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Complete List of Authors:	White, Kyle; Princess Alexandra Hospital; University of Queensland Kinarivala, Mansey; Princess Alexandra Hospital, Internal Medicine and Clinical Epidemiology Scott, Ian; University of Queensland, School of Clinical Medicine; Princess Alexandra Hospital, Department of Internal Medicine and Clinical Epidemiology
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Title Page

Manuscript Title

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

Authors

Dr Kyle White
Princess Alexandra Hospital, Brisbane, Australia
University of Queensland, Brisbane, Australia
BSc, MBBS, FRACP, FCICM, MPH

Dr Mansey Kinarivala
Princess Alexandra Hospital, Brisbane, Australia
MBBS, FRACP

A/Prof Ian Scott
Princess Alexandra Hospital, Brisbane, Australia
University of Queensland, Brisbane, Australia
MEd, MHA, MBBS, FRACP

Corresponding Author

Dr Kyle White
Princess Alexandra Hospital
199 Ipswich Road, Wolloongabba, 4102
Ph: +61731762111
Email: kyle.white@health.qld.gov.au

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Abstract

Importance

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

Objective

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

Data Sources

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

Study Selection

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

Data Extraction and Synthesis

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

Main Outcomes and Measures

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

Results

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

Conclusion and Relevance

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

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

Strength and Limitations

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

Introduction

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

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

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

Methods

Study design

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

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

Data collection and synthesis

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

Data on variables reported as, or able to be converted to, raw numbers, were pooled from all studies and subject to comparative meta-analysis using Review Manager (RevMan, Computer program. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For each variable, the weighted odds ratio (OR) comparing T2MI to T1MI, and its 95% confidence interval (CI), was calculated using the random effects method in anticipation of study heterogeneity of at least moderate degree (I^2 statistic of heterogeneity >50%) (10). In addition to the weighted OR, we also report the crude, unweighted total event rates for each variable subject to meta-analysis in order to provide a more clinically meaningful estimate of the prevalence of these events in each patient group in view of the large sample sizes. Studies reporting mean or median values only are also reproduced as reported in the original study.

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

Patient and Public Involvement

No patient involved.

Results

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

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

Risk of bias assessment

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

Participant characteristics

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

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

Precipitating factors

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

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

Presenting clinical features

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

Investigations

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

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

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

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

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

Management

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

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

Prognosis

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

Discussion

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

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

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

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

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

Coronary angiography and revascularisation were both performed much less frequently in T2MI than in T1MI patients. Treating physicians may perceive invasive strategies as being contraindicated or potentially harmful in the presence of various co-morbidities more commonly seen in T2MI and which are associated with competing mortality risk. In our pooled data, only 1 in 3 T2MI patients who underwent angiography demonstrated obstructive coronary artery disease, although this figure may be an underestimate due to selection bias whereby younger, less multi-morbid patients preferentially underwent angiography. In contrast, in the CASABLANCA cohort study where all consecutive patients with incident T2MI underwent angiography, 47.7% demonstrated ≥70% stenosis in at least 2 major coronary arteries (55). These conflicting findings question whether patients presenting with T2MI would benefit from routine use of invasive strategies that define coronary anatomy and, if plaque rupture or critical stenoses are seen, prompt revascularisation, with resultant improvement in patient outcomes. In one study (19), angiography unmasked acute plaque rupture in 29% of patients classified as T2MI. In another study, among 11.4% of 236 patients with T2MI who underwent revascularisation, the odds of all-cause death were reduced by 67% compared to the remaining 88.6% who were not revascularized (24). In contrast, in a third more rigorous study comparing T2MI versus T1MI patients following PCI within 24 hours of symptom onset, and adjusting results using multivariate logistic regression analysis and inverted probability weighting,(15) in-hospital mortality was lower in patients with T1MI and receiving PCI (OR 0.47; 95% CI 0.40–0.55; $p < 0.001$), but not in those with T2MI receiving PCI (OR 1.09; 95% CI 0.62–1.94; $p = 0.763$). However, all these studies are observational, so completion of randomised trials, such as the Appropriateness of Coronary investigation in myocardial injury and Type 2 myocardial infarction (ACT-2) trial which is currently in recruitment (54), will hopefully provide a more definitive answer.

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

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

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

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

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

Conclusion

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

Tables

Table 1. Pre-existing medical conditions in patients with T2MI versus T1MI.

Pre-existing medical condition	**T2MI**			**T1MI**			**Odds ratio* (95% CI)**
	Number of patients with the specified condition	Total number of patients	%	Number of patients with the specified condition	Total number of patients	%	
CAD	3915	11706	33.4%	27538	110213	25.0%	1.13 [0.96, 1.32]
Type 2 DM	3420	13560	25.2%	27169	110833	24.5%	0.98 [0.86, 1.10]
HTN	8296	12424	66.8%	64648	105505	61.3%	1.22 [1.05, 1.43]
Dyslipidaemia	4626	10652	43.4%	40099	87366	45.9%	0.74 [0.58, 0.94]
Smoker	4213	11332	37.2%	49796	92377	53.9%	0.61 [0.50, 0.74]
Obesity	1225	3672	33.4%	30963	56970	54.3%	0.63 [0.46, 0.87]
Renal failure	2002	7443	26.9%	15969	82882	19.3%	1.89 [1.59, 2.25]
Heart failure	1949	10276	19.0%	7471	91700	8.1%	2.34 [1.87, 2.93]
PVD	584	5856	10.0%	2066	41280	5.0%	1.33 [1.05, 1.69]
CVD	1164	9941	11.7%	7669	105310	7.3%	1.48 [1.30, 1.69]
Atrial fibrillation	836	3645	22.9%	1220	19843	6.1%	3.02 [2.29, 3.99]
COPD	800	5018	15.9%	823	48375	1.7%	1.94 [1.22, 3.08]
Illicit drug Use	46	204	22.5%	8	220	3.6%	8.15 [1.03, 64.46]

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

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

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

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

*Comparing T2MI with T1MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis
Abbreviations: ACEI- Angiotensin converting enzyme inhibitors, ARB- Angiotensin receptor blockers; CI=confidence interval; T2MI=type 2 myocardial infarction; T1MI=type 1 myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft

Table 3. Outcomes in patients with T2MI versus T1MI.

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

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

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

Contribution Statement

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

Competing Interests

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

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Data Sharing Statement

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

Ethic Approval Statement

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

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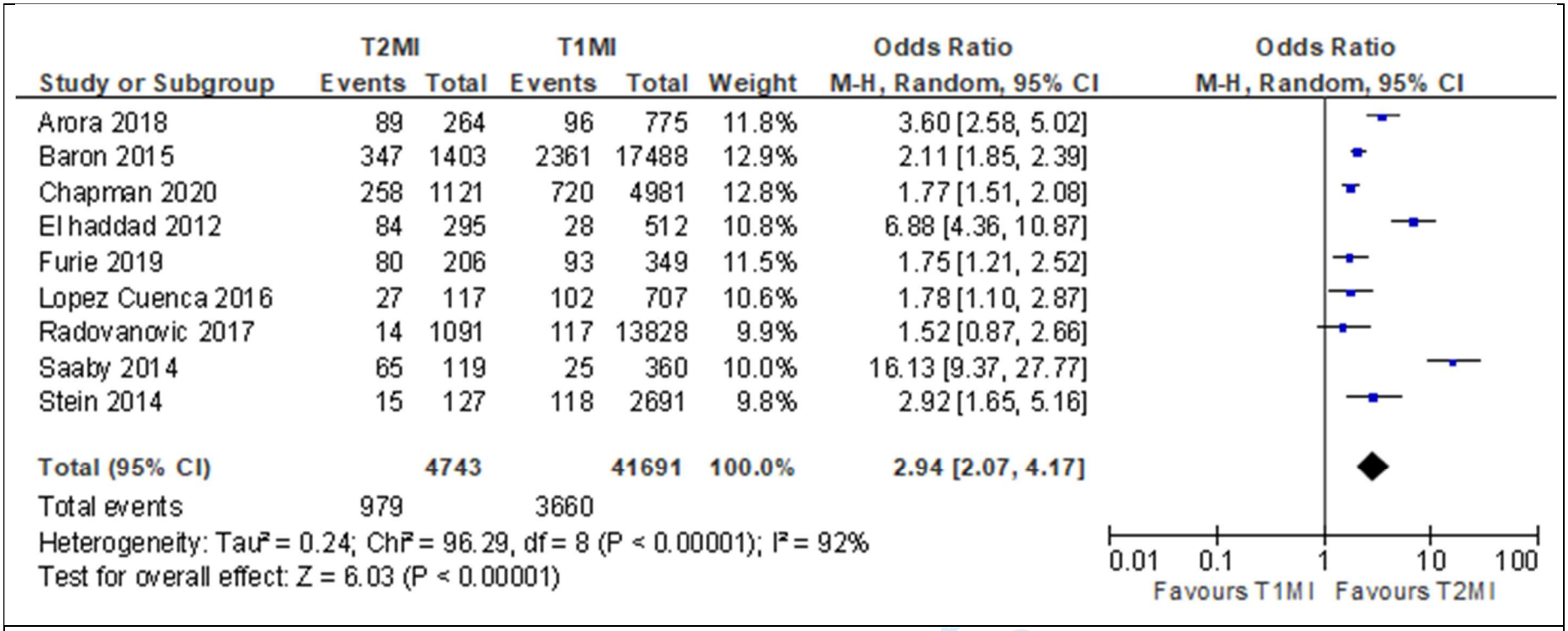


Figure 1. Forest plot of the result of meta-analysis of the risk one year mortality of T2MI patients compared to T1MI patients.

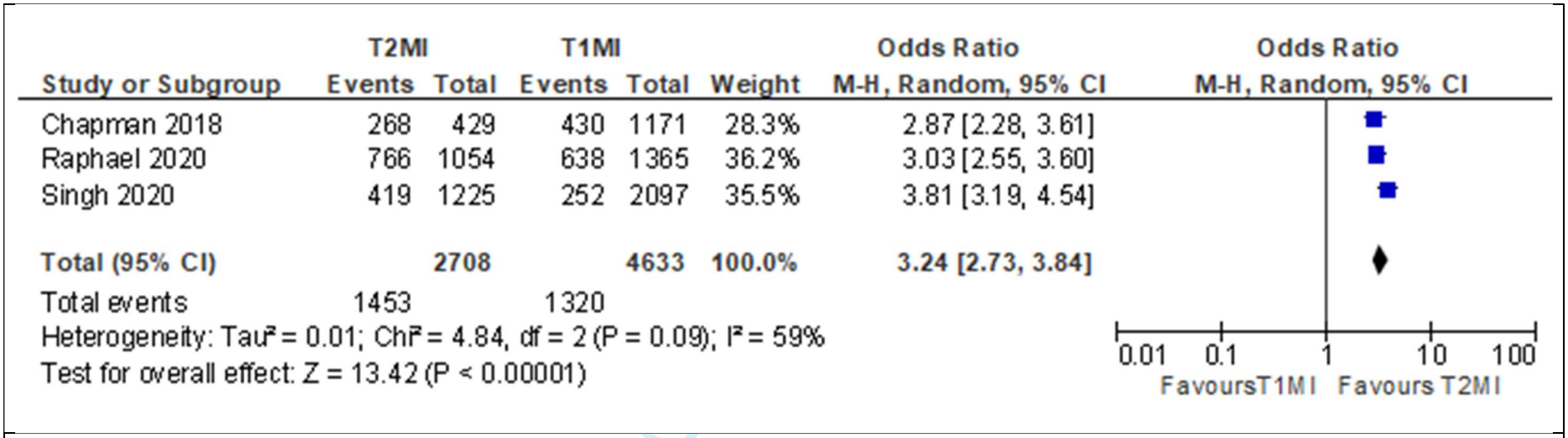


Figure 2. Forest plot of the result of meta-analysis of the risk long-term mortality of T2MI patients compared to T1MI patients.

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

Table S1. MEDLINE search strategy.
(type 2 adj3 myocard*) OR (type-2 adj3 myocard*) OR (type II adj3 myocard*) OR (type-II adj3 myocard*) OR (type 2 adj3 MI) OR (type-2 adj3 MI) OR T2MI OR (supply demand adj3 myocard*)

Table S2. EMBASE search strategy.
('type 2' NEXT/3 myocard*) OR ('type-2' NEXT/3 myocard*) OR ('type ii' NEXT/3 myocard*) OR ('type-ii' NEXT/3 myocard*) OR ('type 2' NEXT/3 mi) OR ('type-2' NEXT/3 mi) OR ('t2mi') OR ('supply demand' NEXT/3 myocard*)

Table S4. Study characteristics.

Author, Year	Patients		Design	Definition of MI	Variables					
	T1MI	T2MI			Pre-existing conditions	Symptoms	Investigations	Troponin Values	Management	Prognosis
Arora, 2018 (1)	775	264	Retrospective	2012	X		X	X	X	X
Balanescu, 2020 (2)	152	49	Retrospective	2018		X	X		X	
Baron, 2015 (3)	17488	1403	Prospective	2007	X	X	X	X	X	X
Baron, 2016 (4)	40501	1313	Prospective	2007	X	X	X	X	X	
Bonaca, 2012 (5)	359	42	Prospective	2007						
Cediel, 2017 (6)	376	194	Retrospective	2012	X	X	X	X		X
Chapman, 2018 (7)	1171	429	Prospective	2012	X		X	X	X	X
Chapman, 2020 (8)	4981	1121	Prospective	2018	X	X	X	X		X
Consuegra-Sanchaz, 2018 (9)	125	75	Retrospective	2012	X	X	X	X		
El-Haddad, 2012 (10)	512	295	Retrospective	2012						X
Etaher, 2020 (11)	97	121	Prospective	2018	X		X		X	
Furie, 2019 (12)	349	206	Retrospective	2012	X	X	X	X	X	X
Guimaraes, 2018 (13)	847	76	Retrospective	2012	X		X		X	X

Hawatmeh, 2020 (14)	664	281	Retrospective	2012	X		X	X	X	
Higuchi, 2019 (15)	12023	491	Retrospective	2012	X		X		X	X
Javed, 2009 (16)	143	64	Retrospective	2007	X		X	X		X
Kadesjo, 2019 (17)	1111	251	Retrospective	2018	X				X	X
Lambrecht, 2018 (18)	360	119	Prospective	2007	X		X	X		X
Landes, 2016 (19)	107	107	Retrospective	2012	X	X	X	X		
Lopez-Cuenca, 2016 (20)	707	117	Retrospective	2012	X	X	X	X	X	X
Meigher, 2016 (21)	340	452	Retrospective	2012	X	X	X	X		X
Nestelberger, 2017 (22)	684	128	Prospective	2012	X		X		X	X
Neumann, 2017 (23)	188	99	Prospective	2012	X		X	X		X
Paiva, 2015 (24)	764	236	Retrospective	2012	X		X	X		X
Pandey, 2020 (25)	97	103	Prospective	2018	X					
Putot, 2018 (26)	2036	847	Prospective	2012	X		X	X		X
Putot, 2019 (27)	365	254	Retrospective	2018	X		X	X		X
Putot, 2020 (28)	3710	862	Retrospective	2012	X		X	X		X
Radovanovic, 2017 (29)	13828	1091	Retrospective	2012	X		X		X	X

Raphael, 2020 (30)	1365	1054	Retrospective	2018	X		X	X	X	X
Reed, 2017 (31)	88	162	Retrospective	2012			X	X	X	
Saaby 2013 (32)	397	144	Prospective	2007	X		X	X		
Saaby, 2014 (33)	360	119	Prospective	2007	X		X	X	X	X
Sandoval, 2014 (34)	66	190	Retrospective	2012	X	X	X	X		X
Sandoval, 2017 (35)	77	140	Prospective	2012	X	X	X	X	X	X
Sato, 2020 (36)	2834	155	Prospective	2012	X		X	X	X	X
Shah, 2015 (37)	1171	429	Prospective	2012	X	X	X	X	X	X
Singh, 2020 (38)	2097	1225	Retrospective	2018	X		X	X	X	X
Smilowitz, 2018 (39)	137	146	Prospective	2012	X	X	X	X	X	X
Stein, 2014 (40)	2691	127	Prospective	2007	X	X	X		X	X
Truong, 2020 (41)	275	175	Retrospective	2012	X	X	X		X	X

Table S5. Risk of bias assessment

Author, Year	Selection				Comparability	Outcome			Summary
	Representative of Exposed Cohort	Selection of Non-exposed	Ascertainment of Exposure	Outcome was not present at start	Comparability of Cohorts	Assessment	Follow-up Length	Adequacy of Follow-Up	
Arora, 2018 (1)	x	x	x	x	x	x	x	x	8 (good quality)
Balanescu, 2020 (2)	0	x	x	x	x	x	0	x	6 (fair quality)
Baron, 2015 (3)	x	x	x	x	x	x	x	x	8 (good quality)
Baron, 2016 (4)	x	x	x	x	x	x	x	x	8 (good quality)
Bonaca, 2012 (5)	x	x	x	x	x	x	x	x	8 (good quality)
Cediel, 2017 (6)	x	x	x	x	x	x	x	x	8 (good quality)
Chapman, 2018 (7)	x	x	x	x	x	x	x	x	8 (good quality)
Chapman, 2020 (8)	x	x	x	x	x	x	x	x	8 (good quality)
Consuegra-Sanchaz, 2018 (9)	0	0	x	x	0	x	0	0	3 (poor quality)
El-Haddad, 2012 (10)	x	x	x	x	x	0	0	0	5 (fair quality)
Etaher, 2020 (11)	x	x	x	x	x	x	x	x	8 (good quality)
Furie, 2019 (12)	x	x	x	x	x	x	x	x	8 (good quality)
Guimaraes, 2018 (13)	0	0	x	x	0	x	0	x	4 (fair quality)

Hawatmeh, 2020 (14)	0	0	x	x	0	x	x	0	4 (fair quality)
Higuchi, 2019 (15)	0	0	x	x	x	x	x	x	5 (fair quality)
Javed, 2009 (16)	x	x	x	x	x	x	x	x	8 (good quality)
Kadesjo, 2019 (17)	x	x	x	x	x	x	x	x	8 (good quality)
Lambrecht, 2018 (18)	x	x	x	x	x	x	x	x	8 (good quality)
Landes, 2016 (19)	x	x	x	x	x	x	x	x	8 (good quality)
Lopez-Cuenca, 2016 (20)	x	x	x	x	x	x	x	x	8 (good quality)
Meigher, 2016 (21)	x	x	x	x	x	x	x	x	8 (good quality)
Nestelberger, 2017 (22)	x	x	x	x	x	x	x	x	8 (good quality)
Neumann, 2017 (23)	x	x	x	x	x	x	x	x	8 (good quality)
Paiva, 2015 (24)	x	x	x	x	x	x	x	x	8 (good quality)
Pandey, 2020 (25)	0	0	x	0	x	0	0	0	2 (poor quality)
Putot, 2018 (26)	x	x	x	x	x	x	x	x	8 (good quality)
Putot, 2019 (27)	x	x	x	x	x	0	x	x	7 (good quality)
Putot, 2020 (28)	x	x	x	x	x	x	x	x	8 (good quality)
Radovanovic, 2017 (29)	x	x	x	x	x	x	x	x	8 (good quality)

Raphael, 2020 (30)	x	x	x	x	x	x	x	x	8 (good quality)
Reed, 2017 (31)	x	x	x	x	x	x	x	x	8 (good quality)
Saaby 2013 (32)	x	x	x	x	x	x	x	x	8 (good quality)
Saaby, 2014 (33)	x	x	x	x	x	x	x	x	8 (good quality)
Sandoval, 2014 (34)	x	x	x	x	x	x	x	x	8 (good quality)
Sandoval, 2017 (35)	x	x	x	x	x	x	x	x	8 (good quality)
Sato, 2020 (36)	0	0	0	x	0	0	x	x	2 (poor quality)
Shah, 2015 (37)	x	x	x	x	x	x	x	x	8 (good quality)
Singh, 2020 (38)	0	0	x	x	x	x	x	x	6 (fair quality)
Smilowitz, 2018 (39)	x	x	0	x	x	x	x	x	7 (good quality)
Stein, 2014 (40)	x	x	0	x	x	x	x	x	7 (good quality)
Truong, 2020 (41)	x	x	x	x	x	x	x	x	8 (good quality)

Table S6. Precipitating conditions for T2MI.

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

Table S7. 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	4344	7335	59.2%	73103	83371	87.7%	0.19 [0.15, 0.26]
Dyspnoea	1681	6080	27.6%	8154	82617	9.9%	2.83 [1.96, 4.08]
Arm or shoulder discomfort	28	330	8.5%	50	143	35.0%	0.18 [0.11, 0.30]
Jaw or neck discomfort	6	140	4.3%	12	77	15.6%	0.24 [0.09, 0.68]
Epigastric discomfort	8	140	5.7%	8	77	10.4%	0.52 [0.19, 1.45]
Nausea or vomiting	46	330	13.9%	39	143	27.3%	0.46 [0.28, 0.74]
Fatigue	5	140	3.6%	5	77	6.5%	0.53 [0.15, 1.90]
Diaphoresis	16	140	11.4%	16	77	20.8%	0.49 [0.23, 1.05]
Other nonspecific symptoms	1252	2932	42.7%	4096	58884	7.0%	4.19 [0.72, 24.39]
Collapse / syncope	99	2125	4.7%	157	7152	2.2%	2.10 [1.05, 4.18]

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

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

Table S8. 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	1265	9417	13.4%	42726	101584	42.1%	0.22 [0.18, 0.28]
ST depression or T wave Inversion	2174	6314	34.4%	14938	68530	21.8%	1.38 [0.94, 2.02]
Pathological Q Waves	30	447	6.7%	177	850	20.8%	0.38 [0.20, 0.71]
Non-specific ST-T wave changes	146	592	24.7%	45	417	10.8%	2.62 [1.81, 3.79]
Left bundle branch block	338	3330	10.2%	3045	60031	5.1%	1.72 [1.40, 2.12]
Atrial fibrillation/flutter	448	1660	27.0%	1871	18272	10.2%	3.70 [2.87, 4.77]
Echocardiograph							
Echocardiogram performed	648	1353	47.9%	1571	2830	55.5%	0.44 [0.20, 0.96]
Presence of RWMA	97	286	33.9%	101	214	47.2%	0.48 [0.06, 3.78]
Angiogram							
Angiogram performed	3686	10721	34.4%	56242	67432	83.4%	0.09 [0.06, 0.12]
Obstructive coronary artery disease present	1246	3663	34.0%	19923	44404	44.9%	0.16 [0.05, 0.54]
Multivessel disease present	593	2147	27.6%	11839	41715	28.4%	0.40 [0.19, 0.82]

*Comparing T2MI with T1MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis
RWMA=regional wall motion abnormalities; CI=confidence interval; T2MI=type 2 myocardial infarction; T1MI=type 1 myocardial infarction

Table S9. 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)	21	5.1-1703	2.8-447
Abbreviations: xULN= times upper limit normal			

Figure S1. PRISMA flow diagram.

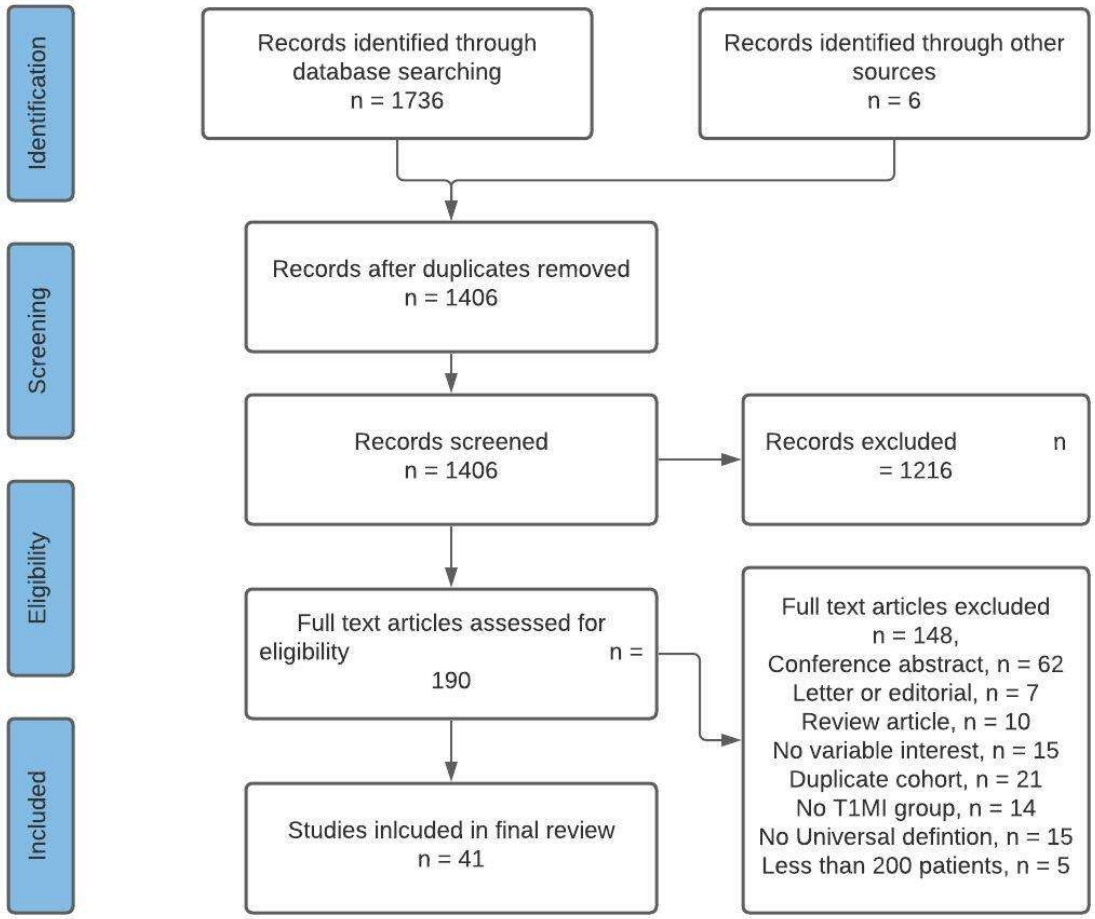


Figure S2. Forest Plot. Ischaemic Heart Disease.

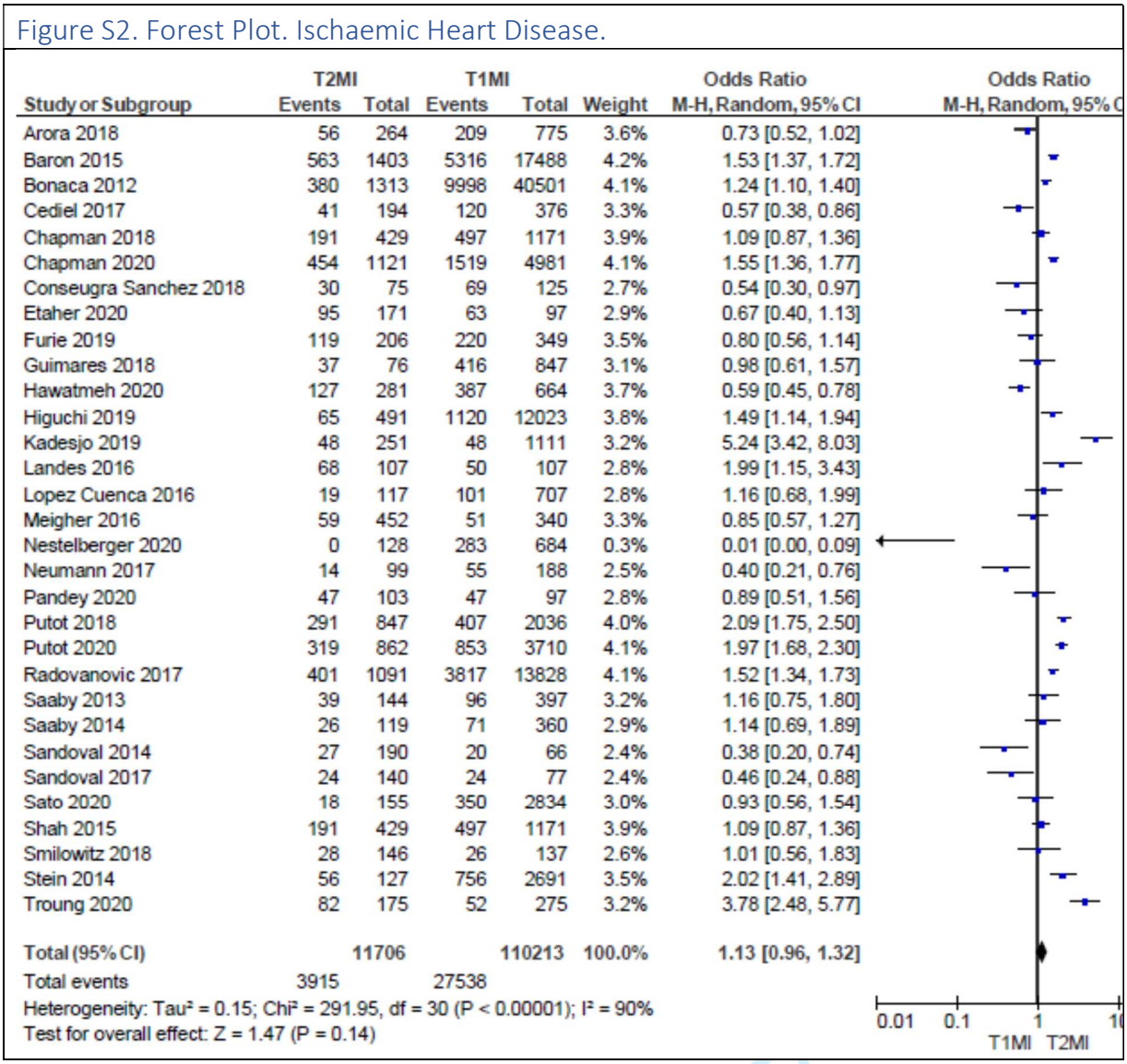


Figure S3. Forest Plot. Type 2 Diabetes Mellitus.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Arora 2018	110	264	371	775	3.3%	0.78 [0.59, 1.03]
Baron 2015	376	1403	3882	17488	3.8%	1.28 [1.13, 1.45]
Baron 2016	306	1313	9395	40501	3.8%	1.01 [0.88, 1.15]
Cediel 2017	73	194	132	376	2.9%	1.12 [0.78, 1.60]
Chapman 2018	93	429	185	1171	3.3%	1.48 [1.12, 1.95]
Chapman 2020	147	1121	802	4981	3.6%	0.79 [0.65, 0.95]
Conseugra Sanchez 2018	29	75	59	125	2.1%	0.71 [0.39, 1.26]
Etaher 2020	64	171	36	97	2.3%	1.01 [0.61, 1.70]
Furie 2019	100	206	199	349	3.0%	0.71 [0.50, 1.00]
Guimares 2018	27	76	419	847	2.4%	0.56 [0.35, 0.92]
Hawatmeh 2020	101	281	303	664	3.2%	0.67 [0.50, 0.89]
Higuchi 2019	148	491	3745	12023	3.6%	0.95 [0.78, 1.16]
Javed 2009	24	64	61	143	2.0%	0.81 [0.44, 1.48]
Kadesjo 2019	56	251	213	1111	3.1%	1.21 [0.87, 1.69]
Lambrecht 2018	28	119	46	360	2.3%	2.10 [1.24, 3.55]
Landes 2016	54	107	54	107	2.3%	1.00 [0.59, 1.71]
Lopez Cuenca 2016	52	117	336	707	2.8%	0.88 [0.60, 1.31]
Meigher 2016	122	452	126	340	3.2%	0.63 [0.46, 0.85]
Nestelberger 2020	26	128	180	684	2.5%	0.71 [0.45, 1.13]
Neumann 2017	12	99	42	188	1.8%	0.48 [0.24, 0.96]
Pandey 2020	47	103	44	97	2.2%	1.01 [0.58, 1.76]
Putot 2018	264	847	504	2036	3.6%	1.38 [1.15, 1.64]
Putot 2019	99	254	138	365	3.1%	1.05 [0.76, 1.46]
Radovanovic 2017	286	1091	2766	13828	3.7%	1.42 [1.23, 1.64]
Raphael 2020	150	1054	313	1365	3.5%	0.56 [0.45, 0.69]
Saaby 2013	40	144	52	397	2.5%	2.55 [1.60, 4.07]
Saaby 2014	28	119	46	360	2.3%	2.10 [1.24, 3.55]
Sandoval 2014	57	190	21	66	2.0%	0.92 [0.50, 1.68]
Sandoval 2017	43	140	32	77	2.1%	0.62 [0.35, 1.11]
Sato 2020	40	155	1015	2834	2.9%	0.62 [0.43, 0.90]
Shah 2015	93	429	185	1171	3.3%	1.48 [1.12, 1.95]
Singh 2020	165	1225	405	2097	3.6%	0.65 [0.53, 0.79]
Smilowitz 2018	58	146	61	137	2.5%	0.82 [0.51, 1.32]
Stein 2014	61	127	945	2691	3.0%	1.71 [1.19, 2.44]
Troung 2020	41	175	56	275	2.6%	1.20 [0.76, 1.89]
Total (95% CI)		13560		110833	100.0%	0.98 [0.86, 1.10]
Total events	3420		27169			

Heterogeneity: Tau² = 0.10; Chi² = 208.56, df = 34 (P < 0.00001); I² = 84%
Test for overall effect: Z = 0.39 (P = 0.70)

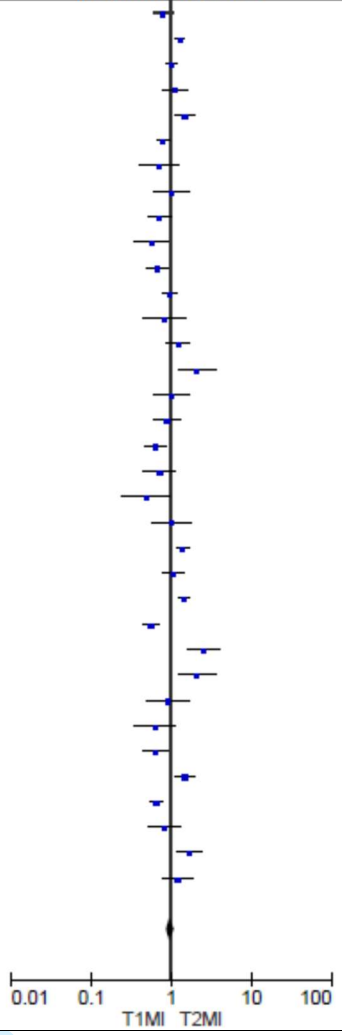
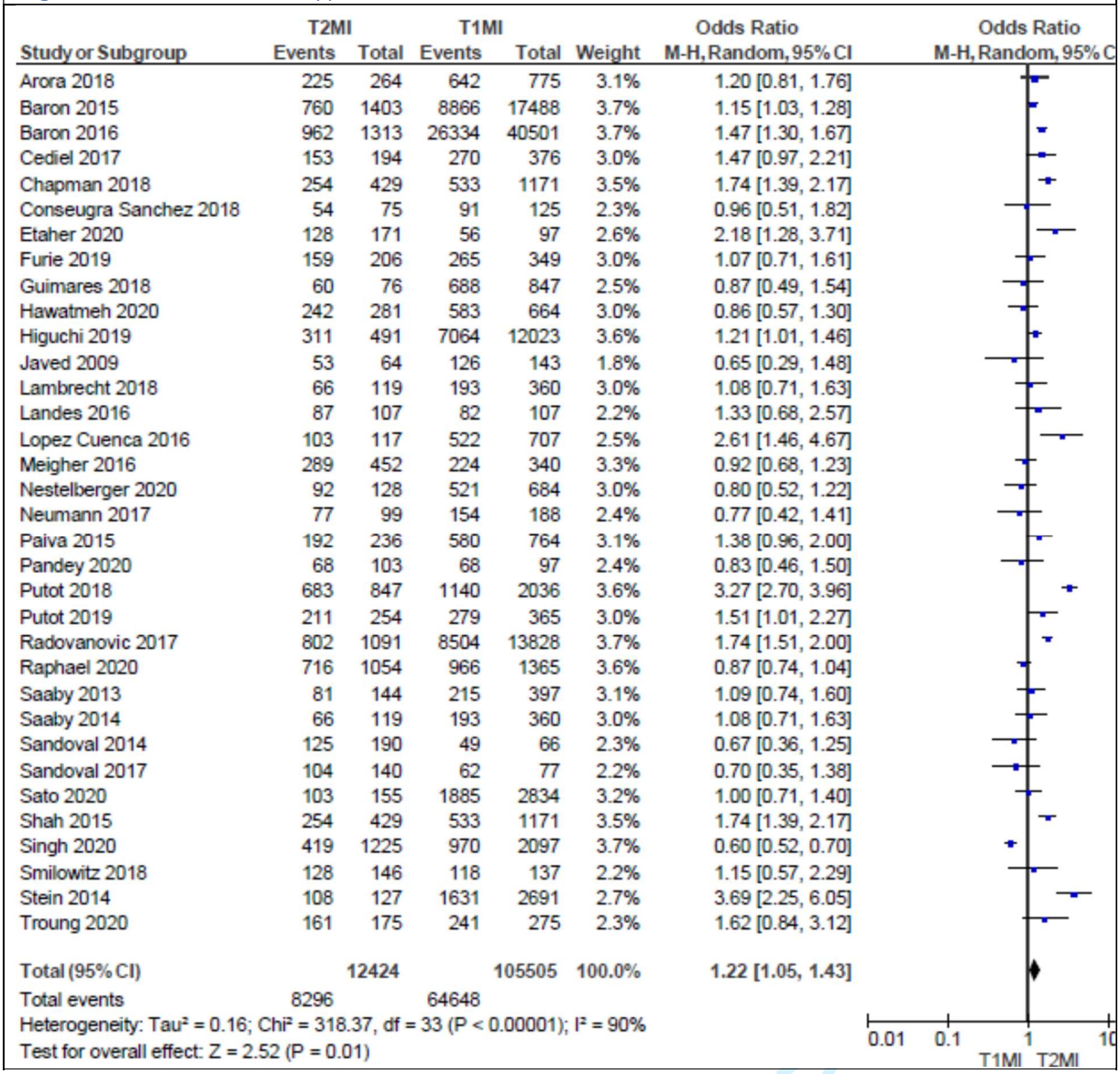


Figure S4. Forest Plot. Hypertension.



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

Heterogeneity: Tau² = 0.16; Chi² = 318.37, df = 33 (P < 0.00001); I² = 90%

Test for overall effect: Z = 2.52 (P = 0.01)

Figure S5. Forest Plot. Dyslipidaemia.

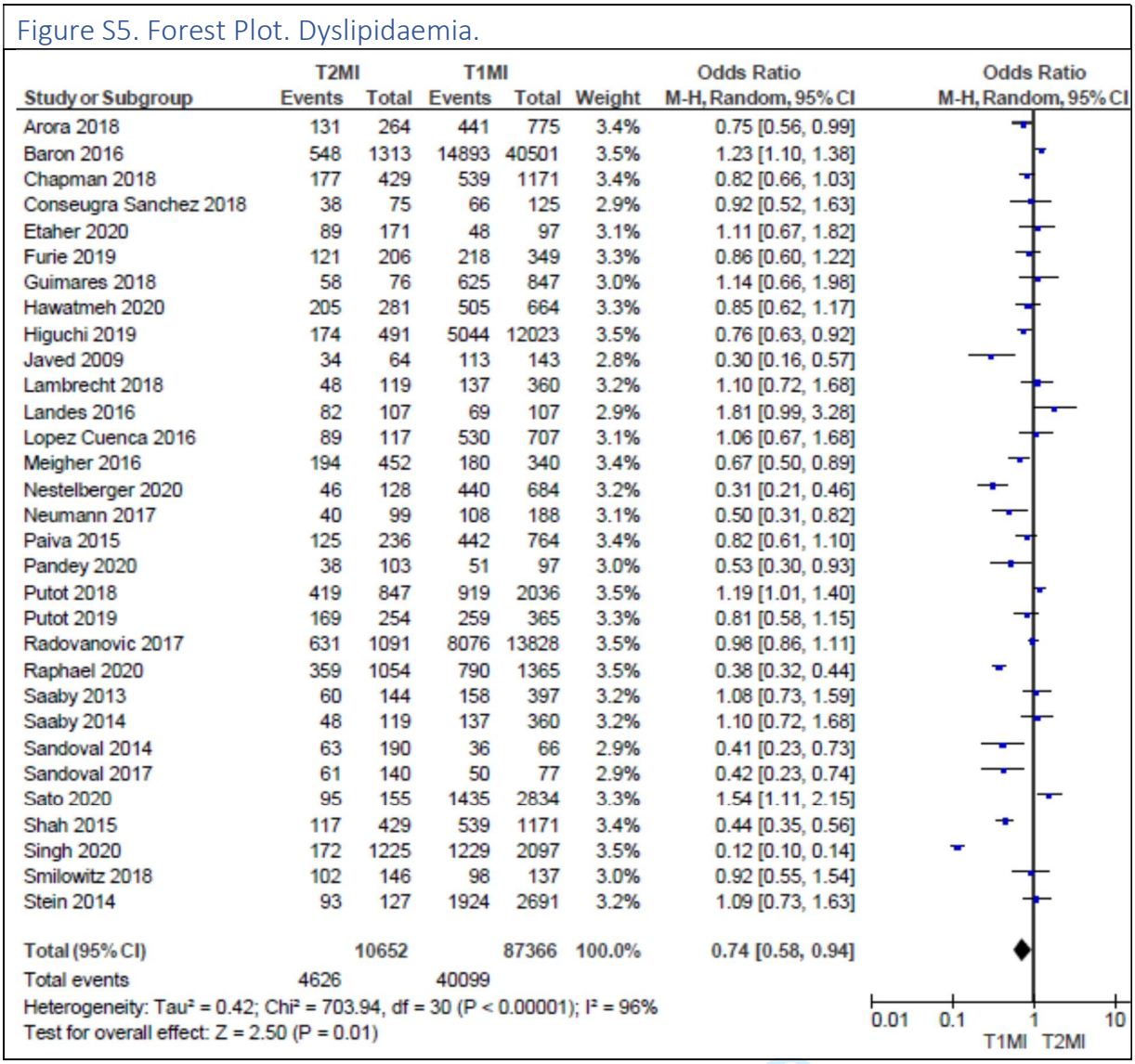


Figure S6. Forest Plot. Smoking.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Arora 2018	80	264	327	775	3.6%	0.60 [0.44, 0.80]
Baron 2015	765	1403	10248	17488	3.9%	0.85 [0.76, 0.94]
Baron 2016	771	1313	24754	40501	3.9%	0.90 [0.81, 1.01]
Cediel 2017	62	194	218	376	3.5%	0.34 [0.24, 0.49]
Chapman 2018	62	429	380	1171	3.6%	0.35 [0.26, 0.47]
Conseugra Sanchez 2018	10	75	27	125	2.4%	0.56 [0.25, 1.23]
Etaher 2020	21	171	30	97	2.8%	0.31 [0.17, 0.59]
Furie 2019	73	206	133	349	3.5%	0.89 [0.62, 1.28]
Guimares 2018	36	76	304	847	3.2%	1.61 [1.00, 2.58]
Hawatmeh 2020	88	281	272	664	3.6%	0.66 [0.49, 0.88]
Javed 2009	30	64	66	143	2.9%	1.03 [0.57, 1.86]
Lambrecht 2018	91	119	284	360	3.1%	0.87 [0.53, 1.42]
Landes 2016	44	107	41	107	3.0%	1.12 [0.65, 1.94]
Lopez Cuenca 2016	23	117	232	707	3.2%	0.50 [0.31, 0.81]
Meigher 2016	172	452	129	340	3.6%	1.00 [0.75, 1.34]
Nestelberger 2020	21	128	181	684	3.1%	0.55 [0.33, 0.90]
Neumann 2017	17	99	52	188	2.8%	0.54 [0.29, 1.00]
Pandey 2020	13	103	16	97	2.4%	0.73 [0.33, 1.61]
Putot 2018	280	847	1271	2036	3.8%	0.30 [0.25, 0.35]
Putot 2019	101	254	243	365	3.5%	0.33 [0.24, 0.46]
Radovanovic 2017	340	1091	5697	13828	3.9%	0.65 [0.57, 0.74]
Raphael 2020	462	1054	907	1365	3.8%	0.39 [0.33, 0.47]
Saaby 2013	35	144	129	397	3.3%	0.67 [0.43, 1.03]
Saaby 2014	91	119	284	360	3.1%	0.87 [0.53, 1.42]
Sandoval 2017	52	140	23	77	2.9%	1.39 [0.76, 2.52]
Sato 2020	51	155	921	2834	3.5%	1.02 [0.72, 1.44]
Shah 2015	62	429	380	1171	3.6%	0.35 [0.26, 0.47]
Singh 2020	244	1225	1063	2097	3.8%	0.24 [0.21, 0.29]
Smilowitz 2018	96	146	89	137	3.2%	1.04 [0.63, 1.69]
Stein 2014	20	127	1095	2691	3.2%	0.27 [0.17, 0.44]
Total (95% CI)		11332		92377	100.0%	0.61 [0.50, 0.74]
Total events	4213		49796			

Heterogeneity: Tau² = 0.25; Chi² = 430.67, df = 29 (P < 0.00001); I² = 93%
Test for overall effect: Z = 5.06 (P < 0.00001)

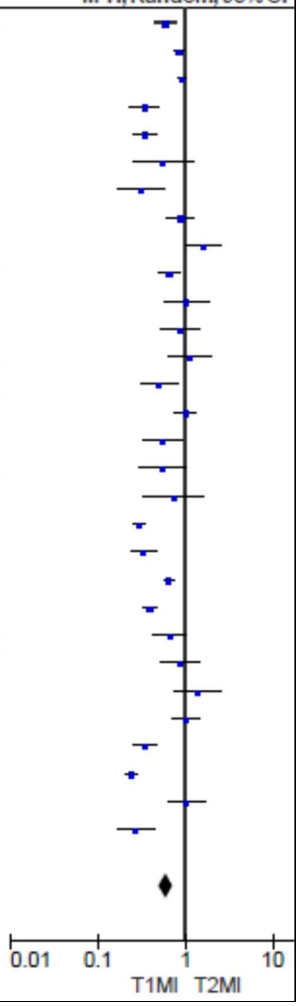


Figure S7. Forest Plot. Obesity.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Baron 2016	824	1313	27283	40501	21.6%	0.82 [0.73, 0.91]
Javed 2009	14	64	54	143	11.0%	0.46 [0.23, 0.91]
Pandey 2020	22	103	22	97	11.2%	0.93 [0.47, 1.81]
Putot 2018	91	847	423	2036	19.7%	0.46 [0.36, 0.58]
Putot 2019	27	254	97	365	15.2%	0.33 [0.21, 0.52]
Radovanovic 2017	247	1091	3084	13828	21.2%	1.02 [0.88, 1.18]
Total (95% CI)		3672		56970	100.0%	0.63 [0.46, 0.87]
Total events	1225		30963			

Heterogeneity: Tau² = 0.12; Chi² = 47.72, df = 5 (P < 0.00001); I² = 90%
Test for overall effect: Z = 2.80 (P = 0.005)

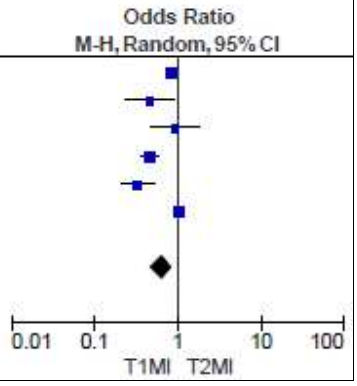


Figure S8. Forest Plot. Chronic Kidney Disease.

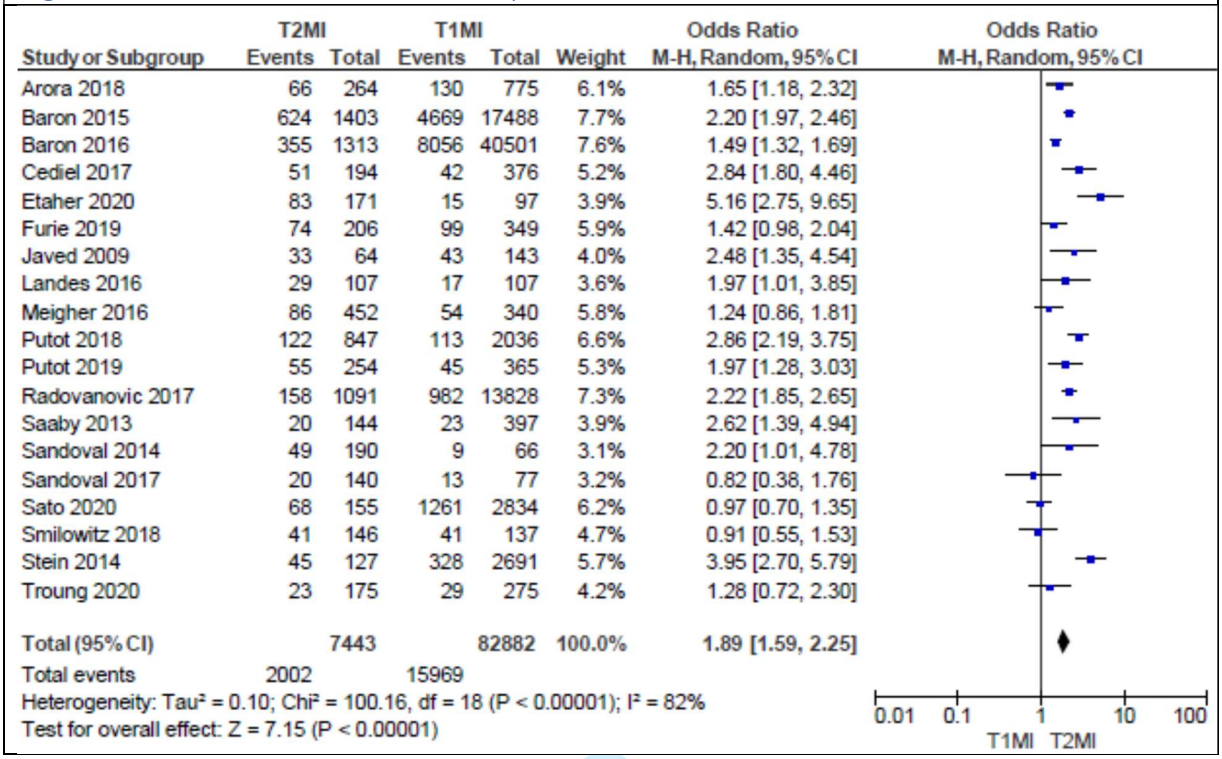


Figure S9. Forest Plot. Heart Failure.

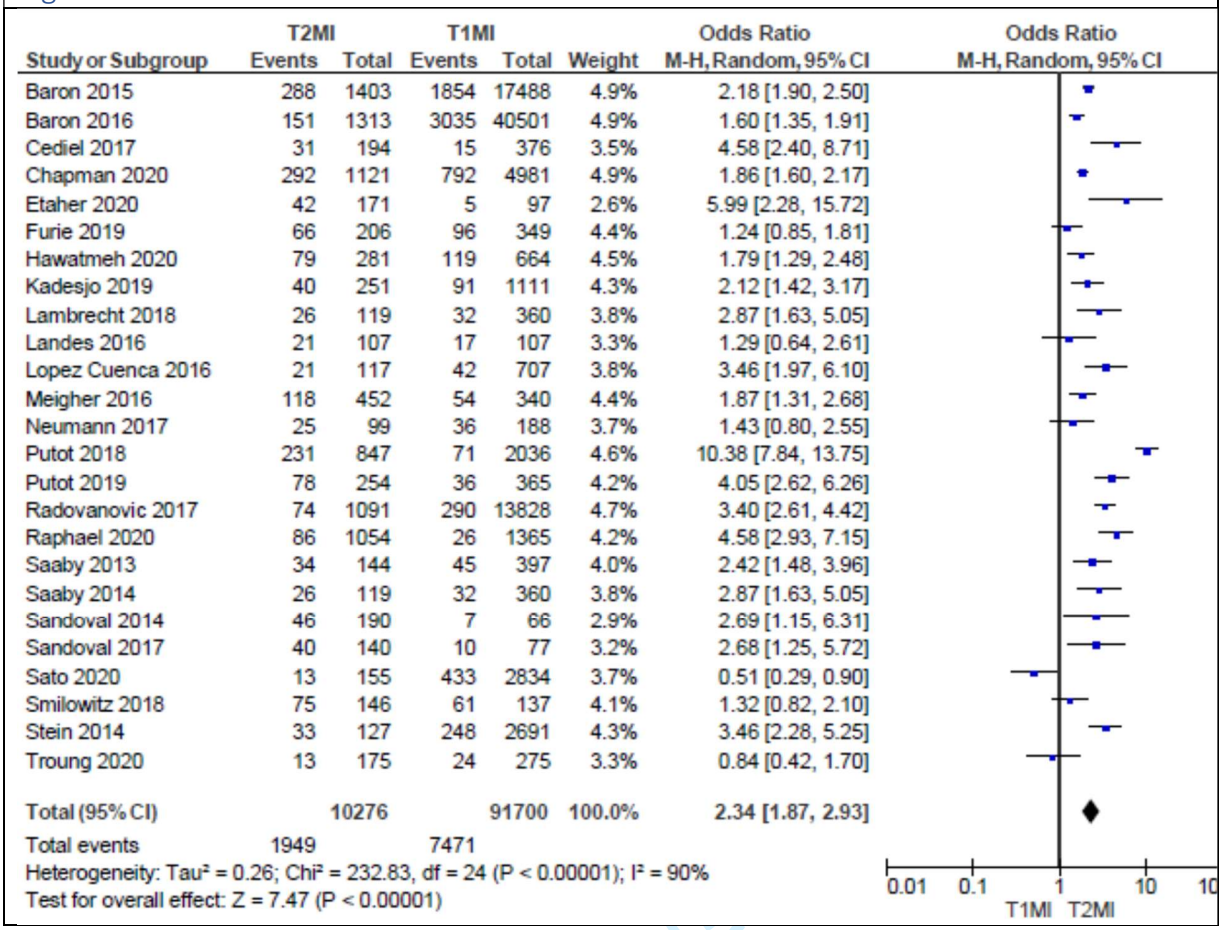


Figure S10. Forest Plot. Peripheral Vascular Disease.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
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 ($P < 0.00001$); $I^2 = 77\%$

Test for overall effect: $Z = 2.36$ ($P = 0.02$)

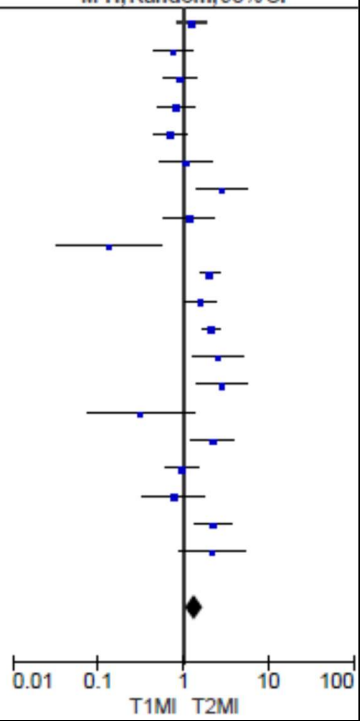


Figure S11. Forest Plot. Cerbrovascular Disease.

