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Review Article

Outcomes of first-generation versus second-generation drug-eluting stents in calcified coronary lesions: A meta-analysis

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Abstract

The choice between first-generation drug-eluting stents (DES) and second-generation DES in managing calcified coronary lesions remains a topic of debate. The aim of this study was to compare outcomes between first-generation DES and second-generation DES in patients with calcified coronary lesions. This meta-analysis study was conducted from October to November 2024. The databases used were Embase, Scopus, and PubMed. Relevant articles were collated, and data regarding outcomes in patients with calcified coronary lesions treated with first-generation and second-generation DES were included to calculate the pooled effect size. The statistical analysis was performed using the Mantel-Haenszel method. Six articles were included in the study. The results indicated that calcified coronary lesions treated with first-generation DES were associated with increased risks of all-cause mortality (Odd ratios (OR): 1.23; 95% confidence interval (95%CI): 1.05–1.45; *p*-Egger= 0.9346; *p*-Heterogeneity: 0.9720; *p*=0.0120), myocardial infarction (OR: 1.48; 95%CI: 1.22–1.80; *p*-Egger: 0.6472; *p*-Heterogeneity: 0.5890; *p*<0.0001); and target lesion revascularization (TLR) (OR: 1.47; 95%CI: 1.24–1.74; *p*-Egger: 0.9982; *p*-Heterogeneity: 0.5950; *p*<0.0001), in comparison with second-generation DES. In contrast, when comparing first- and second-generation DES in terms of cardiac death and major adverse cardiovascular events, a similar risk was depicted. This study compared the outcomes of first-generation and second-generation DES in the management of patients with calcified coronary lesions, which may serve as a reference for selecting DES in the patient population.

Keywords: Drug-eluting stent (DES), first-generation DES, second-generation DES, calcified coronary lesion, meta-analysis

Introduction

Calcified coronary lesions in myocardial infarction patients represent a significant clinical concern that demands serious attention. The prevalence of calcified coronary lesions among these patients varies depending on the detection methods employed [1]. A previous study found that among patients undergoing percutaneous coronary intervention (PCI), 18–24% had calcified coronary lesions [2]. Another study reported an incidence rate of 11%, while the prevalence among all PCI patients could reach as high as 38%, with 12% of these cases classified as severe

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Received: January 12, 2025 - Accepted: May 14, 2025 - Published online: June 2, 2025

calcified lesions [3]. The rate of mortality associated with calcified coronary lesions among patients with myocardial infarction has yet to be ascertained. However, it has been indicated that patients in the severe category of calcified lesions are 10.8% more likely to experience mortality compared to those with mild lesions [4]. This underscores the significant management challenges posed by calcified coronary lesions [4].

Several major concerns arise in the management of patients with calcified coronary lesions. First, calcification creates a diagnostic challenge, as calcified lesions are typically undetectable using standard angiography, making treatment decisions significantly more difficult [1]. Second, procedural difficulties are substantial, with a high risk of complications such as stent malposition, under expansion, and edge dissection, all of which adversely affect patient prognosis [5]. Third, the limitations of traditional angioplasty equipment often result in uneven forces being applied to vessel walls, making them counterproductive. Therefore, advanced techniques, such as atherectomy or lithotripsy, are recommended for achieving optimal outcomes [6]. Given these challenges, patients with calcified coronary lesions require comprehensive management strategies. The use of drug-eluting stents (DES) has proven to be an important intervention for improving clinical outcomes in this condition [7].

A DES is a small, mesh-like tube used to open narrowed arteries during medical procedures [8]. In 1999, Dr. Sousa introduced the DES through a procedure involving a sirolimus-eluting stent (SES) [9]. Since its introduction, DES has been a significant innovation in interventional cardiology, as it has greatly reduced complications such as restenosis following coronary interventions [10]. Evidence indicates that DES outperforms bare-metal stents (BMS) by significantly reducing the risk of recurrent myocardial infarction and the need for target vessel revascularization [11]. Additionally, research has concluded that the incidence of in-stent restenosis is much lower with DES compared to BMS [12]. Since the introduction of DES, advancements in DES technology have focused on improving their safety and efficacy [13]. Early-generation DES, such as SES and paclitaxel-eluting stents (PES), were associated with adverse events like late stent thrombosis and late restenosis, primarily due to delayed healing and inflammation [14].

