University of Genoa
Department of Internal Medicine (Di.M.I.)

PhD course
Translational and Clinical Internal Medicine (TaCIM)

Optimization of Antithrombotic Therapy in Patients Undergoing Percutaneous Coronary Intervention

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Abstract

Background: The optimal management of antiplatelet therapy, both in the periprocedural and chronic phases, in patients undergoing percutaneous coronary intervention (PCI) remains a matter of ongoing debate. Balancing ischemic protection against bleeding risk is central to contemporary treatment strategies, particularly in the era of potent P2Y12 inhibitors and modern drug-eluting stents.

Objectives: To comprehensively evaluate and compare different antiplatelet strategies in both acute (periprocedural) and chronic settings following PCI.

Methods: A systematic review and meta-analysis of randomized controlled trials was performed to assess different durations of dual antiplatelet therapy (DAPT) and subsequent monotherapy strategies. In parallel, a multicenter registry study was conducted to investigate the real-world use of cangrelor, an intravenous P2Y12 inhibitor, in the periprocedural setting and to characterize bleeding risk of patients receiving cangrelor in contemporary practice.

Results: Comparative analyses of DAPT duration consistently demonstrated that abbreviated regimens are associated with a more favorable safety profile, with no significant trade-off in ischemic protection compared with the conventional 12-month strategy. These findings were consistent across clinical presentations and treatment strategies, supporting the feasibility of shorter DAPT durations in a broad PCI population. In the periprocedural setting, real-world data on cangrelor use provided a detailed characterization of patients at increased bleeding risk, identifying key clinical predictors and enabling the development of a dedicated bleeding risk score. This approach allows for improved patient selection and risk stratification in the acute phase of PCI.

Conclusions: Contemporary evidence supports a paradigm shift toward more individualized antiplatelet strategies after PCI. Shortened DAPT durations appear safe and effective for most patients, while tailored approaches in the acute phase—supported by real-world data—may further optimize the balance between ischemic and bleeding risks. Precision-based antiplatelet therapy represents a key step toward improving clinical outcomes in modern interventional cardiology.

Introduction

Percutaneous coronary intervention (PCI) is a cornerstone of contemporary cardiovascular medicine and has profoundly improved the prognosis of patients with acute and chronic coronary syndromes (1, 2). By enabling rapid and effective myocardial revascularization, PCI reduces short-term mortality, limits myocardial injury, and alleviates ischemic symptoms. However, PCI is intrinsically thrombogenic. Mechanical plaque disruption, endothelial injury, and intracoronary device implantation trigger intense platelet activation and aggregation, creating a biological environment in which thrombotic complications may occur despite technically successful procedures. Consequently, the clinical benefits of PCI are inextricably linked to the effectiveness of antiplatelet therapy administered during the procedure and throughout long-term follow-up (3). Antiplatelet therapy has therefore become a fundamental determinant of outcomes after PCI. Insufficient platelet inhibition exposes patients to acute and late ischemic events, including stent thrombosis and recurrent myocardial infarction, whereas excessive platelet inhibition increases bleeding risk, which is now recognized as an independent predictor of morbidity and mortality. The challenge of PCI pharmacotherapy lies in achieving an optimal balance between ischemic protection and bleeding safety, a balance that is not static but evolves over time and differs substantially between clinical settings.

Rationale for dual antiplatelet therapy and a brief overview of conventional and emerging options in clinical practice

Platelets play a central role in coronary thrombosis and PCI-related ischemic complications. Plaque rupture or erosion leads to the exposure of highly thrombogenic substrates, promoting platelet adhesion, activation, and aggregation. These processes are amplified during PCI by balloon inflation and stent deployment, which further disrupt the endothelium and enhance local inflammation. Activated platelets release prothrombotic mediators, propagate thrombin generation, and contribute to microvascular obstruction, particularly in acute coronary syndromes (ACS). This pathophysiological framework provides the rationale for antiplatelet therapy as the cornerstone of PCI management.

Aspirin (acetylsalicylic acid), through irreversible inhibition of cyclooxygenase-1 and suppression of thromboxane A2 synthesis, represents the foundational antiplatelet agent in coronary artery disease (4). The introduction of P2Y12 receptor inhibitors further improved outcomes by targeting a key pathway of platelet activation and aggregation. Dual antiplatelet therapy (DAPT), combining aspirin with a P2Y12 inhibitor, rapidly became standard of care in patients undergoing PCI and still maintains a central role in the vast majority of them. After timely platelet inhibition importance was emphasized in the context of the procedure itself, even pre-procedural administration of oral P2Y12 inhibitor was tested, although with disappointing results (5). This, however, paved the way to the introduction of fast-onset, intravenous P2Y12 inhibitors, aimed at achieving prompt intraprocedural platelet blockage while avoiding the limitations associated with upstream oral drug administration prior to coronary angiography (6-9). Further enriching this complex

landscape, aspirin-free regimens have been recently proposed in the post-procedural phase, showing favorable safety-efficacy profile in randomized studies (10). These and other emerging protocols (e.g., DAPT *de-escalation*) are nowadays recognized as alternatives in selected clinical scenarios (e.g., patients at both high bleeding and high ischemic risk).

Antiplatelet drugs: oral agents

Aspirin remains a universal component of antiplatelet therapy owing to its rapid onset, irreversible platelet inhibition, and extensive evidence base demonstrating reductions in mortality and recurrent ischemic events. Its role as background therapy is consistently endorsed across all clinical scenarios in the absence of contraindications. An intravenous form of aspirin is widely available and can be administered as a faster-onset equivalent to the oral form.

Clopidogrel, a thienopyridine P2Y12 receptor inhibitor, requires hepatic bioactivation and is characterized by delayed onset of action and marked interindividual variability in platelet inhibition. Despite these limitations, clopidogrel has maintained an important role in clinical practice, particularly in patients with chronic coronary syndromes (CCS) or in those with increased bleeding risk, where its more favorable safety profile is advantageous. Prasugrel and ticagrelor provide more potent, rapid, and consistent P2Y12 inhibition (11). Prasugrel irreversibly inhibits the P2Y12 receptor and achieves robust platelet inhibition but is contraindicated in patients with a history of stroke or transient ischemic attack and requires caution in elderly patients and those with low body weight. Ticagrelor, a reversible P2Y12 inhibitor, offers rapid onset and offset of action and does not require metabolic activation, but may be associated with adverse effects such as dyspnea and bradyarrhythmia. Large randomized trials have demonstrated the superiority of prasugrel and ticagrelor over clopidogrel in ACS patients undergoing PCI, with significant reductions in ischemic events and stent thrombosis, albeit at the expense of increased non–procedure-related bleeding (12). These findings underpin contemporary European Society of Cardiology (ESC) guideline recommendations favoring potent P2Y12 inhibitors in ACS, while reserving clopidogrel for selected scenarios, including CCS and high bleeding risk (1, 2).

Antiplatelet drugs: intravenous agents

While oral agents are largely implicated in the longitudinal strategy after PCI, parenteral antiplatelet therapy plays a complementary role in the catheterization laboratory, particularly in high-risk settings.

Intravenous glycoprotein IIb/IIIa inhibitors, by blocking the final common pathway of platelet aggregation, provide the most potent antiplatelet effect currently available. Although routine use has declined, ESC guidelines support their selective or bailout use in the presence of procedural thrombotic complications, where the ischemic benefit may outweigh the bleeding risk (1).

Cangrelor is an intravenous, reversible $P2Y_{12}$ inhibitor that achieves rapid onset and offset of platelet inhibition (13). It is approved for use in patients undergoing PCI who have not received prior oral $P2Y_{12}$ therapy and when oral administration is not feasible. Three large randomized clinical trials (6-9) and pooled

analyses have evaluated cangrelor versus clopidogrel or placebo in PCI populations, demonstrating a reduction in ischemic events, particularly stent thrombosis, with similar rates of severe bleeding but an increase in minor bleeding. Cangrelor may be particularly useful in high-risk or $P2Y_{12}$-naïve patients undergoing PCI or when rapid, short-acting inhibition is required.

Thrombotic and bleeding dominance

A useful conceptual framework for understanding antiplatelet therapy across the spectrum of coronary artery disease is the contrast between thrombotic dominance and bleeding dominance. A relevant example is the clinical context: acute versus chronic presentation. In ACS, particularly in the early phase, clinical outcomes are largely driven by ischemic risk (14). Heightened platelet reactivity, unstable coronary lesions, and systemic inflammation create a setting of thrombotic dominance, in which early and potent antiplatelet strategies are prioritized, even at the cost of a transient increase in bleeding risk. This paradigm is reflected in ESC guidelines, which favor potent P2Y12 inhibition and allow selective use of parenteral antiplatelet agents when clinically indicated. Conversely, in CCS, thrombotic risk is generally lower and more stable over time, while the cumulative impact of bleeding becomes increasingly relevant. This relative bleeding dominance supports treatment simplification, shorter durations of DAPT, and de-escalation strategies aimed at preserving long-term safety without compromising ischemic protection. Contemporary ESC guidelines consistently emphasize individualized risk assessment to guide antiplatelet intensity and duration in this setting (1, 2). Additional major determinants of the bleeding-thrombosis balance certainly include the complexity of coronary anatomy and patient-specific features such as diabetes and kidney function. Although an detailed discussion of these factors is outside the scope of this document, their importance their role should be carefully considered whenever specific antiplatelet strategies are selected.

Bleeding risk and long-term outcomes

Bleeding complications are now recognized as a major determinant of prognosis after PCI. Beyond their immediate clinical consequences, bleeding events are associated with interruption of antiplatelet therapy, increased inflammation, and higher long-term mortality. This recognition has driven a shift toward more personalized antiplatelet strategies (15), balancing ischemic and bleeding risks over time.

Rationale and scope of the present thesis

The present thesis focuses on antiplatelet therapy in patients undergoing PCI across a range of clinical scenarios, including both acute and chronic coronary syndromes and encompassing oral and parenteral antiplatelet medication administered either acutely during the procedural (or immediately post-procedural) phase or chronically.

Specifically, aims of the studies developed during the Philosophy Doctor (PhD) course and herein included were twofold:

1. To compare the safety-efficacy profile of different DAPT durations, ranging from very short (≤3 months) to extended (>12 months) protocols;
2. To characterize the risk of bleeding in patients receiving the parenteral antiplatelet cangrelor and to develop a risk stratification model for the purpose of bleeding risk quantification in a real-world population undergoing PCI with cangrelor.

In short, these contributions aim to refine the use of antiplatelet therapy across the PCI continuum, ultimately seeking to achieve more precise and effective antiplatelet strategies in patients treated with contemporary PCI.

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Very short vs. long dual antiplatelet therapy after second generation drug-eluting stents in 35 785 patients undergoing percutaneous coronary interventions: a meta-analysis of randomized controlled trials

INTRODUCTION

Dual antiplatelet therapy (DAPT) is a therapeutic cornerstone for patients with acute coronary syndrome (ACS) and/or undergoing percutaneous coronary intervention (PCI) (1-3), reducing the incidence of stent thrombosis (ST) and other ischaemic events. Uncertainties, however, persist regarding the optimal duration of DAPT in different clinical scenarios (4-6). Although randomized controlled trials (RCTs) have shown ischaemic benefits for DAPT extended even beyond the 12 months 'standard' (7), the declining incidence of ST (mainly owing to advances in PCI materials and techniques) (8) and a growing focus on adverse impact of haemorrhagic events (9) have prompted RCTs exploring the impact of increasingly shorter DAPT durations (10-12).

A number of meta-analyses have shown net benefits in the ischaemic/bleeding balance for ≤6 months vs. 12 months DAPT in patients with low-ischaemic risk (13, 14). Recent RCTs have enriched the landscape by also investigating very short DAPT regimens and higher-risk populations (10-12, 15, 16).

We performed a systematic review and meta-analysis with the aim of assessing the safety and efficacy of very short (1 or 3 months) vs. 12 months DAPT in patients undergoing PCI with second-generation drug-eluting stents (DES).

METHODS

Study selection and eligibility criteria

The meta-analysis was registered on PROSPERO (ID 153522) and conducted according to the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations (17) (Appendix 1, *Tables S1-S3*). We included RCTs enrolling patients treated with second-generation DES, presenting with either ACS or chronic coronary syndromes (CCS), randomized to very short (<_3 months) or long (~12 months) DAPT regimens (Appendix 1, *Table S4*). No restriction was applied regarding post-DAPT antiplatelet monotherapy (i.e. aspirin or $P2Y_{12}$ inhibitor). We excluded studies: (i) not published in English; (ii) enrolling patients treated conservatively or receiving bare metal stents (BMS) or first-generation DES; (iii) adopting different DAPT durations from those mentioned above; (iv) enrolling patients with a concomitant indication for anticoagulant therapy; (v) adopting antiplatelet agents other than aspirin, clopidogrel, ticagrelor, or prasugrel at dis- charge; and (vi) with observational, cross-sectional, or other non-RCT design.

A systematic digital search was performed between May and October 2019, using MEDLINE/PubMed, Cochrane, Embase, and Web of Science database, TCTMD (https://www.tctmd.com) and ClinicalTrials.gov. We used the following search terms: 'antiplatelet therapy', 'DAPT', 'clopidogrel', 'prasugrel', 'ticagrelor', and 'randomized trial' (*Appendix 1, Table S2*). Previous meta- analyses and abstracts/presentations from

annual meetings of major cardiovascular societies (European Society of Cardiology, American Heart Association, American College of Cardiology and Transcatheter Cardiovascular Therapeutics) were also screened. Reference lists of included articles were screened using a snowball approach. Two independent investigators (S.B. and M.G.) assessed titles and abstracts for eligibility. For each eligible study, full texts, supplementary materials, online appendices, and reference lists were examined for inclusion/exclusion criteria. The following data were extracted: (i) study characteristics (year of publication, trial design, inclusion and exclusion criteria, number of randomized patients, treatment strategy in the intervention and control arms, number of patients per arm, follow-up duration, primary and secondary endpoints); (ii) patients' baseline and procedural characteristics; and (iii) outcome measure (*Appendix 1, Tables S5-S8*). Disagreement was resolved by consensus.

Risk of Bias and Endpoint Definitions

The quality of trials and risk of bias were assessed using the Cochrane's Collaboration Tool (18) (*Appendix 1 Table S9*). The primary efficacy endpoint was major adverse cardiovascular events (MACE) and the primary safety endpoint trial-defined major bleeding through at least 1 year. Secondary endpoints included net clinical benefit, all-cause death, myocardial infarction (MI), definite or probable ST, stroke, target vessel revascularization (TVR), and any bleeding. MACE were extrapolated from each trial according to the definition reported in the protocol; definitions included various combinations of all-cause death, cardiac or cardiovascular death, MI, stroke, definite or probable ST, urgent coronary artery bypass grafting, or TVR (*Appendix 1, Table S5*). Major or any bleeding and net clinical benefit were defined according to trial definitions. We chose the Bleeding Academic Research Consortium (BARC) definition when available; if not provided, or if the trial reported multiple definitions, we chose the Thrombolysis in Myocardial Infarction (TIMI) criteria and Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) criteria (Appendix 1, *Tables S5* and *S6* for endpoint definitions).

Statistical analysis

Analyses were performed at study level. Odds ratio (ORs) with 95% confidence intervals (CIs) were calculated to estimate the effects of different DAPT durations. If data on a certain outcome were not available for a trial, it was excluded from the corresponding pooled analysis for that single endpoint. The Q Cochran test and Higgins I^2 statistics were used to estimate heterogeneity among studies, with I^2 <25%, 25–50%, or >50%, respectively, indicating low, moderate, or high heterogeneity (18). For moderate-to-high heterogeneity, the random-effect model with inverse variance weighting was used, whereas the Mantel–Haenszel fixed-effect model was adopted in case of low heterogeneity. Publication bias was evaluated by visual inspection of funnel plots (Appendix 1, *Figures S10–S18*). To evaluate the robustness of our findings, we performed a sensitivity analysis by sequentially removing each single trial from the pooled effect estimates (Appendix *Table S19*). Three subgroup analyses were also run by dividing the trials according to: (i) post-short DAPT use of aspirin vs. $P2Y_{12}$ inhibitor; (ii) post-short DAPT prevalent use of a potent $P2Y_{12}$

inhibitor (i.e. ticagrelor) vs. other oral antiplatelet agent (i.e. aspirin or clopi-dogrel), and (iii) duration of antiplatelet treatment in the very short arm (i.e. 1 month vs. 3 months) (*Appendix* 1, *Table S20*). Meta-regressions were employed to test the impact of year of publication, absolute percentage of patients presenting with ACS, and ab-solute percentage of patients presenting with troponin-positive ACS, on effect estimates (Appendix 1, *Tables S21-S29*). *P*-values <0.05 were considered significant. Analyses were conducted using Review Manager software version 5.3.5 (Cochrane Collaboration) and R (R Foundation for Statistical Computing, version 3.6.1).

RESULTS

Our search produced 5983 potentially relevant articles, seven of which met the inclusion criteria and entered the meta-analysis. The search strategy is outlined in the PRISMA flow diagram (*Appendix* 1 *Table S3*). The main features of each trial are summarized in *Appendix* 1, *Table S4*. The planned duration of DAPT in the experimental arm was 1 month in two trials and 3 months in the remaining five trials; thereafter, patients received aspirin monotherapy in three trials, oral $P2Y_1$ inhibitor monotherapy (clopidogrel, ticagrelor, or prasugrel) in SMART-CHOICE (11), ticagrelor alone in GLOBAL LEADERS (15) and TWILIGHT (10), and clopidogrel alone in STOPDAPT-2 (12). The antiplatelet regimens in the control arms are shown in *Appendix 1, Table S4*. TWILIGHT randomized all patients (regardless of acute or chronic syndromes) to ticagrelor vs. ticagrelor plus aspirin after 3 month DAPT with aspirin plus ticagrelor (10). The follow-up duration was 24 months in two trials and 12 months in the others. The patients' clinical and procedural characteristics are shown in *Appendix 1, Table S7*. Of note, the proportion of troponin-positive ACS patients ranged from 0% in RESET (19) to 85% in REDUCE (16). Conversely, the percentage of patients presenting with CCS was between 0% in the REDUCE (16) and 60% in the STOPDAPT-2 (12). Only two trials included patients with silent ischaemia, accounting in both cases for <10% of the overall population (10, 20).

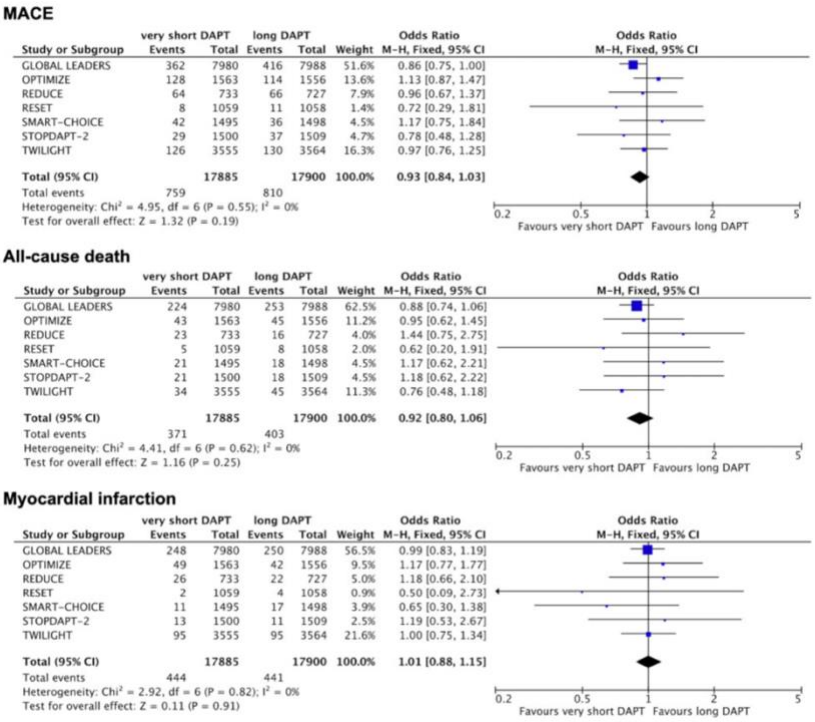
Primary efficacy composite endpoint: trial-defined major adverse cardiovascular events

All seven trials reported this endpoint, involving a total of 35 785 participants. GLOBAL LEADERS (15) had the highest relative weight (51.6%). Heterogeneity among trials was low (I^2 = 0%, P = 0.55). There were 759 recorded events among 17 885 patients treated with very short DAPT vs. 810 among 17 900 patients receiving long DAPT. The pooled effect estimate showed no significant difference between the two groups (OR 0.93, 95% CI 0.84–1.03, P = 0.19, *Figure 1*). Removal of one trial at time did not influence the primary result (*Appendix* 1 *Table S19*). No significant differences were noted according to post-DAPT antiplatelet monotherapy in the experimental arm (aspirin vs. ticagrelor vs. aspirin or clopidogrel) and according to very short DAPT length (1 or 3 months; *Appendix* 1 *Table S20*). Meta-regressions showed no significant associations between moderators and treatment effect (*Appendix* 1 *Table S21*).

Primary safety endpoint: trial-defined major bleeding

All trials except REDUCE (16) reported major bleeding events, involving a total of 34 325 participants. GLOBAL LEADERS (15) had the highest relative weight (27.3%). Heterogeneity among studies was high (I^2= 68%, P = 0.008). Major bleeding occurred in 229 of 17 152 patients treated with very short DAPT and in 299 of 17 173 patients receiving long DAPT, resulting in a 39% significant reduction of major bleeding odds in the very short DAPT arm (OR 0.61, 95% CI 0.40–0.94, P = 0.03, *Figure 2*). Meta-analyses excluding of RESET (19), STOPTDAPT-2 (12), or TWILIGHT (10) were not statistically significant at the 0.05 level, but results were in the same direction of association as the main analysis. (*Appendix 1 Table S19*). After removing GLOBAL LEADERS (15), very short DAPT was associated with an enhanced reduction in major bleeding odds (OR 0.50, 95% CI 0.37– 0.68, P < 0.00001). Analyses according to very short DAPT length showed no significant subgroup differences (P = 0.93); the same was true when trials were grouped according to type of monotherapy following very short DAPT (*Appendix 1 Table S20*). Meta-regressions were non-significant (*Appendix 1 Table S28*).

Figure 1. Major adverse cardiovascular events (MACE), all-cause death, and myocardial infarction.



Secondary endpoints

Net clinical benefit

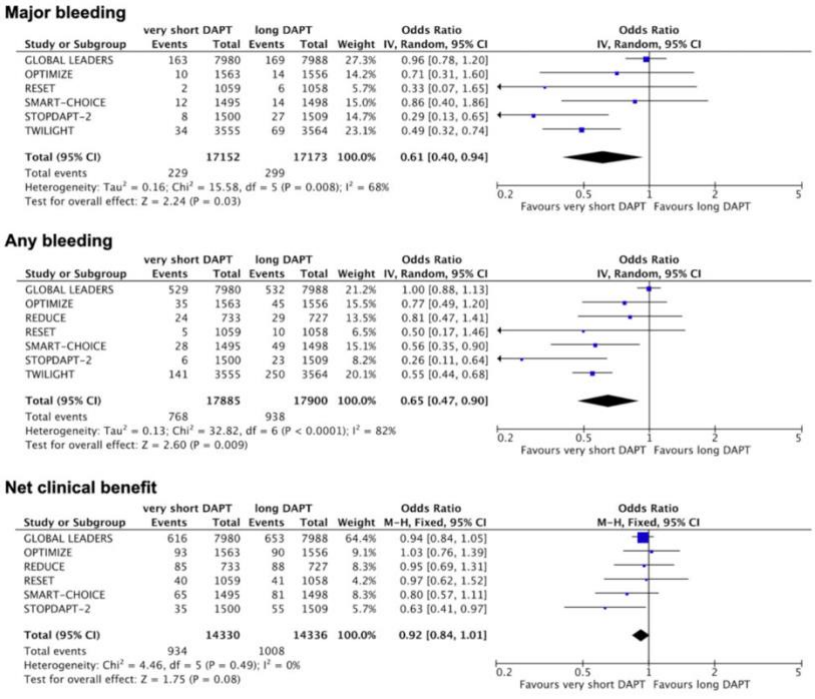
Results for the outcome of net clinical benefit were available for five trials, involving a total of 28 666 patients. Nine-hundred thirty-four out of 14 330 patients in the very short DAPT and 1008 out of 14 336 patients in the long DAPT group developed events. Pooled analysis showed no significant difference between the two treatment arms (OR 0.92, 95% CI 0.84–1.01, P = 0.08, *Figure 3*). Sensitivity and subgroup

analyses did not show substantial changes (*Appendix Tables S19* and *S20*). No significant influence of moderators was shown by meta-regression analyses (*Appendix 1 Table S27*).

Any bleeding

All trials reported results for any bleeding, involving a total of 35 785 patients. Any bleeding occurred in 768 of 17 885 patients treated with very short DAPT and in 930 of 17 900 patients treated with long DAPT, resulting in a 35% significant odds reduction in favour of very short DAPT (OR 0.65, 95% CI 0.47–0.90, P = 0.009, *Figure 2*). Removal of one trial at time did not influence the result of the main analysis (*Appendix 1 Table S19*). Subgroup analyses according to very short DAPT length (P = 0.49) or to type of monotherapy after DAPT (*Appendix Table S20*) showed no significant subgroup differences. Meta-regressions did not yield significant results (*Appendix 1 Table S29*).

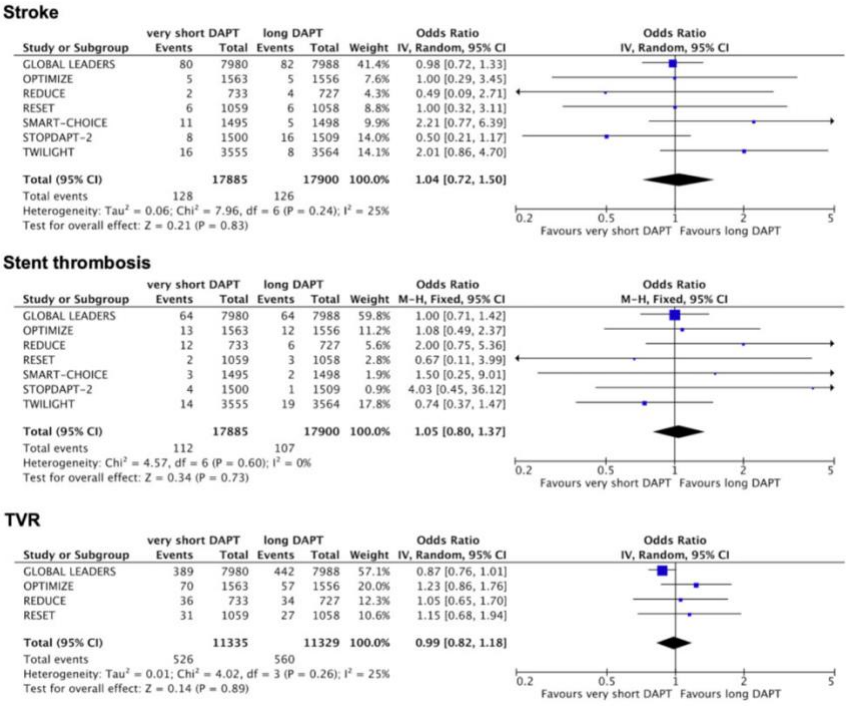
Figure 2. Major bleeding, any bleeding and net clinical benefit



All-cause death, myocardial infarction, stent thrombosis, stroke, and target vessel revascularization

Results for other ischaemic endpoints are shown in *Figures 1 and 3*. Three-hundred seventy-one patients receiving very short DAPT died during follow-up, compared with 403 in the long DAPT arm, with no statistically significant difference between the two treatments (OR 0.92, 95% CI 0.80–1.06, P = 0.25). The two strategies were also comparable with respect to MI (OR 1.01, 95% CI 0.88–1.15, P = 0.91), stroke (OR 1.04, 95% CI 0.72–1.50, P = 0.83), ST (OR 1.05, 95% CI 0.80–1.37, P = 0.73), and TVR (OR 0.99, 95% CI 0.82–1.18, P = 0.89). The results of sensitivity or subgroup analyses were consistent with those of the primary analysis (Appendix 1, *Tables S19-S20*). Results of meta-regression analyses were non-significant (*Appendix 1, Tables S22–S26*).

Figure 3. Stroke, stent thrombosis and target vessel revascularization (TVR)



DISCUSSION

To the best of our knowledge, this is the first meta-analysis investigating the efficacy and safety of very short (<_3 months) compared with long (12–15 months) DAPT regimens in CAD patients undergoing PCI. According to our findings, reducing DAPT after modern PCI to 1 or 3 months does not expose to a higher-ischaemic risk, and may potentially be associated with a substantial safety benefit.

Two decades ago, data from PCI-CURE (2) and CREDO (21) laid the foundation for the co-administration of aspirin and clopidogrel in patients undergoing PCI, for a period that was subsequently crystallized in 12 months (if a first-generation DES was implanted) or 1 month (if a BMS was used). About one decade ago, the appreciation of long-term residual ischaemic risk for ACS patients, along with the late thrombosis scare with first-generation DES, stimulated RCTs, such as the DAPT trial (7), that supported a generalized extension of DAPT duration. The subsequent introduction of second-generation DES, however, clearly associated with a low incidence of stent-related thrombotic events (22), along with the appreciation of the haemorrhagic risks of extended DAPT (13, 23), shifted the emphasis on shortening DAPT after PCI, particularly in patients at high bleeding risk or likely to require early DAPT discontinuation (e.g. with known need for major surgery or malignancy). In this scenario, the Polymer- free Drug-Coated Coronary Stents in Patients at High Bleeding Risk (LEADERS FREE) (24) was the first trial showing, in a high bleeding risk scenario, that a 1 month DAPT strategy following PCI with a biolimus A9-DES was superior to 1 month DAPT after BMS implantation in reducing the rate of thromboembolic events. Subsequent studies have further investigated shortened DAPT after DES implantation in populations of all-comers or low-ischaemic

risk, with encouraging results (19, 20, 25-30). Pooled together, these data demonstrated no difference between ≤6 months vs. 12 months DAPT regarding the incidence of MI and ST, whereas the rate of bleeding decreased with shortened DAPT (31). Of note, a cautionary signal arose from the ACS cohort, in whom the risk of thrombotic events with a short course (particularly 3 month DAPT) was higher, with nullification of the net clinical benefit (31). To date, international consensuses and guidelines support the concept of patient-tailored DAPT regimens, weighed on individual haemorrhagic and ischaemic risk (6, 32). Nevertheless, solid data are still scarce, and the European Society of Cardiology has given a class IIa, level of evidence (LOE) A recommendation for 3 month DAPT and a class IIb, LOE C recommendation for 1 month DAPT exclusively for patients with CCS at, respectively, high and very high bleeding risk (33).

In our meta-analysis, 1 or 3 month DAPT vs. long DAPT offered comparable protection in terms of ischaemic events in a cohort of CCS and ACS patients. Moreover, in line with the evidence from previous meta-analyses (13, 14) our findings confirm that 1 or 3month DAPT significantly reduced major bleeding. The benefit of very short DAPT on bleeding risk, of note, appeared blunted by the inclusion of GLOBAL LEADERS (15). One possible explanation resides in the mandatory ticagrelor monotherapy following very short DAPT compared with aspirin plus clopidogrel DAPT in the control arm for chronic CAD patients. The recently published TWILIGHT (10), instead, randomized a mixed cohort of patients to ticagrelor alone vs. ticagrelor plus aspirin after initial 3 months DAPT, demonstrating a 44% reduction in BARC 2–5 bleeding, with a nearly halved risk of major bleeding, and without parallel increase in ischaemic events with monotherapy.

According to our findings, different post-DAPT regimens did not confer any advantage in terms of safety, and the use of $P2Y_{12}$ inhibitor monotherapy, even with ticagrelor, seemed as safe as aspirin monotherapy. Finally, we did not register significant interactions according to very short DAPT duration, suggesting that 1 or 3 months DAPT may be equally safe and effective. We believe that these results align with current ESC recommendation on CCS patients (33), supporting the shortening of DAPT when the clinical context requires it. On the other hand, they reassure clinicians confirming that very short DAPT may be a viable option also in acute patients, if ischaemic risk is acceptable and longer DAPT is deemed inappropriate.

LIMITATIONS

Our meta-analysis has several limitations. First, this is a study-level meta-analysis, with the limitations of each included study; moreover, in the absence of patient-level data, it was hardly possible to assess the impact of baseline characteristics on outcomes; we did, however, perform sensitivity analyses for different durations of very short antiplatelet therapy and for type of antiplatelet monotherapy. Second, we adopted trial definitions of MACE and bleeding endpoints; however, analyses of individual ischaemic outcomes were additionally performed. Importantly, patients with unstable coronary syndromes were generally underrepresented and subgroup trial data were often lacking. For this reason, and despite two different meta-regressions showing no significant influence of CAD presentation on effect measure, our results should not be immediately generalized to the whole spectrum of CAD patients. Again, due to the absence of RCTs

testing a 'very short' DAPT against 6 months, we could not provide a comparison between these two regimens. Finally, given some heterogeneity across trials in terms of year of publication, trial design, patients enrolled, and type and duration of antiplatelet therapy, the more rigorous random-effects analysis was applied in the presence of moderate-to-high heterogeneity and a meta-regression using the year of publication as covariate was carried out.

