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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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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 Meta-analyses 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% CI 1.53 to 2.28) and chronic heart failure (OR 2.35; 95% CI 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% CI 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% CI 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 1-year 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).

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.

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.

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 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 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 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 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 definition[1] was used in 7 (17.5%) studies,[15 16 27 29 43 44 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 43–45 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 beta-blockers (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)

Outcomes	T2MI			T1MI			
	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).

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 all-cause 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).

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 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.

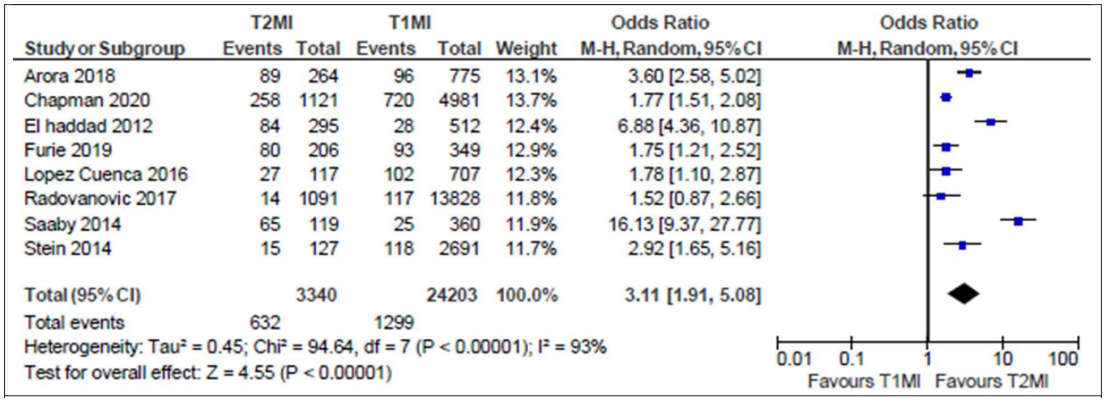

Figure 1 Forest plot of 1-year all-cause mortality of patients with type 2 myocardial infarction (T2MI) compared with patients with type 1 myocardial infarction (T1MI).

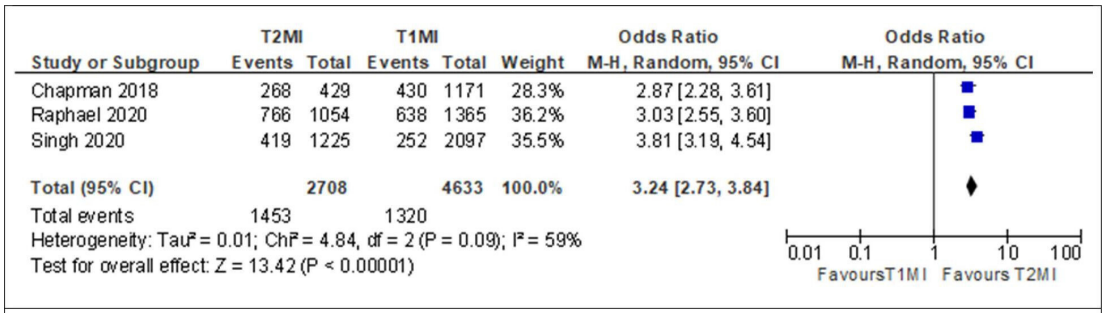

Figure 2 Forest plot of long-term all-cause mortality of patients with type 2 myocardial infarction (T2MI) compared with patients with type 1 myocardial infarction (T1MI).

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 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 investigators[26] 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 review[5] 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 ≥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 review[59] 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 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.

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 characteristics

Author, Year	Patients		Design	Definition of MI	Geographic location	Screening	Troponin Assay
	T1MI	T2MI					
Arora, 2018 (1)	775	264	Retrospective	2012	USA	NSTEMI patients	cTnI
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	cTnI
Chapman, 2018 (6)	1171	429	Prospective	2012	UK	ED with elevated troponin	cTnI
Chapman, 2020 (7)	4981	1121	Prospective	2018	UK	Suspected ACS	cTnI
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	cTnI
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	cTnI
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	cTnI
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	cTnI
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-cTnI

Paiva, 2015 (23)	764	236	Retrospective	2012	Portugal	Admitted to CCU with MI	cTnI
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	cTnI
Putot, 2019 (26)	365	254	Retrospective	2018	France	Hospitalised patients with CAD	cTnI
Putot, 2020 (27)	3710	862	Retrospective	2012	France	Hospitalised patients with MI	cTnI
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	cTnI
Saaby, 2014 (32)	360	119	Prospective	2007	Denmark	Elevated troponin	cTnI
Sandoval, 2014 (33)	66	190	Retrospective	2012	USA	ED patients with troponin measured	cTnI
Sandoval, 2017 (34)	77	140	Prospective	2012	USA	ED patients with troponin measured	cTnI
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	cTnI
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	cTnI
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 syndrome; NSTEMI = non-ST elevation myocardial infarction; CCU = coronary care unit; CAD = coronary artery disease

Table S3b. Study characteristics

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

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

Table S4. Risk of bias assessment

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

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

Table S5. Precipitating conditions for T2MI.

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. Clinical features on presentation in patients with T2MI versus T1MI patients.

Presenting Symptom	T2MI			T1MI			Odds ratio * [95% CI]
	No. patients with presenting symptom	Total number of patients	%	No. patients with presenting symptom	Total number of patients	%	
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

Table S7. Cardiac investigations in patients with T2 MI versus T1MI.

Variable	T2MI			T1MI			Odds ratio* (95% CI)
	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 effects 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 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 upper limit normal			

Figure S1. PRISMA flow diagram.

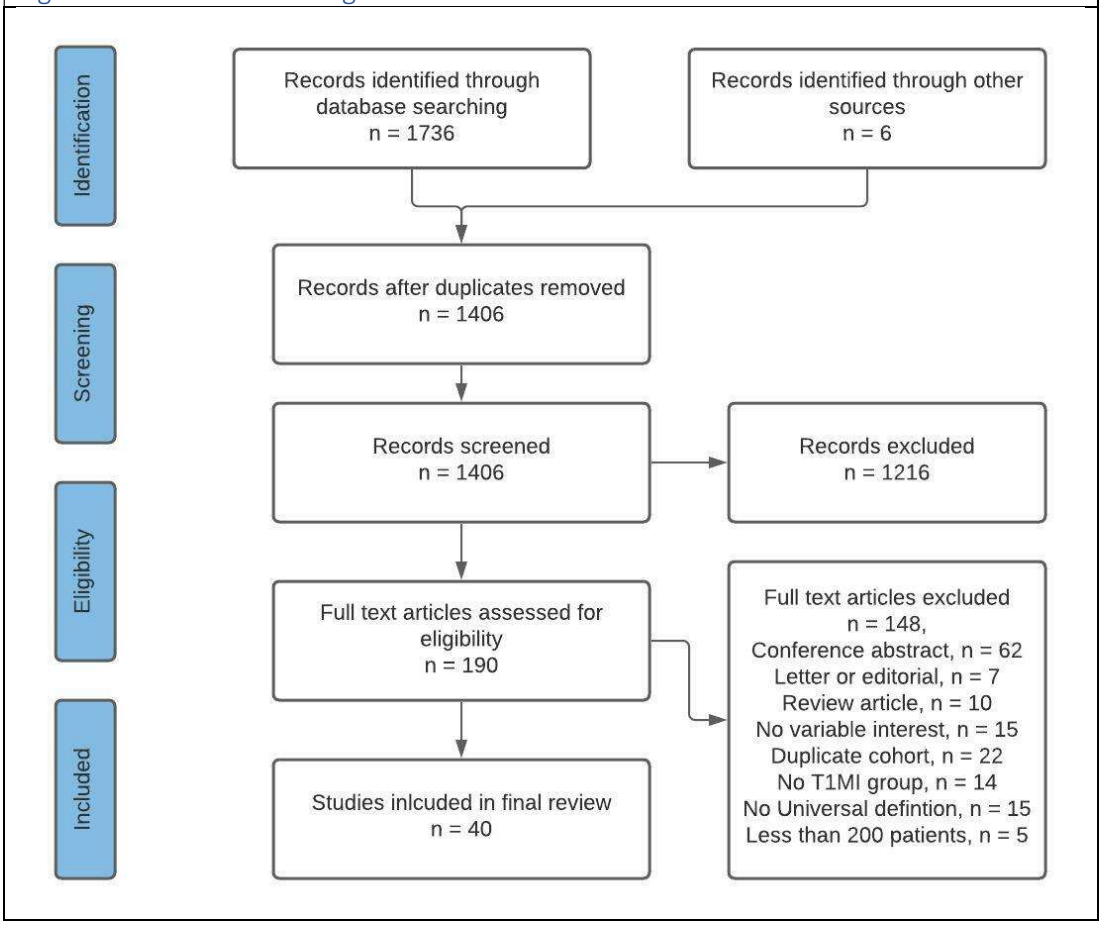


Figure S2. Forest Plot. Presence of Ischaemic Heart Disease.

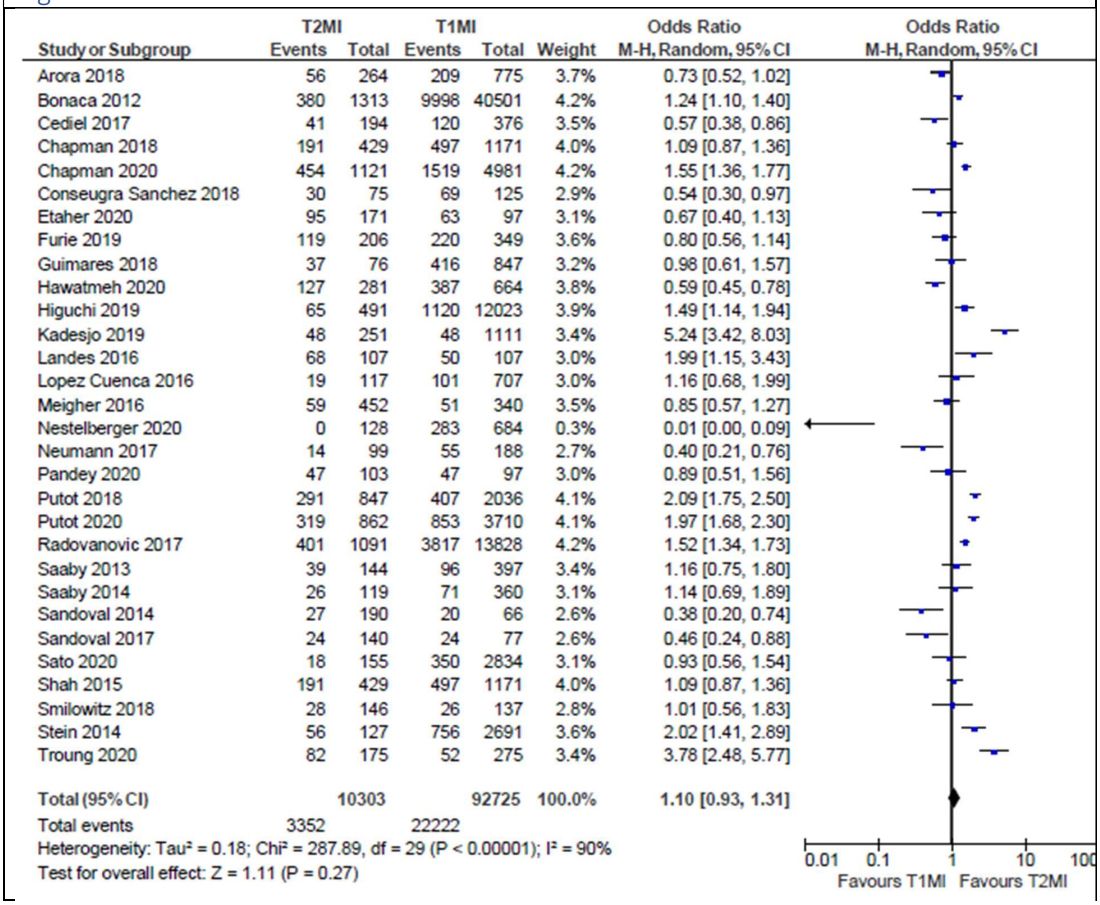


Figure S3. Forest Plot. Presence of Type 2 Diabetes Mellitus.

