CJC Open 2 (2020) 118–128

Original Article

Meta-analysis Comparing Outcomes of Type 2 Myocardial Infarction and Type 1 Myocardial Infarction With a Focus on Dual Antiplatelet Therapy

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ABSTRACT

Background: There are important knowledge gaps in type 2 myocardial infarction (T2MI). Our primary objective was to compare the outcomes of patients with T2MI with those of patients with type 1 myocardial infarction (T1MI). Our secondary objective was to determine whether randomized controlled trials (RCTs) evaluating dual antiplatelets (DAPTs) have explicitly included patients with T2MI.

Methods: We performed a meta-analysis comparing outcomes of patients with T2MI with patients with T1MI and a separate systematic review to evaluate the inclusion of T2MI in RCTs evaluating DAPT. There were 19 cohorts enrolling 48,829 patients (40,604 with T1MI and 5361 with T2MI) and 51 RCTs enrolling 188,132 patients with acute coronary syndrome.

RÉSUMÉ

Contexte : Il existe d'importantes lacunes dans notre connaissance de l'infarctus du myocarde de type 2 (IMT2). Notre objectif principal était de comparer le devenir de patients ayant subi un IMT2 et celui de patients ayant subi un infarctus du myocarde de type 1 (IMT1). Notre objectif secondaire était de déterminer si des essais contrôlés randomisés (ECR) visant à évaluer des bithérapies antiplaquettaires (BA) avaient inclus explicitement des patients ayant subi un IMT2.

Méthodologie : Nous avons réalisé une méta-analyse afin de comparer le devenir de patients ayant subi un IMT2 et celui de patients ayant subi un IMT1. Nous avons aussi effectué une revue systématique distincte des données pour évaluer l'inclusion de cas d'IMT2 dans les ECR visant à évaluer des BA. Il y avait 19 cohortes regroupant 48 829

The term "type 2 myocardial infarction" (T2MI) was first defined by the Second Universal Definition of Myocardial Infarction 2007[1] and was recently updated in 2018 by the Task Force for the Fourth Universal Definition of Myocardial Infarction.[2] T2MI was defined as myocardial infarction (MI) whereby a condition other than atherosclerotic coronary artery disease creates an imbalance between myocardial oxygen supply and demand.[1] Currently, there are no formal management guidelines for patients with T2MI.

Dual antiplatelet therapy (DAPT) (aspirin plus a direct or an indirect P2Y12 inhibitor) is the cornerstone in the management of patients with myocardial infarctions secondary to atherosclerotic coronary plaque rupture (T1MI).[3,4] However, it remains unclear to what extent DAPT has been evaluated in T2MI. Because platelet activation may be less prominent in T2MI, DAPT may not confer the same

Received for publication October 21, 2019. Accepted February 19, 2020.

Ethics Statement: The research reported has adhered to the relevant ethical guidelines.

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See page 125 for disclosure information.

https://doi.org/10.1016/j.cjco.2020.02.005

Results: Patients with T2MI had approximately 2-fold increases in unadjusted odds of long-term mortality compared with patients with T1MI (odds ratio, 2.47; 95% confidence interval, 2.06-2.96; $P < 0.0001$) and a 45% increase in adjusted odds of long-term mortality (odds ratio, 1.45; 95% confidence interval, 1.25-1.69; $P < 0.0001$, respectively). There was no published evaluation of efficacy, effectiveness, and safety of DAPT in patients with T2MI.

Conclusion: Patients with T2MI are at increased risk of adjusted all-cause long-term mortality compared with patients with T1MI. The role of DAPT remains unclear in T2MI.

Résultats : Chez les patients ayant subi un IMT2, la probabilité non corrigée de mortalité à long terme était environ 2 fois plus élevée que chez les patients ayant subi un IMT1 (rapport de cotes : 2,47; intervalle de confiance à 95 % : 2,06-2,96; $p < 0,0001$), et la probabilité corrigée de mortalité à long terme était accrue de 45 % (rapport de cotes : 1,45; intervalle de confiance à 95 % : 1,25-1,69; $p < 0,0001$). Aucune évaluation de l'efficacité (potentielle ou réelle) et de l'innocuité des BA chez les patients ayant subi un IMT2 n'a été publiée.

Conclusion : Le risque corrigé de mortalité à long terme toutes causes confondues est plus élevé chez les patients ayant subi un IMT2 que chez les patients ayant subi un IMT1. Le rôle des BA reste à élucider dans les cas d'IMT2.

potential benefit in patients with T2MI as with T1MI. Notwithstanding, various causes of T2MI may predispose a prothrombotic state, suggesting a potential role for DAPT in patients with T2MI.[5] On the other hand, patients with T2MI may have underlying conditions that can increase bleeding risk with DAPT. Considering the current knowledge gaps, we aim to compare the outcomes of patients with T2MI with patients with T1MI and to appraise the uses of DAPT in patients with T2MI enrolled in randomized controlled trials (RCTs) and observational cohorts.