To address these issues, second-generation DES, including everolimus-eluting stents (EES) and zotarolimus-eluting stents (ZES), have been developed since 2006 [15]. Second-generation DES have thinner struts and more biocompatible polymers, resulting in enhanced safety and efficacy compared to first-generation DES [16]. These advancements are expected to make second-generation DES more effective in treating calcified coronary lesions. Several studies have examined the use of first- and second-generation DES in managing calcified coronary lesions; however, the findings of these studies remain contradictive [17-22], highlighting the need for a meta-analysis. The aim of this study was to compare the outcomes of first- and second-generation DES in cases of calcified coronary lesions using a meta-analytical approach.

Methods

Study design and protocol registration

This systematic review and meta-analysis were conducted by involving the data from articles indexed on Scopus, Embase, and PubMed databases for calculating the cumulative point estimate. The protocol of this systematic review and meta-analysis has been registered with PROSPERO (Registration ID: 637443). The protocol was designed following the checklists of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [23] and the filled PRISMA checklists form is presented in **Underlying data**.

Eligibility criteria

The inclusion criteria for this study were articles with a design of randomized controlled trials (RCTs) or observational study designs that evaluated the outcomes of first-generation versus second-generation DES in calcified coronary lesions. This study included only articles written in English that provided sufficient data for calculating cumulative point estimates. Meanwhile, review articles, commentaries, and letters to the editor were excluded. This study focused on patients with myocardial infarction who had calcified coronary lesions. The intervention involved

PCI using DES. The study compared the effectiveness of first-generation and second-generation DES in managing this condition. The primary outcomes evaluated included major adverse cardiovascular events (MACE), all-cause mortality, cardiac death, recurrent myocardial infarction, and the need for target lesion revascularization (TLR).

Search strategy

A literature search was conducted in Scopus, Embase, and PubMed. An additional search for articles was also conducted from the reference lists of related articles. The literature search was restricted to articles published until November 15, 2024. Articles in languages other than English were excluded. Keywords adapted from medical subject headings (MeSH) terms included: "DES" or "drug-eluting stents" or “drug-eluting stent” and "first-generation" and "second-generation" and "calcified coronary lesions" or “calcified coronary lesion” or “calcified plaque” and "outcomes or “outcome”." The article search for this study was carried out by MSR and JKF.

Quality assessment

In the present study, the Newcastle-Ottawa Scale was applied to assess the quality of observational studies [24], while the modified Jadad scale was applied to assess the quality of RCT studies [25]. The Newcastle-Ottawa Scale included three items of appraisal: sample selection, comparability, and outcome assessment. This rating tool scored between 0 and 9 points. Scores ranging between 0–3 indicated low quality, between 4–6 denoted moderate quality, while scores between 7 and 9 represented high-quality articles [24]. The modified Jadad scale used for assessing the quality considered various components, including randomization, blinding, withdrawals or dropouts, eligibility, adverse events, and statistical analysis. The score ranged from 0 to 8. Articles scoring 0–3 were considered low quality, scores of 4–5 indicated moderate quality, and scores of 6–8 were assigned to high-quality articles [25]. Quality assessment of the articles was carried out by JKF, MCW, YNA, UAK, FEBN, EGB, VST, DJ, WMP, and FT, with JKF providing guidance on the evaluation of article quality. The team was divided into two groups: the first team consisted of MCW, YNA, UAK, FEBN, and EGB, while the second team consisted of VST, DJ, WMP, and FT. Both teams independently assessed the quality of the articles. The results of the article quality evaluation were then gathered and discussed, and any discrepancies were resolved through discussion. A detailed evaluation of article quality is provided in the **Underlying data**.