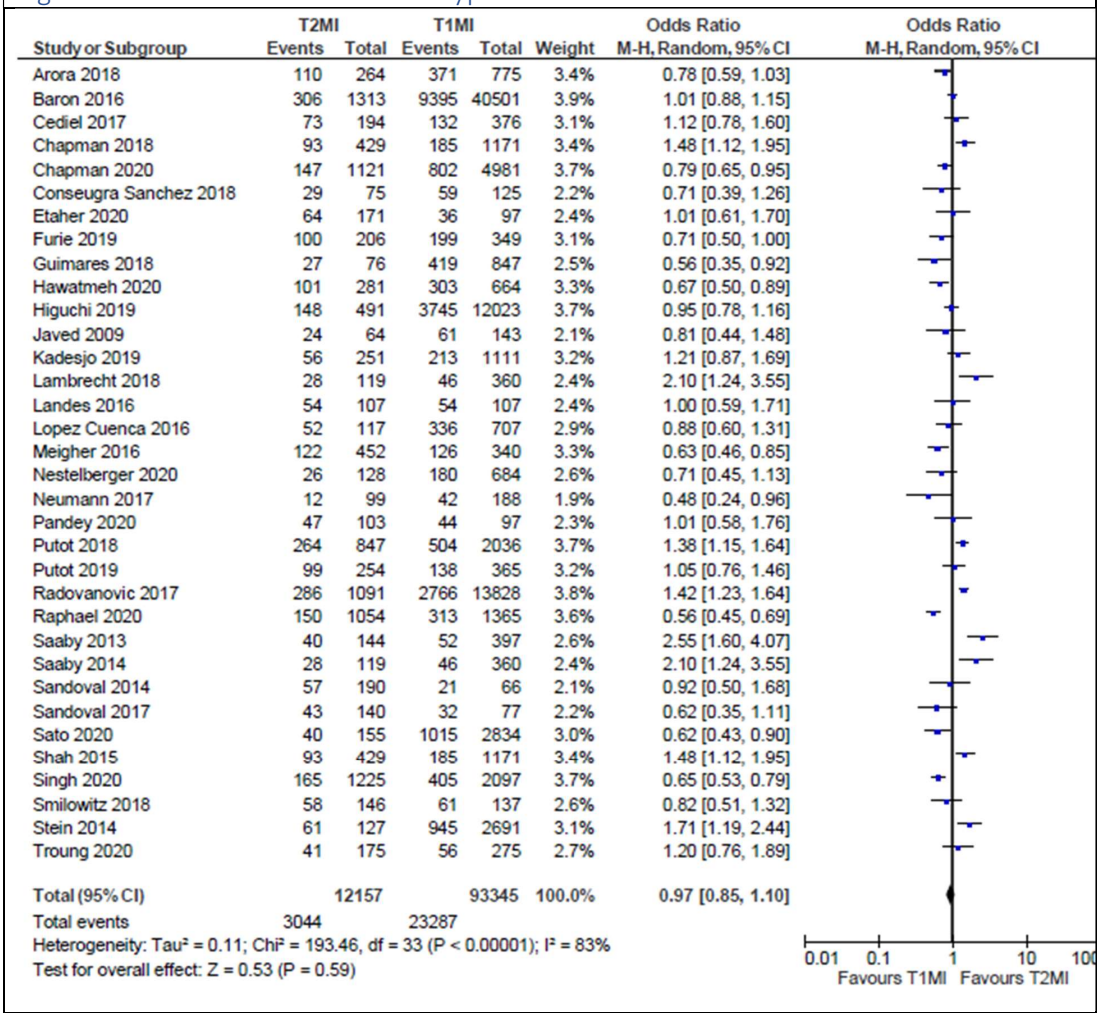


Figure S4. Forest Plot. Presence of Hypertension.

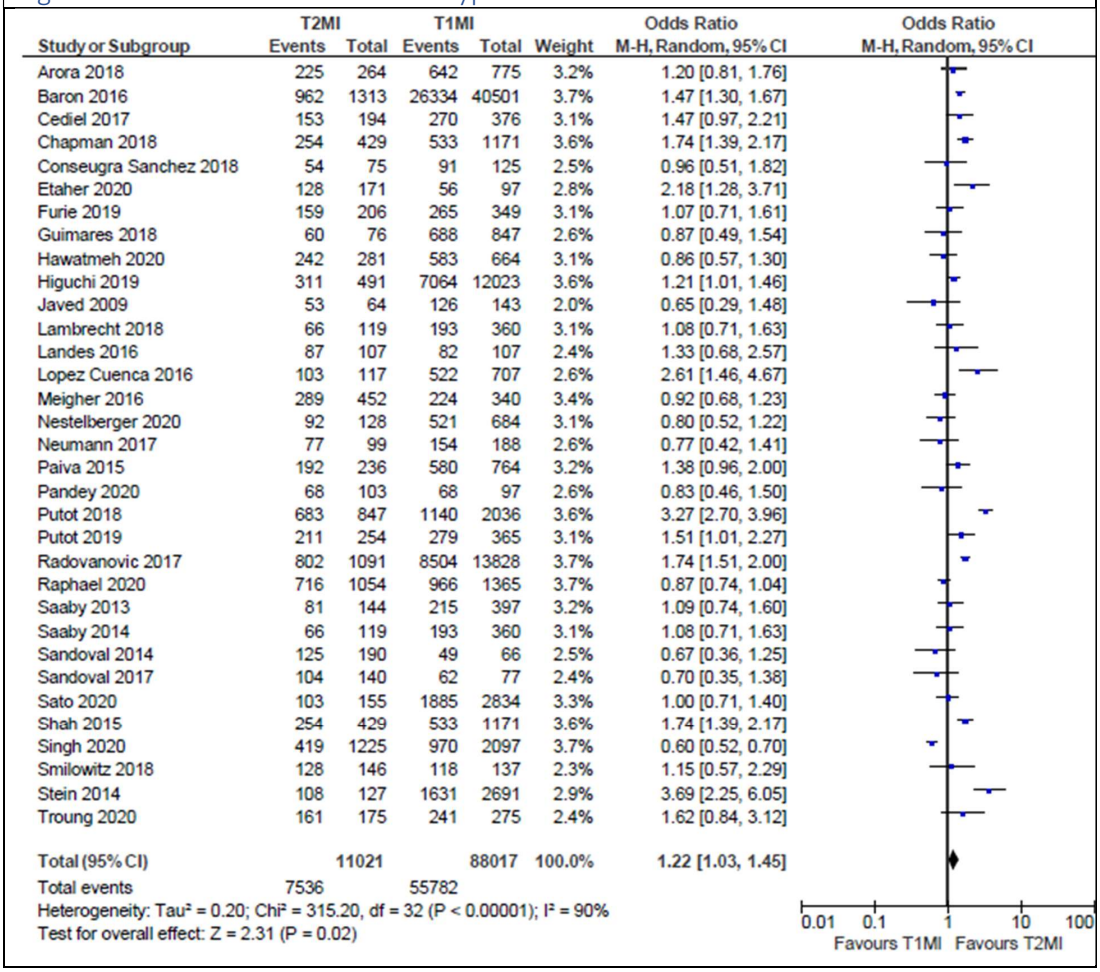


Figure S5. Forest Plot. Presence of Dyslipidaemia.

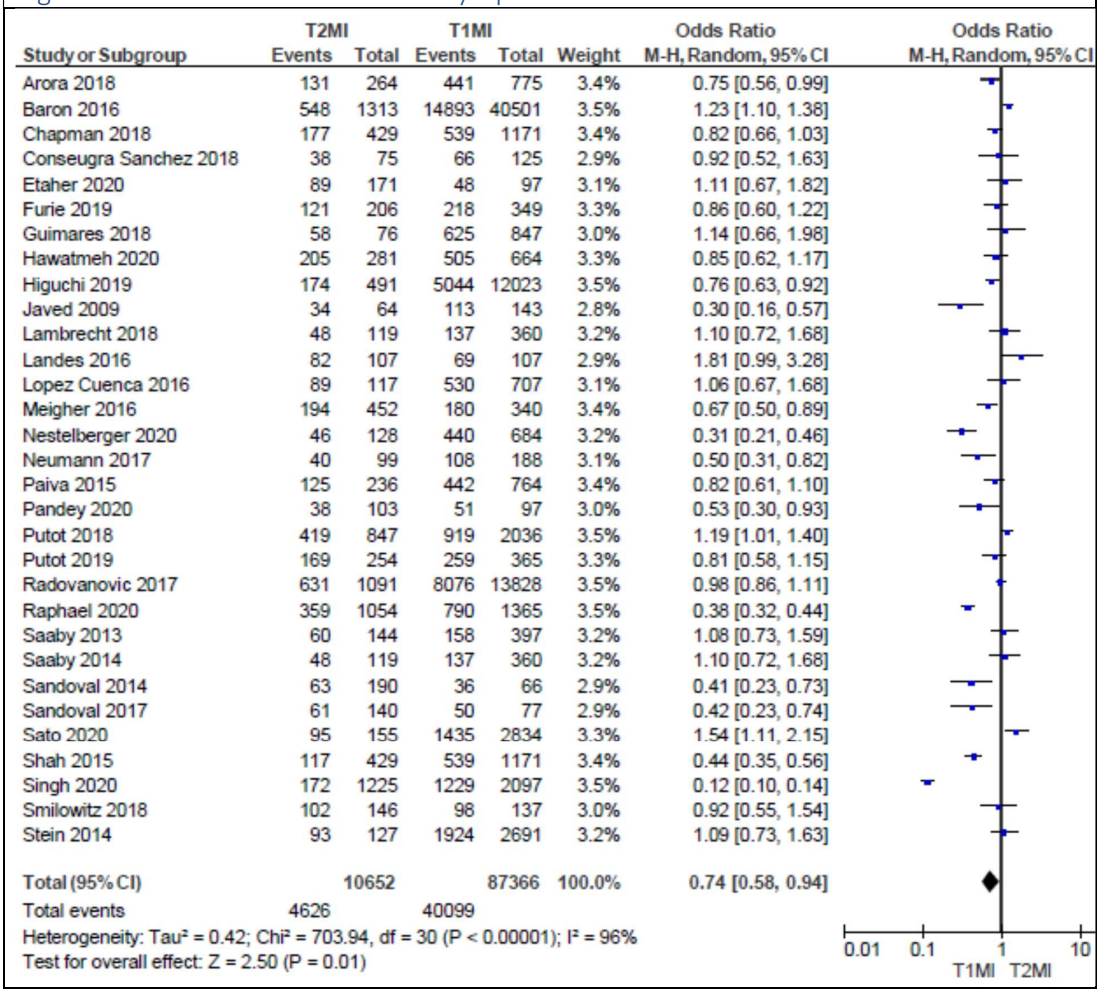


Figure S6. Forest Plot. Smoking Status.

