

Biolimus- versus sirolimus-eluting stents in percutaneous coronary intervention: a comprehensive systematic review and meta-analysis of randomised controlled trials



Ricardo F.O. Suruagy-Motta^{1*}; Leonardo Dexheimer da Silva²; Gabriel Rezende Neves³; Carlos Alexandre Farias⁴; Leonardo Galvão de Oliveira Oldra⁵, MD; Pedro Antonio Machado Gomes de Sousa⁶, MD; Edmundo Damiani Bertoli⁷, MD; Evandro Martins Filho⁸, MD; Pedro Cox-Alomar⁹, MD, MPH, FSCAI; Brunna Pileggi¹⁰, MD; Pedro Craveiro de Melo¹⁰, MD; David de Andrade Nunes¹¹, MD; Lorenzo Azzalini¹², MD, PhD, MSc, FACC, FSCAI; Sant Kumar¹², MD

*Corresponding author: Department of Medicine, Cesmac University Center, Rua Cônego Machado, 984, Maceió, Alagoas, 57051-160, Brazil. E-mail: ricasuruagy1@gmail.com

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ABSTRACT

BACKGROUND: Sirolimus-eluting stents (SES) are a benchmark in percutaneous coronary intervention (PCI), while biolimus-eluting stents (BES), which combine a more lipophilic analogue with a biodegradable polymer, may enhance healing and reduce thrombosis. Whether these BES features translate into improved survival and cardiac outcomes compared with SES remains uncertain.

AIMS: We sought to perform a meta-analysis of randomised controlled trials evaluating BES compared with SES in adult patients undergoing PCI.

METHODS: This meta-analysis encompassed randomised and controlled clinical trials that directly compared BES with SES in the setting of percutaneous coronary intervention. A comprehensive literature search was performed across PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials up to June 2025. The main outcomes assessed were all-cause and cardiac mortality, while secondary endpoints included major adverse cardiovascular events (MACE), myocardial infarction, target lesion revascularisation (TLR), and stent thrombosis (ST). Outcomes were evaluated at ≤ 1 year (early) and >1 -5 years (midterm) using pooled risk ratios (RRs) with 95% confidence intervals (CIs) in random-effects models, with heterogeneity assessed by the I^2 test.

RESULTS: Six trials (12,109 patients: 6,088 BES, 6,021 SES) were analysed. BES reduced 1-year cardiac death by 30% (RR 0.70, 95% CI: 0.52-0.93) and showed a non-significant 19% reduction in all-cause death (RR 0.81; $p=0.058$). MACE, myocardial infarction, and TLR were similar between stents across timepoints. BES showed a non-significant early increase in ST (RR 1.85; $p=0.12$) but a 46% reduction in late ST (RR 0.54, 95% CI: 0.33-0.88). Mortality rates converged after 1 year.

CONCLUSIONS: BES offer a short-term reduction in cardiac mortality and late stent thrombosis compared with SES, with otherwise similar morbidity outcomes. These results support the short-term safety of BES and indicate a possible long-term thrombotic and cardiac survival benefit, warranting confirmation in longer-term trials.

KEYWORDS: biolimus; drug-eluting stent; meta-analysis; percutaneous coronary intervention; sirolimus

As percutaneous coronary revascularisation techniques continue to evolve, stents have naturally become a central target of innovation – not solely to maintain coronary patency but also to address the underlying mechanisms of tissue injury and local inflammatory response. Consequently, drug-eluting stents (DES) have become the gold standard in coronary interventions, utilising antiproliferative agents designed to suppress restenosis and promote more favourable endothelial healing. Among these, sirolimus-eluting stents (SES) and stents eluting its derivatives – such as the more lipophilic biolimus – have gained prominence for their potential to inhibit neointimal proliferation more effectively.^{1,2}

Biologically, sirolimus is a naturally macrolide lactone isolated from *Streptomyces hygroscopicus*, which exerts its antiproliferative effect by inhibiting muscle cell proliferation and migration through early blockade of the mammalian target of rapamycin (mTOR) pathway. As a result, it induces G1 cell-cycle blockade.¹ Accordingly, this mechanism solidified sirolimus as a foundational agent in the first generation of drug-eluting stents. Nonetheless, certain limitations remain, particularly regarding delayed vascular healing and increased thrombotic risk associated with the inflammation induced by durable polymers. These concerns have prompted the search for novel drug formulations with improved safety and performance profiles.²

In response to these challenges, biolimus has emerged as a promising pharmacological alternative. Structurally, it is a semisynthetic derivative of sirolimus, modified with a butyl group at the C40 position, which enhances its lipophilicity. Therefore, it demonstrates superior lipid membrane compatibility, allowing for deeper vascular wall penetration and prolonged local retention while simultaneously reducing systemic exposure.^{3,4} Consequently, biolimus has frequently been paired with biodegradable stent platforms, aiming to minimise restenosis rates and optimise long-term outcomes.^{4,5} Thus, these developments have positioned biolimus-eluting stents (BES) as a potentially superior alternative in the context of long-term percutaneous interventions.

Despite these advances, the clinical distinction between sirolimus- and biolimus-eluting stents remains a subject of ongoing debate.⁶ Hence, a systematic and evidence-based comparison is essential to elucidate their relative therapeutic value. Therefore, the present systematic review and meta-analysis aim to evaluate clinical outcomes through randomised controlled trials, thereby contributing to the current existing literature and informing future haemodynamic strategies based on robust comparative data.

Methods

This systematic review and meta-analysis was conducted in full accordance with the methodological standards outlined

Impact on daily practice

This meta-analysis reveals a distinct, time-dependent clinical profile between these two platforms that directly refines daily practice. In the early phase (<1 year), biolimus-eluting stents (BES) provide a substantial reduction in cardiac mortality compared with sirolimus-eluting stents. Conversely, during midterm follow-up (1-5 years), the benefit of BES shifts to sustained safety. Clinically, these temporal trends dictate that strict adherence to dual antiplatelet therapy (DAPT) is essential during the initial months to bridge the polymer resorption window.

in the Cochrane Handbook for Systematic Reviews of Interventions and adhered to the 2020 PRISMA reporting guidelines. The study protocol was prospectively registered in the PROSPERO database (CRD420251119555).^{7,8}

SEARCH STRATEGY

The search was carried out independently by two authors (R.F.O. Suruagy-Motta and L.D. da Silva) in the databases PubMed/MEDLINE, Cochrane, Web of Science, Embase, and Scopus, including studies that had a comparison between biolimus- and sirolimus-eluting stents in coronary interventions. The search strategy was constructed using Boolean logic, in which the operators “AND” and “OR” were employed to link the key terms: drug-eluting stents, stent, biolimus, sirolimus, percutaneous coronary intervention, and randomised controlled trial.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

The guiding question of this systematic review was defined as follows: “in patients with coronary lesions, which eluting stent is more safe and effective, a biolimus-eluting stent or a sirolimus-eluting stent?” This research question was structured according to the PICOTT model,^{9,10} encompassing the following elements:

Population (P): individual presenting coronary artery disease undergoing percutaneous coronary intervention (PCI) with stent implantation

Intervention (I): biolimus-eluting stent

Comparison (C): sirolimus-eluting stent

Outcomes (O): all-cause mortality, cardiac death, major adverse cardiovascular events (MACE), stent thrombosis, target lesion revascularisation, myocardial infarction

Type of study (T): randomised controlled trials (RCTs)

Time (T): early-stage outcomes (<1 year) and midterm outcomes (1-5 years).

Abbreviations

BES	biolimus-eluting stent	MI	myocardial infarction	SES	sirolimus-eluting stent
CABG	coronary artery bypass grafting	PCI	percutaneous coronary intervention	ST	stent thrombosis
DES	drug-eluting stent	RCT	randomised controlled trial	TLR	target lesion revascularisation
MACE	major adverse cardiovascular events	RoB 2	risk of bias 2		

EXCLUSION CRITERIA

The exclusion parameters applied in this review were the following: (1) non-randomised studies; (2) studies not involving patients in coronary interventions; (3) studies that addressed only patients with in-stent restenosis; (4) studies that had other limus-eluting stents in the intervention group, such as everolimus or ridaforolimus; (5) studies with insufficient outcome reporting. In addition, single-case descriptions, narrative or systematic reviews, congress abstracts, and any non-original research material were excluded from the final selection.

STUDY SELECTION

During the first stage of selection, titles and abstracts were examined to identify studies relevant to the research question, with no filters applied regarding publication year or language. All citations retrieved from the databases were uploaded into the Rayyan web application (<https://www.rayyan.ai>)¹¹ to facilitate blinded evaluation. Duplicate records were automatically detected and manually verified before removal. Subsequently, studies deemed unrelated to the scope of the review were excluded. The screening process was conducted independently by two investigators (G.R. Neves and L.G. Oldra), and any disagreements were discussed and resolved in consultation with a third reviewer (R.F.O. Suruagy-Motta).

ENDPOINTS AND DEFINITIONS

The primary endpoint was mortality, including cardiac death and all-cause mortality, at 1 year and 5 years of follow-up. Other cardiovascular endpoints were also evaluated, such as MACE (defined by a composite of cardiac death, non-fatal myocardial infarction, and target vessel revascularisation), myocardial infarction, stent thrombosis, and target lesion revascularisation (TLR).

DATA EXTRACTION

Information from each eligible study was systematically collected according to predefined inclusion criteria, encompassing authorship, publication year, study location, study design, sample size, mean age, participant characteristics, stent type, postoperative pharmacotherapy, follow-up duration, and principal outcomes. Data extraction and management were performed independently by two investigators (P.A.M.G. de Sousa and C.A. Farias), with all entries organised in a structured Excel (Microsoft) database. Any inconsistencies or uncertainties were discussed and resolved in agreement with a third reviewer (R.F.O. Suruagy-Motta).

QUALITY ASSESSMENT

The risk-of-bias assessment was performed separately by two authors (R.F.O. Suruagy-Motta and L.D. da Silva) using the Risk of Bias 2 (RoB 2) tool for randomised controlled trials,¹² assessing the randomisation process, deviations from interventions, missing outcome data, measurement of outcome, and selection of the reported result; any overall disagreements in the process were resolved through discussion or consultation with a third author (P.A.M.G. de Sousa).

STATISTICAL ANALYSIS

Treatment effects for categorical outcomes were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). Each

outcome was analysed and evaluated through the I^2 statistic test: if $I^2 > 25\%$, it was considered significant; if $I^2 < 25\%$, it was considered low. In the presence of substantial heterogeneity, a random-effects model incorporating the Hartung-Knapp adjustment was used to yield more conservative and robust pooled estimates. Statistical analyses were conducted using RStudio (R Foundation for Statistical Computing).¹³

Results

STUDIES SELECTED

The database search retrieved 1,202 citations in total, distributed as follows: PubMed (n=149), Embase (n=98), Web of Science (n=509), Scopus (n=226), and Cochrane Library (n=220). After the automatic and manual removal of 748 duplicate entries, 454 unique records were retained for the initial title- and abstract-level screening. From these, 23 studies were reviewed in full text, and ultimately six randomised trials satisfied the eligibility criteria and were incorporated into the quantitative synthesis, representing 12,109 participants overall.¹⁴⁻¹⁹ The complete selection workflow is depicted in **Figure 1**.

BASELINE CHARACTERISTICS

Table 1 summarises the baseline characteristics of patients included in the selected randomised clinical trials comparing biolimus- and sirolimus-eluting stents. Across studies, patient populations were predominantly male, with mean ages ranging from approximately 63 to 67 years. Common comorbidities included diabetes, hypertension, and hypercholesterolaemia. The

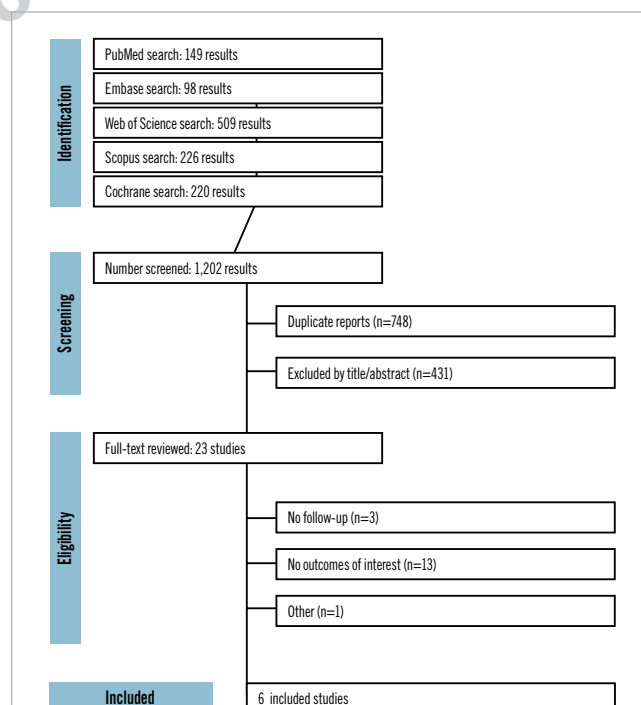


Figure 1. PRISMA flowchart. PRISMA flow diagram summarising the identification, screening, eligibility assessment, and final inclusion of studies.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 1. Baseline characteristics of the studies and patients.