Data extraction

The first team extracted baseline characteristics data from each article, including the principal investigator, study location, study design, participant age, sample size, severity, evaluated outcomes, and follow-up period. Meanwhile, the second team extracted outcome data, which included the incidence of MACE, all-cause mortality, cardiac death, myocardial infarction, and TLR. The data collected from each article included the name of the principal investigator, year of study, study location, study design, participant age, quality of the article, the use of first-generation vs second-generation DES.

Covariates

The predictor covariates in this study were the use of first-generation vs. second-generation DES. The outcome covariates included MACE, all-cause mortality, cardiac death, myocardial infarction, and TLR. The outcomes evaluated were based on the availability of data obtained from each article, with confirmation that sufficient data were available to calculate cumulative point estimates.

Statistical analysis

Data were presented as n (%). Publication bias was detected using the Egger test and funnel plot, with p-value<0.05 and asymmetry in the funnel plot represented the presence of publication bias [26]. The heterogeneity was evaluated using the Q statistic test, where a p-value<0.10 indicated significant heterogeneity. In the presence of heterogeneity, the pooled point estimates were determined by a random effects model, while in the absence of heterogeneity, a fixed effects model was used [27]. The main findings of this study were determined using the Mantel-Haenszel

method [28]. All pooled point estimates were represented as odds ratios (ORs). Data analysis was conducted using Comprehensive Meta-Analysis (CMA, Biostat, Inc, New Jersey, US) and Review Manager (RevMan, Cochrane, London, UK).

Results

Article selection

A total of 114 articles were retrieved from PubMed, 450 from Embase, and 137 from Scopus (**Figure 1**). An additional five articles were identified through the reference lists of relevant publications; however, these were also found within the original search databases. Duplicate removal was subsequently performed using EndNote software (Clarivate, London, UK), resulting in the identification of 150 duplicate records. Following de-duplication, 551 articles remained. Titles and abstracts were screened, and 519 articles were excluded due to irrelevance to the study objectives (**Figure 1**).

