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AIMS AND SCOPE

The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJC mainly publishes articles reporting research results and findings obtained in the field of cardiology and covering a wide range of topics including acute coronary syndromes, aneurysm, angina, arrhythmias, atherosclerosis, atrial fibrillation, cardiomyopathy, congenital heart disease, coronary artery disease, heart failure, hypertension, imaging, infection, myocardial infarction, pathology, peripheral vessels, public health, Raynaud's syndrome, stroke, thrombosis, and valvular disease.

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SYSTEMATIC REVIEWS

Long-term outcomes of titanium-nitride-oxide coated stents and drug-eluting stents in acute coronary syndrome: A systematic review and meta-analysis

Muhammad Ahmed Ali Fahim, Afia Salman, Hira Anas Khan, Syed Muhammad Hasan, Muskan Fatima Bhojani, Sarah Aslam, Amna Zia Ul Haq, Vishal Reddy Bejugam, Beena Muntaha Nasir, Wajiha Gul, Abdul Moeed, Abdelrahman S Abdalla, Muhammad Majid, Muhammad Sohaib Asghar, Md Al Hasibuzzaman

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Abstract

BACKGROUND

In severe cases of coronary artery disease, percutaneous coronary intervention provide promising results. The stent used could be a drug-eluting stent (DES) or a titanium-nitride-oxide coated stent (TiNOS).

AIM

To compare the 5-year effectiveness and safety of the two stent types.

METHODS

The following systematic review and meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analysis

guidelines, and PubMed/MEDLINE, Scopus, and Cochrane Central were searched from inception till August 2023. Primary outcomes were major adverse cardiac events (MACE), cardiac death, myocardial infarction (MI), cardiac death or MI, and ischemia-driven total lesion revascularization (ID-TLR).

RESULTS

Four randomized controlled trials (RCT), which analyzed a sum total of 3045 patients with acute coronary syndrome (ACS) after a median follow-up time of 5 years were included. Though statistically insignificant, an increase in the ID-TLR was observed in patients receiving TiNOSs *vs* DESs. In addition, MI, cardiac death and MI, and definite stent thrombosis (DST) were significantly decreased in the TiNOS arm. Baseline analysis revealed no significant results with meta-regression presenting non-ST elevated MI (NSTEMI) as a statistically significant covariate in the outcome of MACE.

CONCLUSION

TiNOS was found to be superior to DES in terms of MI, cardiac death or MI, and DST outcomes, however, the effect of the two stent types on ID-TLR and MACE was not significant. A greater number of studies are required to establish an accurate comparison of patient outcomes in TiNOS and DES.

Key Words: Stents; Drug-eluting; Major adverse cardiac events; All-cause death; Meta-analysis

Core Tip: Acute coronary syndrome (ACS) is characterized by reduced blood flow to the myocardium. While percutaneous coronary intervention with drug-eluting stents (DES) remains the standard management of ACS patients, titanium-nitride-oxide-coated stents (TiNOS) are a relatively newer intervention with relatively lower host immune reactions. In order to facilitate clinical practice guidelines in ACS patients requiring stent placement, it is imperative to compare and assess the safety and efficacy of DES and TiNOS. Therefore, this meta-analysis compared the two interventions in terms of major adverse cardiac events, cardiac death, myocardial infarction, and ischemia-driven total lesion revascularization outcomes.

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INTRODUCTION

Coronary artery disease (CAD) can be defined as a medical condition where the heart's blood vessels become obstructed, resulting in ischemia and subsequent hypoxia to the cardiac tissue[1]. It is categorized into two groups: acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) with the former differing from the latter mainly in the onset of symptoms[2].

ACS can manifest in a number of ways, namely ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and unstable angina with subsequent arrhythmias. Clinically, a presentation with chest pain localized to the sternum, often described as a sensation of crushing or pressure can be seen. This discomfort may also radiate to the jaw and/or left arm[3].

Percutaneous coronary interventions (PCI) with drug-eluting stents (DES) have been established as the recommended treatment for ACS owing to their superior efficacy compared to bare metal stents (BMS). The introduction of immunosuppressant and anti-proliferative drugs such as sirolimus, everolimus, paclitaxel, and zotarolimus confers the benefit of lower rates of early cellular proliferation, inflammation, and therefore restenosis[4,5]. However, the comparatively newer titanium-nitride-oxide coated stents (TiNOS) have proven to be at par. The titanium-nitride coating affords the benefit of inducing lower levels of host immune reactions compared to other BMS such as non-coated stainless steel, better early vascular healing, lower rates of malapposition, and better stent coverage[6,7]. Additionally, TiNOS have been reported to require a lower duration of post-procedure anticoagulant therapy, owing to their anti-thrombotic nature[8].

In recent years, there have been several randomized controlled trials (RCT) comparing the clinical outcomes of TiNOSs and DESs in patients with ACS with the latest report being on the 5-year follow-up of patients in the TIDE-ACS trial a study that bears a considerable sample size. This study, and the most recent meta-analysis by Daoud *et al*[9] concluded that TiNOSs are a non-inferior and safe alternative to DES in ACS patients[9,10]. However, there is no meta-analysis to date, which has assessed the long-term efficacy and safety of TiNOSs and DESs with a sufficient sample size. Therefore, we aimed to compare the 5-year effectiveness and safety of the two stent types, using the latest data from the RCTs evaluating outcomes 5 years post-procedure.

MATERIALS AND METHODS

Data sources and search strategy

The following systematic review and meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines with a PRISMA checklist[11]. The research questionnaire was formulated utilizing the patient, intervention, control, and outcome (PICO) framework[12] and a search strategy based on the aforementioned questionnaire comprising of the Boolean operators "AND" and "OR" along with various MeSH terms was run on three separate databases: PubMed/MEDLINE, Scopus, and Cochrane Central. These databases were then systematically searched from inception till August 2023, without any restrictions or filters on the basis of language, year of publication, author names, country, institution of publication, or any other aspect applied, and all relevant RCTs and observational studies were selected. The terms utilized in the search strategy included 'bioactive', 'Titanium', 'nitride', 'oxide', 'TiNO', 'TNO', 'BAS', 'stent', 'DES', 'drug' and 'eluting stent'. As this study sees publicly available data, study registry and institutional review board approval were not required. A more detailed overview of the search strategy used is given in Supplementary Table 1. Additionally, to identify grey literature ClinicalTrials.gov, Medrxiv.org, and Google Scholar were searched. This systematic review and meta-analysis is registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42024534358).