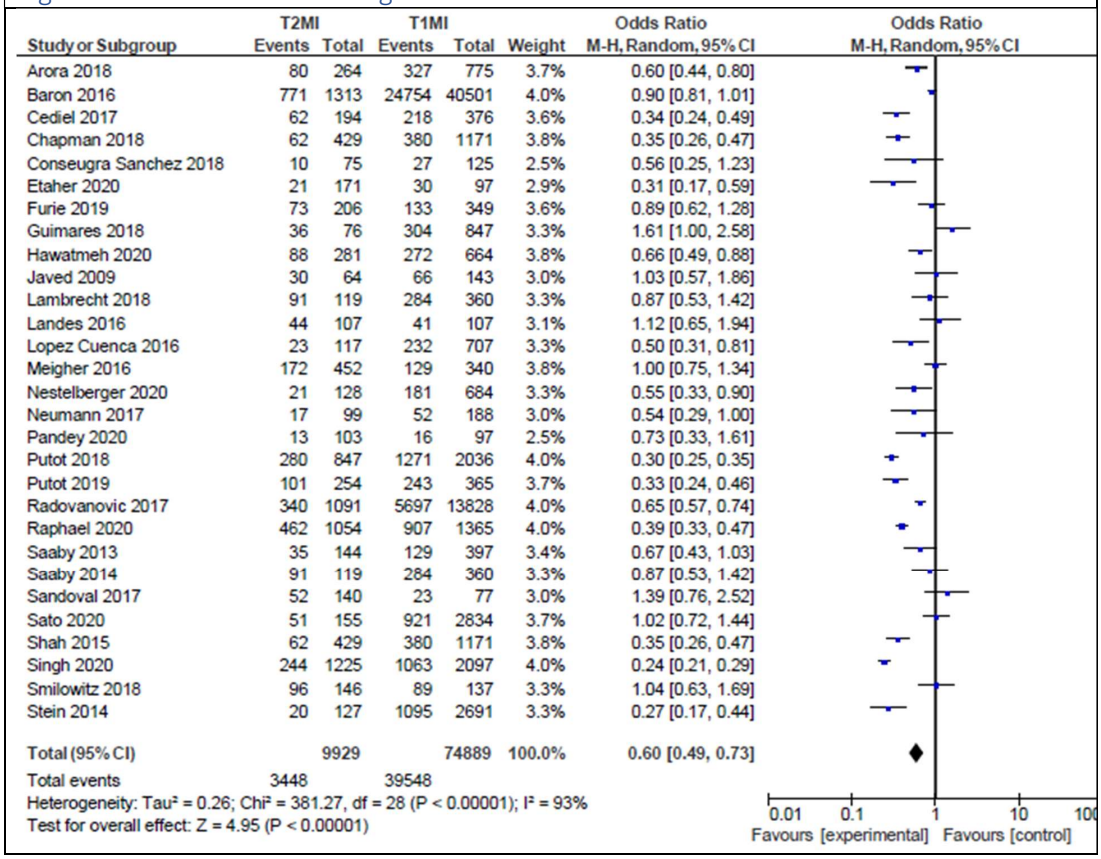


Figure S7. Forest Plot. Obesity Status.

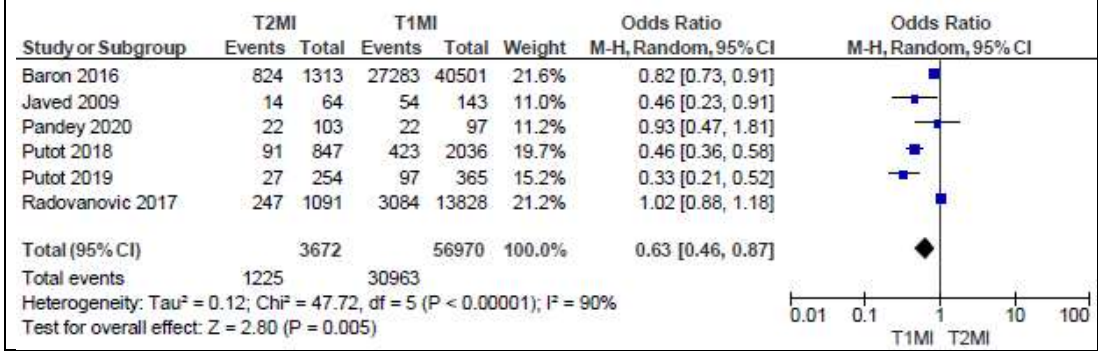


Figure S8. Forest Plot. Presence of Chronic Kidney Disease.

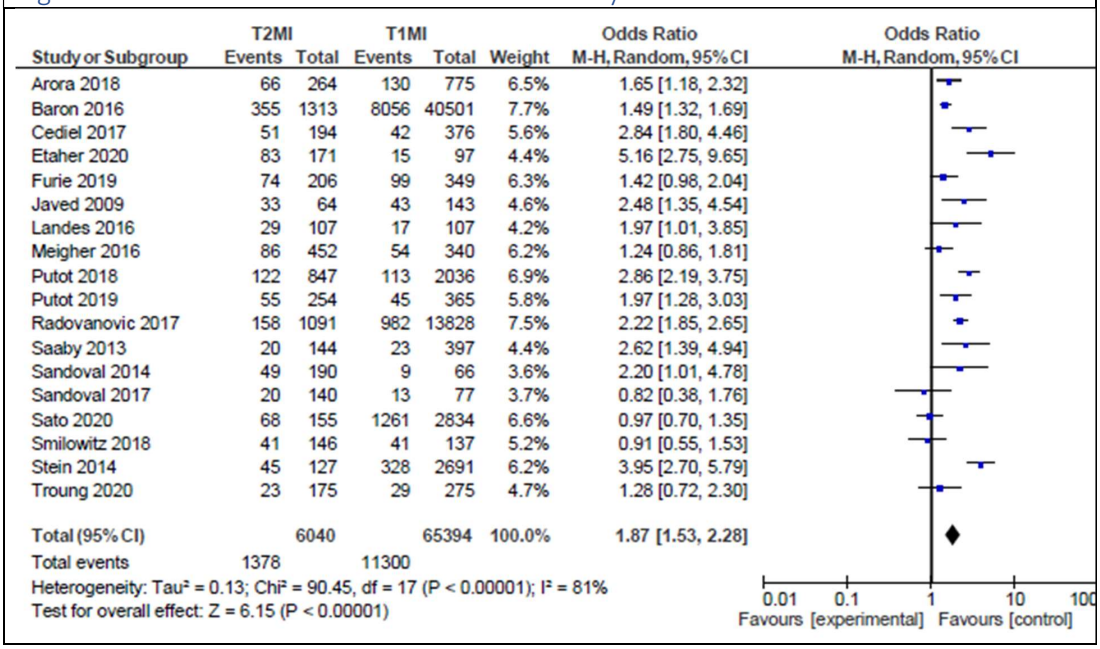


Figure S9. Forest Plot. Presence of Heart Failure.

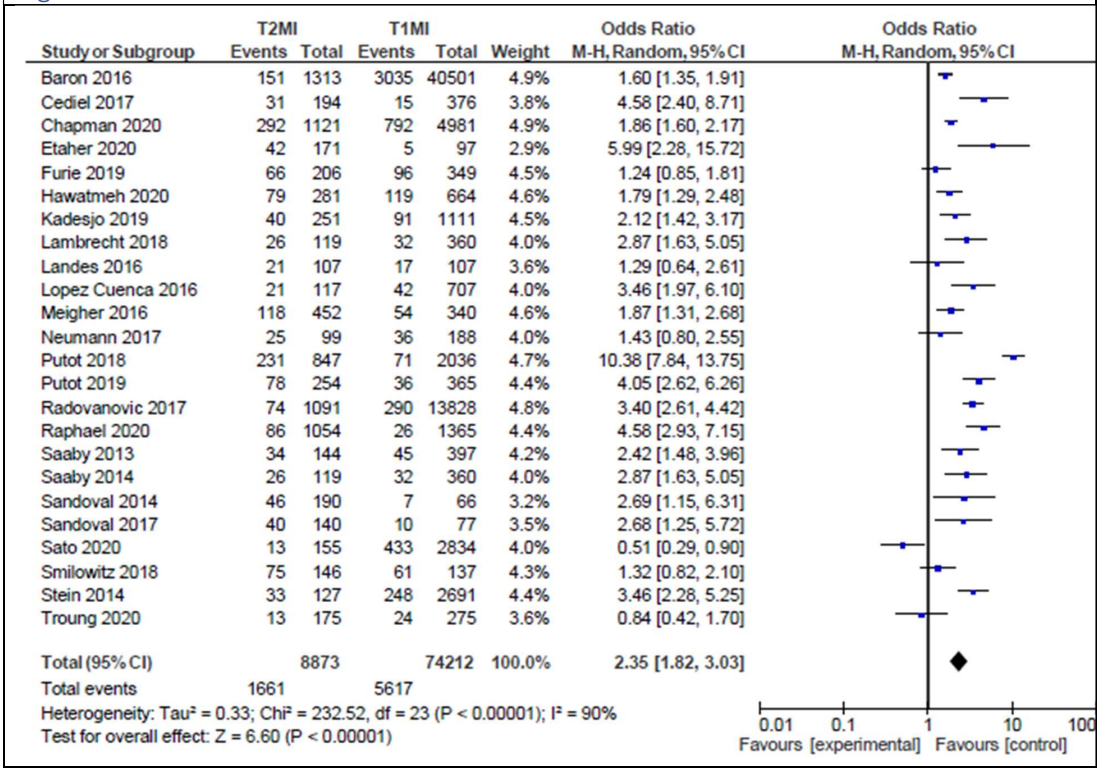


Figure S10. Forest Plot. Presence of Peripheral Vascular Disease.

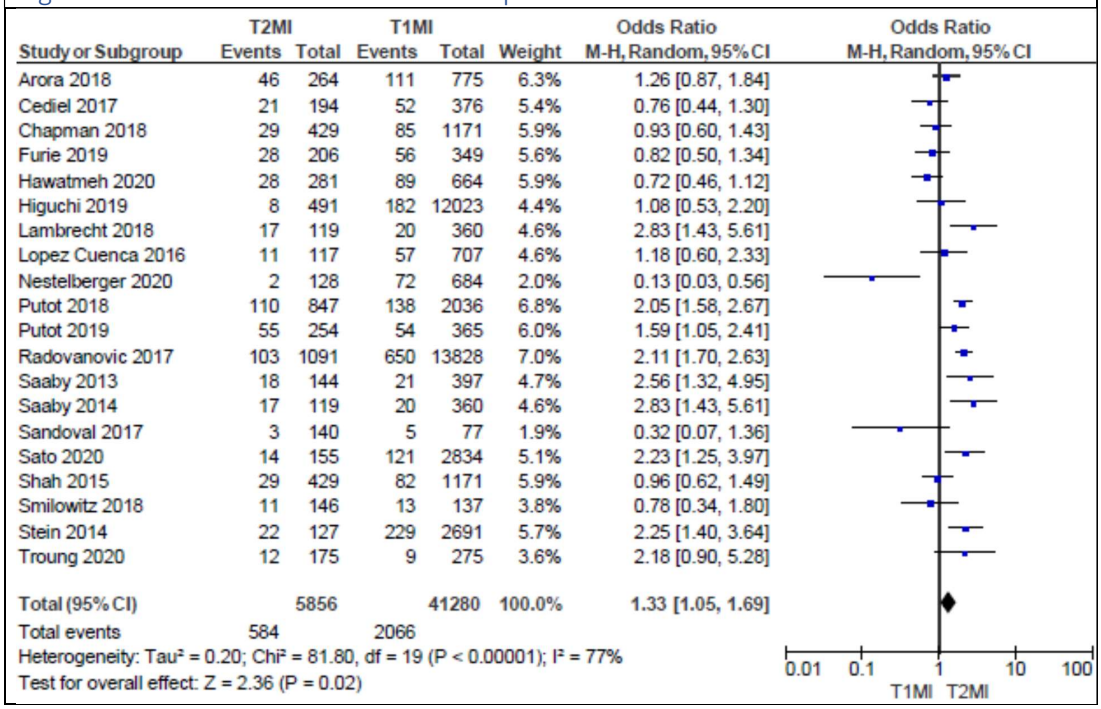


Figure S11. Forest Plot. Presence of Cerebrovascular Disease.