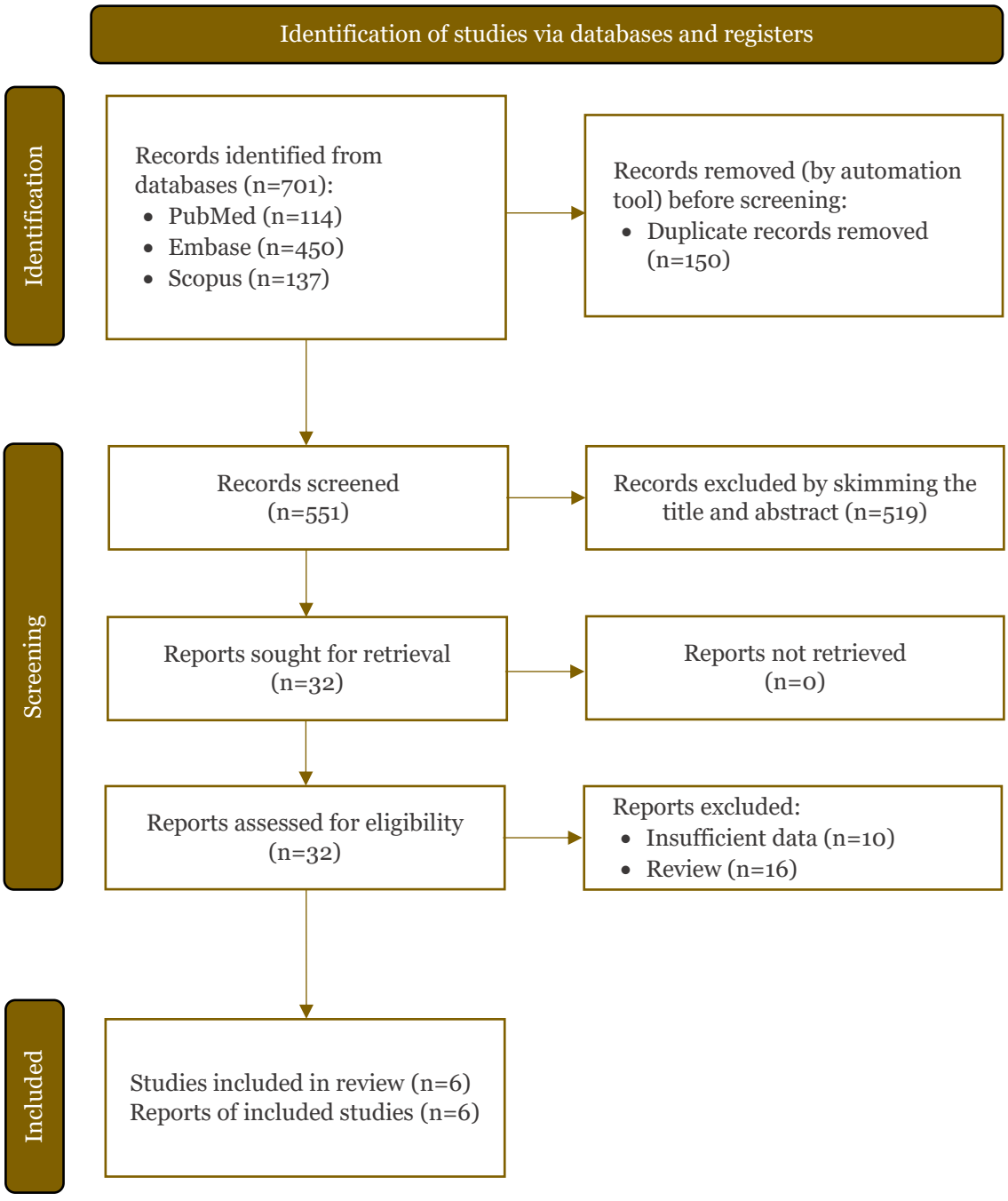

Figure 1. Flowchart of article selection.

Full-text assessments were conducted on the remaining 32 articles. Of these, 10 were excluded due to insufficient data for calculating cumulative point estimates [7,29-37], and 16 were excluded as they were review articles. For this study, data insufficiency was defined as the absence of control data, pre–post comparisons without a control group, cases involving stent thrombosis or stent neoatherosclerosis, comparisons limited to patients with varying degrees of calcification, and studies including only myocardial infarction cases. Ultimately, six articles were included in the final analysis [17-22]. Detailed article selection process is summarized in **Figure 1**.

Baseline characteristics of article in our study

From the six articles we included in this study (**Table 1**), four studies were conducted in the US [17,18,20,22] and two studies were conducted in Japan [19,21]. Regarding study design, two studies had an RCT design [18,21], three studies had a prospective trial design [17,19,20], and one study had a retrospective design [22]. The sample size in each study varied, ranging from 99 patients [22] to 19,833 patients [18]. Regarding the severity of calcified coronary plaque, four studies evaluated severe calcified coronary plaque [17,19,20,22], one study evaluated moderate and severe calcified coronary plaque [18], and one study did not specify the severity [21]. Follow-up periods in each study also varied, ranging from 12 months [22] to 46.8 months [18]. Furthermore, regarding the quality of the articles, five articles were of high quality [17-19,21,22] and one article was of moderate quality [20]. A summary of the quality assessment of the articles in this study is presented in the **Underlying data**.

Comparison of outcomes between first-generation DES and second-generation DES in calcified coronary lesions

Among the variable outcomes (**Figure 2**), the results indicated that the use of first-generation DES was associated with increased all-cause mortality compared to second-generation DES in treating patients with calcified coronary lesions (odd ratios (OR): 1.23; 95% confidence interval (95%CI): 1.05–1.45; *p*-Egger: 0.9346; *p*-Heterogeneity: 0.9720; $p=0.0120$) (**Figure 2A**). An elevated risk of myocardial infarction was observed with the use of first-generation DES compared to second-generation DES in calcified coronary lesions of the patients (OR: 1.48; 95%CI: 1.22–1.80; *p*-Egger: 0.6472; *p*-Heterogeneity: 0.5890; $p<0.0001$) (**Figure 2B**).

