Systematic Review and Meta-Analysis

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Impact of type 2 diabetes mellitus on the long-term mortality in patients who were treated by coronary artery bypass surgery

A systematic review and meta-analysis

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Abstract

Background: Recent scientific reports have mainly focused on the comparison between coronary artery bypass surgery (CABG) and percutaneous coronary intervention. However, the impact of type 2 diabetes mellitus (T2DM) on mortality in patients who were treated by CABG was often ignored. Therefore, we aimed to compare the long-term mortality following CABG in patients with and without T2DM.

Methods: Studies comparing the long-term adverse outcomes following CABG in patients with and without T2DM were searched from electronic databases. Total number of deaths (primary outcome) and events of myocardial infarction (MI), major adverse cerebrovascular and cardiovascular events (MACCEs), stroke, and repeated revascularization (secondary outcomes) were carefully extracted. An analysis was carried out whereby odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the RevMan 5.3 software.

Results: Eleven studies with a total number of 12,965 patients were included. Current results showed that mortality was significantly higher in patients with T2DM with OR: 1.54, 95% CI: 1.37 to 1.72, $P<.00001$; OR: 1.53, 95% CI: 1.36 to 1.72, $P<.00001$; and OR: 1.53, 95% CI: 1.26 to 1.87, $P<.0001$ at 1 to 15, 5 to 15, and 7 to 15 years, respectively. However, MI, repeated revascularization, MACCEs, and stroke were not significantly different with OR: 1.15, 95% CI: 0.81 to 1.64, $P=.44$; OR: 1.09, 95% CI: 0.88 to 1.36, $P=.43$; OR: 1.11, 95% CI: 0.83 to 1.48, $P=.48$; and OR: 1.69, 95% CI: 0.93 to 3.07, $P=.08$, respectively.

Conclusion: Following CABG, a significantly higher rate of mortality was continually observed in patients with T2DM compared to patients without T2DM showing that the former apparently has a high impact on the long-term mortality. However, even if T2DM is an independent risk factor for mortality, it should not be ignored that CABG remains the best revascularization strategy in these patients.

Abbreviations: CABG = coronary artery bypass surgery, CVD = cardiovascular disease, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, T2DM = type 2 diabetes mellitus.

Keywords: cardiovascular diseases, coronary artery bypass surgery, mortality, type 2 diabetes mellitus

1. Introduction

Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular diseases (CVDs).[1] Several studies showed CVDs to have been responsible for more than 80% of death in patients with T2DM, and unfortunately, the actual number of patients with T2DM is estimated to double by the year 2030, indicating a rise in mortality during the coming years.[2]

Recent scientific reports comparing percutaneous coronary intervention (PCI) with coronary artery bypass surgery (CABG) in nondiabetic patients with multivessel coronary artery diseases who were good candidates for either procedure showed that PCI and CABG provided almost similar results following revascularization.[3,4] However, in patients with T2DM, CABG was associated with better long-term clinical outcomes.[5] It was suggested that CABG should be considered the revascularization procedure of choice in patients with T2DM who were complicated with multivessel coronary artery diseases.[6]

Recent scientific reports have mainly focused on the comparison between CABG and PCI. However, the impact of T2DM on mortality in patients who were treated by CABG was often ignored. Therefore, we aimed to compare the long-term mortality following CABG in patients with and without T2DM.

2. Methods

2.1. Data sources and search strategy

Electronic databases (Medline, EMBASE, and the Cochrane Library) were searched for randomized controlled trials (RCTs) and observational studies (English publications) comparing the

Editor: Wilhelm Mistiaen.

Authors' contributions: PKB, AB, and JY were responsible for the conception and design, acquisition of data, analysis and interpretation of data, drafting the initial manuscript, and revising it critically for important intellectual content. PKB wrote this manuscript. All authors read and approved the final manuscript.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:22(e7022)

Received: 12 March 2017 / Received in final form: 20 April 2017 / Accepted: 24 April 2017

http://dx.doi.org/10.1097/MD.0000000000007022

long-term mortality following CABG in patients with and without T2DM. The words "coronary artery bypass surgery and diabetes mellitus" were the searched terms that were used. In addition, the abbreviations "CABG and DM" were also considered in this search strategy.

Apart from the abovementioned terms, the words "coronary artery bypass surgery" were also substituted by the words "surgical revascularization". Reference lists of suitable articles were also reviewed for relevant publications.

2.2. Inclusion and exclusion criteria

Studies were included if:

(1) They were RCTs or observational studies comparing the adverse clinical outcomes following CABG in patients with and without T2DM.
(2) They reported mortality among their clinical endpoints.
(3) They had a follow-up period of 1 or more years.

Studies were excluded if as follows:

(1) They were meta-analyses, case studies, or letters to editors.
(2) They had a shorter follow-up period (<1 year).
(3) They did not report mortality among their clinical endpoints.
(4) They involved patients who were revascularized by CABG without the inclusion of a control group.
(5) They were duplicate studies.

2.3. Outcomes, definitions, and follow-ups

The primary endpoint was mortality and the secondary endpoints were the other adverse cardiovascular outcomes which have been listed below.

These clinical endpoints included the following:

(1) Mortality: consisting of all-cause mortality and cardiac death.
(2) Myocardial infarction (MI).
(3) Stroke.
(4) Major adverse cerebrovascular and cardiovascular events (MACCEs). MACCEs were composed of death, MI, stroke, and repeated revascularization.
(5) Repeated revascularization (target vessel revascularization and target lesion revascularization).

This analysis had a long-term follow-up period (1–15 years). The reported outcomes with their corresponding follow-up periods have been listed in Table 1.

2.4. Data extraction and review

Two authors (PKB and AB) reviewed the relevant articles and carefully assessed the eligibility criteria of each included studies. Information and data concerning the types of study reported the total number of patients with and without T2DM, respectively, the primary and secondary endpoints, as well as data relevant to the baseline features of the patients were carefully extracted. Any disagreement concerning data extraction was solved by the third author (JY). Bias risk was assessed with reference to the Cochrane Collaboration.[7]

2.5. Statistical analysis

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was reported.[8] Possible heterogeneity among the subgroups analyzing the primary and secondary outcomes was assessed using the Cochrane Q-statistic and the I^2-statistic tests, respectively. According to the Q-statistic test, a result with P value $\leq .05$ was considered statistically significant.

