Diabetes Ther (2019) 10:1487–1497
https://doi.org/10.1007/s13300-019-0656-9

ORIGINAL RESEARCH

Short-Term Versus Long-Term Adverse Cardiovascular Outcomes Post Percutaneous Coronary Intervention in Patients with Insulin-Treated Type 2 Diabetes Mellitus: A Simple Meta-Analysis

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Received: May 23, 2019 / Published online: June 29, 2019

ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is a major health issue, especially in patients with coexisting coronary artery disease (CAD). Patients with insulin-treated T2DM (ITDM) have worse outcomes than those with non-insulin-treated T2DM. Very few studies have compared short-term to long-term adverse cardiovascular outcomes following percutaneous coronary intervention (PCI) in patients on insulin therapy. Therefore, in this meta-analysis, we systematically compared short-term to long-term adverse cardiovascular outcomes in a population of patients with ITDM following PCI.

Methods: We searched for English-language publications focusing on PCI in patients with ITDM using specific search terms/phrases. All the participants accepted for inclusion in this meta-analysis were treated with a drug-eluting stent. Post-intervention adverse cardiovascular outcomes observed during short-term and long-term follow-up periods were assessed and compared. Statistical analysis was carried out using the popular RevMan 5.3 software. Odd ratios (OR) with 95% confidence intervals (CI) were calculated.

Results: Six studies comprising 1568 participants with ITDM in total were included in this simple meta-analysis. Patient enrollment periods varied but enrollment occurred during the

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years 1993–2012. When a fixed-effects statistical model was used, post-PCI adverse cardiovascular outcomes—such as major adverse cardiac events (MACEs) (OR 3.33, 95% CI 2.64–4.21; $P = 0.00001$), all-cause mortality (OR 5.73, 95% CI 3.37–9.73; $P = 0.00001$), myocardial infarction (MI) (OR 1.47, 95% CI 1.05–2.07; $P = 0.02$), and repeated revascularization (OR 4.78, 95% CI 3.29–6.94; $P = 0.00001$)—were found to be significantly more likely during the long-term follow-up period. A similar result was observed with a random-effects statistical model.

Conclusion: Adverse cardiovascular outcomes post PCI were significantly more likely during the long-term follow-up period than during the short-term follow-up period in these patients with T2DM on insulin therapy. This hypothesis requires confirmation via new comparative trials that consider short-term and long-term follow-up periods.

Keywords: Drug-eluting stents; Insulin therapy; Long-term cardiovascular outcomes; Major adverse cardiac events; Percutaneous coronary intervention; Short-term cardiovascular outcomes; Type 2 diabetes mellitus

Abbreviations

DES	Drug-eluting stents
ITDM	Insulin-treated type 2 diabetes mellitus
PCI	Percutaneous coronary intervention
T2DM	Type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major health issue, especially in patients with coexisting coronary artery disease (CAD) [1]. Complicated T2DM can lead to sudden cardiac death, silent myocardial infarction, and stroke [2, 3]. Patients with insulin-treated T2DM (ITDM) have worse outcomes than those without insulin therapy following percutaneous coronary intervention (PCI) [4].

A careful assessment of all the cardiovascular research that has been carried out into patients with ITDM who are undergoing PCI indicated that very few studies have compared short-term to long-term adverse cardiovascular outcomes following PCI. Although outcomes after a short period and after a long period have been reported, there has been no comparison of these short-term and long-term outcomes. In the meta-analysis reported in the present paper, we systematically compared the short-term to the long-term adverse cardiovascular outcomes observed in a population of patients with ITDM following PCI.

METHODS

Search Databases

The following search databases were searched:

(a) Web of Science
(b) Excerpta Medica database (EMBASE)
(c) Cochrane Central
(d) Google Scholar
(e) Medical Literature Analysis and Retrieval System Online (MEDLINE, including PubMed)
(f) http://www.ClinicalTrials.gov
(g) Scopus

Search Strategies

English-language publications focusing on PCI in a population of patients with ITDM were searched for using the following search terms or phrases:

(a) "type 2 diabetes mellitus" and "percutaneous coronary intervention"
(b) "diabetes mellitus" and "percutaneous coronary intervention"
(c) "diabetes mellitus" and "PCI"
(d) "diabetes mellitus" and "coronary angioplasty"
(e) "insulin-treated diabetes mellitus" and "percutaneous coronary intervention"
(f) "diabetes mellitus" and "drug eluting stents (DES)"
(g) "diabetes mellitus" and "DES"