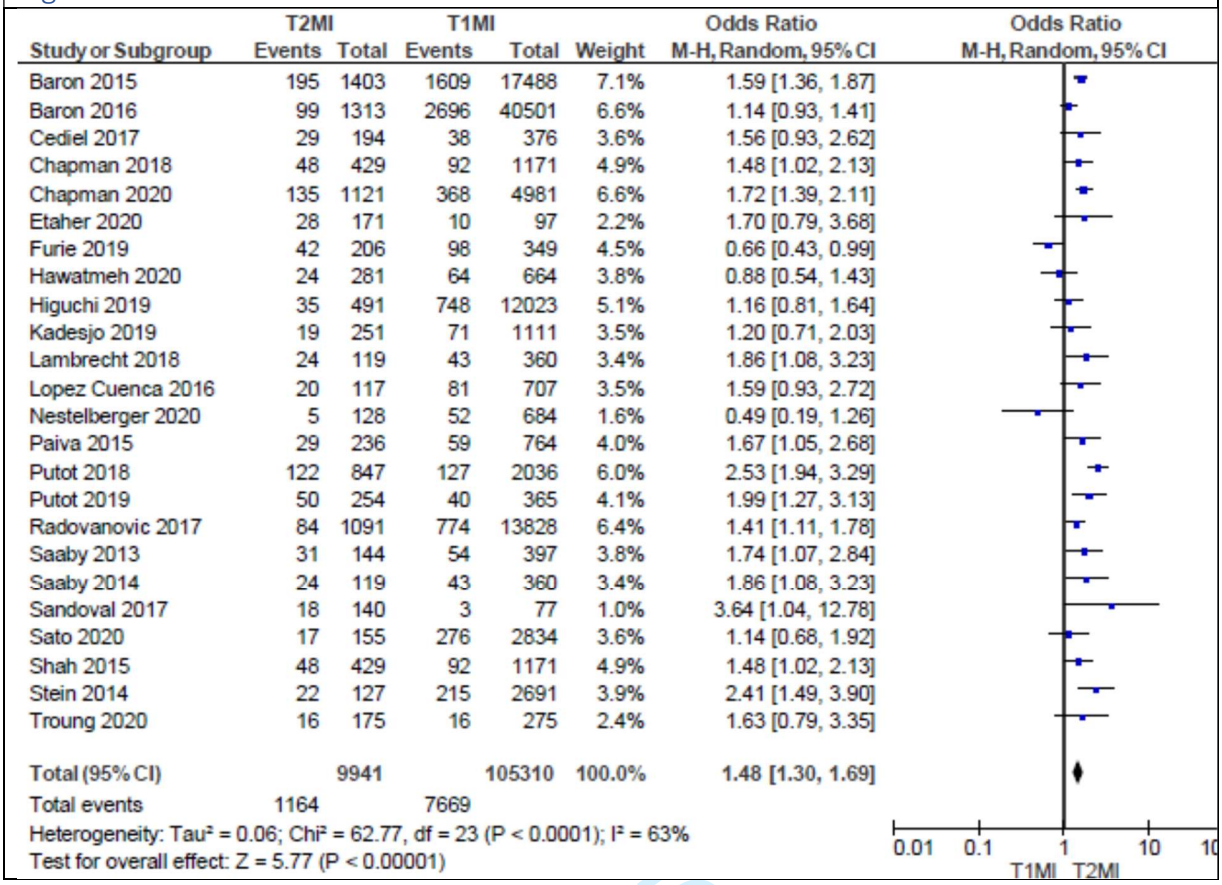


Figure S12. Forest Plot. Illicit Drug Use.

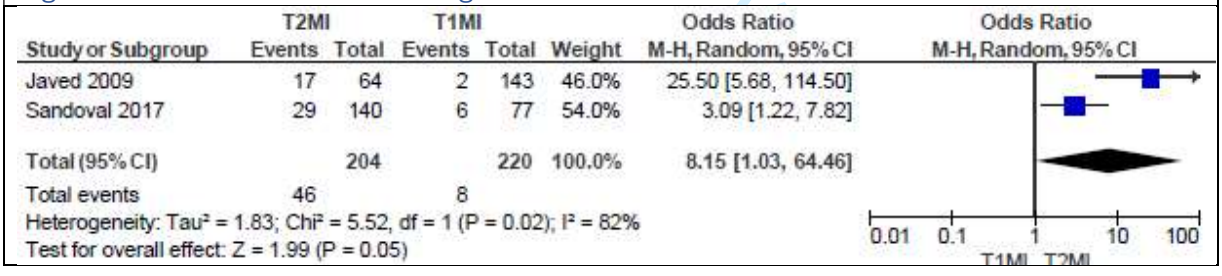


Figure S13. Forest Plot. Atrial Fibrillation.

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

Heterogeneity: Tau² = 0.18; Chi² = 62.33, df = 11 (P < 0.00001); I² = 82%

Test for overall effect: Z = 7.83 (P < 0.00001)

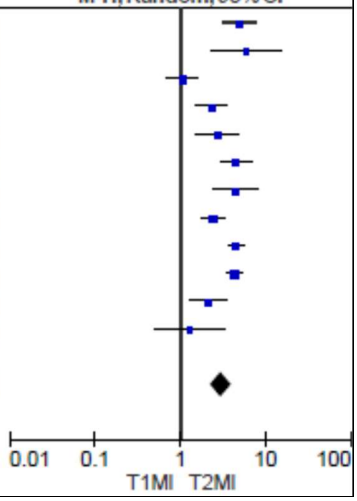


Figure S14. Forest Plot. Chest Pain.

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

Heterogeneity: Tau² = 0.29; Chi² = 280.74, df = 16 (P < 0.00001); I² = 94%

Test for overall effect: Z = 11.30 (P < 0.00001)

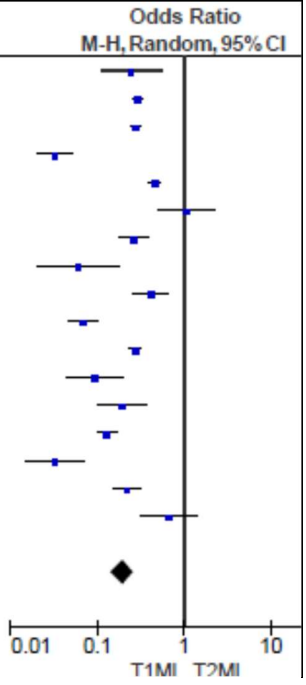


Figure S15. Forest Plot. Dyspnoea.

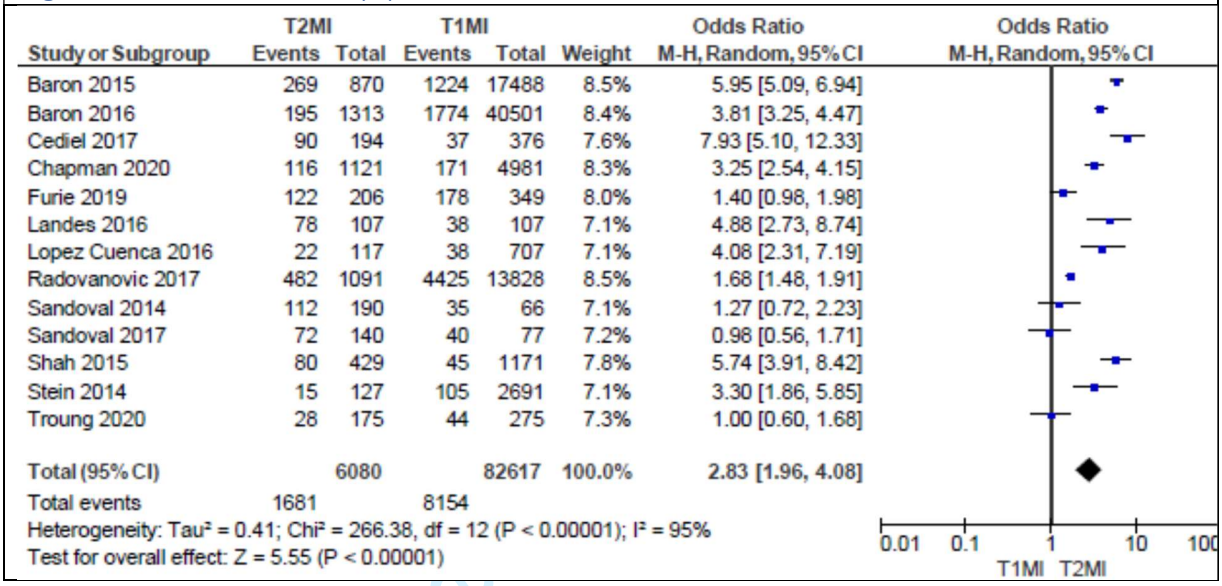


Figure S16. Forest Plot. Arm / Shoulder Discomfort.

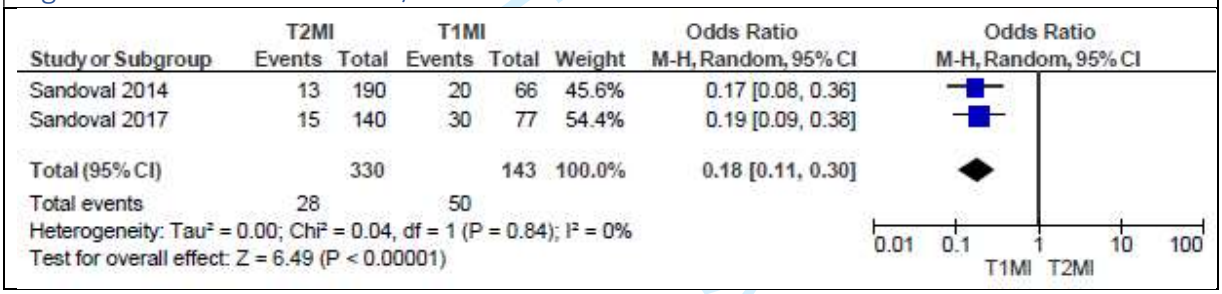


Figure S17. Forest Plot. Jaw / Neck Discomfort.

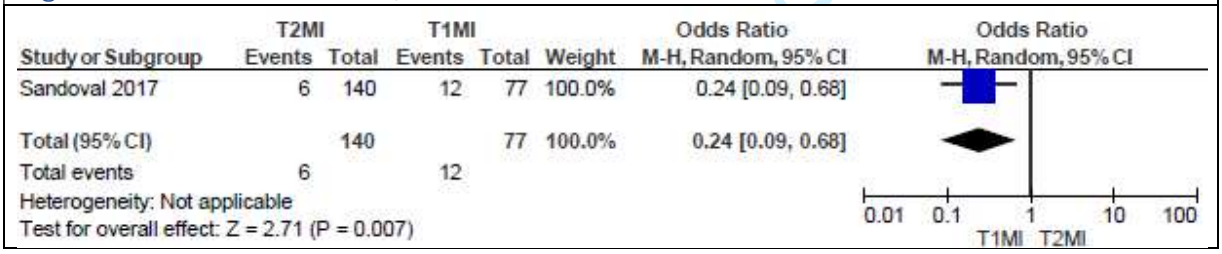


Figure S18. Forest Plot. Epigastric Discomfort.

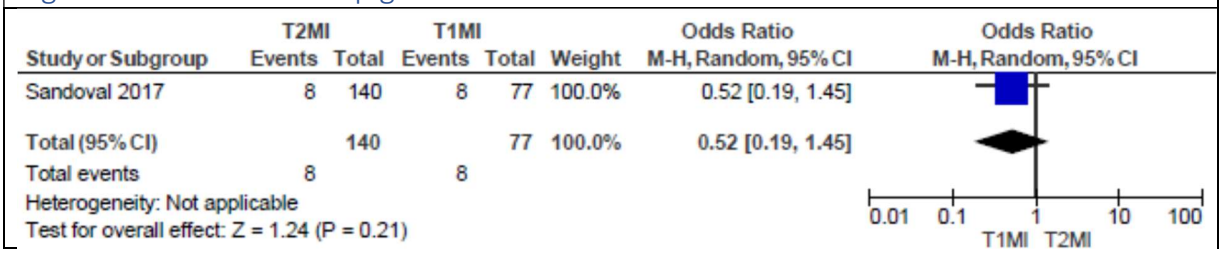


Figure S19. Forest Plot. Nausea / Vomiting.

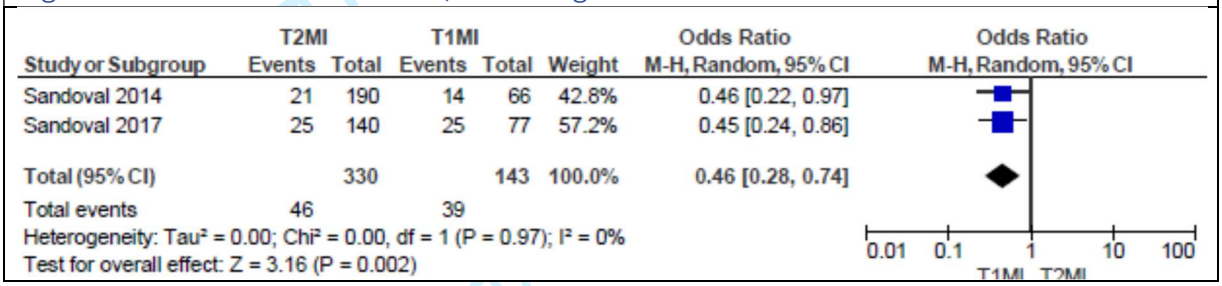


Figure S20. Forest Plot. Fatigue.

Figure S21. Forest Plot. Diaphoresis.

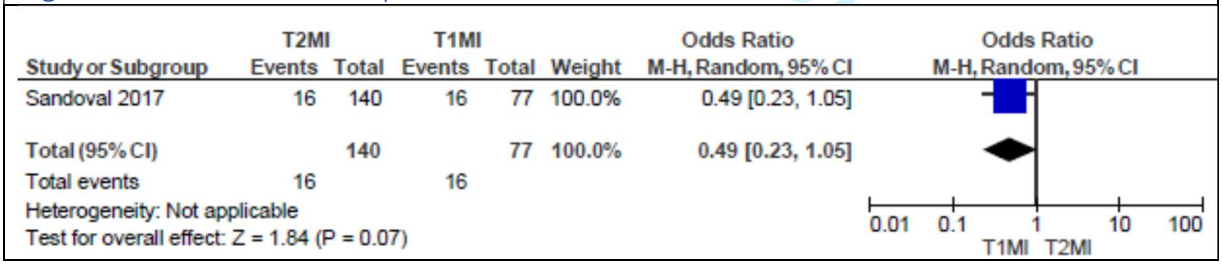


Figure S22. Forest Plot. Non-specific Symptoms.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Baron 2015	264	1403	1434	17488	25.4%	2.59 [2.25, 3.00]
Baron 2016	899	1313	2506	40501	25.5%	32.92 [29.11, 37.24]
Lopez Cuenca 2016	8	117	51	707	24.3%	0.94 [0.44, 2.04]
Neumann 2017	81	99	105	188	24.8%	3.56 [1.98, 6.39]
Total (95% CI)		2932		58884	100.0%	4.19 [0.72, 24.39]
Total events	1252		4096			

Heterogeneity: Tau² = 3.17; Chi² = 760.73, df = 3 (P < 0.00001); I² = 100%
Test for overall effect: Z = 1.59 (P = 0.11)

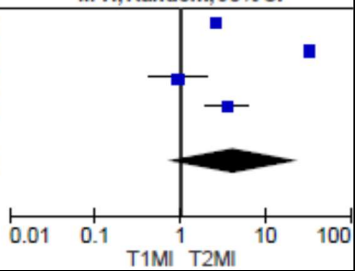


Figure S23. Forest Plot. Collapse / Syncope.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Cediel 2017	15	194	5	376	17.2%	6.22 [2.22, 17.38]
Chapman 2020	38	1121	102	4981	25.6%	1.68 [1.15, 2.45]
Furie 2019	12	206	24	349	21.4%	0.84 [0.41, 1.71]
Shah 2015	31	429	21	1171	23.4%	4.27 [2.42, 7.51]
Troung 2020	3	175	5	275	12.5%	0.94 [0.22, 3.99]
Total (95% CI)		2125		7152	100.0%	2.10 [1.05, 4.18]
Total events	99		157			

Heterogeneity: Tau² = 0.45; Chi² = 19.12, df = 4 (P = 0.0007); I² = 79%
Test for overall effect: Z = 2.10 (P = 0.04)

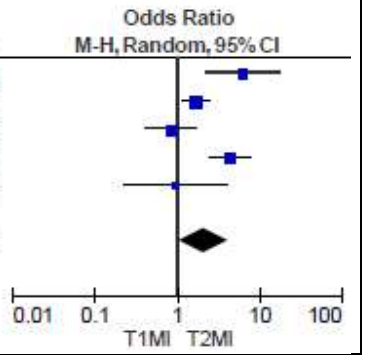


Figure S24. Forest Plot. ST Elevation.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Baron 2015	136	1403	5544	17488	7.8%	0.23 [0.19, 0.28]
Baron 2016	173	1313	14824	40501	7.9%	0.26 [0.22, 0.31]
Cediel 2017	5	194	92	376	3.4%	0.08 [0.03, 0.20]
Chapman 2020	36	1121	870	4981	6.9%	0.16 [0.11, 0.22]
Furie 2019	4	206	18	349	2.7%	0.36 [0.12, 1.09]
Higuchi 2019	288	491	8917	12023	7.8%	0.49 [0.41, 0.59]
Landes 2016	11	107	11	107	3.5%	1.00 [0.41, 2.42]
Lopez Cuenca 2016	1	117	225	707	1.1%	0.02 [0.00, 0.13]
Nestelberger 2020	4	128	115	684	3.0%	0.16 [0.06, 0.44]
Paiva 2015	35	236	417	764	6.6%	0.14 [0.10, 0.21]
Putot 2019	28	254	136	365	6.1%	0.21 [0.13, 0.33]
Putot 2020	207	862	1929	3710	7.8%	0.29 [0.25, 0.35]
Radovanovic 2017	213	1091	7436	13828	7.9%	0.21 [0.18, 0.24]
Raphael 2020	23	1054	198	1365	6.2%	0.13 [0.08, 0.20]
Saaby 2013	5	144	130	397	3.4%	0.07 [0.03, 0.18]
Sandoval 2017	31	140	24	77	4.9%	0.63 [0.34, 1.17]
Shah 2015	40	429	427	1171	6.8%	0.18 [0.13, 0.25]
Stein 2014	25	127	1413	2691	6.2%	0.22 [0.14, 0.35]
Total (95% CI)		9417		101584	100.0%	0.22 [0.18, 0.28]
Total events	1265		42726			

Heterogeneity: Tau² = 0.15; Chi² = 131.14, df = 17 (P < 0.00001); I² = 87%
Test for overall effect: Z = 13.39 (P < 0.00001)

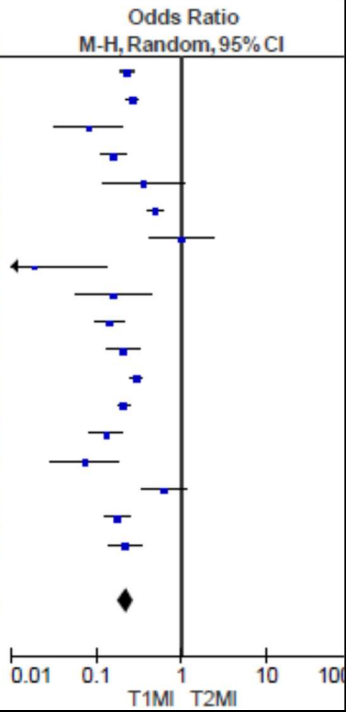


Figure S25. Forest Plot. ST Depression or T Wave Inversion.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Arora 2018	120	264	369	775	7.1%	0.92 [0.69, 1.21]
Baron 2015	446	1403	3970	17488	7.3%	1.59 [1.41, 1.79]
Baron 2016	330	1313	8261	40501	7.3%	1.31 [1.15, 1.49]
Cediel 2017	16	194	94	376	6.4%	0.27 [0.15, 0.47]
Chapman 2020	278	1121	865	4981	7.3%	1.57 [1.35, 1.83]
Conseugra Sanchez 2018	7	75	43	125	5.4%	0.20 [0.08, 0.46]
Hawatmeh 2020	223	281	86	664	6.9%	25.84 [17.90, 37.30]
Landes 2016	71	107	75	107	6.3%	0.84 [0.47, 1.50]
Lopez Cuenca 2016	35	117	152	707	6.8%	1.56 [1.01, 2.41]
Meigher 2016	68	452	61	340	6.9%	0.81 [0.55, 1.18]
Nestelberger 2020	33	128	234	684	6.8%	0.67 [0.44, 1.02]
Saaby 2013	139	144	267	397	5.2%	13.54 [5.41, 33.84]
Sandoval 2017	74	140	40	77	6.4%	1.04 [0.59, 1.81]
Shah 2015	249	429	332	1171	7.2%	3.50 [2.78, 4.40]
Smilowitz 2018	85	146	89	137	6.6%	0.75 [0.46, 1.22]
Total (95% CI)		6314		68530	100.0%	1.38 [0.94, 2.02]
Total events	2174		14938			

Heterogeneity: Tau² = 0.52; Chi² = 416.57, df = 14 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.64 (P = 0.10)

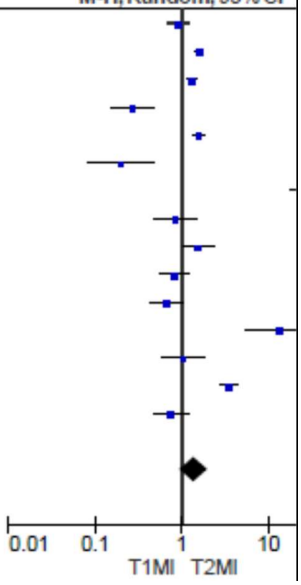


Figure S26. Forest Plot. Q Waves.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Lopez Cuenca 2016	12	117	156	707	48.4%	0.40 [0.22, 0.75]
Sandoval 2014	2	190	6	66	12.8%	0.11 [0.02, 0.54]
Sandoval 2017	16	140	15	77	38.8%	0.53 [0.25, 1.15]
Total (95% CI)		447		850	100.0%	0.38 [0.20, 0.71]
Total events	30		177			

Heterogeneity: Tau² = 0.11; Chi² = 3.09, df = 2 (P = 0.21); I² = 35%
Test for overall effect: Z = 3.03 (P = 0.002)

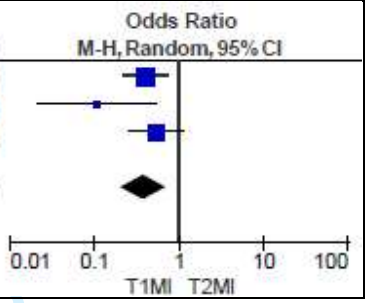


Figure S27. Forest Plot. Non-specific ST Changes.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
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			

Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 5.12 (P < 0.00001)

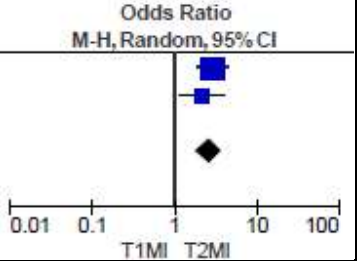


Figure S28. Forest Plot. Left Bundle Branch Block.

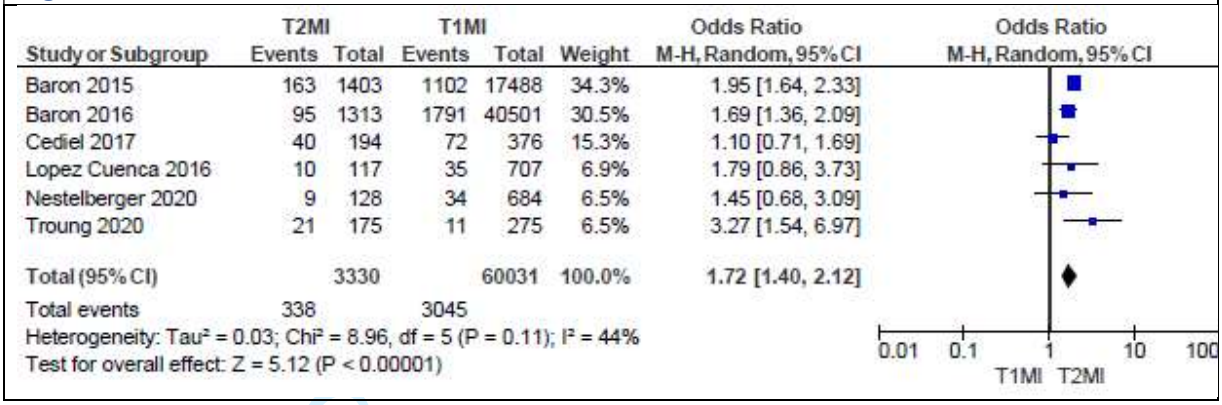


Figure S29. Forest Plot. Atrial Fibrillation.

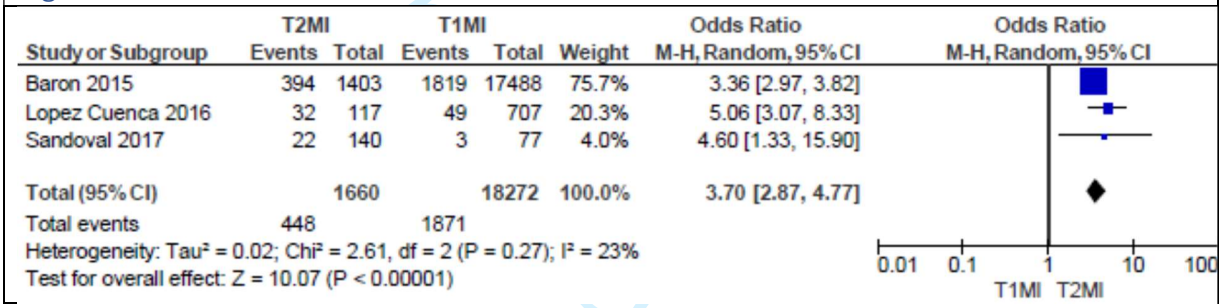


Figure S30. Forest Plot. Angiogram Performed.

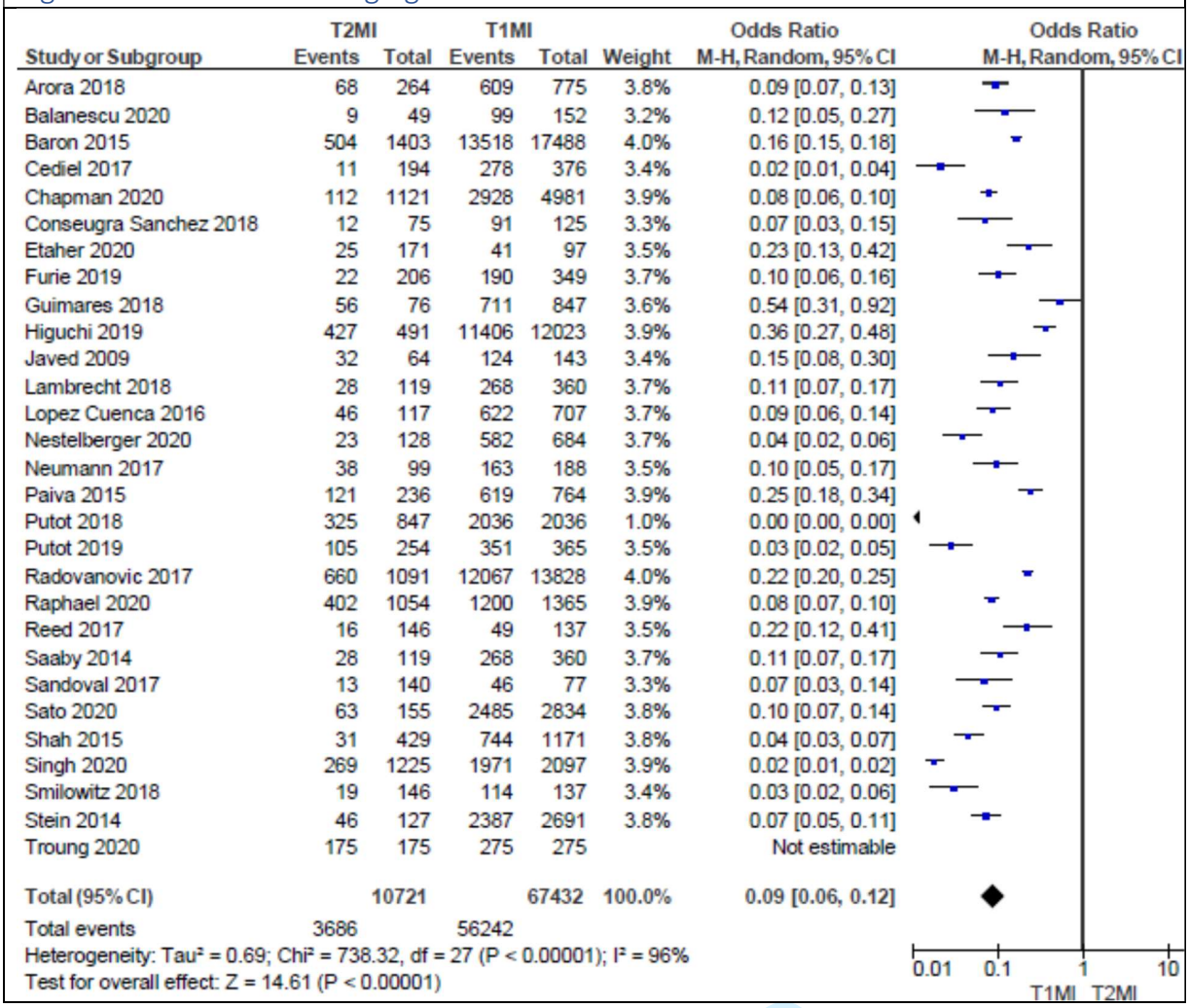


Figure S31. Forest Plot. Obstructive Coronary Artery Disease.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Baron 2016	533	1313	17456	40501	9.6%	0.90 [0.81, 1.01]
Conseugra Sanchez 2018	4	75	82	125	9.0%	0.03 [0.01, 0.09]
Furie 2019	7	206	166	349	9.3%	0.04 [0.02, 0.08]
Javed 2009	25	64	111	143	9.4%	0.18 [0.10, 0.35]
Lopez Cuenca 2016	78	117	64	707	9.5%	20.09 [12.66, 31.90]
Putot 2019	238	254	346	365	9.3%	0.82 [0.41, 1.62]
Raphael 2020	162	1054	1058	1365	9.6%	0.05 [0.04, 0.07]
Saaby 2014	15	119	236	360	9.4%	0.08 [0.04, 0.14]
Sandoval 2017	7	140	42	77	9.2%	0.04 [0.02, 0.11]
Smilowitz 2018	14	146	87	137	9.4%	0.06 [0.03, 0.12]
Troung 2020	163	175	275	275	6.3%	0.02 [0.00, 0.40]
Total (95% CI)		3663		44404	100.0%	0.16 [0.05, 0.54]
Total events	1246		19923			

Heterogeneity: Tau² = 4.01; Chi² = 989.87, df = 10 (P < 0.00001); I² = 99%
Test for overall effect: Z = 2.95 (P = 0.003)

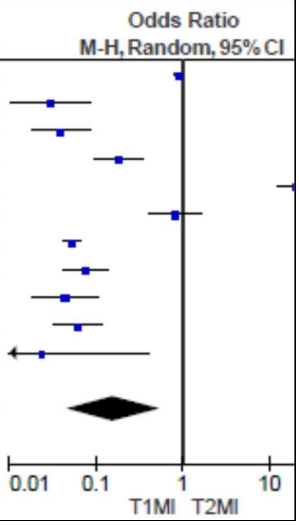


Figure S32. Forest Plot. Multivessel Disease.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Baron 2016	381	1313	11340	40501	22.4%	1.05 [0.93, 1.19]
Putot 2019	59	254	150	365	21.4%	0.43 [0.30, 0.62]
Saaby 2014	11	119	115	360	19.0%	0.22 [0.11, 0.42]
Sandoval 2017	1	140	15	77	8.1%	0.03 [0.00, 0.23]
Smilowitz 2018	1	146	24	137	8.3%	0.03 [0.00, 0.24]
Troung 2020	140	175	195	275	20.7%	1.64 [1.04, 2.58]
Total (95% CI)		2147		41715	100.0%	0.40 [0.19, 0.82]
Total events	593		11839			

Heterogeneity: Tau² = 0.62; Chi² = 68.98, df = 5 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.48 (P = 0.01)

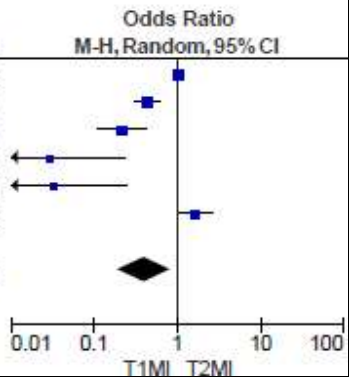


Figure S33. Forest Plot. Echocardiogram Performed.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Cediel 2017	79	194	359	376	14.1%	0.03 [0.02, 0.06]
Furie 2019	103	206	195	349	14.7%	0.79 [0.56, 1.12]
Lambrecht 2018	54	119	180	360	14.6%	0.83 [0.55, 1.26]
Saaby 2014	91	119	321	360	14.2%	0.39 [0.23, 0.68]
Sandoval 2017	72	140	62	77	13.7%	0.26 [0.13, 0.49]
Shah 2015	122	429	340	1171	15.0%	0.97 [0.76, 1.24]
Smilowitz 2018	127	146	114	137	13.7%	1.35 [0.70, 2.60]
Total (95% CI)		1353		2830	100.0%	0.44 [0.20, 0.96]
Total events	648		1571			

Heterogeneity: Tau² = 1.07; Chi² = 138.14, df = 6 (P < 0.00001); I² = 96%
Test for overall effect: Z = 2.05 (P = 0.04)

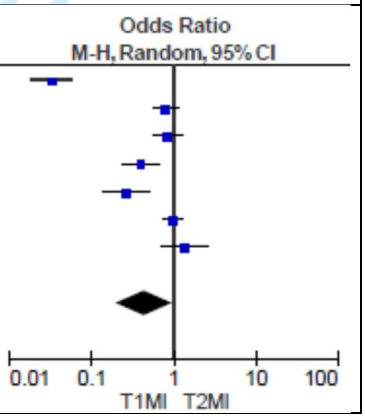


Figure S34. Forest Plot. Regional Wall Motion Abnormalities.

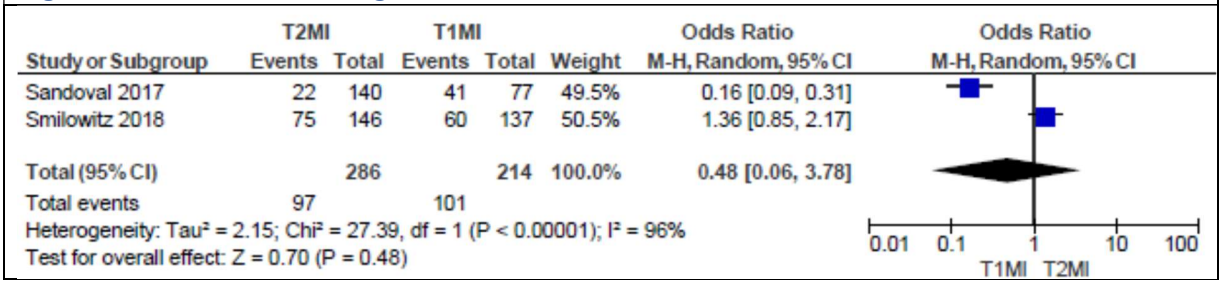


Figure S35. Forest Plot. Beta-Blockers.

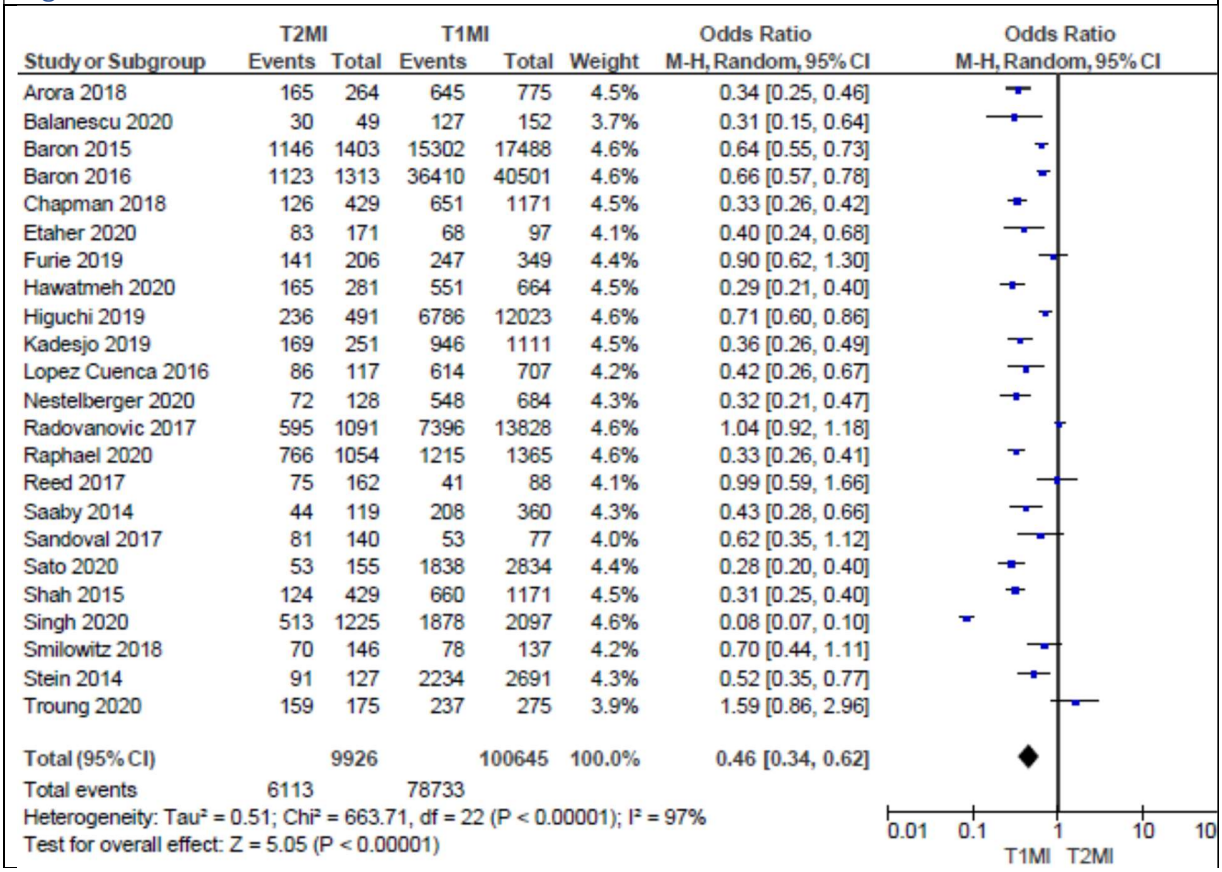


Figure S36. Forest Plot. ACEi/ARB.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Baron 2015	926	1403	13431	17488	5.8%	0.59 [0.52, 0.66]
Baron 2016	945	1313	30781	40501	5.8%	0.81 [0.72, 0.92]
Chapman 2018	156	429	724	1171	5.6%	0.35 [0.28, 0.44]
Etaher 2020	57	171	49	97	4.6%	0.49 [0.29, 0.82]
Hawatmeh 2020	99	281	325	664	5.4%	0.57 [0.43, 0.76]
Higuchi 2019	254	491	7531	12023	5.7%	0.64 [0.53, 0.77]
Kadesjo 2019	118	251	725	1111	5.4%	0.47 [0.36, 0.62]
Lopez Cuenca 2016	53	117	438	707	5.0%	0.51 [0.34, 0.75]
Nestelberger 2020	70	128	546	684	5.0%	0.31 [0.21, 0.45]
Radovanovic 2017	566	1091	7448	13828	5.8%	0.92 [0.82, 1.04]
Raphael 2020	571	1054	976	1365	5.7%	0.47 [0.40, 0.56]
Saaby 2014	38	119	154	360	4.9%	0.63 [0.40, 0.97]
Sandoval 2017	43	140	39	77	4.3%	0.43 [0.24, 0.77]
Sato 2020	93	155	2103	2834	5.3%	0.52 [0.37, 0.73]
Shah 2015	135	429	735	1171	5.6%	0.27 [0.22, 0.34]
Singh 2020	271	1225	1269	2097	5.7%	0.19 [0.16, 0.22]
Smilowitz 2018	62	146	63	137	4.7%	0.87 [0.54, 1.39]
Stein 2014	88	127	2126	2691	5.1%	0.60 [0.41, 0.88]
Troung 2020	147	175	221	275	4.6%	1.28 [0.78, 2.12]
Total (95% CI)		9245		99281	100.0%	0.52 [0.41, 0.66]
Total events	4692		69684			

Heterogeneity: Tau² = 0.24; Chi² = 363.88, df = 18 (P < 0.00001); I² = 95%
Test for overall effect: Z = 5.52 (P < 0.00001)

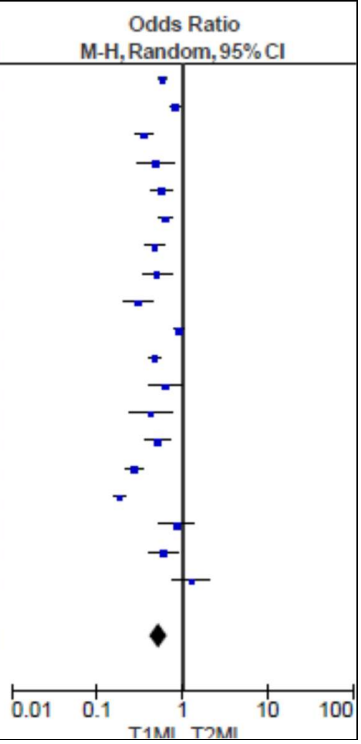


Figure S37. Forest Plot. Antiplatelets.

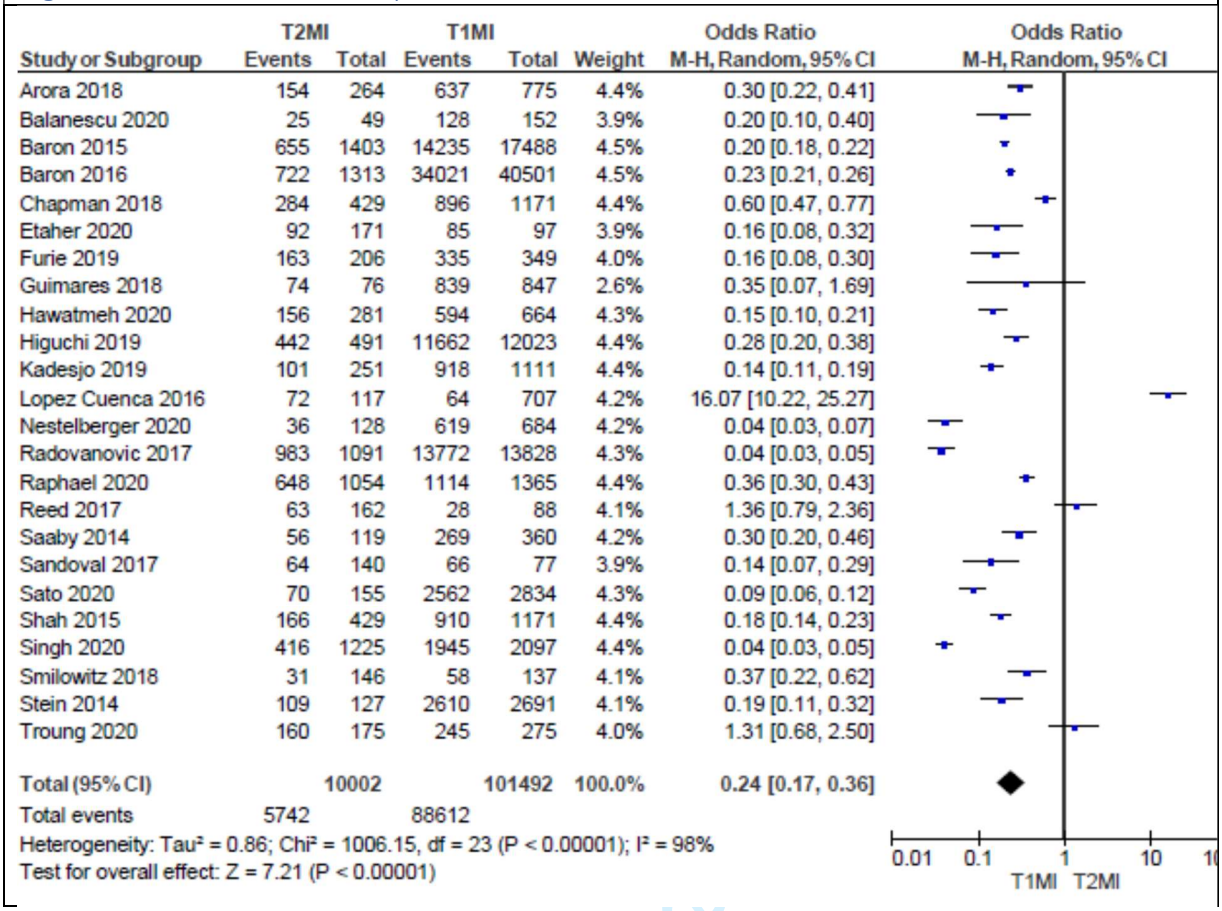


Figure S38. Forest Plot. Anticoagulants.

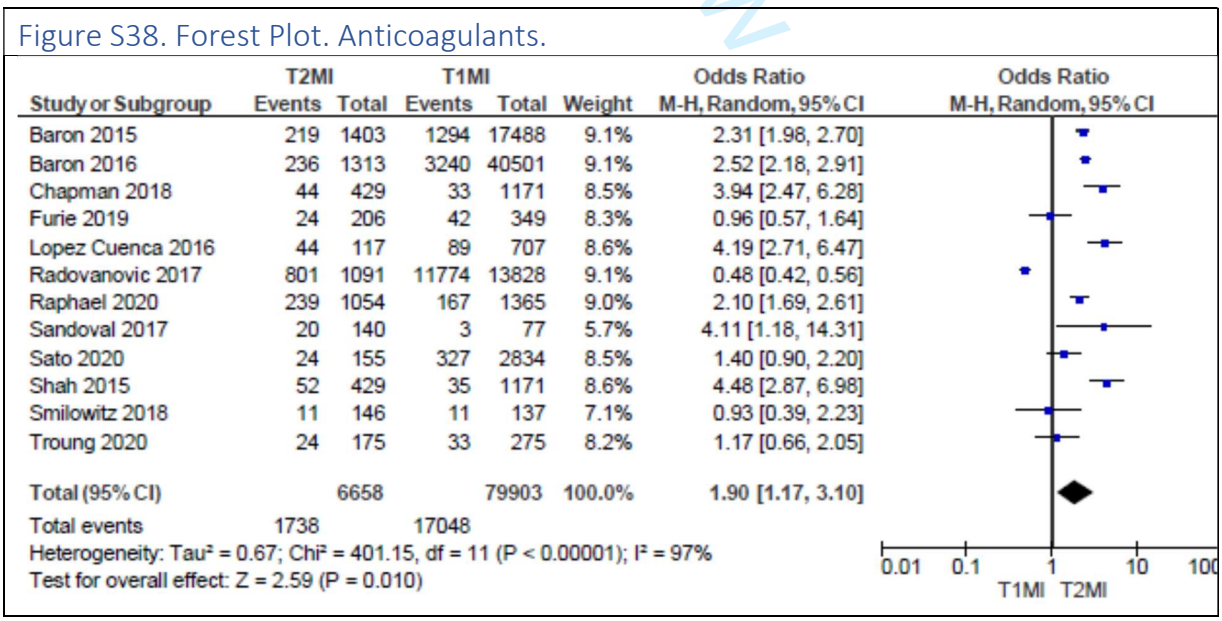


Figure S39. Forest Plot. Antianginals.

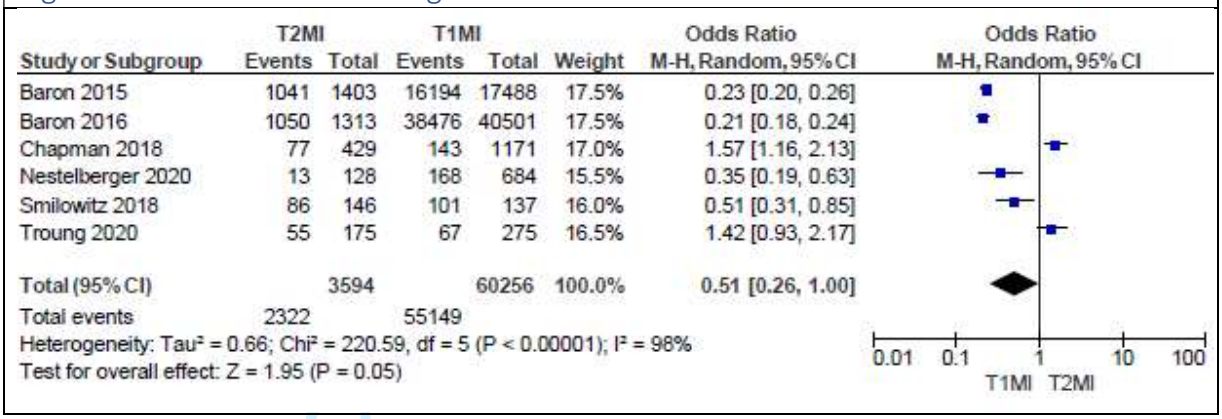


Figure S40. Forest Plot. Diuretics.

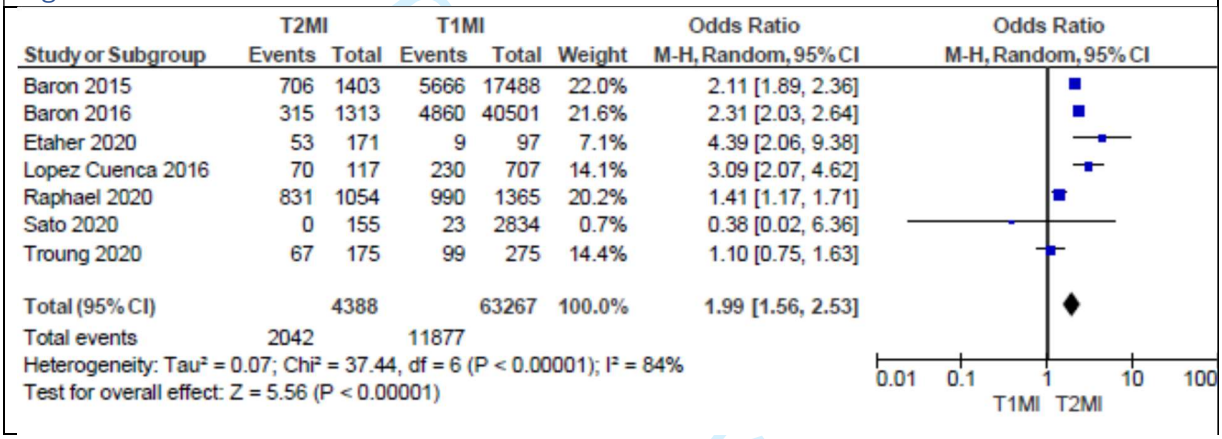


Figure S41. Forest Plot. Statins.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Arora 2018	153	264	646	775	6.0%	0.28 [0.20, 0.37]
Balanescu 2020	29	49	131	152	5.1%	0.23 [0.11, 0.48]
Baron 2015	926	1403	15040	17488	6.3%	0.32 [0.28, 0.36]
Baron 2016	972	1313	37261	40501	6.3%	0.25 [0.22, 0.28]
Chapman 2018	204	429	872	1171	6.1%	0.31 [0.25, 0.39]
Etaher 2020	95	171	81	97	5.4%	0.25 [0.13, 0.46]
Furie 2019	125	206	280	349	5.9%	0.38 [0.26, 0.56]
Hawatmeh 2020	141	281	578	664	6.0%	0.15 [0.11, 0.21]
Higuchi 2019	298	491	9238	12023	6.2%	0.47 [0.39, 0.56]
Kadesjo 2019	92	251	883	1111	6.1%	0.15 [0.11, 0.20]
Lopez Cuenca 2016	92	117	648	707	5.6%	0.34 [0.20, 0.56]
Nestelberger 2020	39	128	606	684	5.8%	0.06 [0.04, 0.09]
Raphael 2020	570	1054	1167	1365	6.2%	0.20 [0.16, 0.24]
Sato 2020	112	155	2303	2834	5.9%	0.60 [0.42, 0.86]
Singh 2020	255	1225	1840	2097	6.2%	0.04 [0.03, 0.04]
Smilowitz 2018	83	146	100	137	5.7%	0.49 [0.30, 0.80]
Troung 2020	158	175	241	275	5.4%	1.31 [0.71, 2.43]
Total (95% CI)		7858		82430	100.0%	0.25 [0.17, 0.36]
Total events	4344		71915			

Heterogeneity: Tau² = 0.57; Chi² = 583.06, df = 16 (P < 0.00001); I² = 97%

Test for overall effect: Z = 7.30 (P < 0.00001)

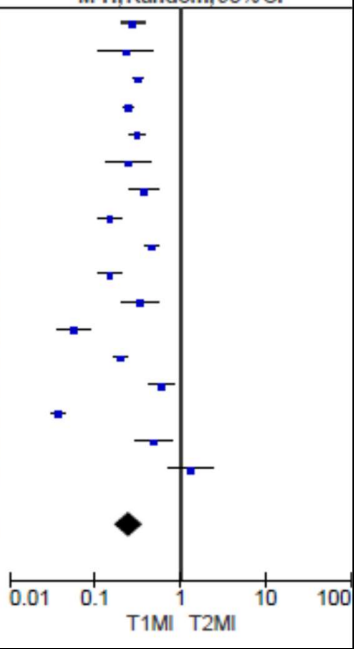


Figure S42. Forest Plot. Percutaneous Coronary Intervention.

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

Heterogeneity: Tau² = 0.99; Chi² = 982.87, df = 23 (P < 0.00001); I² = 98%
Test for overall effect: Z = 12.56 (P < 0.00001)

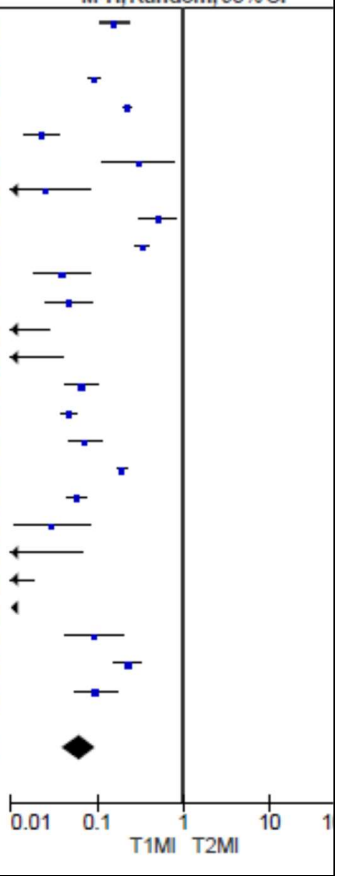


Figure S43. Forest Plot. Coronary Artery Bypass Graft.