The I^2 value also had a major role in this analysis. Heterogeneity increased with a rising I^2 value. That is, the larger the I^2 value, the higher the heterogeneity. If I^2 corresponded to a value less than 50%, a fixed effects model was used. However, if I^2 corresponded to a value greater than 50%, a random effects model was used.

The main analysis was carried out whereby odds ratios (ORs) and 95% confidence intervals (CI) were calculated using the RevMan 5.3 software.

Sensitivity analyses were also carried out by excluding each study one-by-one, and a new analysis was repeated each time.

Since this analysis did not include many trials/observational studies, publication bias was visually estimated by visually assessing funnel plots that were obtained directly from the RevMan software.

Ethical approval was not necessary for this type of study.

All the 3 authors had full access to the data, and they approved the manuscript as written.

3. Results

3.1. Search outcomes

A total of 2621 articles were obtained during the search process. After reviewing/assessing the titles and abstracts, 2578 articles were directly eliminated. Among the 43 remaining articles, 20 duplicated articles were further excluded. A total of 23 full-text

Table 1

Reported outcomes and follow-up periods.

Studies	Outcomes reported	Follow-up periods, years
Abiazaid 2001	Mortality, cerebrovascular events, MI, and repeated revascularization	1
Kappetein 2011	Mortality, stroke, MI, repeated revascularization, and MACCEs	5
Lawrie 1986	Mortality	15
Mahammadi 2007	Cardiac death	12
Marui 2015	Mortality, stroke, MI, repeated revascularization	5
Mulder 2010	Mortality and MI	3
Onuma 2011	Mortality, MACCEs, MI, cerebrovascular events, and repeated revascularization	5
Soares 2006	Mortality	5
Zal 2014	Mortality, MI, stroke, and repeated revascularization	2
Bari 2000	Mortality	7
Koshizaka 2015	Mortality	5

MACCEs = major adverse cerebrovascular and cardiovascular events, MI = myocardial infarction.

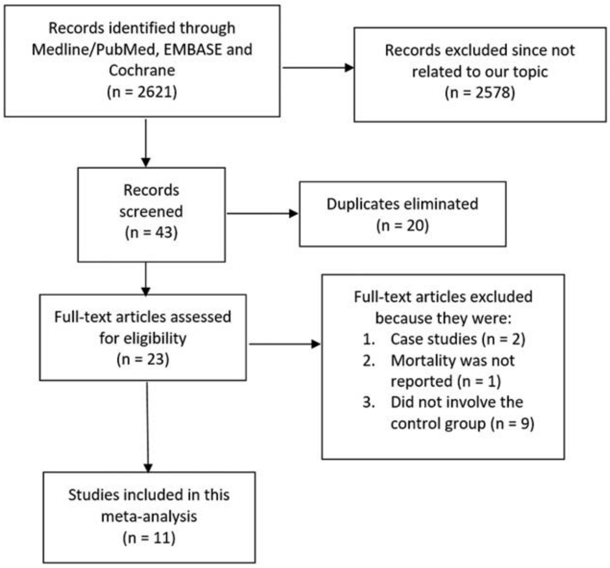

Figure 1. Flow diagram representing the study selection.

articles were assessed for eligibility. A total of 12 publications were further eliminated because of the following reasons: case studies (2), they did not report mortality as their clinical endpoint (1), and they compared CABG with PCI in patients with T2DM without comparing the outcomes in patients without T2DM (9). Finally, only 11 studies (6 RCTs[9–14] and 5 observational studies[15–19]) were included in this meta-analysis as shown in Fig. 1.

3.2. General features of the studies which were included

A total number of 12,965 patients were included in this analysis (4106 patients with T2DM and 8859 patients without T2DM). The general features of the studies which were included in this analysis have been summarized in Table 2.

Number of studies with: 1-year follow-up: 1; 2-year follow-up: 1; 3-year follow-up: 1; 5-year follow-up: 5; 7-year follow-up: 1; 12-year follow-up: 1; 15-year follow-up: 1.

3.3. Baseline features of the patients

The baseline features of the patients have been summarized in Table 3.

The mean age was reported in years, whereas the other features were reported in terms of percentage (%). Mean age of the patients varied between 53.0 and 70.3 years. Majority of the patients in study Marui2015 within both groups had hypertension, whereas study Mahammadi2007 consisted of most patients with dyslipidemia. Overall, except for hypertension that was more prominent in patients with T2DM, there was no other major significant difference in baseline features between patients with and without T2DM who were enrolled in this analysis.

3.4. Mortality analyzed

Results of this study showed that among the 12,965 patients who were analyzed for all-cause death (4106 patients with T2DM and 8859 patients without T2DM), mortality was significantly higher following CABG in patients with T2DM, with OR: 1.54, 95% CI: 1.37 to 1.72; $P<.00001$, $I^2=32\%$ during the long-term follow-up period (1–15 years). Since a low level of heterogeneity (<40%) was reported in this subgroup, a fixed effects model was used during the statistical analysis. This result has been represented in Fig. 2.

When a follow-up period of 5 to 15 years was considered, mortality was still significantly higher in patients with T2DM, with OR: 1.53, 95% CI: 1.36 to 1.72; $P<.00001$, $I^2=47\%$ as shown in Fig. 3. A similar result was again obtained when a follow-up period of 7 to 15 years was considered, with OR: 1.53, 95% CI: 1.26 to 1.87; $P<.0001$, $I^2=0\%$ as shown in Fig. 4.

Several studies reported mortality as their outcome without clearly specifying whether it was all-cause mortality or cardiac death. Therefore, another subgroup analysis was carried out only with studies which specified the type of mortality which was reported. Results of this specific subgroup analysis showed all-cause mortality and cardiac death to significantly favor patients without T2DM with OR: 1.34, 95% CI: 1.12 to 1.60; $P=.001$ and OR: 1.62, 95% CI: 1.31 to 2.00; $P<.00001$, respectively, during this long-term follow-up (Fig. 5).

This analysis was composed of data that were obtained from randomized trials and observational studies. However, separate analyses were further carried out using data that were obtained from randomized trials and observational studies, respectively.

Table 2

General features of the studies which were included.