Author/ Study name, year	Country	Study design	Follow-up time, years	Sample size	Intervention: bio/siro	Male	Age, years	Diabetes	Hypertension	Hypercholester- olaemia	Previous MI	Previous PCI	Previous CABG
Kadota et al, 2012 ¹⁴	Japan	RCT	5	326	194/132	139/95	67.1±10.3/ 67.7±9.3	75/52	149/111	150/108	40/28	63/51	1/4
LEADERS, 2011 ¹⁵	Multicentre	RCT	4	1,707	857/850	643/634	64.6±10.8/ 64.5±10.7	223/191	630/618	560/580	276/227	312/312	90/107
SORT OUT V, 2013 ¹⁶	Denmark	RCT	1	2,468	1,229/1,239	917/930	65.0±10.6/ 65.2±10.3	185/189	682/653	710/730	209/206	205/196	96/71
SORT OUT VII, 2024 ¹⁷	Denmark	RCT	5	1,329	674/655	525/495	63.7±11.5/ 65.1±11.3	114/106	302/310	270/262	103/83	102/83	32/31
SORT OUT IX, 2025 ¹⁸	Denmark	RCT	5	3,151	1,572/1,579	1,219/1,221	66.4±10.7/ 66.1±11.1	304/303	893/850	830/777	224/234	322/311	130/108
SORT OUT XI, 2025 ¹⁹	Denmark	RCT	1	3,136	1,566/1,570	1,221/1,228	66.8±10.4/ 66.4±10.8	299/295	836/867	-	201/210	261/293	87/86

Values are n or mean±SD. Data are presented as biolimus-eluting stent group/sirolimus-eluting stent group. bio: biolimus; CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention; RCT: randomised clinical trial; SD: standard deviation; siro: sirolimus

proportion of patients with a history of myocardial infarction, prior PCI, or coronary artery bypass grafting (CABG) varied between studies, reflecting diverse cardiovascular risk profiles.

The architectural design, strut thickness, and polymer coatings of the evaluated devices varied chronologically across the included trials. In the earlier studies (Kadota et al in 2012, LEADERS in 2011, and SORT OUT V in 2013),¹⁴⁻¹⁶ the intervention group evaluated first-generation biolimus-eluting stents (Nobori [Terumo] or BioMatrix Alpha [Biosensors International Group]), which featured thick stainless-steel struts (120 µm) combined with a biodegradable poly(lactic acid; PLA) polymer applied exclusively to the abluminal surface. In contrast, their respective control arms utilised first-generation sirolimus-eluting stents (Cypher or Cypher Select+ [Cordis]), characterised by thicker stainless-steel struts (140 µm) encapsulated by a durable polymer matrix (polyethylene-co-vinyl acetate [PEVA]/poly-n-butyl methacrylate [PBMA]) with a conformal (360-degree) coating. In the subsequent contemporary trials, device profiles transitioned towards thinner geometries and modified carrier platforms. In SORT OUT VII (2024),¹⁷ the control arm shifted to the ultrathin-strut (60 µm) cobalt-chromium Orsiro (Biotronik) SES, which features an abluminal biodegradable polymer (poly-L-lactic acid [PLLA]). The intervention arms also evolved in SORT OUT IX (2025)¹⁸ and SORT OUT XI (2025),¹⁹ evaluating polymer-free BES platforms (BioFreedom and BioFreedom Ultra [both by Biosensors International Group]) that deliver biolimus directly from a microstructured metallic surface, with strut profiles refining from 120 µm stainless-steel to ultrathin 84 µm cobalt-chromium configurations, respectively.

OUTCOMES

CARDIAC DEATH

In early outcomes (≤1 year), BES were associated with a significant 30% reduction in cardiac death compared with SES (RR 0.70, 95% CI: 0.52-0.93; p=0.015; I²=0%) (Figure 2A). For midterm outcomes (1-5 years), based on three trials involving 6,111 patients (3,063 BES and 3,048 SES), cardiac death rates were similar between groups (RR 1.09, 95% CI: 0.85-1.40; p=0.495) (Figure 2B), with no observed heterogeneity (I²=0%).

ALL-CAUSE MORTALITY

A non-significant 19% reduction in all-cause mortality was observed with BES at early follow-up (RR 0.81, 95% CI: 0.64-1.01; p=0.058; I²=0%) (Figure 3A). At 5 years (3 studies, 3,063 BES and 3,048 SES), all-cause mortality remained similar between groups (RR 1.09, 95% CI: 0.93-1.28; p=0.283; I²=0%) (Figure 3B).

MAJOR ADVERSE CARDIOVASCULAR EVENTS

Five trials enrolling 8,973 patients (4,522 in BES and 4,451 in SES) showed similar MACE rates at ≤1 year (RR 0.95, 95% CI: 0.85-1.07; p=0.44; I²=0%) (Figure 4A). For outcomes between 1 and 5 years (3 studies, 2,995 BES vs 2,972 SES), MACE rates remained comparable (RR 0.98, 95% CI: 0.59-1.63; p=0.90; I²=64%) (Figure 4B).

MYOCARDIAL INFARCTION

Six studies reported myocardial infarction outcomes, showing no significant difference at early follow-up (RR 1.17, 95% CI: 0.94-1.45; p=0.16; I²=0%) (Figure 5).

TARGET LESION REVASCULARISATION

TLR rates were comparable at ≤1 year across all six studies (RR 1.29, 95% CI: 0.68-2.47; p=0.36; I²=74%) (Figure 6A). Between 1 and 5 years (3 studies, 3,016 BES vs 2,991 SES), results remained similar (RR 0.91, 95% CI: 0.46-1.78; p=0.60; I²=43%) (Figure 6B).

STENT THROMBOSIS

All studies reported on stent thrombosis, showing a non-significant early excess with BES (RR 1.85, 95% CI: 0.79-4.34; p=0.12; I²=44%) (Figure 7A). However, from 1 to 5 years (3 studies, 3,103 BES vs 3,084 SES), BES were associated with a significant 46% reduction in stent thrombosis (RR 0.54, 95% CI: 0.33-0.88; p=0.014; I²=0%) (Figure 7B).

SENSITIVITY ANALYSIS

Sensitivity analyses using the leave-one-out and funnel plots methods were performed to investigate sources of heterogeneity (Supplementary Figure 1, Supplementary Figure 2). For 1- to 5-year MACE outcomes, excluding the

LEADERS (2011)¹⁵ trial reduced the heterogeneity to 0% (**Supplementary Figure 2.3B**). For 1-year stent thrombosis, excluding SORT OUT VII (2023)¹⁷ reduced the heterogeneity to 25.9% (**Supplementary Figure 2.6A**). For TLR at 1 year, removing SORT OUT IX (2025)¹⁸ led to a heterogeneity of 53.4% (**Supplementary Figure 2.5A**), and for 1- to 5-year outcomes, excluding LEADERS (2011)¹⁹ reduced the heterogeneity to 0% (**Supplementary Figure 2.5B**).

QUALITY ASSESSMENT

All six RCTs were evaluated using the RoB 2 tool and consistently demonstrated a low risk of bias (**Supplementary Figure 3**), except for Kadota et al (2012) which exhibited a moderate risk, mainly due to heterogeneity in baseline characteristics. Although no statistically significant differences were reported between groups in this study, some variables, such as prior CABG surgery ($p=0.07$), were close to significance. Given the low number of outcome events in this trial, even marginal baseline differences could have influenced the observed results. Regarding publication bias, only the funnel plot for myocardial infarction at 5 years showed some asymmetry, which was supported by a significant Egger's test ($p=0.011$), indicating possible small-study effects or publication bias. However, given the small number of studies included ($n=3$), the reliability of both the visual inspection and statistical tests for publication bias is limited. Despite these issues, the overall findings are likely robust, as the concerns do not seem to have significantly affected the primary outcomes.

Discussion

This systematic review and meta-analysis provide a contemporary and robust comparison between BES and SES, assessing both short- and long-term clinical outcomes based on six randomised controlled trials that enrolled 12,109 patients. In the short term (≤ 1 year), BES were associated with a significant 30% reduction in cardiac death and a non-significant trend towards lower all-cause mortality, while rates of myocardial infarction, MACE, and TLR were comparable between groups. Early stent thrombosis appeared slightly higher in the BES group, though this difference was not statistically significant. Over the long term (1-5 years), clinical outcomes such as cardiac death, all-cause mortality, MACE, and TLR remained similar; however, BES were associated with a significant 46% reduction in stent thrombosis, suggesting a long-term safety advantage.

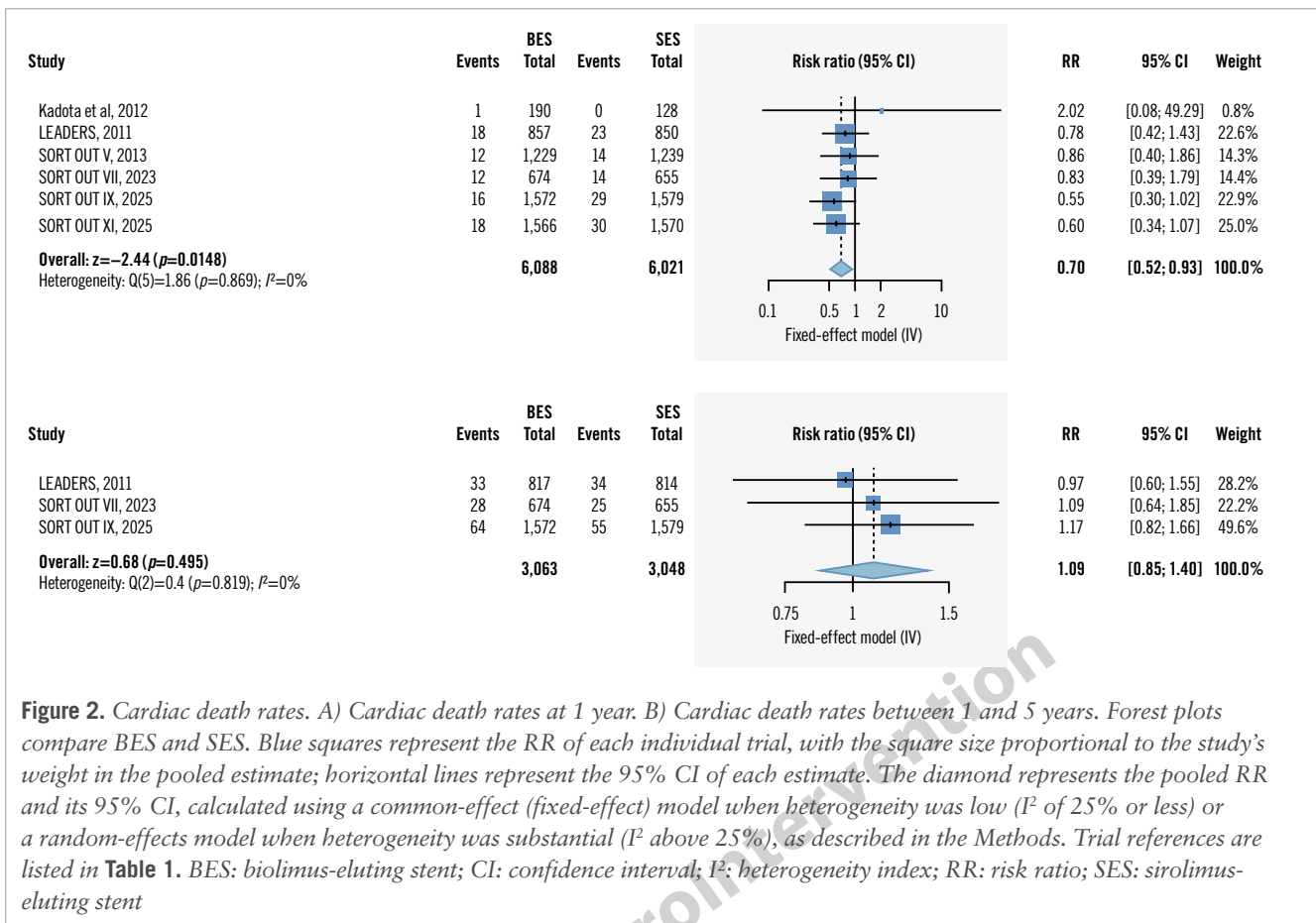
The most striking difference between the two stent platforms was observed in cardiac mortality at short-term follow-up, with BES reducing this risk by 30% compared with SES. Even though the comparison for overall mortality failed to reach statistical significance, the trend favoured BES (RR 0.81; $p=0.058$), suggesting a potential survival benefit. This early reduction in cardiac death may be attributed to differences in vascular healing dynamics and overall biocompatibility between the two stent platforms. Biolimus A9 (Biosensors International Group) is a highly lipophilic sirolimus analogue, enhancing arterial tissue uptake and retention, potentially allowing for more efficient drug delivery to the vessel wall.²⁰ When delivered via an abluminal coating on a biodegradable or polymer-free platform, this pharmacological profile may

promote a more physiological endothelial recovery, with reduced inflammatory response and less fibrin deposition.²¹ These properties may collectively contribute to the observed early safety advantage of BES by facilitating more complete and rapid vascular healing.

An apparent paradox in our short-term findings warrants careful pathophysiological consideration: BES achieved a significant 30% reduction in cardiac mortality despite displaying a non-significant, numerical excess in early stent thrombosis (RR 1.85). Given that early thrombotic events are often catastrophic, this divergent trend is likely explained by the mechanical and biological limitations of the first-generation durable-polymer SES comparators used in the earlier trials. These legacy SES platforms featured thick stainless-steel struts (140 μm) and rigid durable polymers that frequently triggered severe local hypersensitivity, persistent fibrin deposition, and impaired coronary vasomotion. These combined factors could cause sudden, non-thrombotic ischaemic cardiac mortality. Conversely, the abluminal biodegradable polymer or polymer-free design of the evaluated BES platforms minimises this chronic hypersensitivity burden early on. In addition, because the absolute event rates for early stent thrombosis were exceptionally low across all cohorts, the minor numerical imbalance in acute thrombotic events did not offset the broader early survival benefit derived from the enhanced biocompatibility and rapid endothelial healing characteristics of the BES systems.