CONCLUSIONS

The present meta-analysis in patients undergoing PCI with second-generation DES indicates comparable ischaemic hazards with 1 or 3 month DAPT vs. 12 month DAPT. The odds of major or any bleeding were reduced by 1/3 with shortened regimens. Consistent efficacy and safety results were seen for aspirin vs. $P2Y_{12}$ inhibitor monotherapy after initial DAPT, and for 1 vs. 3 month DAPT. Overall, the findings support the use of very short DAPT in CAD–PCI patients, but durations should be tailored to individual risk-benefit profiles.

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Duration of dual antiplatelet therapy and subsequent monotherapy type in patients undergoing drug eluting stent implantation: a network meta-analysis

INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is the cornerstone of secondary prevention of thrombotic events after drug-eluting stent (DES) implantation or acute coronary syndromes (ACS). Powerful platelet inhibition, however, increases bleeding risk. Importantly, whereas the thrombotic risk spikes in the first months after DES implantation, bleeding events increase more linearly with DAPT exposure (1) and are linked to increased mortality, especially when DAPT is prolonged for ≥12 months (2). In a recent meta-analysis of randomized control trials (RCTs), we conclude that very short (3 or even 1 month) DAPT may be a viable option not only in stable patients, as we were unable to show any ischemic trade-off of the expected reduction in bleedings, even in the ACS subgroup (3). Those data expand on previous meta-analyses comparing the "standard" 12 months with 6 or >12 months DAPT durations (4,5). Yet, due to the absence of randomized comparisons, previous works could not clarify the safety and efficacy of ≤3 months regimens compared to 6 or >12 months. In addition, they could not stratify the durations according to the subsequent monotherapy, which instead has been largely debated in the last few years, since a growing number of RCTs has supported a strategy of aspirin (rather than $P2Y_{12}$ inhibitor) drop after ≤3 months DAPT (6–9).

Thus, we have performed a hierarchical network meta-analysis (NMA) with the aim to compare safety and efficacy across different antiplatelet schemes and durations in patients receiving DES.

METHODS

This meta-analysis observes the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations (10) (*Appendix 2, Table S1*). The protocol was registered in PROSPERO (CRD42020173010).

Study selection and quality assessment

Included RCTs fulfilled the following criteria: 1) patients presented with either ACS or chronic coronary syndromes (CCS) and underwent successful percutaneous coronary intervention (PCI) with DES implantation 2) participants were randomized to receive different DAPT durations: very short (≤3 months), short (6 months), standard (12 months) or extended (>12 months) 3) a single antiplatelet drug, either aspirin or a $P2Y_{12}$ inhibitor, was continued thereafter. We considered only articles in English language. We excluded studies: 1) enrolling patients treated with oral anticoagulation and/or undergoing BMS implantation and/or managed conservatively 2) with non-RCT design.

Between November 2019 and January 2020, we accomplished a systematic search of the literature using Medline/PubMed, Web of Science, Embase, Cochrane, ClinicalTrials.gov and TCTMD (https://www.tctmd.com). Search terms were: "dual antiplatelet therapy", "drug-eluting stent", "ticagrelor",

"prasugrel", "clopidogrel" and combinations between them (*Appendix 2, Table S2* outlines the full search strategy). Previous meta-analyses on the same topic were examined. Abstract and presentations from major cardiovascular society congresses (European Society of Cardiology, American College of Cardiology, American Heart Association and Transcatheter Cardiovascular Therapeutics) were also screened. References of the included articles were inspected with a snowball approach. The online search was re-ran before proceeding to the final data analysis. Candidate trials were identified by two independent investigators (SB and GC) screening titles and abstracts. Full texts and supplementary materials were thus assessed to confirm whether inclusion criteria were met.

We extracted information regarding: a) study characteristics (trial design, inclusion and exclusion criteria, primary and secondary endpoints, number of randomized patients, treatment strategy in the intervention and control arms, number of patients per arm, follow-up duration, year of publication); b) patients' baseline and procedural characteristics; c) outcome measure. In case of discrepancies, consensus was achieved. The Cochrane Collaboration's Tool (11) was applied to assess the risk of bias.

Endpoints definitions

The primary efficacy endpoint (PEP) was a composite of cardiac death, myocardial infarction (MI) and stent thrombosis (ST). The primary safety endpoint (PSP) was major bleeding. All-cause death, cardiac death, MI, stroke, ST, net clinical benefit and any bleeding were the secondary endpoints. Outcome definitions derived from each trial were applied (*Appendix 2, Table S3-S4*). Net clinical benefit was defined as a composite of one or more ischemic endpoint and a major bleeding. As for bleeding endpoints, we elected to use the Bleeding Academic Research Consortium (BARC) definition if provided. If not, we chose the available definition preferring the Thrombolysis in Myocardial Infarction (TIMI) (12).

Statistical analysis

We performed a Bayesian NMA to obtain a simultaneous comparison of multiple regimens, combining direct and indirect evidences (13) and postulating the absence of discrepancy between them (that is, *evidence consistency*). We chose the more conservative random-effect model to account for heterogeneity between studies (14). The Markov chain Monte Carlo method was used to estimate odds ratios (ORs) and associated 95% confidence interval (CI), running four chains with 30.000 interactions after a burn-in of 10000. A patients/year (P/Y) approach was adopted to address with different follow-up time and non-informative priors were set. Heterogeneity was measured through the I^2 statistic, with <25%, 25-50% and >50% I^2 indicating, respectively, a low, moderate or high heterogeneity (15). Comparison-adjusted funnel plot and Egger's regressions were employed for publication bias, as previously described (16). Convergence was evaluated graphically according to Gelman and Rubin (17). Consistency was assessed comparing direct and indirect evidences with the node-splitting technique. A ranking of treatment regimens was achieved by computing the surface under the cumulative ranking curve (SUCRA) values for each endpoint, with higher SUCRA indicating well-performing treatments.

Subgroup analyses focusing on the ACS population and on patients receiving 2nd generation DES were carried out. Acknowledging that the RCTs investigating ≤3 months DAPT differ regarding the monotherapy following DAPT, we aimed to investigate the impact of the monotherapy by dividing those RCTs according to the foresaw regimen (i.e. very short with early aspirin drop and prolonged $P2Y_{12}$ and very short with long-term aspirin) and conducted further sensitivity analyses by excluding studies with a $P2Y_{12}$ inhibitor monotherapy or a ticagrelor monotherapy following DAPT and by subdividing the $P2Y_{12}$ monotherapies (i.e. very short with early aspirin drop and prolonged $P2Y_{12}$) with clopidogrel versus potent $P2Y_{12}$ (i.e. ticagrelor or prasugrel). Sensitivity analyses on the primary and secondary endpoints were also conducted repeating the analysis with a frequentist approach (using random-effect models with inverse variance) and including only studies in which randomization among different DAPT durations occurred during the index hospitalization or procedure. We repeated the analysis including the SMART-DATE (20) trial as short vs. extended instead of short vs. standard DAPT as in the principal analysis, as the study compared 6 vs. 12 months or longer DAPT (with a median DAPT duration in the control arm of more than 17 months). Finally, meta-regressions were carried out on the primary efficacy and safety endpoints with the purpose of assessing the impact of multiple covariates on outcome estimates. The covariates of interest included age and the proportions of diabetic, ACS, 2nd generation DES-treated and clopidogrel-treated patients, and were estimated as pooled mean trial-level values. The goodness of fit of the regression models was compared with those of the original model by means of the Deviance Information Criterion (DIC), considering a 5-units DIC reduction suggestive for a goodness-of-fit improvement. R (The R Foundation for Statistical Software, version 3.6.0) was used to implement the analysis.

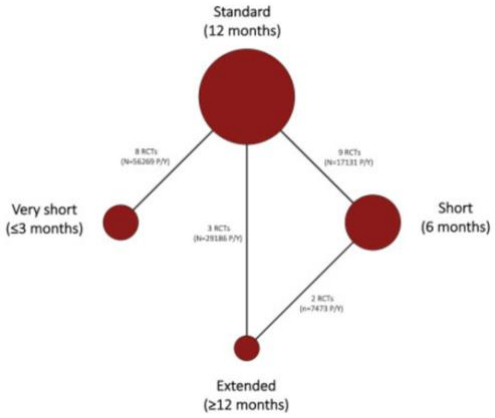
RESULTS

Of 22155 results achieved with our search, 22 met the inclusion criteria and were included in the NMA (*Appendix 2, Table S5* for the PRISMA flow-chart).

Appendix 2, Table S6-S10 report the references and main features of included studies. The overall population amounts at 110059 P/Y with 1417 primary efficacy events and 1155 primary safety events. Of 22 trials, nine compared short vs. standard DAPT (n=17131 P/Y), eight very short vs. standard (n=56269 P/Y), two short vs. extended (n=7473 P/Y) and three standard vs. extended (n=29186 P/Y). Follow-up duration ranged from 9 months to 3 years. In 17/22 trials, after DAPT the experimental arm was shifted to aspirin. GLOBAL LEADERS (6), TWILIGHT (9) and TICO (18) trials adopted a ticagrelor monotherapy, whereas clopidogrel was chosen in STOPDAPT (7), and SMART-CHOICE allowed any oral $P2Y_{12}$, (clopidogrel was preferred in 3/4th of patients) (8). Appendix table S6 provides the treatment strategy for the control groups. The proportion of ACS patients ranged from 0% (e.g. OPTIMIZE (19), which only enrolled chronic patients) to 100% for DAPT-STEMI (20), REDUCE (21) and TICO (18).

Treatment network is shown in Figure 1. We chose standard DAPT as the reference treatment because this duration has been investigated in most of the included trials. Bias assessment is reported in *Appendix 2, Table S11*.

Figure 1. Treatment network



Bayesian NMA results

Results for the efficacy endpoints are displayed in Figure 2. There was no significant difference across different DAPT durations, though extended DAPT was associated with a near-significant odds reduction with respect to PEP (extended vs. standard OR 0.70 95% CI 0.50-1.0, short vs. standard OR 1.1 95% CI 0.78-1.50, very short vs. standard OR 1.0 95% CI 0.74-1.40). Similarly, a trend toward a reduction in ST in favour of extended DAPT was noted (extended vs. standard OR 0.48 95% CI 0.29-1.0), whereas all other regimens yielded similar odds for this endpoint. Extended DAPT was associated with reduced odds of MI (OR 0.56, 95% CI 0.44-0.77), without significant differences between standard and other strategies. All treatments were comparable with respect to all-cause death, cardiac
death and stroke. Figure 3 shows the results for the safety endpoints and for net clinical benefit. Very short significantly reduced the odds of PSP, whereas there was no difference when short or extended DAPT were analysed (extended vs. standard OR 1.3 95% CI 0.81-2.30, short vs. standard OR 0.70 95% CI 0.44-1.10, very short vs. standard OR 0.61 95% CI 0.39-0.87). Both short and very short DAPT were associated with lower odds of any bleeding (short vs. standard OR 0.61 95% CI 0.38-0.90, very short vs. standard OR 0.65 95% CI 0.46-0.87). Finally, for net clinical benefit, the odds were similar for the four treatments (Figure 3).

Heterogeneity, node-split analysis and publication bias

Appendix 2, Table S12 reports the I^2 for individual comparisons and the global I^2 for each endpoint, heterogeneity ranging from low to high. Node-split did not show significant inconsistency between direct and indirect evidences (Figure 4 for the primary endpoints and *Appendix 2, Table S13*). Comparison-adjusted funnel plots and Egger's regressions were not suggestive of significant publication bias (*Appendix 2, Table S14*).

Figure 2. *Results for efficacy endpoints. MI, myocardial infarction; PEP, primary endpoint; ST, stent thrombosis.*

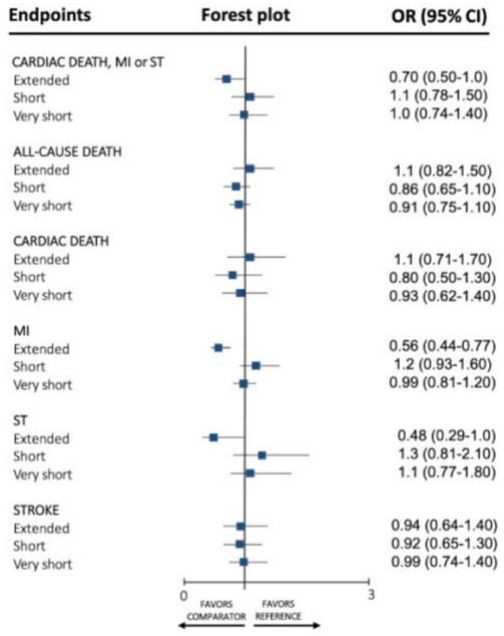


Figure 3. *Results for safety endpoints and net clinical benefit.*

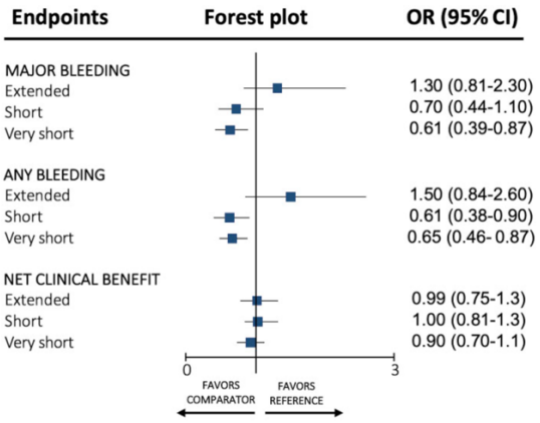
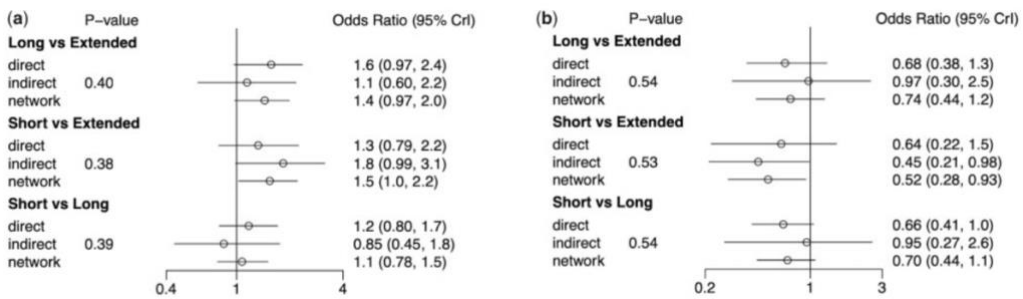


Figure 4. *Node-split analyses for the primary efficacy (A) and safety (B) endpoints. Each forest plot shows the direct, indirect, and network esti- mates for each of the direct comparisons of the main network. P < 0.05 indicates significant inconsistency.*

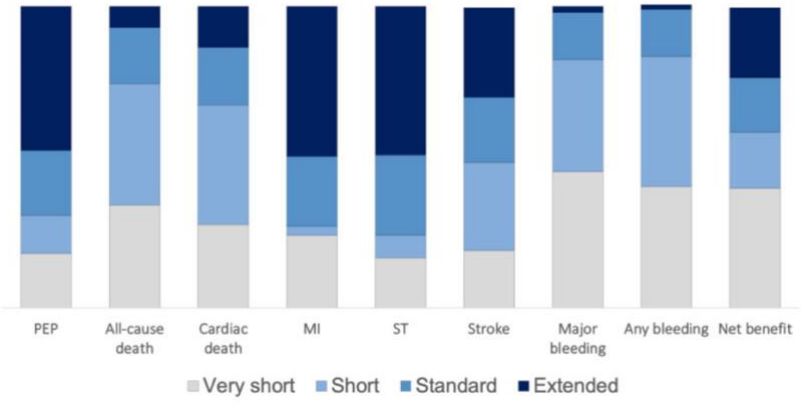


Treatment ranking

Treatment rankings according to SUCRA values are displayed in Figure 5. Extended treatment was first-placed for the PEP and for the individual components of MI and ST. There was a reverse relation between

SUCRA for PSP and treatment duration, with very short DAPT ranked first for this endpoint. Short DAPT was the treatment of choice with respect to all-cause and cardiac death and very short DAPT achieved the highest SUCRA for net clinical benefit. Short and very short DAPT yielded the best SUCRA for any bleeding. Results for stroke were conflicting, with extended treatment ranked first, equal merit with short and followed by standard.

Figure 5. *Coloured bars show the surface under the cumulative ranking curve values for each endpoint on a scale from 0 to 1, with ranking indicating probability that each dual antiplatelet therapy duration is the first 'best', the second 'best', etc. to reduce the given endpoint. Therefore, higher bars, corresponding to higher surface under the cumulative ranking curve, indicate better performing treatments***.**



Bayesian NMA results in ACS patients

Results in the ACS population are summarized in *Appendix 2, Table S15*, also reporting the references of the published sub-analyses. The ACS subgroup included 24838 P/Y, 487 primary efficacy events and 260 primary safety events. Importantly, in the ACS subgroup there was no direct RCT comparing short vs. very-short DAPT, and a direct comparison between standard and extended DAPT was also lacking for net clinical benefit and stroke. Extended, as compared to standard DAPT, significantly reduced the odds of PEP (OR 0.39 95% CI 0.14-0.94) and ST (OR 0.24 95% CI 0.06-0.71), and increased that of any bleeding (OR 2.20 95% CI 1.20-4.40), whereas the rate of MI was comparable (OR 0.48 95% CI 0.20-1.30). There was, unlike the overall population, no significant benefit of shorter regimens with respect to both major and any bleeding (any bleeding: short vs. standard OR 0.65 95% CI 0.33-1.20, very short vs. standard OR 0.72 95% CI 0.49-1.10; major bleeding: short vs. standard OR 0.51 95% CI 0.17-1.40, very short vs. standard OR 0.60 95% CI 0.29-1.20).

Bayesian NMA results in RCTs of 2nd generation DES

Fifteen RCTs were included in the sub-analysis focusing on 2nd generation DES, for an overall sample of 73270 P/Y. Among them, those treated with extended DAPT were significantly less represented (n=3735 P/Y). The direct comparison between extended and long DAPT was missing. The results are summarized in *Appendix 2, Table S16*. No advantage of extended compared to standard was present across all the endpoints.

Particularly, the point estimates of extended vs. standard DAPT for MI (OR 0.92, 95% CI 0.42-2.10) and ST (OR 0.77, 95% CI 0.23-2.50) were in the same direction as the main analysis, albeit loosing statistical significance. Short and very short did not differ from standard for all endpoints at the exception of any bleeding, which was reduced by very short (OR 0.65, 95% CI 0.46-0.87).

Sensitivity analyses

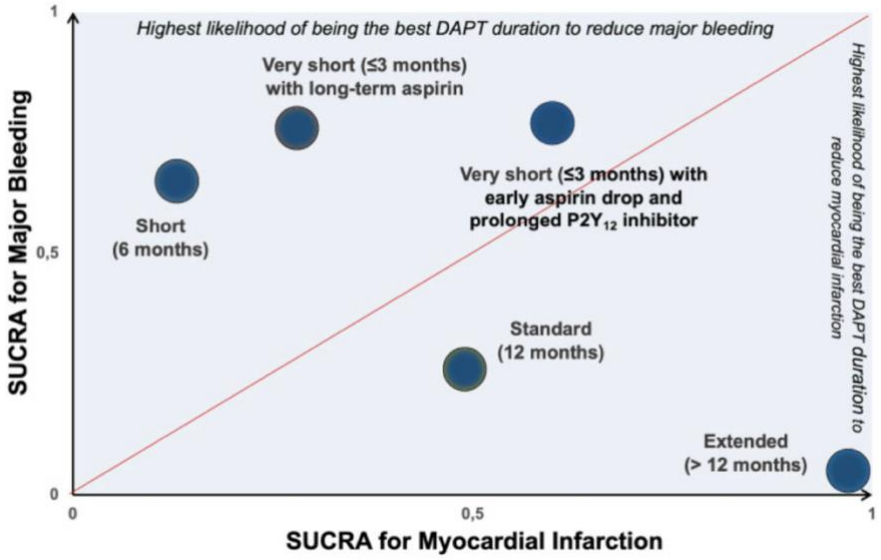
Antiplatelet therapy following DAPT

At the end of very short DAPT, 24037 P/Y were treated with a $P2Y_{12}$ inhibitor and 4088 P/Y with aspirin. After dividing the two monotherapy groups, the Bayesian NMA (*Appendix 2, Table S17*) was consistent with the main analysis regarding all the efficacy endpoints. Major bleeding was significantly reduced in case of ≤3 months DAPT with early aspirin drop and prolonged $P2Y_{12}$ inhibitor (OR 0.61, 95% CI 0.36-0.94), while it was not in case of long-term aspirin (OR 0.55, 95% CI 0.19-1.40). Similarly, the benefit of ≤3 months DAPT with early aspirin drop and prolonged $P2Y_{12}$ inhibitor on any bleeding was preserved (OR 0.62, 95% CI 0.39-0.89), as opposite to long-term aspirin (OR 0.72, 95% CI 0.40-1.30). When treatments were ranked according to the SUCRA values (*Appendix 2, Table S17*), extended was again first for MI whereas very short with early aspirin drop and prolonged $P2Y_{12}$ inhibitor yielded the highest SUCRA for major bleeding (equal merit with very short + aspirin), being second-ranked for MI (Figure 6). Consistently, we found no benefit of very short regimen on the safety endpoints when RCTs of post-DAPT $P2Y_{12}$ monotherapy were excluded (*Appendix 2, Table S18*), whereas similar results as the main analysis were observed after excluding all ticagrelor monotherapy studies (*Appendix 2, Table S19*). Dichotomizing the $P2Y_{12}$ type, dropping aspirin early remained consistently associated with an any (but not major) bleeding reduction only in the clopidogrel group (*Appendix 2, Table S20*).

Other sensitivity analyses and meta-regressions

Appendix 2, Table S21 provides the results of the frequentist NMA. Overall, they were consistent with those of the Bayesian analysis except for the reduction in PEP and ST in favour of extended treatment, which reached statistical significance. Including only RCTs with randomization at the time of index procedure/hospitalization gave neutral results across all endpoints (*Appendix 2, Table S22*). Finally, considering SMART-DATE a short vs. extended trial (*Appendix 2, Table S23*), we obtained neutral results for MI. Meta-regressions results are reported in the *Appendix 2, Table S24*.

Figure 6. *Trade-off between major bleeding and myocardial infarction across different dual antiplatelet therapy (DAPT) durations and subsequent monotherapies. SUCRA, surface under the cumulative ranking.*



DISCUSSION

The main findings of our network metanalysis can be summarized as follows: 1) Compared to 12 months, 3 and 6 months DAPT show comparable efficacy on the PEP, a composite of cardiac death, MI and ST. 2) Extending DAPT beyond 12 months reduces MI and, by using a more sensitive approach, also reduces PEP and ST. 3) Very short (≤3 months) DAPT reduces major bleedings by ~40%. 4) A similar effect on safety is observed with 6 months DAPT, albeit only if a composite of major and minor bleedings is considered. 5) When stratifying the very short regimens according to the subsequent monotherapy, dropping aspiring early and prolonging the $P2Y_{12}$ inhibition is the strategy of choice to minimize the combination of MI and major bleeding. Whereas DAPT is still the paradigm of secondary prevention after coronary stent implantation and its efficacy in reducing thrombotic events is unquestioned, its optimal duration is still a matter of concern. Indeed, the appreciation that DAPT, especially after an ACS, protects from ischemic events well beyond the old "standard" of 12 months required after 1st generation DES has been coupled with a heightened attention to the accrual of bleedings episodes. Recently, new evidence is accumulating in support of shortening DAPT in most cases (3).

It should be noted that, due to a landmark analysis limiting its benefit to the first month post stenting (22), the need for 12 month DAPT was already unsuccessfully challenged at the time of PCI-CURE (23) and CREDO (24). Later, the unheralded increase in very late ST observed with 1st generation DES paved the way for RCTs that explored extended DAPT regimens, with reduced emphasis on the safety component (25). More recently, 2nd generation-DES have finally minimized the dreaded risk of ST, particularly very late after stenting (26), and DAPT discontinuation guided by a physician decision has been shown to be safer than interruption after a bleeding event (the so called DAPT "disruption") (27). Unsurprisingly, thus, the recently presented Onyx-ONE trial (28) has shown that a 1 month DAPT regimen in a large, unselected, cohort of patients treated with a modern zotarolimus-eluting stent is non-inferior to the same regimen applied to patients treated with a polymer-free DES specifically designed and tested in high-bleeding risk patients (29). Our results supports the concept that 12 months, the recommended DAPT duration for most patients in guidelines published between 2011 and 2014, and still the preferred length for all high-risk patients in the

last European Society of Cardiology (ESC) guidelines on myocardial revascularization (30), should be comprehensively reconsidered. Indeed, not only short, but even very short DAPT may be as effective as 12 months DAPT with 2nd generation DES. Notably, despite ESC recommending ≤3-months DAPT only in CCS and according to bleeding risk (31), we found consistent results also in the ACS sub-population. Dropping aspirin while continuing $P2Y_{12}$ monotherapy might guarantee a sufficient antithrombotic power in this high thrombotic risk subset, avoiding the excess of bleeding specifically ascribable to aspirin (32). Data from the *post-hoc* ACS sub-analysis of the GOBAL-LEADERS, in fact, reveal that continuing DAPT with ticagrelor from one month up to one year post-PCI does not clearly reduce ischemic events as compared to ticagrelor monotherapy, instead increasing the bleeding hazard (33). More generally, TWILIGHT showed a net benefit of dropping aspirin at three months in event-free patients at high-risk for ischemia and/or bleeding, supporting the paradigm of a "tailored" DAPT in complex patients, in which these attitudes may coexist (9). Interestingly, very short DAPT followed by $P2Y_{12}$ continuation achieved the highest SUCRA for major bleeding and was second-ranked (after extended) for MI, supporting this as the best DAPT combination and timing, even if caution should be applied due to the small number of RCTs testing this strategy. The counterintuitive absence of bleeding reduction with ≤3 months DAPT followed by aspirin, instead, is likely due to the low statistical power of the analysis.

Conversely, we did observe a stronger efficacy of extended DAPT in reducing the individual component of MI and, in the frequentist analysis, PEP and ST. This benefit, of note, was lost when studies in which randomization occurred after PCI were omitted. In fact, patients at high bleeding risk or with previous bleeding events were unlikely to be included in those RCTs. Therefore, the reduction in thrombotic events observed in extended as compared to standard DAPT cannot be generalized, and may only refer to patients fulfilling the inclusion/exclusion criteria of the individual RCTs, e.g. high thrombotic risk without concomitant bleeding concerns, as recommended by the ESC guidelines (31).

Additionally, we found that six and ≤3-months DAPT reduce the odds for any bleeding events in a roughly similar measure, whereas only very short DAPT achieves a significant reduction in major bleeding. Although DAPT interruption before 6 months is already contemplated by international guidelines (31), there is no definite evidence, at present, that ≤3 months DAPT guarantees better safety compared to 6 months. This concept, suggested by our results, is all the more relevant in light of the prognostic value of major bleedings (34). This result was less definite in the ACS subgroup, probably due to the higher prevalence of potent $P2Y_{12}$ inhibitors and concomitant additional antithrombotic therapy, which may increase the rate of events in the early phase. Although the bleeding reduction was only preserved in the clopidogrel monotherapy subgroup, this result is affected by the very small number of RCTs and low statistical power of this subanalysis.

We believe that the results of the present meta-analysis, interpreted in the light of contemporary stenting, strongly question the concept of 12 months DAPT for most patients. Indeed, considering that we found no difference in terms of ischemic events between standard and both short and very short DAPT strategies, and taking into account the limitations of the available scores for evaluating bleeding risk during the initial

hospitalization (35), the main focus after a PCI with DES implantation should be on the reduction of bleeding events. Therefore, a short DAPT regimen, ideally 3 months for most patients (e.g. CCS) should probably be the standard therapy prescribed at discharge. This timeframe should be extended to at least 6, but potentially (according to clinical judgement) more than 12 months in ACS or CCS undergoing high risk coronary interventions without high bleeding risk, and shortened to 1 months in selected cases (3). In case of concomitant clues of high ischemic and bleeding risk (e.g. ACS at high bleeding risk), dropping aspirin at 1 or 3 months and continuing thereafter with a $P2Y_{12}$-inhibitor might be preferable. Additionally, we believe that bleeding risk, a moving target, should be often reassessed to select patients for further extension of DAPT, with the aim of reducing ischemic events in the long-term.

Compared to another meta-analysis on the same topic (36), our work offers different novelties, like the inclusion of the recently published TICO trial (18), which improve the quality of data related to P2Y12 monotherapy, and, importantly, the exclusion of BMS-treated patients. We also provide a unique insight into the differences between ≤3 and 6 months DAPT.

Limitations

Firstly, the present is a study-level meta-analysis, suffering from unavoidable problems in terms of studies' designs and endpoints. However, we performed several sub-analyses and meta-regressions to account for baseline feature and possible confounding factors. Secondly, we acknowledge that most trials used clopidogrel (instead of newer and more powerful drugs) as the $P2Y_{12}$ inhibitor of choice; however, this supports our main message of shortening DAPT whenever possible, as bleeding risk is even higher if more potent $P2Y_{12}$ drugs are used. Thirdly, published data on ACS were not available for all studies, resulting in smaller sample size (and less power than in the main analysis) for this subanalysis. Fourthly, studies comparing short and extended DAPT did not report data for stroke and net clinical benefit. Fifthly, we could not perform a sub-analysis according to the subtypes of P2Y12 employed as monotherapy; however, such an analysis would be likely underpowered and thus scarcely informative. Finally, timing of randomization in the included trials may affect results, as in inclusion the follow-up period (as opposed to randomization in the before stenting or during initial hospitalization) may select patients with higher thrombotic and lower bleeding risk.

CONCLUSIONS

The efficacy of short and very short DAPT duration is comparable with that of standard DAPT after DES implantation, while extended DAPT reduces MI and ST rate and should be the strategy of choice when the ischemic risk certainly overcomes the bleeding one. Regarding safety, very short and short regimens are better than standard, 12 months DAPT. Dropping aspirin early and prolonging the $P2Y_{12}$ after very short DAPT might be the best option when the risk of MI recurrence and major bleeding are expected to coexist. Therefore, standard DAPT as recommended by current guidelines does not seem to be the best option in most patients.

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ICARUS score for predicting peri-procedural bleeding in patients undergoing percutaneous coronary intervention with cangrelor

INTRODUCTION

As the very early phase after percutaneous coronary intervention (PCI) is characterized by a prominent risk of thrombotic complications compared to bleeding (1-3), maximizing platelet inhibition throughout the periprocedural phase has been a topic of intense interest (4). Cangrelor is an intravenous nucleotide analogue that rapidly blocks the $P2Y_{12}$ receptor. Its effect wanes off in a timely manner after withdrawing the infusion, resulting in versatile platelet inhibition. Because of its pharmacokinetics, cangrelor can be administered immediately after coronary angiography to pursue full platelet inhibition in combination with aspirin during *ad hoc* PCI, thus avoiding the downsides of pre-treating with an oral $P2Y_{12}$ inhibitor (4,5). Since the publication of the landmark CHAMPION trials (6-9), where cangrelor was shown to reduce myocardial infarction (MI) and stent thrombosis (ST) compared to clopidogrel in a mixed cohort of stable and unstable PCI patients, international guidelines recommend its use to minimize thrombotic complications in patients naïve to oral $P2Y_{12}$ receptor inhibitors and deemed suitable for PCI (10).

As coronary revascularization techniques and technologies have evolved (11-13), the focus in recent years has shifted from maximizing antithrombotic therapy during PCI to achieving an optimal trade-off between thrombotic and bleeding risk (14-18). As a result, risk stratification based on bleeding propensity and tailored antithrombotic strategies are now strongly recommended by guidelines and expert consensus documents across the spectrum of coronary artery disease (10,19). While this "bleeding-centered" approach is increasingly guiding the choice of post-procedural antithrombotic strategies (20-24), there is a paucity of data on the effect of potent, yet rapidly reversible, platelet inhibition with cangrelor on the risk of periprocedural bleeding (25), and whether this risk can be predicted. This contributes to the poor penetrance of intravenous antiplatelets in clinical practice (26,27).

We designed a real-world study to reflect the current use of cangrelor in clinical practice and to derive a risk score for the prediction of periprocedural bleeding in patients undergoing PCI with cangrelor.

METHODS

Protocol overview, inclusion and exclusion criteria, data collection

The Intravenous CAngrelor in high-bleeding Risk patients Undergoing percutaneouS coronary intervention (ICARUS) is an investigator-initiated, multicenter, observational, retrospective study conducted in 7 high-volume centers in Italy. Protocol details have been previously registered (clinicaltrials.gov ID: NCT05505591). Consecutive patients aged ≥18 years who underwent PCI and received cangrelor were included. Patients receiving cangrelor as a bridge to surgery were excluded. Medical records were reviewed to collect clinical, procedural, and follow-up data. Data were anonymously recorded using an Excel (Microsoft Corporation) spreadsheet. The requirement for written informed consent was waived due to the retrospective nature of the study. The study protocol complied with the Declaration of Helsinki.

