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ORIGINAL RESEARCH

# Ischaemic and bleeding events after complex versus non-complex PCI: a systematic review and meta-analysis

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ABSTRACT

**BACKGROUND:** Complex percutaneous coronary intervention (PCI) is increasingly performed among patients undergoing myocardial revascularisation.

**AIMS:** We conducted a systematic review and meta-analysis to evaluate the association between complex PCI and the risk of ischaemic and bleeding outcomes.

**METHODS:** Hazard ratios (HRs) were pooled using a random-effects model within a Bayesian framework. The primary analysis was restricted to studies providing adjusted risk estimates, whereas the secondary analysis included unadjusted risk estimates. The primary outcomes were myocardial infarction and major bleeding. The secondary outcomes were all-cause death, stent thrombosis, cardiovascular death, target lesion or vessel revascularisation, and stroke. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for prognostic studies was used to determine the level of certainty in the association between complex PCI and the risk of events.

**RESULTS:** We included 290,039 patients, of whom 94,633 (33%) underwent complex PCI. Compared with non-complex PCI, patients undergoing complex PCI had a higher risk of myocardial infarction (adjusted HR 1.71, 95% credible interval [CrI]: 1.49-1.96), major bleeding (adjusted HR 1.24, 95% CrI: 1.14-1.35), all-cause death (adjusted HR 1.21, 95% CrI: 1.12-1.32), cardiovascular death (adjusted HR 1.29, 95% CrI: 1.15-1.46), stent thrombosis (adjusted HR 1.76, 95% CrI: 1.49-2.14), target lesion or vessel revascularisation (adjusted HR 1.99, 95% CrI: 1.58-2.50), and stroke (adjusted HR 1.21, 95% CrI: 1.03-1.42). The posterior probability of a higher risk associated with complex versus non-complex PCI was >99% for all study outcomes. Except for stroke (which was low certainty), the certainty of evidence was moderate to high for all other outcomes. Secondary analysis, including unadjusted risk estimates, provided consistent results.

**CONCLUSIONS:** Patients undergoing complex PCI have an increased risk of both ischaemic and bleeding events compared with patients undergoing non-complex PCI (PROSPERO: CRD420250656254).

**KEYWORDS:** bleeding risk; complex PCI; coronary; ischaemic risk; PCI





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Advances in pharmacological treatments, equipment, and devices have allowed percutaneous coronary intervention (PCI) to be performed in expanding subsets of patients with a large burden of comorbidities and anatomical complexity[1]. In this context, the term complex PCI has been introduced in the past decade to identify a broad spectrum of interventions with challenging anatomical features in common, including severe calcification, chronic total occlusion, bifurcation lesions, or multivessel treatment[2,3]. So far, data on the association between complex PCI and the risk of adverse events have been sparsely reported, and whether complex PCI is independently associated with higher adjusted risks of ischaemic and bleeding events is uncertain. Such information would provide important clinical utility given the implications for procedural strategy and antithrombotic management.

Against this background, we performed a systematic review and Bayesian meta-analysis to evaluate the association between complex PCI and the risk of ischaemic and bleeding outcomes.

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## Impact on daily practice

Complex percutaneous coronary intervention (PCI) refers to a broad spectrum of interventions characterised by challenging anatomical features, such as severe calcification, chronic total occlusion, bifurcation lesions, or multivessel treatment. Data from several studies indicate a higher baseline risk profile of patients undergoing complex PCI. Compared with non-complex PCI, complex PCI was associated with a significantly higher risk of ischaemic events, including myocardial infarction, stent thrombosis, and target lesion or vessel revascularisation, as well as an increased risk of bleeding events. Complex PCI represents a specific subset of patients requiring tailored strategies aimed at reducing both ischaemic and bleeding events.

## Methods

We followed the Prognosis Research Strategy (PROGRESS) group recommendations[4-7] and the guidance for systematic reviews and meta-analyses of prognostic studies[8]. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD420250656254).

### DATA SOURCES AND SEARCHES

Studies were identified by searching MEDLINE, Embase, and PubMed (excluding MEDLINE records) databases from inception to December 2024; **Supplementary Table 1** provides the full search strings for each database. We manually screened the reference lists of the eligible articles to check if any relevant articles were missed. The search was restricted to human studies, with no restrictions on language or year of publication.

### STUDY SELECTION

The review question was structured using the Population, Index prognostic factor, Comparator prognostic factors, Outcome, Timing and Setting (PICOTS) framework **(Supplementary Table 2)**[8]. Both observational and randomised studies were eligible. Studies were included if complex PCI was defined using more than one of the following procedural criteria: ≥3 stents implanted, ≥3 vessels treated, ≥3 lesions treated, bifurcation lesions requiring implantation of ≥2 stents, total stent length >60 mm, chronic total occlusion PCI, left main PCI, in-stent restenosis, or use of atherectomy. We adopted this definition of complex PCI to account for the heterogeneous distribution of complexity criteria in real-world practice, where individual procedural characteristics frequently coexist. Therefore, including studies that employed a single criterion-based definition would have limited the interpretation of our findings. In case of overlap between studies, we selected the largest study. Two investigators (A.P. Vitale and A. Laino) independently screened titles and abstracts against the eligibility criteria using the Rayyan platform (https://www.rayyan.ai), with potentially eligible studies undergoing full-text assessment. Disagreements were resolved through discussion to achieve consensus.

### OUTCOMES

The two prespecified outcomes of interest were myocardial infarction and major bleeding, given the well-known trade-off between ischaemic and bleeding complications. Additional outcomes included all-cause death, stent thrombosis, cardiovascular (or cardiac) death, target lesion or vessel revascularisation, and stroke. Myocardial infarction was categorised as spontaneous or periprocedural. When available, risk estimates were preferentially extracted according to the Fourth Universal Definition of Myocardial Infarction; otherwise, we extracted the study-level definition **(Supplementary Table 3)**. For major bleeding, we preferentially extracted risk estimates for the composite of Type 3 or 5 bleeding, according to the Bleeding Academic Research Consortium (BARC) scale[9]. If unavailable, we sequentially extracted risk estimates for Thrombolysis in Myocardial Infarction (TIMI) major bleeding, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO) moderate or severe bleeding, or Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) major bleeding. Further details on outcome definitions are reported in **Supplementary Table 3**. *Post hoc* outcomes were a device-oriented composite endpoint (DOCE), as defined in each included study, spontaneous myocardial infarction, and target vessel myocardial infarction.

### DATA EXTRACTION AND QUALITY ASSESSMENT

Data extraction was performed using a predesigned data extraction sheet, developed according to the modified version of the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling

## Abbreviations

**BARC** Bleeding Academic Research Consortium **CAD** coronary artery disease **PCI** percutaneous coronary intervention

Studies (CHARMS) for prognostic factors[8,10]. The definition of complex PCI for each included study is detailed in **Supplementary Table 4**. Two reviewers independently collected hazard ratios (HRs) for the outcomes of interest and assessed the risk of bias of included studies, using the Quality in Prognosis Studies (QUIPS) tool[11]. This tool includes six potential domains of bias: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement, and statistical analysis and reporting. Disagreements were resolved through discussion until consensus was reached.

### DATA SYNTHESIS AND STATISTICAL ANALYSIS

The primary analysis was conducted in studies that provided adjusted risk estimates (the covariates used by each study are listed in **Supplementary Table 5**). Secondary analysis using unadjusted risk estimates was also performed but reported separately. All analyses were carried out using random-effects models within a Bayesian framework. This approach was chosen because it improves clinicians' interpretation of the meta-analysis results and the evaluation of between-study heterogeneity[12]. Specifically, we selected vague priors: for the log of the HR, we used a normally distributed prior with a mean of 0 and a standard deviation of 2; for the heterogeneity parameter ($\tau$), we used a half-normal prior with a scale of 0.5. Risk estimates were summarised using pooled HRs with 95% credible intervals (CrIs). In addition, we reported the posterior probabilities of complex PCI being associated with a higher risk of an event compared with non-complex PCI (i.e., the probability that the HR was >1). As a sensitivity analysis, we used non-informative priors given the anticipated high number of studies included in the quantitative meta-analysis, as well as a frequentist random-effects meta-analysis created by pooling HRs, with a generic inverse-variance model (using the Hunter-Schmidt estimates of the between-study variance)[13]. We evaluated heterogeneity across studies with $\tau$ and $I^2$ statistics. Small-study effects were evaluated by visual assessment of the contour-enhanced funnel plots and using the formal Egger's regression test[14].

We investigated potential sources of heterogeneity in the primary outcomes by *post hoc* meta-regression analyses, including information on baseline characteristics, known predictors of ischaemia[15], known predictors of bleeding[15], antithrombotic therapies, complex PCI components, and year of study publication. In addition, sensitivity analyses were performed for both primary (prespecified) and secondary (*post hoc*) outcomes by separately evaluating observational versus randomised studies, as well as studies enrolling patients with acute coronary syndrome and those including patients with chronic coronary syndrome.

Two reviewers evaluated the overall certainty in pooled estimates using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. These estimates were categorised into one of four levels of certainty: high, moderate, low, or very low. In accordance with GRADE guidance for prognostic studies, cohort data are considered high-certainty evidence[16]. All statistical analyses were performed using R software (R Foundation for Statistical Computing; using the bayesmeta package)[17].

## Results

### STUDY SELECTION AND PATIENT POPULATION

From 13,616 articles, 460 were identified as potentially eligible records after the initial screening **(Supplementary Figure 1)**. Of these, 374 were excluded due to incompatible populations, 40 for incomplete data, 7 for missing outcomes, and 3 for overlapping populations. As a result, we included 36 studies with 290,039 patients, of whom 94,633 (33%) underwent complex PCI and 195,406 (67%) underwent non-complex PCI **(Table 1)**. The criteria used for defining complex PCI are shown in **Table 1. Supplementary**

**Table 1. Characteristics of the population included in the meta-analysis.**

| Population | Value |
|---|---|
| Sample size | 290,039 |
| Complex PCI | 28.3% |
| Females in complex PCI group | 24.1% |
| Diabetic patients in complex PCI group | 35% |
| ACS in complex PCI group | 51.9% |
| Median follow-up, years | 1 |
| **Components of complex PCI** | |
| ≥3 stents implanted | 16.05 (9.23-21.35) |
| ≥3 vessels treated | 3.14 (2.35-5.45) |
| ≥3 lesions treated | 7.5 (5.2-10.2) |
| Bifurcation with ≥2 stents implanted | 5.6 (3.1-9.5) |
| Total stent length >60 mm implanted | 14.85 (8.8-19.95) |
| Chronic total occlusion PCI | 5 (3.98-8.92) |
| Saphenous vein graft PCI | 5 (5.1-5.2) |
| Left main coronary artery PCI | 4 (3.5-6.4) |
| In-stent restenosis | 2.8 (2.0-3.6) |
| Rotational atherectomy | 8.2 (2.1-8.4) |
| **Population** | **No. of studies** |
| Continent of study | |
| Europe | 11 (30) |
| North America | 9 (25) |
| Asia/Oceania | 16 (45) |
| Africa | 0 (0) |
| Study design | |
| Observational | 24 (67) |
| Randomised | 12 (33) |
| Multicentre study | |
| No | 9 (25) |
| Yes | 27 (75) |
| Presentation at index PCI | |
| Acute coronary syndrome | 7 (20) |
| Chronic coronary syndrome | 4 (11) |
| Acute or chronic coronary syndrome | 25 (69) |
| Risk estimates | |
| Adjusted | 27 (75) |
| Unadjusted | 9 (25) |

Categorical variables are expressed as median percentages. Other data are given as n, n (%), or median (IQR). ACS: acute coronary syndrome; IQR: interquartile range; PCI: percutaneous coronary intervention

**Table 6**-**Supplementary Table 11** summarise the patient-level and study-level characteristics. The median age of complex PCI patients was 65.5 years (interquartile range [IQR] 63.9-68.9). The median proportion of patients with diabetes in the complex PCI group was 35% (IQR 32.8-43.0). Acute coronary syndrome was the indication for PCI in 51.95% (IQR 35.5-70.0) of complex PCI patients. From the 36 included studies, a total of 27 studies reporting adjusted HRs were included in the primary analysis, while 27 studies, which provided unadjusted risk estimates, were included in the secondary analysis. The median follow-up duration was 1 year. The studies were published between 2016 and 2024, and most studies were observational (24 out of 36). Overall, the antithrombotic therapies used during and after PCI were comparable between patients undergoing complex PCI versus non-complex PCI.

## RISK OF BIAS

**Supplementary Table 12** presents the risk-of-bias assessment. Most of the studies were at low to moderate risk of bias. All unadjusted studies were deemed at high risk of bias due to the lack of adjustments for other prognostic factors.

## PRIMARY ANALYSIS (ADJUSTED RISK ESTIMATES)

Out of the 222,001 included participants, 78,520 (35%) underwent complex PCI.

### MYOCARDIAL INFARCTION

A total of 19 studies, including 150,213 participants, of whom 57,626 underwent complex PCI, contributed to the analysis of myocardial infarction. Using a Bayesian random-effects model with vague priors, patients undergoing complex PCI had a higher risk of myocardial infarction (adjusted HR 1.71, 95% CrI: 1.49-1.96; moderate to substantial heterogeneity [$\tau$=0.24, $I^2$=70%]; high certainty). We found a 99.9% posterior probability that complex PCI was associated with an increased risk of myocardial infarction **(Figure 1)**. These findings were consistent when using uninformative priors and a frequentist approach **(Figure 1A)**.

### MAJOR BLEEDING

Data from 13 studies, comprising 101,096 patients, of whom 33,740 underwent complex PCI, were analysed. Using a Bayesian random-effects model with vague priors, patients undergoing complex PCI had a higher risk of major bleeding compared with those undergoing non-complex PCI (adjusted HR 1.24, 95% CrI: 1.14-1.35; low heterogeneity [$\tau$=0.08, $I^2$=24%]; high certainty). There was a 99.9% posterior probability that complex PCI was associated with an increased risk of major bleeding **(Figure 2)**. Findings were consistent when using uninformative priors and a frequentist model **(Figure 2A)**.

### ALL-CAUSE DEATH

A total of 21 studies, including 150,744 patients, of whom 56,746 underwent complex PCI, contributed to the analysis of all-cause death. The risk of all-cause death was higher in patients undergoing complex versus non-complex PCI (adjusted HR 1.21, 95% CrI: 1.12-1.32; moderate heterogeneity [$\tau$=0.12, $I^2$=43%]; moderate certainty), with a 99.9% posterior probability **(Figure 3, Supplementary Figure 2)**. Results were confirmed using uninformative priors and a frequentist model **(Figure 3)**.

### OTHER OUTCOMES

A total of 16 studies, enrolling 144,138 participants (50,168 underwent complex PCI), provided data regarding stent thrombosis. Complex PCI was associated with a higher risk of stent thrombosis (adjusted HR 1.71, 95% CrI: 1.45-2.04, posterior probability 99.9%; low heterogeneity [$\tau$=0.10, $I^2$=24%]; high certainty) **(Figure 4, Supplementary Figure 3)**. Fifteen studies, including 127,100 patients, contributed to the analysis of cardiovascular death. Complex PCI was associated with a higher risk of cardiovascular death (adjusted HR 1.29, 95% CrI: 1.15-1.46, posterior probability 99.9%; low heterogeneity [$\tau$=0.12, $I^2$=24%]; high certainty) **(Supplementary Figure 4, Supplementary Figure 5)**. Sixteen studies with a total of 125,057 participants provided data on target lesion or vessel revascularisation. Complex PCI showed an increased risk of target lesion or vessel revascularisation (adjusted HR 1.99, 95% CrI: 1.58-2.49, posterior probability 99.9%; high heterogeneity [$\tau$=0.39, $I^2$=92%]; moderate certainty) **(Supplementary Figure 6, Supplementary Figure 7)**. Stroke was evaluated in 10 studies with 69,091 participants. Patients undergoing complex PCI showed an increased risk of stroke (adjusted HR 1.21, 95% CrI: 1.03-1.42, posterior probability 98.4%; moderate heterogeneity [$\tau$=0.08, $I^2$=30%]; low certainty) **(Supplementary Figure 8, Supplementary Figure 9)**.

### POST HOC OUTCOMES

Patients undergoing complex PCI had a greater risk of the DOCE, spontaneous myocardial infarction, and target vessel myocardial infarction compared with patients undergoing non-complex PCI **(Supplementary Appendix 1-Supplementary Appendix 3)**.

## SECONDARY ANALYSIS (UNADJUSTED RISK ESTIMATES)

We analysed 186,788 participants from 27 studies, including 56,908 patients undergoing complex PCI. Principal results are shown in **Supplementary Figure 10**-**Supplementary Figure 16**.

**Supplementary Table 13** summarises the results of the Bayesian analysis. Overall, the unadjusted and adjusted analyses were largely consistent **(Central illustration)**.

## META-REGRESSION ANALYSIS

Meta-regression analysis revealed that ethnicity, the proportion of patients with acute coronary syndrome, prior myocardial infarction, prior cerebrovascular accident, elderly status, and the proportion of patients with a stent >60 mm implanted were the major sources of the heterogeneity observed for the primary outcomes **(Supplementary Table 14-Supplementary Table 19)**.

## SUBGROUP ANALYSIS

Results remained consistent when data were restricted to observational studies, randomised trials, studies including patients with chronic coronary syndrome, and studies including patients with acute coronary syndrome **(Supplementary Table 20)**.

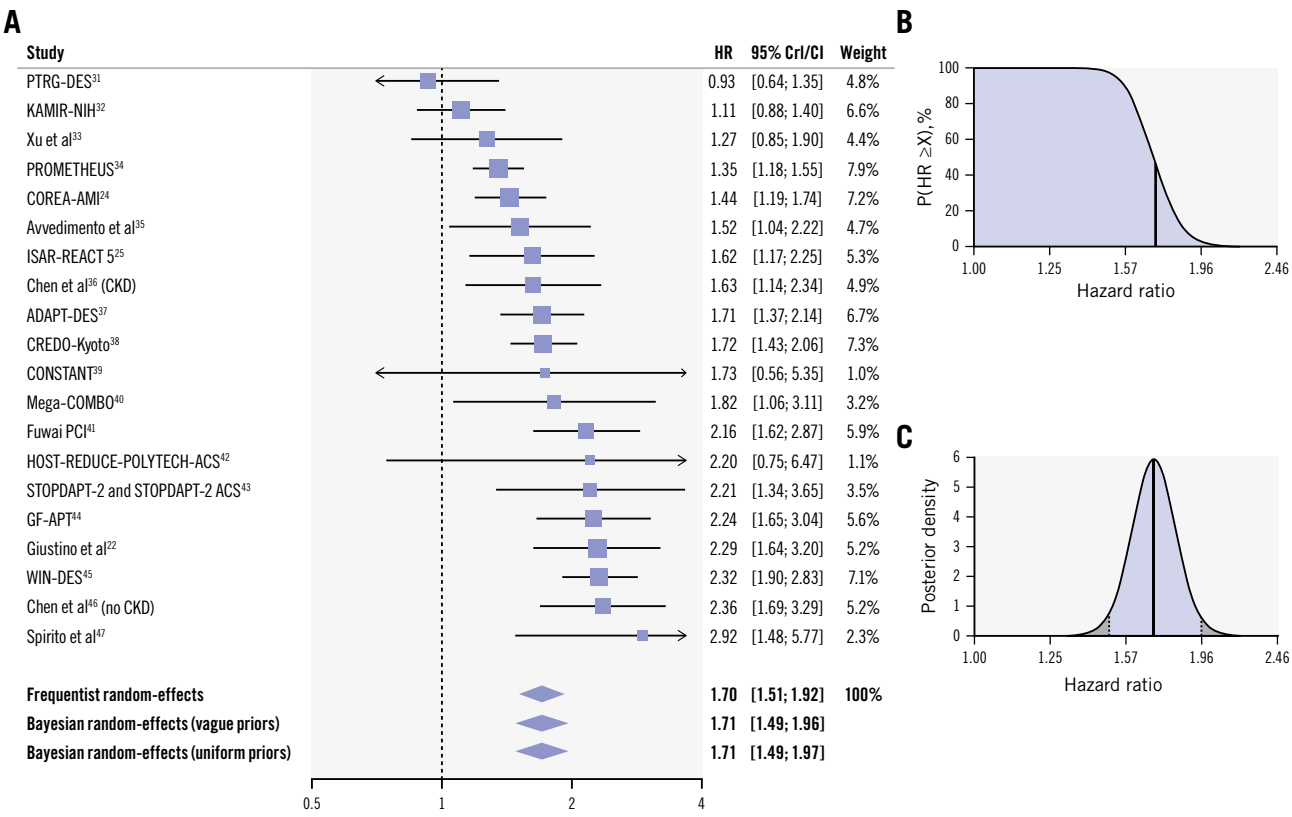



**Figure 1.** *Adjusted risk of myocardial infarction in patients undergoing complex versus non-complex PCI. A) Forest plot of adjusted analysis for myocardial infarction. B) Cumulative posterior distribution of the estimated adjusted hazard ratio for myocardial infarction. On the y-axis, there is the probability (P) that the hazard ratio is greater than or equal to the value on the x-axis (X). The bold vertical line indicates the median value. The blue area is indicative of a good prognostic ability of complex PCI criteria (probability that the hazard ratio is greater than or equal to 1). C) Full posterior distribution of the estimated adjusted hazard ratio for myocardial infarction. The bold vertical line indicates the median value, and the area highlighted in blue indicates the percentile-based 95% credible interval. CI: confidence interval; CKD: chronic kidney disease; CrI: credible interval; HR: hazard ratio; PCI: percutaneous coronary intervention*

### REPORTING BIAS AND LEVEL OF EVIDENCE

No publication bias was detected based on the funnel plots or Egger's tests **(Supplementary Figure 17-Supplementary Figure 23)**. The GRADE assessment rated the evidence as high or moderate certainty, except for stroke (which was low certainty) **(Supplementary Table 21)**.

## Discussion

In the present systematic review and meta-analysis of 290,039 patients from 36 studies, we evaluated the association between complex PCI and several clinically relevant outcomes. Our main findings are as follows: (1) 1 out of 3 patients treated with percutaneous revascularisation underwent complex PCI; (2) complex PCI was associated with a ~70% relative increase in the adjusted risk of myocardial infarction, with ~99% posterior probability and a high certainty of evidence; (3) complex PCI was associated with a ~25% relative increase in the risk of major bleeding, with ~99% posterior probability and a high certainty of evidence; (4) compared with non-complex PCI, patients undergoing complex PCI had a ~20% higher risk of all-cause death (moderate certainty), ~70% higher risk of stent thrombosis (high certainty), ~100% higher risk of target lesion or vessel revascularisation (moderate certainty), and ~20% higher risk of stroke (low certainty).

The present analysis is the first systematic, comprehensive study mapping the prognostic impact of complex PCI on major cardiovascular outcomes. Coronary artery disease (CAD) complexity and high-risk patient characteristics are well-known predictors of adverse events. Prior large-scale analyses were primarily focused on the predictive value of CAD complexity by relying on anatomical factors[18] or combining clinical and procedural factors[19]. However, the definition of complex PCI deviates from the concepts related to CAD complexity or high-risk patient profiles. While the latter can be categorised as patient- or lesion-focused, complex PCI includes a broader range of lesion and procedural characteristics[20] and, in the past few years, has emerged as a key subgroup of interest in randomised trials across several domains. Despite the lack of universally agreed criteria for complex PCI, the definitions of complex PCI were largely consistent across the included studies.

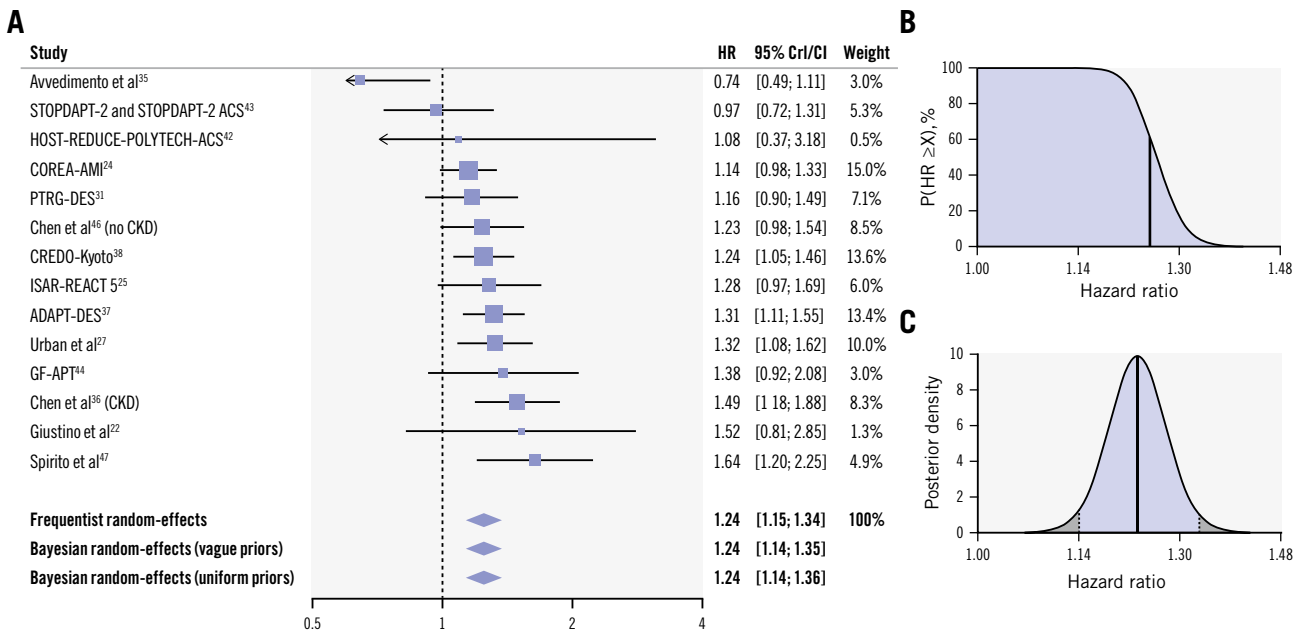



**Figure 2.** *Adjusted risk of major bleeding in patients undergoing complex versus non-complex PCI. A) Forest plot of adjusted analysis for major bleeding. B) Cumulative posterior distribution of the estimated adjusted hazard ratio for major bleeding. On the y-axis, there is the probability (P) that the hazard ratio is greater than or equal to the value on the x-axis (X). The bold vertical line indicates the median value. The blue area is indicative of a good prognostic ability of complex PCI criteria (probability that the hazard ratio is greater than or equal to 1). C) Full posterior distribution of the estimated adjusted hazard ratio for major bleeding. The bold vertical line indicates the median value, and the area highlighted in blue indicates the percentile-based 95% credible interval. CI: confidence interval; CKD: chronic kidney disease; CrI: credible interval; HR: hazard ratio; PCI: percutaneous coronary intervention*

The impact of complex PCI on clinical outcomes has been investigated in prior analyses; however, our study is the first attempt to quantitatively define the magnitude of this association. We found that patients undergoing complex PCI had a ~70% relative increase in the risk of myocardial infarction, a finding that remained largely unchanged in the unadjusted analyses. A similar increase in the order of 70-100% was also found for other ischaemic events, such as stent thrombosis and target lesion or vessel revascularisation. These findings align well with prior studies showing an elevated ischaemic risk in patients treated with complex PCI[21,22]. The underlying reasons for the heightened ischaemic risk after complex PCI are mechanistically plausible and somewhat expected. Patients undergoing complex PCI have a more severe and advanced atherosclerotic burden, along with greater plaque instability. In addition, the complexity of intervened lesions (e.g., long lesions, bifurcations, severe calcifications) often requires multiple and overlapping stents, potentially leading to delayed endothelisation, stent malapposition, and incomplete lesion coverage, with a higher risk of vessel injury or dissection, all predisposing to stent thrombosis or periprocedural myocardial infarction[23,24]. Moreover, multivessel CAD is often associated with incomplete myocardial revascularisation, with the corollary effect of a greater burden of untreated residual coronary lesions that predispose patients to future acute events.

Although the magnitude of association was lower compared with myocardial infarction, complex PCI was associated with an approximately 20% increased risk of major bleeding. Prior evidence regarding the impact of complex PCI on bleeding events was inconclusive. An analysis from Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 and a pooled analysis of six trials did not find any difference in the risk of major bleeding between complex and non-complex PCI[22-25]. Conversely, in a large, unselected cohort of patients undergoing PCI, both ischaemic and bleeding events were increased among patients undergoing complex, in comparison with non-complex, PCI[24]. Mechanistically, the increased risk of bleeding could be explained by the more frequent use of femoral access, larger sheaths, and more potent antithrombotic therapy during complex PCI. Moreover, several patient-related factors are more commonly found among patients undergoing complex PCI, including advanced age, comorbidities, chronic oral anticoagulation, anaemia, gastrointestinal disease, or malignancy[26]. Interestingly, many of these features overlap with high bleeding risk (HBR) criteria, such as older age, renal dysfunction, anaemia, and chronic anticoagulation – further supporting the relationship between complex PCI and HBR status[27].

