BMJ Open 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 used a universal definition of MI and reported quantitative data on at least one variable of interest.

Data extraction and synthesis Data were pooled using random-effect meta-analysis. Risk of bias was assessed using Newcastle-Ottawa quality assessment tool. Preferred Reporting Items for Systematic Reviews and Metaanalyses 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 patients with T1MI and 13 803 patients with T2MI were included. Compared with T1MI, patients with T2MI were: more likely to have pre-existing chronic kidney disease (OR 1.87; 95% Cl 1.53 to 2.28) and chronic heart failure (OR 2.35; 95% Cl 1.82 to 3.03), less likely to present with typical cardiac symptoms of chest pain (OR 0.19; 95% CI 0.13 to 0.26) and more likely to present with dyspnoea (OR 2.64; 95% Cl 1.86 to 3.74); more likely to demonstrate non-specific ST-T wave changes on ECG (OR 2.62; 95% CI 1.81 to 3.79) and less likely to show ST elevation (OR 0.22; 95% Cl 0.17 to 0.28); less likely to undergo coronary angiography (OR 0.09; 95% CI 0.06 to 0.12) and percutaneous coronary intervention (OR 0.06; 95% CI 0.04 to 0.10) or receive cardioprotective medications, such as statins (OR 0.25; 95% CI 0.16 to 0.38) and beta-blockers (OR 0.45; 95% CI 0.33 to 0.63). T2MI had greater risk of all cause 1year mortality (OR 3.11; 95% CI 1.91 to 5.08), with no differences in short-term mortality (OR 1.34; 95% CI 0.63 to 2.85).

Strengths and limitations of this study

- Inclusion of all contemporary cohort studies in the troponin era.
- Analyses of large population of patients with type 2 myocardial infarction and type 1 myocardial infarction which provided high level of precision.
- 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.

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 with T1MI.

INTRODUCTION

The clinical definition of myocardial infarction (MI) 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 Document² 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 prognosis³ (see online supplemental table S1 for more detail).

In clinical practice, distinguishing T2MI from T1MI based on clinical presentation, 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 T1MI⁴⁻⁸ 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 1 January 2009, and 31 December 2020, using search terms to identify all studies related to T2MI (see online supplemental table S2). Reference lists of all relevant articles were also assessed to identify additional relevant studies. The study PRISMA flow chart is shown in online supplemental 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 were used 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 (I^2 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 online supplemental 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 online supplement, online supplemental figure S2–S44.

The 2007 definition¹ was used in 7 (17.5%) studies, $^{15\ 16\ 27\ 29\ 43\ 44\ 52}$ the 2012 definition² in 25 (62.5%) studies, $^{13\ 17\ 19-21\ 23-26\ 30-35\ 37\ 39\ 40\ 42\ 45-48\ 50\ 51}$ and the 2018 definition³ 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 43-45 47 48 50 51 and 23 (57.5%) were retrospective. $^{13\ 14\ 17\ 20\ 21\ 23-28\ 30-32\ 35\ 38-42\ 46\ 49\ 52}$

 Table 1
 Pre-existing medical conditions in patients with type 2 myocardial infarction (T2MI) versus type 1 myocardial infarction (T1MI)

	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	%	OR* (95% CI)
CAD	3352	10 303	32.5	22 222	92 725	24	1.1 (0.93 to 1.31)
Type 2 DM	3044	12 157	25	23 287	93 345	24.9	0.97 (0.85 to 1.10)
HTN	7536	11 021	66.4	55 782	88 017	63.4	1.22 (1.03 to 1.45)
Dyslipidaemia	4626	10 652	43.4	40 099	87 366	45.9	0.74 (0.58 to 0.94)
Smoker	3448	9929	34.7	39 548	74 889	52.8	0.60 (0.49 to 0.73)
Obesity	1225	3672	33.4	30 963	56 970	54.3	0.63 (0.46 to 0.87)
Chronic kidney disease	1378	6040	22.8	11 300	65 394	17.3	1.87 (1.53 to 2.28)
Heart failure	1661	8873	13.1	5617	74 212	7.6	2.35 (1.82 to 3.03)
PVD	584	5856	10.0	2066	41 280	5.0	1.33 (1.05 to 1.69)
CVD	969	8538	11.3	6060	87 822	6.9	1.47 (1.27 to 1.71)
Atrial fibrillation	836	3645	22.9	1220	19 843	6.1	3.02 (2.29 to 3.99)
COPD	800	5018	15.9	823	48 375	1.7	1.94 (1.22 to 3.08)
Illicit drug use	46	204	22.5	8	220	3.6	8.15 (1.03 to 64.46)

*Comparing patients with T2MI with those with T1MI, with OR adjusted according to study weighting using random effects meta-analysis. BMI, body mass index; CAD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; HTN, hypertension; PVD, peripheral vascular disease.

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 ^{21 24–26 49} and 3 (7.5%) as poor quality,^{20 36 47} as summarised in online supplemental 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 (online supplemental figures S45 and 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 with 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), patients with T2MI compared with patients with T1MI were more likely to have chronic kidney disease (22.8% vs 17.3%; OR 1.87; 95% CI 1.53 to 2.28), chronic heart

failure (13.1% vs 7.6%; OR 2.35; 95% CI 1.82 to 3.03), atrial fibrillation (22.9% vs 6.1%; OR 3.02; 95% CI 2.29 to 3.99) and hypertension (66.4% vs 63.4%; OR 1.22; 95% CI 1.03 to 1.45). Patients with T2MI were less likely to have dyslipidaemia (43.4% vs 45.9%; OR 0.74; 95% CI 0.58 to 0.94) and smoking history (34.7% vs 52.8%; OR 0.6; 95% CI 0.49 to 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=18; 45%) included data on precipitating factors associated with T2MI. ¹³ ¹⁵ ¹⁷ ¹⁹ ^{21–24} ²⁷ ³¹ ³² ³⁵ ⁴⁰ ⁴⁴ ⁴⁵ ^{50–52} Data on each precipitating factor were not consistently available across the studies; for example, only 17 studies representing 45% of patients with T2MI assessed the presence of arrythmia.