Studies	Type of study	No of patients with T2DM (n)	No of patients without T2DM (n)	Total no of patients (n)
Abiazaid 2001[9]	RCT	96	509	605
Kappetein 2011[10]	RCT	221	676	897
Lawrie 1986[15]	Observational	212	1222	1434
Mahammadi 2007[16]	Observational	912	1505	2417
Marui 2015[17]	Observational	933	861	1794
Mulder 2010[18]	Observational	216	720	936
Onuma 2011[11]	RCT	96	488	584
Soares 2006[12]	RCT	59	144	203
Zal 2014[19]	Observational	42	125	167
Bari 2000[13]	RCT	180	734	914
Koshizaka 2015[14]	RCT	1139	1875	3014
Total no of patients (n)				
		4106	8859	12,965

RCT = randomized controlled trial, T2DM = type 2 diabetes mellitus.

Table 3

Baseline features.

Studies	Mean age DM/NDM	Males DM/NDM	Hypertension DM/NDM	Dyslipidemia DM/NDM	Smoker DM/NDM
Abiazaid 2001	62.6/61.0	68.8/77.4	56.3/42.8	49.0/59.3	16.7/27.6
Kappetein 2011	65.4/65.0	71.0/79.9	70.0/65.0	82.0/77.0	16.0/22.0
Lawrie 1986	55.0/53.0	83.5/88.8	27.7/17.1	–	65.1/73.6
Mahammadi 2007	62.6/64.0	67.9/78.4	70.0/52.2	86.5/89.2	–
Marui 2015	68.3/70.3	70.0/75.0	86.0/85.0	–	25.0/24.0
Mulder 2010	65.5/67.0	67.9/78.3	55.7/52.5	61.1/60.0	32.0/31.1
Onuma 2011	63.0/61.0	69.0/77.0	56.0/43.0	49.0/59.0	–
Soares 2006	60.0/60.0	67.0/74.0	73.0/58.0	–	–
Zal 2014	69.7/64.7	58.1/77.8	90.7/72.2	51.2/71.4	39.5/57.1
Bari 2000	–	77.9/86.4	–	–	77.5/85.4
Koshizaka 2015	63.0/64.0	74.6/81.9	84.2/69.5	79.8/74.2	17.1/26.4

DM = diabetes mellitus, NDM = nondiabetes mellitus.

The results that were obtained showed mortality to still be significantly higher in patients with T2DM, OR: 1.69, 95% CI: 1.45 to 1.96; $P<.00001$ and OR: 1.38, 95% CI: 1.17 to 1.63; $P=.0001$, respectively (Fig. 6).

Mortality was further subdivided into a short-term (1 year ≤ mortality < 5 years), middle-term (5 years ≤ mortality < 7 years), and long-term (7 years ≤ mortality ≤ 15 years) follow-ups. Significantly higher mortality rates were observed in patients with T2DM, OR: 1.65, 95% CI: 1.07 to 2.54, $P=.02$; OR: 1.53, 95% CI: 1.32 to 1.76, $P<.00001$; and OR: 1.53, 95% CI: 1.26 to 1.87, $P<.0001$ during a short-term, mid-term, and long-term follow-up periods, respectively (Fig. 7).

3.5. Other adverse cardiovascular outcomes that were analyzed

In this study, we also analyzed the other cardiovascular outcomes which were reported. Following CABG, MI, repeated revascularization, and MACCEs were not significantly different in patients with and without T2DM with OR: 1.15, 95% CI: 0.81 to 1.64, $P=.44$, $I^2=0\%$; OR: 1.09, 95% CI: 0.88 to 1.36, $P=.43$, $I^2=0\%$; and OR: 1.11, 95% CI: 0.83 to 1.48, $P=.48$, $I^2=0\%$, respectively, as shown in Fig. 2.

However, even if stroke was higher in the diabetic group with OR: 1.69, 95% CI: 0.93 to 3.07; $P=.08$, $I^2=55\%$, the result was not statistically significant (Fig. 8).

The main result of this current analysis has been summarized in Table 4.

Sensitivity analyses yielded consistent results. In addition, there has been only little evidence of publication bias observed across all the studies which were involved in assessing the primary and secondary endpoints (Figs. 9 and 10).

4. Discussion

Even though T2DM is considered as a major risk factor contributing to the development of CVDs, the relationship between CVDs and T2DM is complicated.[20,21]

This study aimed to show the impact of T2DM on the long-term mortality following CABG. The current results showed mortality to have been consistently higher in patients with T2DM following CABG. Even when data that were obtained from randomized trials and observational studies were separately analyzed, T2DM was still associated with a significantly higher mortality rate. When the other cardiovascular outcomes were compared between patients with and without T2DM, no significant differences were observed among the subgroups analyzing MI, MACCEs, and repeated revascularization. However, following CABG, even if a higher rate of stroke was observed in patients with T2DM, the result was not statistically significant.

Even if all the data that were obtained have contributed significantly to the final results, the weight of each study was different during this analysis. When mortality was analyzed, study Bari2000 had a weight of 11.6%, study Kappetein2013 had a weight of 6.4%, study Koshizaka2015 had a weight of 30.0%, study Lawrie1986 had a weight of 14.9%, study Mahammadi2007 had a weight of 8.0%, and study Marui2015 had a weight of 24.4%. However, even excluding each study one-by-one, or even excluding the study apparently with the highest weight did not affect the results that were previously obtained. Therefore, it was clear that the main result that was obtained was not influenced by the result of 1 particular study.

Previously, when CABG was compared with PCI in patients with T2DM, PCI was associated with a significantly higher rate of repeated revascularization.[22] However, a lower revascularization rate was reported following CABG, as reflected in this current analysis. Despite being higher in patients with T2DM, the result representing stroke was not statistically significant. To further support this point, Bundhun et al also recently compared PCI and CABG in patients with insulin-treated diabetes mellitus (ITDM). Their result showed CABG to be associated with a higher rate of stroke without statistically significance.[6] However, when the same outcome was compared in patients with ITDM and noninsulin-treated T2DM (NITDM), a significantly higher rate of stroke was associated with insulin therapy.[23] This current analysis only showed an insignificantly high rate of stroke observed among patients with T2DM. To note, this present study involved patients with T2DM as a whole, including patients with ITDM and NITDM combined together thus showing a slightly different result compared to the previously mentioned study. Munnee et al[23] also showed a significantly higher rate of mortality and major adverse events associated with ITDM. However, results for MACCEs in this current analysis differed from theirs could be due to the fact that patients with T2DM were combined and analyzed without further being classified into ITDM and NITDM.

