9%	Odds Ratio M-H, Random, 95% CI 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05] 0.46 [0.40, 0.53] 1.08 [0.51, 2.28] 0.26 [0.18, 0.38] 0.06 [0.02, 0.18] 0.42 [0.26, 0.67] 0.07 [0.05, 0.10] 0.27 [0.23, 0.32]		
Study or Subgroup Balanescu 2020 Baron 2016 Cediel 2017 Chapman 2020 Conseugra Sanchez 2018 Furie 2019 Landes 2016 Lopez Cuenca 2016 Meigher 2016 Radovanovic 2017 Sandoval 2014 Sandoval 2017	T Even 7. 8. 7. 8. 8. 8. 8. 8. 8. 8. 8. 8. 8. 8. 8. 8.	2MI atts Total 8 49 99 1313 42 194 49 1121 62 75 88 206 65 107 87 117 41 452 53 1091 65 190 22 140	T11 Events 67 35883 337 4061 102 258 103 618 201 12846 56 38	MI <u>Total</u> 152 40501 376 4981 125 349 107 707 340 13828 66 77 1171	Weight 5.2% 7.4% 6.5% 6.5% 6.9% 4.3% 6.5% 6.8% 7.3% 5.5% 5.9% 7.1%	Odds Ratio M-H, Random, 95% CI 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05] 0.46 [0.40, 0.53] 1.08 [0.51, 2.28] 0.26 [0.18, 0.38] 0.26 [0.18, 0.38] 0.42 [0.26, 0.67] 0.07 [0.05, 0.10] 0.27 [0.23, 0.32] 0.09 [0.04, 0.19] 0.19 [0.10, 0.36]		
Study or Subgroup Balanescu 2020 Baron 2016 Cediel 2017 Chapman 2020 Conseugra Sanchez 2018 Furie 2019 Landes 2016 Lopez Cuenca 2016 Meigher 2016 Radovanovic 2017 Sandoval 2014 Sandoval 2017 Shah 2015 Smilowitz 2018 Stein 2014	T Even 7. 8	2MI Its Total 8 49 99 1313 42 194 49 1121 62 75 88 206 65 107 87 117 41 452 53 1091 65 190 22 140 17 429 46 146 69 127	T11 Events 67 35883 337 4061 102 258 103 618 201 12846 56 38 1041 128 2274	MI Total 152 40501 376 4981 125 349 107 707 340 13828 66 77 1171 137 2691	Weight 5.2% 7.4% 6.5% 6.5% 6.9% 6.5% 6.8% 7.3% 5.5% 5.9% 7.1% 5.4% 6.9%	Odds Ratio M-H, Random, 95% CI 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05] 0.46 [0.40, 0.53] 1.08 [0.51, 2.28] 0.26 [0.18, 0.38] 0.06 [0.02, 0.18] 0.42 [0.26, 0.67] 0.07 [0.05, 0.10] 0.27 [0.23, 0.32] 0.09 [0.04, 0.19] 0.19 [0.10, 0.36] 0.13 [0.10, 0.17] 0.03 [0.02, 0.07] 0.22 [0.15, 0.31]		
Study or Subgroup Balanescu 2020 Baron 2016 Cediel 2017 Chapman 2020 Conseugra Sanchez 2018 Furie 2019 Landes 2016 Lopez Cuenca 2016 Meigher 2016 Radovanovic 2017 Sandoval 2014 Sandoval 2017 Shah 2015 Smilowitz 2018	T Even 7. 8	2MI Its Total 8 49 99 1313 42 194 49 1121 62 75 88 206 65 107 87 117 41 452 53 1091 65 190 22 140 17 429 46 146	T11 Events 67 35883 337 4061 102 258 103 618 201 12846 56 38 1041 128	MI Total 152 40501 376 4981 125 349 107 707 340 13828 66 77 1171 137 2691	Weight 5.2% 7.4% 6.5% 6.5% 6.9% 6.5% 6.8% 7.3% 5.5% 5.9% 7.1% 5.4% 6.9%	Odds Ratio M-H, Random, 95% CI 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05] 0.46 [0.40, 0.53] 1.08 [0.51, 2.28] 0.26 [0.18, 0.38] 0.06 [0.02, 0.18] 0.42 [0.26, 0.67] 0.07 [0.05, 0.10] 0.27 [0.23, 0.32] 0.09 [0.04, 0.19] 0.19 [0.10, 0.36] 0.13 [0.10, 0.17] 0.03 [0.02, 0.07]		
Study or Subgroup Balanescu 2020 Baron 2016 Cediel 2017 Chapman 2020 Conseugra Sanchez 2018 Furie 2019 Landes 2016 Lopez Cuenca 2016 Meigher 2016 Radovanovic 2017 Sandoval 2014 Sandoval 2017 Shah 2015 Smilowitz 2018 Stein 2014	T Even 7. 8	2MI Its Total 8 49 99 1313 42 194 49 1121 62 75 88 206 65 107 87 117 41 452 53 1091 65 190 22 140 17 429 46 146 69 127	T11 Events 67 35883 337 4061 102 258 103 618 201 12846 56 38 1041 128 2274	MI <u>Total</u> 152 40501 376 4981 125 349 107 707 340 13828 66 77 1171 137 2691 275	Weight 5.2% 7.4% 6.5% 6.5% 6.9% 6.5% 6.8% 7.3% 5.5% 5.9% 7.1% 5.4% 6.9%	Odds Ratio M-H, Random, 95% CI 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05] 0.46 [0.40, 0.53] 1.08 [0.51, 2.28] 0.26 [0.18, 0.38] 0.06 [0.02, 0.18] 0.42 [0.26, 0.67] 0.07 [0.05, 0.10] 0.27 [0.23, 0.32] 0.09 [0.04, 0.19] 0.19 [0.10, 0.36] 0.13 [0.10, 0.17] 0.03 [0.02, 0.07] 0.22 [0.15, 0.31]		
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Study or Subgroup Balanescu 2020 Baron 2016 Cediel 2017 Chapman 2020 Conseugra Sanchez 2018 Furie 2019 Landes 2016 Lopez Cuenca 2016 Meigher 2016 Radovanovic 2017 Sandoval 2014 Sandoval 2017 Shah 2015 Smilowitz 2018 Stein 2014 Troung 2020 Total (95% CI) Total events Heterogeneity: Tau ² = 0.40	T Even 8 7 8 8 8 8 1 1 1 1 1 1 1 1 1 1 1 1 1 1	2MI 8 49 99 1313 42 194 449 1121 62 75 88 206 65 107 87 117 41 452 53 1091 65 190 22 140 17 429 46 146 69 127 61 175 5932 74 278.78, df	T11 Events 67 35883 337 4061 102 258 103 618 201 12846 56 38 1041 12846 56 38 1041 128 2274 260 58273 = 15 (P	MI <u>Total</u> 152 40501 3766 4981 125 349 107 707 340 13828 66 77 1171 137 2691 275 65883	Weight 5.2% 7.4% 6.5% 7.4% 5.5% 6.9% 4.3% 6.5% 6.8% 7.3% 5.5% 5.9% 7.1% 5.4% 6.9% 5.4%	Odds Ratio M-H, Random, 95% CI 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05] 0.46 [0.40, 0.53] 1.08 [0.51, 2.28] 0.26 [0.18, 0.38] 0.26 [0.18, 0.38] 0.42 [0.26, 0.67] 0.07 [0.05, 0.10] 0.27 [0.23, 0.32] 0.09 [0.04, 0.19] 0.19 [0.10, 0.36] 0.13 [0.10, 0.17] 0.03 [0.02, 0.07] 0.22 [0.15, 0.31] 0.66 [0.31, 1.41] 0.19 [0.13, 0.26]		
Balanescu 2020 Baron 2016 Cediel 2017 Chapman 2020 Conseugra Sanchez 2018 Furie 2019 Landes 2016 Lopez Cuenca 2016 Meigher 2016 Radovanovic 2017 Sandoval 2014 Sandoval 2017 Shah 2015 Smilowitz 2018 Stein 2014 Troung 2020 Total (95% CI) Total events	T Even 8 7 8 8 8 8 1 1 1 1 1 1 1 1 1 1 1 1 1 1	2MI 8 49 99 1313 42 194 449 1121 62 75 88 206 65 107 87 117 41 452 53 1091 65 190 22 140 17 429 46 146 69 127 61 175 5932 74 278.78, df	T11 Events 67 35883 337 4061 102 258 103 618 201 12846 56 38 1041 12846 56 38 1041 128 2274 260 58273 = 15 (P	MI <u>Total</u> 152 40501 3766 4981 125 349 107 707 340 13828 66 77 1171 137 2691 275 65883	Weight 5.2% 7.4% 6.5% 7.4% 5.5% 6.9% 4.3% 6.5% 6.8% 7.3% 5.5% 5.9% 7.1% 5.4% 6.9% 5.4%	Odds Ratio M-H, Random, 95% CI 0.25 [0.11, 0.56] 0.28 [0.25, 0.32] 0.03 [0.02, 0.05] 0.46 [0.40, 0.53] 1.08 [0.51, 2.28] 0.26 [0.18, 0.38] 0.06 [0.02, 0.18] 0.42 [0.26, 0.67] 0.07 [0.05, 0.10] 0.27 [0.23, 0.32] 0.09 [0.04, 0.19] 0.19 [0.10, 0.36] 0.13 [0.10, 0.31] 0.66 [0.31, 1.41] 0.19 [0.13, 0.26]		M-H, Random, 95% CI