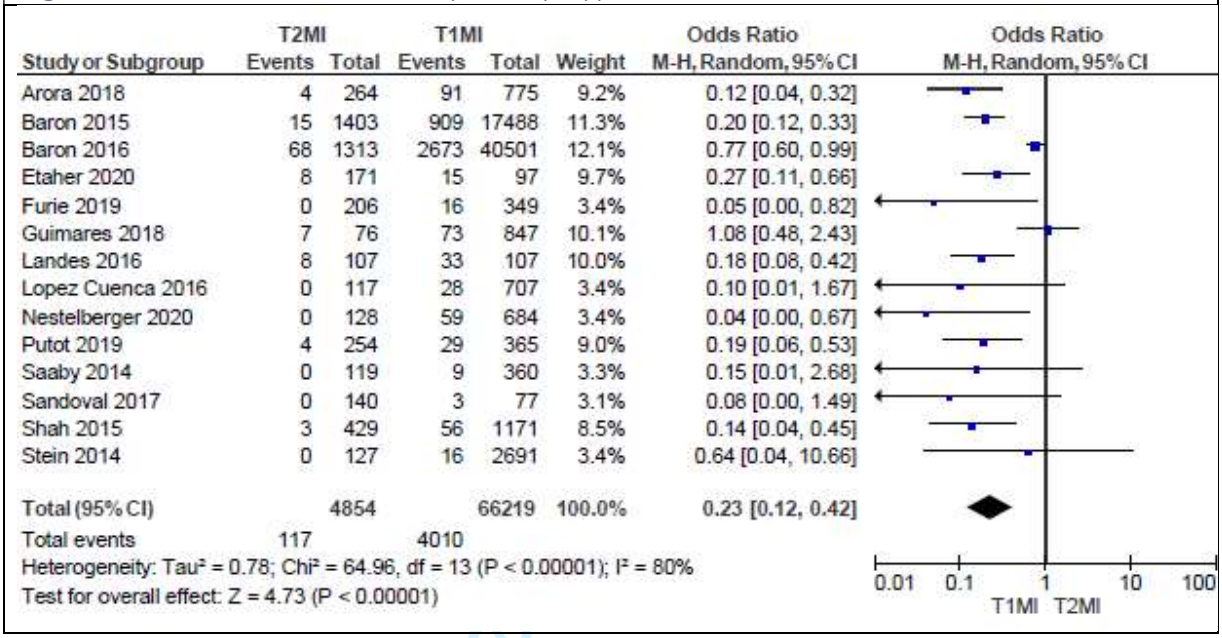


Figure S44. All cause In-hospital mortality. T2MI compared to T1MI.

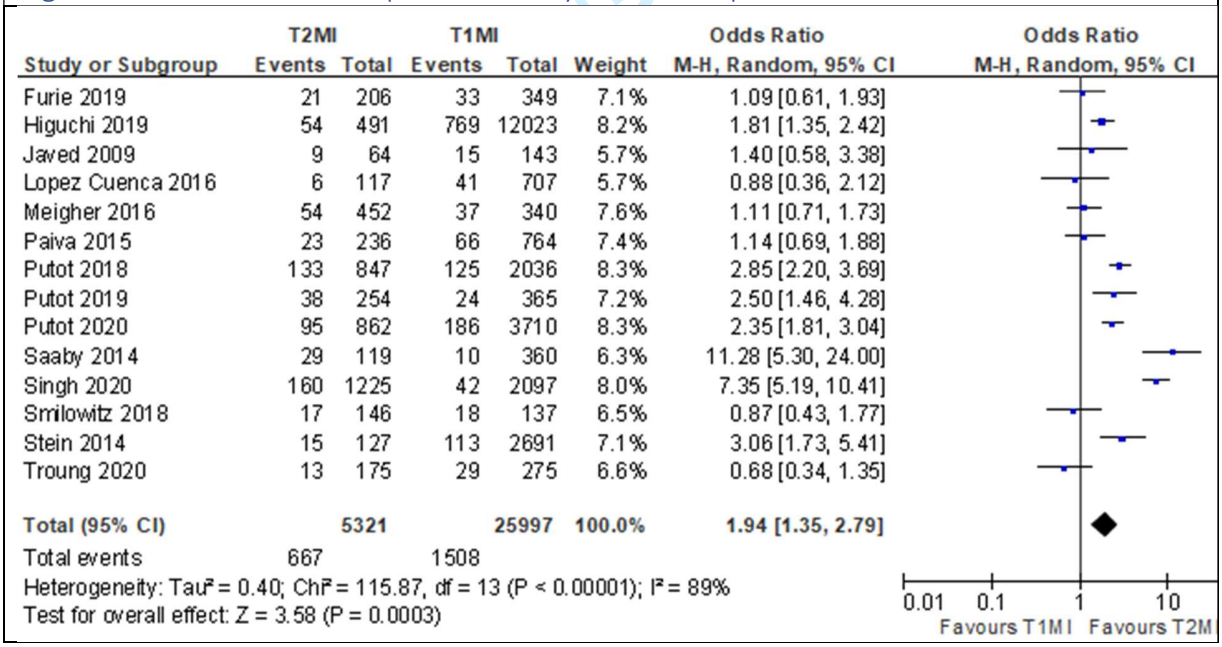


Figure S45. Short-term all-cause mortality. T2MI compared to T1MI.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Nestelberger 2020	1	128	42	684	10.4%	0.12 [0.02, 0.88]
Sandoval 2014	51	190	15	66	29.6%	1.25 [0.65, 2.41]
Sandoval 2017	18	140	6	77	23.4%	1.75 [0.66, 4.60]
Shah 2015	134	429	187	1171	36.7%	2.39 [1.85, 3.09]
Total (95% CI)		**887**		**1998**	**100.0%**	**1.34 [0.63, 2.85]**
Total events	204		250			

Heterogeneity: Tau² = 0.38; Chi² = 12.11, df = 3 (P = 0.007); I² = 75%
Test for overall effect: Z = 0.77 (P = 0.44)

0.01 0.1
Favours T

Figure S47. Two-year all-cause mortality. T2MI compared to T1MI.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Cediel 2017	77	194	74	376	19.0%	2.69 [1.83, 3.94]
Guimares 2018	19	76	156	847	15.9%	1.48 [0.85, 2.55]
Neumann 2017	14	99	18	188	12.5%	1.56 [0.74, 3.28]
Paiva 2015	62	236	92	764	19.3%	2.60 [1.81, 3.74]
Smilowitz 2018	45	146	41	137	16.6%	1.04 [0.63, 1.73]
Troung 2020	29	175	47	275	16.6%	0.96 [0.58, 1.60]
Total (95% CI)		**926**		**2587**	**100.0%**	**1.63 [1.11, 2.41]**
Total events	246		428			

Heterogeneity: Tau² = 0.17; Chi² = 19.10, df = 5 (P = 0.002); I² = 74%
Test for overall effect: Z = 2.48 (P = 0.01)

0.01 0.1
Favours T

Figure S48. Three-year all-cause mortality. T2MI compared to T1MI.

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

Heterogeneity: Tau² = 0.27; Chi² = 14.69, df = 2 (P = 0.0006); I² = 86%
Test for overall effect: Z = 2.16 (P = 0.03)

0.01 0.1
Favours

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PRISMA 2020 Checklist

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

PRISMA 2020 Checklist

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

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

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Title Page

Manuscript Title

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

Authors

Dr Kyle White
Princess Alexandra Hospital, Brisbane, Australia
University of Queensland, Brisbane, Australia
BSc, MBBS, FRACP, FCICM, MPH

Dr Mansey Kinarivala
Princess Alexandra Hospital, Brisbane, Australia
MBBS, FRACP

Prof Ian Scott
Princess Alexandra Hospital, Brisbane, Australia
University of Queensland, Brisbane, Australia
MEd, MHA, MBBS, FRACP

Corresponding Author

Dr Kyle White
Princess Alexandra Hospital
199 Ipswich Road, Wolloongabba, 4102
Ph: +61731762111
Email: kyle.white@health.qld.gov.au

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Abstract

Importance

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

Objective

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

Data Sources

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

Study Selection

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

Data Extraction and Synthesis

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

Main Outcomes and Measures

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

Results

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

Conclusion and Relevance

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

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

Strength and Limitations

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

Introduction

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

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

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

Methods

Study design

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

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

Data collection and synthesis

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

Data on variables reported as, or able to be converted to, raw numbers, were pooled from all studies and subject to comparative meta-analysis using Review Manager (RevMan, Computer program. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For each variable, the weighted odds ratio (OR) comparing T2MI to T1MI, and its 95% confidence interval (CI), was calculated using the random effects method. As specified in the registered study protocol, the random effects method was used in anticipation of study heterogeneity of at least moderate degree (I^2 statistic of heterogeneity >50%) (10). In addition to the weighted OR, we also report the crude, unweighted total event rates for each variable subject to meta-analysis in order to provide a more clinically meaningful estimate of the prevalence of these events in each patient group in view of the large sample sizes. Studies reporting mean or median values only were reproduced as reported in the original study.

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

Patient and Public Involvement

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

Results

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

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

Risk of bias assessment

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

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

Participant characteristics

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

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

Precipitating factors

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

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

Presenting clinical features

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

Investigations

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

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

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

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

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

Management

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

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

Prognosis

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

Conclusion

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

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

Tables

Table 1. Pre-existing medical conditions in patients with T2MI versus T1MI.

Pre-existing medical condition	T2MI			T1MI			Odds ratio* (95% CI)
	Number of patients with the specified condition	Total number of patients	%	Number of patients with the specified condition	Total number of patients	%	
CAD	3915	11706	33.4%	27538	110213	25.0%	1.13 [0.96, 1.32]
Type 2 DM	3420	13560	25.2%	27169	110833	24.5%	0.98 [0.86, 1.10]
HTN	8296	12424	66.8%	64648	105505	61.3%	1.22 [1.05, 1.43]
Dyslipidaemia	4626	10652	43.4%	40099	87366	45.9%	0.74 [0.58, 0.94]
Smoker	4213	11332	37.2%	49796	92377	53.9%	0.61 [0.50, 0.74]
Obesity	1225	3672	33.4%	30963	56970	54.3%	0.63 [0.46, 0.87]
Renal failure	2002	7443	26.9%	15969	82882	19.3%	1.89 [1.59, 2.25]
Heart failure	1949	10276	19.0%	7471	91700	8.1%	2.34 [1.87, 2.93]
PVD	584	5856	10.0%	2066	41280	5.0%	1.33 [1.05, 1.69]
CVD	1164	9941	11.7%	7669	105310	7.3%	1.48 [1.30, 1.69]
Atrial fibrillation	836	3645	22.9%	1220	19843	6.1%	3.02 [2.29, 3.99]
COPD	800	5018	15.9%	823	48375	1.7%	1.94 [1.22, 3.08]
Illicit drug Use	46	204	22.5%	8	220	3.6%	8.15 [1.03, 64.46]

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

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

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

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

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

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

Table 3. Outcomes in patients with T2MI versus T1MI.

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

*Comparing T1MI with T2MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis
Abbreviations: CV= Cardiovascular, MACE= Major adverse cardiovascular events; T2MI=type 2 myocardial infarction; T1MI=type 1 myocardial infarction; CI=confidence interval

Figures

Figure S38. Forest Plot. Percutaneous Coronary Intervention Performed.

Contribution Statement

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

Competing Interests

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

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Data Sharing Statement

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

Ethic Approval Statement

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

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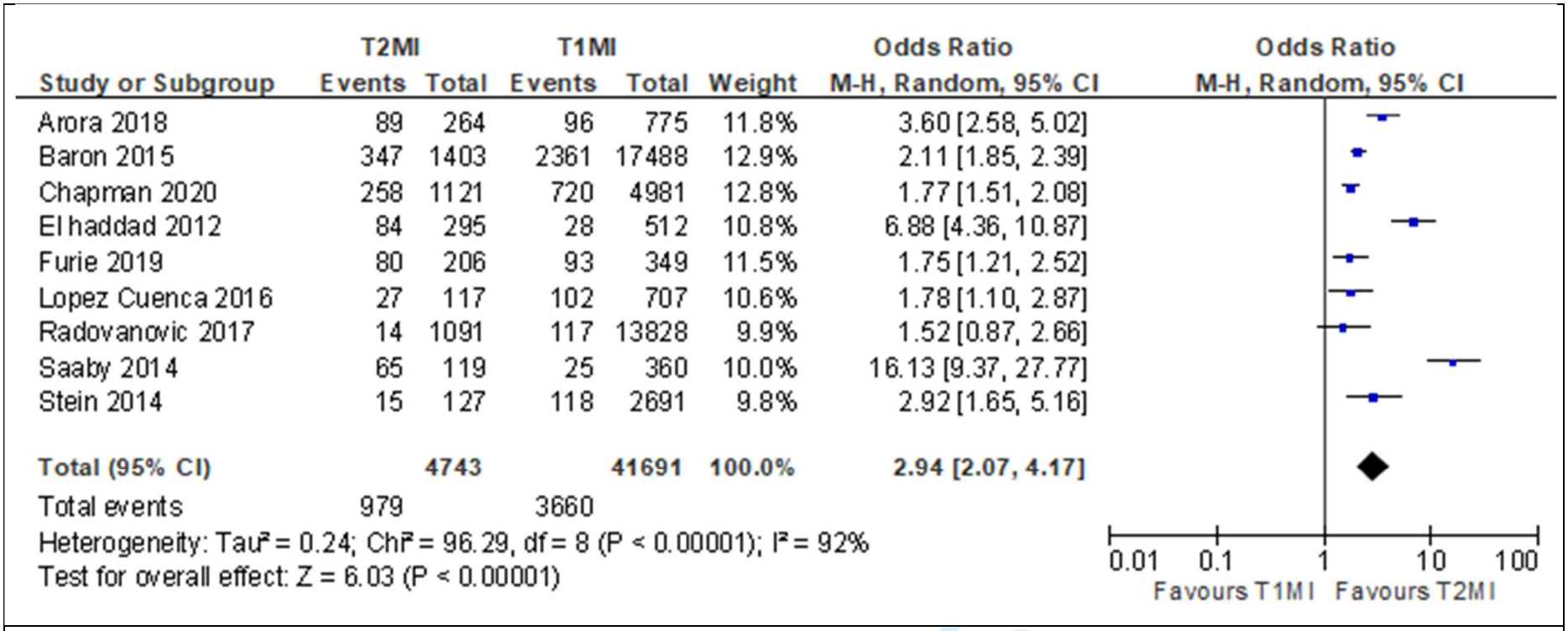


Figure 1. Forest plot of the result of meta-analysis of the risk one year mortality of T2MI patients compared to T1MI patients.

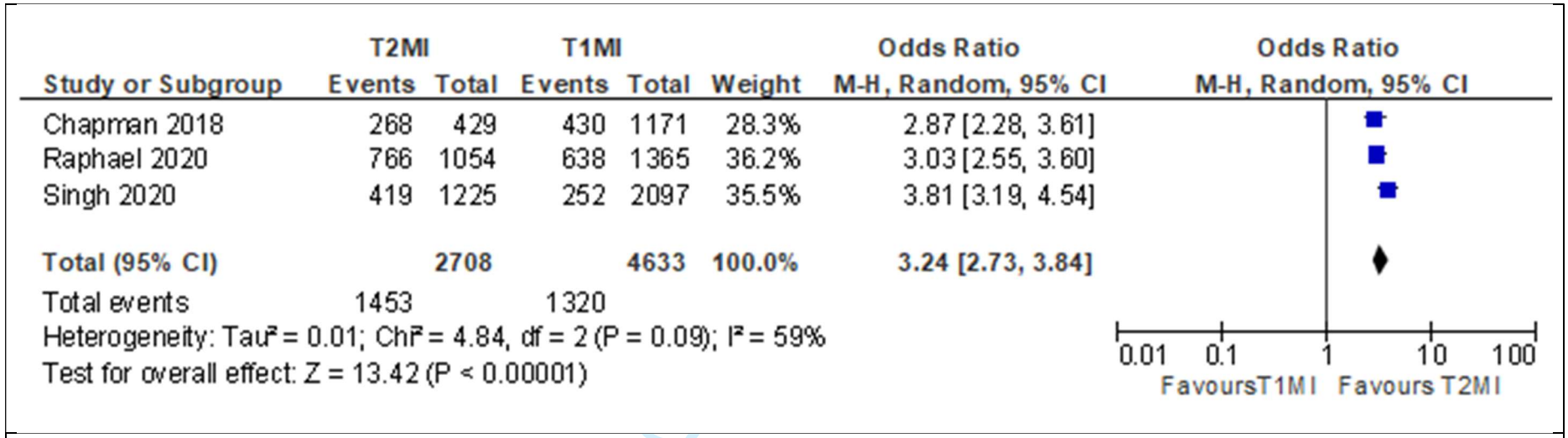


Figure 2. Forest plot of the result of meta-analysis of the risk long-term mortality of T2MI patients compared to T1MI patients.

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, 2015 (3)	17488	1403	Prospective	2007	Sweden	AMI patients	hs-cTnT
Baron, 2016 (4)	40501	1313	Prospective	2007	Sweden	AMI patients	hs-cTnT
Bonaca, 2012 (5)	359	42	Prospective	2007	Multinational	TRITON TIMI 38 trial	N/A
Cediel, 2017 (6)	376	194	Retrospective	2012	Spain	ED patients with at least 1 troponin	cTnI
Chapman, 2018 (7)	1171	429	Prospective	2012	UK	ED with elevated troponin	cTnI
Chapman, 2020 (8)	4981	1121	Prospective	2018	UK	Suspected ACS	cTnI
Consuegra-Sanchaz, 2018 (9)	125	75	Retrospective	2012	Spain	ED patients with at least 1 troponin	cTnI hs-cTnT
El-Haddad, 2012 (10)	512	295	Retrospective	2012	USA	Patients with elevated troponin	N/A
Etaher, 2020 (11)	97	121	Prospective	2018	Australia	Patients with elevated troponin	N/A
Furie, 2019 (12)	349	206	Retrospective	2012	Israel	NSTEMI on general ward	Unknown
Guimaraes, 2018 (13)	847	76	Retrospective	2012	Multinational	ACS during TRACER trial	N/A
Hawatmeh, 2020 (14)	664	281	Retrospective	2012	USA	NSTEMI patients	cTnI
Higuchi, 2019 (15)	12023	491	Retrospective	2012	Tokyo	Admitted to CCU	N/A
Javed, 2009 (16)	143	64	Retrospective	2007	USA	Patients with elevated troponin	cTnI
Kadesjo, 2019 (17)	1111	251	Retrospective	2018	Sweden	MI, Registry	N/A
Lambrecht, 2018 (18)	360	119	Prospective	2007	Denmark	Hospitalised patients with troponin measured	cTnI
Landes, 2016 (19)	107	107	Retrospective	2012	Israel	Diagnosed with T2MI and T1MI	cTnT
Lopez-Cuenca, 2016 (20)	707	117	Retrospective	2012	Spain	Diagnosed with T2MI and T1MI	hs-cTnT
Meigher, 2016 (21)	340	452	Retrospective	2012	Germany	ED patients with elevated troponin	cTnI
Nestelberger, 2017 (22)	684	128	Prospective	2012	Multinational	ED patients with MI	N/A

Neumann, 2017 (23)	188	99	Prospective	2012	Germany	ED patients with suspected MI	hs-cTnI
Paiva, 2015 (24)	764	236	Retrospective	2012	Portugal	Admitted to CCU with MI	cTnI
Pandey, 2020 (25)	97	103	Prospective	2018	USA	MI	N/A
Putot, 2018 (26)	2036	847	Prospective	2012	France	ED or cardiology ward with elevated troponin	cTnI
Putot, 2019 (27)	365	254	Retrospective	2018	France	Hospitalised patients with CAD	cTnI
Putot, 2020 (28)	3710	862	Retrospective	2012	France	Hospitalised patients with MI	cTnI
Radovanovic, 2017 (29)	13828	1091	Retrospective	2012	Switzerland	Diagnosed AMI	N/A
Raphael, 2020 (30)	1365	1054	Retrospective	2018	USA	Raised troponin	cTnT
Reed, 2017 (31)	88	162	Retrospective	2012	USA	Underwent vascular surgery procedure	cTnT
Saaby 2013 (32)	397	144	Prospective	2007	Denmark	Troponin measured	cTnI
Saaby, 2014 (33)	360	119	Prospective	2007	Denmark	Elevated troponin	cTnI
Sandoval, 2014 (34)	66	190	Retrospective	2012	USA	ED patients with troponin measured	cTnI
Sandoval, 2017 (35)	77	140	Prospective	2012	USA	ED patients with troponin measured	cTnI
Sato, 2020 (36)	2834	155	Prospective	2012	Japan	Hospitalised patient with MI	N/A
Shah, 2015 (37)	1171	429	Prospective	2012	UK	Admitted with elevated troponin	cTnI
Singh, 2020 (38)	2097	1225	Retrospective	2018	USA	Age <50, MI or raised troponin	N/A
Smilowitz, 2018 (39)	137	146	Prospective	2012	USA	Admitted with raised troponin	cTnI
Stein, 2014 (40)	2691	127	Prospective	2007	Israel	Admitted to cardiology	N/A
Truong, 2020 (41)	275	175	Retrospective	2012	Russia	MI, undergoing angiogram	N/A

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, 2015 (3)	17488	1403	X	X	X	X	X	X
Baron, 2016 (4)	40501	1313	X	X	X	X	X	
Bonaca, 2012 (5)	359	42						
Cediel, 2017 (6)	376	194	X	X	X	X		X
Chapman, 2018 (7)	1171	429	X		X	X	X	X
Chapman, 2020 (8)	4981	1121	X	X	X	X		X
Consuegra-Sanchaz, 2018 (9)	125	75	X	X	X	X		
El-Haddad, 2012 (10)	512	295						X
Etaher, 2020 (11)	97	121	X		X		X	
Furie, 2019 (12)	349	206	X	X	X	X	X	X
Guimaraes, 2018 (13)	847	76	X		X		X	X
Hawatmeh, 2020 (14)	664	281	X		X	X	X	
Higuchi, 2019 (15)	12023	491	X		X		X	X
Javed, 2009 (16)	143	64	X		X	X		X
Kadesjo, 2019 (17)	1111	251	X				X	X
Lambrecht, 2018 (18)	360	119	X		X	X		X
Landes, 2016 (19)	107	107	X	X	X	X		
Lopez-Cuenca, 2016 (20)	707	117	X	X	X	X	X	X
Meigher, 2016 (21)	340	452	X	X	X	X		X
Nestelberger, 2017 (22)	684	128	X		X		X	X
Neumann, 2017 (23)	188	99	X		X	X		X
Paiva, 2015 (24)	764	236	X		X	X		X
Pandey, 2020 (25)	97	103	X					
Putot, 2018 (26)	2036	847	X		X	X		X
Putot, 2019 (27)	365	254	X		X	X		X
Putot, 2020 (28)	3710	862	X		X	X		X
Radovanovic, 2017 (29)	13828	1091	X		X		X	X

Raphael, 2020 (30)	1365	1054	X		X	X	X	X
Reed, 2017 (31)	88	162			X	X	X	
Saaby 2013 (32)	397	144	X		X	X		
Saaby, 2014 (33)	360	119	X		X	X	X	X
Sandoval, 2014 (34)	66	190	X	X	X	X		X
Sandoval, 2017 (35)	77	140	X	X	X	X	X	X
Sato, 2020 (36)	2834	155	X		X		X	X
Shah, 2015 (37)	1171	429	X	X	X	X	X	X
Singh, 2020 (38)	2097	1225	X		X		X	X
Smilowitz, 2018 (39)	137	146	X	X	X	X	X	X
Stein, 2014 (40)	2691	127	X	X	X		X	X
Truong, 2020 (41)	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, 2015 (3)	x	x	x	x	x	8 (good quality)
Baron, 2016 (4)	x	x	x	x	x	8 (good quality)
Bonaca, 2012 (5)	x	x	x	x	x	8 (good quality)
Cediel, 2017 (6)	x	x	x	x	x	8 (good quality)
Chapman, 2018 (7)	x	x	x	x	x	8 (good quality)
Chapman, 2020 (8)	x	x	x	x	x	8 (good quality)
Consuegra-Sanchaz, 2018 (9)	0	0	x	0	0	3 (poor quality)
El-Haddad, 2012 (10)	x	x	0	0	0	5 (fair quality)
Etaher, 2020 (11)	x	x	x	x	x	8 (good quality)
Furie, 2019 (12)	x	x	x	x	x	8 (good quality)
Guimaraes, 2018 (13)	0	0	x	0	x	4 (fair quality)
Hawatmeh, 2020 (14)	0	0	x	x	0	4 (fair quality)
Higuchi, 2019 (15)	0	0	x	x	x	5 (fair quality)
Javed, 2009 (16)	x	x	x	x	x	8 (good quality)
Kadesjo, 2019 (17)	x	x	x	x	x	8 (good quality)
Lambrecht, 2018 (18)	x	x	x	x	x	8 (good quality)
Landes, 2016 (19)	x	x	x	x	x	8 (good quality)
Lopez-Cuenca, 2016 (20)	x	x	x	x	x	8 (good quality)
Meigher, 2016 (21)	x	x	x	x	x	8 (good quality)
Nestelberger, 2017 (22)	x	x	x	x	x	8 (good quality)

Neumann, 2017 (23)	x	x	x	x	x	8 (good quality)
Paiva, 2015 (24)	x	x	x	x	x	8 (good quality)
Pandey, 2020 (25)	0	0	0	0	0	2 (poor quality)
Putot, 2018 (26)	x	x	x	x	x	8 (good quality)
Putot, 2019 (27)	x	x	0	x	x	7 (good quality)
Putot, 2020 (28)	x	x	x	x	x	8 (good quality)
Radovanovic, 2017 (29)	x	x	x	x	x	8 (good quality)
Raphael, 2020 (30)	x	x	x	x	x	8 (good quality)
Reed, 2017 (31)	x	x	x	x	x	8 (good quality)
Saaby 2013 (32)	x	x	x	x	x	8 (good quality)
Saaby, 2014 (33)	x	x	x	x	x	8 (good quality)
Sandoval, 2014 (34)	x	x	x	x	x	8 (good quality)
Sandoval, 2017 (35)	x	x	x	x	x	8 (good quality)
Sato, 2020 (36)	0	0	0	x	x	2 (poor quality)
Shah, 2015 (37)	x	x	x	x	x	8 (good quality)
Singh, 2020 (38)	0	0	x	x	x	6 (fair quality)
Smilowitz, 2018 (39)	x	x	x	x	x	7 (good quality)
Stein, 2014 (40)	x	x	x	x	x	7 (good quality)
Truong, 2020 (41)	x	x	x	x	x	8 (good quality)

Table S5. Precipitating conditions for T2MI.

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

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	4344	7335	59.2%	73103	83371	87.7%	0.19 [0.15, 0.26]
Dyspnoea	1681	6080	27.6%	8154	82617	9.9%	2.83 [1.96, 4.08]
Arm or shoulder discomfort	28	330	8.5%	50	143	35.0%	0.18 [0.11, 0.30]
Jaw or neck discomfort	6	140	4.3%	12	77	15.6%	0.24 [0.09, 0.68]
Epigastric discomfort	8	140	5.7%	8	77	10.4%	0.52 [0.19, 1.45]
Nausea or vomiting	46	330	13.9%	39	143	27.3%	0.46 [0.28, 0.74]
Fatigue	5	140	3.6%	5	77	6.5%	0.53 [0.15, 1.90]
Diaphoresis	16	140	11.4%	16	77	20.8%	0.49 [0.23, 1.05]
Other nonspecific symptoms	1252	2932	42.7%	4096	58884	7.0%	4.19 [0.72, 24.39]
Collapse / syncope	99	2125	4.7%	157	7152	2.2%	2.10 [1.05, 4.18]

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

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

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	1265	9417	13.4%	42726	101584	42.1%	0.22 [0.18, 0.28]
ST depression or T wave Inversion	2174	6314	34.4%	14938	68530	21.8%	1.38 [0.94, 2.02]
Pathological Q Waves	30	447	6.7%	177	850	20.8%	0.38 [0.20, 0.71]
Non-specific ST-T wave changes	146	592	24.7%	45	417	10.8%	2.62 [1.81, 3.79]
Left bundle branch block	338	3330	10.2%	3045	60031	5.1%	1.72 [1.40, 2.12]
Atrial fibrillation/flutter	448	1660	27.0%	1871	18272	10.2%	3.70 [2.87, 4.77]
Echocardiograph							
Echocardiogram performed	648	1353	47.9%	1571	2830	55.5%	0.44 [0.20, 0.96]
Presence of RWMA	97	286	33.9%	101	214	47.2%	0.48 [0.06, 3.78]
Angiogram							
Angiogram performed	3686	10721	34.4%	56242	67432	83.4%	0.09 [0.06, 0.12]
Obstructive coronary artery disease present	1246	3663	34.0%	19923	44404	44.9%	0.16 [0.05, 0.54]
Multivessel disease present	593	2147	27.6%	11839	41715	28.4%	0.40 [0.19, 0.82]

*Comparing T2MI with 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)	21	5.1-1703	2.8-447
Abbreviations: xULN= times upper limit normal			

Figure S1. PRISMA flow diagram.

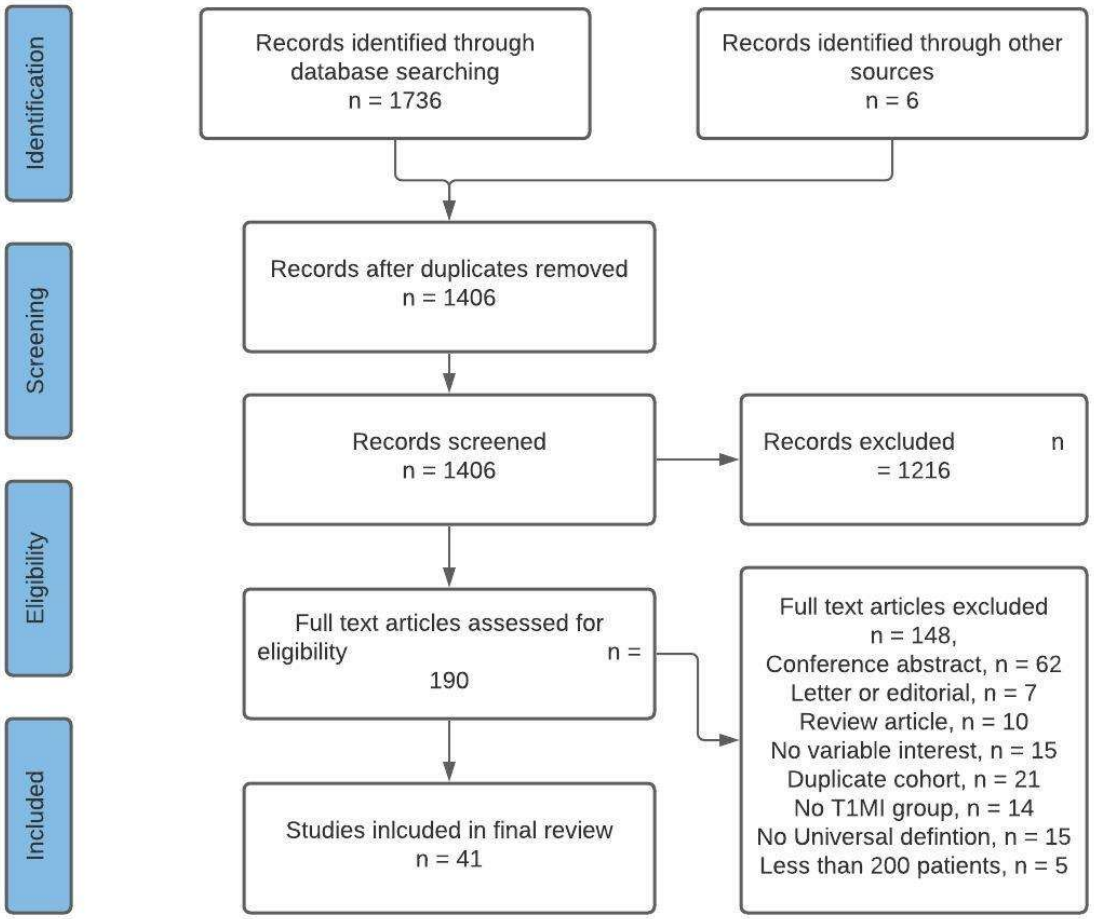


Figure S2. Forest Plot. Presence of Ischaemic Heart Disease.

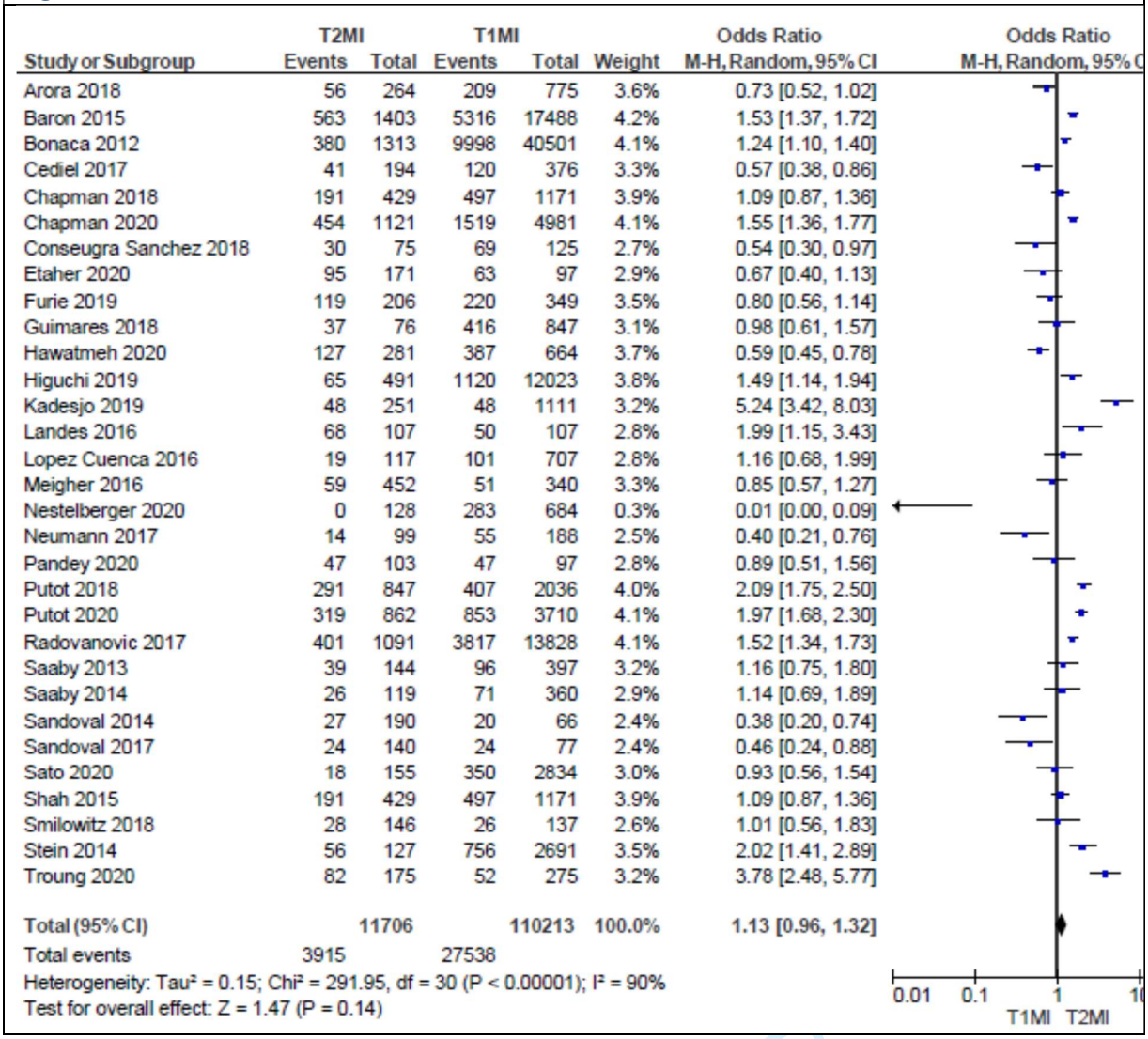


Figure S3. Forest Plot. Presence of Type 2 Diabetes Mellitus.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Arora 2018	110	264	371	775	3.3%	0.78 [0.59, 1.03]
Baron 2015	376	1403	3882	17488	3.8%	1.28 [1.13, 1.45]
Baron 2016	306	1313	9395	40501	3.8%	1.01 [0.88, 1.15]
Cediel 2017	73	194	132	376	2.9%	1.12 [0.78, 1.60]
Chapman 2018	93	429	185	1171	3.3%	1.48 [1.12, 1.95]
Chapman 2020	147	1121	802	4981	3.6%	0.79 [0.65, 0.95]
Conseugra Sanchez 2018	29	75	59	125	2.1%	0.71 [0.39, 1.26]
Etaher 2020	64	171	36	97	2.3%	1.01 [0.61, 1.70]
Furie 2019	100	206	199	349	3.0%	0.71 [0.50, 1.00]
Guimares 2018	27	76	419	847	2.4%	0.56 [0.35, 0.92]
Hawatmeh 2020	101	281	303	664	3.2%	0.67 [0.50, 0.89]
Higuchi 2019	148	491	3745	12023	3.6%	0.95 [0.78, 1.16]
Javed 2009	24	64	61	143	2.0%	0.81 [0.44, 1.48]
Kadesjo 2019	56	251	213	1111	3.1%	1.21 [0.87, 1.69]
Lambrecht 2018	28	119	46	360	2.3%	2.10 [1.24, 3.55]
Landes 2016	54	107	54	107	2.3%	1.00 [0.59, 1.71]
Lopez Cuenca 2016	52	117	336	707	2.8%	0.88 [0.60, 1.31]
Meigher 2016	122	452	126	340	3.2%	0.63 [0.46, 0.85]
Nestelberger 2020	26	128	180	684	2.5%	0.71 [0.45, 1.13]
Neumann 2017	12	99	42	188	1.8%	0.48 [0.24, 0.96]
Pandey 2020	47	103	44	97	2.2%	1.01 [0.58, 1.76]
Putot 2018	264	847	504	2036	3.6%	1.38 [1.15, 1.64]
Putot 2019	99	254	138	365	3.1%	1.05 [0.76, 1.46]
Radovanovic 2017	286	1091	2766	13828	3.7%	1.42 [1.23, 1.64]
Raphael 2020	150	1054	313	1365	3.5%	0.56 [0.45, 0.69]
Saaby 2013	40	144	52	397	2.5%	2.55 [1.60, 4.07]
Saaby 2014	28	119	46	360	2.3%	2.10 [1.24, 3.55]
Sandoval 2014	57	190	21	66	2.0%	0.92 [0.50, 1.68]
Sandoval 2017	43	140	32	77	2.1%	0.62 [0.35, 1.11]
Sato 2020	40	155	1015	2834	2.9%	0.62 [0.43, 0.90]
Shah 2015	93	429	185	1171	3.3%	1.48 [1.12, 1.95]
Singh 2020	165	1225	405	2097	3.6%	0.65 [0.53, 0.79]
Smilowitz 2018	58	146	61	137	2.5%	0.82 [0.51, 1.32]
Stein 2014	61	127	945	2691	3.0%	1.71 [1.19, 2.44]
Troung 2020	41	175	56	275	2.6%	1.20 [0.76, 1.89]
Total (95% CI)		13560		110833	100.0%	0.98 [0.86, 1.10]
Total events	3420		27169			

Heterogeneity: Tau² = 0.10; Chi² = 208.56, df = 34 (P < 0.00001); I² = 84%
Test for overall effect: Z = 0.39 (P = 0.70)

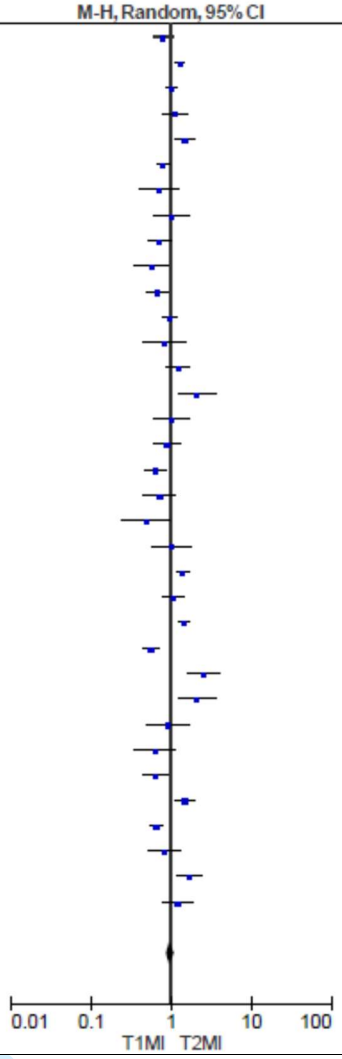


Figure S4. Forest Plot. Presence of Hypertension.

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

Heterogeneity: Tau² = 0.16; Chi² = 318.37, df = 33 (P < 0.00001); I² = 90%

Test for overall effect: Z = 2.52 (P = 0.01)

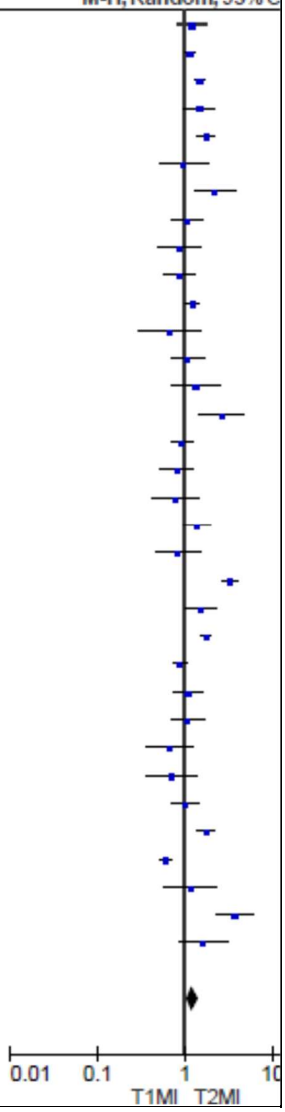


Figure S5. Forest Plot. Presence of Dyslipidaemia.

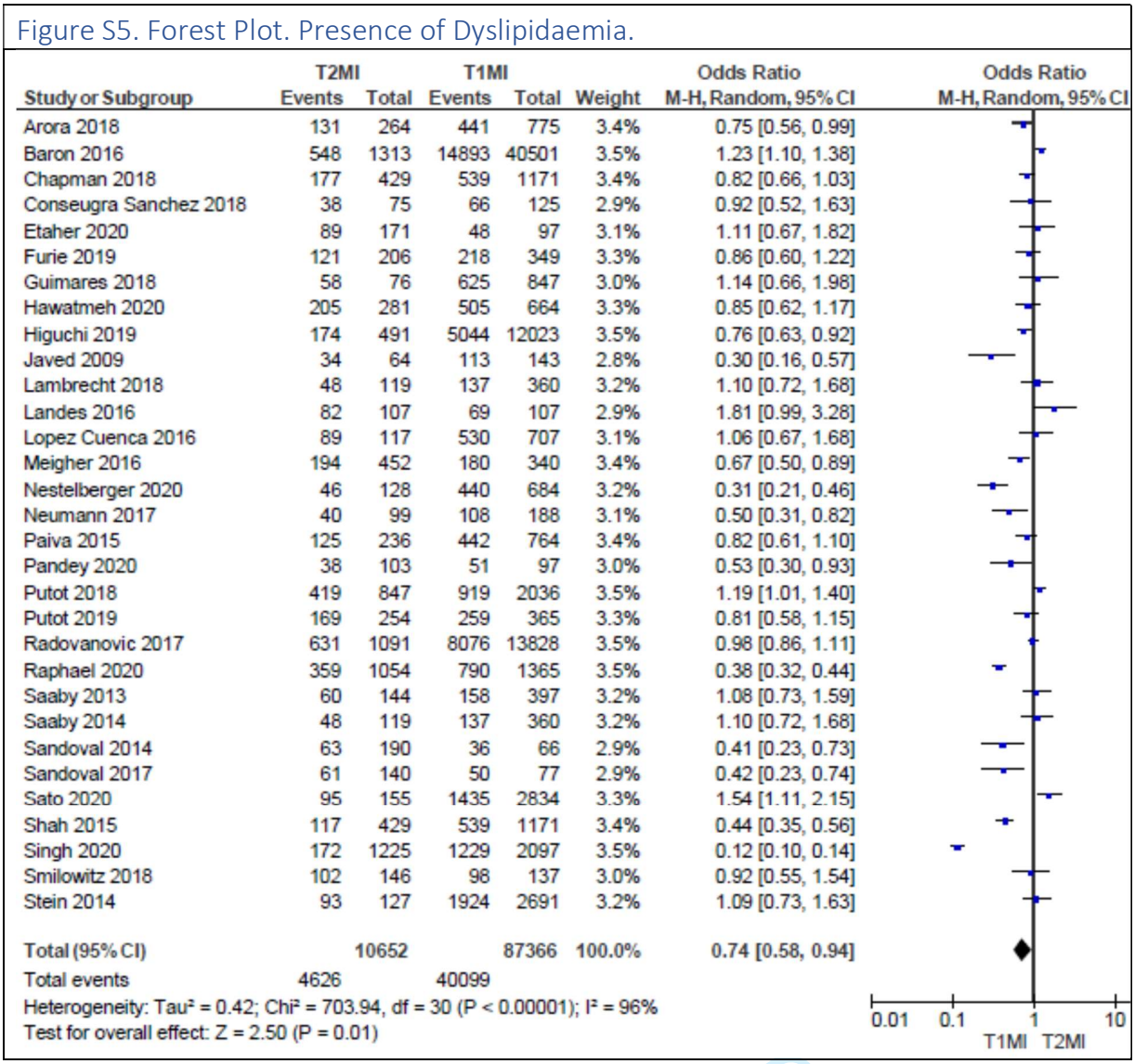


Figure S6. Forest Plot. Smoking Status.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Arora 2018	80	264	327	775	3.6%	0.60 [0.44, 0.80]
Baron 2015	765	1403	10248	17488	3.9%	0.85 [0.76, 0.94]
Baron 2016	771	1313	24754	40501	3.9%	0.90 [0.81, 1.01]
Cediel 2017	62	194	218	376	3.5%	0.34 [0.24, 0.49]
Chapman 2018	62	429	380	1171	3.6%	0.35 [0.26, 0.47]
Conseugra Sanchez 2018	10	75	27	125	2.4%	0.56 [0.25, 1.23]
Etaher 2020	21	171	30	97	2.8%	0.31 [0.17, 0.59]
Furie 2019	73	206	133	349	3.5%	0.89 [0.62, 1.28]
Guimares 2018	36	76	304	847	3.2%	1.61 [1.00, 2.58]
Hawatmeh 2020	88	281	272	664	3.6%	0.66 [0.49, 0.88]
Javed 2009	30	64	66	143	2.9%	1.03 [0.57, 1.86]
Lambrecht 2018	91	119	284	360	3.1%	0.87 [0.53, 1.42]
Landes 2016	44	107	41	107	3.0%	1.12 [0.65, 1.94]
Lopez Cuenca 2016	23	117	232	707	3.2%	0.50 [0.31, 0.81]
Meigher 2016	172	452	129	340	3.6%	1.00 [0.75, 1.34]
Nestelberger 2020	21	128	181	684	3.1%	0.55 [0.33, 0.90]
Neumann 2017	17	99	52	188	2.8%	0.54 [0.29, 1.00]
Pandey 2020	13	103	16	97	2.4%	0.73 [0.33, 1.61]
Putot 2018	280	847	1271	2036	3.8%	0.30 [0.25, 0.35]
Putot 2019	101	254	243	365	3.5%	0.33 [0.24, 0.46]
Radovanovic 2017	340	1091	5697	13828	3.9%	0.65 [0.57, 0.74]
Raphael 2020	462	1054	907	1365	3.8%	0.39 [0.33, 0.47]
Saaby 2013	35	144	129	397	3.3%	0.67 [0.43, 1.03]
Saaby 2014	91	119	284	360	3.1%	0.87 [0.53, 1.42]
Sandoval 2017	52	140	23	77	2.9%	1.39 [0.76, 2.52]
Sato 2020	51	155	921	2834	3.5%	1.02 [0.72, 1.44]
Shah 2015	62	429	380	1171	3.6%	0.35 [0.26, 0.47]
Singh 2020	244	1225	1063	2097	3.8%	0.24 [0.21, 0.29]
Smilowitz 2018	96	146	89	137	3.2%	1.04 [0.63, 1.69]
Stein 2014	20	127	1095	2691	3.2%	0.27 [0.17, 0.44]
Total (95% CI)		11332		92377	100.0%	0.61 [0.50, 0.74]
Total events	4213		49796			

Heterogeneity: Tau² = 0.25; Chi² = 430.67, df = 29 (P < 0.00001); I² = 93%

Test for overall effect: Z = 5.06 (P < 0.00001)

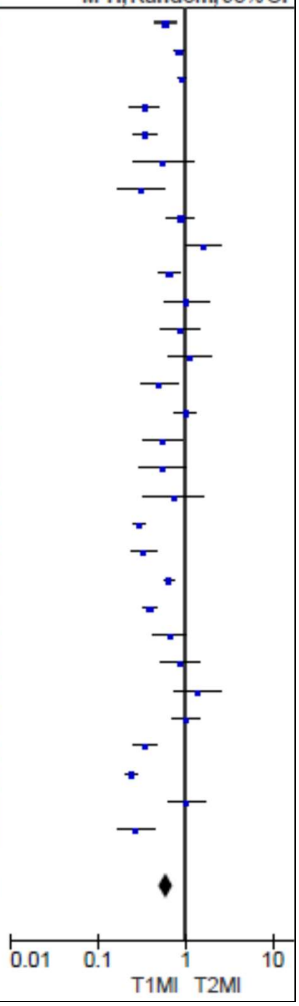


Figure S7. Forest Plot. Obesity Status.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Baron 2016	824	1313	27283	40501	21.6%	0.82 [0.73, 0.91]
Javed 2009	14	64	54	143	11.0%	0.46 [0.23, 0.91]
Pandey 2020	22	103	22	97	11.2%	0.93 [0.47, 1.81]
Putot 2018	91	847	423	2036	19.7%	0.46 [0.36, 0.58]
Putot 2019	27	254	97	365	15.2%	0.33 [0.21, 0.52]
Radovanovic 2017	247	1091	3084	13828	21.2%	1.02 [0.88, 1.18]
Total (95% CI)		3672		56970	100.0%	0.63 [0.46, 0.87]
Total events	1225		30963			

Heterogeneity: Tau² = 0.12; Chi² = 47.72, df = 5 (P < 0.00001); I² = 90%

Test for overall effect: Z = 2.80 (P = 0.005)

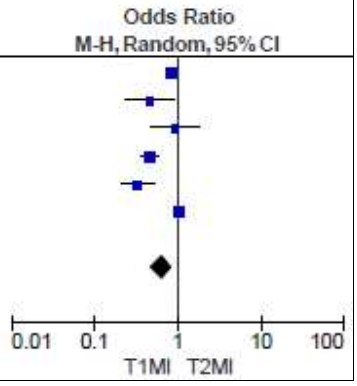


Figure S8. Forest Plot. Presence of Chronic Kidney Disease.

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

Heterogeneity: Tau² = 0.10; Chi² = 100.16, df = 18 (P < 0.00001); I² = 82%
Test for overall effect: Z = 7.15 (P < 0.00001)

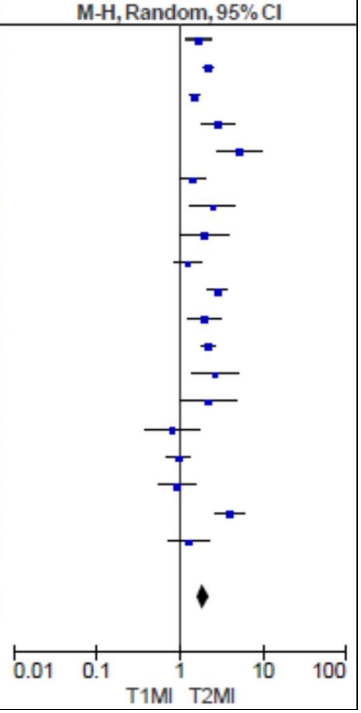


Figure S9. Forest Plot. Presence of Heart Failure.

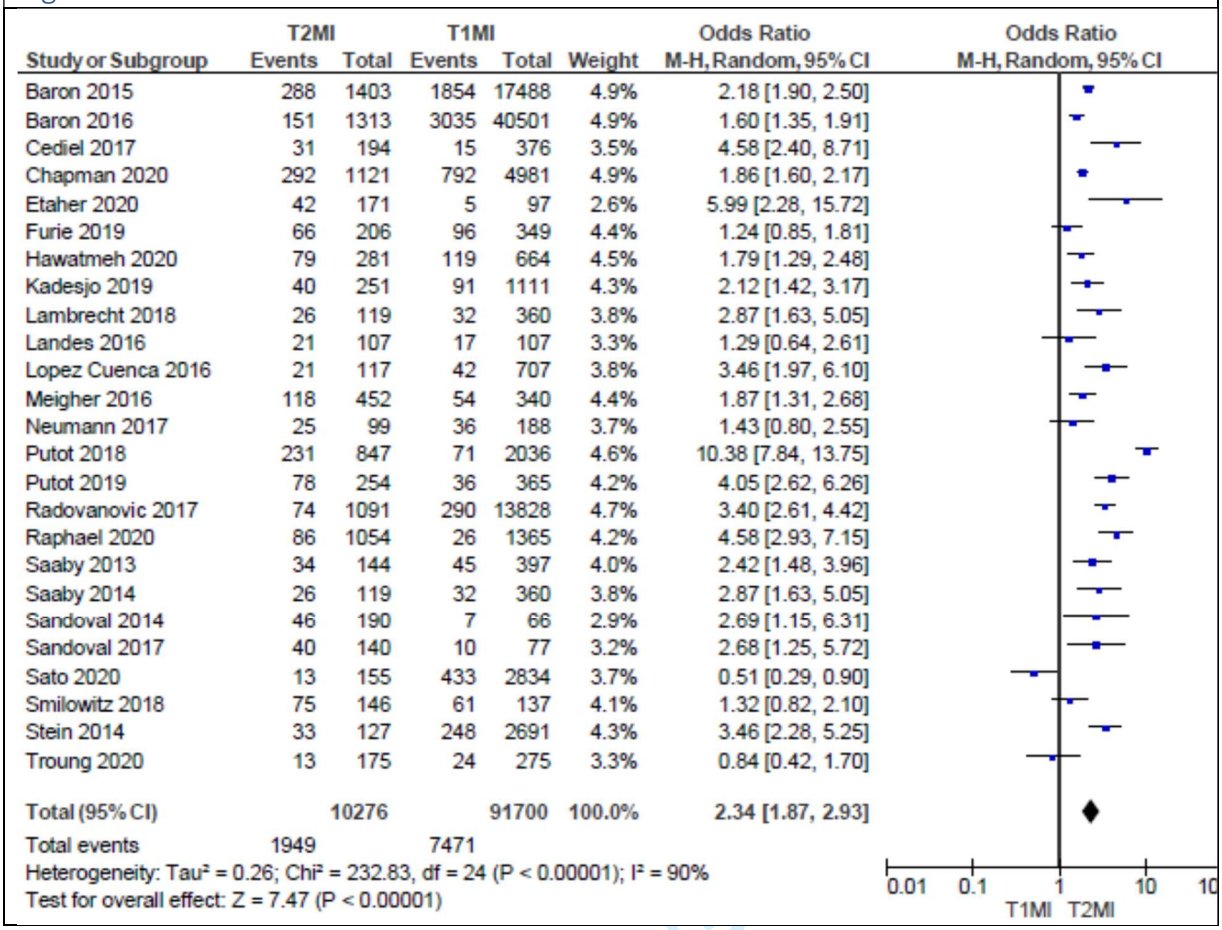


Figure S10. Forest Plot. Presence of Peripheral Vascular Disease.

