

Review

# Safer Heart Stents: Drug-Eluting Stents and the Duration of Antiplatelet Therapy in the Post-Myocardial Infarction Period

Valeria Trivelloni<sup>1</sup>, Stefano Salvini<sup>1</sup>, Ilenia Monaco<sup>1</sup>, Fatima Samet Bouhaik<sup>1</sup>,  
Insaf Chouarfia<sup>1</sup>, Iheb Guefrachi<sup>1</sup>, Yassine Bencharef<sup>1</sup>, Mouhand Charaf<sup>1</sup>, Mounia Sedrati<sup>1</sup>,  
Guezzi Embarek<sup>1</sup>, Dario Bottiglierio<sup>1,2,\*</sup> 

<sup>1</sup>Centre Hospitalier Général Victor Jousselin de Dreux, 28100 Dreux, France

<sup>2</sup>Head of the Cardiology and Cardiac Intensive Care Unit at Victor Jousselin Hospital, 28100 Dreux, France

\*Correspondence: [bottiglieriodario56@gmail.com](mailto:bottiglieriodario56@gmail.com) (Bottiglierio Dario)

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## Abstract

Percutaneous coronary intervention (PCI) has significantly improved the management of ischemic heart disease, particularly with the advent of drug-eluting stents (DES), which have substantially lowered the incidence of stent thrombosis compared to bare-metal stents (BMS). Despite this progress, complications such as stent thrombosis, though less frequent, remain clinically relevant. From a pharmacological perspective, dual antiplatelet therapy (DAPT) plays an essential role in minimizing the risk of stent thrombosis, albeit at the cost of an increased bleeding risk. Over time, the duration of DAPT has been progressively shortened, largely attributable to advancements in DES technology, which offer improved safety and efficacy profiles. This review examines clinical trials, randomized controlled studies, and meta-analyses conducted between 2020 and 2024 to evaluate the effectiveness of short-term DAPT in patients receiving DES, with a particular emphasis on the post-myocardial infarction (MI) setting. Emerging data indicate that shorter DAPT regimens do not elevate the risk of stent thrombosis while markedly reducing bleeding complications, thereby endorsing a more concise treatment approach without compromising safety outcomes. Furthermore, the impact of novel technologies and the increasing adoption of personalized therapeutic strategies are explored, underscoring their importance in optimizing clinical outcomes.

## Keywords

percutaneous coronary intervention (PCI); drug-eluting stents (DES); stent thrombosis; dual antiplatelet therapy (DAPT); post-myocardial infarction (MI); bleeding risk; thrombosis prevention; antiplatelet therapy duration; advanced stent technology; cardiovascular guidelines; emerging technologies in cardiology; genetic biomarkers in treatment

## Introduction

The introduction of drug-eluting stents (DES) has transformed the treatment paradigm for coronary artery disease by significantly decreasing the risk of stent thrombosis, a complication more frequently associated with bare-metal stents (BMS) or earlier interventional techniques [1–14]. While DES have demonstrated considerable clinical advantages, post-percutaneous coronary intervention (PCI) management, particularly regarding the duration of antiplatelet therapy, remains a complex and evolving challenge. Historically, long-term dual antiplatelet therapy (DAPT) was considered the standard of care for preventing stent thrombosis. However, advancements in DES technology have enabled shorter DAPT durations without compromising safety. This article provides an in-depth analysis of recent evidence on post-PCI management, focusing on the clinical implications of utilizing next-generation DES and determining the optimal duration of DAPT.

## Methods

This systematic review was conducted through an extensive search of the PubMed database, employing the keywords “antiplatelet” and “coronary” to identify relevant studies published between 2020 and 2024. Inclusion criteria specified the following: articles written in English, studies involving human participants aged 18 years or older, a minimum sample size of 1000 patients, studies that included stent thrombosis as a primary or secondary endpoint, and only randomized controlled trials (RCTs). The initial search yielded 447 records, which were reduced to 420 after duplicate removal. Following abstract screening, 167 studies were excluded, leaving 253 articles for detailed full-text evaluation.

Among these, 200 studies were excluded for reasons such as insufficient population size (fewer than 1000 patients) or endpoints not directly related to stent thrombosis. Consequently, 53 studies met the eligibility criteria and

were included in the final analysis. These comprised RCTs, clinical trials, and meta-analyses focusing on the duration of DAPT and the efficacy of DES in both urgent and elective clinical settings.

This systematic review was conducted in accordance with the PRISMA guidelines to ensure transparency and comprehensive reporting of the methodology and findings.