Inclusion and Exclusion Criteria

The following inclusion criteria for the studies were applied:

- Studies that reported *both* short-term and long-term adverse cardiovascular outcomes in a population of patients with ITDM following PCI
- Studies that involved PCI with DES
- Studies in which participants with ITDM were separately assessed and not combined with participants with non-insulin-treated T2DM

The following exclusion criteria for the studies were employed:

- Studies that reported patients with T2DM but did not separately assess patients with ITDM
- Studies that reported adverse cardiovascular outcomes for either a short-term or a long-term follow-up period but not both
- Studies that did not report adverse cardiovascular outcomes post PCI
- Studies that were duplicates or were repeated in different search databases

Types of Participants

This analysis included ITDM patients with the following features (Table 1):

- Coronary artery disease + PCI
- Multivessel disease + PCI
- Native coronary artery lesions + PCI

All the participants included in the meta-analysis were treated with a DES.

Assessed Outcomes

The following adverse cardiovascular endpoints were assessed (Table 1):

- Major adverse cardiac events (MACEs): death, myocardial infarction (MI), and revascularization. Major adverse cardiovascular and cerebrovascular events (MACCEs, i.e., MACEs as well as stroke) were also included in this category.
- All-cause mortality.
- MI.
- Repeated revascularization, including target vessel revascularization and target lesion revascularization.

The follow-up periods reported in the original studies are also listed in Table 1. Short-term outcomes (in-hospital or within 1 month) were compared with long-term outcomes (from 6 months to 5 years).

Data Extraction and Quality Assessment

Seven reviewers were involved in the data extraction process. Data including the types of participants (patients with coronary artery disease with a single lesion or multivessel disease or those with native coronary lesions), the total number of participants receiving insulin treatment, the type and quality of the studies, baseline features such as comorbidities, mean age and gender, as well as the total numbers of events associated with specific outcomes were carefully extracted.

Any disagreement was discussed among the authors and the corresponding author made the final decision.

The bias risk for the trials was assessed based on the recommendations suggested by the Cochrane Collaboration [5], whereas the bias risk for prospective/retrospective studies were assessed using the Newcastle–Ottawa Scale (NOS) [6].

Statistical Analysis

Statistical analysis was carried out using the popular RevMan 5.3 software. Odd ratios (OR) with 95% confidence intervals (CI) were calculated. Heterogeneity was assessed by the commonly used Q statistical test, whereby a P value of ≤ 0.05 generated during analysis indicated a statistically significant difference. Any P value above 0.05 indicated a statistically nonsignificant difference. Heterogeneity was also assessed

Table 1 Types of participants, endpoints reported, and follow-up period duration(s)

Study	Type of participant	Endpoints reported	Follow-up period duration(s)
Abizaid et al. [8]	T2DM patients with native CAL treated with Palmaz–Schatz stents	MACEs, death, MI	In-hospital versus 1 year
Akin et al. [9]	T2DM patients with CAD + PCI	All-cause mortality, MI, stroke, MACCEs	In-hospital versus 1 year
Dangas et al. [10]	T2DM patients with MVD + PCI	MACCEs, repeated revascularization	1 month versus 1 year versus 5 years
Kuchulakanti et al. [11]	T2DM patients with CAD + PCI	Death, MI, repeated revascularization, ST, MACEs	In-hospital versus 1 month versus 6 months
Mehran et al. [12]	T2DM patients with MVD + PCI	Mortality, MI, TLR	In-hospital versus 1 year
Voudris et al. [13]	T2DM patients with MVD + PCI	Death, MI, ST, repeated revascularization, MACEs	In-hospital versus $\geq$ 1 year

T2DM type 2 diabetes mellitus, *CAL* coronary artery lesion, *CAD* coronary artery disease, *PCI* percutaneous coronary intervention, *MVD* multivessel disease, *MACEs* major adverse cardiac events, *MACCEs* major adverse cardiac and cerebrovascular events, *MI* myocardial infarction, *ST* stent thrombosis

by the I^2 statistical test: the larger the I^2 value, the greater the heterogeneity.

In this study, a fixed-effects statistical model and a random-effects statistical model were used. Sensitivity analysis was also carried out to exclude any excessively influential study from the results. In addition, publication bias was assessed visually with a funnel plot.