Study selection

Following the comprehensive literature search, all articles retrieved were exported to the EndNote Reference library (Version X7.5; Clarivate Analytics, Philadelphia, PA, United Sates), where duplicates were identified and removed accordingly. Two independent authors (Muhammad Ahmed Ali Fahim and Afia Salman) initially screened the remaining articles on the basis of Title and Abstract, after which full texts were evaluated to confirm relevance. Any disagreements between the two authors were resolved after discussion with a third author (Hira Anas Khan).

Studies complying with the following inclusion criteria were included in our analysis: Presented their findings in english literature; patients above 18 years of age; patients with CAD who received coronary PCI; comparative studies involving implantation of either a TiNOS or DES; outcomes reported at a 5-year follow-up; provided the outcomes as risk ratios (RR), odd ratios or raw data that could be utilized to calculate them; studies reporting one or more of our primary and or secondary outcomes. Our exclusion criteria included conference abstracts, letters, case reports, and studies containing inadequate original data for further analysis.

Study outcomes

We defined our primary outcomes of interest as major adverse cardiac event [MACE, which we defined as a composite of cardiac death, myocardial infarction (MI) or ischemia-driven total lesion revascularization (ID-TLR)], cardiac death, MI, cardiac death or MI and ID-TLR. Our secondary outcomes of interest were defined as all-cause death and definite stent thrombosis (DST).

Statistical analysis

For this study, the program RevMan (version 5.4.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020) was used for all meta-analyses and subgroup analysis with the study population being divided into ACS or ACS and CCS subgroups. While Comprehensive Meta Analyst (version 3.7) was used for all meta-regression analyses. A random-effects model was used, for both, and RR along with their 95% Confidence Intervals (CI) were pooled. A P value of > 0.05 was considered statistically significant for all outcomes. Furthermore, heterogeneity was assessed with the Higgins I^2 test. A value of I^2 = 25%-50% was considered mild, 50%-75% moderate, and > 75% significant heterogeneity. Meta-regression results were reported as coefficients (Coeff) and P values.

Data extraction

The study, baseline patient, procedural, and angiographic characteristics were extracted onto an Excel Sheet and verified by two independent authors (Muhammad Ahmed Ali Fahim and Afia Salman). Any disagreements were resolved after consultation with a third author (Hira Anas Khan). Extracted data included, study name, year of publication, study design, study location, sample size, type of DES, study outcomes number of patients in each group, follow-up period, general patient characteristics (age and sex), comorbidities (diabetes mellitus, hypertension), risk factors (smoking, family history) prior cardiac events/procedures [MI, PCI, coronary artery bypass graft (CABG)], cause of PCI (NSTEMI, STEMI, unstable angina), reference vessel diameter, lesion length, total stents per lesion, direct stenting, stents per (culprit) Lesion, stent diameter, primary and secondary endpoints. For certain studies particular baseline and study characteristics were not accessible in the documents pertaining to the 5-year outcomes. As a result, the publication of the same trial for 1-year outcomes was utilized to comprehensively extract these characteristics for further analysis and regression[13-15].

Quality assessment

The Revised Cochrane risk-of-bias tool for randomized trials (ROB 2)[16] tool was used by two independent authors (Muhammad Ahmed Ali Fahim and Afia Salman) to assess the quality of each RCT reported in this meta-analysis. The studies were analyzed according to their randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. All inconsistencies were resolved with discussion and agreement. Additionally, the quality of evidence of each outcome was assessed utilizing GRADEpro[17].

RESULTS

After retrieval of a total of 320 studies from the aforementioned resources, 4 studies[10,18-20], all being RCTs, were narrowed down and included in the meta-analysis. A more detailed explanation of the process is represented in the PRISMA flow chart as shown in Figure 1. The following outcomes of MACE, ID-TLR, cardiac death, MI, cardiac death or MI, DST, and all-cause death were extracted, pooled and analyzed for a sum total of 3045 patients with ACS after a median follow-up time of 5 years. The studies that presented patient data as pooled ACS and CCS were sub-grouped accordingly. Tables 1 and 2 identify the study characteristics and baseline patient, procedural, and angiographic characteristics of the included studies respectively.

Risk of bias assessment

The risks of bias of the included RCTs are demonstrated in Supplementary Figure 1. The overall risk of bias across the RCTs is 75%. Two studies had a high risk of bias for deviation from the intended interventions (TIDE, TITAX-AMI). Additionally, one study represented a high risk of bias for the measurement of the outcomes (BASE-ACS). Furthermore, potential bias existed in one study for the measurement of outcomes (TIDES-ACS). The individual risk of bias summary for each RCT is given in Supplementary Figure 2.

Baseline analysis

An analysis was performed on the following compiled categorical and continuous baseline patient, procedural and angiographic characteristics of age, gender, diabetes mellitus, hypertension, smoking, family history for ischemic heart disease (IHD) or CAD, prior MI, prior PCI, prior CABG, reference vessel diameter, lesion length, stent per (culprit) lesion, stent diameter, total stent length per lesion, direct stenting, and NSTEMI the results of which are given in Supplementary Tables 2 and 3. Analysis results for all revealed a P value of greater than 0.05 indicating no significant differences in characteristics between the 2 arms patients were randomized in.

Primary outcomes

ID-TLR was an outcome of interest across all 4 studies. Upon pooling the results, a slightly increased occurrence of ID-TLR was observed in patients receiving TiNOSs as compared to those receiving DES. However, this disparity did not achieve statistical significance. (RR = 1.06, 95%CI = 0.84-1.35; P = 0.62; I^2 = 0%). Pooling data from three studies that evaluated the incidence of MI underscored a significant risk reduction associated with TiNOSs between the 2 groups (RR = 0.59, 95%CI = 0.43-0.80; P = 0.0008; I^2 = 0%). Additionally, all four studies assessed cardiac death and analysis demonstrated a lower incidence of the outcome in the TiNOS group when compared to the DES group; however, this divergence did not attain statistical significance (RR = 0.54, 95%CI = 0.28-1.03; P = 0.06; I^2 = 44%). The composite endpoint of cardiac death or MI was reported by all 4 studies and a statistically significant reduction in risk was apparent in patients treated with TiNOSs as opposed to those with DESs (RR = 0.59, 95%CI = 0.47-0.75; P < 0.0001; I^2 = 0%). In terms of MACE, a collective analysis of all studies exhibited a decrease in TiNOS in patients randomized between the two groups but no statistically significant divergence (RR = 0.86, 95%CI = 0.70-1.06; P = 0.17; I^2 = 29%). Forest plots for primary outcomes are represented in Figure 2.