To ensure the methodological rigor and reliability of the included studies, a systematic quality assessment was performed. Key methodological parameters, such as randomization, blinding, and the reporting of withdrawals or dropouts, were evaluated using the Jadad Scale. Each study underwent independent evaluation by two reviewers, with disagreements resolved through discussion or consultation with a third reviewer. The risk of bias was categorized as low, unclear, or high for each domain. Additionally, the GRADE framework was applied to determine the overall certainty of the evidence, considering variables such as study design, consistency of results, and identified risks of bias. This comprehensive quality assessment underpins the strength of the review's conclusions and ensures that the findings are reliable and evidence-based.

## Results and Discussion

Determining the appropriate duration of DAPT is fundamental to optimizing clinical outcomes for patients undergoing PCI. The primary aim of DAPT is to reduce the incidence of thrombotic complications, such as stent thrombosis and myocardial infarction, through the inhibition of platelet aggregation. However, prolonging DAPT increases the likelihood of bleeding events, which can be severe. Hence, it is essential to carefully balance the benefits of preventing thrombosis with the risk of bleeding.

The duration of DAPT should be individualized based on each patient's ischemic risk (e.g., thrombosis or recurrent myocardial infarction) and bleeding propensity. Several factors influence this determination, including demographic variables (e.g., age), comorbid conditions (e.g., diabetes, hypertension, chronic kidney disease), the type of stent deployed, prior bleeding history, and the clinical presentation (e.g., stable coronary artery disease or acute coronary syndrome). Tailoring therapy in this manner mitigates thrombotic and bleeding complications, ensuring optimal clinical outcomes while avoiding unnecessary adverse effects. Further research remains essential to refine therapeutic strategies, particularly for high-risk populations, to enhance both safety and efficacy.

The European Society of Cardiology (ESC) guidelines define short DAPT as a regimen of dual antiplatelet agents administered for less than six months. This approach is commonly used in patients undergoing coronary stent placement to prevent stent thrombosis and reduce ischemic events. For individuals at low ischemic risk, a duration of one to three months may suffice, whereas higher-risk

patients may require treatment extending to 12 months or longer. The decision should be guided by an assessment of the balance between ischemic and bleeding risks, tailored to the patient's specific clinical circumstances [1].

Advances in DES technology have significantly reduced the risk of stent thrombosis, a complication more prevalent with BMS. These stents deliver antiproliferative agents to inhibit vascular smooth muscle cell growth, thereby preventing restenosis and limiting thrombotic events [3–17].

Recent studies, including STOPDAPT-2 [18] and STOPDAPT-3 [19], have evaluated short-term versus long-term DAPT in patients treated with DES. Results indicate that shorter DAPT durations do not compromise stent thrombosis prevention, as modern DES effectively maintain coronary patency [20]. Third-generation DES, such as those utilizing everolimus or zotarolimus, have further enhanced long-term outcomes, reducing thrombotic risks while maintaining safety [21]. Moreover, advances in diagnostic imaging, particularly optical coherence tomography (OCT), have facilitated precise evaluation of stent endothelialization and thrombotic risk, improving therapeutic decision-making and outcomes [22].

Optical coherence tomography provides high-resolution imaging of coronary lesions, enabling precise stent placement during PCI. A meta-analysis of 32 RCTs involving 22,684 patients demonstrated that PCI guided by intravascular imaging, including OCT, achieved superior outcomes compared to angiography-guided PCI. This approach was associated with significant reductions in major adverse cardiovascular events (MACE), cardiovascular mortality, myocardial infarction (MI), stent thrombosis, and target lesion revascularization (TLR). The benefits were particularly pronounced in patients with acute coronary syndrome (ACS), highlighting the utility of OCT in complex cases.

Despite robust evidence supporting OCT-guided PCI, its clinical adoption remains limited due to barriers such as hospital resource constraints, insufficient training, and cost considerations. Intravascular imaging is routinely implemented in Japan, but its use remains sporadic globally. Addressing these challenges could promote broader adoption of intravascular imaging and enhance procedural and clinical outcomes.

This meta-analysis further compared angiography-guided, intravascular imaging-guided, and functionally guided PCI strategies. Intravascular imaging-guided PCI was associated with the most favorable outcomes, including reduced risks of MACE, cardiovascular death, stent thrombosis, and TLR, particularly among ACS patients. Functionally guided PCI also demonstrated superiority over angiography guidance in reducing MACE and MI. Trials evaluating second-generation or newer DES reinforced these findings, underscoring the efficacy of advanced PCI techniques.