Ethical Approval

This study is a meta-analysis involving data that were previously published in original studies. No experiment involving humans or animals was carried out by any of the authors. Therefore, ethical approval was not required for this simple meta-analysis.

RESULTS

Search Outcomes

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline was followed [7]. After carefully searching through the electronic databases, a total of 3276 publications were retrieved. The relevance of each paper to this meta-analysis was assessed based on the title and abstract of the article. 3152 irrelevant papers were eliminated. 124 full-text articles that met the inclusion and exclusion criteria were assessed for eligibility. Most of these full-text articles were eliminated for the following reasons:

(a) They were systematic reviews and meta-analyses (5 papers)
(b) They were literature reviews (3)
(c) They focused on patients with T2DM without specifying the number of participants with ITDM (32)
(d) They focused on patients with T2DM but did not classify the participants into ITDM; instead, all participants were combined into one category (18)
(e) They only showed data relating to a short-term or a long-term follow-up period, not to both (39)
(f) They were duplicated studies (21)

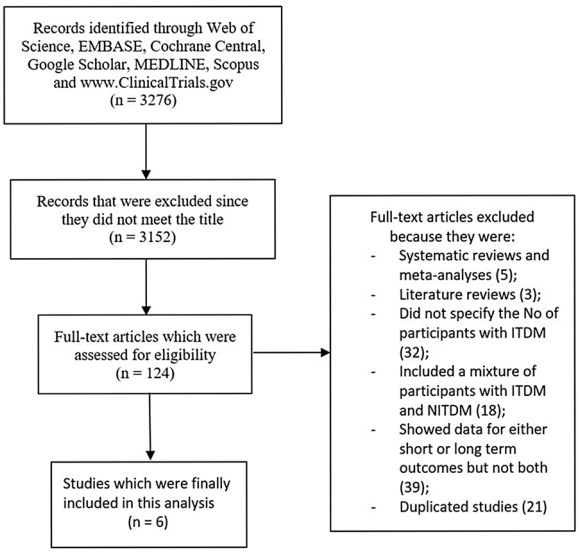

Fig. 1 Flow diagram for the study selection process in this meta-analysis

Ultimately, only six full-text articles [8–13] were accepted for inclusion in this meta-analysis, as shown in Fig. 1.

General and Baseline Features

Six studies comprising a total of 1568 participants with ITDM were included in this simple meta-analysis. Patient enrollment occurred during the years 1993–2012. All participants were implanted with a DES, such as a sirolimus-eluting stent (SES) or a paclitaxel-eluting stent (PES), as shown in Table 2. The antiplatelet drugs that were used are also listed in Table 2.

Upon assessing the quality of the studies, a moderate risk of bias was observed.

The baseline features of the participants are listed in Table 3. Most of the participants were males, with mean ages ranging from 63.0 to 66.9 years. The mean percentages of participants with hypertension, dyslipidemia, current smoker status, and glycated hemoglobin are listed in Table 3. Based on the data shown in Table 3, there was no significant difference in cardiovascular risk factors between the patients assigned to the short-term follow-up group and those assigned to the long-term follow-up group.

Main Results

When a fixed-effects statistical model was used in this meta-analysis, it was found that adverse post-PCI cardiovascular outcomes, including MACEs (OR 3.33, 95% CI 2.64–4.21; $P = 0.00001$), all-cause mortality (OR 5.73, 95% CI 3.37–9.73; $P = 0.00001$), MI (OR 1.47, 95% CI 1.05–2.07; $P = 0.02$), and repeated revascularization (OR 4.78, 95% CI 3.29–6.94; $P = 0.00001$), were significantly more likely during the long-term follow-up period as compared to the short-term follow-up period in patients with ITDM, as shown in Fig. 2.

When a random statistical model was used, it was found that adverse post-PCI cardiovascular outcomes, including MACEs (OR 3.95, 95% CI 2.06–7.56; $P = 0.0001$), all-cause mortality (OR 4.97, 95% CI 2.00–12.35; $P = 0.0005$), and repeated revascularization (OR 4.92, 95% CI 1.97–12.29; $P = 0.0007$), were still significantly more likely during the long-term follow-up period as compared to the short-term follow-up period in the patients with ITDM, as shown in Fig. 3.