Furthermore, a distinct temporal effect was observed in our subanalysis, demonstrating that the early reduction in cardiac mortality was largely driven by contemporary, late-era trials published around 2025, such as SORT OUT IX and SORT OUT XI.^{18,19} This chronological shift reflects the major iterative breakthroughs in stent architecture over the last decade. While earlier trials evaluated first-generation BES with thick stainless-steel platforms coated with biodegradable polymers, the 2025 trials investigated advanced polymer-free BES designs (BioFreedom and BioFreedom Ultra) that deliver biolimus directly from microstructured surfaces, accompanied by a reduction in strut thickness to 84 μm . By entirely eliminating the carrier polymer, these modern platforms completely bypass the transient local inflammatory phase traditionally caused by polymer degradation during the first year. This design allows for exceptionally rapid, high-quality re-endothelialisation and optimised local drug-elution dynamics. Consequently, this architectural evolution explains why the short-term survival benefit of BES became prominent and pronounced only in the contemporary era, even when evaluated against modern, ultrathin-strut SES comparators.^{14,20-23}

These safety advantages, however, appear to be time dependent. While BES were numerically associated with a higher risk of early stent thrombosis (RR 1.85; $p=0.12$), this difference was not statistically significant and may reflect a brief phase of thrombotic vulnerability during polymer resorption and incomplete endothelial coverage.²² Importantly, beyond the first year, BES conferred a 46% relative reduction in stent thrombosis ($p=0.014$), with consistent results across trials ($I^2=0\%$). However, it is important to note that most biolimus-eluting stents were combined with biodegradable polymers, making it difficult to disentangle the effects of



the drug from those of the polymer.^{14,20} This co-association introduces a potential bias, as the observed benefits may partly reflect the favourable biological response to a reduced polymer burden, such as lower inflammation and improved healing, rather than the drug alone. Supporting this, a recent meta-analysis showed a significant reduction in very late stent thrombosis with biodegradable-polymer DES compared with durable-polymer counterparts.²³

In contrast, the efficacy endpoints for myocardial infarction, MACE, and TLR remained comparable between stents in both timeframes. Myocardial infarction rates were similar at early and midterm follow-up (RR 1.17 and 0.91, respectively), consistent with prior randomised trials demonstrating non-inferiority among newer-generation DES in preventing ischaemic complications.¹⁹ TLR rates also did not differ significantly between BES and SES, though a high degree of heterogeneity was observed in the early period ($I^2 = 74\%$). This variability likely reflects differences in trial populations and procedural factors rather than intrinsic differences between stent platforms. The neutrality in these endpoints highlights that both stents effectively suppress neointimal proliferation, which is expected given that both sirolimus and biolimus are potent mTOR inhibitors with established antirestenotic properties.

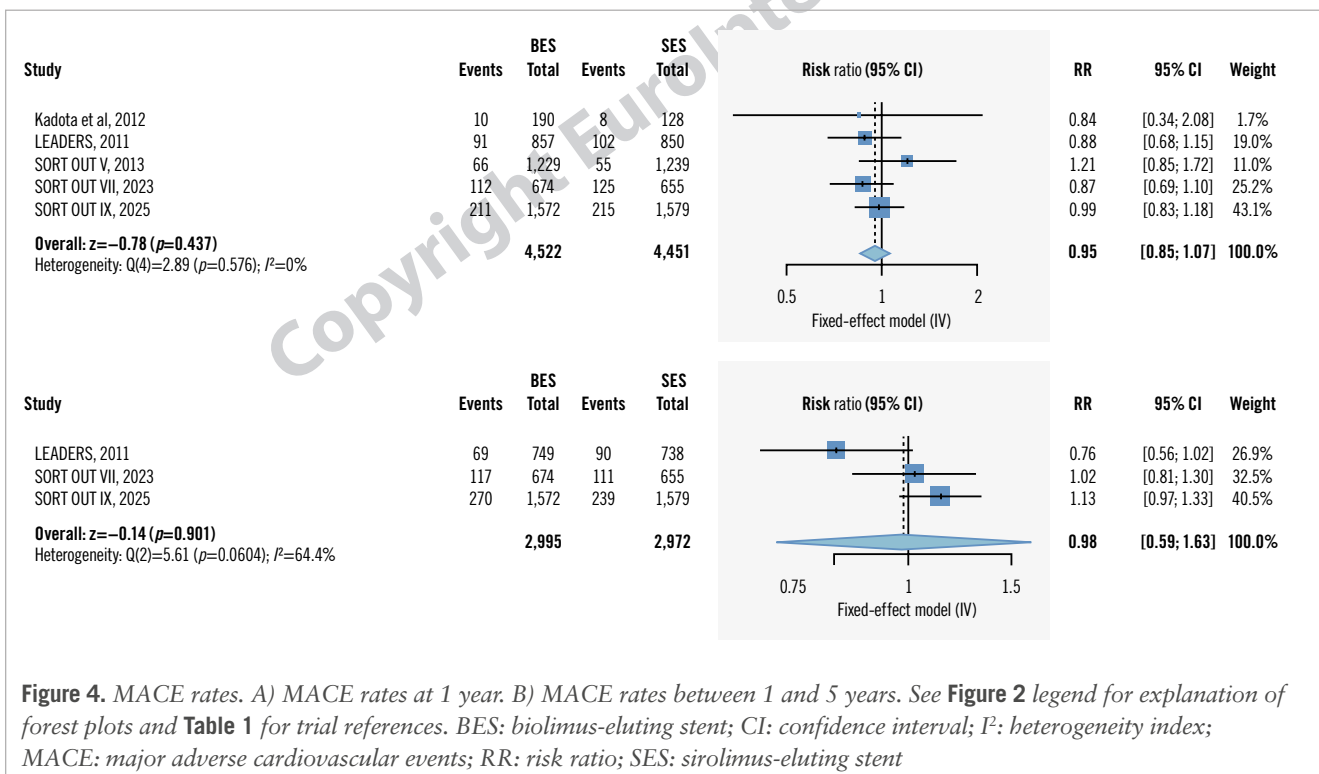
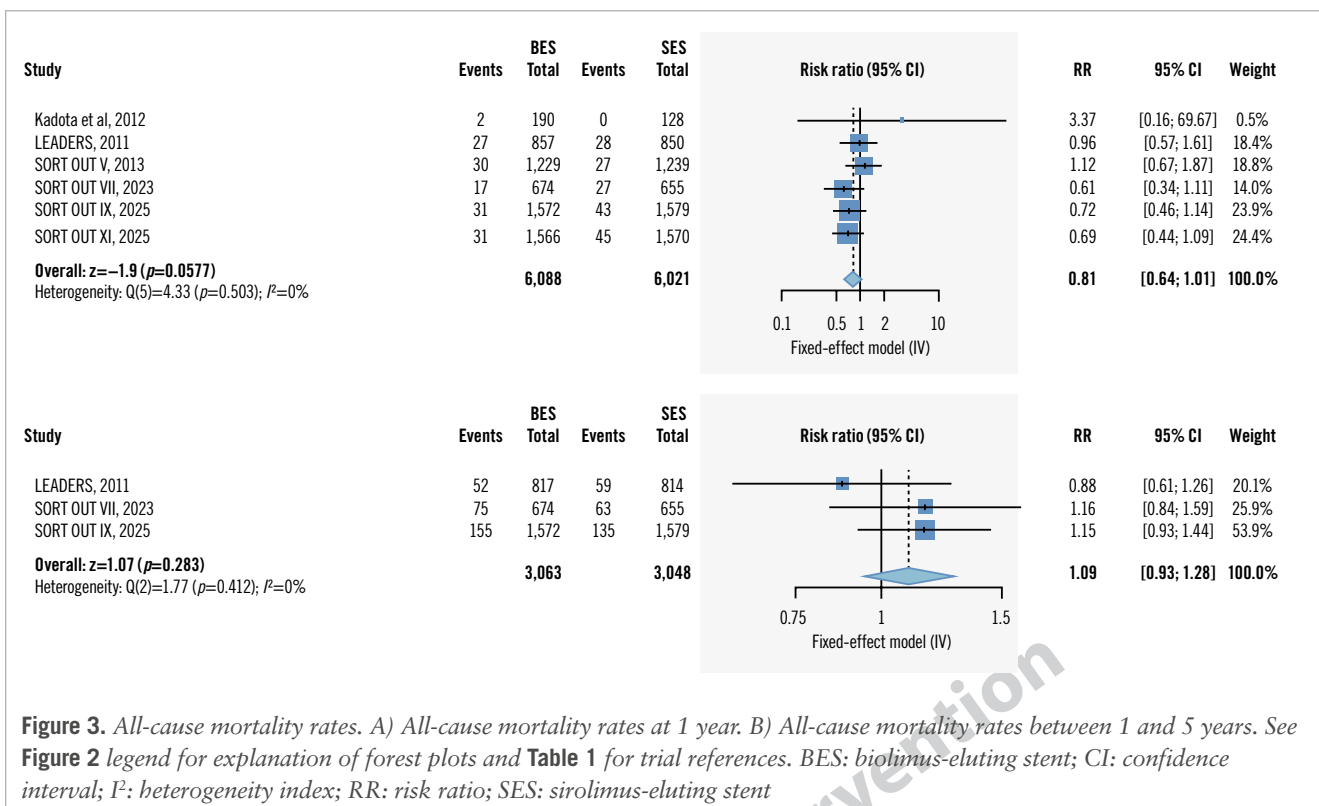
Furthermore, the temporal convergence of mortality rates after the first year, characterised by a late catch-up in mortality within the BES group, warrants physiological clarification. This phenomenon is primarily driven by the degradation kinetics of the biodegradable-polymer platforms. The localised

biocompatibility advantages of BES are most pronounced during the first 6 to 12 months, a critical window when active polymer resorption occurs and standard durable polymers are most prone to inducing hypersensitivity and delayed endothelialisation. Once the biodegradable matrix is fully resorbed, the remaining metallic construct behaves similarly across advanced platforms, causing the initial survival curves to run parallel or converge over midterm follow-up. Additionally, late clinical outcomes beyond 1 year are increasingly dictated by systemic neoatherosclerosis and the natural progression of native coronary artery disease rather than device-specific components, which naturally dilutes the early localised safety benefits offered by the BES platform.¹⁶⁻²³

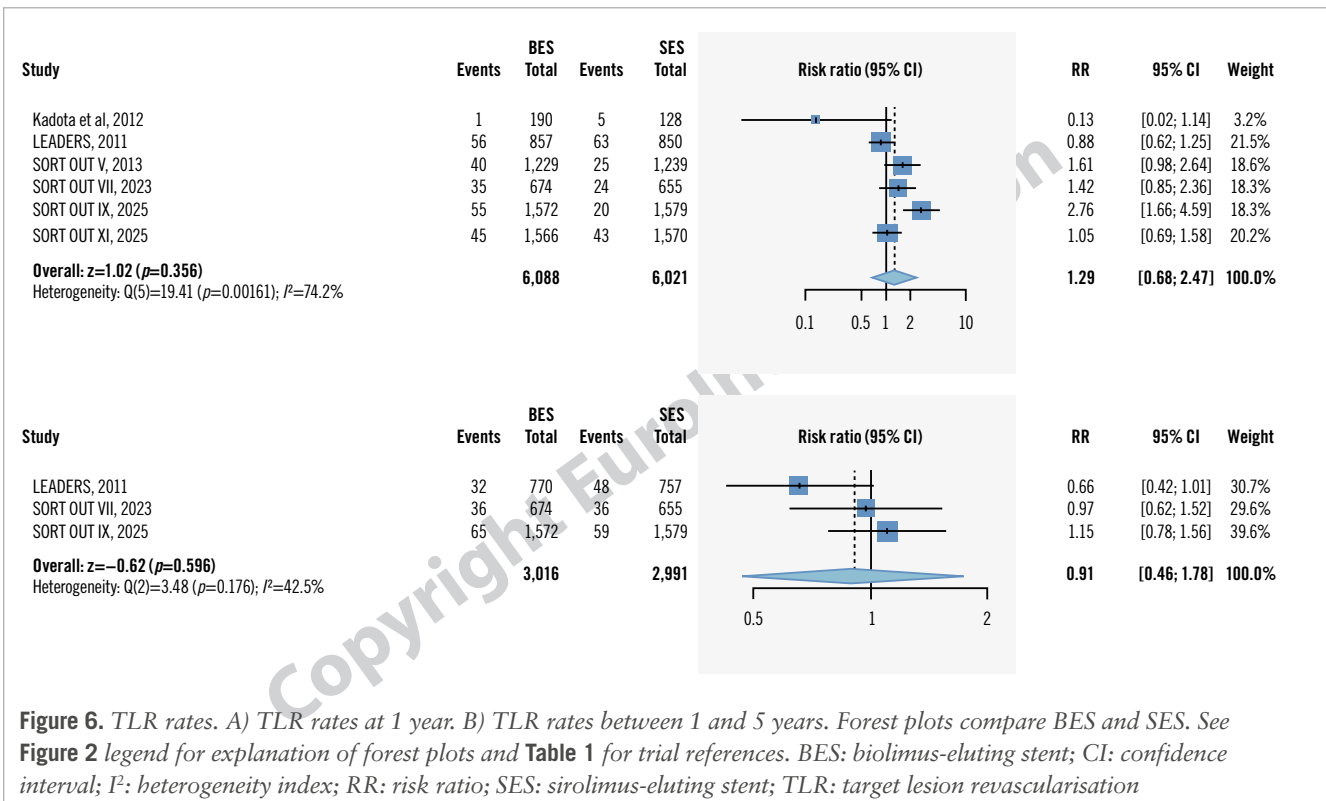
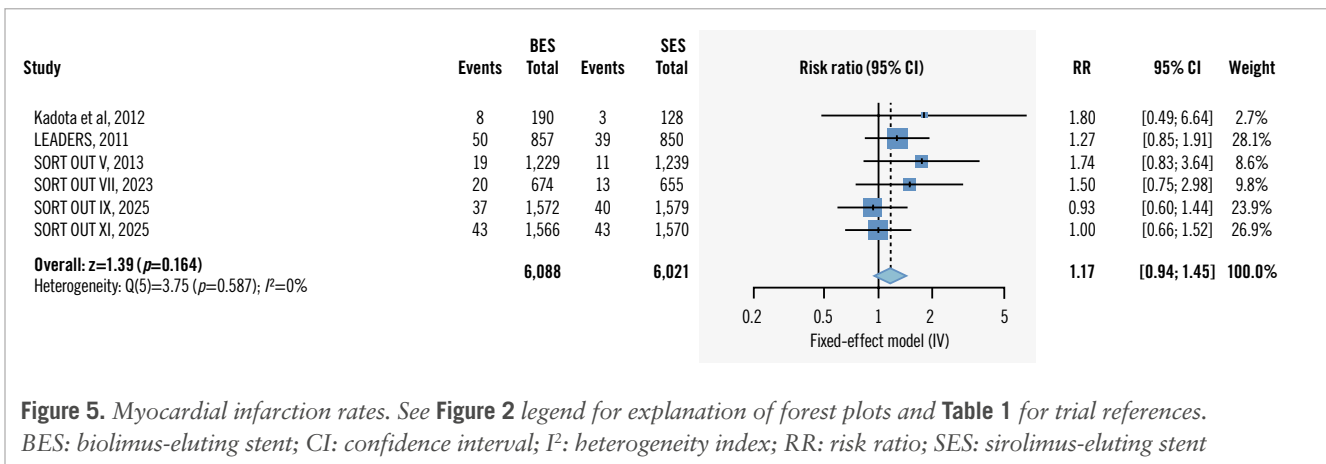
Beyond the observed outcomes, the clinical interpretation of these findings must also consider the heterogeneity in stent design, such as strut thickness, polymer type, and coating techniques, which represents an important confounding factor when comparing DES platforms. These structural characteristics can independently influence vascular healing, inflammation, and thrombotic risk, making it challenging to isolate the clinical impact of the antiproliferative drug alone. These considerations highlight the need for future studies using more standardised stent designs to better delineate the individual impact of the drug, polymer, and structural features on clinical endpoints.