The most common precipitants were sepsis (35.9%) and heart failure (35.9%, followed by arrythmia (29.8%) (online supplemental 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 online supplemental table S6, compared with patients with T1MI, patients with T2MI were less likely to present with typical cardiac symptoms of chest pain (58.6% vs 88.4%; OR 0.19; 95% CI 0.13 to 0.26) or discomfort in the arm or shoulder (8.5% vs 35%;

OR 0.18; 95% CI 0.11 to 0.3), but more likely to present with dyspnoea (27.1% vs 10.6%; OR 2.64; 95% CI 1.86 to 3.74).

Investigations

ECG findings on presentation (online supplemental table S7) such as ST elevation (14.1% vs 44.2%; OR 0.22; 95% CI 0.17 to 0.28) and pathological Q waves (6.7% vs 20.8%; OR 0.38; 95% CI 0.20 to 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 to 3.79), and atrial arrythmias (21% vs 6.6%; OR 4.99; 95% CI 3.14 to 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, 4 studies (10%) reported the use of high-sensitivity cTn assays, 21 (53%) reported sensitive assays and 14 (35%) did not specify what generation assay was used (online supplemental tables S3a and 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 1, 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 ULN for each assay to allow direct comparison (online supplemental table S8). For peak troponin, patients with T1MI had a higher and wider range of between 5 and 1702 times the ULN compared with 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 cTn assays was more predictive of T2MI or T1MI compared with 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 patients with T2MI than those with T1MI (47.9% vs 55.5%; OR 0.44; 95% CI 0.20 to 0.96) and when reported (online supplemental 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 patients with T1MI and 40%–56% in patients with T2MI.

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

Management

Patients with T2MI, compared with patients with T1MI, were significantly less likely to receive conventional cardioprotective medications (table 2), comprising betablockers (58.3% vs 76.3%; OR 0.45; 95% CI 0.33 to 0.63), antiplatelet agents (70.8% vs 88.5%; OR 0.25; 95% CI 0.16 to 0.38) and statins (52.9% vs 87.6%; OR 0.25; 95% CI 0.16 to 0.38). Of note, patients with T2MI were more likely to receive diuretics (44.8% vs 13.6%; OR 1.98; 95%

 Table 2
 Pharmacological management and invasive interventions in patients with type 2 myocardial infarction (T2MI) versus type 1 myocardial infarction (T1MI)

	T2MI T1MI						
Intervention	No. patients receiving intervention	Total number of patients	%	No. patients receiving intervention	Total number of patients	%	OR* (95% CI)
Medication							
Beta blockers	4967	8523	58.3	63 431	83 157	76.3	0.45 (0.33 to 0.63)
ACEI/ARB	3766	7842	48	56 253	81 793	68.8	0.52 (0.40 to 0.67)
Antiplatelets	5087	8599	70.8	74 377	84 004	88.5	0.25 (0.16 to 0.38)
Anticoagulants	1519	5255	28.9	15 754	62 415	25.2	1.87 (1.06 to 3.30)
Antianginal agents	1281	2191	58.5	38 955	42 768	91.1	0.61 (0.21 to 1.74)
Diuretics	1336	2985	44.8	6211	45 779	13.6	1.98 (1.37 to 2.86)
Statins	3418	6455	52.9	56 875	64 942	87.6	0.25 (0.16 to 0.38)
Invasive							
PCI	2092	9936	21.1	67 411	86 425	78.0	0.06 (0.04 to 0.10)
CABG	102	3451	2.9	3101	48 731	6.4	0.23 (0.12 to 0.45)

Comparing patients with T2MI with those with T1MI, with OR adjusted according to study weighting using random effects meta-analysis. ACEI, ACE inhibitors; ARB, angiotensin receptor blockers; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Table 3 Outcomes in patients with type 2 myocardial infarction (T2MI) versus type 1 myocardial infarction (T1MI)											
	T2MI			T1MI							
Outcomes	No. patients with outcome	Total number of patients	%	No. patients with outcome	Total number of patients	%	OR* (95% CI)				
CV in-hospital mortality	184	2109	8.7	331	6248	5.3	1.61 (1.17 to 2.22)				
All-cause in-hospital mortality	667	5321	12.5	1508	25 997	5.8	1.94 (1.35 to 2.79)				
Short-term all-cause mortality	204	887	23.0	250	1998	12.5	1.34 (0.63 to 2.85)				
1-year all-cause mortality	632	3340	18.9	1299	24 203	5.4	3.11 (1.91 to 5.08)				
2-year all-cause mortality	246	926	26.6	428	2587	16.5	1.63 (1.11 to 2.41)				
3-year all-cause mortality	193	525	36.8	710	4305	16.5	2.00 (1.07 to 3.76)				
Long-term all-cause mortality	1453	2708	53.7	1320	4633	28.5	3.24 (2.73 to 3.84)				

*Comparing patients with T1MI with those with T2MI, with OR adjusted according to study weighting using random effects meta-analysis. CV, cardiovascular.

CI 1.37 to 2.86) or anticoagulants (28.9% vs 25.2%; OR 1.87; 95% CI 1.06 to 3.30).

DISCUSSION

Percutaneous coronary intervention (PCI) (21.1% vs 78.0%; OR 0.06; 95% CI 0.04 to 0.10) and coronary artery bypass surgery (2.9% vs 6.4%; OR 0.23; 95% CI 0.12 to 0.45) were also significantly less likely to be performed in patients with T2MI than patients with T1MI.

Prognosis

Patients with T2MI had significantly increased risk of allcause death compared with patients with T1MI in both short-term and long-term follow-up (table 3). Specifically, compared with patients with T1MI, T2MI demonstrated increased all-cause mortality in-hospital (12.5% vs 5.8%; OR 1.94; 95% CI 1.35 to 2.79, online supplemental figure S40), at 1 year (18.9% vs 5.4%; OR 3.11; 95% CI 1.91 to 5.08, figure 1) and at 5–10 years (53.7% vs 28.5%, OR 3.24; 95% CI 2.73 to 3.84, figure 2). In contrast, there were no differences between patients with T2MI and T1MI in the risk of short-term mortality at 120–180 days (23.0% vs 12.5%; OR 1.34; 95% CI 0.63 to 2.85). 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 MIs 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 with 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, patients with T2MI demonstrated more medical comorbidities than patients with T1MI, 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 patients with T2MI.