The sensitivity analysis indicated that there was no excessively influential study. Publication bias was assessed visually using a funnel plot (Fig. 4) generated by the RevMan 5.3 software.

DISCUSSION

We performed a simple meta-analysis in order to systematically compare the short-term to the long-term adverse cardiovascular outcomes post percutaneous coronary intervention (PCI) in a population of patients with ITDM. As we have previously mentioned, there are various published studies that focus on T2DM patients with PCI. However, only a few studies separately report the outcomes of patients with ITDM following intervention. Even fewer report both short-term and long-term outcomes for the same patients in the same study, and those studies report the short-term and long-term outcomes separately and without comparing them. Therefore, in a novel approach, we combined the patient data from all relevant studies and then compared the short-term to the long-

Table 2 Main features of the studies included in this meta-analysis

Studies	Type of study	Enrollment period of patients	Total number of participants with ITDM (*n*)	Stent type(s)	Antiplatelet treatment
Abizaid et al. [8]	OS	1994–1996	97	DES	ASA 325 mg od indefinitely + ticlopidine 250 mg bd for 1 month
Akin et al. [9]	OS	2005–2006	581	SES and PES	ASA + clopidogrel
Dangas et al. [10]	RCT	2004–2012	325	SES and PES	ASA + clopidogrel
Kuchulakanti et al. [11]	OS	2003	351	SES and PES	ASA 325 mg od + clopidogrel 75 mg od or ticlopidine 250 mg bd
Mehran et al. [12]	OS	1993–1999	81	–	ASA 325 mg od indefinitely + clopidogrel 75 mg od or ticlopidine 250 mg bd for 4 weeks
Voudris et al. [13]	OS	2002–2005	133	DES	ASA + clopidogrel
Total number of patients (*n*)			1568		

ITDM insulin-treated type 2 diabetes mellitus, *NITDM* non-insulin-treated type 2 diabetes mellitus, *OS* observational study, *RCT* randomized controlled trials, *DES* drug-eluting stent, *SES* sirolimus-eluting stent, *PES* paclitaxel-eluting stent, *ASA* aspirin, *bd* twice daily

Table 3 Baseline features of the participants (extracted from the original studies)

Study	Age (years) ST/LT	Male (%) ST/LT	HBP (%) ST/LT	DL (%) ST/LT	CS (%) ST/LT	HbA1c (%) ST/LT
Abizaid et al. [8]	63.0/63.0	49.4/49.5	73.3/73.3	60.0/60.0	48.9/48.9	–
Akin et al. [9]	66.9/66.9	65.4/65.4	92.4/92.4	80.7/80.7	14.9/14.9	–
Dangas et al. [10]	63.2/63.2	61.9/61.9	86.8/86.8	–	18.2/18.2	8.50/8.50
Kuchulakanti et al. [11]	65.1/65.1	60.5/60.5	89.0/89.0	88.5/88.5	16.0/16.0	–
Mehran et al. [12]	63.0/63.0	52.0/52.0	77.0/77.0	71.0/71.0	11.0/11.0	–
Voudris et al. [13]	65.0/65.0	70.7/70.7	79.7/79.7	94.7/94.7	56.4/56.4	–

ITDM insulin-treated type 2 diabetes mellitus, *ST* short-term follow-up, *LT* long-term follow-up, *HBP* high blood pressure, *DL* dyslipidemia, *CS* current smoker, *HbA1c* glycated hemoglobin