Limitations

This study has several strengths, including the exclusive inclusion of randomised trials, stratification by follow-up



duration, and low heterogeneity across most outcomes. However, some limitations warrant consideration. First, the SES comparators varied significantly between studies, encompassing different device generations with substantial heterogeneity in strut thickness, polymer composition (durable vs biodegradable), and coating techniques. This structural variation across control groups introduces a chronological and technical bias, as variations in mechanical profiles can independently impact vessel injury and long-term re-endothelialisation, making a uniform benchmark comparison challenging. Second, an inherent methodological limitation is the confounding interplay



between the antiproliferative drug and its carrier platform. Because the evaluated BES technologies are coupled with biodegradable polymers, it is mathematically and clinically difficult to isolate whether the long-term safety benefits are driven by the specific properties of biolimus or by the gradual resorption of the polymer matrix. Third, the availability of long-term data was limited, as only three of the six trials provided midterm (1- to 5-year) outcomes. This reduction in sample size effectively halves the total evaluable patient population for the midterm period, limiting the statistical power to detect differences in rare but critical endpoints, such as late stent thrombosis. All of these factors may have directly influenced the clinical outcomes evaluated in this study. Fourth, a moderate risk of bias due to baseline characteristic imbalances was identified in one included trial (Kadota et al [2012]). Although this trial represents a small proportion of

the overall cohort, its marginal baseline variations could have disproportionately influenced its specific endpoints due to a low absolute event rate, thereby introducing minor residual confounding to the pooled estimates.

Conclusions

This meta-analysis of six randomised trials demonstrates that, from a holistic perspective, BES and SES yield highly comparable overall outcomes, displaying equivalent efficacy in reducing myocardial infarction, MACE, and TLR across all time frames. Within this landscape of clinical similarity, BES exhibit targeted safety advantages, characterised by a significant early reduction in cardiac mortality and a substantial long-term reduction in stent thrombosis compared with SES. These findings highlight the clinical relevance of polymer biodegradability and drug release

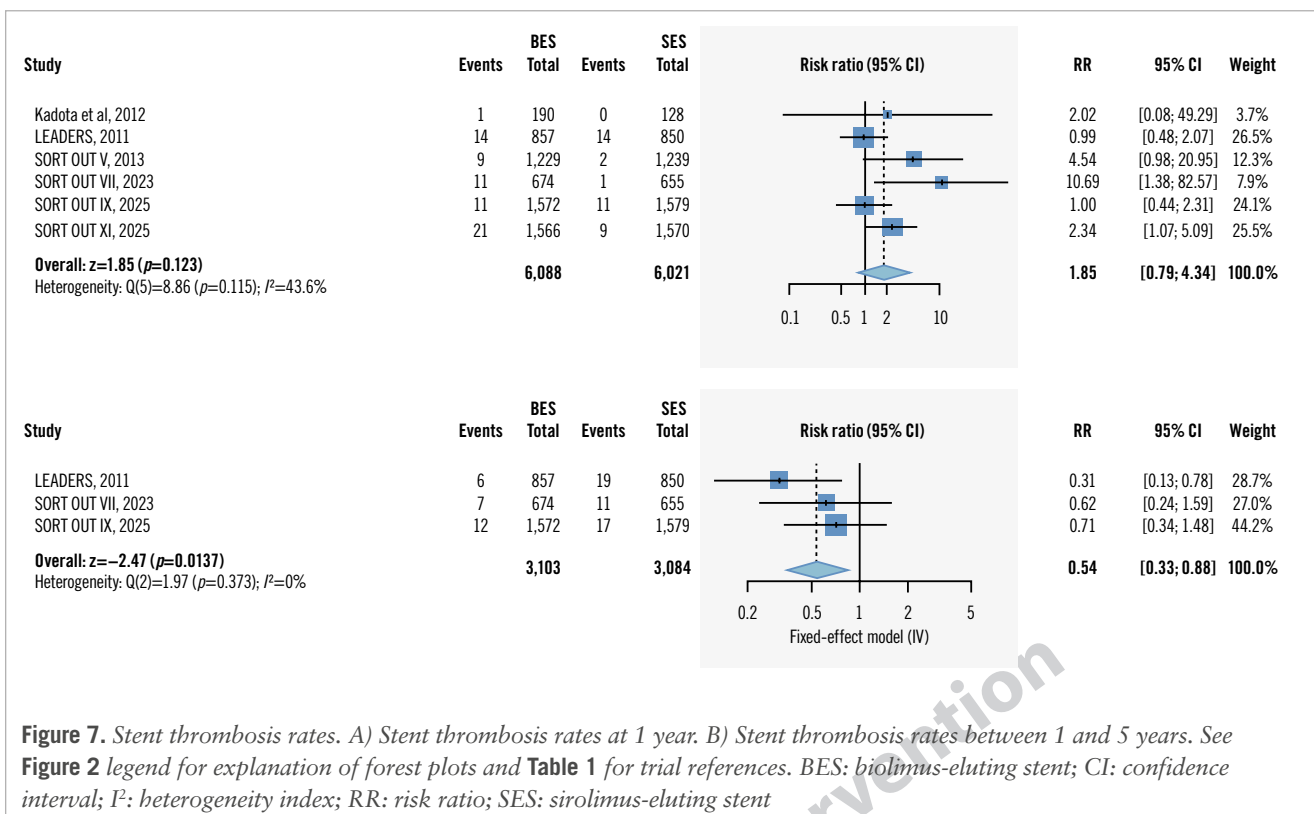


Figure 7. Stent thrombosis rates. A) Stent thrombosis rates at 1 year. B) Stent thrombosis rates between 1 and 5 years. See Figure 2 legend for explanation of forest plots and Table 1 for trial references. BES: biolimus-eluting stent; CI: confidence interval; I^2 : heterogeneity index; RR: risk ratio; SES: sirolimus-eluting stent

kinetics in shaping safety outcomes, without shifting the devices' overall morbidity profile. Additional randomised investigations will be essential to isolate the effect of the drug itself by controlling structural stent factors, allowing a more accurate assessment of the clinical benefits attributable to the antiproliferative agent.

Authors' affiliations

1. Department of Medicine, Cesmac University Center, Maceió, Brazil; 2. Department of Medicine, University of São Paulo, São Paulo, Brazil; 3. Department of Medicine, State University of Pará, Belém, Brazil; 4. Department of Medicine, 9 of July University, São Paulo, Brazil; 5. Department of Medicine, Anhembi Morumbi University, São Paulo, Brazil; 6. Department of Medicine, Federal University of Uberlândia, Uberlândia, Brazil; 7. Department of Internal Medicine, Hospital and Maternity Marieta Konder Bornhausen, Itajaí, Brazil; 8. Division of Interventional Cardiology, Santa Casa de Misericórdia de Maceió, Maceió, Brazil; 9. Division of Interventional Cardiology, University of Miami, Miami, FL, USA; 10. Division of Interventional Cardiology, InCor, São Paulo, Brazil; 11. Division of Interventional Cardiology, Dante Pazzanese Institute of Cardiology, São Paulo, Brazil; 12. Division of Cardiology, Department of Medicine, University of Washington, Seattle, WA, USA

AI statement

Artificial intelligence (ChatGPT) was used to cross-verify the manual data extraction performed independently by two reviewers and to refine the technical English phrasing of the manuscript. The authors take full responsibility for the veracity of all data included in this paper.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. PRISMA 2020 main checklist.

Supplementary Appendix 2. PRISMA abstract checklist.

Supplementary Figure 1. Funnel plots.

Supplementary Figure 2. Leave-one-out sensitivity analysis.

Supplementary Figure 3. RoB 2.0 of included studies.

The supplementary data are published online at:

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Supplementary data

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Supplementary Appendix 1. PRISMA 2020 main checklist.

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	Pg. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg. 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg. 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg. 4
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg. 4
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	Pg. 4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg. 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg. 4,5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg. 4
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pg. 4,5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg. 5

Topic	No.	Item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	Pg. 4,5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Pg. 4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pg 4,5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pg. 4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg, 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	Pg. 4-5, 8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pg. 8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pg. 5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pg. 8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Figure 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Pg. 6-7
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	Pg. 6-8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pg. 6-8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pg. 8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Supplementary Figure 1, Supplementary Figure 2

Topic	No.	Item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supplementary Figure 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pg. 8
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg. 8-9
	23b	Discuss any limitations of the evidence included in the review.	Pg. 8-10
	23c	Discuss any limitations of the review processes used.	Pg. 9-10
	23d	Discuss implications of the results for practice, policy, and future research.	Pg 9-10
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	CRD420251119555
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg. 3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Pg.3-4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	None
Competing interests	26	Declare any competing interests of review authors.	Pg. 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

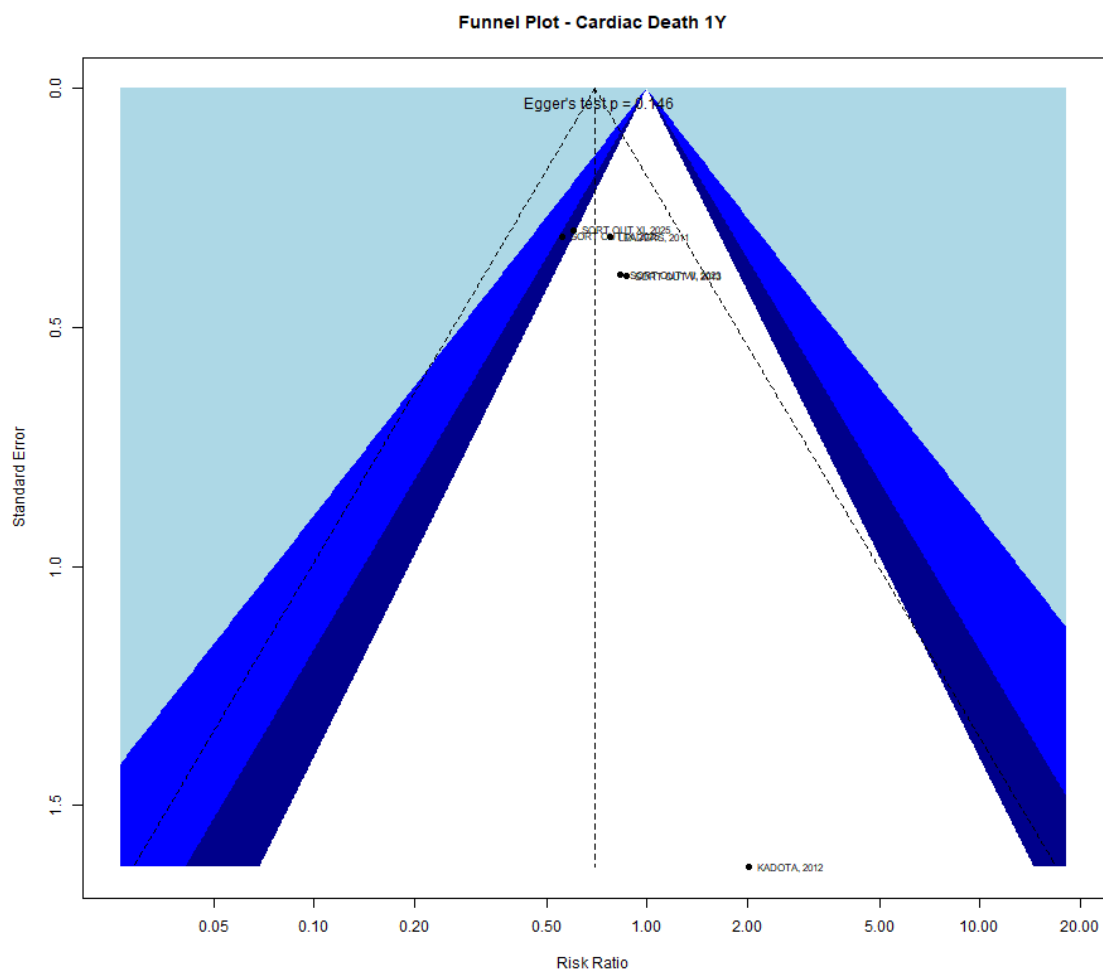
Abbreviations: MS, manuscript; sup., supplement.