This study also revealed that the incidence of TLR was higher with first-generation DES compared to second-generation DES in patients with calcified coronary lesions (OR: 1.47; 95%CI: 1.24–1.74; *p*-Egger: 0.9982; *p*-Heterogeneity: 0.5950; $p<0.0001$) (**Figure 2C**). Conversely, no significant difference was found between first-generation and second-generation DES regarding MACE (OR: 1.20; 95%CI: 0.93–1.55; *p*-Egger: 0.4036; *p*-Heterogeneity: 0.1780; $p=0.1730$) and cardiac death (OR: 1.15; 95%CI: 0.92–1.44; *p*-Egger: 0.8279; *p*-Heterogeneity: 0.4470; $p=0.2120$) among patients with calcified coronary lesions. The comparison of the outcome between first-generation and second-generation DES is summarized in **Table 2**.

Heterogeneity and potential publication bias

The Egger test showed that all variables had $p\geq0.05$ and a symmetric funnel plot (**Underlying data**), indicating no potential for publication bias. The funnel plot is presented in the **Underlying data**. Regarding data heterogeneity, the Q statistic test revealed that all variables had *p*-heterogeneity≥0.10, indicating no evidence of heterogeneity in the data. Therefore, a fixed-effect model has been applied to all variables in this study. A summary of the Egger test and Q statistic results is presented in **Table 2**.

Table 1. Baseline characteristics of studies included in our analysis

Study	Country	Design	Age (years)	Sample size	Severity	Outcomes	Follow up (months)	Quality assessment
Genereux *et al.*, 2016 [17]	US	Prospective trial	71.4±0.5	443	Severe	MACE, death, cardiac death, TLR	25.1	High
Guedeney *et al.*, 2020 [18]	US	RCT	65.3±10.5	19833	Moderate and severe	All - cause mortality, myocardial infarction, cardiac death, TLR	46.8	High
Kobayashi 2014 *et al.*, [19]	Japan	Prospective trial	NA	116	Severe	Restenosis, TLR, MACE	23±2	High
Kovacic *et al.*, 2011 [20]	US	Prospective trial	70.1±10.4	1593	Severe	In-hospital death, myocardial infarction, TVR, MACE,	NA	Moderate
Nishida *et al.*, 2018 [21]	Japan	RCT	69.3±9.6	6090	NA	TLR, TVR, death, myocardial infarction	36	High
Tian *et al.*, 2015 [22]	US	Retrospective	70.8±9.7	99	Severe	All - cause death, cardiac death, myocardial infarction, TLR, MACE	12	High

MACE: major adverse cardiovascular events; NA: not available; RCT: randomized controlled trials; TLR: target lesion revascularization; TVR: target vessel revascularization

Table 2. Summary of the comparative analysis between first-generation and second-generation drug-eluting stents in calcified coronary lesions

Covariates	1st generation DES, n (%)	2nd generation DES, n (%)	Model	Number of studies	Odd ratio (OR)	95%CI	*p*-Egger	*p*-Heterogeneity	*p*-value
Major adverse cardiovascular events (MACE)	107 (6.61)	241 (12.27)	Fixed	5	1.20	0.93–1.55	0.4036	0.1780	0.1730
All-cause mortality	272 (12.26)	426 (10.10)	Fixed	4	1.23	1.05–1.45	0.9346	0.9720	0.0120
Cardiac death	137 (6.17)	226 (5.36)	Fixed	4	1.15	0.92–1.44	0.8279	0.4470	0.2120
Myocardial infarction	206 (9.60)	254 (6.50)	Fixed	3	1.48	1.22–1.80	0.6472	0.5890	<0.0001
Target lesion revascularization (TLR)	284 (12.36)	373 (8.65)	Fixed	5	1.47	1.24–1.74	0.9982	0.5950	<0.0001