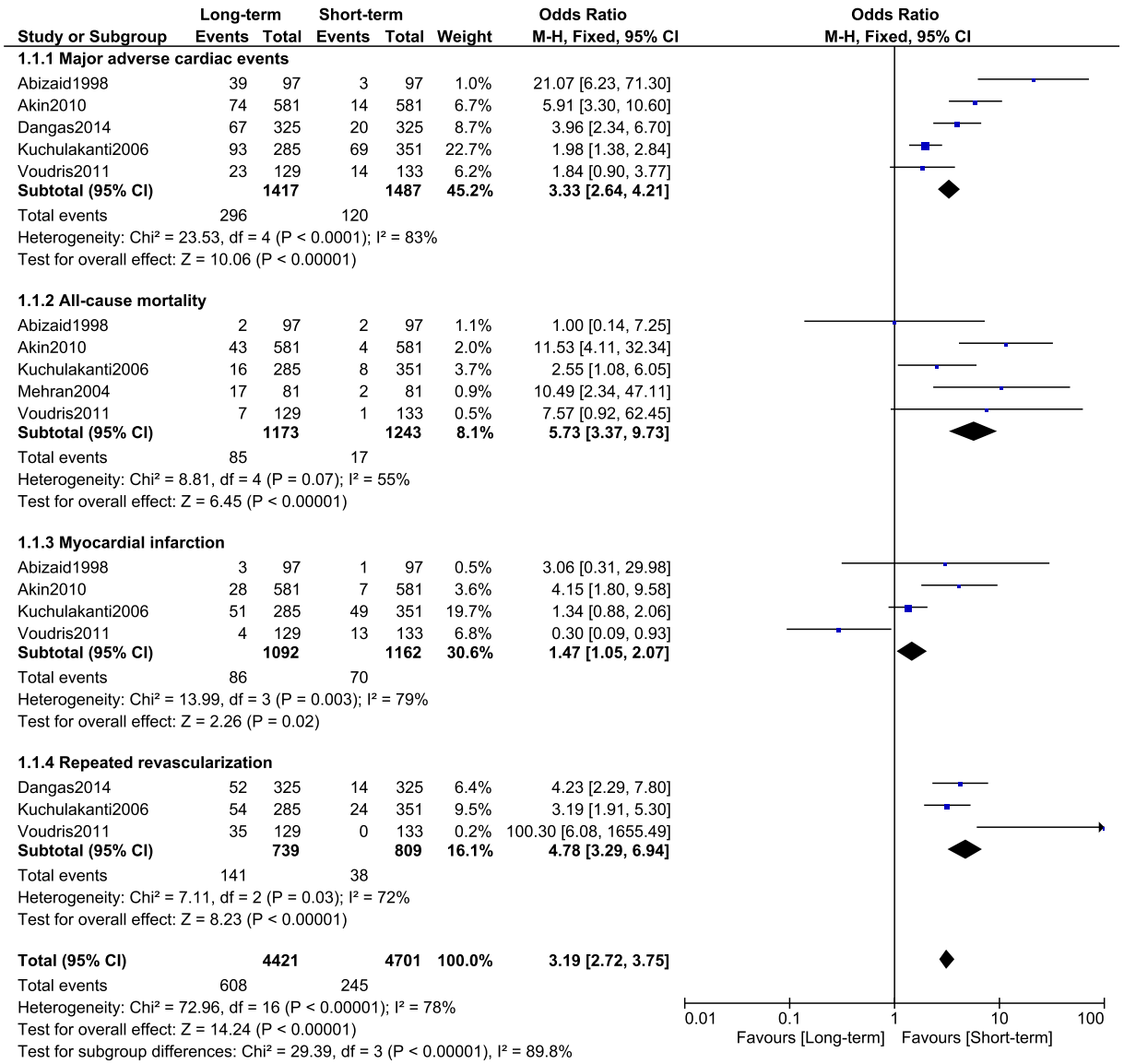

Fig. 2 Adverse post-PCI cardiovascular outcomes that were observed during the short-term and the long-term follow-up periods in patients with ITDM (fixed-effects statistical model)

term adverse cardiovascular outcomes observed in this subgroup of patients with T2DM following PCI.

Previously, several meta-analyses of major trials showed that ITDM was associated with worse adverse cardiovascular outcomes than observed in patients with non-insulin-treated T2DM following PCI [14, 15]. A meta-analysis published by Bundhun et al. comparing the adverse outcomes in patients with ITDM and non-insulin-treated T2DM showed that both short-term and long-term adverse outcomes were significantly more likely in the ITDM subgroup following PCI [16]. However, even when both short-term and long-term outcomes were assessed and reported in the same study, they were analyzed separately and were not compared with each other.

