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Temporal trends in clinical outcomes after percutaneous coronary intervention: a systematic review of 66,327 patients from 25 all-comers trials

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KEYWORDS

- ACS/NSTE-ACS
- drug-eluting stent
- stable angina

Abstract

Background: With the improvements of percutaneous coronary intervention (PCI) technology and post-PCI patient management, several registry studies reported temporal trends in post-PCI clinical outcomes. However, their results are inconclusive, potentially reflecting region-specific trends, based on site-reported events without external validity.

Aims: This study aimed to investigate temporal trends in post-PCI clinical outcomes in all-comers randomised controlled trials (RCTs) involving coronary stents.

Methods: We performed a systematic review identifying RCTs comparing a clinical outcome as a primary endpoint among different coronary stents with an all-comers design and independent clinical event adjudication, extracting the study start year, patient baseline characteristics, and one- and five-year clinical outcomes. Temporal trends in clinical outcomes (cardiac death, myocardial infarction [MI], target lesion revascularisation [TLR], stent thrombosis [ST]) were assessed using random-effects meta-regression analyses, estimating the relationship between clinical outcomes and study start year.

Results: Overall, 25 all-comers trials (51 device arms, 66,327 patients) conducted between 2003 and 2018 fulfilled the eligibility criteria. Random-effects meta-regression analysis revealed significant decreasing trends in one- and five-year cardiac death, one-year TLR, and five-year ST incidences (relative risk per 10-year increase: 0.69 [0.51-0.92], 0.66 [0.44-0.98], 0.60 [0.41-0.88], and 0.18 [0.07-0.44], respectively). There was no significant trend in myocardial infarction incidences.

Conclusions: This is the first attempt to clarify and quantify the temporal trends of post-PCI outcome incidence. The 15-year improvements in PCI therapy and post-therapeutic patient management are associated with reduced incidences of cardiac death and PCI-related adverse events.

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Abbreviations

CEC	clinical events committee
DES	drug-eluting stents
MI	myocardial infarction
NSTE-ACS	acute coronary syndrome without ST-segment elevation
PCI	percutaneous coronary intervention
RCT	randomised controlled trial
RR	relative risk
ST	stent thrombosis
STEMI	ST-segment elevation myocardial infarction
TLR	target lesion revascularisation

Introduction

Percutaneous coronary intervention (PCI) technology has advanced since the first human coronary balloon angioplasty in 1977, with coronary stents (including drug-eluting stents [DES]) ensuring better safety and efficacy after PCI[1]. Furthermore, patient management strategies for acute coronary syndrome (ACS) and adjunct pharmacological therapy (e.g., antiplatelet and lipid-lowering therapy) have improved. Considering this combination of developments, the degree of improvement in post-PCI clinical outcomes is of paramount interest. While several registries have reported temporal trends in post-PCI clinical outcomes, their generalisability is limited because the majority of the included patients are from a particular region or institution. Nationwide registries have also reported temporal trends in post-PCI clinical outcomes. However, they did not sufficiently measure the impact of therapeutic developments *per se*, as they reported only crude outcomes such as all-cause mortality, including deaths from non-cardiac causes[2]. Furthermore, these studies were limited by a relatively low patient follow-up rate and lack of objective adjudication of site-reported clinical outcomes. Recent prospective randomised controlled trials (RCTs) have commonly applied an independent clinical events committee (CEC) for objective event adjudication. Considering the limitations of registry reports, the current study aimed to clarify and quantify the temporal trends in post-PCI clinical outcomes using historical data from all-comers RCTs evaluating the efficacy and safety of coronary stents, with independent clinical event adjudication based on a comprehensive systematic review and meta-analytic approach.

Editorial, see page 1283

Methods

SEARCH STRATEGY AND SELECTION CRITERIA

Eligible studies for the systematic review and current meta-analysis were RCTs comparing different coronary stents with an all-comers design based on minimal patient exclusion criteria, presumably reflecting routine clinical practices. Eligible studies included RCTs (1) investigating the safety and efficacy of a DES compared to other stent(s), designed with clinical outcomes as primary endpoints rather than being surrogate markers (e.g., angiographic parameters); (2) with the studied coronary stents being approved by CE marking; (3) with clinical event adjudication by independent CECs; and (4) with an all-comers design. An all-comers trial was defined as a trial without the major exclusion criteria listed in the **Supplementary Table 1**. As there is no clear definition of an all-comers trial in the literature, our selection was based on consensus among the authors. In the current analysis, trials investigating bifurcation-dedicated, covered, self-expandable stents or bioresorbable scaffolds were excluded for consistency, although we imposed no language, publication date, or publication status restrictions. We searched for relevant trials through Medline, Embase, the Cochrane database, and abstracts and presentations from major cardiovascular meetings, using the keywords "randomized controlled trial", "coronary artery disease", and "stent" **(Supplementary Table 2)**. The systematic review was conducted in accordance with PRISMA guidelines[3]. Two independent investigator teams (M. Ono/A. Saito and T. Kanie/Y. Takaoka) reviewed the titles, abstracts, and texts for trial eligibility. Disagreements were resolved by consulting another investigator (T. Asano). To identify all-comers trials, we first restricted the target RCTs to those conducted in non-specific populations by excluding specific population trials with particular patient characteristics, clinical settings, or anatomical conditions (e.g., diabetes, high bleeding risk, ST-segment elevation myocardial infarction [STEMI], chronic total occlusion, or left main disease). We then assessed the inclusion and exclusion criteria of these trials and determined their eligibility. Study quality was assessed using the Cochrane Collaboration's tool for assessing bias risk. The current systematic review was registered and published in PROSPERO (CRD42020108188).

ENDPOINTS AND DEFINITIONS

The investigated clinical outcomes included cardiac death, myocardial infarction (MI), target lesion revascularisation (TLR), and stent thrombosis (ST) one year after the index procedure. In the included trials, the relevant outcomes at five years were also collected, if applicable. The clinical outcomes were defined as applied in each trial. To reduce bias, we included only TLR incidences reported as repeat revascularisation with objective clinical indication, such as clinically indicated TLR defined by the Academic Research Consortium (ARC)[4]. Clinically indicated TLR was defined as a reintervention for clinically significant stenosis, confirmed by quantitative coronary angiography, with functional or clinical factors justifying the indication of the reintervention. ST was defined as definite ST according to the ARC definition or relevant definitions in trials before the ARC definition was published[4]. The initial iterations of DES (i.e., CYPHER® sirolimus-eluting stent [Cordis, Santa Clara, CA, USA] and TAXUS™ paclitaxel-eluting stent [Boston Scientific, Marlborough, MA, USA]) and later iterations of DES were categorised as early and new DES, respectively.

STATISTICAL ANALYSIS

Inclusion and exclusion criteria, study start year, participating countries, patient demographics, comorbidities, and incidences of the clinical outcomes in each study arm were extracted from

the publications. Temporal trends in post-PCI clinical outcomes were examined using random-effects meta-regression analysis with a restricted maximum likelihood (REML) estimation method and time (i.e., study start year) as a moderator. Log-transformed incidences were applied in each meta-regression model. Relative risk (RR) per 10 years was calculated based on an exponentiated beta coefficient in the regression model. Results were exponentiated for interpretation and visualisation in figures. The pooled incidence rates were calculated for clinical outcomes, along with 95% confidence intervals (CIs) using the random effects model with REML. The pooled values were also calculated for subgroups stratified by every five years of the first patient enrolment and were presented in forest plots.

The pooled patient follow-up rates in the included trials (i.e., the rate of patients with available clinical status at the one- and five-year follow-ups) were calculated. The homogeneity assumption between treatment effects in different trials was tested using the Q test and further quantified using the τ^2 and I^2 statistics. The amount of heterogeneity accounted for by the moderator was given under the R^2 statistic. For the sensitivity analysis, we repeated the analyses in a more consistent population by including only trials conducted in European countries. Incidences were calculated based on an intention-to-treat analysis and $p<0.05$ was considered statistically significant. All statistical analyses were conducted using R version 3.62 (R Foundation for Statistical Computing, Vienna, Austria). The meta-regression model fitting and pooled outcome measure calculations were performed using the metafor package, and the results were visualised with the ggplot2 package.

Results

Of 10,139 citations identified by the initial database search performed in September 2020, there were 49 eligible RCTs (95 device arms, 97,465 non-specific patients). After assessing the inclusion and exclusion criteria, we identified 25 all-comers trials (51 device arms) enrolling 66,327 patients from 2003-2018 (publication year: 2005-2020) **(Supplementary Figure 1)**. The included trials were conducted in Europe, North and South America, East Asia and the Middle East, and Oceania. Twenty trials with 44,943 patients were conducted in European countries alone. The included trials **(Table 1)** had 9 study arms with 12,510 patients receiving early DES and 42 study arms with 53,817 patients receiving new DES. The inclusion and exclusion criteria of the included trials, along with the 49 eligible trials enrolling non-specific patients, are presented in the **Supplementary Table 3**. All 25 all-comers trials reported one-year clinical outcomes at nine or 12 months, whereas 13 with 34,463 patients reported five-year clinical outcome incidences. The pooled patient follow-up rates of the included trials were 99.0% (95% CI: 98.6-99.3) at one year and 98.4% (95% CI: 97.6-99.2) at five years. Detailed information regarding the included trials with the applied definitions for clinical outcomes and the results of the bias assessment are reported in **Supplementary Table 4**-**Supplementary Table 7**.

Among the one-year clinical outcomes, we observed a decreasing trend over time in cardiac death (RR per 10 years: 0.69 [95% CI: 0.51-0.92]; R^2=0.23, p=0.01) and TLR (RR per 10 years: 0.60 [0.41-0.88]; R^2=0.15, p=0.01), whereas we observed no significant trend in MI incidence (RR per 10 years: 1.15 [0.76-1.74]; R^2=0.00, p=0.50) **(Figure 1)**. Our analysis also revealed a decreasing trend in five-year cardiac death incidence (RR per 10 years: 0.66 [0.44-0.98]; R^2=0.15, p=0.04) but not in five-year MI or TLR incidence **(Figure 2)**. The forest plots in **Figure 1** and **Figure 2** summarise the pooled incidences of one- and five-year clinical outcomes stratified by each period (study start year: 2003-2007, 2008-2012, and 2013-2016). The pooled incidence of one-year cardiac death was 1.63% (95% CI: 1.27-1.99) in 2003-2007, subsequently decreasing to 1.09% (95% CI: 0.85-1.34) in 2013-2016. The five-year incidence of cardiac death also decreased from 5.27% (95% CI: 4.39-6.15) to 4.64% (95% CI: 4.20-5.09) over 10 years. The incidence of one-year TLR decreased from 4.32% (95% CI: 2.57-6.08) to 2.55% (95% CI: 2.05-3.04) between 2003-2007 and 2013-2016.

Figure 3 presents temporal trends in one- and five-year ST incidences. There was a significant declining tendency in five-year ST incidence (RR per 10 years: 0.18 [0.07-0.44]; R^2=0.50, p<0.01), while there were no significant trends in one-year ST incidence (RR per 10 years: 0.66 [0.39-1.11]; R^2=0.07, p=0.12). The pooled five-year ST incidence in 2003-2007 was 2.80% (95% CI: 1.89-3.72), decreasing to 1.20% (95% CI: 0.92-1.47) in 2008-2012.

The sensitivity analysis of the 20 Europe-only trials conducted between 2003 and 2018 revealed similar trends in clinical outcomes. **Supplementary Figure 2** includes the detailed results of the sensitivity analysis.