	T2M		T1N	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Baron 2016	195	1313	1774	40501	9.4%	3.81 [3.25, 4.47]	
Cediel 2017	90	194	37	376	8.3%	7.93 [5.10, 12.33]	
Chapman 2020	116	1121	171	4981	9.2%	3.25 [2.54, 4.15]	-
Furie 2019	122	206	178	349	8.8%	1.40 [0.98, 1.98]	
Landes 2016	78	107	38	107	7.6%	4.88 [2.73, 8.74]	
Lopez Cuenca 2016	22	117	38	707	7.7%	4.08 [2.31, 7.19]	
Radovanovic 2017	482	1091	4425	13828	9.5%	1.68 [1.48, 1.91]	-
Sandoval 2014	112	190	35	66	7.7%	1.27 [0.72, 2.23]	
Sandoval 2017	72	140	40	77	7.7%	0.98 [0.56, 1.71]	
Shah 2015	80	429	45	1171	8.6%	5.74 [3.91, 8.42]	-
Stein 2014	15	127	105	2691	7.6%	3.30 [1.86, 5.85]	
Troung 2020	28	175	44	275	7.9%	1.00 [0.60, 1.68]	+
Total (95% CI)		5210		65129	100.0%	2.64 [1.86, 3.74]	•
Total events	1412		6930				
Heterogeneity: Tau ² =	0.33; Chi ²	= 163.9	95, df = 1	1 (P < 0	.00001); l ²	= 93%	1 0,1 1 10
Test for overall effect:	Z = 5.46 (P < 0.0	0001)				irs [experimental] Favours [cont

	T2M	I	T1M	L		Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	1	M-H, Rand	om, 95% Cl	
Sandoval 2014	13	190	20	66	45.6%	0.17 [0.08, 0.36]		-		
Sandoval 2017	15	140	30	77	54.4%	0.19 [0.09, 0.38]				
Total (95% CI)		330		143	100.0%	0.18 [0.11, 0.30]		+		
Total events	28		50							
Heterogeneity: Tau ² =	0.00; Chi ²	= 0.04	df = 1 (P	= 0.84	$1); 1^2 = 0\%$		0.01	01	1 10	G

	T2M	I	T1M	L		Odds Ratio		Odds Ra	atio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random	, 95% CI	
Sandoval 2014	13	190	20	66	45.6%	0.17 [0.08, 0.36]				
Sandoval 2017	15	140	30	77	54.4%	0.19 [0.09, 0.38]				
Total (95% CI)		330		143	100.0%	0.18 [0.11, 0.30]		•		
Total events	28		50							
Heterogeneity: Tau ² = Test for overall effect:				0.01	.,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		0.01	77577	10 2MI	100
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igure S17. Fore	est Plot.	Nau	sea / V	′omit	ing as	Presenting Featu	re.			
igure S17. Fore	est Plot. T2MI		sea / V T1MI		ing as	Presenting Featu	re.	Odds Ra	tio	
	T2MI				0		re.	Odds Ra M-H, Random,		
Study or Subgroup	T2MI		T1MI		0	Odds Ratio	re.			
Figure S17. Fore Study or Subgroup Sandoval 2014 Sandoval 2017	T2MI Events	Total	T1MI Events	Total	Weight	Odds Ratio M-H, Random, 95% Cl	re.			
Study or Subgroup Sandoval 2014 Sandoval 2017	T2MI Events 21	Total 190	T1MI Events 14	Total 66 77	Weight 42.8%	Odds Ratio M-H, Random, 95% CI 0.46 [0.22, 0.97]	re.			
Study or Subgroup Sandoval 2014 Sandoval 2017 Total (95% CI)	T2MI Events 21	Total 190 140	T1MI Events 14	Total 66 77	Weight 42.8% 57.2%	Odds Ratio M-H, Random, 95% CI 0.46 [0.22, 0.97] 0.45 [0.24, 0.86]	re.			
Study or Subgroup	T2MI Events 21 25 46	Total 190 140 330	T1MI Events 14 25 39	Total 66 77 143	Weight 42.8% 57.2% 100.0%	Odds Ratio M-H, Random, 95% CI 0.46 [0.22, 0.97] 0.45 [0.24, 0.86]	re.			100