In the present analysis, adverse post-PCI cardiovascular outcomes, including MACEs, MI, all-cause mortality, and repeated revascularization, were significantly more likely in the long-

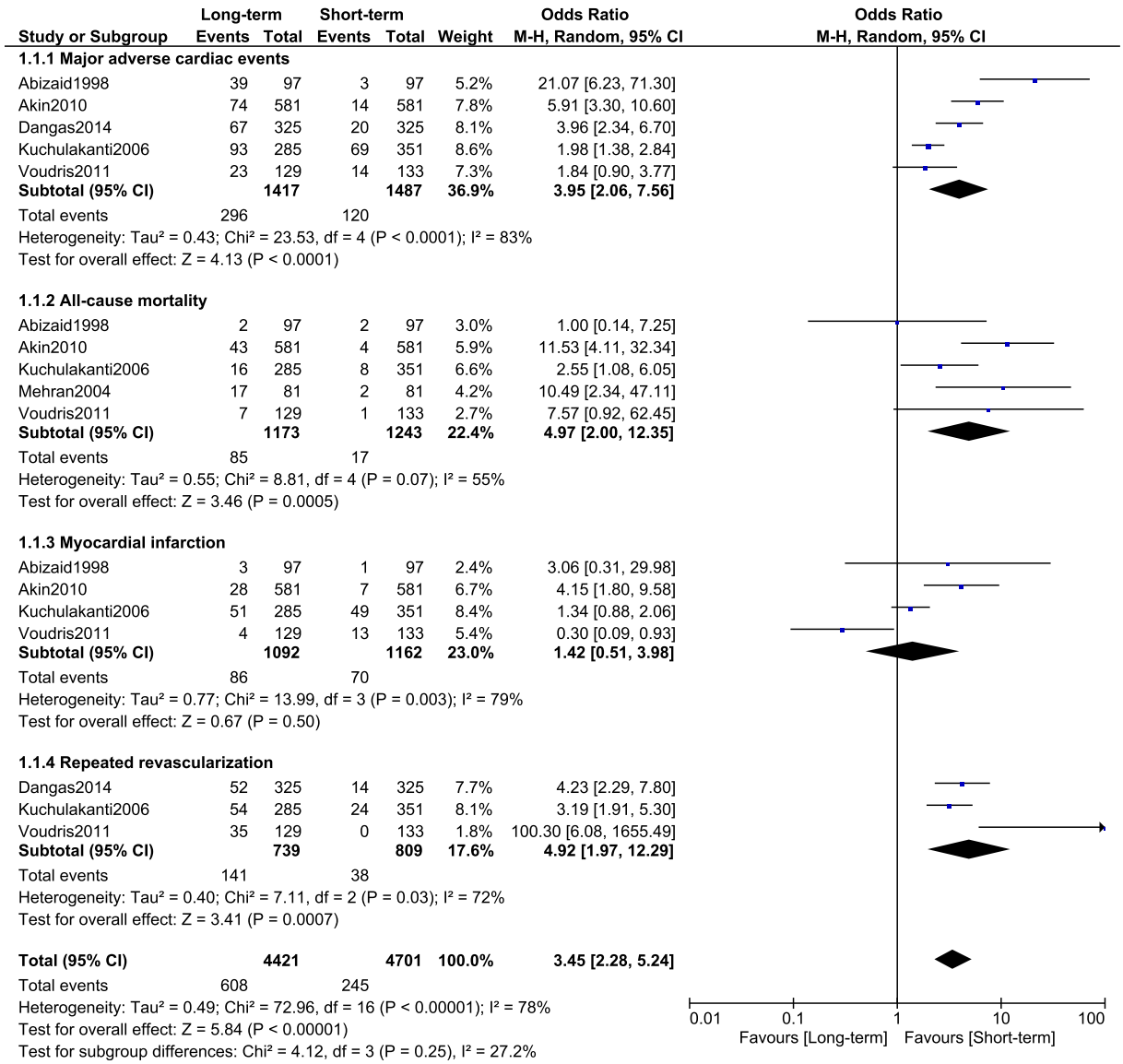

Fig. 3 Adverse post-PCI cardiovascular outcomes that were observed during the short-term and long-term follow-up periods in patients with ITDM (random-effects statistical model)

term follow-up subgroup, favoring the short-term follow-up subgroup. Long-term adverse cardiovascular outcomes were significantly more likely than short-term adverse cardiovascular outcomes in patients with ITDM.

The Comparison of Bioactive Stent to the Everolimus-Eluting Stent in Acute Coronary Syndrome (BASE ACS) trial, which was published online on 27 May 2016, showed that long-term outcomes were significantly more likely in patients with T2DM, supporting the results of this meta-analysis [17]. MACEs and all-cause mortality were all significantly more likely during the long-term follow-up period. However, it should be noted that the outcomes were compared between patients with and without T2DM, and ITDM as well as non-insulin-treated T2DM patients were assessed together in the T2DM group.