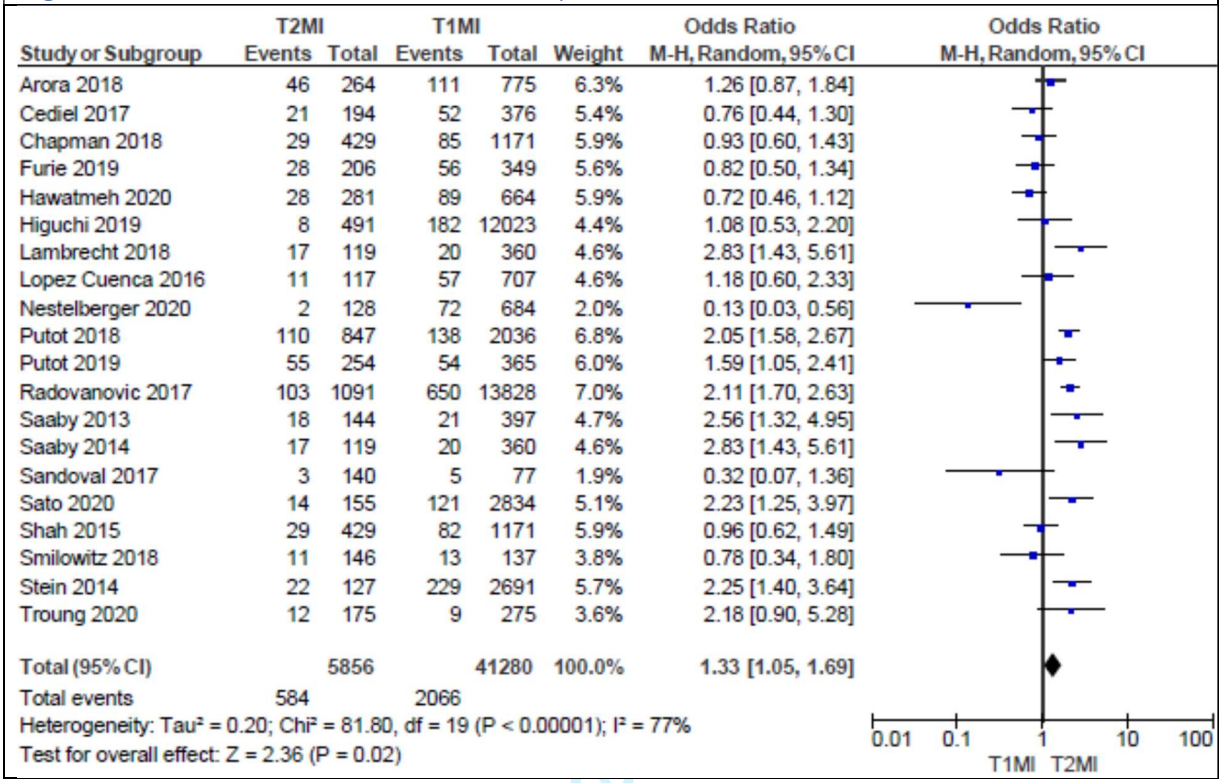


Figure S11. Forest Plot. Presence of Cerebrovascular Disease.

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

Heterogeneity: Tau² = 0.06; Chi² = 62.77, df = 23 (P < 0.0001); I² = 63%
Test for overall effect: Z = 5.77 (P < 0.00001)

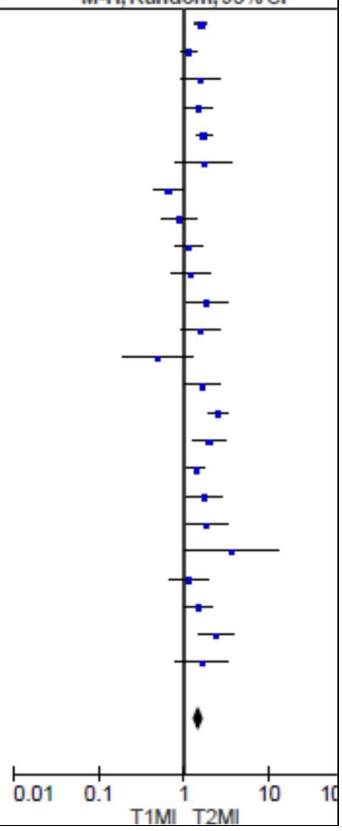


Figure S12. Forest Plot. Presence of Illicit Drug Use.

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

Heterogeneity: Tau² = 1.83; Chi² = 5.52, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 1.99 (P = 0.05)

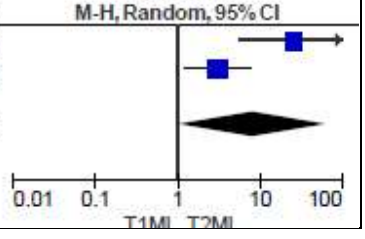


Figure S13. Forest Plot. Presence of Atrial Fibrillation.

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

Heterogeneity: Tau² = 0.18; Chi² = 62.33, df = 11 (P < 0.00001); I² = 82%
Test for overall effect: Z = 7.83 (P < 0.00001)

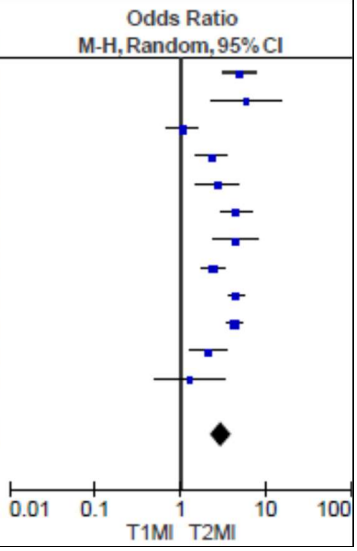


Figure S14. Forest Plot. Chest Pain as Presenting Feature.

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

Heterogeneity: Tau² = 0.29; Chi² = 280.74, df = 16 (P < 0.00001); I² = 94%
Test for overall effect: Z = 11.30 (P < 0.00001)

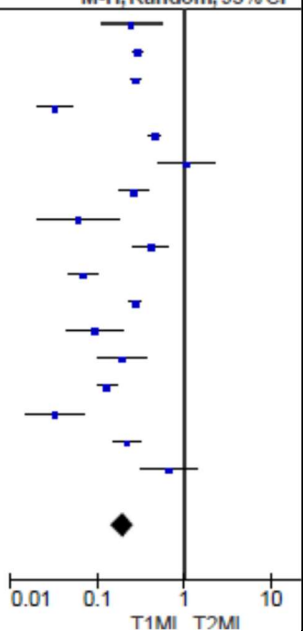


Figure S15. Forest Plot. Dyspnoea as Presenting Feature.

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

Heterogeneity: Tau² = 0.41; Chi² = 266.38, df = 12 (P < 0.00001); I² = 95%
Test for overall effect: Z = 5.55 (P < 0.00001)

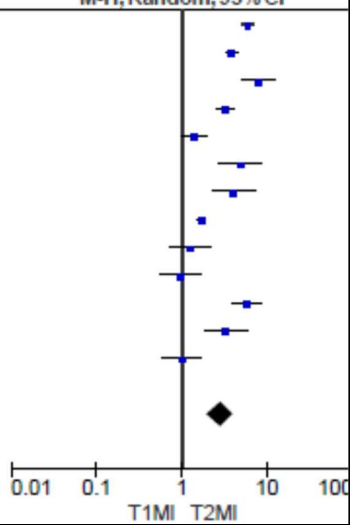


Figure S16. Forest Plot. Arm / Shoulder Discomfort as Presenting Feature.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Sandoval 2014	13	190	20	66	45.6%	0.17 [0.08, 0.36]
Sandoval 2017	15	140	30	77	54.4%	0.19 [0.09, 0.38]
Total (95% CI)		330		143	100.0%	0.18 [0.11, 0.30]
Total events	28		50			

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 6.49 (P < 0.00001)

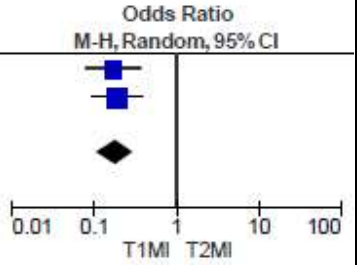


Figure S17. Forest Plot. Nausea / Vomiting as Presenting Feature.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Sandoval 2014	21	190	14	66	42.8%	0.46 [0.22, 0.97]
Sandoval 2017	25	140	25	77	57.2%	0.45 [0.24, 0.86]
Total (95% CI)		330		143	100.0%	0.46 [0.28, 0.74]
Total events	46		39			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 3.16 (P = 0.002)

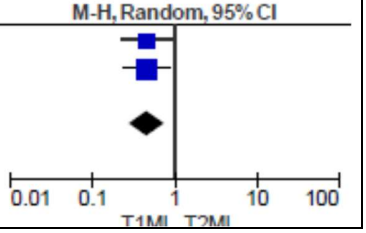


Figure S18. Forest Plot. Non-specific Symptoms as Presenting Features.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Baron 2015	264	1403	1434	17488	25.4%	2.59 [2.25, 3.00]
Baron 2016	899	1313	2506	40501	25.5%	32.92 [29.11, 37.24]
Lopez Cuenca 2016	8	117	51	707	24.3%	0.94 [0.44, 2.04]
Neumann 2017	81	99	105	188	24.8%	3.56 [1.98, 6.39]
Total (95% CI)		2932		58884	100.0%	4.19 [0.72, 24.39]
Total events	1252		4096			

Heterogeneity: Tau² = 3.17; Chi² = 760.73, df = 3 (P < 0.00001); I² = 100%
Test for overall effect: Z = 1.59 (P = 0.11)

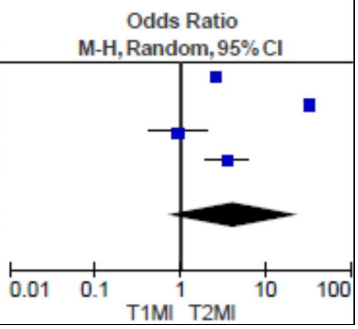


Figure S19. Forest Plot. Collapse / Syncope as Presenting Features.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Cediel 2017	15	194	5	376	17.2%	6.22 [2.22, 17.38]
Chapman 2020	38	1121	102	4981	25.6%	1.68 [1.15, 2.45]
Furie 2019	12	206	24	349	21.4%	0.84 [0.41, 1.71]
Shah 2015	31	429	21	1171	23.4%	4.27 [2.42, 7.51]
Troung 2020	3	175	5	275	12.5%	0.94 [0.22, 3.99]
Total (95% CI)		2125		7152	100.0%	2.10 [1.05, 4.18]
Total events	99		157			

Heterogeneity: Tau² = 0.45; Chi² = 19.12, df = 4 (P = 0.0007); I² = 79%
Test for overall effect: Z = 2.10 (P = 0.04)

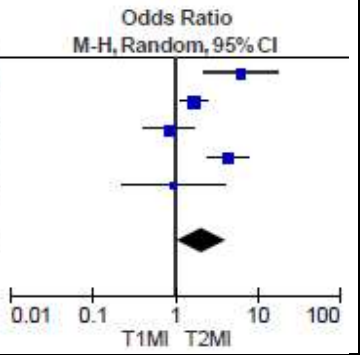


Figure S20. Forest Plot. ST Elevation on ECG.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Baron 2015	136	1403	5544	17488	7.8%	0.23 [0.19, 0.28]
Baron 2016	173	1313	14824	40501	7.9%	0.26 [0.22, 0.31]
Cediel 2017	5	194	92	376	3.4%	0.08 [0.03, 0.20]
Chapman 2020	36	1121	870	4981	6.9%	0.16 [0.11, 0.22]
Furie 2019	4	206	18	349	2.7%	0.36 [0.12, 1.09]
Higuchi 2019	288	491	8917	12023	7.8%	0.49 [0.41, 0.59]
Landes 2016	11	107	11	107	3.5%	1.00 [0.41, 2.42]
Lopez Cuenca 2016	1	117	225	707	1.1%	0.02 [0.00, 0.13]
Nestelberger 2020	4	128	115	684	3.0%	0.16 [0.06, 0.44]
Paiva 2015	35	236	417	764	6.6%	0.14 [0.10, 0.21]
Putot 2019	28	254	136	365	6.1%	0.21 [0.13, 0.33]
Putot 2020	207	862	1929	3710	7.8%	0.29 [0.25, 0.35]
Radovanovic 2017	213	1091	7436	13828	7.9%	0.21 [0.18, 0.24]
Raphael 2020	23	1054	198	1365	6.2%	0.13 [0.08, 0.20]
Saaby 2013	5	144	130	397	3.4%	0.07 [0.03, 0.18]
Sandoval 2017	31	140	24	77	4.9%	0.63 [0.34, 1.17]
Shah 2015	40	429	427	1171	6.8%	0.18 [0.13, 0.25]
Stein 2014	25	127	1413	2691	6.2%	0.22 [0.14, 0.35]
Total (95% CI)		9417		101584	100.0%	0.22 [0.18, 0.28]
Total events	1265		42726			

Heterogeneity: Tau² = 0.15; Chi² = 131.14, df = 17 (P < 0.00001); I² = 87%
Test for overall effect: Z = 13.39 (P < 0.00001)

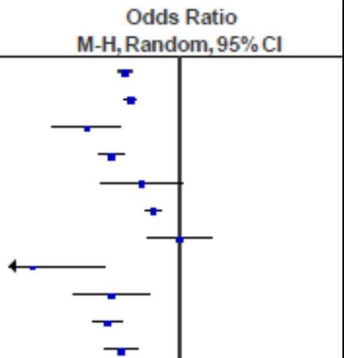


Figure S21. Forest Plot. ST Depression or T Wave Inversion on ECG.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Arora 2018	120	264	369	775	7.1%	0.92 [0.69, 1.21]
Baron 2015	446	1403	3970	17488	7.3%	1.59 [1.41, 1.79]
Baron 2016	330	1313	8261	40501	7.3%	1.31 [1.15, 1.49]
Cediel 2017	16	194	94	376	6.4%	0.27 [0.15, 0.47]
Chapman 2020	278	1121	865	4981	7.3%	1.57 [1.35, 1.83]
Conseugra Sanchez 2018	7	75	43	125	5.4%	0.20 [0.08, 0.46]
Hawatmeh 2020	223	281	86	664	6.9%	25.84 [17.90, 37.30]
Landes 2016	71	107	75	107	6.3%	0.84 [0.47, 1.50]
Lopez Cuenca 2016	35	117	152	707	6.8%	1.56 [1.01, 2.41]
Meigher 2016	68	452	61	340	6.9%	0.81 [0.55, 1.18]
Nestelberger 2020	33	128	234	684	6.8%	0.67 [0.44, 1.02]
Saaby 2013	139	144	267	397	5.2%	13.54 [5.41, 33.84]
Sandoval 2017	74	140	40	77	6.4%	1.04 [0.59, 1.81]
Shah 2015	249	429	332	1171	7.2%	3.50 [2.78, 4.40]
Smilowitz 2018	85	146	89	137	6.6%	0.75 [0.46, 1.22]
Total (95% CI)		6314		68530	100.0%	1.38 [0.94, 2.02]
Total events	2174		14938			

Heterogeneity: Tau² = 0.52; Chi² = 416.57, df = 14 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.64 (P = 0.10)

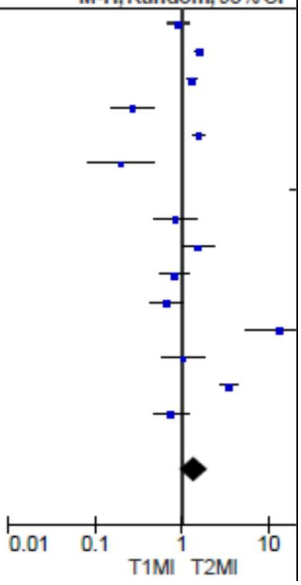


Figure S22. Forest Plot. Q Waves on ECG.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Lopez Cuenca 2016	12	117	156	707	48.4%	0.40 [0.22, 0.75]
Sandoval 2014	2	190	6	66	12.8%	0.11 [0.02, 0.54]
Sandoval 2017	16	140	15	77	38.8%	0.53 [0.25, 1.15]
Total (95% CI)		447		850	100.0%	0.38 [0.20, 0.71]
Total events	30		177			

Heterogeneity: Tau² = 0.11; Chi² = 3.09, df = 2 (P = 0.21); I² = 35%
Test for overall effect: Z = 3.03 (P = 0.002)

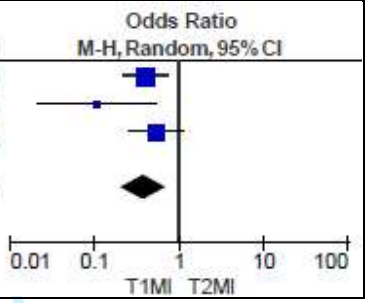


Figure S23. Forest Plot. Non-specific ST Changes on ECG.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
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			

Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 5.12 (P < 0.00001)

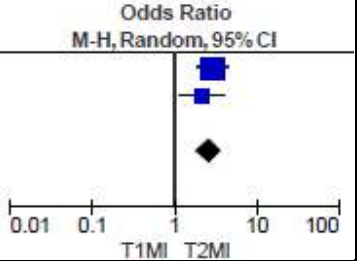


Figure S24. Forest Plot. Left Bundle Branch Block on ECG.

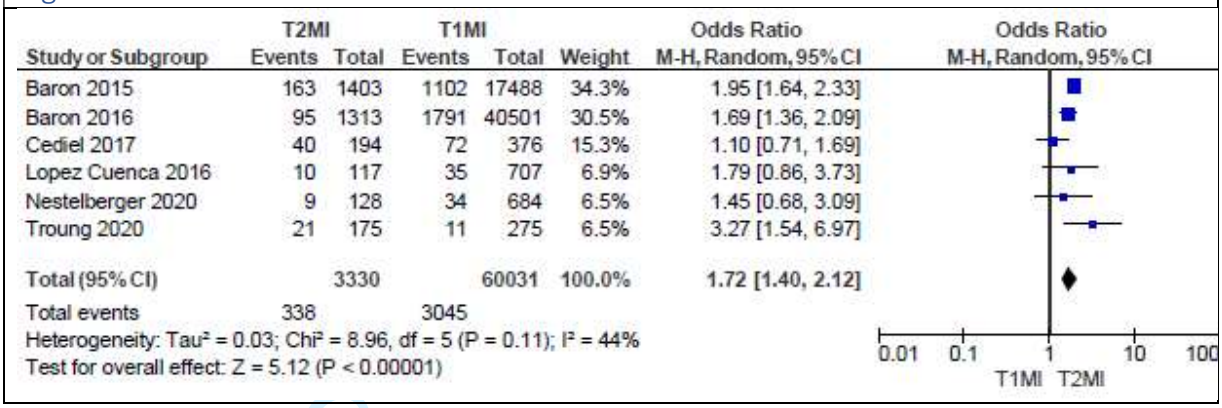


Figure S25. Forest Plot. Atrial Fibrillation on ECG.

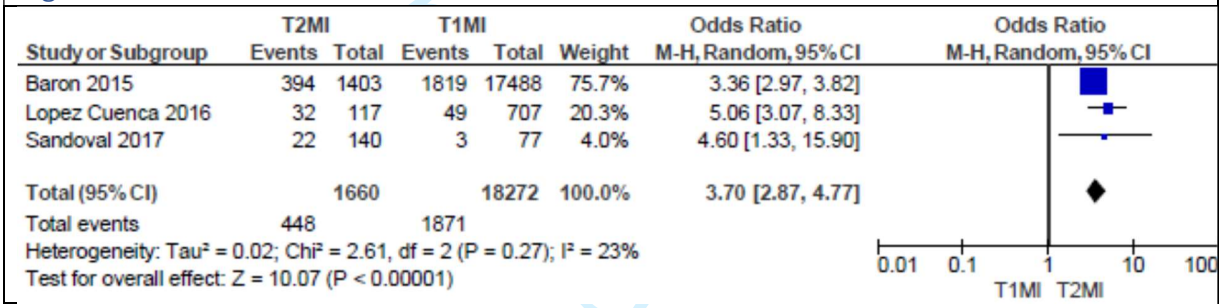


Figure S26. Forest Plot. Coronary Angiogram Performed.

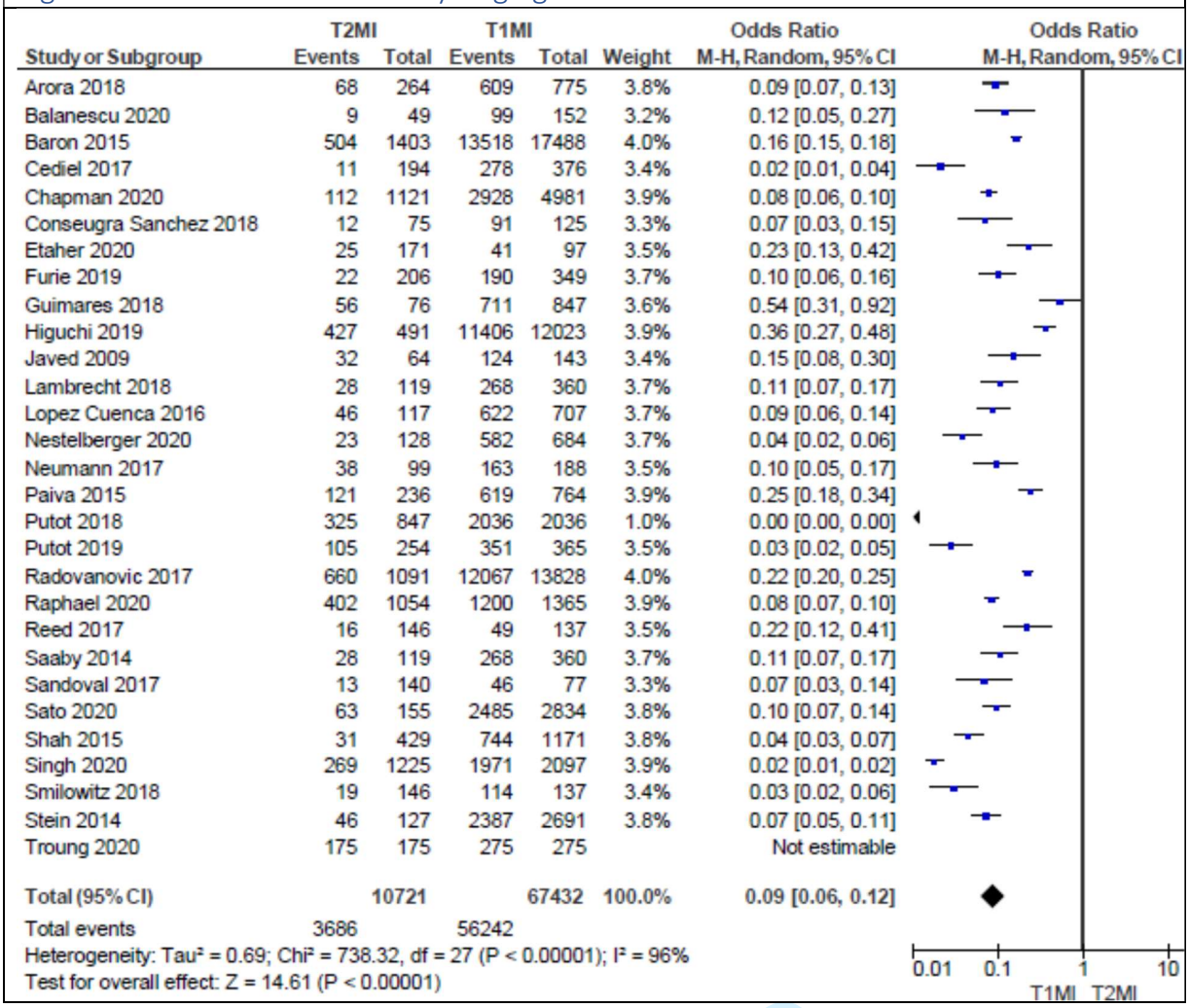


Figure S27. Forest Plot. Obstructive Coronary Artery Disease on Coronary Angiogram.

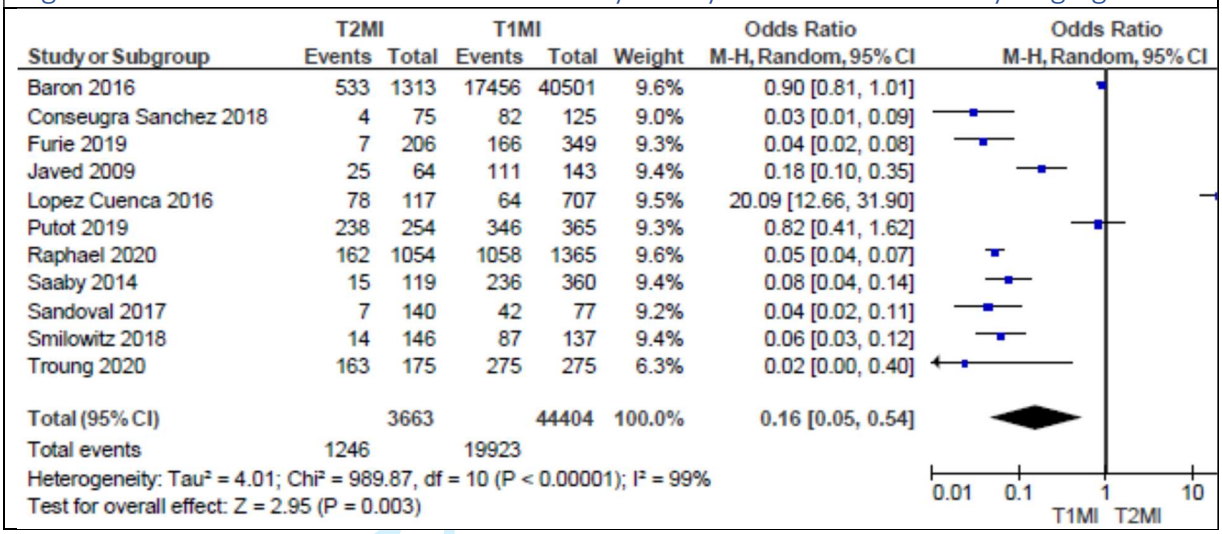


Figure S28. Forest Plot. Multivessel Disease on Coronary Angiogram.

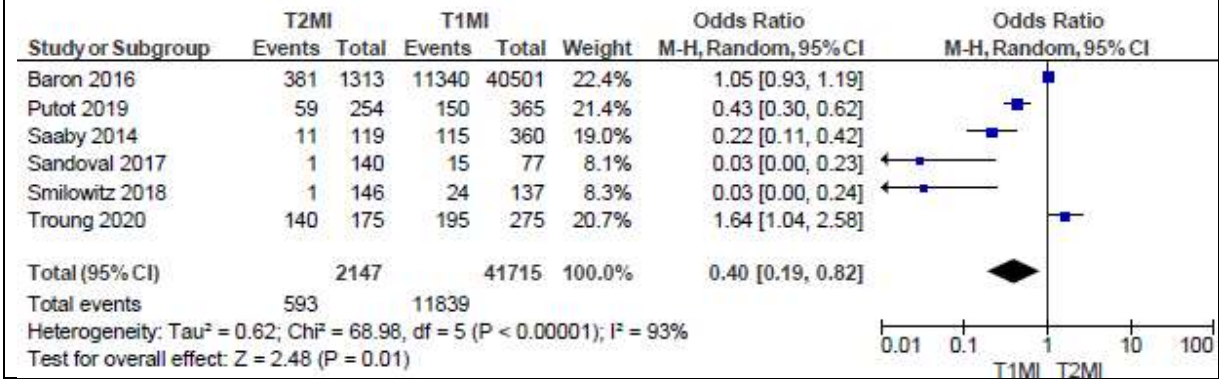


Figure S29. Forest Plot. Echocardiogram Performed.

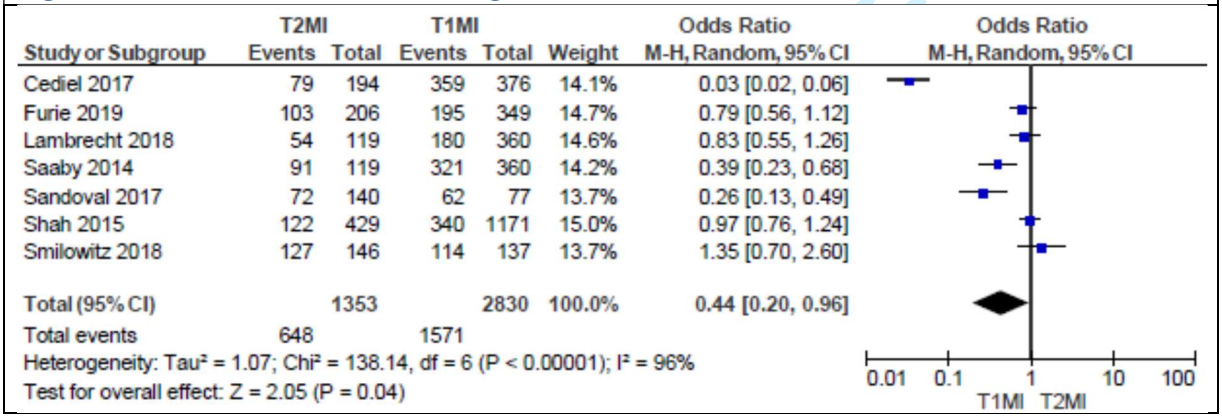


Figure S30. Forest Plot. Regional Wall Motion Abnormalities on Echocardiogram.

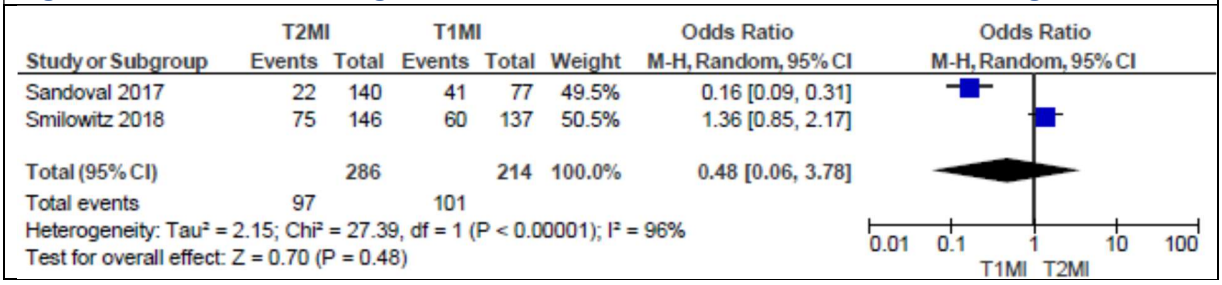


Figure S31. Forest Plot. Beta-Blockers Prescribed.

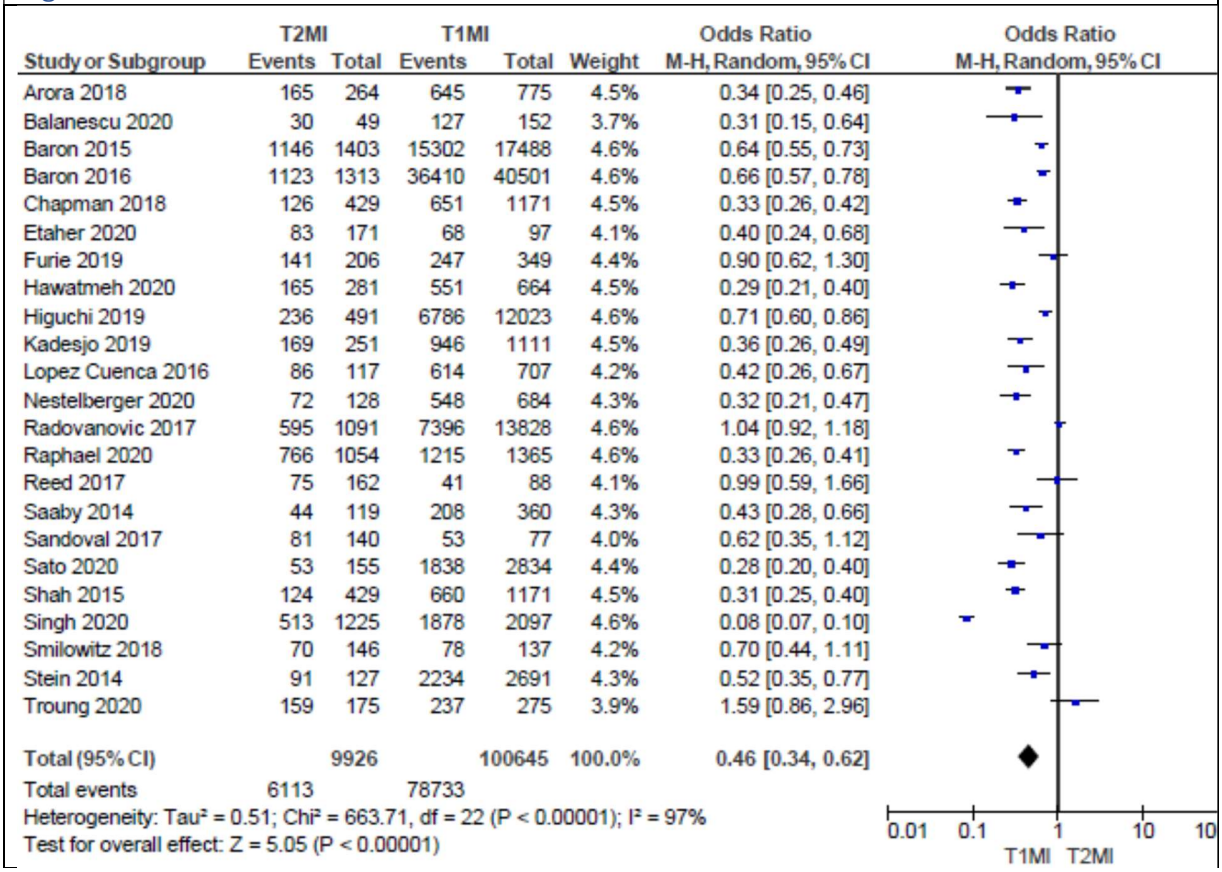


Figure S32. Forest Plot. ACEi/ARB Prescribed.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Baron 2015	926	1403	13431	17488	5.8%	0.59 [0.52, 0.66]
Baron 2016	945	1313	30781	40501	5.8%	0.81 [0.72, 0.92]
Chapman 2018	156	429	724	1171	5.6%	0.35 [0.28, 0.44]
Etaher 2020	57	171	49	97	4.6%	0.49 [0.29, 0.82]
Hawatmeh 2020	99	281	325	664	5.4%	0.57 [0.43, 0.76]
Higuchi 2019	254	491	7531	12023	5.7%	0.64 [0.53, 0.77]
Kadesjo 2019	118	251	725	1111	5.4%	0.47 [0.36, 0.62]
Lopez Cuenca 2016	53	117	438	707	5.0%	0.51 [0.34, 0.75]
Nestelberger 2020	70	128	546	684	5.0%	0.31 [0.21, 0.45]
Radovanovic 2017	566	1091	7448	13828	5.8%	0.92 [0.82, 1.04]
Raphael 2020	571	1054	976	1365	5.7%	0.47 [0.40, 0.56]
Saaby 2014	38	119	154	360	4.9%	0.63 [0.40, 0.97]
Sandoval 2017	43	140	39	77	4.3%	0.43 [0.24, 0.77]
Sato 2020	93	155	2103	2834	5.3%	0.52 [0.37, 0.73]
Shah 2015	135	429	735	1171	5.6%	0.27 [0.22, 0.34]
Singh 2020	271	1225	1269	2097	5.7%	0.19 [0.16, 0.22]
Smilowitz 2018	62	146	63	137	4.7%	0.87 [0.54, 1.39]
Stein 2014	88	127	2126	2691	5.1%	0.60 [0.41, 0.88]
Troung 2020	147	175	221	275	4.6%	1.28 [0.78, 2.12]
Total (95% CI)		9245		99281	100.0%	0.52 [0.41, 0.66]
Total events	4692		69684			

Heterogeneity: Tau² = 0.24; Chi² = 363.88, df = 18 (P < 0.00001); I² = 95%
Test for overall effect: Z = 5.52 (P < 0.00001)

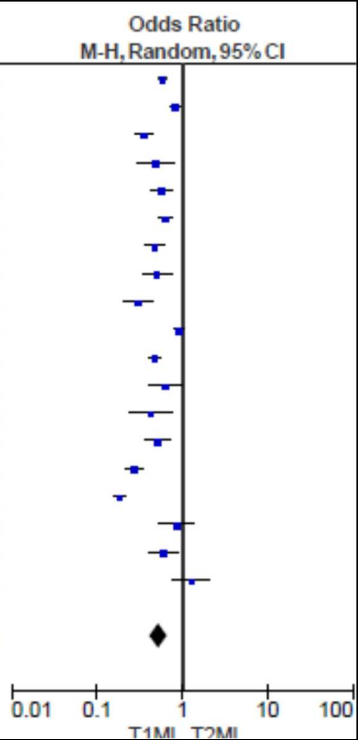
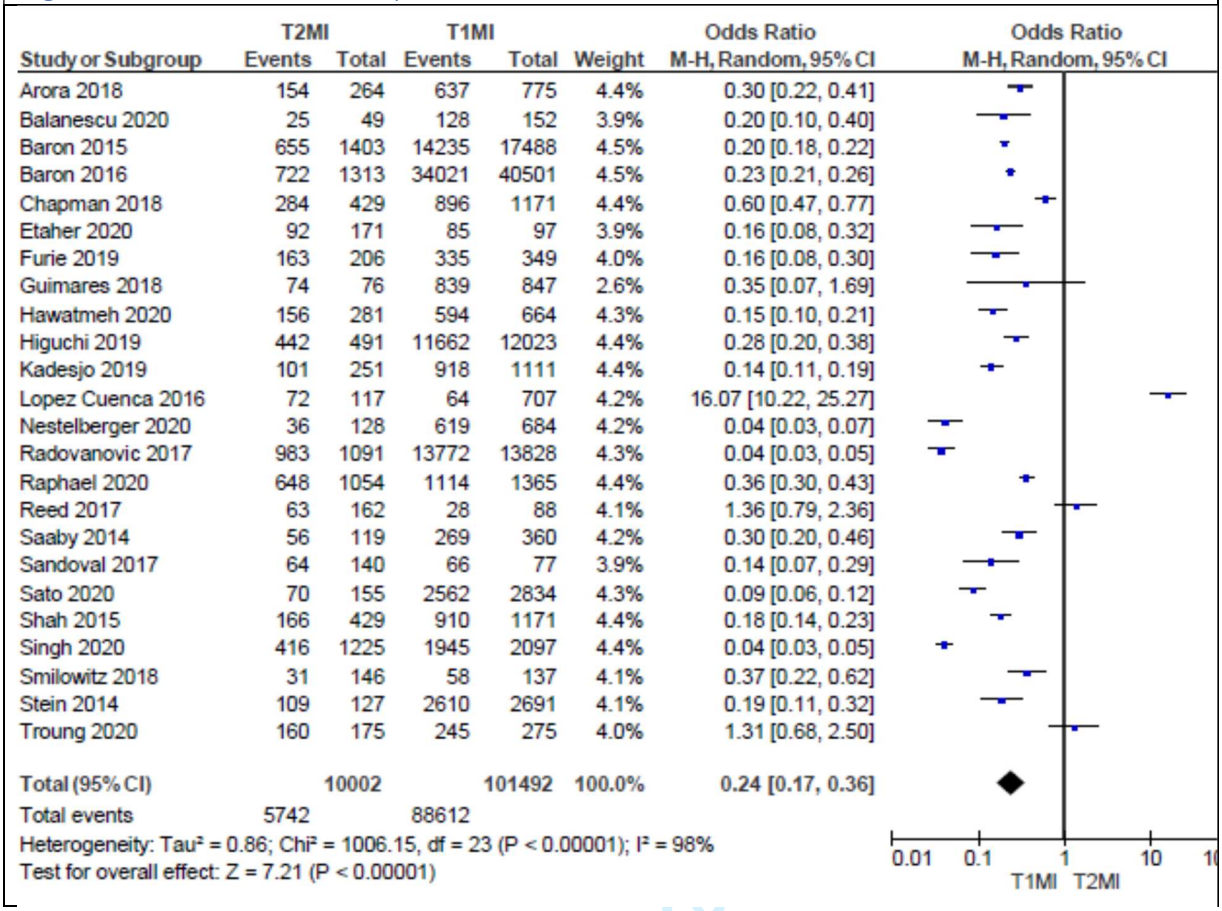


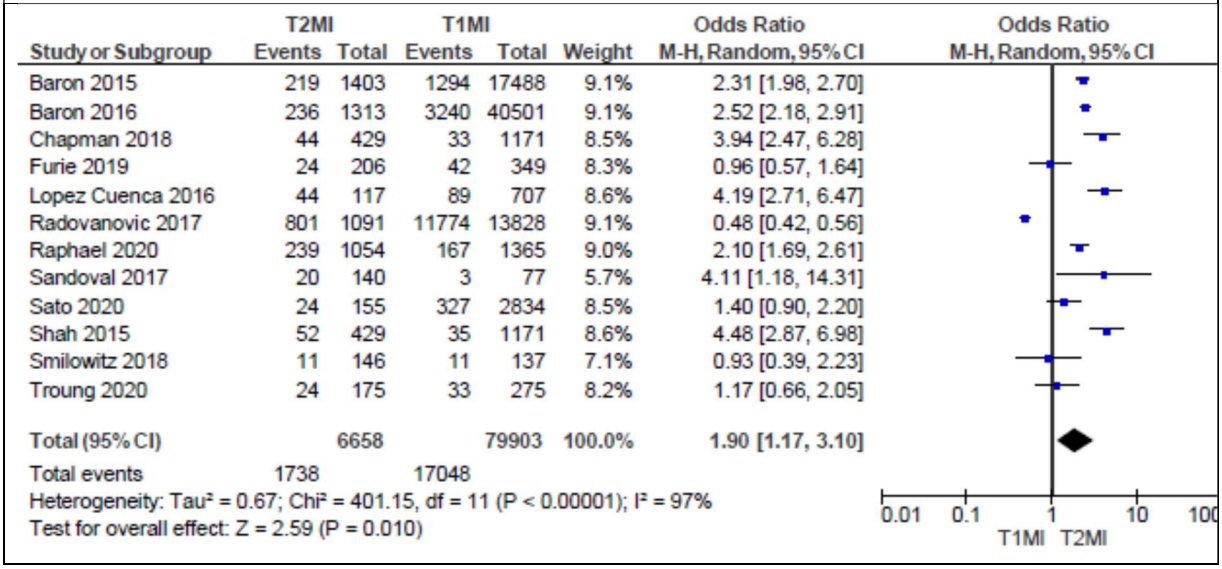
Figure S33. Forest Plot. Antiplatelets Prescribed.



Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Arora 2018	154	264	637	775	4.4%	0.30 [0.22, 0.41]
Balanescu 2020	25	49	128	152	3.9%	0.20 [0.10, 0.40]
Baron 2015	655	1403	14235	17488	4.5%	0.20 [0.18, 0.22]
Baron 2016	722	1313	34021	40501	4.5%	0.23 [0.21, 0.26]
Chapman 2018	284	429	896	1171	4.4%	0.60 [0.47, 0.77]
Etaher 2020	92	171	85	97	3.9%	0.16 [0.08, 0.32]
Furie 2019	163	206	335	349	4.0%	0.16 [0.08, 0.30]
Guimares 2018	74	76	839	847	2.6%	0.35 [0.07, 1.69]
Hawatmeh 2020	156	281	594	664	4.3%	0.15 [0.10, 0.21]
Higuchi 2019	442	491	11662	12023	4.4%	0.28 [0.20, 0.38]
Kadesjo 2019	101	251	918	1111	4.4%	0.14 [0.11, 0.19]
Lopez Cuenca 2016	72	117	64	707	4.2%	16.07 [10.22, 25.27]
Nestelberger 2020	36	128	619	684	4.2%	0.04 [0.03, 0.07]
Radovanovic 2017	983	1091	13772	13828	4.3%	0.04 [0.03, 0.05]
Raphael 2020	648	1054	1114	1365	4.4%	0.36 [0.30, 0.43]
Reed 2017	63	162	28	88	4.1%	1.36 [0.79, 2.36]
Saaby 2014	56	119	269	360	4.2%	0.30 [0.20, 0.46]
Sandoval 2017	64	140	66	77	3.9%	0.14 [0.07, 0.29]
Sato 2020	70	155	2562	2834	4.3%	0.09 [0.06, 0.12]
Shah 2015	166	429	910	1171	4.4%	0.18 [0.14, 0.23]
Singh 2020	416	1225	1945	2097	4.4%	0.04 [0.03, 0.05]
Smilowitz 2018	31	146	58	137	4.1%	0.37 [0.22, 0.62]
Stein 2014	109	127	2610	2691	4.1%	0.19 [0.11, 0.32]
Troung 2020	160	175	245	275	4.0%	1.31 [0.68, 2.50]
Total (95% CI)		10002		101492	100.0%	0.24 [0.17, 0.36]
Total events	5742		88612			

Heterogeneity: Tau² = 0.86; Chi² = 1006.15, df = 23 (P < 0.00001); I² = 98%
Test for overall effect: Z = 7.21 (P < 0.00001)

Figure S34. Forest Plot. Anticoagulants Prescribed.



Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Baron 2015	219	1403	1294	17488	9.1%	2.31 [1.98, 2.70]
Baron 2016	236	1313	3240	40501	9.1%	2.52 [2.18, 2.91]
Chapman 2018	44	429	33	1171	8.5%	3.94 [2.47, 6.28]
Furie 2019	24	206	42	349	8.3%	0.96 [0.57, 1.64]
Lopez Cuenca 2016	44	117	89	707	8.6%	4.19 [2.71, 6.47]
Radovanovic 2017	801	1091	11774	13828	9.1%	0.48 [0.42, 0.56]
Raphael 2020	239	1054	167	1365	9.0%	2.10 [1.69, 2.61]
Sandoval 2017	20	140	3	77	5.7%	4.11 [1.18, 14.31]
Sato 2020	24	155	327	2834	8.5%	1.40 [0.90, 2.20]
Shah 2015	52	429	35	1171	8.6%	4.48 [2.87, 6.98]
Smilowitz 2018	11	146	11	137	7.1%	0.93 [0.39, 2.23]
Troung 2020	24	175	33	275	8.2%	1.17 [0.66, 2.05]
Total (95% CI)		6658		79903	100.0%	1.90 [1.17, 3.10]
Total events	1738		17048			

Heterogeneity: Tau² = 0.67; Chi² = 401.15, df = 11 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.59 (P = 0.010)

Figure S35. Forest Plot. Antianginal Drugs Prescribed.

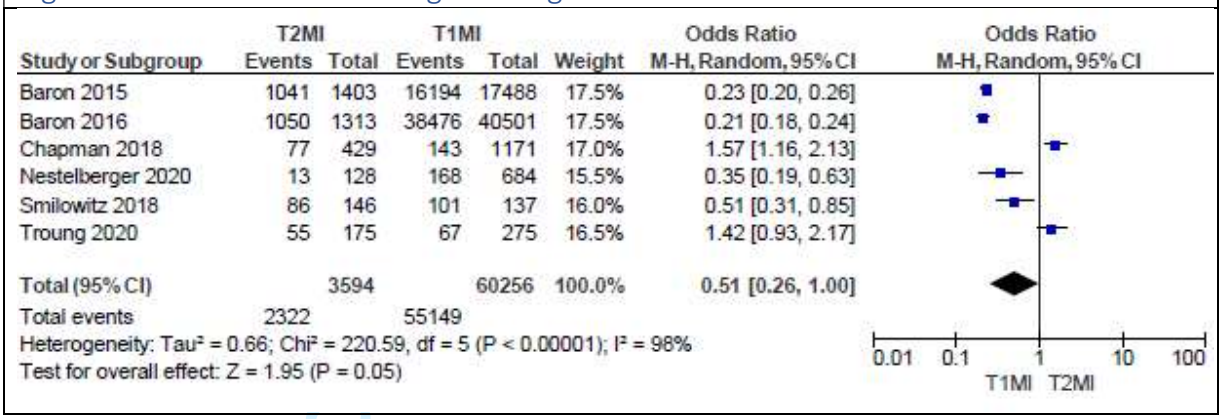


Figure S36. Forest Plot. Diuretics Prescribed.

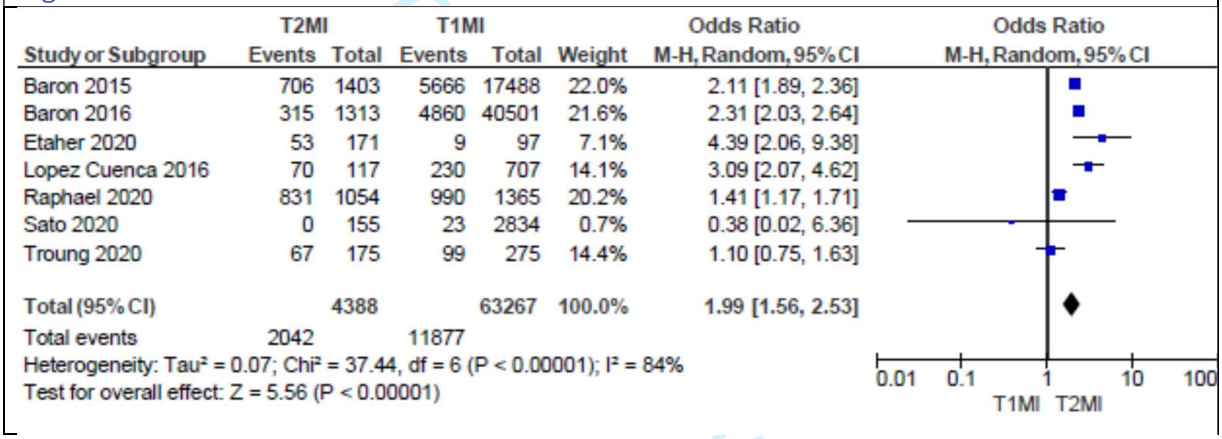


Figure S37. Forest Plot. Statins Prescribed.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Arora 2018	153	264	646	775	6.0%	0.28 [0.20, 0.37]
Balanescu 2020	29	49	131	152	5.1%	0.23 [0.11, 0.48]
Baron 2015	926	1403	15040	17488	6.3%	0.32 [0.28, 0.36]
Baron 2016	972	1313	37261	40501	6.3%	0.25 [0.22, 0.28]
Chapman 2018	204	429	872	1171	6.1%	0.31 [0.25, 0.39]
Etaher 2020	95	171	81	97	5.4%	0.25 [0.13, 0.46]
Furie 2019	125	206	280	349	5.9%	0.38 [0.26, 0.56]
Hawatmeh 2020	141	281	578	664	6.0%	0.15 [0.11, 0.21]
Higuchi 2019	298	491	9238	12023	6.2%	0.47 [0.39, 0.56]
Kadesjo 2019	92	251	883	1111	6.1%	0.15 [0.11, 0.20]
Lopez Cuenca 2016	92	117	648	707	5.6%	0.34 [0.20, 0.56]
Nestelberger 2020	39	128	606	684	5.8%	0.06 [0.04, 0.09]
Raphael 2020	570	1054	1167	1365	6.2%	0.20 [0.16, 0.24]
Sato 2020	112	155	2303	2834	5.9%	0.60 [0.42, 0.86]
Singh 2020	255	1225	1840	2097	6.2%	0.04 [0.03, 0.04]
Smilowitz 2018	83	146	100	137	5.7%	0.49 [0.30, 0.80]
Troung 2020	158	175	241	275	5.4%	1.31 [0.71, 2.43]
Total (95% CI)		7858		82430	100.0%	0.25 [0.17, 0.36]
Total events	4344		71915			

Heterogeneity: Tau² = 0.57; Chi² = 583.06, df = 16 (P < 0.00001); I² = 97%

Test for overall effect: Z = 7.30 (P < 0.00001)

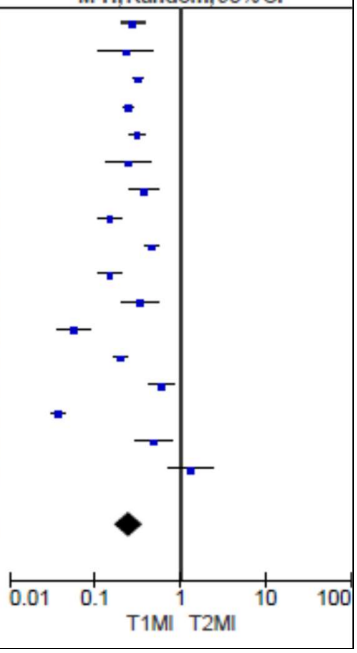


Figure S38. Forest Plot. Percutaneous Coronary Intervention Performed.

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

Heterogeneity: Tau² = 0.99; Chi² = 982.87, df = 23 (P < 0.00001); I² = 98%
Test for overall effect: Z = 12.56 (P < 0.00001)

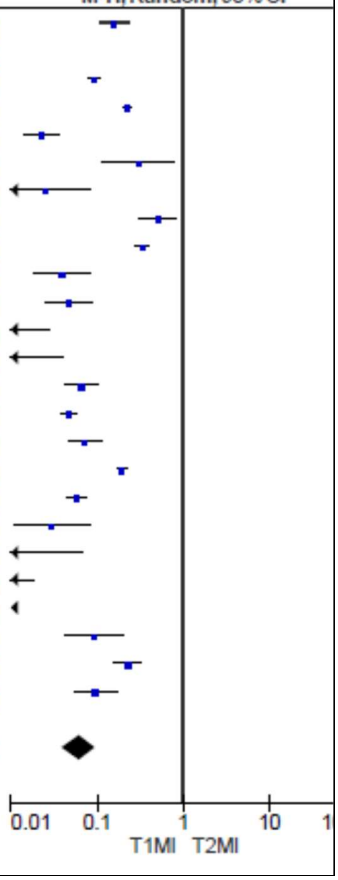
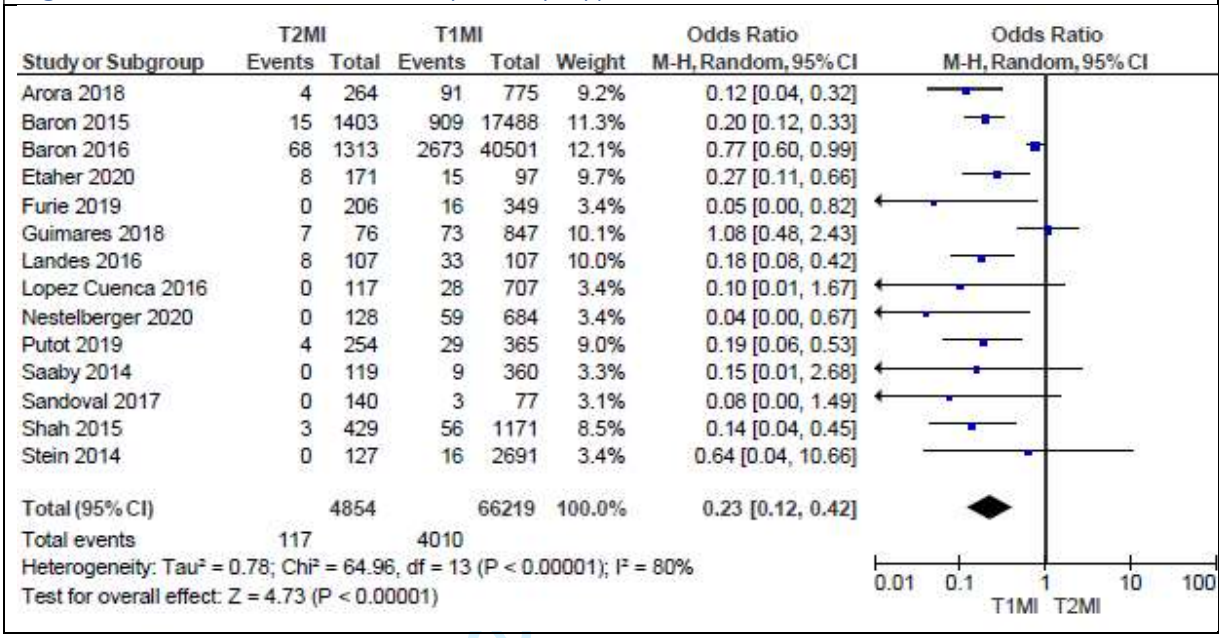


Figure S39. Forest Plot. Coronary Artery Bypass Graft Performed.