Supplementary Appendix 2. PRISMA abstract checklist.

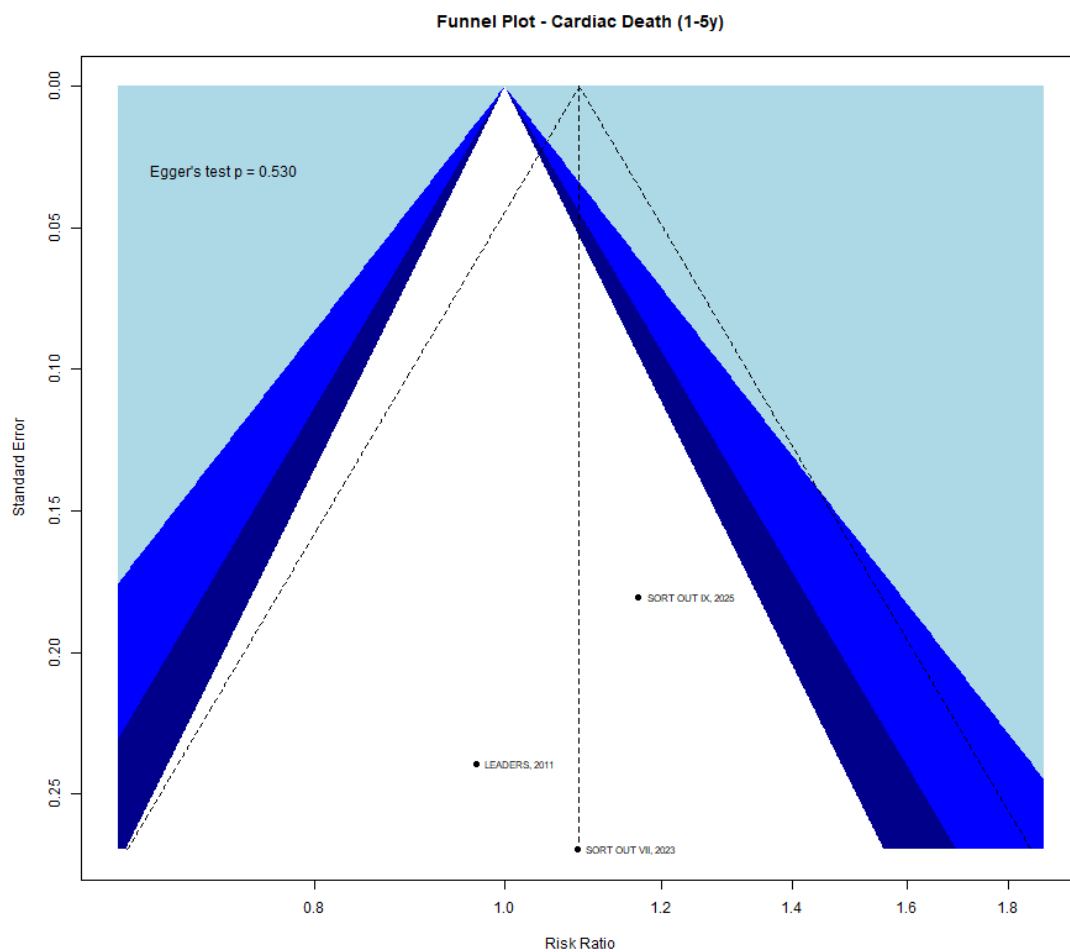
Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g., databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	-
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarize relevant characteristics of studies.	-
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e., which group is favored).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g., study risk of bias, inconsistency and imprecision).	-
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	None
Registration	12	Provide the register name and registration number.	Yes

Supplementary Figure 1. Funnel plots.

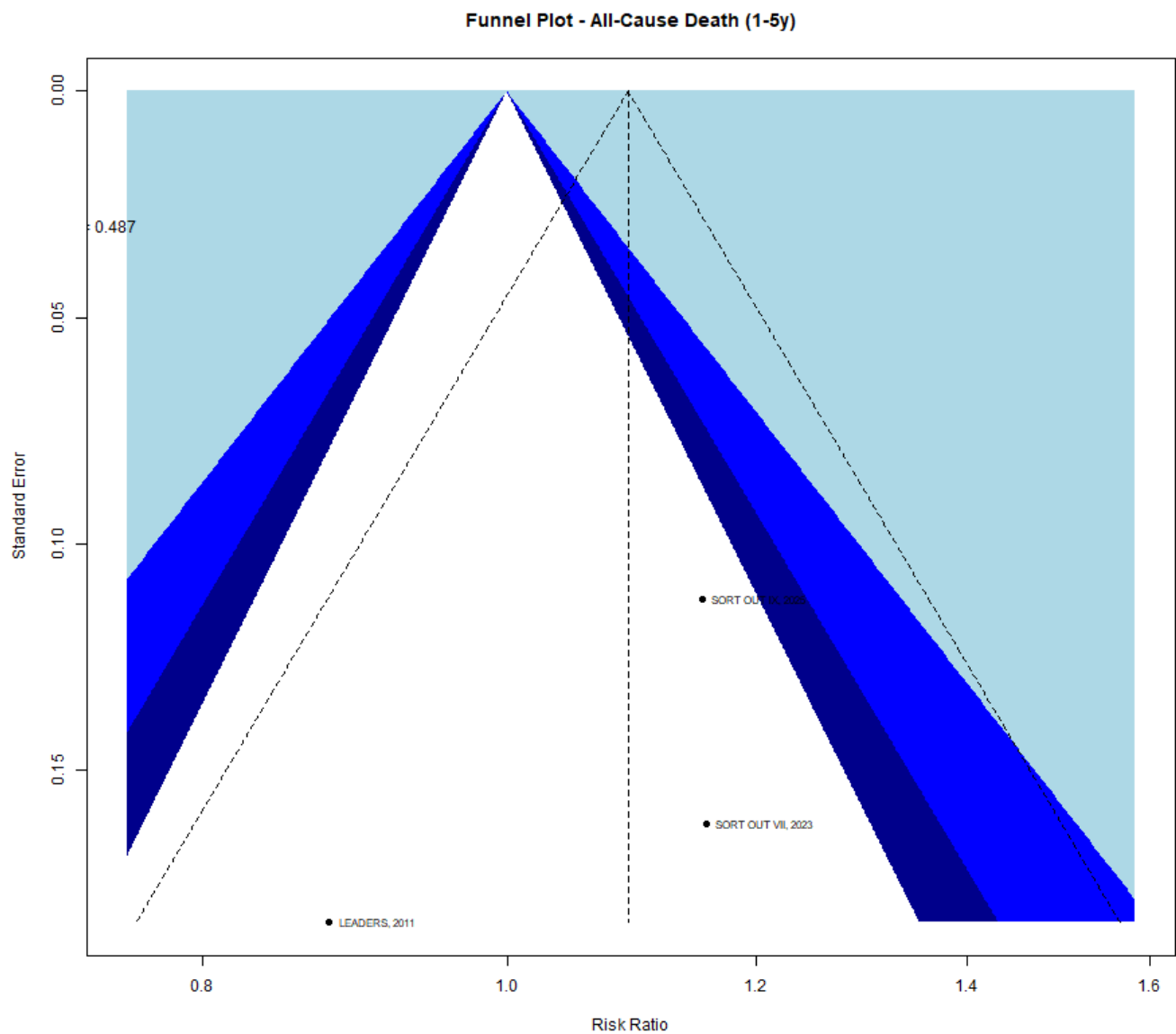
Contour-enhanced funnel plots assessing small-study effects and potential publication bias for each outcome and follow-up period, plotting the risk ratio (RR, x-axis, log scale) of each included trial against its standard error (y-axis). Shaded contour bands denote conventional levels of statistical significance (p below 0.10, p below 0.05, and p below 0.01); studies falling in the unshaded, outer region are non-significant at the two-sided 10% level. The dashed vertical line indicates the pooled effect estimate. The p-value from Egger's test for funnel plot asymmetry is displayed on each plot. RR: Risk Ratio.



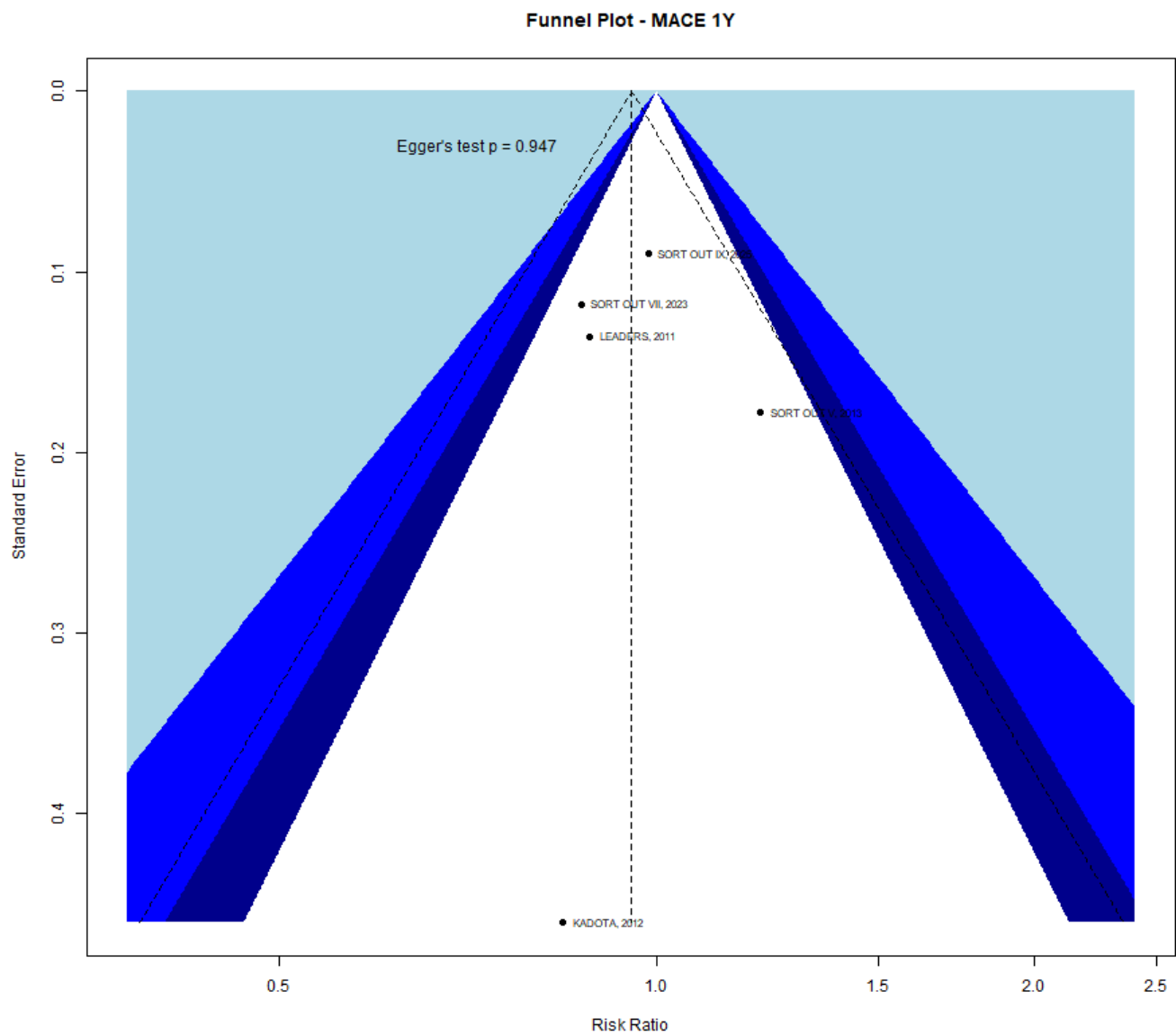
Supplementary Figure 1.1A. Funnel plot for cardiac death (1 year).