Although there is compelling evidence for intravascular imaging-guided and functionally guided PCI, angiography remains the predominant approach worldwide, except in Japan. This continued reliance may reflect trial limitations, inconsistent findings, or variations in patient populations. For example, while the FAME trial [23] supported fractional flow reserve (FFR)-guided PCI, the FLOWER MI trial did not demonstrate its superiority, likely due to differing study populations, such as stable coronary artery disease versus post-ST elevation MI patients.

Data from over 20,000 patients confirm that intravascular imaging-guided PCI significantly improves outcomes, particularly in ACS patients, by reducing cardiovascular complications. Current guidelines, however, assign only a Class IIa recommendation to intravascular imaging-guided PCI, and its real-world adoption remains modest. Barriers include institutional practices, physician training, and cost constraints. In spite of these challenges, intravascular imaging, including intravascular ultrasound (IVUS), has shown potential for enhancing procedural success and reducing mortality. Greater efforts are required to overcome these obstacles and integrate intravascular imaging more effectively into routine clinical practice [22].

#### *Duration of Antiplatelet Therapy: Balancing Bleeding and Thrombosis Risk*

The risk of stenosis in patients undergoing PCI with DES placement is influenced by various clinical and biological factors. Identifying variables linked to early, late, and very late stent thrombosis (ST) is critical for improving risk management. In a 2024 study by Gerald Chi *et al.* [17], data from 8741 patients undergoing PCI with DES for acute coronary syndrome (ACS) were analyzed to identify variables both positively and negatively associated with different phases of ST. These variables were instrumental in constructing risk assessment models for stenosis. After multivariable adjustment, factors such as age  $\geq 75$  years [hazard ratio (HR) = 2.13; 95% confidence interval (CI): 1.26–3.60], a history of prior myocardial infarction [HR = 1.81; 95% CI: 1.22–2.68], low hemoglobin levels [HR = 2.34; 95% CI: 1.59–3.44], and high white blood cell (WBC) count [HR = 1.58; 95% CI: 1.02–2.46] were associated with an increased risk of overall stenosis. Conversely, DES use [HR = 0.56; 95% CI: 0.38–0.83] and rivaroxaban therapy [HR = 0.63; 95% CI: 0.44–0.88] reduced stenosis risk up to 720 days. Low hemoglobin levels and high WBC counts were linked specifically to early stenosis (low hemoglobin: HR = 2.35; 95% CI: 1.34–4.12; high WBC count: HR = 2.11; 95% CI: 1.17–3.81). Late stenosis was associated with low hemoglobin levels [HR = 2.32; 95% CI: 1.26–4.27] or prior myocardial infarction [HR = 2.98; 95% CI: 1.67–5.31], while DES use reduced the risk [HR = 0.33; 95% CI: 0.16–0.67]. Very late stenosis was primarily associated with age  $\geq 75$  years [17]. For nearly two decades, American and European guidelines

have recommended a 12-month duration for DAPT in ACS. This class I recommendation established 12-month DAPT as the global standard for ACS patients undergoing PCI. The CURE trial (Clopidogrel in Unstable Angina to Prevent Recurrent Events) formed the basis for this duration, comparing DAPT to no DAPT. However, the trial did not investigate the optimal DAPT length and had a mean treatment duration of nine months rather than 12 [24–26]. Subsequent studies primarily focused on comparing different DAPT agents (e.g., prasugrel or ticagrelor vs. clopidogrel) rather than treatment duration. Despite this, their findings reinforced the 12-month standard, even as median durations varied, with nine months for ticagrelor and 15 months for prasugrel. Over time, evidence began challenging the 12-month standard, suggesting shorter therapy for patients with high bleeding risk and extended therapy for those at greater ischemic risk who could tolerate it [26–34].

Hong S.J. *et al.* (2024) [33] showed that combining aspirin with ticagrelor did not significantly improve thrombosis outcomes but increased gastrointestinal and intracranial bleeding risks, particularly in elderly or comorbid patients. Shorter DAPT durations have emerged as an effective strategy for high-bleeding-risk patients, minimizing bleeding without compromising thrombosis prevention. Bajraktari *et al.* (2024) [34] reported that reducing DAPT duration significantly lowered bleeding events without increasing stent thrombosis risk.