Discussion

In the current analysis, we aimed to clarify and quantify the temporal trends in the incidence of post-PCI clinical outcomes. Our analysis revealed significant decreasing trends in the incidences of one- and five-year cardiac death (31% and 34% decrease per 10 years, respectively) and TLR (40% decrease per 10 years) and five-year ST (82% decrease per 10 years) over time. However, we observed no significant trends in the MI incidence **(Central illustration)**.

To our knowledge, this is the first analysis to investigate temporal trends in clinical outcomes after PCI quantitatively using data from all-comers RCTs (presumably reflecting routine practice) with a substantial patient follow-up rate and objective event adjudication. Indeed, there are considerable discrepancies between objective event adjudication and site reports on which registry studies are generally based. A discordance between investigator-reported and CEC-adjudicated events was reported in a prospective substudy (GLASSY: GLOBAL LEADERS Adjudication Sub-StudY) of the GLOBAL LEADERS trial for the detection of clinical events—especially MI, target vessel revascularisation, and major bleeding—which investigated the safety and efficacy of ticagrelor monotherapy one month after DES implantation[5].

Table 1. Summary table of the included studies.

Trial name	Author	Study period	Publication year	Device	No. of enrolled patients	DES generation	Primary endpoint	Country	1-year clinical outcome					5-year clinical outcome				
									Follow-up rate (%)	Cardiac death (%)	MI (%)	TLR (%)	ST (%)	Follow-up rate (%)	Cardiac death (%)	MI (%)	TLR (%)	ST (%)
SIRTAX[17]	Windecker	2003-2004	2005	CYPHER	503	Early	Cardiac death, MI, ischaemia-driven TLR	Switzerland	100	1.4	3.2	5.8	2.0	97.6	5.9	6.7	13.4	4.7
				TAXUS Express	509	Early			100	2.2	3.9	10.2	1.6	96.1	5.9	7.2	15.7	4.3
LEADERS[18]	Windecker	2006-2007	2008	BioMatrix	857	New	Cardiac death, MI, ischaemia-driven TVR	European countries	98.7	2.1	5.9	5.2	2.0	96.3	8.0	9.9	10.1	2.7
				CYPHER	850	Early			98.8	2.7	4.6	5.8	2.0	95.2	8.5	10.4	12.5	4.4
SORT OUT III[19]	Rasmussen	2006-2007	2014	Endeavor	1,162	New	Cardiac death, MI, TVR	Denmark	100	1.2	1.8	5.3	1.1	99.7	4.1	5.5	7.6	1.2
				CYPHER	1,170	Early			100	0.9	0.5	1.4	0.3	99.7	4.6	5.6	6.0	2.1
COMPARE[20]	Kedhi	2007-2008	2010	XIENCE	897	New	All death, MI, TVR	the Netherlands	99.8	1.2	1.7	1.7	0.4	99.4	4.5	7.1	5.0	2.2
				TAXUS Liberté	903	Early			99.9	1.1	3.1	4.8	2.0	99.6	4.7	11.6	8.3	4.0
PROTECT[21]	Camenzind	2007-2008	2012	Endeavor	4,357	New	Definite or probable stent thrombosis	Asia, Australia, New Zealand, Europe, the Middle East, and North and South America	99.3				0.6	95.9	3.6	5.0	6.3	
				CYPHER	4,352	Early			99.0				0.5	96.3	4.1	6.6	5.0	
SORT OUT IV[22]	Jensen	2007-2009	2012	XIENCE/PROMUS	1,390	New	Cardiac death, MI, ST, ischaemia-driven TVR	Denmark	100	1.9	1.1	1.4	0.1	99.9	4.6	4.1	4.8	0.4
				CYPHER	1,384	Early			99.9	1.4	1.4	1.7	0.7	99.9	4.7	5.6	7.0	2.0
Resolute All-Comers[23]	Serruys	2008-2008	2010	Resolute	1,140	New	Cardiac death, target vessel MI, ischaemia-driven TLR	European countries	98.2	1.3	4.6	3.9	1.3	98.5	6.5	7.1	7.8	1.6
				XIENCE	1,152	New			97.7	1.7	4.4	3.4	0.4	98.4	5.7	6.8	7.1	0.8
COMPARE II[24]	Smits	2009-2011	2013	Nobori	1,795	New	Cardiac death, MI, ischaemia-driven TVR	the Netherlands	99.4	0.8	2.9	2.1	0.7	98.4	4.6	7.8	6.5	1.5
				XIENCE	912	New			99.1	0.8	2.5	1.8	0.4	97.7	4.0	7.2	5.5	0.9
SORT OUT V[25]	Christiansen	2009-2011	2013	Nobori	1,229	New	Cardiac death, MI, ST, ischaemia-driven TVR	Denmark	99.9	1.0	1.5	3.3	0.7	99.9	3.8	6.2	6.2	1.9
				CYPHER	1,239	Early			100	1.1	0.9	2.0	0.2	99.9	4.8	6.0	6.4	1.5
RESET[26]	Kimura	2010-2010	2012	XIENCE	1,597	New	TLR	Japan	98.0	1.0	3.0	2.9	0.3					
				CYPHER	1,600	Early			98.8	1.3	3.5	3.7	0.4					
DUTCH PEERS[27]	von Birgelen	2010-2012	2014	Resolute	906	New	Cardiac death, target vessel MI, ischaemia-driven TVR	the Netherlands	99.9	1.7		2.2	0.3	99.2	4.4			1.1
				XIENCE	905	New			100	1.1		2.2	0.7	99.3	4.9			1.1
HOST-ASSURE[28]	Park	2010-2011	2014	PROMUS	2,503	New	Cardiac death, target vessel MI, ischaemia-driven TLR	South Korea	98.7	1.4	1.1	1.3	0.2					
				Resolute	1,252	New			98.7	1.4	1.4	1.2	0.2					
PLATINUM PLUS[29]	Fajadet	2010-2012	2017	PROMUS	1,952	New	Cardiac death, target vessel MI, ischaemia-driven TVR	European countries	95.4	1.1	1.6	2.0	0.3					
				XIENCE	1,028	New			96.0	1.0	0.8	1.6	0.3					
NEXT[30]	Natsuaki	2011-2011	2013	Nobori	1,617	New	TLR	Japan	99.0	1.6	3.3	2.9	0.2	74.3	4.4	5.3	7.7	0.5
				XIENCE/PROMUS	1,618	New			99.4	1.2	3.1	2.9	0.1	74.5	3.9	5.0	7.4	0.3

Table 1. Summary table of the included studies. (cont'd)

Trial name	Author	Study period	Publication year	Device	No. of enrolled patients	DES generation	Primary endpoint	Country	1-year clinical outcome					5-year clinical outcome				
									Follow-up rate (%)	Cardiac death (%)	MI (%)	TLR (%)	ST (%)	Follow-up rate (%)	Cardiac death (%)	MI (%)	TLR (%)	ST (%)
SORT OUT VI[31]	Raungaard	2011-2012	2015	Resolute	1,502	New	Cardiac death, target vessel MI, ischaemia-driven TLR	Denmark	99.9	1.5	2.1	3.5	0.6					
				BioMatrix	1,497	New			99.9	1.7	2.0	3.1	0.4					
BIOSCIENCE[32]	Pilgrim	2012-2013	2014	Orsiro	1,063	New	Cardiac death, target vessel MI, ischaemia-driven TLR	Switzerland	97.0	1.9	4.0	3.4	0.9	93.5	4.6	10.0	10.4	1.6
				XIENCE	1,056	New			98.1	2.1	4.3	2.4	0.4	96	3.9	11.6	9.6	1.6
BIO-RESORT[33]	von Birgelen	2012-2015	2016	SYNERGY	1,172	New	Cardiac death, target vessel MI, ischaemia-driven TVR	the Netherlands	99.1	0.9	2.2	1.5	0.3					
				Resolute	1,173	New			99.3	0.9	2.7	1.5	0.3					
				Orsiro	1,169	New			99.5	0.9	2.5	1.5	0.3					
SORT OUT VII[34]	Jensen	2012-2014	2016	Orsiro	1,261	New	Cardiac death, target vessel MI, ischaemia-driven TLR	Denmark	99.9	1.3	1.6	2.0	0.4					
				Nobori	1,264	New			99.9	1.4	2.5	2.9	1.2					
ReCre8[35]	Rozemeijer	2014-2017	2019	Resolute	744	New	Cardiac death, target vessel MI, ischaemia-driven TLR	European countries	99.1	1.3	3.2		0.5					
				Cre8	747	New			99.5	1.3	3.9		0.9					
SORT OUT VIII[36]	Maeng	2014-2015	2019	SYNERGY	1,385	New	Cardiac death, target vessel MI, ischaemia-driven TLR	Denmark	100	1.5	1.9	2.3	0.7					
				BioMatrix	1,379	New			99.9	1.3	3.4	2.5	0.9					
DESSOLVE III[37]	Winter	2015-2015	2017	Mistent	703	New	Cardiac death, target vessel MI, ischaemia-driven TLR	European countries	99.7	2.0	2.4	2.6	0.4					
				XIENCE	695	New			100	1.6	2.2	3.7	0.7					
SORT OUT IX[38]	Jensen	2015-2018	2020	BioFreedom	1,572	New	Cardiac death, target vessel MI, ischaemia-driven TLR	Denmark	100	0.4	2.4	3.5	0.7					
				Orsiro	1,579	New			100	0.8	2.5	1.3	0.7					
BIONYX[14]	von Birgelen	2015-2016	2018	Resolute Onyx	1,243	New	Cardiac death, target vessel MI, ischaemia-driven TVR	the Netherlands, Belgium, Israel	98.1	0.6	1.6	2.5	0.1					
				Orsiro	1,245	New			97.4	1.1	1.6	2.0	0.6					
TARGET All Comers[39]	Lansky	2015-2016	2018	FIREHAWK	823	New	Cardiac death, target vessel MI, ischaemia-driven TVR	European countries	96.0	1.1	5.2	1.1	1.1					
				XIENCE	830	New			96.0	0.9	4.6	2.3	1.1					
TALENT[40]	Zaman	2016-2017	2019	Supraflex	720	New	Cardiac death, target vessel MI, ischaemia-driven TLR	European countries	96.5	1.0	3.2	2.7	0.7					
				XIENCE	715	New			98.3	0.3	3.7	4.0	0.7					

DES: drug-eluting stent; MI: myocardial infarction; No.: number; ST: stent thrombosis; TLR: target lesion revascularisation; TVR: target vessel revascularisation BioFreedom™ (Biosensors, Singapore); BioMatrix™ (Biosensors, Singapore); Cre8™ (Alvimedica, Istanbul, Turkey); CYPHER® (Cordis Santa Clara, CA, USA); Endeavor® (Medtronic, Minneapolis, MN, USA); FIREHAWK® (MicroPort, Shanghai, China); MiStent® (Micell Technologies, Durham, NC, USA); Nobori® (Terumo,Tokyo, Japan); Osiro (Biotronik, Berlin Germany); PROMUS™ (Boston Scientific, Marlborough, MA, USA); Resolute™ (Medtronic, Minneapolis, MN, USA); Resolute Onyx™ (Medtronic, Minneapolis, MN, USA); Supraflex™ (Sahajanand Medical Technologies, Mumbai, India); SYNERGY™ (Boston Scientific, Marlborough, MA, USA); TAXUS Express (Boston Scientific, Marlborough, MA, USA); TAXUS™ Liberté™ (Boston Scientific, Marlborough, MA, USA); XIENCE® (Abbott Laboratories, Abbott Park, IL, USA)