DES: drug-eluting stents

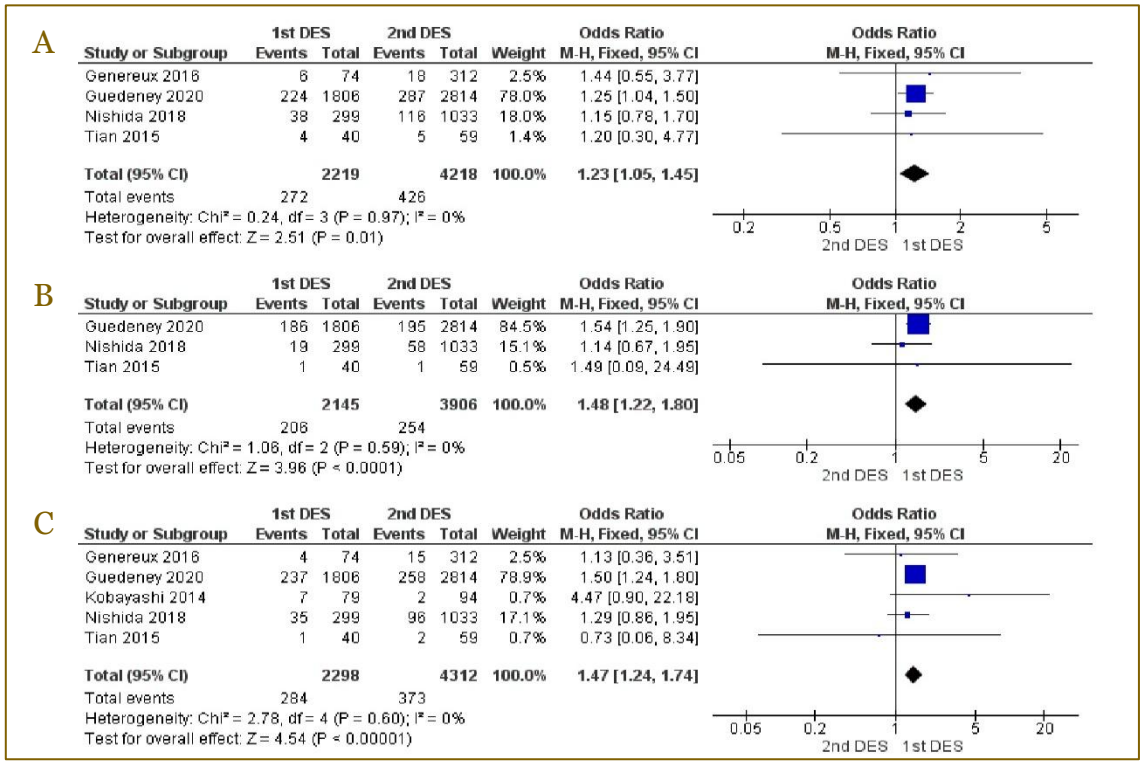

Figure 2. Clinical outcomes of first-generation vs second-generation drug-eluting stents (DES) in calcified coronary lesions. (A) Comparative analysis of all-cause mortality rates between first-generation and second-generation DES. (B) Evaluation of myocardial infarction risk in patients treated with first-generation DES versus second-generation DES. (C) Assessment of target lesion revascularization rates between first-generation DES and second-generation DES.