Secondary outcomes

DST was evaluated across three out of four studies, revealing a statistically significant decrease in TiNOSs over DESs (RR = 0.31, 95%CI = 0.17-0.58; P = 0.0002; I^2 = 8%). Lastly, the analysis of all-cause death, inclusive of all studies, demonstrated a statistically non-significant decrease in TiNOS patients as compared to DES patients (RR = 0.90, 95%CI = 0.68-1.19; P = 0.45; I^2 = 4%). Forest plots for secondary outcomes are represented in Figure 3.

Subgroup analysis

Studies were sub-grouped according to the representation of patients as ACS or ACS and CCS wherever possible. The outcome of ID-TLR had no heterogeneity overall and this trend continued when studies were sub-grouped. Similar to the overall effect both subgroups presented with the result of a non-significant increase in ID-TLR in TiNOS patients when compared with DES patients. [RR = 1.02, 95%CI = 0.79-1.33, I^2 = 0% P = 0.85; RR = 1.25, 95%CI = 0.71-2.18, I^2 = not available (NA), P = 0.44]. Furthermore, no subgroup differences were found (I^2 = 0%). Similarly, for MI no heterogeneity was present overall or when studies sub-grouped, with both subgroups showing a decrease in MI in the TiNOS patients arm. However, this decrease was significant in the ACS subgroup while insignificant in the ACS and CCS one. (RR = 0.57, 95%CI = 0.41-0.80, I^2 = 0%, P = 0.0010; RR = 0.72, 95%CI = 0.30-1.73, I^2 = NA, P = 0.46). Additionally, no differences between both were shown (I^2 = 0%). When assessing cardiac death mild heterogeneity was shown overall and when studies sub-grouped with the ACS subgroup it showed a slight decrease. The results of both subgroups differed greatly with the ACS subgroup showing a significant decrease in cardiac death while the ACS and CCS subgroup showed a non-significant increase in the aforementioned outcome when TiNOSs were compared with DESs. (RR = 0.46, 95%CI = 0.23-0.90, I^2 = 42%, P = 0.02; RR = 1.23, 95%CI = 0.34-4.50, I^2 = NA, P = 0.75). Subgroup differences having mild heterogeneity were seen (I^2 = 43.9%). No heterogeneity was seen overall or in subgroups for the composite outcome of cardiac death or MI. Both subgroups showed a decrease in the outcome for the TiNOS arm however this decrease was significant in the ACS subgroup and insignificant in the ACS and CCS one. (RR = 0.57, 95%CI = 0.44-0.73, I^2 = 0%, P < 0.0001; RR = 0.85, 95%CI = 0.40-1.77, I^2 = NA, P = 0.66). Slight subgroup differences were shown (I^2 = 1.1%). MACE showed moderate heterogeneity overall but when subgroup analysis was performed and the TIDE study was isolated from the ACS studies the heterogeneity of the ACS subgroup decreased greatly. The results of both subgroups differed with the ACS subgroup

Table 1 Study characteristics

Study name	Year of publication	Study design	Study location	Sample size	Intervention	Control	Study outcomes	Follow-up duration
TIDE	2011	RCT	Switzerland	302	TiNO-coated stent	Zotarolimus-eluting stent	In-stent late lumen loss; MACE; death; cardiac death; MI; clinically-indicated TLR; clinically-indicated TVR; repeat vascular-ization; cardiac death or MI; stroke; cardiac death, MI, or clinically indicated TLR	5 years
BASE ACS	2016	RCT	Finland	827	TiNO-coated stent	Everolimus-eluting stent	MACE; cardiac death; non-cardiac death; total death; non-fatal MI; cardiac death or MI; ischemia-driven TLR; DST	5 years (median)
TITAX AMI	2013	RCT	Finland	425	TiNO-coated stent	Paclitaxel-eluting stent	MACE; cardiac death; recurrent MI; cardiac death or recurrent MI; ischemia-driven TLR; DST; all-cause death	5 years
TIDES ACS	2023	RCT	Five European countries	1491	TiNO-coated stent	Everolimus-eluting stent	Cardiac death; MI; ischemia-driven TLR; major bleeding; cardiac death or MI; stent thrombosis; non-cardiac death; all-cause death	5 years

RCT: Randomized controlled trial; TiNO: Titanium-nitride-oxide; MACE: Major adverse cardiovascular event; MI: Myocardial infarction; TLR: Target lesion revascularization; TVR: Target vessel revascularization; DST: Definite stent thrombosis.

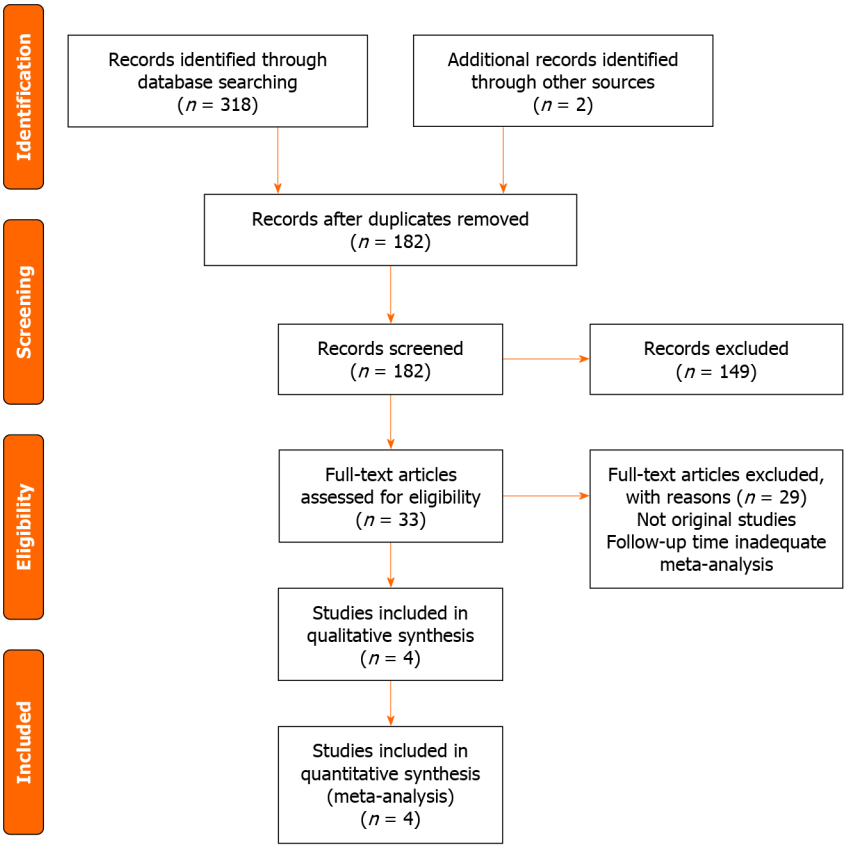


Figure 1 Preferred reporting items for systematic review and meta-analyses flowchart.