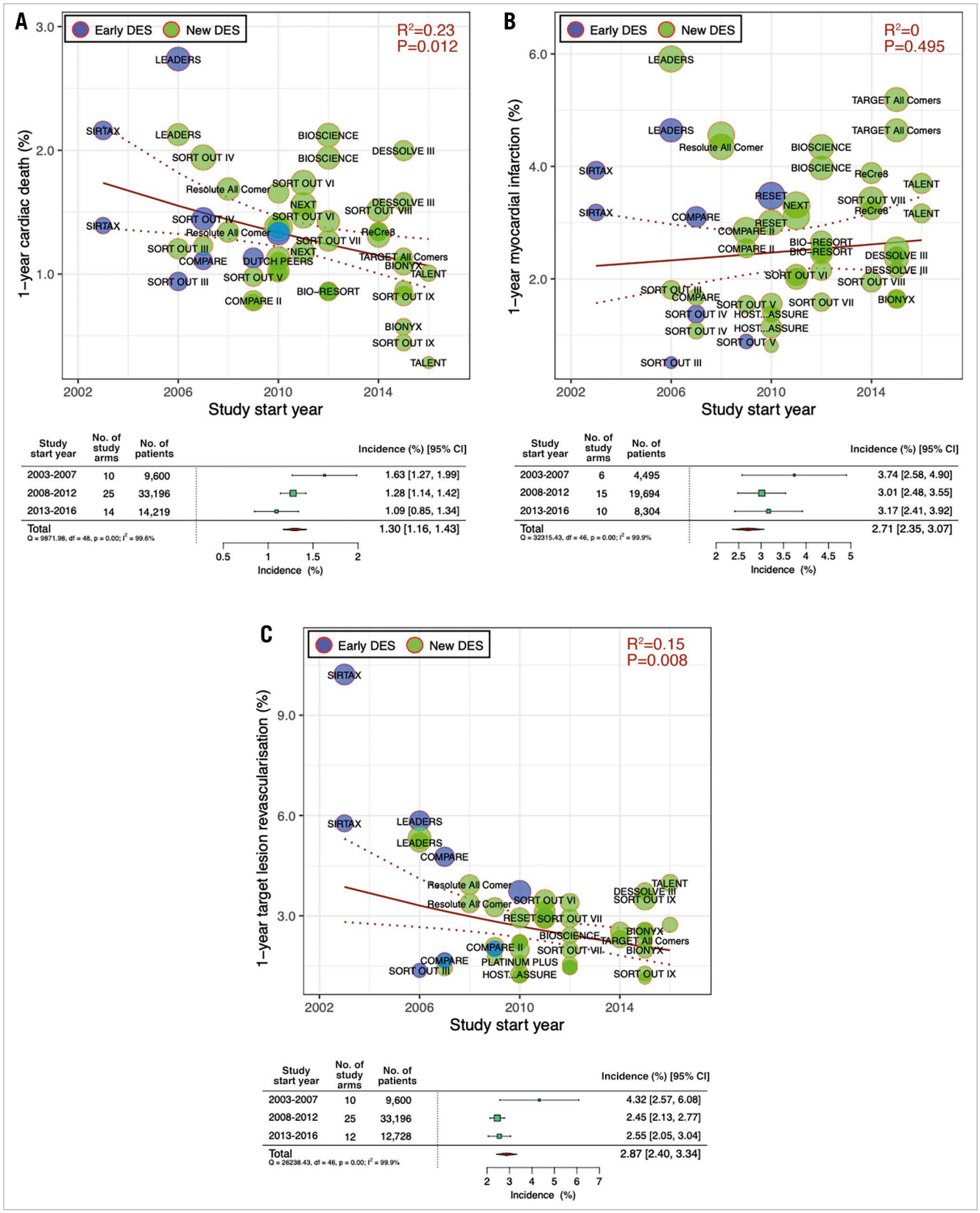


Figure 1. *Meta-regression analysis for temporal trends trends at one year. One-year incidences of A) cardiac death, B) myocardial infarction and C) target lesion revascularisation. Bubbles are plotted in accordance with the study start year and incidences of clinical outcomes for each study (device) arm. The size of each bubble is correlated with a weight in the analysis. Forest plots summarise the pooled estimated incidences of each clinical outcome divided into three periods (2003-2007, 2008-2012, and 2013-2016). CI: confidence interval; DES: drug-eluting stents; No.: number*

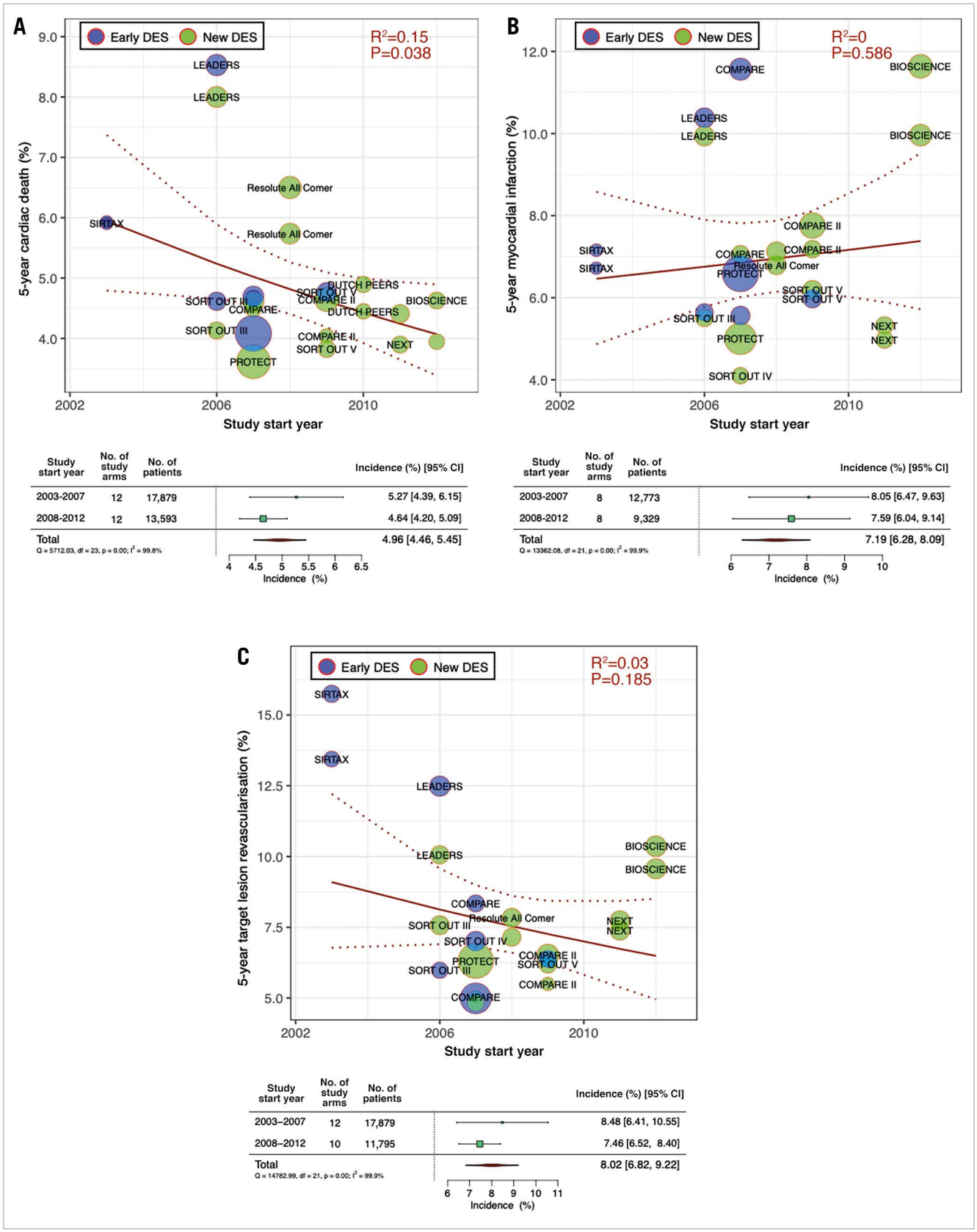


Figure 2. *Meta-regression analysis for temporal trends at five years. Five-year incidences of A) cardiac death, B) myocardial infarction and C) target lesion revascularisation. Bubbles are plotted in accordance with the study start year and incidences of clinical outcomes for each study (device) arm. The size of bubble is correlated with a weight in the analysis. Forest plots summarise the pooled estimated incidences of each clinical outcome divided into two periods (2003-2007 and 2008-2012). CI: confidence interval; DES: drug-eluting stents; No.: number*

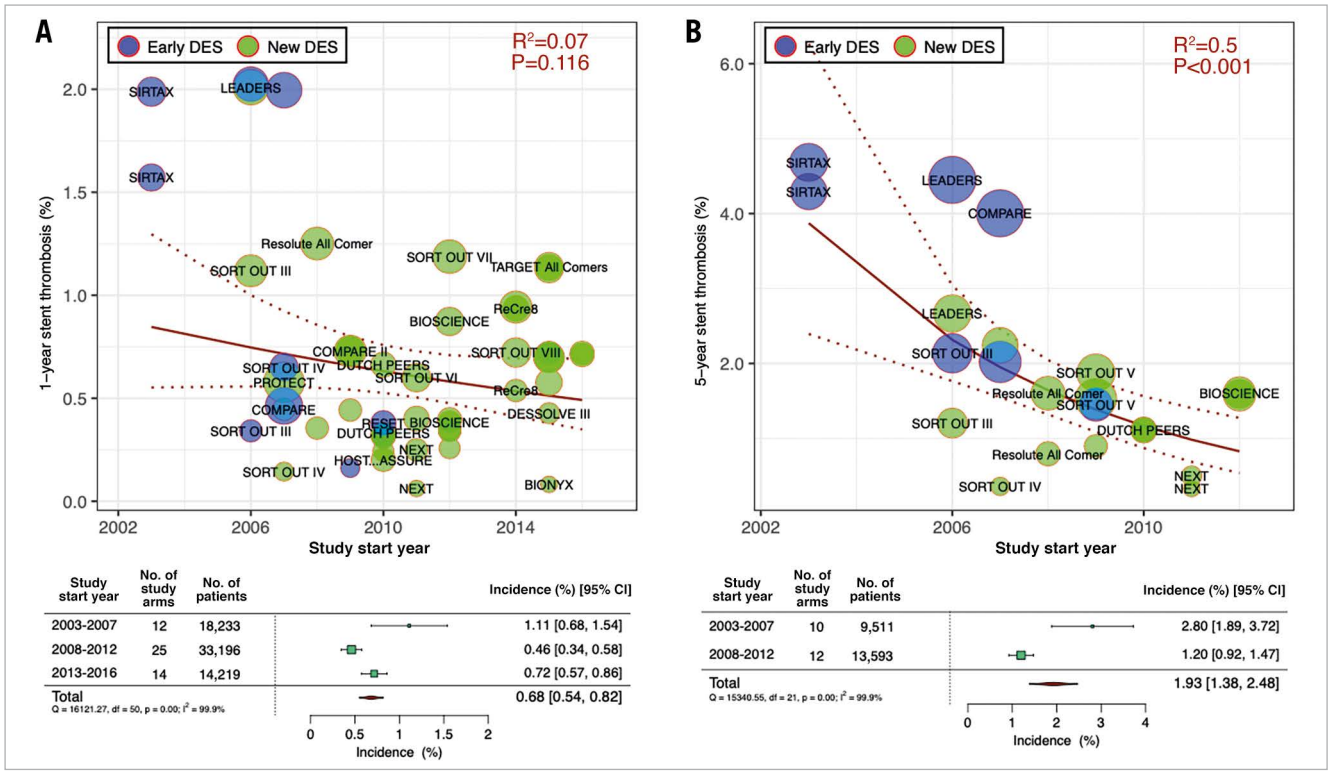
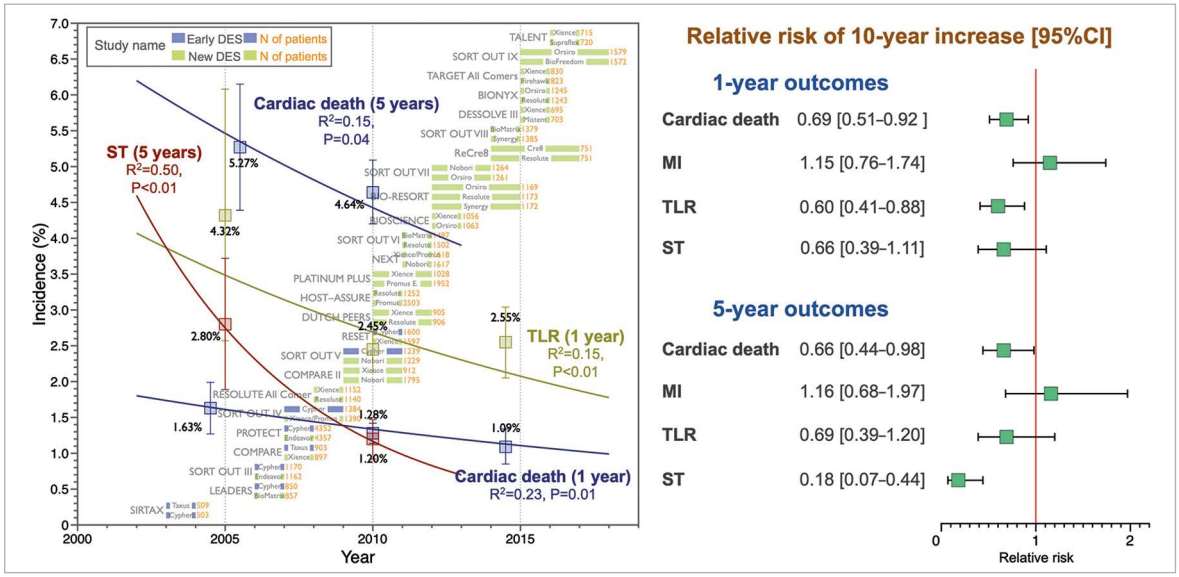