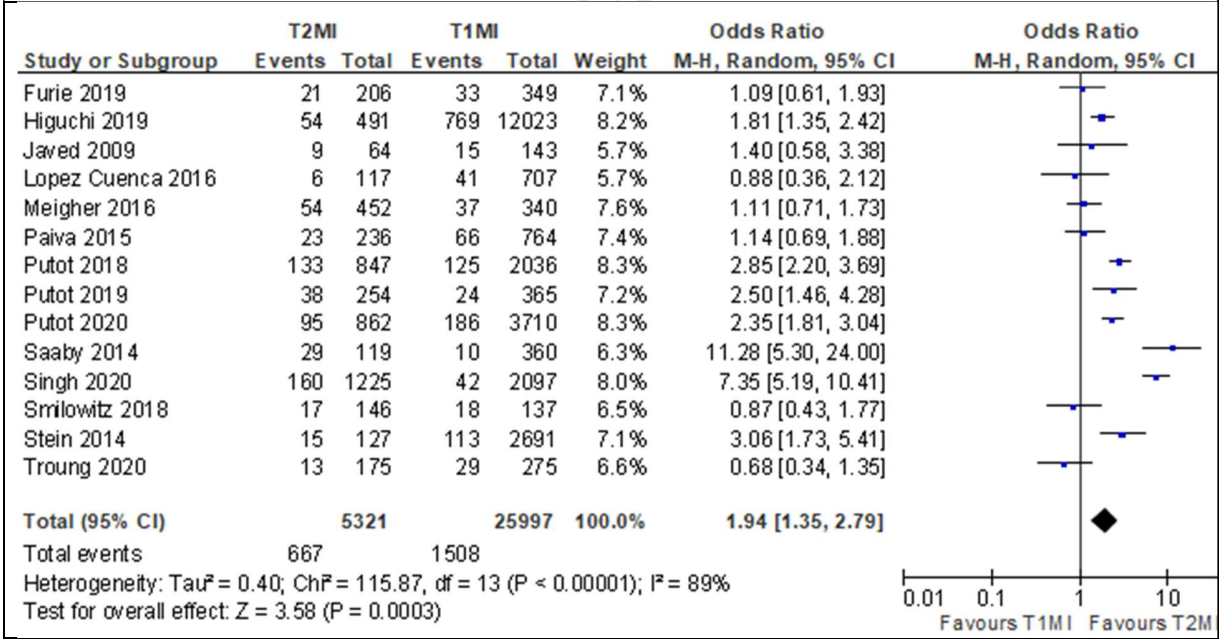


Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Arora 2018	4	264	91	775	9.2%	0.12 [0.04, 0.32]
Baron 2015	15	1403	909	17488	11.3%	0.20 [0.12, 0.33]
Baron 2016	68	1313	2673	40501	12.1%	0.77 [0.60, 0.99]
Etaher 2020	8	171	15	97	9.7%	0.27 [0.11, 0.66]
Furie 2019	0	206	16	349	3.4%	0.05 [0.00, 0.82]
Guimares 2018	7	76	73	847	10.1%	1.08 [0.48, 2.43]
Landes 2016	8	107	33	107	10.0%	0.18 [0.08, 0.42]
Lopez Cuenca 2016	0	117	28	707	3.4%	0.10 [0.01, 1.67]
Nestelberger 2020	0	128	59	684	3.4%	0.04 [0.00, 0.67]
Putot 2019	4	254	29	365	9.0%	0.19 [0.06, 0.53]
Saaby 2014	0	119	9	360	3.3%	0.15 [0.01, 2.68]
Sandoval 2017	0	140	3	77	3.1%	0.08 [0.00, 1.49]
Shah 2015	3	429	56	1171	8.5%	0.14 [0.04, 0.45]
Stein 2014	0	127	16	2691	3.4%	0.64 [0.04, 10.66]
Total (95% CI)		4854		66219	100.0%	0.23 [0.12, 0.42]
Total events	117		4010			

Heterogeneity: Tau² = 0.78; Chi² = 64.96, df = 13 (P < 0.00001); I² = 80%

Test for overall effect: Z = 4.73 (P < 0.00001)

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



Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Furie 2019	21	206	33	349	7.1%	1.09 [0.61, 1.93]
Higuchi 2019	54	491	769	12023	8.2%	1.81 [1.35, 2.42]
Javed 2009	9	64	15	143	5.7%	1.40 [0.58, 3.38]
Lopez Cuenca 2016	6	117	41	707	5.7%	0.88 [0.36, 2.12]
Meigher 2016	54	452	37	340	7.6%	1.11 [0.71, 1.73]
Paiva 2015	23	236	66	764	7.4%	1.14 [0.69, 1.88]
Putot 2018	133	847	125	2036	8.3%	2.85 [2.20, 3.69]
Putot 2019	38	254	24	365	7.2%	2.50 [1.46, 4.28]
Putot 2020	95	862	186	3710	8.3%	2.35 [1.81, 3.04]
Saaby 2014	29	119	10	360	6.3%	11.28 [5.30, 24.00]
Singh 2020	160	1225	42	2097	8.0%	7.35 [5.19, 10.41]
Smilowitz 2018	17	146	18	137	6.5%	0.87 [0.43, 1.77]
Stein 2014	15	127	113	2691	7.1%	3.06 [1.73, 5.41]
Troung 2020	13	175	29	275	6.6%	0.68 [0.34, 1.35]
Total (95% CI)		**5321**		**25997**	**100.0%**	**1.94 [1.35, 2.79]**
Total events	667		1508			

Heterogeneity: Tau² = 0.40; Chi² = 115.87, df = 13 (P < 0.00001); I² = 89%

Test for overall effect: Z = 3.58 (P = 0.0003)

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

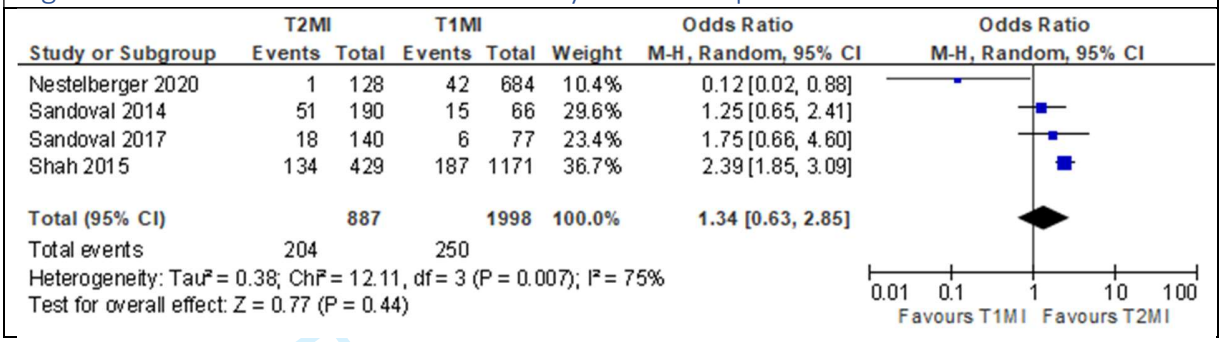


Figure S42. Two-year all-cause mortality. T2MI compared to T1MI.

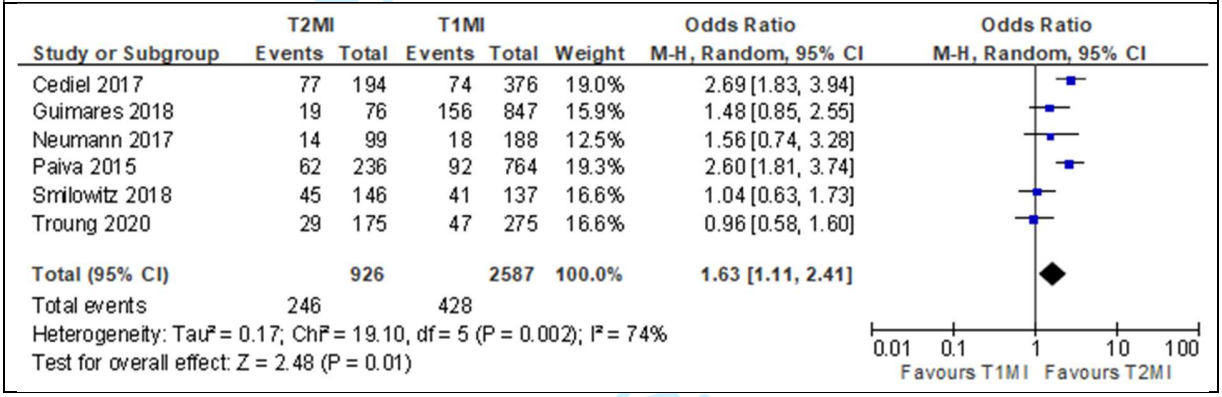
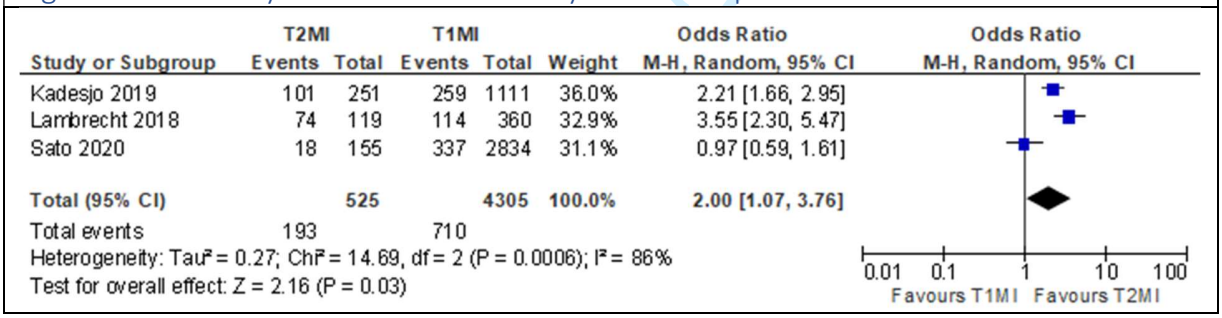


Figure S43. Three-year all-cause mortality. T2MI compared to T1MI.



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PRISMA 2020 Checklist

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

PRISMA 2020 Checklist

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

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

PRISMA 2020 Checklist

10.1136/bmj.n71

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

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Title Page

Manuscript Title

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

Authors

Dr Kyle White
Princess Alexandra Hospital, Brisbane, Australia
University of Queensland, Brisbane, Australia
BSc, MBBS, FRACP, FCICM, MPH

Dr Mansey Kinarivala
Princess Alexandra Hospital, Brisbane, Australia
MBBS, FRACP

Prof Ian Scott
Princess Alexandra Hospital, Brisbane, Australia
University of Queensland, Brisbane, Australia
MEd, MHA, MBBS, FRACP

Corresponding Author

Dr Kyle White
Princess Alexandra Hospital
199 Ipswich Road, Wolloongabba, 4102
Ph: +61731762111
Email: kyle.white@health.qld.gov.au

Manuscript Word Count

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Abstract

Importance

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

Objective

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

Data Sources

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

Study Selection

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

Data Extraction and Synthesis

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

Main Outcomes and Measures

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

Results

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

Conclusion and Relevance

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

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

Strength and Limitations

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

Introduction

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

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

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

Methods

Study design

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

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

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

Data collection and synthesis

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

Data on variables reported as, or able to be converted to, raw numbers, were pooled from all studies and subject to comparative meta-analysis using Review Manager (RevMan, Computer program. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For each variable, the odds ratio (OR) comparing T2MI to T1MI, and its 95% confidence interval (CI), was calculated and weighted using the random effects method. As specified in the registered study protocol, the random effects method was used in anticipation of study heterogeneity of at least moderate degree (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.

Patient and Public Involvement

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

Results

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

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

Risk of bias assessment

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

Participant characteristics

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

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

Precipitating factors

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

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

Presenting clinical features

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

Investigations

ECG findings on presentation (Table S7) such as ST elevation (14.1% vs 44.2%; OR 0.22; 95%CI 0.17-0.28) and pathological Q waves (6.7% vs 20.8%; OR 0.38; 95%CI 0.20-0.71) were less evident in T2MI than in T1MI. In contrast, non-specific ST-T wave changes (24.7% vs 10.8%; OR 2.62; 95%CI 1.81-3.79), and atrial arrythmias (21% vs 6.6%; OR 4.99; 95%CI 3.14-7.93) were more common among T2MI. No differences between groups were seen in the frequency of ST depression or T wave inversion.

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

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

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

Management

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

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

Prognosis

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

Conclusion

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

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

Tables

Table 1. Pre-existing medical conditions in patients with T2MI versus T1MI.

Pre-existing medical condition	T2MI			T1MI			Odds ratio* (95% CI)
	Number of patients with the specified condition	Total number of patients	%	Number of patients with the specified condition	Total number of patients	%	
CAD	3352	10303	32.5%	22222	92725	24%	1.1 [0.93, 1.31]
Type 2 DM	3044	12157	25%	23287	93345	24.9%	0.97 [0.85, 1.10]
HTN	7536	11021	66.4%	55782	88017	63.4%	1.22 [1.03, 1.45]
Dyslipidaemia	4626	10652	43.4%	40099	87366	45.9%	0.74 [0.58, 0.94]
Smoker	3448	9929	34.7%	39548	74889	52.8%	0.60 [0.49, 0.73]
Obesity	1225	3672	33.4%	30963	56970	54.3%	0.63 [0.46, 0.87]
Renal failure	1378	6040	22.8%	11300	65394	17.3%	1.87 [1.53, 2.28]
Heart failure	1661	8873	13.1%	5617	74212	7.6%	2.35 [1.82, 3.03]
PVD	584	5856	10.0%	2066	41280	5.0%	1.33 [1.05, 1.69]
CVD	969	8538	11.3%	6060	87822	6.9%	1.47 [1.27, 1.71]
Atrial fibrillation	836	3645	22.9%	1220	19843	6.1%	3.02 [2.29, 3.99]
COPD	800	5018	15.9%	823	48375	1.7%	1.94 [1.22, 3.08]
Illicit drug Use	46	204	22.5%	8	220	3.6%	8.15 [1.03, 64.46]

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

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

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

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

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

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

Table 3. Outcomes in patients with T2MI versus T1MI.

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

*Comparing T1MI with T2MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis
Abbreviations: CV= Cardiovascular, MACE= Major adverse cardiovascular events; T2MI=type 2 myocardial infarction; T1MI=type 1 myocardial infarction; CI=confidence interval

Figures

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

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

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

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

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

Contribution Statement

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

Competing Interests

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

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Data Sharing Statement

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

Ethic Approval Statement

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

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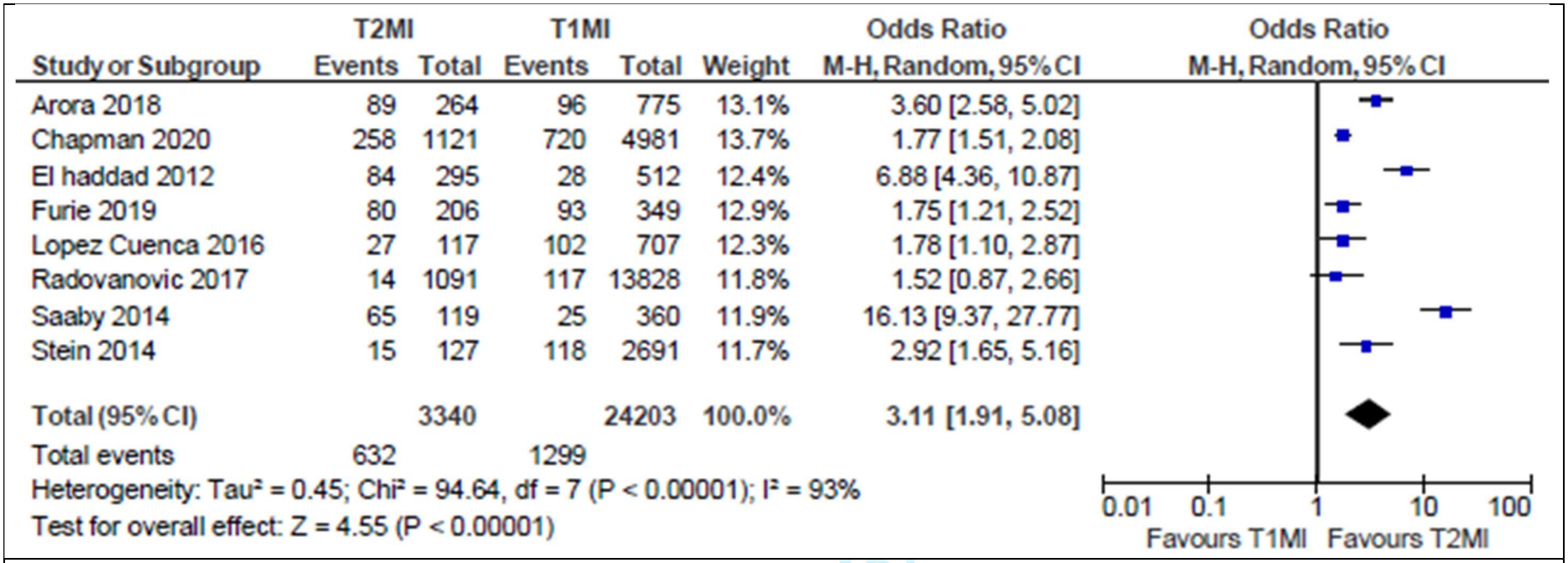


Figure 1. Forest plot of the result of meta-analysis of the risk one-year mortality of T2MI patients compared to T1MI patients.

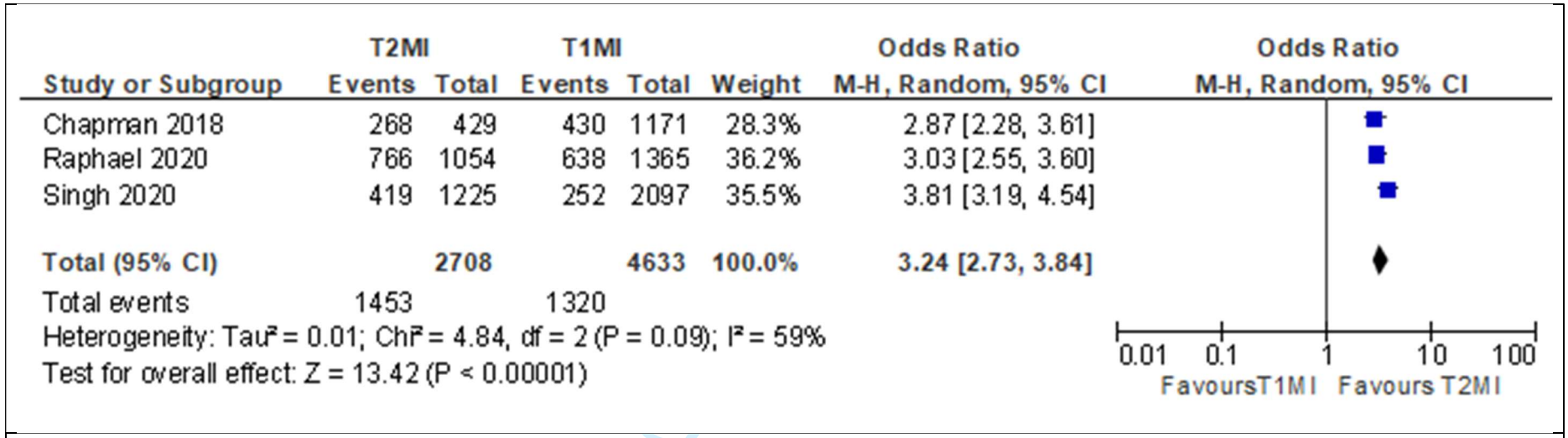


Figure 2. Forest plot of the result of meta-analysis of the risk long-term mortality of T2MI patients compared to T1MI patients.

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.

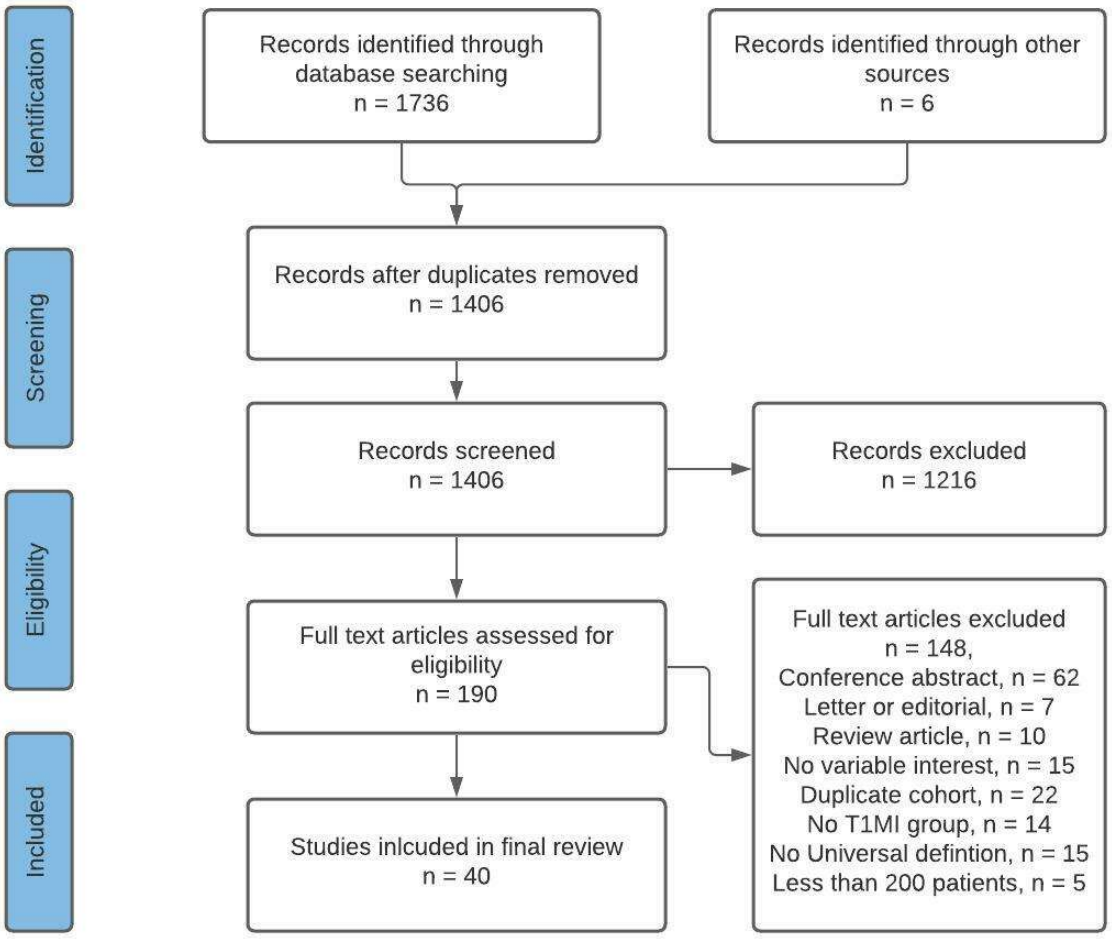


Figure S2. Forest Plot. Presence of Ischaemic Heart Disease.

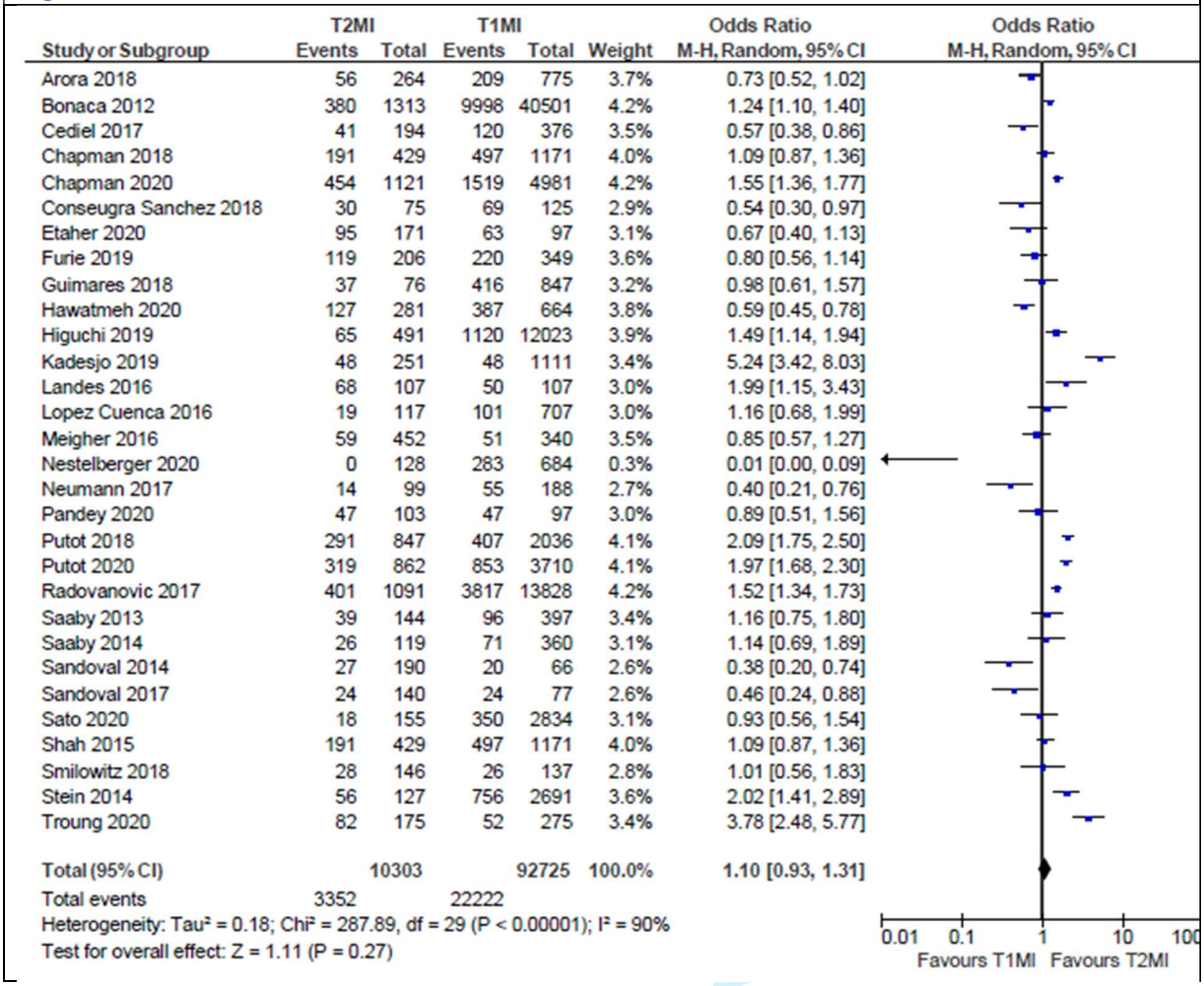


Figure S3. Forest Plot. Presence of Type 2 Diabetes Mellitus.

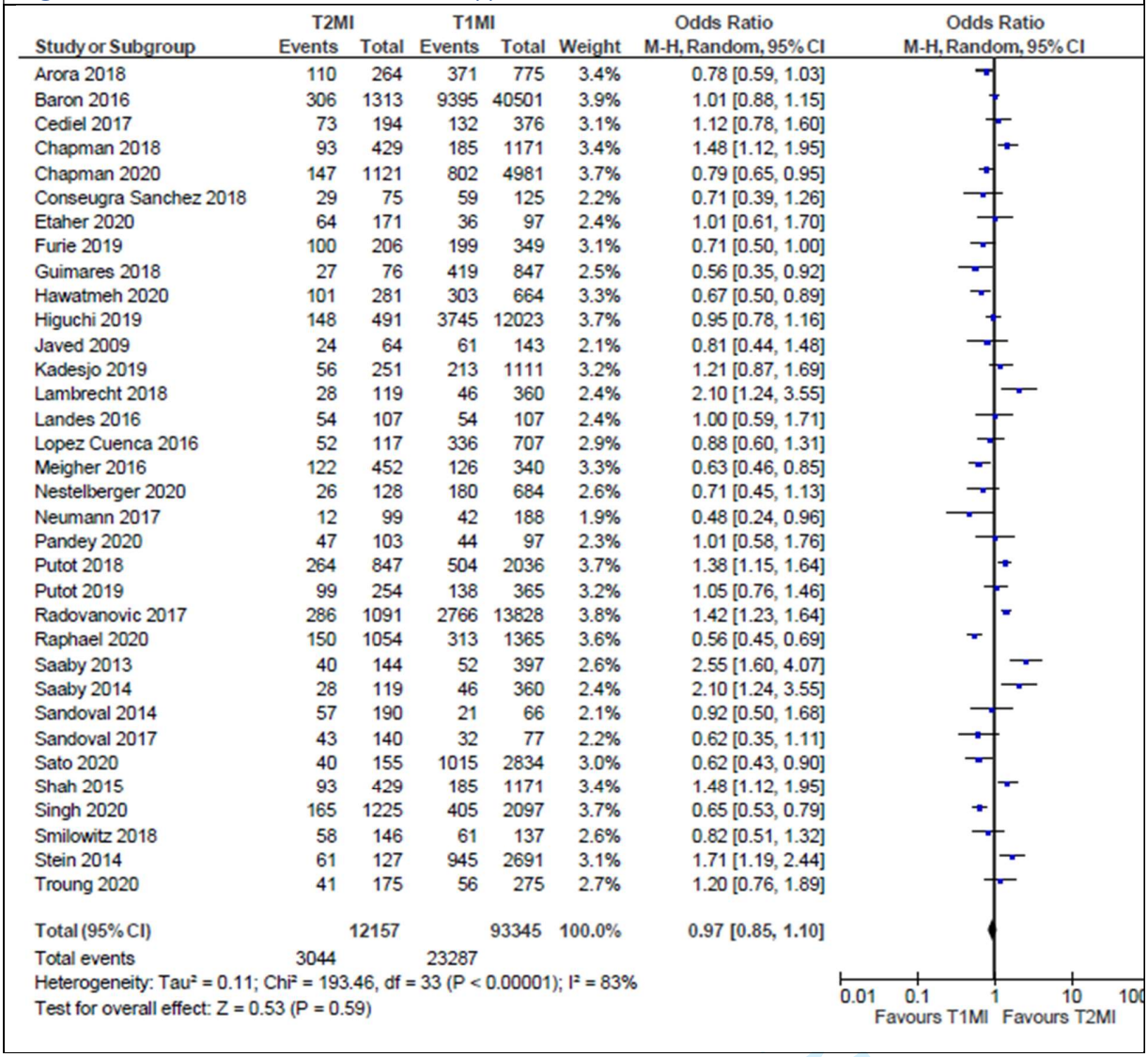


Figure S4. Forest Plot. Presence of Hypertension.

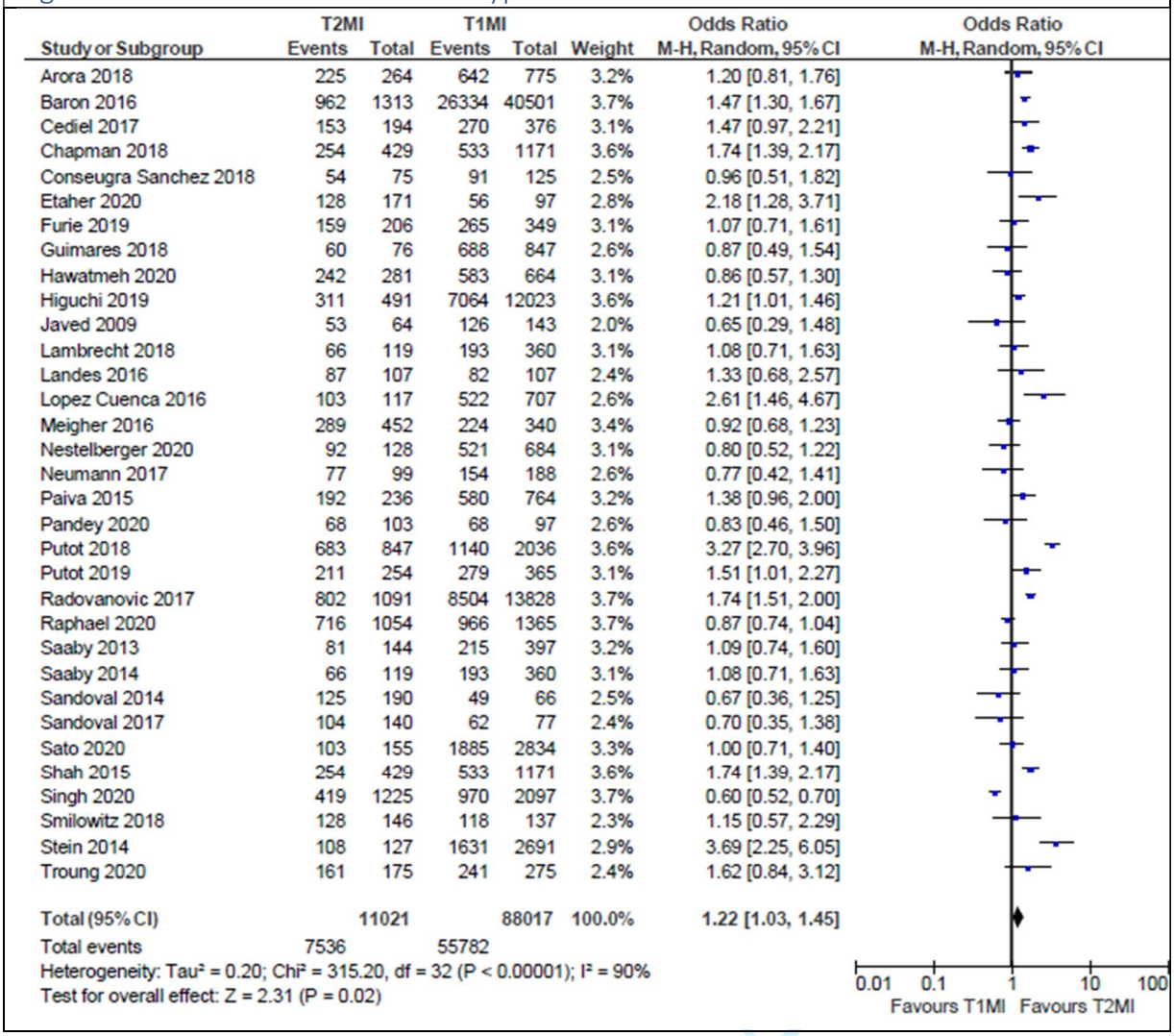


Figure S5. Forest Plot. Presence of Dyslipidaemia.

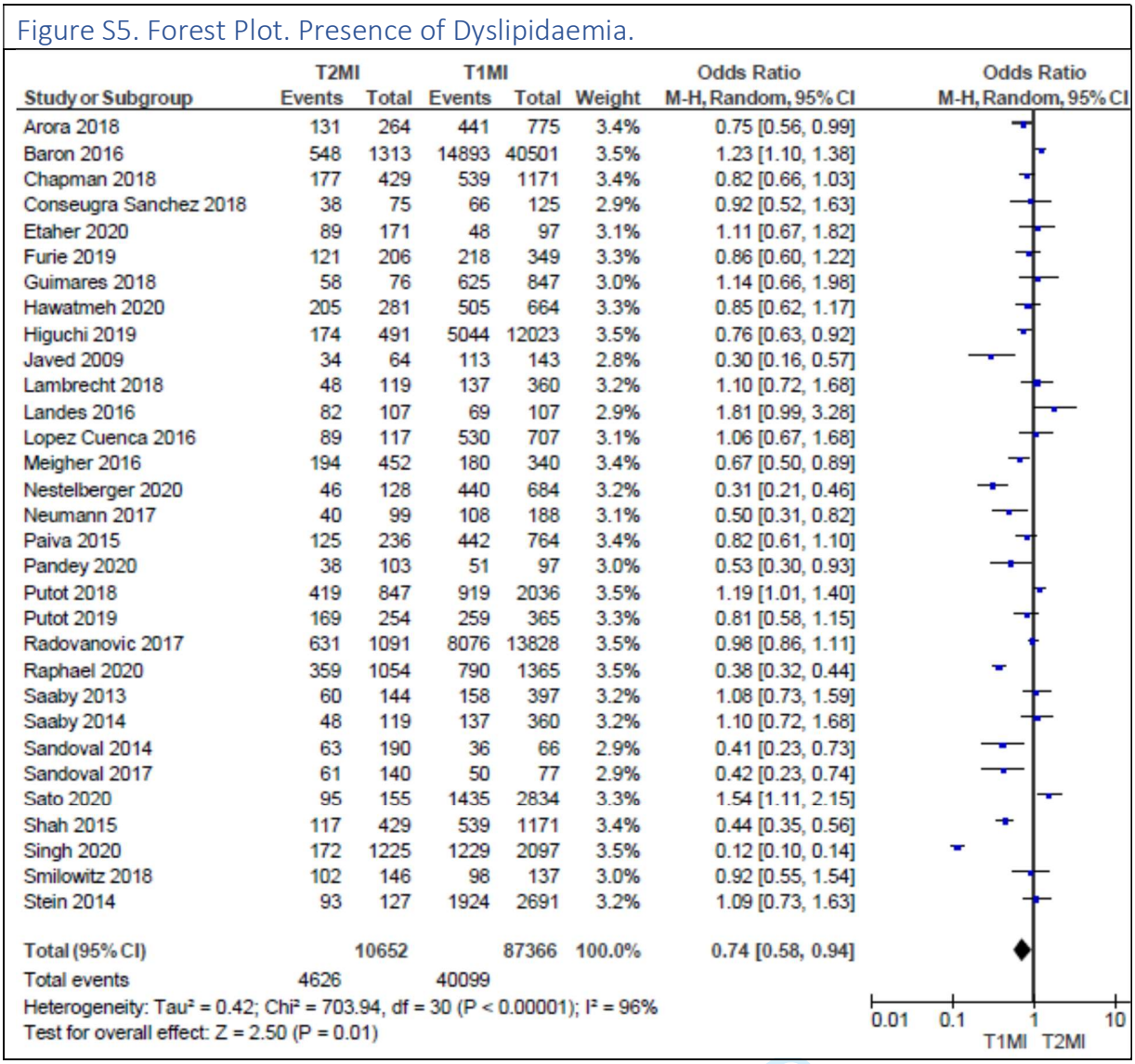


Figure S6. Forest Plot. Smoking Status.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio 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: Tau² = 0.26; Chi² = 381.27, df = 28 (P < 0.00001); I² = 93%
Test for overall effect: Z = 4.95 (P < 0.00001)

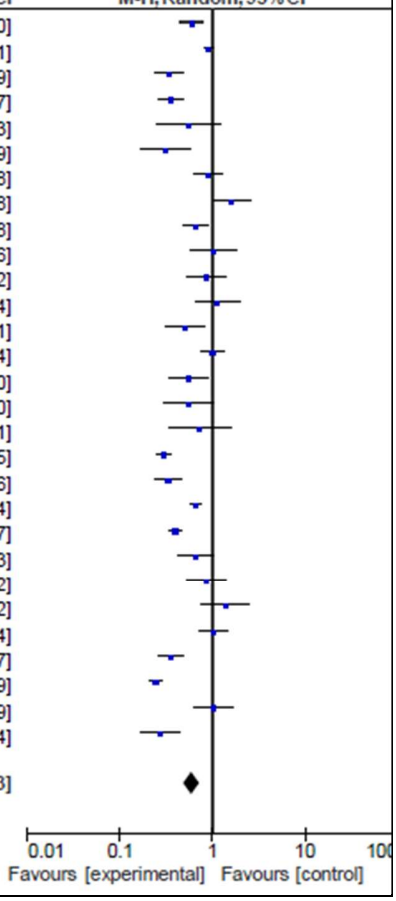


Figure S7. Forest Plot. Obesity Status.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Baron 2016	824	1313	27283	40501	21.6%	0.82 [0.73, 0.91]
Javed 2009	14	64	54	143	11.0%	0.46 [0.23, 0.91]
Pandey 2020	22	103	22	97	11.2%	0.93 [0.47, 1.81]
Putot 2018	91	847	423	2036	19.7%	0.46 [0.36, 0.58]
Putot 2019	27	254	97	365	15.2%	0.33 [0.21, 0.52]
Radovanovic 2017	247	1091	3084	13828	21.2%	1.02 [0.88, 1.18]
Total (95% CI)		3672		56970	100.0%	0.63 [0.46, 0.87]
Total events	1225		30963			

Heterogeneity: Tau² = 0.12; Chi² = 47.72, df = 5 (P < 0.00001); I² = 90%
Test for overall effect: Z = 2.80 (P = 0.005)

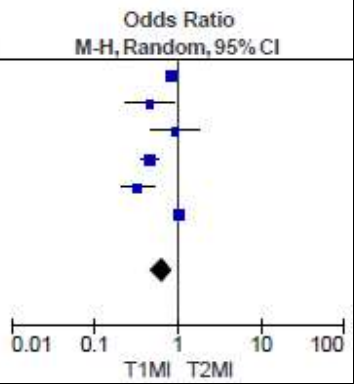


Figure S8. Forest Plot. Presence of Chronic Kidney Disease.

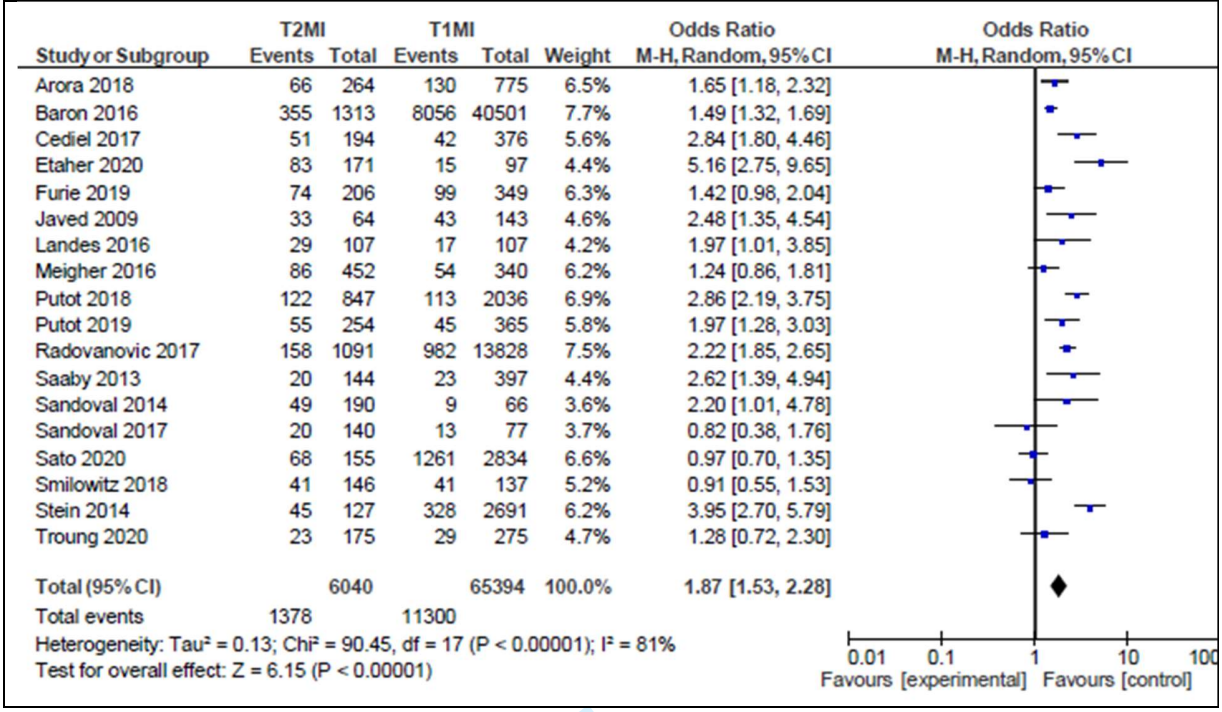


Figure S9. Forest Plot. Presence of Heart Failure.

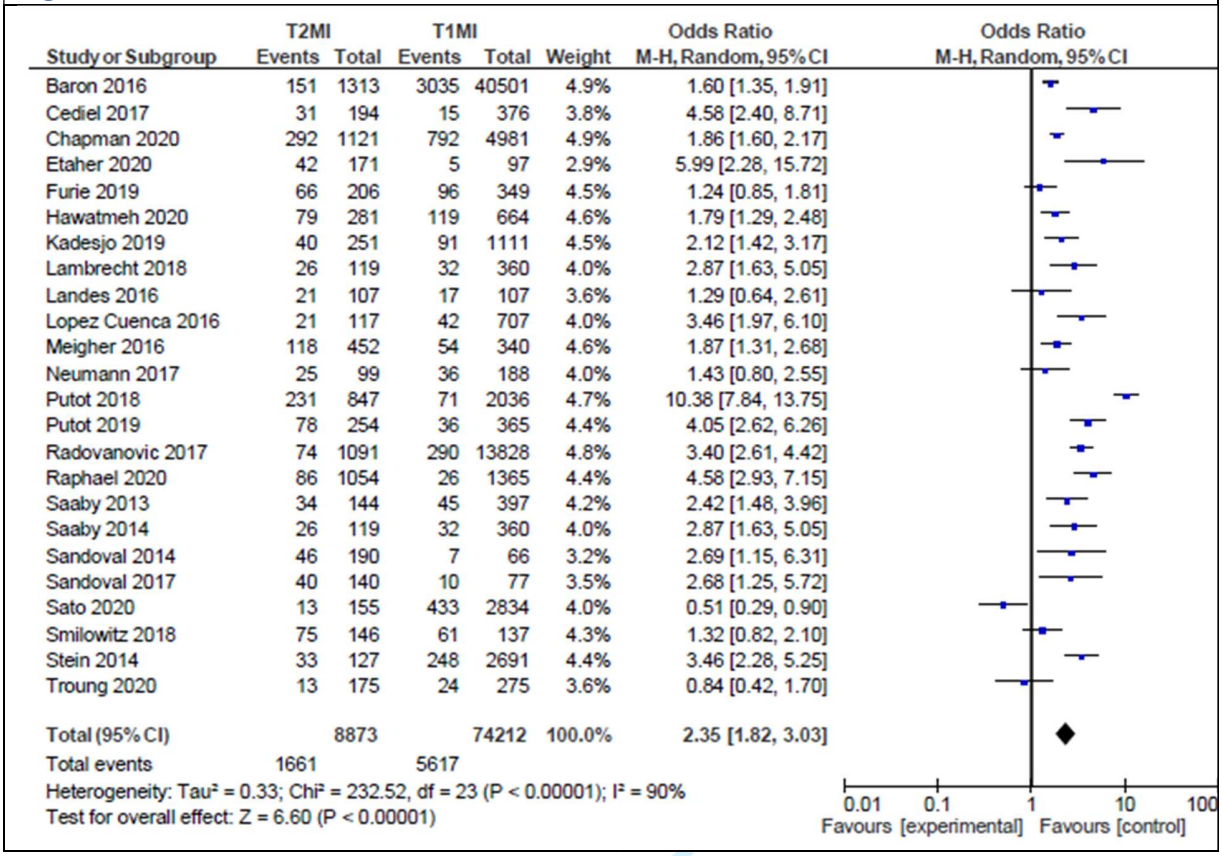


Figure S10. Forest Plot. Presence of Peripheral Vascular Disease.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
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 ($P < 0.00001$); $I^2 = 77\%$

Test for overall effect: $Z = 2.36$ ($P = 0.02$)

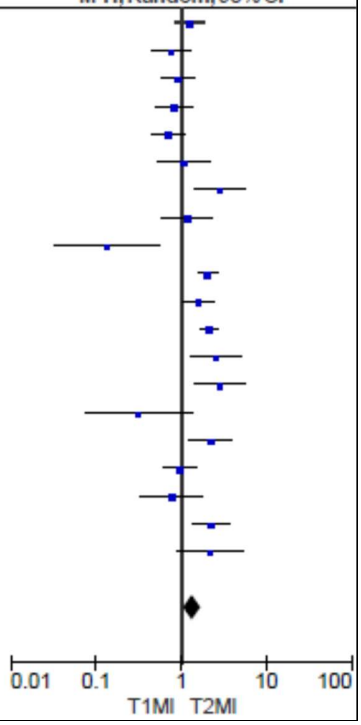


Figure S11. Forest Plot. Presence of Cerebrovascular Disease.

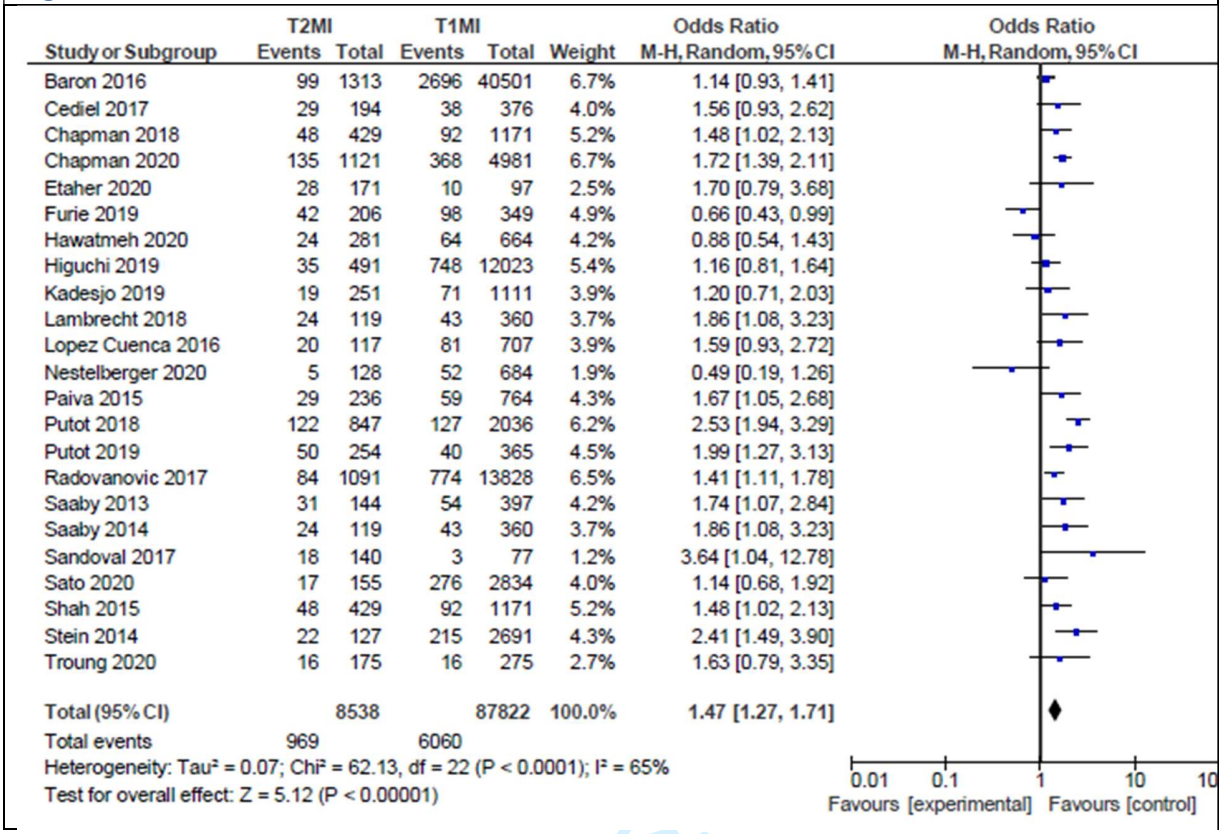


Figure S12. Forest Plot. Presence of Illicit Drug Use.

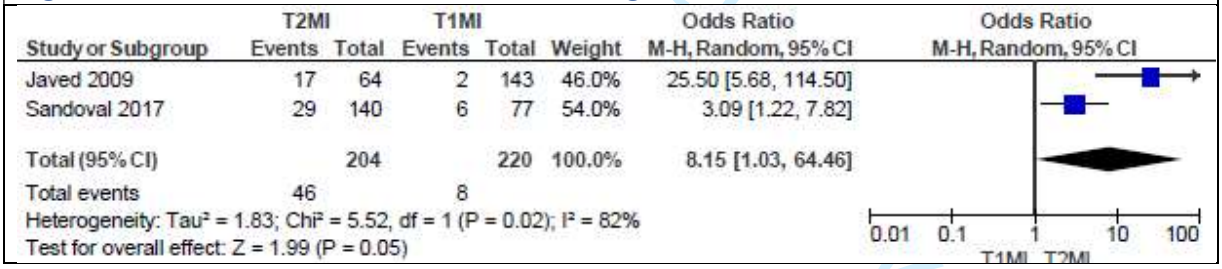


Figure S13. Forest Plot. Presence of Atrial Fibrillation.

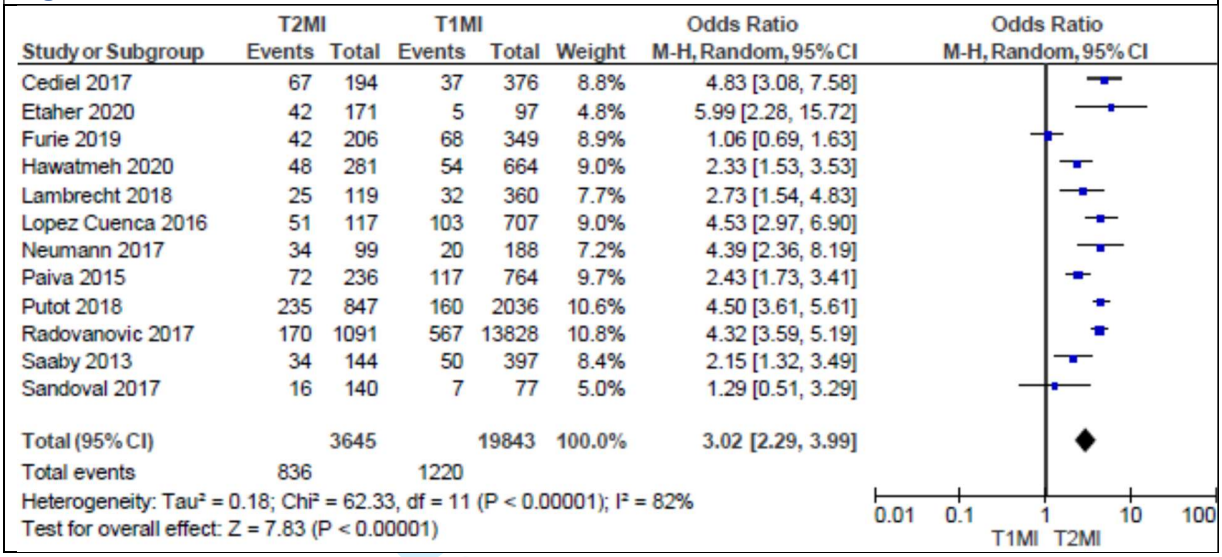


Figure S14. Forest Plot. Chest Pain as Presenting Feature.