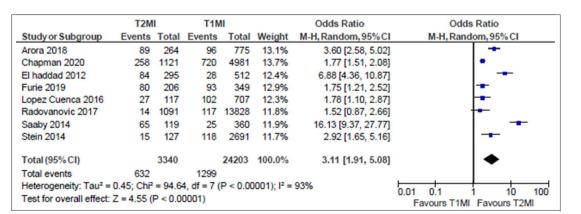


Figure 1 Forest plot of 1-year all-cause mortality of patients with type 2 myocardial infarction (T2MI) compared with patients with type 1 myocardial infarction (T1MI).

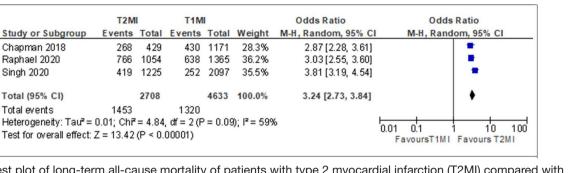


Figure 2 Forest plot of long-term all-cause mortality of patients with type 2 myocardial infarction (T2MI) compared with patients with type 1 myocardial infarction (T1MI).

Sepsis¹⁰ ¹⁶ ²⁷ and anaemia⁵¹ 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 with non-cardiac surgery, hypotension, anaemia or hypoxia.²⁹ In another study, shock syndromes were triggers portending a worse prognosis compared with all other triggers.³² In our analysis, non-cardiac surgery as a trigger was less frequent than reported by other investigators²⁶ whereby perioperative 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 review⁵ reporting cTn values 30%–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 patients with T2MI than those with T1MI. Treating physicians may perceive invasive strategies as being contraindicated or potentially harmful in the presence of various comorbidities more commonly seen in T2MI and associated with competing mortality risk. In our pooled data, only one in three patients with T2MI who underwent angiography demonstrated obstructive coronary artery disease, although this figure may be an underestimate due to selection bias whereby younger, less multimorbid patients preferentially underwent angiography. In the Catheter Sampled Blood Archive in Cardiovascular Disease (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 \geq 70% stenosis in at least 2 major coronary arteries.⁵⁴ 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, lead to 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 with the remaining 209 non-revascularised patients.²³ In contrast, in a third more rigorous study comparing patients with T2MI versus patients with T1MI 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 to 0.55; p<0.001), but not in those with T2MI receiving PCI (OR 1.09; 95% CI 0.62 to 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 T2MI (ACT-2) trial, which is currently in recruitment,⁵⁵ will hopefully provide a more definitive answer.

Given that a third of patients with T2MI 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 multimorbid patients with T2MI. The higher use of diuretics in the T2MI population likely reflects the higher prevalence of heart failure and hypertension. Recognising 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 1-year mortality in patients with T2MI compared with patients with T1MI, similar to the twofold greater mortality rate in T2MI noted in a recent systematic review of nine 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 comorbidities, rather than underlying obstructive coronary artery disease which was seen in 30%-50% of patients with T2MI.^{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 yielded 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 third and fourth universal definitions were applied.⁵⁶ In another study which compared separate T2MI cohorts, as defined by the 2007 and the 2012 definitions, comorbidities and use of cardioprotective medications were less frequent in the 2012 cohort, likely due to less severe MIs being included as a result of the use of 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 57% 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 with those of T1MI were of smaller magnitude. Similarly, 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.^{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 vs 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. However, 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 yielding 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 metaregression 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 review⁵⁹ which compared patients with T1MI with those with T2MI, 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 postdischarge mortality due to their omission in the datasets.

CONCLUSION

This review has identified differences between patients with T2MI and T1MI 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 interhospital 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, revascularisation strategies and cardioprotective medications in patients with T2MI that warrant more randomised trials that enrol such patients.

Contributors All authors 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 were responsible for drafting manuscript and final approval of the version to be published. All authors 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. IS is the guarantor and accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

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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 art disease contributes to an imbalance between myocardial oxygen supply and/or deman 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.

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*)