Figure 3. *Meta-regression analysis for temporal at one and five years. Incidence of A) one-year and B) five-year stent thrombosis. Bubbles are plotted in accordance with the study start year and incidences of clinical outcomes for each study (device) arm. The size of each bubble is correlated with a weight in the analysis. Forest plots summarise the pooled estimated incidences of each clinical outcome divided into three periods (2003-2007, 2008-2012, and 2013-2016). CI: confidence interval; DES: drug-eluting stents; No.: number*

TEMPORAL TRENDS IN CARDIAC DEATH AFTER PCI

In a recent study investigating the temporal trend of mortality after PCI using British Cardiovascular Intervention Society PCI Registry data collected between 2007 and 2014, the mean age of patients receiving PCI increased from 63.8 to 65.1 years, with more recent years being associated with higher mortality[2].



Central illustration. *Temporal trends in the incidence of post-PCI clinical outcomes. In the meta-regression analysis including 25 all-comers RCTs, there were significant decreasing trends in the incidence of one- and five-year cardiac death, one-year TLR, and five-year ST whereas there were no trends in MI incidences. CI: confidence interval; DES: drug-eluting stent; MI: myocardial infarction; RCT: randomised controlled trial; RR: relative risk; ST: stent thrombosis; TLR: target lesion revascularisation*

Mortality was also affected by other comorbidities such as cancer, even after age and sex adjustment. Similarly, in the current analysis, the mean age of the patients gradually increased over time (2.30 years per 10 years [95% CI: 0.82-3.77], p<0.001 for trend). However, the cardiac death incidence following PCI tended to decrease, whereas all-cause death did not have decreasing trends at one and five years (RR per 10 years: 0.97 [0.78-1.22] at one year and 1.08 [0.76-1.54] at five years) **(Supplementary Figure 3)**. Interestingly, the incidences of non-cardiac death had increasing tendencies (RR per 10 years: 1.53 [1.08-2.17] at one year and 1.63 [0.94-2.85] at five years) **(Supplementary Figure 3)**. In a more aged population, all-cause death may counterbalance the incidence with other increased comorbidities due to ageing.

Improving the prognosis of coronary artery disease is one of the major goals of PCI therapy. To date, a great deal of effort has been made in various approaches for achieving this goal. Patient management for acute coronary syndrome (ACS) (timing and completeness of revascularisation, mechanical circulatory support device, and acute cardiac care after PCI), general cardiovascular risk control (medical treatment and lifestyle modification), PCI device (DES, intravascular imaging, and guidewire), invasive functional assessment, and antiplatelet therapy after PCI have improved over the years. The observed decreasing trend in the incidence of cardiac death may be attributed to the integration of these developments, suggesting that measures taken thus far have been in the proper direction.

Major contributing factors to the observed decreasing trend in cardiac death incidence might be the improvement of the patient management including cardiovascular risk control and medical treatment rather than improvements in PCI technology and technique. This is because no major trials have demonstrated a significant benefit of revascularisation in mortality for patients with chronic coronary syndrome, who were mainly enrolled in the included trials[6]. However, it is likely that additional technological and technical improvements in PCI will lead to further decreases in the incidence of TLR and ST, which may in turn improve prognosis among affected patients. In a large patient-level meta-analysis including 32,524 patients, TLR after PCI was an independent predictor of long-term mortality (hazard ratio: 1.23 [1.04-1.45])[7]. In a recent report from a large registry in the USA, functional fractional flow reserve (FFR) prior to PCI gradually increased from 44% to 75% between 2009 and 2017, and FFR-guided PCI was associated with a lower risk of one-year mortality than angiography-guided PCI[8].

TEMPORAL TRENDS IN PCI-RELATED OUTCOMES

The observed improvement in the incidence of PCI-related outcomes (i.e., TLR and ST) was potentially associated with improvements in PCI technologies and techniques, and medical therapies represented by $P2Y_{12}$ inhibitors and lipid-lowering therapy. The SYNTAX II trial investigated the impact of the integration of new developments in PCI practice (usage of a contemporary DES, intravascular ultrasound, and pressure wire for the physiological assessment) on clinical outcomes in patients with multivessel disease. The results were compared with those of the SYNTAX I trial conducted nine years earlier[9]. The SYNTAX II study revealed significant decreases in the incidence of repeat revascularisation and ST, in accordance with our findings.

Second-generation DES with modified drug elution, thinner struts, and biocompatible polymers have been associated with improved efficacy and reduced incidence of repeat revascularisation when compared with first-generation DES[1]. However, no additional positive impact of the thinner strut of the contemporary DES on TLR incidence has been reported[10]. The results of the current analysis are consistent with those of these previous findings. The pooled one-year incidence of TLR decreased from the first to the second period (2003-2007, 2008-2012, respectively), while the incidences were comparable between the second and latest periods (2008-2012, 2013-2016, respectively) **(Figure 1)**. Furthermore, the significant trend in TLR incidence observed at one year became non-significant at five years (adjusted RR: 0.65 [0.38-1.12]). This suggests that the impact of difference in DES generations on long-term TLR incidence became less obvious at five years. Several RCTs reported their extended results beyond five years (7-10 years), in which differences in clinical outcomes (TLR and ST) between different DES became less significant in the very long term[11].

Potential technical factors influencing TLR incidence include the utilisation of intravascular imaging during PCI[12]. Nevertheless, the penetration rate of intravascular imaging is still low at 5-15% in the USA and European countries, in which the majority of the included trials were conducted[13]. Although the included trials rarely reported the prevalence of intravascular imaging-guided PCI, the BIONYX trial conducted in European countries and Israel between 2015 and 2016 reported a 1.2% utilisation rate of intracoronary imaging[14].

In the current analysis, the five-year ST incidence decreased significantly over time (RR per 10 years: 0.18 [0.07-0.44], p<0.01). This is potentially attributed to the development of coronary stents with thinner struts and biocompatible polymers with or without biodegradation, the advent of potent $P2Y_{12}$ inhibitors, and improvement in lipid lowering therapy presumably inhibiting the progression of neoatherosclerosis[15].

IMPLICATIONS OF THE CURRENT RESULTS AND STUDY LIMITATIONS

The current analysis observed several significant trends in clinical outcomes after PCI in the all-comers RCTs. The observed trends were ascribed to the composite of miscellaneous factors mainly associated with time course, which included developments in PCI technologies and techniques, invasive functional assessment, medical therapies ($P2Y_{12}$ inhibitors, lipid-lowering therapy, etc.), and cardiovascular prevention measures. The current analysis has a limitation in discriminating specific factors attributed to each endpoint because of the lack of individual data especially for medical treatment including antiplatelet therapy. Furthermore, in the across-study comparison, between-study heterogeneity is hardly

eliminated, even if multiple-covariate adjustment is applied. The results should be interpreted with caution considering the potential existence of spurious or collinear effects. Other limitations to the current analysis are as follows. First, the included population was not necessarily representative of the real-world population, although they were selected from all-comers trials with minimal exclusion criteria. In their study, de Boer et al reported that applying the all-comers design did not result in the inclusion of all consecutive patients in the *post hoc* analysis of the LEADERS and RESOLUTE all-comers trials[16]. The current analysis may have included selected populations with undetected biases. Second, the definitions of clinical outcomes, especially MI, varied as shown in **Supplementary Table 5** and **Supplementary Table 6**. This may have precluded an unbiased assessment of temporal trends in clinical outcomes. Recent MI definitions include an assessment using sensitive cardiac markers (i.e., cardiac troponins). Consequently, the events which were adjudicated as unstable angina according to the old definitions were adjudicated as MI with the recent definitions, potentially resulting in underestimation of improvements in terms of MI prevention. Third, the performance of TLR is susceptible to the bias of investigators. The early trials tended to include a subgroup with scheduled angiographic follow-up **(Supplementary Table 8)**. It should be noted that in the SIRTAX trial which reported a high TLR incidence, nearly 50% of the patients underwent follow-up angiography at both one and five years. In those trials, the oculostenotic reflex potentially triggered the performance of TLR, although we applied only clinically indicated TLR adjudicated by an independent CEC based on the objective definition. Fourth, our study lacked investigation regarding bleeding events after PCI. PCI therapy has been developed by balancing thrombotic events with bleeding events besides the development of antiplatelet therapy including modification of the duration of dual antiplatelet therapy. Novel $P2Y_{12}$ inhibitors potentially reduce thrombotic events represented by MI and ST, whereas more potent antiplatelet therapy might introduce an increased incidence of bleeding events. A small number of the included trials (six out of 25 trials) reported the bleeding event incidence with various definitions across the trials. This imposed a limitation on demonstrating the temporal trend of the bleeding event rate. We tabulated the summary of the reported bleeding event incidences and antiplatelet regimen of the included trials in **Supplementary Table 9**. Fifth, the current analysis was conducted by splitting each trial into individual arms to clarify the impact of the device difference. However, this methodology eventually disbanded a within-trial integrity based on the randomisation.

Conclusions

Our meta-regression analysis, which included all-comers RCTs for DES use between 2003 and 2018, revealed significant decreasing trends in one-year cardiac death (31% decrease per 10 years) and TLR (40% decrease per 10 years) incidences, and five-year cardiac death (34% decrease per 10 years) and ST (82% decrease per 10 years) incidences but no significant trends in the MI incidence over time. Our analysis indicated that 15-year developments in PCI therapy and post-therapeutic patient care were associated with decreased incidence. PCI procedures and meticulous patient management such as post-PCI MI prevention strategies may be critical for ensuring better clinical outcomes.