Discussion

The findings indicated that the utilization of first-generation DES, as compared with second-generation DES, was associated with an increased risk of all-cause mortality, myocardial infarction, and TLR in patients with calcified coronary lesions. Direct comparison of results between studies was not possible, as this is the first study to compare the outcomes of first- and second-generation DES in calcified coronary lesions. However, only one meta-analysis has compared the outcomes between DES and BMS in patients with calcified coronary lesions. This meta-analysis included five articles and found that DES significantly reduced the incidence of TLR when compared to BMS. However, it was unable to show differences in stent thrombosis, cardiac death, and myocardial infarction between DES and BMS [38]. Regarding the comparison between the first-generation DES and second-generation DES, no previous study has employed a meta-analysis approach. Therefore, the outcomes of this study contribute to understanding the differences between first-generation DES and second-generation DES in patients with calcified coronary lesions and may aid clinicians make more informed decisions when selecting DES for their patients.

Theoretically, factors that could account for a higher risk of all-cause mortality with first-generation DES, compared to second-generation DES in patients with calcified coronary lesions, are not yet clearly explained. However, we propose several potential explanations, including differences in stent design and polymer coating [39], and their relationships to clinical outcomes and mortality rates in patients with calcified coronary lesions [1]. The design of the stent and polymer coating varies across generations. First-generation DES, such as SES and PES, are coated with durable polymers, which may contribute to a persistent inflammatory response [39]. Furthermore, this inflammatory response could result in delayed vascular healing and increase the risk of late stent thrombosis following discontinuation of dual antiplatelet therapy (DAPT) [40,41]. On the other hand, second-generation DES, including EES, have thinner struts and bioresorbable polymers. This might improve the chances of recovery with minimal local

inflammation [42]. Moreover, when discussing problems concerning the creation of DES and its correlation to clinical outcomes and mortality rates in patients suffering from calcified coronary lesions, it is important to note that these patients are at a higher risk for procedural complications and restenosis [1,43]. First-generation DESs may enhance these conditions by an inflammatory response, possibly resulting in higher rates of adverse events, including mortality [42]. Second-generation DESs have a better safety profile, which makes them more suitable for patients with calcified coronary lesions by reducing thrombosis-related risks and improving vascular healing [44]. This may theoretically explain our findings that first-generation DES is associated with a higher risk of all-cause mortality compared to second-generation DES in patients with calcified coronary lesions.

These findings also indicated that the increased risk of myocardial infarction was associated with first-generation DES compared to second-generation DES in patients with calcified coronary lesions. Stent design, biocompatibility [39], and interaction with inflammatory response are some of the reasons for these findings [45]. Regarding stent design and biocompatibility, first-generation DES have thicker struts and employ durable polymers. These aspects can provoke an immense inflammatory response. It promotes further inflammation, leading to an enhanced risk of stent thrombosis, delayed vascular wall healing, and thus poor outcomes, especially in complex lesions [39,46]. Consequently, this may result in instability of plaques, which further increases the risk of myocardial infarction [47,48]. However, the second generation of DES uses much thinner struts coupled with more biocompatible materials; this may provide better endothelialization and reduce inflammation [49]. Additionally, this may enhance the healing of arterial walls and minimize the occurrence of late stent thrombosis [50]. Indeed, several studies have reported that second-generation DES significantly decreases the rates of very late stent thrombosis by 67–76% compared to first-generation DES, which is critical in preventing subsequent myocardial infarction [14,51]. Regarding inflammation and vascular healing, the inflammatory response triggered by first-generation DES promotes deleterious vascular remodeling that enhances thrombogenicity. Inflammatory injury can thus further deteriorate the condition and increase the risk of myocardial infarction, which is already high for such patients owing to calcified lesions [45]. This explanation may provide the theoretical basis supporting our results, which show that first-generation DES is related to a higher risk of myocardial infarction compared to second-generation DES in calcified coronary lesion patients.