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup					Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Baron 2016	899	1313	2506	40501	34.0%	32.92 [29.11, 37.24]	
Lopez Cuenca 2016	8	117	51	707	32.8%	0.94 [0.44, 2.04]	i —
Neumann 2017	81	99	105	188	33.3%	3.56 [1.98, 6.39]	
Total (95% CI)		1529		41396	100.0%	4.90 [0.48, 50.33]	
Total events	988		2662				

	T2M	1	T1M	1		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H,	Random, 95% CI	
Cediel 2017	15	194	5	376	17.2%	6.22 [2.22, 17.38]			
Chapman 2020	38	1121	102	4981	25.6%	1.68 [1.15, 2.45]			
Furie 2019	12	206	24	349	21.4%	0.84 [0.41, 1.71]			
Shah 2015	31	429	21	1171	23.4%	4.27 [2.42, 7.51]			
Troung 2020	3	175	5	275	12.5%	0.94 [0.22, 3.99]	18		
Total (95% CI)		2125		7152	100.0%	2.10 [1.05, 4.18]		•	
Total events	99		157						
Heterogeneity: Tau ² =	0.45; Chi ²	= 19.1	2, df = 4 (P = 0.0	007); l ² =	79%	0.01 0.1		100
Test for overall effect:	Z = 2.10 (P = 0.0	4)				0.01 0.1	1 10 T1MI T2MI	100

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Baron 2016	173	1313	14824	40501	8.3%	0.26 [0.22, 0.31]	-
Cediel 2017	5	194	92	376	3.9%	0.08 [0.03, 0.20]	
Chapman 2020	36	1121	870	4981	7.4%	0.16 [0.11, 0.22]	
Furie 2019	4	206	18	349	3.2%	0.36 [0.12, 1.09]	
Higuchi 2019	288	491	8917	12023	8.2%	0.49 [0.41, 0.59]	+
Landes 2016	11	107	11	107	4.1%	1.00 [0.41, 2.42]	
Lopez Cuenca 2016	1	117	225	707	1.3%	0.02 [0.00, 0.13]	·
Nestelberger 2020	4	128	115	684	3.5%	0.16 [0.06, 0.44]	
Paiva 2015	35	236	417	764	7.1%	0.14 [0.10, 0.21]	-
Putot 2019	28	254	136	365	6.7%	0.21 [0.13, 0.33]	
Putot 2020	207	862	1929	3710	8.2%	0.29 [0.25, 0.35]	-
Radovanovic 2017	213	1091	7436	13828	8.3%	0.21 [0.18, 0.24]	-
Raphael 2020	23	1054	198	1365	6.7%	0.13 [0.08, 0.20]	
Saaby 2013	5	144	130	397	3.9%	0.07 [0.03, 0.18]	
Sandoval 2017	31	140	24	77	5.5%	0.63 [0.34, 1.17]	
Shah 2015	40	429	427	1171	7.3%	0.18 [0.13, 0.25]	
Stein 2014	25	127	1413	2691	6.7%	0.22 [0.14, 0.35]	-
Total (95% CI)		8014		84096	100.0%	0.22 [0.17, 0.28]	◆
Total events	1129		37182				
Heterogeneity: Tau ² =	0.18: Chi ²	= 130.4	47. df = 1	6 (P < 0	.00001): 1	= 88%	0.01 0.1 1 10

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	T2M	1.	T1N	11		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	
Arora 2018	120	264	369	775	7.5%	0.92 [0.69, 1.21]	-	
Baron 2016	330	1313	8261	40501	7.7%	1.31 [1.15, 1.49]	-	
Cediel 2017	16	194	94	376	7.0%	0.27 [0.15, 0.47]		
Chapman 2020	278	1121	865	4981	7.7%	1.57 [1.35, 1.83]	-	
Conseugra Sanchez 2018	7	75	43	125	6.1%	0.20 [0.08, 0.46]		
Hawatmeh 2020	223	281	86	664	7.4%	25.84 [17.90, 37.30]		-
Landes 2016	71	107	75	107	6.9%	0.84 [0.47, 1.50]		
Lopez Cuenca 2016	35	117	152	707	7.3%	1.56 [1.01, 2.41]		
Meigher 2016	68	452	61	340	7.4%	0.81 [0.55, 1.18]		
Nestelberger 2020	33	128	234	684	7.3%	0.67 [0.44, 1.02]	-	
Saaby 2013	139	144	267	397	6.0%	13.54 [5.41, 33.84]		•
Sandoval 2017	74	140	40	77	7.0%	1.04 [0.59, 1.81]	+	
Shah 2015	249	429	332	1171	7.6%	3.50 [2.78, 4.40]	-	
Smilowitz 2018	85	146	89	137	7.2%	0.75 [0.46, 1.22]	-+	
Total (95% CI)		4911		51042	100.0%	1.36 [0.85, 2.17]	•	
Total events	1728		10968					
Heterogeneity: Tau ² = 0.74;	Chi ² = 416	6.55, df	= 13 (P <	0.0000	1); l ² = 979	%	0.01 0.1 1 1	0

	T2M	1	T1M	I		Odds Ratio		Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95	% CI	
Lopez Cuenca 2016	12	117	156	707	48.4%	0.40 [0.22, 0.75]				
Sandoval 2014	2	190	6	66	12.8%	0.11 [0.02, 0.54]	-			
Sandoval 2017	16	140	15	77	38.8%	0.53 [0.25, 1.15]		- -		
Total (95% CI)		447		850	100.0%	0.38 [0.20, 0.71]		•		
Total events	30		177							
Heterogeneity: Tau ² =	0.11; Chi2	= 3.09,	df = 2 (F	= 0.21); I ² = 35%	6	0.01	01 1	10	100
Test for overall effect:	Z = 3.03 (I	P = 0.0	02)				0.01	T1MI T2MI	10	100