Table S3a. Study ch	aracteris	stics	-				
Author, Year	Pati	ents	Design	Definition	Geographic	Screening	Troponin
	T1MI	T2MI	_	of MI	location	_	Assay
Arora, 2018 (1)	775	264	Retrospective	2012	USA	NSTEMI patients	cTnl
Balanescu, 2020 (2)	152	49	Retrospective	2018	USA	AMI patients	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 least 1 troponin	cTnl
Chapman, 2018 (6)	1171	429	Prospective	2012	UK	ED with elevated troponin	cTnl
Chapman, 2020 (7)	4981	1121	Prospective	2018	UK	Suspected ACS	cTnl
Consuegra-Sanchaz, 2018 (8)	125	75	Retrospective	2012	Spain	ED patients with at least 1 troponin	cTnI hs-cTnT
El-Haddad, 2012 (9)	512	295	Retrospective	2012	USA	Patients with elevated 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 general ward	Unknown
Guimaraes, 2018 (12)	847	76	Retrospective	2012	Multinational	ACS during TRACER trial	N/A
Hawatmeh, 2020 (13)	664	281	Retrospective	2012	USA	NSTEMI patients	cTnl
Higuchi, 2019 (14)	12023	491	Retrospective	2012	Tokyo	Admitted to CCU	N/A
Javed, 2009 (15)	143	64	Retrospective	2007	USA	Patients with elevated 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	cTnl
Landes, 2016 (18)	107	107	Retrospective	2012	Israel	Diagnosed with T2MI and T1MI	cTnT
Lopez-Cuenca, 2016 (19)	707	117	Retrospective	2012	Spain	Diagnosed with T2MI and T1MI	hs-cTnT
Meigher, 2016 (20)	340	452	Retrospective	2012	Germany	ED patients with elevated 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	N/A	
Putot, 2018 (25)	2036	847	Prospective	2012	France	ED or cardiology ward with elevated troponin	cTnl	
Putot, 2019 (26)	365	254	Retrospective	2018	France	Hospitalised patients with CAD	cTnl	
Putot, 2020 (27)	3710	862	Retrospective	2012	France	Hospitalised patients with MI	cTnl	
Radovanovic, 2017 (28)	13828	1091	Retrospective	2012	Switzerland	Diagnosed AMI	N/A	
Raphael, 2020 (29)	1365	1054	Retrospective	2018	USA	Raised troponin	cTnT	
Reed, 2017 (30)	88	162	Retrospective	2012	USA	Underwent vascular surgery procedure	cTnT	
Saaby 2013 (31)	397	144	Prospective	2007	Denmark	Troponin measured	cTnl	
Saaby, 2014 (32)	360	119	Prospective	2007	Denmark	Elevated troponin	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 troponin measured	cTnl	
Sato, 2020 (35)	2834	155	Prospective	2012	Japan	Hospitalised patient with MI	N/A	
Shah, 2015 (36)	1171	429	Prospective	2012	UK	Admitted with elevated troponin	cTnl	
Singh, 2020 (37)	2097	1225	Retrospective	2018	USA	Age <50, MI or raised troponin	N/A	
Smilowitz, 2018 (38)	137	146	Prospective	2012	USA	Admitted with raised troponin	cTnl	
Stein, 2014 (39)	2691	127	Prospective	2007	Israel	Admitted to cardiology	N/A	
Truong, 2020 (40)	275	175	Retrospective	2012	Russia	MI, undergoing angiogram	N/A	
cTnI = cardiac troponin I; cTnT = cardiac troponin T; hs- = high sensitivity; AMI = acute myocardial infarction; MI = myocardial infarction; ACS =								
acute coronary syndro	me; NSTEI	MI = non-	ST elevation myoc	ardial infarc	tion; CCU = coron	ary care unit; CAD = coronary artery disea	se	

Author, Year	Pati	ents	Variables								
	T1MI	T2MI	Pre-existing conditions	Symptoms	Investigation s	Troponin Values	Management	Prognosis			
Arora, 2018 (1)	775	264	Х		X	Х	X	Х			
Balanescu, 2020 (2)	152	49		Х	Х		X				
Baron, 2016 (3)	40501	1313	X	Х	X	Х	X				
Bonaca, 2012 (4)	359	42									
Cediel, 2017 (5)	376	194	X	Х	Х	Х		Х			
Chapman, 2018 (6)	1171	429	Х		Х	Х	X	Х			
Chapman, 2020 (7)	4981	1121	Х	Х	Х	Х		Х			
Consuegra-Sanchaz, 2018 (8)	125	75	Х	Х	X	Х					
El-Haddad, 2012 (9)	512	295						Х			
Etaher, 2020 (10)	97	121	X		X		X				
Furie, 2019 (11)	349	206	X	Х	X	Х	X	Х			
Guimaraes, 2018 (12)	847	76	Х		X		X	Х			
Hawatmeh, 2020 (13)	664	281	Х		X	Х	X				
Higuchi, 2019 (14)	12023	491	X		X		X	Х			
Javed, 2009 (15)	143	64	Х		Х	Х		Х			
Kadesjo, 2019 (16)	1111	251	Х				X	Х			
Lambrecht, 2018 (17)	360	119	Х		X	Х		Х			
Landes, 2016 (18)	107	107	Х	Х	Х	Х					
Lopez-Cuenca, 2016 (19)	707	117	Х	Х	Х	Х	X	Х			
Meigher, 2016 (20)	340	452	Х	Х	X	Х		Х			
Nestelberger, 2017 (21)	684	128	Х		Х		X	Х			
Neumann, 2017 (22)	188	99	Х		X	Х		Х			
Paiva, 2015 (23)	764	236	Х		Х	Х		Х			
Pandey, 2020 (24)	97	103	Х								
Putot, 2018 (25)	2036	847	Х		Х	Х		Х			
Putot, 2019 (26)	365	254	Х		Х	Х		Х			
Putot, 2020 (27)	3710	862	Х		Х	Х		Х			
Radovanovic, 2017 (28)	13828	1091	Х		Х		X	Х			
Raphael, 2020 (29)	1365	1054	Х		Х	Х	Х	Х			

Reed, 2017 (30)	88	162			Х	Х	X	
Saaby 2013 (31)	397	144	Х		Х	X		
Saaby, 2014 (32)	360	119	Х		Х	X	Х	X
Sandoval, 2014 (33)	66	190	Х	Х	Х	X		X
Sandoval, 2017 (34)	77	140	Х	Х	Х	X	Х	X
Sato, 2020 (35)	2834	155	Х		Х		Х	X
Shah, 2015 (36)	1171	429	Х	Х	Х	X	Х	X
Singh, 2020 (37)	2097	1225	Х		Х		X	X
Smilowitz, 2018 (38)	137	146	Х	Х	Х	X	Х	X
Stein, 2014 (39)	2691	127	Х	Х	Х		Х	Х
Truong, 2020 (40)	275	175	Х	Х	Х		Х	X