Several theories can explain our findings on higher TLR risk with first-generation DES compared with second-generation DES in patients with calcified coronary lesions. First-generation DES have thicker struts that increase mechanical stress on the arterial wall, thus enhancing neointimal hyperplasia and delaying vascular healing [49]. Additionally, first-generation DES were manufactured using resilient polymers that allow drugs to be released slowly, prolonging the exposure of the arterial wall to antiproliferative agents. This predisposes to a risk of prolonged inflammation and resultant tissue damage [14]. On the contrary, second-generation DESs have thinner struts, which may minimize mechanical injury to the arterial wall, accelerating endothelialization while minimalizing neointimal growth [52]. Besides that, second-generation DES bioabsorbable polymers degrade over time at a controlled rate. This provides for controlled drug elution without prolonged irritation of the arterial wall. Hence, this may reduce the duration of inflammation and promote healthier vascular healing [16,53]. Another factor that could contribute to our results is the biological response. First-generation DES triggered a more pronounced inflammatory response due to the use of durable polymers, which slow overall vascular recovery. This delay makes it more susceptible to restenosis and often requires complementary interventions such as TLR [8]. In contrast, second-generation DES, with thinner struts and bioabsorbable coatings, supports rapid closure of endothelium with minimal inflammation. This accelerated healing may reduce the likelihood of restenosis and, ultimately, decrease the need for TLR procedures [47]. This explanation may provide the theoretical background supporting our results of higher risks of TLR with first-generation DES compared to second-generation DES in patients with calcified coronary lesions.

The current study has some advantages and clinical implications. This is the first meta-analysis comparing outcomes between first-generation DES and second-generation DES. Thus, the present study may help elucidate the ongoing debate between first-generation and second-

generation DES for cases of calcified coronary lesions. Our results may help clinicians choose the appropriate DES for managing patients with calcified coronary lesions, potentially improving clinical outcomes in complex lesions. This study also suggests that second-generation DES is related to superior clinical outcomes, especially in patients with calcified coronary lesions, which is generally considered a more challenging condition to treat [1]. The better effectiveness of the second-generation DES might imply more effective management of high-risk patients. Furthermore, these results support the current evolving treatment strategies for PCI [54], emphasizing the necessity for continuous reassessment and adoption of new technologies. By showing superior performance of second-generation DES, this study encourages clinicians to consider their use in treating calcified lesions, thus assuring better patient care and outcomes.

Although this study provides important information in the management of patients with calcified coronary lesions, several limitations need to be mentioned. The various possible confounding factors were not assessed, such as characterization of calcium distribution, lesion preparation, management of procedural risks, and comprehensive assessment of the patient. In addition, only six articles were included in our study, which is a small sample size for calculating cumulative outcomes. The studies were conducted only within the US and Japan, which may limit the generalizability of our findings to other populations. Moreover, the severity of calcified coronary lesions varied across the included studies, potentially influencing the risk of bias in our analysis. The follow-up periods ranged from 12 to 46.8 months, which may also have affected the final result of our study. Further studies overcoming these limitations are needed to yield more valid results.

Conclusion

The use of first-generation DES significantly increased the risk of all-cause mortality, myocardial infarction, and TLR when compared to second-generation DES in treating patients with calcified coronary lesions. These findings might provide further insight to support clinicians in choosing an appropriate DES for the treatment of calcified coronary lesions. Nevertheless, further research is needed to address the limitations of this study and obtain more comprehensive results.

Ethics approval

Not required.

Acknowledgments

We thank *Lembaga Pengelola Dana Pendidikan* (LPDP), Republic of Indonesia, for supporting this project.

Competing interests

All the authors declare that there are no conflicts of interest.

Funding

This study received no external funding.

Underlying data

Derived data supporting the findings of this study are available Figshare (https://doi.org/10.6084/m9.figshare.28190537).

Declaration of artificial intelligence use

This study utilized artificial intelligence (AI) tools in the following capacities: ChatGPT and Quillbot were employed for language refinement, including improving grammar, sentence structure, and readability of the manuscript. We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were made solely by the authors.

How to cite

Rohman MS, Fajar JK, Widyaningsih MC, *et al*. Outcomes of first-generation versus second-generation drug-eluting stents in calcified coronary lesions: A meta-analysis. Narra J 2025; 5 (2): e2100 - http://doi.org/10.52225/narra.v52.2100.

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