Koshizaka et al[14] also showed T2DM to be associated with increased mortality compared to non-T2DM after 5 years

Study or Subgroup	DM Events	DM Total	Non-DM Events	Non-DM Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Mortality						
Abiazaid2001	3	96	14	509	0.5%	1.14 [0.32, 4.05]
Bari2000	80	180	244	734	6.8%	1.61 [1.15, 2.24]
Kappetein2013	26	221	68	676	3.8%	1.19 [0.74, 1.93]
Koshizaka2015	247	1139	234	1875	17.7%	1.94 [1.60, 2.36]
Lawrie1986	109	212	480	1222	8.8%	1.64 [1.22, 2.19]
Mahammadi2007	881	912	1442	1505	4.7%	1.24 [0.80, 1.92]
Marui2015	166	933	132	861	14.4%	1.20 [0.93, 1.53]
Mulder2010	25	216	45	720	2.3%	1.96 [1.17, 3.28]
Onuma2011	8	96	35	488	1.3%	1.18 [0.53, 2.62]
Soares2006	9	59	23	144	1.4%	0.95 [0.41, 2.19]
Zal2014	5	42	14	125	0.8%	1.07 [0.36, 3.18]
Subtotal (95% CI)		**4106**		**8859**	**62.7%**	**1.54 [1.37, 1.72]**
Total events	1559		2731			
Heterogeneity: Chi² = 14.77, df = 10 (P = 0.14); I² = 32%						
Test for overall effect: Z = 7.56 (P < 0.00001)						
1.1.2 Myocardial Infarction						
Abiazaid2001	3	96	21	509	0.8%	0.75 [0.22, 2.56]
Kappetein2013	11	221	22	676	1.3%	1.56 [0.74, 3.26]
Marui2015	28	933	24	861	3.1%	1.08 [0.62, 1.88]
Mulder2010	4	216	10	720	0.6%	1.34 [0.42, 4.31]
Onuma2011	5	96	29	488	1.2%	0.87 [0.33, 2.31]
Zal2014	2	42	2	125	0.1%	3.08 [0.42, 22.54]
Subtotal (95% CI)		**1604**		**3379**	**7.1%**	**1.15 [0.81, 1.64]**
Total events	53		108			
Heterogeneity: Chi² = 2.48, df = 5 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.77 (P = 0.44)						
1.1.3 Repeated Revascularization						
Abiazaid2001	3	96	18	509	0.7%	0.88 [0.25, 3.05]
Kappetein2013	28	221	82	676	4.5%	1.05 [0.66, 1.66]
Marui2015	127	933	107	861	12.3%	1.11 [0.84, 1.46]
Onuma2011	10	96	42	488	1.6%	1.23 [0.60, 2.56]
Zal2014	0	42	2	125	0.2%	0.58 [0.03, 12.35]
Subtotal (95% CI)		**1388**		**2659**	**19.2%**	**1.09 [0.88, 1.36]**
Total events	168		251			
Heterogeneity: Chi² = 0.43, df = 4 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.43)						
1.1.4 Major adverse cardiovascular and cerebrovascular events (MACCEs)						
Kappetein2013	59	221	167	676	7.7%	1.11 [0.79, 1.57]
Onuma2011	22	96	103	488	3.3%	1.11 [0.66, 1.88]
Subtotal (95% CI)		**317**		**1164**	**11.0%**	**1.11 [0.83, 1.48]**
Total events	81		270			
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**7415**		**16061**	**100.0%**	**1.38 [1.26, 1.51]**
Total events	1861		3360			
Heterogeneity: Chi² = 28.71, df = 23 (P = 0.19); I² = 20%						
Test for overall effect: Z = 6.93 (P < 0.00001)						
Test for subgroup differences: Chi² = 11.03, df = 3 (P = 0.01), I² = 72.8%						

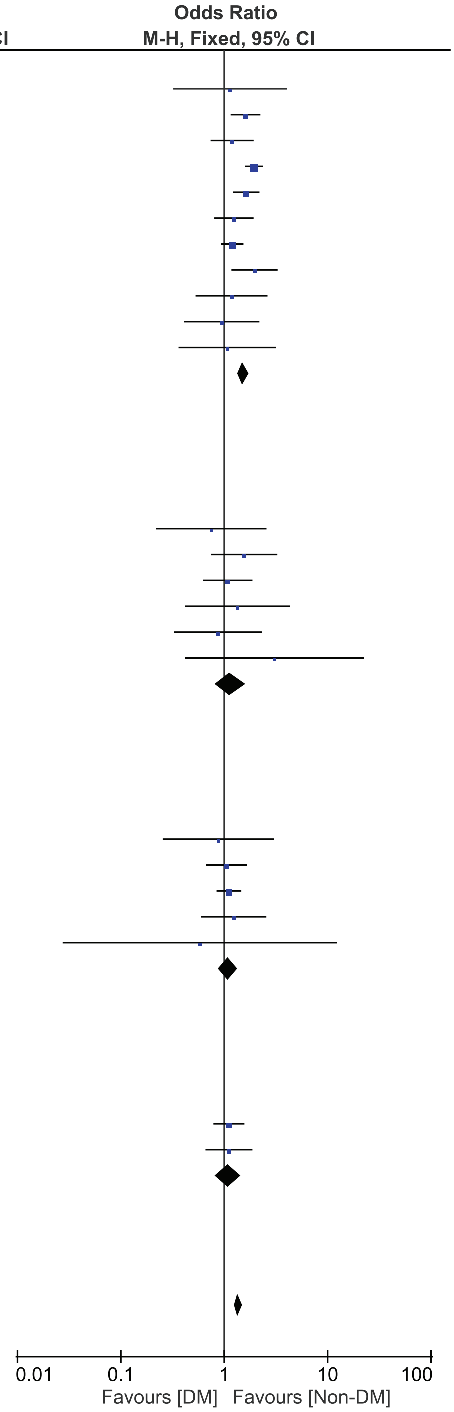

Figure 2. Mortality and adverse cardiovascular outcomes reported between type 2 diabetes mellitus (T2DM) and non-T2DM following revascularization by coronary artery bypass surgery (1–15 years).

following CABG. It should be noted that data from the PRoject of Ex-vivo Vein graft ENgineering via Transfection IV Trial (PREVENT IV) were used. In addition, a subgroup of the patients was monitored on the basis of whether they had insulin therapy before CABG or not. Several studies have also shown significantly higher mortality rate to be associated with T2DM patients on insulin treatment.