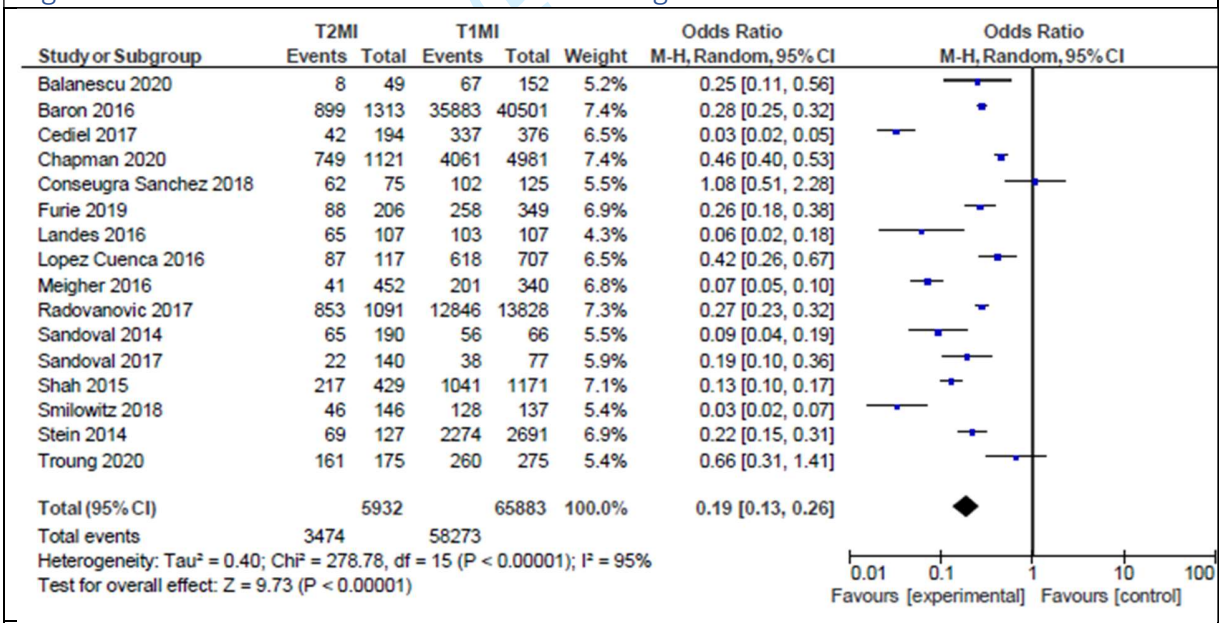


Figure S15. Forest Plot. Dyspnoea as Presenting Feature.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Baron 2016	195	1313	1774	40501	9.4%	3.81 [3.25, 4.47]
Cediel 2017	90	194	37	376	8.3%	7.93 [5.10, 12.33]
Chapman 2020	116	1121	171	4981	9.2%	3.25 [2.54, 4.15]
Furie 2019	122	206	178	349	8.8%	1.40 [0.98, 1.98]
Landes 2016	78	107	38	107	7.6%	4.88 [2.73, 8.74]
Lopez Cuenca 2016	22	117	38	707	7.7%	4.08 [2.31, 7.19]
Radovanovic 2017	482	1091	4425	13828	9.5%	1.68 [1.48, 1.91]
Sandoval 2014	112	190	35	66	7.7%	1.27 [0.72, 2.23]
Sandoval 2017	72	140	40	77	7.7%	0.98 [0.56, 1.71]
Shah 2015	80	429	45	1171	8.6%	5.74 [3.91, 8.42]
Stein 2014	15	127	105	2691	7.6%	3.30 [1.86, 5.85]
Troung 2020	28	175	44	275	7.9%	1.00 [0.60, 1.68]
Total (95% CI)		5210		65129	100.0%	2.64 [1.86, 3.74]
Total events	1412		6930			

Heterogeneity: Tau² = 0.33; Chi² = 163.95, df = 11 (P < 0.00001); I² = 93%
Test for overall effect: Z = 5.46 (P < 0.00001)

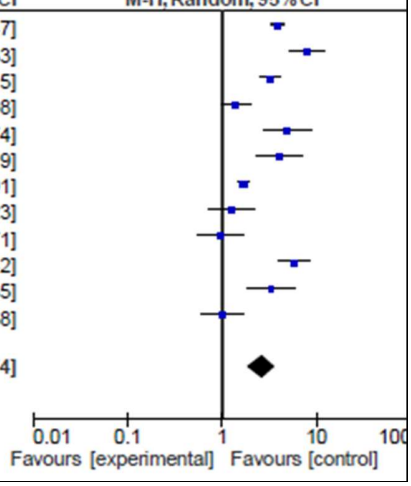


Figure S16. Forest Plot. Arm / Shoulder Discomfort as Presenting Feature.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Sandoval 2014	13	190	20	66	45.6%	0.17 [0.08, 0.36]
Sandoval 2017	15	140	30	77	54.4%	0.19 [0.09, 0.38]
Total (95% CI)		330		143	100.0%	0.18 [0.11, 0.30]
Total events	28		50			

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 6.49 (P < 0.00001)

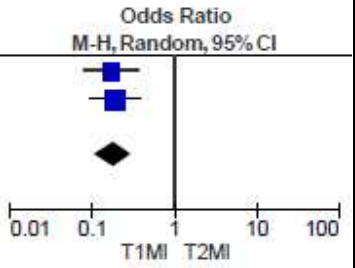


Figure S17. Forest Plot. Nausea / Vomiting as Presenting Feature.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Sandoval 2014	21	190	14	66	42.8%	0.46 [0.22, 0.97]
Sandoval 2017	25	140	25	77	57.2%	0.45 [0.24, 0.86]
Total (95% CI)		330		143	100.0%	0.46 [0.28, 0.74]
Total events	46		39			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 3.16 (P = 0.002)

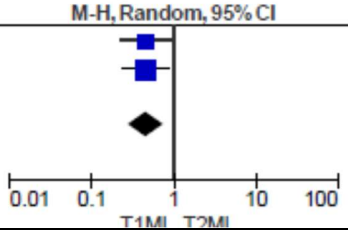


Figure S18. Forest Plot. Non-specific Symptoms as Presenting Features.

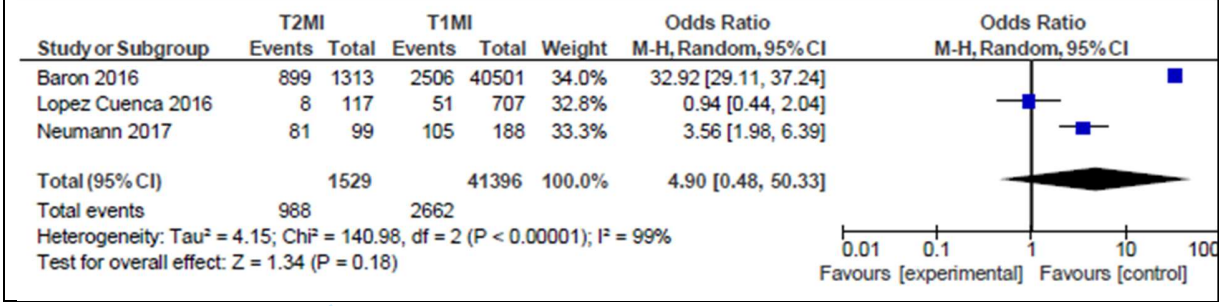


Figure S19. Forest Plot. Collapse / Syncope as Presenting Features.

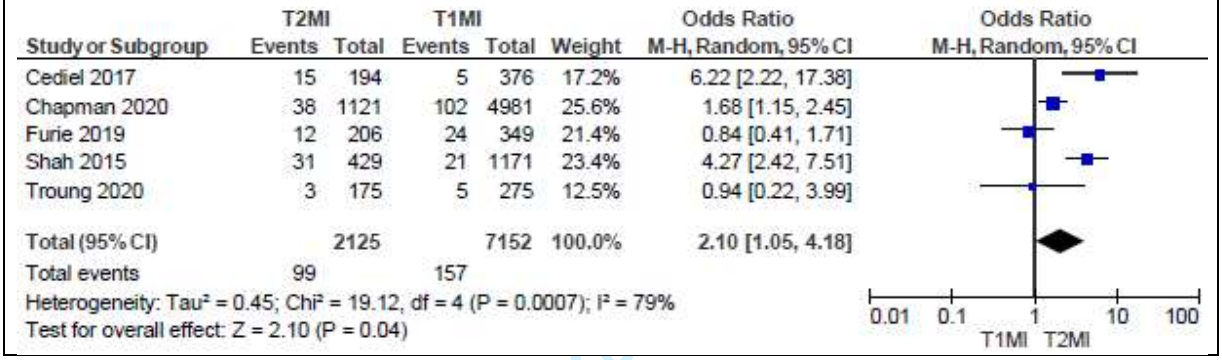


Figure S20. Forest Plot. ST Elevation on ECG.

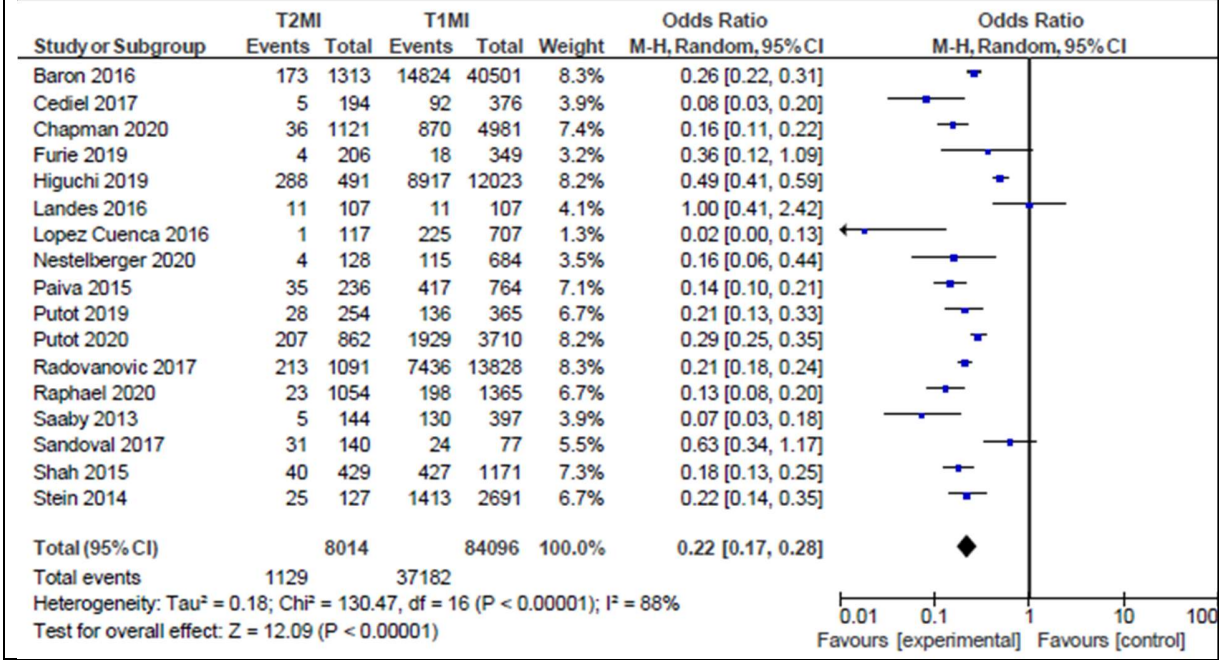


Figure S21. Forest Plot. ST Depression or T Wave Inversion on ECG.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio 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]
Total (95% CI)		4911		51042	100.0%	1.36 [0.85, 2.17]
Total events	1728		10968			

Heterogeneity: Tau² = 0.74; Chi² = 416.55, df = 13 (P < 0.00001); I² = 97%

Test for overall effect: Z = 1.28 (P = 0.20)

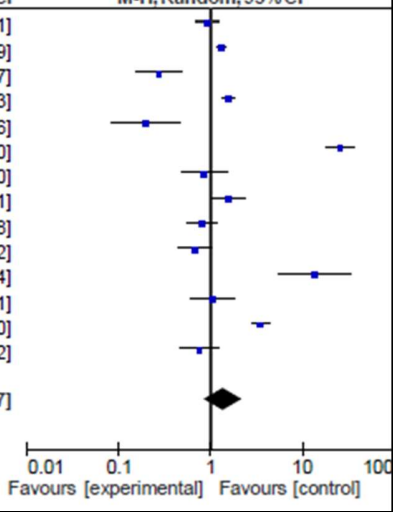


Figure S22. Forest Plot. Q Waves on ECG.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Lopez Cuenca 2016	12	117	156	707	48.4%	0.40 [0.22, 0.75]
Sandoval 2014	2	190	6	66	12.8%	0.11 [0.02, 0.54]
Sandoval 2017	16	140	15	77	38.8%	0.53 [0.25, 1.15]
Total (95% CI)		447		850	100.0%	0.38 [0.20, 0.71]
Total events	30		177			

Heterogeneity: Tau² = 0.11; Chi² = 3.09, df = 2 (P = 0.21); I² = 35%

Test for overall effect: Z = 3.03 (P = 0.002)

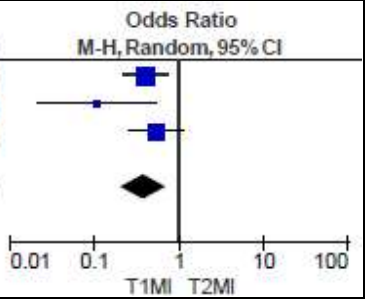


Figure S23. Forest Plot. Non-specific ST Changes on ECG.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
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			

Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 1 (P = 0.48); I² = 0%

Test for overall effect: Z = 5.12 (P < 0.00001)

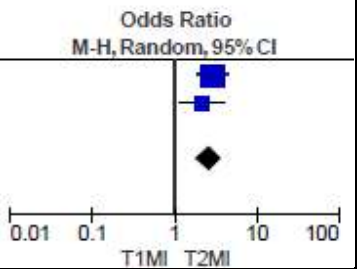


Figure S24. Forest Plot. Left Bundle Branch Block on ECG.

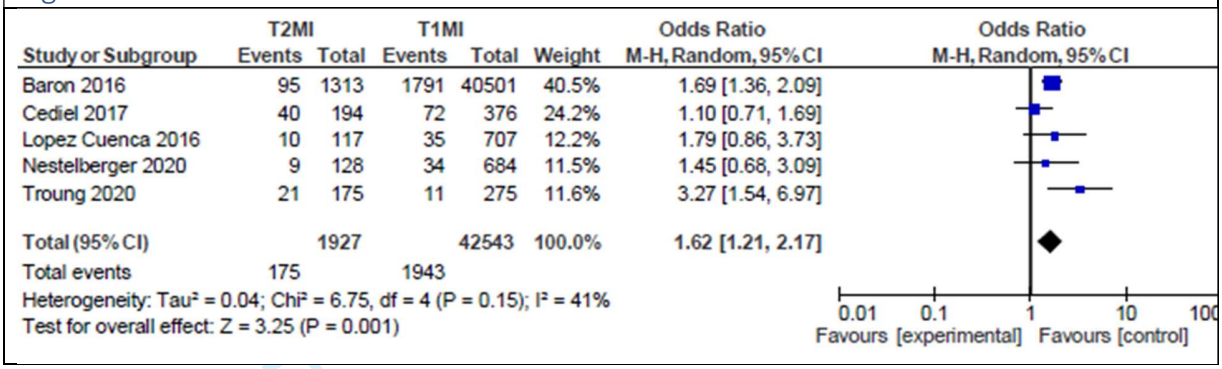


Figure S25. Forest Plot. Atrial Fibrillation on ECG.

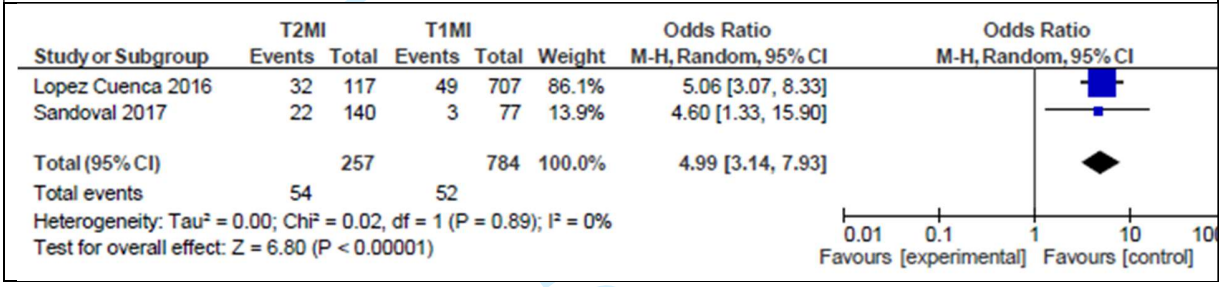


Figure S26. Forest Plot. Coronary Angiogram Performed.

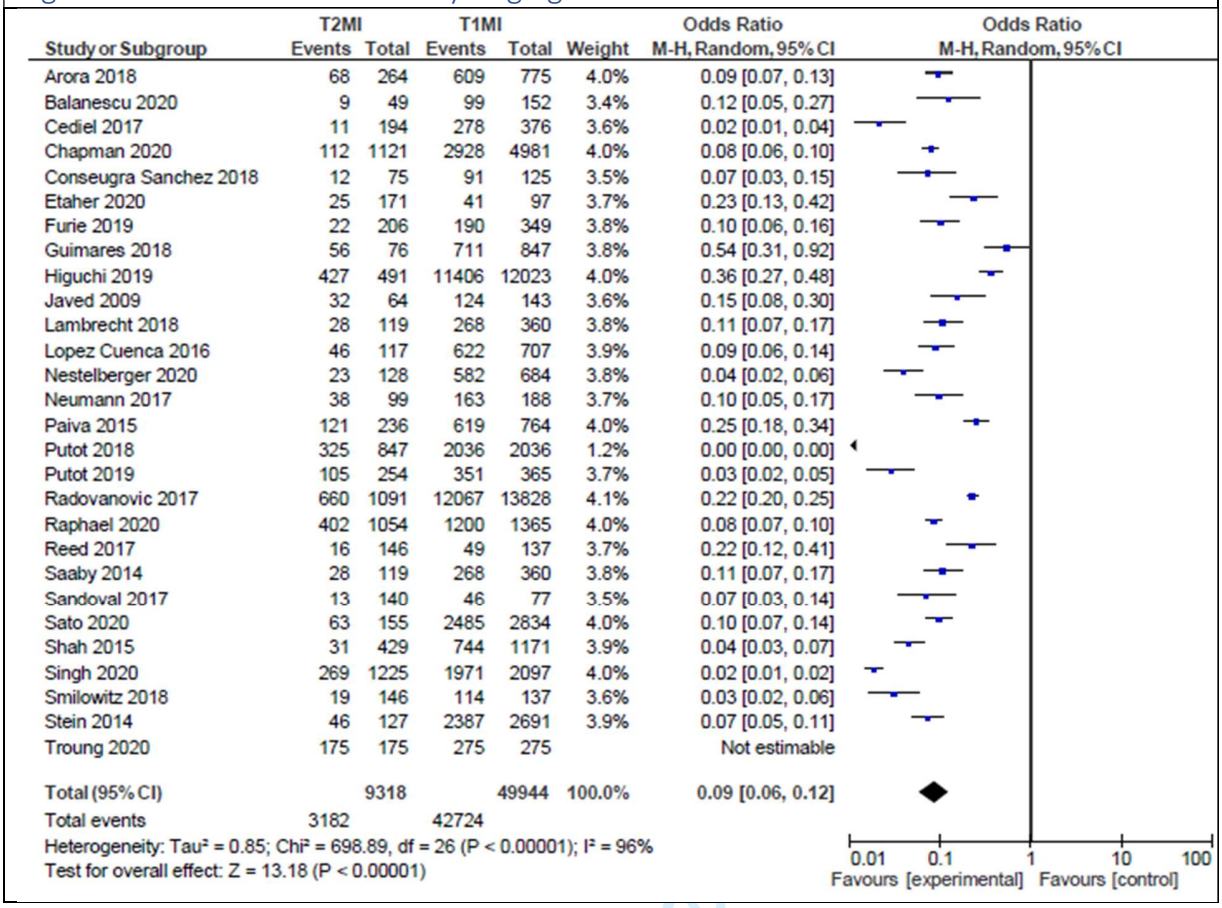


Figure S27. Forest Plot. Obstructive Coronary Artery Disease on Coronary Angiogram.

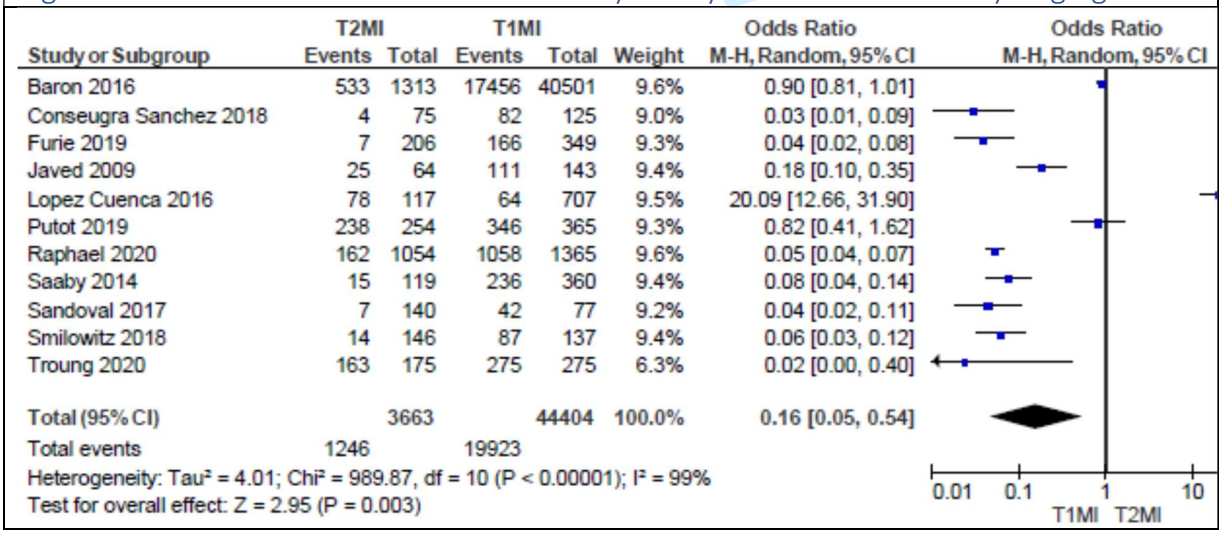


Figure S28. Forest Plot. Multivessel Disease on Coronary Angiogram.

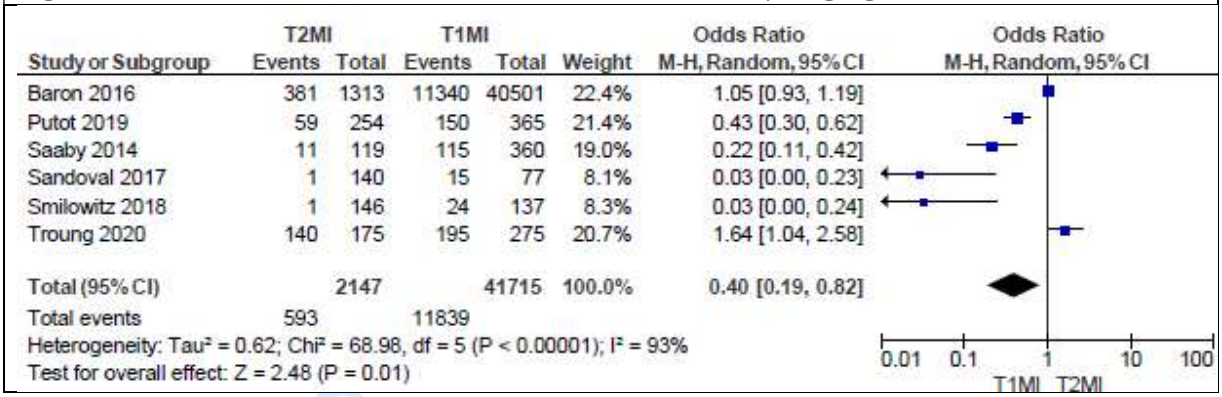


Figure S29. Forest Plot. Echocardiogram Performed.

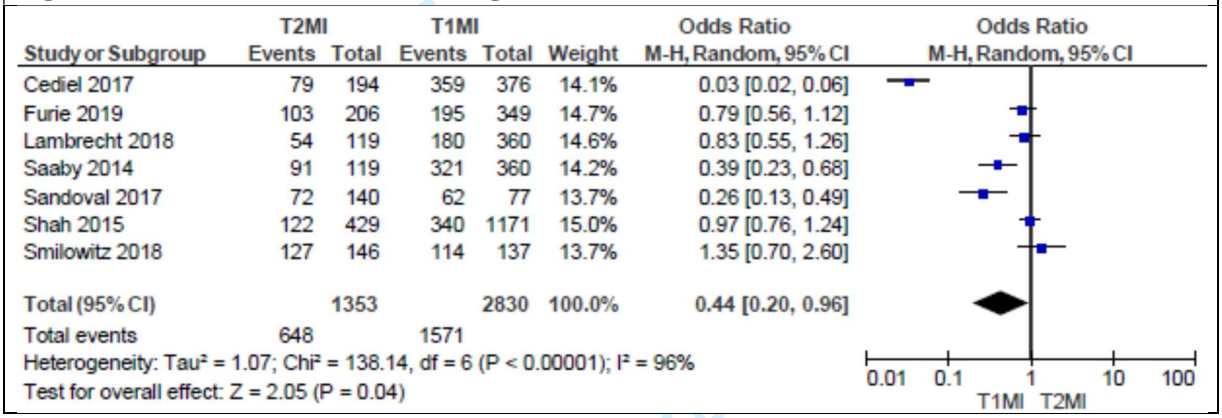


Figure S30. Forest Plot. Regional Wall Motion Abnormalities on Echocardiogram.

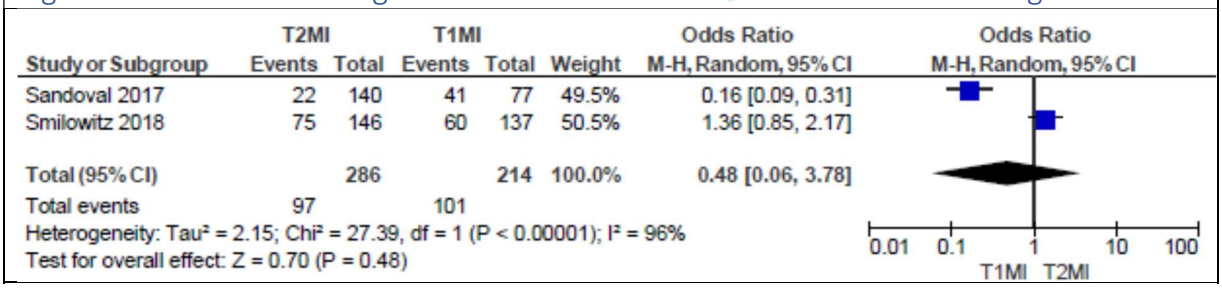


Figure S31. Forest Plot. Beta-Blockers Prescribed.

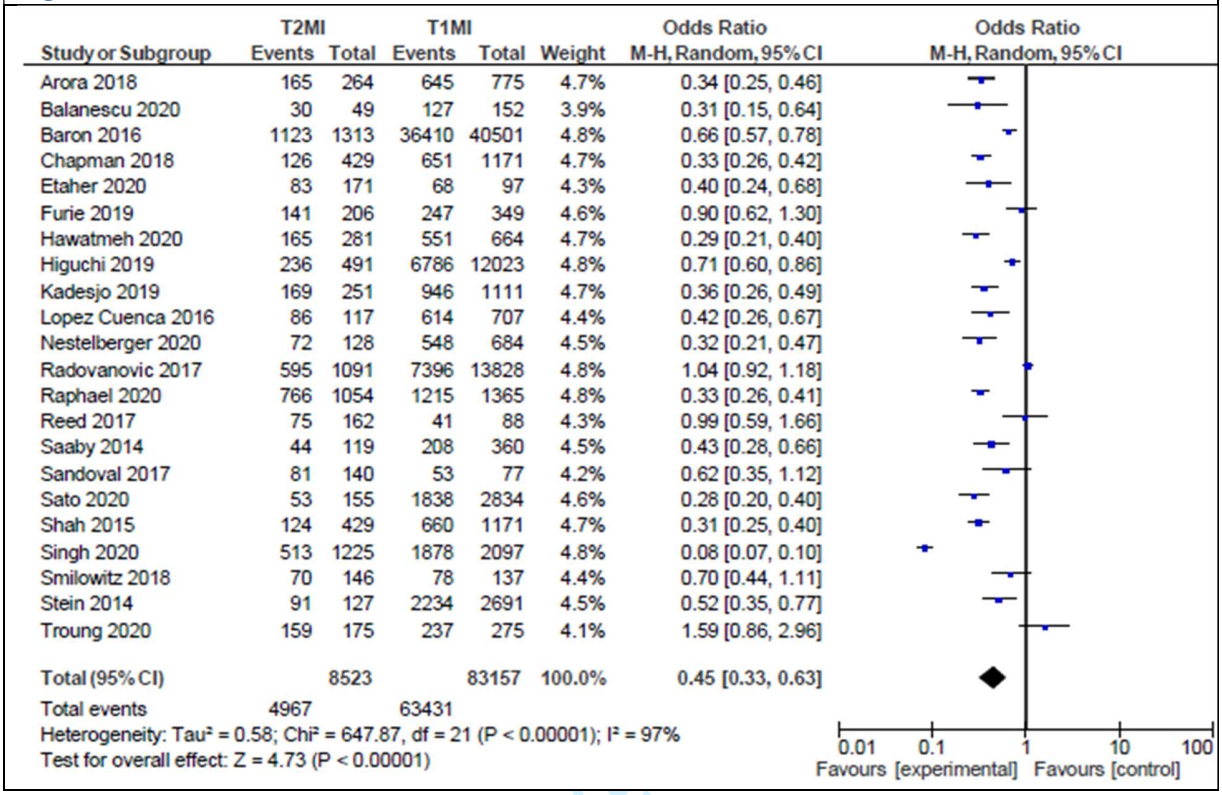


Figure S32. Forest Plot. ACEi/ARB Prescribed.

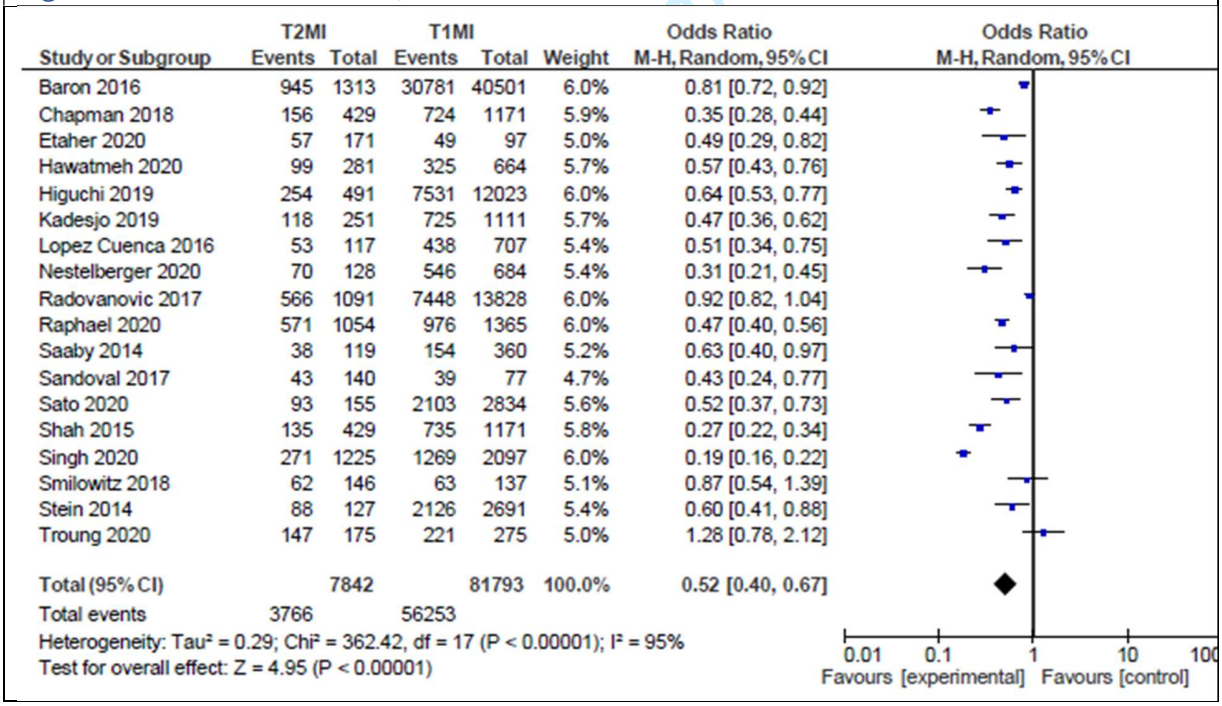


Figure S33. Forest Plot. Antiplatelets Prescribed.

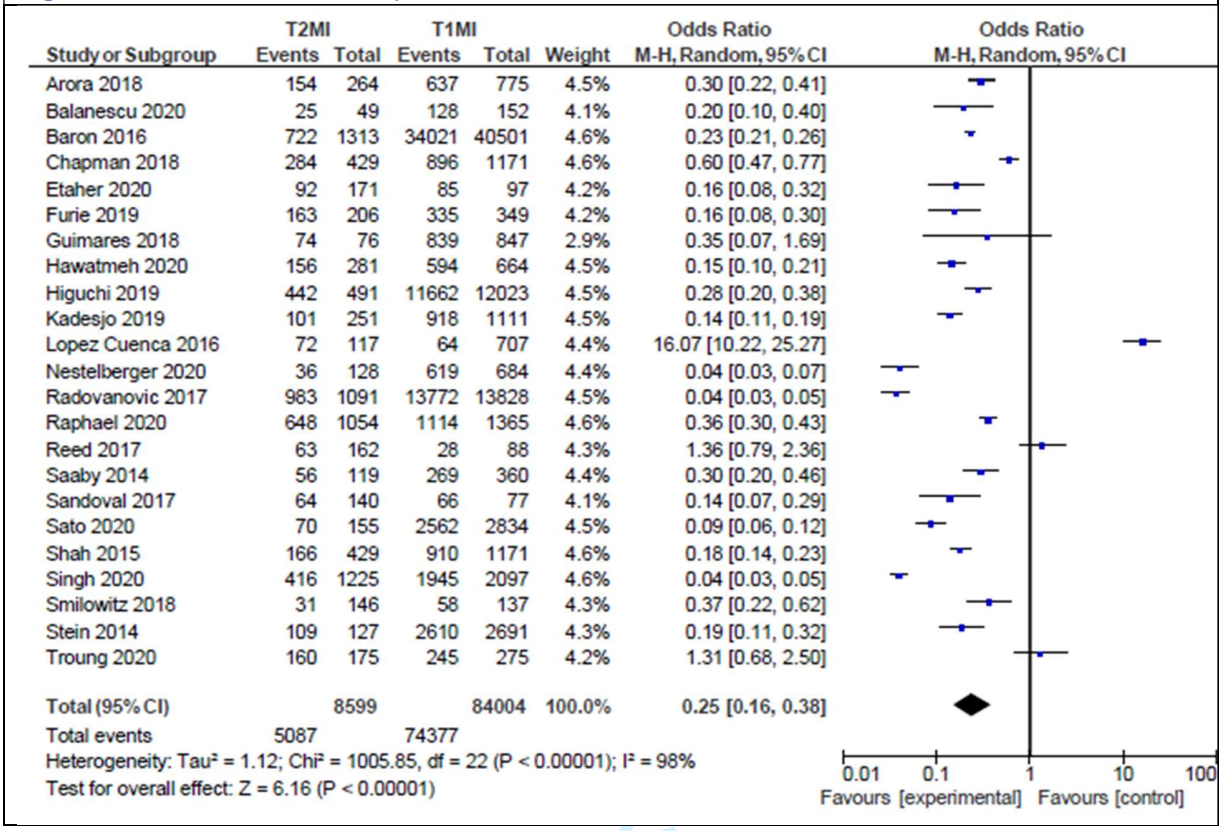


Figure S34. Forest Plot. Anticoagulants Prescribed.

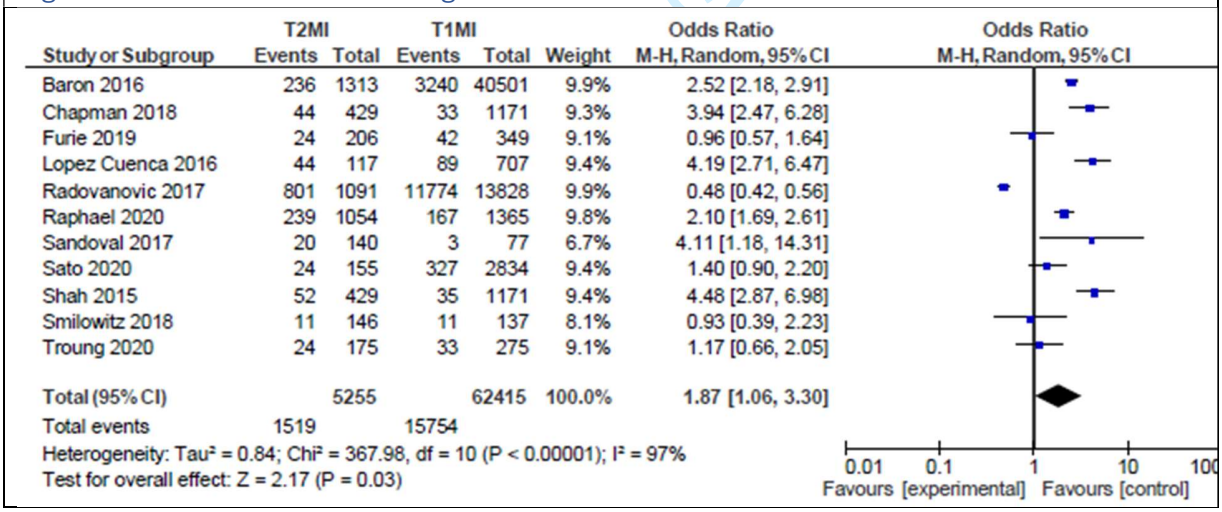


Figure S35. Forest Plot. Antianginal Drugs Prescribed.

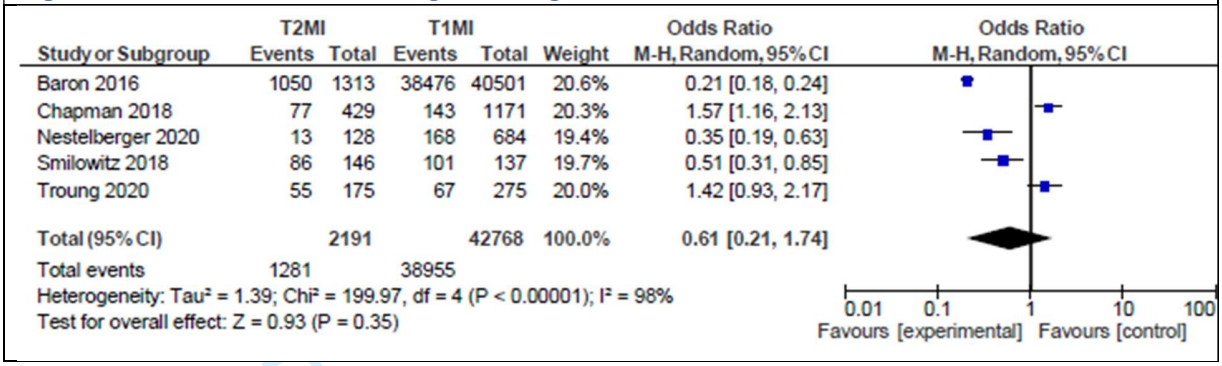


Figure S36. Forest Plot. Diuretics Prescribed.

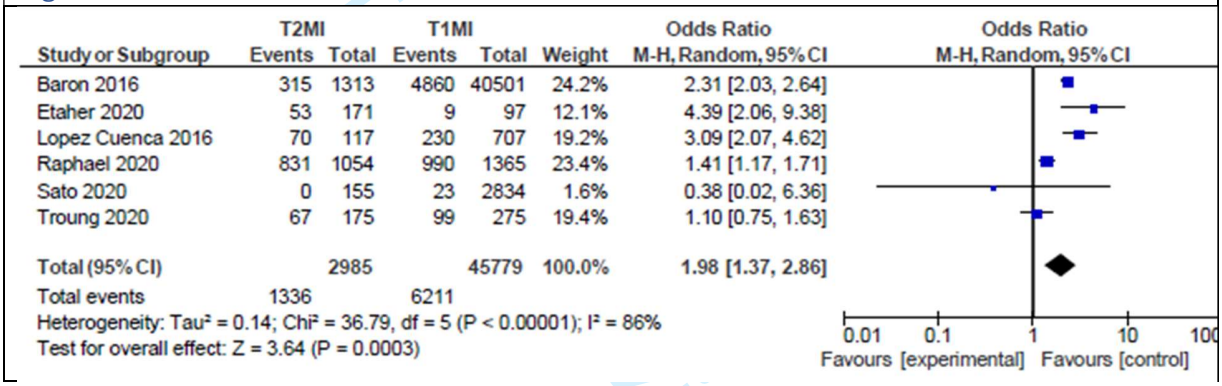


Figure S37. Forest Plot. Statins Prescribed.

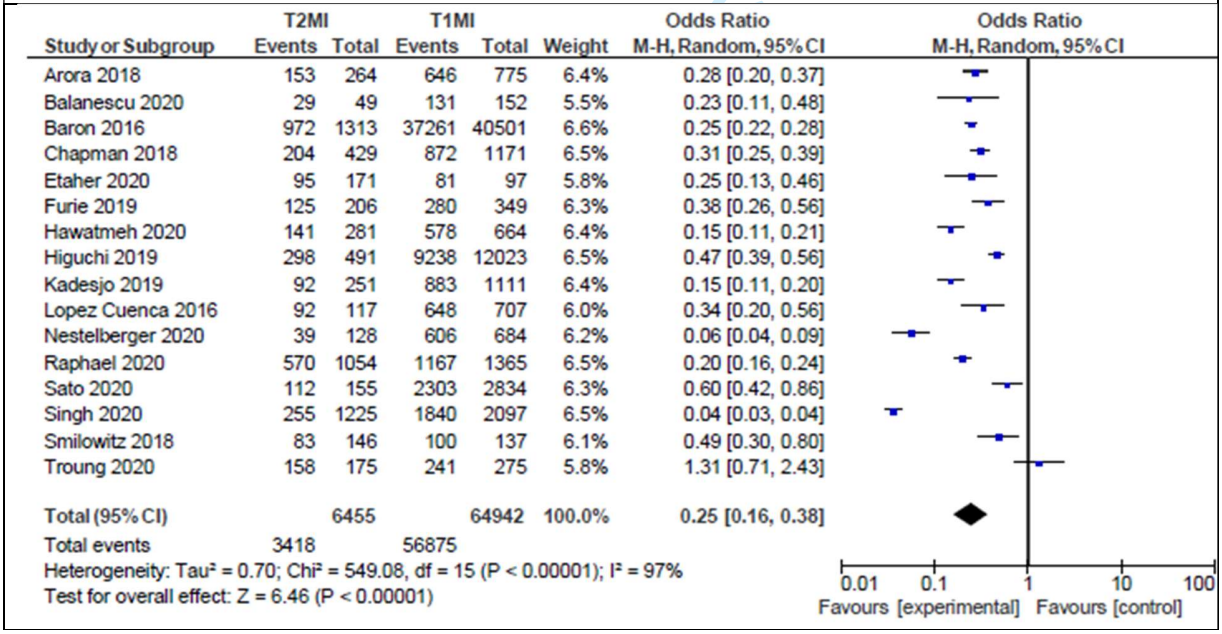


Figure S38. Forest Plot. Percutaneous Coronary Intervention Performed.

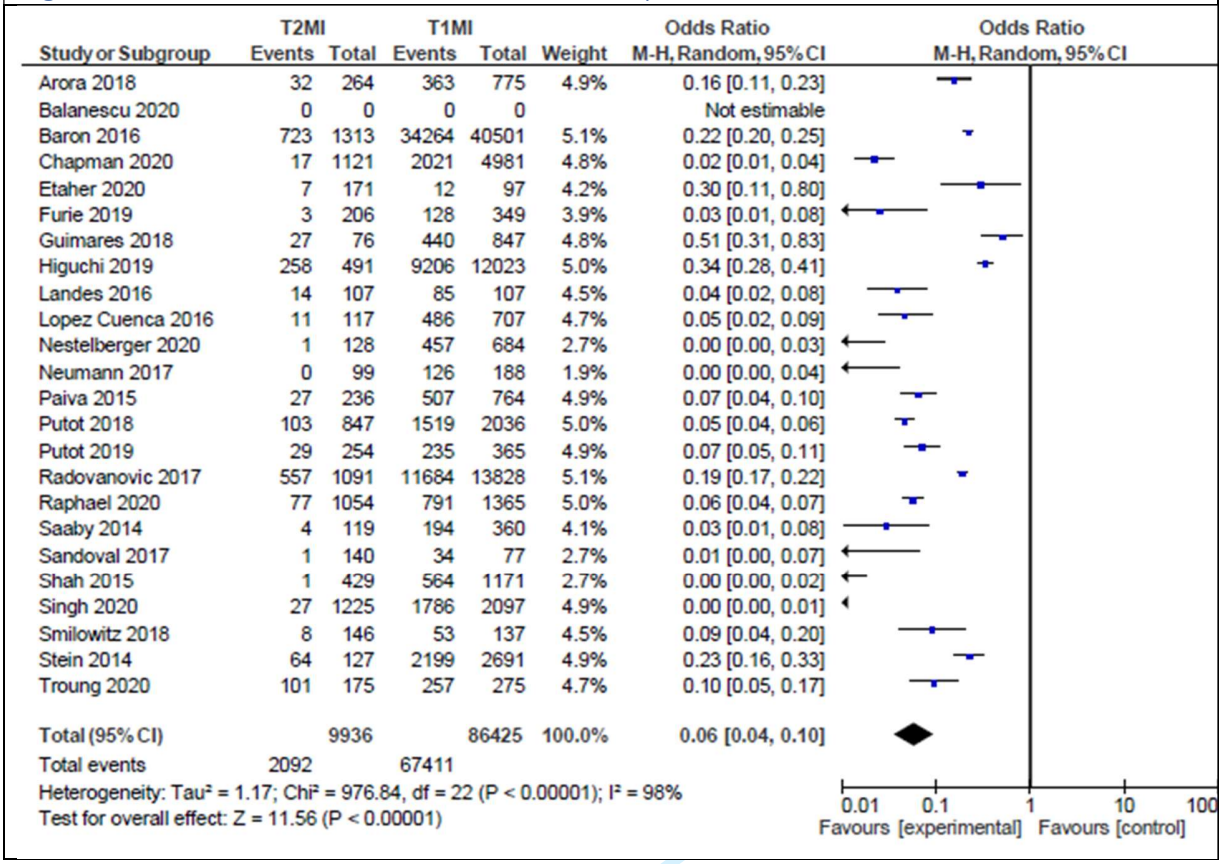


Figure S39. Forest Plot. Coronary Artery Bypass Graft Performed.

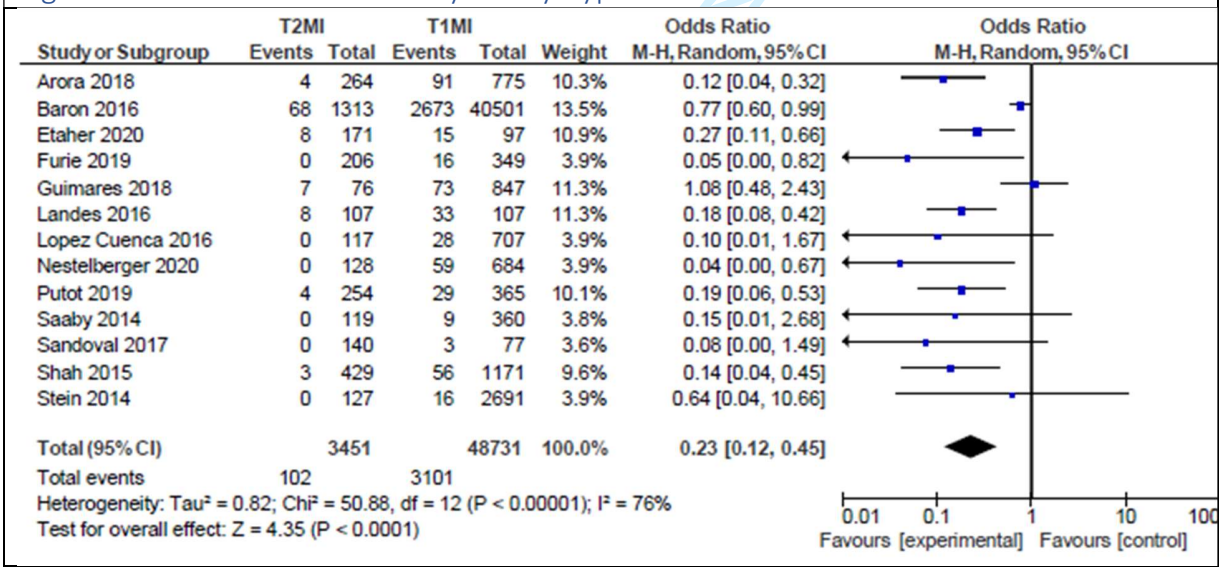


Figure S40. All cause In-hospital mortality. T2MI compared to T1MI.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Furie 2019	21	206	33	349	7.1%	1.09 [0.61, 1.93]
Higuchi 2019	54	491	769	12023	8.2%	1.81 [1.35, 2.42]
Javed 2009	9	64	15	143	5.7%	1.40 [0.58, 3.38]
Lopez Cuenca 2016	6	117	41	707	5.7%	0.88 [0.36, 2.12]
Meigher 2016	54	452	37	340	7.6%	1.11 [0.71, 1.73]
Paiva 2015	23	236	66	764	7.4%	1.14 [0.69, 1.88]
Putot 2018	133	847	125	2036	8.3%	2.85 [2.20, 3.69]
Putot 2019	38	254	24	365	7.2%	2.50 [1.46, 4.28]
Putot 2020	95	862	186	3710	8.3%	2.35 [1.81, 3.04]
Saaby 2014	29	119	10	360	6.3%	11.28 [5.30, 24.00]
Singh 2020	160	1225	42	2097	8.0%	7.35 [5.19, 10.41]
Smilowitz 2018	17	146	18	137	6.5%	0.87 [0.43, 1.77]
Stein 2014	15	127	113	2691	7.1%	3.06 [1.73, 5.41]
Troung 2020	13	175	29	275	6.6%	0.68 [0.34, 1.35]
Total (95% CI)		**5321**		**25997**	**100.0%**	**1.94 [1.35, 2.79]**
Total events	667		1508			

Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 115.87$, df = 13 ($P < 0.00001$); $I^2 = 89\%$
Test for overall effect: Z = 3.58 (P = 0.0003)

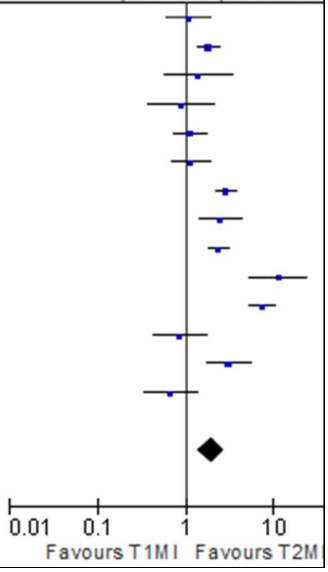


Figure S41. Short-term all-cause mortality. T2MI compared to T1MI.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Nestelberger 2020	1	128	42	684	10.4%	0.12 [0.02, 0.88]
Sandoval 2014	51	190	15	66	29.6%	1.25 [0.65, 2.41]
Sandoval 2017	18	140	6	77	23.4%	1.75 [0.66, 4.60]
Shah 2015	134	429	187	1171	36.7%	2.39 [1.85, 3.09]
Total (95% CI)		**887**		**1998**	**100.0%**	**1.34 [0.63, 2.85]**
Total events	204		250			

Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 12.11$, df = 3 ($P = 0.007$); $I^2 = 75\%$
Test for overall effect: Z = 0.77 (P = 0.44)

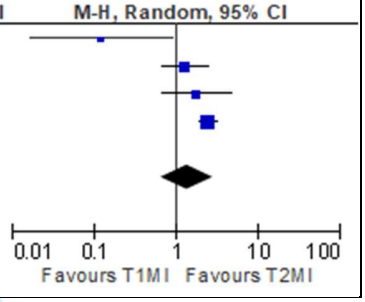


Figure S42. Two-year all-cause mortality. T2MI compared to T1MI.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Cediel 2017	77	194	74	376	19.0%	2.69 [1.83, 3.94]
Guimares 2018	19	76	156	847	15.9%	1.48 [0.85, 2.55]
Neumann 2017	14	99	18	188	12.5%	1.56 [0.74, 3.28]
Paiva 2015	62	236	92	764	19.3%	2.60 [1.81, 3.74]
Smilowitz 2018	45	146	41	137	16.6%	1.04 [0.63, 1.73]
Troung 2020	29	175	47	275	16.6%	0.96 [0.58, 1.60]
Total (95% CI)		**926**		**2587**	**100.0%**	**1.63 [1.11, 2.41]**
Total events	246		428			

Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 19.10$, df = 5 ($P = 0.002$); $I^2 = 74\%$
Test for overall effect: Z = 2.48 (P = 0.01)

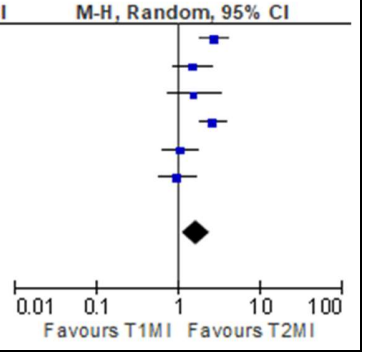


Figure S43. Three-year all-cause mortality. T2MI compared to T1MI.