	T2M	1	T1M	1		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M	H, Random, 95% Cl
Meigher 2016	90	452	27	340	65.4%	2.88 [1.83, 4.55]		-
Sandoval 2017	56	140	18	77	34.6%	2.19 [1.17, 4.09]		
Total (95% CI)		592		417	100.0%	2.62 [1.81, 3.79]		•
Total events	146		45					a

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Baron 2016	95	1313	1791	40501	40.5%	1.69 [1.36, 2.09]	
Cediel 2017	40	194	72	376	24.2%	1.10 [0.71, 1.69]	+
Lopez Cuenca 2016	10	117	35	707	12.2%	1.79 [0.86, 3.73]	+ - -
Nestelberger 2020	9	128	34	684	11.5%	1.45 [0.68, 3.09]	- +
Troung 2020	21	175	11	275	11.6%	3.27 [1.54, 6.97]	
Total (95% CI)		1927		42543	100.0%	1.62 [1.21, 2.17]	♦
Total events	175		1943				
Heterogeneity: Tau ² =	0.04 · Chi ²	= 6.75	df = 4 (F)	P = 0.15	$ ^2 = 41\%$	F	0.01 0.1 1 10

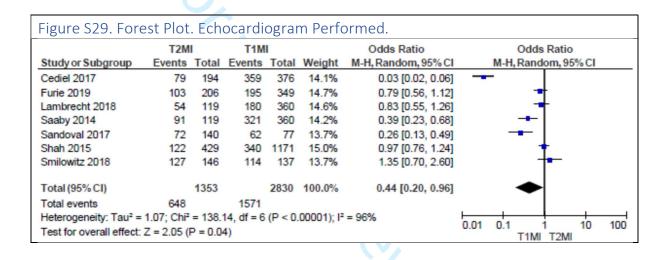
	T2M	1	T1M	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% CI
Lopez Cuenca 2016	32	117	49	707	86.1%	5.06 [3.07, 8.33]]
Sandoval 2017	22	140	3	77	13.9%	4.60 [1.33, 15.90]	1
Total (95% CI)		257		784	100.0%	4.99 [3.14, 7.93]	ı 🔶
Total events	54		52				

lect: Z = 6.80 (P < 0.0000);

	T2M		T1N	11		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	om, 95% CI
Arora 2018	68	264	609	775	4.0%	0.09 [0.07, 0.13]	-	
Balanescu 2020	9	49	99	152	3.4%	0.12 [0.05, 0.27]		
Cediel 2017	11	194	278	376	3.6%	0.02 [0.01, 0.04]		
Chapman 2020	112	1121	2928	4981	4.0%	0.08 [0.06, 0.10]	+	
Conseugra Sanchez 2018	12	75	91	125	3.5%	0.07 [0.03, 0.15]		
Etaher 2020	25	171	41	97	3.7%	0.23 [0.13, 0.42]		
Furie 2019	22	206	190	349	3.8%	0.10 [0.06, 0.16]		
Guimares 2018	56	76	711	847	3.8%	0.54 [0.31, 0.92]		1
Higuchi 2019	427	491	11406	12023	4.0%	0.36 [0.27, 0.48]	-	
Javed 2009	32	64	124	143	3.6%	0.15 [0.08, 0.30]		
Lambrecht 2018	28	119	268	360	3.8%	0.11 [0.07, 0.17]		
Lopez Cuenca 2016	46	117	622	707	3.9%	0.09 [0.06, 0.14]	_	
Nestelberger 2020	23	128	582	684	3.8%	0.04 [0.02, 0.06]	_	
Neumann 2017	38	99	163	188	3.7%	0.10 [0.05, 0.17]	_	
Paiva 2015	121	236	619	764	4.0%	0.25 [0.18, 0.34]	+	
Putot 2018	325	847	2036	2036	1.2%	0.00 [0.00, 0.00]	•	
Putot 2019	105	254	351	365	3.7%	0.03 [0.02, 0.05]		
Radovanovic 2017	660	1091	12067	13828	4.1%	0.22 [0.20, 0.25]		
Raphael 2020	402	1054	1200	1365	4.0%	0.08 [0.07, 0.10]	-	
Reed 2017	16	146	49	137	3.7%	0.22 [0.12, 0.41]		
Saaby 2014	28	119	268	360	3.8%	0.11 [0.07, 0.17]		
Sandoval 2017	13	140	46	77	3.5%	0.07 [0.03, 0.14]		
Sato 2020	63	155	2485	2834	4.0%	0.10 [0.07, 0.14]	-	
Shah 2015	31	429	744	1171	3.9%	0.04 [0.03, 0.07]		
Singh 2020	269	1225	1971	2097	4.0%	0.02 [0.01, 0.02]	-	
Smilowitz 2018	19	146	114	137	3.6%	0.03 [0.02, 0.06]		
Stein 2014	46	127	2387	2691	3.9%	0.07 [0.05, 0.11]		
Troung 2020	175	175	275	275		Not estimable		
Total (95% CI)		9318		49944	100.0%	0.09 [0.06, 0.12]	•	
Total events	3182		42724					
Heterogeneity: Tau ² = 0.85	; Chi ² = 698	3.89, df	= 26 (P <	0.0000	1); l ² = 96 ⁶	%	0.01 0.1	1 10

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95%
Baron 2016	533	1313	17456	40501	9.6%	0.90 [0.81, 1.01]	
Conseugra Sanchez 2018	4	75	82	125	9.0%	0.03 [0.01, 0.09]	I
Furie 2019	7	206	166	349	9.3%	0.04 [0.02, 0.08]	
Javed 2009	25	64	111	143	9.4%	0.18 [0.10, 0.35]	
Lopez Cuenca 2016	78	117	64	707	9.5%	20.09 [12.66, 31.90]	
Putot 2019	238	254	346	365	9.3%	0.82 [0.41, 1.62]	
Raphael 2020	162	1054	1058	1365	9.6%	0.05 [0.04, 0.07]	-
Saaby 2014	15	119	236	360	9.4%	0.08 [0.04, 0.14]	
Sandoval 2017	7	140	42	77	9.2%	0.04 [0.02, 0.11]	
Smilowitz 2018	14	146	87	137	9.4%	0.06 [0.03, 0.12]	
Troung 2020	163	175	275	275	6.3%	0.02 [0.00, 0.40]	·
Total (95% CI)		3663		44404	100.0%	0.16 [0.05, 0.54]	-
Total events	1246		19923				