Endpoints definition and adjudication

The primary endpoint was Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding within 48 hours after PCI. Endpoint events were centrally adjudicated by a committee comprising four interventional and clinical cardiologists affiliated with the coordinating centers (Ospedale Policlinico San Martino, Genova, and A.O.R.N. Sant'Anna e San Sebastiano, Caserta). Access site and non-access site related bleeding were also adjudicated and appraised separately.

Statistical analysis

Categorical variables were reported as frequencies and percentages and compared using the Student-t test or Fisher's test, as appropriate. Continuous variables were tested for normality using the Kolmogorov-Smirnov test, reported as mean ± standard deviation (SD) or median (interquartile range [IQR]), and compared with the Student-t test or Wilcoxon-Mann-Whitney test, as appropriate. Comparisons of event rates were performed using pairwise Fisher's tests. In the present analysis, only patients with complete information on periprocedural bleeding were included. Missing values accounted for <1% of the total dataset and a maximum of ~2% within each individual variable. To minimize data loss, missing values were imputed using a multiple imputation algorithm. The imputed dataset was then randomly split in a 3:1 ratio to obtain the derivation and validation cohorts, respectively.

Candidate risk predictors were selected based on clinical (known bleeding predictors from previous literature) and statistical (variables whose prevalence differed significantly between patients experiencing bleeding vs. not) considerations and entered into univariable binary logistic regressions using BARC 2, 3, or 5 bleeding within 48 hours after PCI as the dependent variable. Putative predictors included: baseline clinical characteristics (age, sex, body mass index); risk factors and comorbidities (diabetes, hypertension, family history of coronary artery disease, smoking habit, chronic kidney disease, heart failure); laboratory data (platelet count, white blood cell count, hemoglobin); clinical presentation (acute vs. chronic coronary syndrome); periprocedural factors (pre-treatment with a $P2Y_{12}$ inhibitor, use of glycoprotein IIb/IIIa inhibitors [GPI], unfractionated heparin dosage, cangrelor infusion duration, 3-vessel disease, femoral access, post-procedural use of a newer $P2Y_{12}$ inhibitor [ticagrelor or prasugrel]). Independent variables not linearly related to the dependent variable were categorized (28). Hemoglobin (Hb) was dichotomized using the threshold of 110 g/L (29), age using the cut-off of 75 years (29), and estimated glomerular filtration rate (eGFR) was categorized in three levels (i.e., >60, 60-30, and ≤29 ml/min) (29). A Variance Inflation Criterion value <5 was considered indicative of absence of collinearity. Significant univariable predictors ($p<0.05$) were entered into a multivariable model, from which only independent predictors ($p<0.05$) were retained in the final model. Odds ratios (ORs) and associated 95% confidence intervals (CI) were derived. ORs were then rounded to the nearest integer value to obtain the individual weights of each variable in the score. Model discrimination was tested in the derivation and validation datasets using receiver operator characteristic

(ROC) curves. Calibration was assessed by comparing predicted and observed event rates across progressive score strata.

We sought to determine the score threshold able to identify the subgroup at the highest risk of periprocedural bleeding by comparing the rates of 48-hour BARC 2, 3, or 5 bleeding across progressive score strata. We compared the accuracy of the resulting score threshold with the PRECISE-DAPT and Academic Research Consortium-High Bleeding Risk (ARC-HBR) scores (10,30-32) using the DeLong's test. The accuracy of the score was also tested in a sensitivity analysis limited to access-related bleeding and compared with previous scores. Two-tailed P values <0.05 were considered statistically significant. Statistical analysis was performed using "R" (version 3.6.2). The corresponding author had full access to the study dataset and takes responsibility for its integrity and the data analysis.

RESULTS

Baseline characteristics

The total study cohort consisted of 1076 patients who underwent PCI from January 2019 to May 2023, of whom 5 were excluded due to missing clinical outcome data (Figure 1). Of the resulting 1071 patients (total amount of missing values <1%), 54 (5%) had a primary endpoint event of BARC 2, 3, or 5 bleeding [35 (65%) BARC 2 bleeding, 12 (22%) BARC 3a bleeding, 6 (11%) BARC 3b bleeding and 1 (2%) BARC 5a bleeding], of whom 24 (44%) due to access site-related events. Baseline clinical characteristics of the study population, stratified by patients who did or did not bleed during follow-up, are reported in Table I. In the overall population, mean age was 68±12 years and 24% of patients were female, with a numerically higher proportion of women among patients experiencing bleeding. There were no differences with respect to cardiovascular risk factors and comorbidities except for a higher prevalence of chronic kidney disease in patients with bleeding (28% vs. 15%, p=0.02). This group was also more likely to present with acute coronary syndrome (ACS) (94% vs. 72%, p<0.001) or cardiogenic shock (15% vs. 3%, p<0.001), and to receive GPI (9% vs. 2%, p=0.01), femoral access (30% vs. 7%, p<0.001), or mechanical support (17% vs 3%, p<0.001). There was no difference in the use of $P2Y_{12}$ inhibitor pre-treatment, type of $P2Y_{12}$ inhibitor administered after the procedure, unfractionated heparin dosage, use of bolus-only cangrelor administration, and duration of cangrelor infusion.

Risk score derivation and performance in the training dataset

The training dataset included 793 randomly selected patients, of whom 37 (4.7%) experienced BARC 2, 3 or 5 bleeding. The results of the binary logistic regression models are summarized in Table II. The final multivariable model identified three independent predictors of BARC 2, 3, or 5 bleeding at 48 hours after PCI: age ≥75 years (OR 2.58, 95% CI 1.21-5.48, p=0.01), ACS at presentation (OR 8.14, 95% CI 2.28-52, p=0.01) and femoral access (OR 6.21, 95% CI 2.71-14, p<0.001). Multicollinearity was excluded as VIF values were always below 2. The final risk score, the ICARUS score, was developed by assigning 3 points to age ≥75 years, 8 points in case of ACS at presentation, and 6 points if femoral access was used. The total

integer score ranged between a minimum of 0 and a maximum of 17 points. The ROC curve is presented in Figure 2, panel A, and shows a good discrimination ability with an AUC of 0.78 (95% CI 0.70-0.85) in the derivation cohort. Predicted and observed rates of BARC 2, 3, or 5 bleeding across progressive score strata are presented in Figure 2, panel B, showing excellent calibration.

Figure 1. *Study flow-chart. Abbreviations: ARC-HBR: Academic Research Consortium-High Bleeding Risk; PRECISE-DAPT: PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Antiplatelet Therapy.*

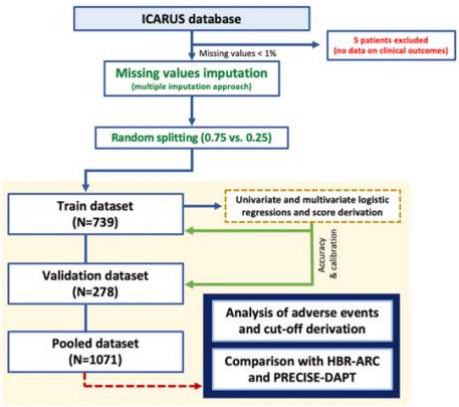
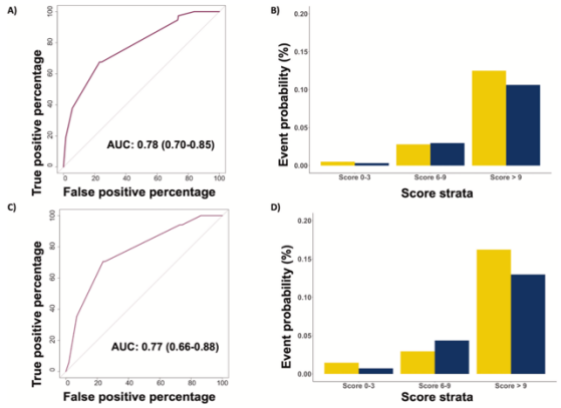


Figure 2. *Discrimination and calibration in the derivation (panels A and B) and validation (panels C and D) cohorts. Panel A shows the receiver operator characteristic (ROC) analysis. Panel B and D show the comparison between predicted (navy blue bars) and observed (golden bars) rates of 48-h BARC 2, 3, or 5 bleeding. Abbreviations: AUC: area under the curve. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)*



Risk score validation in the test dataset

The novel risk score was validated using a test dataset of 278 patients, of whom 17 (6.1%) experienced the primary endpoint. At validation analysis, the discrimination ability of the ICARUS score for the prediction of periprocedural BARC 2, 3, or 5 bleeding was good, with an AUC of 0.77 (95% CI 0.66-0.88 – Figure 2, panel C), akin to that of the derivation cohort. Calibration of the new score for BARC 2, 3, or 5 bleeding at 48 hours was also good in the validation dataset and similar to the derivation analysis (Figure 2, panel D).

Table I. *Baseline characteristics of patients with and without bleeding*

	Overall (N=1071)	Bleeding (N=54)	No-bleeding (N=1017)	P-value
Clinical history				
Age, years	68 ± 12	70 ± 13	68 ± 12	0.09
Age ≥75 years	304 (28)	281 (28)	23 (43)	0.03
Female sex	255 (24)	19 (35)	236 (23)	0.06
BMI, Kg/m2	27 ± 5	26 ± 5	27 ± 5	0.18
Hypertension	796 (74)	41 (76)	755 (74)	0.93
Dyslipidemia	684 (64)	31 (57)	653 (64)	0.38
Diabetes	280 (26)	17 (31)	263 (26)	0.45
Smoker	349 (33)	15 (28)	334 (33)	0.52
Family history of CAD	234 (22)	9 (17)	225 (22)	0.44
COPD	120 (11)	7 (13)	113 (11)	0.85
Peripheral arterial disease	132 (12)	3 (6)	129 (13)	0.14
Atrial fibrillation	98 (9)	7 (13)	91 (9)	0.46
Previous stroke or TIA	40 (4)	4 (7)	36 (4)	0.14
Previous myocardial infarction	176 (16)	6 (11)	170 (17)	0.37
Previous PCI	196 (18)	5 (9)	191 (19)	0.11
Previous CABG	39 (4)	1 (2)	38 (4)	0.72
Chronic kidney disease	170 (16)	15 (28)	155 (15)	0.02
Creatinine, mg/dl	1.09 ± 1.11	1.08 ± 1.11	1.35 ± 1.20	0.08
Dialysis	15 (1)	2 (4)	13 (1)	0.17
Active cancer	32 (3)	3 (6)	29 (3)	0.22
Heart failure	117 (11)	8 (15)	109 (11)	0.48
Presentation				
Acute coronary syndrome	782 (73)	51 (94)	731 (72)	<0.001
Cardiogenic shock	41 (4)	8 (15)	33 (3)	<0.001
Cardiac arrest	56 (5)	7 (13)	49 (5)	0.02
Procedural characteristics				
Access				<0.001
NA	1 (0)	0 (0)	1 (0)	
Radial	982 (92)	38 (70)	944 (93)	
Femoral	87 (8)	16 (30)	71 (7)	
Culprit vessel				<0.001
NA	1 (0)	1 (2)	0 (0)	

LMS	65 (6)	9 (17)	56 (6)	
LAD	567 (53)	26 (48)	541 (53)	
LCx	171 (16)	3 (6)	168 (17)	
RCA	264 (25)	15 (28)	249 (25)	
SVG	2 (0)	0 (0)	2 (0)	
Number of vessels treated				<0.001
NA	13 (1)	4 (7)	9 (1)	
1	792 (74)	35 (65)	757 (75)	
2	231 (22)	13 (24)	218 (21)	
3	34 (3)	2 (4)	32 (3)	
Thrombus	357 (33)	28 (52)	329 (32)	0.005
DES implanted	1035 (97)	46 (85)	989 (97)	<0.001
Total stent lenght, mm	42 ± 25	52 ± 31	41 ± 24	0.01
Mechanical support	39 (4)	9 (17)	30 (3)	<0.001
Pharmacology				
P2Y12 inhibitors pre-PCI				
Clopidogrel	41 (4)	1 (2)	40 (4)	0.68
600 mg	37 (95)	0 (0)	37 (97)	0.04
Ticagrelor	35 (3)	2 (4)	33 (3)	> 0.99
Prasugrel	0 (0)	0 (0)	0 (0)	> 0.99
Procedural medications				
Total UFH dose, UI	7071 ± 2549	7370 ± 2760	7055 ± 2538	0.38
GpIIbIIIa inhibitor	25 (2)	5 (9)	20 (2)	0.01
Cangrelor bolus only	16 (1)	1 (2)	15 (1)	0.57
Cangrelor bolus + infusion	1023 (96)	52 (96)	971 (96)	> 0.99
Cangrelor infusion duration, min	128 ± 32	126 ± 26	128 ± 33	0.55
Cangrelor infusion duration < 120 min	40 (4)	6 (11)	34 (3)	0.01
P2Y12 inhibitor post-PCI				
Clopidogrel	375 (35)	15 (28)	360 (36)	0.35
600 mg	348 (97)	12 (80)	336 (97)	0.01
Ticagrelor	617 (58)	33 (62)	584 (58)	0.61
Prasugrel	52 (5)	1 (2)	51 (5)	0.48

Table II. Logistic regression analysis results

Covariate	Univariable analysis	Multivariable analysis

	OR (95% CI)	P value	OR (95% CI)	P value
Age ≥75 years	2.41 (1.24 – 4.72)	0.01	2.58 (1.21 – 5.48)	0.01
Female sex	1.84 (0.89 – 3.63)	0.09		
BMI	0.93 (0.86-1.01)	0.09		
Diabetes	1.38 (0.66 – 2.75)	0.37		
Hypertension	1.23 (0.58-2.92)	0.61		
Family history of CAD	0.77 (0.30-1.68)	0.54		
Heart failure	1.71 (0.63 – 3.95)	0.25		
Major anemia*	3.76 (1.35 – 9.02)	0.01	1.95 (0.61 – 5.56)	0.23
Chronic kidney disease				
eGFR 30 - 60, ml/min	1.97 (0.88 - 4.12)	0.08	1.04 (0.42 – 2.42)	0.92
eGFR <30, ml/min	4.99 (1.37 – 14.4)	0.01	1.92 (0.45 – 6.82)	0.34
White blood cells on admission	1.05 (0.99 – 1.11)	0.09		
Platelet on admission	0.99 (0.99 – 1)	0.38		
Acute coronary syndrome	6.82 (2.06 – 42)	0.01	8.14 (2.28 – 52)	0.01
Femoral access	8.52 (4.12 – 17)	<0.001	6.21 (2.71 – 14)	<0.001
$P2Y_{12}$ inhibitor pre-treatment	0.73 (0.12 – 2.48)	0.67		
Cangrelor infusion duration, min	0.99 (0.98 – 1)	0.93		
Mechanical support	6.77 (2.35 – 17)	<0.001	1.72 (0.50 – 5.38)	0.37
Three-vessel disease	1.21 (0.55-2.47)	0.61		
Ejection fraction	0.96 (0.93 – 0.99)	0.01	0.99 (0.96 – 1.02)	0.74
Glycoprotein IIbIIIa inhibitors	3.24 (0.74 – 10)	0.07		
UFH dose	1 (0.99-1.0002)	0.38		
Post-procedural ticagrelor or prasugrel	0.88 (0.46-1.77)	0.73		

Correlation with clinical events and comparison with current risk scores

In the pooled dataset, including 1071 patients undergoing PCI with cangrelor, there was a significant trend toward higher rates of periprocedural BARC 2, 3, or 5 bleeding in patients with a higher score (high-risk group, score: >9 points, N=274) compared to patients in the intermediate-risk group (score: 6-9 points, N=529) and low-risk group (score: ≤3 points, N=268) (13.5% vs. 2.8% vs. 0.7%, respectively; p for trend <0.001). Comparison analyses showed weak evidence for difference in BARC 2, 3, or 5 bleeding rates between patients in the low-risk group (score ≤3) vs. intermediate-risk group (6-9 points) (p=0.05); both these groups had significantly lower rates of periprocedural BARC 2, 3, or 5 bleeding compared to the high-risk group (>9 points) (p<0.001 for both comparisons – Figure 3). The ARC-HBR and PRECISE-DAPT

scores were available for all patients in both the original and imputed dataset. At ROC analysis (Figure 4, panel A), an ICARUS score >9 points yielded a higher discrimination (AUC 0.72, 95% CI 0.66-0.79) compared to an ARC-HBR score ≥1 (AUC 0.61, 95% CI 0.54-0.68, p<0.001) and a PRECISE-DAPT score ≥25 (AUC 0.58, 95% CI 0.52-0.65, p<0.001) for the prediction of periprocedural BARC 2, 3, or 5 bleeding, whereas there was no difference between the latter two scores (p=0.448). Sensitivity and specificity values are summarized in Figure 4, panel B. When restricting the analysis to access-site related bleeding (*Appendix 3, Figure S1 and Table SI*), results were consistent except for a further lower discrimination of the PRECISE-DAPT score, which performed significantly worse than the ICARUS and the ARC-HBR scores.

Figure 3. *BARC 2, 3, or 5 bleeding rates across progressive risk score strata. Pairwise comparisons between events rates were significant between patients with score > 9 vs. score 6–8 and between score > 9 vs. score ≤ 3 (both p < 0.001) but not between score ≤ 3 and score 6–8 (p = 0.05).*

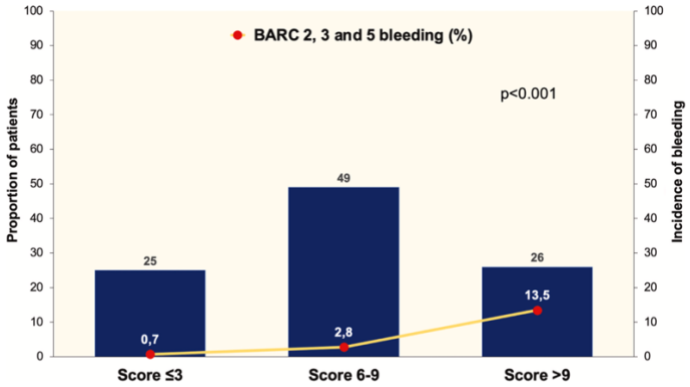
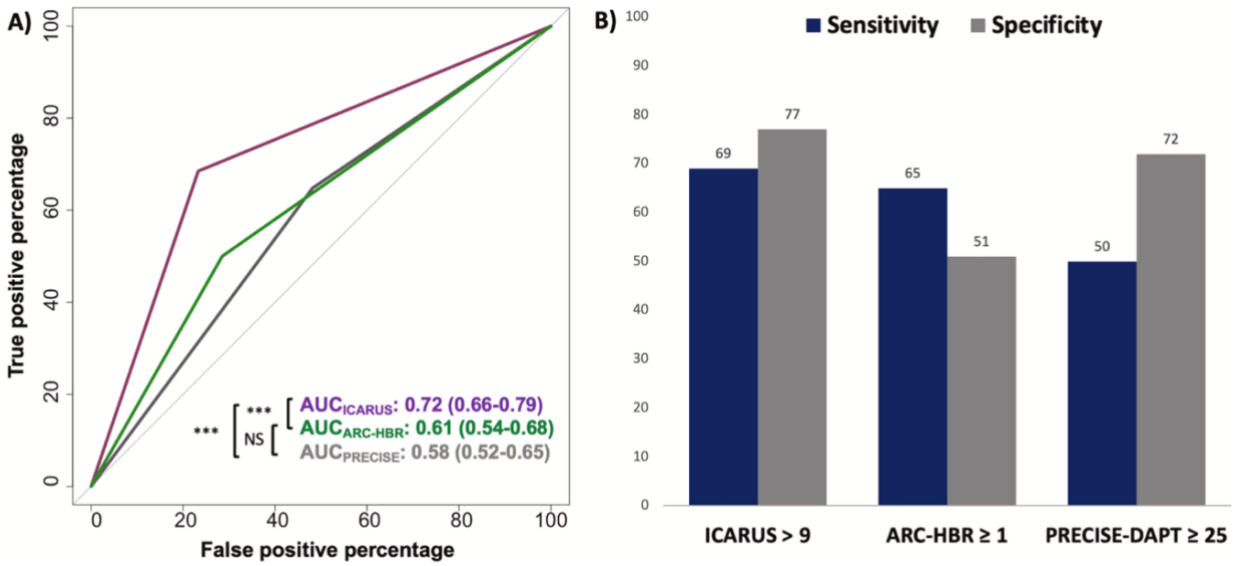


Figure. 4. *Receiver operator characteristic (ROC) for an ICARUS score > 9 compared to an ARC-HBR score ≥ 1 and a PRECISE-DAPT score ≥ 25 (panel A) and sensitivity and specificity across the same risk scores and thresholds (panel B). Abbreviations: ARC-HBR: Academic Research Consortium-High Bleeding Risk; AUC: area under the curve; PRECISE-DAPT: PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Antiplatelet Therapy. NS stands for non-significant; *** for p < 0.001.*



DISCUSSION

In this multicenter study, we derived and validated a novel risk score, the ICARUS score (age, ACS at presentation, and femoral access), which showed to accurately predict the risk of periprocedural BARC 2, 3, or 5 bleeding in patients undergoing PCI and receiving cangrelor. When the study population was stratified using the new score, approximatively 1 in 4 patients with a score of >9 points were identified as being at high risk of periprocedural bleeding, accounting for almost 70% of the total bleeding events. In the high-risk group, the risk of BARC 2, 3, or 5 bleeding was more than 4-fold higher than the intermediate-risk group (6-9 points) and roughly 14-fold higher than the low-risk group (≤3 points). The discrimination ability for periprocedural bleeding of the new risk score outperformed that of the risk scores that are currently recommended by international guidelines for bleeding risk prediction (10,33).

In contrast to post-procedural antithrombotic regimens, current recommendations for the use of cangrelor do not consider the importance of on-treatment, periprocedural bleeding risk. Despite the short duration of infusion (usually ~2 hours) and very fast offset of action, cangrelor was shown to increase the risk of bleeding in the CHAMPION studies (9). Although in these trials cangrelor was only compared with clopidogrel whereas potent $P2Y_{12}$ inhibitors, which have different pharmacodynamic profiles and clinical efficacy (31,34,35), were not administered, contemporary real-world data support a similar effect of clopidogrel and ticagrelor on bleeding events in patients at HBR (36,37). Furthermore, despite the excess risk associated with cangrelor was mainly driven by minor bleeding events, the CHAMPION program excluded HBR patients and predominantly enrolled young patients (<65 years) with a few comorbidities, potentially at low bleeding risk. This contrasts with the current practice of most centers, where elderly and multimorbid patients are increasingly frequent (38). In real-world populations, the potential harm of cangrelor in terms of increased risk of bleeding may be more pronounced, and therefore warrants further investigation. In addition, although bleeding in PCI patients continues to be perceived mainly as a post-discharge issue, several studies have shown a time-dependent distribution, with a predominant bleeding risk during the early post-PCI phase, followed by a plateau (1), suggesting that a timely implementation of bleeding-avoidance strategies is important to optimize patient outcomes (2,39). However, neither the randomized CHAMPION trials nor the subsequent real-world studies have fully addressed the issue of bleeding risk stratification in cangrelor-recipients (40-42). Recently, the ARCANGELO registry showed a modest absolute risk of bleeding in a cohort of PCI patients treated with cangrelor and transitioned to any (including potent) $P2Y_{12}$ inhibitors; however, this study included only patients with ACS and none of the reported analyses focused on bleeding risk stratification (43).

The novel ICARUS score yielded good accuracy in predicting periprocedural bleeding and has the advantage of being easy to use (including simple and readily available variables) and calculate (no need for web-based calculator). Each item of the ICARUS score has been previously associated with an increased risk of bleeding, also in patients on cangrelor. In a prespecified subgroup analysis of the CHAMPION-PHOENIX trial (44), elderly patients (≥75 years) experienced a 3-fold higher rate of moderate or severe bleeding. ACS at presentation has been also shown to be associated with bleeding risk and to potentially improve risk

stratification over and above validated risk tools (45). This observation was confirmed in our study where acute presentation maintained its independent predictive ability after accounting for possible confounders, including the use of $P2Y_{12}$ inhibitor pre-treatment or GPI, the dosage of heparin, the duration of cangrelor infusion, and the use of a potent $P2Y_{12}$ inhibitor (ticagrelor or prasugrel) in the post-procedural phase. Although these factors often accompany ACS presentation, none was independently associated with bleeding in our study. The use of femoral access has also been consistently associated with periprocedural bleeding (20). In this regard, given that a significant proportion of bleeding in the acute peri-PCI phase is related to the access site, we performed a sensitivity analysis focusing on this specific complication, which showed similar discrimination compared to the main analysis and superior performance of the ICARUS score compared to other risk scores. These results are not unexpected considering that both the ARC-HBR criteria and the PRECISE-DAPT score were developed to predict post-discharge, rather than periprocedural, bleeding. Moreover, the PRECISE-DAPT score derivation dataset excluded in-hospital events (46), giving account of the very low accuracy of the score in our study (47).

Our observations have several clinical implications. First, they provide reassurance on the safety profile of cangrelor in real-world patients. Indeed, in our study, only 1 in 4 patients belongs to the high-risk group (i.e., those presenting with at least two concomitant score items), whereas the rate of periprocedural BARC 2, 3, or 5 bleeding was relatively low (<3%) in the majority of patients undergoing PCI with cangrelor. Yet, our data underscore the need for specific risk stratification tools for periprocedural bleeding in cangrelor recipients and indicate that current risk scores, which were designed to predict mainly post-discharge events, cannot be used for this purpose. Our findings promote treatment personalization of patients undergoing PCI in several different respects. First, the ICARUS score may assist interventional cardiologists in identifying high-risk patients, in whom cangrelor administration might have an unfavorable effect due to an excess risk of peri-procedural bleeding. In these patients, the exclusive use of oral P2Y12 inhibitors may be a safer treatment option. Moreover, the novel score may inform about the main determinants of peri-procedural bleeding risk in patients receiving cangrelor, and thereby potentially guide decision-making for access site selection (e.g., avoiding the use of femoral access when cangrelor use is planned). Furthermore, our findings suggest the necessity for intensified post-procedural monitoring when cangrelor is used in high-risk patients identified by the ICARUS score (e.g., those with a score >9 points).

LIMITATIONS

This study was conceived with an observational and retrospective design, which introduces inherent selection bias, carries the risk of data loss and makes our results hypothesis-generating. Further evaluation and validation of the novel score in prospective studies are needed. These limitations were partially mitigated by the decision to assess the endpoints within the hospitalization period. In addition, bleeding events were adjudicated by a central committee. Furthermore, the amount of missing data was extremely low, and data loss was further minimized thanks to missing values imputation. We randomly selected a subgroup of patients to validate our score in a cohort not used for score derivation; however, further external validation

studies in larger populations with different clinical profiles and ethnicities are necessary. The incidence of severe or life-threatening bleeding was low. Therefore, larger studies are needed to confirm the accuracy of the identified risk model for risk stratification of more severe events. Finally, because there was no control group receiving only oral $P2Y_{12}$ inhibitors, we cannot infer whether avoiding cangrelor in the high-risk group may have reduced the rate of bleeding.

CONCLUSIONS

In this study, we developed and validated the ICARUS score, a simple 3-item risk score for the prediction of periprocedural bleeding in patients undergoing PCI with cangrelor. The ICARUS score (age, acute clinical presentation, and femoral access) identified patients at high risk of periprocedural bleeding in whom the use of cangrelor should be considered cautiously and close postprocedural monitoring is desirable. Prospective validation studies of this novel score are warranted.

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Summary of main scientific contributions

Across the individual studies included in this thesis, several key themes have emerged with consistency and clinical relevance.

First, this thesis highlights bleeding as a central outcome, rather than a secondary safety consideration, across both the chronic and procedural phases of PCI. In this respect, the included studies were inspired by the realization of the importance of bleeding risk as a co-equal component of therapeutic effectiveness (1, 2). The included studies confirm that intensive platelet inhibition, when tailored to both procedural context and thrombotic risk, can be associated with improved control of ischemic complications while minimizing haemorrhagic ones. These patterns align with contemporary randomized data suggesting that modulation of antiplatelet intensity in the periprocedural and subacute period may offer net clinical benefit (3).

A recurrent theme that the included studies hint at is the importance of dynamic adjustment of antiplatelet intensity over time and based on individualized clinical judgement. The data herein presented emphasize the feasibility and safety of shorter term DAPT in the post-PCI phase and, in fact, the lack of rationale for considering a "fixed" duration of treatment the standard for most individuals (*one size fits all* approach) (3-5). Besides, they underscore the feasibility of risk-stratifying candidates for cangrelor infusion, even despite the requirement for prompt administration in acute clinical settings in which other key determinants of bleeding risk may not be readily available. In this respect, despite the lack of direct comparison with a control group, the real-world data herein presented also hold potential to inform future research aimed at further clarifying the safety–efficacy profile of cangrelor, compared with oral P2Y12 inhibitors, across bleeding risk strata.

Scientific contextualization of the project and alignment with contemporary evidence

The body of evidence presented in this thesis was generated during a period of notable evolution in antiplatelet therapy for patients undergoing PCI. During this timeframe, accumulating evidence and evolving clinical practice have increasingly shaped how antiplatelet strategies are conceptualized, evaluated, and implemented in diverse patient populations (5, 6). Consequently, the findings should be understood not as isolated, static observations, but rather as part of a dynamic continuum that interacts with ongoing advances in antiplatelet pharmacotherapy. Collectively, this emerging evidence supports a progressive shift away from the historical paradigm of uniform 12-month DAPT toward more flexible strategies, including shortened DAPT durations, early aspirin discontinuation, and P2Y12 inhibitor monotherapy in selected patients.

Among the most influential recent contributions is the MASTER DAPT trial, which evaluated an abbreviated antiplatelet strategy in patients at high bleeding risk undergoing PCI with contemporary drug-eluting stents (7). The TARGET-FIRST trial investigated P2Y12 inhibitor monotherapy after 1 month of DAPT in patients undergoing primary PCI for myocardial infarction with early complete revascularization (8). Conversely, the NEO-MINDSET trial evaluated an even earlier antiplatelet simplification strategy, testing immediate post-PCI aspirin withdrawal in favor of potent P2Y12 inhibitor monotherapy in a broader acute coronary

syndrome population (9). Beyond individual trials, recent meta-analytical evidence has provided further support for shortened DAPT strategies (5).

Importantly, apart from the ICARUS registry presented herein, no major registry or randomized trial specifically focusing on bleeding risk stratification in cangrelor-treated patients has been published recently. This underscores the scientific value of the study and establishes a robust platform for future substudies in this uniquely characterized and sizeable real-world cohort.

Conclusions

In conclusion, this PhD thesis provides robust evidence on how antiplatelet therapy influences outcomes after PCI and demonstrates the value of dynamic, individualized treatment strategies. The findings, developed over a period of rapid evolution in the field, align closely with emerging evidence from contemporary trials and reinforce the paradigm of flexible, patient-centered antiplatelet care. This perspective has significant clinical relevance and may help clinicians optimize antiplatelet therapy to achieve the best balance between efficacy and safety in patients undergoing PCI.