Impact on daily practice

Our analysis revealed a decreasing trend in one- and five-year cardiac death, one-year TLR, and five-year ST incidences after PCI in all-comers stent trials conducted over the last 15 years; however, no such trends for MI incidence were observed. The integration of miscellaneous therapeutic developments might have contributed to these decreases. Further improvements in PCI-related outcomes, post-PCI MI prevention strategies, and therapeutic approaches may clarify the effects of PCI on patient prognosis.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Stefanini GG, Byrne RA, Windecker S, Kastrati A. State of the art: coronary artery stents - past, present and future. *EuroIntervention.* 2017;13:706-16.

2. Hulme WJ, Sperrin M, Martin GP, Curzen N, Ludman P, Kontopantelis E, Mamas MA; British Cardiovascular Intervention Society and the National Institute of Cardiovascular Outcomes Research. Temporal trends in relative survival following percutaneous coronary intervention. *BMJ Open.* 2019;9:e024627.

3. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;339:b2700.

4. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.

5. Franzone A, McFadden E, Leonardi S, Piccolo R, Vranckx P, Serruys PW, Benit E, Liebetrau C, Janssens L, Ferrario M, Zurakowski A, Diletti R, Dominici M, Huber K, Slagboom T, Buszman P, Bolognese L, Tumscitz C, Bryniarski K, Aminian A, Vrolix M, Petrov I, Garg S, Naber C, Prokopczuk J, Hamm C, Steg PG, Heg D, Jüni P, Windecker S, Valgimigli M; GLASSY Investigators. Ticagrelor Alone Versus Dual Antiplatelet Therapy From 1 Month After Drug-Eluting Coronary Stenting. *J Am Coll Cardiol.* 2019;74:2223-34.

6. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, Chaitman BR, Senior R, Lopez-Sendon J, Alexander KP, Lopes RD, Shaw LJ, Berger JS, Newman JD, Sidhu MS, Goodman SG, Ruzyllo W, Gosselin G, Maggioni AP, White HD, Bhargava B, Min JK, Mancini GBJ, Berman DS, Picard MH, Kwong RY, Ali ZA, Mark DB, Spertus JA, Krishnan MN, Elghamaz A, Moorthy N, Hueb WA, Demkow M, Mavromatis K, Bockeria O, Peteiro J, Miller TD, Szwed H, Doerr R, Keltai M, Selvanayagam JB, Steg PG, Held C, Kohsaka S, Mavromichalis S, Kirby R, Jeffries NO, Harrell FE, Jr., Rockhold FW, Broderick S, Ferguson TB Jr, Williams DO, Harrington RA, Stone GW, Rosenberg Y; ISCHEMIA Research Group. Initial Invasive or Conservative Strategy for Stable Coronary Disease. *N Engl J Med.* 2020;382:1395-407.

7. Palmerini T, Della Riva D, Biondi-Zoccai G, Leon MB, Serruys PW, Smits PC, von Birgelen C, Ben-Yehuda O, Généreux P, Bruno AG, Jenkins P, Stone GW. Mortality Following Nonemergent, Uncomplicated Target Lesion Revascularization After Percutaneous Coronary Intervention: An Individual Patient Data Pooled Analysis of 21 Randomized Trials and 32,524 Patients. *JACC Cardiovasc Interv.* 2018;11:892-902.

8. Parikh RV, Liu G, Plomondon ME, Sehested TSG, Hlatky MA, Waldo SW, Fearon WF. Utilization and Outcomes of Measuring Fractional Flow Reserve in Patients With Stable Ischemic Heart Disease. *J Am Coll Cardiol.* 2020;75:409-19.

9. Escaned J, Collet C, Ryan N, De Maria GL, Walsh S, Sabate M, Davies J, Lesiak M, Moreno R, Cruz-Gonzalez I, Hoole SP, Ej West N, Piek JJ, Zaman A, Fath-Ordoubadi F, Stables RH, Appleby C, van Mieghem N, van Geuns RJ, Uren N, Zueco J, Buszman P,

Iniguez A, Goicolea J, Hildick-Smith D, Ochala A, Dudek D, Hanratty C, Cavalcante R, Kappetein AP, Taggart DP, van Es GA, Morel MA, de Vries T, Onuma Y, Farooq V, Serruys PW, Banning AP. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. *Eur Heart J.* 2017;38:3124-34.

10. Bangalore S, Toklu B, Patel N, Feit F, Stone GW. Newer-Generation Ultrathin Strut Drug-Eluting Stents Versus Older Second-Generation Thicker Strut Drug-Eluting Stents for Coronary Artery Disease. *Circulation.* 2018;138:2216-26.

11. Yamaji K, Räber L, Zanchin T, Spitzer E, Zanchin C, Pilgrim T, Stortecky S, Moschovitis A, Billinger M, Schönenberger C, Eberli F, Jüni P, Lüscher TF, Heg D, Windecker S. Ten-year clinical outcomes of first-generation drug-eluting stents: the Sirolimus-Eluting vs. Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) VERY LATE trial. *Eur Heart J.* 2016;37:3386-95.

12. Hong SJ, Kim BK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Kang WC, Her AY, Kim YH, Hur SH, Hong BK, Kwon H, Jang Y, Hong MK; IVUS-XPL Investigators. Effect of Intravascular Ultrasound-Guided vs Angiography-Guided Everolimus-Eluting Stent Implantation: The IVUS-XPL Randomized Clinical Trial. *JAMA.* 2015;314:2155-63.

13. Koskinas KC, Nakamura M, Raber L, Colleran R, Kadota K, Capodanno D, Wijns W, Akasaka T, Valgimigli M, Guagliumi G, Windecker S, Byrne RA. Current Use of Intracoronary Imaging in Interventional Practice - Results of a European Association of Percutaneous Cardiovascular Interventions (EAPCI) and Japanese Association of Cardiovascular Interventions and Therapeutics (CVIT) Clinical Practice Survey. *Circ J.* 2018;82:1360-8.

14. von Birgelen C, Zocca P, Buiten RA, Jessurun GAJ, Schotborgh CE, Roguin A, Danse PW, Benit E, Aminian A, van Houwelingen KG, Anthonio RL, Stoel MG, Somi S, Hartmann M, Linssen GCM, Doggen CJM, Kok MM. Thin composite wire strut, durable polymer-coated (Resolute Onyx) versus ultrathin cobalt-chromium strut, bioresorbable polymer-coated (Orsiro) drug-eluting stents in allcomers with coronary artery disease (BIONYX): an international, single-blind, randomised non-inferiority trial. *Lancet.* 2018;392:1235-45.

15. Torrado J, Buckley L, Duran A, Trujillo P, Toldo S, Valle Raleigh J, Abbate A, Biondi-Zoccai G, Guzman LA. Restenosis, Stent Thrombosis, and Bleeding Complications: Navigating Between Scylla and Charybdis. *J Am Coll Cardiol.* 2018; 71:1676-95.

16. de Boer SP, Lenzen MJ, Oemrawsingh RM, Simsek C, Duckers HJ, van der Giessen WJ, Serruys PW, Boersma E. Evaluating the 'all-comers' design: a comparison of participants in two 'all-comers' PCI trials with non-participants. *Eur Heart J.* 2011;32:2161-7.

17. Windecker S, Remondino A, Eberli FR, Jüni P, Räber L, Wenaweser P, Togni M, Billinger M, Tüller D, Seiler C, Roffi M, Corti R, Sütsch G, Maier W, Lüscher T, Hess OM, Egger M, Meier B. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization (SIRTAX). *N Engl J Med.* 2005;353:653-62.

18. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Jüni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet.* 2008;372:1163-73.

19. Rasmussen K, Maeng M, Kaltoft A, Thayssen P, Kelbaek H, Tilsted HH, Abildgaard U, Christiansen EH, Engstrøm T, Krusell LR, Ravkilde J, Hansen PR, Hansen KN, Abildstrøm SZ, Aarøe J, Jensen JS, Kristensen SD, Bøtker HE, Madsen M, Johnsen SP, Jensen LO, Sørensen HT, Thuesen L, Lassen JF; SORT OUT III study group. Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial. *Lancet.* 2010;375:1090-9.

20. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet.* 2010;375:201-9.

21. Camenzind E, Wijns W, Mauri L, Kurowski V, Parikh K, Gao R, Bode C, Greenwood JP, Boersma E, Vranckx P, McFadden E, Serruys PW, O'Neil WW, Jorissen B, Van Leeuwen F, Steg PG; PROTECT Steering Committee and Investigators. Stent thrombosis and major clinical events at 3 years after zotarolimus-eluting or sirolimus-eluting coronary stent implantation: a randomised, multicentre, open-label, controlled trial. *Lancet.* 2012;380:1396-1405.

22. Jensen LO, Thayssen P, Hansen HS, Christiansen EH, Tilsted HH, Krusell LR, Villadsen AB, Junker A, Hansen KN, Kaltoft A, Maeng M, Pedersen KE, Kristensen SD, Bøtker HE, Ravkilde J, Sanchez R, Aarøe J, Madsen M, Sørensen HT, Thuesen L, Lassen JF; Scandinavian Organization for Randomized Trials With Clinical Outcome IV (SORT OUT IV) Investigators. Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention: the Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV). *Circulation.* 2012;125:1246-55.

23. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbæk H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med.* 2010;363:136-46.

24. Smits PC, Hofma S, Togni M, Vázquez N, Valdés M, Voudris V, Slagboom T, Goy JJ, Vuillomenet A, Serra A, Nouche RT, den Heijer P, van der Ent M. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. *Lancet.* 2013;381:651-60.

25. Christiansen EH, Jensen LO, Thayssen P, Tilsted HH, Krusell LR, Hansen KN, Kaltoft A, Maeng M, Kristensen SD, Bøtker HE, Terkelsen CJ, Villadsen AB, Ravkilde J, Aarøe J, Madsen M, Thuesen L, Lassen JF; Scandinavian Organization for Randomized Trials with Clinical Outcome (SORT OUT) V investigators. Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): a randomised non-inferiority trial. *Lancet.* 2013;381:661-9.

26. Kimura T, Morimoto T, Natsuaki M, Shiomi H, Igarashi K, Kadota K, Tanabe K, Morino Y, Akasaka T, Takatsu Y, Nishikawa H, Yamamoto Y, Nakagawa Y, Hayashi Y, Iwabuchi M, Umeda H, Kawai K, Okada H, Kimura K, Simonton CA, Kozuma K; RESET Investigators. Comparison of everolimus-eluting and sirolimus-eluting coronary stents: 1-year outcomes from the Randomized Evaluation of Sirolimus-eluting Versus Everolimus-eluting stent Trial (RESET). *Circulation.* 2012;126:1225-36.

27. von Birgelen C, Sen H, Lam MK, Danse PW, Jessurun GA, Hautvast RW, van Houwelingen GK, Schramm AR, Gin RM, Louwerenburg JW, de Man FH, Stoel MG, Löwik MM, Linssen GC, Saïd SA, Nienhuis MB, Verhorst PM, Basalus MW, Doggen CJ, Tandjung K. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. *Lancet.* 2014;383:413-23.

28. Park KW, Kang SH, Kang HJ, Koo BK, Park BE, Cha KS, Rhew JY, Jeon HK, Shin ES, Oh JH, Jeong MH, Kim S, Hwang KK, Yoon JH, Lee SY, Park TH, Moon KW, Kwon HM, Hur SH, Ryu JK, Lee BR, Park YW, Chae IH, Kim HS; HOST-ASSURE Investigators. A randomized comparison of platinum chromium-based everolimus-eluting stents versus cobalt chromium-based Zotarolimus-Eluting stents in all-comers receiving percutaneous coronary intervention: HOST-ASSURE (harmonizing optimal strategy for treatment of coronary artery stenosis-safety & effectiveness of drug-eluting stents & anti-platelet regimen), a randomized, controlled, noninferiority trial. *J Am Coll Cardiol.* 2014;63:2805-16.