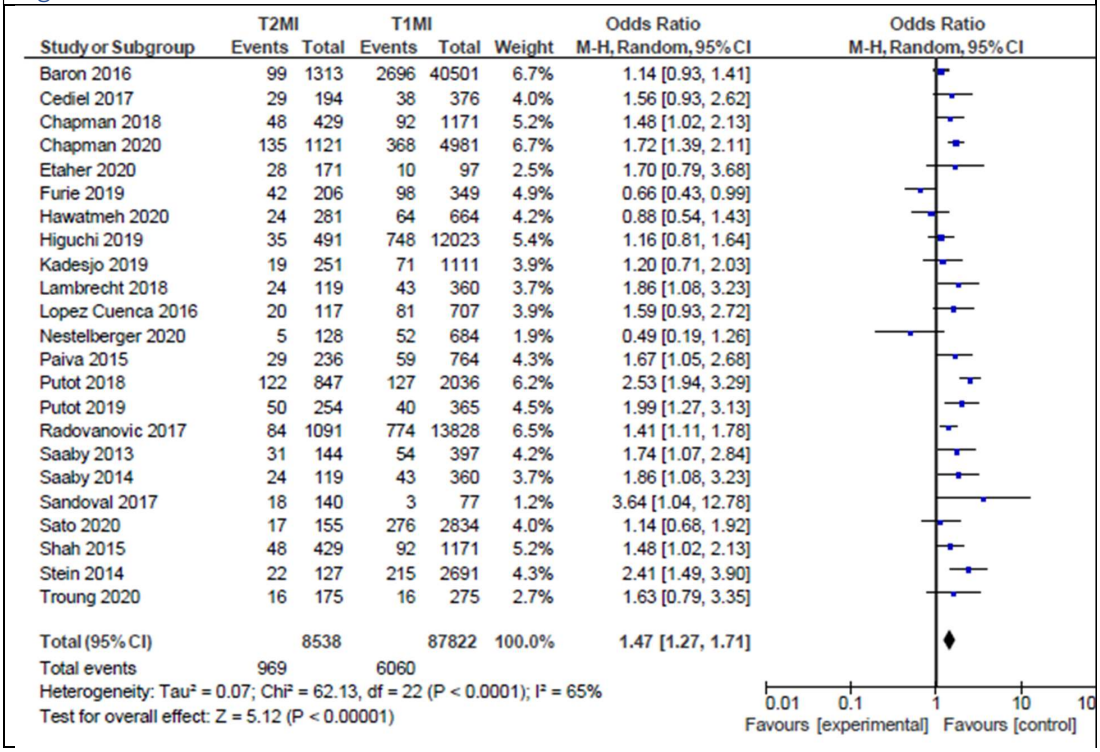


Figure S12. Forest Plot. Presence of Illicit Drug Use.

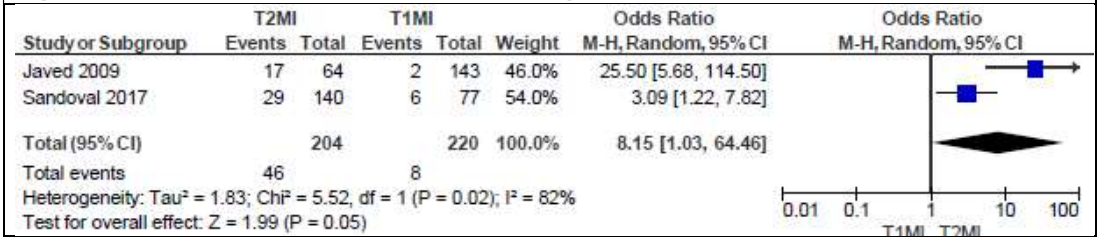


Figure S13. Forest Plot. Presence of Atrial Fibrillation.

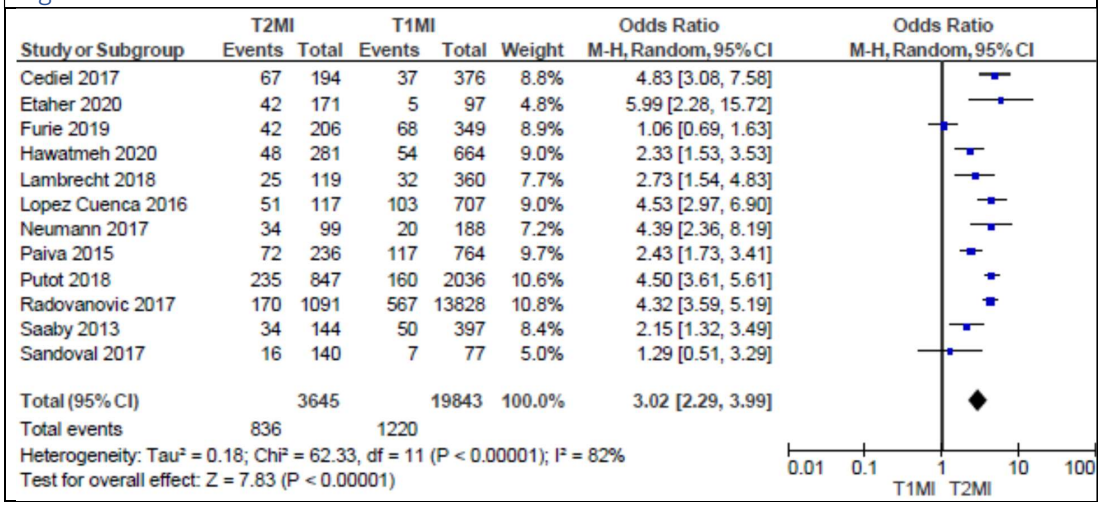


Figure S14. Forest Plot. Chest Pain as Presenting Feature.

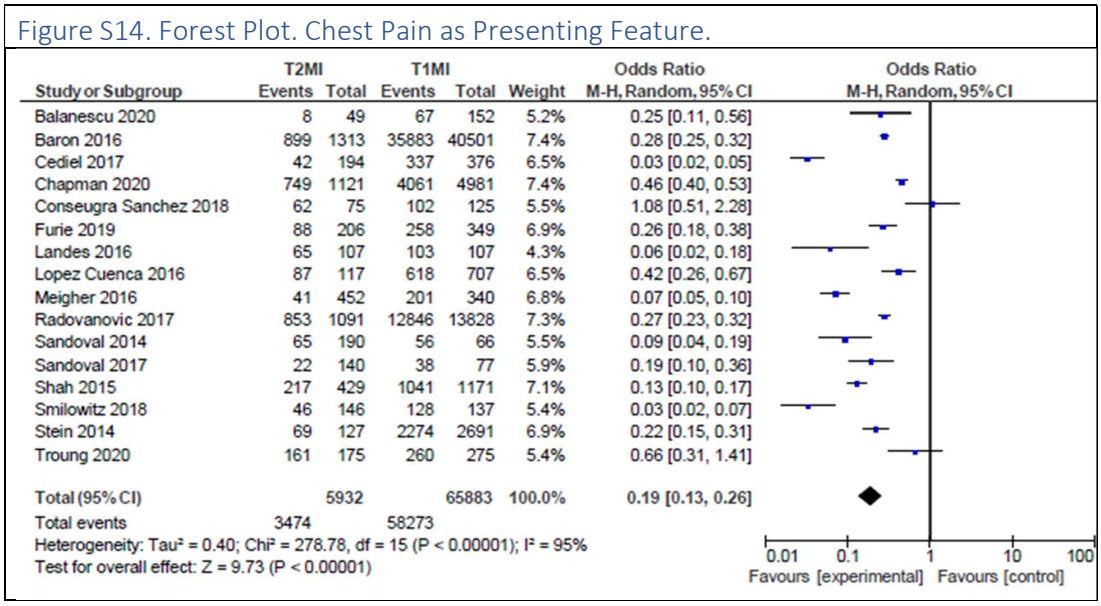


Figure S15. Forest Plot. Dyspnoea as Presenting Feature.

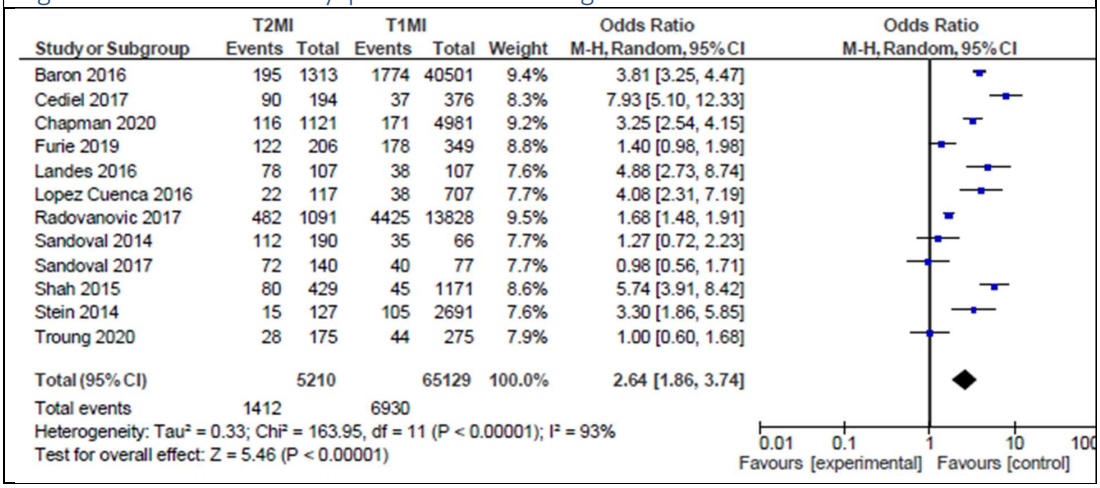


Figure S16. Forest Plot. Arm / Shoulder Discomfort as Presenting Feature.

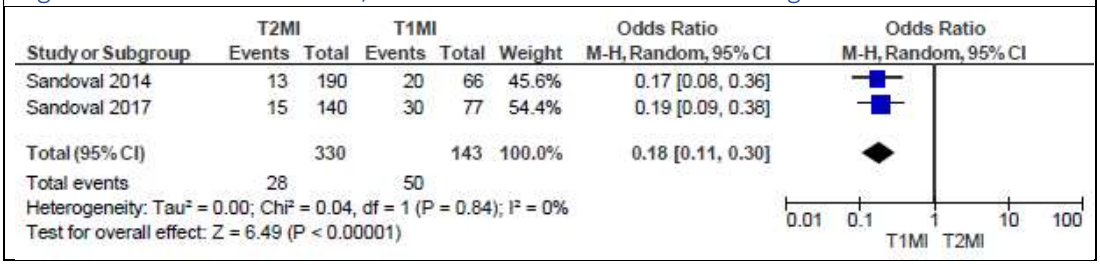


Figure S17. Forest Plot. Nausea / Vomiting as Presenting Feature.

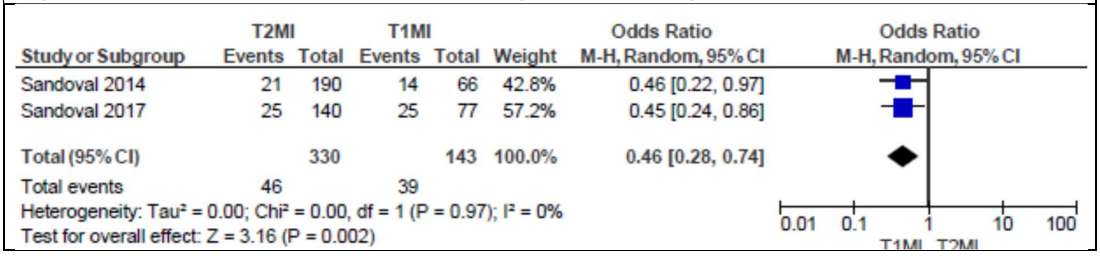


Figure S18. Forest Plot. Non-specific Symptoms as Presenting Features.

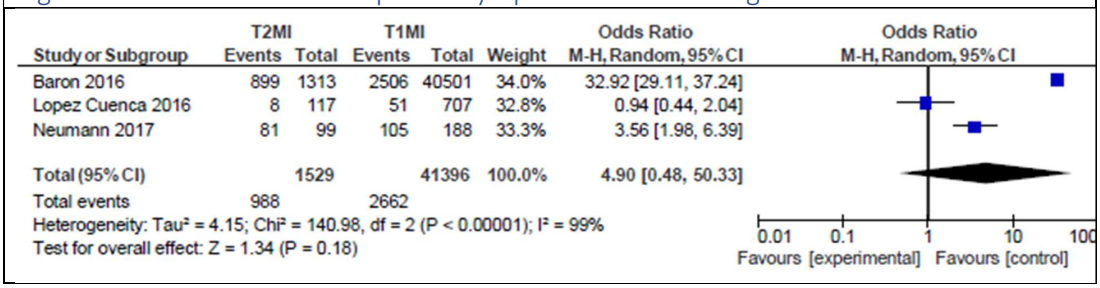


Figure S19. Forest Plot. Collapse / Syncope as Presenting Features.