Methods

We performed a systematic review and meta-analysis following the standards set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[6] and the guidelines for reporting meta-analysis of observational studies as proposed by the MOOSE group.[7] We conducted 2 independent literature searches in PubMed, EMBASE, and Science Direct. The first search aimed to identify any studies pertaining directly to T2MI. We used the following search terms: type 2 myocardial infarction, secondary MI, supply-demand mismatch, demand ischemia, secondary ischemia, myocardial ischemia, type 2 ischemia, myocardial injury, myocardial necrosis, and silent ischemia. The second search targeted all studies evaluating DAPT in acute coronary syndrome (ACS) using the keywords myocardial infarction, acute coronary syndrome, clopidogrel, prasugrel, ticagrelor, and heart attack. We specifically excluded RCTs evaluating ticlodipine because this drug is rarely if ever used in this contemporary era. Both searches had no language restriction and covered all studies published since 1999 (release of the first DAPT trial **C**lopidogrel in **U**nstable Angina to Prevent **R**ecurrent Ischemic **E**vents [CURE]) to February 12, 2020.

We used the definitions of T1MI and T2MI as defined by the Fourth Universal Definition of Myocardial Infarction.[2] We defined reinfarction as reported in each publication. We additionally included any available RCTs or observational studies of T2MI. We excluded editorials, reviews, letters, animal studies, case reports, and conference abstracts. We also excluded studies that evaluated exclusively postoperative myocardial infarction because the term "T2MI" vs postoperative troponin elevation and myocardial injury was often interchangeably used in these instances. Furthermore, the management and outcomes of these patients were inconsistently described. We excluded observational studies that did not report the rates or number of events for T2MI and T1MI separately. For the second search, we included all RCTs that evaluated DAPT in ACS to determine whether any of these trials specifically included patients with T2MI.

Three reviewers (CR, AAT, and TH) extracted data independently. Disagreements were resolved by consensus and the third reviewer (TH). We extracted data about baseline characteristics of study subjects (age, sex, and comorbidities), management, study inclusion and exclusion criteria, and in-hospital and long-term mortality and reinfarction.

We summarized the outcomes (short/intermediate and long-term all-cause mortality and reinfarction). We defined short/intermediate-term mortality as all deaths occurring at less than 1 year and long-term mortality as all deaths occurring during a follow-up of at least 1 year. We computed weighted means of baseline characteristics and rates of outcomes. We pooled the unadjusted and adjusted comparisons of long-term mortality of patients with T1MI and T2MI of the observational studies. We examined the funnel plot to identify potential publication bias. All meta-analyses were completed with random-effects models with Comprehensive Meta-Analysis, Version 3, 2014. We chose random-effect models because of the marked heterogeneity seen in the fixed-effect models.

Results

We retrieved 2048 citations of studies of T2MI and 1669 citations of studies evaluating DAPT in ACS (Fig. 1). For the final evaluation, we retained 19 cohorts enrolling 48,829 patients (43,468 with T1MI and 5361 with T2MI)[8-27] (Table 1) and 51 RCTs enrolling 188,132 patients[25-77] (Fig. 1). We described the characteristics of the patients enrolled in the observational studies in Supplemental Table S1. No RCTs evaluating DAPT in ACS have explicitly included patients with T2MI. The effectiveness and safety of DAPT were also not appraised in any observational study of T2MI.

Compared with patients with T1MI, patients with T2MI were older (69 vs 65 years, $P = 0.02$), more often female (44% vs 30%, $P < 0.0001$), and more often had diabetes mellitus (30% vs 27%) and hypertension (70% vs 67%, $P = 0.03$)