Historically, complex PCI has been recognised as a high ischaemic risk condition, with bleeding risk often overlooked. Conversely, our analysis supports the concept that complex PCI confers a dual hazard with increases in both ischaemic and bleeding risks. This highlights the need to pursue bleeding-avoidance strategies also in patients undergoing complex

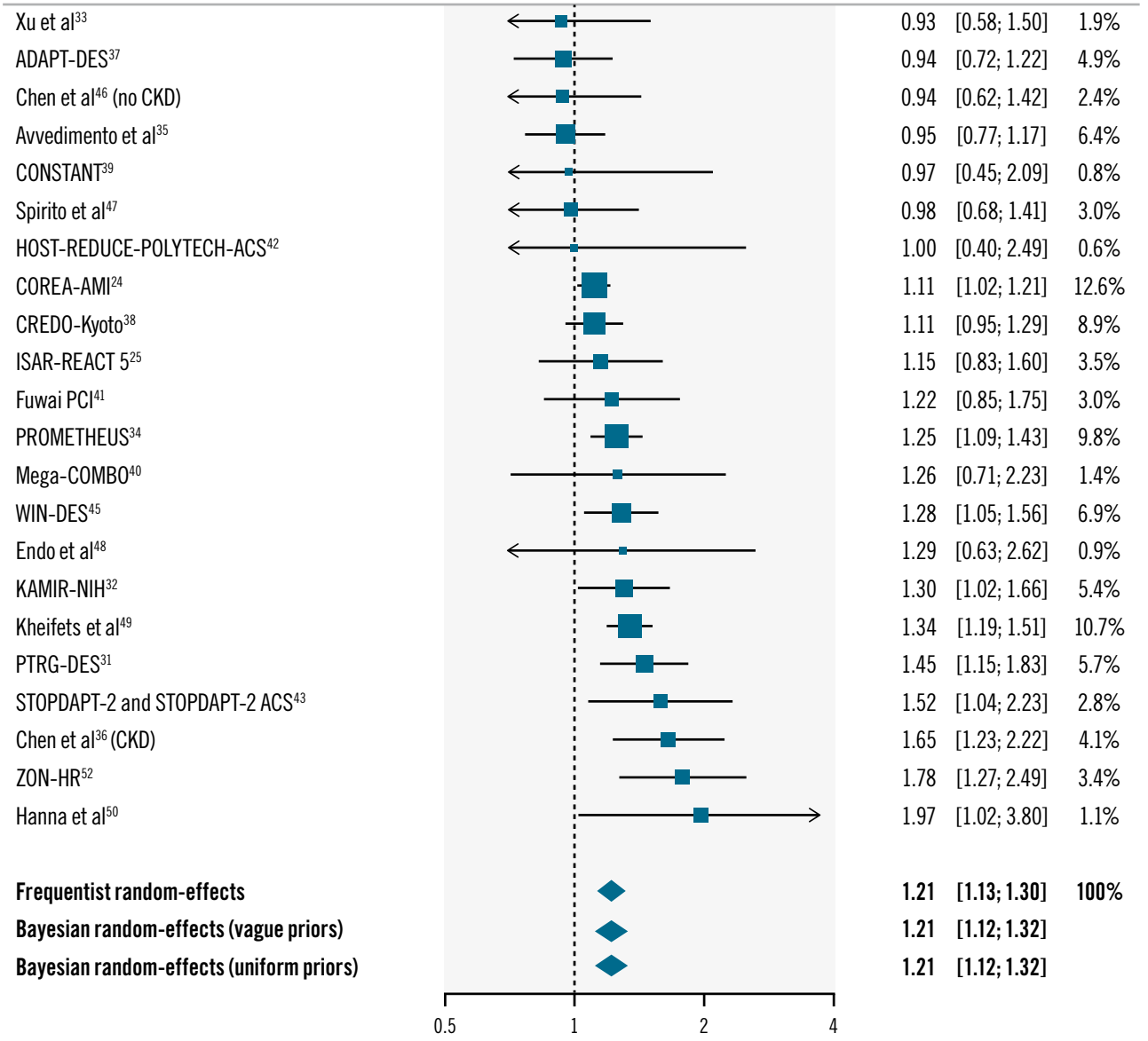



**Figure 3.** *Adjusted risk of all-cause death in patients undergoing complex versus non-complex PCI. CI: confidence interval; CKD: chronic kidney disease; CrI: credible interval; HR: hazard ratio; PCI: percutaneous coronary intervention*

PCI. During the periprocedural period, the preferential use of radial access, the implementation of ultrasound-guided femoral access, and careful selection of anticoagulant therapy may mitigate the bleeding risk[28]. On the other hand, the excess of ischaemic events, including stent thrombosis, repeat revascularisation, and myocardial infarction, among patients undergoing complex PCI deserves careful attention when these procedures are performed. In this context, the extensive use of intracoronary imaging, which has proved to be particularly useful in reducing ischaemic recurrences[29], may be helpful for complex PCI procedures. With respect to antithrombotic strategies, our results, which align with prior studies[21,30], provide further evidence supporting the prioritisation of bleeding over ischaemic risk assessment when selecting the appropriate dual antiplatelet therapy regimen for CAD patients. Therefore, long-term antiplatelet strategies, including de-escalation or $P2Y_{12}$ inhibitor monotherapy, should also be considered in this population given their similar efficacy and improved safety – also in the context of complex PCI[2,21]. However, it should be acknowledged that our findings were influenced by the high prevalence of patients with HBR undergoing complex PCI. Unfortunately, subgroup analyses comparing HBR versus non-HBR patients were not feasible. Therefore, our analyses cannot determine whether such risk stratification may identify a subset of complex PCI patients who could benefit from more intensive dual antiplatelet therapy.

## Limitations

Our study has several limitations. First, we observed a moderate to high degree of between-study heterogeneity

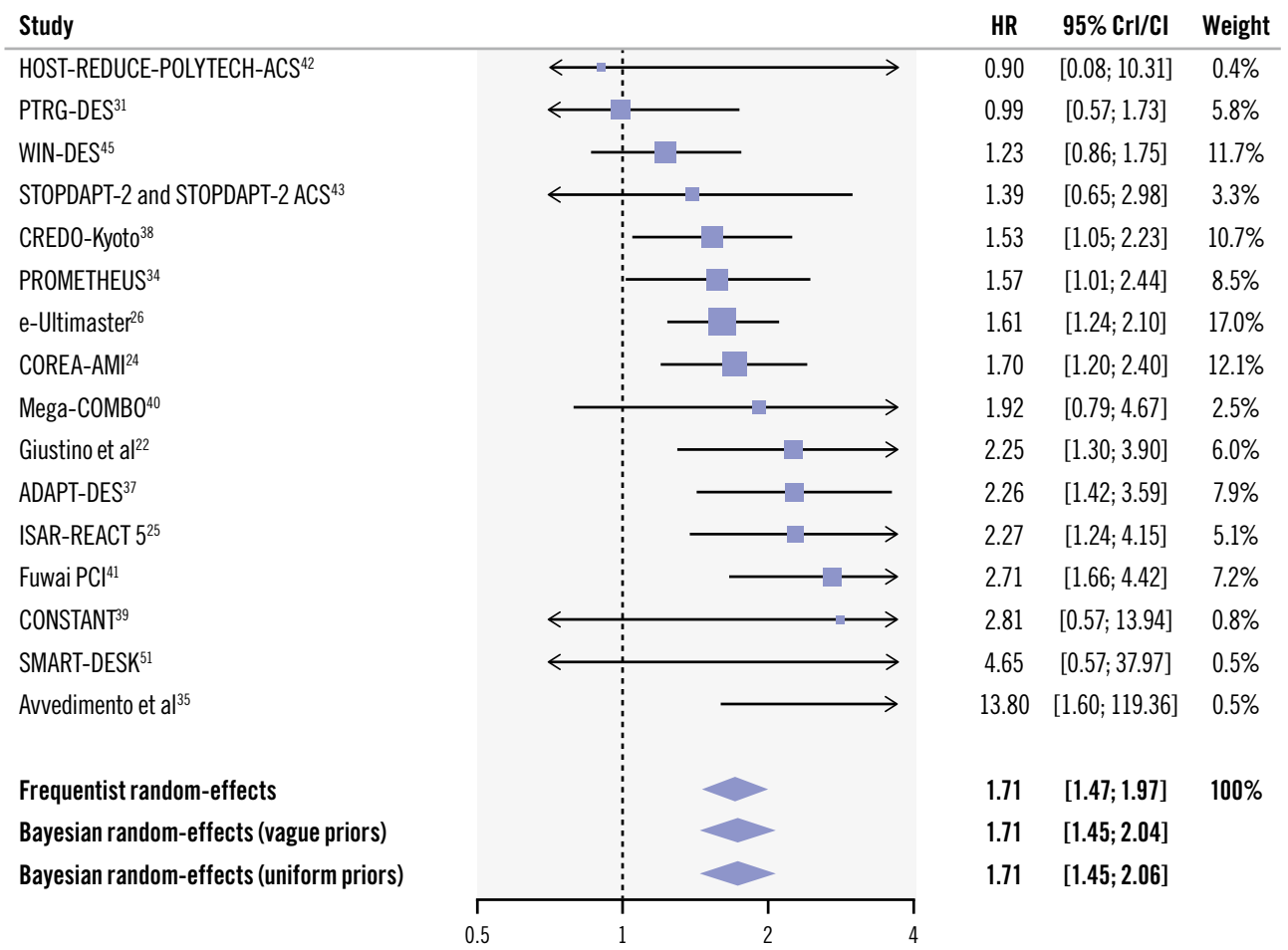
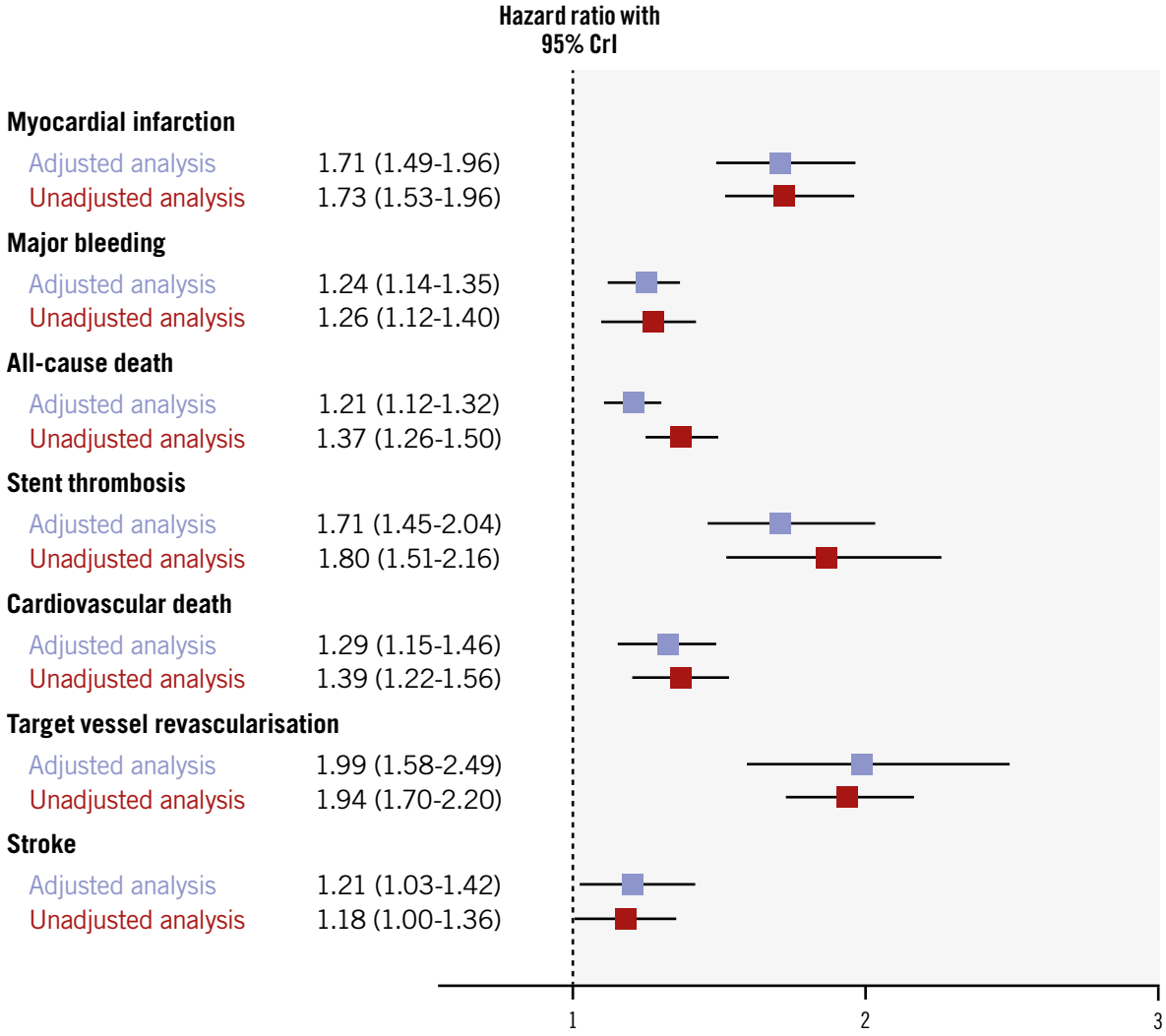



**Figure 4.** *Adjusted risk of stent thrombosis in patients undergoing complex versus non-complex PCI. CI: confidence interval; CrI: credible interval; HR: hazard ratio: PCI: percutaneous coronary intervention*

in some analyses. This finding is common in meta-analyses of prognostic studies and may reflect differences in the definition of complex PCI, outcome definitions, covariates included in adjustment models, and inconsistencies in the definition and measurement of these covariates across studies. In this context, our results were generally consistent across multiple subgroup and meta-regression analyses. However, the use of study-level rather than individual-level data precluded a comprehensive assessment of the influence of these potential modifiers on the observed treatment effects. Second, we were unable to provide separate analyses for early versus late outcomes. This analysis would have been important to disentangle the periprocedural risk associated with complex PCI from the long-term risk. Third, our study demonstrated the association between complex PCI and increased risks of both ischaemic and bleeding events. Although these findings are informative for risk stratification, they do not directly guide the selection of antithrombotic treatment strategies after PCI. These associations should be interpreted with caution and ideally confirmed in adequately powered randomised clinical trials that are specifically designed to evaluate antithrombotic strategies stratified by PCI complexity. Fourth, several included studies were not specifically designed to enrol patients with complex CAD. Therefore, highly complex forms or subsets may have been underrepresented or excluded. Fifth, so far, there is no universal definition of complex PCI. As a result, different subtypes of complex PCI, which may carry distinct prognostic implications, are often grouped under the same diagnostic category. Currently, data are not systematically reported in a way that allows detection of these differences, thereby limiting the ability to explore the differential prognostic implications of specific complex PCI patterns. This limitation may have introduced a degree of bias into our analyses and contributed to residual heterogeneity that could not be adequately accounted for. Finally, although our meta-regression analyses did not identify any interaction between antithrombotic therapies and the observed treatment effects, some limitations should be taken into consideration. These analyses, which were powered only when a high number of studies were included, were conducted on a *post hoc* basis. In addition, information regarding antithrombotic therapy was inconsistently reported across studies. As a result, the lack of relationship between antithrombotic therapy and treatment effect should be interpreted with caution.

**Summary forest plot for each outcome included in the adjusted and unadjusted analyses.**

## Ischaemic and bleeding events after complex versus non-complex PCI: a systematic review and meta-analysis




- 1 out of 3 patients undergoing PCI received a complex intervention
- Patients undergoing complex PCI are at increased risk of ischaemic events
- Patients undergoing complex PCI are at increased risk of major bleeding

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*CrI: credible interval; PCI: percutaneous coronary intervention*

## Conclusions

In conclusion, our systematic review and meta-analysis, which included 290,039 patients from 36 studies, found that complex PCI was associated with a higher risk of ischaemic events, including myocardial infarction, stent thrombosis, and target lesion or vessel revascularisation, than non-complex PCI. Additionally, complex PCI carried a higher risk of major bleeding. While the magnitude and certainty of these risks vary, the associations were consistent across both adjusted and unadjusted analyses. Collectively, these findings underscore the increased risks of complex PCI in terms of both ischaemic and bleeding complications.

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## Conflict of interest statement

G. Esposito reports personal fees from Amgen, Boehringer Ingelheim, Edwards Lifesciences, and Sanofi, outside the submitted work; and research grants to the institution from Boston Scientific and Medtronic. The other authors have no conflicts of interest to declare.

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## Supplementary data

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*The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-01204*

**Supplementary data**

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**Supplementary Appendix 1.** Complex PCI and risk of DOCE: a *post hoc* analysis.

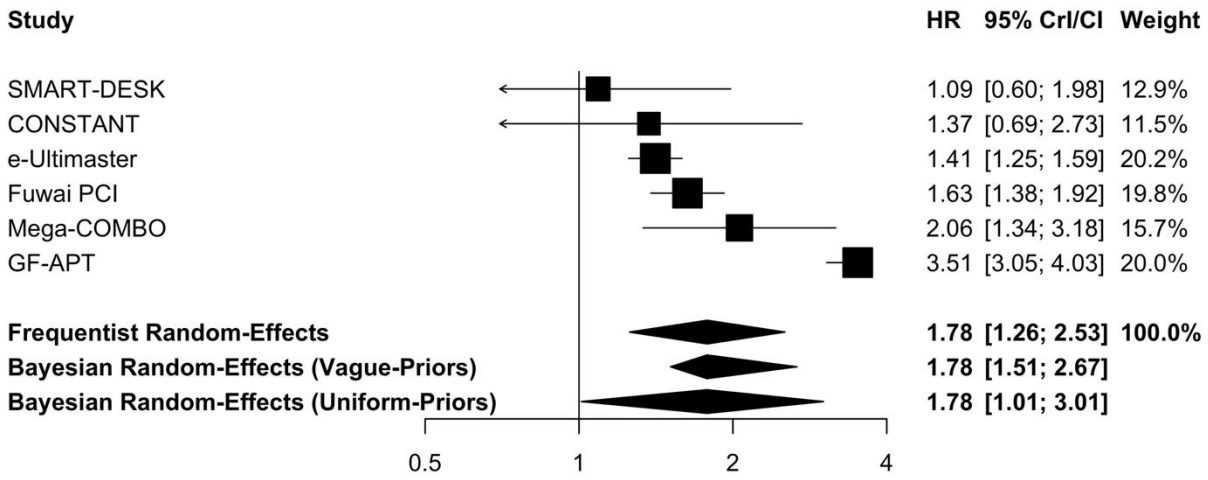
To explore the prognostic significance of complex PCI for a device oriented composite endpoint (DOCE), we retrospectively collected data for the adjusted risk of DOCE in patients undergoing complex vs. non-complex PCI and performed a quantitative synthesis. DOCE definition across included studies and results from the quantitative synthesis, were presented as follows:

**DOCE definition across included studies.**

| Study | Year | Outcome definition |
|---|---|---|
| ADAPT-DES | 2018 | Not included in the quantitative synthesis |
| Avvedimento et al. | 2024 | Not included in the quantitative synthesis |
| Chen et al. | 2023 | Not included in the quantitative synthesis |
| CONSTANT | 2018 | **TVF**: cardiac death, myocardial infarction, ID-TVR |
| COREA-AMI | 2021 | Not included in the quantitative synthesis |
| CREDO-Kyoto | 2020 | Not included in the quantitative synthesis |
| e-Ultimaster | 2020 | **TLF**: cardiac death, TV-MI, ID-TVR |
| Endo et al. | 2020 | Not included in the quantitative synthesis |
| Fuwai PCI | 2020 | **MACE**: cardiac death, myocardial infarction, stent thrombosis, TLR |
| GF-APT | 2020 | **MACE**: cardiac death, myocardial infarction, CD-TVR |
| Giustino et al. | 2016 | Not included in the quantitative synthesis |
| Hanna et al. | 2023 | Not included in the quantitative synthesis |
| HOST-REDUCE-POLYTECH-ACS | 2022 | Not included in the quantitative synthesis |
| ISAR-REACT 5 | 2021 | Not included in the quantitative synthesis |
| KAMIR-NIH | 2023 | Not included in the quantitative synthesis |
| Kheifets et al. | 2022 | Not included in the quantitative synthesis |
| Mega-COMBO | 2023 | **TLF**: cardiac death, TV-MI, CD-TLR |
| PROMETHEUS | 2018 | Not included in the quantitative synthesis |
| PTRG-DES | 2014 | Not included in the quantitative synthesis |
| Riku et al. | 2022 | Not included in the quantitative synthesis |
| SMART-DESK | 2019 | **TLF**: cardiac death, TV-MI, TLR |
| Spirito et al. | 2023 | Not included in the quantitative synthesis |
| STOPDAPT-2 and STOPDAPT-2 ACS | 2023 | Not included in the quantitative synthesis |
| Urban et al. | 2021 | Not included in the quantitative synthesis |
| WIN-DES | 2016 | Not included in the quantitative synthesis |
| Xu et al. | 2023 | Not included in the quantitative synthesis |
| ZON-HR | 2024 | Not included in the quantitative synthesis |

CD-TLR: clinically driven target lesion revascularization; ID-TVR: ischemia driven target vessel revascularization; TLF: target lesion failure; TVF: target vessel failure; TLR: target lesion revascularization; TV-MI: target vessel myocardial infarction.

**Forest plot of adjusted analysis for DOCE in patients undergoing complex PCI vs. non-complex PCI.**

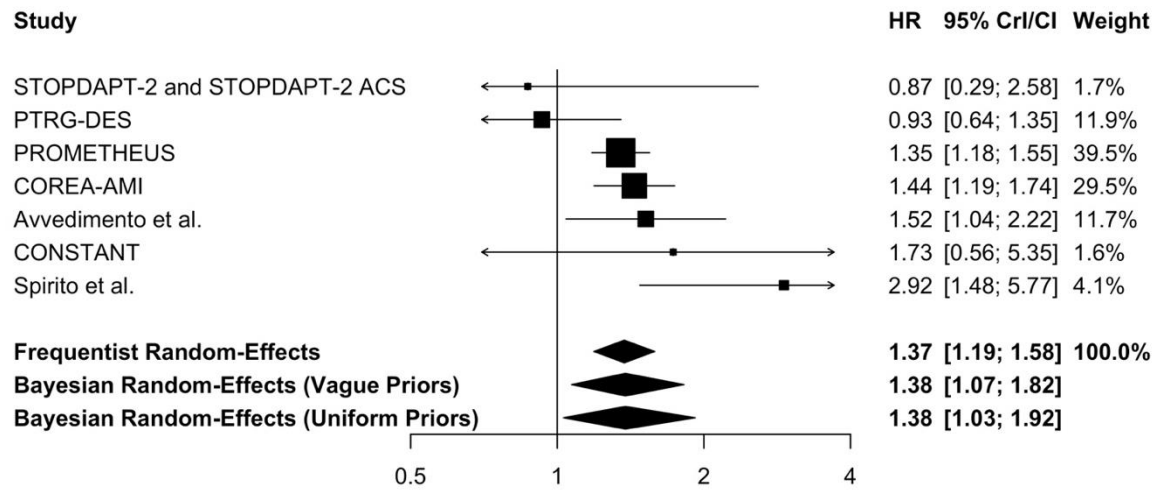



CI: confidence interval; CrI: credible interval; HR: hazard ratio.

**Supplementary Appendix 2.** Complex PCI and risk of spontaneous myocardial infarction: a *post hoc* analysis.

To explore the prognostic significance of complex PCI for spontaneous myocardial infarction, we retrospectively collected data for the adjusted risk of spontaneous myocardial infarction in patients undergoing complex vs. non-complex PCI and performed a quantitative synthesis. Results from the quantitative synthesis, were presented as follows:

**Forest plot of adjusted analysis for spontaneous myocardial infarction in patients undergoing complex PCI vs. non-complex PCI.**

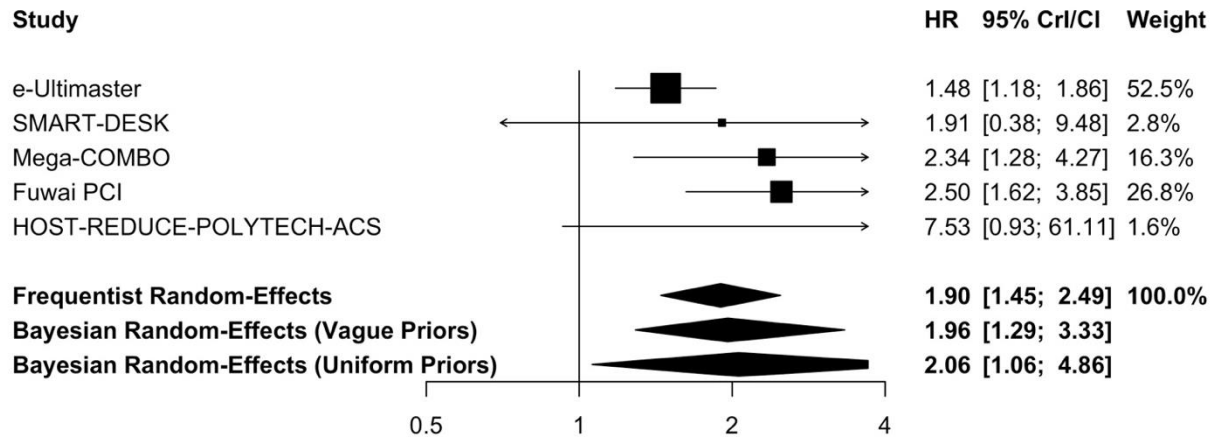



CI: confidence interval; CrI: credible interval; HR: hazard ratio.

**Supplementary Appendix 3.** Complex PCI and risk of target vessel myocardial infarction: a *post hoc* analysis.

To explore the prognostic significance of complex PCI for target vessel myocardial infarction, we retrospectively collected data for the adjusted risk of target vessel myocardial infarction in patients undergoing complex vs. non-complex PCI and performed a quantitative synthesis. Results from the quantitative synthesis, were presented as follows:

**Forest plot of adjusted analysis for target vessel myocardial infarction in patients undergoing complex PCI vs. non-complex PCI.**




CI: confidence interval; CrI: credible interval; HR: hazard ratio.

**Supplementary Table 1.** Search string for the retrieved databases.

| MEDLINE | Search terms | No. citations | EMBASE | Search terms | No. citations | PUBMED (not MEDLINE) | Search terms | No. citations |
|---|---|---|---|---|---|---|---|---|
| **#1** | coronary AND artery AND disease:ab,ti AND [medline]/lim | 166104 | **#1** | coronary AND artery AND disease:ab,ti AND [embase]/lim | 253224 | **#1** | coronary AND artery AND disease:ab,ti AND [pubmed-not-medline]/lim | 407 |
| **#2** | acute AND coronary AND syndrome:ab,ti AND [medline]/lim | 30334 | **#2** | acute AND coronary AND syndrome:ab,ti AND [embase]/lim | 62919 | **#2** | acute AND coronary AND syndrome:ab,ti AND [pubmed-not-medline]/lim | 131 |
| **#3** | myocardial AND infarction:ab,ti AND [medline]/lim | 201088 | **#3** | myocardial AND infarction:ab,ti AND [embase]/lim | 305286 | **#3** | myocardial AND infarction:ab,ti AND [pubmed-not-medline]/lim | 594 |
| **#4** | percutaneous AND coronary AND intervention:ab,ti AND [medline]/lim | 41621 | **#4** | percutaneous AND coronary AND intervention:ab,ti AND [embase]/lim | 79566 | **#4** | percutaneous AND coronary AND intervention:ab,ti AND [pubmed-not-medline]/lim | 138 |
| **#5** | chronic AND coronary AND syndrome:ab,ti AND [medline]/lim | 5832 | **#5** | chronic AND coronary AND syndrome:ab,ti AND [embase]/lim | 12591 | **#5** | chronic AND coronary AND syndrome:ab,ti AND [pubmed-not-medline]/lim | 21 |
| **#6** | pci:ab,ti AND [medline]/lim | 30469 | **#6** | pci:ab,ti AND [embase]/lim | 75085 | **#6** | pci:ab,ti AND [pubmed-not-medline]/lim | 168 |
| **#7** | #1 OR #2 OR #3 OR #4 OR #5 OR #6 | 371634 | **#7** | #1 OR #2 OR #3 OR #4 OR #5 OR #6 | 574913 | **#7** | #1 OR #2 OR #3 OR #4 OR #5 OR #6 | 1228 |
| **#8** | complex AND pci AND [medline]/lim | 2396 | **#8** | complex AND pci AND [embase]/lim | 6113 | **#8** | complex AND pci AND [pubmed-not-medline]/lim | 24 |
| **#9** | complex AND percutaneous AND coronary AND intervention AND [medline]/lim | 3980 | **#9** | complex AND percutaneous AND coronary AND intervention AND [embase]/lim | 7720 | **#9** | complex AND percutaneous AND coronary AND intervention AND [pubmed-not- | 11 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | medline]/lim | |
| **#10** | complexity AND procedure AND [medline]/lim | 8244 | **#10** | complexity AND procedure AND [embase]/lim | 13222 | **#10** | complexity AND procedure AND [pubmed-not-medline]/lim | 299 |
| **#11** | 'high risk' AND features AND 'ischemic events':ab,ti AND [medline]/lim | 55 | **#11** | 'high risk' AND features AND 'ischemic events':ab,ti AND [embase]/lim | 91 | **#11** | 'high risk' AND features AND 'ischemic events':ab,ti AND [pubmed-not-medline]/lim | 0 |
| **#12** | criteria AND pci AND 'high bleeding' AND risk:ti,ab AND [medline]/lim | 62 | **#12** | criteria AND pci AND 'high bleeding' AND risk:ti,ab AND [embase]/lim | 144 | **#12** | criteria AND pci AND 'high bleeding' AND risk:ti,ab AND [pubmed-not-medline]/lim | 0 |
| **#13** | stenting AND complexity AND procedural:ti AND [medline]/lim | 9 | **#13** | stenting AND complexity AND procedural:ti AND [embase]/lim | 17 | **#13** | stenting AND complexity AND procedural:ti AND [pubmed-not-medline]/lim | 0 |
| **#14** | complex AND 'non complex' AND lesions:ti AND [medline]/lim | 13 | **#14** | complex AND 'non complex' AND lesions:ti AND [embase]/lim | 26 | **#14** | complex AND 'non complex' AND lesions:ti AND [pubmed-not-medline]/lim | 1 |
| **#15** | 'clinical outcomes' AND 'high bleeding risk' AND criteria AND pci:ab,ti AND [medline]/lim | 13 | **#15** | 'clinical outcomes' AND 'high bleeding risk' AND criteria AND pci:ab,ti AND [embase]/lim | 36 | **#15** | 'clinical outcomes' AND 'high bleeding risk' AND criteria AND pci:ab,ti AND [pubmed-not-medline]/lim | 0 |
| **#16** | complex AND lesions AND pci AND 'stent implantation' AND [medline]/lim | 73 | **#16** | complex AND lesions AND pci AND 'stent implantation' AND [embase]/lim | 213 | **#16** | complex AND lesions AND pci AND 'stent implantation' AND [pubmed-not-medline]/lim | 1 |
| **#17** | #8 OR #9 OR #10 OR #11 OR #12 OR | 12838 | **#17** | #8 OR #9 OR #10 OR #11 OR #12 OR | 22725 | **#17** | #8 OR #9 OR #10 OR #11 OR #12 OR | 329 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | #13 OR #14 OR #15 OR #16 | | | #13 OR #14 OR #15 OR #16 | | | #13 OR #14 OR #15 OR #16 | |
| **#20** | #7 AND #17 | 4210 | **#20** | #7 AND #17 | 9384 | **#20** | #7 AND #17 | 20 |

**Supplementary Table 2.** PICOTS algorithm to define the research question.

| Questions | Answers |
|---|---|
| **Population** | Patients undergoing complex PCI defined as those meeting more than one of the following criteria: ≥ 3 vessels treated, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation lesions requiring implantation of ≥ 2 stents, total stent length of > 60 mm, chronic total occlusions PCI, left main PCI, in-stent restenosis, rotational atherectomy. |
| **Index prognostic factor** | Complex PCI. |
| **Comparator prognostic factors** | The following clinical covariates were of interest: smoking status, diabetes, dyslipidemia, hypertension, prior MI, prior PCI, prior CABG, CHF, use of intracoronary imaging, use of non-transfemoral approach, use of MCS device, and stent type. |
| **Outcome** | The following outcomes of interest were investigated: myocardial infarction, major bleeding, all-cause death, cardiovascular death, stent thrombosis, target-vessel (or target-lesion) revascularization, and stroke. |
| **Timing** | Prognostic factors were evaluated at baseline and during PCI. |
| **Setting** | Complex PCI was studied to provide prognostic information about patients undergoing PCI. This information may be of clinical utility for the care of patients undergoing complex revascularization procedures. |

CABG: coronary artery bypass grafting; CHF: chronic heart failure; DAPT: dual antiplatelet therapy; MCS: mechanical circulatory support; MI: myocardial infarction; PCI: percutaneous coronary intervention.