	T2M	I	T1N	11		Odds Ratio	Odd	ls Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Ran	dom, 95% Cl
Baron 2016	381	1313	11340	40501	22.4%	1.05 [0.93, 1.19]		(.
Putot 2019	59	254	150	365	21.4%	0.43 [0.30, 0.62]	-	
Saaby 2014	11	119	115	360	19.0%	0.22 [0.11, 0.42]		
Sandoval 2017	1	140	15	77	8.1%	0.03 [0.00, 0.23]	+ • • • • • • • • • • • • • • • • • • •	
Smilowitz 2018	1	146	24	137	8.3%	0.03 [0.00, 0.24]	←	
Troung 2020	140	175	195	275	20.7%	1.64 [1.04, 2.58]		
Total (95% CI)		2147		41715	100.0%	0.40 [0.19, 0.82]	•	•
Total events	593		11839					



	T2M	1	T1M	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Sandoval 2017	22	140	41	77	49.5%	0.16 [0.09, 0.31]	
Smilowitz 2018	75	146	60	137	50.5%	1.36 [0.85, 2.17]	-
Total (95% CI)		286		214	100.0%	0.48 [0.06, 3.78]	
Total events	97		101				

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	T2M		T1N			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% CI
Arora 2018	165	264	645	775	4.7%	0.34 [0.25, 0.46]	-
Balanescu 2020	30	49	127	152	3.9%	0.31 [0.15, 0.64]	
Baron 2016	1123	1313	36410	40501	4.8%	0.66 [0.57, 0.78]	-
Chapman 2018	126	429	651	1171	4.7%	0.33 [0.26, 0.42]	-
Etaher 2020	83	171	68	97	4.3%	0.40 [0.24, 0.68]	
Furie 2019	141	206	247	349	4.6%	0.90 [0.62, 1.30]	
Hawatmeh 2020	165	281	551	664	4.7%	0.29 [0.21, 0.40]	-
Higuchi 2019	236	491	6786	12023	4.8%	0.71 [0.60, 0.86]	+
Kadesjo 2019	169	251	946	1111	4.7%	0.36 [0.26, 0.49]	-
Lopez Cuenca 2016	86	117	614	707	4.4%	0.42 [0.26, 0.67]	
Nestelberger 2020	72	128	548	684	4.5%	0.32 [0.21, 0.47]	-
Radovanovic 2017	595	1091	7396	13828	4.8%	1.04 [0.92, 1.18]	i t
Raphael 2020	766	1054	1215	1365	4.8%	0.33 [0.26, 0.41]	-
Reed 2017	75	162	41	88	4.3%	0.99 [0.59, 1.66]	
Saaby 2014	44	119	208	360	4.5%	0.43 [0.28, 0.66]	
Sandoval 2017	81	140	53	77	4.2%	0.62 [0.35, 1.12]	
Sato 2020	53	155	1838	2834	4.6%	0.28 [0.20, 0.40]	-
Shah 2015	124	429	660	1171	4.7%	0.31 [0.25, 0.40]	-
Singh 2020	513	1225	1878	2097	4.8%	0.08 [0.07, 0.10]	+
Smilowitz 2018	70	146	78	137	4.4%	0.70 [0.44, 1.11]	
Stein 2014	91	127	2234	2691	4.5%	0.52 [0.35, 0.77]	
Troung 2020	159	175	237	275	4.1%	1.59 [0.86, 2.96]	· +-
Total (95% CI)		8523		83157	100.0%	0.45 [0.33, 0.63]	▲
Total events	4967		63431				
Heterogeneity: Tau ² =	0.58; Chi ²	= 647.0	87, df = 2	1 (P < 0	.00001); 13	² = 97%	0.01 0.1 1 10
Test for overall effect:	Z = 4.73 (P < 0.0	0001)			1	Favours [experimental] Favours [control

	T2M	1	T1N	41		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Baron 2016	945	1313	30781	40501	6.0%	0.81 [0.72, 0.92]	-
Chapman 2018	156	429	724	1171	5.9%	0.35 [0.28, 0.44]	+
Etaher 2020	57	171	49	97	5.0%	0.49 [0.29, 0.82]	
Hawatmeh 2020	99	281	325	664	5.7%	0.57 [0.43, 0.76]	-
Higuchi 2019	254	491	7531	12023	6.0%	0.64 [0.53, 0.77]	-
Kadesjo 2019	118	251	725	1111	5.7%	0.47 [0.36, 0.62]	-
Lopez Cuenca 2016	53	117	438	707	5.4%	0.51 [0.34, 0.75]	
Nestelberger 2020	70	128	546	684	5.4%	0.31 [0.21, 0.45]	
Radovanovic 2017	566	1091	7448	13828	6.0%	0.92 [0.82, 1.04]	
Raphael 2020	571	1054	976	1365	6.0%	0.47 [0.40, 0.56]	
Saaby 2014	38	119	154	360	5.2%	0.63 [0.40, 0.97]	
Sandoval 2017	43	140	39	77	4.7%	0.43 [0.24, 0.77]	
Sato 2020	93	155	2103	2834	5.6%	0.52 [0.37, 0.73]	
Shah 2015	135	429	735	1171	5.8%	0.27 [0.22, 0.34]	-
Singh 2020	271	1225	1269	2097	6.0%	0.19 [0.16, 0.22]	•
Smilowitz 2018	62	146	63	137	5.1%	0.87 [0.54, 1.39]	-+
Stein 2014	88	127	2126	2691	5.4%	0.60 [0.41, 0.88]	
Troung 2020	147	175	221	275	5.0%	1.28 [0.78, 2.12]	↓ •-
Total (95% CI)		7842		81793	100.0%	0.52 [0.40, 0.67]	•
Total events	3766		56253				