29. Fajadet J, Neumann FJ, Hildick-Smith D, Petronio S, Zaman A, Spence M, Wöhrle J, Elhadad S, Roberts D, Hovasse T, Valdés M, Silber S. Twelve-month results of a prospective, multicentre trial to assess the everolimus-eluting coronary stent system (PROMUS Element): the PLATINUM PLUS all-comers randomised trial. *EuroIntervention.* 2017;12:1595-604.

30. Natsuaki M, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, Akasaka T, Igarashi K, Tanabe K, Morino Y, Ishikawa T, Nishikawa H, Awata M, Abe M, Okada H, Takatsu Y, Ogata N, Kimura K, Urasawa K, Tarutani Y, Shiode N, Kimura T; NEXT Investigators. Biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent: a randomized, controlled, noninferiority trial. *J Am Coll Cardiol.* 2013;62:181-90.

31. Raungaard B, Jensen LO, Tilsted HH, Christiansen EH, Maeng M, Terkelsen CJ, Krusell LR, Kaltoft A, Kristensen SD, Bøtker HE, Thuesen L, Aarøe J, Jensen SE, Villadsen AB, Thayssen P, Veien KT, Hansen KN, Junker A, Madsen M, Ravkilde J, Lassen JF; Scandinavian Organization for Randomized Trials with Clinical Outcome (SORT OUT). Zotarolimus-eluting durable-polymer-coated stent versus a biolimus-eluting biodegradable-polymer-coated stent in unselected patients undergoing percutaneous coronary intervention (SORT OUT VI): a randomised non-inferiority trial. *Lancet.* 2015;385:1527-35.

32. Pilgrim T, Heg D, Roffi M, Tüller D, Muller O, Vuilliomenet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Fahrni T, Moschovitis A, Noble S, Eberli FR, Wenaweser P, Jüni P, Windecker S. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial. *Lancet.* 2014;384:2111-22.

33. von Birgelen C, Kok MM, van der Heijden LC, Danse PW, Schotborgh CE, Scholte M, Gin R, Somi S, van Houwelingen KG, Stoel MG, de Man FHAF, Louwerenburg JHW, Hartmann M, Zocca P, Linssen GCM, van der Palen J, Doggen CJM, Löwik MM. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in all-comers with coronary artery disease (BIO-RESORT): a three-arm, randomised, non-inferiority trial. *Lancet.* 2016;388:2607-17.

34. Jensen LO, Thayssen P, Maeng M, Ravkilde J, Krusell LR, Raungaard B, Junker A, Terkelsen CJ, Veien KT, Villadsen AB, Kaltoft A, Tilsted HH, Hansen KN, Aaroe J, Kristensen SD, Hansen HS, Jensen SE, Madsen M, Bøtker HE, Berencsi K, Lassen JF,

Christiansen EH. Randomized Comparison of a Biodegradable Polymer Ultrathin Strut Sirolimus-Eluting Stent With a Biodegradable Polymer Biolimus-Eluting Stent in Patients Treated With Percutaneous Coronary Intervention: the SORT OUT VII Trial. *Circ Cardiovasc Interv.* 2016;9:e003610.

35. Rozemeijer R, Stein M, Voskuil M, van den Bor R, Frambach P, Pereira B, Koudstaal S, Leenders GE, Timmers L, Rittersma SZ, Kraaijeveld AO, Agostoni P, Roes KC, Doevendans PA, Stella PR; ReCre8 Study Investigators. Randomized All-Comers Evaluation of a Permanent Polymer Zotarolimus-Eluting Stent Versus a Polymer-Free Amphilimus-Eluting Stent. *Circulation.* 2019;139:67-77.

36. Maeng M, Christiansen EH, Raungaard B, Kahlert J, Terkelsen CJ, Kristensen SD, Carstensen S, Aaroe J, Jensen SE, Villadsen AB, Lassen JF, Thim T, Eftekhari A, Veien KT, Hansen KN, Junker A, Botker HE, Jensen LO; SORT OUT VIII Investigators. Everolimus-Eluting Versus Biolimus-Eluting Stents With Biodegradable Polymers in Unselected Patients Undergoing Percutaneous Coronary Intervention: A Randomized Noninferiority Trial With 1-Year Follow-Up (SORT OUT VIII Trial). *JACC Cardiovasc Interv.* 2019;12:624-33.

37. de Winter RJ, Katagiri Y, Asano T, Milewski KP, Lurz P, Buszman P, Jessurun GAJ, Koch KT, Troquay RPT, Hamer BJB, Ophuis TO, Wöhrle J, Wyderka R, Cayla G, Hofma SH, Levesque S, Zurakowski A, Fischer D, Kośmider M, Goube P, Arkenbout EK, Noutsias M, Ferrari MW, Onuma Y, Wijns W, Serruys PW. A sirolimus-eluting bioabsorbable polymer-coated stent (MiStent) versus an everolimus-eluting durable polymer stent (Xience) after percutaneous coronary intervention (DESSOLVE III): a randomised, single-blind, multicentre, non-inferiority, phase 3 trial. *Lancet.* 2018;391:431-40.

38. Jensen LO, Maeng M, Raungaard B, Kahlert J, Ellert J, Jakobsen L, Villadsen AB, Veien KT, Kristensen SD, Ahlehoff O, Carstensen S, Christensen MK, Terkelsen CJ, Engstroem T, Hansen KN, Botker HE, Aaroe J, Thim T, Thuesen L, Freeman P, Aziz A, Eftekhari A, Junker A, Jensen SE, Lassen JF, Hansen HS, Christiansen EH; Sort Out IX Study Group. Randomized Comparison of the Polymer-Free Biolimus-Coated BioFreedom Stent With the Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Orsiro Stent in an All-Comers Population Treated With Percutaneous Coronary Intervention: The SORT OUT IX Trial. *Circulation.* 2020;141: 2052-63.

39. Lansky A, Wijns W, Xu B, Kelbaek H, van Royen N, Zheng M, Morel MA, Knaapen P, Slagboom T, Johnson TW, Vlachojannis G, Arkenbout KE, Holmvang L, Janssens L, Ochala A, Brugaletta S, Naber CK, Anderson R, Rittger H, Berti S, Barbato E, Toth GG, Maillard L, Valina C, Buszman P, Thiele H, Schächinger V, Baumbach A; TARGET All Comers Investigators. Targeted therapy with a localised abluminal groove, low-dose sirolimus-eluting, biodegradable polymer coronary stent (TARGET All Comers): a multicentre, open-label, randomised non-inferiority trial. *Lancet.* 2018;392:1117-26.

40. Zaman A, de Winter RJ, Kogame N, Chang CC, Modolo R, Spitzer E, Tonino P, Hofma S, Zurakowski A, Smits PC, Prokopczuk J, Moreno R, Choudhury A, Petrov I, Cequier A, Kukreja N, Hoye A, Iniguez A, Ungi I, Serra A, Gil RJ, Walsh S, Tonev G, Mathur A, Merkely B, Colombo A, Ijsselmuiden S, Soliman O, Kaul U, Onuma Y, Serruys PW; TALENT trial investigators. Safety and efficacy of a sirolimus-eluting coronary stent with ultra-thin strut for treatment of atherosclerotic lesions (TALENT): a prospective multicentre randomised controlled trial. *Lancet.* 2019;393:987-97.

Supplementary data

Supplementary Table 1. Definition of an all-comers trial.

Supplementary Table 2. Search strategy.

Supplementary Table 3. Inclusion and exclusion criteria of the eligible and included trials.

Supplementary Table 4. Patient baseline characteristics and medication of the included trials.

Supplementary Table 5. Definitions of myocardial infarction in the included trials.

Supplementary Table 6. Definitions of cardiac death and clinically indicated target lesion revascularisation.

Supplementary Table 7. Bias assessment of the included trials.

Supplementary Table 8. Performance of routine angiographic follow-up in the included trials.

Supplementary Table 9. List of antiplatelet therapy regimens and bleeding event rates in the included trials.

Supplementary Figure 1. Study selection process.

Supplementary Figure 2. The results of sensitivity analysis.

Supplementary Figure 3. Temporal trends of all-cause death and non-cardiac death.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00192

Supplementary data

Supplementary Table 1. Definition of an all-comers trial.

An all-comers trial was defined as one enrolling patients without the major exclusion criteria listed below.

a	Stenting for multiple lesions or vessels (>3 lesions or stents)
b	Low ejection fraction of left ventricular (<30 or 35%)
c	Haemodialysis
d	ST-segment elevation myocardial infarction
e	Non-ST-segment elevation acute coronary syndrome
f	Severely calcified lesion
g	Thrombotic lesion
h	Chronic total occlusion
i	In-stent restenosis
j	Saphenous vein graft
k	Arterial graft
l	Unprotected left main coronary artery
m	Bifurcated lesion with side branch (>2 mm) or requiring two stents
n	Aorto-ostial lesion
o	Long lesion with length over 30 mm

Supplementary Table 2. Search strategy.

PubMed		**N of publications**
#1	"Coronary Artery Disease"[Mesh]	64,648
#2	coronary[TIAB]	401,835
#3	#1 OR #2	412,330
#4	"Stents"[Mesh]	80,154
#5	stent*[TIAB]	103,181
#6	#4 OR #5	118,029
#7	#3 AND #6	34,902
#8	"randomized controlled trial"[Publication Type]	526,106
#9	"randomized controlled trials as topic"[MeSH Terms]	144,239
#10	#8 OR #9	662,528
#11	#7 AND #10	4,499
Embase		
#1	'coronary artery disease'/exp	339,681
#2	coronary	737,700
#3	#1 OR #2	739,876
#4	'stent'/exp	175,261
#5	stent*	212,905
#6	#4 OR #5	215,209
#7	#3 AND #6	40,842
#8	#7 AND ('controlled clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de)	3,948
Cochrane Library		
#1	MeSH descriptor: [Coronary Artery Disease] explode all trees	6,525
#2	coronary:ti,ab,kw	56,852
#3	#1 or #2	56,852
#4	MeSH descriptor: [Stents] explode all trees	4,232
#5	stent*:ti,ab,kw	15,567
#6	#4 or #5	15,617
#7	#3 and #6	8,533
#8	#7 in Trials	8,509
#9	#8 not pubmed:an	4,204
#10	#9 not embase:an	1,692

Supplementary Table 3. Inclusion and exclusion criteria of the eligible and included trial.