showing a significant decrease in MACE while the ACS and CCS subgroup showed a nonsignificant increase in the outcome in patients treated with TiNOSs as compared to DESs. (RR = 0.81, 95%CI = 0.67-0.99, I^2 = 10%, P = 0.04; RR = 1.16, 95%CI = 0.74-1.82, I^2 = NA, P = 0.51). Subgroup differences having moderate heterogeneity were seen (I^2 = 50.3%). The outcome of All-Cause Death revealed slight heterogeneity overall and none in the ACS subgroup. The results of both subgroups were insignificant but differed in the sense that the ACS subgroup showed a decrease in all-cause death while the ACS and CCS subgroups showed an increase in the outcome for the TiNOS arm. (RR = 0.84, 95%CI = 0.63-1.12, I^2 = 0%, P = 0.23; RR = 1.60, 95%CI = 0.68-3.76, I^2 = NA, P = 0.28). Subgroup differences having mild heterogeneity were seen (I^2 = 49.7%).

Table 2 Baseline patient, procedural, and angiographic characteristics, *n* (%)

		TIDE (2011)	BASE ACS (2016)	TITAX AMI (2013)	TIDES ACS (2023)
Sample size *n* (TiNOS/DES)		302 (152/150)	827 (417/410)	425 (214/211)	1491 (989/502)
Age (yr), mean ± SD	TiNOS	65.9 ± 9.0	62.9 ± 12.0	64 ± 11	62.7 ± 10.9
	DES	63.4 ± 10.5	63.0 ± 11.8	64 ± 11	62.6 ± 10.5
Male sex, *n*	TiNOS	124	317	162	745
	DES	118	312	157	383
Female sex, *n*	TiNOS	28	100	52	244
	DES	32	98	54	119
Diabetes mellitus	TiNOS	30 (19.7)	65 (15.6)	48 (22)	140 (14.2)
	DES	28 (18.7)	75 (18.3)	33 (16)	63 (12.5)
Hypertension	TiNOS	105 (69.1)	201 (48.2)	122 (57)	463 (46.8)
	DES	113 (75.3)	212 (51.7)	106 (50)	219 (43.6)
Current smoking/smoking	TiNOS	53 (34.9)	144 (34.5)	113 (53)	309 (31.2)
	DES	43 (28.7)	134 (32.7)	97 (46)	180 (35.9)
Family history of IHD/CAD	TiNOS	45 (29.6)	192 (46.0)	103 (48)	503 (50.9)
	DES	47 (31.3)	185 (45.1)	95 (45)	247 (49.2)
Prior MI	TiNOS	42 (27.6)	56 (13.4)	33 (15)	75 (7.6)
	DES	32 (21.3)	40 (9.8)	20 (9)	45 (9.0)
Prior PCI	TiNOS	39 (25.7)	40 (9.6)	22 (10)	69 (7.0)
	DES	38 (25.3)	43 (10.5)	10 (5)	33 (6.6)
Prior CABG	TiNOS	12 (7.9)	20 (4.8)	16 (7)	6 (6.0)
	DES	4 (2.7)	17 (4.1)	13 (6)	6 (1.2)
STEMI	TiNOS	0 (0)	162 (38.8)	83 (39)	444 (44.9)
	DES	0 (0)	159 (38.8)	97 (46)	239 (47.6)
Unstable angina	TiNOS	14 (9.2)	49 (11.8)	0 (0)	126 (12.7)
	DES	16 (10.7)	64 (15.6)	0 (0)	61 (12.2)
NSTEMI	TiNOS	50 (32.9)	206 (49.4)	131 (61)	458 (46.3)
	DES	63 (42.0)	187 (45.6)	114 (54)	226 (45.0)
Reference vessel diameter (mm), mean ± SD	TiNOS	2.88 ± 0.47	3.13 ± 0.43	3.16 ± 0.45	3.20 ± 0.45
	DES	2.90 ± 0.53	3.14 ± 0.43	3.11 ± 0.50	3.21 ± 0.45
Lesion length (mm), mean ± SD	TiNOS	13.1 ± 8.1	14.4 ± 5.4	13.6 ± 5.6	14.9 ± 6.5
	DES	14.2 ± 8.9	14.3 ± 6.5	13.2 ± 6.4	14.8 ± 5.9
Direct stenting	TiNOS	76 (33.2)	134 (32.1)	26 (12)	225 (22.8)
	DES	66 (29.7)	126 (30.7)	32 (15)	145 (28.9)
Total stent length per lesion (mm), mean ± SD	TiNOS	19.3 ± 11.1	20.8 ± 9.4	18.5 ± 6.4	20.5 ± 7.8
	DES	19.6 ± 10.0	20.6 ± 8.2	19.2 ± 7.2	20.6 ± 7.2
Stents per (culprit) lesion, mean ± SD	TiNOS	1.28 ± 0.55	1.15 ± 0.38	1.1 ± 0.3	1.13 ± 0.38
	DES	1.17 ± 0.45	1.14 ± 0.36	1.1 ± 0.4	1.14 ± 0.37
Stent diameter (mm), mean ± SD	TiNOS	3.02 ± 0.46	3.15 ± 0.44	3.16 ± 0.42	3.22 ± 1.14
	DES	3.01 ± 0.50	3.15 ± 0.45	3.11 ± 0.45	3.19 ± 0.43

n: Number of participants; TiNOS: Titanium-nitride-oxide-coated stent; DES: Drug-eluting stent; IHD: Ischemic heart disease; CAD: Coronary artery

disease; MACE: Major adverse cardiovascular event; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction.

Meta-regression

We assessed age, male gender, female gender, diabetes mellitus, hypertension, smoking, family history for IHD or CAD, prior MI, prior PCI, prior CABG, NSTEMI, reference vessel diameter, lesion length, direct stenting, total stent length per lesion, stent per (culprit) lesion, and stent diameter as covariates having an impact on specific outcomes. The outcomes assessed in the meta-regression included MACE, ID-TLR, cardiac death, cardiac death or MI, and all-cause death the results for which are represented in Supplementary Tables 4-8. All covariates for all outcomes revealed an insignificant 2-sided *P* value except for the covariate of NSTEMI% which had a significant result when assessed for the outcome of MACE (Coeff: -0.0369, $P = 0.0416$). Scatter plots are presented in the Supplementary Figures 3-87.