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Supplementary Table S1. PRISMA checklist

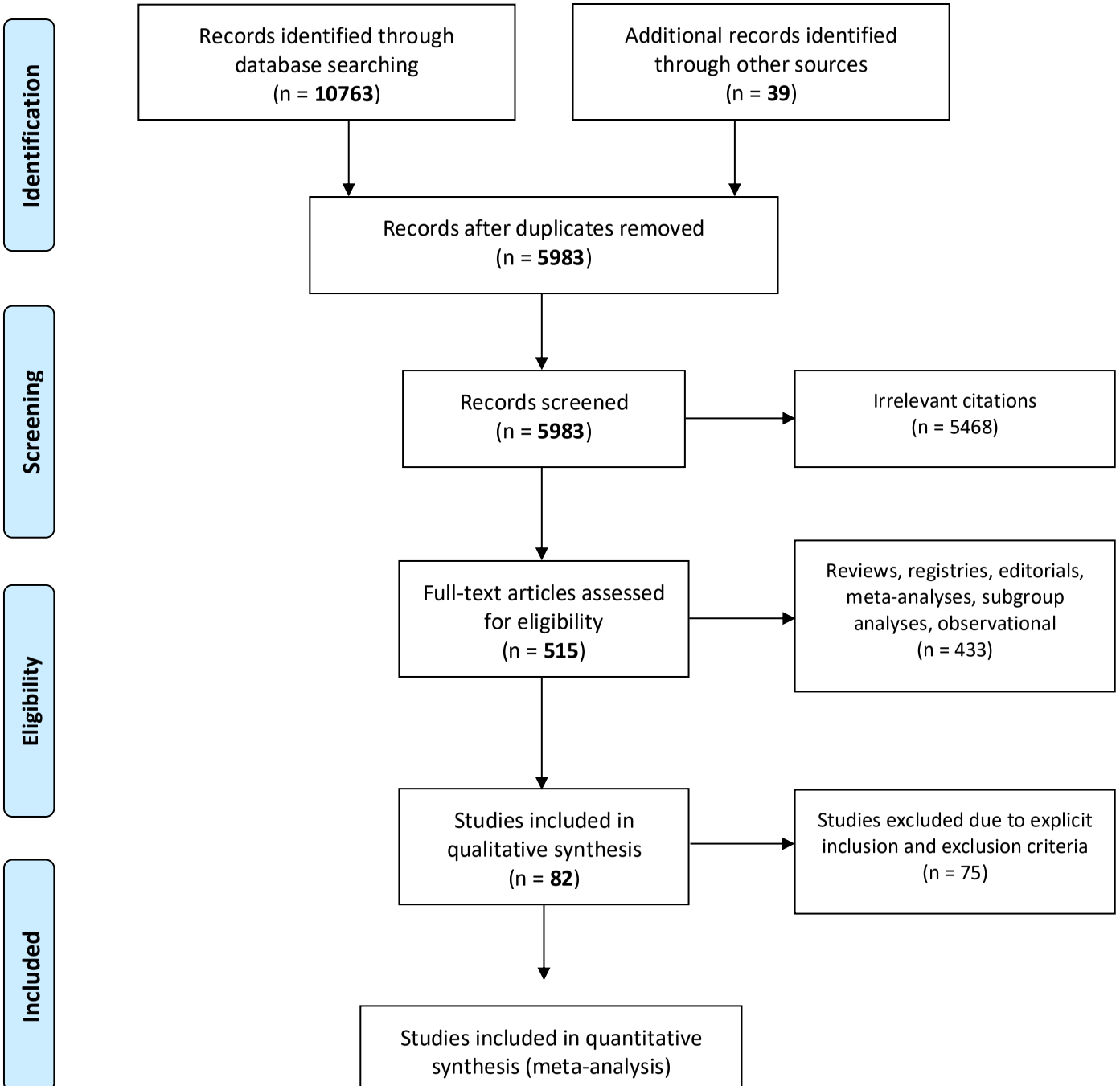
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Under registration in PROSPERO, ID 153522
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5 Supp. S4-S7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supp. S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Supp. S3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Supplementary Table S2. Full electronic search in MEDLINE database through October 1, 2019

Research	Query	Items found
1	Dual antiplatelet therapy	4993
2	Single antiplatelet therapy	2053
3	Dual antiplatelet therapy AND duration	812
4	Dual antiplatelet therapy AND short	356
5	Dual antiplatelet therapy AND long	940
6	Clopidogrel	13780
7	Ticagrelor	2451
8	Prasugrel	2295
9	Ticagrelor AND random*	775
10	Clopidogrel AND random*	3315
11	Prasugrel AND random*	663
12	Dual antiplatelet therapy AND randomized trial	1228
13	Dual Antiplatelet therapy AND clopidogrel	2375
14	Dual antiplatelet therapy AND Ticagrelor	589
15	Dual antiplatelet therapy AND Prasugrel	535

Supplementary Table S3. PRISMA flowchart



Supplementary Table S4. Characteristics of included Trials

Name	Design	Inclusion criteria	Main exclusion criteria	Study enrolment	Enrolled patients	Time of randomization	Daily DAPT regimen (mg)	DAPT duration	Primary composite end point	Follow up (months)
GLOBAL LEADERS (6)	open-label	≥18 years; ≥1 stenosis ≥ 50% in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation with RVD ≥2.25 mm.	Intolerance to aspirin, P2Y12 inhibitors, bivalirudin, stainless steel or biolimus; intake of a strong CYP3A4 inhibitor; moderate to severe hepatic impairment; planned surgery, including CABG as a staged procedure, ≤ 12 month, unless DAPT is maintained throughout the peri-surgical period; oral anti-coagulation therapy; active major bleeding or major surgery within the last 30 days; history of ICH; stroke (any type) ≤ 30 days; pregnancy or breastfeeding.	Jul 2013 – Nov 2015	15968	Index procedure	Experimental arm: Ticagrelor 90 bid + Aspirin 75-100 (1month) followed by Ticagrelor monotherapy Control arm: Aspirin 75-100 + Ticagrelor 90 bid (in ACS) or Clopidogrel 75 (in stable patients)	1 month (n=7980) 12 months (n=7988)	All-cause mortality or new Q-wave MI	24
OPTIMIZE (3)	open-label	Stable angina, silent ischemia or low risk ACS; ≥1 lesion with stenosis >50% (MVD allowed) in a native vessel >2.5 mm diameter.	STEMI; PCI with BMS in non-target lesions <6 months; previous treatment with any DES; scheduled elective surgery ≤12 months after index procedure; contraindication to study drugs; lesion in a saphenous vein graft; in-stent restenosis of DES.	Apr 2010 – Mar 2012	3119	Index procedure	First 3 months: Clopidogrel 75 + Aspirin 100 After 3 months: -Experimental monotherapy: Aspirin 100 -Control arm: Clopidogrel 75 + Aspirin 100	3 months (n=1563) 12 months (n=1566)	All-cause death, MI, stroke, or major bleeding	12
REDUCE (2)	open-label	≥18 years; ACS undergoing successful PCI with COMBO stent.	Cardiogenic shock; recent major bleeding; contraindication to DAPT; planned cardiac surgery or intervention for another lesion after index hospital discharge; any revascularization with other stents than COMBO; need for transplantation; need for permanent DAPT; life	Jun 2014 – May 2016	1496	Index procedure	First 3 months: Aspirin 100-200 + Ticagrelor 90 bid or Prasugrel 10 or Clopidogrel 75 (at discretion of the treating physician, with P and T preferred over C) After 3 months:	3 months (n=729) 12 months (n=733)	All cause death, MI, definite/probable ST, stroke, TVR or BARC II-V bleeding	24

			expectancy <2 years; pregnancy.				-Experimental monotherapy: Aspirin 100 -Control arm: Aspirin 100 + Ticagrelor 90 bid or Prasugrel 10 or Clopidogrel 75			
RESET (1)	open-label	≥20 years old; undergoing successful elective PCI in a coronary artery with ≥50% DS by visual estimation; RVD ≥2.5-4.0 mm.	Contraindication to study drugs; bleeding history ≤3 months; prior CVE (not TIA), occlusive PAD, thromboembolic disease, ST, Severe hepatic/renal dysfunction; leukopenia, neutropenia, thrombocytopenia, anaemia, or known bleeding diathesis; cardiogenic shock; LVEF <40%; pregnancy or potential childbearing; life expectancy <3 year; STEMI ≤ 48 hours after onset of symptoms; LM disease requiring PCI; bifurcation lesion treated with a two-stent technique; in-stent restenosis; CTO; prior DES implantation; overlapped DESs (only allowed in the long-lesion subgroup)	Apr 2009 – Dec 2010	2148	Index procedure	First 3 months: Clopidogrel 75 + Aspirin 100 After 3 months: -Experimental monotherapy: Aspirin 100 -Control arm: Clopidogrel 75 + Aspirin 100	3 months (n=1059) 12 months (n=1058)	CV death, MI, ST, ID-TVR, and TIMI major or minor bleeding	12
SMART-CHOICE (5)	open-label	≥20 years; ≥1 coronary artery stenosis ≥ 50% in a native coronary artery with visually estimated diameter ≥ 2.25 mm and ≤ 4.25 mm amenable to stent implantation, undergone PCI.	Contraindication to study drugs; hemodynamic instability or cardiogenic shock; active pathologic bleeding; DES implantation within 12 months before the index procedure; childbearing potential; noncardiac comorbidities with a life expectancy < 2 years.	Mar 2014 – Jul 2017	2993	Index procedure or at 3-months follow-up visit	First 3 months: Aspirin 100 + Clopidogrel 75 (in stable patients) or Clopidogrel 75 /Ticagrelor 90 bid/Prasugrel 10 (in ACS) After 3 months: -Experimental monotherapy: P2Y12 inhibitor (C	3 months (n=1495) 12 months (n=1498)	All-cause death, MI, or stroke	12

							in stable patients; C/T/P in ACS) -Control arm: Aspirin 100 + Clopidogrel 75 (stable patients) or Clopidogrel 75 /Ticagrelor 90 bid/Prasugrel 10 (ACS)			
STOPDAPT-2 (4)	open-label	Successful PCI with CoCr-EES without other types of DES or in-hospital major complications other than peri-procedural MI	Anticoagulation or antiplatelet therapy other than aspirin and P2Y12 receptor blockers; history of intracranial bleeding; intolerance to clopidogrel.	Dec 2015 – Dec 2017	3045	After PCI, before hospital discharge	First month: Clopidogrel 75 or Prasugrel 10 + Aspirin 81-200 After 1 month: -Experimental monotherapy: Clopidogrel (Prasugrel was switched to Clopidogrel if necessary) -Control arm: Clopidogrel 75 or + Aspirin 81-200	1 month (n=1523) 12 months (n=1522)	CV death, MI, definite ST, stroke, or TIMI major or minor bleeding	12

TWILIGHT (7)	double-blind	Successful DES implantation with at list one of the following: ≥65 years, female sex, troponin-positive ACS, vascular disease, DM treated with medication, CKD, MVD, TSL >30 mm, thrombotic target lesion, bifurcation lesion treated with two stents, LM or proximal LAD obstruction, atherectomy	STEMI; cardiogenic shock; ongoing long-term treatment with oral anticoagulants; contraindication to aspirin or ticagrelor	Jul 2015 – Dec 2017	9006	After 3-months from index procedure	First 3 months: Ticagrelor 90 bid + Aspirin (81-100) After 3 months, in event-free patients: -Experimental monotherapy: Ticagrelor 90 bid -Control arm: Ticagrelor 90 bid + Aspirin (81-100)	3 month (n=3555) 15 month (n=3564)	BARC 2, 3, or 5 bleeding	12

Abbreviations: ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; BMS: bare metal stent; C: clopidogrel; CABG: coronary artery bypass graft; CAD: coronary artery disease; CoCr-EES: cobalt-chromium everolimus-eluting stent; CKD: chronic kidney disease; CTO: chronic total occlusion; CVE: cerebrovascular event; DES: drug-eluting stent; DM: diabetes mellitus ICH: intracranial haemorrhage; ID-TLR: ischemia-driven target lesion revascularization; LAD: left anterior descending; LM: left main; LVEF; left ventricle ejection fraction; MI: myocardial infarction; MVD: multi-vessel disease; P: prasugrel; PCI: percutaneous coronary intervention; RVD: reference vessel diameter; ST: stent thrombosis; STEMI: ST-elevation myocardial infarction; T: ticagrelor; TIMI: Thrombolysis in Myocardial Infarction; TSL: total stent length.

Supplementary Table S5. Trial-defined major adverse cardiac events and bleeding definitions for each included trial

Study	Trial defined MACE	Trial defined Major Bleeding	Trial defined Any bleeding
GLOBAL LEADERS **(6)**	All-cause death, stroke, new Q-wave MI	BARC 3-5	BARC 2-5
OPTIMIZE **(3)**	All cause death, MI, urgent CABG or TLR	GUSTO severe/REPLACE2 major	Major bleeding plus bleeding events that did not meet criteria for major, severe or life-threatening bleeding according to modified major REPLACE-2 and severe or life- threatening GUSTO criteria
REDUCE **(2)**	Cardiovascular death, MI, definite/probable ST, stroke, MI, TVR	-	BARC 2-5
RESET **(1)**	Death from any cause, MI, ST	TIMI major	TIMI major and minor
SMART CHOICE **(5)**	All-cause death, MI, stroke	BARC 3-5	BARC 2-5
STOPDAPT **(4)**	Cardiovascular death, MI, definite ST, stroke	BARC 3-5	TIMI major and minor
TWILIGHT (**7**)	Cardiovascular death, MI, ischemic stroke	BARC 3-5	BARC 2-5

Abbreviations: CABG: coronary artery bypass graft; MI: myocardial infarction; ST: stent thrombosis TLR: target lesion revascularization; TVR: target vessel revascularization

Supplementary Table S6. Efficacy and safety outcome definitions for each included trial

Study	MI	ST	Stroke	TVR	Net clinical benefit	Bleeding
GLOBAL LEADERS (6)	Third universal definition (8)	ARC definition (9)	Rapid onset of focal/global neurological deficit lasting ≥24 hours or <24 hours if therapeutic intervention, neuro-imaging or death. No other causes (e.g. tumour, drug side effect, trauma, etc.). Confirmation by at least 1 of: a neurologist or neurosurgeon; neuro-imaging; lumbar puncture; other compelling evidence of stroke	NR	Composite of all-cause death, stroke, myocardial infarction, or BARC 3-5 bleeding	BARC (10)
OPTIMIZE (3)	WHO definition (11)	ARC definition (9)	Acute neurological event with duration ≥24 hours with confirmation by CT, MRI or pathology. Classified as as haemorrhagic or ischemic	New percutaneous or surgical re-intervention (CABG) of a target vessel	Composite of all-cause death, myocardial infarction, stroke, or major bleeding	REPLACE2 (12) GUSTO (13)
REDUCE (2)	Third universal definition (8)	ARC definition (9)	NR	NR	All cause death, myocardial infarction, stent thrombosis, stroke, target vessel revascularization or BARC 2-5 bleeding	BARC (10)
RESET (1)	ARC definition (9, 11)	ARC definition (9)	Sudden onset of vertigo, numbness, aphasia, or dysarthria resulting from vascular lesions of the brain, including haemorrhage, embolism, thrombosis, or rupturing aneurysm	Repeat PCI or CABG of the TV according to each physician with following findings: ischemic symptoms or positive stress test and angiographic minimal lumen diameter stenosis ≥50% by QCA analysis; or angiographic diameter stenosis ≥70% by QCA	Composite of death from cardiovascular cause, myocardial infarction, ischemia-driven target-vessel revascularization, or bleeding	TIMI (14)

				analysis without either ischemic symptoms or positive stress test.		
SMART-CHOICE (5)	Elevated Troponin or CK-MB > ULN with ischemic symptoms or ECG findings indicative of ischemia. Periprocedural enzymes elevation ≤ 48 hours after the index procedure without concomitant ischemic symptoms or ECG findings indicative of ischemia was excluded in the assessment of end points	ARC definition (9)	Any non-convulsive focal or global neurologic deficit of abrupt onset lasting > 24 hours or leading to death, which was caused by ischemia or haemorrhage	-	Composite of all-cause death, myocardial infarction, stroke or BARC 2-5 bleedings	BARC (10)
STOPDAPT-2 (4)	ARC definition (9)	ARC definition (9)	Acute onset of a neurological deficit that persists ≥24 hours due to ischemia or haemorrhage. TIA were not classified in this category	PCI performed in the target vessel or revascularization by CABG, including TLR	Composite of cardiovascular death, myocardial infarction, definite stent thrombosis, stroke, or TIMI major or minor bleeding	BARC (10) TIMI (14)
TWILIGHT (7)	Third Universal definition (8)	ARC definition (9)	Acute symptomatic neurological dysfunction, lasting >24 hours in the absence of therapeutic intervention; death due to cerebral, spinal or retinal tissue injury as evidenced by neuroimaging or lumbar puncture	-	-	BARC (10)

Abbreviations: ARC: Academic Research Consortium; BARC: Bleeding Academic Research Consortium; CABG: coronary artery bypass graft; CK: creatine-kinase; CT: computed tomography; GUSTO: Global Utilization of Streptokinase And Tpa For Occluded Arteries; MRI: Magnetic Resonance Imaging; MI: myocardial infarction; NR: not reported; PCI: percutaneous coronary intervention; QCA: quantitative coronary angiography; REPLAE-2: Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events; ST: stent thrombosis; TIMI: Thrombolysis in Myocardial Infarction; TV: target vessel; TVR: target vessel revascularization; UAP: unstable angina pectoris; WHO: World Health Organization

Supplementary Table S7. Baseline and clinical patients' characteristics

	GLOBAL LEADERS (6)		OPTIMIZE (3)		REDUCE (2)		RESET (1)		SMART-CHOICE (5)		STOPDAPT-2 (4)		TWILIGHT (7)	
	1m (n=7980)	12m (n=7988)	3m (n=1563)	12m (n=1556)	3m (n=751)	12m (n=745)	3m (n=1059)	12m (n=1058)	3m (n=1495)	12m (n=1498)	1m (n=1500)	12m (n=1509)	3 m (3555)	15m (3564)
Age (mean, SD or median Q1-Q3)	64.5 (10.3)	64.6 (10.3)	61.3 (10.4)	61.9 (10.6)	61 (53-69)	60 (52-68)	62.4 (9.4)	62.4 (9.8)	64.6 (10.7)	64.4 (10.7)	68.1 (10.9)	69.1 (10.4)	65.2 (10.3)	65.1 (10.4)
Women, n (%)	1865 (23.4)	1849 (23.1)	571 (36.5)	574 (36.9)	131 (17.4)	169 (22.7)	377 (35.6)	393 (37.1)	408 (27.3)	387 (25.8)	317 (21.1)	355 (23.5)	846 (23.8)	852 (23.9)
Diabetes, n (%)	2049 (25.7)	1989 (24.9)	554 (35.4)	549 (35.3)	162 (21.6)	145 (19.5)	316 (29.8)	305 (28.8)	570 (38.2)	552 (36.8)	585 (39)	574 (38)	1319 (37.1)	1301 (36.5)
Hypertension, n (%)	5882 (74)	5883 (73.3)	1350 (86.4)	1371 (88.2)	379 (50.7)	375 (50.7)	660 (62.3)	650 (61.4)	921 (61.6)	919 (61.3)	1105 (73.7)	1116 (74)	2580 (72.6)	2574 (72.2)
Smoking, n (%)	2066 (25.9)	2103 (26.3)	290 (18.6)	269 (17.3	313 (42.1)	314 (42.7)	267 (25.2)	241 (22.8)	424 (28.4)	367 (24.2)	399 (26.6)	311 (20.6)	726 (20.4)	822 (23.1)
Dyslipidaemia, n (%)	5345 (69.3)	5423 (70)	953 (63.2)	952 (63.7)	346 (46.3)	333 (44.9)	611 (57.7)	634 (59.9)	673 (45.1)	679 (45.5)	1116 (74.4)	1128 (74.8)	2157 (60.7)	2146 (60.2)
Family history of CAD, n (%)	NR	NR	564 (41.3)	583 (42.8)	260 (35)	265 (36)	NR	NR	NR	NR	NR	NR	NR	NR
Previous ACS, n (%)	1831 (23)	1879 (23.6)	541 (34.6)	542 (34.8)	94 (12.5)	88 (11.8)	19 (1.8)	17 (1.6)	62 (4.1)	65 (4.3)	207 (13.8)	199 (13.2)	1020 (28.7)	1020 (28.6)
Previous PCI, n (%)	2609 (32.7)	2612 (32.7)	327 (20.9)	297 (19.1)	88 (11.7)	73 (9.8)	37 (3.5)	32 (3)	NR	NR	503 (33.5)	529 (35.1)	1502 (42.3)	1496 (42)
Previous CABG, n (%)	448 (5.6)	495 (6.2)	111 (7.1)	128 (8.2)	21 (2.8)	21 (2.8)	2 (0.2)	6 (0.6)	NR	NR	17 (1.1)	42 (2.8)	362 (10.2)	348 (9.8)
Previous stroke or TIA, n (%)	210 (2.6)	211 (2.6)	38 (2.5)	38 (2.5)	11 (1.5)	15 (2)	NR	NR	99 (6.6)	102 (6.8)	81 (5.4)	105 (7)	NR	NR
CHF, n (%)	NR	NR	67 (4.3)	64 (4.2)	NR	NR	120 (11.3)	125 (11.8)	NR	NR	115 (7.7)	107 (7.1)	NR	NR
CKD, n (%)	1099 (13.9)	1072 (13.5)	114 (7.4)	89 (5.8)	NR	NR	NR	NR	44 (2.9)	53 (3.5)	82 (5.5)*	84 (5.6)*	572 (16.8)	573 (16.7)
PAD, n (%)	467 (6)	529 (6.7)	43 (2.8)	46 (3)	NR	NR	NR	NR	NR	NR	96 (6.4)	100 (6.6)		
	Clinical presentation													
ACS														

STEMI	1062 (13.3)	1030 (12.9)	NR	NR	370 (49.3)	336 (45.2)	NR	NR	164 (11)	150 (10)	291 (19.4)	270 (17.9)	-	-
NSTEMI	1684 (21.1)	1689 (21.1)	84 (5.4)	84 (5.4)	267 (35.6)	305 (41)	NR	NR	239 (16)	230 (15.4)	81 (5.4)	99 (6.6)	1024 (28.8)	1096 (30.8)
UAP	1004 (12.6)	1018 (12.7)	NR	NR	114 (15.2)	103 (13.8)	432 (40.8)	422 (39.9)	467 (31.2)	491 (32.8)	193 (12.9)	214 (14.2)	1249 (35.1)	1245 (34.9)
Stable CAD, n (%)	4230 (53)	4251 (53.2)	935 (59.8)	911 (58.6)	-	-	471 (44.5)	490 (46.3)	625 (41.8)	625 (41.8)	935 (62.3)	926 (61.4)	1047 (29.5)	999 (28)
Silent ischemia, n (%)	-	-	134 (8.6)	143 (9.2)	-	-	-	-	-	-	-	-	234 (6.6)	223 (6.3)
Angiographic features														
Treated vessel, n (%)														
LM	197 (1.9)	190 (1.8)	24 (1.2)	30 (1.5)	NR	NR	NR	NR	23 (1.2)	35 (1.9)	43 (2.9)	37 (2.5)	166 (4.7)	187 (5.2)
LAD	4283 (41.2)	4383 (42)	986 (47.9)	960 (46.6)	360 (48)	329 (44.2)	707 (52.7)	722 (53.6)	903 (48.8)	950 (50.4)	828 (55.2)	854 (56.6)	1993 (56.1)	2010 (56.4)
LCX	2524 (24.3)	2553 (24.5)	481 (23.4)	501 (24.3)	NR	NR	281 (21)	259 (19.2)	399 (21.6)	376 (19.9)	268 (17.9)	305 (20.2)	1151 (32.4)	1146 (32.2)
RCA	3284 (31.6)	3206 (30.7)	567 (27.6)	571 (27.7)	NR	NR	353 (26.3)	365 (27.1)	524 (28.3)	524 (27.8)	436 (29.1)	410 (27.2)	1243 (35)	1257 (35.3)
Stent type, (%)	BES (94.8) Other (6.4)	BES (94.4) Other (6.7)	ZES (100)	ZES (100)	COMBO stent (100)	COMBO stent (100)	E-ZES (100)	E-ZES (0)	CoCr-EES (35.1)	CoCr-EES (35.1)	CoCr-EES (100)	CoCr-EES (100)	II gen DES (97.8)	II gen DES (97.7)
							SES (0)	SES (28.5)	PtCr-EES (32.7)	PtCr-EES (31.9)				
							EES (0)	EES (30)	SES (32.2)	SES (32.8)				
							R-ZES (0)	R-ZES (41.5)	ZES (0)	ZES (0.1)				
									PCE (0)	PCE (0.1)				

All data are presented as mean and standard deviation or absolute numbers and percentage

Abbreviations: ACS: acute coronary syndrome; BES: biolimus A9-eluting stent; CAD: coronary artery disease; CHF: chronic heart failure; CKD: chronic kidney disease; CoCr-EES: cobalt-chromium everolimus-eluting stent; LAD: left anterior descending; LCX: left circumflex; LM: left main;

MI: myocardial infarction; NR: not reported; NSTEMI; non-ST elevation myocardial infarction; PAD: peripheral arterial disease; PCE: paclitaxel-cilostazol eluting; PCI: percutaneous coronary intervention; PtCr-EES: platinum-chromium Everolimus-eluting stent; RCA: right coronary artery; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent; STEMI: ST-elevation myocardial infarction; TIA: transient ischemic attack; UAP: unstable angina pectoris;

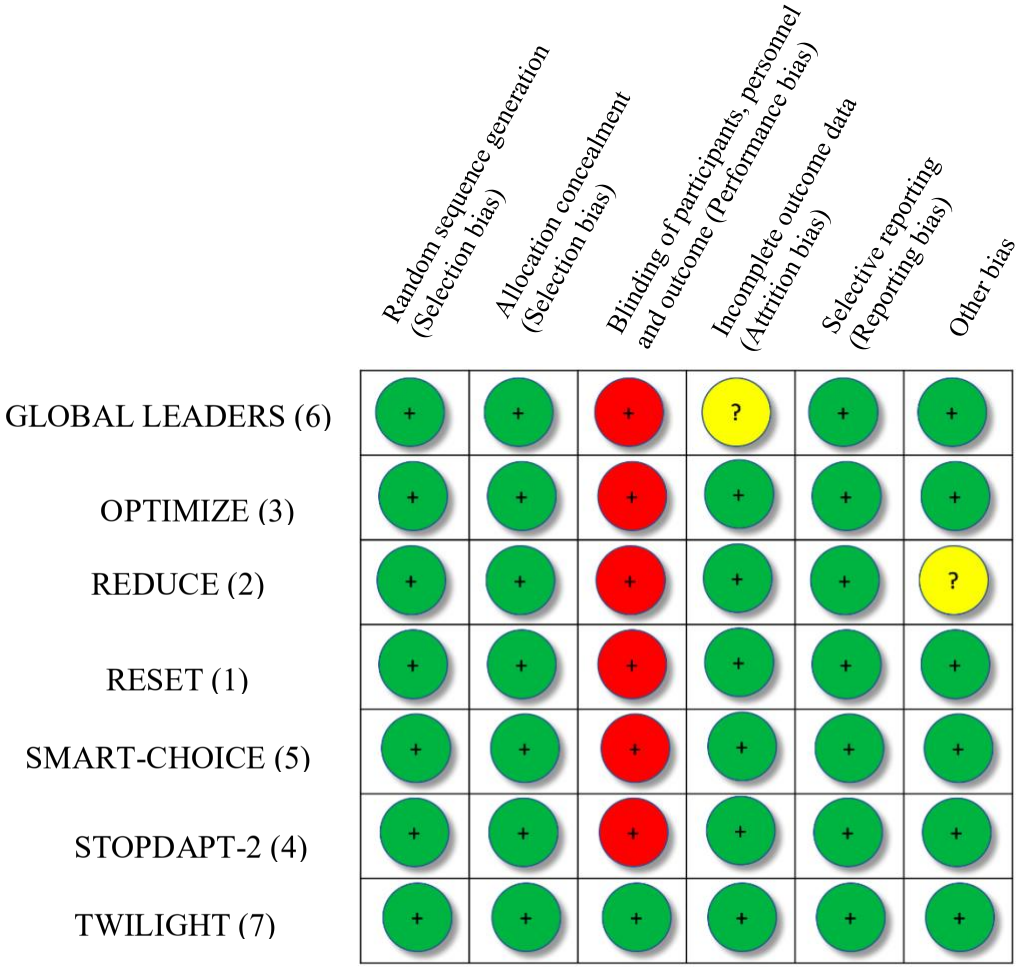
*these data refer to severe CKD (eGFR < 30 ml/min/1.73m^2), as reported by the study authors

Supplementary Table S8. Trial reported clinical outcomes

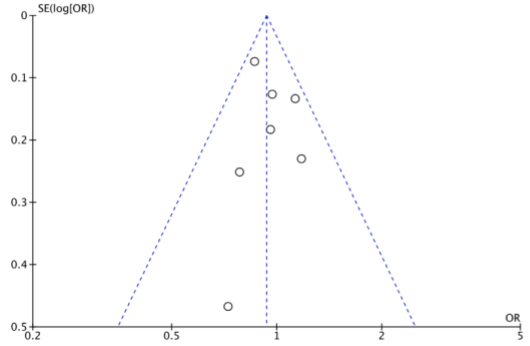
	GLOBAL LEADERS (6)		OPTIMIZE (3)		REDUCE (2)		RESET(1)		SMART-CHOICE (5)		STOPDAPT-2 (4)		TWILIGHT (7)	
	1m (n=7980)	12m (n=7988)	3m (n=1563)	12m (n=1556)	3m (n=733)	12m (n=727)	3m (n=1059)	12m (n=1058)	3m (n=1495)	12m (n=1498)	1m (n=1500)	12m (n=1509)	3m (n=3555)	15m (n=3564)
Trial defined MACE	362 (4.54)	416 (5.21)	128 (8.3)	114 (7.4)	64 (8.7)	66 (9.1)	8 (0.8)	11 (1.3)	42 (2.9)	36 (2.5)	29 (1.96)	37 (2.51)	126 (3.6)	130 (3.7)
Net benefit	616 (7.72)	653 (8.17)	93 (6)	90 (5.8)	85 (11.6)	88 (12.1)	40 (4.7)	41 (4.7)	65 (4.5)	81 (5.6)	35 (2.36)	55 (3.7)	-	-
All-cause death	224 (2.81)	253 (3.17)	43 (2.8)	45 (2.9)	23 (3.1)	16 (2.2)	5 (0.5)	8 (1)	21 (1.4)	18 (1.2)	21 (1.42)	18 (1.21)	34 (1)	45 (1.3)
MI	248 (3.11)	250 (3.13)	49 (3.2)	42 (2.7)	26 (3.5)	22 (3)	2 (0.2)	4 (0.4)	11 (0.8)	17 (1.2)	13 (0.88)	11 (0.75)	95 (2.7)	95 (2.7)
Stroke	80 (1)	82 (1.03)	5 (0.3)	5 (0.3)	2 (0.3)	4 (0.6)	6 (0.6)	6 (0.7)	11 (0.8)	5 (0.3)	8 (0.54)	16 (1.09)	16 (0.5)	8 (0.2)
ST	64 (0.8)	64 (0.8)	13 (0.8)	12 (0.8)	12 (1.6)	6 (0.8)	2 (0.2)	3 (0.3)	3 (0.2)	2 (0.1)	4 (0.27)	1 (0.07)	14 (0.4)	19 (0.6)
TVR	389 (4.87)	442 (5.54)	70 (4.6)	57 (3.8)	36 (4.9)	34 (4.7)	31 (3.9)	27 (3.7)	-	-	-	-	-	-
Major bleeding	163 (2.04)	169 (2.12)	10 (0.6)	14 (0.9)	-	-	2 (0.2)	6 (0.6)	12 (0.8)	14 (1)	8 (0.54)	27 (1.81)	34 (1)	69 (2)
Any bleeding	529 (6.63)	532 (6.66)	35 (2.3)	45 (2.9)	24 (3.3)	29 (4)	5 (0.5)	10 (1.9)	28 (2.0)	49 (3.4)	6 (0.41)	23 (1.54)	141 (4)	250 (7.1)

All data are presented as absolute numbers and percentage

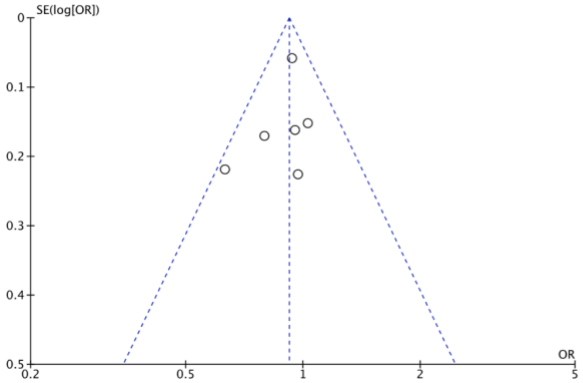
Supplementary Table S9. Risk of bias of individual studies by Cochrane risk assessment tool



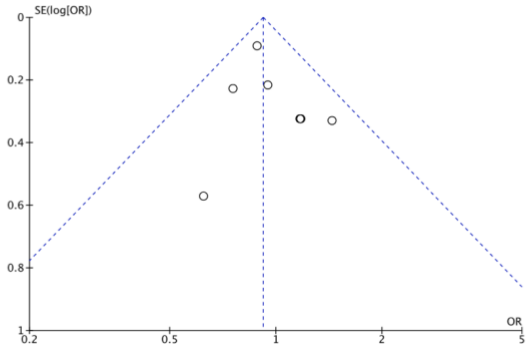
Supplementary Table S10. Funnel plot for trial-defined MACE



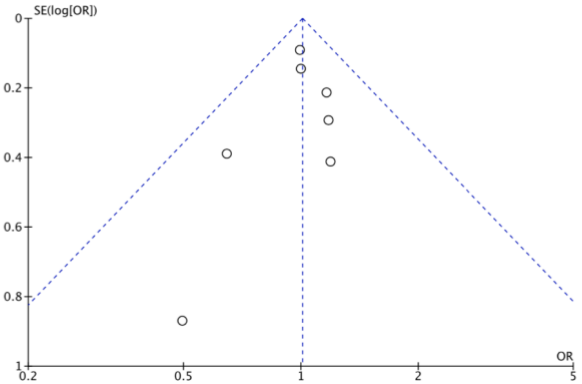
Supplementary Table S11. Funnel plot for net clinical benefit



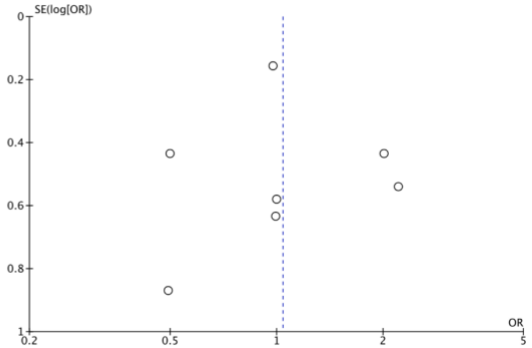
Supplementary Table S12. Funnel plot for all-cause death