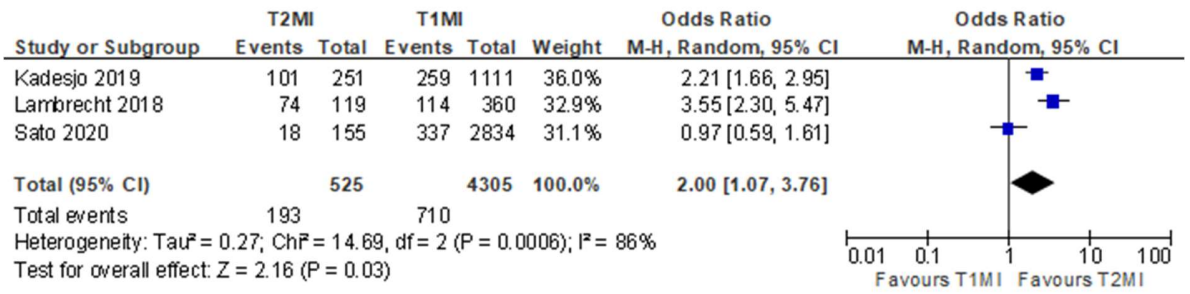
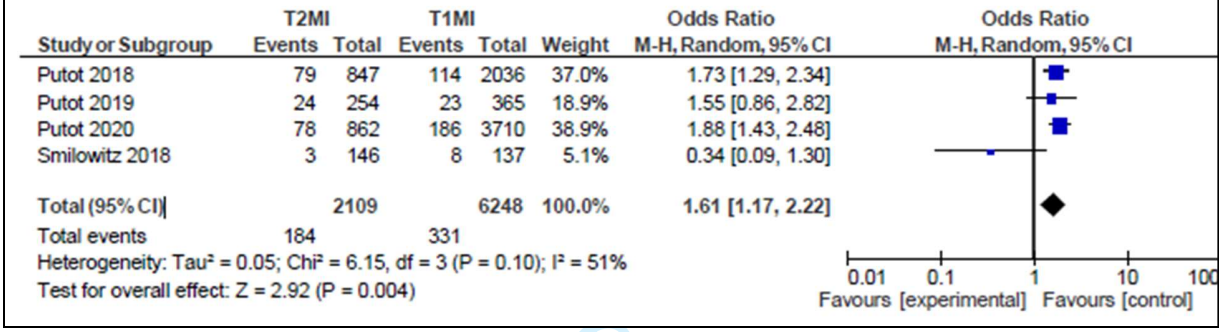


Figure S44. CVS In-hospital mortality. T2MI compared to T1MI.



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PRISMA 2020 Checklist

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

PRISMA 2020 Checklist

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

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

PRISMA 2020 Checklist

10.1136/bmj.n71

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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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Manuscript ID	bmjopen-2021-055755.R3
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Date Submitted by the Author:	17-Jan-2022
Complete List of Authors:	White, Kyle; Princess Alexandra Hospital; University of Queensland Kinarivala, Mansey; Princess Alexandra Hospital, Internal Medicine and Clinical Epidemiology Scott, Ian; University of Queensland, School of Clinical Medicine; Princess Alexandra Hospital, Department of Internal Medicine and Clinical Epidemiology
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Title Page

Manuscript Title

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

Authors

Dr Kyle White
Princess Alexandra Hospital, Brisbane, Australia
University of Queensland, Brisbane, Australia
BSc, MBBS, FRACP, FCICM, MPH

Dr Mansey Kinarivala
Princess Alexandra Hospital, Brisbane, Australia
MBBS, FRACP

Prof Ian Scott
Princess Alexandra Hospital, Brisbane, Australia
University of Queensland, Brisbane, Australia
MEd, MHA, MBBS, FRACP

Corresponding Author

Dr Kyle White
Princess Alexandra Hospital
199 Ipswich Road, Wolloongabba, 4102
Ph: +61731762111
Email: kyle.white@health.qld.gov.au

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Abstract

Importance

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

Objective

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

Data Sources

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

Study Selection

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

Data Extraction and Synthesis

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

Main Outcomes and Measures

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

Results

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

Conclusion and Relevance

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

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

Strength and Limitations

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

Introduction

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

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

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

Methods

Study design

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

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

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

Data collection and synthesis

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

Data on variables reported as, or able to be converted to, raw numbers, were pooled from all studies and subject to comparative meta-analysis using Review Manager (RevMan, Computer program. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For each variable, the odds ratio (OR) comparing T2MI to T1MI, and its 95% confidence interval (CI), was calculated and weighted using the random effects method. As specified in the registered study protocol, the random effects method was used in anticipation of study heterogeneity of at least moderate degree (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 Table S3. They comprised a total of 127,620 participants of whom 98,930 participants (77.5%) were classified as T1MI and 13,803 (10.8%) as T2MI. In the following text, we report key findings; more information and forest plots for each analysis involving more than one study and more than 100 total cases can be found in the on-line supplement, Figures S2-S44.

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

Risk of bias assessment

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

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

Participant characteristics

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

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

Precipitating factors

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

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

Presenting clinical features

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

Investigations

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

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

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

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

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

Management

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

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

Prognosis

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

Conclusion

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

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

Tables

Table 1. Pre-existing medical conditions in patients with T2MI versus T1MI.

Pre-existing medical condition	T2MI			T1MI			Odds ratio* (95% CI)
	Number of patients with the specified condition	Total number of patients	%	Number of patients with the specified condition	Total number of patients	%	
CAD	3352	10303	32.5%	22222	92725	24%	1.1 [0.93, 1.31]
Type 2 DM	3044	12157	25%	23287	93345	24.9%	0.97 [0.85, 1.10]
HTN	7536	11021	66.4%	55782	88017	63.4%	1.22 [1.03, 1.45]
Dyslipidaemia	4626	10652	43.4%	40099	87366	45.9%	0.74 [0.58, 0.94]
Smoker	3448	9929	34.7%	39548	74889	52.8%	0.60 [0.49, 0.73]
Obesity	1225	3672	33.4%	30963	56970	54.3%	0.63 [0.46, 0.87]
Renal failure	1378	6040	22.8%	11300	65394	17.3%	1.87 [1.53, 2.28]
Heart failure	1661	8873	13.1%	5617	74212	7.6%	2.35 [1.82, 3.03]
PVD	584	5856	10.0%	2066	41280	5.0%	1.33 [1.05, 1.69]
CVD	969	8538	11.3%	6060	87822	6.9%	1.47 [1.27, 1.71]
Atrial fibrillation	836	3645	22.9%	1220	19843	6.1%	3.02 [2.29, 3.99]
COPD	800	5018	15.9%	823	48375	1.7%	1.94 [1.22, 3.08]
Illicit drug Use	46	204	22.5%	8	220	3.6%	8.15 [1.03, 64.46]

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

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

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

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

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

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

Table 3. Outcomes in patients with T2MI versus T1MI.

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

*Comparing T1MI with T2MI patients, with odds ratio adjusted according to study weighting using random effects meta-analysis
Abbreviations: CV= Cardiovascular, MACE= Major adverse cardiovascular events; T2MI=type 2 myocardial infarction; T1MI=type 1 myocardial infarction; CI=confidence interval

Figures

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

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

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

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

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

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

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

Contribution Statement

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

Competing Interests

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

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Data Sharing Statement

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

Ethic Approval Statement

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

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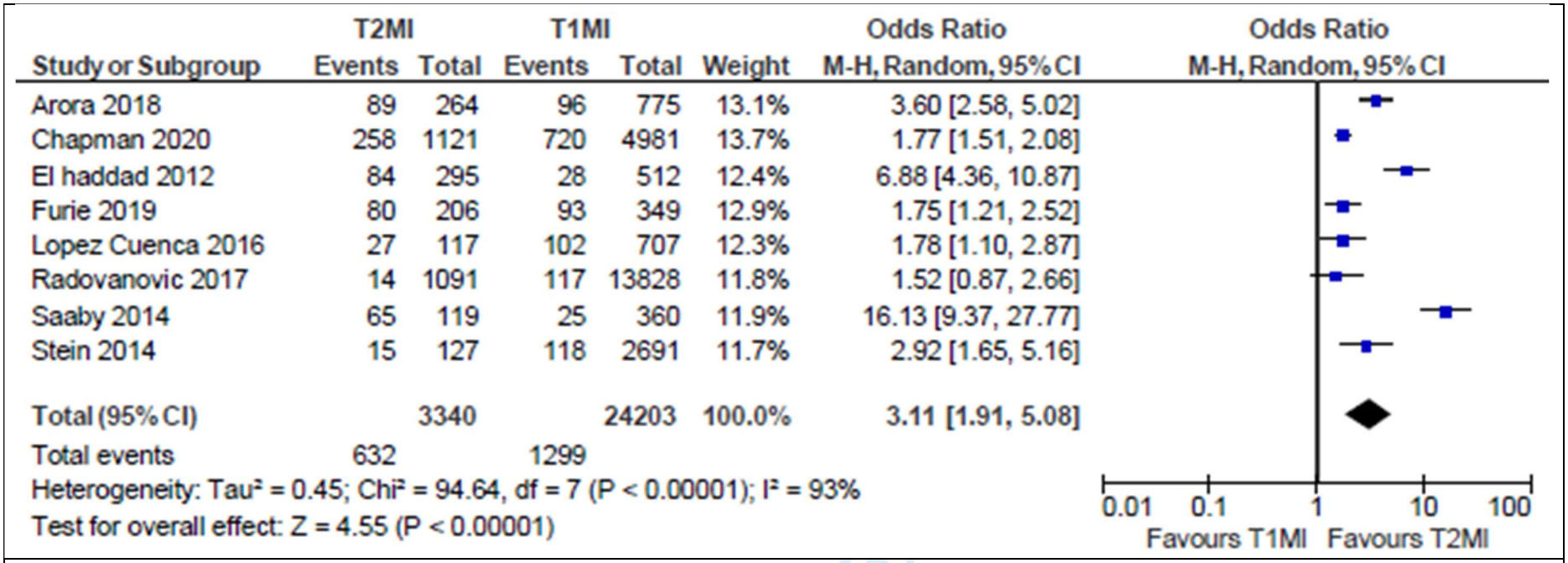


Figure 1. Forest plot of the result of meta-analysis of the risk one-year mortality of T2MI patients compared to T1MI patients.

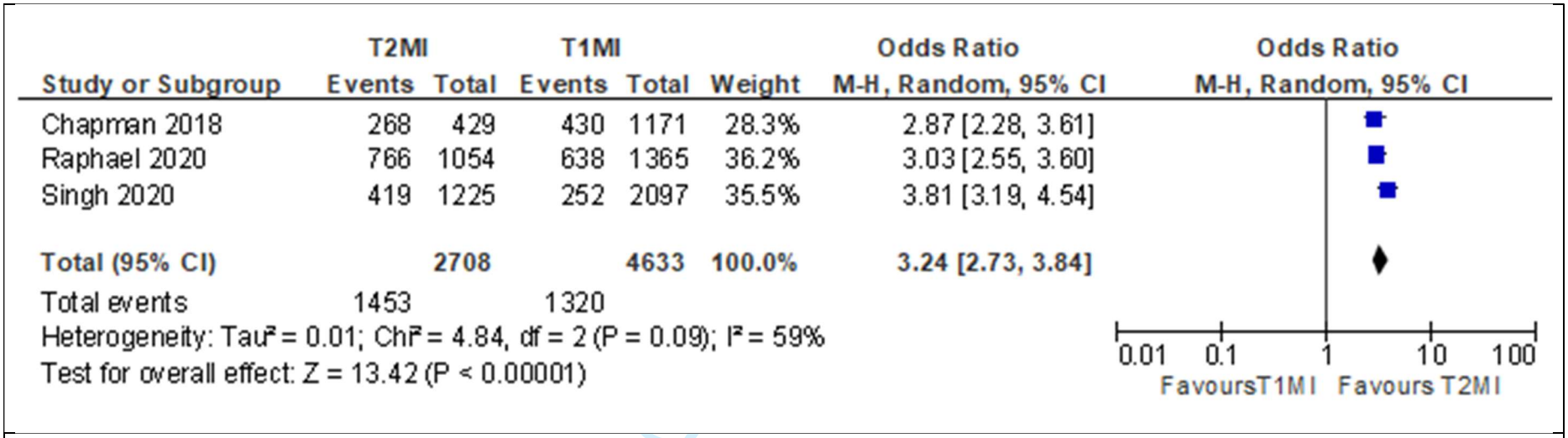


Figure 2. Forest plot of the result of meta-analysis of the risk long-term mortality of T2MI patients compared to T1MI patients.

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.

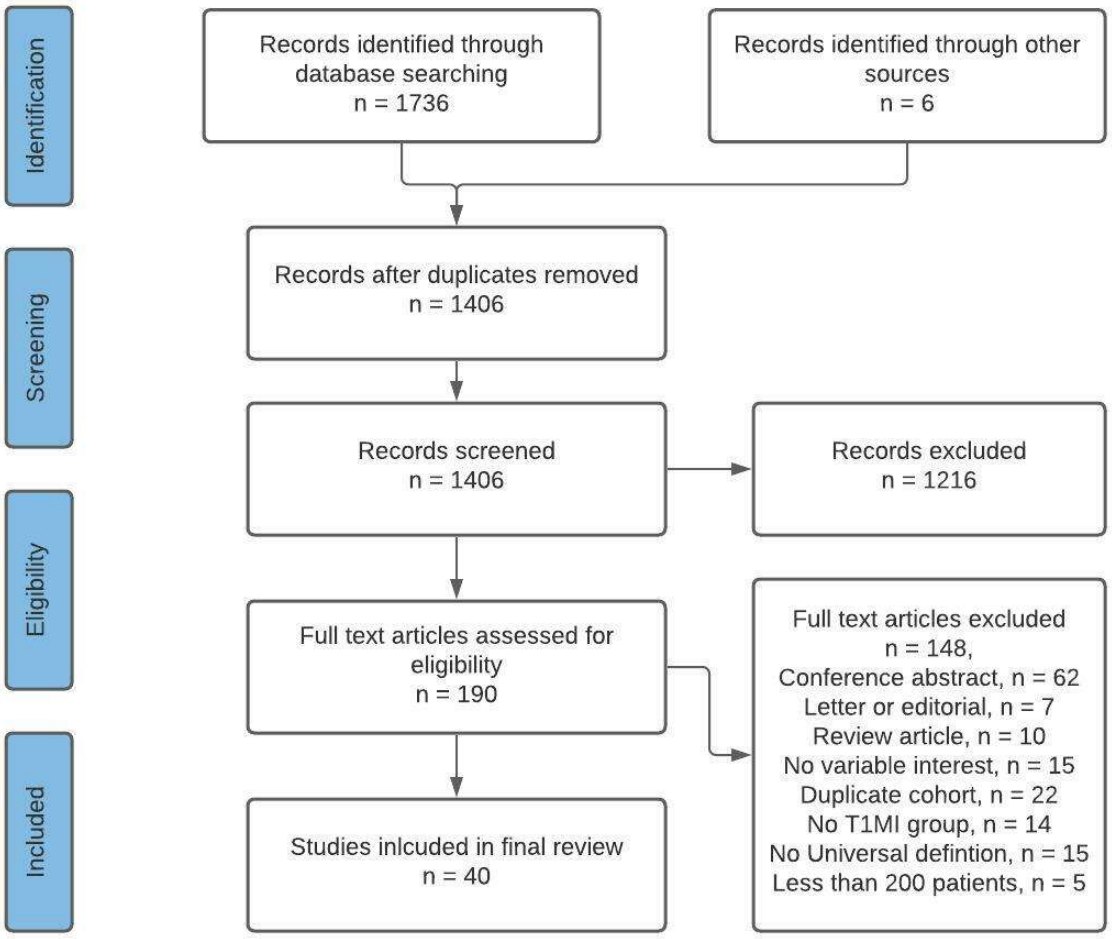


Figure S2. Forest Plot. Presence of Ischaemic Heart Disease.

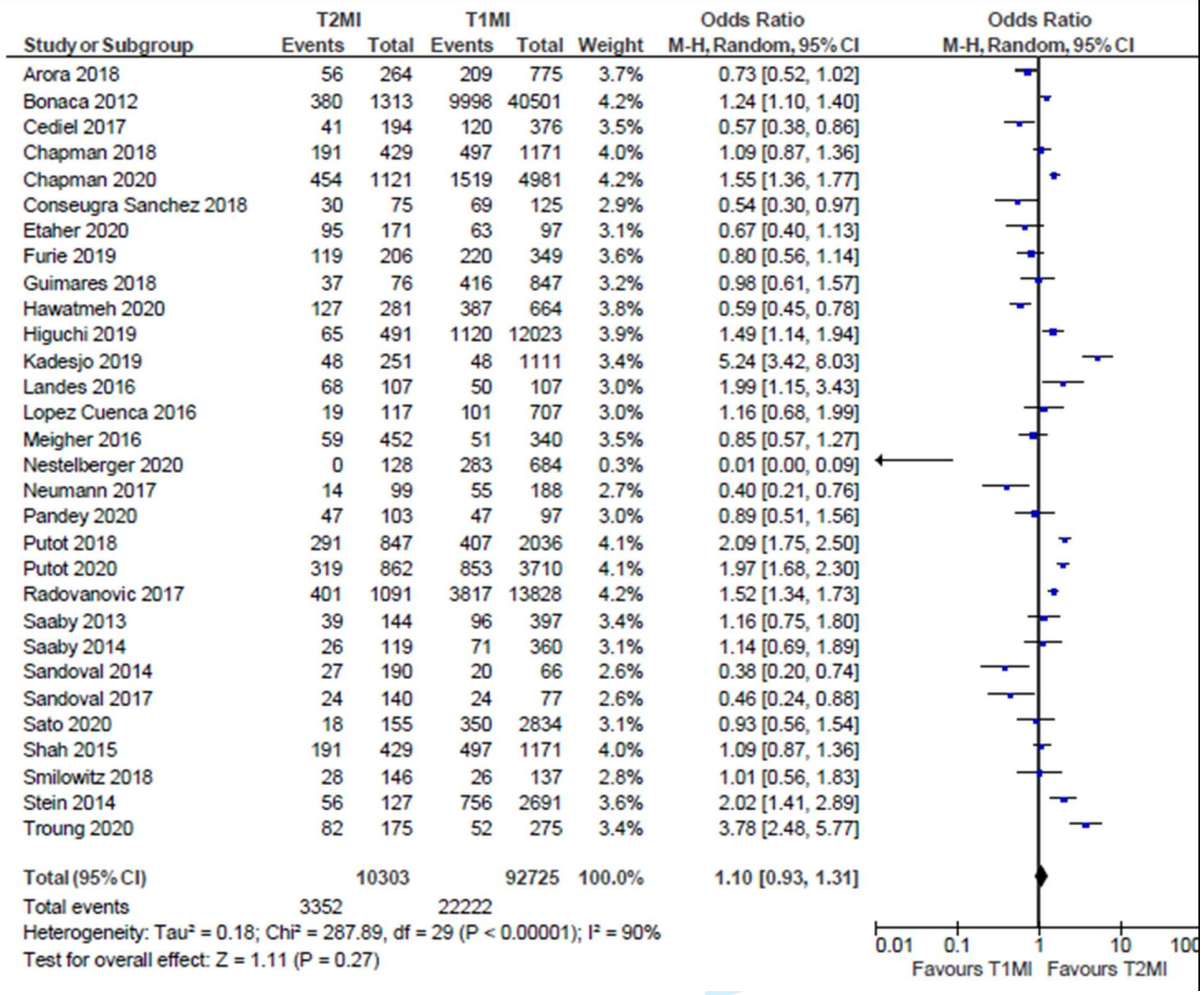


Figure S3. Forest Plot. Presence of Type 2 Diabetes Mellitus.

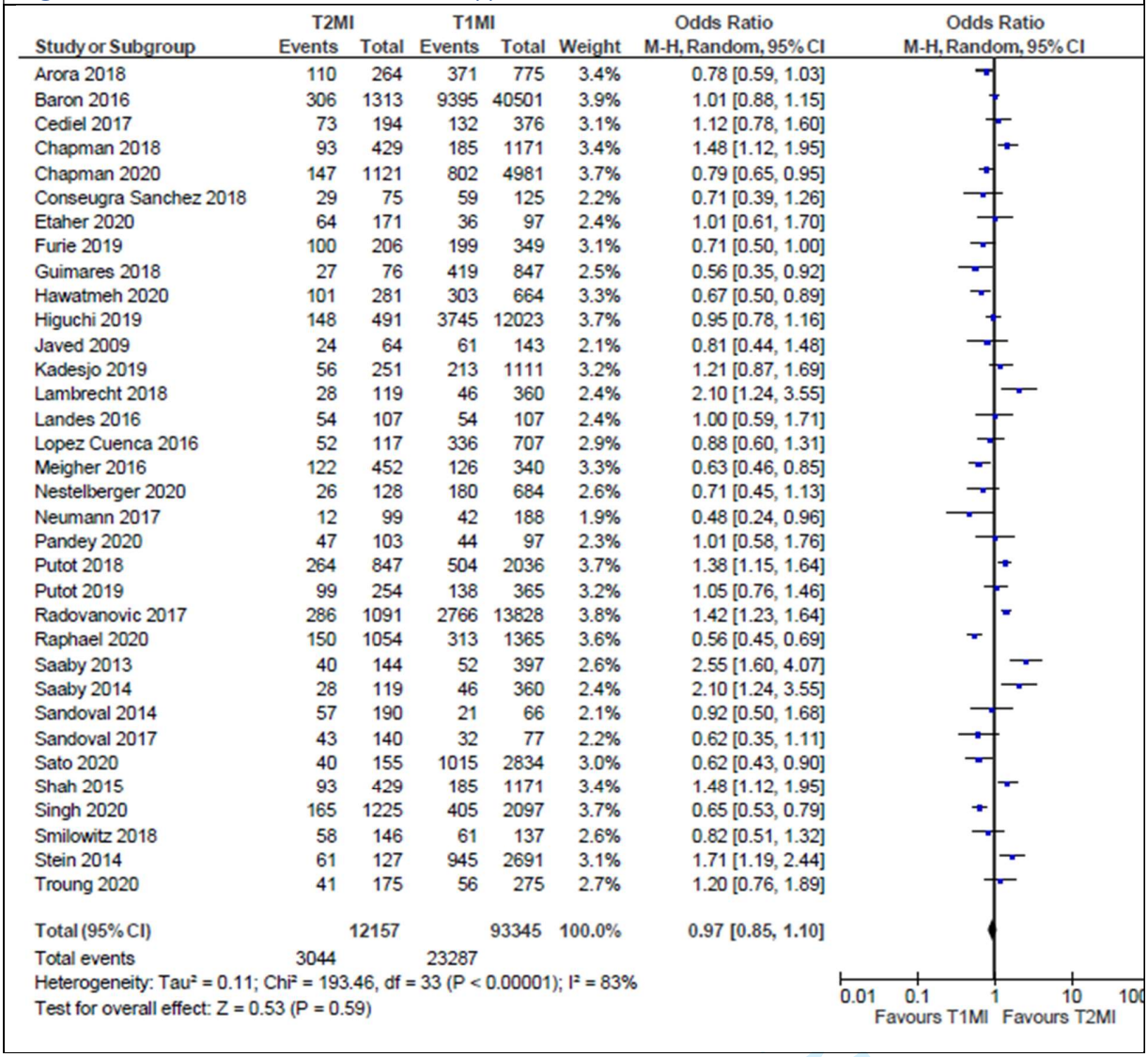


Figure S4. Forest Plot. Presence of Hypertension.

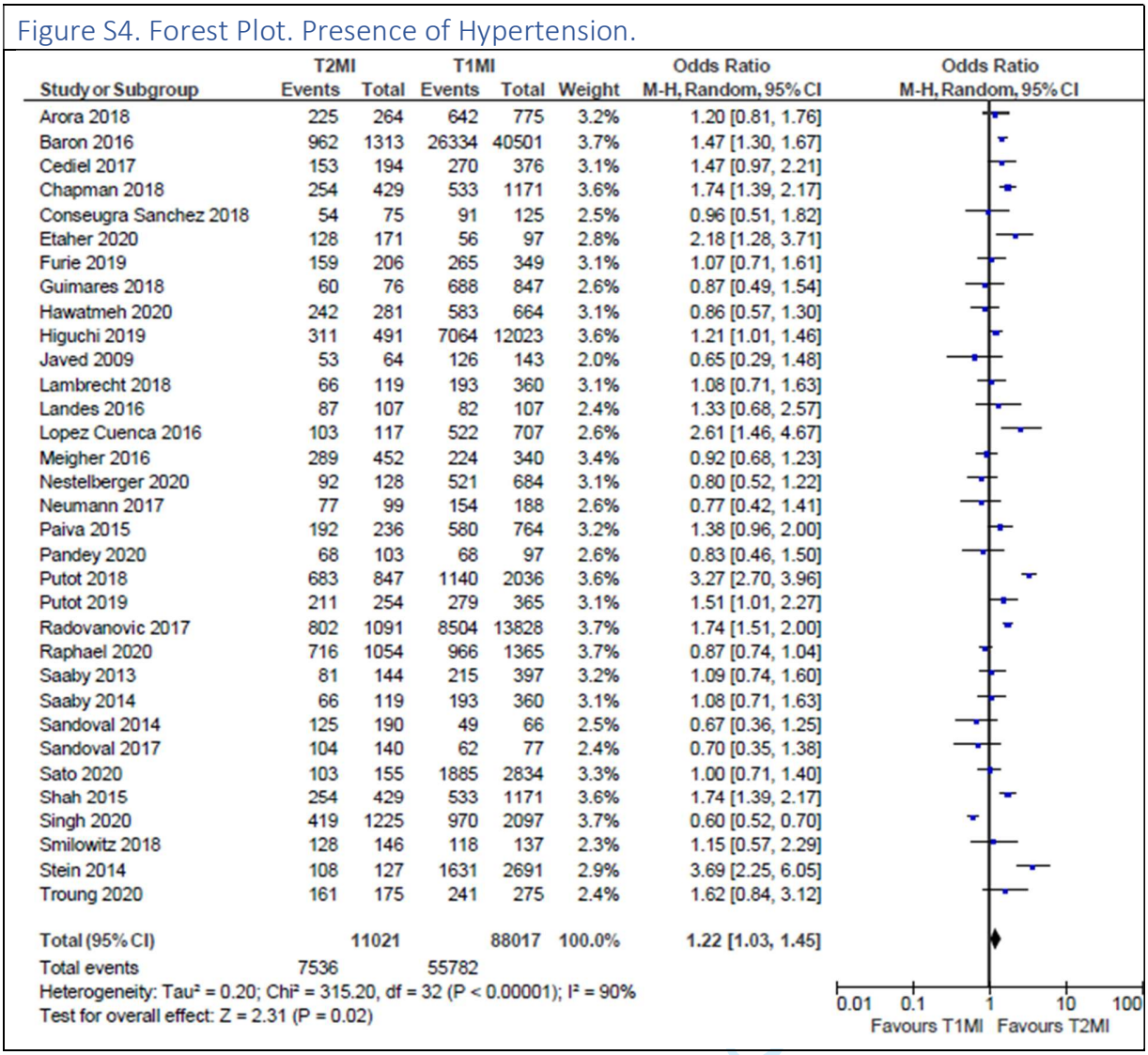


Figure S5. Forest Plot. Presence of Dyslipidaemia.

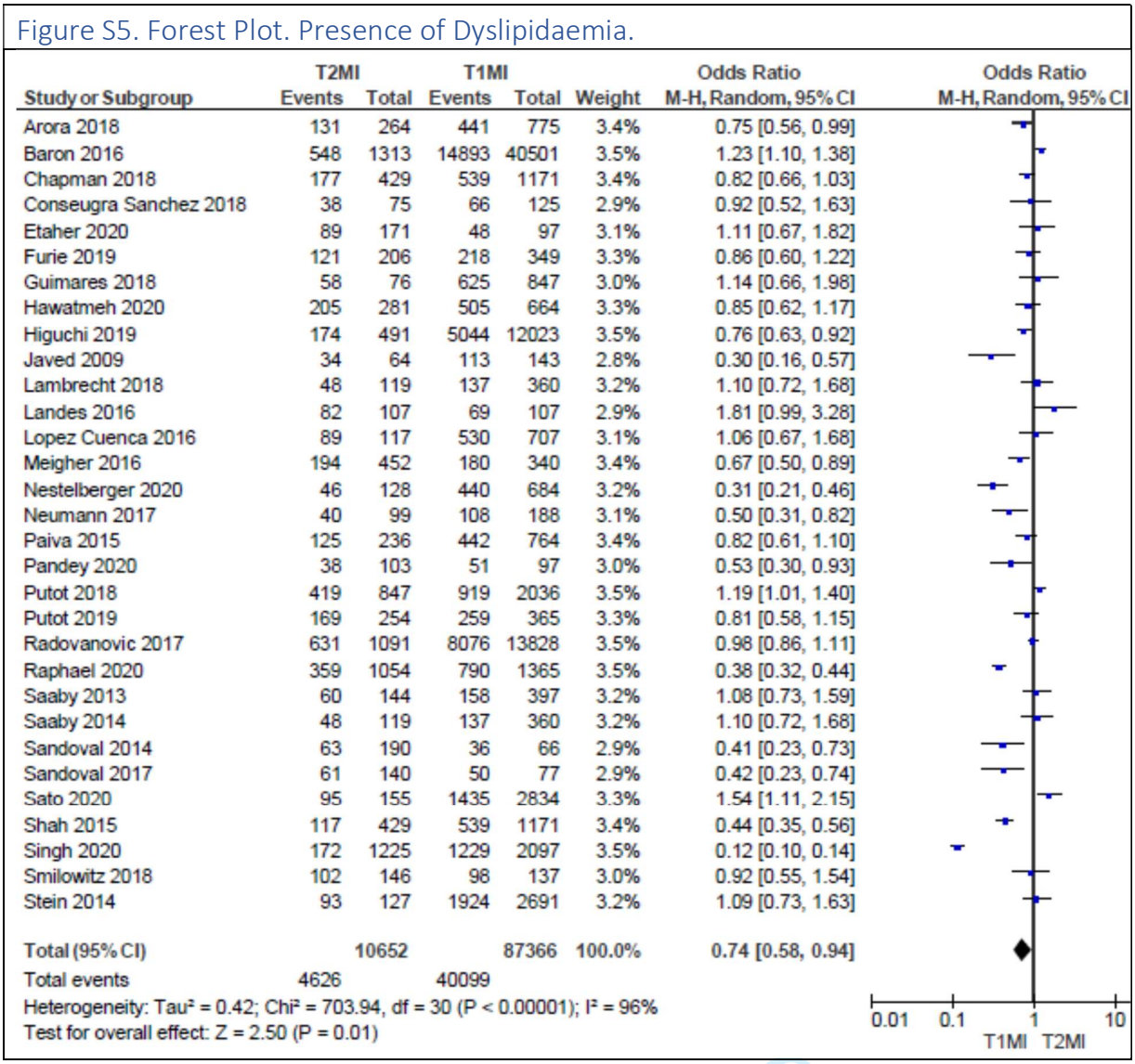


Figure S6. Forest Plot. Smoking Status.

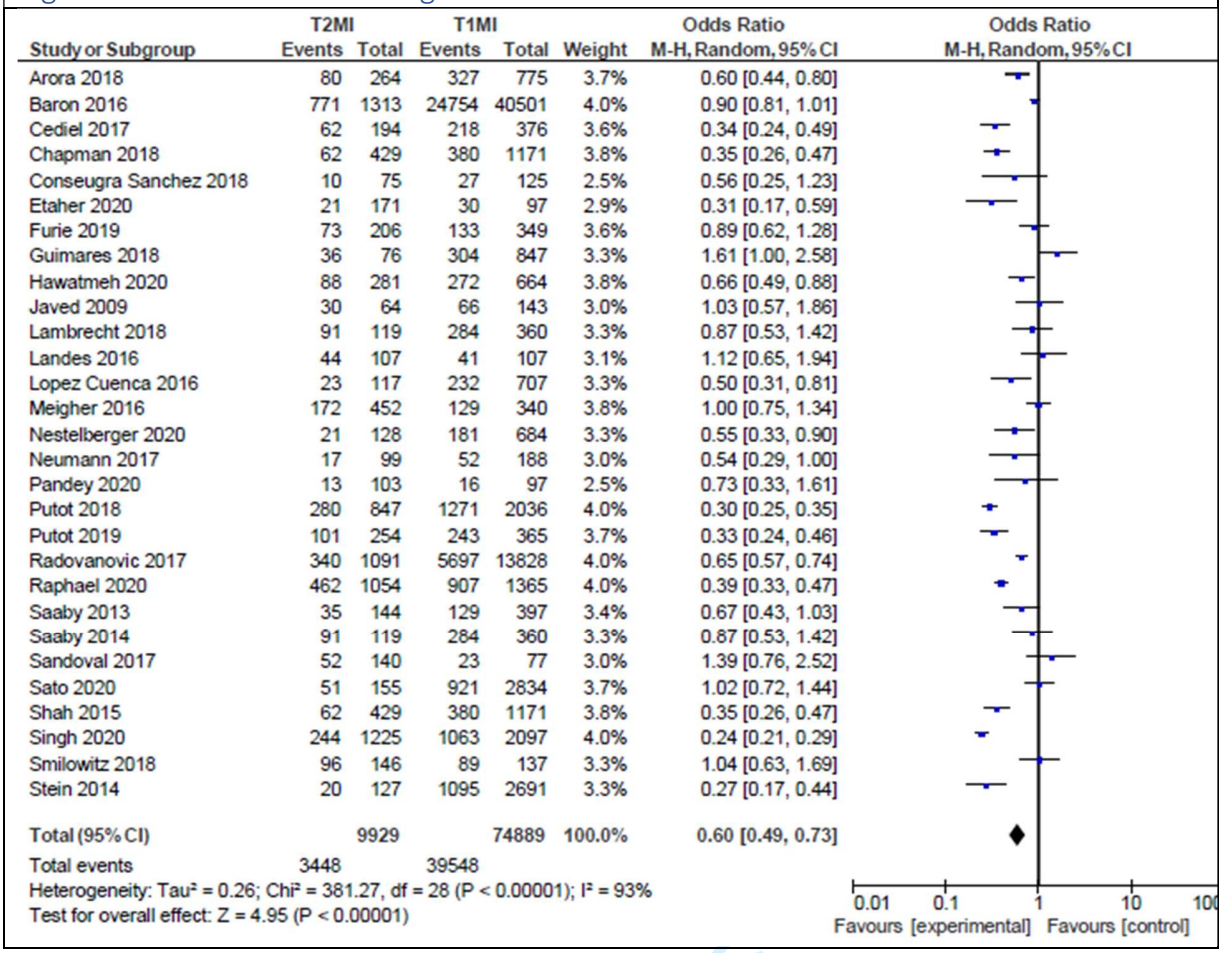


Figure S7. Forest Plot. Obesity Status.

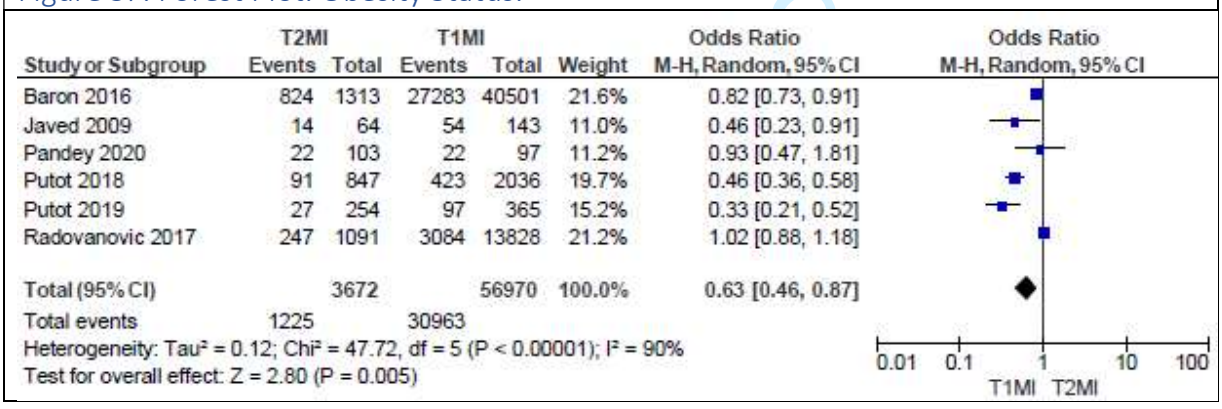


Figure S8. Forest Plot. Presence of Chronic Kidney Disease.

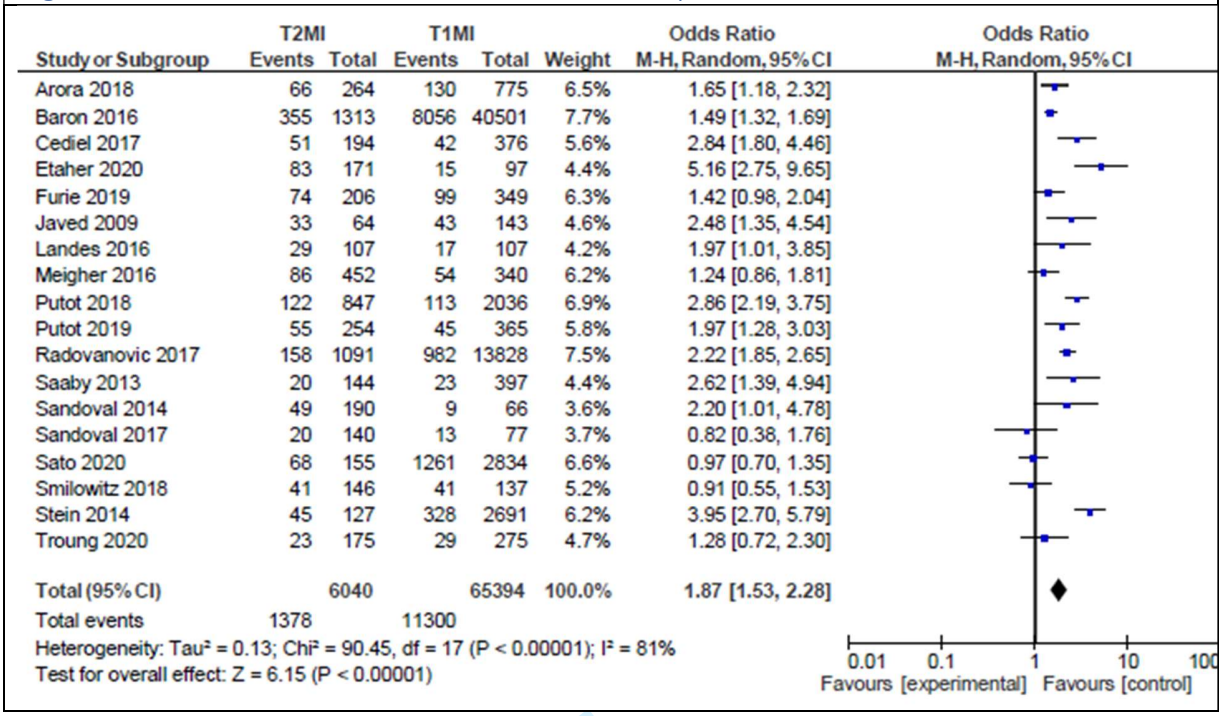


Figure S9. Forest Plot. Presence of Heart Failure.

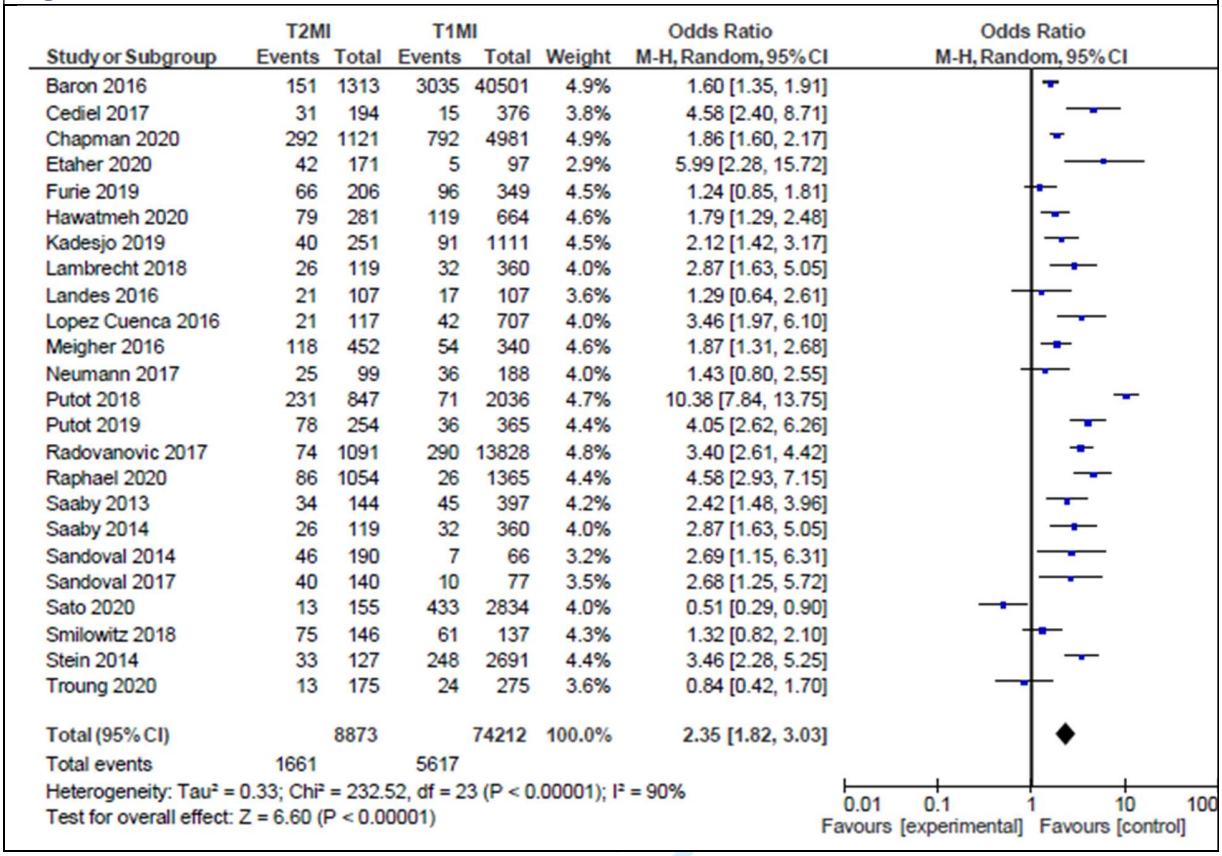


Figure S10. Forest Plot. Presence of Peripheral Vascular Disease.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
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 ($P < 0.00001$); $I^2 = 77\%$

Test for overall effect: $Z = 2.36$ ($P = 0.02$)

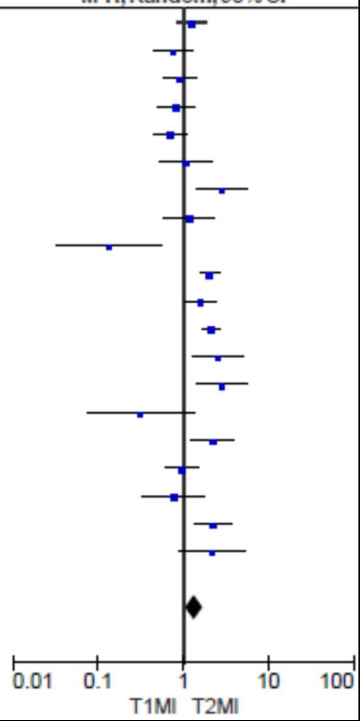


Figure S11. Forest Plot. Presence of Cerebrovascular Disease.

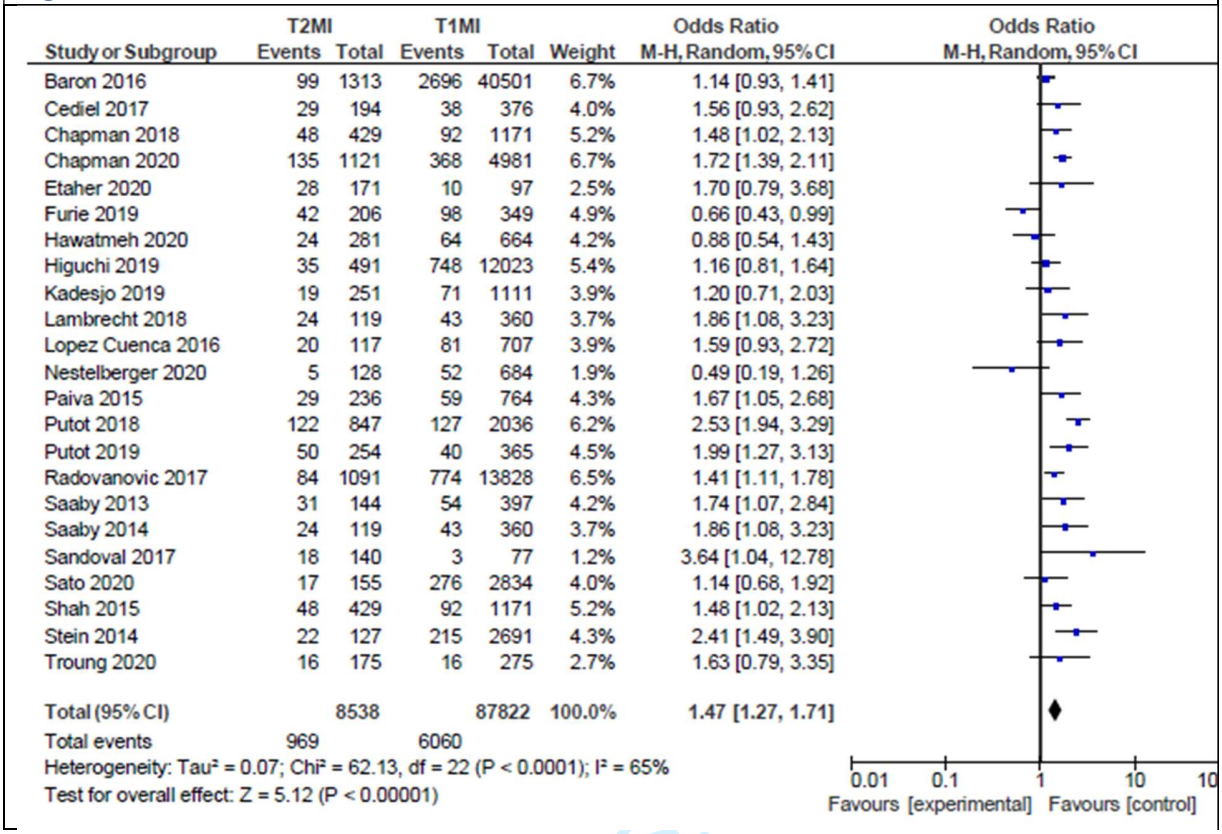


Figure S12. Forest Plot. Presence of Illicit Drug Use.

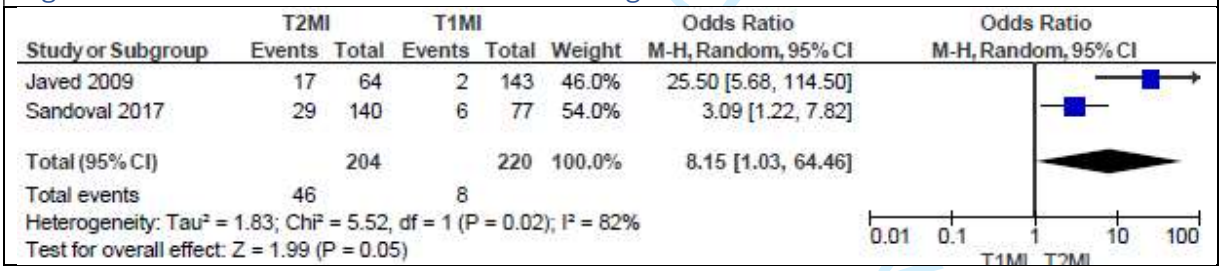


Figure S13. Forest Plot. Presence of Atrial Fibrillation.

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

Heterogeneity: Tau² = 0.18; Chi² = 62.33, df = 11 (P < 0.00001); I² = 82%
Test for overall effect: Z = 7.83 (P < 0.00001)

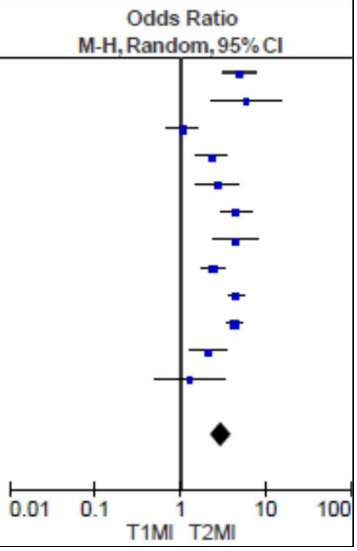


Figure S14. Forest Plot. Chest Pain as Presenting Feature.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Balanescu 2020	8	49	67	152	5.2%	0.25 [0.11, 0.56]
Baron 2016	899	1313	35883	40501	7.4%	0.28 [0.25, 0.32]
Cediel 2017	42	194	337	376	6.5%	0.03 [0.02, 0.05]
Chapman 2020	749	1121	4061	4981	7.4%	0.46 [0.40, 0.53]
Conseugra Sanchez 2018	62	75	102	125	5.5%	1.08 [0.51, 2.28]
Furie 2019	88	206	258	349	6.9%	0.26 [0.18, 0.38]
Landes 2016	65	107	103	107	4.3%	0.06 [0.02, 0.18]
Lopez Cuenca 2016	87	117	618	707	6.5%	0.42 [0.26, 0.67]
Meigher 2016	41	452	201	340	6.8%	0.07 [0.05, 0.10]
Radovanovic 2017	853	1091	12846	13828	7.3%	0.27 [0.23, 0.32]
Sandoval 2014	65	190	56	66	5.5%	0.09 [0.04, 0.19]
Sandoval 2017	22	140	38	77	5.9%	0.19 [0.10, 0.36]
Shah 2015	217	429	1041	1171	7.1%	0.13 [0.10, 0.17]
Smilowitz 2018	46	146	128	137	5.4%	0.03 [0.02, 0.07]
Stein 2014	69	127	2274	2691	6.9%	0.22 [0.15, 0.31]
Troung 2020	161	175	260	275	5.4%	0.66 [0.31, 1.41]
Total (95% CI)		5932		65883	100.0%	0.19 [0.13, 0.26]
Total events	3474		58273			

Heterogeneity: Tau² = 0.40; Chi² = 278.78, df = 15 (P < 0.00001); I² = 95%
Test for overall effect: Z = 9.73 (P < 0.00001)

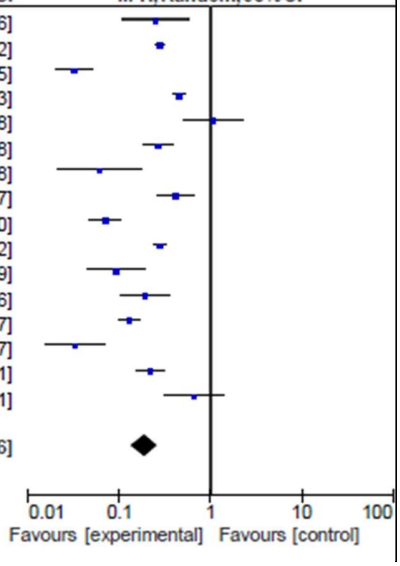


Figure S15. Forest Plot. Dyspnoea as Presenting Feature.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Baron 2016	195	1313	1774	40501	9.4%	3.81 [3.25, 4.47]
Cediel 2017	90	194	37	376	8.3%	7.93 [5.10, 12.33]
Chapman 2020	116	1121	171	4981	9.2%	3.25 [2.54, 4.15]
Furie 2019	122	206	178	349	8.8%	1.40 [0.98, 1.98]
Landes 2016	78	107	38	107	7.6%	4.88 [2.73, 8.74]
Lopez Cuenca 2016	22	117	38	707	7.7%	4.08 [2.31, 7.19]
Radovanovic 2017	482	1091	4425	13828	9.5%	1.68 [1.48, 1.91]
Sandoval 2014	112	190	35	66	7.7%	1.27 [0.72, 2.23]
Sandoval 2017	72	140	40	77	7.7%	0.98 [0.56, 1.71]
Shah 2015	80	429	45	1171	8.6%	5.74 [3.91, 8.42]
Stein 2014	15	127	105	2691	7.6%	3.30 [1.86, 5.85]
Troung 2020	28	175	44	275	7.9%	1.00 [0.60, 1.68]
Total (95% CI)		5210		65129	100.0%	2.64 [1.86, 3.74]
Total events	1412		6930			

Heterogeneity: Tau² = 0.33; Chi² = 163.95, df = 11 (P < 0.00001); I² = 93%
Test for overall effect: Z = 5.46 (P < 0.00001)

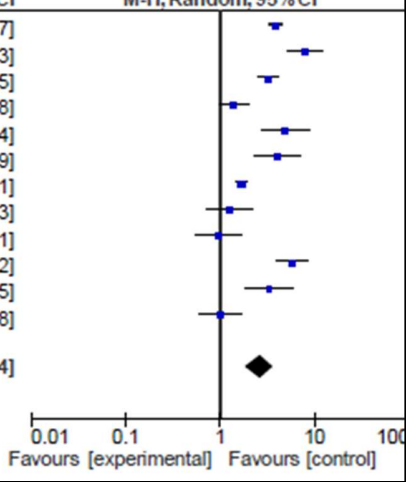


Figure S16. Forest Plot. Arm / Shoulder Discomfort as Presenting Feature.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Sandoval 2014	13	190	20	66	45.6%	0.17 [0.08, 0.36]
Sandoval 2017	15	140	30	77	54.4%	0.19 [0.09, 0.38]
Total (95% CI)		330		143	100.0%	0.18 [0.11, 0.30]
Total events	28		50			

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 6.49 (P < 0.00001)

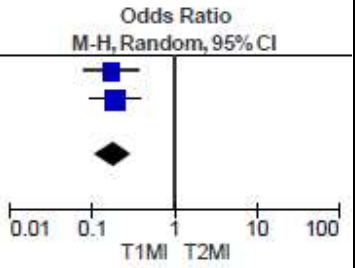


Figure S17. Forest Plot. Nausea / Vomiting as Presenting Feature.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Sandoval 2014	21	190	14	66	42.8%	0.46 [0.22, 0.97]
Sandoval 2017	25	140	25	77	57.2%	0.45 [0.24, 0.86]
Total (95% CI)		330		143	100.0%	0.46 [0.28, 0.74]
Total events	46		39			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 3.16 (P = 0.002)

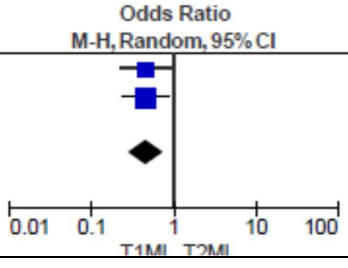


Figure S18. Forest Plot. Non-specific Symptoms as Presenting Features.

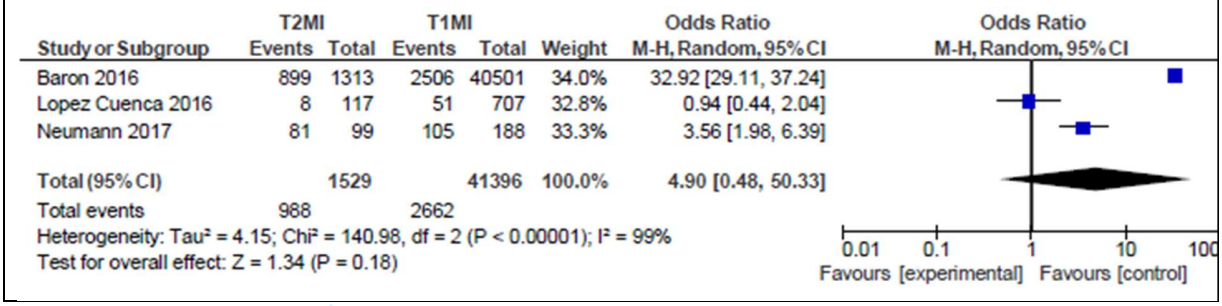


Figure S19. Forest Plot. Collapse / Syncope as Presenting Features.