Quality assessment of evidence

The quality of evidence was graded 'High' or 'Moderate' after assessment using GRADEpro with the results of ID TLR, Cardiac Death, All Cause Death and MACEs being rated as 'Moderate' quality after downgrading evidence in the field of 'Imprecision' due to individual studies having wide CIs and results being opposite. The remaining outcomes of MI, cardiac death or MI and DST being graded as 'High'. A detailed explanation of each outcome is offered in Supplementary Table 9.

DISCUSSION

The findings of our meta-analysis and systematic review grossly favor TiNOSs over DESs. ID-TLR, the primary outcome being assessed, was found to be numerically higher with TiNOSs, whereas all other outcomes, namely cardiac death, MI, DST, MACE, and all-cause death were significantly lower in PCI with TiNOSs when compared to the occurrence of the same outcomes with DES. Meta-regression was performed for multiple variables such as age (years), male gender, female gender, diabetes mellitus, hypertension, smoking, family history for IHD or CAD, prior MI, prior PCI, prior CABG, reference vessel diameter (mm), lesion length (mm), NSTEMI, stent diameter (mm), total stent per lesion (mm) and stent per (culprit) lesion. However, none were found to be significant contributors to any outcomes being measured in our analysis except for NSTEMI for the outcome of MACE. Furthermore, a baseline analysis found no significant difference between the characteristics of the 2 arms proving that all statistically significant outcomes in our study were not due to any baseline angiographic or procedural discrepancies between the TiNOS or DES groups.

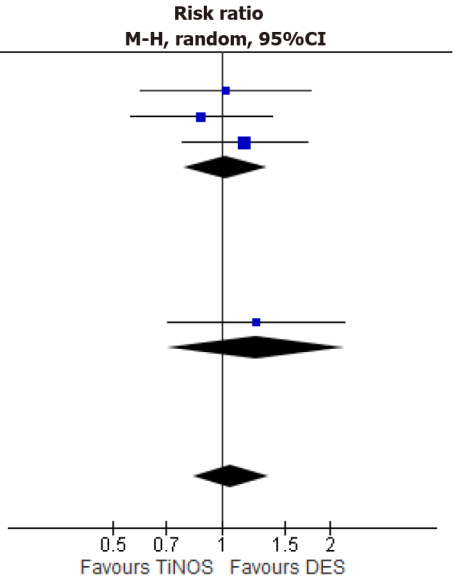
ID-TLR was found to be higher with TiNOSs (RR = 1.06, 95%CI = 0.84-1.35; $P = 0.62$; $I^2 = 0\%$), although statistically insignificant, as compared to DESs which is in coherence with the findings of a previous meta-analysis by Daoud *et al*[9], as well as a comparative study by Limacher *et al*[21]. Although there is insufficient literature highlighting the exact cause of this occurrence, possible reasons for this could be the increased incidence of diabetes mellitus and peripheral arterial disease in patients undergoing PCI with TiNOSs in the TIDE ACS trial, a major contributor to our pooled data. Both factors have been identified as independent predictors of ID-TLR for between 2 and 4 years after PCI by a study conducted by Kurihara *et al*[22]. However, the validity of this hypothesis may be challenged as the mentioned study shows outcomes after treatment with DESs rather than TiNOSs. When assessed through meta-regression diabetes mellitus showed no significant association with this outcome. Early studies, such as one conducted by Varho *et al*[23] suggest that TiNOSs may cause greater early neointimal hyperplasia [Median (interquartile range) neointimal hyperplasia of 203 (106) μm *vs* 42.2 (41) μm] but similar coronary flow reserve, and fractional flow rate (FFR) compared to DES. As FFR has emerged as a valuable predictor of ID-TLR[24], this accentuates the statistical insignificance of increased ID-TLR with the TiNOS arm of this study.

TiNOSs showed statistically significant lower rates of DST *vs* DESs (RR = 0.31, 95%CI = 0.17-0.58; $P = 0.0002$; $I^2 = 8\%$). These findings are consistent with those of Daoud *et al*[9]. According to a study, TiNOSs afford better endothelization than other BMS due to their biocompatibility which results in a less aggressive host response against the inserted stent, lower resultant inflammation, and hence, less likely thrombosis. Additionally, they have exhibited lower fibrinogen and platelet deposition, key modulators in the process[5,6]. Other important contributors to stent thrombosis are stent malapposition and insufficient stent coverage as they create a prothrombotic state due to low endothelial shear stress which causes the production of various chemical factors and according to a cohort study by Sia *et al*[7], Varho *et al*[23] and an RCT by Karjalainen *et al*[25], the incidence of malapposed and uncovered stents is lower with TiNOSs. The clinicians may reconsider their choice of stent types based on the different stent thrombosis outcomes. This also calls for further studies that investigate the optimal patient selection criteria based on the coagulation profile and the medical comorbidities.

These arguments can also be extended to explain the lower rates of MACE (RR = 0.86, 95%CI = 0.70-1.06; $P = 0.17$; $I^2 = 29\%$), cardiac death (RR = 0.54, 95%CI = 0.28-1.03; $P = 0.06$; $I^2 = 44\%$), MI (RR = 0.59, 95%CI = 0.43-0.80; $P = 0.0008$; $I^2 = 0\%$), the composite endpoint of cardiac death or MI (RR = 0.59, 95%CI = 0.47-0.75; $P < 0.0001$; $I^2 = 0\%$), along with the fact that while Varho *et al*[23] reports the opposite, as mentioned earlier, TiNOSs have the advantage of lower neointimal hyperplasia and resultant restenosis as reported by a more recent study conducted on rabbit iliac artery specimens[26]. The overall impact is satisfactory perfusion and therefore, lower probability of cardiac death. However, this is contradicted by Pilgrim *et al*[15] who showed an increased incidence of in-stent late loss, defined as loss in diameter in the