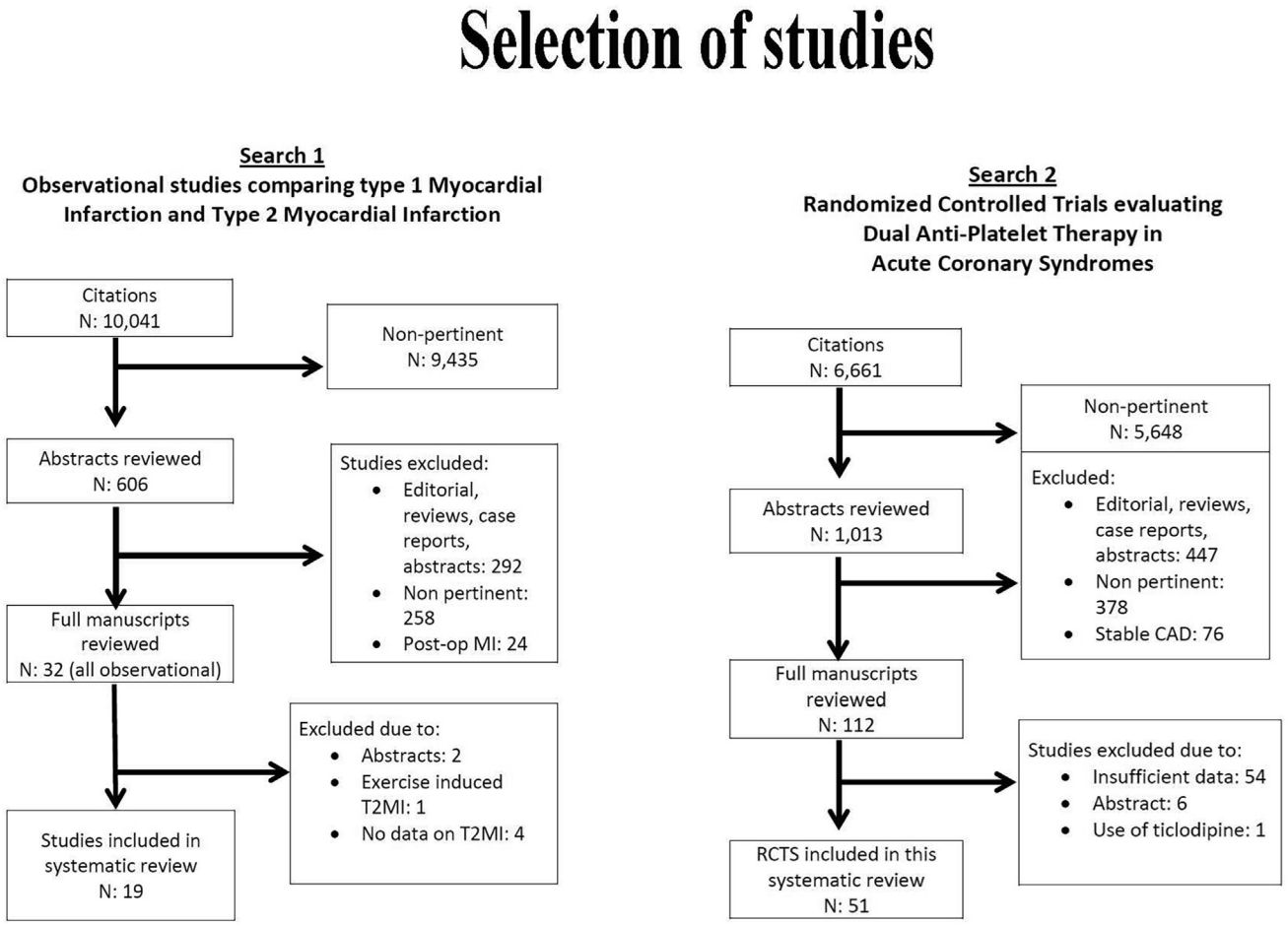

Figure 1. Selection of studies. RCT, randomized controlled trial; T2MI, type 2 myocardial infarction.

(Table 2). DAPT use in patients with T2MI was reported in only 7 observational studies.[7,8,13,15,17,19,21,23] The aggregate mean use was 20.8% in patients with T2MI and 74.2% in patients with T1MI (Table 3). Patients with T2MI were 91% less likely to use DAPT and 80% less likely to undergo percutaneous coronary intervention (Table 3).

wPatients enrolled in the RCTs had the best unadjusted long-term survival compared with patients with T1MI and T2MI in the observational studies. Compared with patients with T1MI, patients with T2MI had 2.5-fold increase in unadjusted long-term mortality (Table 3 and Fig. 2) and an approximately 45% increase in adjusted long-term mortality (odds ratio, 1.45; 95% confidence interval, 1.25-1.69; $P < 0.0001$) (Table 3 and Fig. 3). The comparisons of long-term mortality between T2MI and T1MI were generally adjusted for age, sex, baseline characteristics, and comorbidities, except for the study by Newman et al.,[15] in which long-term mortality was adjusted only for age, sex, and prior coronary artery disease.

The precipitating factors of T2MI were reported in 7 studies.[7-9,12,14,21-22] Arrhythmia, anemia/bleeding, respiratory diseases, heart failure, and infection/sepsis were the most common reported precipitating factors for T2MI (Table 4). There was no obvious publication bias detected as the funnel plot appeared to be symmetrical (Fig. 4).