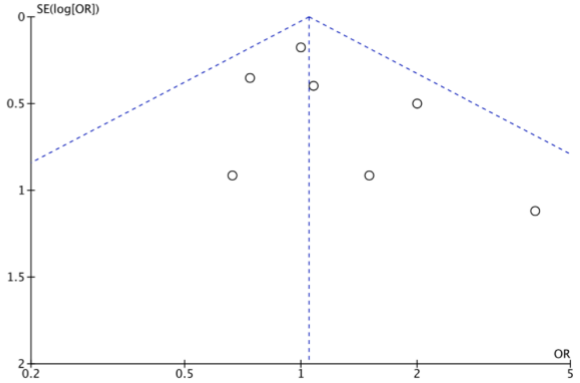
Supplementary Table S13. Funnel plot for myocardial infarction



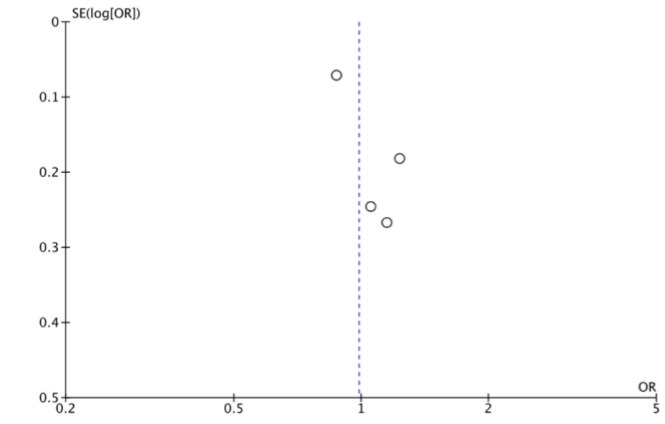
Supplementary Table S14. Funnel plot for stroke



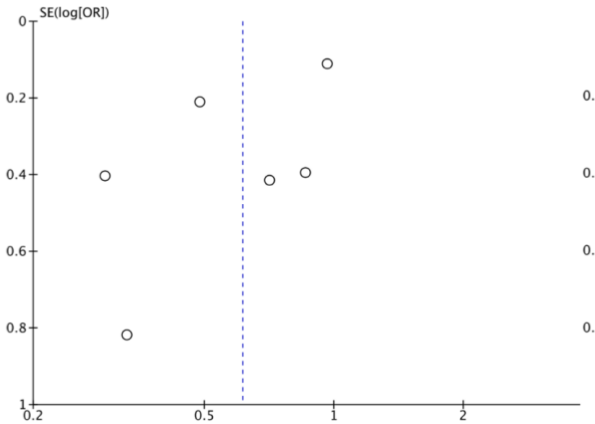
Supplementary Table S15. Funnel plot for stent thrombosis



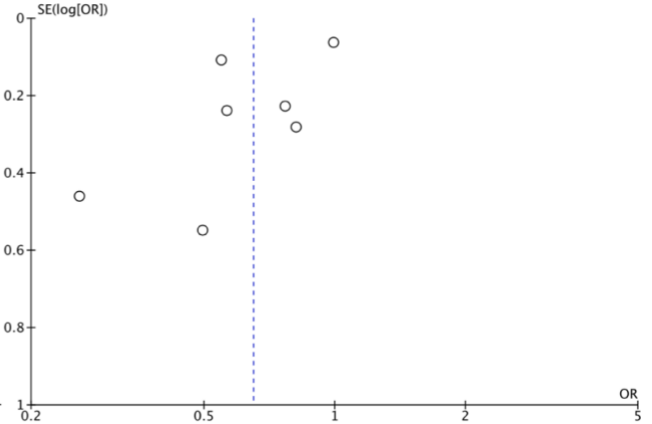
Supplementary Table S16. Funnel plot for target vessel revascularization



Supplementary Table S17. Funnel plot for major bleeding



Supplementary Table S18. Funnel plot for any bleeding



Supplementary Table S19. Sensitivity analysis for primary and secondary endpoints after individual removal of each study from the corresponding pooled analysis

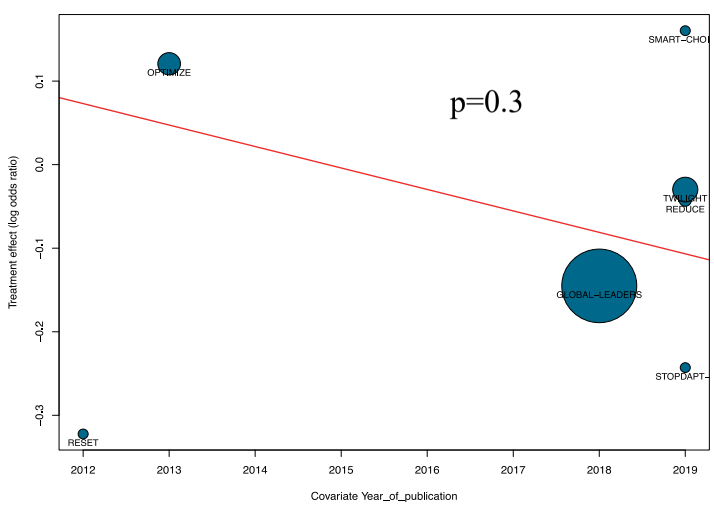
Supplementary Table S20. Subgroup analyses according to very short DAPT duration and to antiplatelet monotherapy following very short DAPT

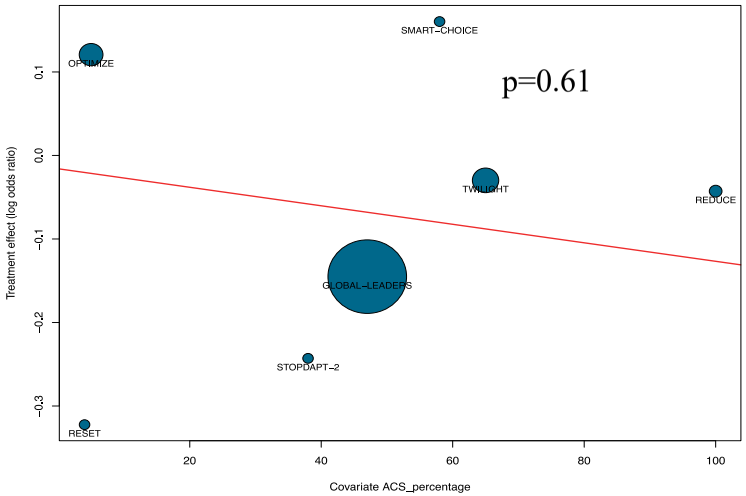
				Trial removed																
	GLOBAL LEADERS (6)			OPTIMIZE (3)			REDUCE (2)			RESET(1)			SMART-CHOICE (5)			STOPDAPT-2 (4)			TWILIGHT (7)		
	OR	CI	p	OR	CI	p	OR	CI	p	OR	CI	p	OR	CI	p	OR	CI	p	OR	CI	p
MACE	1.01	0.87-1.16	0.93	0.90	0.81-1.01	0.07	0.93	0.84-1.04	0.19	0.94	0.85-1.04	0.21	0.92	0.83-1.02	0.13	0.94	0.85-1.04	0.25	0.93	0.83-1.04	0.18
Net benefit	0.89	0.76-1.04	0.13	0.91	0.83-1.00	0.06	0.92	0.83-1.01	0.08	0.92	0.84-1.01	0.08	0.93	0.85-1.03	0.15	0.94	0.85-1.03	0.19	-	-	-
All-cause death	0.98	0.78-1.23	0.86	0.92	0.79-1.06	0.25	0.90	0.78-1.04	0.15	0.93	0.83-1.07	0.29	0.91	0.78-1.05	0.19	0.91	0.78-1.05	0.19	0.94	0.81-1.09	0.42
MI	1.03	0.84-1.26	0.80	0.99	0.86-1.14	0.90	1.00	0.87-1.15	0.98	1.01	0.89-1.16	0.86	1.02	0.89-1.17	0.75	1.00	0.88-1.15	0.97	1.01	0.87-1.17	0.91
Stroke	1.08	0.62-1.87	0.78	1.05	0.68-1.61	0.82	1.08	0.73-1.60	0.70	1.05	0.68-1.62	0.82	0.96	0.69-1.34	0.82	1.09	0.84-1.42	0.50	0.95	0.73-1.23	0.70
ST	1.12	0.74-1.69	0.60	1.04	0.79-1.38	0.77	0.99	0.75-1.31	0.95	1.06	0.81-1.38	0.68	1.04	0.79-1.36	0.78	1.02	0.78-1.33	0.89	1.11	0.83-1.49	0.46
TVR	1.16	0.90-1.49	0.24	0.90	0.79-1.03	0.12	1.01	0.79-1.29	0.95	0.99	0.79-1.23	0.90	-	-	-	-	-	-	-	-	-
Major bleedings	0.50	0.37-0.68	**<0.00001**	0.59	0.36-0.97	**0.04**	-	-	-	0.64	0.41-0.99	0.05	0.57	0.34-0.94	**0.03**	0.71	0.48-1.05	0.08	0.66	0.40-1.07	0.09
Any bleeding	0.58	0.49-0.68	**<0.00001**	0.62	0.43-0.91	**0.01**	0.62	0.43-0.90	**0.01**	0.66	0.47-0.93	**0.02**	0.66	0.46-0.95	**0.03**	0.71	0.51-0.97	**0.03**	0.69	0.49-0.97	**0.03**

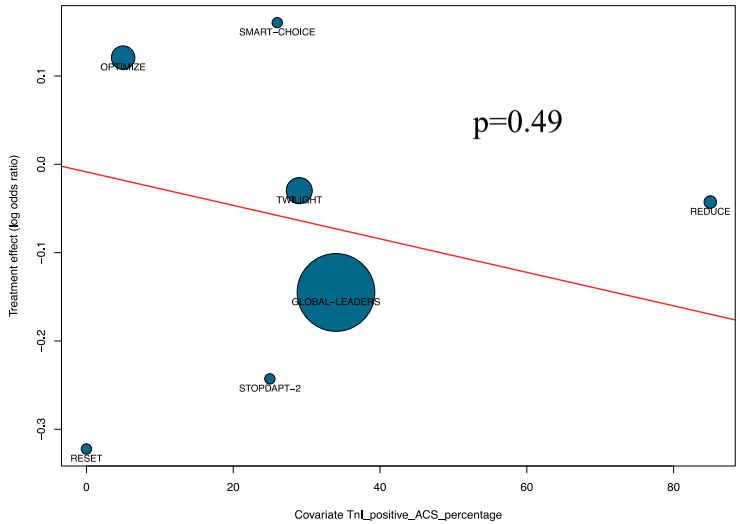
	MACE			Net benefit			All-cause death			MI			ST			Stroke			TVR			Major bleedings			Any bleeding		
1 vs. 3 months DAPT																											
	OR	**CI**	**p***	**OR**	**CI**	**p***	**OR**	**CI**	**p***	**OR**	**CI**	**p***	**OR**	**CI**	**p***	**OR**	**CI**	**p***	**OR**	**CI**	**p***	**OR**	**CI**	**p***	**OR**	**CI**	**p***
1 month	0.86	0.75-0.99	0.08	0.91	0.82-1.02	0.82	0.90	0.76-1.08	0.73	1.00	0.84-1.19	0.91	1.05	0.74-1.47	0.99	0.90	0.67-1.20	0.39	0.87	0.76-1.01	0.05	0.57	0.18-1.81	0.99	0.55	0.15-2.03	0.90
3 months	1.03	0.89-1.20		0.94	0.79-1.11		0.95	0.74-1.22		1.02	0.83-1.25		1.05	0.68-1.60		1.20	0.66-2.17		1.16	0.90-1.49		0.56	0.41-0.78		0.60	0.50-0.70	
Aspirin vs. P2Y12 monotherapy following DAPT																											
Aspirin	1.05	0.85-1.29	0.22	0.99	0.81-1.20	0.41	1.02	0.73-1.43	0.48	1.13	0.81-1.57	0.46	1.28	0.72-2.27	0.43	0.86	0.41-1.82	0.65	1.16	0.90-1.49	0.05	0.61	0.29-1.25	0.97	0.75	0.54-1.05	0.42
P2Y12	0.90	0.80-1.01		0.90	0.81-1.00		0.90	0.77-1.05		0.99	0.85-1.14		0.99	0.73-1.34		1.04	0.80-1.35		0.87	0.76-1.01		0.62	0.36-1.05		0.60	0.37-0.95	
Ticagrelor vs. aspirin or clopidogrel monotherapy																											
Ticagrelor	1.03	0.86-1.22	0.20	0.89	0.76-1.04	0.56	1.08	0.82-1.41	0.17	1.05	0.79-1.39	0.74	1.41	0.84-2.39	0.19	0.89	0.55-1.43	0.52	1.16	0.90-1.49	0.05	0.53	0.31-0.93	0.53	0.61	0.44-0.85	0.57
Other	0.89	0.79-1.01		0.94	0.84-1.05		0.86	0.73-1.02		1.00	0.86-1.16		0.94	0.69-1.28		1.07	0.80-1.43		0.87	0.76-1.01		0.70	0.36-1.37		0.74	0.41-1.33	

p*= p value for subgroup differences

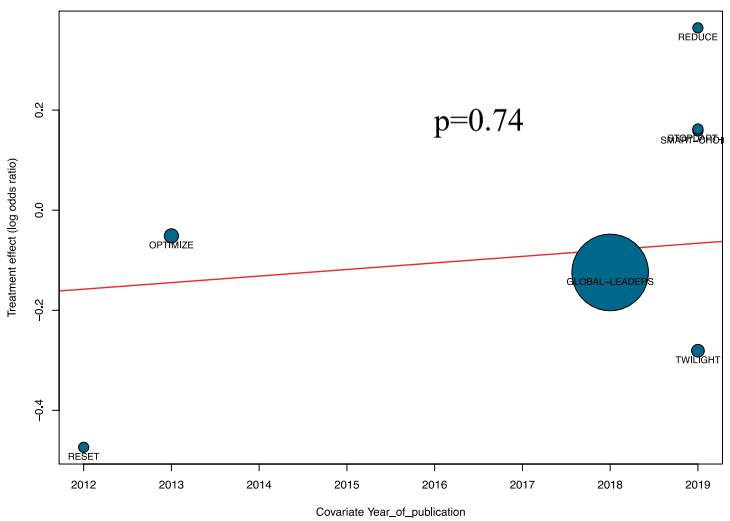
Supplementary Table S21. Bubble plots for MACE

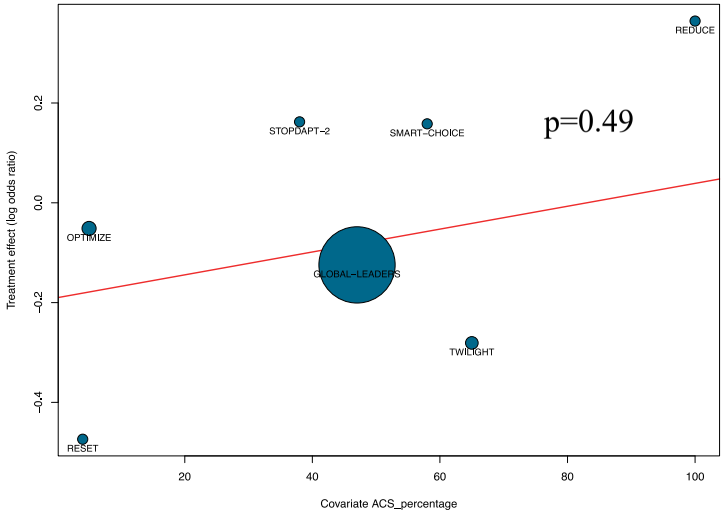


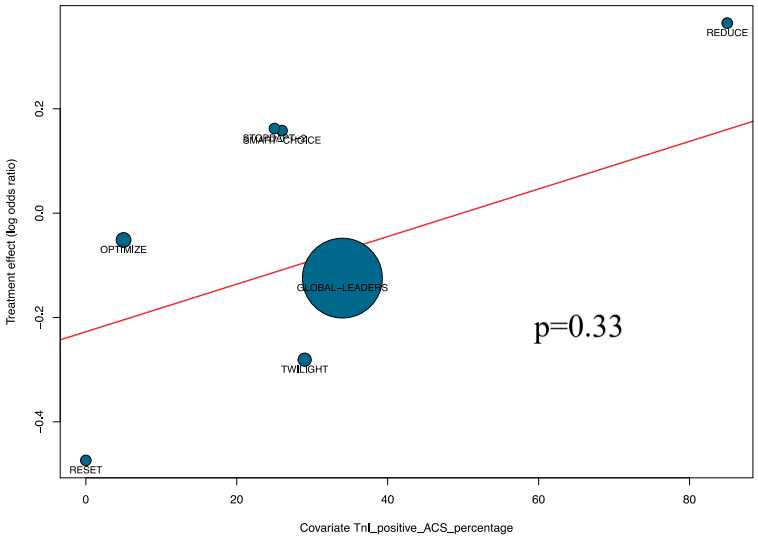




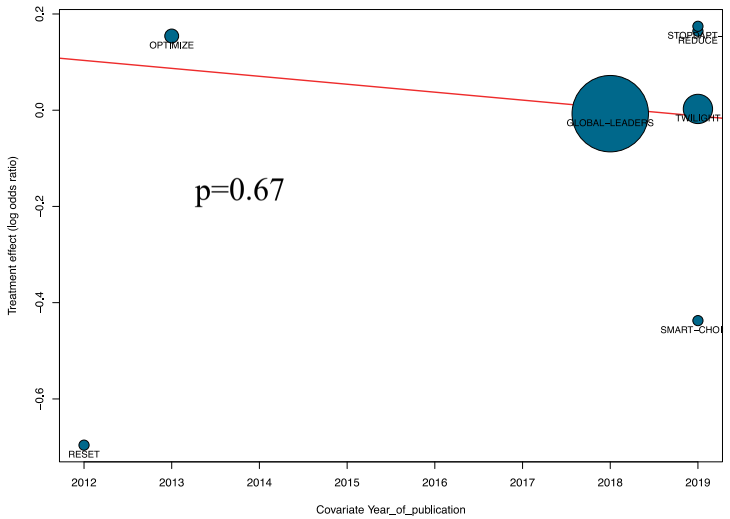
Supplementary Table S22. Bubble plots for all-cause death

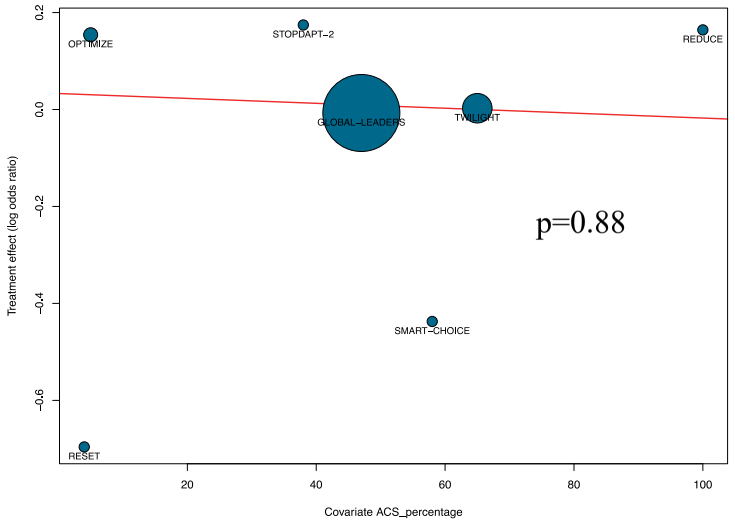


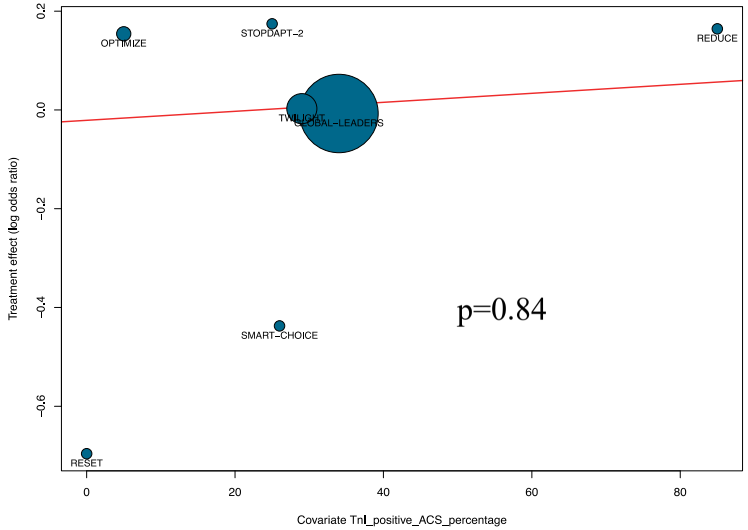




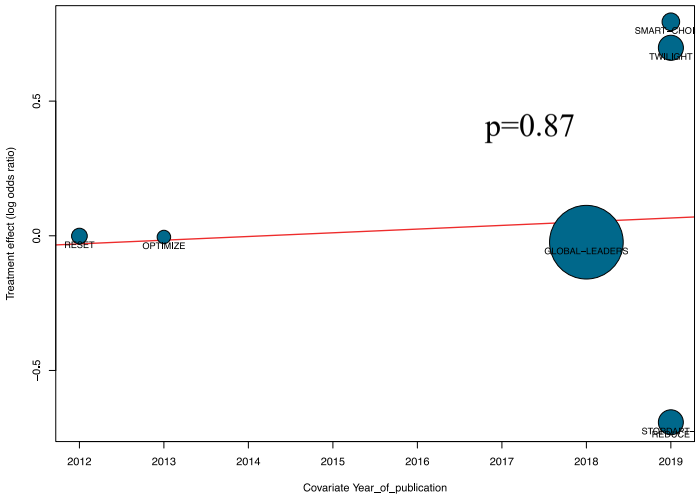
Supplementary Table S23. Bubble plots for myocardial infarction

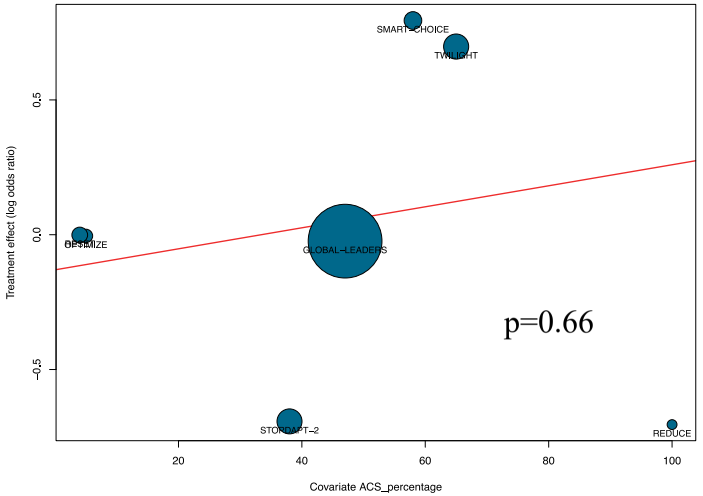


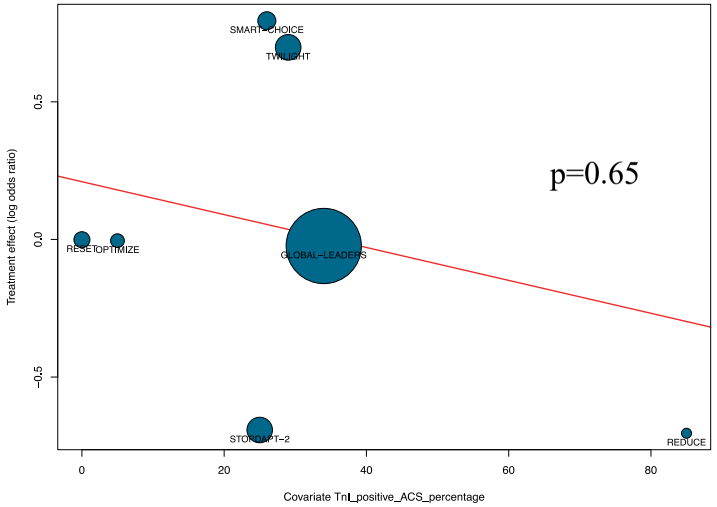




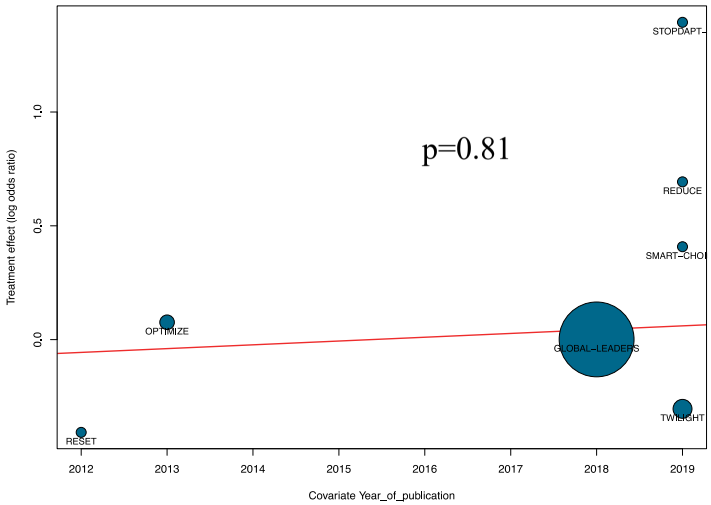
Supplementary Table S24. Bubble plots for stroke

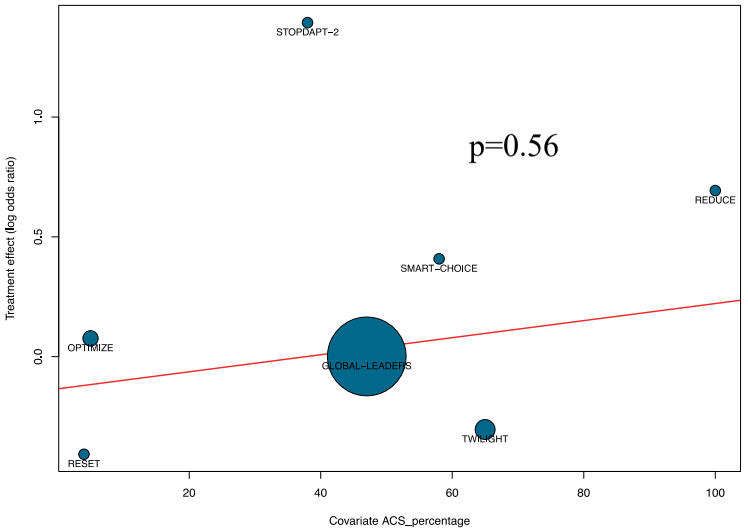


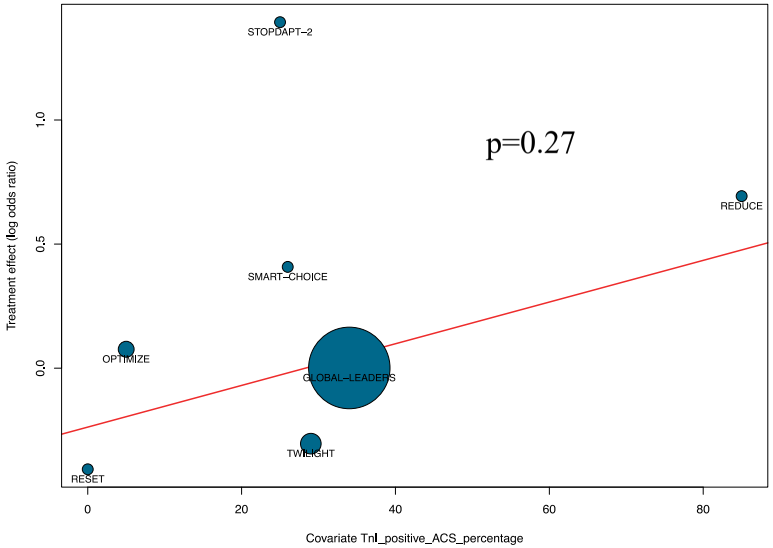




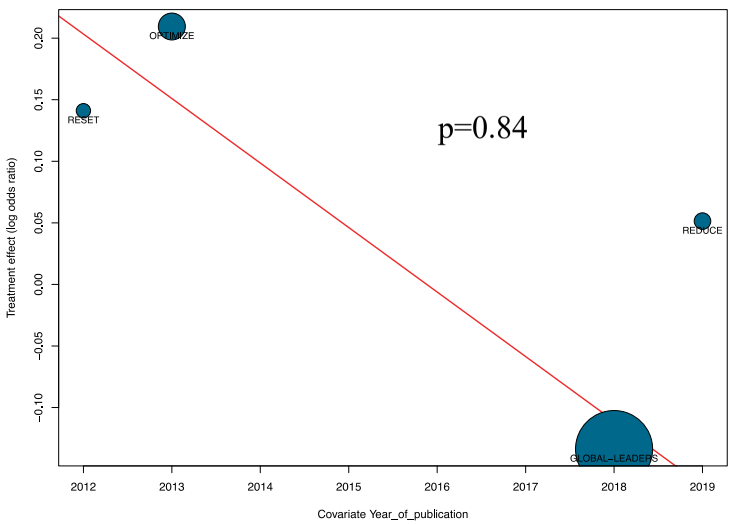
Supplementary Table S25. Bubble plots for stent thrombosis

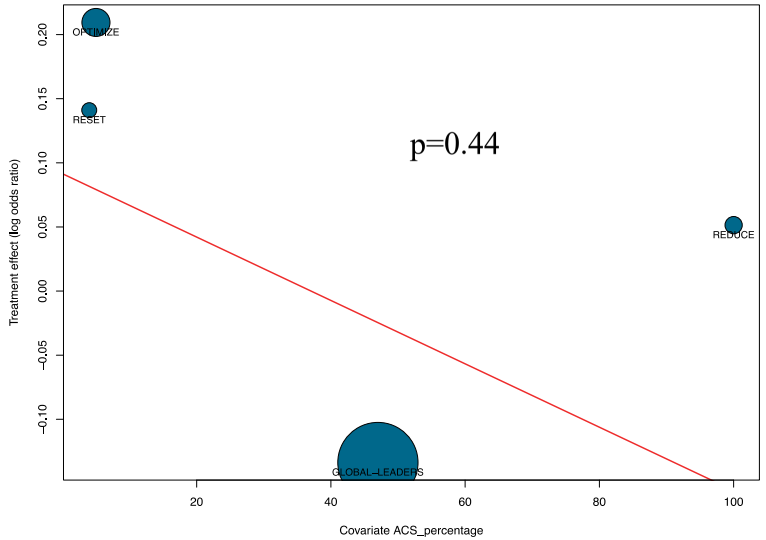


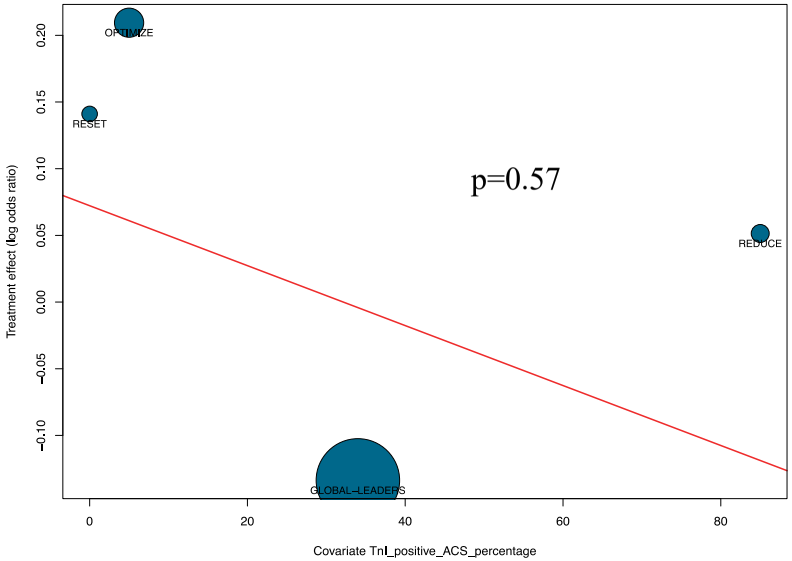




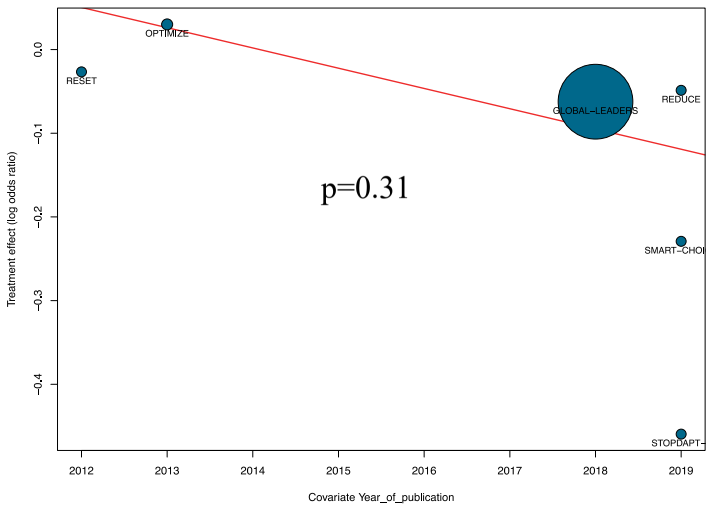
Supplementary Table S26. Bubble plots for TVR