Even in the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease

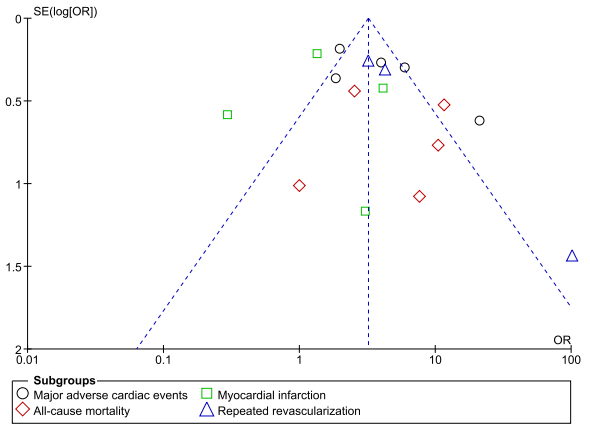

Fig. 4 Funnel plot that was used to visually assess the publication bias

(FREEDOM) trial, a significantly higher rate of adverse post-intervention cardiovascular outcomes was observed in patients with ITDM during a 5-year follow-up period, again supporting the results of this meta-analysis [10]. However, as we previously mentioned, studies have seldom compared short-term to long-term cardiovascular outcomes in similar subgroups of patients.

Recently, Chen et al. conducted a meta-analysis which showed that the rate of early stent thrombosis was significantly higher in patients with ITDM, whereas the rates of late and very late stent thrombosis were not significantly different between ITDM patients and those with non-insulin-treated T2DM [18]. Even though that well-supported and well-written meta-analysis showed that the rate of early stent thrombosis was significantly higher in patients with ITDM, the authors did not compare the rates of short-term and long-term stent thrombosis in those patients. It should be noted that, even though our meta-analysis compared long-term to short-term outcomes following PCI, data were limited, so we could not compare rates of stent thrombosis.

LIMITATIONS

This analysis had certain limitations. First of all, the total number of participants was only 1568, which is smaller than in other meta-analyses, although it was sufficient to be able to draw a reliable conclusion. Secondly, the long-term follow-up period was not the same in all the studies, which may have had a minor effect on the results. Another limitation was the fact that important cardiovascular outcomes such as stent thrombosis were not assessed, as these outcomes were only reported in a minority of studies. Furthermore, the types of CAD, the total number of vessels that were obstructed, and the use of antiplatelet agents might also have influenced the main outcomes, and thus represent other limitations of this analysis. Finally, this analysis did not involve new-generation DESs. Studies involving ITDM patients with new-generation DESs in which both short-term and long-term cardiovascular outcomes are reported are still lacking, and might only be available in the future.

CONCLUSIONS

Adverse cardiovascular outcomes post percutaneous coronary intervention were significantly more likely to be observed during the long-term follow-up period than during the short-term follow-up period in these patients with ITDM. This hypothesis requires confirmation via new comparative trials that consider both short-term and long-term follow-up periods.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or the publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. Dr. Hongtao Lu, Dr. Bing Tang, Dr. Yanhua Zhou, Dr. Chenhong Xu, Dr. Pravesh Kumar Bundhun, Dr. Zhangui

Tang, and Dr. Hong Bao were responsible for the conception and design of this meta-analysis, the acquisition of data, and the analysis and interpretation of that data, for drafting the initial manuscript, and for revising it critically for important intellectual content. Dr. Hongtao Lu, Dr. Bing Tang, and Dr. Yanhua Zhou wrote the final draft of the manuscript and are the co-first authors. All the authors approved the final manuscript.

Disclosures. The authors Dr. Hongtao Lu, Dr. Bing Tang, Dr. Yanhua Zhou, Dr. Chenhong Xu, Dr. Pravesh Kumar Bundhun, Dr. Zhangui Tang, and Dr. Hong Bao have nothing to disclose.

Compliance with Ethics Guidelines. This meta-analysis is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. Consequently, ethical approval was not required for this simple meta-analysis. Data were extracted from previously published original studies, and references for each of these studies are provided in the "Search Outcomes" subsection of the "Results" section, as well as in the tables. All data are directly available in the original referenced studies [8–13].

Data Availability. All data generated or analyzed during this study were extracted from previously published original studies and have been included in the present article (tables and figures).

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