Discussion

Our meta-analysis of observational studies showed that compared with patients with T1MI, patients with T2MI were older and more often female, had more hypertension, and had diabetes mellitus. Compared with patients with T1MI, patients with T2MI were 90% less likely to be treated with DAPT and 80% less likely to undergo percutaneous coronary intervention. Patients with T2MI had approximately 45% increase in adjusted odds of all-cause long-term mortality compared with patients with T1MI. The efficacy, effectiveness, and safety of DAPT have never been formally appraised in RCTs or observational studies.

There were marked differences in unadjusted short- and long-term mortality rates among the 3 groups of patients (patients with ACS enrolled in the RCTs, T1MI, and T2MI in the observational cohorts). Although both short- and long-term mortality were less than 5% in patients with ACS enrolled in the RCTs that evaluated DAPT, unadjusted short- and long-term mortality were 7% and 11%, respectively, for patients with T1MI in the observational studies. The higher unadjusted short- and long-term mortality of patients in the observational studies likely would be due to the enrollment of patients without MI, with younger age, and with fewer comorbid conditions in the RCTs than patients in the observational studies.[78]

Table 1. Characteristics of observational studies comparing T2MI with T1MI

Study first author (year of publication)	Design	Countries	Enrollment periods	No. of patients with MI	No. of centres/ countries	Key inclusion criteria	Key exclusion criteria
Arora (2018)	Retrospective	United States	2013-2014	1039	Single centre	All patients with NSTEMI	STEMI, transferred in, no available troponins, cardiac arrest
Baron (2014)	Prospective (SWEDEHEART Study)	Sweden	2011	18,891	73 Swedish hospitals	MI hospitalized in Sweden	None
Cediel (2016)	Retrospective	Spain	2012-2013	570	Single university centre	All adults with at least 1 value of troponin tested	Cardiac arrest, alternate diagnoses other than MI, lived far
Chapman (2018)	Prospective	Scotland	2009-2009	1600	1 tertiary centre	All patients with elevated troponin values	Admitted for elective procedures, incomplete electronic hospital records, and nonresidents
Gonzalez (2011)	Retrospective	United States	2004-2007	348	1 tertiary centre	All MI with $\geq$ 50% coronary stenosis on angiogram and $\geq$ 24-mo follow-up	Terminal diseases, refused standard MI treatment, no obstructive coronary artery disease
Greenslade (2017)	Pooled study of 1 prospective observational and 1 interventional study	Australia	2008-2014	152	Single tertiary centre	Adults with MI who could provide consent, enrollment during regular working hours	Pregnant, lived far
Javed (2009)	Prospective	United States	2009	207	Single centre	All adults with $\geq$ 1 abnormal troponin value who provided consent	Refusal to participate
Lambrecht (2018)	Prospective study	Denmark	2010	479	Single centre	All patients with at least 1 troponin $\geq$ 99th percentile normal value	Pregnant, lived outside catchment area
Lopez-Cuenca (2016)	Retrospective	Spain	2012-2013	824	Single veterans tertiary centre	All patients with MI	None
Nestelberger (2017)	Retrospective	Switzerland, Italy, Germany, Spain, Poland	2006-2015	924	12 centres/5 countries	Adults within 12 h of ischemic symptoms	Unclear diagnosis
Neumann (2017)	Prospective	Germany	2013-2016	287	Single university centre	Adults with suspected MI who could provide consent	Missing troponins, STEMI
Radovanovic (2016)	Prospective (AMIS-PLUS)	Switzerland	2009-2015	14,920	53 Swiss hospitals	All patients hospitalized with MI in Switzerland	None
Raphael (2020)	Prospective	United States	2003-2012	2, 436	Mayo Clinic and Olmstead Medical Center	Adults with $\geq$ 1 available troponin value	Prior MI, refused to consent, unclear cause for elevation of troponin
Saaby (2014)	Prospective	Denmark	2010	488	Single centre	Adults with $\geq$ 1 available troponin value	Outside catchment area, troponins administered outside the hospital

Continued

Table 1. Continued.

Study first author (year of publication)	Design	Countries	Enrollment periods	No. of patients with MI	No. of centres/ countries	Key inclusion criteria	Key exclusion criteria
Sandoval (2015)	Retrospective	United States	2013	310	Single centre	Adults with ≥ 1 available troponin value	None
Sandoval (2017)	Prospective (UTROPIA Study)	United States	2011	217	Single centre	All patients who provided consent and with ≥ 2 troponins and 1 ECG within 24 h	Pregnant,transferred in patients, did not present to the emergency department
Shah (2015)	Prospective	Scotland	2014	1600	Single centre	All patients with troponin I ≥ 50 ng/L	None
Smilowitz (2018)	Prospective	United States	2012-2013	283	Single veterans tertiary centre	All patients with elevated troponin values	None
Stein (2014)	Prospective national Israel registry (ACSIS Registry)	Israel	2008-2010	2818	Nationwide Israel multicentres (26 intensive and 37 medical wards)	All patients with MI	None