Reasons that have been suggested for this higher rate of adverse cardiovascular outcomes associated with insulin therapy were: more aggressive disease or several health complications presented in these patients, with a more advanced stage of T2DM.[24] In addition, adverse effects of insulin could also be another reason contributing to a higher rate of mortality in patients with ITDM.[24] Also, iatrogenic hyperinsulinemia promoting proinflammatory macrophage response and stimulating hormonal hyperactivation of signal transduction pathway,[25,26] endogenous hyperinsulinemia which could increase hepatic synthesis of cholesterol[27] could all be mechanisms suggested to contribute to

Study or Subgroup	DM Events	DM Total	Non-DM Events	Non-DM Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Mortality						
Bari2000	80	180	244	734	11.6%	1.61 [1.15, 2.24]
Kappetein2013	26	221	68	676	6.4%	1.19 [0.74, 1.93]
Koshizaka2015	247	1139	234	1875	30.0%	1.94 [1.60, 2.36]
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Marui2015	166	933	132	861	24.4%	1.20 [0.93, 1.53]
Onuma2011	8	96	35	488	2.3%	1.18 [0.53, 2.62]
Soares2006	9	59	23	144	2.5%	0.95 [0.41, 2.19]
Subtotal (95% CI)		**3752**		**7505**	**100.0%**	**1.53 [1.36, 1.72]**
Total events	1526		2658			
Heterogeneity: Chi² = 13.27, df = 7 (P = 0.07); I² = 47%						
Test for overall effect: Z = 7.23 (P < 0.00001)						
Total (95% CI)		**3752**		**7505**	**100.0%**	**1.53 [1.36, 1.72]**
Total events	1526		2658			
Heterogeneity: Chi² = 13.27, df = 7 (P = 0.07); I² = 47%						
Test for overall effect: Z = 7.23 (P < 0.00001)						
Test for subgroup differences: Not applicable						

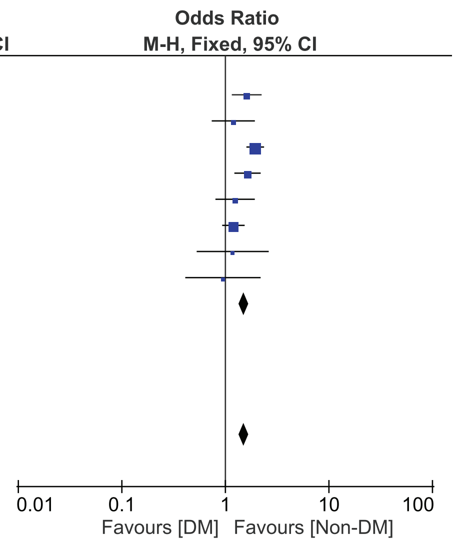

Figure 3. Long-term mortality observed between type 2 diabetes mellitus (T2DM) and non-T2DM following revascularization by coronary artery bypass surgery (5–15 years).

Study or Subgroup	DM Events	DM Total	Non-DM Events	Non-DM Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Mortality						
Bari2000	80	180	244	734	33.5%	1.61 [1.15, 2.24]
Lawrie1986	109	212	480	1222	43.3%	1.64 [1.22, 2.19]
Mahammadi2007	881	912	1442	1505	23.2%	1.24 [0.80, 1.92]
Subtotal (95% CI)		**1304**		**3461**	**100.0%**	**1.53 [1.26, 1.87]**
Total events	1070		2166			
Heterogeneity: Chi² = 1.15, df = 2 (P = 0.56); I² = 0%						
Test for overall effect: Z = 4.26 (P < 0.0001)						
Total (95% CI)		**1304**		**3461**	**100.0%**	**1.53 [1.26, 1.87]**
Total events	1070		2166			
Heterogeneity: Chi² = 1.15, df = 2 (P = 0.56); I² = 0%						
Test for overall effect: Z = 4.26 (P < 0.0001)						
Test for subgroup differences: Not applicable						

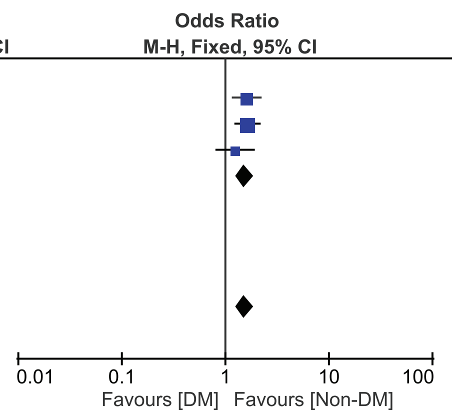

Figure 4. Long-term mortality observed between type 2 diabetes mellitus (T2DM) and non-T2DM following revascularization by coronary artery bypass surgery (7–15 years).

this high rate of adverse events in this particular subgroup of T2DM patients.[28,29] Unfortunately, this current analysis had limited data on patients with ITDM.

The retrospective study by Carson et al[30] which aimed to show the impact of T2DM on the short-term mortality and morbidity in patients undergoing CABG indicated that T2DM was an important risk factor in patients undergoing CABG. Their study, which involved 434 hospitals in North America and included 41,663 patients with T2DM and 105,123 patients without T2DM, had a follow-up period of only 30 days. This current analysis showed T2DM to be independently associated with a long-term mortality following CABG in different subgroups of patients.

The study by Banning et al[31] that compared the outcomes between CABG and paclitaxel eluting stents showed a comparable result among patients with and without T2DM who were revascularized by CABG in terms of composite endpoints including stroke, MI, and death altogether. However, the results of this present study showed death to significantly be lower in patients without T2DM, whereas MI was comparable between these 2 groups while stroke, despite being higher in the diabetic group, was not statistically significant.