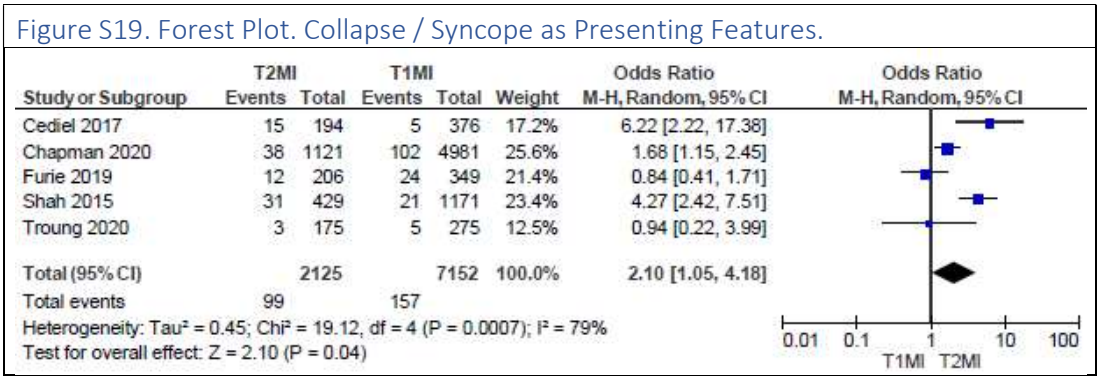


Figure S20. Forest Plot. ST Elevation on ECG.

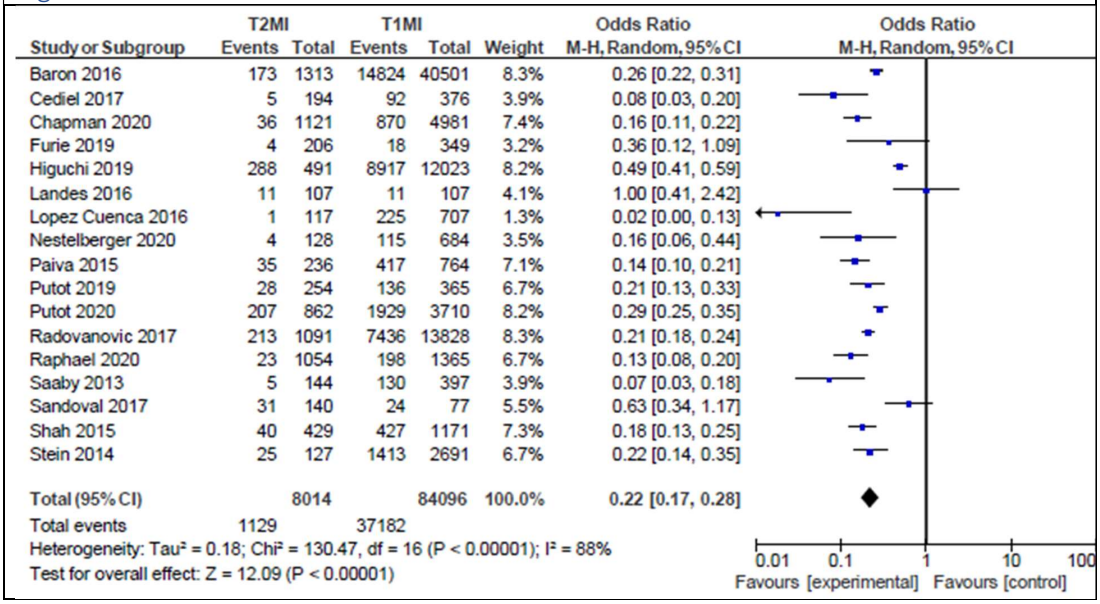


Figure S21. Forest Plot. ST Depression or T Wave Inversion on ECG.

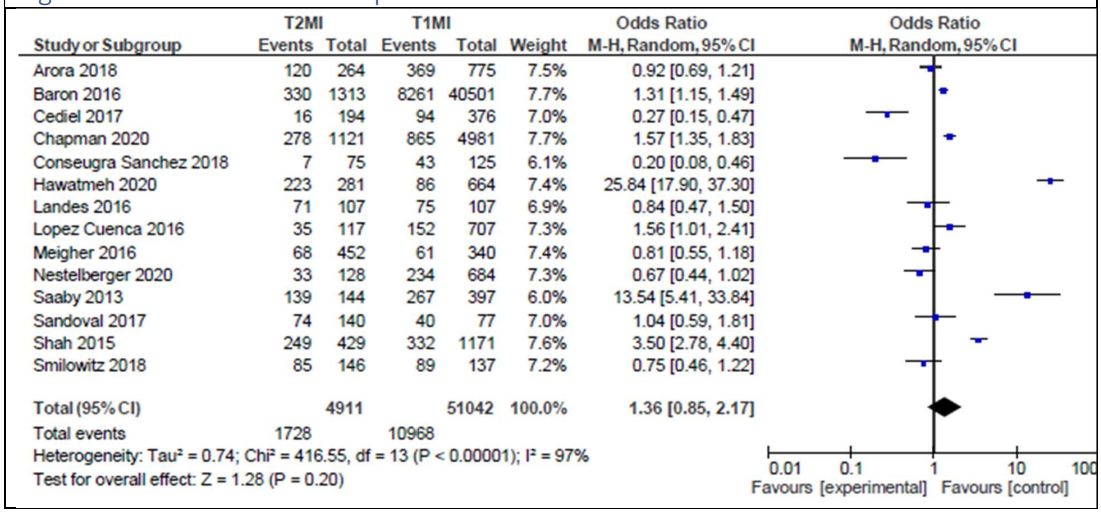


Figure S22. Forest Plot. Q Waves on ECG.

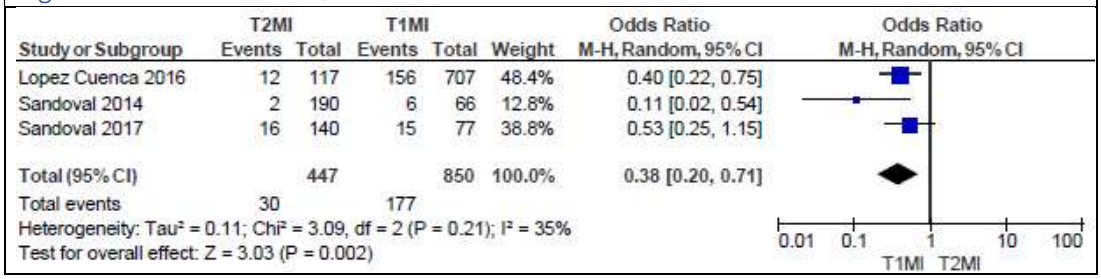


Figure S23. Forest Plot. Non-specific ST Changes on ECG.

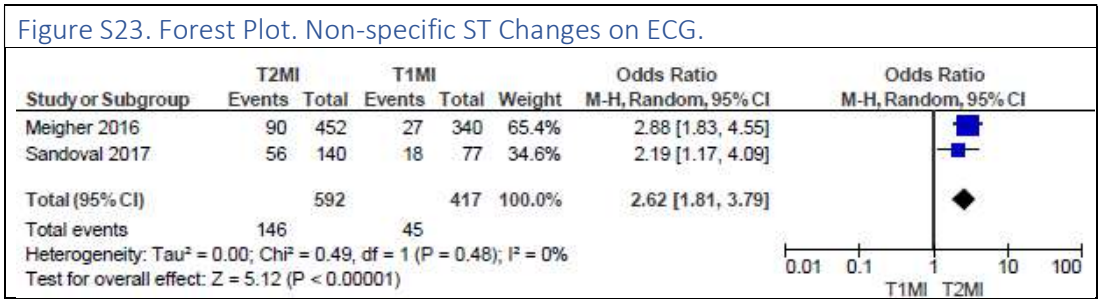


Figure S24. Forest Plot. Left Bundle Branch Block on ECG.

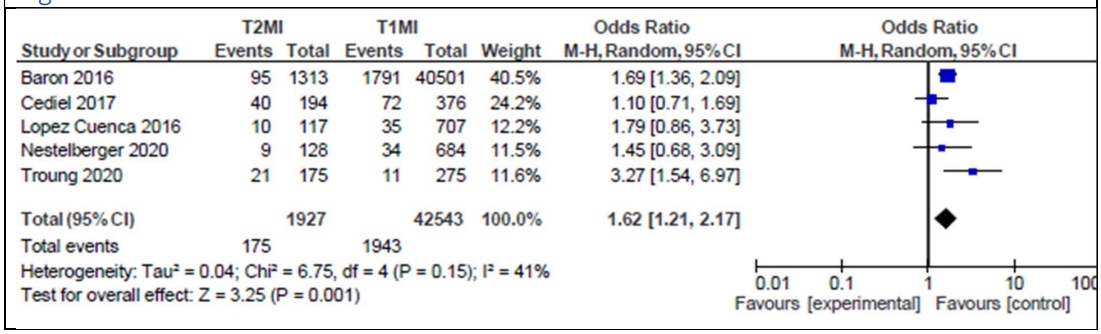


Figure S25. Forest Plot. Atrial Fibrillation on ECG.

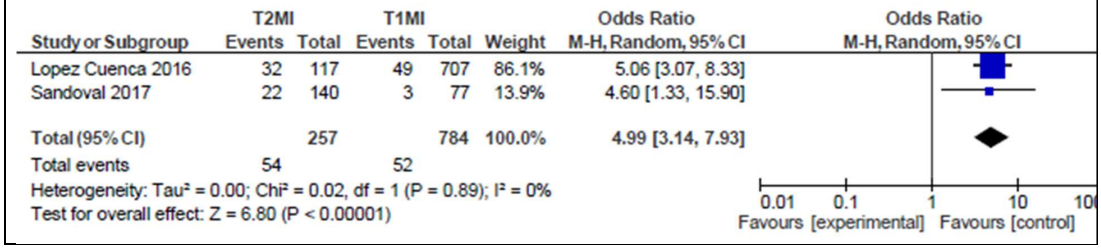


Figure S26. Forest Plot. Coronary Angiogram Performed.

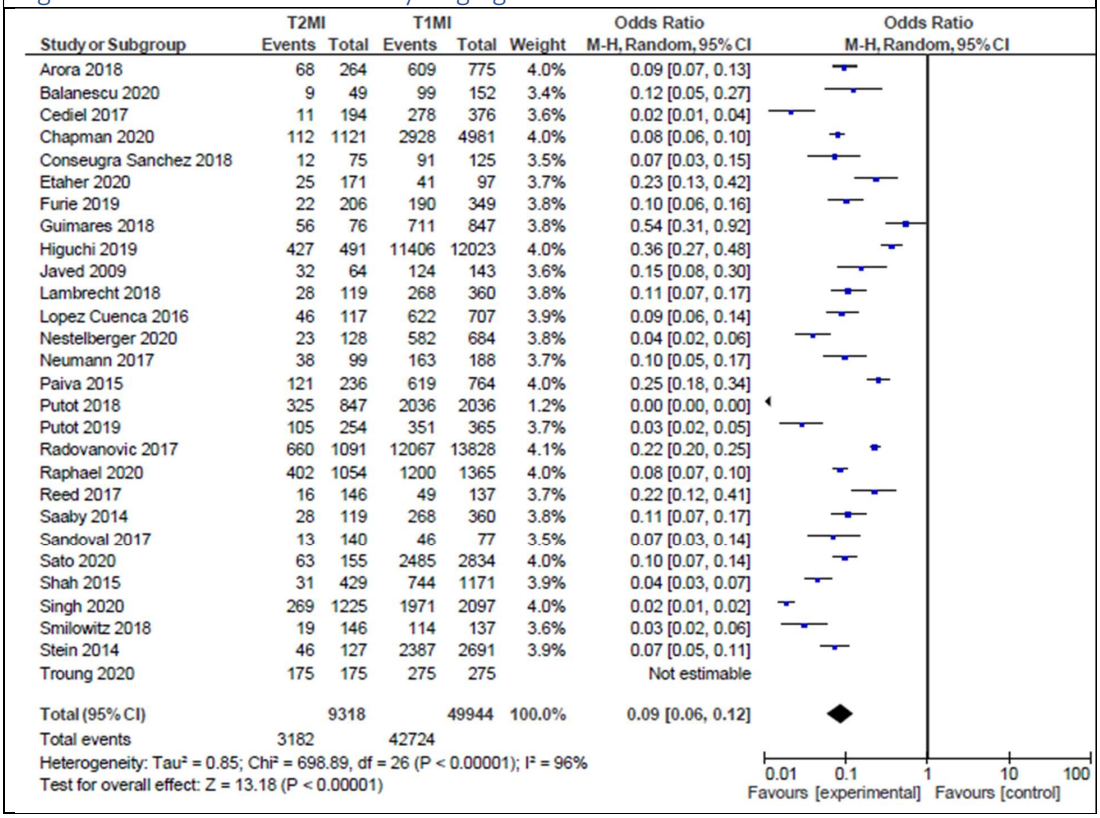


Figure S27. Forest Plot. Obstructive Coronary Artery Disease on Coronary Angiogram.