**Supplementary Table 3.** Outcome definitions across included studies.

| Study | Year | Outcome | Definition |
|---|---|---|---|
| ADAPT-DES | 2018 | Myocardial infarction | ACUTY criteria |
| | | Major bleeding | TIMI major or minor, GUSTO severe or moderate, ACUITY major, any clinically significant bleeding event requiring medical attention |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiovascular death |
| | | Target vessel or lesion revascularization | Not included in the quantitative synthesis |
| | | Stroke | Not included in the quantitative synthesis |
| Avvedimento et al. | 2024 | Myocardial infarction | VARC-2 criteria |
| | | Major bleeding | VARC-2 criteria |
| | | Stent thrombosis | Not defined |
| | | Cardiac or cardiovascular death | Cardiovascular death |
| | | Target vessel or lesion revascularization | Target vessel revascularization |
| | | Stroke | VARC-2 criteria |
| BIOFLOW II-IV-V | 2022 | Myocardial infarction | Not included in the quantitative synthesis |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiac death |
| | | Target vessel or lesion revascularization | Clinically driven target lesion revascularization |
| | | Stroke | Not included in the quantitative synthesis |
| BIOSTEMI | 2023 | Myocardial infarction | 4 UDMI |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiac death |
| | | Target vessel or lesion revascularization | Target lesion revascularization |
| | | Stroke | Any |
| Chen et al. | 2023 | Myocardial infarction | 3 UDMI |
| | | Major bleeding | BARC 3 - 5 |

| | | | |
|---|---|---|---|
| | | Stent thrombosis | Not included in the quantitative synthesis |
| | | Cardiac or cardiovascular death | Not included in the quantitative synthesis |
| | | Target vessel or lesion revascularization | Target vessel revascularization |
| | | Stroke | Not included in the quantitative synthesis |
| CONSTANT | 2020 | Myocardial infarction | 3 UDMI |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiac death |
| | | Target vessel or lesion revascularization | Target vessel revascularization |
| | | Stroke | Not included in the quantitative synthesis |
| COREA-AMI | 2021 | Myocardial infarction | 3 UDMI |
| | | Major bleeding | BARC 3 - 5 |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiac death |
| | | Target vessel or lesion revascularization | Target vessel revascularization |
| | | Stroke | Ischemic stroke |
| CREDO-Kyoto | 2020 | Myocardial infarction | Arterial Revascularization Therapies Study definition |
| | | Major bleeding | GUSTO moderate or severe |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiac death |
| | | Target vessel or lesion revascularization | Target lesion revascularization |
| | | Stroke | Any |
| e-Ultimaster | 2020 | Myocardial infarction | Not included in the quantitative synthesis |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiac death |
| | | Target vessel or lesion revascularization | Clinically driven target lesion revascularization |
| | | Stroke | Not included in the quantitative synthesis |
| Endo et al. | 2020 | Myocardial infarction | Not included in the quantitative synthesis |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Not included in the quantitative synthesis |

| | | | |
|---|---|---|---|
| | | Cardiac or cardiovascular death | Not included in the quantitative synthesis |
| | | Target vessel or lesion revascularization | Not included in the quantitative synthesis |
| | | Stroke | Not included in the quantitative synthesis |
| Fuwai PCI | 2020 | Myocardial infarction | 3 UDMI |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiac death |
| | | Target vessel or lesion revascularization | Target vessel revascularization |
| | | Stroke | Any |
| GF-APT | 2020 | Myocardial infarction | 3 UDMI |
| | | Major bleeding | BARC 3 - 5 |
| | | Stent thrombosis | Not included in the quantitative synthesis |
| | | Cardiac or cardiovascular death | Cardiac death |
| | | Target vessel or lesion revascularization | Target vessel revascularization |
| | | Stroke | Not included in the quantitative synthesis |
| Giustino et al. | 2016 | Myocardial infarction | According to trial definition included in the pooled analysis |
| | | Major bleeding | TIMI major, BARC 3 – 5 and REPLACE major |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiac death |
| | | Target vessel or lesion revascularization | Target vessel revascularization |
| | | Stroke | Not included in the quantitative synthesis |
| GLOBAL LEADERS | 2022 | Myocardial infarction | 3 UDMI |
| | | Major bleeding | BARC 3- 5 |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Not included in the quantitative synthesis |
| | | Target vessel or lesion revascularization | Target vessel revascularization |
| | | Stroke | Any |
| Goel et al. | 2020 | Myocardial infarction | Not included in the quantitative synthesis |
| | | Major bleeding | Not defined |
| | | Stent thrombosis | Not included in the quantitative synthesis |
| | | Cardiac or cardiovascular death | Not included in the quantitative synthesis |

| | | | |
|---|---|---|---|
| | | Target vessel or lesion revascularization | Not included in the quantitative synthesis |
| | | Stroke | Not included in the quantitative synthesis |
| Hanna et al. | 2021 | Myocardial infarction | Not defined |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Not included in the quantitative synthesis |
| | | Cardiac or cardiovascular death | Cardiovascular death |
| | | Target vessel or lesion revascularization | Target lesion revascularization |
| | | Stroke | Not included in the quantitative synthesis |
| HOST-REDUCE-POLYTECH-ACS | 2022 | Myocardial infarction | 3 UDMI |
| | | Major bleeding | BARC 3 - 5 |
| | | Stent thrombosis | Not defined |
| | | Cardiac or cardiovascular death | Cardiovascular death |
| | | Target vessel or lesion revascularization | Target vessel revascularization |
| | | Stroke | Not included in the quantitative synthesis |
| ISAR-REACT 5 | 2021 | Myocardial infarction | 3 UDMI |
| | | Major bleeding | BARC 3 - 5 |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Not included in the quantitative synthesis |
| | | Target vessel or lesion revascularization | Not included in the quantitative synthesis |
| | | Stroke | Any |
| KAMIR-NIH | 2023 | Myocardial infarction | Not defined |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Not included in the quantitative synthesis |
| | | Cardiac or cardiovascular death | Cardiac death |
| | | Target vessel or lesion revascularization | Not included in the quantitative synthesis |
| | | Stroke | Not included in the quantitative synthesis |
| Kheifets et al. | 2022 | Myocardial infarction | Not included in the quantitative synthesis |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Not included in the quantitative synthesis |
| | | Cardiac or cardiovascular death | Not included in the quantitative synthesis |
| | | Target vessel or lesion revascularization | Not included in the quantitative synthesis |

| | | | |
|---|---|---|---|
| | | Stroke | Not included in the quantitative synthesis |
| MASTER DAPT | 2022 | Myocardial infarction | 3 UDMI |
| | | Major bleeding | BARC 3 - 5 |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiovascular death |
| | | Target vessel or lesion revascularization | Not included in the quantitative synthesis |
| | | Stroke | Any |
| Mega-COMBO | 2023 | Myocardial infarction | Not defined |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiovascular death |
| | | Target vessel or lesion revascularization | Clinically driven target lesion revascularization |
| | | Stroke | Any |
| PENDULUM | 2021 | Myocardial infarction | Not included in the quantitative synthesis |
| | | Major bleeding | BARC 3 – 5 |
| | | Stent thrombosis | Not included in the quantitative synthesis |
| | | Cardiac or cardiovascular death | Not included in the quantitative synthesis |
| | | Target vessel or lesion revascularization | Not included in the quantitative synthesis |
| | | Stroke | Not included in the quantitative synthesis |
| PROMETHEUS | 2018 | Myocardial infarction | Not defined |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Not included in the quantitative synthesis |
| | | Target vessel or lesion revascularization | Not included in the quantitative synthesis |
| | | Stroke | Not included in the quantitative synthesis |
| PTRG-DES | 2024 | Myocardial infarction | 3 UDMI |
| | | Major bleeding | BARC 3 - 5 |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Not included in the quantitative synthesis |
| | | Target vessel or lesion revascularization | Not included in the quantitative synthesis |
| | | Stroke | Any |

| | | | |
|---|---|---|---|
| Riku et al. | 2022 | Myocardial infarction | Not included in the quantitative synthesis |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Not included in the quantitative synthesis |
| | | Cardiac or cardiovascular death | Not included in the quantitative synthesis |
| | | Target vessel or lesion revascularization | Target vessel revascularization |
| | | Stroke | Not included in the quantitative synthesis |
| Sidney-2 | 2023 | Myocardial infarction | ARC-2 definition and 3 UDMI |
| | | Major bleeding | BARC 3 – 5 |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiovascular death |
| | | Target vessel or lesion revascularization | Not included in the quantitative synthesis |
| | | Stroke | Any |
| SMART-DESK | 2019 | Myocardial infarction | Not included in the quantitative synthesis |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiac death |
| | | Target vessel or lesion revascularization | Target lesion revascularization |
| | | Stroke | Not included in the quantitative synthesis |
| Spirito et al. | 2023 | Myocardial infarction | 3 UDMI |
| | | Major bleeding | BARC 3 - 5 |
| | | Stent thrombosis | Not included in the quantitative synthesis |
| | | Cardiac or cardiovascular death | Not included in the quantitative synthesis |
| | | Target vessel or lesion revascularization | Target vessel revascularization |
| | | Stroke | Any |
| STOPDAPT-2 and STOPDAPT-2 ACS | 2023 | Myocardial infarction | ARC definition |
| | | Major bleeding | BARC 3 - 5 |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiovascular death |
| | | Target vessel or lesion revascularization | Target vessel revascularization |
| | | Stroke | Any |
| STOPDAPT-3 | 2024 | Myocardial infarction | ARC definition |

| | | | |
|---|---|---|---|
| | | Major bleeding | BARC 3 - 5 |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiovascular death |
| | | Target vessel or lesion revascularization | Target lesion revascularization |
| | | Stroke | Any |
| Urban et al. | 2021 | Myocardial infarction | Not included in the quantitative synthesis |
| | | Major bleeding | BARC 3 – 5 |
| | | Stent thrombosis | Not included in the quantitative synthesis |
| | | Cardiac or cardiovascular death | Not included in the quantitative synthesis |
| | | Target vessel or lesion revascularization | Not included in the quantitative synthesis |
| | | Stroke | Not included in the quantitative synthesis |
| Vogel et al. | 2018 | Myocardial infarction | Not defined |
| | | Major bleeding | Not defined |
| | | Stent thrombosis | Not defined |
| | | Cardiac or cardiovascular death | Cardiac death |
| | | Target vessel or lesion revascularization | Ischemia driven target lesion revascularization |
| | | Stroke | Not included in the quantitative synthesis |
| WIN-DES | 2021 | Myocardial infarction | According to trial definition included in the pooled analysis |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Definite and probable according to ARC definition |
| | | Cardiac or cardiovascular death | Cardiac death |
| | | Target vessel or lesion revascularization | Target lesion revascularization |
| | | Stroke | Not included in the quantitative synthesis |
| Xu et al. | 2023 | Myocardial infarction | 3 UDMI |
| | | Major bleeding | Not included in the quantitative synthesis |
| | | Stent thrombosis | Not included in the quantitative synthesis |
| | | Cardiac or cardiovascular death | Cardiac death |
| | | Target vessel or lesion revascularization | Not included in the quantitative synthesis |
| | | Stroke | Any |
| ZON-HR | 2018 | Myocardial infarction | Not included in the quantitative synthesis |
| | | Major bleeding | Not included in the quantitative synthesis |

| | | | |
|---|---|---|---|
| | | Stent thrombosis | Not included in the quantitative synthesis |
| | | Cardiac or cardiovascular death | Not included in the quantitative synthesis |
| | | Target vessel or lesion revascularization | Not included in the quantitative synthesis |
| | | Stroke | Not included in the quantitative synthesis |

ARC: Academic research consortium; BARC: Bleeding academic research consortium; GUSTO: Global Use of Streptokinase and t-PA for Occluded Coronary Arteries; UDMI: Universal definition of myocardial infarction; REPLACE-2: Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events; TIMI: Thrombolysis in Myocardial Infarction.

**Supplementary Table 4.** Complex PCI definitions across included studies.

| Study | Year | Complex PCI definition |
|---|---|---|
| ADAPT-DES | 2018 | – ≥ 3 drug eluting stents implanted,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– left main PCI,<br>– saphenous vein graft PCI,<br>– use of atherectomy. |
| Avvedimento et al. | 2024 | – ≥ 3 vessels treated,<br>– ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 60 mm,<br>– chronic total occlusion PCI. |
| BIOFLOW II-IV-V | 2022 | – ≥ 3 lesions treated,<br>– ≥ 3 stents implanted,<br>– total stent length ≥ 60 mm.<br>– multivessel PCI. |
| BIOSTEMI | 2017 | – ≥ 3 drug eluting stents implanted,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– left main PCI,<br>– saphenous vein graft PCI,<br>– use of atherectomy. |
| Chen et al. | 2023 | – ≥ 3 vessels treated,<br>– ≥ 3 lesions treated,<br>– ≥ 3 stents implanted,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 60 mm,<br>– chronic total occlusion PCI. |
| CONSTANT | 2018 | – ≥ 3 lesions treated,<br>– ≥ 3 vessels treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 60 mm,<br>– severe calcified lesions PCI,<br>– left main PCI,<br>– chronic total occlusion PCI. |
| COREA-AMI | 2021 | – ≥ 3 stents implanted,<br>– ≥ 3 lesions treated, |

| | | |
|---|---|---|
| | | – bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 60 mm,<br>– multivessel PCI,<br>– in-stent restenosis,<br>– left main PCI,<br>– chronic total occlusion PCI. |
| CREDO-Kyoto | 2020 | – ≥ 3 vessels treated,<br>– ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 60 mm,<br>– chronic total occlusion PCI. |
| e-Ultimaster | 2020 | – ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length > 60 mm,<br>– multivessel PCI<br>– chronic total occlusion PCI. |
| Endo et al. | 2020 | – ≥ 3 vessels treated,<br>– ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 60 mm,<br>– left main PCI,<br>– chronic total occlusion PCI,<br>– use of atherectomy. |
| Fuwai PCI | 2020 | – ≥ 3 vessels treated,<br>– ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length > 60 mm,<br>– in-stent restenosis,<br>– severely calcified lesion,<br>– left main PCI,<br>– chronic total occlusion PCI. |
| GF-APT | 2020 | – ≥ 3 vessels treated,<br>– ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 60 mm, |

| | | |
|---|---|---|
| | | – left main PCI,<br>– surgical bypass graft PCI,<br>– chronic total occlusion PCI. |
| Giustino et al. | 2016 | – ≥ 3 vessels treated,<br>– ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 60 mm,<br>– chronic total occlusion PCI. |
| GLOBAL LEADERS | 2024 | – ≥ 3 vessels treated,<br>– ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length > 60 mm,<br>– chronic total occlusion PCI. |
| Goel et al. | 2022 | – ≥ 3 lesions treated,<br>– ≥ 3 stents implanted,<br>– total stent length ≥ 60 mm,<br>– multivessel PCI. |
| Hanna et al. | 2023 | – ≥ 3 vessels treated<br>– ≥ 2 vessels if including left main coronary artery, or proximal left anterior descending artery,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– lesions with severe calcification,<br>– left main PCI,<br>– saphenous vein graft PCI,<br>– chronic total occlusion PCI<br>– use of atherectomy. |
| HOST-REDUCE-POLYTECH-ACS | 2022 | – ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– bifurcation lesion PCI,<br>– total stent length ≥ 60 mm,<br>– left main PCI,<br>– lesions with severe calcification. |
| ISAR-REACT 5 | 2021 | – ≥ 2 vessels disease in the presence of right dominance,<br>– ≥ 3 vessels disease in the presence of left dominance,<br>– ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– total stent length ≥ 60mm. |

| | | |
|---|---|---|
| KAMIR-NIH | 2023 | – ≥ 3 stents implanted,<br>– total stent length ≥ 38 mm implanted,<br>– multivessel PCI,<br>– left main coronary artery PCI. |
| Kheifets et al. | 2022 | – ≥ 3 drug eluting stents implanted,<br>– bifurcation with ≥ 2 stents,<br>– left main PCI,<br>– total stent length ≥ 60 mm,<br>– saphenous vein graft PCI,<br>– chronic total occlusion PCI. |
| MASTER DAPT | 2023 | – ≥ 3 vessels treated,<br>– ≥ 3 lesions treated,<br>– ≥ 3 stents implanted,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 60 mm,<br>– chronic total occlusion PCI. |
| Mega-COMBO | 2023 | – ≥ 3 stents implanted,<br>– ≥ 3 target vessels treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– moderate-to-severe lesion calcification,<br>– total stent length ≥ 60 mm implanted,<br>– left main PCI,<br>– saphenous vein graft PCI. |
| PENDULUM | 2023 | – ≥ 3 stents implanted,<br>– ≥ 3 vessels treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 60 mm,<br>– moderate-to-severe lesion calcification,<br>– left main PCI,<br>– saphenous vein graft. |
| PROMETHEUS | 2018 | – bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 30 mm,<br>– moderate or severely calcified lesion,<br>– left main PCI. |
| PTRG-DES | 2014 | – ≥ 3 vessels treated,<br>– ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 60mm, |

| | | |
|---|---|---|
| | | – left main PCI,<br>– chronic total occlusion PCI. |
| Riku et al. | 2022 | – ≥ 3 stents implanted,<br>– bifurcation with ≥ 2 stents,<br>– total stent length ≥ 60mm,<br>– left main PCI,<br>– chronic total occlusion PCI. |
| Sidney-2 | 2018 | – ≥ 3 lesions treated,<br>– ≥ 3 vessels treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length > 60 mm,<br>– severe calcified lesions,<br>– left main PCI,<br>– chronic total occlusion PCI. |
| SMART-DESK | 2019 | – bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 40 mm,<br>– minimal stent diameter ≤ 2.5 mm implanted,<br>– left main PCI. |
| Spirito et al. | 2023 | – ≥ 3 stents implanted,<br>– ≥ 3 vessels treated,<br>– ≥ 3 lesions treated,<br>– total stent length ≥ 60mm,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– left main PCI,<br>– saphenous vein graft PCI,<br>– chronic total occlusion PCI. |
| STOPDAPT-2 and STOPDAPT-2 ACS | 2023 | – ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 60mm,<br>– chronic total occlusion PCI. |
| STOPDAPT-3 | 2021 | – ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– left main PCI,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 60 mm,<br>– multivessel PCI,<br>– in-stent restenosis,<br>– chronic total occlusion PCI. |

| | | |
|---|---|---|
| Urban et al. | 2021 | – ≥ 3 vessels treated,<br>– ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– chronic total occlusion PCI. |
| Vogel et al. | 2020 | – ≥ 3 stents implanted,<br>– ≥ 3 lesions treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length > 60 mm,<br>– multivessel PCI,<br>– chronic total occlusion PCI. |
| WIN-DES | 2016 | – ≥ 2 stents implanted,<br>– ≥ 2 lesions treated,<br>– total stent length ≥ 30mm,<br>– bifurcation requiring implantation of ≥ 2 stents. |
| Xu et al. | 2023 | – ≥ 2 stents implanted,<br>– ≥ 2 lesions treated,<br>– bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 40mm,<br>– moderately-to-severely calcified lesion,<br>– left main PCI,<br>– chronic total occlusion PCI. |
| ZON-HR | 2024 | – bifurcation requiring implantation of ≥ 2 stents,<br>– total stent length ≥ 60 mm,<br>– saphenous vein graft PCI,<br>– chronic total occlusion PCI. |

DES: drug eluting stent; PCI: percutaneous coronary intervention, SVG: saphenous venous graft

**Supplementary Table 5.** Covariates used for adjustments across included studies.

| Study | Year | Adjustment variables |
|---|---|---|
| ADAPT-DES | 2018 | Clinical: age, gender, smoking, BMI, diabetes, hemoglobin, creatinine clearance, white blood cell count, platelet cell count, platelet count, peripheral artery disease, CHF, HPR, prior PCI, prior CABG and clinical presentation as ACS.<br>Procedural: use of ultrasound imaging, multivessel disease, pre-procedural TIMI flow grade 2-3, thrombus and target LAD vessel revascularization. |
| Avvedimento et al. | 2024 | Clinical: gender, dyslipidemia, previous CAD and prior PCI.<br>Procedural: non-transfemoral approach of catheterization. |
| Chen et al. | 2023 | Clinical: age, hypertension, diabetes, peripheral artery disease, prior PCI, prior CABG and prior ACS.<br>Procedural: not available. |
| CONSTANT | 2018 | Clinical: age, gender, smoking, diabetes and ACS.<br>Procedural: not available. |
| COREA-AMI | 2021 | Clinical: age, diabetes, prior MI, prior CABG, established vascular disease, atrial fibrillation, CKD, LVEF dysfunction, medications at discharge and extended DAPT.<br>Procedural: cardiogenic shock with use of ECMO/IABP and prior PCI. |
| CREDO-Kyoto | 2020 | Clinical: age, gender, BMI, smoking, hypertension, diabetes, hemoglobin, platelet count, COPD, cirrhosis, cancer, atrial fibrillation, CKD, prior MI, prior stroke, peripheral vascular disease, HF and use of medication (statins, beta blockers, ACE-I/ARB).<br>Procedural: use of DES. |
| e-Ultimaster | 2020 | Clinical: age, gender, smoking, hypertension, diabetes, dyslipidemia, renal impairment, clinical presentation as acute vs. chronic coronary syndrome, prior MI, prior PCI and prior CABG.<br>Procedural: not available. |
| Endo et al. | 2020 | Clinical: age, CKD.<br>Procedural: PCI complication, complete revascularization and use of MCS device. |
| Fuwai PCI | 2020 | Clinical: age, gender, smoking, BMI, hypertension, diabetes, CKD, hemoglobin, platelet count, DAPT duration, prior MI, prior PCI, prior CABG and clinical presentation as ACS.<br>Procedural: mean stent diameter and type of DES implanted. |
| GF-APT | 2020 | Clinical: age, gender, BMI, smoking, hypertension, diabetes, dyslipidemia, CKD, prior MI, prior PCI and prior ischemic stroke.<br>Procedural: not available. |

| | | |
|---|---|---|
| Giustino et al. | 2016 | Clinical: age, gender, smoking, hypertension, diabetes, prior PCI, prior CABG, prior MI, clinical presentation as CS (non–ST-segment elevation MI or ST-segment elevation MI) and stent type.<br>Procedural: not available. |
| Hanna et al. | 2023 | Clinical: age, gender, race, BMI, frailty, hypertension, diabetes, dyslipidemia, marital status, anemia, CKD, prior MI, prior PCI, prior CABG, prior stroke, CHF, peripheral artery disease, severe valvular disease, atrial fibrillation, COPD, cancer, cirrhosis, alcohol dependence, gastrointestinal bleeding, depression and use of medication as: aspirin, anticoagulation, P2Y12 inhibitor, high-intensity statin, beta-blocker, renin-angiotensin system blocker or angiotensin-converting enzyme inhibitor.<br>Procedural: not available. |
| HOST-REDUCE-POLYTECH-ACS | 2022 | Clinical: age, diabetes, smoking, CKD and LVEF.<br>Procedural: not available. |
| ISAR-REACT 5 | 2021 | Clinical: participating center, ACS presentation type and use of medication (ticagrelor or prasugrel).<br>Procedural: not available. |
| KAMIR-NIH | 2023 | Clinical: age, gender, smoking, hypertension, diabetes, peak troponin-I, blood glucose, total cholesterol, triglyceride, LVEF, DBP, ACS presentation (atypical chest pain, dyspnea, ST-segment depression, Killip class II/III) and GRACE risk score.<br>Procedural: door-ballon-time and access to EMS. |
| Kheifets et al. | 2022 | Clinical: age, hypertension, diabetes, CHF, severe LVEF reduction, prior myocardial injury, prior ACS, cardiogenic shock and renal failure.<br>Procedural: not available. |
| Mega-COMBO | 2023 | Clinical: age, hypertension, smoking, diabetes, dyslipidemia, prior MI, prior CABG, CKD and indication for PCI.<br>Procedural: not available. |
| PROMETHEUS | 2018 | Clinical: age, race, hypertension, BMI, diabetes, eGFR, hemoglobin, derivation center, prior PCI and CAD presentation.<br>Procedural: multivessel disease, bivalirudin use, use of medication (prasugrel) and stent type. |
| PTRG-DES | 2024 | Clinical: age, gender, BMI, hypertension, diabetes, dyslipidemia, CKD and CHF.<br>Procedural: not available. |
| Riku et al. | 2022 | Clinical: clinical presentation as ACS, prior MI, prior PCI and prior CABG.<br>Procedural: number of stents, total stent length, minimal stent size and target vessel revascularization (LM, LAD, LCX, RCA) |
| SMART-DESK | 2019 | Clinical: age, gender, smoking, dyslipidemia, hemoglobin, creatinine, prior cerebrovascular event, prior MI, prior PCI, peak of CK-MB, LVEF, clinical presentation as ACS<br>Procedural: multivessel disease, bifurcation, coronary lesion type B2/C and revascularization of LAD |

| | | |
|---|---|---|
| Spirito et al. | 2023 | Clinical: age, sex, race, smoking, hypertension, dyslipidemia, diabetes, prior PCI, prior MI, prior CABG, atrial fibrillation, dialysis and clinical presentation as (ACS vs. CCS).<br>Procedural: not available. |
| STOPDAPT-2 and STOPDAPT-2 ACS | 2023 | Clinical: clinical presentation as (ACS or CCS) and parent study.<br>Procedural: not available. |
| Urban et al. | 2021 | Clinical: age, diabetes, smoking, hemoglobin, dyslipidemia, creatinine, platelet count, prior MI, CHF, liver disease, peripheral arterial disease, prior PCI and clinical presentation as ACS (non-ST-segment elevation MI or ST-segment elevation MI).<br>Procedural: not available. |
| WIN-DES | 2016 | Clinical: smoking, BMI, family history of CAD, and clinical presentation as ACS.<br>Procedural: number of stents per patient and type of lesions B2/C. |
| Xu et al. | 2023 | Clinical: age, gender, diabetes, creatinine, LVEF, prior MI and ACS type.<br>Procedural: ostial lesions, de novo lesion, type B2/C lesions and mean diameter of stents. |
| ZON-HR | 2024 | Clinical: diabetes, serum creatinine, multivessel coronary artery disease, CKD and prior MI.<br>Procedural: not available. |

ACE-I: angiotensin converting enzyme inhibitor; ACS: acute coronary syndrome; ARB: angiotensin receptor blocker; BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; CCS: chronic coronary syndrome; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; DAPT: dual antiplatelet therapy; DBP: diastolic blood pressure; DES: drug eluting stent; ECMO: extracorporeal membrane oxygenation; eGFR: estimated glomerular filtration rate; EMS: emergency medical service; HF: heart failure, HPR: high platelet reactivity; IABP: intra-aortic balloon pump; LAD: left anterior descending artery; LCX: left circumflex artery; LMT: left main; LVEF: left ventricular ejection fraction; MI: myocardial infarction; MCS: mechanical circulatory support; PCI: percutaneous coronary intervention; RCA: right coronary artery.