Nevertheless, a few studies support the fact that patients with T2DM who were revascularized by CABG had substantially higher risk of major adverse events especially among ITDM.[32] This present study reported a significantly higher rate of mortality in patients with T2DM following CABG, but however, results for MACCEs were not statistically significant and involved only 2 studies for comparison which was not sufficient to reach a conclusion in terms of this particular outcome. Results from the CABG Patch Trial Database showed that during a follow-up period of 4 years, T2DM was not a predictor of mortality after CABG.[33] But the Trial involved only patients with left ventricular dysfunction with several comorbidities. However, in this current analysis, majority of patients with T2DM also suffer from hypertension which could have also influenced the mortality rate following CABG.

Study or Subgroup	DM Events	DM Total	Non-DM Events	Non-DM Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 All-Cause Mortality						
Kappetein2013	26	221	68	676	8.6%	1.19 [0.74, 1.93]
Lawrie1986	109	212	480	1222	20.0%	1.64 [1.22, 2.19]
Marui2015	166	933	132	861	32.7%	1.20 [0.93, 1.53]
Subtotal (95% CI)		**1366**		**2759**	**61.3%**	**1.34 [1.12, 1.60]**
Total events	301		680			
Heterogeneity: Chi² = 2.81, df = 2 (P = 0.24); I² = 29%						
Test for overall effect: Z = 3.24 (P = 0.001)						
1.1.2 Cardiac Mortality						
Kappetein2013	13	221	30	676	4.0%	1.35 [0.69, 2.63]
Lawrie1986	54	212	181	1222	11.6%	1.97 [1.39, 2.78]
Mahammadi2007	881	912	1442	1505	10.7%	1.24 [0.80, 1.92]
Marui2015	80	933	45	861	12.4%	1.70 [1.17, 2.48]
Subtotal (95% CI)		**2278**		**4264**	**38.7%**	**1.62 [1.31, 2.00]**
Total events	1028		1698			
Heterogeneity: Chi² = 2.97, df = 3 (P = 0.40); I² = 0%						
Test for overall effect: Z = 4.45 (P < 0.00001)						
Total (95% CI)		**3644**		**7023**	**100.0%**	**1.45 [1.26, 1.66]**
Total events	1329		2378			
Heterogeneity: Chi² = 7.76, df = 6 (P = 0.26); I² = 23%						
Test for overall effect: Z = 5.33 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.79, df = 1 (P = 0.18), I² = 44.2%						

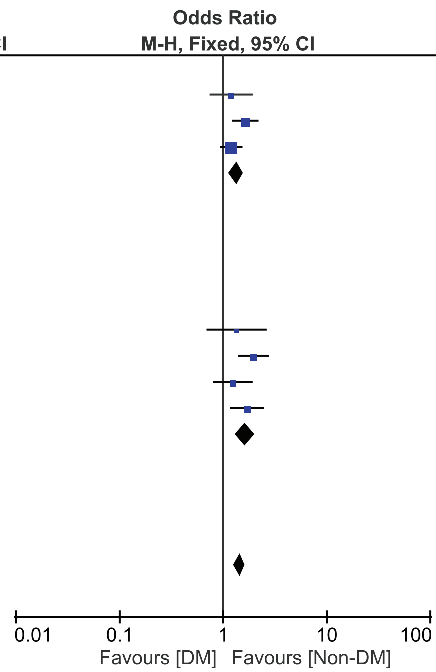

Figure 5. All-cause mortality and cardiac death observed between type 2 diabetes mellitus (T2DM) and non-T2DM following revascularization by coronary artery bypass surgery.

Even if T2DM has a high impact on mortality in patients undergoing revascularization with CABG during the long-term, in comparison to patients without T2DM, CABG remains the most effective revascularization procedure in patients with T2DM.[10] Mortality might have also been attributable to the age of the patients and their clinical conditions. And when compared to PCI, neither revascularization procedure could completely eliminate attacks of the heart but were more effective

Study or Subgroup	DM Events	DM Total	Non-DM Events	Non-DM Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Mortality only using data from randomized trials						
Abiazaid2001	3	96	14	509	0.9%	1.14 [0.32, 4.05]
Bari2000	80	180	244	734	10.9%	1.61 [1.15, 2.24]
Kappetein2013	26	221	68	676	6.0%	1.19 [0.74, 1.93]
Koshizaka2015	247	1139	234	1875	28.2%	1.94 [1.60, 2.36]
Onuma2011	8	96	35	488	2.1%	1.18 [0.53, 2.62]
Soares2006	9	59	23	144	2.3%	0.95 [0.41, 2.19]
Subtotal (95% CI)		**1791**		**4426**	**50.4%**	**1.69 [1.45, 1.96]**
Total events	373		618			
Heterogeneity: Chi² = 7.03, df = 5 (P = 0.22); I² = 29%						
Test for overall effect: Z = 6.78 (P < 0.00001)						
1.1.2 Mortality only using data from observational studies						
Lawrie1986	109	212	480	1222	14.0%	1.64 [1.22, 2.19]
Mahammadi2007	881	912	1442	1505	7.5%	1.24 [0.80, 1.92]
Marui2015	166	933	132	861	23.0%	1.20 [0.93, 1.53]
Mulder2010	25	216	45	720	3.7%	1.96 [1.17, 3.28]
Zal2014	5	42	14	125	1.3%	1.07 [0.36, 3.18]
Subtotal (95% CI)		**2315**		**4433**	**49.6%**	**1.38 [1.17, 1.63]**
Total events	1186		2113			
Heterogeneity: Chi² = 4.80, df = 4 (P = 0.31); I² = 17%						
Test for overall effect: Z = 3.87 (P = 0.0001)						
Total (95% CI)		**4106**		**8859**	**100.0%**	**1.54 [1.37, 1.72]**
Total events	1559		2731			
Heterogeneity: Chi² = 14.77, df = 10 (P = 0.14); I² = 32%						
Test for overall effect: Z = 7.56 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.09, df = 1 (P = 0.08), I² = 67.6%						

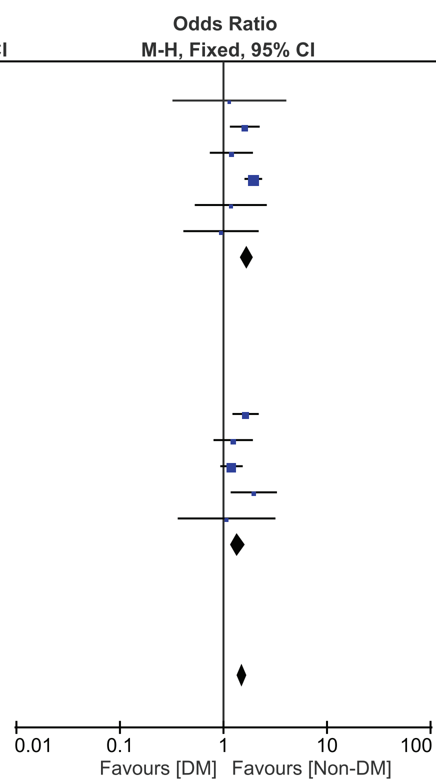

Figure 6. Randomized controlled trials and observational studies analyzed separately for long-term mortality.