	T2M	1	T1N	11		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	om, 95% CI
Arora 2018	154	264	637	775	4.5%	0.30 [0.22, 0.41]	-	
Balanescu 2020	25	49	128	152	4.1%	0.20 [0.10, 0.40]		
Baron 2016	722	1313	34021	40501	4.6%	0.23 [0.21, 0.26]	*	
Chapman 2018	284	429	896	1171	4.6%	0.60 [0.47, 0.77]	+	
Etaher 2020	92	171	85	97	4.2%	0.16 [0.08, 0.32]		
Furie 2019	163	206	335	349	4.2%	0.16 [0.08, 0.30]		
Guimares 2018	74	76	839	847	2.9%	0.35 [0.07, 1.69]		-
Hawatmeh 2020	156	281	594	664	4.5%	0.15 [0.10, 0.21]		
Higuchi 2019	442	491	11662	12023	4.5%	0.28 [0.20, 0.38]	-	
Kadesjo 2019	101	251	918	1111	4.5%	0.14 [0.11, 0.19]	-	
Lopez Cuenca 2016	72	117	64	707	4.4%	16.07 [10.22, 25.27]		
Nestelberger 2020	36	128	619	684	4.4%	0.04 [0.03, 0.07]		
Radovanovic 2017	983	1091	13772	13828	4.5%	0.04 [0.03, 0.05]		
Raphael 2020	648	1054	1114	1365	4.6%	0.36 [0.30, 0.43]	-	
Reed 2017	63	162	28	88	4.3%	1.36 [0.79, 2.36]	-	•
Saaby 2014	56	119	269	360	4.4%	0.30 [0.20, 0.46]		
Sandoval 2017	64	140	66	77	4.1%	0.14 [0.07, 0.29]		
Sato 2020	70	155	2562	2834	4.5%	0.09 [0.06, 0.12]	+	
Shah 2015	166	429	910	1171	4.6%	0.18 [0.14, 0.23]	-	
Singh 2020	416	1225	1945	2097	4.6%	0.04 [0.03, 0.05]	-	
Smilowitz 2018	31	146	58	137	4.3%	0.37 [0.22, 0.62]		
Stein 2014	109	127	2610	2691	4.3%	0.19 [0.11, 0.32]		
Troung 2020	160	175	245	275	4.2%	1.31 [0.68, 2.50]	-	-
Total (95% CI)		8599		84004	100.0%	0.25 [0.16, 0.38]	•	
Total events	5087		74377					

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Baron 2016	236	1313	3240	40501	9.9%	2.52 [2.18, 2.91]	
Chapman 2018	44	429	33	1171	9.3%	3.94 [2.47, 6.28]	
Furie 2019	24	206	42	349	9.1%	0.96 [0.57, 1.64]	
Lopez Cuenca 2016	44	117	89	707	9.4%	4.19 [2.71, 6.47]	
Radovanovic 2017	801	1091	11774	13828	9.9%	0.48 [0.42, 0.56]	-
Raphael 2020	239	1054	167	1365	9.8%	2.10 [1.69, 2.61]	-
Sandoval 2017	20	140	3	77	6.7%	4.11 [1.18, 14.31]	
Sato 2020	24	155	327	2834	9.4%	1.40 [0.90, 2.20]	
Shah 2015	52	429	35	1171	9.4%	4.48 [2.87, 6.98]	
Smilowitz 2018	11	146	11	137	8.1%	0.93 [0.39, 2.23]	
Troung 2020	24	175	33	275	9.1%	1.17 [0.66, 2.05]	+
Total (95% CI)		5255		62415	100.0%	1.87 [1.06, 3.30]	•
Total events	1519		15754				

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	I M-H, Random, 95% CI
Baron 2016	1050	1313	38476	40501	20.6%	0.21 [0.18, 0.24]	
Chapman 2018	77	429	143	1171	20.3%	1.57 [1.16, 2.13]	I −
Nestelberger 2020	13	128	168	684	19.4%	0.35 [0.19, 0.63]	
Smilowitz 2018	86	146	101	137	19.7%	0.51 [0.31, 0.85]	_ _ _
Troung 2020	55	175	67	275	20.0%	1.42 [0.93, 2.17]	ı † ∙-
Total (95% CI)		2191		42768	100.0%	0.61 [0.21, 1.74]	
Total events	1281		38955				

	T2M	1	T1N	41		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% CI
Baron 2016	315	1313	4860	40501	24.2%	2.31 [2.03, 2.64]]
Etaher 2020	53	171	9	97	12.1%	4.39 [2.06, 9.38]	1 –
Lopez Cuenca 2016	70	117	230	707	19.2%	3.09 [2.07, 4.62]	i 🛛 🛨
Raphael 2020	831	1054	990	1365	23.4%	1.41 [1.17, 1.71]	i 🖛
Sato 2020	0	155	23	2834	1.6%	0.38 [0.02, 6.36]	i — — —
Troung 2020	67	175	99	275	19.4%	1.10 [0.75, 1.63]	i 🕇
Total (95% CI)		2985		45779	100.0%	1.98 [1.37, 2.86]	ı ♦
Total events	1336		6211				
Heterogeneity: Tau ² =	0.14; Chi ²	= 36.79	9, df = 5 (P < 0.00	0001); l ² =	86%	0.01 0.1 1 10
Test for overall effect:	Z = 3.64 (P = 0.0	003)				Favours [experimental] Favours [cont
							avouro [experimental] + avouro [een

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Arora 2018	153	264	646	775	6.4%	0.28 [0.20, 0.37]	-
Balanescu 2020	29	49	131	152	5.5%	0.23 [0.11, 0.48]	
Baron 2016	972	1313	37261	40501	6.6%	0.25 [0.22, 0.28]	-
Chapman 2018	204	429	872	1171	6.5%	0.31 [0.25, 0.39]	+
Etaher 2020	95	171	81	97	5.8%	0.25 [0.13, 0.46]	
Furie 2019	125	206	280	349	6.3%	0.38 [0.26, 0.56]	-
Hawatmeh 2020	141	281	578	664	6.4%	0.15 [0.11, 0.21]	-
Higuchi 2019	298	491	9238	12023	6.5%	0.47 [0.39, 0.56]	+
Kadesjo 2019	92	251	883	1111	6.4%	0.15 [0.11, 0.20]	-
Lopez Cuenca 2016	92	117	648	707	6.0%	0.34 [0.20, 0.56]	
Nestelberger 2020	39	128	606	684	6.2%	0.06 [0.04, 0.09]	
Raphael 2020	570	1054	1167	1365	6.5%	0.20 [0.16, 0.24]	-
Sato 2020	112	155	2303	2834	6.3%	0.60 [0.42, 0.86]	-
Singh 2020	255	1225	1840	2097	6.5%	0.04 [0.03, 0.04]	-
Smilowitz 2018	83	146	100	137	6.1%	0.49 [0.30, 0.80]	
Troung 2020	158	175	241	275	5.8%	1.31 [0.71, 2.43]	
Total (95% CI)		6455		64942	100.0%	0.25 [0.16, 0.38]	•
Total events	3418		56875				
Heterogeneity: Tau ² =	0.70; Chi ²	= 549.0	08. df = 1	5 (P < 0	.00001): P	² = 97%	0.01 0.1 1 10