**Supplementary Table 6.** Main features of included studies.

| Study | PMID† | DOI† | Participants, n | Population included | Patients undergoing complex PCI, n (%) | Mean age in complex PCI, yrs | Females in complex PCI, n (%) | Diabetes in complex PCI, n (%) | Acute coronary syndrome in complex PCI, n (%) | Follow-up, yrs |
|---|---|---|---|---|---|---|---|---|---|---|
| ADAPT-DES | 30041804 | 10.1016/j.jcard.2018.03.103 | 8,582 | Patients undergoing PCI with DES | 2,255 (26.3) | 65.5 | 473 (21) | 806 (35.7) | 1057 (46.9) | 2 |
| Avvedimento et al. | 38763211 | 10.1016/j.rec.2024.05.002 | 1,550 | Patients with severe AS and concomitant CAD who underwent PCI 3 months before TAVR | 454 (29.3) | 80.9 | 161 (35.5) | 164 (36.1) | 0 (0) | 2 |
| BIOFLOW II-IV-V | 35212802 | 10.1007/s00392-022-01994-4 | 2,350 | Patients undergoing PCI with BP-SES or DP-EES | 348 (14.8) | 65.3 | 113 (32.6) | 101 (29) | 123 (35.3) | 3 |
| BIOSTEMI | 36807456 | 10.1002/ccd.30600 | 1,700 | Patients undergoing primary PCI | 421 (24.8) | 63.9 | 57 (13) | 96 (23) | 421 (100) | 2 |
| Chen et al. (CKD) | 36691863 | 10.1002/ccd.30569 | 4,537 | Patients undergoing PCI with DES | 1,151 (25.4) | 72 | 356 (30.9) | 640 (55.6) | 503 (44) | 1 |
| Chen et al. (No-CKD) | 36691863 | 10.1002/ccd.30569 | 10,534 | Patients undergoing PCI with DES | 2,983 (28.3) | 63.7 | 614 (20.6) | 1,271 (43.6) | 1,180 (40) | 1 |
| CONSTANT | 36341214 | 10.1016/j.jacasi.2021.08.006 | 926 | Patients undergoing PCI with second generation DES | 249 (26.9) | 64 | 58 (23.3) | 82 (32.9) | 174 (70) | 2 |
| COREA-AMI | 36013097 | 10.3390/jcm11164853 | 10,329 | Patients with ACS undergoing PCI | 6,144 (59.4) | 65.5 | 1,850 (39.1) | 2,495 (40.6) | 6,144 (100) | 1 |
| CREDO-Kyoto | 33064372 | 10.1002/ccd.29335 | 7,871 | Patients with stable CAD undergoing PCI | 2,777 (35.3) | 68.5 | 730 (26) | 1,246 (45) | 0 (0) | 5 |
| e-Ultimaster | 32588821 | 10.4244/EIJ-D-20-00361 | 37,198 | Patients undergoing PCI with new-generation DES | 10,241 (27.3) | 64.9 | 2,217 (22) | 3,256 (32.1) | 4,836 (47.2) | 1 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Endo et al. | 31350706 | 10.1007/s12928-019-00608-7 | 1,062 | Patients undergoing PCI with new-generation DES | 358 (33.7) | 69 | 59 (16) | 161 (45) | 55 (15) | 1.9 |
| Fuwai PCI | 32405273 | 10.1155/2020/2985435 | 10,167 | Patients undergoing PCI | 3,651 (35.9) | 58.6 | 754 (21) | 1,202 (33) | 2,058 (56) | 2.5 |
| GF-APT | 34881313 | 10.3389/fcvm.2021.768190 | 15,459 | Patients with stable CAD (prior MI >12 month; prior coronary revascularization >12-month, stenosis >50%) undergoing PCI | 6,335 (41.0) | 59.1 | 1,249 (19.7) | 2176 (34) | 0 (0) | 1 |
| Giustino et al. | 27595509 | 10.1016/j.jacc.2016.07.760 | 9,577 | Pooled analysis from EXCELLENT, PRODIGY, OPTIMIZE, RESET, SECURITY, ITALIC PLUS trials | 1,680 (17.5) | 63.6 | 526 (31) | 602 (35.8) | 796 (47.4) | 1.1 |
| GLOBAL LEADERS | 31397487 | 10.1093/eurheartj/ehz453 | 16,450 | Patients undergoing PCI with BES | 4,570 (27.8) | 65.2 | 1,200 (26) | 975 (21) | 2,221 (49) | 2 |
| Goel et al. | - | - | 4,278 | Patients with HBR undergoing PCI | 1,393 (32.6) | NA | NA | NA | NA | 1 |
| Hanna et al. | 37776222 | 10.1161/JAHA.122.029057 | 513 | Elderly (≥75 years) patients undergoing PCI | 288 (56.1) | 81.1 | 94 (32.6) | 97 (34) | 0 (0) | 1 |
| HOST-REDUCE-POLYTECH-ACS | 35262625 | 10.1001/jamacardio.2022.0052 | 2,271 | Patients with ACS undergoing PCI | 705 (31.0) | 59.7 | 82 (11) | 326 (46.2) | 705 (100) | 1 |
| ISAR-REACT 5 | 34468709 | 10.1093/ehjacc/zuab077 | 3,377 | Prasugrel vs. ticagrelor in ACS patients undergoing PCI | 1,429 (43.2) | 65.9 | 294 (21.6) | 333 (23.3) | 1,429 (100) | 1 |
| KAMIR-NIH | 37752278 | 10.1038/s41598-023-43385-3 | 4,373 | Patients with NSTEMI undergoing PCI | 2,106 (48.1) | 66 | 602 (28.6) | 723 (34) | 2,106 (100) | 3 |
| Kheifets et al. | 35811722 | 10.3389/fcvm.2022.913588 | 20,301 | Patients undergoing PCI | 5,647 (27.8) | 66.3 | 1,208 (21.4) | 2,677 (47.4) | NA | 1 |
| MASTER DAPT | 35580836 | 10.1093/eurheartj/ehac284 | 4,579 | Patients with HBR undergoing PCI with | 1,196 (26.1) | 76.6 | 405 (33.9) | 349 (29) | 0 (0) | 1 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Ultimaster SES implantation | | | | | | |
| Mega-COMBO | 37866281 | 10.1016/j.amjcard.2023.09.081 | 2,425 | Patients undergoing PCI with COMBO stent implantation | 923 (38.1) | 65.1 | NA | NA | 497 (54.9) | 1 |
| PENDULUM | 32624464 | 10.4244/EIJ-D-20-00345 | 6,267 | Patients undergoing PCI with DES implantation | 1,712 (27.3) | NA | NA | NA | NA | 1 |
| PROMETHEUS | 29475531 | 10.1016/j.cjca.2017.12.023 | 19,914 | Patients with ACS and undergoing PCI | 9,735 (48.9) | 65.2 | 3,045 (31.3) | 3,946 (40.5) | 9,735 (100) | 1 |
| PTRG-DES | 38463677 | 10.1016/j.jacasi.2023.10.011 | 11,714 | Patients undergoing PCI | 3,152 (26.9) | 64.4 | 985 (31) | 1,216 (38.6) | 1,786 (56.7) | 1 |
| Riku et al. | 35967938 | 10.18999/nagjms.84.2.352 | 383 | Patients undergoing PCI with SES implantation | 84 (21.9) | 66.3 | 21 (25) | 42 (50) | 23 (27.4) | 1 |
| Sidney-2* | 36754514 | 10.1016/j.jacc.2022.11.041 | 22,941 | Pooled analysis of GLASSY, SMART CHOICE, STOP DAPT 2, TICO, TWILIGHT trials | 4,685 (20.4) | 64.9 | 1,547 (33) | 974 (20.8) | 2,857 (61) | 1 |
| SMART DESK | 30468035 | 10.4070/kcj.2018.0097 | 1,999 | Patients undergoing PCI with BES or EES implantation | 1,145 (57.3) | 64.3 | 373 (32.5) | 396 (34.6) | 631 (55.1) | 2 |
| Spirito et al. | 38639154 | 10.1002/ccd.31055 | 2,657 | Elderly (>80 years) patients undergoing PCI | 1,387 (52.0) | 84.2 | 474 (34.2) | 491 (35.4) | 669 (48.2) | 1 |
| STOPDAPT-2 and STOPDAPT-2 ACS* | 36873770 | 10.1016/j.jacasi.2022.09.011 | 5,997 | Patients undergoing PCI with EES implantation | 999 (16.7) | 69.1 | 201 (20) | 421 (42.1) | 654(65.5) | 1 |
| STOPDAPT-3 | 38749592 | 10.1016/j.jcin.2024.03.017 | 5,966 | Patients with HBR undergoing PCI | 1,230 (20.6) | 72.4 | 632 (51.4) | 246 (20) | 861 (70) | 1 |
| Urban et al. | 33404627 | 10.1001/jamacardio.2020.6814 | 6,641 | Pooled analysis of HRB studies (CENTURY, ZEUS, LEADERS FREE, LEADERS FREE II, SENIOR, and PARIS) | 2,289 (34.5) | NA | NA | NA | NA | 1 |
| Vogel et al. | - | - | 3,507 | Patients with HBR undergoing PCI with XIENCE implantation | 558 (15.9) | NA | NA | NA | NA | 4 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| WIN-DES | 27056305 | 10.1016/j.jcin.2015.12.013 | 10,241 | Female patients undergoing PCI with DES from the following trials: RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, TAXUS, TAXUS II SR, TAXUS IV, TAXUS V, SIRTAX, ENDEAVOR II, ENDEAVOR III, ENDEAVOR, IV, PROTECT, RESOLUTE AC, TWENTW, SPIRIT II, SPIRIT III, SPIRIT IV, COMPARE I, BASKET-PROVE, EXCELLENT, RESET, LEADERS, PRODIGY, COMPARE II, ISAR TEST 4 | 4,629 (45.0) | 67.7 | 4,629 (100) | 1,574 (34) | 2,001 (43.2) | 3 |
| Xu et al. | 36848178 | 10.1097/CM9.0000000000000002450 | 7,712 | Patients undergoing PCI | 4,882 (63.3) | 58 | 1,089 (22.3) | 1519 (31) | 2,848 (58.3) | 2 |
| ZON-HR | - | - | 3,691 | Patients undergoing PCI | 842 (22.8) | 66.1 | 826 (29) | 783 (28) | 1,927 (68) | 1 |

ACS: acute coronary syndrome; AS: aortic stenosis; BES: biolimus-eluting stent; BP-SES: biodegradable-polymer sirolimus-eluting stent; CAD: coronary artery disease; CKD: chronic kidney disease; DES: drug-eluting stent; DP-EES: durable polymer everolimus-eluting stent; EES: everolimus-eluting stent; HBR: high bleeding risk; MI: myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; SES: sirolimus-eluting stent; TAVR: transcatheter aortic valve replacement.

*Data from STOPDAPT-2 and STOPDAPT-2 ACS were used for the adjusted analysis whereas data from Sidney-2 were used in the unadjusted analysis.

† not reported for Goel et al. (https://doi.org/10.1016/S0735-1097(20)32031-3), Vogel et al. (https://doi.org/10.1016/j.jacc.2018.08.1723) and ZON-HR (https://doi.org/10.1093/eurheartj/ehae666.2394) because presented as abstract.

**Supplementary Table 7.** Baseline characteristics of patients undergoing complex versus non-complex PCI.

| Study | Subgroup | Age* (mean) | Female patients (%) | Asian patients (%) | Black patients (%) | Caucasian patients (%) |
|---|---|---|---|---|---|---|
| ADAPT-DES | Complex PCI | 65.6 | 21.0 | NA | NA | NA |
| | Non-complex PCI | 62.9 | 27.7 | NA | NA | NA |
| Avvedimento et al. | Complex PCI | 80.9 | 35.5 | NA | NA | NA |
| | Non-complex PCI | 81.3 | 44.7 | NA | NA | NA |
| BIOFLOW II-IV-V | Complex PCI | 65.3 | 29.0 | NA | NA | 32.6 |
| | Non-complex PCI | 64.4 | 24.8 | NA | NA | 32.6 |
| BIOSTEMI | Complex PCI | 63.4 | 22.8 | NA | NA | NA |
| | Non-complex PCI | 61.5 | 23.9 | NA | NA | NA |
| Chen et al. (CKD) | Complex PCI | 72.0 | 30.9 | 11.9 | 8.9 | 52.9 |
| | Non-complex PCI | 71.7 | 38.5 | 13.6 | 13.1 | 44.3 |
| Chen et al. (no CKD) | Complex PCI | 63.7 | 20.6 | 18.4 | 7.8 | 48.2 |
| | Non-complex PCI | 63.6 | 27.3 | 19.5 | 10.4 | 41.6 |
| CONSTANT | Complex PCI | 64.0 | 23.3 | 100 | 0 | 0 |
| | Non-complex PCI | 63.7 | 28.8 | 100 | 0 | 0 |
| COREA-AMI | Complex PCI | 65.1 | 26.8 | 100 | 0 | 0 |
| | Non-complex PCI | 61.3 | 27.0 | 100 | 0 | 0 |
| CREDO-Kyoto | Complex PCI | 68.5 | 26.0 | 100 | 0 | 0 |
| | Non-complex PCI | 68.7 | 29.0 | 100 | 0 | 0 |
| e-Ultimaster | Complex PCI | 64.9 | 21.6 | NA | NA | NA |
| | Non-complex PCI | 63.9 | 24.9 | NA | NA | NA |
| Endo et al. | Complex PCI | 69.0 | 16.0 | 100 | NA | 0 |
| | Non-complex PCI | 67.0 | 19.0 | 100 | NA | 0 |
| Fuwai PCI | Complex PCI | 58.6 | 20.0 | 100 | 0 | 0 |
| | Non-complex PCI | 58.2 | 24.1 | 100 | 0 | 0 |
| GF-APT | Complex PCI | 59.1 | 19.7 | 100 | 0 | 0 |
| | Non-complex PCI | 59.3 | 24.3 | 100 | 0 | 0 |
| Giustino et al. | Complex PCI | 63.6 | 31.3 | NA | NA | NA |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Non-complex PCI | 63.4 | 32.3 | NA | NA | NA |
| GLOBAL LEADERS | Complex PCI | 65.3 | 21.8 | NA | NA | NA |
| | Non-complex PCI | 64.2 | 24.2 | NA | NA | NA |
| Goel et al | Complex PCI | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA |
| Hanna et al. | Complex PCI | 80.0 | 21.3 | NA | NA | 97.3 |
| | Non-complex PCI | 81.0 | 32.6 | NA | NA | 95.5 |
| HOST-REDUCE-POLYTECH-ACS | Complex PCI | 59.7 | 11.6 | 100 | 0 | 0 |
| | Non-complex PCI | 58.5 | 10.5 | 100 | 0 | 0 |
| ISAR-REACT 5 | Complex PCI | 65.9 | 20.6 | NA | NA | NA |
| | Non-complex PCI | 63.6 | 21.5 | NA | NA | NA |
| KAMIR-NIH | Complex PCI | 64.6 | 26.1 | 100 | 0 | 0 |
| | Non-complex PCI | 61.8 | 25.3 | 100 | 0 | 0 |
| Kheifets et al. | Complex PCI | 66.3 | 21.4 | NA | NA | NA |
| | Non-complex PCI | 65.6 | 21.8 | NA | NA | NA |
| Mega-COMBO | Complex PCI | 65.1 | NA | 0 | 0 | 100 |
| | Non-complex PCI | 61.7 | NA | 0 | 0 | 100 |
| PROMETHEUS | Complex PCI | 65.2 | 31.3 | NA | NA | NA |
| | Non-complex PCI | 63.6 | 32.0 | NA | NA | NA |
| MASTER DAPT | Complex PCI | 76.5 | 29.1 | NA | NA | NA |
| | Non-complex PCI | 75.9 | 31.3 | NA | NA | NA |
| PENDULUM | Complex PCI | NA | NA | 100 | 0 | 0 |
| | Non-complex PCI | NA | NA | 100 | 0 | 0 |
| PTRG-DES | Complex PCI | 65.0 | 31.2 | 100 | 0 | 0 |
| | Non-complex PCI | 64.1 | 32.4 | 100 | 0 | 0 |
| Riku et al. | Complex PCI | 66.3 | 25.0 | 100 | 0 | 0 |
| | Non-complex PCI | 66.2 | 24.4 | 100 | 0 | 0 |
| SMART-DESK | Complex PCI | 64.3 | 32.6 | 100 | 0 | 0 |
| | Non-complex PCI | 63.5 | 28.6 | 100 | 0 | 0 |
| Sidney-2 | Complex PCI | 64.9 | 20.8 | 36.9 | 36.9 | NA |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Non-complex PCI | 64.9 | 24.0 | 45.2 | 45.2 | NA |
| Spirito et al. | Complex PCI | 84.2 | 34.2 | 6.0 | 5.9 | 71.7 |
| | Non-complex PCI | 84.0 | 44.5 | 5.4 | 7.8 | 58.5 |
| STOPDAPT-2 and STOPDAPT-2 ACS | Complex PCI | 69.1 | 20.1 | 100 | 0 | 0 |
| | Non-complex PCI | 67.7 | 21.9 | 100 | 0 | 0 |
| STOPDAPT-3 | Complex PCI | 72.4 | 20.0 | 100 | 0 | 0 |
| | Non-complex PCI | 71.5 | 24.3 | 100 | 0 | 0 |
| Urban et al. | Complex PCI | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA |
| Vogel et al. | Complex PCI | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA |
| WIN-DES | Complex PCI | 67.7 | 100 | NA | NA | NA |
| | Non-complex PCI | 66.7 | 100 | NA | NA | NA |
| Xu et al. | Complex PCI | 58.4 | 22.3 | 100 | 0 | 0 |
| | Non-complex PCI | 57.6 | 24.2 | 100 | 0 | 0 |
| ZON-HR | Complex PCI | 66.1 | 29.0 | NA | NA | NA |
| | Non-complex PCI | 68.0 | 25.0 | NA | NA | NA |

*Age in years.
CKD: chronic kidney disease; NA: not available; PCI: percutaneous coronary intervention.

**Supplementary Table 8.** Predictors of ischaemic events in patients undergoing complex versus non-complex PCI.

| Study | Subgroup | ACS (%) | Smoking (%) | PAD (%) | Prior MI (%) | Prior PCI (%) | Prior CVA (%) | Diabetes† (%) | Intracoronary imaging‡ (%) |
|---|---|---|---|---|---|---|---|---|---|
| ADAPT-DES | Complex PCI | 46.9 | 19.7 | 14.0 | 28.2 | 45.6 | NA | 35.7 | 38.9 |
| | Non-complex PCI | 53.4 | 23.6 | 8.9 | 24.1 | 41.9 | NA | 31.2 | 39.3 |
| Avvedimento et al. | Complex PCI | 25.9 | 9.6 | 25.5 | 23.4 | 73.1 | NA | 36.1 | NA |
| | Non-complex PCI | 22.2 | 9.5 | 23.1 | 25.9 | 65.7 | NA | 36.9 | NA |
| BIOFLOW II-IV-V | Complex PCI | 35.3 | 62.6 | NA | 27.8 | 32.4 | 5.2 | 32.6 | NA |
| | Non-complex PCI | 30.2 | 60.5 | NA | 27.8 | 42.6 | 6.8 | 32.6 | NA |
| BIOSTEMI | Complex PCI | 100 | 40.8 | 3.1 | 3.1 | 3.8 | 1.9 | 13.5 | NA |
| | Non-complex PCI | 100 | 43.1 | 2.3 | 4.3 | 5.5 | 2.8 | 12.0 | NA |
| Chen et al. (CKD) | Complex PCI | 42.2 | 18.8 | 15.2 | 27.2 | 42.1 | 14.5 | 55.6 | NA |
| | Non-complex PCI | 45.3 | 8.4 | 14.2 | 24.4 | 44.1 | 15.4 | 55.2 | NA |
| Chen et al. (no CKD) | Complex PCI | 39.3 | 22.8 | 7.2 | 21.3 | 38.7 | 8.2 | 42.6 | NA |
| | Non-complex PCI | 45.2 | 16.9 | 7.2 | 20.5 | 38.3 | 8.6 | 46.1 | NA |
| CONSTANT | Complex PCI | 69.9 | 35.3 | NA | 1.6 | 6.4 | 11.2 | 32.9 | 44.1 |
| | Non-complex PCI | 68.2 | 34.9 | NA | 2.4 | 9.6 | 9.2 | 31.3 | 42.9 |
| COREA-AMI | Complex PCI | 100 | 38.2 | NA | 4.1 | 6.8 | 8.3 | 33.4 | NA |
| | Non-complex PCI | 100 | 43.7 | NA | 3.0 | 4.7 | 5.7 | 32.9 | NA |
| CREDO-Kyoto | Complex PCI | 8.8 | 27.0 | 9.9 | 21.0 | NA | 13.0 | 45.0 | 49.0 |
| | Non-complex PCI | 12.0 | 27.0 | 10.2 | 11.0 | NA | 11.0 | 38.0 | 47.0 |
| e-Ultimaster | Complex PCI | 47.2 | 24.2 | NA | 26.0 | 28.1 | NA | 32.1 | NA |
| | Non-complex PCI | 58.2 | 27.2 | NA | 21.6 | 25.2 | NA | 27.0 | NA |
| Endo et al. | Complex PCI | 15.0 | 63.0 | NA | NA | NA | NA | 55.0 | 99.4 |
| | Non-complex PCI | 25.0 | 66.0 | NA | NA | NA | NA | 63.0 | 98.4 |
| Fuwai PCI | Complex PCI | 56.4 | 58.5 | 3.0 | 22.6 | 26.5 | 10.8 | 32.9 | 9.3 |
| | Non-complex PCI | 61.9 | 56.4 | 2.4 | 16.8 | 22.3 | 10.5 | 28.2 | 3.3 |
| GF-APT | Complex PCI | 25.7 | 57.5 | NA | 25.7 | 18.8 | 11.5 | 34.3 | NA |
| | Non-complex PCI | 20.8 | 59.9 | NA | 20.8 | 22.0 | 10.9 | 31.9 | NA |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Giustino et al. | Complex PCI | 47.4 | 26.5 | NA | 23.1 | 13.2 | NA | 35.8 | NA |
| | Non-complex PCI | 43.0 | 26.1 | NA | 17.4 | 14.7 | NA | 30.8 | NA |
| GLOBAL LEADERS | Complex PCI | 48.6 | 26.7 | 6.9 | 21.4 | 29.4 | 2.8 | 26.3 | NA |
| | Non-complex PCI | 46.3 | 25.9 | 6.0 | 23.8 | 33.7 | 2.5 | 24.6 | NA |
| Goel et al | Complex PCI | NA | NA | NA | NA | NA | 21.0 | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | 20.1 | NA | NA |
| Hanna et al. | Complex PCI | 23.1 | 66.3 | 27.1 | 19.9 | 35.1 | 12.0 | 35.6 | 34.7 |
| | Non-complex PCI | 23.1 | 65.3 | 28.9 | 23.1 | 39.2 | 14.2 | 34.0 | 16.3 |
| HOST-REDUCE-POLYTECH-ACS | Complex PCI | 100 | 31.9 | 1.3 | 3.8 | 10.6 | 2.0 | 46.2 | 41.0 |
| | Non-complex PCI | 100 | 37.2 | 1.3 | 3.5 | 11.5 | 1.0 | 40.8 | 30.4 |
| ISAR-REACT 5 | Complex PCI | 100 | 33.8 | NA | 15.5 | 22.3 | NA | 23.3 | NA |
| | Non-complex PCI | 100 | 36.5 | NA | 14.9 | 22.1 | NA | 21.1 | NA |
| KAMIR-NIH | Complex PCI | 100 | NA | NA | NA | 9.8 | 6.3 | 37.2 | 27.9 |
| | Non-complex PCI | 100 | NA | NA | NA | 10.1 | 5.0 | 25.2 | 23.1 |
| Kheifets et al. | Complex PCI | 63.2 | 35.6 | NA | 63.2 | NA | NA | 47.4 | NA |
| | Non-complex PCI | 55.5 | 36.2 | NA | 55.5 | NA | NA | 49.4 | NA |
| Mega-COMBO | Complex PCI | 16.8 | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | 25.8 | NA | NA | NA | NA | NA | NA | NA |
| PROMETHEUS | Complex PCI | 100 | 24.1 | 13.6 | 29.9 | 25.9 | 13.3 | 40.5 | NA |
| | Non-complex PCI | 100 | 26.1 | 10.8 | 31.8 | 24.7 | 10.7 | 35.7 | NA |
| MASTER DAPT | Complex PCI | 47.7 | 7.2 | 11.5 | 22.5 | 26.1 | 13.0 | 33.9 | NA |
| | Non-complex PCI | 48.5 | 9.7 | 10.3 | 17.6 | 25.9 | 12.3 | 33.5 | NA |
| PENDULUM | Complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| PTRG-DES | Complex PCI | 26.8 | 28.0 | 12.1 | 7.2 | 13.6 | 8.0 | 38.6 | 38.6 |
| | Non-complex PCI | 29.1 | 28.0 | 12.5 | 8.1 | 13.3 | 6.6 | 33.2 | NA |
| Riku et al. | Complex PCI | NA | NA | NA | 20.2 | 22.6 | NA | 50.0 | NA |
| | Non-complex PCI | NA | NA | NA | 9.4 | 12.4 | NA | 50.1 | NA |
| SMART-DESK | Complex PCI | 56.0 | 27.0 | NA | 7.2 | 12.8 | 5.9 | 34.6 | NA |
| | Non-complex PCI | 55.0 | 26.0 | NA | 8.0 | 11.0 | 5.5 | 34.6 | NA |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sidney-2 | Complex PCI | 61.0 | 27.2 | 6.9 | 19.8 | 29.3 | 2.8 | 33.0 | NA |
| | Non-complex PCI | 59.6 | 26.7 | 6.2 | 18.6 | 30.6 | 3.1 | 31.3 | NA |
| Spirito et al. | Complex PCI | 24.6 | 17.5 | 13.8 | 24.6 | 39.3 | 14.7 | 35.4 | NA |
| | Non-complex PCI | 21.7 | 5.8 | 12.7 | 21.7 | 45.3 | 14.8 | 37.1 | NA |
| STOPDAPT-2 and STOPDAPT-2 ACS | Complex PCI | 65.5 | 27.9 | 4.8 | 12.7 | 17.4 | 6.9 | 42.1 | 99.2 |
| | Non-complex PCI | 69.7 | 29.7 | 3.9 | 9.1 | 17.2 | 5.1 | 32.2 | 97.2 |
| STOPDAPT-3 | Complex PCI | 70.0 | 23.9 | NA | 7.9 | 14.5 | 9.8 | 51.4 | 94.8 |
| | Non-complex PCI | 76.3 | 23.5 | NA | 7.7 | 15.9 | 9.2 | 44.0 | 92.7 |
| Urban et al. | Complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| Vogel et al. | Complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| WIN-DES | Complex PCI | 19.5 | 26.1 | NA | 19.5 | 20.9 | NA | 34.0 | NA |
| | Non-complex PCI | 17.7 | 27.7 | NA | 17.7 | 21.4 | NA | 29.9 | NA |
| Xu et al. | Complex PCI | 19.1 | 56.9 | 2.9 | 19.1 | 21.9 | 10.6 | 31.1 | 6.9 |
| | Non-complex PCI | 17.2 | 56.5 | 2.0 | 17.2 | 27.4 | 9.3 | 27.7 | 2.2 |
| ZON-HR | Complex PCI | 68.0 | NA | 8.0 | 25.0 | NA | 0.3 | 19.0 | NA |
| | Non-complex PCI | 54.0 | NA | 15.0 | 31.0 | NA | 0.3 | 26.0 | NA |

ACS: acute coronary syndrome; CI: confidence interval; CKD: chronic kidney disease; NA: not available; PAD: peripheral artery disease; PCI: percutaneous coronary intervention.
† Predictor of both ischemic and bleeding events.
‡ IVUS or OCT.