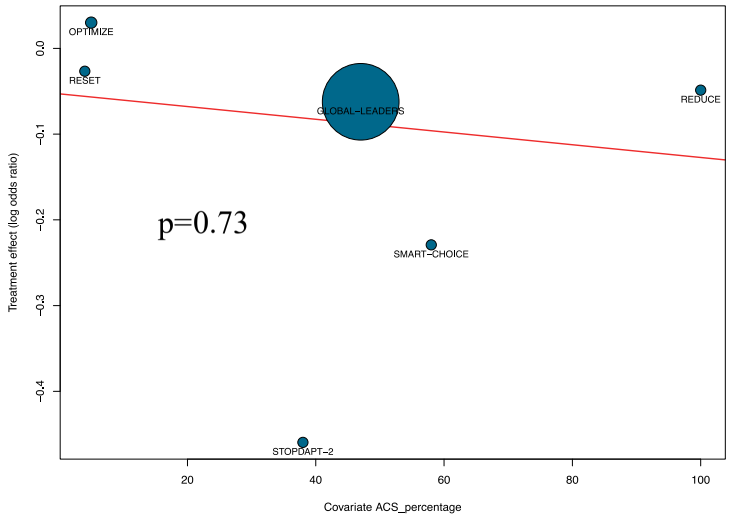


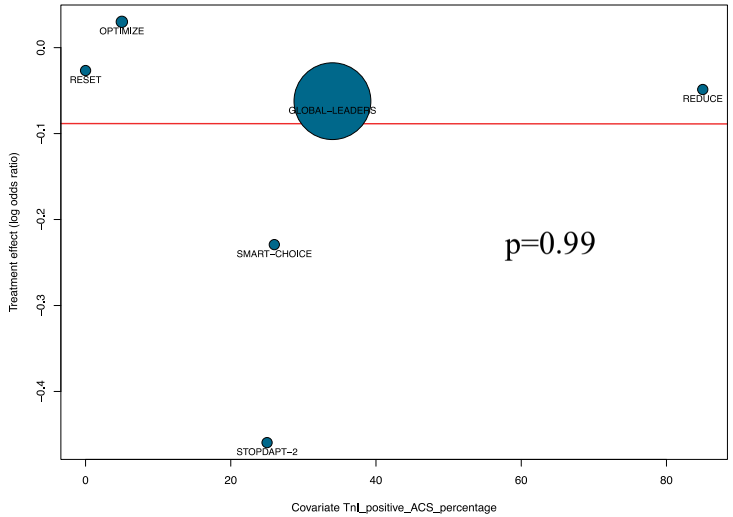




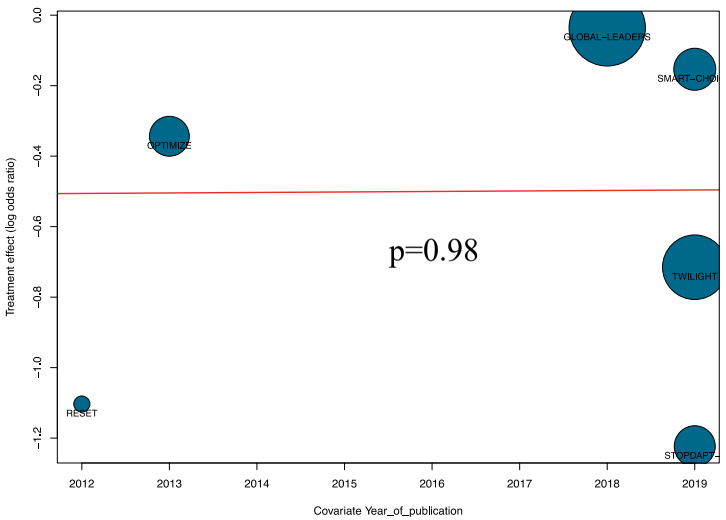
Supplementary Table S27. Bubble plots for net clinical benefit

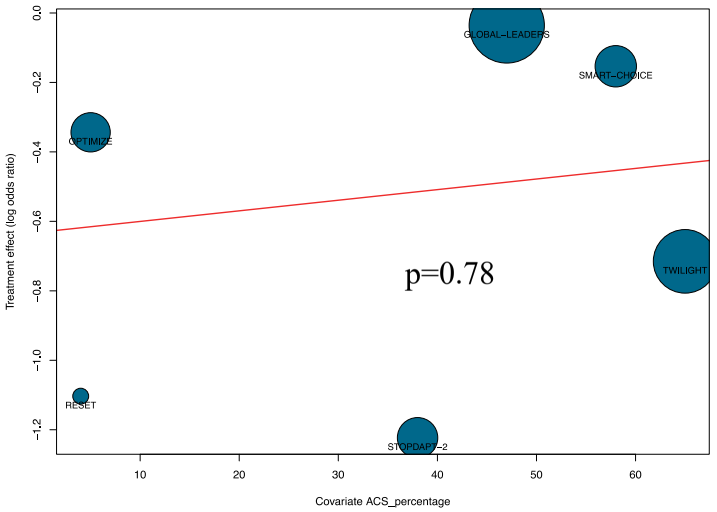


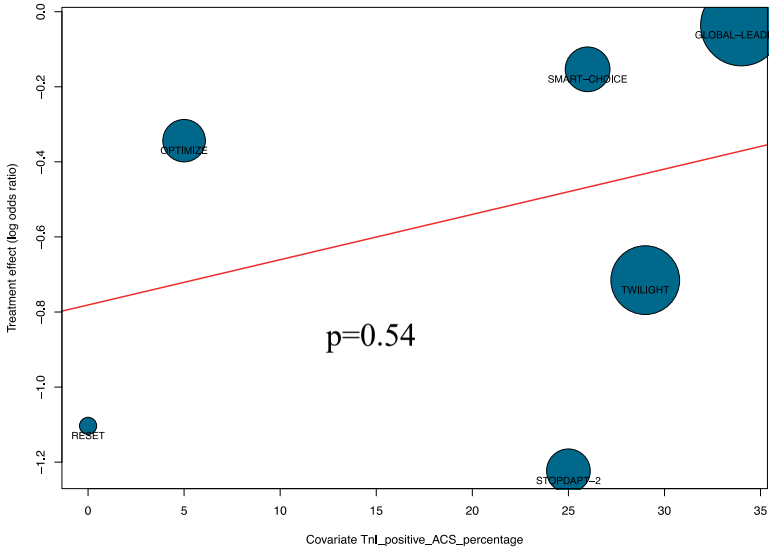




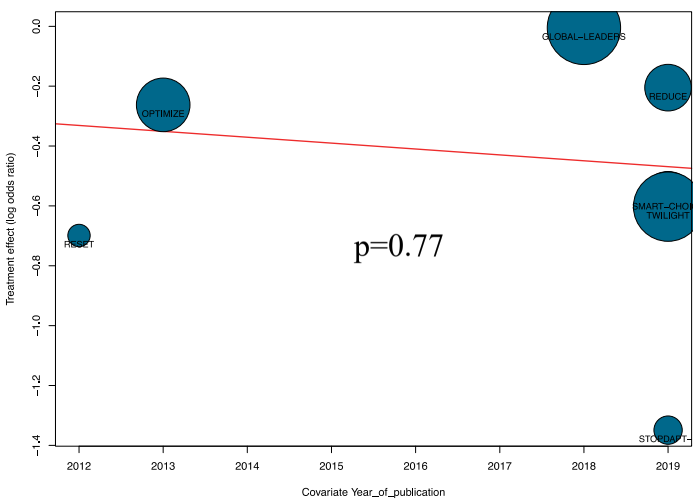
Supplementary Table S28. Bubble plots for major bleeding

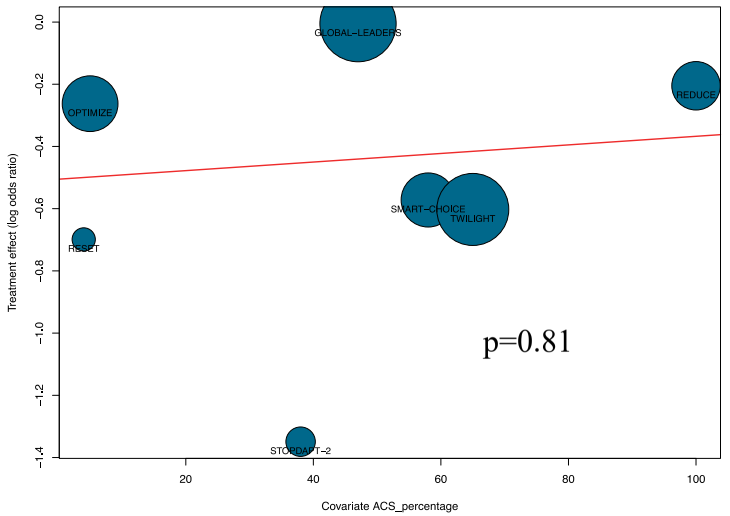


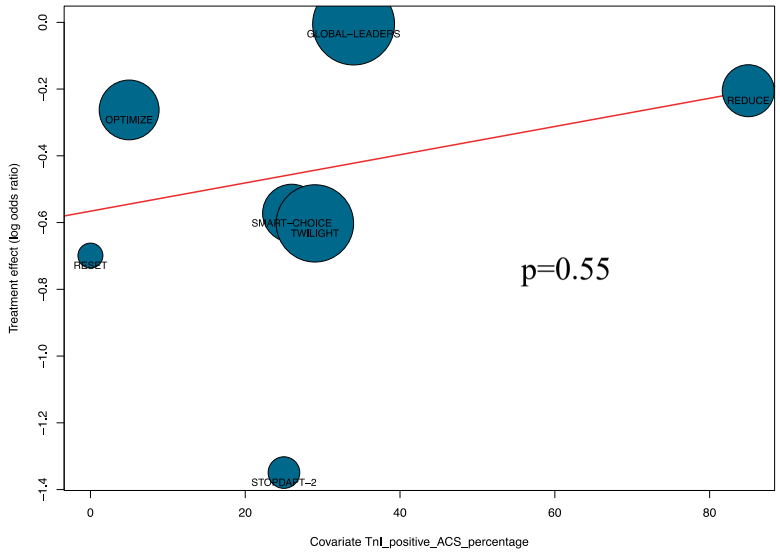




Supplementary Table S29. Bubble plots for any bleeding







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Supplementary Appendix 2

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Supplementary Table S1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis).	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: 1) Background: main objectives; 2)Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis; 3) Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity. 4) Discussion/Conclusions: limitations; conclusions and implications of findings. 5) Other: primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, including mention of why a network meta-analysis has been conducted.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	PROSPERO CRD42020173010
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3-4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supp. S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3-4

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3-4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3-4
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	3-4
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Supp. S11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.	5-6
Planned method of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: handling of multi-group trials; Selection of variance structure; Selection of prior distributions in Bayesian analyses; and Assessment of model fit.	5-6
Assessment of inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	5-6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Supp. S11
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: sensitivity or subgroup analyses; Meta-regression analyses; Alternative formulations of the treatment network; and Use of alternative prior distributions for Bayesian analyses (if applicable).	5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6-9
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	6-9
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	6-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-9

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	6-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches may be needed to deal with information from larger networks.	6-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g., placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	6-9
Exploration of inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	6-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	6-9
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth).	6-9
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, researchers, and policymakers).	10-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).	10-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	-

Supplementary Table S2. Full electronic search in MEDLINE/Pubmed database through January 11, 2020

Research	Query	Items found
1	Dual antiplatelet therapy	4918
2	Drug-eluting stent	16153
3	Dual antiplatelet therapy AND random*	1322
4	Drug eluting stent AND random*	3905
5	Dual antiplatelet therapy AND drug-eluting stent	1379
6	Dual antiplatelet therapy AND drug-eluting stent AND random*	454
7	Dual antiplatelet therapy AND Ticagrelor	604
8	Dual antiplatelet therapy AND Prasugrel	525
9	Dual antiplatelet therapy AND Clopidogrel	2335

Supplementary Table S3. Efficacy endpoint definitions

Study	Cardiac Death	MI	ST	Stroke
ARTIC-Interruption	All deaths unless there was a definite noncardiac cause	ARC criteria	ARC criteria	ARC criteria
DAPT	Any death due to an evident cardiac cause, any death related to PCI, unwitnessed death, or death of unknown causes	ARC criteria	ARC criteria	Sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as haemorrhage, embolism, thrombosis, or rupturing aneurysm that either: 1. persists >24 h or results in death in< 24 h 2. persists <24 h duration if the following treatments are used: a. pharmacologic, i.e. thrombolytic drug administration, or b. non-pharmacologic, i.e. neuro- interventional procedure (e.g. intracranial angioplasty) 3. persists <24 h but has neuro-radiological (MRI or CT) diagnostic changes suggestive of acute tissue injury
DAPT STEMI	Any death due to immediate cardiac cause; unwitnessed death and death of unknown cause; procedure-related CV deaths including those related to concomitant treatment	ARC criteria	ARC criteria	Acute neurological event of ≥24 h of duration, with focal signs and symptoms, confirmed by CT or MRI or pathological confirmation. Aetiology: - haemorrhagic stroke: including intraparenchymal, subarachnoid haemorrhage and subdural hematomas) - ischemic stroke - unknown cause: in which case there was no brain imaging
DES LATE	All deaths unless there was a definite noncardiac cause	Universal definition (*Circulation*. 2007;116:2634–2653)	ARC criteria	New neurological deficit, confirmed by a neurologist and imaging

EXCELLENT	All deaths unless there was a definite noncardiac cause	ARC criteria Periprocedural MI: ≤ 48 h after PCI: an increase of cardiac enzyme (CK-MB or troponin T/troponin I) 3 times > ULN in stable patients - in patients with elevated baseline levels of cardiac enzyme: a subsequent increase of 2-fold from baseline values > 48 h after PCI: clinical signs of MI combined with a CK-MB fraction or troponin T/troponin I increase > ULN	ARC criteria	A new neurological deficit, was confirmed by a neurologist and on imaging.
GLOBAL LEADERS		Third universal definition	ARC criteria	Rapid onset of focal/global neurological deficit lasting ≥24 h or <24 h if therapeutic intervention, neuro-imaging or death. No other causes (e.g. tumour, drug side effect, trauma, etc.). Confirmation by at least 1 of: a neurologist or neurosurgeon; neuro-imaging; lumbar puncture; other compelling evidence of stroke
I -LOVE -IT 2	Any death due to an evident cardiac cause, any death related to PCI, unwitnessed death, or death of unknown causes	Universal definition (*Circulation*. 2007;116:2634–2653)	-	-
ISAR SAFE	-	- new Q-waves - pathologic evidence (such as autopsy) showing a new MI - ST-segment elevation (>l mm in 2 contiguous leads) accompanied by ischemic chest pain lasting for >20minutes - hemodynamic decompensation	ARC criteria	Acute neurological event of ≥24 h of duration, with focal signs and symptoms and without evidence supporting any alternative explanation, confirmed by CT/MRI or pathological confirmation
ITALIC	All deaths unless there was a definite noncardiac cause	- Q-wave MI: recurrence of symptoms and/or development of new pathological Q waves in 2 or more contiguous leads with elevated CK-MB, or troponin levels - non–Q-wave MI: >2-fold CK elevation with elevated CK-MB or troponin without new pathological Q waves	ARC criteria	Acute new neurological deficit ending in death or lasting longer than 24 h, diagnosed as stroke by a physician
IVUS-XPL	All deaths unless there was a definite non-cardiac cause	Presence of consistent clinical symptoms, ECG change, or abnormal imaging findings combined with a CK myocardial band fraction increase > ULN or an increase in troponin I to > 99th percentile of the ULN	ARC criteria	A new neurological deficit confirmed using a neurological examination and imaging

NIPPON	-	Periprocedural: CK-MB level > ULN were not considered as new MI, but as MI at registration - CK-MB level >3x the ULN within 48 h after PCI -a serum troponin or serum CK-MB level >5x the ULN ≤72 h after CABG - a new Q-wave, LBB, new occlusion of the native vessel or graft, or reduction of viable myocardium on diagnostic imaging. Spontaneous: myocardial enzymes are at or above the ULN, it should be considered as MI at registration -serum level of troponin or CK-MB > ULN,>48 h after PCI or ≤72 h after CABG Re-infarction: blood levels of biomarkers measured twice after the onset of MI are stable or decrease and the values at 3 to 6 h after PCI show a > 20% increase compared with those obtained at IP	ARC criteria	Cerebrovascular accident: cerebral infarction (ischemic stroke) or cerebral hemorrhage or subarachnoid hemorrhage (hemorrhagic stroke). Stroke: sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or ruptured aneurysm
OPTIDUAL	-	Third universal definition	ARC criteria	Acute episode of neurologic dysfunction attributed to a central nervous system vascular cause, documented by imaging. Evidence obtained from autopsy can confirm the diagnosis
OPTIMA-C	ARC criteria	ARC criteria	ARC criteria	ARC criteria
OPTIMIZE	-	WHO definition (ref)	ARC criteria	Acute neurological event of ≥24 h with confirmed by CT, MRI or pathology. Classified as haemorrhagic or ischemic.
REDUCE		Third universal definition	ARC criteria	-

RESET		ARC criteria	ARC criteria	Sudden onset of vertigo, numbness, aphasia, or dysarthria resulting from vascular lesions of the brain, including haemorrhage, embolism, thrombosis, or rupturing aneurysm
SECURITY	Any death without a non-cardiac cause	1. Cardiac enzyme elevation (troponin T/I or CK-MB) above the ULN associated with at least 1 ischemic symptom 2. New Q waves on the ECG 3. ECG changes indicative of ischemia or coronary artery intervention	ARC criteria	Any new neurological deficit lasting >24 h associated with neuroimaging evidence (CT/ MRI)
SMART CHOICE		1. Elevated Troponin or CK-MB > ULN with ischemic symptoms or ECG findings indicative of ischemia 2. Periprocedural enzymes elevation ≤ 48 h after the IP without concomitant ischemic symptoms 3. ECG findings indicative of ischemia was excluded in the assessment of end points	ARC criteria	Any non-convulsive focal or global neurologic deficit of abrupt onset lasting > 24 h or leading to death, which was caused by ischemia or haemorrhage
SMART DATE	All deaths unless there was a definite noncardiac cause	Elevated cardiac enzymes (cardiac troponin or CK-MB) above the upper reference limit with ischaemic symptoms or ECG findings indicative of ischaemia that was not related to the IP	ARC criteria	Any non-convulsive focal or global neurological deficit of abrupt onset lasting more than 24 h leading to death, which was caused by ischemia or hemorrhage within the brain
STOP DAPT2		ARC criteria	ARC criteria	Acute onset of a neurological deficit that persists ≥24 h due to ischemia or haemorrhage. TIA were not classified in this category
TICO	Death due to myocardial infarction, cardiac perforation or pericardial tamponade, arrhythmia or conduction abnormalities stroke ≤ 30 days of procedure, or related to the procedure or any case in which a cardiac cause was not excluded	Third universal definition	ARC criteria	Acute cerebrovascular event that caused death, a neurological deficit lasting > 24 hours, or an acute infarction shown by imaging studies
TWILIGHT		Third Universal definition	ARC criteria	Acute symptomatic neurological dysfunction, lasting >24 h in the absence of therapeutic intervention; death due to cerebral, spinal or retinal tissue injury as evidenced by neuroimaging or lumbar puncture

Abbreviations: ARC: Academic Research Consortium; BARC: Bleeding Academic Research Consortium; CABG: coronary artery bypass graft; CK: creatine-kinase; CT: computed tomography; GUSTO: Global Utilization of Streptokinase And Tpa For Occluded Arteries; IP: index procedure; MRI: Magnetic Resonance Imaging; LBB: left bundle block; MI: myocardial infarction; NR: not reported; PCI: percutaneous coronary intervention; QCA: quantitative coronary angiography; REPLAE-2: Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events; ST: stent thrombosis; TIA: transient ischemic attack TIMI: Thrombolysis in Myocardial Infarction; TV: target vessel; TVR: target vessel revascularization; UAP: unstable angina pectoris; ULN: upper limit normal; WHO: World Health Organization.

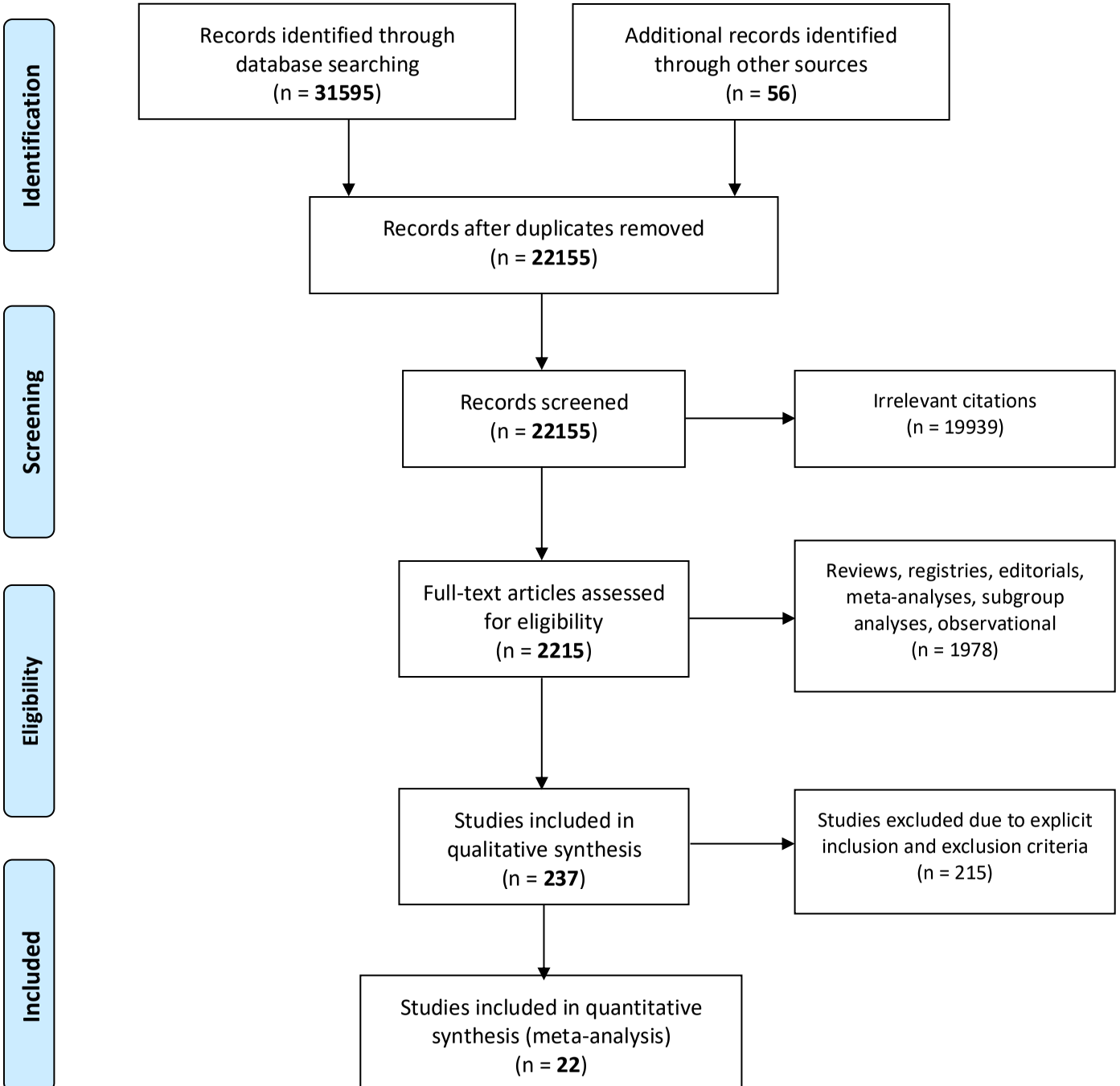
Supplementary Table S4. Safety endpoint and net clinical benefit definitions

Trial name	Net benefit	Major bleeding	Any bleeding
ARTIC-Interruption	Any death, myocardial infarction, stent thrombosis, stroke or TIA, urgent revascularization, TIMI major bleed	STEEPLE major	STEEPLE major or minor
DAPT	NA	GUSTO moderate or severe	BARC 2-5
DAPT STEMI	All-cause mortality, any myocardial infarction, stent thrombosis, stroke, and TIMI major bleeding.	TIMI major	NA
DES LATE	Cardiac death, myocardial infarction, stroke, stent thrombosis, or TIMI major bleeding	TIMI major	NA
EXCELLENT	Death, myocardial infarction, stroke, stent thrombosis, or TIMI major bleeding	TIMI major	TIMI major or minor
GLOBAL LEADERS	All-cause mortality, Stroke, Myocardial infarction, or BARC 3-5 Bleeding	BARC 3-5	BARC 2-5
I -LOVE -IT 2	All-cause death, all MI, stroke, and BARC 3-5 bleeding	BARC 3-5	NA
ISAR SAFE	Death, myocardial infarction, definite, or probable stent thrombosis, stroke or TIMI major bleeding	TIMI major	TIMI major or minor
ITALIC	All-cause mortality, MI, stroke, TVR or TIMI major bleeding	TIMI major	TIMI major or minor
IVUS-XPL	Cardiac death, MI, stroke, or TIMI major bleeding	TIMI major	NA
NIPPON	All-cause death, nonfatal myocardial infarction, nonfatal stroke, or major bleeding according to modified REPLACE-2 definition	Intracranial bleeding, intraocular bleeding, retroperitoneal bleeding, clinically evident bleeding causing a decrease of hemoglobin by >3 g/dl, all bleeding causing a decrease of hemoglobin by >4 g/dl, and bleeding leading to transfusion of packed red blood cells or ≥2 U of whole blood	NA
OPTIDUAL	Death, MI, stroke or TIMI major bleeding	TIMI major	BARC 2-5
OPTIMA-C	NA	TIMI major	NA
OPTIMIZE	Death from all causes, MI, stroke, or major REPLACE-2/GUSTO bleeding	Intracranial, intraocular, or retroperitoneal hemorrhage; clinically overt blood loss resulting hemoglobin decrease >3 g/dL, any hemoglobin decrease >4 g/dL, or transfusion of ≥ 1 units of packed red blood cells or whole blood; or intracranial hemorrhage or bleeding causing hemodynamic compromise and requiring intervention (modified REPLACE-2)	REPLACE-2/GUSTO minor
REDUCE	NA	NA	BARC 2-5

RESET	NA	TIMI major	TIMI major or minor
SECURITY	NA	BARC 3-5	BARC 2-5
SMART CHOICE	NA	BARC 3-5	BARC 2-5
SMART DATE	NA	BARC 3-5	BARC 2-5
STOP DAPT2	NA	BARC 3-5	TIMI minor or major
TICO	Death, MI, stent thrombosis, stroke, target vessel revascularization and a major bleeding	TIMI major	TIMI major or minor
TWILIGHT	NA	BARC 3-5	BARC 2-5

Abbreviations: NA: not available; MI; myocardial infarction; TIA: transient ischemic attack; TVR: target vessel revascularization.

Supplementary Table S5. PRISMA flowchart



Supplementary Table S6. List and references of the included trial

OPTIMA-C [1]	OPTIMIZE [2]	ITALIC [3]	GLOBAL LEADERS[4]	DAPT-STEMI [5]
I-LOVE-IT 2 [6]	EXCELLENT [7]	OPTIDUAL [8]	TWILIGHT [9]	IVUS XPL [10]
RESET [11]	DAPT [12]	REDUCE [13]	ISAR SAFE [14]	SMART-DATE [15]
DES LATE [16]	SMART-CHOICE [17]	SECURITY [18]	NIPPON [19]	ARTIC-Interruption [20]
STOPDAPT-2 [21]	TICO[22]			

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Supplementary Table S7. Trials' designs and main features

Name	Design	Inclusion criteria	Main exclusion criteria	Study enrolment	Enrolled patients	Time of randomization	Daily DAPT regimen (mg)	DAPT duration	Primary composite end point	F-U (months)
ARTIC	Open label	- age ≥18 years - eligible for PCI with planned use of at least one DES - patients without use of a GPIIb/IIIa inhibitor at the time of randomization	- indication for anticoagulation with vitamin K antagonists - contraindication to aspirin or clopidogrel or GPIIb/IIIa inhibitors or to increased dose regimen of aspirin or clopidogrel - ongoing bleeding or recent bleeding or recent major surgery - severe liver insufficiency - thrombopenia - treatment with GPIIb/IIIa before randomization - STEMI - prior history of major bleeding with contraindication to DAPT - any scheduled surgery during the year after enrolment 10 - high-risk feature of poor compliance to DAPT	January 2011 - March 2012	1286	12 months after PCI	12 months ASA + C 18-30 month ASA + C	12 months (n=624) 18-30 months (n=635)	Death, MI, ST, stroke, or urgent revascularisation	17
DAPT	Double-blind	- age> 18 years - PCI with stent deployment ≤24 hours	- index procedure stent placement with stent diameter <2.25 mm or >4.0 mm - pregnant women - planned surgery necessitating discontinuation of antiplatelet therapy within the 30 months following enrolment. - current medical condition with a life expectancy of < 3 years - anticoagulant therapy - contraindication to study drugs - subject treated with both DES and BMS during the index procedure.	August 2009 - July 2011	25682	12 months after PCI	12 months ASA 75-162 + C 75/P 10 30 months ASA 75-162 + C 75/P 10	12 months (n=4941) 30 months (n=5020)	ST; MACCE (composite of death, MI, or stroke)	33
DAPT STEMI	Open label	STEMI patients between 18-85 years, who underwent primary PCI with a secondgeneration DES implantation	- contraindication to study drugs - known bleeding diathesis or coagulopathy - planned elective surgical procedure necessitating interruption of DAPT during the first 6 months after randomization. - history of stent thrombosis - DES in main left coronary artery - active bleeding, known bleeding diathesis or known coagulopathy. - oral anticoagulant therapy with Coumadin derivates - life expectancy of <1 year - pregnancy or potential childbearing	December 2011 - August 2017	1100	6 months after PCI	6 months ASA 75–100 + P 10/T 90 bid 12 months ASA 75–100 + P 10/T 90 bid	ASA only (n=433) 12 months (n=437)	All-cause mortality, any MI, any revascularization, stroke and major bleeding	18

DES LATE	Open label	- DES at least 12 months before enrolment - no MACE (myocardial infarction, stroke, or repeat revascularization) or major bleeding since implantation - DAPT on board	- contraindication to study drugs - concomitant vascular disease that required the long-term use of clopidogrel or other established indications for clopidogrel therapy (eg, recent ACS) - life expectancy of <1 year.	July 2007 - July 2011	5045	12 to 18 months after PCI	12 months ASA 100 or 200 + C 75 36 months ASA 100 or 200 + C 75	12 months (n=2514) 36 months (n=2531).	Cardiac death, MI, or stroke	24
EXCELLENT	Open label	- lesion in a native coronary vessel with a reference diameter of 2.25 to 4.25 mm - stenosis of >50% - evidence of myocardial ischemia such as stable/unstable angina - recent MI - silent ischemia - a positive functional study - reversible changes on ECG consistent with ischemia - documentation of ischemia was not mandatory for lesions with ≥ 75% stenosis	- MI ≤ 72 hours - LVEF ≤25% - cardiogenic shock - any stent implantation in the target vessel before enrolment - severe hepatic/renal dysfunction - leukopenia, neutropenia, thrombocytopenia, anaemia - contraindication to study drugs - major bleeding ≤ 3 months or major surgery ≤ 2 months - elective surgical procedure planned ≤ 12 months - life expectancy <1 year - significant LM disease (≥ 50% stenosis) - CTO - true bifurcation lesions requiring a planned 2-stent strategy	June 2008 - July 2009	1443	Index procedure	6 months ASA 100 + C 75 12 months ASA 100 + C 75	6 months (n= 722) 12 months (n= 721)	Cardiac death, MI, or TVR	12
GLOBAL LEADERS	Open label	- ≥18 years - ≥1 stenosis ≥ 50% in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation with RVD ≥2.25 mm.	- contraindication to study drugs - moderate to severe hepatic impairment - planned surgery, including CABG as a staged procedure, ≤ 12 month, unless DAPT is maintained throughout the peri-surgical period - oral anti-coagulation therapy - active major bleeding or major surgery ≤30 days -history of ICH -stroke (any type) ≤ 30 days -pregnancy or breastfeeding	July 2013 – November 2015	15968	Index procedure	Experimental arm: Ticagrelor 90 bid + Aspirin 75-100 (1month) followed by Ticagrelor monotherapy Control arm: Aspirin 75-100 + Ticagrelor 90 bid (in ACS) or Clopidogrel 75 (in stable patients)	1 month (n=7980) 12 months (n=7988)	All-cause mortality or new Q-wave MI	24