Table S4. Risk of bia	as assessment					
			Outcome			
Author, Year	Representative of Exposed Cohort	Selection of Non-exposed	Assessment	Follow-up Length	Adequacy of Follow- Up	Summary
Arora, 2018 (1)	x	х	х	x	х	8 (good quality)
Balanescu, 2020 (2)	0	х	х	0	х	6 (fair quality)
Baron, 2016 (3)	x	х	х	x	х	8 (good quality)
Bonaca, 2012 (4)	x	х	х	x	х	8 (good quality)
Cediel, 2017 (5)	x	х	х	x	х	8 (good quality)
Chapman, 2018 (6)	x	х	х	x	х	8 (good quality)
Chapman, 2020 (7)	x	х	х	x	х	8 (good quality)
Consuegra-Sanchaz, 2018 (8)	0	0	x	0	0	3 (poor quality)
El-Haddad, 2012 (9)	x	х	0	0	0	5 (fair quality)
Etaher, 2020 (10)	х	х	х	x	х	8 (good quality)
Furie, 2019 (11)	x	х	х	x	х	8 (good quality)
Guimaraes, 2018 (12)	0	0	x	0	x	4 (fair quality)
Hawatmeh, 2020 (13)	0	0	x	x	0	4 (fair quality)
Higuchi, 2019 (14)	0	0	х	x	х	5 (fair quality)
Javed, 2009 (15)	x	х	х	x	х	8 (good quality)
Kadesjo, 2019 (16)	x	х	х	x	х	8 (good quality)
Lambrecht, 2018 (17)	x	х	x	x	x	8 (good quality)
Landes, 2016 (18)	х	х	х	x	х	8 (good quality)
Lopez-Cuenca, 2016 (19)	x	х	x	x	x	8 (good quality)
Meigher, 2016 (20)	х	х	х	x	х	8 (good quality)
Nestelberger, 2017 (21)	x	х	x	x	x	8 (good quality)
Neumann, 2017 (22)	х	х	х	x	х	8 (good quality)

					r	
Paiva, 2015 (23)	Х	x	Х	Х	Х	8 (good quality)
Pandey, 2020 (24)	0	0	0	0	0	2 (poor quality)
Putot, 2018 (25)	х	x	х	х	х	8 (good quality)
Putot, 2019 (26)	х	x	0	х	х	7 (good quality)
Putot, 2020 (27)	х	x	х	х	х	8 (good quality)
Radovanovic, 2017 (28)	х	x	x	х	х	8 (good quality)
Raphael, 2020 (29)	х	x	х	х	х	8 (good quality)
Reed, 2017 (30)	х	x	х	х	х	8 (good quality)
Saaby 2013 (31)	х	x	х	х	х	8 (good quality)
Saaby, 2014 (32)	х	x	х	х	х	8 (good quality)
Sandoval, 2014 (33)	х	x	х	х	х	8 (good quality)
Sandoval, 2017 (34)	х	x	х	х	х	8 (good quality)
Sato, 2020 (35)	0	0	0	х	х	2 (poor quality)
Shah, 2015 (36)	х	x	х	х	х	8 (good quality)
Singh, 2020 (37)	0	0	х	х	х	6 (fair quality)
Smilowitz, 2018 (38)	х	х	х	х	х	7 (good quality)
Stein, 2014 (39)	х	х	х	х	х	7 (good quality)
Truong, 2020 (40)	Х	х	х	Х	х	8 (good quality)

Table S5. Precipitating conditions for T 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	1	592	0.2%

Table S6. Clini	cal features	on preser	ntation ir	n patients wi	th T2MI ve	ersus T1I	MI patients.
		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% CI]
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

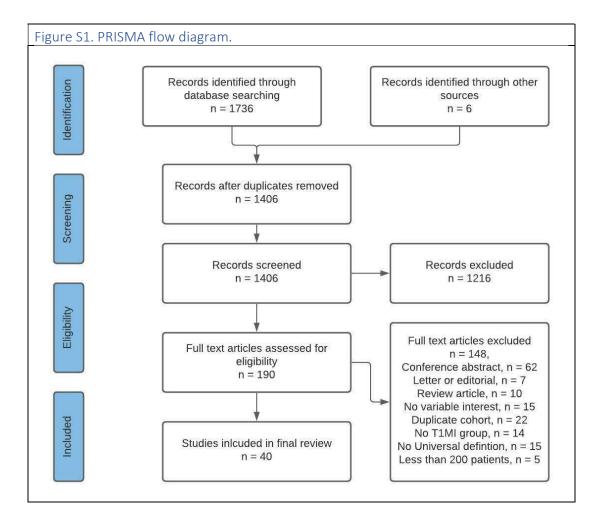
Abbreviations: URL- upper reference limit; STEMI- ST elevation myocardial infarction; NSTEMI- Non- ST elevation myocardial infarction; MI- Myocardial infarction; cTn- cardiac troponin; T1MI- Type 1 myocardial infarction; T2MI- Type 2 myocardial infarction; ECG- electrocardiogram; CAD- coronary artery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

		T2MI			T1MI			
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 T1MI patients, with odds ratio adjusted according to study weighting using random effect: meta-analysis

ECG=electrocardiograph; RWMA=regional wall motion abnormalities; CI=confidence interval; T2MI=type 2 myocardial infarction; T1MI=type 1 myocardial infarction

Table S8. Troponin mea	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		•									



	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
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%	6	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% 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]	1
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); I ² = 83%	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% CI	M-H, Random, 95% CI
Arora 2018	225	264	642	775	3.2%	1.20 [0.81, 1.76]	
Baron 2016	962	1313	26334	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]	
Meigher 2016	289	452	224	340	3.4%	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%	1.74 [1.51, 2.00]	-
Raphael 2020	716	1054	966	1365	3.7%	0.87 [0.74, 1.04]	+
Saaby 2013	81	144	215	397	3.2%	1.09 [0.74, 1.60]	+
Saaby 2014	66	119	193	360	3.1%	1.08 [0.71, 1.63]	+
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]	<u>+-</u>
Total (95% CI)		11021		88017	100.0%	1.22 [1.03, 1.45]	•
Total events	7536		55782				
Heterogeneity: Tau ² = 0.20;	Chi ² = 315	.20, df =	= 32 (P <	0.00001); I ² = 90%		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%
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]		- F
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]		ł
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]		+
Fotal (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%	6	<u> </u>	
Test for overall effect: Z = 2							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, 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]	
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]	-
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]	+
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]	+
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]	+
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]	-
Total (95% CI)		9929		74889	100.0%	0.60 [0.49, 0.73]	•
Total events	3448		39548				
Heterogeneity: Tau ² = 0.26	5; Chi ² = 381	1.27, df	= 28 (P <	0.0000	1); I ² = 939	%	0.01 0.1 1 10
Test for overall effect: Z =	4.95 (P < 0.	00001)					0.01 0.1 1 10 avours [experimental] Favours [con

	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 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]	•	
10(01 00/001)			30963					