**Supplementary Table 9.** Predictors of bleeding events in patients undergoing complex versus non-complex PCI.

| Study | Subgroup | Anemia (%) | Cancer (%) | CKD† (%) | Elderly status* (%) | Liver disease (%) | Prior bleeding (%) | Transfusion‡ (%) | Femoral access (%) |
|---|---|---|---|---|---|---|---|---|---|
| ADAPT-DES | Complex PCI | NA | NA | 19.4 | NA | NA | NA | NA | 96.5 |
| | Non-complex PCI | NA | NA | 15.3 | NA | NA | NA | NA | 95.0 |
| Avvedimento et al. | Complex PCI | NA | NA | 51.8 | NA | NA | NA | NA | 79.2 |
| | Non-complex PCI | NA | NA | 55.7 | NA | NA | NA | NA | 79.2 |
| BIOFLOW II-IV-V | Complex PCI | NA | 10.4 | 8.1 | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | 8.9 | 7.6 | NA | NA | NA | NA | NA |
| BIOSTEMI | Complex PCI | NA | NA | 14.4 | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | 10.3 | NA | NA | NA | NA | NA |
| Chen et al. (CKD) | Complex PCI | 60.5 | NA | 100 | NA | NA | NA | NA | 84.0 |
| | Non-complex PCI | 62.6 | NA | 100 | NA | NA | NA | NA | 87.7 |
| Chen et al. (no CKD) | Complex PCI | 31.1 | NA | 0 | NA | NA | NA | NA | 79.3 |
| | Non-complex PCI | 31.9 | NA | 0 | NA | NA | NA | NA | 81.0 |
| CONSTANT | Complex PCI | NA | NA | 7.6 | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | 2.7 | NA | NA | NA | NA | NA |
| COREA-AMI | Complex PCI | NA | NA | 5.0 | 24.5 | NA | NA | NA | 81.1 |
| | Non-complex PCI | NA | NA | 4.5 | 18.5 | NA | NA | NA | 81.6 |
| CREDO-Kyoto | Complex PCI | 34.0 | 9.1 | 42.0 | 31.0 | 2.5 | NA | NA | 63.0 |
| | Non-complex PCI | 32.0 | 11.0 | 39.0 | 32.0 | 2.8 | NA | NA | 46.0 |
| e-Ultimaster | Complex PCI | NA | NA | NA | NA | NA | NA | NA | 23.3 |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | 15.7 |
| Endo et al. | Complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| Fuwai PCI | Complex PCI | NA | NA | 4.3 | NA | NA | NA | NA | 10.3 |
| | Non-complex PCI | NA | NA | 3.8 | NA | NA | NA | NA | 8.0 |
| GF-APT | Complex PCI | 1.0 | NA | 1.8 | NA | NA | 3.6 | NA | NA |
| | Non-complex PCI | 1.1 | NA | 1.5 | NA | NA | 3.6 | NA | NA |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Giustino et al. | Complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| GLOBAL LEADERS | Complex PCI | NA | NA | 14.1 | NA | NA | NA | NA | 31.3 |
| | Non-complex PCI | NA | NA | 13.5 | NA | NA | NA | NA | 25.3 |
| Goel et al | Complex PCI | 70.9 | 16.2 | 53 | 46.8 | NA | 3.7 | NA | NA |
| | Non-complex PCI | 68.5 | 18.1 | 54.0 | 46.8 | NA | 3.5 | NA | NA |
| Hanna et al. | Complex PCI | 5.3 | 24.4 | 19.9 | 100 | 0.4 | 4.9 | NA | 44.0 |
| | Non-complex PCI | 9.0 | 19.8 | 18.4 | 100 | 0.9 | 6.9 | NA | 31.6 |
| HOST-REDUCE-POLYTECH-ACS | Complex PCI | NA | NA | 5.1 | 0 | NA | 0 | NA | NA |
| | Non-complex PCI | NA | NA | 1.7 | 0 | NA | 0 | NA | NA |
| ISAR-REACT 5 | Complex PCI | NA | NA | NA | NA | NA | NA | NA | 64.3 |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | 62.1 |
| KAMIR-NIH | Complex PCI | NA | NA | NA | NA | NA | NA | NA | 49.6 |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | 44.2 |
| Kheifets et al. | Complex PCI | NA | NA | NA | NA | NA | NA | NA | 55.0 |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | 49.4 |
| Mega-COMBO | Complex PCI | NA | NA | NA | NA | NA | NA | NA | 33 |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | 27.3 |
| PROMETHEUS | Complex PCI | 16.0 | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | 13.1 | NA | NA | NA | NA | NA | NA | NA |
| MASTER DAPT | Complex PCI | NA | 16.4 | 21.2 | 65.3 | 1.3 | 5.5 | NA | 14.2 |
| | Non-complex PCI | NA | 14.9 | 18.4 | 70.1 | 1.3 | 7.5 | NA | 14.3 |
| PENDULUM | Complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| PTRG-DES | Complex PCI | 27.4 | NA | 22.9 | NA | NA | NA | NA | NA |
| | Non-complex PCI | 24.0 | NA | 20.0 | NA | NA | NA | NA | NA |
| Riku et al. | Complex PCI | NA | NA | 3.6 | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | 2.7 | NA | NA | NA | NA | NA |
| SMART-DESK | Complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sidney-2 | Complex PCI | NA | NA | 16.9 | NA | 0.2 | 1.1 | NA | 31.0 |
| | Non-complex PCI | NA | NA | 16.8 | NA | 0.2 | 1.2 | NA | 26.8 |
| Spirito et al. | Complex PCI | 58.1 | NA | 47.5 | 100 | NA | NA | NA | 82.8 |
| | Non-complex PCI | 55.7 | NA | 49.0 | 100 | NA | NA | NA | 84.2 |
| STOPDAPT-2 and STOPDAPT-2 ACS | Complex PCI | 32.0 | 7.8 | 33.3 | 32.4 | NA | 1.2 | NA | 12.1 |
| | Non-complex PCI | 24.6 | 7.5 | 32.0 | 29.8 | NA | 1.1 | NA | 12.1 |
| STOPDAPT-3 | Complex PCI | NA | 10.9 | 13.7 | 48.0 | NA | NA | NA | 23.3 |
| | Non-complex PCI | NA | 10.1 | 10.8 | 45.2 | NA | NA | NA | 16.6 |
| Urban et al. | Complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| Vogel et al. | Complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| WIN-DES | Complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| Xu et al. | Complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA | NA |
| ZON-HR | Complex PCI | 6.0 | NA | 47.5 | NA | NA | 0.3 | NA | NA |
| | Non-complex PCI | 9.0 | NA | 49.0 | NA | NA | 0.6 | NA | NA |

CKD: chronic kidney disease; NA: not available; PCI: percutaneous coronary intervention.
* Age ≥ 75 years.
† Predictor of both ischemic and bleeding events.
‡ Prior or in-hospital.

**Supplementary Table 10.** Antithrombotic therapy in patients undergoing complex versus non-complex PCI.

| Study | Subgroup | Clopidogrel (%) | Potent oral $P2Y_{12}$ inhibitors (%) | Prasugrel (%) | Ticagrelor (%) | GPIIb/IIIa inhibitors (%) | Anticoagulants (%) | DAPT >12 months (%) |
|---|---|---|---|---|---|---|---|---|
| ADAPT-DES | Complex PCI | 80.7 | 0 | 0 | 0 | NA | 6.9 | 44.0 |
| | Non-complex PCI | 80.4 | 0 | 0 | 0 | NA | 5.0 | 44.0 |
| Avvedimento et al. | Complex PCI | NA | NA | NA | NA | NA | 2.9 | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | 3.1 | NA |
| BIOFLOW II-IV-V | Complex PCI | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA |
| BIOSTEMI | Complex PCI | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA |
| Chen et al. (CKD) | Complex PCI | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA |
| Chen et al. (no CKD) | Complex PCI | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA |
| CONSTANT | Complex PCI | 88.8 | NA | NA | NA | NA | NA | 85.7 |
| | Non-complex PCI | 86.8 | NA | NA | NA | NA | NA | 80.7 |
| COREA-AMI | Complex PCI | 87.2 | 11.9 | 6.3 | 5.6 | 31.5 | 2.2 | 54.8 |
| | Non-complex PCI | 84.9 | 14.8 | 9.0 | 5.8 | 30.9 | 2.2 | 56.2 |
| CREDO-Kyoto | Complex PCI | 10.0 | NA | NA | NA | NA | 7.6 | NA |
| | Non-complex PCI | 9.6 | NA | NA | NA | NA | 7.0 | NA |
| e-Ultimaster | Complex PCI | NA | NA | NA | NA | NA | NA | 29.7 |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | 34.2 |
| Endo et al. | Complex PCI | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA |
| Fuwai PCI | Complex PCI | 100 | 0 | 0 | 0 | 21.9 | NA | NA |
| | Non-complex PCI | 100 | 0 | 0 | 0 | 13.0 | NA | NA |
| GF-APT | Complex PCI | 86.0 | 17.7 | 0 | 17.7 | NA | 0 | NA |
| | Non-complex PCI | 86.0 | 10.4 | 0 | 13.4 | NA | 0 | NA |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Giustino et al. | Complex PCI | 100 | 0 | 0 | 0 | NA | NA | NA |
| | Non-complex PCI | 100 | 0 | 0 | 0 | NA | NA | NA |
| GLOBAL LEADERS | Complex PCI | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA |
| Goel et al | Complex PCI | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA |
| Hanna et al. | Complex PCI | NA | NA | NA | NA | 3.6 | 24.4 | NA |
| | Non-complex PCI | NA | NA | NA | NA | 1.7 | 24.7 | NA |
| HOST-REDUCE-POLYTECH-ACS | Complex PCI | 0 | 100 | 100 | 0 | NA | NA | NA |
| | Non-complex PCI | 0 | 100 | 100 | 0 | NA | NA | NA |
| ISAR-REACT 5 | Complex PCI | 0 | 100 | 51.3 | 48.7 | 11.9 | NA | NA |
| | Non-complex PCI | 0 | 100 | 49.7 | 50.3 | 12.7 | NA | NA |
| KAMIR-NIH | Complex PCI | 69.7 | 29.3 | 9.0 | 19.1 | 9.5 | 2.2 | NA |
| | Non-complex PCI | 71.8 | 27.1 | 9.0 | 16.2 | 7.5 | 2.1 | NA |
| Kheifets et al. | Complex PCI | NA | NA | NA | NA | NA | 10.4 | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | 8.5 | NA |
| Mega-COMBO | Complex PCI | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA |
| PROMETHEUS | Complex PCI | 79.3 | 20.7 | 20.7 | 0 | 24.0 | NA | NA |
| | Non-complex PCI | 79.9 | 20.1 | 20.1 | 0 | 21.9 | NA | NA |
| MASTER DAPT | Complex PCI | NA | NA | NA | NA | NA | 34.7 | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | 37.0 | NA |
| PENDULUM | Complex PCI | NA | NA | NA | 0 | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | 0 | NA | NA | NA |
| PTRG-DES | Complex PCI | 100 | 0 | 0 | 0 | NA | 0 | NA |
| | Non-complex PCI | 100 | 0 | 0 | 0 | NA | 0 | NA |
| Riku et al. | Complex PCI | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA |
| SMART-DESK | Complex PCI | 100 | 0 | 0 | 0 | NA | NA | NA |
| | Non-complex PCI | 100 | 0 | 0 | 0 | NA | NA | NA |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Sidney-2 | Complex PCI | 21.1 | 78.9 | 0.9 | 78.0 | 5.8 | 0 | NA |
| | Non-complex PCI | 32.3 | 67.7 | 1.0 | 66.7 | 4.8 | 0 | NA |
| Spirito et al. | Complex PCI | 88.6 | 10.2 | 1.2 | 9.0 | NA | 18.5 | NA |
| | Non-complex PCI | 90.1 | 8.2 | 1.3 | 6.9 | NA | 16.1 | NA |
| STOPDAPT-2 and STOPDAPT-2 ACS | Complex PCI | 56.9 | 42.9 | 42.9 | 0 | NA | 0.4 | NA |
| | Non-complex PCI | 57.3 | 42.6 | 42.6 | 0 | NA | 0.5 | NA |
| STOPDAPT-3 | Complex PCI | NA | 100 | 100 | 0 | NA | 13.1 | 0 |
| | Non-complex PCI | NA | 100 | 100 | 0 | NA | 12.5 | 0 |
| Urban et al. | Complex PCI | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA |
| Vogel et al. | Complex PCI | NA | NA | NA | NA | NA | NA | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | NA | NA |
| WIN-DES | Complex PCI | NA | NA | NA | NA | NA | 0 | NA |
| | Non-complex PCI | NA | NA | NA | NA | NA | 0 | NA |
| Xu et al. | Complex PCI | 98.6 | 1.4 | NA | 1.4 | 15.1 | NA | 100 |
| | Non-complex PCI | 98.4 | 1.6 | NA | 1.6 | 8.8 | NA | 100 |
| ZON-HR | Complex PCI | 28.2 | 67.0 | NA | NA | NA | NA | 74.0 |
| | Non-complex PCI | 48.0 | 52.0 | NA | NA | NA | NA | 83.0 |

CI: confidence interval; GP: glycoprotein; NA: not available; PCI: percutaneous coronary intervention.

**Supplementary Table 11.** Distribution of complex PCI criteria across included studies.

| Study | ≥ 3 stents implanted | ≥ 3 vessels treated | ≥ 3 lesions treated | Bifurcation with ≥ 2 stents implanted | Total stent length > 60 mm implanted | Chronic total occlusion PCI | Saphenous vein graft PCI | Left main PCI | In-stent restenosis | Use of rotational atherectomy |
|---|---|---|---|---|---|---|---|---|---|---|
| ADAPT-DES | 1,528 (17.8) | NA | NA | NA | NA | NA | 429 (5) | 319 (3.7) | NA | 180 (2.1) |
| Avvedimento et al. | 342 (22.1) | 83 (5.4) | 181 (11.7) | 142 (9.2) | 267 (17.2) | 12 (0.8) | NA | NA | NA | NA |
| BIOFLOW II-IV-V | 124 (5.2) | NA | 27 (1.1) | NA | 90 (3.8) | NA | NA | NA | NA | NA |
| BIOSTEMI | 1,229 (72.2) | 40 (2.4) | 340 (20.0) | 529 (31.1) | 728 (42.8) | 49 (2.9) | NA | NA | NA | NA |
| Chen et al. | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| CONSTANT | NA | 27 (2.9) | 47 (5.0) | 18 (2.0) | 125 (13.5) | 74 (8.0) | NA | 59 (6.4) | NA | NA |
| COREA-AMI | 1,219 (11.8) | NA | 1,053 (10.2) | 145 (1.4) | 351 (3.4) | 454 (4.4) | NA | 330 (3.2) | 124 (1.2) | NA |
| CREDO-Kyoto | 1,876 (23.8) | 439 (5.6) | 850 (10.8) | 460 (5.8) | 1,557 (20.0) | 1,166 (14.8) | NA | NA | NA | NA |
| e-Ultimaster | 4,575 (12.3) | NA | 1,934 (5.2) | 1,004 (2.7) | 3,273 (8.8) | 1,823 (4.9) | NA | NA | NA | NA |
| Endo et al. | 66 (6.2) | 55 (5.2) | 82 (7.7) | 41 (3.9) | 93 (8.8) | 119 (11.2) | NA | 92 (8.7) | NA | 89 (8.4) |
| Fuwai PCI | 2,389 (23.5) | 224 (2.2) | 732 (7.2) | 426 (4.2) | 2,054 (20.2) | 833 (8.2) | NA | 264 (2.6) | 447 (4.4) | 50 (0.5) |
| GF-APT | 2,953 (19.1) | 77 (0.5) | 556 (3.6) | 1,067 (6.9) | 3,571 (23.1) | 2,164 (14.0) | 77 (0.5) | 757 (4.9) | NA | NA |
| Giustino et al. | 804 (8.4) | 124 (1.3) | 268 (2.8) | 660 (6.9) | 612 (6.4) | 192 (1.9) | NA | NA | NA | NA |
| GLOBAL LEADERS | 2,768 (17.9) | 1,301 (8.4) | NA | 473 (3.1) | 2,077 (13.4) | NA | NA | NA | NA | NA |
| Goel et al. | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Hanna et al. | NA | NA | NA | 59 (11.5) | NA | 38 (7.4) | 35 (6.8) | 18 (3.5) | NA | 42 (8.2) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| HOST-REDUCE-POLYTECH-ACS | 324 (14.3) | NA | 172 (7.5) | 128 (5.6) | 451 (19.8) | NA | NA | 9 (4.0) | NA | NA |
| ISAR-REACT 5 | 806 (35.4) | NA | 1,154 (50.8) | NA | 219 (9.6) | NA | NA | NA | NA | NA |
| KAMIR-NIH | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Kheifets et al. | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| MASTER DAPT | 860 (19.0) | 190 (4.0) | 439 (10.0) | 184 (4.0) | 801 (17.0) | 214 (5.0) | NA | 169 (4.0) | NA | NA |
| Mega-COMBO | 458 (18.9) | NA | 179 (7.4) | 1,074 (44.3) | 451 (18.6) | NA | 124 (5.1) | 179 (7.4) | NA | NA |
| PENDULUM | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| PROMETHEUS | 2,036 (10.2) | 291 (1.4) | 1,515 (7.6) | 2,122 (10.6) | 1,654 (8.3) | NA | NA | 667 (3.3) | NA | NA |
| PTRG-DES | 1,277 (10.9) | 435 (3.7) | 1,122 (9.6) | 572 (4.9) | 821 (7.0) | NA | NA | 572 (4.9) | NA | NA |
| Riku et al. | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Sidney-2 | 9,268 (40.4) | 1,927 (8.4) | 6,561 (28.6) | 3,303 (14.4) | 14,659 (63.9) | 2,546 (11.1) | NA | NA | NA | NA |
| SMART-DESK | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Spirito et al. | 202 (7.6) | 335 (12.6) | 199 (7.5) | 252 (9.5) | 547 (20.6) | 133 (5.0) | 138 (5.2) | 284 (10.7) | NA | 773 (29.1) |
| STOPDAPT-2 and STOPDAPT-2 ACS | 529 (8.8) | 186 (3.1) | 302 (5.0) | 34 (0.6) | 756 (12.6) | 237 (4.0) | NA | NA | NA | NA |
| STOPDAPT-3 | 530 (8.9) | 143 (2.4) | 310 (5.2) | 71 (1.2) | 966 (16.2) | 232 (3.9) | NA | NA | NA | NA |
| Urban et al. | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Vogel et al. | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| WIN-DES | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Xu et al. | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| ZON-HR | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |

NA: not available; PCI: percutaneous coronary intervention.

**Supplementary Table 12.** Risk-of-bias assessment of the included studies according to the QUIPS tool.

| Study | Year | Study Participation | Study Attrition | Prognostic Factor Measurement | Outcome Measurement | Adjustment for Other Prognostic Factors | Statistical Analysis and Reporting |
|---|---|---|---|---|---|---|---|
| **ADAPT-DES** | 2018 | Low ROB | Low ROB | Moderate ROB | Low ROB | Low ROB | Low ROB |
| **Avvedimento et al.** | 2024 | Low ROB | Low ROB | Moderate ROB | Moderate ROB | Moderate ROB | Moderate ROB |
| **BIOFLOW II-IV-V** | 2022 | Low ROB | Low ROB | Moderate ROB | Low ROB | High ROB | Moderate ROB |
| **BIOSTEMI** | 2017 | Low ROB | Low ROB | Moderate ROB | Low ROB | High ROB | Moderate ROB |
| **Chen et al.** | 2023 | Moderate ROB | Low ROB | Moderate ROB | High ROB | Low ROB | Moderate ROB |
| **CONSTANT** | 2018 | Low ROB | Low ROB | Moderate ROB | Moderate ROB | Moderate ROB | Moderate ROB |
| **COREA-AMI** | 2021 | Low ROB | Moderate ROB | Moderate ROB | Low ROB | Low ROB | Low ROB |
| **CREDO-Kyoto** | 2020 | Low ROB | Low ROB | Moderate ROB | Low ROB | Low ROB | Low ROB |
| **e-Ultimaster** | 2020 | Low ROB | Low ROB | Moderate ROB | Low ROB | Moderate ROB | Low ROB |
| **Endo et al.** | 2020 | High ROB | Moderate ROB | Moderate ROB | Moderate ROB | Low ROB | Moderate ROB |
| **Fuwai PCI** | 2020 | Moderate ROB | Moderate ROB | Moderate ROB | Low ROB | Low ROB | Low ROB |
| **GF-APT** | 2021 | Moderate ROB | Low ROB | Moderate ROB | Low ROB | Low ROB | Low ROB |
| **Giustino et al.** | 2016 | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |
| **GLOBAL LEADERS** | 2024 | Low ROB | Low ROB | Low ROB | Moderate ROB | High ROB | Low ROB |
| **Goel et al.** | 2022 | Moderate ROB | Moderate ROB | High ROB | High ROB | High ROB | Moderate ROB |
| **Hanna et al.** | 2023 | Low ROB | Low ROB | Moderate ROB | Moderate ROB | Low ROB | Moderate ROB |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **HOST-REDUCE-POLYTECH-ACS** | 2022 | Moderate ROB | Low ROB | Low ROB | Moderate ROB | Moderate ROB | Moderate ROB |
| **ISAR-REACT 5** | 2021 | Low ROB | Low ROB | Moderate ROB | Low ROB | Moderate ROB | Low ROB |
| **KAMIR-NIH** | 2023 | Low ROB | Low ROB | Moderate ROB | Low ROB | Low ROB | Moderate ROB |
| **Kheifets et al.** | 2022 | Moderate ROB | High ROB | Moderate ROB | Low ROB | Low ROB | Low ROB |
| **MASTER DAPT** | 2023 | Low ROB | Low ROB | Low ROB | Moderate ROB | High ROB | Low ROB |
| **Mega-COMBO** | 2023 | Low ROB | High ROB | Moderate ROB | Moderate ROB | Low ROB | Low ROB |
| **PENDULUM** | 2023 | Moderate ROB | Low ROB | Moderate ROB | High ROB | High ROB | Moderate ROB |
| **PROMETHEUS** | 2018 | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Moderate ROB |
| **PTRG-DES** | 2024 | Low ROB | Low ROB | Moderate ROB | Low ROB | Moderate ROB | Low ROB |
| **Riku et al.** | 2022 | High ROB | Moderate ROB | Moderate ROB | Moderate ROB | Low ROB | High ROB |
| **Sidney-2** | 2021 | Low ROB | Low ROB | Low ROB | Low ROB | High ROB | Low ROB |
| **SMART-DESK** | 2019 | Low ROB | Low ROB | Moderate ROB | Low ROB | Low ROB | Low ROB |
| **Spirito et al.** | 2023 | Low ROB | Moderate ROB | Moderate ROB | Low ROB | Low ROB | Low ROB |
| **STOPDAPT-2 and STOPDAPT-2 ACS** | 2023 | Low ROB | Low ROB | Moderate ROB | Low ROB | High ROB | Moderate ROB |
| **STOPDAPT-3** | 2023 | Low ROB | Low ROB | Low ROB | Low ROB | High ROB | Low ROB |
| **Urban et al.** | 2021 | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |
| **Vogel et al.** | 2018 | Low ROB | Moderate ROB | Moderate ROB | High ROB | High ROB | High ROB |
| **WIN-DES** | 2016 | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB | Low ROB |
| **Xu et al.** | 2023 | Moderate ROB | Low ROB | Moderate ROB | Low ROB | Low ROB | Moderate ROB |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **ZON-HR** | 2024 | Moderate ROB | Moderate ROB | Moderate ROB | Low ROB | High ROB | High ROB |

ROB: risk of bias.

**Supplementary Table 13.** Summary statistics for adjusted and unadjusted Bayesian analyses.

| Outcomes | Studies | Patients (N) | Posterior Probability | Prediction interval | τ (95% CrI) | $I^2$ (95% CI) |
|---|---|---|---|---|---|---|
| **Adjusted analysis** | | | | | | |
| Myocardial infarction | 19 | 150,213 | 99.9% | 1.01 to 2.89 | 0.24 (0.13 to 0.37) | 70% (50% to 81%) |
| Major bleeding | 13 | 101,096 | 99.9% | 0.99 to 1.55 | 0.08 (0.01 to 0.18) | 24% (0% to 59%) |
| All-cause death | 21 | 150,744 | 99.9% | 0.92 to 1.61 | 0.12 (0.02 to 0.29) | 43% (6% to 66%) |
| Stent thrombosis | 16 | 144,138 | 99.9% | 1.12 to 2.68 | 0.10 (0.01 to 0.35) | 24% (0% to 58%) |
| CV death | 15 | 127,100 | 99.9% | 0.94 to 1.81 | 0.12 (0.01 to 0.25) | 24% (0% to 59%) |
| TVR or TLR | 14 | 136,825 | 99.9% | 0.85 to 4.61 | 0.39 (0.23 to 0.59) | 92% (88% to 94%) |
| Stroke | 10 | 69,0911 | 98.4% | 0.85 to 1.72 | 0.08 (0.01 to 0.31) | 30% (0% to 67%) |
| **Unadjusted analysis** | | | | | | |
| Myocardial infarction | 20 | 148,456 | 99.9% | 1.09 to 2.75 | 0.21 (0.08 to 0.34) | 56% (28% to 73%) |
| Major bleeding | 16 | 133,610 | 99.9% | 0.87 to 1.79 | 0.15 (0.02 to 0.28) | 51% (15% to 72%) |
| All-cause death | 23 | 172,353 | 96.6% | 1.02 to 1.84 | 0.13 (0.05 to 0.21) | 46% (12% to 66%) |
| Stent thrombosis | 16 | 120,480 | 99.9% | 1.17 to 2.83 | 0.15 (0.01 to 0.35) | 15% (0% to 52%) |
| CV death | 17 | 104,914 | 99.9% | 0.99 to 1.91 | 0.12 (0.01 to 0.25) | 30% (0% to 61%) |
| TVR or TLR | 16 | 91,288 | 99.6% | 1.24 to 3.03 | 0.20 (0.10 to 0.32) | 79% (7% to 88%) |
| Stroke | 13 | 113,213 | 96.7% | 0.80 to 1.64 | 0.12 (0.01 to 0.29) | 18% (0% to 56%) |

CrI: credible interval; CI: confidence interval; CV: cardiovascular; MI: myocardial infarction; TVR: target vessel revascularization; TLR: target lesion revascularization.

**Supplementary Table 14.** Meta-regression analyses of the primary outcomes by the baseline characteristics of patients undergoing complex versus non-complex PCI.

| Covariate | Outcomes | Number of studies | β coefficient | 95% CI | p value |
|---|---|---|---|---|---|
| Age* (mean) | Myocardial infarction | 20 | 0.006 | -0.015 to 0.028 | 0.56 |
| | Major bleeding | 14 | 0.002 | -0.010 to 0.013 | 0.80 |
| Female patients (%) | Myocardial infarction | 19 | 0.004 | -0.002 to 0.009 | 0.23 |
| | Major bleeding | 14 | 0.004 | -0.009 to 0.017 | 0.55 |
| Asian patients (%) | Myocardial infarction | 14 | -0.003 | -0.007 to 0.001 | 0.12 |
| | Major bleeding | 9 | -0.002 | -0.004 to -0.001 | **0.03** |
| Black patients (%) | Myocardial infarction | 15 | 0.025 | -0.013 to 0.065 | 0.19 |
| | Major bleeding | 10 | 0.019 | 0.008 to 0.037 | **0.04** |
| Caucasian patients (%) | Myocardial infarction | 15 | 0.004 | -0.002 to 0.009 | 0.16 |
| | Major bleeding | 11 | 0.004 | 0.0006 to 0.007 | **0.02** |

*Age in years.
CI: confidence interval.
Data of the overall population were used for adjustment.

**Supplementary Table 15.** Meta-regression analyses of the primary outcomes for predictors of ischaemic events in patients undergoing complex versus non-complex PCI.

| Covariate | Outcomes | Number of studies | β coefficient | 95% CI | p value |
|---|---|---|---|---|---|
| ACS (%) | Myocardial infarction | 20 | -0.003 | -0.006 to -0.002 | **0.04** |
| | Major bleeding | 14 | -0.001 | -0.003 to 0.001 | 0.37 |
| Smoking (%) | Myocardial infarction | 19 | -0.001 | -0.010 to 0.008 | 0.82 |
| | Major bleeding | 14 | -0.003 | -0.010 to 0.003 | 0.31 |
| PAD (%) | Myocardial infarction | 12 | -0.015 | -0.040 to 0.008 | 0.19 |
| | Major bleeding | 10 | -0.001 | -0.023 to 0.021 | 0.92 |
| Prior MI (%) | Myocardial infarction | 19 | 0.014 | -0.003 to 0.030 | 0.11 |
| | Major bleeding | 14 | 0.008 | 0.005 to 0.017 | **0.04** |
| Prior PCI (%) | Myocardial infarction | 19 | 0.003 | -0.007 to 0.012 | 0.60 |
| | Major bleeding | 14 | -0.001 | -0.007 to 0.006 | 0.88 |
| Prior CVA (%) | Myocardial infarction | 13 | 0.027 | -0.019 to 0.074 | 0.25 |
| | Major bleeding | 9 | 0.033 | 0.007 to 0.058 | **0.01** |
| Diabetes† (%) | Myocardial infarction | 19 | 0.004 | -0.001 to 0.020 | 0.65 |
| | Major bleeding | 14 | 0.005 | -0.004 to 0.014 | 0.28 |
| Intracoronary imaging‡ (%) | Myocardial infarction | 8 | 0.003 | -0.004 to 0.001 | 0.36 |
| | Major bleeding | 4 | -0.005 | -0.011 to 0.001 | 0.09 |

ACS: acute coronary syndrome; CI: confidence interval; CKD: chronic kidney disease; CVA: cerebrovascular accident; PAD: peripheral artery disease; PCI: percutaneous coronary intervention.
† Predictor of both ischemic and bleeding events.
‡ IVUS or OCT.
Data of the overall population were used for adjustment.

**Supplementary Table 16.** Meta-regression analyses of the primary outcomes for predictors of bleeding events in patients undergoing complex versus non-complex PCI.

| Covariate | Outcomes | Number of studies | β coefficient | 95% CI | p value |
|---|---|---|---|---|---|
| Anemia (%) | Myocardial infarction | 8 | 0.002 | -0.009 to 0.012 | 0.74 |
| | Major bleeding | 8 | 0.005 | -0.001 to 0.010 | 0.11 |
| Cancer (%) | Myocardial infarction | 0 | - | - | - |
| | Major bleeding | 3 | 0.057 | -0.067 to 0.182 | 0.37 |
| CKD† (%) | Myocardial infarction | 14 | -0.001 | -0.006 to 0.003 | 0.48 |
| | Major bleeding | 12 | 0.001 | -0.001 to 0.004 | 0.21 |
| Elderly status* (%) | Myocardial infarction | 6 | 0.008 | -0.003 to 0.017 | 0.06 |
| | Major bleeding | 7 | 0.004 | 0.001 to 0.008 | **0.03** |
| Liver disease (%) | Myocardial infarction | 0 | - | - | - |
| | Major bleeding | 3 | 0.032 | -0.089 to 0.153 | 0.61 |
| Prior bleeding (%) | Myocardial infarction | 3 | 0.005 | -0.197 to 0.208 | 0.95 |
| | Major bleeding | 4 | 0.146 | -0.023 to 0.316 | 0.09 |
| Transfusion‡ (%) | Myocardial infarction | 1 | - | - | - |
| | Major bleeding | 0 | - | - | - |
| Femoral access (%) | Myocardial infarction | 12 | -0.013 | -0.006 to 0.003 | 0.57 |
| | Major bleeding | 9 | 0.003 | -0.001 to 0.007 | 0.15 |

CI: confidence interval; CKD: chronic kidney disease.
* Age ≥ 75 years.
† Predictor of both ischemic and bleeding events.
‡ Prior or in-hospital.
Data of the overall population were used for adjustment.

**Supplementary Table 17.** Meta-regression analyses of antithrombotic therapy and the primary outcomes in patients undergoing complex versus non-complex PCI.

| Covariate | Outcomes | Number of studies | β coefficient | 95% CI | p value |
|---|---|---|---|---|---|
| Clopidogrel (%) | Myocardial infarction | 14 | -0.001 | -0.005 to 0.003 | 0.59 |
| | Major bleeding | 10 | 0.001 | -0.002 to 0.002 | 0.77 |
| Potent oral $P2Y_{12}$ inhibitors (%) | Myocardial infarction | 13 | 0.001 | -0.005 to 0.005 | 0.97 |
| | Major bleeding | 10 | -0.001 | -0.004 to 0.002 | 0.59 |
| Prasugrel (%) | Myocardial infarction | 11 | 0.001 | -0.006 to 0.009 | 0.73 |
| | Major bleeding | 8 | -0.003 | -0.007 to 0.002 | 0.31 |
| Ticagrelor (%) | Myocardial infarction | 12 | -0.002 | -0.010 to 0.010 | 0.97 |
| | Major bleeding | 8 | 0.002 | -0.004 to 0.008 | 0.59 |
| GP IIb/IIIa inhibitors (%) | Myocardial infarction | 6 | 0.004 | -0.014 to 0.021 | 0.69 |
| | Major bleeding | 0 | - | - | - |
| Anticoagulants (%) | Myocardial infarction | 10 | 0.022 | -0.022 to 0.066 | 0.33 |
| | Major bleeding | 9 | 0.005 | -0.002 to 0.012 | 0.16 |
| DAPT >12 months (%) | Myocardial infarction | 6 | -0.003 | -0.013 to 0.007 | 0.58 |
| | Major bleeding | 4 | -0.010 | -0.029 to 0.009 | 0.29 |

CI: confidence interval; DAPT: dual antiplatelet therapy; GP: glycoprotein.
Data of the overall population were used for adjustment.