Study name	All-comers trial	N of major exclusion criteria	Multiple lesions or vessels	Low EF	Haemodialysis	STEMI	NSTE-ACS	Severe calcification	Thrombus	CTO	ISR	SVG	Arterial graft	Left main	Bifurcation	Aorto-ostium	Long lesion
TAXUS I	NO	14	Excluded	Excluded	Excluded	Excluded	Excluded	Included	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Not reported	Excluded
SIRIUS	NO	13	Excluded	Included	Not reported	Excluded	Included	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
TAXUS IV	NO	13	Excluded	Included	Excluded	Excluded	Included	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
TAXUS VI	NO	12	Excluded	Excluded	Not reported	Excluded	Included	Excluded	Not reported	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Included
SIRTAX	YES	0	Included	Included	Not reported	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
TAXUS V	NO	11	Included	Included	Excluded	Excluded	Included	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Included
ENDEAVOR II	NO	12	Excluded	Excluded	Not reported	Excluded	Excluded	Excluded	Not reported	Not reported	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
ENDEAVOR IV	NO	14	Excluded	Excluded	Not reported	Excluded	Included	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
LEADERS	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
SPIRIT IV	NO	13	Excluded	Excluded	Not reported	Excluded	Included	Excluded	Not reported	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
ZEST	NO	3	Included	Included	Not reported	Excluded	Included	Included	Included	Included	Excluded	Included	Included	Excluded	Included	Included	Included
SORT OUT III	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
ISAR-TEST 4	NO	5	Included	Included	Included	Included	Included	Included	Included	Included	Excluded	Excluded	Excluded	Excluded	Included	Not reported	Included
COMPARE	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
PERSEUS	NO	7	Excluded	Not reported	Not reported	Excluded	Included	Included	Not reported	Not reported	Excluded	Excluded	Excluded	Not reported	Included	Not reported	Excluded
Kadota et al	NO	7	Excluded	Excluded	Excluded	Excluded	Included	Included	Included	Not reported	Excluded	Included	Included	Excluded	Included	Included	Excluded
PROTECT	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
SORT OUT IV	YES	0	Included	Not reported	Not reported	Included	Included	Not reported	Included	Included	Not reported	Included	Included	Included	Included	Not reported	Included
Resolute All Comer	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
ISAR-TEST 5	NO	5	Included	Included	Excluded	Included	Included	Included	Included	Included	Excluded	Excluded	Excluded	Excluded	Included	Included	Included
TWENTE	NO	2	Included	Included	Excluded	Excluded	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
ECO-PLEASANT	NO	5	Included	Excluded	Excluded	Excluded	Included	Included	Included	Included	Excluded	Not reported	Not reported	Excluded	Included	Not reported	Included
PLATINUM	NO	14	Included	Excluded	Not reported	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
COMPARE II	YES	0	Included	Not reported	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
SORT OUT V	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
RESET	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included

DUTCH PEERS	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
HOST–ASSURE	YES	1	Included	Included	Not reported	Included	Included	Not reported	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
BASKET-PROVE II	NO	5	Included	Not reported	Not reported	Included	Included	Not reported	Included	Included	Excluded	Excluded	Excluded	Excluded	Included	Not reported	Included	
PLATINUM PLUS	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Not reported	Included	
NEXT	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
PROMISE	NO	7	Included	Not reported	Excluded	Excluded	Included	Not reported	Included	Excluded	Excluded	Excluded	Not reported	Excluded	Excluded	Not reported	Included	
SORT OUT VI	YES	0	Included	Not reported	Not reported	Included	Included	Not reported	Included	Included	Included	Included	Not reported	Included	Included	Included	Included	
BIOSCIENCE	YES	0	Included	Not reported	Not reported	Included	Included	Not reported	Included	Included	Included	Included	Included	Included	Included	Included	Included	
CENTURY II	NO	3	Included	Excluded	Excluded	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	
EVOLVE II	NO	6	Included	Not reported	Not reported	Excluded	Included	Not reported	Not reported	Excluded	Excluded	Excluded	Excluded	Excluded	Not Reported	Not reported	Included	
BIO-RESORT	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Not reported	Included	
SORT OUT VII	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Not reported	Included	
BIOFLOW-IV	NO	15	Excluded	Excluded	Excluded	Excluded	Included	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	
BIONICS	NO	7	Excluded	Excluded	Excluded	Excluded	Included	Included	Not reported	Included	Included	Included	Included	Not reported	Excluded	Not reported	Excluded	
HARMONEE	NO	10	Included	Excluded	Excluded	Excluded	Included	Included	Included	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Not reported	Excluded	
ReCre8	YES	1	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
SORT OUT VIII	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
BIOFLOW V	NO	10	Included	Excluded	Excluded	Excluded	Included	Included	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Not reported	Included	
DESSOLVE III	YES	1	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Not reported	Included	
BIONYX	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
SORT OUT IX	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
TARGET All Comers	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included
TALENT	YES	0	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included	Included

All the eligible 49 trials enrolling non-specific population are listed. The included all-comers trials are highlighted in red.
CTO: chronic total occlusion; EF: ejection fraction; ISR: in-stent restenosis; N: number; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; SVG: saphenous vein graft

Supplementary Table 4. Patient baseline characteristics and medication of the included trials.

Trial name	Device	N of patients	N of lesions	Mean age	Male (%)	Hypertension (%)	Diabetes (%)	Dyslipidaemia (%)	STEMI (%)	NSTE-ACS (%)	Prior MI (%)	Renal insufficiency (%)	N of lesions treated	Beta-blocker (%)	Statin (%)	ACEI/ ARB (%)	DAPT at one year (%)
SIRTAX	CYPHER	503	693	62	75.9	60	21.5	60.6	23.3	27.8	28.8		1.4				
	TAXUS Express	509	708	62	78.4	62.3	18.3	57	21.6	30.1	29.7		1.4				
LEADERS	BioMatrix	857	1,257	64.6	75	73.5	26	65.3	15.8	39.1	32.2		1.5				
	CYPHER	850	1,215	64.5	74.6	72.7	22.5	68.2	16.5	39.2	32.6		1.4				
SORT OUT III	Endeavor	1,162	1,619	64.3	73.3	54	15	70	6	37.5	25						
	CYPHER	1,170	1,611	64.3	73.7	51	14	68	8.5	38.1	26						
COMPARE	XIENCE	897	1,286	62.9	69	46.5	17.1	49.8	26.8	33.6	15	3	1.4				70
	TAXUS Liberté	903	1,294	63.6	72.4	49.5	19	49.9	23.5	35.7	18	3	1.4				70
PROTECT	Endeavor	4,357	6,151	62.3	76.7	64.6	26.9	61.8	8.2	17.6	20		1.4				87
	CYPHER	4,352	6,140	62.1	76	63.4	28.4	62.8	8.8	17.1	21		1.39				88
SORT OUT IV	XIENCE/PROMUS	1,390	1,805	64.2	75.9	56.7	14	71.1	8.8	32.9	21.5		1.3				
	CYPHER	1,384	1,779	64	75.2	53.8	14.2	71.1	10.5	32.7	20.6		1.3				
Resolute All Comer	Resolute	1,140	1,661	64.4	76.7	71.1	23.5	63.9	34.5	19.4	28.9		1.46				
	XIENCE	1,152	1,705	64.2	77.2	71.3	23.4	67.7	33.7	18.9	30.4		1.48				
COMPARE II	Nobori	1,795	2,638	63	74.4	54.8	21.8		20.7	37.2	20.3	4.3	1.5				66.6
	XIENCE	912	1,387	62.7	74.3	56.3	21.6		21.6	36.2	18.8	4.4	1.5				65.9
SORT OUT V	Nobori	1,229	1,532	65	74.6	55.5	15.1	57.8	18.3	30.3	17.7		1.25				
	CYPHER	1,239	1,555	65.2	75.1	52.7	15.3	58.9	18.3	31	17.3		1.26				
RESET	XIENCE	1,597	1,967	68.9	77.5	79.5	45.5	74.5	6.5	11.3	29	2.1	1.23	36.8	77.4	61.8	11.1

	CYPHER	1,600	1,960	69.3	76.1	80.6	44.6	75.3	5.2	13.3	31	2.4	1.23	37.7	77.4	60.9	10.4
DUTCH PEERS	Resolute	906	1,205	64	73.4	55.2	18.4	46.1	19.3	39.6	23	4					
	XIENCE	905	1,166	65	72.6	53	17.3	47.5	21.5	36.8	21	3					
HOST–ASSURE	PROMUS	2,503	3,426	63.1	69.8	68.2	31.8	64	11.3	18.1	4.6	2.4		68.3	84.8	65.4	91.1
	Resolute	1,252	1,661	63.5	65.6	68.1	32	65.7	10.9	16.7	3.9	2.9		67.5	85.9	66.2	92.6
PLATINUM PLUS	PROMUS	1,952	3,289	65.7	77.7	68	29.1	63.4	8.7	28.1	21.7		1.6				59.4
	XIENCE	1,028	1,711	66.1	78.4	68.6	27.2	62.2	9.3	27.6	24.3		1.6				61.2
NEXT	Nobori	1,617	1,985	69.1	77	81.4	46.1	78.2	5.1	11.6	28	2.5	1.27				86.7
	XIENCE/PROMUS	1,618	1,947	69.3	77.4	81.8	45.7	78.1	4.4	11.1	28	2.6	1.24				87.5
SORT OUT VI	Resolute	1,502	1,883	65.7	76.2	59.7	17.6	59.3	19.6	31	18.7		1.3				
	BioMatrix	1,497	1,791	65.8	75.8	58.1	18	59.1	16.9	33.9	19.7		1.3				
BIOSCIENCE	Orsiro	1,063	1,594	66.1	77	68.5	24.2	67	19.8	34.4	21		1.5	47.3	53.6	25.9	83.4
	XIENCE	1,056	1,545	65.9	77.3	66.9	21.7	67.8	18.6	33.9	19.3		1.46	45.4	54.2	26.6	82.1
BIO-RESORT	SYNERGY	1,172	1,532	64	72.1	44.4	17.3	36	32.2	37.5	16	3					85.5
	Resolute	1,173	1,580	63.6	72.3	47.2	17.9	38.4	27.8	41.7	21	3					86.3
	Orsiro	1,169	1,551	64.2	73.1	47	18	39.6	31.7	38.3	18	4					85.1
SORT OUT VII	Orsiro	1,261	1,590	66.1	74.9	58.1	18.7	57.6	21.3	30.8	17.4		1.3				
	Nobori	1,264	1,588	64.8	75.2	56.4	18.6	56.7	20.7	32.6	17.8		1.3				
ReCre8	Resolute	744	1,024	65.1	77.6	55.2	20	45.7	22.4	25	21.2						40.1
	Cre8	747	1,087	64.7	75.6	55.2	20.7	43.5	24.2	22.6	18.6						39.4
SORT OUT VIII	SYNERGY	1,385	1,725	66	76.5	56.1	18.1	54			18						
	BioMatrix	1,379	1,670	66	76.6	57.7	19	52.5			17						
DESSOLVE III	MiStent	703	1,037	66.4	70.3	72	26.6	60.8	14.7	44.2	27	7	1.49				

	XIENCE	695	993	66.3	73.8	75	27.1	60	15.7	43	28	7	1.44	
SORT OUT IX	BioFreedom	1,572	1,966	66.4	77.5	56.8	16.7	52.8	23.3	32	14.7		1.3	
	Orsiro	1,579	1,985	66.1	77.3	53.8	16.6	49.2	25.1	32	15.2		1.3	
BIONYX	Resolute Onyx	1,243	1,646	64.1	76.1	51.5	20.9	45.4	22.7	48.1	16.1	6.7		83.9
	Orsiro	1,245	1,593	63.9	76.1	53.2	20.1	46.4	27.2	43.9	15.6	6.7		82.2
TARGET All Comers	FIREHAWK	823	1,221	64.9	78.1	59.9	24	53	8.4	35.4	21.7	5.5	1.5	
	XIENCE	830	1,179	65.3	76.4	62.5	23	51.2	8.9	35.4	24.8	7	1.4	
TALENT	Supraflex	720	1,046	66	75.8	65.3	21.8	61.8	16.5	43.1	18.9	2.8	1.45	
	XIENCE	715	1,030	65	76	66	24.9	60.2	16.4	40.3	17.9	2	1.44	

ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker; AHA/ACC: American Heart Association/American College of Cardiology; DAPT: dual antiplatelet therapy; LVEF: left ventricular ejection fraction; N: number; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction

Supplementary Table 5. Definitions of myocardial infarction in the included trials.