	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		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	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]	+
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]	−
Lambrecht 2018	26	119	32	360	4.0%	2.87 [1.63, 5.05]	
Landes 2016	21	107	17	107	3.6%	1.29 [0.64, 2.61]	
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]	-
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	4.4%	4.05 [2.62, 6.26]	-
Radovanovic 2017	74	1091	290	13828	4.8%	3.40 [2.61, 4.42]	
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]	_ →
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]	+
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	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	46	264	111	775	6.3%	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	5.9%	0.93 [0.60, 1.43]		+	
Furie 2019	28	206	56	349	5.6%	0.82 [0.50, 1.34]			
Hawatmeh 2020	28	281	89	664	5.9%	0.72 [0.46, 1.12]			
Higuchi 2019	8	491	182	12023	4.4%	1.08 [0.53, 2.20]		+	
Lambrecht 2018	17	119	20	360	4.6%	2.83 [1.43, 5.61]			
Lopez Cuenca 2016	11	117	57	707	4.6%	1.18 [0.60, 2.33]		- - -	
Nestelberger 2020	2	128	72	684	2.0%	0.13 [0.03, 0.56]		·	
Putot 2018	110	847	138	2036	6.8%	2.05 [1.58, 2.67]		-	
Putot 2019	55	254	54	365	6.0%	1.59 [1.05, 2.41]		-	
Radovanovic 2017	103	1091	650	13828	7.0%	2.11 [1.70, 2.63]		+	
Saaby 2013	18	144	21	397	4.7%	2.56 [1.32, 4.95]			
Saaby 2014	17	119	20	360	4.6%	2.83 [1.43, 5.61]			
Sandoval 2017	3	140	5	77	1.9%	0.32 [0.07, 1.36]	-		
Sato 2020	14	155	121	2834	5.1%	2.23 [1.25, 3.97]			
Shah 2015	29	429	82	1171	5.9%	0.96 [0.62, 1.49]		+	
Smilowitz 2018	11	146	13	137	3.8%	0.78 [0.34, 1.80]			
Stein 2014	22	127	229	2691	5.7%	2.25 [1.40, 3.64]			
Troung 2020	12	175	9	275	3.6%	2.18 [0.90, 5.28]			
Total (95% CI)		5856		41280	100.0%	1.33 [1.05, 1.69]		•	
Total events	584		2066						
Heterogeneity: Tau ² =	0.20: Chi ²	= 81.80), df = 19	(P < 0.0)	00001): I ²	= 77%	0.01 0	1 1 10	1

	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	Odd	Is Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Ran	idom, 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					

	T2M	1	T1N	11		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	lom, 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); l ² :	= 82%	0.01 0.1	1 10

	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
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					

	T2M	1	T1N	41		Odds Ratio	Odds	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Rando	m, 95% CI
Baron 2016	195	1313	1774	40501	9.4%	3.81 [3.25, 4.47	מ	-
Cediel 2017	90	194	37	376	8.3%	7.93 [5.10, 12.33	3]	-
Chapman 2020	116	1121	171	4981	9.2%	3.25 [2.54, 4.15	5]	-
Furie 2019	122	206	178	349	8.8%	1.40 [0.98, 1.98	3]	-
Landes 2016	78	107	38	107	7.6%	4.88 [2.73, 8.74	4]	
Lopez Cuenca 2016	22	117	38	707	7.7%	4.08 [2.31, 7.19	9]	
Radovanovic 2017	482	1091	4425	13828	9.5%	1.68 [1.48, 1.91	1]	-
Sandoval 2014	112	190	35	66	7.7%	1.27 [0.72, 2.23	3] -	_
Sandoval 2017	72	140	40	77	7.7%	0.98 [0.56, 1.71	ŋ 	_
Shah 2015	80	429	45	1171	8.6%	5.74 [3.91, 8.42	2]	-
Stein 2014	15	127	105	2691	7.6%	3.30 [1.86, 5.85	5]	
Troung 2020	28	175	44	275	7.9%	1.00 [0.60, 1.68	8] -	_
Total (95% CI)		5210		65129	100.0%	2.64 [1.86, 3.74	ŋ	•
Total events	1412		6930					
Heterogeneity: Tau ² =	0.33; Chi ²	= 163.9	95, df = 1	1(P < 0)	.00001); l ²	= 93%	0.01 0.1 1	

	T2M		T1M			Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rando	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	$1^2 = 0\%$		0.01	01	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% 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	1	M-H, Rand	om, 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]	_	—	
Neumann 2017	81	99	105	188	33.3%	3.56 [1.98, 6.39	1			
Total (95% CI)		1529		41396	100.0%	4.90 [0.48, 50.33	1	-		
Total events	988		2662							
Heterogeneity: Tau ² = 4	4.15; Chi ²	= 140.9	98. df = 2	(P < 0.0	00001); l ²	= 99%	0.01	01	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, Rand	lom, 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]				
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 =	0.45; Chi ²	= 19.12	2, df = 4 (P = 0.0	0007); l ² =	79%	-	1		
Test for overall effect:					14800 5 801800		0.01	0.1 T1MI	1 10 T2MI	1

	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	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); I	= 88%	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	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]	-1
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 = 97	%	0.01 0.1 1 10

	T2M	1	T1M	I		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]		
Total (95% CI)		447		850	100.0%	0.38 [0.20, 0.71]	•	
Total events	30		177					

	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	
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 (P	P = 0.15	$ ^2 = 41\%$		0.01 0.1 1 10

Sandoval 2017 22 140 3 77 13.9% 4.60 [1.33, 15.90]	95% CI
	-
	-
Total (95% CI) 257 784 100.0% 4.99 [3.14, 7.93]	•
Total events 54 52	

	T2M	-	T1N			Odds Ratio		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		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); I ² = 96	%	0.01 0.1	1 10

Figure S27. Forest P	lot. Ob	struc	tive Co	orona	ry Arte	ry Disease on Col	ronary Angiogram.
	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% Cl
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				
Heterogeneity: Tau ² = 4.01;	Chi ² = 989	.87, df	= 10 (P <	0.0000	1); I ² = 999	%	0.01 0.1 1 10
Test for overall effect: Z = 2.	95 (P = 0.	003)	-				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, Rand	om, 95% Cl
Baron 2016	381	1313	11340	40501	22.4%	1.05 [0.93, 1.19]	0.000	
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					