I -LOVE -IT 2	Open label	- >18 years -1 coronary lesion with stenosis >70% in a vessel with reference diameter of 2.5 to 4.0 mm. -if with multivessel disease: complete revascularization <1 month using the same study stents if needed.	- known intolerance to a study drug, metal alloys, or contrast media - life expectancy <1 year - restenosed lesions - stent implantation <1 year - LVEF <40% - severe renal or hepatic dysfunction - hemodynamic instability - planned surgery<6 months after index procedure - pregnancy or potential childbearing - clinical indications of the inability to tolerate DAPT for 12 months	October 2012 - June 2013	1829	Index procedure	6 months ASA 100 + C 75 12 months ASA 100 + C 75	6 months (n=909) 12 months (n=920)	Cardiac death, TVMI, or clinically indicated TLR	18
ISAR SAFE	Double-blind	Clopidogrel therapy at 6 months after DES implantation	- clinical symptoms, proof of ischemia, and/or presence of angiographic lesions requiring revascularization - previous ST - DES implantation in LM coronary artery - MI during the 6 months after DES implantation - life expectancy of ≤1 year - planned major surgery within the next 6 months with need to discontinue antiplatelet therapy - active bleeding; bleeding diathesis - history of intracranial bleeding - oral anticoagulation therapy with coumarin derivatives - contraindication to study drugs - pregnancy or potential childbearing	October 2008 - April 2014	4005	6 months after index procedure	6 months ASA 100 + C 75 12 months ASA 100 + C 75	6 months (n=1998) 12 months (n=2007)	Death, MI, ST (definite or probable), stroke, or TIMI major bleeding	9
ITALIC	Open label	-age>18years -eligible for (PCI) -implanted with at least 1 Xience V DES -all clinical situations excluding primary PCI for acute MI and treatment of the LMA	- prior DES implantation < 1 year - thrombocytopenia or known haemorrhagic diathesis - oral anticoagulation therapy or abciximab treatment during hospital stay - contraindication to study drugs - major surgery within the preceding 6 weeks - evidence of active gastrointestinal or urogenital bleeding - severe liver failure - any surgery scheduled during the year after enrolment - severe concomitant disease with <2 years' life expectancy.	November 2008 - December 2010 (ITALIC) January 2012 - November 2013 (ITALIC PLUS)	2031	Index hospitalization	6 months ASA 75-160 + C 75/P 10/T 90 bid 24 months ASA 75-160 + C 75/P 10/T 90 bid	6months (n=926) 24 months (n= 924)	Death, MI, repeat emergency TVR, stroke, or TIMI major bleeding	36

IVUS-XPL	Open label	- age > 20 years - typical chest pain or evidences of myocardial ischemia - non-emergent conditions - patients who provide signed informed consent -stent length ≥28 mm based on angiographic estimation - significant coronary artery stenosis (>50%) considered for coronary revascularization with stent implantation - reference vessel diameter 2.5- 4.0 mm based on operator assessment	- STEMI < 48 hrs - contraindication for anti-platelet agents and bleeding history <3 months - contraindication to study drugs - prior CVE (not TIA) - peripheral artery occlusive disease - thromboembolic disease - ST - age>80 years - severe hepatic/renal dysfunction. - significant leucopenia, neutropenia, thrombocytopenia, anemia, or known bleeding diathesis - cardiogenic shock. - LVEF<40% - pregnancy or potential childbearing - life expectancy <1 year - LM disease requiring PCI - bifurcation lesion with 2-stent technique - CTO - previous DES <6 months - in-stent restenosis	October 2010 - July 2014	NA	Index procedure	6 months ASA 100 + C 75 12 months ASA 100 + C 75	6 months (n=699) 12-months (n=701)	Cardiac death, target lesion-related MI, or ischemia-driven TLR	12
NIPPON	Open label	- age > 20 years and <80 years - indication for PCI	- cardiogenic shock at the time of PCI - concomitant disease for which a thienopyridine was essential for treatment - history of ST - contraindication to study drugs - subject was unable to give informed consent. - LVEF<30% - Pregnancy - life expectancy < 1year - any active bleeding condition - inability to undergo complete clinical follow-up - coronary artery not eligible for PCI with the Nobori stent - planned surgery necessitating discontinuation of antiplatelet therapy (>14 days) within 18 months following enrolment. - index stent procedure for a saphenous vein graft - in-stent restenosis - unprotected LMT lesion - history of intracranial bleeding or ischemic stroke < 6 months before enrolment. - DES for another lesion < 6 months prior to index PCI - bleeding predisposition or history of coagulation abnormality - long-term warfarin (or similar anticoagulant) therapy	December 2011 - June 2015	3773	Index hospitalization	6 months ASA 81 to 162 + C 75/Ticlopidine 200 12 months ASA 81 to 162 + C 75/Ticlopidine 200	6 months (n=1653) 18 months (n=1654)	All cause death, Q-wave or non–Q-wave MI, CVE, and major bleeding	36

OPTIDUAL	Open label	- symptoms of stable angina - silent ischaemia - ACS (i.e. unstable angina, NSTEMI, STEMI) - ≥1 lesion with stenosis ≥50% located in a native vessel ≥2.25 mm in diameter and who were implanted with ≥1 DES of any type.	- age <18 y - oral anticoagulation therapy - DES in an unprotected LM coronary artery -contemporaneous enrolment in a different clinical trial - life expectancy <2 years - contraindication to study drugs - other revascularization with a DES ≤9 months or other revascularization with a BMS ≤1 month prior to this study	January 2009 - January 2013	1799	At 12 ± 3 months after PCI	12 months ASA 75-160 + C 75 36 months ASA 75-160 + C 75	12 months (n=690) 36 months (n=695)	All-cause mortality, MI, stroke and major bleeding events.	36
OPTIMA-C	Open label	- >20 years -evidence of myocardial ischemia -significant coronary artery stenosis (>50%) amenable for coronary revascularization with a single stent (diameter of 2.75-4.0 mm and length of ≤ 30 mm). -de novo stenotic lesion located in a native coronary artery with visually estimated reference artery diameter of 2.5-4.0 mm and lesion length of ≤ 28 mm.	- STEMI - contraindication to study drugs - clinical conditions requiring systemic immune suppression over 2 weeks or anti-cancer therapy - prior ST - thromboembolic disease - pregnancy or potential childbearing - thrombocytopenia, anaemia, or known bleeding diathesis known coagulopathy (HIT) or refused blood transfusions - gastrointestinal or genitourinary bleeding < 3 months or major surgery <2 months - non cardiac comorbid conditions - life expectancy <1 year - LVEF < 35% - cardiogenic shock. - severe hepatic/renal dysfunction - LM disease requiring PCI - true bifurcation lesions requiring 2 stents - target lesions with CTO or with in-stent restenosis - previous DES implantation within 1 year	April 2011 - May 2014	1368	Index procedure	6 months ASA 100 + C 75 12 months ASA 100 + C 75	6 months (n=7980) 12 months (n=7988)	Cardiac death, TVR, MI, ischemia driven TLR	12
OPTIMIZE	Open label	-stable angina -silent ischemia or low risk ACS -≥1 lesion with stenosis >50% (MVD allowed) in a native vessel >2.5 mm diameter.	- STEMI - PCI with BMS in non-target lesions <6 months - previous treatment with any DES - scheduled elective surgery ≤1y after index procedure - contraindication to study drugs - lesion in a saphenous vein graft - in-stent restenosis.	April 2010 – March 2012	3211	Index procedure	3 months ASA 100 + C 75 12 months ASA 100 + C 75	3 months (n=1563) 12 months (n=1556)	All-cause death, MI, stroke, or major bleeding	12
REDUCE	Open label	-≥18 years -ACS undergoing successful PCI with COMBO stent	- cardiogenic shock - recent major bleeding - contraindication to DAPT - planned cardiac surgery or intervention for another lesion after index hospital discharge - any revascularization with other stents than COMBO - need for transplantation - need for permanent DAPT - life expectancy <2 years - pregnancy	June 2014 – May 2016	1496	Index procedure	3 months ASA + C 75/P 10/T 90 bid 12 months ASA + C 75/P 10/T 90 bid	3 months (n=729) 12 months (n=733)	All cause death, MI, definite/probable ST, stroke, TVR or BARC II-V bleeding	24

RESET	Open label	- age≥20 years old - undergoing successful elective PCI in a coronary artery with ≥50% DS by visual estimation - RVD ≥2.5-4.0 mm.	- contraindication to study drugs - bleeding history ≤3 months - prior CVE (not TIA) - occlusive PAD - thromboembolic disease - severe hepatic/renal dysfunction - leukopenia, neutropenia, thrombocytopenia, anaemia - known bleeding diathesis - cardiogenic shock - LVEF <40% - pregnancy or potential childbearing - life expectancy <3 year - STEMI ≤ 48 hours after onset of symptoms - LM disease requiring PCI - bifurcation lesion treated with a two-stent technique - in-stent restenosis - CTO - prior DES implantation - overlapped DESs (only allowed in the long-lesion subgroup)	April 2009 – December 2010	2148	Index procedure	3 months ASA 100 + C 75 12 months ASA 100 + C 75	3 months (n=1059) 12 months (n=1058)	CV death, MI, ST, ID-TVR, and TIMI major or minor bleeding	12
SECURITY	Double-blind	- symptoms of stable/unstable angina - documented silent ischemia - DES implantation in the target lesion ≤24h -presence ≥1 de novo stenosis ≥ 70% in a native coronary artery -age>18 years -no other DES implanted before the target procedure -no BMS implanted in the 3 months before the target procedure.	- treatment for saphenous vein graft - in-stent restenosis - unprotected LM coronary artery - STEMI ≤48 h - NSTEMI ≤6 months - LVFE <30% - contraindication to study drugs - history of significant thrombocytopenia with aspirin or thienopyridines - severe renal dysfunction - pregnancy or potential childbearing - active bleeding or significant risk of bleeding - uncontrolled hypertension - life expectancy <2y - any medical condition that could preclude follow-up, as defined in the protocol	July 2009 - June 2014	1404	Index procedure	6 months ASA + C/T/P 12 months ASA + C/T/P	6 months (n = 682) 12 months (n = 717)	Cardiac death, MI, stroke, definite or probable ST, or BARC 3-5 bleeding	24

SMART CHOICE	Open label	- ≥20 years - ≥1 coronary artery stenosis ≥ 50% in a native coronary artery with visually estimated diameter ≥ 2.25 mm and ≤ 4.25 mm amenable to stent implantation, undergone PCI	- contraindication to study drugs - hemodynamic instability or cardiogenic shock - active pathologic bleeding - DES implantation within 12 months before the index procedure - childbearing potential - noncardiac comorbidities with a life expectancy < 2 years.	Mar 2014 – Jul 2017	2993	Index procedure or at 3-months follow-up	First 3 months: ASA 100 + C 75 (in stable patients) or C 75 /T 90 bid/P 10 (in ACS) After 3 months: -Experimental monotherapy: P2Y12 inhibitor (C in stable patients; C/T/P in ACS) -Control arm: ASA 100 + C 75 (stable patients) or C 75 /T 90 bid/P 10 (ACS)	3 months (n=1495) 12 months (n=1498)	All-cause death, MI, or stroke	12
SMART-DATE	Open label	- ACS that included unstable angina, NSTEMI and STEMI. - one lesion in a native coronary vessel with reference diameter of 2·25–4·25 mm and stenosis >50% amenable for PCI with stents.	- contraindication to study drugs - active pathological bleeding - major bleeding within the previous 3 months - major surgery within the previous 2 months - history of bleeding diathesis or known coagulopathy - life expectancy <2 years - an elective surgical procedure planned <1y - active participation in another drug or device investigational study	September 2012 - December 2015	2712	Index procedure	6 months ASA 100 + C 75 12 months ASA 100 + C 75 After December 2014 P 10 or T 90 bid could be used instead of C	6 months (n=1357) 12 months (n=1355)	All-cause mortality, MI, or stroke	18
STOP DAPT 2	Open label	Successful PCI with CoCr-EES without other types of DES or in-hospital major complications other than peri-procedural MI	- anticoagulation or antiplatelet therapy other than aspirin and P2Y12 receptor blockers - history of intracranial bleeding - intolerance to clopidogrel	Dec 2015 – Dec 2017	3045	After PCI, before hospital discharge	First month: C 75 or P 10 + ASA 81-200 After 1 month: -Experimental monotherapy: C (P was switched to C if necessary) -Control arm: C 75 or + ASA 81-200	1 month (n=1523) 12 months (n=1522)	CV death, MI, definite ST, stroke, or TIMI major or minor bleeding	12

TICO	Open-label	- ≥ 19 years - Bioabsorbable polymer sirolimus eluting stent placed for ACS	≥ 80 years Increased bleeding risk due to: - any prior haemorrhagic stroke - ischemic stroke, dementia, brain surgery ≤ 6 months - intracranial tumour - aortic dissection - internal bleeding ≤ 6 months - active bleeding or bleeding diathesis - anaemia or thrombocytopenia - major surgery or traumatic injury resulting in any impairment of physical activity within the past 3 weeks Need for oral anticoagulation Life expectancy <1 year Treatment with strong cytochrome P450A4 inhibitors Moderate to severe hepatic disfunction Increased risk of bradycardia-related symptoms	August 2015 – October 2018	3056	Index procedure/ hospitalization	First 3 months: ASA + T 90 BID After 3 months: Experimental arm: Ticagrelor 90 BID Control arm: ASA + T 90 BID	3 months (n=1527) 12 months (n=1529)	Major bleeding, death, MI, ST, stroke, target-vessel revascularization	12
TWILIGHT	Double-blind	Successful DES implantation with at list one of the following: - ≥65 years - female sex - troponin-positive ACS - vascular disease - DM treated with medication - CKD - MVD - TSL >30 mm - thrombotic target lesion - bifurcation lesion treated with two stents - LM or proximal LAD obstruction atherectomy	- STEMI - cardiogenic shock - ongoing long-term treatment with oral anticoagulants - contraindication to aspirin or ticagrelor	July 2015 – December 2017	9006	3-months after PCI	First 3 months: Ticagrelor 90 bid + ASA 81-100 After 3 months, in event-free patients: -Experimental monotherapy: Ticagrelor 90 bid -Control arm: Ticagrelor 90 bid + ASA 81-100	3 months (n=3555) 15 months (n=3564)	BARC 2, 3, or 5 bleeding	12

Abbreviations: ACS: acute coronary syndrome; ASA: acetylsalicylic acid; BARC: Bleeding Academic Research Consortium; BMS: bare metal stent; C: clopidogrel; CABG: coronary artery bypass graft; CAD: coronary artery disease; CoCr-EES: cobalt-chromium everolimus-eluting stent; CKD: chronic kidney disease; CTO: chronic total occlusion; CVE: cerebrovascular event; DAPT= dual antiplatelet therapy ; DES: drug-eluting stent; DM: diabetes mellitus; F-U : follow up ICH: intracranial haemorrhage; ID-TLR: ischemia-driven target lesion revascularization; LAD: left anterior descending; LM: left main; LVEF; left ventricle ejection fraction; M : month; MACCE : major adverse cardiac and cerebrovascular events MI: myocardial infarction; MVD: multi-vessel disease; P: prasugrel; PCI: percutaneous coronary intervention; RVD: reference vessel diameter; ST: stent thrombosis; STEMI: ST-elevation myocardial infarction; T: ticagrelor; TIMI: Thrombolysis in Myocardial Infarction; TLF: target organ failure; TLR: target lesion revascularization; TSL: total stent length; TVMI: target vessel myocardial infarction.

Supplementary Table S8. Baseline patients' characteristics

Trial name	Group	Age (mean, SD or median Q1-Q3)	Women, n (%)	Diabetes, n (%)	Hypertension, n (%)	Smoking, n (%)	Dyslipidaemia, n (%)	Family history of CAD, n (%)	Previous ACS, n (%)	Previous PCI, n (%)	Previous CABG, n (%)	Previous stroke or TIA, n (%)	CHF, n (%)	CKD, n (%)	PAD, n (%)
ARTIC	12 m (n=624)	64	121 (19)	222 (36)	388 (62)	152 (24)	426 (68)	-	186 (30)	249 (40)	35 (6)	38 (6)	23 (4)	-	-
	>12 m (n=635)	64	127 (20)	198 (31)	376 (59)	147 (23)	428 (67)	-	197 (31)	273 (43)	47 (7)	28 (4)	20 (3)	-	-
DAPT	12 m (n=4941)	61.6 (± 10.1)	1284 (26)	1481 (30.1)	3649 (74)	1210 (24.7)	-	-	1026 (21.1)	1529 (31)	581 (11.8)	169 (3.4)	223 (4.5)	-	284 (5.8)
	30 m (n=5020)	61.8 (± 10.2)	1242 (24.7)	1556 (31.1)	3796 (75.8)	1222 (24.6)	-	-	1092 (22)	15!8 (30.4)	568 (11.3)	155 (3.1)	238 (4.8)	-	284 (5.8)
DAPT STEMI	6 m (n=433)	59.8 (±10.7)	-	54 (13)	193 (45)	218 (51)	120 (28)	143 (33)	26 (6)	29 (7)	8 (2)	14 (3)	16 (4)	-	16 (4)
	12 m (n=437)	60.2 (±10.3)	-	61 (14)	195 (45)	205 (47)	125 (29)	144 (33)	20 (5)	18 (4)	2 (0.5)	8 (2)	19 (4)	-	9 (2)
DES LATE	12 m (n=2514)	62.3 (±10.1)	-	709 (28.2)	1423 (56.6)	722 (28.7)	-	-	92 (3.7)	276 (11)	-	89 (3.5)	-	-	-
	24 m (n=2531)	62.5 (±10)	-	709 (28)	1479 (58.4)	693 (27.4)	-	-	103 (4.1)	313 (12.4)	-	15 (4.5)	-	-	-
EXCELLENT	6 m (n=722)	63 (±9.6)	-	272 (37.7)	525 (72.7)	198 (27.4)	543 (75.2)	-	47 (6.5)	67 (9.3)	11 (1.5)	47 (6.5)	4 (0.6)	6 (0.8)	-
	12 m (n=721)	62.4 (±10.4)	-	278 (38.6)	532 (73.8)	186 (25.8)	550 (76.3)	-	27 (3.7)	62 (8.6)	7 (1)	48 (6.7)	5 (0.7)	9 (1.2)	-
GLOBAL LEADERS	1m (n=7980)	64.5 (10.3)	1865 (23.4)	2049 (25.7)	5882 (74)	2066 (25.9)	5345 (69.3)	-	1831 (23)	2609 (32.7)	448 (5.6)	210 (2.6)	-	1099 (13.9)	467 (6)
	12m (n=7988)	64.6 (10.3)	1849 (23.1)	1989 (24.9)	5883 (73.3)	2103 (26.3)	5423 (70)	-	1879 (23.6)	2612 (32.7)	495 (6.2)	211 (2.6)	-	1072 (13.5)	529 (6.7)
I LOVE IT-2	6 m (n=909)	60.4 (10.2)	-	211 (23.2)	554 (61)	333 (36.6)	230 (25.3)	57 (6.3)	156 (17.2)	77 (8.5)	4 (0.4)	84 (9.2)	-	-	13 (1.4)
	12 m (n=920)	60 (10)	-	203 (22.1)	596 (64.8)	352 (38.3)	215 (23.4)	47 (5.1)	145 (15.8)	60 (6.5)	4 (0.4)	87 (9.5)	-	-	10 (1.1)
ISAR SAFE	6 m (n=1997)	67.2 (59.3-73.3)	386 (19.3)	495 (24.8)	1797 (87.5)	292 (14.6)	1747 (87.5)	-	516 (25.9)	-	152 (7.7)	-	-	-	-
	12 m (n=2003)	67.2 (59.1-73.7)	391 (19.5)	484 (24.2)	1830 (91.5)	306 (15.3)	1748 (87.4)	-	491 (24.5)	-	149 (7.5)	-	-	-	-
ITALIC	6 m (n=912)	61.7 (±10.9)	-	331 (36.3)	595 (65.2)	464 (50.9)	612 (67.1)	322 (35.3)	142 (15.6)	220 (24.1)	61 (6.7)	-	-	28 (3.1)	-

	24 m (n=910)	61.5 (±11.1)	-	344 (37.8)	589 (64.7)	480 (52.7)	611 (67.1)	325 (35.7)	134 (14.7)	205 (22.5)	45 (4.9)	-	-	25 (2.7)	-
IVUS-XPL	6 m (n = 699)	63 (±9)	-	249 (36)	443 (63)	171 (25)	473 (68)	-	34 (5)	72 (10)	22 (3)	-	-	-	-
	12 m (n =701)	64 (±9)	-	257 (37)	455 (65)	165 (25)	456 (65)	-	29 (4)	73 (10)	14 (2)	-	-	-	-
NIPPON	6 m (n=1886)	67.3 (±9.7)	-	700 (37.1)	1315 (69.7)	1084 (57.5)	1272 (67.4)	-	218 (11.6)	454 (24.1)	24 (1.3)	84 (4.5)	-	-	66 (3.5)
	18 m (n=1887)	67.2 (± 9.9)	-	707 (37.5)	1342 (71.1)	1130 (59.9)	1278 (67.7)	-	212 (11.2)	481 (25.5)	29 (1.5)	75 (4)	-	-	48 (2.5)
OPTIDUAL	12 m (n=690)	64.2 (± 11.5)	143 (20.7)	222 (32.2)	417 (60.4)	399 (57.8)	-	224 (32.5)	122 (17.7)	186 (27)	35 (5.1)	25 (3.6)	8 (1.2)	-	45 (6.5)
	48 m (n=695)	64.1 (±10.8)	127 (18.3)	213 (30.6)	396 (57)	425 (61.2)	-	195 (28.1)	119 (17.1)	180 (25.9)	37 (5.3)	29 (4.2)	4 (0.6)	-	34 (4.9)
OPTIMA-C	6 m (n=683)	62.8 (10.8)	-	199 (29.1)	426 (62.4)	184 (26.9)	204 (29.9)	-	-	-	-	-	12 (1.8)	-	-
	12 m (n=684)	64.4 (10.3)	-	203 (29.7)	437 (63.9)	184 (26.9)	195 (28.5)	-	-	-	-	-	19 (2.8)	-	-
OPTIMAZE	3 m (n=1563)	61.3 (10.4)	571 (36.5)	554 (35.4)	1350 (86.4)	290 (18.6)	953 (63.2)	564 (41.3)	541 (34.6)	327 (20.9)	111 (7.1)	38 (2.5)	67 (4.3)	114 (7.4)	43 (2.8)
	12 m (n=1556)	61.9 (10.6)	574 (36.9)	549 (35.3)	1371 (88.2)	269 (17.3)	952 (63.7)	583 (42.8)	542 (34.8)	297 (19.1)	128 (8.2)	38 (2.5)	64 (4.2)	89 (5.8)	46 (3)
REDUCE	3m (n=751)	61 (53-69)	131 (17.4)	162 (21.6)	379 (50.7)	313 (42.1)	346 (46.3)	260 (35)	94 (12.5)	88 (11.7)	21 (2.8)	11 (1.5)	-	-	-
	12m (n=745)	60 (52-68)	169 (22.7)	145 (19.5)	375 (50.7)	314 (42.7)	333 (44.9)	265 (36)	88 (11.8)	73 (9.8)	21 (2.8)	15 (2)	-	-	-
RESET	3 m (n=1059)	62.4 (9.4)	377 (35.6)	316 (29.8)	660 (62.3)	267 (25.2)	611 (57.7)	-	19 (1.8)	37 (3.5)	2 (0.2)	-	120 (11.3)	-	-
	12 m (n=1058)	62.4 (9.8)	393 (37.1)	305 (28.8)	650 (61.4)	241 (22.8)	634 (59.9)	-	17 (1.6)	32 (3)	6 (0.6)	-	125 (11.8)	-	-
SECURITY	6 m (n=682)	64.9 (±10.2)	153 (22.4)	206 (30.4)	508 (74.5)	139 (20.5)	446 (65.4)	-	145 (21.2)	132 (19.4)	38 (5.6)	-	-	-	-
	12 m (n=717)	65.5 (±10.1)	166 (23.2)	223 (31.4)	510 (71.1)	172 (24.4)	436 (60.8)	-	144 (20.1)	116 (16.2)	39 (5.4)	-	-	-	-
SMART CHOICE	3 m (n=1495)	64.6 (10.7)	408 (27.3)	570 (38.2)	921 (61.6)	424 (28.4)	673 (45.1)	-	62 (4.1)	-	-	99 (6.6)	-	44 (2.9)	-
	12 m (n=1498)	64.4 (10.7)	387 (25.8)	552 (36.8)	919 (61.3)	367 (24.2)	679 (45.5)	-	65 (4.3)	-	-	102 (6.8)	-	53 (3.5)	-
SMART DATE	6 m (n=1357)	62 (11.5)	341 (25.1)	365 (26.9)	669 (49.9)	506 (38)	322 (24.2)	-	30 (2.3)	65 (4.9)	52 (3.9)	-	13 (1)	-	
	12 m (n=1355)	62.2 (11.9)	327 (24.1)	379 (28.1)	654 (48.7)	536 (40.1)	336 (25.2)	-	23 (1.7)	52 (3.9)	58 (4.4)	-	6 (0.5)	-	
	1 m (n=1500)	68.1 (10.9)	317 (21.1)	585 (39)	1105 (73.7)	399 (26.6)	1116 (74.4)	-	207 (13.8)	503 (33.5)	17 (1.1)	81 (5.4)	115 (7.7)	82 (5.5)	96 (6.4)

STOP DAPT 2	12 m (n=1509)	69.1 (10.4)	355 (23.5)	574 (38)	1116 (74)	311 (20.6)	1128 (74.8)	-	199 (13.2)	529 (35.1)	42 (2.8)	105 (7)	107 (7.1)	84 (5.6)	100 (6.6)
TICO	3 m (n=1527)	61 (11)	323 (21)	418 (27)	760 (50)	555 (36)	924 (61)	-	64 (4)	135 (9)	8 (1)	60 (4)	-	292 (19)	-
	12 m (n=1529)	61 (11)	305 (20)	417 (27)	781 (51)	587 (38)	922 (60)	-	49 (3)	127 (8)	10 (1)	66 (4)	-	328 (22)	-
TWILIGHT	3 m (n=3555)	65.2 (10.3)	846 (23.8)	1319 (37.1)	2580 (72.6)	726 (20.4)	2157 (60.7)	-	1020 (28.7)	1502 (42.3)	362 (10.2)	-	-	572 (16.8)	-
	15m (n=3564)	65.1 (10.4)	852 (23.9)	1301 (36.5)	2574 (72.2)	822 (23.1)	2146 (60.2)	-	1020 (28.6)	1496 (42)	348 (9.8)	-	-	573 (16.7)	-

All data are presented as mean and standard deviation or absolute numbers and percentage

Supplementary Table S9. Clinical presentation

Trial Name		ACS			Stable CAD, n (%)	Silent ischemia, n (%)
		STEMI	NSTEMI	UAP		
ARTIC	12 m	-	-	-	-	-
	12 +6/18m	-	-	-	-	-
DAPT	12 m	511 (10.3)	767 (15.5)	825 (16.7)	1870 (37.8)	-
	30 m	534 (10.6)	776 (15.5)	838 (16.7)	1882 (37.5)	-
DAPT STEMI	6 m	433 (49)	-	-	-	-
	12 m	447 (51)	-	-	-	-
DES LATE	12 m	314 (12.5)	266 (10.6)	971 (38.6)	956 (38)	-
	24 m	314 (12.4)	268 (10.6)	930 (36.7)	1011 (39.9)	-
EXCELLENT	6 m	19 (2.6)	350 (48.5)	353 (48.9)	6 m	19 (2.6)
	12 m	26 (3.6)	349 (48.4)	346 (48)	12 m	26 (3.6)
GLOBAL LEADERS	1 m	1062 (13.3)	1684 (21.1)	1004 (12.6)	4230 (53)	-
	12 m	1030 (12.9)	1689 (21.1)	1018 (12.7)	4251 (53.2)	-
I LOVE-IT 2	6 m	122 (13.4)	103 (11.3)		527 (58)	
	12 m	126 (13.7)	98 (10.7)		520 (56.5)	
ISAR SAFE	6 m	158 (7.9)	207 (10.4)	429 (21.5)	969 (48.6)	218 (10.9)
	12 m	166 (8.3)	203 (10.1)	438 (21.9)	956 (47.8)	227 (11.3)
ITALIC	6 m	1 (0.1)	67 (7.3)	143 (15.7)	375 (41.1)	185 (20.3)
	24 m	3 (0.3)	65 (7.1)	149 (16.4)	378 (41.5)	183 (20.1)
IVUS-XPL	6 m	106 (51)	-	237 (34)	356 (51)	-

	12 m	112 (16)	-	231 (33)	358 (51)	-
NIPPON	6 m	234 (12.4)	42 (2.2)	335 (17.8)	846 (44.9)	-
	18 m	242 (12.8)	34 (1.8)	365 (19.3)	814 (43.1)	-
OPTIDUAL	12 m	82 (11.9)	117 (17)	63 (9.1)	207 (30)	151 (21.9)
	48 m	214 (19.9)	99 (14.2)	66 (9.5)	240 (34.5)	138 (19.9)
OPTIMA-C	6 m	-	90 (13.2)	254 (37.2)	339 (49.1)	-
	12 m	-	95 (13.9)	253 (37.0)	336 (49.1)	-
OPTMAZE	3 m	-	84 (5.4)	-	935 (59.8)	134 (8.6)
	12 m	-	84 (5.4)	-	911 (58.6)	143 (9.2)
REDUCE	3 m	370 (49.3)	267 (35.6)	114 (15.2)	-	-
	12 m	336 (45.2)	305 (41)	103 (13.8)	-	-
RESET	3 m	-	-	432 (40.8)	471 (44.5)	-
	12 m	-	-	422 (39.9)	490 (46.3)	-
SECURITY	6 m	-	-	213 (38.4)	341 (61.6)	-
	12 m	-	-	229 (38.4)	368 (61.6)	-
SMART CHOICE	3 m	164 (11)	239 (16)	467 (31.2)	625 (41.8)	-
	12 m	150 (10)	230 (15.4)	491 (32.8)	625 (41.8)	-
SMART DATE	6 m	509 (37.5)	428 (31.5)	420 (31)	-	-
	15 m	-	1096 (30.8)	1245 (34.9)	999 (28)	223 (6.3)
STOP DAPT 2	1 m	291 (19.4)	81 (5.4)	193 (12.9)	935 (62.3)	-
	12 m	270 (17.9)	99 (6.6)	214 (14.2)	926 (61.4)	-
TICO	3 m	546 (36)	539 (35)	442 (29)	-	-

	12 m	557 (36)	488 (32)	484 (32)	-	-
TWILIGHT	3 m	-	1024 (28.8)	1249 (35.1)	1047 (29.5)	234 (6.6)
	15 m	-	1096 (30.8)	1245 (34.9)	999 (28)	223 (6.3)

Supplementary Table S10. Procedural characteristics

	DAPT	Treated vessel (%) LM	LAD	LCX	RCA	Stent Type (%)	
ARTIC-Interruption	12 m	23 (4)	325 (52)	181 (29)	222 (36)	1st generation PCE and SES (40)	2nd generation DES (64)
	12+6/18 m	18 (3)	342 (54)	209 (33)	191 (30)	1st generation PCE and SES (43)	2nd generation DES (62)
DAPT	12 m	55 (0.9)	2586 (40.4)	1506 (23.5)	2057 (32.1)	EES (Xience and Promus) (47.7) PCE (Taxus) (26.6)	ZES (Endeavor) (12.6) SES (Cypher) (10.9)
	30 m	55 (0.8)	2715 (41.2)	1473 (22.4)	2153 (32.7)	EES (Xience and Promus) (47.7) PCE (Taxus) (26.6)	ZES (Endeavor) (12.6) SES (Cypher)(10.9)
DAPT STEMI	6 m	-	169 (39)	-	175 (41)	ZES (Resolute) (93)	Others (7)
	12 m	-	188 (43)	-	179 (41)	ZES (Resolute) (93)	Others (7)
DES LATE	12 m	90 (2.6)	1768 (50.6)	651 (18.6)	972 (27.8)	1st generation SES (44.3) 1st generation PCE (20.3) 2nd generation ZES (19.0)	2nd generation EES (10.4) Other 2nd generation DES (6.0)
	24 m	112 (3.1)	1781 (49.5)	715 (19.9)	976 (27.1)	1st generation SES (43.5) 1st generation PCE (20.5) 2nd generation ZES (18.9)	2nd generation EES (11.9) Other 2nd generation DES (5.3)
EXCELLENT	6 m	-	452 (63)	-	-	EES (Xience and Promus) (74.8)	SES (Cypher) (25.2)
	12 m	-	452 (63)	-	-	EES (Xience and Promus) (74.8)	SES (Cypher) (25.2)
GLOBAL LEADERS	1 m	197 (1.9)	4283 (41.2)	2524 (24.3)	3284 (31.6)	BES (94.8)	Others (6.4)
	12 m	190 (1.8)	4383 (42)	2553 (24.5)	3206 (30.7)	BES (94.4)	Others (6.7)
I LOVE-IT 2	6 m	23 (1.9)	569 (45.9)	284 (22.9)	364 (29.4)	BP-SES (Tivoli) (100)	
	12 m	21 (1.7)	569 (45.3)	279 (22.2)	386 (30.8)	BP-SES (Tivoli) (100)	
ISAR SAFE	6 m	9 (0.5)	794 (39.8)	528 (26.4)	636 (31.8)	1st generation PES (2.2) 1st generation SES (25) EES (47.5) ZES (Endeavor) (4.3)	ZES (Resolute) (11.4) BES (8.3) Other (0.9)