**Supplementary Table 18.** Meta-regression analyses of the primary outcomes and complex PCI criteria distribution across included studies.

| Covariate | Outcomes | Number of studies | β coefficient | 95% CI | p value |
|---|---|---|---|---|---|
| ≥ 3 stents implanted | Myocardial infarction | 13 | 0.006 | -0.008 to 0.022 | 0.40 |
| | Major bleeding | 11 | -0.002 | -0.007 to 0.012 | 0.61 |
| ≥ 3 vessels treated | Myocardial infarction | 9 | 0.001 | -0.053 to 0.060 | 0.97 |
| | Major bleeding | 7 | -0.030 | -0.063 to 0.002 | 0.07 |
| ≥ 3 lesions treated | Myocardial infarction | 13 | -0.003 | -0.014 to 0.007 | 0.53 |
| | Major bleeding | 10 | 0.001 | -0.006 to 0.008 | 0.79 |
| Bifurcation with ≥ 2 stents implanted | Myocardial infarction | 12 | 0.002 | -0.014 to 0.018 | 0.78 |
| | Major bleeding | 9 | -0.019 | -0.047 to 0.009 | 0.18 |
| > 60 mm stent implanted | Myocardial infarction | 13 | 0.020 | 0.006 to 0.035 | **0.01** |
| | Major bleeding | 10 | 0.001 | -0.011 to 0.011 | 0.99 |
| Chronic total occlusion PCI | Myocardial infarction | 8 | 0.007 | -0.017 to 0.031 | 0.57 |
| | Major bleeding | 7 | 0.011 | -0.008 to 0.031 | 0.24 |
| Saphenous venous graft PCI | Myocardial infarction | 4 | -0.048 | -0.127 to 0.030 | 0.22 |
| | Major bleeding | 3 | -0.032 | -0.127 to 0.064 | 0.51 |
| Left main PCI | Myocardial infarction | 10 | 0.032 | -0.042 to 0.105 | 0.39 |
| | Major bleeding | 6 | -0.027 | -0.071 to 0.016 | 0.22 |
| In-stent restenosis | Myocardial infarction | 0 | - | - | - |
| | Major bleeding | 1 | - | - | - |
| Use of atherectomy | Myocardial infarction | 3 | 0.005 | -0.014 to 0.024 | 0.61 |
| | Major bleeding | 0 | - | - | - |

CI: confidence interval; PCI: percutaneous coronary intervention.
Data of the complex PCI group were used for adjustment.

**Supplementary Table 19.** Meta-regression analyses of the primary outcomes and study-level covariates.

| Covariate | Outcomes | Number of studies | β coefficient | 95% CI | p value |
|---|---|---|---|---|---|
| Year of study publication | Myocardial infarction | 20 | -0.011 | -0.040 to 0.019 | 0.48 |
| | Major bleeding | 14 | -0.004 | -0.020 to 0.011 | 0.60 |

CI: confidence interval.
Data of the overall population were used for adjustment

**Supplementary Table 20.** Subgroup analyses.

| Subgroup | Outcomes | Number of studies | Number of participants | HR | 95% CrI |
|---|---|---|---|---|---|
| Observational studies | Myocardial infarction | 14 | 118,750 | 1.61 | 1.37 to 1.89 |
| | Major bleeding | 8 | 73,233 | 1.25 | 1.11 to 1.40 |
| | All-cause death | 17 | 128,872 | 1.20 | 1.10 to 1.33 |
| | Stent thrombosis | 12 | 108,592 | 1.75 | 1.43 to 2.19 |
| | CV death | 11 | 112,672 | 1.27 | 1.11 to 1.48 |
| | TVR or TLR | 14 | 106,548 | 1.99 | 1.55 to 2.60 |
| | Stroke | 8 | 46,554 | 1.16 | 0.96 to 1.37 |
| Randomized studies | Myocardial infarction | 5 | 31,463 | 2.12 | 1.60 to 2.74 |
| | Major bleeding | 5 | 27,863 | 1.22 | 0.94 to 1.59 |
| | All-cause death | 5 | 21,866 | 1.27 | 0.95 to 1.70 |
| | Stent thrombosis | 3 | 18,509 | 1.41 | 1.24 to 2.21 |
| | CV death | 4 | 31,463 | 1.62 | 1.06 to 2.53 |
| | TVR or TLR | 3 | 18,509 | 1.76 | 1.12 to 3.24 |
| | Stroke | 2 | 9,373 | 1.90 | 0.93 to 3.83 |
| Studies including only patients with acute coronary syndrome | Myocardial infarction | 7 | 50,694 | 1.41 | 1.20 to 1.71 |
| | Major bleeding | 5 | 26,407 | 1.22 | 0.94 to 1.59 |
| | All-cause death | 7 | 50,694 | 1.18 | 1.04 to 1.36 |
| | Stent thrombosis | 6 | 46,321 | 1.66 | 1.24 to 2.22 |
| | CV death | 6 | 30,780 | 1.24 | 1.02 to 1.58 |
| | TVR or TLR | 3 | 18,597 | 1.62 | 0.97 to 3.24 |
| | Stroke | 3 | 19,703 | 1.40 | 0.85 to 2.64 |
| Studies including only patients with chronic coronary syndrome | Myocardial infarction | 4 | 29,542 | 1.87 | 1.42 to 2.51 |
| | Major bleeding | 4 | 29,029 | 1.18 | 0.81 to 1.62 |
| | All-cause death | 4 | 14,083 | 1.06 | 0.79 to 1.55 |
| | Stent thrombosis | 3 | 13,570 | 2.67 | 1.19 to 7.33 |
| | CV death | 4 | 29,029 | 1.33 | 0.85 to 2.09 |
| | TVR or TLR | 4 | 23,393 | 2.11 | 0.87 to 4.49 |

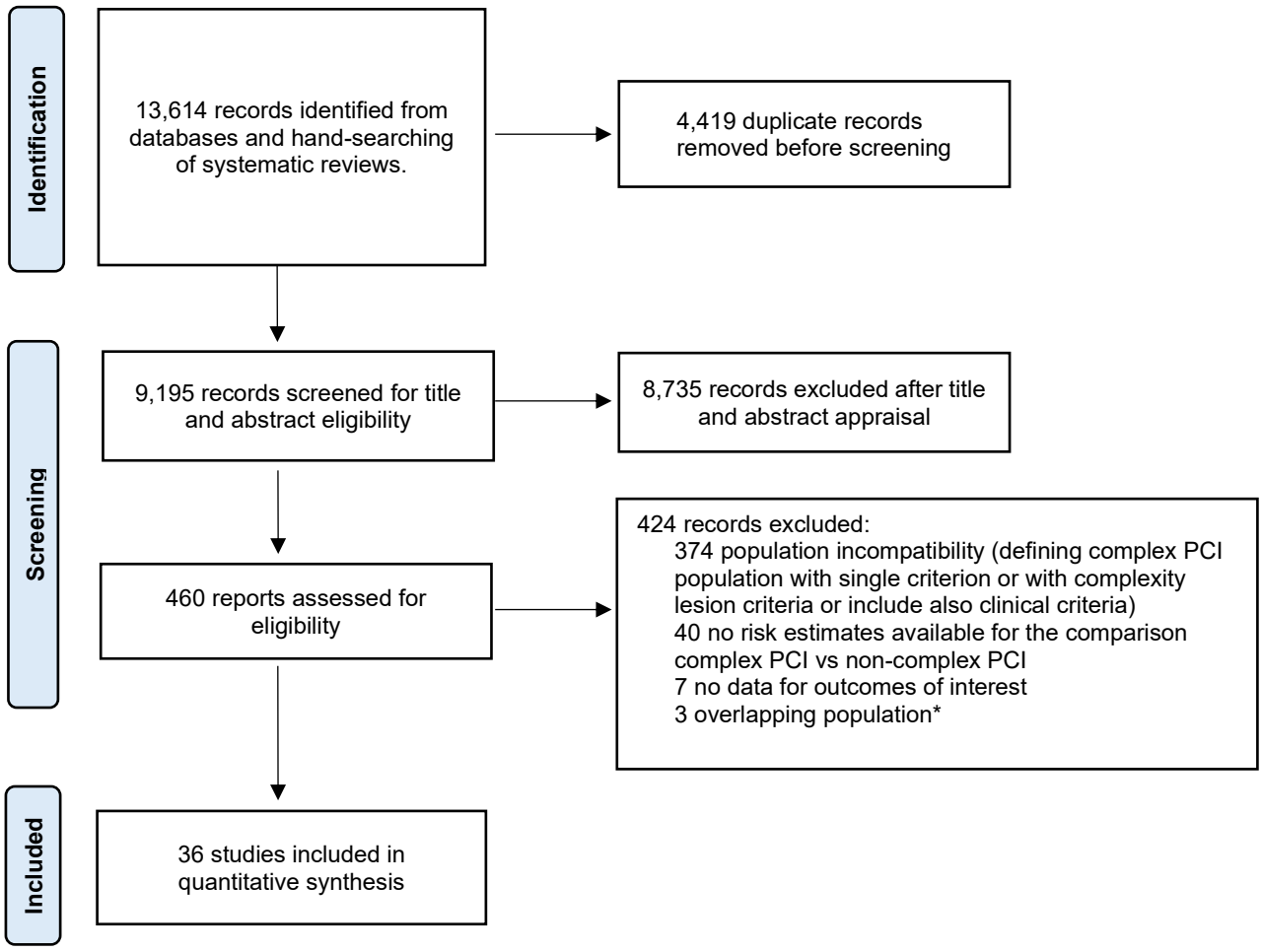
| | | | | | |
|---|---|---|---|---|---|
| | Stroke | 2 | 9,421 | 1.40 | 0.85 to 2.64 |

CrI: credible interval. CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction; TVR: target vessel revascularization; TLR: target lesion revascularization.

**Supplementary Table 21.** GRADE table for systematic reviews of prognostic studies included in the primary adjusted analysis.

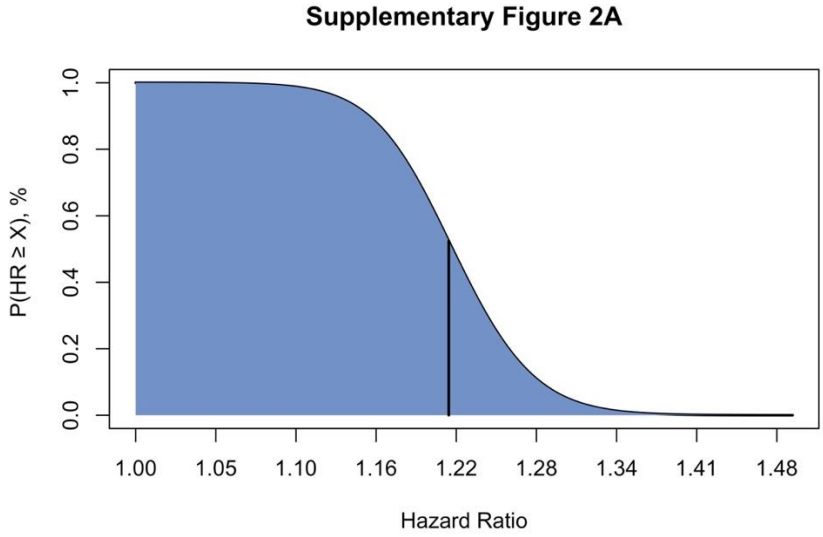
| Outcome | Number of Studies | Risk of Bias | Inconsistency | Imprecision | Publication Bias | Moderate/large effect size | Dose effect | Overall Quality |
|---|---|---|---|---|---|---|---|---|
| Myocardial infarction | 21 | ✓ | ✓ | ✓ | ✓ | ✓ | Unclear | HIGH |
| Major bleeding | 15 | ✓ | ✓ | ✓ | ✓ | ✓ | Unclear | HIGH |
| All-cause Death | 24 | X | ✓ | ✓ | ✓ | ✓ | Unclear | MODERATE |
| Stent thrombosis | 17 | ✓ | ✓ | ✓ | ✓ | ✓ | Unclear | HIGH |
| CV death | 18 | ✓ | ✓ | ✓ | ✓ | ✓ | Unclear | HIGH |
| TVR or TLR | 19 | X | ✓ | ✓ | ✓ | ✓ | Unclear | MODERATE |
| Stroke | 11 | X | X | X | ✓ | ✓ | Unclear | LOW |

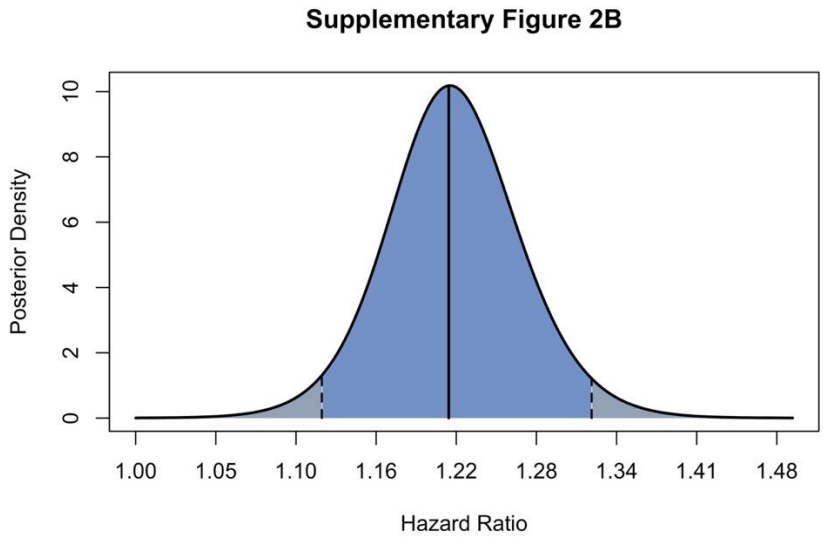
MI: myocardial infarction; CV: cardiovascular; ST: stent thrombosis; TVR: target vessel revascularization; TLR: target lesion revascularization; X: serious limitations; ✓: no serious limitations




**Supplementary Figure 1.** Flowchart for the selection process of studies included in the quantitative analysis.

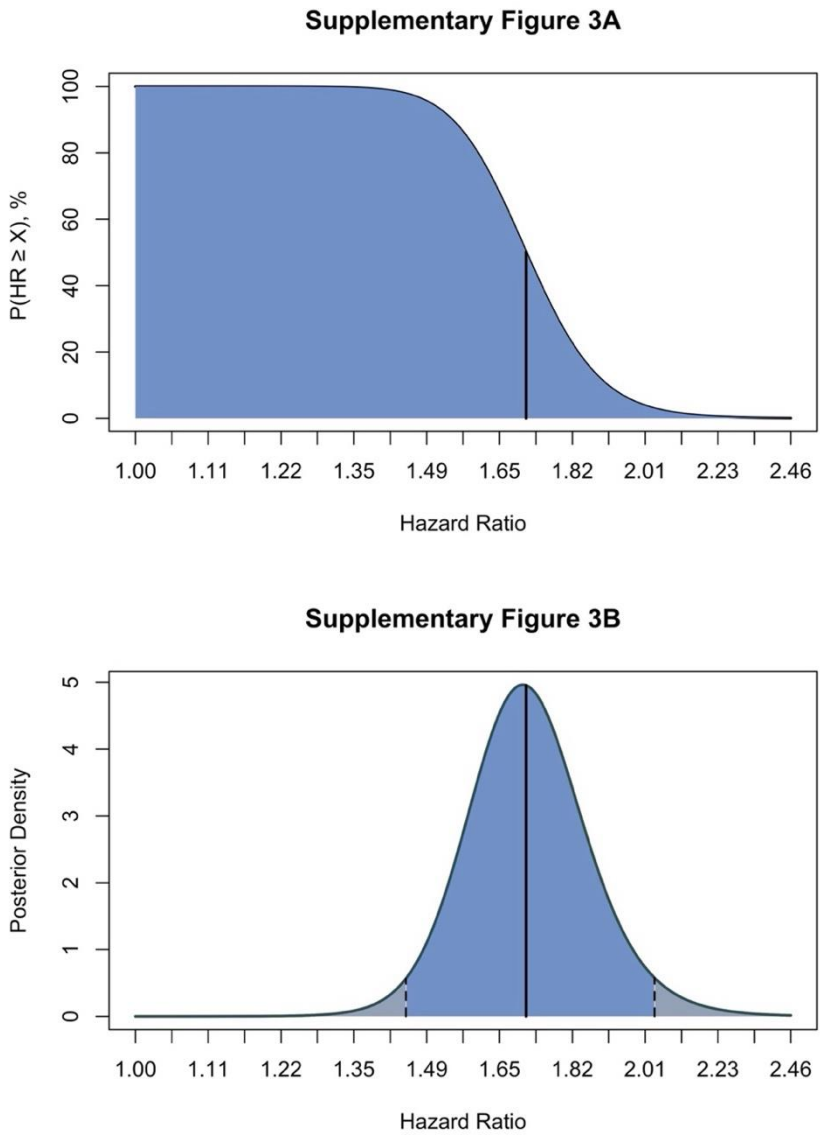
*The Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents (SMART-CHOICE) and Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trials were excluded for overlapping and included in the individual patient data meta-analysis Sidney-2. The Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent (STOPDAPT)-2 trial was excluded for overlapping and included in the individual patient data meta-analysis STOPDAPT-2 and STOPDAPT-2 ACS.



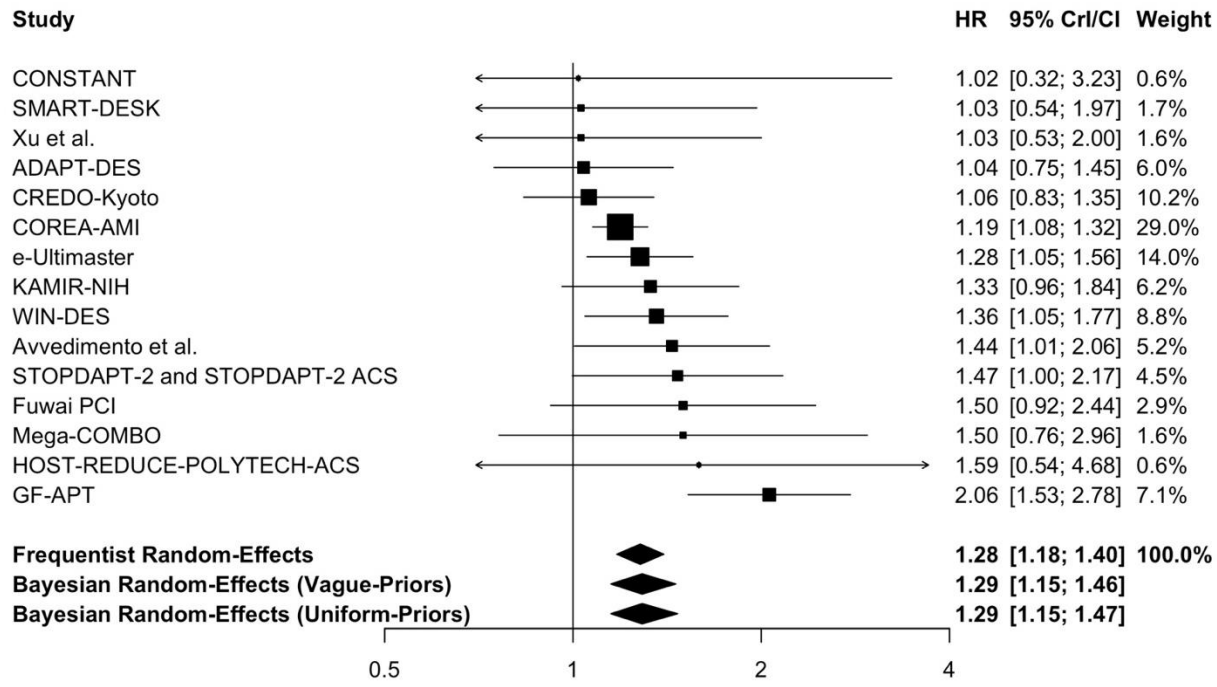

**Supplementary Figure 2.** Cumulative posterior distribution and full posterior distribution of the estimated adjusted hazard ratio for all-cause death.

**Panel A: Cumulative posterior distribution of the estimated adjusted hazard ratio for all-cause death.** On the y-axis there is the probability that the hazard ratio is greater than or equal to the value on the x-axis. The bold vertical line indicates the median value. The blue area is indicative of a good prognostic ability of complex PCI criteria (probability that hazard ratio is greater than or equal to 1).
**Panel B: Full posterior distribution of the estimated adjusted hazard ratio for all-cause death.** The bold vertical line indicates the median value, and the area highlighted in blue indicating the percentile based 95% credible interval.
HR: hazard ratio.



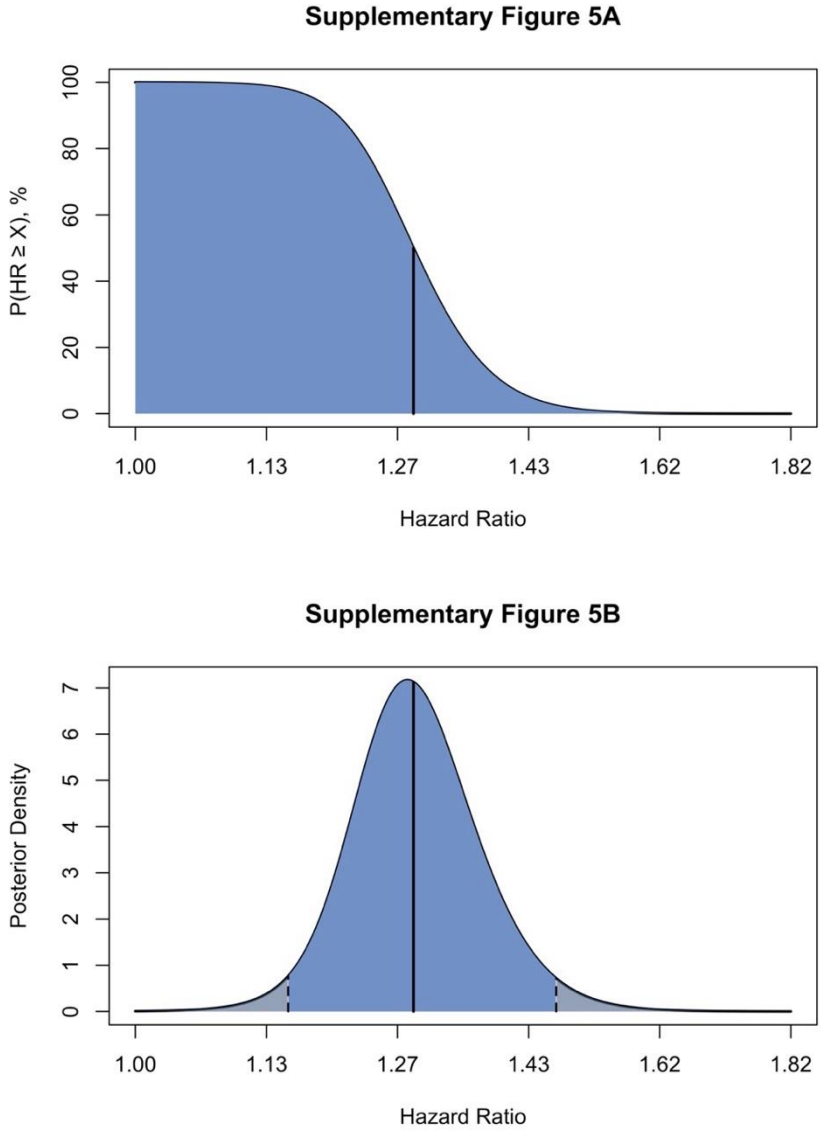

**Supplementary Figure 3.** Cumulative posterior distribution and full posterior distribution of the estimated adjusted hazard ratio for stent thrombosis.

**Panel A: Cumulative posterior distribution of the estimated adjusted hazard ratio for stent thrombosis.** On the y-axis there is the probability that the hazard ratio is greater than or equal to the value on the x-axis. The bold vertical line indicates the median value. The blue area is indicative of a good prognostic ability of complex PCI criteria (probability that hazard ratio is greater than or equal to 1).
**Panel B: Full posterior distribution of the estimated adjusted hazard ratio for for stent thrombosis.** The bold vertical line indicates the median value, and the area highlighted in blue indicating the percentile based 95% credible interval.
HR: hazard ratio.



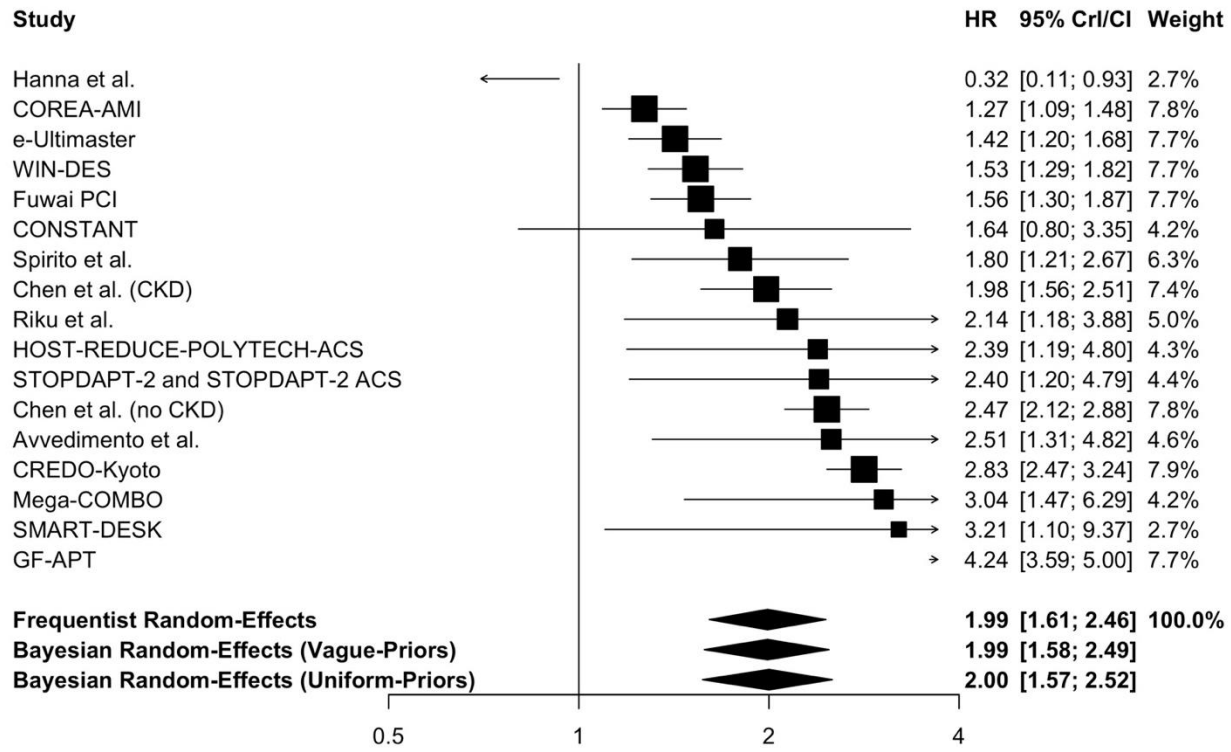

**Supplementary Figure 4.** Forest plot of adjusted analysis for cardiovascular death in patients undergoing complex PCI versus non-complex PCI.

CI: confidence interval; CrI: credible interval; HR: hazard ratio.



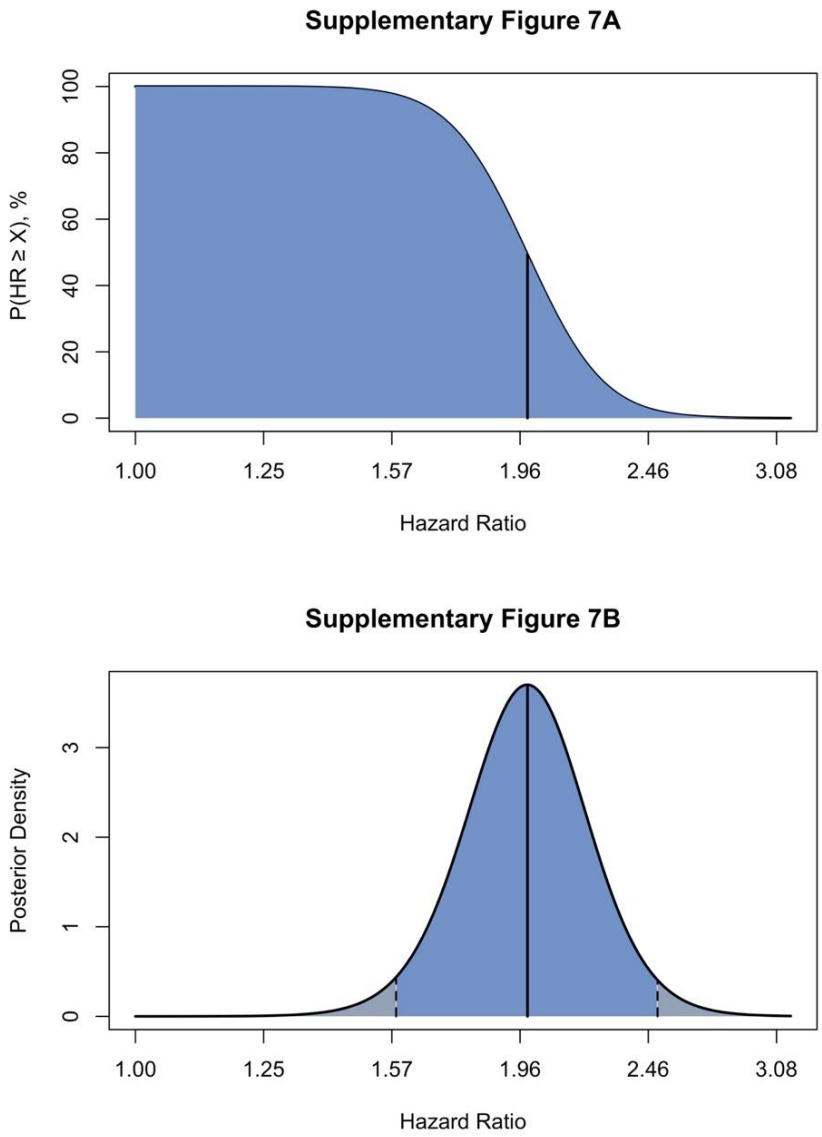

**Supplementary Figure 5.** Cumulative posterior distribution and full posterior distribution of the estimated adjusted hazard ratio for cardiovascular death.