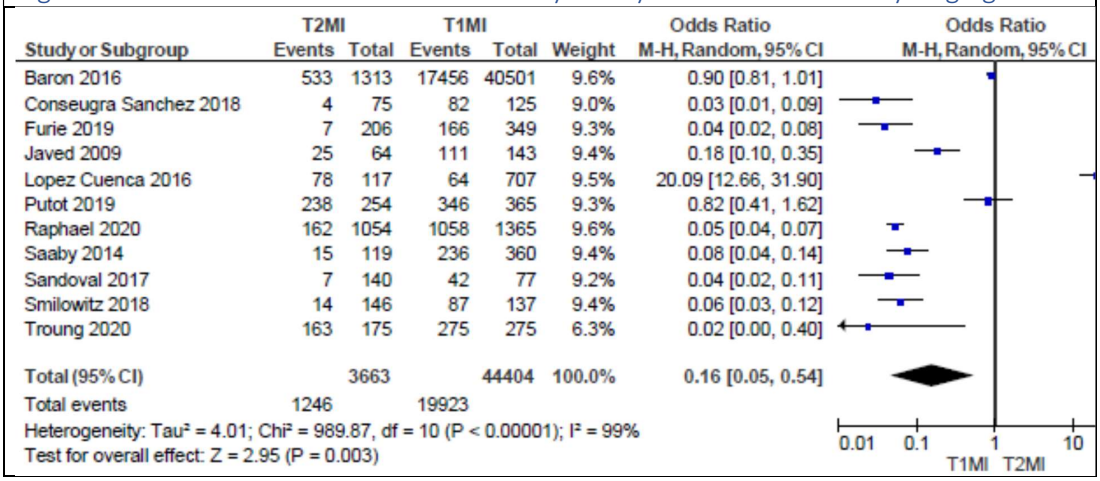


Figure S28. Forest Plot. Multivessel Disease on Coronary Angiogram.

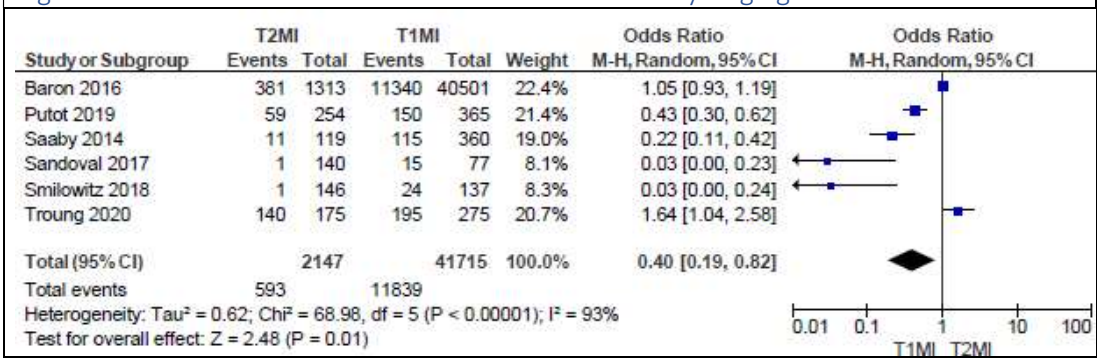


Figure S29. Forest Plot. Echocardiogram Performed.

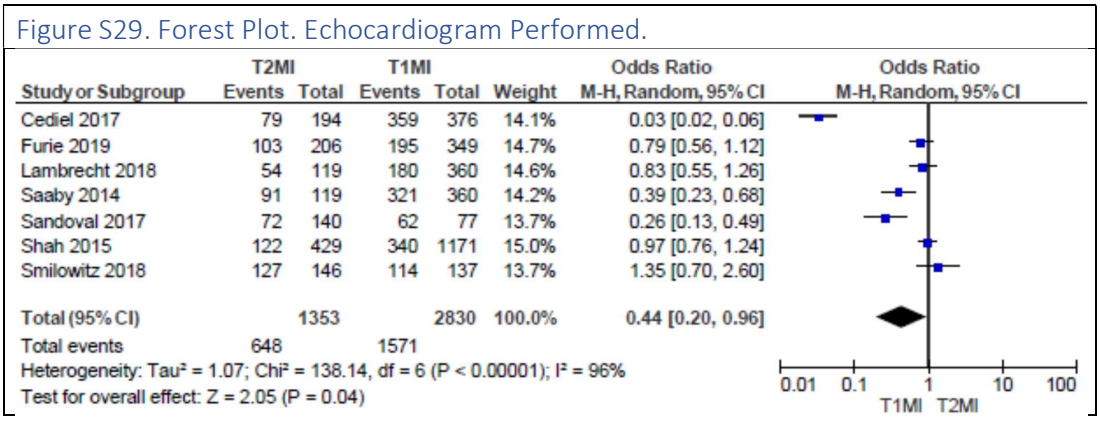


Figure S30. Forest Plot. Regional Wall Motion Abnormalities on Echocardiogram.

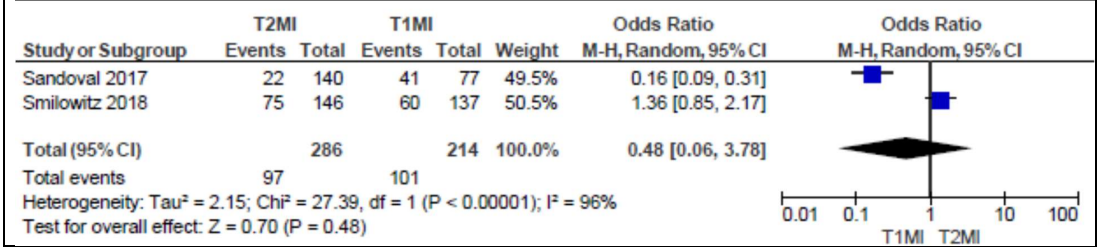


Figure S31. Forest Plot. Beta-Blockers Prescribed.

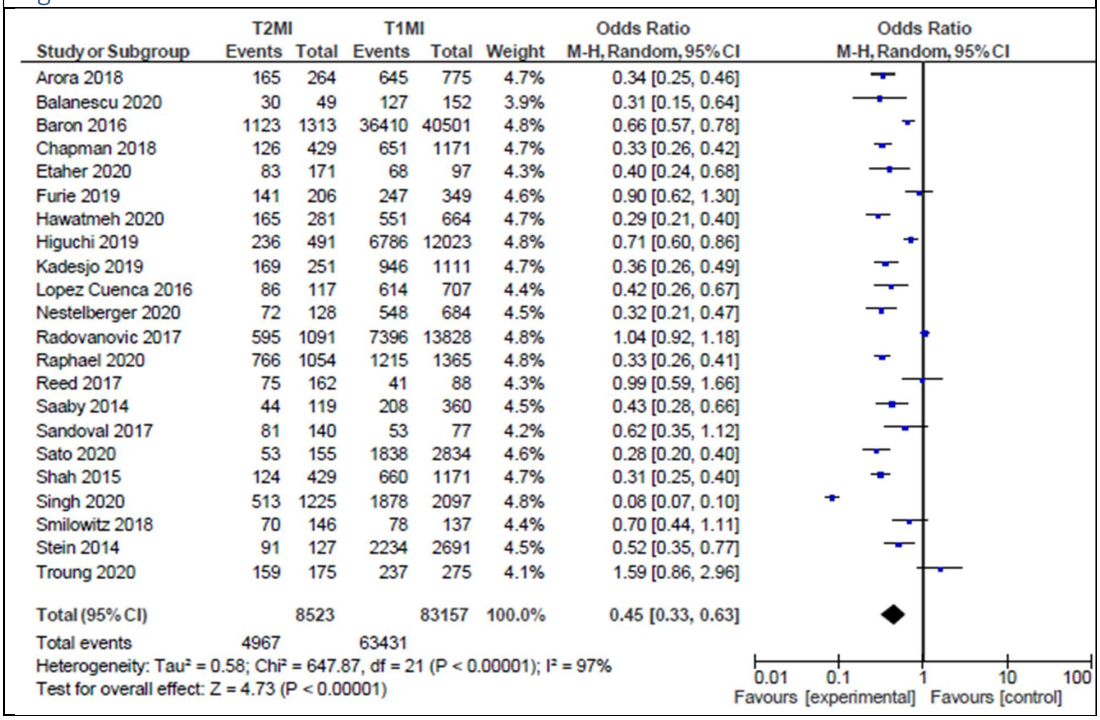


Figure S32. Forest Plot. ACEi/ARB Prescribed.

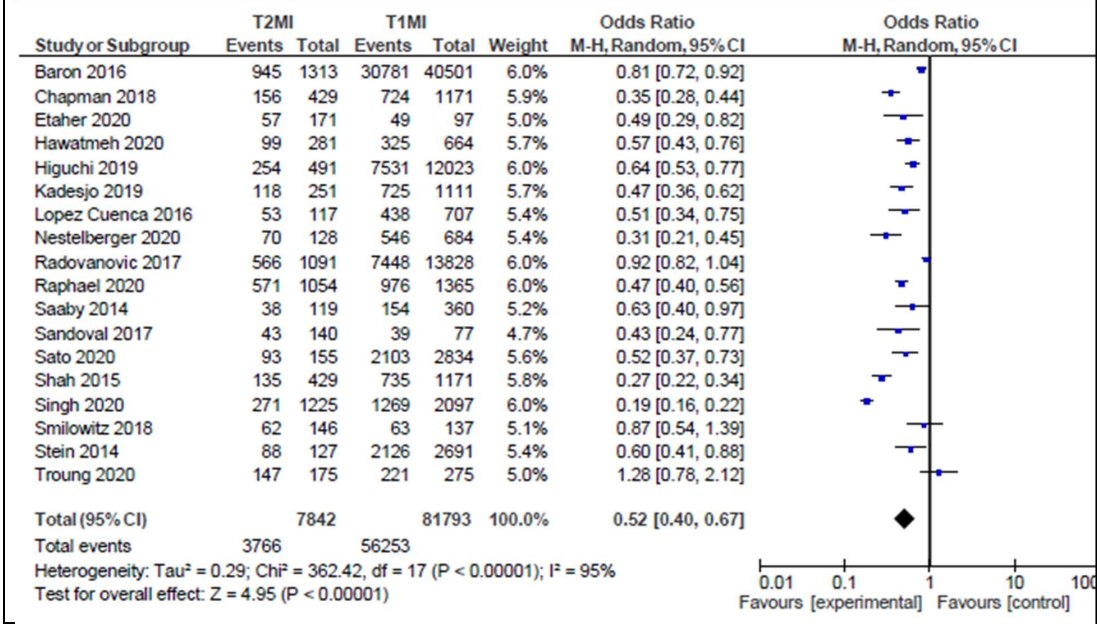


Figure S33. Forest Plot. Antiplatelets Prescribed.