A network meta-analysis using the netmeta package in R Studio (version 4.3.3), developed by RStudio PBC (Posit), based in Boston, Massachusetts, USA, was conducted to analyze 25 studies involving 65,115 patients. The studies were identified through a computer search of PubMed (National Library of Medicine, Bethesda, Maryland, USA), Cochrane Library (Oxford, England, UK), Web of Science (Clarivate Analytics, Philadelphia, Pennsylvania, USA), Embase (Elsevier, Amsterdam, Netherlands), and Scopus (Elsevier, Amsterdam, Netherlands) databases up until April 1st, 2024, comparing outcomes such as cardiac death, MI, stent thrombosis, stroke, and major bleeding (BARC 3-5) across various regimens, including single antiplatelet therapy (SAPT), DAPT, and triple antiplatelet therapy (TAPT) with cilostazol. The results showed no significant differences in cardiac death risk for TAPT (RR = 0.74; 95% CI: 0.40–1.35;  $p = 0.33$ ) or DAPT (RR = 1.01; 95% CI: 0.84–1.19;  $p = 0.87$ ) compared to SAPT. Similar trends were observed for MI, stent thrombosis, and stroke.

However, TAPT and DAPT both increased major bleeding risks relative to SAPT, with statistical significance for DAPT (RR = 1.43; 95% CI: 1.09–1.88;  $p = 0.0107$ ). These findings highlight that while TAPT and DAPT increase bleeding risks, they do not differ significantly in other primary outcomes [35].

Recent evidence underscores bleeding risk as a critical factor in determining DAPT duration. Strategies such as switching to clopidogrel, reducing prasugrel or

ticagrelor doses, or shortening DAPT followed by ticagrelor monotherapy have consistently demonstrated reduced bleeding risks without increasing cardiovascular or cerebrovascular ischemic events compared to 12-month regimens [26–66].

The MASTER DAPT trial demonstrated that abbreviated DAPT (one month) significantly reduced major and clinically relevant nonmajor bleeding compared to standard DAPT ( $\geq 3$  months), with similar rates of net adverse clinical events (NACE: all-cause death, myocardial infarction [MI], stroke and major bleeding) and major adverse cardiovascular and cerebral events (MACCE). Diabetes status did not influence these outcomes. Similarly, a meta-analysis comparing 1–3 months of DAPT followed by monotherapy to a 12-month regimen reported reduced bleeding (OR 0.67; 95% CI: 0.44–1.00;  $p = 0.05$ ) without significant differences in cardiovascular outcomes. Stent-related outcomes, such as stent thrombosis and target vessel revascularization, were also comparable, supporting abbreviated DAPT as a safe and effective strategy [36,37].

Contemporary DAPT strategies, such as short-term DAPT and uniform de-escalation, show promise for managing ACS in elderly patients. A network meta-analysis of 16 RCTs involving 47,911 patients found that uniform de-escalation provided superior net clinical benefits compared to potent P2Y<sub>12</sub> inhibitors. While short-term DAPT reduced major bleeding, it was less effective for MACE. These findings emphasize the importance of personalized approaches based on individual bleeding and ischemic risks, with further trials needed to confirm benefits in elderly populations [38].

Despite these advancements, the 12-month DAPT guideline remains the only class I recommendation for ACS patients, frequently leading to overtreatment. Updating clinical guidelines to reflect current evidence on optimal DAPT duration is essential to reduce unnecessary risks and improve patient outcomes [1,39].

#### Guideline Recommendations for Noncardiac Surgery

Current guidelines suggest postponing elective noncardiac surgery for at least 6 to 12 months after DES placement, while continuing aspirin perioperatively to prevent stent thrombosis even beyond one year after PCI and withholding P2Y<sub>12</sub> inhibitors for 5 to 7 days before surgery [1,2,33,67]. These recommendations are based on observational studies that have shown a significant link between premature discontinuation of antiplatelet therapy and fatal stent thrombosis, especially following first-generation DES implantation [20]. Furthermore, a secondary analysis of an RCT demonstrated that continued aspirin use reduced the risk of myocardial infarction in patients with prior PCI. However, several observational studies have questioned the necessity of discontinuing antiplatelet therapy before noncardiac surgery, showing no significant asso-

ciation between therapy interruption and adverse cardiac events during the perioperative period [33,67–69]. A recent study involving over 1000 patients compared aspirin monotherapy to the complete cessation of antiplatelet therapy (with therapy discontinued days before surgery and resumed within 48 hours post-procedure in the absence of complications) for patients with DES implantation over one year prior and scheduled for low-to-moderate-risk elective noncardiac surgery. The results indicated that the incidence of major bleeding did not differ significantly between the groups (6.5% vs. 5.2%;  $p = 0.39$ ), although minor bleeding was significantly more frequent in the aspirin group (14.9% vs. 10.1%;  $p = 0.027$ ). These findings suggest that, in specific cases, discontinuing antiplatelet therapy may not be necessary, particularly for patients with a longer interval since DES implantation who are undergoing low-risk surgery [70].