Study or Subgroup 8			T1M			Odds Ratio	Odds Ratio	
	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]	1	
Total (95% CI)		1353		2830	100.0%	0.44 [0.20, 0.96]	•	
Total events	648		1571					
Heterogeneity: Tau ² = 1.0	07; Chi ²	= 138.1	14, df = 6	(P < 0.	00001); l ²	= 96%	0.01 0.1 1 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% 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	I	T1N	41		Odds Ratio	Odds Ratio
study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
vora 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]	
urie 2019	141	206	247	349	4.6%	0.90 [0.62, 1.30]	-+
lawatmeh 2020	165	281	551	664	4.7%	0.29 [0.21, 0.40]	-
liguchi 2019	236	491	6786	12023	4.8%	0.71 [0.60, 0.86]	+
adesjo 2019	169	251	946	1111	4.7%	0.36 [0.26, 0.49]	-
opez Cuenca 2016	86	117	614	707	4.4%	0.42 [0.26, 0.67]	
lestelberger 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]	- +
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]	
roung 2020	159	175	237	275	4.1%	1.59 [0.86, 2.96]	<u> </u>
fotal (95% CI)		8523		83157	100.0%	0.45 [0.33, 0.63]	•
otal events leterogeneity: Tau ² =	4967		63431				

	T2M		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	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]	i -
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				
Heterogeneity: Tau ² =	0.29; Chi ²	= 362.4	12, df = 1	7 (P < 0	.00001); P	= 95%	0.01 0.1 1 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% Cl
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]		F
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]	-	<u>†</u>
Total (95% CI)		8599		84004	100.0%	0.25 [0.16, 0.38]	•	
Total events	5087		74377					
Heterogeneity: Tau ² =	1.12; Chi ²	= 1005	.85, df =	22 (P <	0.00001);	l ² = 98%	0.01 0.1	1 10

	T2M	1	T1N	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	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]	
opez 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]	
Froung 2020	24	175	33	275	9.1%	1.17 [0.66, 2.05]	· +-
Fotal (95% CI)		5255		62415	100.0%	1.87 [1.06, 3.30]	◆
Total events	1519		15754				

	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	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]	-
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]	-
Total (95% CI)		2191		42768	100.0%	0.61 [0.21, 1.74]	-
Total events	1281		38955				
Heterogeneity: Tau ² =	1.39; Chi ²	= 199.9	97. df = 4	(P<0.0	00001); l ² =	98%	01 0.1 1 10

	T2M	I	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	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]	
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]	+
Total (95% CI)		2985		45779	100.0%	1.98 [1.37, 2.86]	•
Total events	1336		6211				
Heterogeneity: Tau ² = (0.14; Chi ²	= 36.79	9, df = 5 (P < 0.00	0001); l ² = 8	36%	0.01 0.1 1 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
Arora 2018	153	264	646	775	6.4%	0.28 [0.20, 0.3]	7] —	
Balanescu 2020	29	49	131	152	5.5%	0.23 [0.11, 0.44	B]	
Baron 2016	972	1313	37261	40501	6.6%	0.25 [0.22, 0.20	B] 🔫	
Chapman 2018	204	429	872	1171	6.5%	0.31 [0.25, 0.39	9] 🗕 🛨	
Etaher 2020	95	171	81	97	5.8%	0.25 [0.13, 0.4	6]	
Furie 2019	125	206	280	349	6.3%	0.38 [0.26, 0.56	6]	
Hawatmeh 2020	141	281	578	664	6.4%	0.15 [0.11, 0.2	1] —	
Higuchi 2019	298	491	9238	12023	6.5%	0.47 [0.39, 0.56	6] 🗕 🛨	
Kadesjo 2019	92	251	883	1111	6.4%	0.15 [0.11, 0.20	0] —	
Lopez Cuenca 2016	92	117	648	707	6.0%	0.34 [0.20, 0.5	6]	
Nestelberger 2020	39	128	606	684	6.2%	0.06 [0.04, 0.09	9] —	
Raphael 2020	570	1054	1167	1365	6.5%	0.20 [0.16, 0.24	4] 🗕 🖛	
Sato 2020	112	155	2303	2834	6.3%	0.60 [0.42, 0.86	6]	
Singh 2020	255	1225	1840	2097	6.5%	0.04 [0.03, 0.04	4] 🖛	
Smilowitz 2018	83	146	100	137	6.1%	0.49 [0.30, 0.80	oj —	
Troung 2020	158	175	241	275	5.8%	1.31 [0.71, 2.43	3] -	-
Total (95% CI)		6455		64942	100.0%	0.25 [0.16, 0.34	8] 🔶	
Total events	3418		56875					

	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
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]	← -	
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]	+	1
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]	\leftarrow	
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 = Test for overall effect:				2 (P < 0.	.00001); l²	= 98%	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	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				
Heterogeneity: Tau ² = (0.82; Chi ²	= 50.88	3, df = 12	(P < 0.0	00001); I ²	= 76%	0.01 0.1 1 10