Study or Subgroup	DM Events	DM Total	Non-DM Events	Non-DM Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Mortality (1 to < 5 years)						
Abiazaid2001	3	96	14	509	0.9%	1.14 [0.32, 4.05]
Mulder2010	25	216	45	720	3.7%	1.96 [1.17, 3.28]
Zal2014	5	42	14	125	1.3%	1.07 [0.36, 3.18]
Subtotal (95% CI)		**354**		**1354**	**5.9%**	**1.65 [1.07, 2.54]**
Total events	33		73			
Heterogeneity: Chi² = 1.37, df = 2 (P = 0.50); I² = 0%						
Test for overall effect: Z = 2.26 (P = 0.02)						
1.1.2 Mortality (5 to < 7 years)						
Kappetein2013	26	221	68	676	6.0%	1.19 [0.74, 1.93]
Koshizaka2015	247	1139	234	1875	28.2%	1.94 [1.60, 2.36]
Marui2015	166	933	132	861	23.0%	1.20 [0.93, 1.53]
Onuma2011	8	96	35	488	2.1%	1.18 [0.53, 2.62]
Soares2006	9	59	23	144	2.3%	0.95 [0.41, 2.19]
Subtotal (95% CI)		**2448**		**4044**	**61.7%**	**1.53 [1.32, 1.76]**
Total events	456		492			
Heterogeneity: Chi² = 12.11, df = 4 (P = 0.02); I² = 67%						
Test for overall effect: Z = 5.84 (P < 0.00001)						
1.1.3 Mortality (> 7 to 15 years)						
Bari2000	80	180	244	734	10.9%	1.61 [1.15, 2.24]
Lawrie1986	109	212	480	1222	14.0%	1.64 [1.22, 2.19]
Mahammadi2007	881	912	1442	1505	7.5%	1.24 [0.80, 1.92]
Subtotal (95% CI)		**1304**		**3461**	**32.4%**	**1.53 [1.26, 1.87]**
Total events	1070		2166			
Heterogeneity: Chi² = 1.15, df = 2 (P = 0.56); I² = 0%						
Test for overall effect: Z = 4.26 (P < 0.0001)						
Total (95% CI)		**4106**		**8859**	**100.0%**	**1.54 [1.37, 1.72]**
Total events	1559		2731			
Heterogeneity: Chi² = 14.77, df = 10 (P = 0.14); I² = 32%						
Test for overall effect: Z = 7.56 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.11, df = 2 (P = 0.95), I² = 0%						

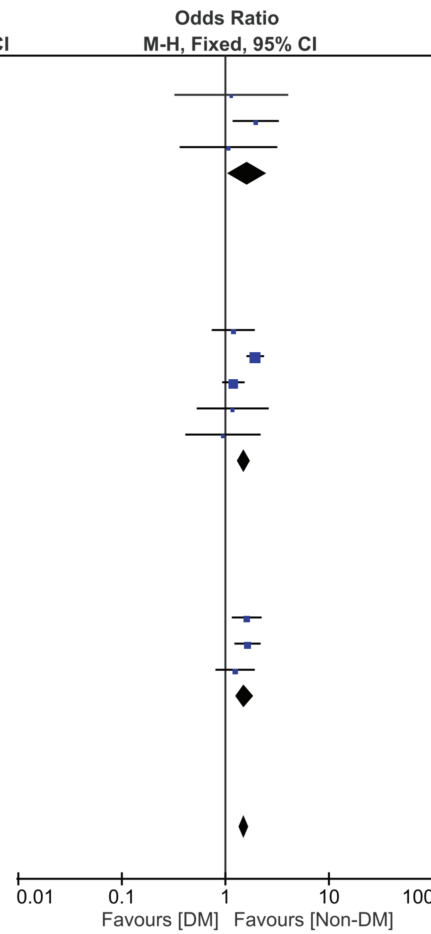

Figure 7. Mortality at different time period observed between type 2 diabetes mellitus (T2DM) and non-T2DM following revascularization by coronary artery bypass surgery.

compared to medical therapy.[12] However, since a significantly higher repeated revascularization rate was observed with PCI, and due to the fact that CABG could restore blood flow to a larger extent, and blockade sites could be more accessible compared to PCI, CABG should be considered more effective in patients with T2DM. However, after revascularization with CABG, precautions such as implementing a heart healthy lifestyle, increasing regular physical exercises, smoking cessation, blood pressure and cholesterol control with diet and medications, and weight loss should all be considered in these T2DM patients with CVDs.[34]

Study or Subgroup	DM Events	DM Total	Non-DM Events	Non-DM Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Stroke						
Abiazaid2001	6	96	6	509	16.1%	5.59 [1.76, 17.71]
Kappetein2013	9	221	22	676	23.7%	1.26 [0.57, 2.78]
Marui2015	73	933	65	861	35.7%	1.04 [0.73, 1.47]
Onuma2011	6	96	14	488	19.3%	2.26 [0.84, 6.03]
Zal2014	1	42	2	125	5.3%	1.50 [0.13, 16.98]
Subtotal (95% CI)		**1388**		**2659**	**100.0%**	**1.69 [0.93, 3.07]**
Total events	95		109			
Heterogeneity: Tau² = 0.23; Chi² = 8.98, df = 4 (P = 0.06); I² = 55%						
Test for overall effect: Z = 1.72 (P = 0.08)						
Total (95% CI)		**1388**		**2659**	**100.0%**	**1.69 [0.93, 3.07]**
Total events	95		109			
Heterogeneity: Tau² = 0.23; Chi² = 8.98, df = 4 (P = 0.06); I² = 55%						
Test for overall effect: Z = 1.72 (P = 0.08)						
Test for subgroup differences: Not applicable						