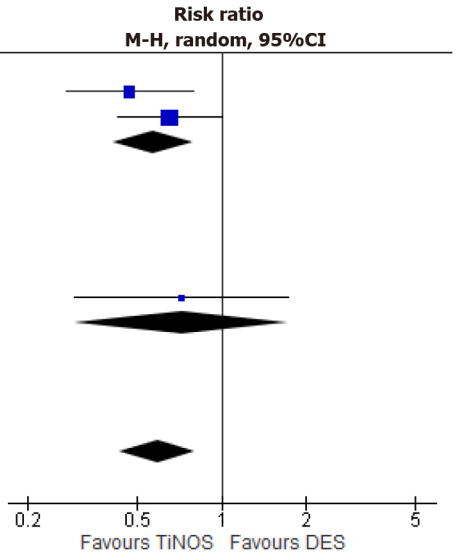
A

Study or subgroup	TiNOS Events	TiNOS Total	DES Events	DES Total	Weight	Risk ratio M-H, random, 95%CI	Year
1.1.1 ACS							
TITAX AMI	24	214	23	211	19.3%	1.03 [0.60, 1.76]	2013
BASE ACS	33	417	37	410	27.8%	0.88 [0.56, 1.37]	2016
TIDES ACS	73	989	32	502	34.8%	1.16 [0.78, 1.73]	2023
Subtotal (95% CI)		**1620**		**1123**	**82.0%**	**1.02 [0.79, 1.33]**	
Total events	130		92				
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 2 (P = 0.66); I² = 0%							
Test for overall effect: Z = 0.18 (P = 0.85)							
1.1.2 ACS & CCS							
TIDE	24	152	19	150	18.0%	1.25 [0.71, 2.18]	2011
Subtotal (95% CI)		**152**		**150**	**18.0%**	**1.25 [0.71, 2.18]**	
Total events	24		19				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.77 (P = 0.44)							
Total (95% CI)		**1772**		**1273**	**100.0%**	**1.06 [0.84, 1.35]**	
Total events	154		111				
Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 3 (P = 0.75); I² = 0%							
Test for overall effect: Z = 0.49 (P = 0.62)							
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%							



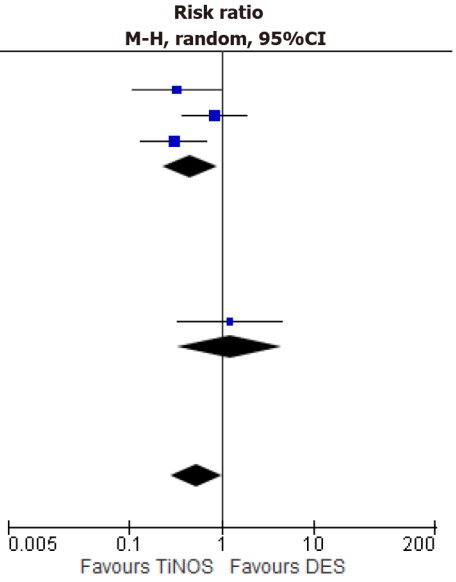
B

Study or subgroup	TiNOS Events	TiNOS Total	DES Events	DES Total	Weight	Risk ratio M-H, random, 95%CI	Year
6.1.1 ACS							
TITAX AMI	18	214	38	211	34.8%	0.47 [0.28, 0.79]	2013
TIDES ACS	45	989	35	502	52.8%	0.65 [0.43, 1.00]	2023
Subtotal (95% CI)		**1203**		**713**	**87.6%**	**0.57 [0.41, 0.80]**	
Total events	63		73				
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0%							
Test for overall effect: Z = 3.30 (P = 0.0010)							
6.1.2 ACS & CCS							
TIDE	8	152	11	150	12.4%	0.72 [0.30, 1.73]	2011
Subtotal (95% CI)		**152**		**150**	**12.4%**	**0.72 [0.30, 1.73]**	
Total events	8		11				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.74 (P = 0.46)							
Total (95% CI)		**1355**		**863**	**100.0%**	**0.59 [0.43, 0.80]**	
Total events	71		84				
Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 2 (P = 0.56); I² = 0%							
Test for overall effect: Z = 3.35 (P = 0.0008)							
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%							



C

Study or subgroup	TiNOS Events	TiNOS Total	DES Events	DES Total	Weight	Risk ratio M-H, random, 95%CI	Year
3.1.1 ACS							
TITAX AMI	4	214	12	211	21.4%	0.33 [0.11, 1.00]	2013
BASE ACS	11	417	13	410	31.1%	0.83 [0.38, 1.84]	2016
TIDES ACS	9	989	15	502	30.1%	0.30 [0.13, 0.69]	2023
Subtotal (95% CI)		**1620**		**1123**	**82.5%**	**0.46 [0.23, 0.90]**	
Total events	24		40				
Heterogeneity: Tau² = 0.15; Chi² = 3.47, df = 2 (P = 0.18); I² = 42%							
Test for overall effect: Z = 2.27 (P = 0.02)							
3.1.2 ACS & CCS							
TIDE	5	152	4	150	17.5%	1.23 [0.34, 4.50]	2011
Subtotal (95% CI)		**152**		**150**	**17.5%**	**1.23 [0.34, 4.50]**	
Total events	5		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.32 (P = 0.75)							
Total (95% CI)		**1772**		**1273**	**100.0%**	**0.54 [0.28, 1.03]**	
Total events	29		44				
Heterogeneity: Tau² = 0.19; Chi² = 5.34, df = 3 (P = 0.15); I² = 44%							
Test for overall effect: Z = 1.86 (P = 0.06)							
Test for subgroup differences: Chi² = 1.78, df = 1 (P = 0.18), I² = 43.9%							