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Arora 2018	32	264	363	775	4.9%	0.16 [0.11, 0.23]	
Balanescu 2020	0	0	0	0		Not estimable	
Baron 2016	723	1313	34264	40501	5.1%	0.22 [0.20, 0.25]	*
Chapman 2020	17	1121	2021	4981	4.8%	0.02 [0.01, 0.04]	
Etaher 2020	7	171	12	97	4.2%	0.30 [0.11, 0.80]	
Furie 2019	3	206	128	349	3.9%	0.03 [0.01, 0.08]	<u>←</u>
Guimares 2018	27	76	440	847	4.8%	0.51 [0.31, 0.83]	
Higuchi 2019	258	491	9206	12023	5.0%	0.34 [0.28, 0.41]	+
Landes 2016	14	107	85	107	4.5%	0.04 [0.02, 0.08]	
Lopez Cuenca 2016	11	117	486	707	4.7%	0.05 [0.02, 0.09]	
Nestelberger 2020	1	128	457	684	2.7%	0.00 [0.00, 0.03]	←
Neumann 2017	0	99	126	188	1.9%	0.00 [0.00, 0.04]	←
Paiva 2015	27	236	507	764	4.9%	0.07 [0.04, 0.10]	-
Putot 2018	103	847	1519	2036	5.0%	0.05 [0.04, 0.06]	-
Putot 2019	29	254	235	365	4.9%	0.07 [0.05, 0.11]	
Radovanovic 2017	557	1091	11684	13828	5.1%	0.19 [0.17, 0.22]	
Raphael 2020	77	1054	791	1365	5.0%	0.06 [0.04, 0.07]	
Saaby 2014	4	119	194	360	4.1%	0.03 [0.01, 0.08]	
Sandoval 2017	1	140	34	77	2.7%	0.01 [0.00, 0.07]	·
Shah 2015	1	429	564	1171	2.7%	0.00 [0.00, 0.02]	←
Singh 2020	27	1225	1786	2097	4.9%	0.00 [0.00, 0.01]	•
Smilowitz 2018	8	146	53	137	4.5%	0.09 [0.04, 0.20]	_ _
Stein 2014	64	127	2199	2691	4.9%	0.23 [0.16, 0.33]	-
Troung 2020	101	175	257	275	4.7%	0.10 [0.05, 0.17]	
Total (95% CI)		9936		86425	100.0%	0.06 [0.04, 0.10]	•
Total events	2092		67411				

	T2M	1	T1N	11		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Arora 2018	4	264	91	775	10.3%	0.12 [0.04, 0.32]	
Baron 2016	68	1313	2673	40501	13.5%	0.77 [0.60, 0.99]	-
Etaher 2020	8	171	15	97	10.9%	0.27 [0.11, 0.66]	
Furie 2019	0	206	16	349	3.9%	0.05 [0.00, 0.82]	·
Guimares 2018	7	76	73	847	11.3%	1.08 [0.48, 2.43]	_ _
Landes 2016	8	107	33	107	11.3%	0.18 [0.08, 0.42]	
Lopez Cuenca 2016	0	117	28	707	3.9%	0.10 [0.01, 1.67]	· · · · · · · · · · · · · · · · · · ·
Nestelberger 2020	0	128	59	684	3.9%	0.04 [0.00, 0.67]	← -
Putot 2019	4	254	29	365	10.1%	0.19 [0.06, 0.53]	
Saaby 2014	0	119	9	360	3.8%	0.15 [0.01, 2.68]	· · · · · · · · · · · · · · · · · · ·
Sandoval 2017	0	140	3	77	3.6%	0.08 [0.00, 1.49]	<+
Shah 2015	3	429	56	1171	9.6%	0.14 [0.04, 0.45]	
Stein 2014	0	127	16	2691	3.9%	0.64 [0.04, 10.66]	
Total (95% CI)		3451		48731	100.0%	0.23 [0.12, 0.45]	•
Total events	102		3101				

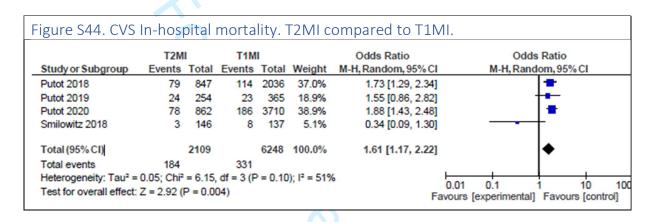
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$\begin{array}{c} 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 9\\ 50\\ 51\\ 52\\ 53\\ 54\end{array}$	
55 56 57 58 59 60	

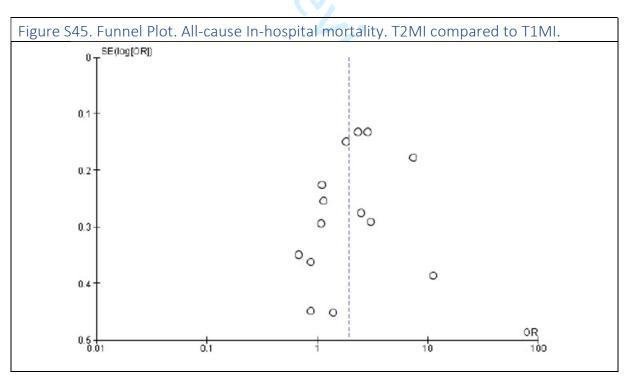
	T2M	I	T1N	I		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rando	om, 95% CI
Furie 2019	21	206	33	349	7.1%	1.09 [0.61, 1.93]	-	-
Higuchi 2019	54	491	769	12023	8.2%	1.81 [1.35, 2.42]		-
Javed 2009	9	64	15	143	5.7%	1.40 [0.58, 3.38]	+	
Lopez Cuenca 2016	6	117	41	707	5.7%	0.88 [0.36, 2.12]		
Meigher 2016	54	452	37	340	7.6%	1.11 [0.71, 1.73]	+	-
Paiva 2015	23	236	66	764	7.4%	1.14 [0.69, 1.88]	-	-
Putot 2018	133	847	125	2036	8.3%	2.85 [2.20, 3.69]		-
Putot 2019	38	254	24	365	7.2%	2.50 [1.46, 4.28]		
Putot 2020	95	862	186	3710	8.3%	2.35 [1.81, 3.04]		-
Saaby 2014	29	119	10	360	6.3%	11.28 [5.30, 24.00]		
Singh 2020	160	1225	42	2097	8.0%	7.35 [5.19, 10.41]		-
Smilowitz 2018	17	146	18	137	6.5%	0.87 [0.43, 1.77]		_
Stein 2014	15	127	113	2691	7.1%	3.06 [1.73, 5.41]		
Troung 2020	13	175	29	275	6.6%	0.68 [0.34, 1.35]		-
Total (95% CI)		5321		25997	100.0%	1.94 [1.35, 2.79]		◆
Total events	667		1508					
Heterogeneity: Tau ² =	0.40; Chř	= 115.	87, df = 1	3 (P < 0	.00001); P	²= 89%		10
Test for overall effect:	Z = 3.58 (P = 0.0	003)				0.01 0.1 1 Favours T1MI	