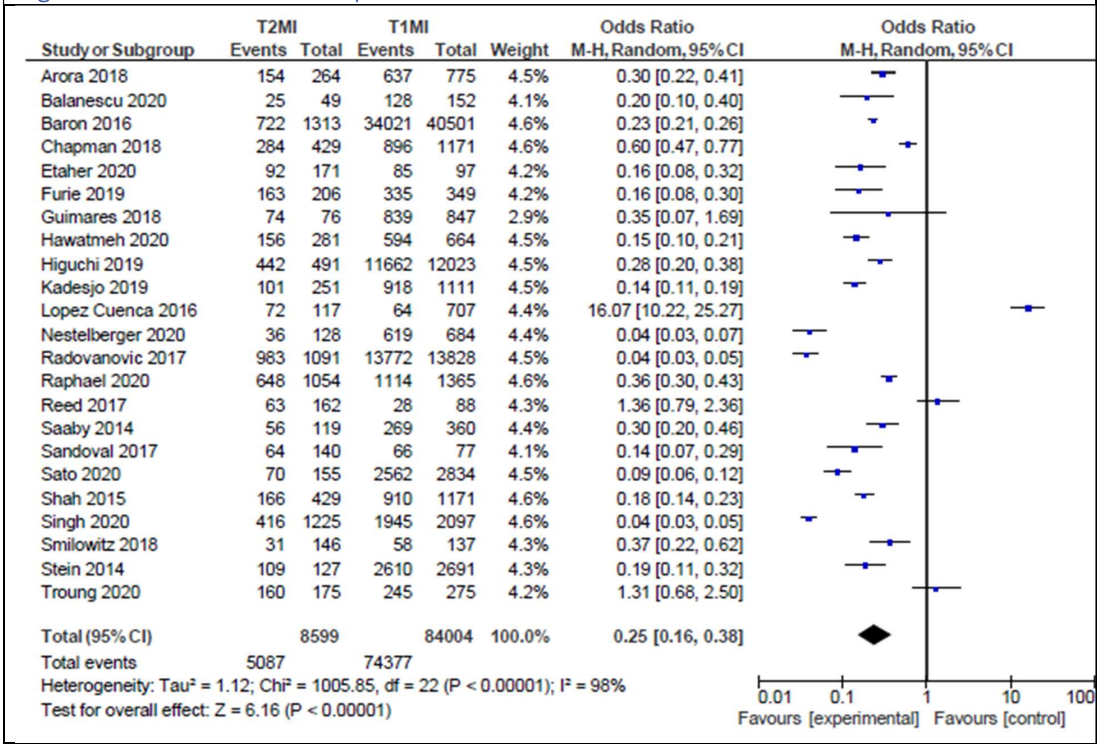


Figure S34. Forest Plot. Anticoagulants Prescribed.

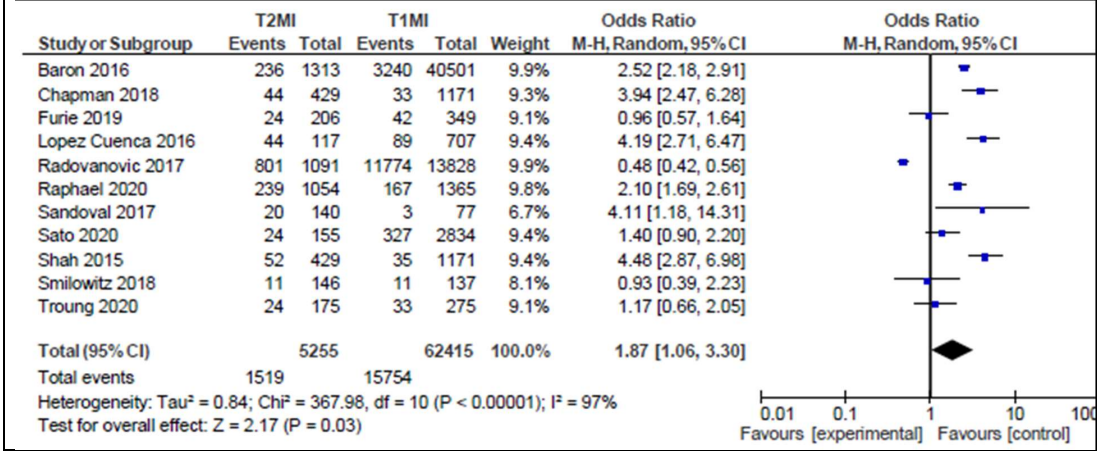


Figure S35. Forest Plot. Antianginal Drugs Prescribed.

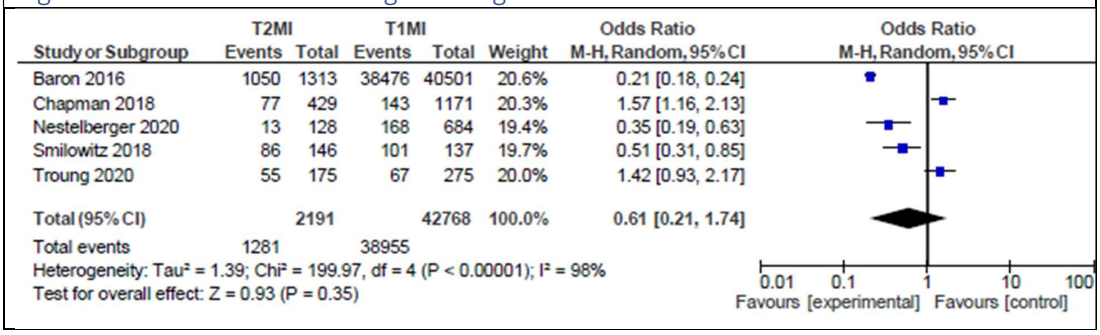


Figure S36. Forest Plot. Diuretics Prescribed.

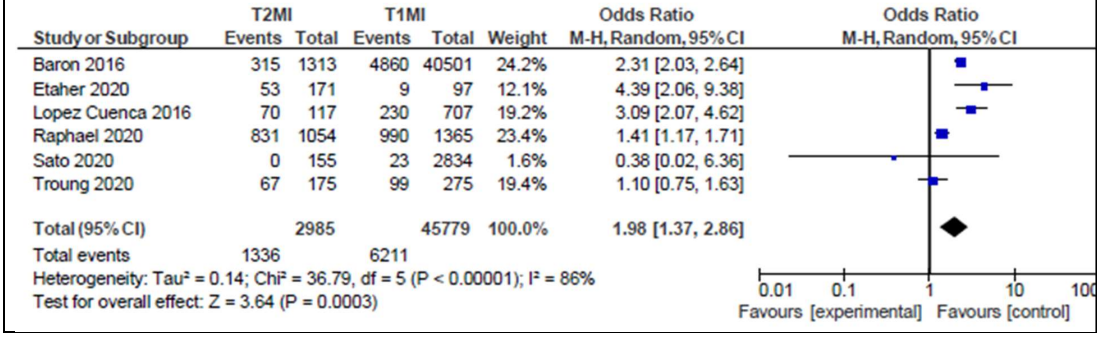


Figure S37. Forest Plot. Statins Prescribed.

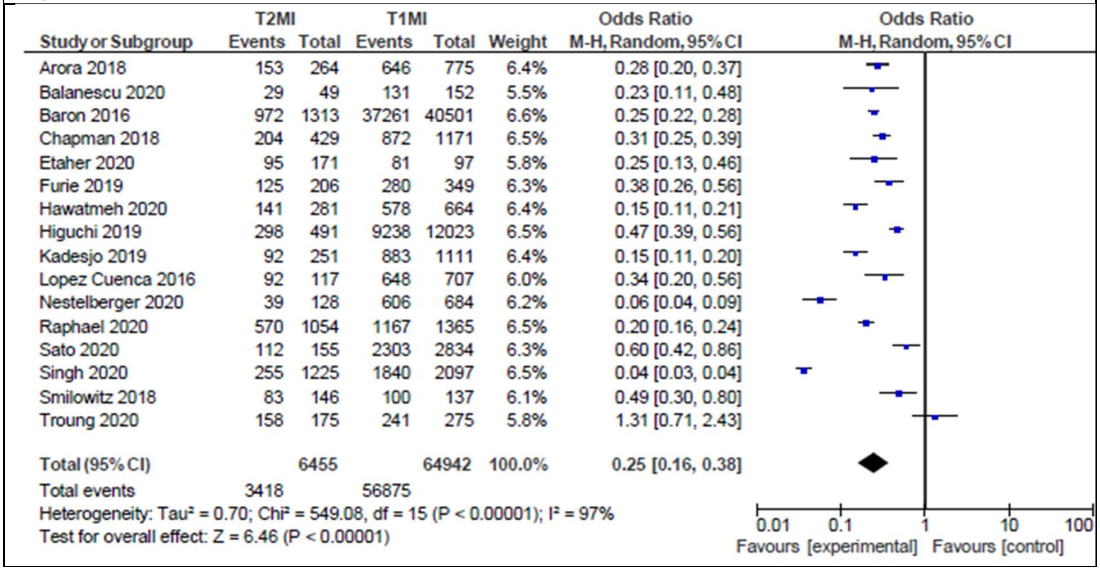


Figure S38. Forest Plot. Percutaneous Coronary Intervention Performed.

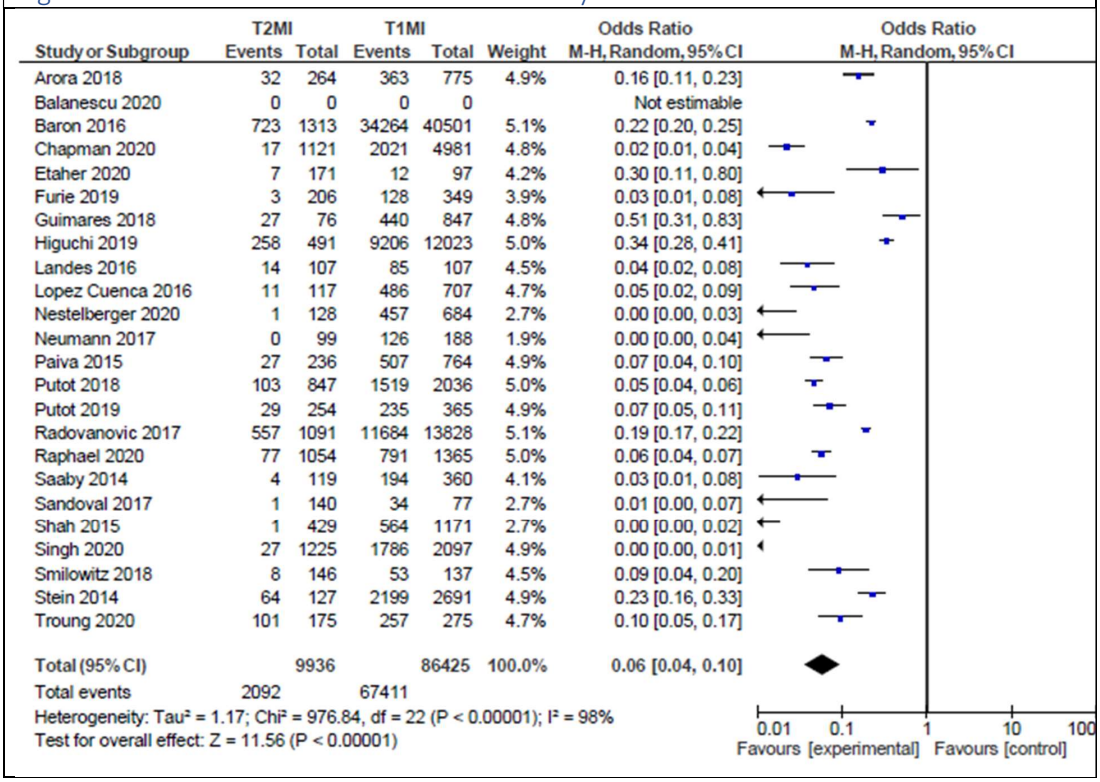


Figure S39. Forest Plot. Coronary Artery Bypass Graft Performed.

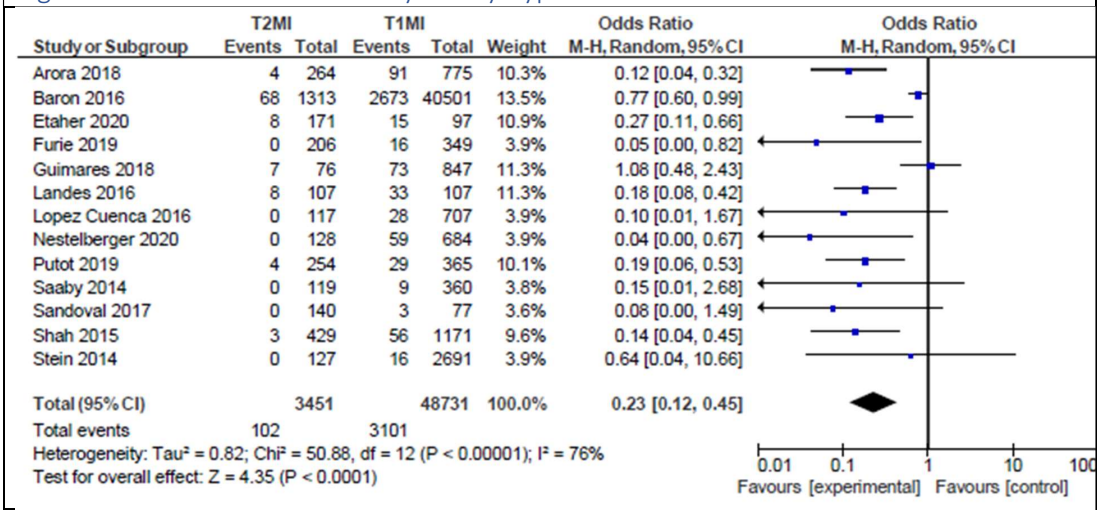


Figure S40. All cause In-hospital mortality. T2MI compared to T1MI.