ACSIS, Acute Coronary Syndrome Israeli Survey; AMIS-PLUS, National Registry of Acute Myocardial Infarction in Switzerland; ECG, electrocardiogram; MI, myocardial infarction; NSTEMI, non−ST-segment myocardial infarction; STEMI, ST-segment elevation myocardial infarction; SWEDEHEART, **S**wedish **W**eb-System for **E**nhancement and **D**evelopment of **E**vidence-Based Care in **H**eart Disease **E**valuated **A**ccording to **R**ecommended **T**herapies; T1MI, type 1 myocardial infarction; T2MI, type 2 myocardial infarction; UTROPIA, **U**se of **Tropo**nin in **A**cute Coronary Syndromes.

The lack of significant heterogeneity in our random-effects model of adjusted odds was markedly in contrast to the heterogeneity observed in the random-effects model of unadjusted odds of long-term mortality. By using adjusted odds, we were able to make the populations more comparable between studies and between patients with T1MI and T2MI. Therefore, our estimate suggested a true increase in odd of long-term mortality in patients with T2MI compared with patients with T1MI, adjusted for the increased age and higher comorbidities of patients with T2MI.

In a meta-analysis of 9 observational studies, Gupta et al.[79] reported a 3-fold increase in short and intermediate-term mortalities in patients with T2MI compared with patients with T1MI. Compared with the previous meta-analysis,[79] our study provided more long-term information with 7 studies reporting data beyond 1-year follow-up. Most important, our adjusted estimate for long-term mortality may be less confounded by differences in clinical characteristics between patients with T2MI and T1MI.

Short- and long-term mortality were high in patients with T2MI with weighted mean rates of 15% and 30%, respectively. This finding implied that approximately 1 in 3 patients with T2MI may die beyond 1 year after the index event. Even after adjustment for their increased age and comorbidities, patients with T2MI remained at higher risk of long-term all-cause mortality compared with patients with T1MI. Although the increased mortality of a T2MI may not be entirely due to cardiovascular diseases, its occurrence indicates worse outcome that would justify close follow-up of these patients.

Recognizing the triggers of T2MI is imperative to prevent its occurrence. The most frequently reported condition associated with T2MI was arrhythmia, which could be tachyarrhythmia or bradyarrhythmia. Although clinicians may be aware that tachyarrhythmia can increase myocardial oxygen demand,[1,2] it is not always recognized that severe bradyarrhythmia might precipitate T2MI because of a reduction in myocardial oxygen supply. Anemia and bleeding were also common precipitating factors of T2MI. Expedient control of bleedings or transfusion of blood products may be valuable to prevent T2MI in susceptible patients. Because we excluded studies evaluating exclusively postoperative myocardial injury, we could not examine the frequency of its occurrence in T2MI.

At present, there is a lack of contemporary management guidelines for patients with T2MI. Beyond control of the underlying conditions, the efficacy of DAPT had never been formally evaluated for patients with T2MI in RCTs. Kidd et al.[5] demonstrated a reduction of T2MI with vorapaxar in patients with T2MI, suggesting that antiplatelets may reduce the occurrence of T2MI in patients at risk. Nevertheless, the benefits observed with vorapaxar may not be able to be replicated with direct and indirect P2Y12 receptor inhibitors because of their different mechanisms of actions.

The incidence of T2MI will likely escalate with the increasing use of high-sensitivity troponin assays. Although our detection of T2MI may be enhanced, knowledge gaps concerning the optimal management of these patients persist. The high mortality rates of these patients underlined the need for future research evaluating the role of conventional ACS therapy (eg, DAPT and coronary intervention) in patients with T2MI.[80]

Table 2. Baseline characteristics of patients enrolled in RCTs and observational studies

	RCT			Observational studies				
	95% CI	No. of studies (No. of patients)	*P* values RCT vs observational studies	T1MI (95% CI)	No. of studies (No. of patients)	T2MI (95% CI)	No. of studies (No. of patients)	*P* values T1MI vs T2MI
Age, y	62.1 (61.3-62.9)	51 (188,132)	< 0.0001	64.9 (65.0-68.9)	14 (36,592)	69.2 (66.1-72.4)	15 (3930)	0.02
Female, %	25.5 (24.0-27.1)	51 (188,132)	< 0.0001	29.8 (26.6-33.3)	17 (38,352)	44.2 (40.5-49.0)	21 (4842)	< 0.0001
Diabetes mellitus, %	24.0 (22.0-26.1)	49 (142,096)	0.04	26.8 (23.3-30.7)	17 (37,840)	29.5 (25.5-33.9)	18 (4771)	0.05
Hypertension, %	63.3 (58.3-67.9)	45 (170,988)	0.32	67.1 (62.5-71.5)	16 (35,276)	69.9 (57.7-80.0)	16 (8533)	0.03
Prior MI, %	18.5 (15.0-22.5)	34 (147,006)	0.003	28.4 (25.2-31.8)	11 (23,296)	32.8 (25.9-40.6)	11 (2877)	0.21
Heart failure, %	8.3 (4.7-14.2)	6 (27,556)	0.25	14.7 (7.2-27.9)	9 (32,619)	21.1 (13.7-31.0)	9 (3331)	0.08