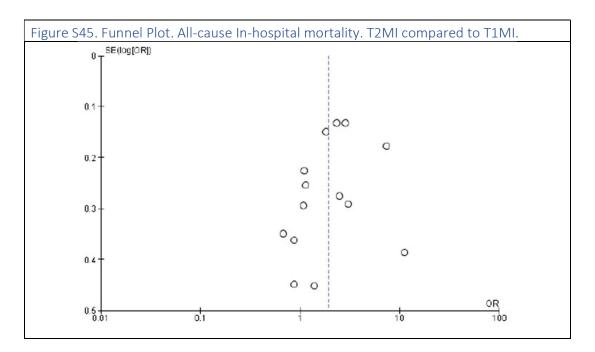
T2M	E	T1M			Odds Ratio	Odds Ratio
Events				Weight		
21	206	33	349	7.1%	1.09 [0.61, 1.93]	+-
54	491	769	12023	8.2%	1.81 [1.35, 2.42]	-
9	64	15	143	5.7%	1.40 [0.58, 3.38]	- -
6	117	41	707	5.7%	0.88 [0.36, 2.12]	
54	452	37	340	7.6%	1.11 [0.71, 1.73]	+-
23	236	66	764	7.4%	1.14 [0.69, 1.88]	+-
133	847	125	2036	8.3%	2.85 [2.20, 3.69]	+
38	254	24	365	7.2%	2.50 [1.46, 4.28]	
95	862	186	3710	8.3%	2.35 [1.81, 3.04]	-
29	119	10	360	6.3%	11.28 [5.30, 24.00]	
160	1225	42	2097	8.0%	7.35 [5.19, 10.41]	-
17	146	18	137	6.5%	0.87 [0.43, 1.77]	-
15	127	113	2691	7.1%	3.06 [1.73, 5.41]	
13	175	29	275	6.6%	0.68 [0.34, 1.35]	-+
	5321		25997	100.0%	1.94 [1.35, 2.79]	•
667		1508				
0.40; Chř	= 115.	87, df = 1	3 (P < 0	.00001); P	²= 89%	
	Events 21 54 9 6 54 23 133 38 95 29 160 17 15 13 667 0.40; Chř	Events Total 21 206 54 491 9 64 6 117 54 452 23 236 133 847 38 254 95 862 29 119 160 1225 17 146 15 127 13 175 5321 667 0.40; Chr = 115.1	Events Total Events 21 206 33 54 491 769 9 64 15 6 117 41 54 452 37 23 236 666 133 847 125 38 254 24 95 862 186 29 119 10 160 1225 42 17 146 18 15 127 113 13 175 29 5321 5321 5328	Events Total Events Total 21 206 33 349 54 491 769 12023 9 64 15 143 6 117 41 707 54 452 37 340 23 236 66 764 133 847 125 2036 38 254 24 365 95 862 186 3710 29 119 10 360 160 1225 42 2097 17 146 18 137 15 127 113 2691 13 175 29 275 5321 25997 667 1508 0.40; ChF = 115.87, df = 13 (P < 0	Events Total Events Total Weight 21 206 33 349 7.1% 54 491 769 12023 8.2% 9 64 15 143 5.7% 6 117 41 707 5.7% 54 452 37 340 7.6% 23 236 66 764 7.4% 133 847 125 2036 8.3% 38 254 24 365 7.2% 95 862 186 3710 8.3% 29 119 10 360 6.3% 160 1225 42 2097 8.0% 17 146 18 137 6.5% 15 127 113 2691 7.1% 13 175 29 275 6.6% 5321 2597 100.0% 667 1508 0.40; ChF = 115.87, df =	Events Total Events Total Weight M-H, Random, 95% CI 21 206 33 349 7.1% 1.09 [0.61, 1.93] 54 491 769 12023 8.2% 1.81 [1.35, 2.42] 9 64 15 143 5.7% 1.40 [0.58, 3.38] 6 117 41 707 5.7% 0.88 [0.36, 2.12] 54 452 37 340 7.6% 1.11 [0.71, 1.73] 23 236 66 764 7.4% 1.14 [0.69, 1.88] 133 847 125 2036 8.3% 2.85 [2.20, 3.69] 38 254 24 365 7.2% 2.50 [1.46, 4.28] 95 862 186 3710 8.3% 2.35 [1.81, 3.04] 29 119 10 360 6.3% 11.28 [5.30, 24.00] 160 1225 42 2097 8.0% 7.35 [5.19, 10.41] 17 146 18 137 6.5%

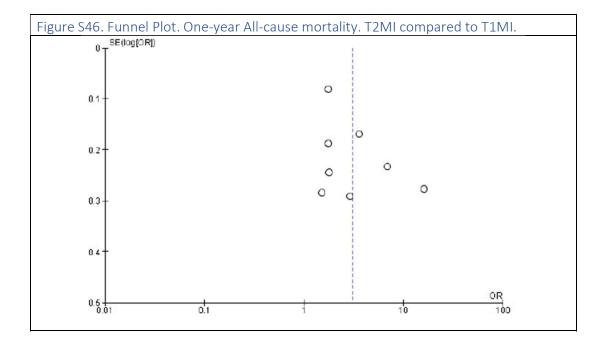
T2M		T1M			Odds Ratio	Odds Ratio
Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1	128	42	684	10.4%	0.12 [0.02, 0.88]	
51	190	15	66	29.6%	1.25 [0.65, 2.41]	
18	140	6	77	23.4%	1.75 [0.66, 4.60]	+
134	429	187	1171	36.7%	2.39 [1.85, 3.09]	
	887		1998	100.0%	1.34 [0.63, 2.85]	•
204		250				
.38; Chr	= 12.1	1. df = 3 (P = 0.0)07); I ² = 7	5%	
	Events 1 51 18 134 204	Events Total 1 128 51 190 18 140 134 429 887 204	Events Total Events 1 128 42 51 190 15 18 140 6 134 429 187 887 204 250	Events Total Events Total 1 128 42 684 51 190 15 66 18 140 6 77 134 429 187 1171 887 1998 204 250	Events Total Events Total Weight 1 128 42 684 10.4% 51 190 15 66 29.6% 18 140 6 77 23.4% 134 429 187 1171 36.7% 887 1998 100.0% 204 250	Events Total Events Total Weight M-H, Random, 95% CI 1 128 42 684 10.4% 0.12 [0.02, 0.88] 51 190 15 66 29.6% 1.25 [0.65, 2.41] 18 140 6 77 23.4% 1.75 [0.66, 4.60] 134 429 187 1171 36.7% 2.39 [1.85, 3.09] 887 1998 100.0% 1.34 [0.63, 2.85]

	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	1	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% 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					
Heterogeneity: Tau ² = I	0.27: Chr	= 14.6	9. df = 2 (P = 0.0)006); I ² =	86%		1 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% 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				
Heterogeneity: Tau ² =	0.05: Chi ²	= 6.15.	df = 3 (P	= 0.10); ² = 51%	6 0.01	0.1 1 10





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