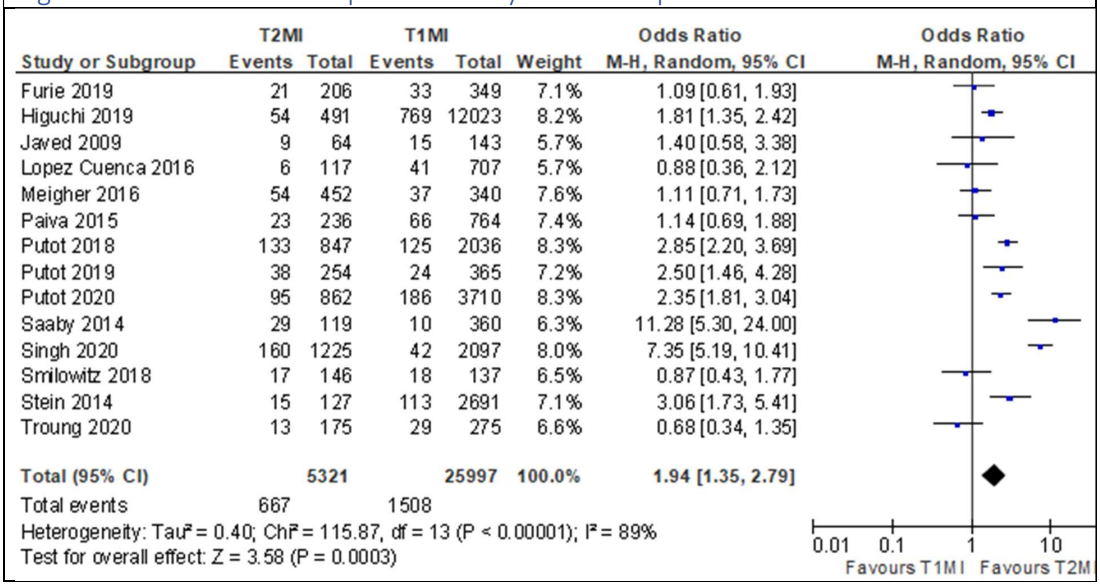


Figure S41. Short-term all-cause mortality. T2MI compared to T1MI.

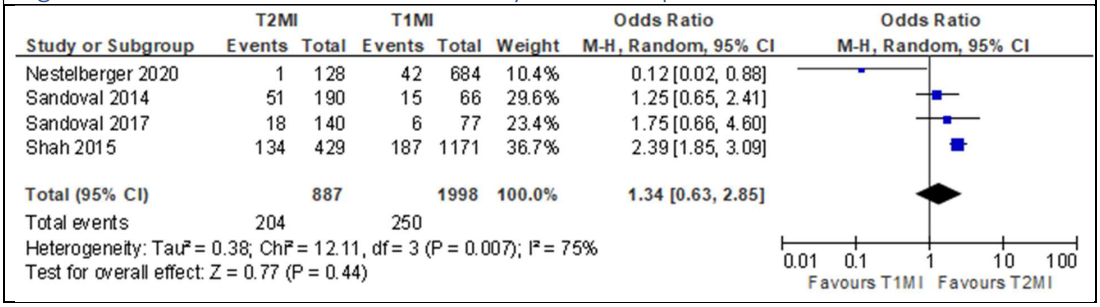


Figure S42. Two-year all-cause mortality. T2MI compared to T1MI.

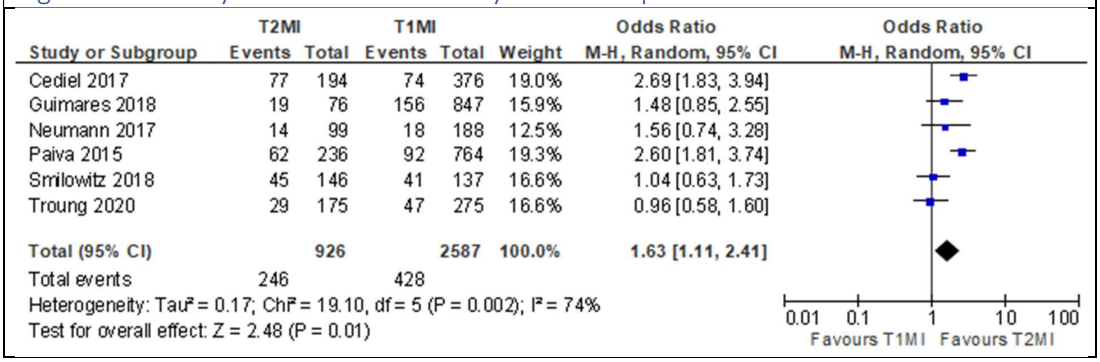


Figure S43. Three-year all-cause mortality. T2MI compared to T1MI.

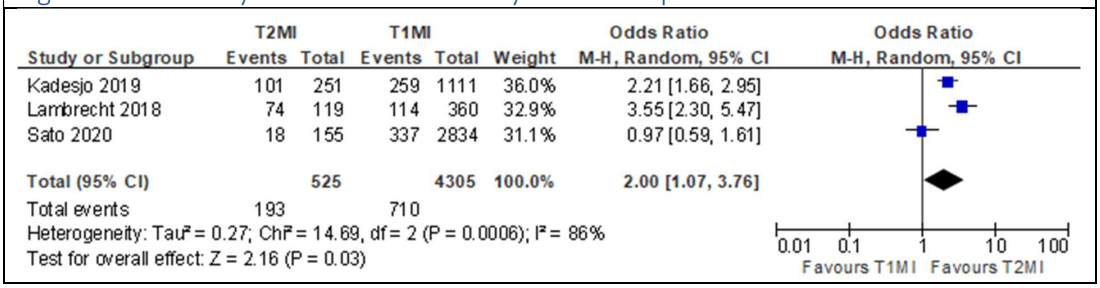


Figure S44. CVS In-hospital mortality. T2MI compared to T1MI.

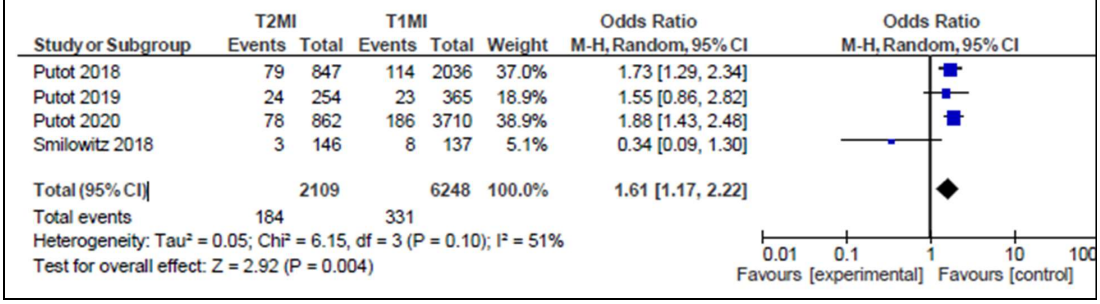


Figure S45. Funnel Plot. All-cause In-hospital mortality. T2MI compared to T1MI.

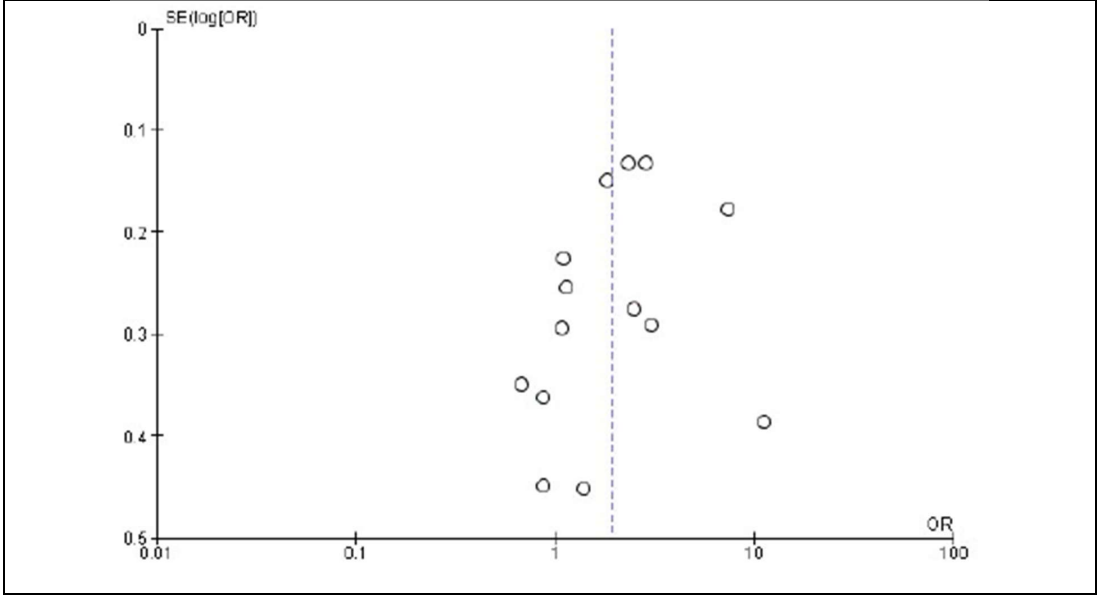
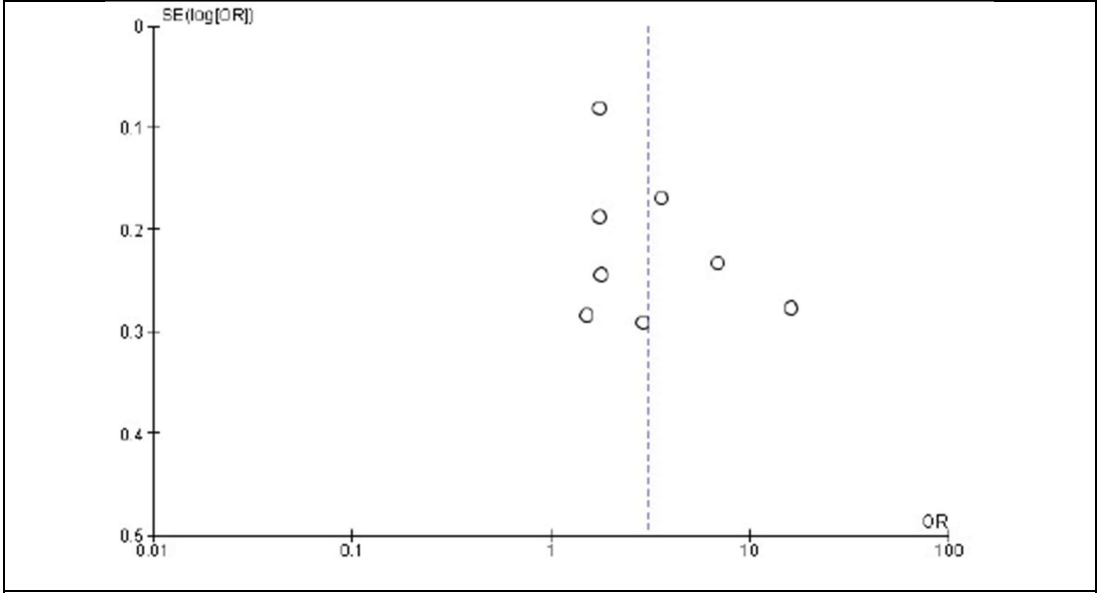


Figure S46. Funnel Plot. One-year All-cause mortality. T2MI compared to T1MI.



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