CI, confidence interval; DAPT, dual antiplatelet; MI, myocardial infarction; RCT, randomized controlled trial; T1MI, type 1 myocardial infarction; T2MI, type 2 myocardial infarction.

Table 3. Management and outcomes of patients

	RCT			Observational studies				
	No. of studies (No. of patients)	Weighted mean, % (95% CI)	*P* values RCT vs observational studies	No. of studies comparing T1MI and T2MI (No. of patients)	T1MI weighted mean, % (95% CI)	T2MI observational studies % weighted mean, (95% CI)	*P* values T1MI vs T2MI	ORs of T2MI compared with T1MI (95% CI)
In-hospital initiation of DAPT	NA	NA	NA	6 (19,480)	74.2 (66.0-81.0)	20.8 (4.1-34.2)	< 0.0001	0.09 (0.04-0.21)
Coronary angiography	35 (83,466)	99.8 (99.7-99.9)	< 0.0001	8 (35,795)	82.9 (77.8-87.0)	28.2 (18.5-40.4)	< 0.0001	0.28 (0.20-0.39)
PCI	34 (78,358)	99.8 (99.6-99.9)	< 0.0001	9 (36,825)	64.4 (52.8-74.6)	10.3 (4.3-22.6)	< 0.0001	0.17 (9.1-32.7)
Reinfarction	4 (5,321)	3.3 (2.6-4.2)	< 0.0001	5 (5396)	9.8 (6.3-14.9)	6.4 (4.0-10.1)	0.002	0.62 (0.47-0.84)*
Short-term mortality	12 (97,269)	2.9 (1.7-4.9)	< 0.0001	8 (7249)	7.1 (5.5-8.8)	15.6 (10.3-20.8)	0.0006	1.86 (1.20-2.88)*
Long-term mortality	4 (33,593)	3.6 (2.3-5.4)	< 0.0001	16 (46,947) 11 (42,912)	11.3 (6.4-19.2)	27.7 (20.6-36.1)	< 0.0001	2.47 (2.06-2.96)* 1.45 (1.25-1.69)†

CI, confidence interval; DAPT, dual antiplatelet therapy; NA, nonapplicable (due to randomized comparison of dual antiplatelet therapy vs placebo); PCI, percutaneous coronary intervention; RCT, randomized controlled trials; T1MI, type 1 myocardial infarction; T2MI, type 2 myocardial infarction.

* Unadjusted comparison.

† Adjusted comparison.