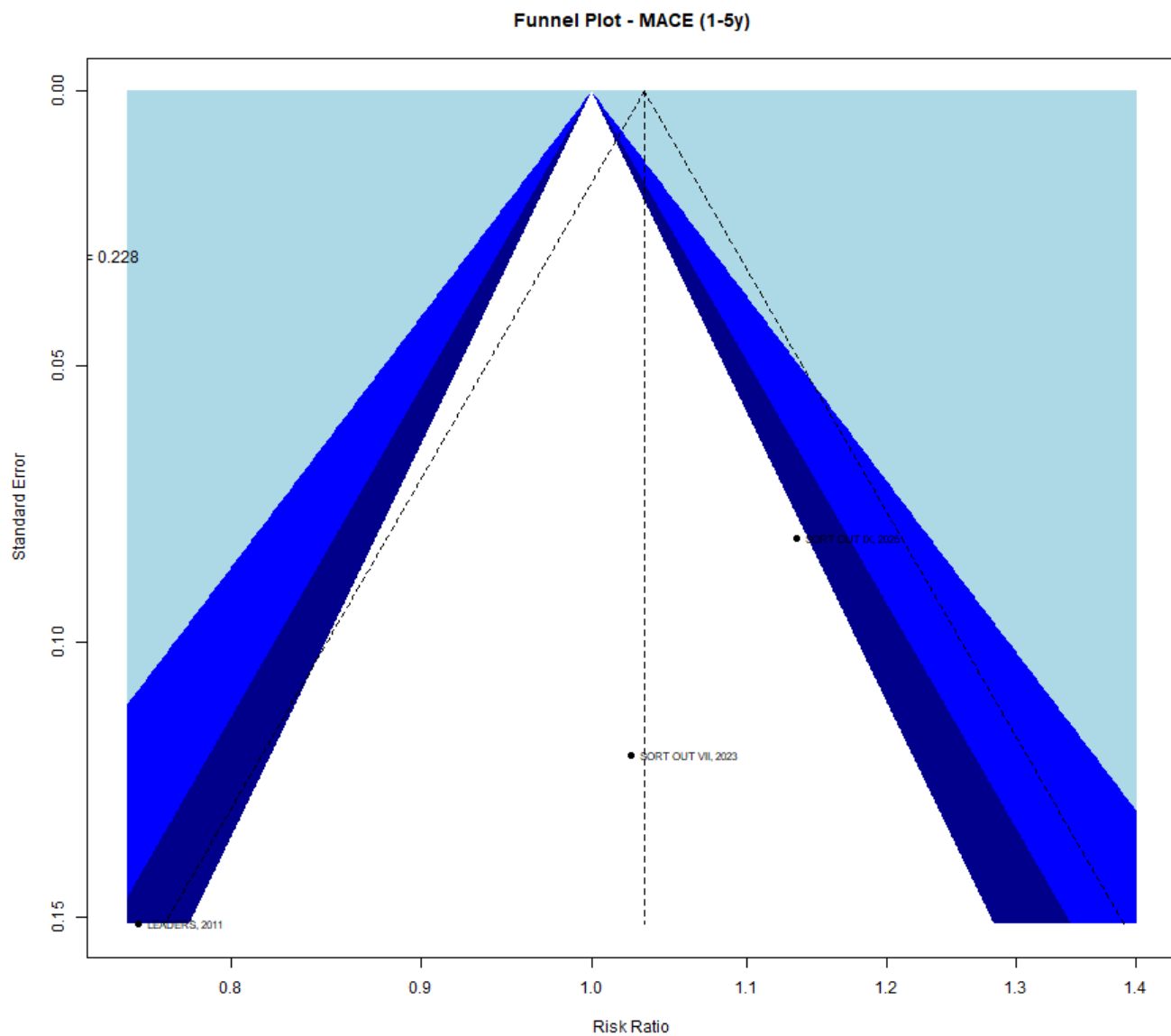
Supplementary Figure 1.1B. Funnel plot for cardiac death (1-5 year).



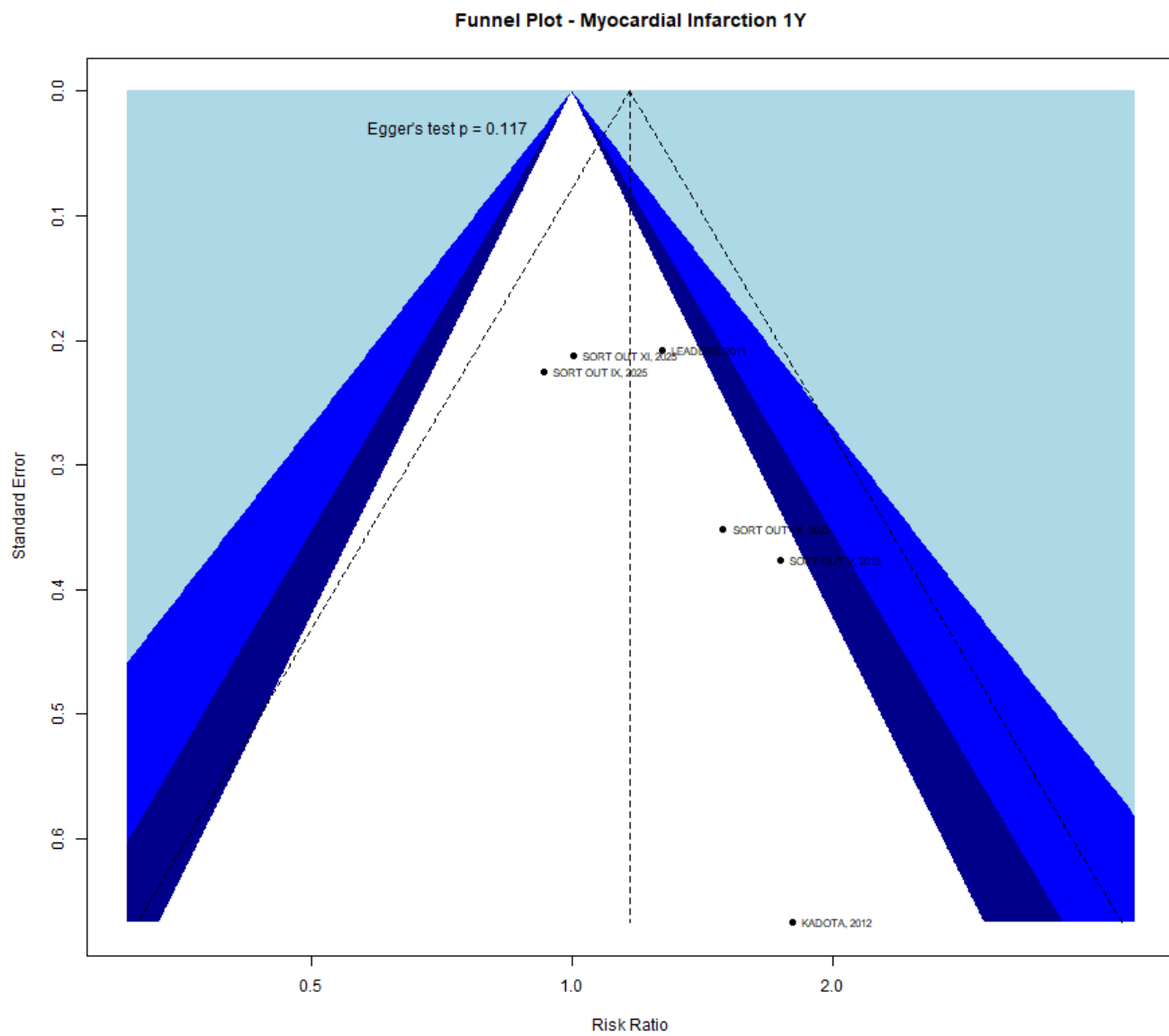
Supplementary Figure 1.2B. Funnel plot for all-cause mortality (1-5 year).



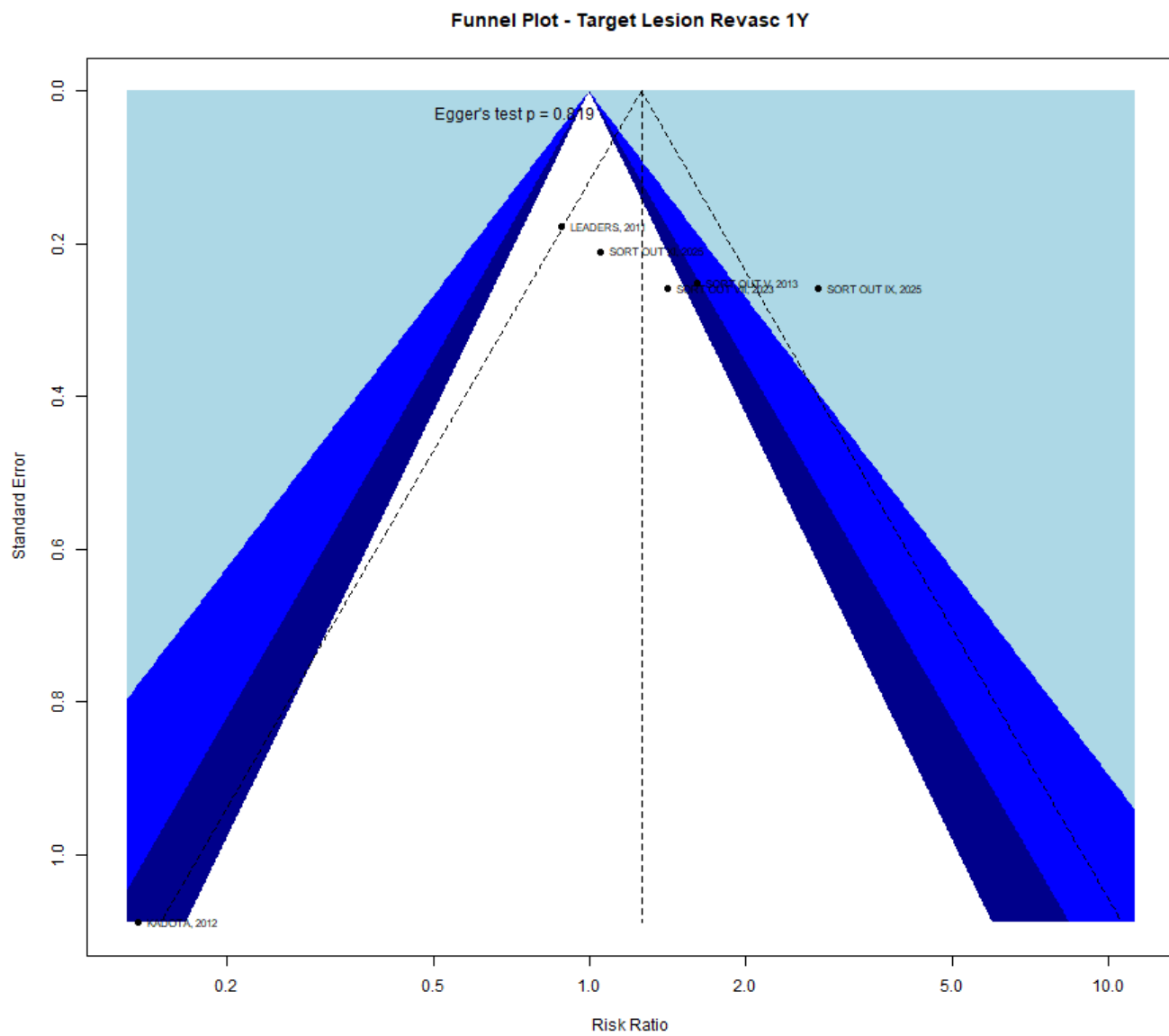
Supplementary Figure 1.3A. Funnel plot for major adverse cardiovascular events (1 year).



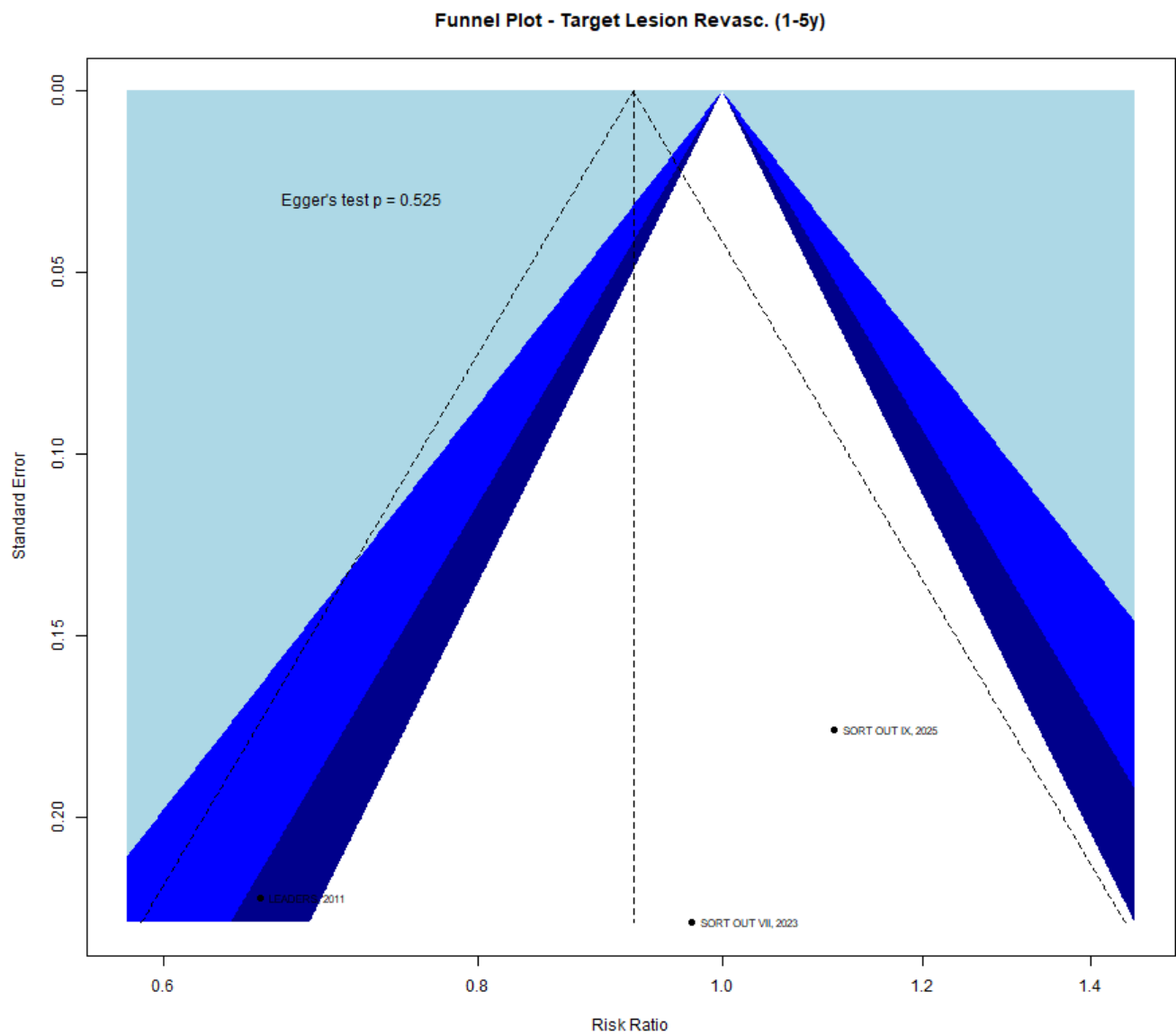
Supplementary Figure 1.3B. Funnel plot for major adverse cardiovascular events (1-5 year).