**Panel A: Cumulative posterior distribution of the estimated adjusted hazard ratio for cardiovascular death.** On the y-axis there is the probability that the hazard ratio is greater than or equal to the value on the x-axis. The bold vertical line indicates the median value. The blue area is indicative of a good prognostic ability of complex PCI criteria (probability that hazard ratio is greater than or equal to 1).
**Panel B: Full posterior distribution of the estimated adjusted hazard ratio for cardiovascular death.** The bold vertical line indicates the median value, and the area highlighted in blue indicating the percentile based 95% credible interval.
HR: hazard ratio.



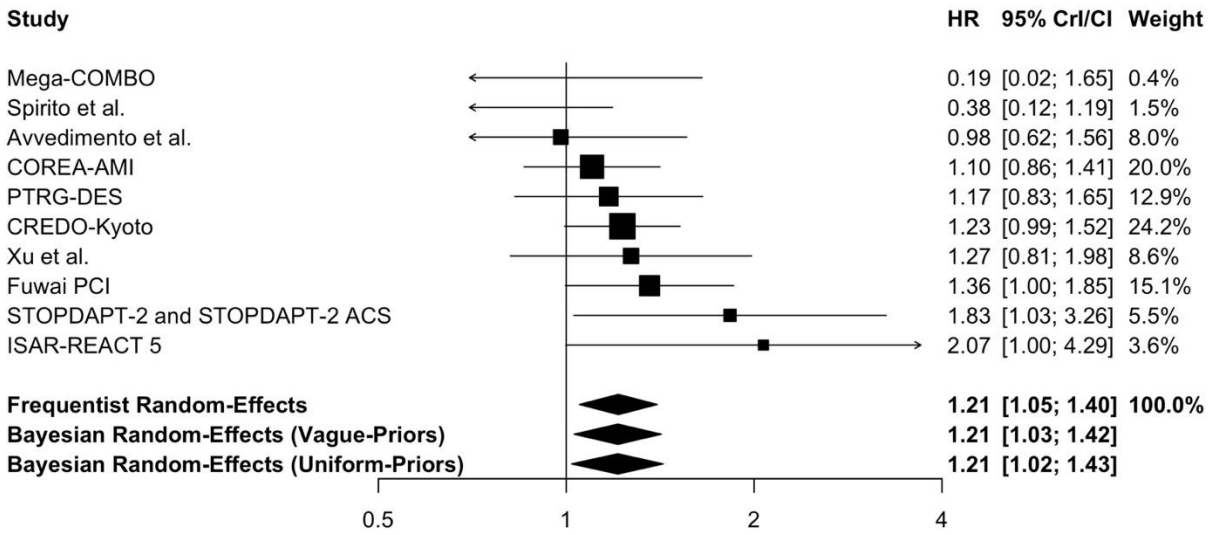

**Supplementary Figure 6.** Forest plot of adjusted analysis for target lesion or vessel revascularisation in patients undergoing complex PCI versus non-complex PCI.

CI: confidence interval; CrI: credible interval; HR: hazard ratio.



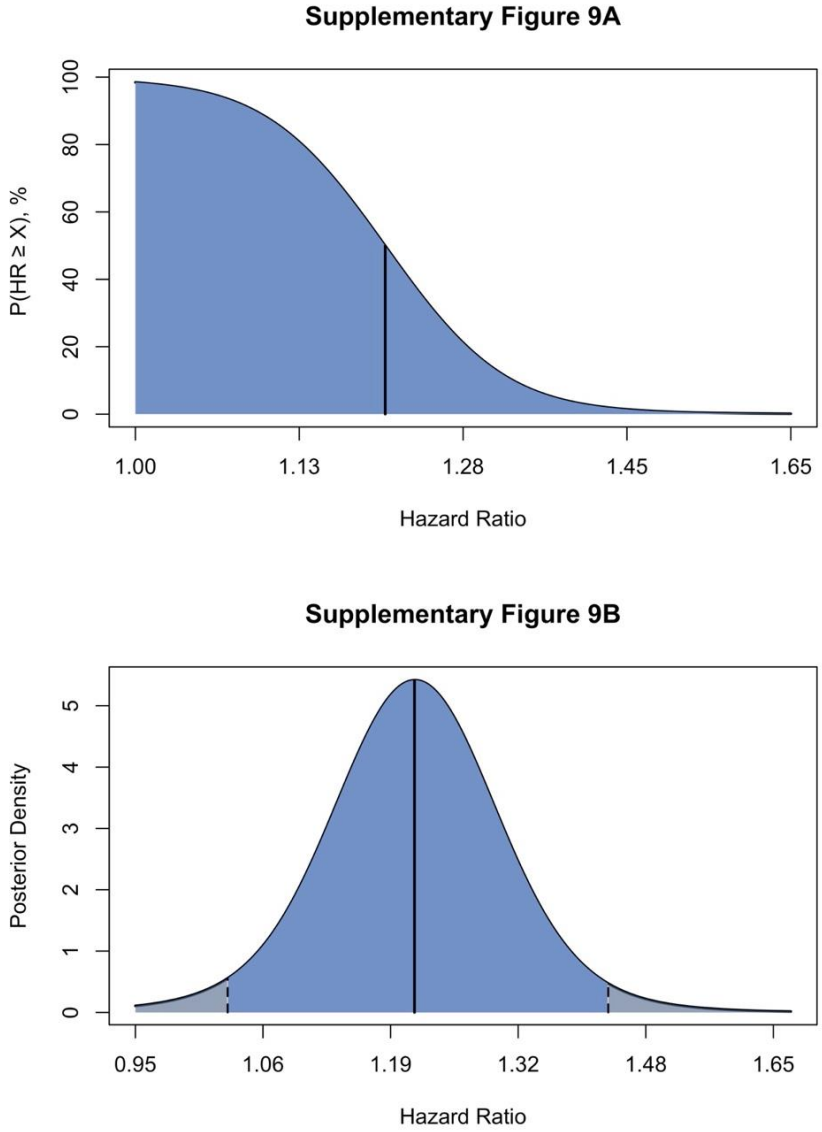

**Supplementary Figure 7.** Cumulative posterior distribution and full posterior distribution of the estimated adjusted hazard ratio for target lesion or vessel revascularisation.

**Panel A: Cumulative posterior distribution of the estimated adjusted hazard ratio for target or vessel revascularization.** On the y-axis there is the probability that the hazard ratio is greater than or equal to the value on the x-axis. The bold vertical line indicates the median value. The blue area is indicative of a good prognostic ability of complex PCI criteria (probability that hazard ratio is greater than or equal to 1).
**Panel B: Full posterior distribution of the estimated adjusted hazard ratio for target or vessel revascularization.** The bold vertical line indicates the median value, and the area highlighted in blue indicating the percentile based 95% credible interval.
HR: hazard ratio.




**Supplementary Figure 8.** Forest plot of adjusted analysis for stroke in patients undergoing complex PCI versus non-complex PCI.

CI: confidence interval; CrI: credible interval; HR: hazard ratio.



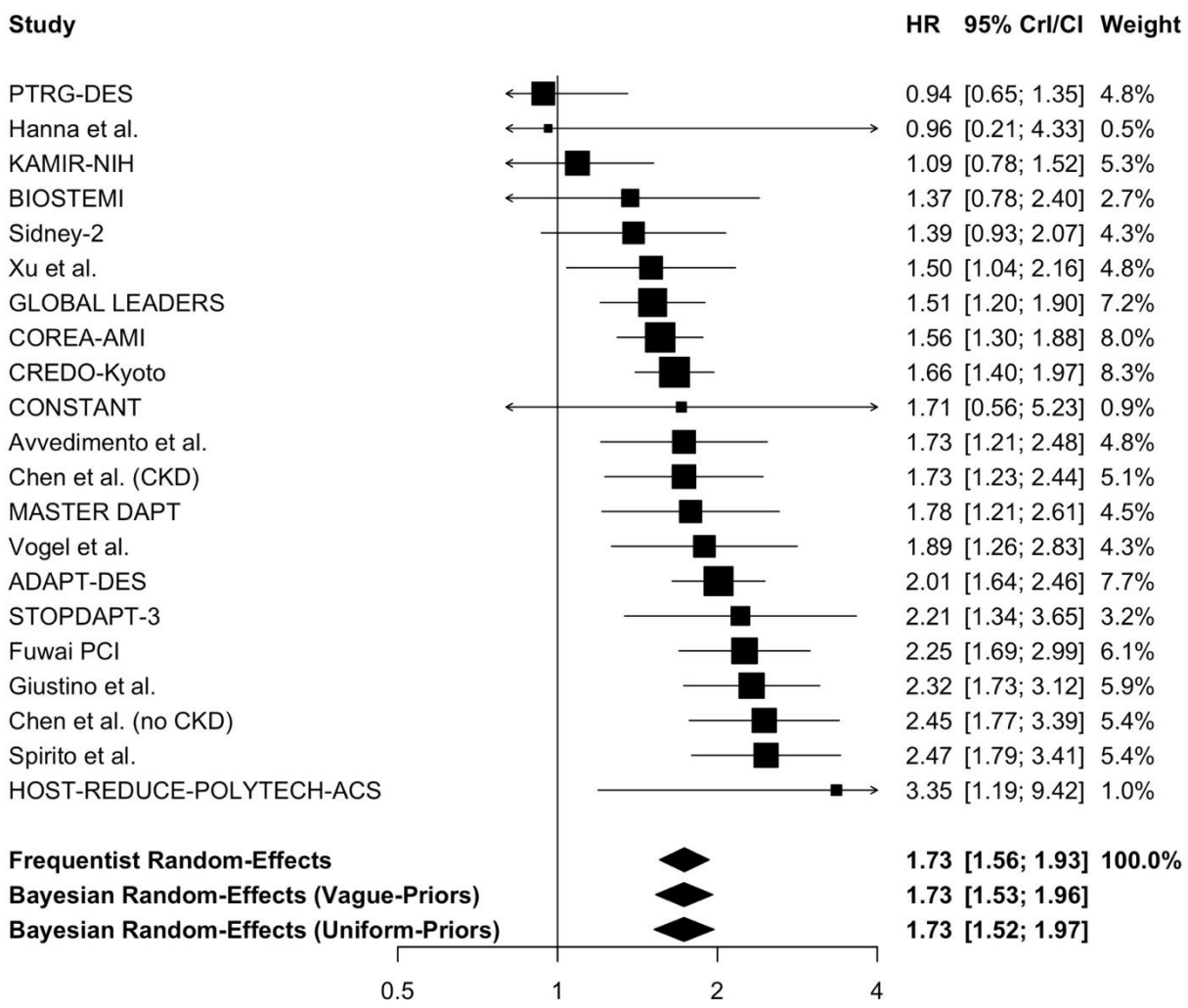

**Supplementary Figure 9.** Cumulative posterior distribution and full posterior distribution of the estimated adjusted hazard ratio for stroke.

**Panel A: Cumulative posterior distribution of the estimated adjusted hazard ratio for stroke.** On the y-axis there is the probability that the hazard ratio is greater than or equal to the value on the x-axis. The bold vertical line indicates the median value. The blue area is indicative of a good prognostic ability of complex PCI criteria (probability that hazard ratio is greater than or equal to 1).

**Panel B: Full posterior distribution of the estimated adjusted hazard ratio for stroke.**

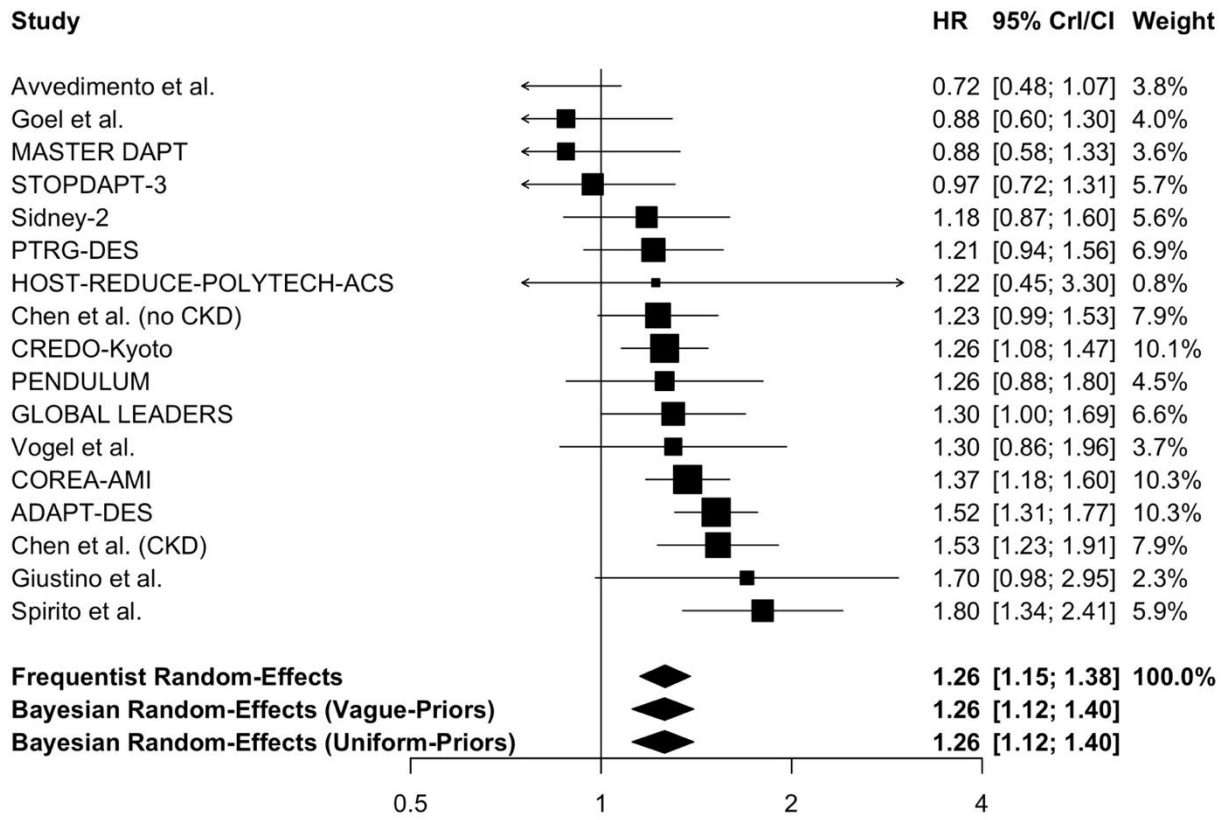
The bold vertical line indicates the median value, and the area highlighted in blue indicating the percentile based 95% credible interval.

HR: hazard ratio.



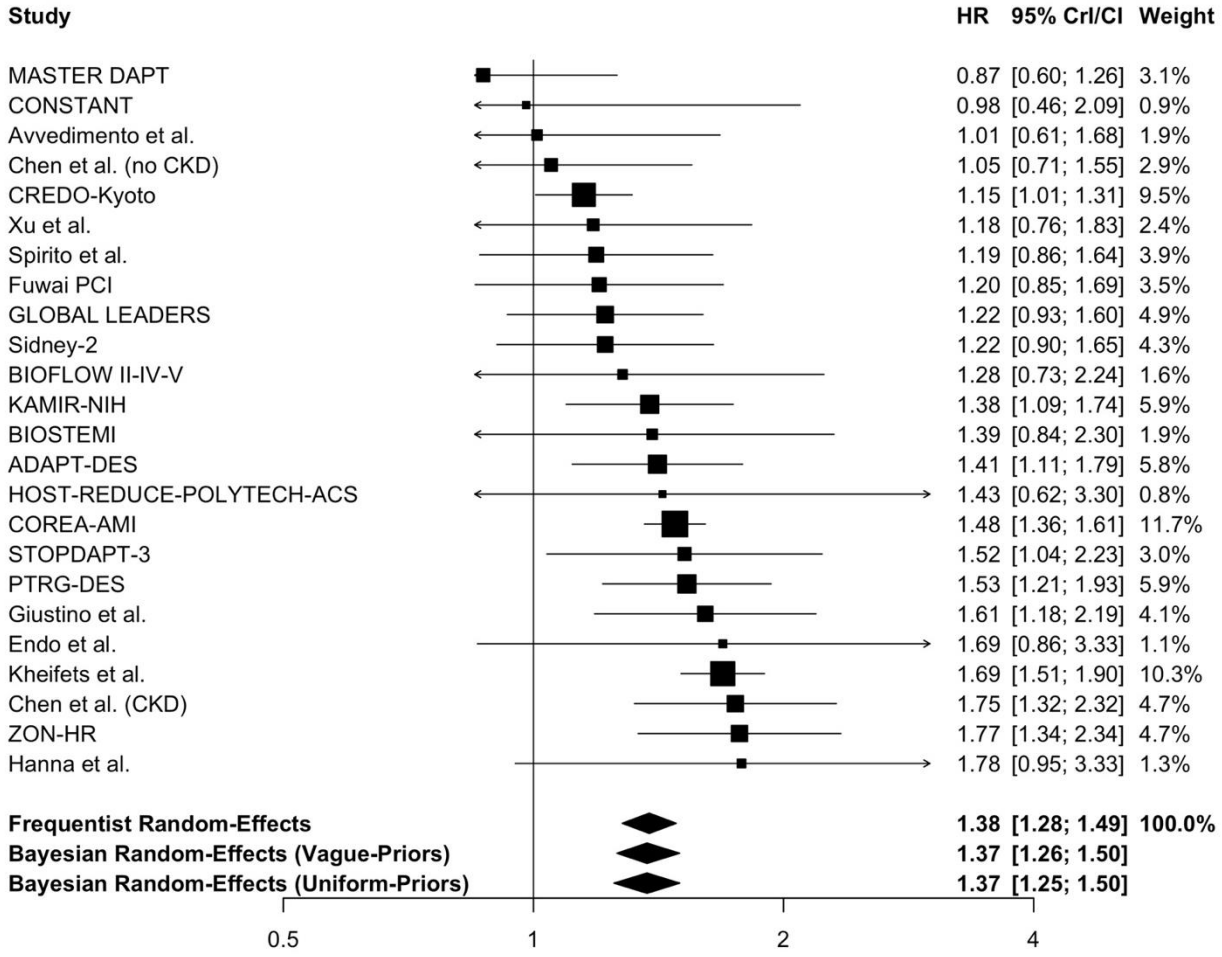

**Supplementary Figure 10.** Unadjusted analysis for myocardial infarction in patients undergoing complex PCI versus non-complex PCI.

CI: confidence interval; CrI: credible interval; HR: hazard ratio.



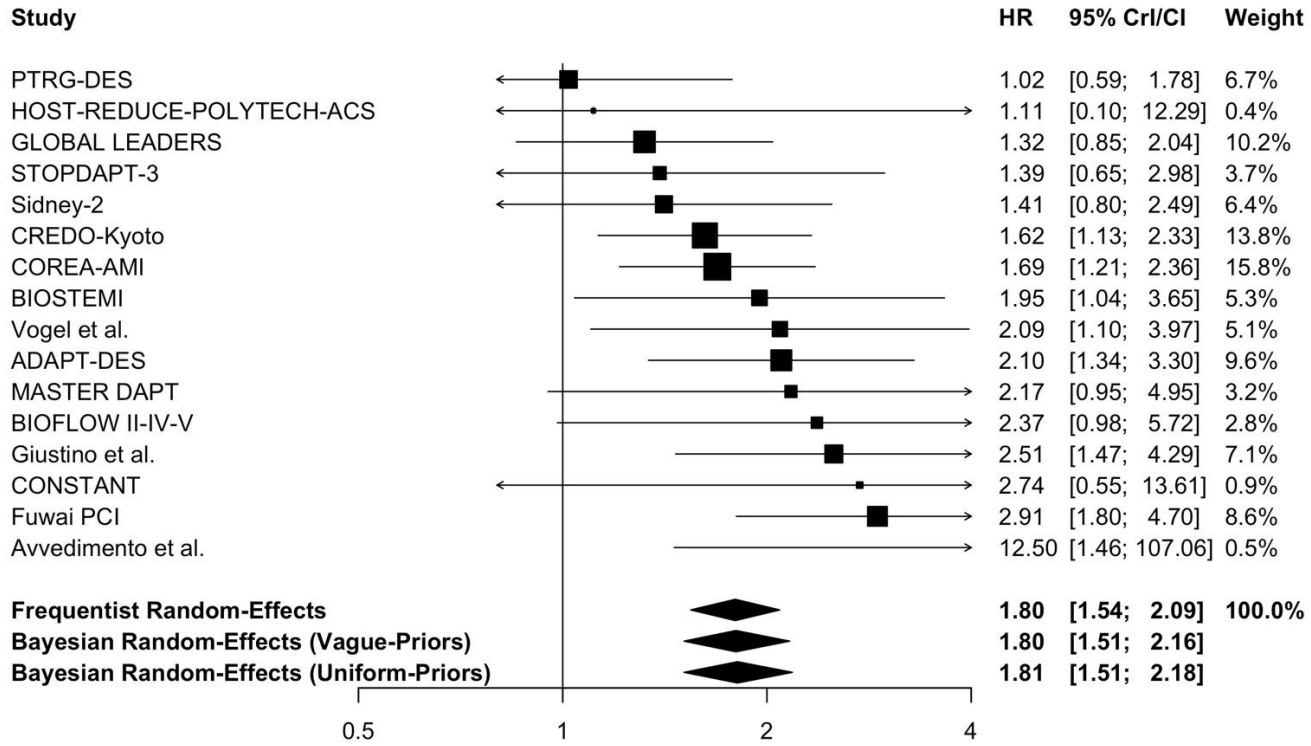

**Supplementary Figure 11.** Unadjusted analysis for major bleeding in patients undergoing complex PCI versus non-complex PCI.

CI: confidence interval; CrI: credible interval; HR: hazard ratio.



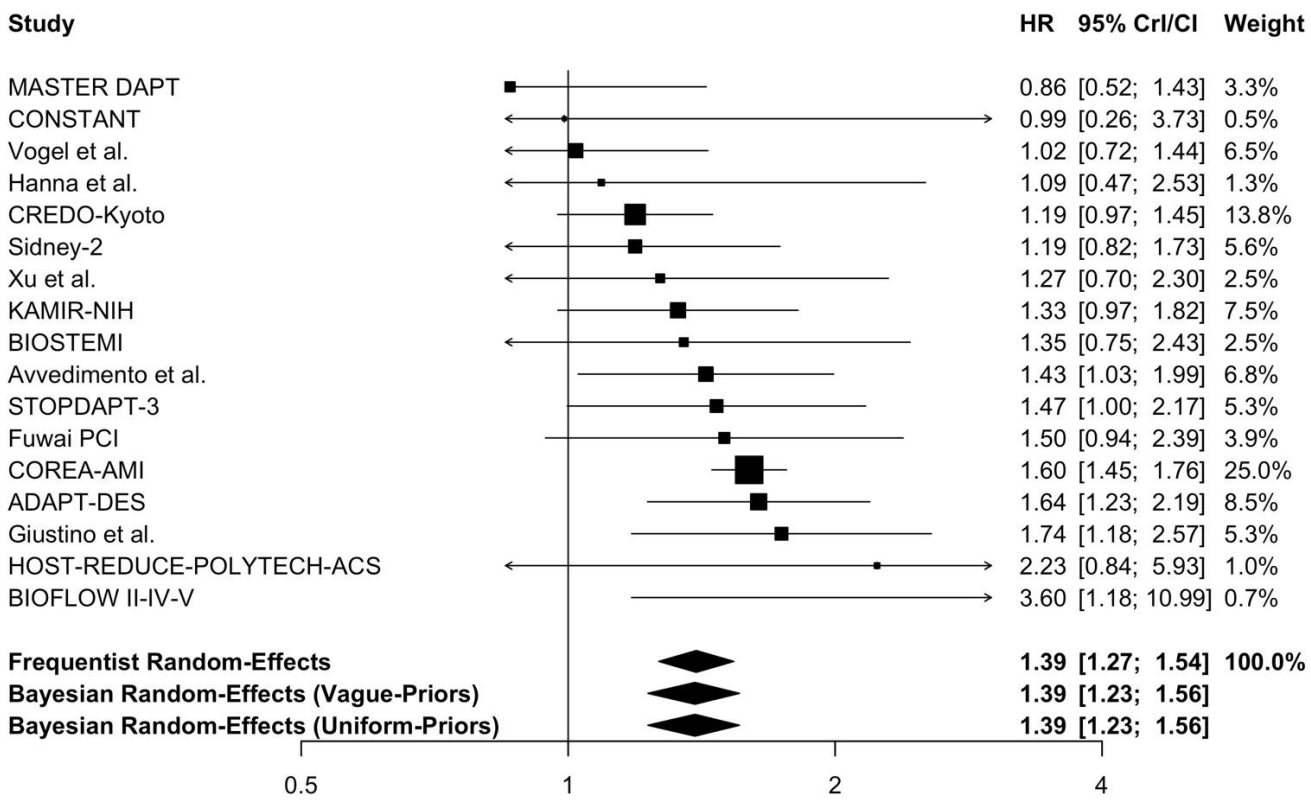

**Supplementary Figure 12.** Unadjusted analysis for all-cause death in patients undergoing complex PCI versus non-complex PCI.

CI: confidence interval; CrI: credible interval; HR: hazard ratio.



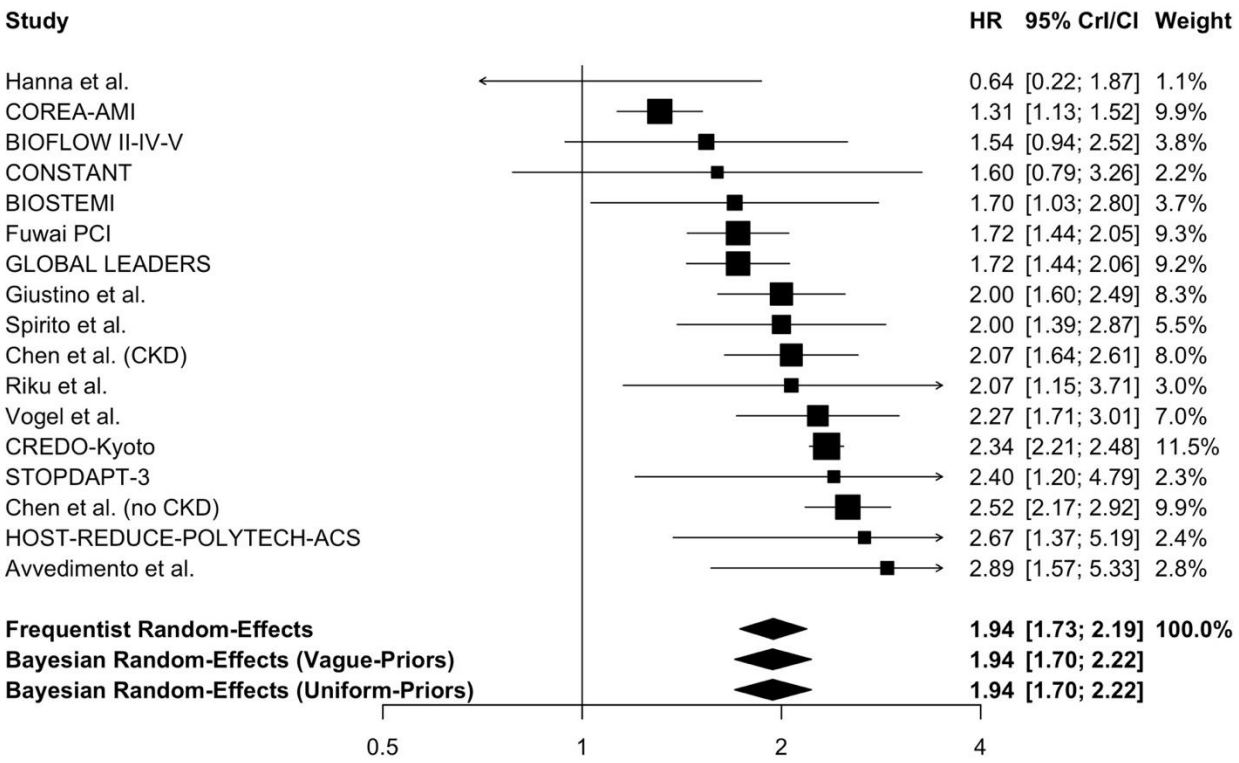

**Supplementary Figure 13.** Unadjusted analysis for stent thrombosis in patients undergoing complex PCI versus non-complex PCI.

CI: confidence interval; CrI: credible interval; HR: hazard ratio.