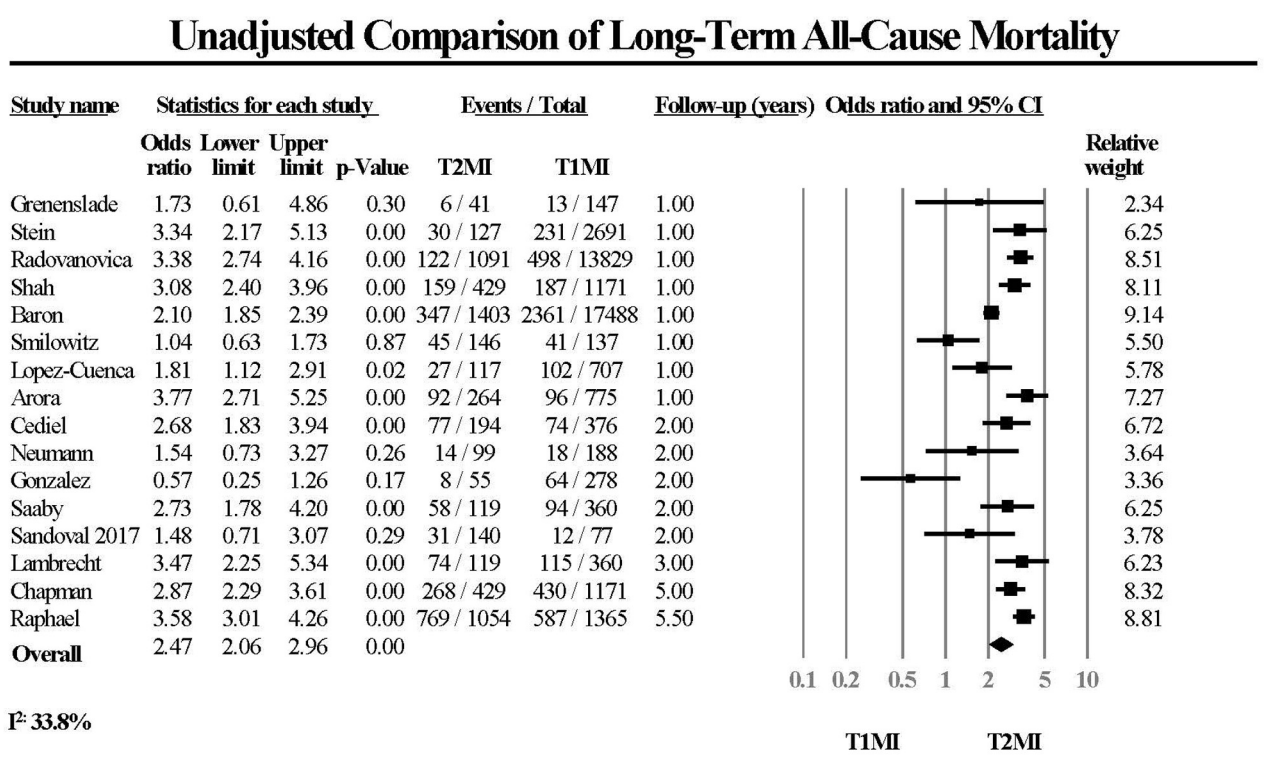

Figure 2. Unadjusted comparison of long-term all-cause mortality. CI, confidence interval; T1MI, type 1 myocardial infarction; T2MI, type 2 myocardial infarction.

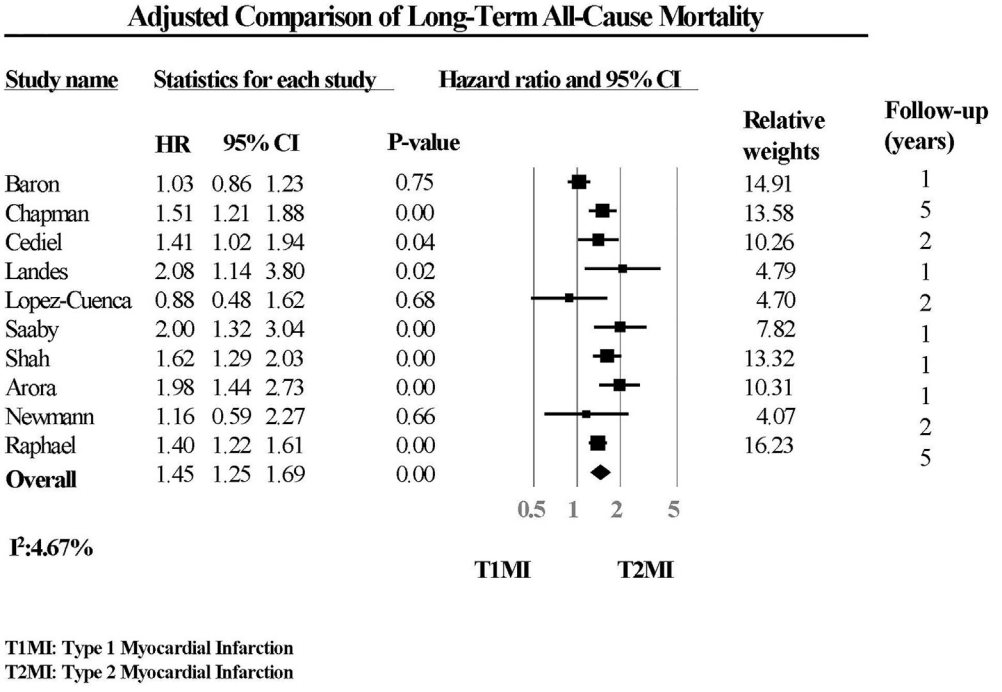

Figure 3. Adjusted comparison of long-term all-cause mortality. CI, confidence interval; HR, hazard ratio; T1MI, type 1 myocardial infarction; T2MI, type 2 myocardial infarction.

Table 4. Triggers of type 2 myocardial infarction

Triggers of type 2 myocardial infarction	No. of studies (No. of patients)	Weighed mean, % (95% CIs)
Arrhythmia	9 (36,592)	22.4 (16.1-30.3)
Anemia/bleeding	8 (35,044)	15.9 (11.6-21.4)
Respiratory diseases	5 (12,682)	13.7 (8.3-21.8)
Heart failure	4 (25,066)	13.7 (8.3-21.8)
Hypertensive crisis	6 (11,204)	11.5 (6.6-19.2)
Sepsis/infection	5 (24,387)	10.1 (5.2-18.8)

CI, confidence interval.