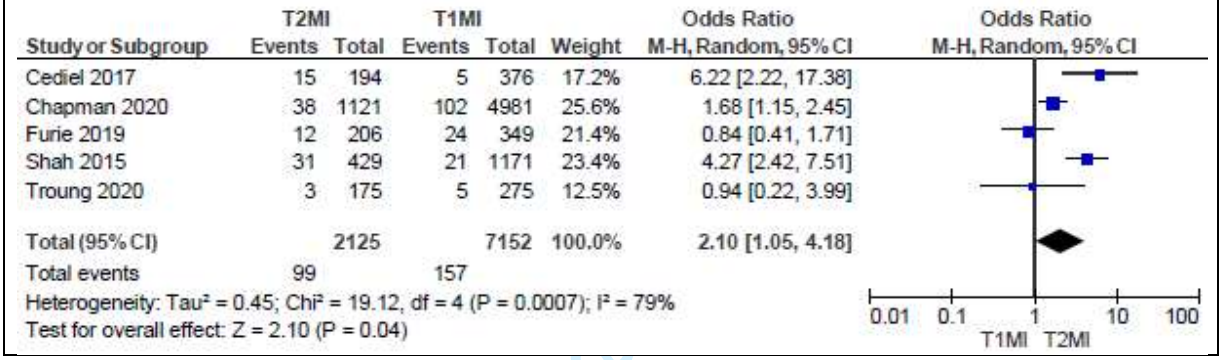


Figure S20. Forest Plot. ST Elevation on ECG.

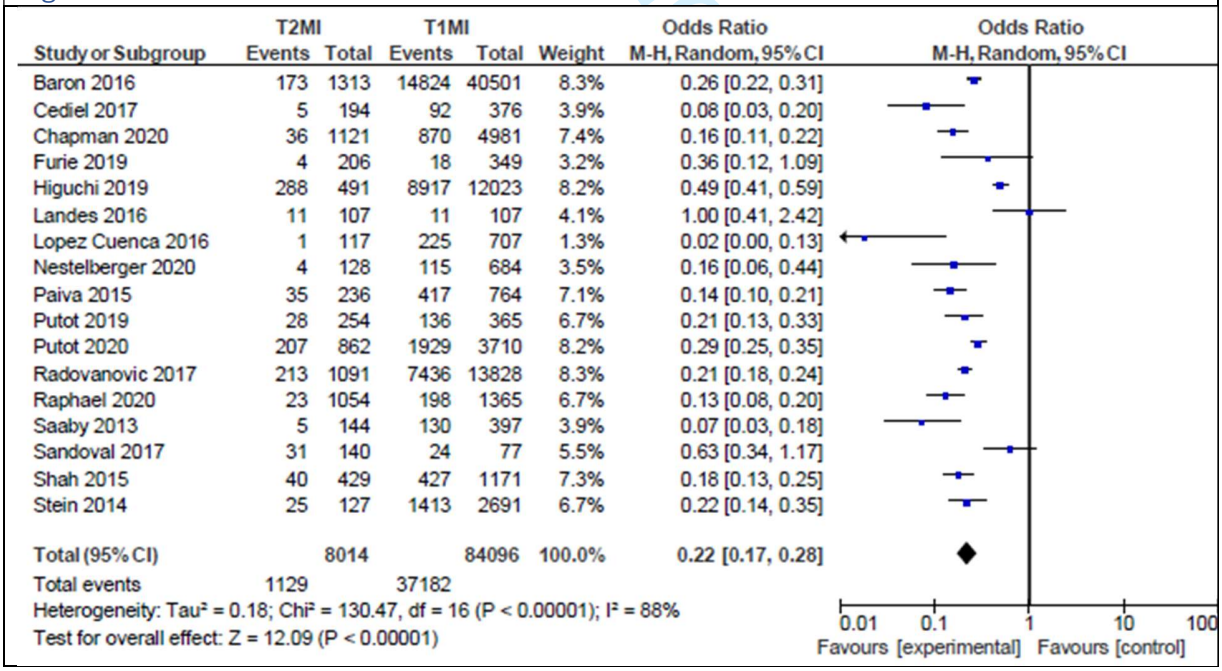


Figure S21. Forest Plot. ST Depression or T Wave Inversion on ECG.

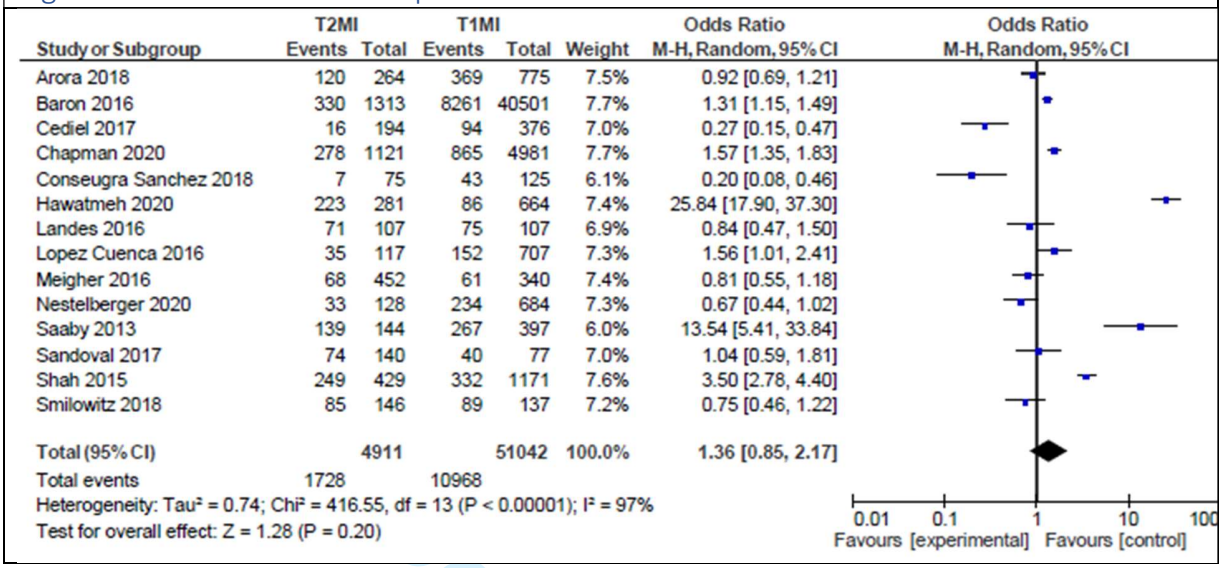


Figure S22. Forest Plot. Q Waves on ECG.

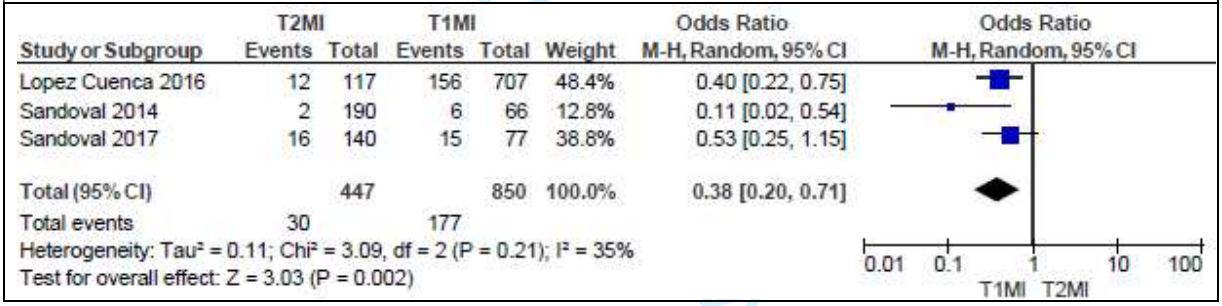


Figure S23. Forest Plot. Non-specific ST Changes on ECG.

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

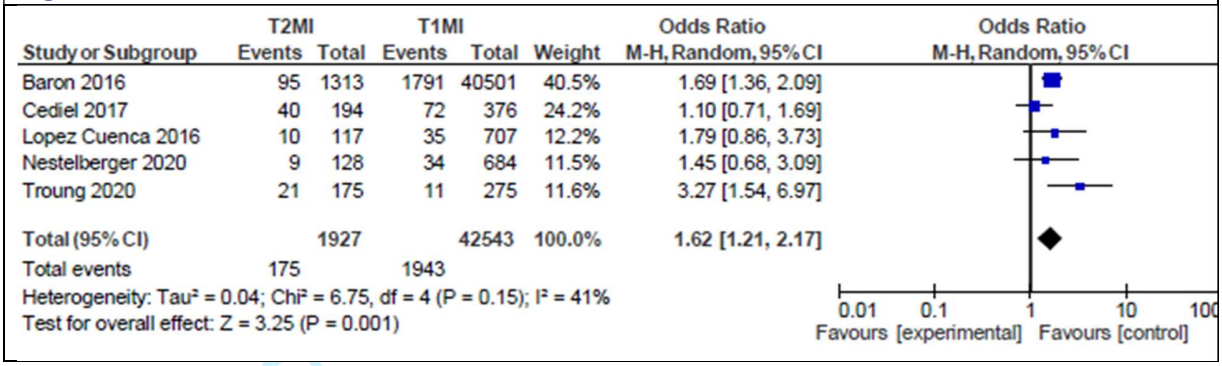


Figure S25. Forest Plot. Atrial Fibrillation on ECG.

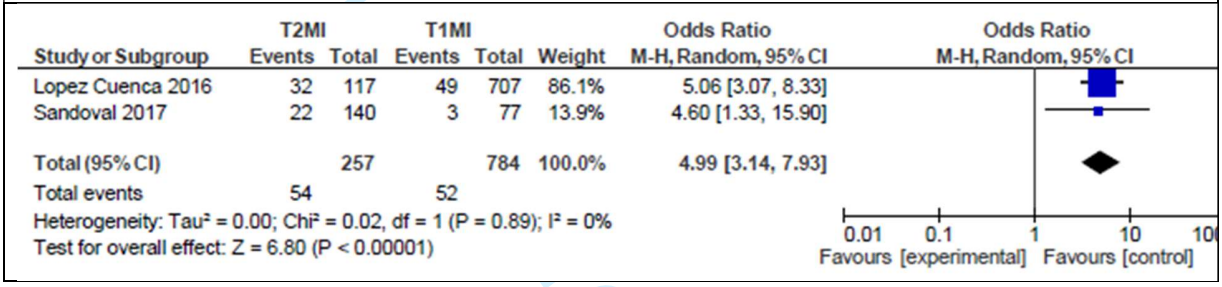


Figure S26. Forest Plot. Coronary Angiogram Performed.

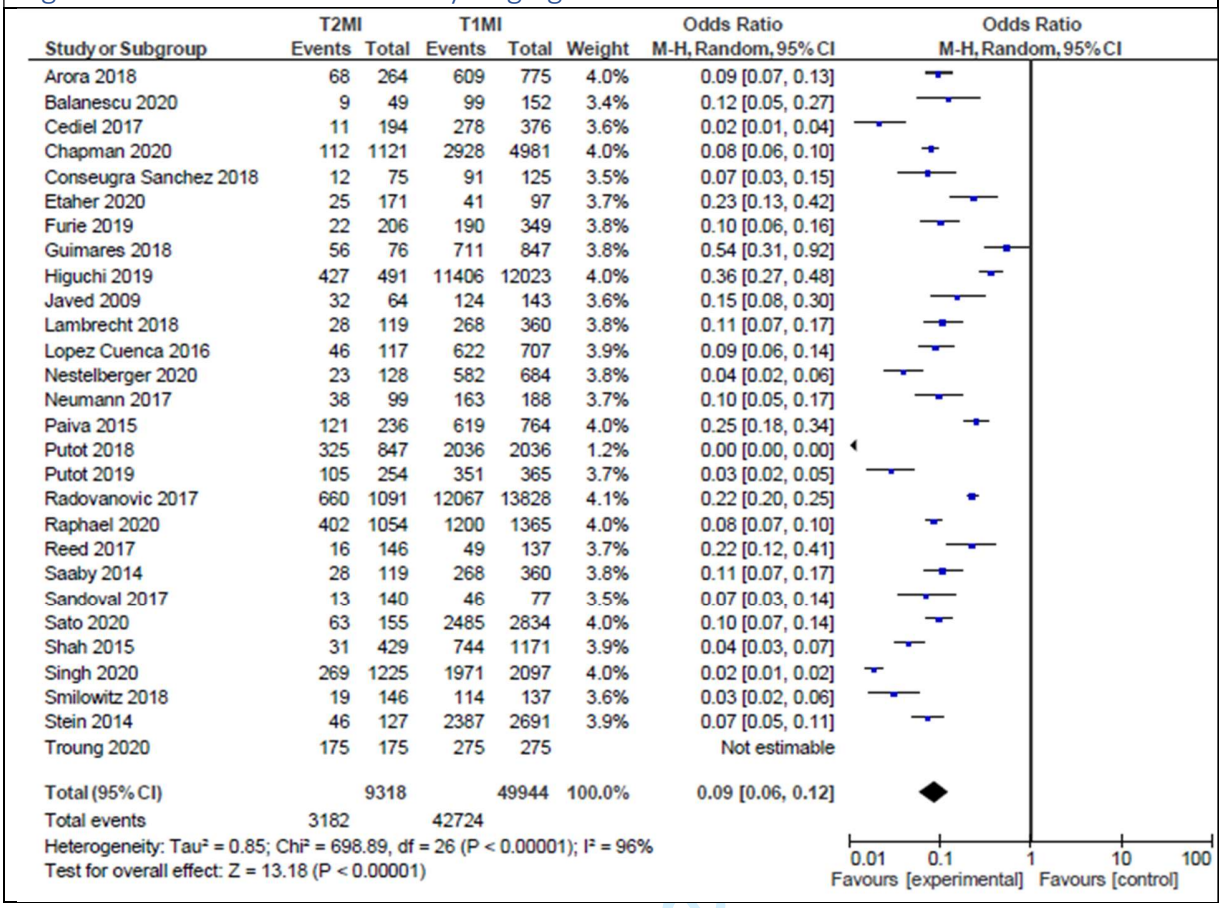


Figure S27. Forest Plot. Obstructive Coronary Artery Disease on Coronary Angiogram.

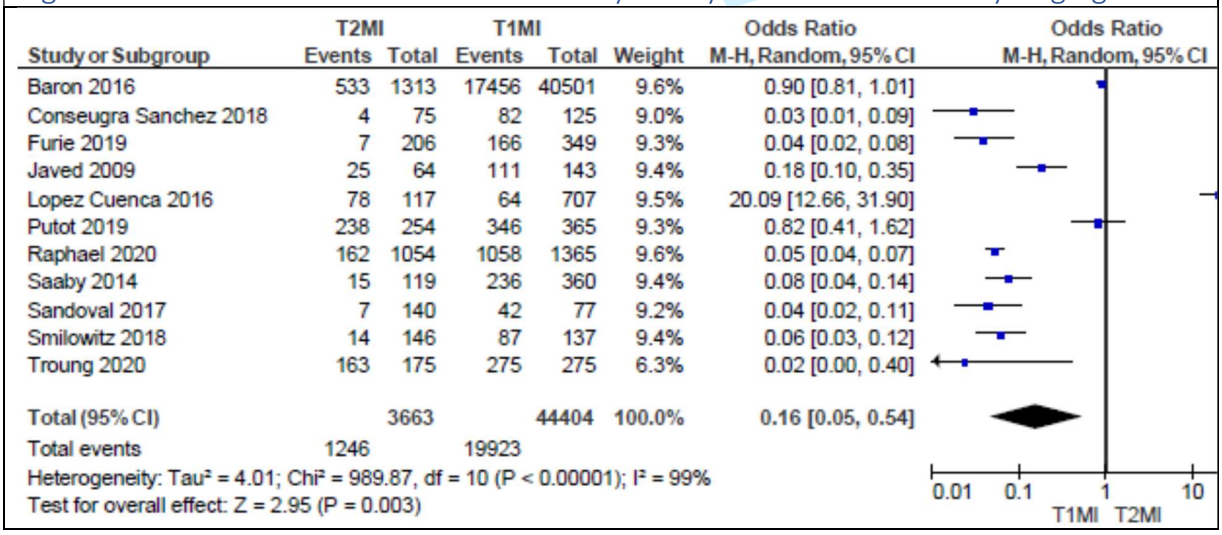


Figure S28. Forest Plot. Multivessel Disease on Coronary Angiogram.

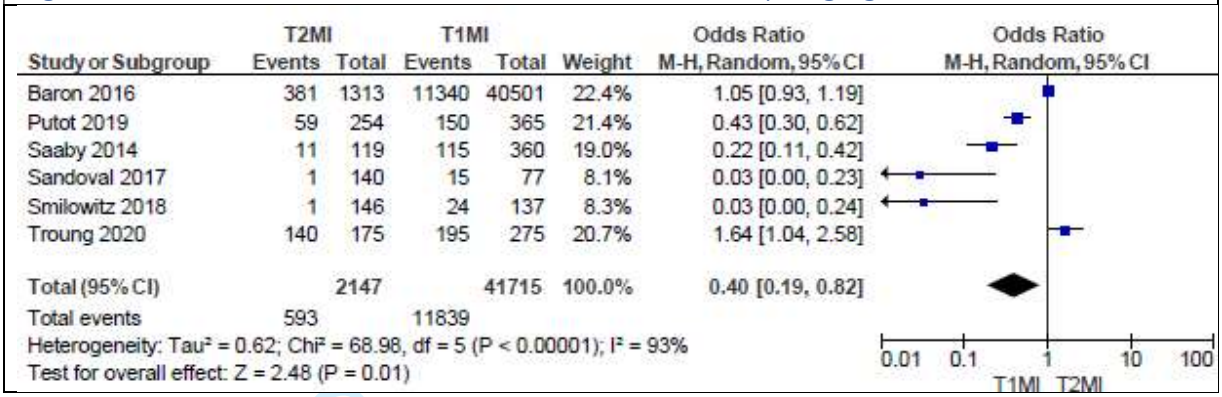


Figure S29. Forest Plot. Echocardiogram Performed.

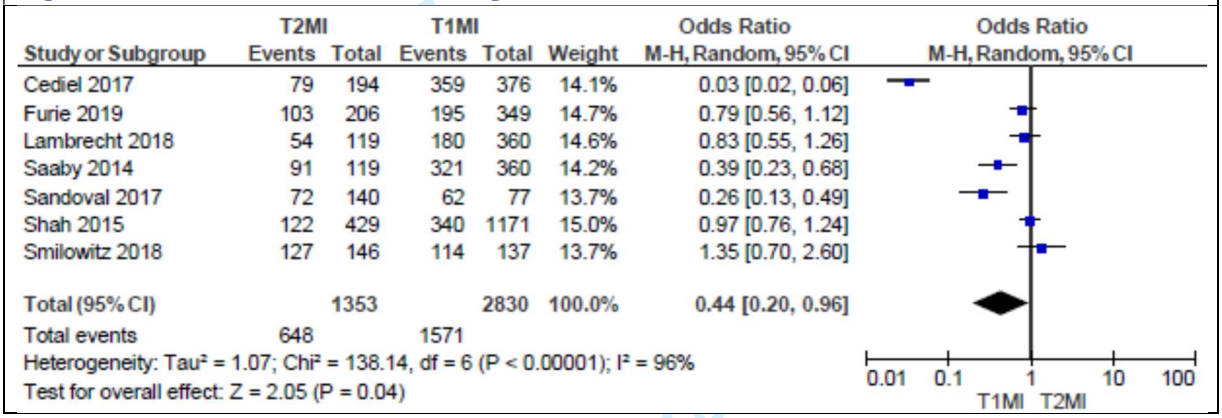


Figure S30. Forest Plot. Regional Wall Motion Abnormalities on Echocardiogram.

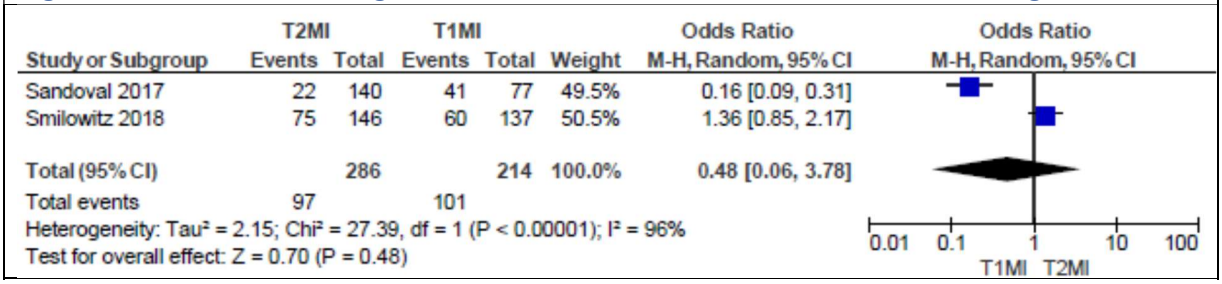


Figure S31. Forest Plot. Beta-Blockers Prescribed.

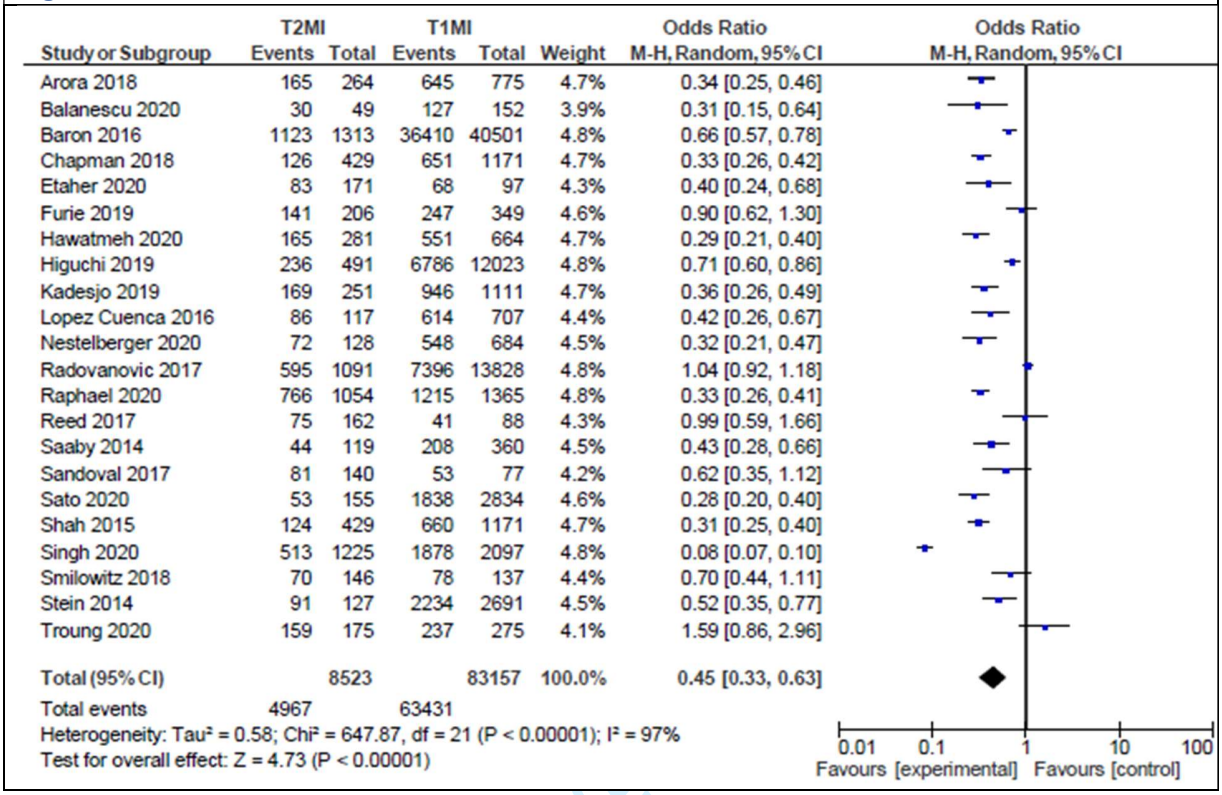


Figure S32. Forest Plot. ACEi/ARB Prescribed.

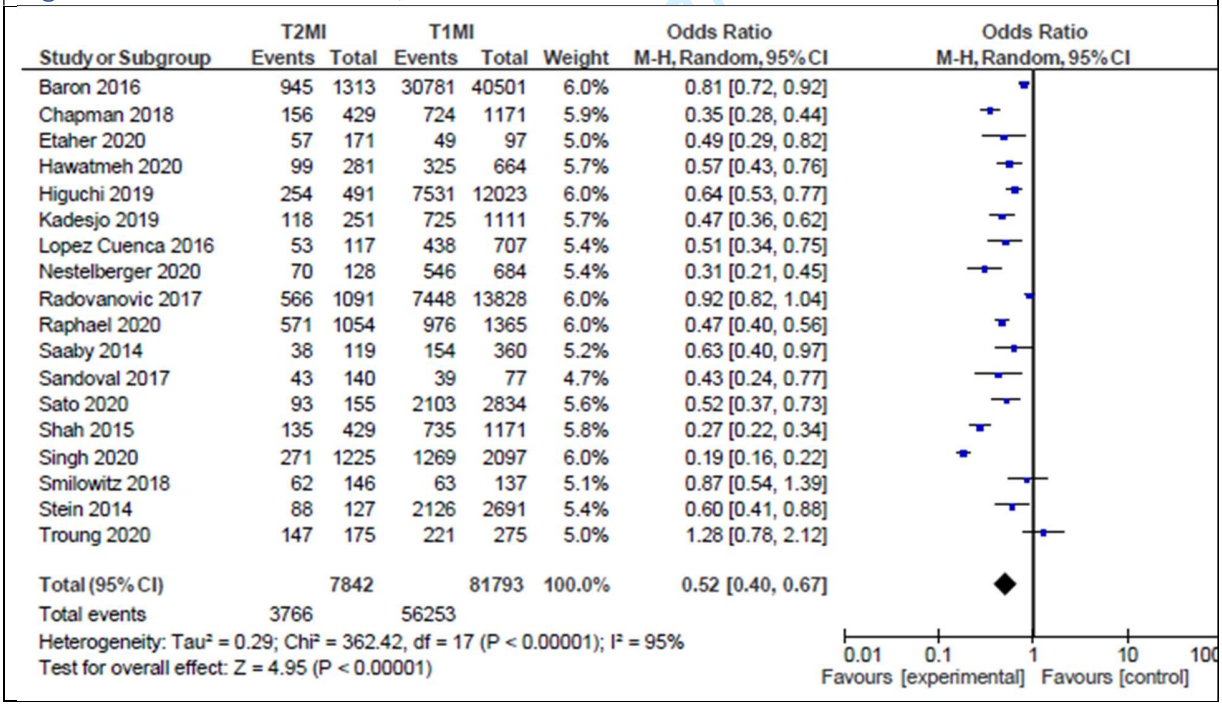


Figure S33. Forest Plot. Antiplatelets Prescribed.

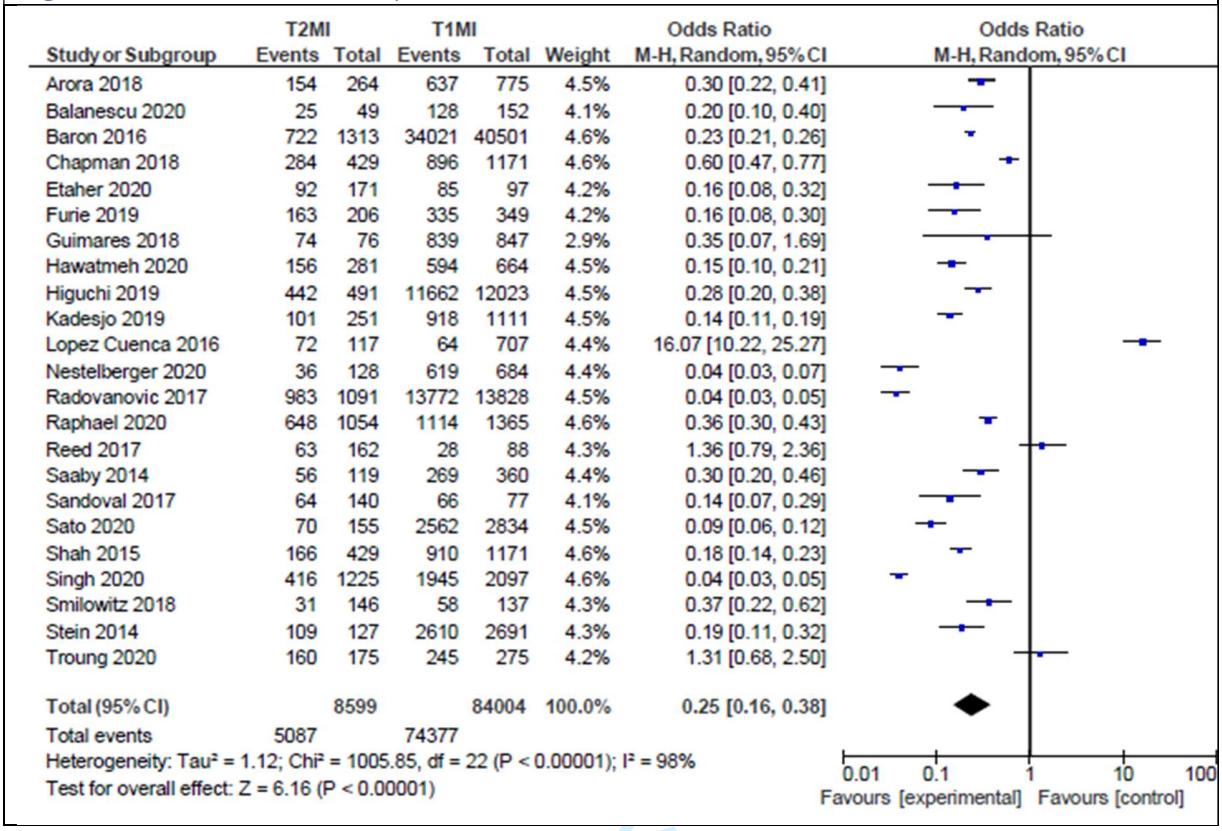


Figure S34. Forest Plot. Anticoagulants Prescribed.

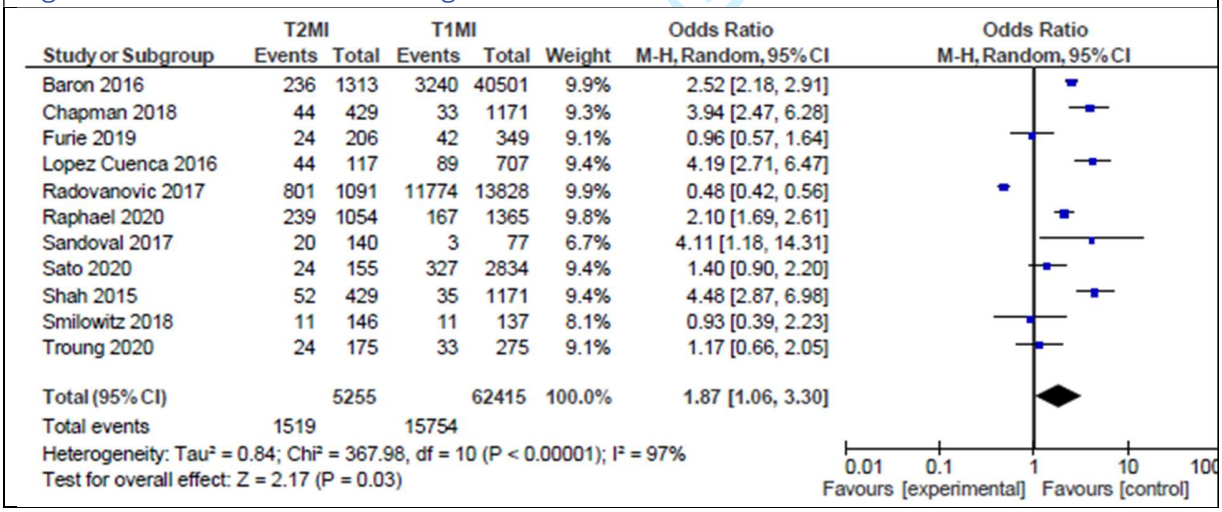


Figure S35. Forest Plot. Antianginal Drugs Prescribed.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio 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: Tau² = 1.39; Chi² = 199.97, df = 4 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.93 (P = 0.35)

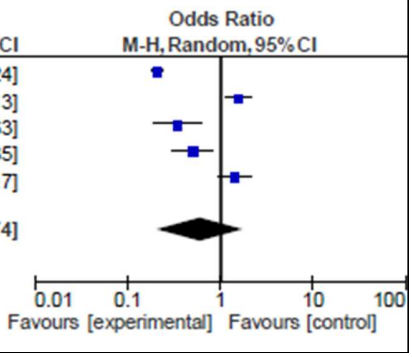


Figure S36. Forest Plot. Diuretics Prescribed.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio 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: Tau² = 0.14; Chi² = 36.79, df = 5 (P < 0.00001); I² = 86%
Test for overall effect: Z = 3.64 (P = 0.0003)

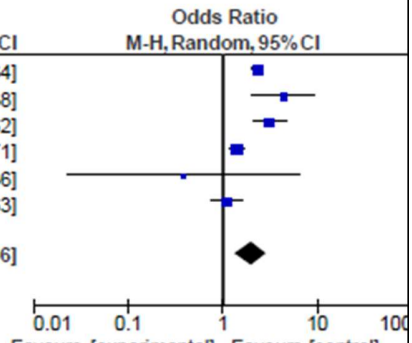


Figure S37. Forest Plot. Statins Prescribed.

Study or Subgroup	T2MI Events	T2MI Total	T1MI Events	T1MI Total	Weight	Odds Ratio M-H, Random, 95% CI
Arora 2018	153	264	646	775	6.4%	0.28 [0.20, 0.37]
Balanescu 2020	29	49	131	152	5.5%	0.23 [0.11, 0.48]
Baron 2016	972	1313	37261	40501	6.6%	0.25 [0.22, 0.28]
Chapman 2018	204	429	872	1171	6.5%	0.31 [0.25, 0.39]
Etaher 2020	95	171	81	97	5.8%	0.25 [0.13, 0.46]
Furie 2019	125	206	280	349	6.3%	0.38 [0.26, 0.56]
Hawatmeh 2020	141	281	578	664	6.4%	0.15 [0.11, 0.21]
Higuchi 2019	298	491	9238	12023	6.5%	0.47 [0.39, 0.56]
Kadesjo 2019	92	251	883	1111	6.4%	0.15 [0.11, 0.20]
Lopez Cuenca 2016	92	117	648	707	6.0%	0.34 [0.20, 0.56]
Nestelberger 2020	39	128	606	684	6.2%	0.06 [0.04, 0.09]
Raphael 2020	570	1054	1167	1365	6.5%	0.20 [0.16, 0.24]
Sato 2020	112	155	2303	2834	6.3%	0.60 [0.42, 0.86]
Singh 2020	255	1225	1840	2097	6.5%	0.04 [0.03, 0.04]
Smilowitz 2018	83	146	100	137	6.1%	0.49 [0.30, 0.80]
Troung 2020	158	175	241	275	5.8%	1.31 [0.71, 2.43]
Total (95% CI)		6455		64942	100.0%	0.25 [0.16, 0.38]
Total events	3418		56875			

Heterogeneity: Tau² = 0.70; Chi² = 549.08, df = 15 (P < 0.00001); I² = 97%
Test for overall effect: Z = 6.46 (P < 0.00001)

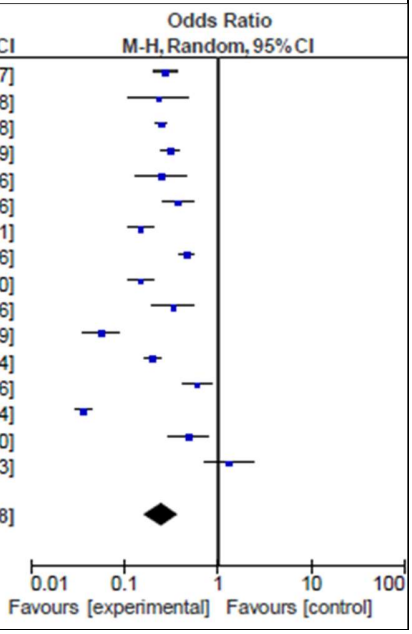


Figure S38. Forest Plot. Percutaneous Coronary Intervention Performed.

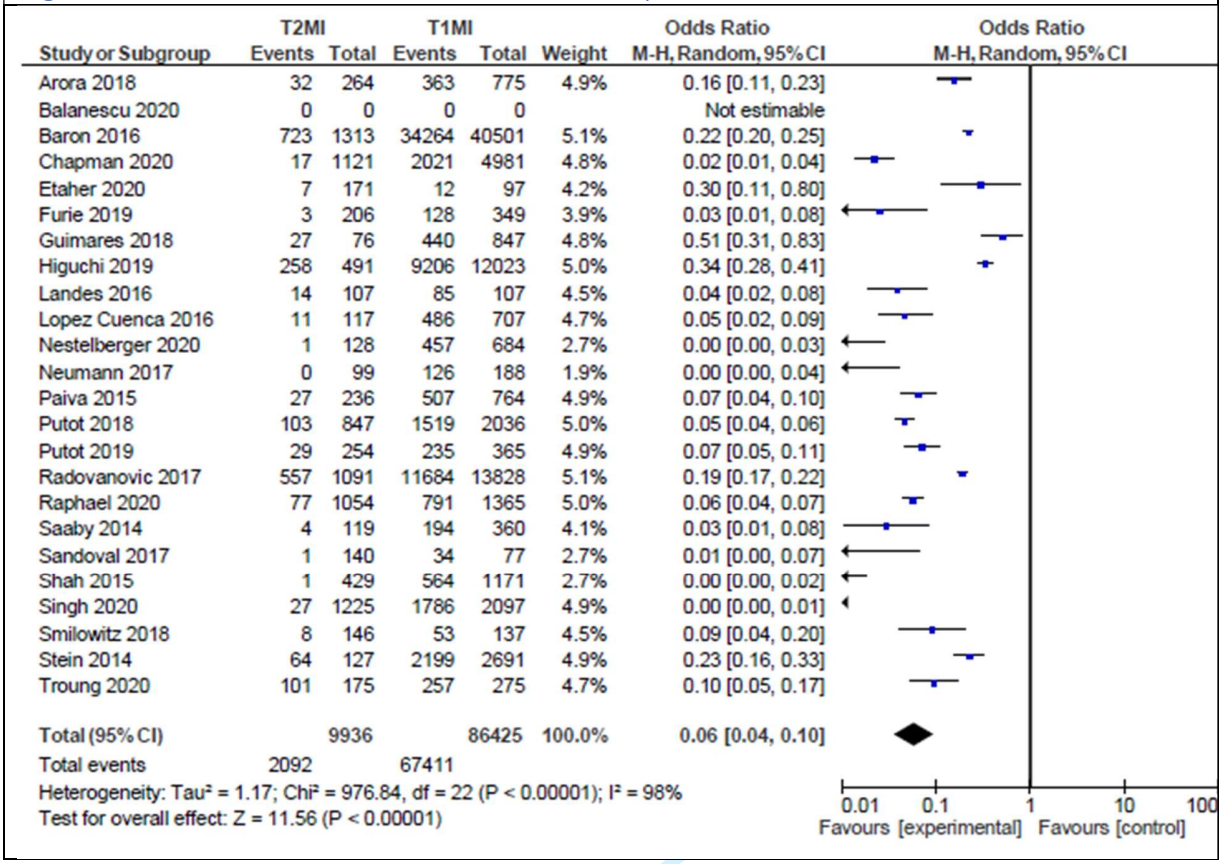


Figure S39. Forest Plot. Coronary Artery Bypass Graft Performed.

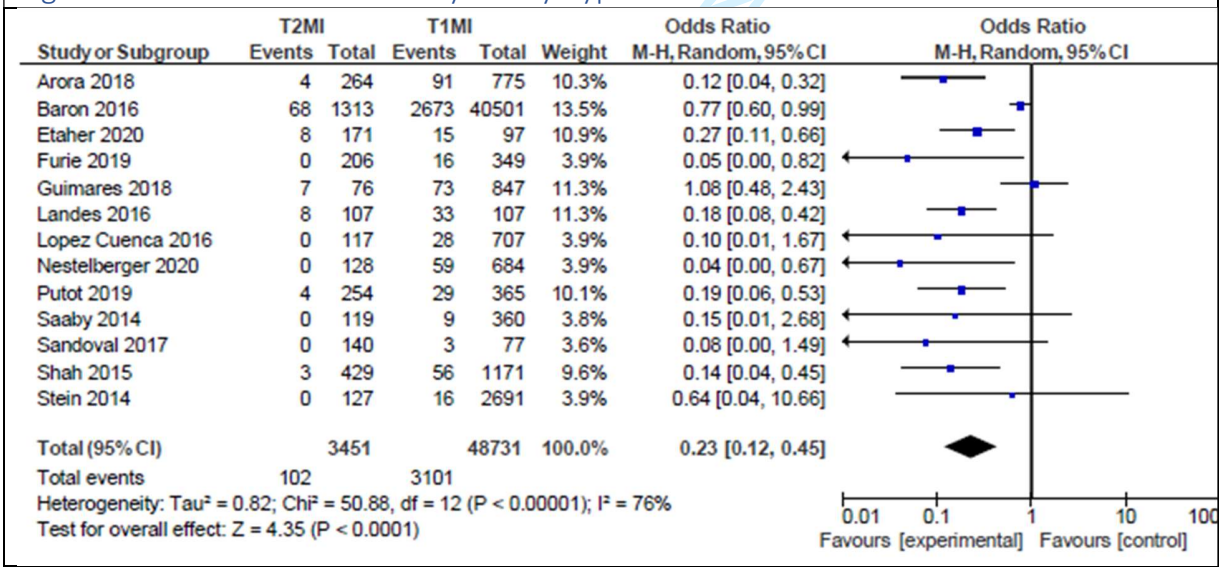


Figure S40. All cause In-hospital mortality. T2MI compared to T1MI.

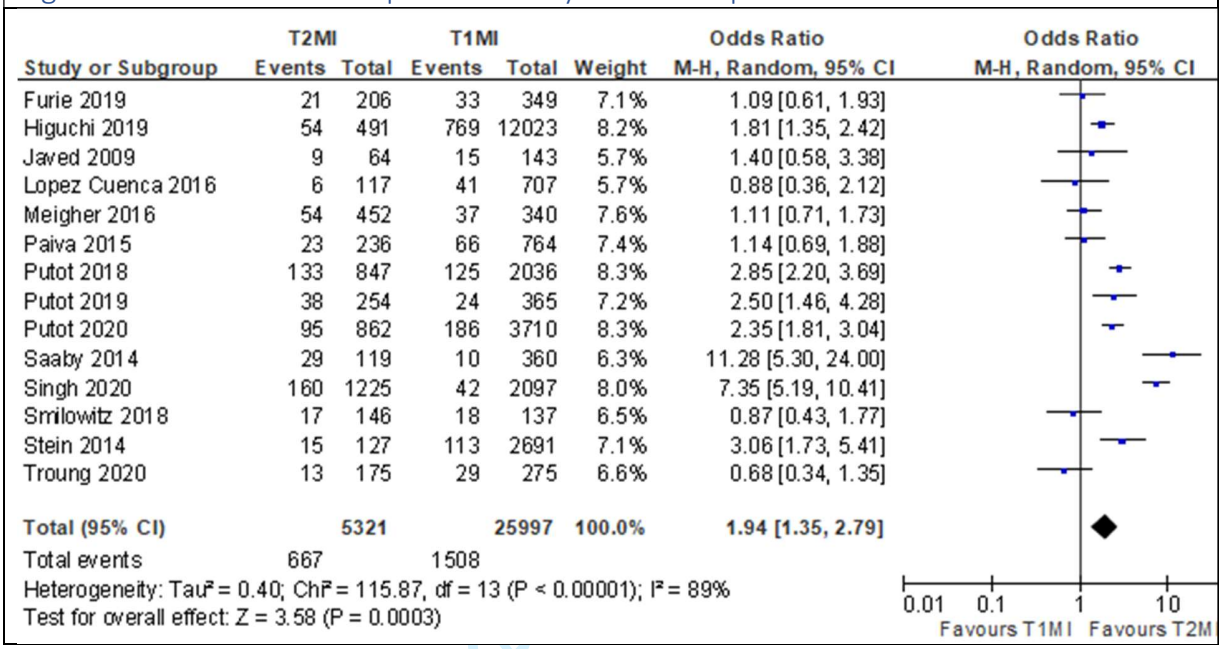


Figure S41. Short-term all-cause mortality. T2MI compared to T1MI.

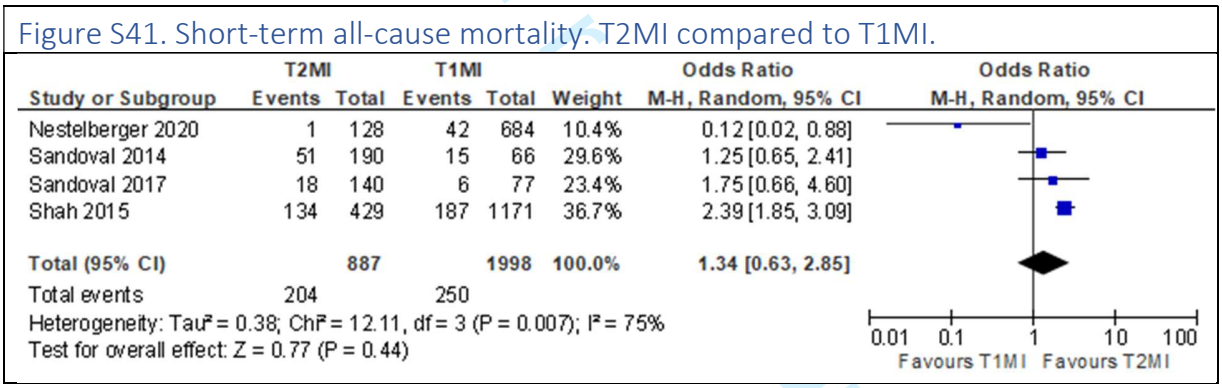


Figure S42. Two-year all-cause mortality. T2MI compared to T1MI.

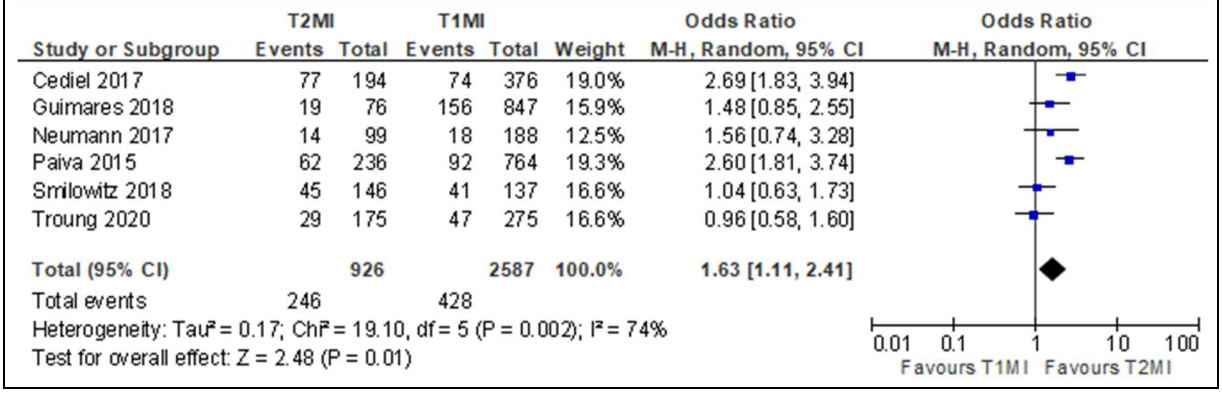


Figure S43. Three-year all-cause mortality. T2MI compared to T1MI.

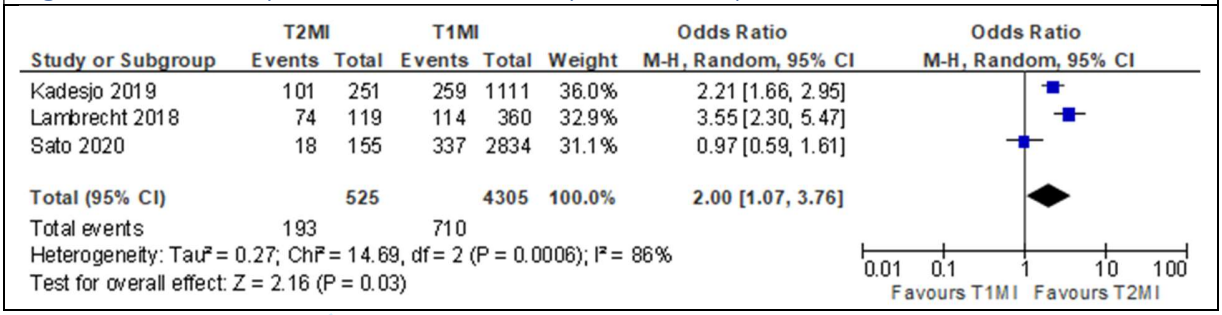


Figure S44. CVS In-hospital mortality. T2MI compared to T1MI.

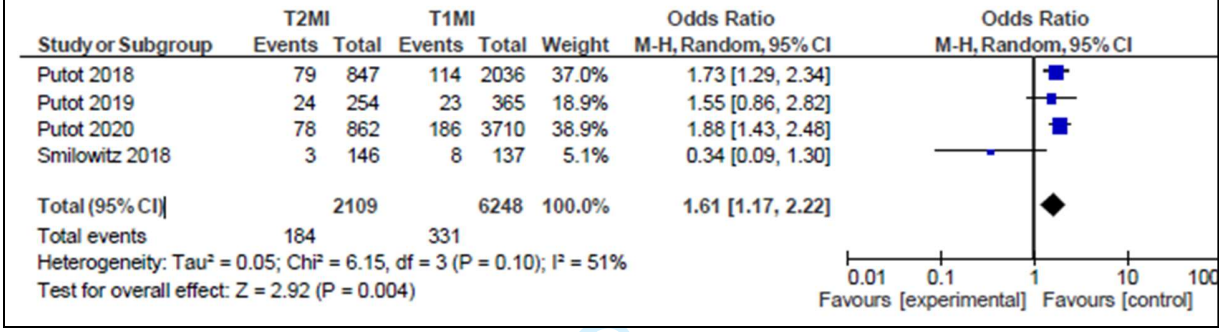


Figure S45. Funnel Plot. All-cause In-hospital mortality. T2MI compared to T1MI.

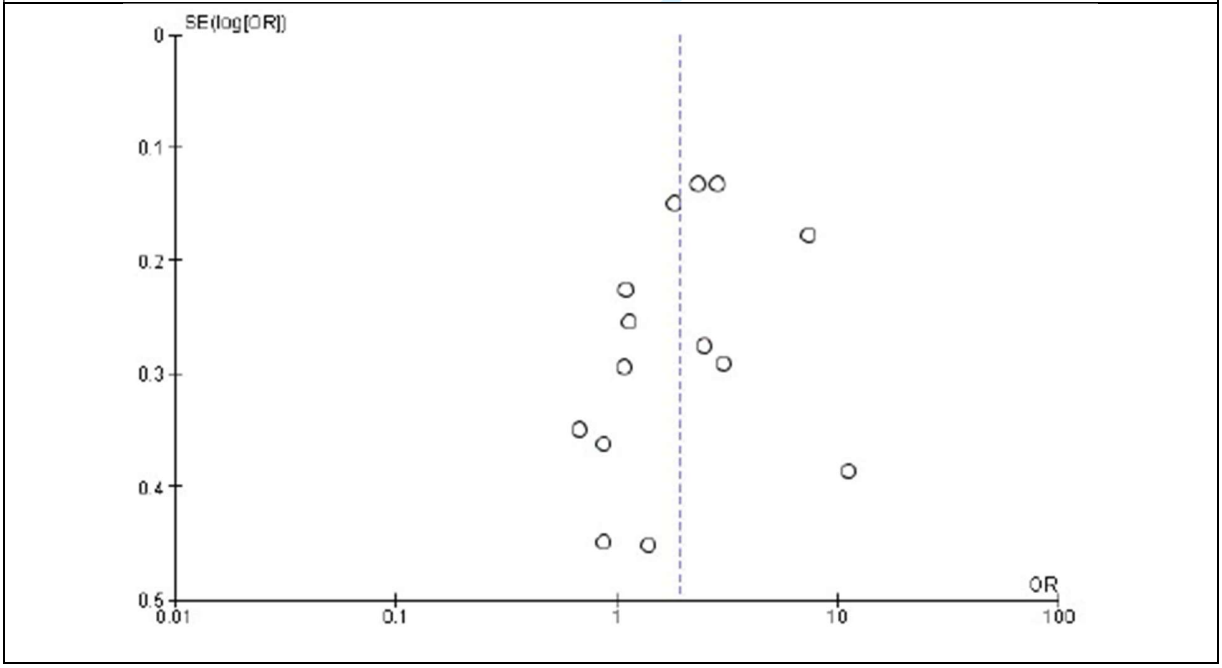
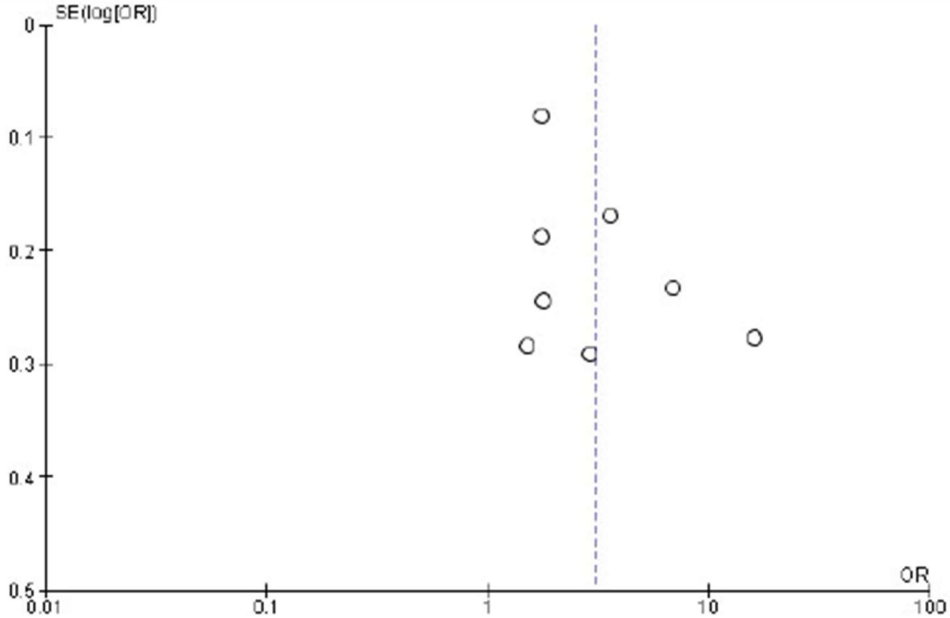


Figure S46. Funnel Plot. One-year All-cause mortality. T2MI compared to T1MI.



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PRISMA 2020 Checklist

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

PRISMA 2020 Checklist

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

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

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