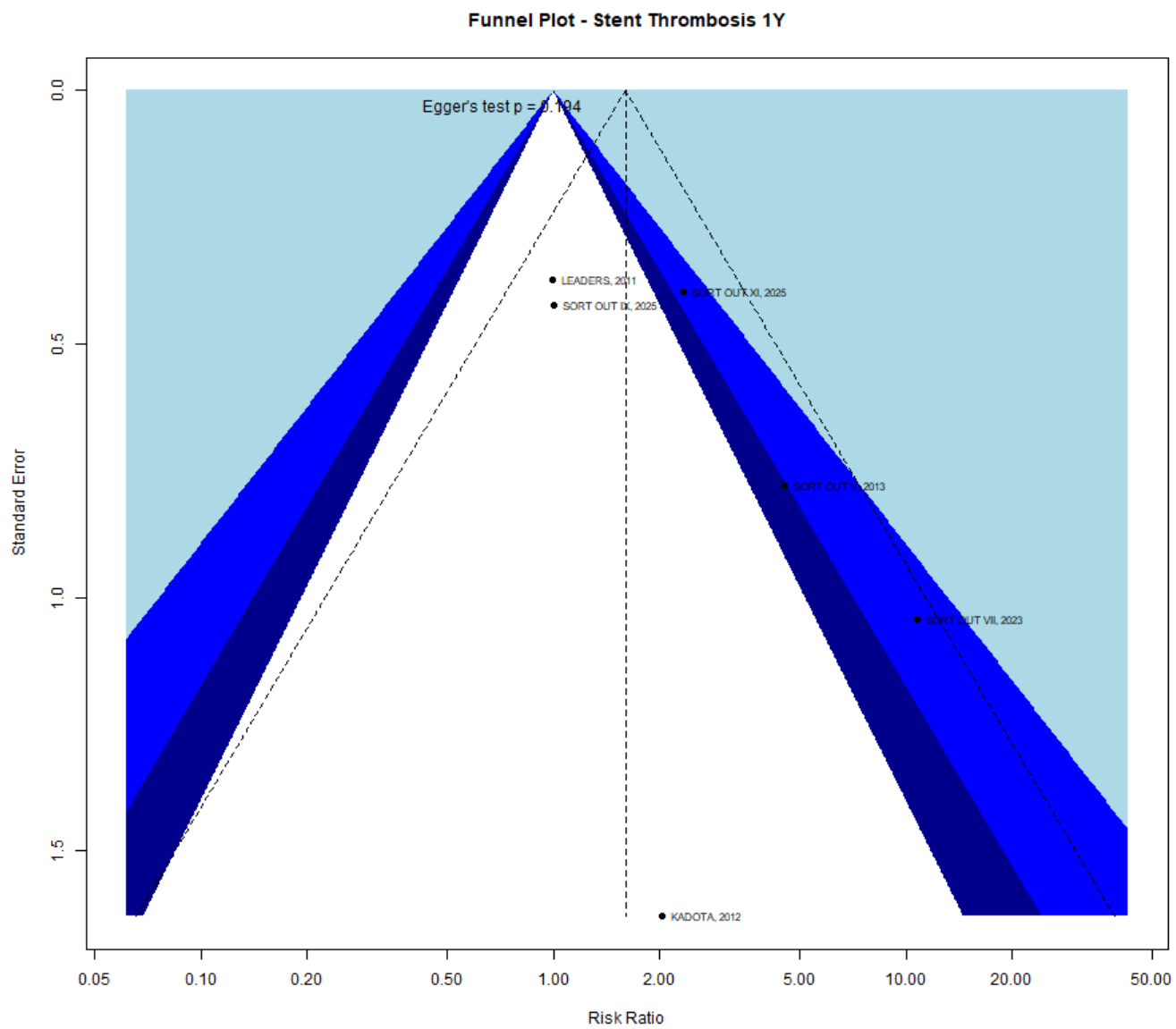
Supplementary Figure 1.4. Funnel plot for myocardial infarction (1 year).



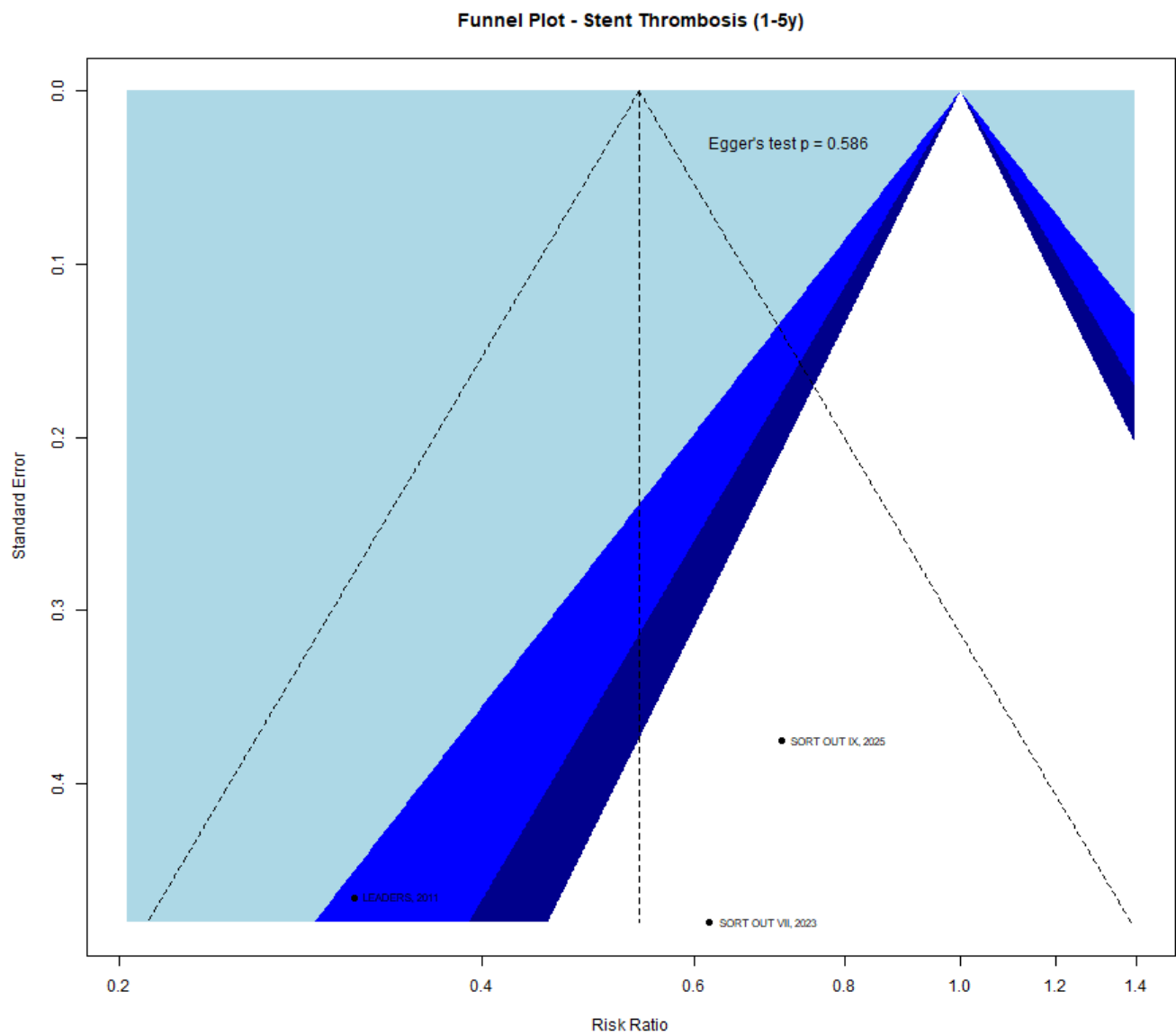
Supplementary Figure 1.5A. Funnel plot for target lesion revascularisation (1 year).



Supplementary Figure 1.5B. Funnel plot for target lesion revascularisation (1-5 year).



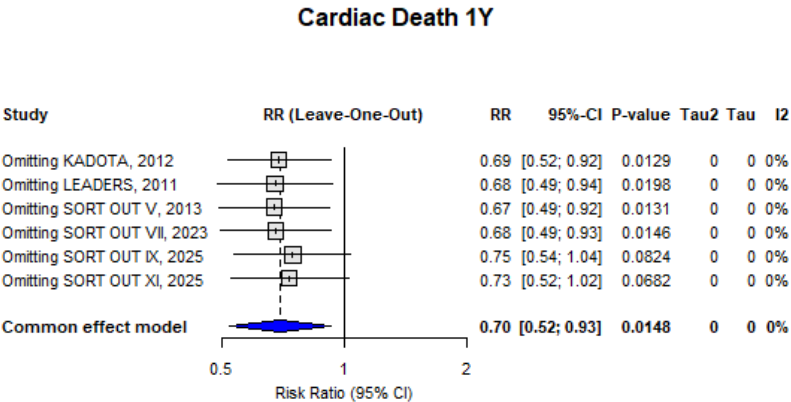
Supplementary Figure 1.6A. Funnel plot for stent thrombosis (1 year).



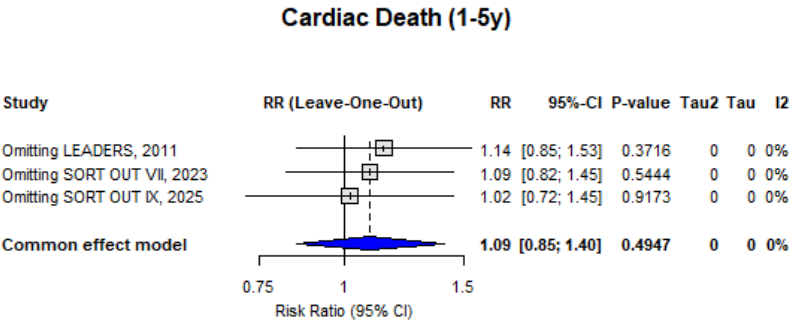
Supplementary Figure 1.6B. Funnel plot for stent thrombosis (1-5 year).

Supplementary Figure 2. Leave-one-out analysis.

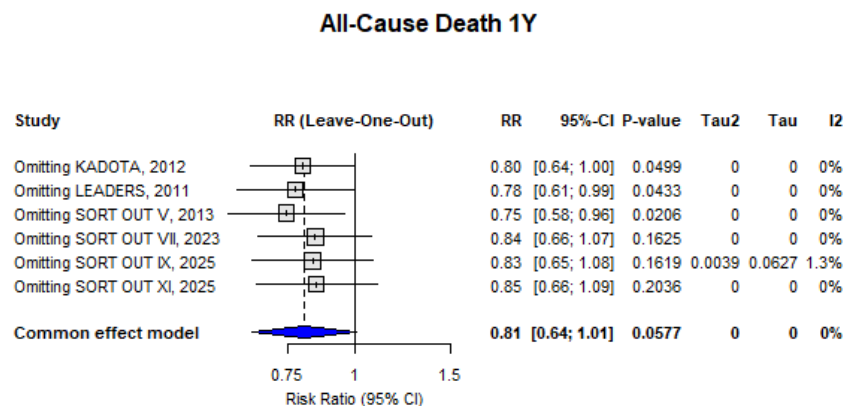
Leave-one-out sensitivity analysis for each outcome and follow-up period. Each row shows the pooled risk ratio (RR) and 95% confidence interval (CI) recalculated after sequentially omitting one study at a time, to assess the influence of individual studies on the overall effect estimate and on heterogeneity; the bottom row (diamond) shows the pooled estimate with all studies included (common-effect model). RR: Risk Ratio; CI: Confidence Interval; Tau²: between-study variance; Tau: square root of Tau², i.e. the standard deviation of true effect sizes across studies; I²: heterogeneity index



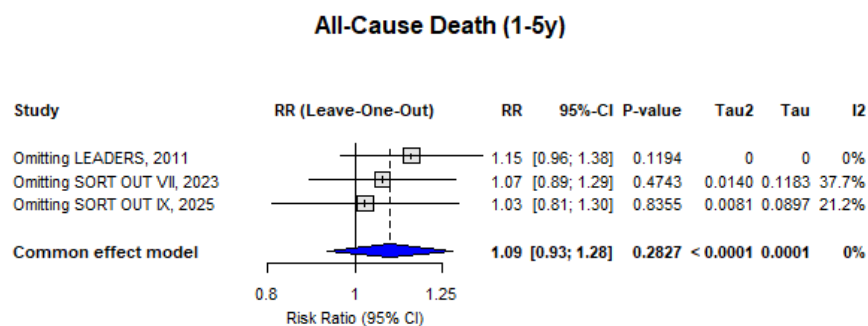
Supplementary Figure 2.1A. Leave-one-out for cardiac death (1 year).