	12 m	3 (0.2)	812 (40.6)	480 (24)	682 (34)	1st generation PES (2.3) 1st generation SES (24.1) EES (49.3) ZES (Endeavor) (3.8)	ZES (Resolute) (10.9) BES (8.5) Others (0.6)
ITALIC	6 m	14 (1.5)	669 (73.4)	456 (50)	489 (53.6)	EES (Xience V) (100)	
	24 m	8 (0.9)	658 (72.3)	436 (47.9)	474 (52.1)	EES (Xience V) (100)	
IVUS-XPL	6 m	-	518 (55)	187 (20)	239 (25)	EES (Xience Prime) (100)	
	12 m	-	530 (56)	175 (18)	245 (26)	EES (Xience Prime) (100)	
NIPPON	6 m	8 (0.4)	1091 (52.1)	414 (19.8)	582 (27.8)	BP-BES (Nobori) (100)	
	18 m	16 (0.8)	1133 (53.1)	410 (19.2)	573 (26.9)	BP-BES (Nobori) (100)	
OPTIDUAL	12 m	-	443 (64)	214 (31)	268 (39)	1st generation SES (17.5) 1st generation PCE (16.0)	2nd generation ZES (10.8) EES (49.2) Other (6.5)
	48 m	-	397 (57)	225 (32)	280 (40)	1st generation SES (19.9) 1st generation PCE (15.2)	2nd generation ZES (8.3) EES (50.2) Other (6.4)
OPTIMA-C	6 m	-	394 (57.7)	134 (19.6)	155 (22.7)	BES (Biomatrix) (49.8) ZES (Resolute) (50.2)	
	12 m	-	353 (51.6)	165 (24.1)	166 (24.3)	BES (Biomatrix) (49.9) ZES (Resolute) (50.1)	
OPTIMIZE	3 m	24 (1.2)	986 (47.9)	481 (23.4)	567 (27.6)	ZES (Endeavor) (100)	
	12 m	30 (1.5)	960 (46.6)	501 (24.3)	571 (27.7)	ZES (Endeavor) (100)	
REDUCE	3 m	-	360 (48)	-	-	Combo stent (100)	
	12 m	-	329 (44,2)	-	-	Combo stent (100)	
RESET	3 m	-	707 (52.7)	281 (21)	353 (26.3)	ZES (Endeavor) (100)	
	12 m	-	722 (53.6)	259 (19.2)	365 (27.1)	SES (Cypher) (28.5) EES (Xience) (30) ZES (Resolute) (41.5)	
SECURITY	6 m	-	402 (43)	133 (14.3)	206 (22)	2nd generation ZES (Endeavor and Resolute) (42.1) BP-BES (Nobori) (25.3) BES (Biomatrix) (7.2)	EES (Promus) (11.3) EES (Xience) (8.8)

	12 m	-	423 (44)	137 (14.2)	207 (21.6)	2nd generation ZES (Endeavor and Resolute) (40.3) BP-BES (Nobori) (27.3) BES (Biomatrix) (7.5)	EES (Promus) (10.8) EES (Xience) (9.5)
SMART CHOICE	3 m	23 (1.2)	903 (48.8)	399 (21.6)	524 (27.8)	EES (Xience) (35.1) EES (Promus and Synergy) (32.7)	SES (Orsiro) (32.2)
	12 m	35 (1.9)	950 (50.4)	376 (19.9)	524 (27.8)	EES (Xience) (35.1) EES (Promus and Synergy) (31.9)	SES (Orsiro) (32.8)
SMART DATE	6 m	29 (2.1)	767 (56.6)	31 (24.4)	504 (37.2)	EES (Xience) (35.1) ZES (Resolute) (33.8)	BES (Biomatrix) (29.9) Others (0.5)
	12 m	17 (1.3)	826 (61)	340 (25.1)	490 (36.2)	EES (Xience) (34.1) ZES (Resolute) (33.9)	BES (Biomatrix) (30.9) Others (0.7)
STOP DAPT 2	1 m	43 (2.9)	828 (55.2)	268 (17.9)	436 (29.1)	EES (Xience) (100)	
	12 m	37 (2.5)	854 (56.6)	305 (20.2)	410 (27.2)	EES (Xience) (100)	
TICO	3 m	49 (3)	912 (48)	358 (19)	565 (30)	BP-SES (Orsiro) (100)	
	12 m	45 (2)	909 (48)	353 (19)	588 (31)	BP-SES (Orsiro) (100)	
TWILIGHT	3 m	166 (4.7)	1993 (56.1)	1151 (32.4)	1243 (35)	2nd generation DES (97.8)	
	15 m	187 (5.2)	2010 (56.4)	1146 (32.2)	1257 (35.3)	2nd generation DES (97.7)	

Abbreviations: BES: biolimus A9-eluting stent; BP-BES: biodegradable polymer-biolimus eluting stent; BP-SES: biodegradable polymer-sirolimus eluting stent; LAD: left anterior descending; LCX: left circumflex; LM: left main; NR: not reported; PCE: paclitaxel-cilostazol eluting; RCA: right coronary artery; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent;

Supplementary Table S11. Risk of Bias assessment

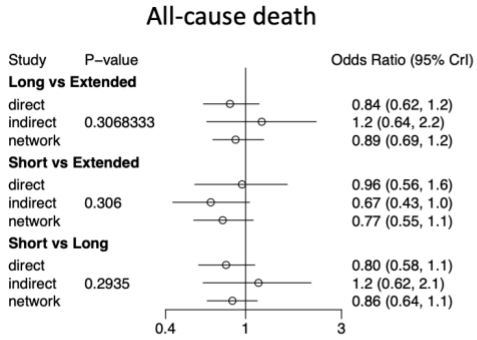
Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants, personnel and outcome (Performance bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)	Other bias
ARTIC	+	+	-	+	+	?
DAPT	?	?	+	+	+	-
DAPT STEMI	+	?	-	+	+	?
DES LATE	+	?	-	+	+	?
EXCELLENT	+	+	-	+	+	?
GLOBAL LEADERS	+	+	-	?	+	+
I LOVE IT 2	+	-	-	+	+	-
ISAR SAFE	+	+	+	+	+	?
ITALIC	+	?	-	+	+	-
IVUS-XPL	+	+	-	+	?	-
NIPPON	+	+	-	+	+	+

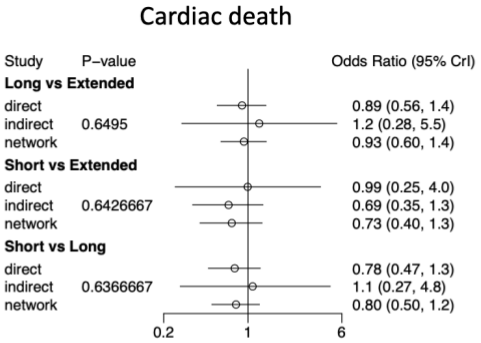
OPTIDUAL	+	+	-	+	+	?
OPTIMA C	+	+	-	+	+	?
OPTIMIZE	+	+	-	+	+	?
REDUCE	+	+	-	+	+	?
RESET	+	+	-	+	+	?
SECURITY	+	+	+	?	+	?
SMART CHOICE	+	+	-	+	+	?
SMART DATE	+	+	-	+	+	+
STOP DAPT2	+	+	-	+	+	+
TWILIGHT	+	+	+	+	+	+
TICO	+	+	-	+	+	+

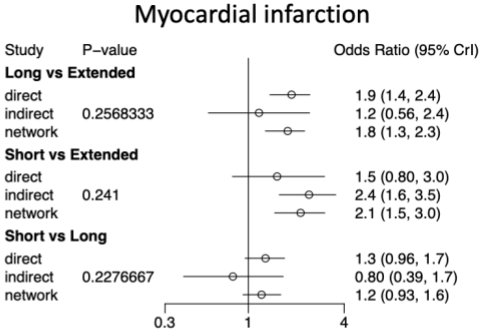
Supplementary Table S12. Heterogeneity across analyses

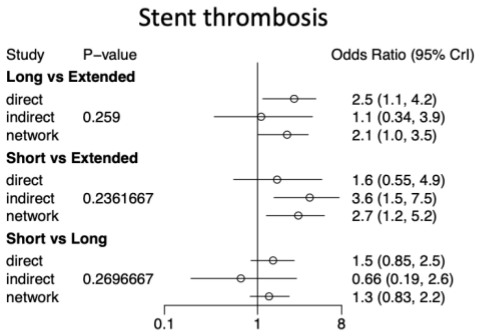
Endpoint	I^2 Extended vs. Standard	I^2 Extended vs. Short	I^2 Standard vs. Short	I^2 Standard vs. Very Short	Global I^2
PEP	84.7	0	0	28	51
All-cause death	49.9	64.8	0	0	1
Cardiac death	0	0	0	0	0
MI	53	0	1.6	0	0
ST	68	2.6	32.5	0	8.15
Stroke	0	0	0	20	0
Major bleeding	0	61	4	75	55.2
Any bleeding	72	0	34	87	81
Net clinical benefit	35	0	0	60	0

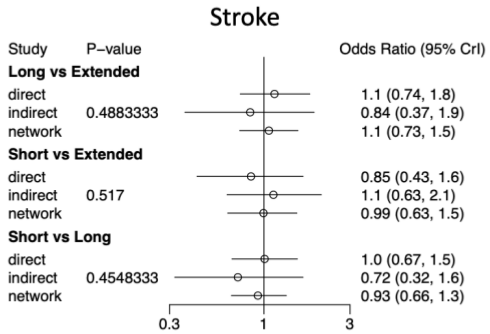
Supplementary Table S13. Node-split for the secondary endpoints (main analysis)

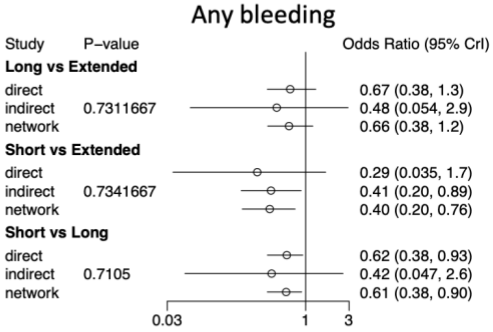


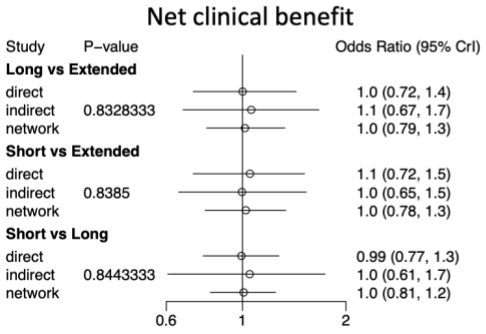




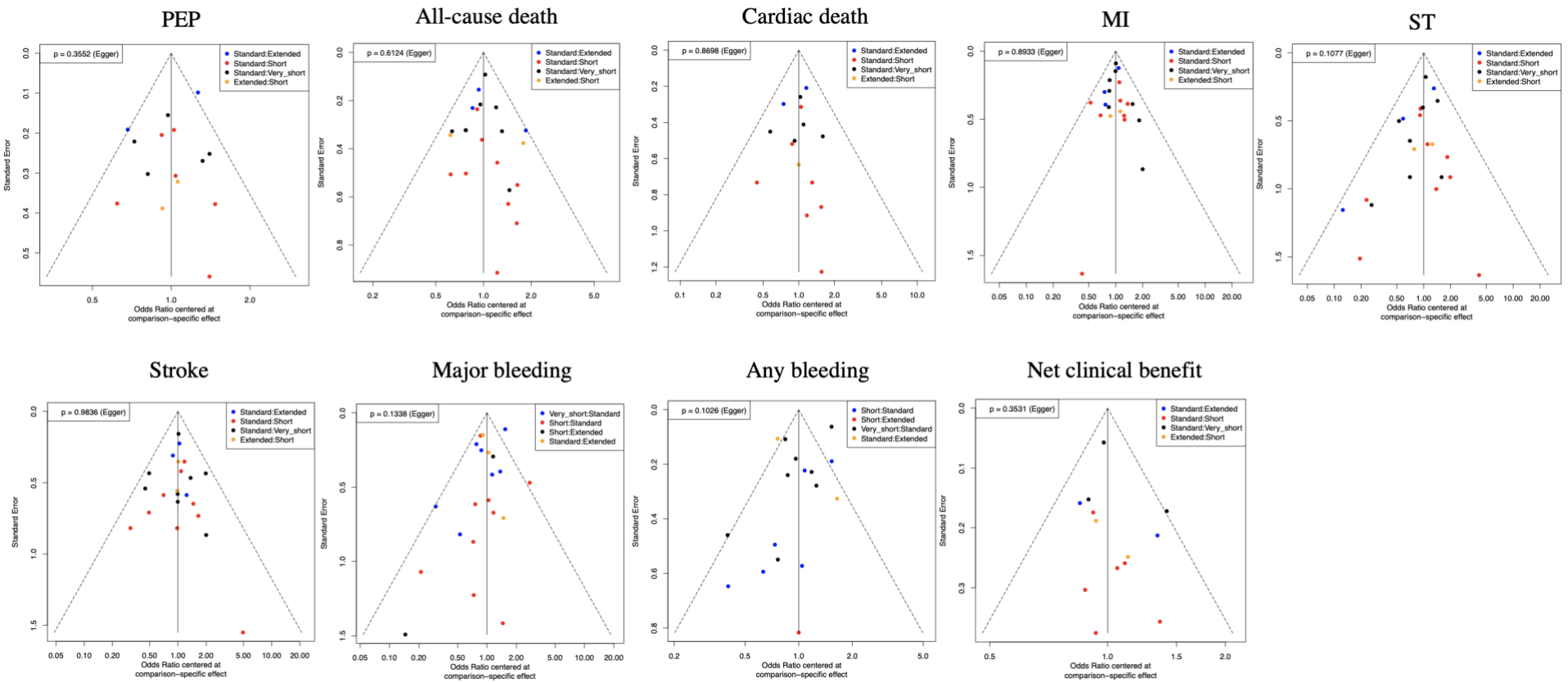








Supplementary Table S14. Comparison-adjusted funnel plots



Supplementary Table S15. Results of random-effects Bayesian NMA for ACS subgroup according to published data

Endpoint	Extended vs. standard		Short vs. standard		Very short vs. standard	
	OR	95% CI	OR	95% CI	OR	95% CI
PEP	**0.39**	**0.14-0.94**	1.1	0.50-2.40	1.0	0.46-2.30
All-cause death	0.72	0.24-1.6	0.87	0.43-1.7	0.88	0.50-1.7
Cardiac death	0.41	0.03-2.0	0.88	0.21-5.3	0.98	0.18-5.0
MI	0.48	0.20-1.3	1.3	0.57-2.5	0.76	0.37-1.50
ST	**0.24**	**0.06-0.71**	1.3	0.51-3.3	1.4	0.65-3.10
Stroke	NA	NA	1.0	0.41-2.6	0.88	0.39-1.70
Major bleeding	1.6	0.50-5.2	0.51	0.17-1.40	0.60	0.29-1.2
Any bleeding	**2.2**	**1.20-4.40**	0.65	0.33-1.20	0.72	0.49-1.1
Net clinical benefit	0.43	0.092-1.90	0.78	0.43-1.40	0.67	0.46-1.0

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Supplementary Table S16. Results of random-effects Bayesian NMA for RCTs of 2nd generation DES

Endpoint	Extended vs. standard		Short vs. standard		Very short vs. standard	
	OR	95% CI	OR	95% CI	OR	95% CI
PEP	0.79	0.41-1.50	1.10	0.80-1.50	1.00	0.79-1.30
All-cause death	0.79	0.42-1.50	1.10	0.80-1.50	1.00	0.79-1.30
Cardiac death	0.72	0.16-3.10	0.70	0.40-1.20	0.93	0.62-1.40
MI	0.92	0.42-2.10	1.40	0.94-2.20	0.99	0.79-1.20
ST	0.77	0.23-2.50	1.20	0.69-2.20	1.10	0.79-1.70
Stroke	1.10	0.44-2.90	0.94	0.53-1.60	1.10	0.70-1.40
Major bleeding	1.40	0.42-7.00	0.81	0.40-1.80	0.59	0.32-0.96
Any bleeding	2.7	0.47-25.0	0.81	0.45-1.50	**0.65**	**0.46-0.87**
Net clinical benefit	0.95	0.54-1.70	1.00	0.68-1.50	0.89	0.66-1.10

Supplementary Table S17. Results of random-effects Bayesian NMA after dividing very short DAPT according to the subsequent monotherapy (i.e. very short with early aspirin drop and prolonged $P2Y_{12}$ and very short with long-term aspirin): a) Odds ratios and 95% confidence intervals; b) SUCRA values

a)

Endpoint	Extended vs. standard		Short vs. standard		Very short with long-term aspirin vs. standard		Very short with aspirin drop and prolonged $P2Y_{12}$ vs. standard	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
PEP	0.70	0.51-1.00	1.10	0.78-1.50	1.20	0.76-1.90	0.88	0.57-1.40
All-cause death	1.10	0.82-1.50	0.86	0.63-1.10	1.00	0.68-1.50	0.89	0.69-1.10
Cardiac death	1.10	0.70-1.70	0.80	0.51-1.30	1.10	0.63-1.90	0.78	0.43-1.40
MI	**0.57**	**0.44-0.80**	1.20	0.91-1.60	1.10	0.75-1.60	0.96	0.73-1.20
ST	0.49	0.28-1.00	1.30	0.80-2.20	1.30	0.60-2.70	1.10	0.66-2.00
Stroke	0.94	0.65-1.40	0.93	0.65-1.30	0.85	0.38-1.90	1.00	0.73-1.50
Major bleeding	1.40	0.78-2.40	0.70	0.43-1.10	0.55	0.19-1.40	**0.61**	**0.36-0.94**
Any bleeding	0.62	0.81-2.70	**0.60**	**0.37-0.91**	0.72	0.40-1.30	**0.62**	**0.39-0.89**
Net clinical benefit	0.98	0.74-1.30	1.00	0.79-1.20	1.00	0.65-1.60	0.86	0.60-1.10

b)

Endpoint	Extended	Short	Standard	Very short with aspirin drop and prolonged $P2Y_{12}$	Very short with long-term aspirin
PEP	0.92	0.30	0.45	0.65	0.18
All-cause death	0.19	0.78	0.40	0.72	0.40
Cardiac death	0.29	0.74	0.40	0.73	0.33
MI	0.99	0.14	0.49	0.60	0.28
ST	0.97	0.22	0.57	0.45	0.29
Stroke	0.54	0.56	0.40	0.37	0.62
Major bleeding	0.05	0.64	0.26	0.77	0.76
Any bleeding	0.03	0.80	0.27	0.79	0.61
Net clinical benefit	0.47	0.40	0.40	0.83	0.39

Supplementary Table S18. Results of random-effect Bayesian NMA excluding trials with a post-DAPT $P2Y_{12}$ monotherapy

Endpoint	Extended vs. Standard		Short vs. Standard		Very Short vs. Standard	
	OR	95% CI	OR	95% CI	OR	95% CI
PEP	0.70	0.49-1.10	1.1	0.78-1.50	1.2	0.74-2.0
All-cause death	1.1	0.75-1.5	0.85	0.60-1.20	1.0	0.64-1.60
Cardiac death	1.1	0.69-1.70	0.79	0.51-1.30	1.1	0.61-1.90
MI	**0.58**	**0.43-0.86**	1.2	0.90-1.60	1.1	0.71-1.70
ST	0.52	0.28-1.20	1.3	0.77-2.40	1.3	0.53-3.0
Stroke	0.94	0.65-1.40	0.93	0.64-1.30	0.86	0.39-1.90
Major bleeding	1.4	0.80-2.3	0.70	0.44-1.1	0.56	0.21-1.40
Any bleeding	1.6	0.80-2.60	**0.63**	**0.37-0.91**	0.73	0.41-1.30
Net clinical benefit	0.98	0.76-1.3	1.0	0.81-1.2	1.0	0.68-1.5

Supplementary Table S19. Results of random-effect Bayesian NMA excluding trials with a post-DAPT Ticagrelor monotherapy

Endpoint	Extended vs. Standard		Short vs. Standard		Very Short vs. Standard	
	OR	95% CI	OR	95% CI	OR	95% CI
PEP	0.69	0.50-1.00	1.10	0.78-1.50	1.10	0.78-1.60
All-cause death	1.1	0.77-1.50	0.86	0.62-1.10	1.10	0.76-1.50
Cardiac death	1.1	0.70-1.70	0.79	0.51-1.20	1.00	0.66-1.60
MI	**0.58**	**0.43-0.83**	1.20	0.91-1.60	1.00	0.72-1.40
ST	0.51	0.28-1.20	1.30	0.79-2.30	1.50	0.74-3.10
Stroke	0.93	0.64-1.40	0.93	0.64-1.30	0.90	0.52-1.50
Major bleeding	1.40	0.78-2.40	0.70	0.43-1.10	**0.51**	**0.25-0.95**
Any bleeding	1.6	0.82-2.70	**0.62**	**0.37-0.91**	**0.59**	**0.36-0.91**
Net clinical benefit	0.98	0.76-1.30	1.0	0.80-1.20	1.0	0.69-1.50

Supplementary Table S20. Results of random-effect Bayesian NMA after dividing the monotherapies according to the $P2Y_{12}$ type (i.e. clopidogrel or potent $P2Y_{12}$)

Endpoint	Extended vs. standard		Short vs. standard		Very short with long-term aspirin vs. standard		Very short with early aspirin drop and prolonged potent $P2Y_{12}$ vs. standard		Very short with early aspirin drop and prolonged clopidogrel vs. standard	
	OR	95% CI	OR	OR	95% CI	95% CI	OR	95% CI	OR	95% CI
PEP	0.70	0.50-1.10	1.10	0.77-1.50	1.20	0.75-2.0	0.74	0.34-1.50	0.98	0.55-1.7
All-cause death	1.1	0.81-1.5	0.86	0.64-1.10	1.0	0.68-1.50	0.83	0.60-1.10	1.20	0.71-2.0
Cardiac death	1.1	0.70-1.70	0.80	0.51-1.30	1.10	0.62-1.90	0.57	0.19-1.60	0.90	0.44-1.80
MI	**0.57**	**0.44-0.81**	1.20	0.92-1.60	1.10	0.74-1.70	0.97	0.72-1.20	0.86	0.47-1.60
ST	0.49	0.29-1.0	1.30	0.81-2.20	1.30	0.62-2.70	0.96	0.55-1.70	2.50	0.60-14
Stroke	0.94	0.63-1.40	0.93	0.64-1.40	0.85	0.38-2.0	1.10	0.70-1.70	0.93	0.45-1.90
Major bleeding	1.40	0.78-1.40	0.70	0.42-1.10	0.55	0.19-1.50	0.67	0.36-1.20	0.46	0.17-1.10
Any bleeding	1.50	0.81-2.60	**0.61**	**0.37-0.91**	0.73	0.40-1.30	0.71	0.44-1.10	**0.42**	**0.20-0.84**
Net clinical benefit	0.98	0.74-1.30	1.0	0.80-1.30	1.0	0.66-0.60	0.86	0.62-1.10	NA	NA

Supplementary Table S21. Results of random-effect frequentist NMA (IV method)

Endpoint	Extended vs. Standard		Short vs. Standard		Very Short vs. Standard	
	OR	95% CI	OR	95% CI	OR	95% CI
PEP	**0.68**	**0.51-0.90**	1.15	0.89-1.49	1.03	0.79-1.33
All-cause death	1.16	0.93-1.44	0.88	0.69-1.14	0.91	0.79-1.04
Cardiac death	1.07	0.77-1.48	0.81	0.54-1.21	0.93	0.66-1.30
MI	**0.55**	**0.44-0.67**	1.19	0.92-1.52	1.00	0.87-1.14
ST	0.42	0.28-0.64	1.21	0.79-1.83	1.05	0.81-1.37
Stroke	0.93	0.68-1.26	0.92	0.66-1.28	0.99	0.78-1.26
Major bleeding	1.32	0.87-2.00	0.75	0.51-1.10	**0.63**	**0.45-0.87**
Any bleeding	1.50	0.89-2.50	**0.62**	**0.42-0.92**	**0.65**	**0.49-0.86**
Net clinical benefit	1.00	0.81-1.22	1.02	0.85-1.23	0.92	0.83-1.02

Supplementary Table S22. Results of random-effects NMA excluding trials with randomization after the index procedure/hospitalization

Endpoint	Extended vs. Standard		Short vs. Standard		Very Short vs. Standard	
	OR	95% CI	OR	95% CI	OR	95% CI
PEP	0.93	0.27-2.90	1.50	0.81-2.7	1.2	0.82-2.00
All-cause death	0.83	0.42-1.60	0.80	0.53-1.20	0.95	0.75-1.20
Cardiac death	0.83	0.42-1.60	0.80	0.54-1.10	0.94	0.77-1.20
MI	0.83	0.42-1.60	0.80	0.54-1.20	0.94	0.76-1.20
ST	0.94	0.25-3.00	1.5	0.81-2.80	1.20	0.81-2.00
Stroke	1.20	0.49-3.00	1.0	0.59-1.70	0.91	0.60-1.30
Major bleeding	1.20	0.49-3.00	1.00	0.60-1.70	0.92	0.61-1.30
Any bleeding	0.92	0.27-3.10	1.50	0.81-2.70	1.20	0.80-2.00
Net clinical benefit	0.91	0.24-3.1	1.5	0.81-2.70	1.20	0.82-2.20

Supplementary Table S23. Results of random-effects NMA considering SMART-DATE a trial of short vs. extended DAPT

Endpoint	Extended vs. Standard		Short vs. Standard		Very Short vs. Standard	
	OR	95% CI	OR	95% CI	OR	95% CI
PEP	0.76	0.42-1.60	1.00	0.68-1.50	1.00	0.79-1.30
All-cause death	0.71	0.35-1.40	0.66	0.37-1.10	0.92	0.75-1.10
Cardiac death	0.82	0.30-2.20	0.66	0.30-1.40	0.93	0.62-1.40
MI	0.61	0.30-1.30	1.10	0.72-1.90	0.99	0.80-1.20
ST	0.71	0.24-2.00	1.10	0.49-2.40	1.10	0.78-1.60
Stroke	1.10	0.44-2.80	0.94	0.48-1.90	0.99	0.69-1.40
Major bleeding	1.90	0.59-6.30	1.10	0.44-2.70	**0.60**	**0.35-0.91**
Any bleeding	1.60	0.51-5.70	0.96	0.39-2.20	**0.65**	**0.45-0.88**
Net clinical benefit	0.95	0.54-1.60	1.00	0.68-1.50	0.89	0.66-1.10

Supplementary Table S24. Results for the meta-regression analyses for the primary efficacy and safety endpoints

	Covariate	Beta coefficient	95% Confidence Interval	DIC
Primary efficacy endpoint	**Age**	0.06	-0.35 – 0.49	50.5
	Percentage of diabetic patients	0.003	-0.43 – 0.47	50.5
	Percentage of clopidogrel-treated patients	0.26	-0.14 – 0.65	49.2
	Percentage of 2nd generation DES-treated patients	-0.08	-0.61 – 0.43	50.4
	Percentage of ACS patients	-0.003	-0.44 – 0.39	50.24

	Covariate	Beta coefficient	95% Confidence Interval	DIC
Primary safety endpoint	**Age**	-0.36	-1.04 – 0.25	73.8
	Percentage of diabetic patients	-0.52	-1.10 – 0.11	73.9
	Percentage of clopidogrel-treated patients	-0.22	-0.82 – 0.37	75
	Percentage of 2nd generation DES-treated patients	0.16	-0.58 – 1.06	74.8
	Percentage of ACS patients	0.03	-0.50 – 0.69	75.2

The beta coefficient represents the change in effect estimates for the mean covariate value. The reference model (namely, that without covariates) had a DIC of 49.5, suggesting that taking into account the covariates did not improve the goodness of fit for both the endpoints.

Supplementary Appendix 3

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Supplementary Table S1. Missing values counts and percentages across the variable adjusted for in the predictive models

Supplementary Table S2. Balance statistics before and after inverse probability of treatment weighing

Supplementary Figure S1. Love plot displaying balance statistics before and after inverse probability of treatment weighing

Supplementary Table S1. Missing values counts and percentages across the variable adjusted for in the predictive models

Variable	Missing Count	Missing %
Female sex	0	0
Hypertension	2	0.19
Family history of CAD	0	0
Smoker	3	0.28
PAD	3	0.28
CKD	3	0.28
HF	3	0.28
ACS	0	0
AF	4	0.37
LM	1	0.09
BMI	6	0.56
Post PCI Clopidogrel	6	0.56
Total UFH dose	4	0.37
Femoral access	1	0.09
Infusion duration	17	1.59

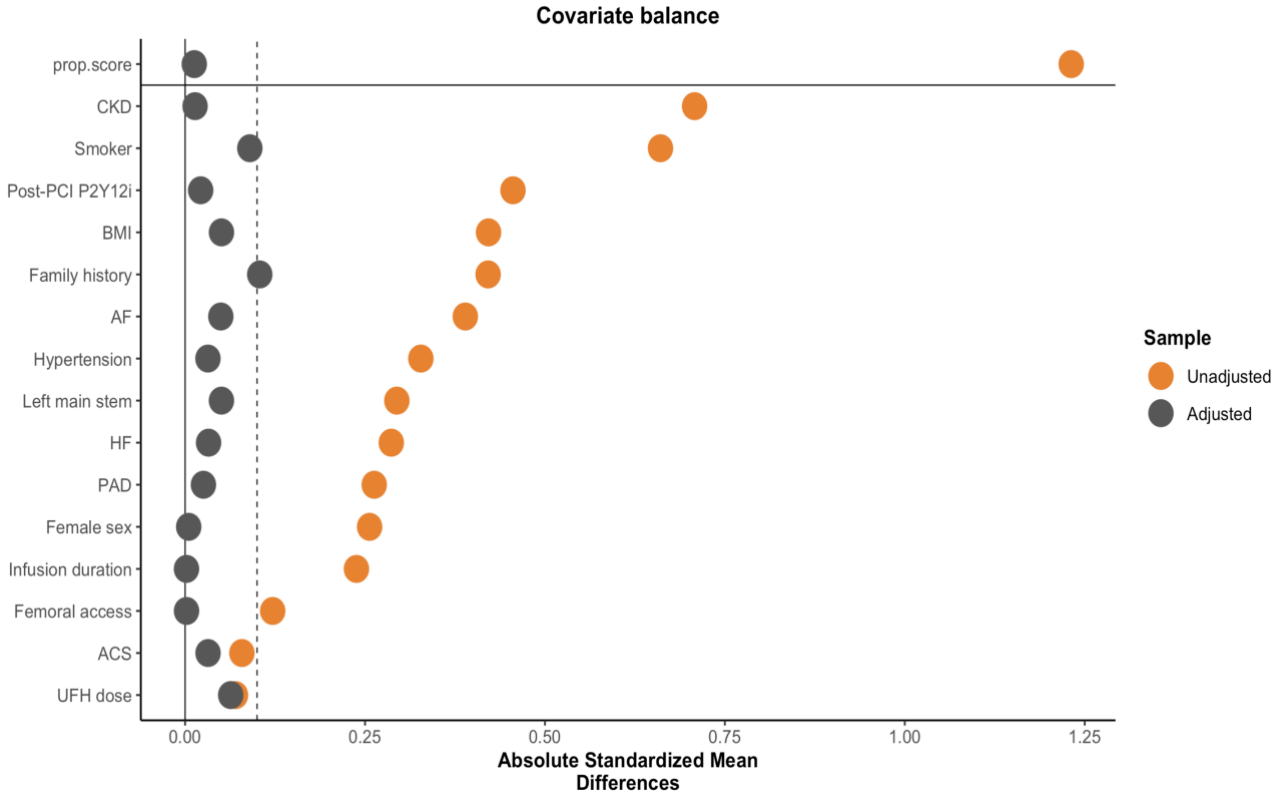
Abbreviations: ACS: acute coronary syndrome; AF: atrial fibrillation; BMI: body mass index; CAD: coronary artery disease; CKD: chronic kidney disease; HF: heart failure; LM: left main; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention; UFH: unfractionated heparin.

Supplementary Table S2. Balance statistics before and after inverse probability of treatment weighing

	SMD unadjusted	SMD adjusted	Mean threshold
Propensity score	1.4148464236237	0.075007936591124	<0.1
Female sex	0.10793433652531	-0.019614495206374	<0.1
Hypertension	0.146443228454172	0.020217255229408	<0.1
Family history of CAD	-0.18221614227086	-0.012053662870412	<0.1
Smoker	-0.2921340629275	-0.019389817473777	<0.1
PAD	0.16846785225718	0.011274641719499	<0.1
CKD	0.25437756497948	0.032199820926996	<0.1
HF	0.085567715458276	-0.0012109009382149	<0.1
ACS	-0.13467852257182	0.01126376195743	<0.1
AF	0.13173734610123	0.0044792115132405	<0.1
LM	0.066210670314637	0.026591331718805	<0.1
BMI	-0.45462474990109	-0.075993896035969	<0.1
Femoral access	0.019904240766074	0.01290488983122	<0.1
Infusion duration	-0.30129931343555	0.013193439959329	<0.1
Post PCI Clopidogrel	0.30868673050616	0.0023714268970712	<0.1
Total UFH dose	0.25035244070951	-0.042866703613969	<0.1

Abbreviations as per Supplementary Table 1.

Supplementary Figure S1. Love plot displaying balance statistics before and after inverse probability of treatment weighing



Abbreviations as per Supplementary Table 1.