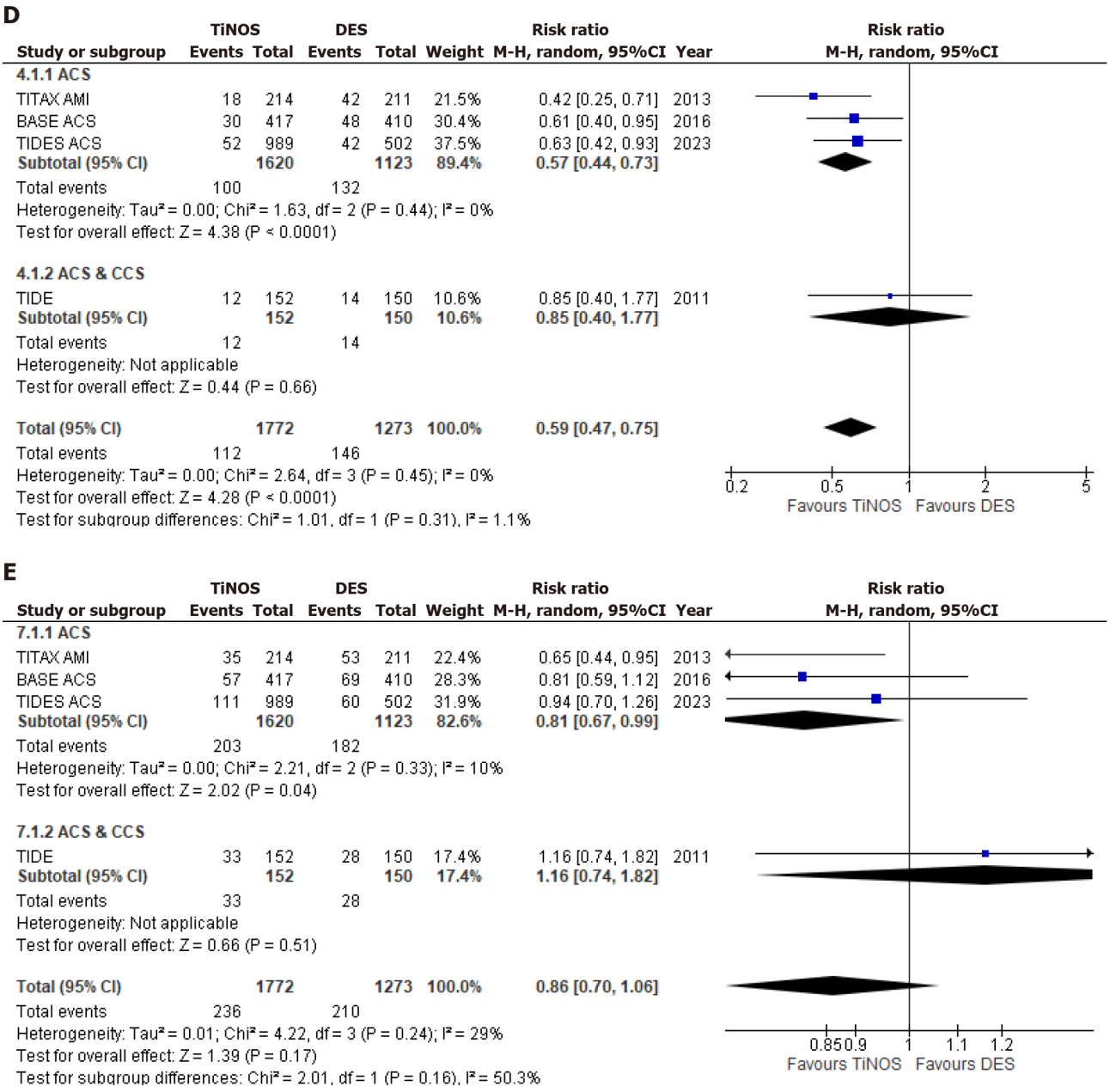


Figure 2 Forest plots for primary outcomes. A: Ischemia-driven target lesion revascularization forest plot; B: Myocardial infarction forest plot; C: Cardiac death forest plot; D: Cardiac death or myocardial infarction forest plot; E: Major adverse cardiovascular event forest plot. TiNOS: Titanium-nitride-oxide-coated stent; DES: Drug-eluting stent; M-H: Mantel-Haenszel; ACS: Acute coronary syndrome; CCS: Chronic coronary syndrome.

lumen following PCI and in segment binary restenosis with TiNOSs compared to DES. However, it is important to note that this study reports outcomes 1-year post-procedure without any further follow-up reports, which were not assessed in our study.

Upon subgroup analysis, the ACS subgroup displayed a statistically significant difference in favor of TiNOSs for MACE (RR = 0.81, 95%CI = 0.67-0.99; P = 0.04) and cardiac death (RR = 0.46, 95%CI = 0.23-0.90; P = 0.02). The significance in ACS-only studies with regard to this result can be explained by the greater likelihood of early stent thrombosis in ACS compared to CCS, as concluded by Yamamoto *et al*[27] which can eventually result in cardiac death as already discussed. In this setting, TiNOSs anticoagulant properties in a thrombotic environment which is found in ACS aid the prognosis in patients. However, our meta-regression reported no significant association of Cardiac death or MI with any of our analyzed covariates. The argument is supported further by Karjalainen *et al*[28], who report a significantly lower incidence of MI and MACE after the use of BMS.

As stated previously, pooling data from three studies underscored a significant risk reduction associated with TiNOSs in MI (RR = 0.59, 95%CI = 0.43-0.80; P = 0.0008; I^2 = 0%). The I^2 = 0% suggests that there was no significant variability among the pool of subjects of all three studies, hence, strengthening the reliability of the pool data analysis. Previous studies such as the one conducted by Bouisset *et al*[10] also display that there is a significant decrease in the risk of MI occurring after using TiNOSs as compared to DESs. Daoud *et al*[9], further support this by highlighting that there is a lower risk of recurrent non-fatal MI occurring when TiNOSs are used.