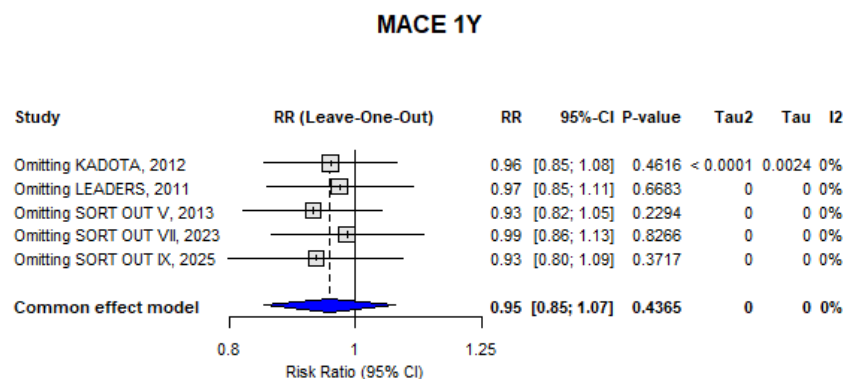
Supplementary Figure 2.1B. Leave-one-out for cardiac death (1-5 year).



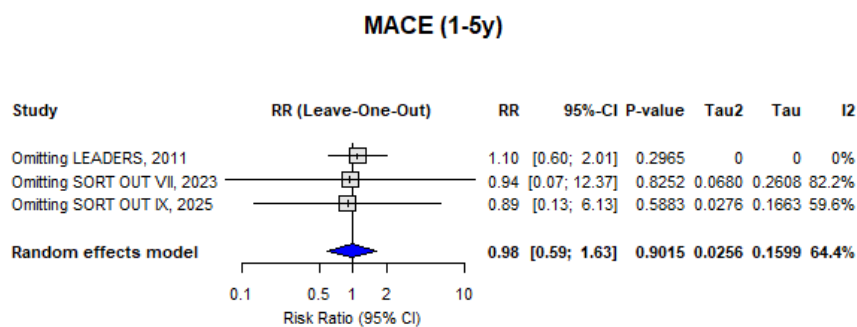
Supplementary Figure 2.2A. Leave-one-out for all-cause mortality (1 year).



Supplementary Figure 2.2B. Leave-one-out for all-cause mortality (1-5 year).

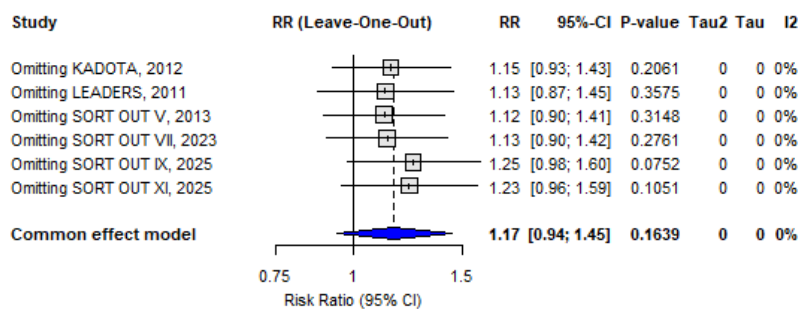


Supplementary Figure 2.3A. Leave-one-out for major adverse cardiovascular events (1 year).

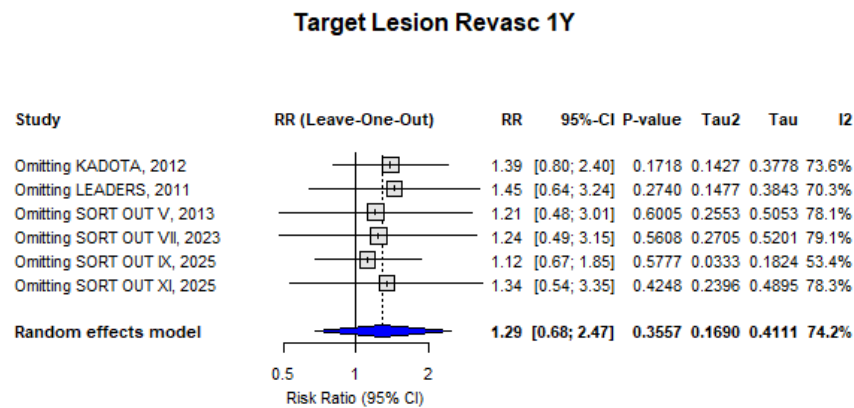


Supplementary Figure 2.3B. Leave-one-out for major adverse cardiovascular events (1-5 year).

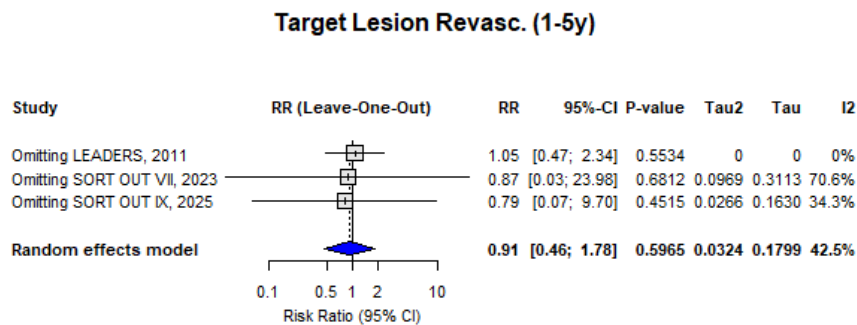
Myocardial Infarction 1Y



Supplementary Figure 2.4A. Leave-one-out for myocardial infarction (1 year).

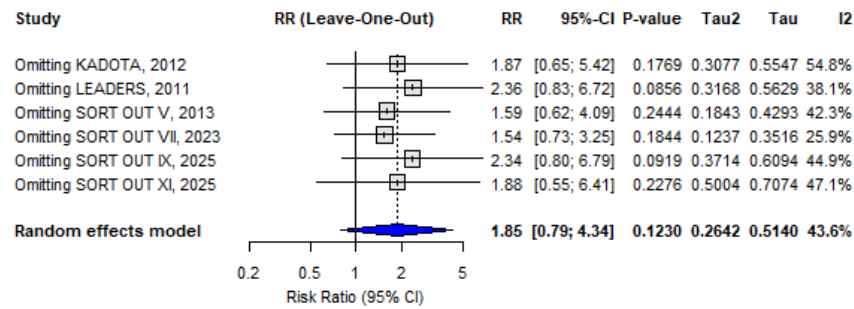


Supplementary Figure 2.5A. Leave-one-out for target lesion revascularisation (1 year).



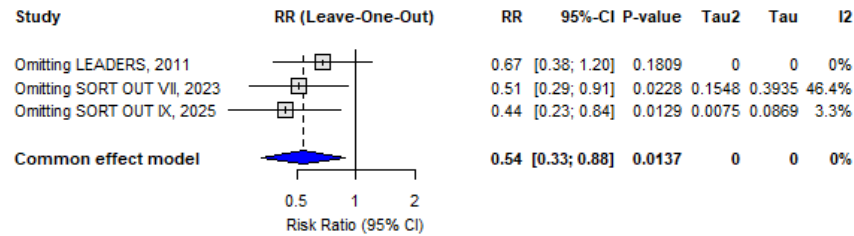
Supplementary Figure 2.5B. Leave-one-out for target lesion revascularization (1-5 year).

Stent Thrombosis 1Y



Supplementary Figure 2.6A Leave-one-out for stent thrombosis (1 year).

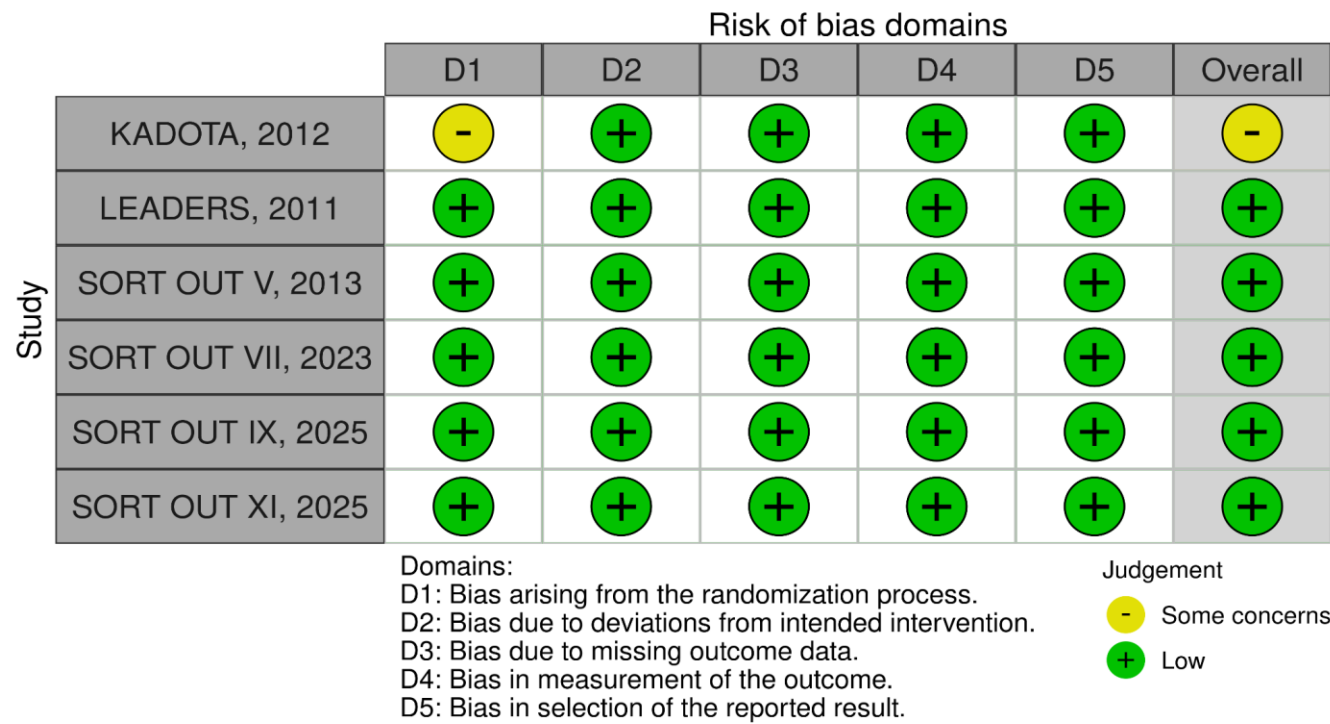
Stent Thrombosis (1-5y)



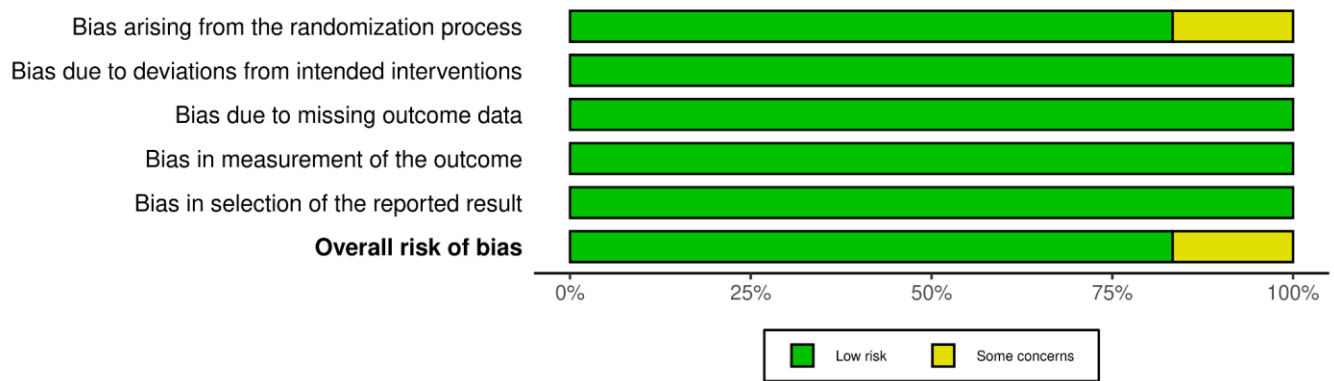
Supplementary Figure 2.6B. Leave-one-out for stent thrombosis (1-5 year).

Supplementary Figure 3. Risk of Bias (RoB) 2.0 of included studies.

Risk-of-bias assessment of included randomized controlled trials using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool. (A) Traffic-light plot displaying the risk-of-bias judgment for each domain in each included trial. (B) Weighted bar plot summarizing, across all studies, the overall proportion of trials at each risk-of-bias level for each domain. D1: bias arising from the randomization process; D2: bias due to deviations from intended interventions; D3: bias due to missing outcome data; D4: bias in measurement of the outcome; D5: bias in selection of the reported result. Green indicates low risk of bias; yellow indicates some concerns. RoB 2.0: Risk of Bias 2.0 tool.



Supplementary Figure 3A. “Traffic light” plot of the domain-level judgments for each study.



Supplementary Figure 3B. Summary of the overall weighted bar plot of risk-of-bias judgments within each bias domain.