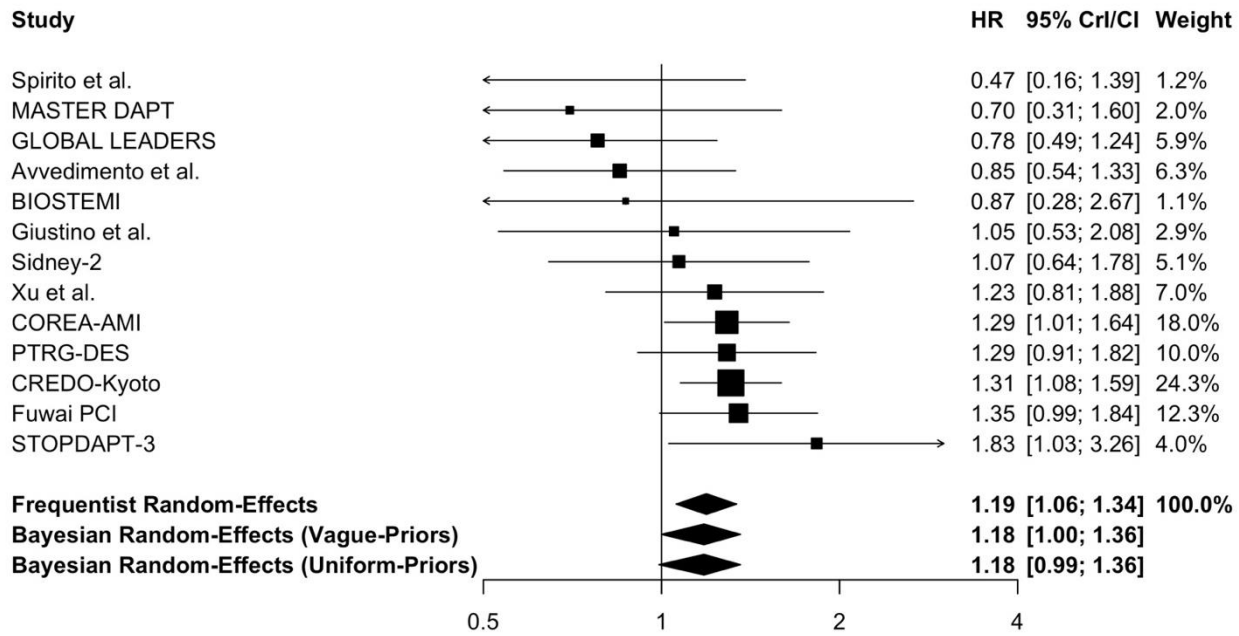

**Supplementary Figure 14.** Unadjusted analysis for cardiovascular death in patients undergoing complex PCI versus non-complex PCI.

CI: confidence interval; CrI: credible interval; HR: hazard ratio.



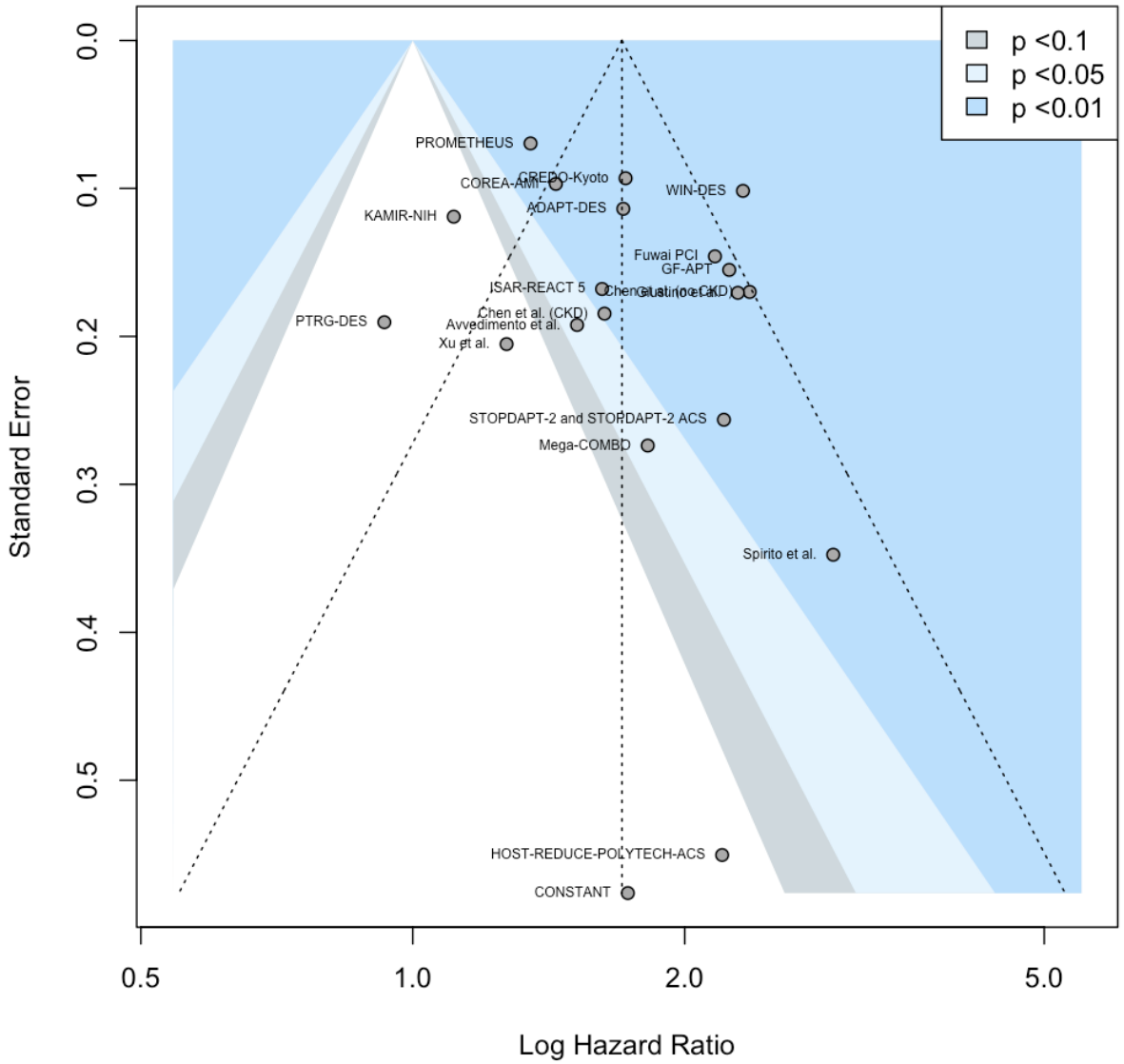

**Supplementary Figure 15.** Unadjusted analysis for target lesion or vessel revascularisation in patients undergoing complex PCI versus non-complex PCI.

CI: confidence interval; CrI: credible interval; HR: hazard ratio.



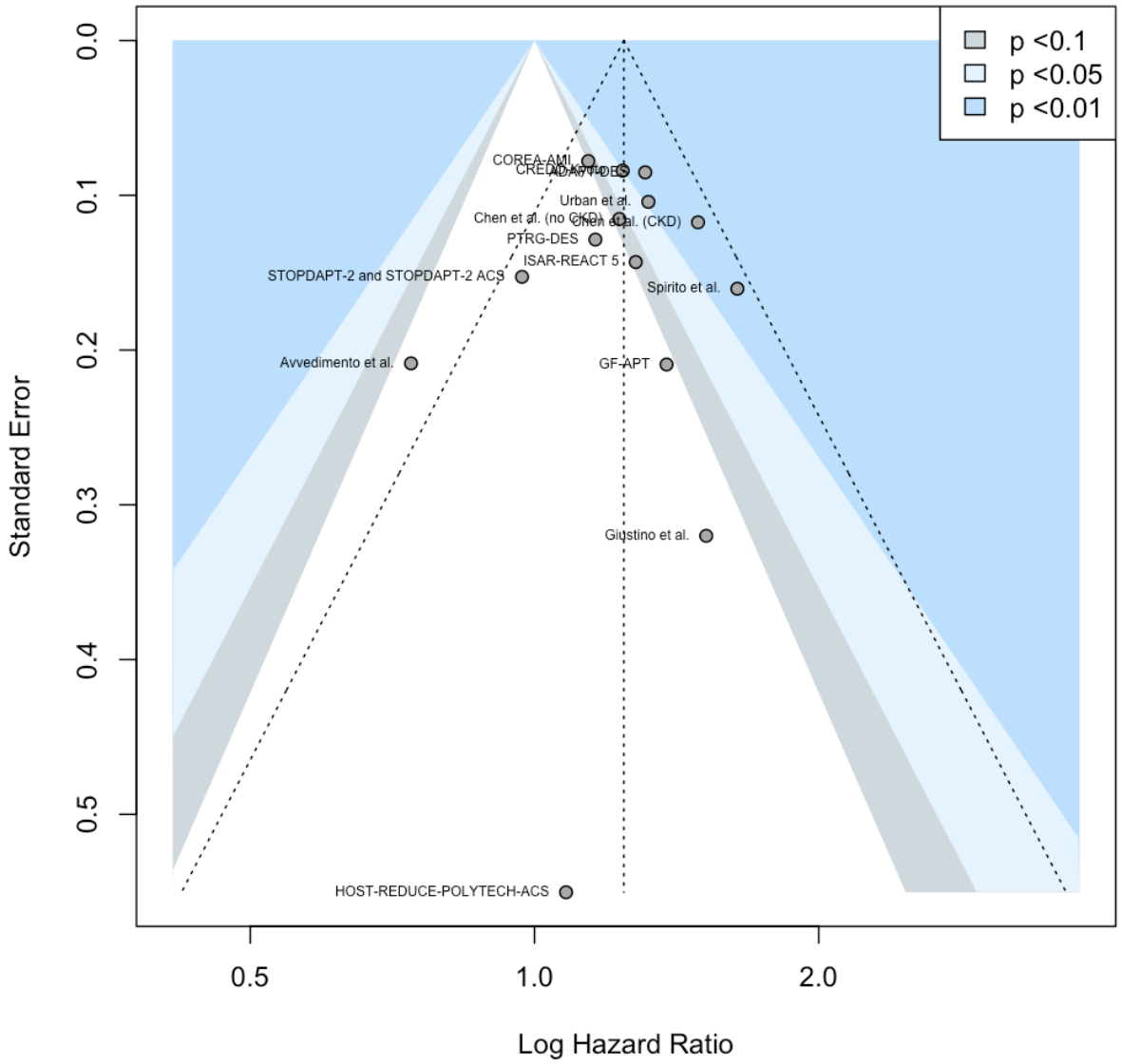

**Supplementary Figure 16.** Unadjusted analysis for stroke in patients undergoing complex PCI versus non-complex PCI.

CI: confidence interval; CrI: credible interval; HR: hazard ratio.



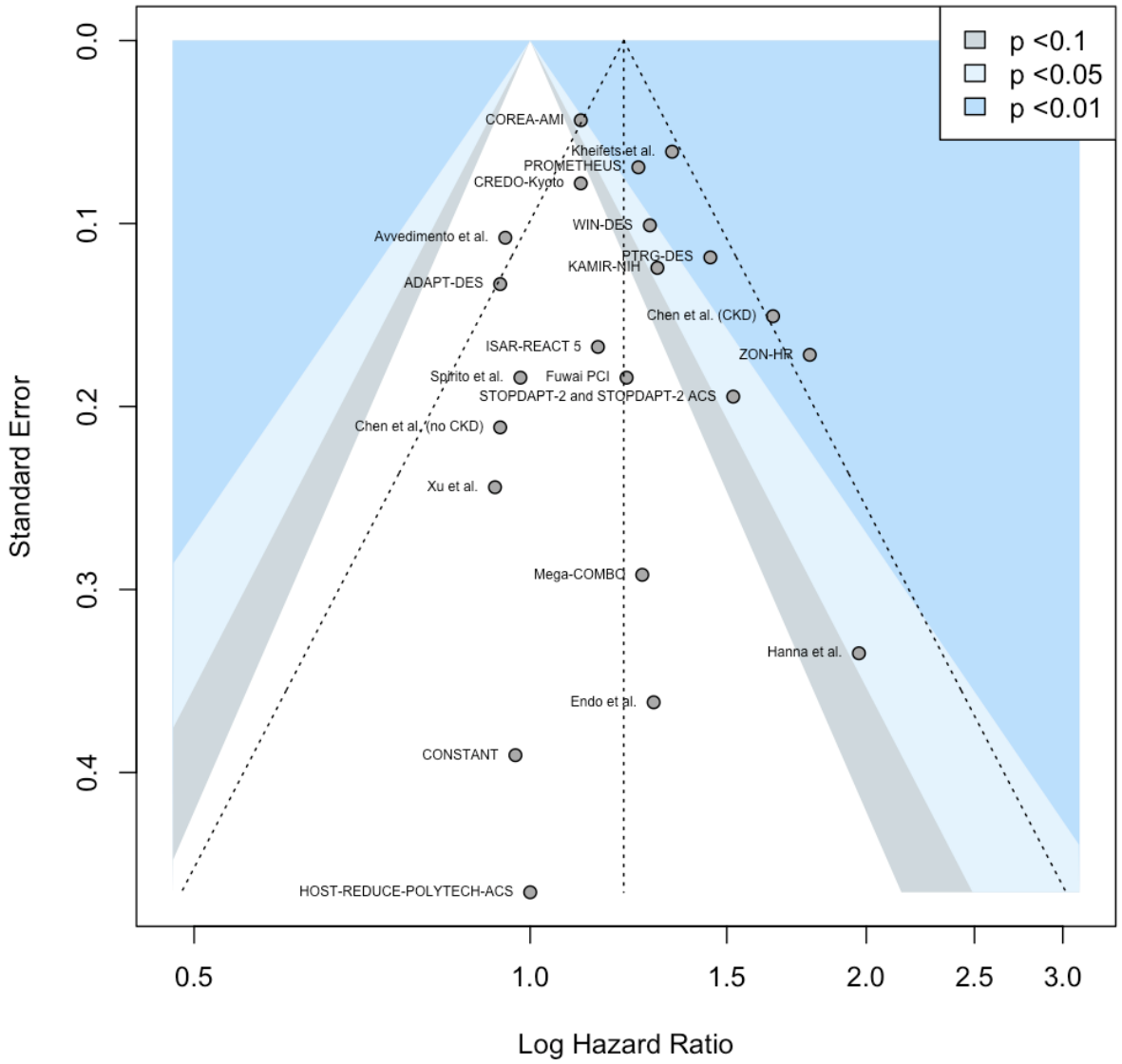

**Supplementary Figure 17.** Funnel plot and Egger's regression test for studies included in the analysis of the risk of myocardial infarction.

P = 0.85.



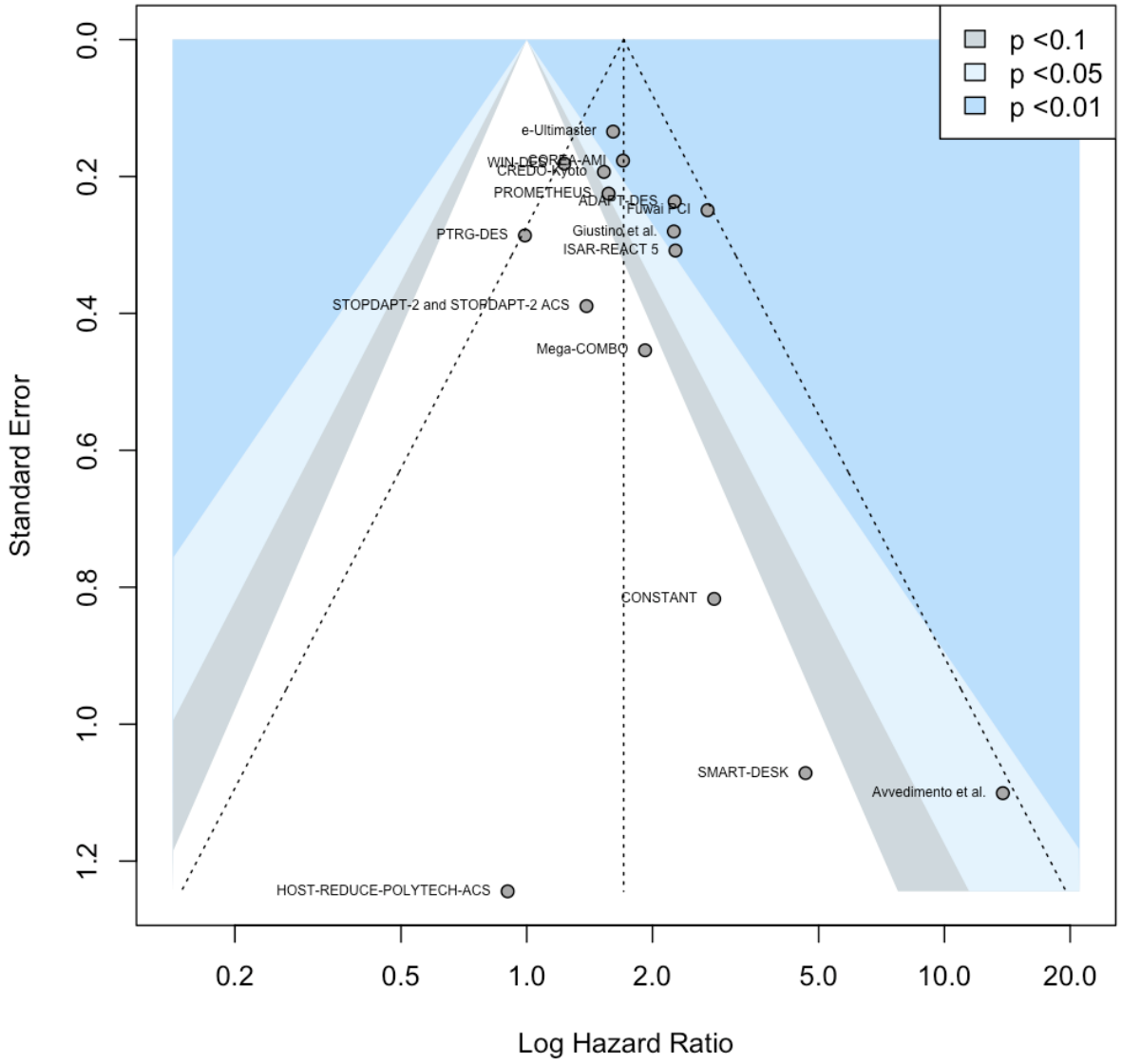

**Supplementary Figure 18.** Funnel plot and Egger's regression test for studies included in the analysis of the risk of major bleeding.

P = 0.25



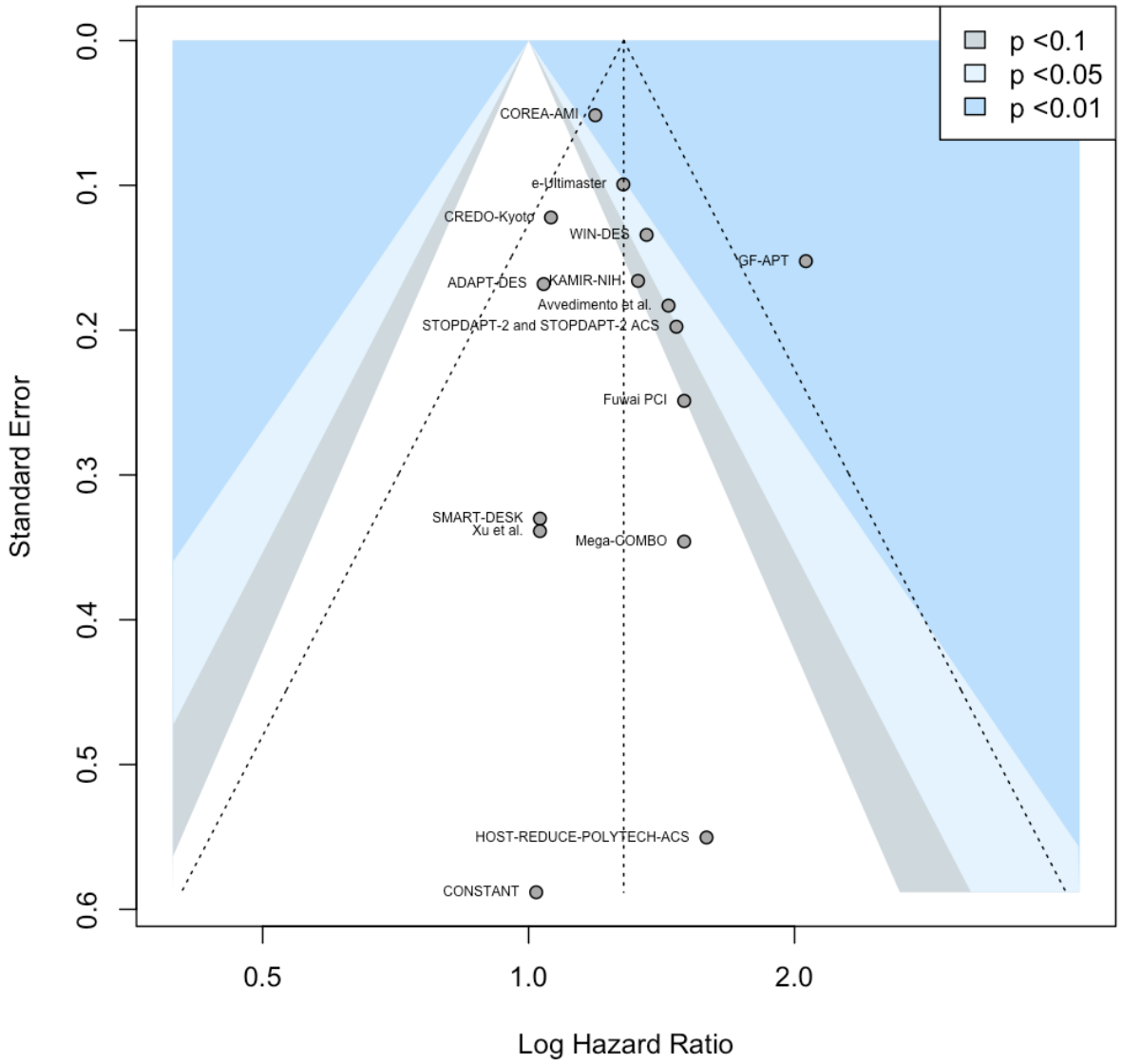

**Supplementary Figure 19.** Funnel plot and Egger's regression test for studies included in the analysis of the risk of all-cause death.

P = 0.58.



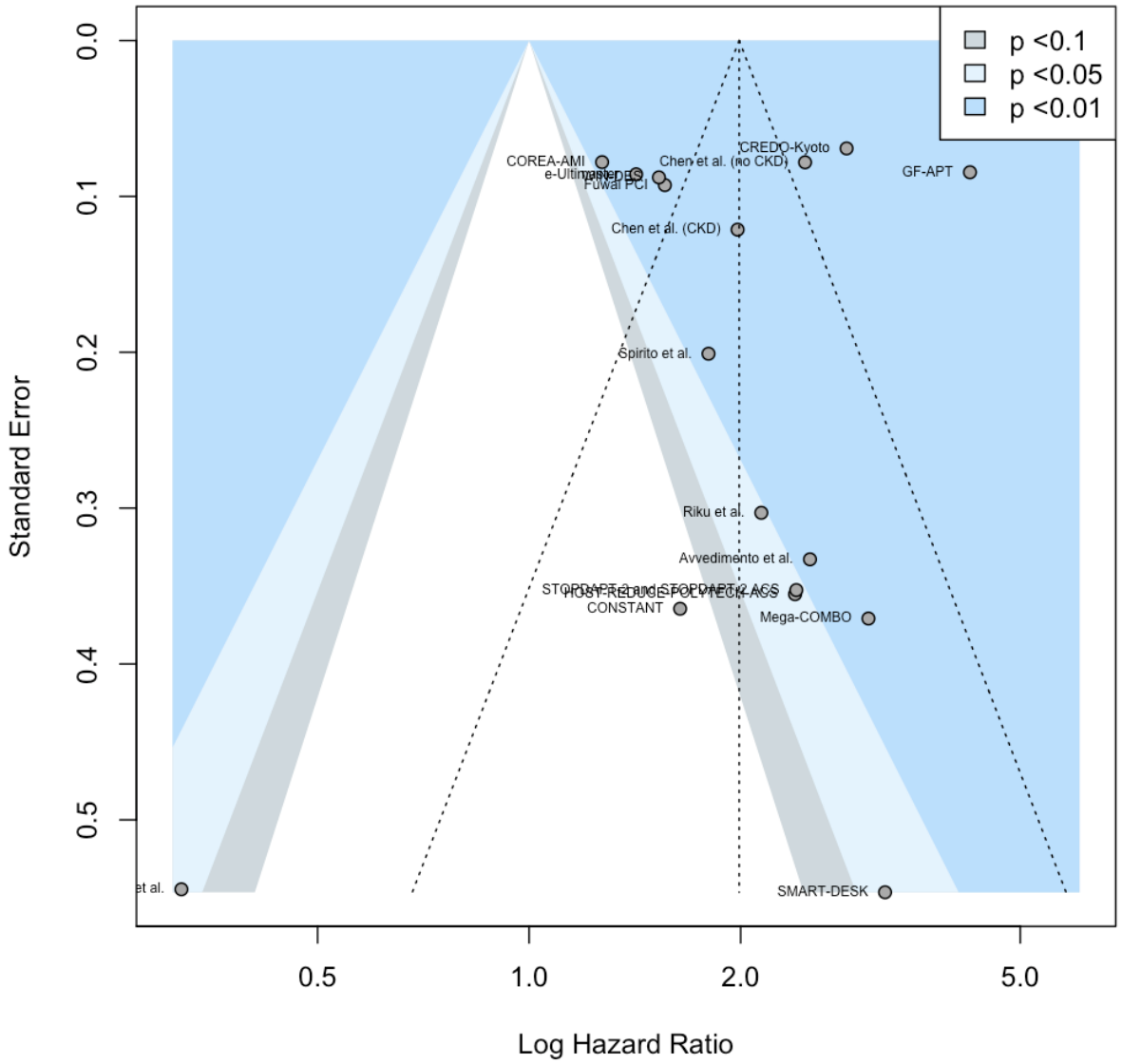

**Supplementary Figure 20.** Funnel plot and Egger's regression test for studies included in the analysis of the risk of stent thrombosis.

P = 0.13.



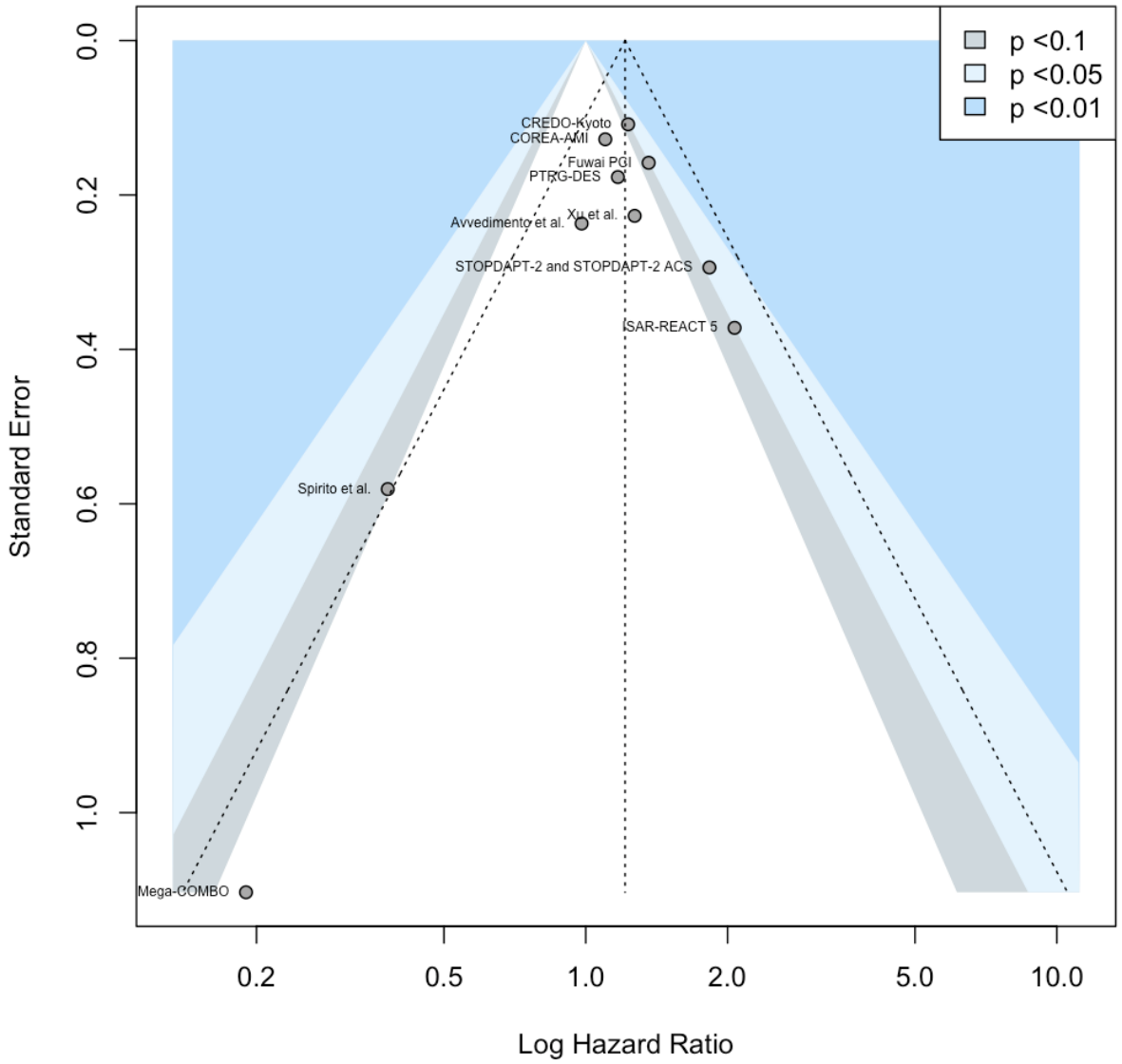

**Supplementary Figure 21.** Funnel plot and Egger's regression test for studies included in the analysis of the risk of cardiovascular death.

P = 0.36.




**Supplementary Figure 22.** Funnel plot and Egger's regression test for studies included in the analysis of the risk of target lesion or vessel revascularisation.

P = 0.80.




**Supplementary Figure 23.** Funnel plot and Egger's regression test for studies included in the analysis of the risk of stroke.

P = 0.40.