#### New Guidelines and Personalized Treatments

Updated guidelines from the ESC and the American College of Cardiology (ACC) now recommend a shorter duration of DAPT for patients at low or moderate risk of thrombosis, proposing treatment durations as brief as 3 months. For patients at high risk of thrombosis, the recommended duration may be extended to 6–12 months [1,2]. Studies, such as Natsuaki *et al.* (2024) [19], have demonstrated that reducing the duration of DAPT does not compromise safety while significantly lowering the risk of bleeding complications.

Moreover, the use of personalized treatment strategies, supported by genetic biomarkers and advanced monitoring technologies such as OCT, is increasingly being emphasized.

Personalized DAPT involves tailoring therapy based on individual patient characteristics, including ischemic and bleeding risks, stent type, comorbid conditions, and genetic responsiveness to medications. This strategy allows for the adjustment of both the choice of antiplatelet agents and the duration of therapy to maximize safety and efficacy [24,25,70–72]. Research by Min *et al.* (2024) [73] underscores the value of adapting DAPT duration to a patient's risk profile, demonstrating reductions in both thrombotic and bleeding events.

#### Emerging Technologies and Future Therapies

Recent advances in stent technology, such as biodegradable stents, represent a promising step forward in reducing thrombosis risk and long-term complications. These devices, which eliminate the need for permanent polymers, may further decrease the likelihood of post-PCI thrombosis. Ongoing studies, including SPARTAN, HOST-REDUCE-POLYTECH-ACS, and the BIO-RESORT Trial, are evaluating the safety and efficacy of biodegradable stents with encouraging preliminary results [14,74,75].



The results of two registries assessed the safety and efficacy of different drug-eluting stents in patients with symptomatic coronary artery disease. The first registry, the S-FLEX UK-II registry, evaluated the Supraflex Cruz Sirolimus-eluting Stent (SES) in 1835 patients (mean age 65.2 years) who underwent implantation of 2973 Supraflex Cruz SES. The primary endpoint was target lesion failure (TLF), defined as cardiac death, target vessel myocardial infarction (TV-MI), and clinically indicated target lesion revascularization (CI-TLR). At 30 days, TLF occurred in 0.7% of patients (12 patients), with 0.3% cardiac death, 0.2% TV-MI, and 0.2% CI-TLR. At 12 months, TLF was observed in 2.3% (43 patients), with 0.8% cardiac death, 0.8% TV-MI, and 0.8% CI-TLR. The definite stent thrombosis rate was 0.3% across the population at 12 months. Subgroup analyses indicated higher rates of TLF (6.2%) and stent thrombosis (1%) in diabetic patients, while lower rates of TLF and stent thrombosis were seen in patients with bifurcation lesions or long coronary lesions (>20 mm).

The second registry, a single-center prospective registry, compared the Genoss and Orsiro drug-eluting stents in 751 and 931 patients, respectively. The primary endpoint was a device-oriented composite outcome (DOCO), including cardiac death, TV-MI, and CI-TLR. After propensity score matching, no significant differences were found in clinical and angiographic characteristics between the two groups. During a median follow-up of 730 days, the DOCO rate was 3.1% in the Genoss DES group and 2.9% in the Orsiro DES group (log-rank  $p = 0.847$ ), indicating comparable safety and efficacy between the two devices. These findings highlight favorable outcomes for both the Supraflex Cruz SES and the Genoss and Orsiro DES, demonstrating low rates of TLF and stent thrombosis in patients with complex coronary artery disease. However, RCTs are warranted to validate these results [76,77].

The BIO-RESORT trial, a large-scale, randomized study, evaluated the health outcomes and costs associated with three new-generation DES—Orsiro SES, Synergy everolimus-eluting stent (EES), and Resolute Integrity zotarolimus-eluting stent (ZES). The trial included 3514 all-comer patients undergoing PCI across four Dutch centers, with broad inclusion criteria to reflect a diverse patient population. Patients were followed for three years, with health outcomes assessed in quality-adjusted life years (QALYs) and adverse cardiovascular events. Costs were retrospectively calculated, incorporating PCI procedures, hospital stays, follow-ups, and repeat revascularizations, adjusted to 2020 values.