Limitations

Our systematic reviews had a few noteworthy limitations. First, the lack of patient-level data precluded us from computing adjusted odds ratios for short-term/intermediate mortality and reinfarction. Second, our adjusted comparison of long-term mortality may still be flawed by residual confounders that may not have been accounted for in the individual studies. Third, we could not compare the risk of cardiovascular mortality in patients with T2MI with that of patients with T1MI because only 3 studies reported cardiovascular mortality.[19,26,27] Fourth, because we excluded studies of myocardial injury after surgeries, our summary estimates of T2MI could not be extrapolated to patients with postoperative T2MI. Finally, it was possible that some patients with T2MI might have only myocardial injury without actual myocardial necrosis. Because patients with myocardial injury generally had better outcomes than patients with myocardial infarction,[79,81] our evaluations of odds of mortality may be underestimated because of the potential inclusion of patients with myocardial injury.

Conclusion

Even after accounting for their increased comorbidities, patients with T2MI still have higher all-cause long-term mortality compared with patients with T1MI. The efficacy, effectiveness, and safety of DAPT in T2MI have not been formally appraised in any RCTs or observational study. Therefore, the role of DAPT in T2MI remains undefined. This knowledge gap underscores the need for future studies evaluating DAPT in patients with T2MI to optimize the management of these high-risk patients.

Funding Sources

There are no funding sources to declare.

Disclosures

Andrew Yan received research grant support from AstraZeneca. Jean-Francois Tanguay received research grant support and speaker/consulting honoraria from Abbott Vascular, Amgen, AstraZeneca, Bayer, Biosensors, Idorsia, Medtronic, Sanofi, and Servier. Shamir Mehta received institutional research grant support from AstraZeneca, Abbott, Boston Scientific, and Sanofi. Shaun Goodman received research grant support and speaker/consulting honoraria from AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi-Sankyo, Eli Lilly, Merck, and Sanofi. Thao Huynh received research grant support and speaker/consulting

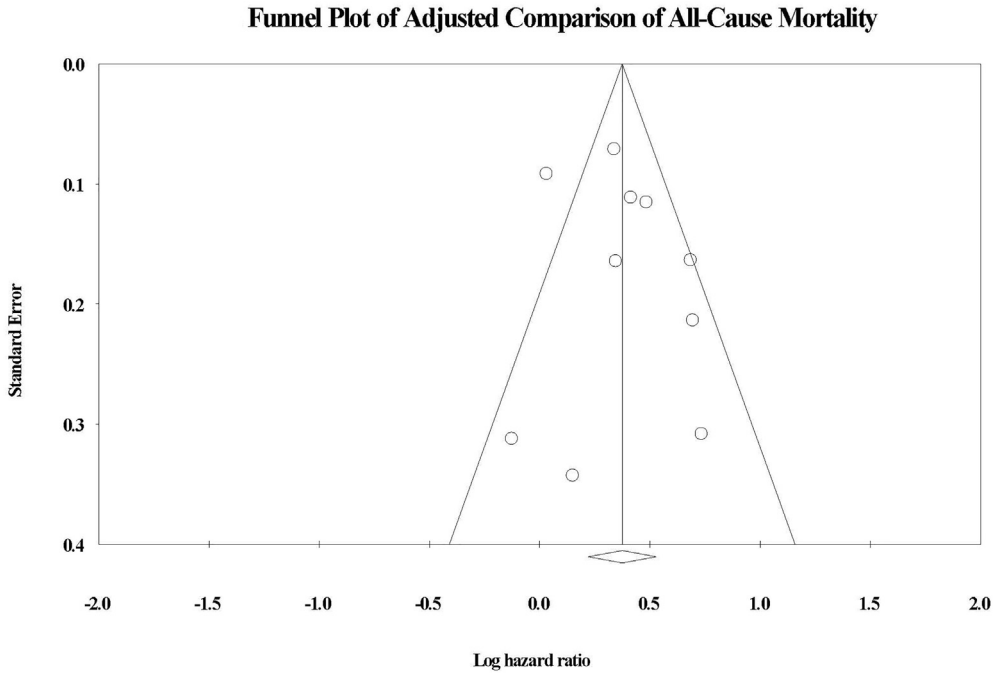

Figure 4. Funnel plot of adjusted comparison of all-cause mortality.

honoraria from AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi-Sankyo, Eli Lilly, Merck, and Sanofi.

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Supplementary Material

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