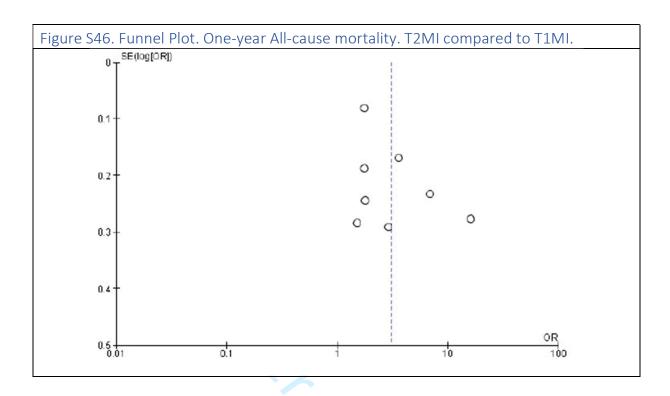
	T2M	1	T1M	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Nestelberger 2020	1	128	42	684	10.4%	0.12[0.02, 0.88]	
Sandoval 2014	51	190	15	66	29.6%	1.25 [0.65, 2.41]	
Sandoval 2017	18	140	6	77	23.4%	1.75 [0.66, 4.60]	+
Shah 2015	134	429	187	1171	36.7%	2.39 [1.85, 3.09]	-
Total (95% CI)		887		1998	100.0%	1.34 [0.63, 2.85]	•
Total events	204		250				
Heterogeneity: Tau ² =	50%						

igure S42. Two	-year al	l-cau	se mo	rtalit	y. T2M	I compared to T1	MI.
	T2M		T1M	I	-	Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cediel 2017	77	194	74	376	19.0%	2.69 [1.83, 3.94]	-
Guimares 2018	19	76	156	847	15.9%	1.48 [0.85, 2.55]	+
Neumann 2017	14	99	18	188	12.5%	1.56 [0.74, 3.28]	+
Paiva 2015	62	236	92	764	19.3%	2.60 [1.81, 3.74]	-
Smilowitz 2018	45	146	41	137	16.6%	1.04 [0.63, 1.73]	-
Troung 2020	29	175	47	275	16.6%	0.96 [0.58, 1.60]	+
Total (95% CI)		926		2587	100.0%	1.63 [1.11, 2.41]	◆
Total events	246		428				-
Heterogeneity: Tau ² =	0.17: Chr	= 19.1	0 df = 5 (Έ = Π Γ	102) [,] I ² = 7	4%	

	T2MI		T1MI		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Kadesjo 2019	101	251	259	1111	36.0%	2.21 [1.66, 2.95]	-
Lambrecht 2018	74	119	114	360	32.9%	3.55 [2.30, 5.47]	
Sato 2020	18	155	337	2834	31.1%	0.97 [0.59, 1.61]	+
Total (95% CI)		525		4305	100.0%	2.00 [1.07, 3.76]	•
Total events	193		710				







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PRISMA 2020 Checklist

		BMJ Open	36/bmjope	Page 60 of 6
PRIS	MA 2	020 Checklist	P	
			2021-	
Section and Topic	ltem #	Checklist item	-055755	Location where item is reported
TITLE			0n	
Title	1	Identify the report as a systematic review.	17	1
ABSTRACT			н Ф Ф	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	rua	3
INTRODUCTION			₹ 2	
2 Rationale	3	Describe the rationale for the review in the context of existing knowledge.	022	4
3 Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.		4
METHODS			owh	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	load	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to date when each source was last searched or consulted.	dentify studies. Specify the ∃	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	O M	Supp
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many rev and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in		4
2 Data collection 3 process 4	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of a process.		4
5 Data items 6	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which result		4
8	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, fundia assumptions made about any missing or unclear information.	sources). Describe any	4
 Study risk of bias assessment 	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how ma study and whether they worked independently, and if applicable, details of automation tools used in the process.	by reviewers assessed each	5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation	<u>່ງ</u> ດຸ of results.	5
2 Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study inter comparing against the planned groups for each synthesis (item #5)).	ention characteristics and ज	5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing sumn conversions.	⊊ Pary statistics, or data Ø	5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	. ד ס	5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was per model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.		5
0	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analys	ð.	5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	¢ , , , , , , , , , , , , , , , , , , ,	N/A
2 Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biase	vp xay	5
Certainty	15	Describe any methods used to assess centainty (on confidence) in the body of avidence for a butcontern	Ħ.	N/A

PRISMA 2020 Checklist

Page 61 of 61		BMJ Open	
PRIS	MA 2	020 Checklist	
Section and Topic	ltem #	Checklist item	Location where item is reported
assessment		O n	
RESULTS	I		
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the redimber of studies included in the review, ideally using a flow diagram.	5
1	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5
2 Study characteristics	17	Cite each included study and present its characteristics.	Supp
4 Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supp
6 Results of 7 individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supp
8 Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supp
9 syntheses 0	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Supp
1	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Supp
22	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
4 Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
25 Certainty of 26 evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION		_	
28 Discussion 29 30	23a	Provide a general interpretation of the results in the context of other evidence.	7
	23b	Discuss any limitations of the evidence included in the review.	9
31	23c	Discuss any limitations of the review processes used.	9
32	23d	Discuss implications of the results for practice, policy, and future research.	9
OTHER INFORMA	TION	4 	
³⁴ Registration and ³⁵ protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
6 6	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
37	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
38 Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and dther materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