The analysis revealed that SES achieved the highest QALYs (2.566 per patient) and the lowest costs (€14,670 per patient) compared to EES and ZES. SES was dominant in 79% of scenarios versus ZES and in 71% versus EES. Although the per-patient differences were small, these findings could translate into substantial cost savings at a population level given the high annual volume of PCI

procedures. Key findings highlighted SES as the most cost-effective option across willingness-to-pay thresholds up to €100,000 per QALY. While stent prices and healthcare costs vary depending on local agreements and market dynamics, these results emphasize the importance of cost-effectiveness analyses in high-volume interventions like PCI.

Further studies comparing economic feasibility across healthcare systems and patient demographics could refine clinical decision-making and optimize resource allocation [78].

Additionally, the use of genetic biomarkers has the potential to revolutionize treatment personalization by determining the optimal DAPT duration for individual patients, thereby reducing both thrombosis and bleeding risks. Studies, including Claassens *et al.* (2019) [71] and Lee *et al.* (2022) [72], have demonstrated how genetic biomarkers can guide therapeutic decisions and improve clinical outcomes. For example, in patients undergoing primary PCI, a CYP2C19 genotype-guided strategy for selecting oral P2Y12 inhibitors was shown to be noninferior to standard treatment with ticagrelor or prasugrel for thrombotic events at 12 months.

In a study involving 2488 patients (1242 in the genotype-guided group and 1246 in the standard treatment group), the genotype-guided approach significantly reduced bleeding incidence. The combined primary outcome, encompassing death from any cause, myocardial infarction, stent thrombosis, stroke, or major bleeding, occurred in 5.1% of the genotype-guided group and 5.9% of the standard treatment group. Bleeding incidence was notably lower in the genotype-guided group (9.8% vs. 12.5% in the standard-treatment group). Importantly, the use of clopidogrel in patients without a CYP2C19 loss-of-function allele was associated with reduced bleeding compared to more potent P2Y12 inhibitors. These findings suggest that genotype-guided therapy offers similar thrombotic protection with improved bleeding outcomes, supporting its integration into clinical practice for patients undergoing PCI [70].

### Limitations

While this review provides a comprehensive analysis of the key studies on short-duration DAPT, several limitations must be acknowledged. First, heterogeneity may arise due to variations in study design, patient populations, and treatment protocols, potentially limiting the generalizability of the findings. In addition, some studies lacked detailed long-term follow-up data, which could impact the evaluation of the long-term safety and efficacy of short DAPT regimens. Another limitation is the potential for publication bias, as studies reporting negative or neutral results may be underrepresented. Furthermore, while the quality of the included studies was assessed using standard risk-of-

bias tools, inherent biases, such as selection or performance biases, may still influence the validity of the conclusions. These factors should be considered when interpreting the findings of this review.

The lack of access to individual patient data limited the ability to analyze specific subgroup outcomes, assess temporal trends, or evaluate multivariable predictors. Moreover, inconsistencies in the definitions of MACE, MI, and revascularization events across trials further complicate comparisons. The included studies were conducted in diverse geographic regions and medical centers over varying time periods, using different PCI devices and performed by operators with differing levels of expertise, factors not accounted for in this analysis. Lastly, the significant variation in sample sizes across the RCTs underscores the need for larger, more standardized trials to confirm these findings.

## Conclusion

The introduction of DES has markedly advanced the management of PCI patients by reducing stent thrombosis risk and enabling shorter DAPT durations. Current guidelines highlight a personalized approach, incorporating factors such as thrombosis risk, bleeding risk, and the type of stent used. Technological advancements, including the development of biodegradable stents and the growing integration of intraprocedural imaging techniques, are contributing to safer and more effective post-PCI management. Nevertheless, continued research is crucial to further refine treatment strategies, with a particular focus on personalized therapies guided by genetic biomarkers and the exploration of emerging technologies to improve patient outcomes.

## Author Contributions

TV, SS, and BD designed the research study. MI, SBF, CI, GI, BY, CM, SM, and GE collected and curated the data. BD conceptualized the study and developed the methodology. TV, SS, and BD collected and curated the data. TV and BD prepared the initial draft of the manuscript. TV and SS reviewed and edited the manuscript. TV, SS, and BD analyzed the data. BD supervised the research and manuscript preparation. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Conflict of Interest

The authors declare no conflict of interest.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.59958/hsf.8273>.

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