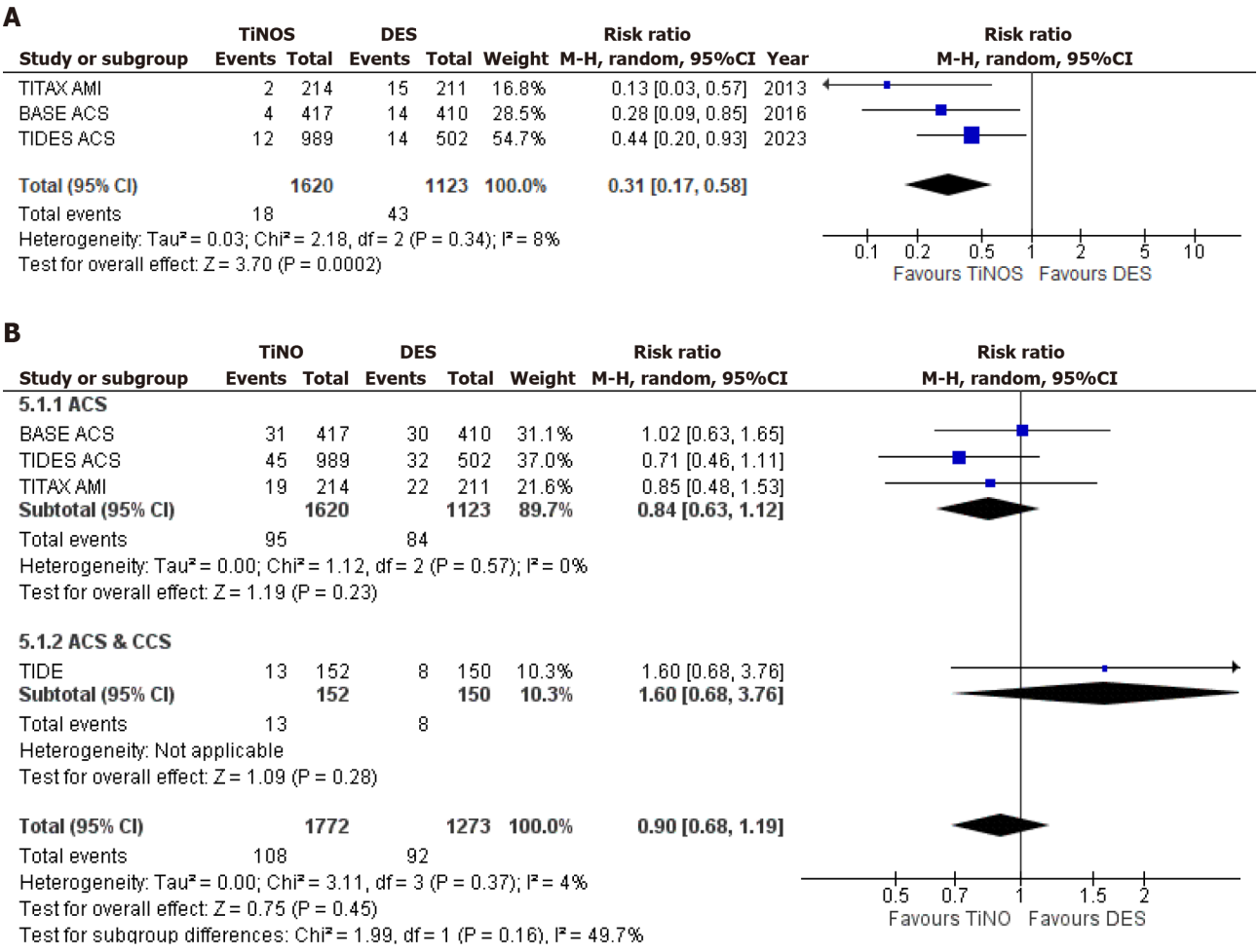


Figure 3 Forest plots for secondary outcomes. A: Definite stent thrombosis forest plot; B: All-cause death forest plot. TiNOS: Titanium-nitride-oxide-coated stent; DES: Drug-eluting stent; M-H: Mantel-Haenszel; ACS: Acute coronary syndrome; CCS: Chronic coronary syndrome.

The analysis of all-cause death suggests a broad measure of mortality. Our analysis of all-cause death, inclusive of all studies, demonstrated no statistically significant distinction between TiNOSs and DESs (RR = 0.90, 95%CI = 0.68-1.19; P = 0.45; I^2 = 4%). This infers that there is a possibility that the observed difference in mortality of the two stents could have occurred due to chance which leads it to being not significant with little variability among the studies. Upon subgroup analysis, as well as regression for the mentioned covariates, the non-significant trend persisted suggesting that the lack of statistical significance is not influenced by subgroup factors without any association between all-cause death and other factors. Similarly, as per the study conducted by Brener *et al*[29], there is no significant difference in cardiovascular *vs* non-cardiovascular mortality post-PCI regardless of the stent used.

While assessing NSTEMI as a covariate to possibly have an effect on the outcomes, we observed a statistically significant association with MACE. A multitude of previous research has presented an association of STEMI with MACE [30-33]. Ours as well as Fath-Ordoubadi *et al*[34] are among the few that have presented the contrary. This may possibly be due to the fact that long-term follow-up studies have smaller sample sizes and incomplete reporting of outcomes of interest[35].

It is important to note that this study may be limited in its extent to elucidate the comparison between TiNOSs and DESs accurately. Due to the limited number of studies, the data may not be representative. Furthermore, all pooled data has been derived from European countries without subgroup studies on participant ethnicities which limits its generalizability. Since the prognosis for ACS and subsequent PCI as a whole is multifactorial including race as a potential risk factor[36], this warrants a detailed study that focuses on the differences in outcomes in people of different races and ethnicities. The data used included patients with both ACS and CCS. However, subgroup studies were conducted to tackle this discrepancy. The trials included also displayed a difference in the type of DES used which could have impacted the results of each and hence, our analysis, even if only to a very limited extent. Another factor that limits the accuracy of our results is the bias due to the deviation from intended intervention specifically in the TIDE and TITAX-AMI studies. For example, in the TITAX-AMI trial, a greater percentage of patients were administered glycoprotein IIa/IIIb inhibitors in patients being treated with TiNOSs than DESs. Additionally, most trials are limited due to the lack of angiographic follow up which may have a possible contribution to the results favoring DESs with regard to ID-TLR or other outcomes favoring TiNOSs over DESs.

The findings of this systematic review and meta-analysis spark international collaborations and consensus efforts among researchers to share larger data sizes in order to optimal stent selection strategies in the management of ACS. Future studies could delve deeper into patient-reported outcomes and quality-of-life measures associated with different stent types. Moreover, the available evidence can be utilized to reinforce the refinement of TiNOSs and further development of novel stent strategies. Further studies can conduct a comparative analysis of healthcare costs associated with different ACS treatment approaches, which can lead to a lesser financial burden on the healthcare systems. Lastly, with the advent of newer technologies, the development of clinical practice guidelines is crucial to the management of ACS patients requiring stent placement.

CONCLUSION

Although DES was deemed to be an evolutionary move from BMS, resulting in their frequent use in PCI, TiNOSs have proved to be comparable if not superior to DESs with regard to efficacy and safety in the management of ACS. It has proven to elicit rapid healing and lower rates of long-term complications such as MI and ST even in patients with comorbidities such as diabetes. Nonetheless, it is important to conduct more studies to further evaluate these findings and fill in gaps in the literature to get better insight into the true potential of these stents.

FOOTNOTES

Author contributions: Fahim MAA, Salman A, Khan HA and Moeed A participated in the conceptualization, data curation, investigation, methodology, project administration, resources, supervision, validation, visualization, and writing of the original draft; Hasan SM, Bhojani MF, Aslam S, Haq AZU, Bejugam VR, Nasir BM and Gul W were involved in project administration, and writing of the original draft; Fahim MAA, Moeed A, Abdalla AS, Majid M, Asghar MS and Hasibuzzaman MA were involved in the formal analysis, project administration, supervision, validation, visualization, and writing - review & editing; All authors have read and approved the final manuscript.

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