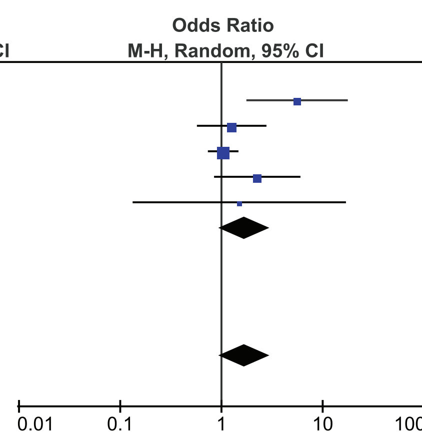

Figure 8. Stroke reported between type 2 diabetes mellitus (T2DM) and non-T2DM following revascularization by coronary artery bypass surgery (1–15 years).

Table 4

Results of this analysis.

Outcomes analyzed	OR with 95% CI	P	I^2, %
Mortality (1–15 y)	1.54 (1.37–1.72)	.00001	32
Mortality (5–15 y)	1.53 (1.36–1.72)	.00001	47
Mortality (7–15 y)	1.53 (1.26–1.87)	.0001	0
MACCEs	1.11 (0.83–1.48)	.48	0
MI	1.15 (0.81–1.64)	.44	0
Repeated revascularization	1.09 (0.88–1.36)	.43	0
Stroke	1.69 (0.93–3.07]	.08	55

CI = confidence interval, MACCEs = major adverse cerebrovascular and cardiovascular events, MI = myocardial infarction, OR = odds ratio.

5. Novelty

This study is new in the way that it is among the first meta-analyses showing the impact of T2DM on the long-term mortality rate in patients who were treated by CABG. Moreover, this study included a larger number of patients which were extracted from randomized trials and observational studies. Previous studies did not involve such a large number of patients. Also, this analysis compared long-term mortality during different sets of follow-up periods, and even separately compared mortality using data which were obtained from randomized trials and observational studies respectively. Cardiac death was also separately analyzed. A low level of heterogeneity among the different subgroups which were analyzed could also contribute to the novelty in this study.

6. Limitations

This study has limitations. First of all, due to the limited number of patients analyzed, this study might not generate very good results. Also, a moderate level of heterogeneity was observed when analyzing mortality during a follow-up period between 1 and 15 years, and 5 to 15 years, respectively. This could have been partly due to the involvement of data which were obtained from observational studies. In addition, this analysis was limited only to English publications which could lead to the introduction of selection and publication bias. Moreover, only 1 study had a follow-up period of 1, 2, 7, 12, and 15 years, respectively. The remaining studies had a follow-up period of 3 and 5 years, respectively. Therefore, even if a follow-up period ranging from 1 to 15 years was considered justified, it was limited to different follow-up periods. However, this point was further improved when an analysis considering a short-term (1 to < 5 years), mid-term (5 to < 7 years), and long-term (7 to 15 years) follow-up was carried out. Moreover, a high percentage of T2DM also suffered from hypertension showing that the latter might have partly contributed to this high mortality rate. Also, the drug history (cardiac medications used) prior and post CABG were not known. These medication uses could have had an influence on the results too. In addition, the large gap between study Lawrie1986 and the other studies might be a possible confounder because of significant recent advances in cardiovascular surgeries as compared to the year 1986. However, fortunately excluding study Lawrie1986 did not affect the results of this analysis. Finally, due to limited data reporting the number of patients on insulin therapy, we could not carry out another subgroup analysis based only on patients who were being treated by insulin.

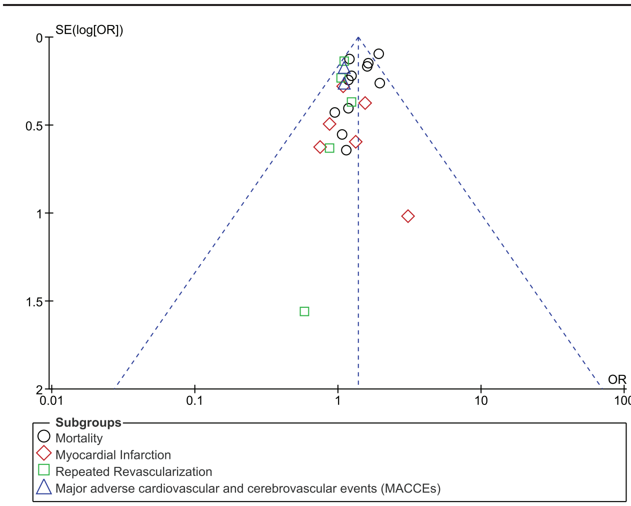

Figure 9. Funnel plot showing publication bias of 4 subgroups.

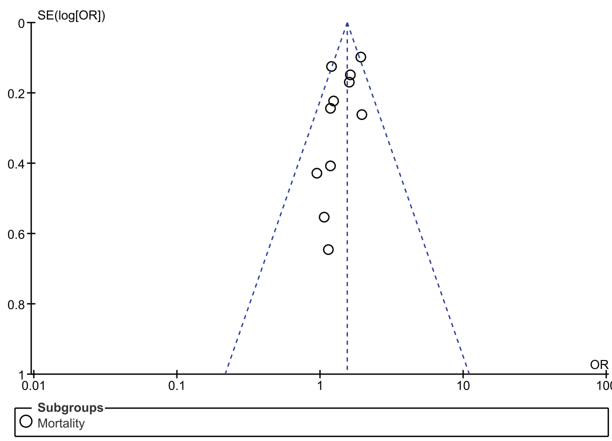

Figure 10. Funnel plot showing publication bias of 1 subgroup.

7. Conclusion

Following CABG, a significantly higher rate of mortality was continually observed in patients with T2DM compared to patients without T2DM showing that the former apparently has a high impact on the long-term mortality. However, even if T2DM is an independent risk factor for mortality, it should not be ignored that CABG remains the best revascularization strategy in these patients.

Acknowledgment

No written assistance was required and no external source of funding was required for this research.

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