Trial name	Study start year	Definition of spontaneous MI
SIRTAX	2003	Q or CKMB/cTn>2ULN
LEADERS	2006	ECG or (CK>2ULN + CKMB/cTn>1ULN)
SORT OUT III	2006	Clinical/ECG + cTn>1ULN [Universal definition][70]
COMPARE	2007	Clinical/ECG + CKMB/cTn>1ULN
PROTECT	2007	ECG or (clinical + CKMB/cTn>1ULN)
SORT OUT IV	2007	Clinical/ECG + cTn>1ULN [Universal definition]
Resolute All Comer	2008	(Clinical + Q + cTn/CK>1ULN) or (CK>2ULN + CKMB/cTn>1ULN) or CKMB/cTn>3ULN [Extended historical][71]
COMPARE II	2009	Clinical/ECG + CKMB/cTn>1ULN
SORT OUT V	2009	Clinical/ECG + cTn>1ULN [Universal definition]
DUTCH PEERS	2010	(Clinical + Q + cTn/CK>1ULN) or (CK>2ULN + CKMB/cTn>1ULN) or CKMB/cTn>3ULN [Extended historical]
HOST–ASSURE	2010	Clinical/ECG + cTn>1ULN [Universal definition]
PLATINUM PLUS	2010	(Q + CKMB/cTn>1ULN) or (ECG/clinical + CKMB/cTn>2ULN)
RESET	2010	CKMB/cTn>1ULN [ARC]
NEXT	2011	CKMB/cTn>1ULN [ARC]
SORT OUT VI	2011	Clinical/ECG + cTn>1ULN [Universal definition]
BIO-RESORT	2012	(Clinical + Q + cTn/CK>1ULN) or (CK>2ULN + CKMB/cTn>1ULN) or CKMB/cTn>3ULN [Extended historical]
BIOSCIENCE	2012	Clinical/ECG + cTn>1ULN [Universal definition]
SORT OUT VII	2012	Clinical/ECG + cTn>1ULN [Universal definition]
ReCre8	2014	CKMB/cTn>1ULN [ARC]
SORT OUT VIII	2014	Clinical/ECG + cTn>1ULN [Universal definition]
BIONYX	2015	(Clinical + Q + cTn/CK>1ULN) or (CK>2ULN + CKMB/cTn>1ULN) or CKMB/cTn>3ULN [Extended historical]
DESSOLVE III	2015	(Clinical + Q + cTn/CK>1ULN) or (CK>2ULN + CKMB/cTn>1ULN) or CKMB/cTn>3ULN [Extended historical]
SORT OUT IX	2015	Clinical/ECG + cTn>1ULN [Universal definition]
TARGET All Comers	2015	Clinical/ECG + cTn>1ULN [Universal definition]
TALENT	2016	Clinical/ECG + cTn>1ULN [Universal definition]

ARC: Academic Research Consortium; CKMB: creatine kinase myocardial band; Clinical: clinical findings related to myocardial infarction; cTn: cardiac troponin; ECG: ischaemic change in electrocardiograph; MI: myocardial infarction; Q: Q-wave detected on electrocardiograph; SCAI: Society for Cardiovascular Angiography and Interventions; ULN: upper limit of normal

Summary Table for the definition of spontaneous myocardial infarction

2003 -2007	**N of trials**
clinical/ECG + cTn>1ULN **[Universal definition]**[70]	2
ECG or (CK>2ULN + CKMB/cTn>1ULN)	1
Q or CKMB/cTn>2ULN	1
Clinical/ECG + CKMB/cTn>1ULN	1
ECG or (clinical + CKMB/cTn>1ULN)	1
2008 - 2012	
clinical/ECG + cTn>1ULN **[Universal definition]**[70]	5
(clinical + Q + cTn/CK>1ULN) or (CK>2ULN + CKMB/cTn>1ULN) or CKMB/cTn>3ULN **[Extended historical]**[71]	3
CKMB/cTn>1ULN **[ARC]**[72]	2
(Q + CKMB/cTn>1ULN) or (ECG/clinical + CKMB/cTn>2ULN)	1
2013 - 2016	
clinical/ECG + cTn>1ULN **[Universal definition]**[70]	4
(clinical + Q + cTn/CK>1ULN) or (CK>2ULN + CKMB/cTn>1ULN) or CKMB/cTn>3ULN **[Extended historical]**[71]	2
CKMB/cTn>1ULN **[ARC]**[72]	1

ARC: Academic Research Consortium; CKMB: creatine kinase myocardial band; Clinical: clinical findings related to myocardial infarction; cTn: cardiac troponin; ECG: ischaemic change on electrocardiograph; N: number; Q: Q-wave detected on electrocardiograph; SCAI: Society for Cardiovascular Angiography and Interventions; ULN: upper limit of normal

Supplementary Table 6. Definitions of cardiac death and clinically indicated target lesion revascularisation.

Trial name	Definition for cardiac death	Definition for clinically indicated TLR
SIRTAX	Definition not reported	ARC
LEADERS	ARC	ARC
SORT OUT III	ARC	N/A[#]
COMPARE	ARC	ARC
PROTECT	ARC	N/A[#]
SORT OUT IV	ARC	Clinically driven
Resolute All Comer	ARC	ARC
COMPARE II	ARC	ARC
SORT OUT V	ARC	Clinically driven
DUTCH PEERS	ARC	ARC
HOST–ASSURE	ARC	ARC
PLATINUM PLUS	Death due to MI; arrhythmia or conduction disturbance; deaths related to the procedure; stroke prior to hospital discharge; and death of unknown cause	ARC*
RESET	ARC	ARC
NEXT	ARC	ARC
SORT OUT VI	ARC	Clinically driven
BIO-RESORT	ARC	ARC*
BIOSCIENCE	ARC	ARC*
SORT OUT VII	ARC	Clinically driven
ReCre8	ARC	N/A[#]
SORT OUT VIII	ARC	Clinically driven
BIONYX	ARC	ARC
DESSOLVE III	ARC	ARC
SORT OUT IX	ARC	Clinical-driven
TARGET All Comers	Definition not reported	Definition not reported (ischaemia-driven)
TALENT	ARC	ARC

[#] Trial did not report the incidence of clinically indicated TLR. * The ARC definition was applied but quantitative coronary angiography was not performed at an independent angiographic core laboratory.

ARC: Academic Research Consortium; MI: myocardial infarction; TLR: target lesion revascularisation

Supplementary Table 7. Bias assessment of the included trials.

Trial name	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL*	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER BIAS
SIRTAX	Low	Low	High	Low	Low	Low	Low
LEADERS	Low	Low	High	Low	Low	Low	Low
SORT OUT III	Low	Low	High	Low	Low	Low	Low
COMPARE	Low	Low	High	Low	Low	Low	Low
PROTECT	Low	Low	High	Low	Low	Low	Low
SORT OUT IV	Low	Low	High	Low	Low	Low	Low
Resolute All Comer	Low	Low	High	Low	Low	Low	Low
COMPARE II	Low	Low	High	Low	Low	Low	Low
SORT OUT V	Low	Low	High	Low	Low	Low	Low
RESET	Low	Low	High	Low	Low	Low	Low
DUTCH PEERS	Low	Low	High	Low	Low	Low	Low
HOST–ASSURE	Low	Low	High	Low	Low	Low	Low
PLATINUM PLUS	Low	Low	High	Low	Low	Low	Low
NEXT	Low	Low	High	Low	Low	Low	Low
SORT OUT VI	Low	Low	High	Low	Low	Low	Low
BIOSCIENCE	Low	Low	High	Low	Low	Low	Low
BIO-RESORT	Low	Low	High	Low	Low	Low	Low
SORT OUT VII	Low	Low	High	Low	Low	Low	Low
ReCre8	Low	Low	High	Low	Low	Low	Low
SORT OUT VIII	Low	Low	High	Low	Low	Low	Low
DESSOLVE III	Low	Low	High	Low	Low	Low	Low
BIONYX	Low	Low	High	Low	Low	Low	Low
SORT OUT IX	Low	Low	High	Low	Low	Low	Low
TARGET All Comers	Low	Low	High	Low	Low	Low	Low
TALENT	Low	Low	High	Low	Low	Low	Low

* In all trials, the operator was not blinded while the assessors (clinical events committee, core laboratory, and statistician) were blinded. Awareness of the allocated stent possibly introduces a bias in the operator's procedure (e.g., lesion preparation, post-dilatation, etc.).

Supplementary Table 8. Performance of routine angiographic follow-up in the included trials.

Study name	Device	N of patients	Month at angio FU	N of patients undergoing angio FU	Patients with angio FU (%)	Month at 1Y TLR	1Y TLR (%)	Angio FU performed before 1Y result
SIRTAX	CYPHER	503	8	267	53.1%	12	5.8%	YES
	TAXUS Express	509		273	53.6%		10.2%	
LEADERS	BioMatrix	857	9	168	19.6%	12	5.2%	YES
	CYPHER	850		167	19.6%		5.8%	
SORT OUT III	Endeavor	1,162	No angio FU			12	5.3%	
	CYPHER	1,170					1.4%	
COMPARE	XIENCE	897	No angio FU			12	1.7%	
	TAXUS Liberté	903					4.8%	
PROTECT	Endeavor	4357	No angio FU			12		
	CYPHER	4,352						
SORT OUT IV	XIENCE/PROMUS	1,390	No angio FU			9	1.4%	
	CYPHER	1,384					1.7%	
Resolute All Comer	Resolute	1,140	13	142	12.5%	12	3.9%	NO
	XIENCE	1,152		130	11.3%		3.4%	
COMPARE II	Nobori	1,795	No angio FU			12	2.1%	
	XIENCE	912					1.8%	
SORT OUT V	Nobori	1,229	No angio FU			12	3.3%	
	CYPHER	1,239					2.0%	
DUTCH PEERS	Resolute	906	No angio FU			12	2.2%	
	XIENCE	905					2.2%	
HOST–ASSURE	PROMUS	2,503	No angio FU			12	1.3%	
	Resolute	1,252					1.2%	
PLATINUM PLUS	PROMUS Element	1,952	No angio FU			12	2.0%	
	XIENCE	1,028					1.6%	
RESET	XIENCE	1,597	8	235	14.7%	12	2.9%	YES
	CYPHER	1,600		247	15.4%		3.7%	
NEXT	Nobori	1,617	8	227	14.0%	12	2.9%	YES
	XIENCE/PROMUS	1,618		230	14.2%		2.9%	
SORT OUT VI	Resolute	1,502	No angio FU			12	3.5%	
	BioMatrix	1,497					3.1%	
BIO-RESORT	SYNERGY	1,172	No angio FU			12	1.5%	
	Resolute	1,173					1.5%	
	Orsiro	1,169					1.5%	
BIOSCIENCE	Orsiro	1,063	No angio FU			12	3.4%	
	XIENCE	1,056					2.4%	
SORT OUT VII	Orsiro	1,261	No angio FU			12	2.0%	
	Nobori	1,264					2.9%	
ReCre8	Resolute	751	No angio FU			12		
	Cre8	751						
SORT OUT VIII	SYNERGY	1,385	No angio FU			12	2.3%	
	BioMatrix	1,379					2.5%	
BIONYX	Resolute Onyx	1,243	No angio FU			12	2.5%	
	Orsiro	1,245					2.0%	

DESSOLVE III	MiStent	703	No angio FU			12	2.6%	
	XIENCE	695					3.7%	
SORT OUT IX	BioFreedom	1,572	No angio FU			12	3.5%	
	Orsiro	1,579					1.3%	
TARGET All Comers	FIREHAWK	823	13	71	8.6%	12	1.1%	NO
	XIENCE	830		66	8.0%		2.3%	
TALENT	Supraflex	720	No angio FU			12	2.7%	
	XIENCE	715					4.0%	

angio: angiography; FU: follow-up; N: number; TLR: target lesion revascularisation; Y: year

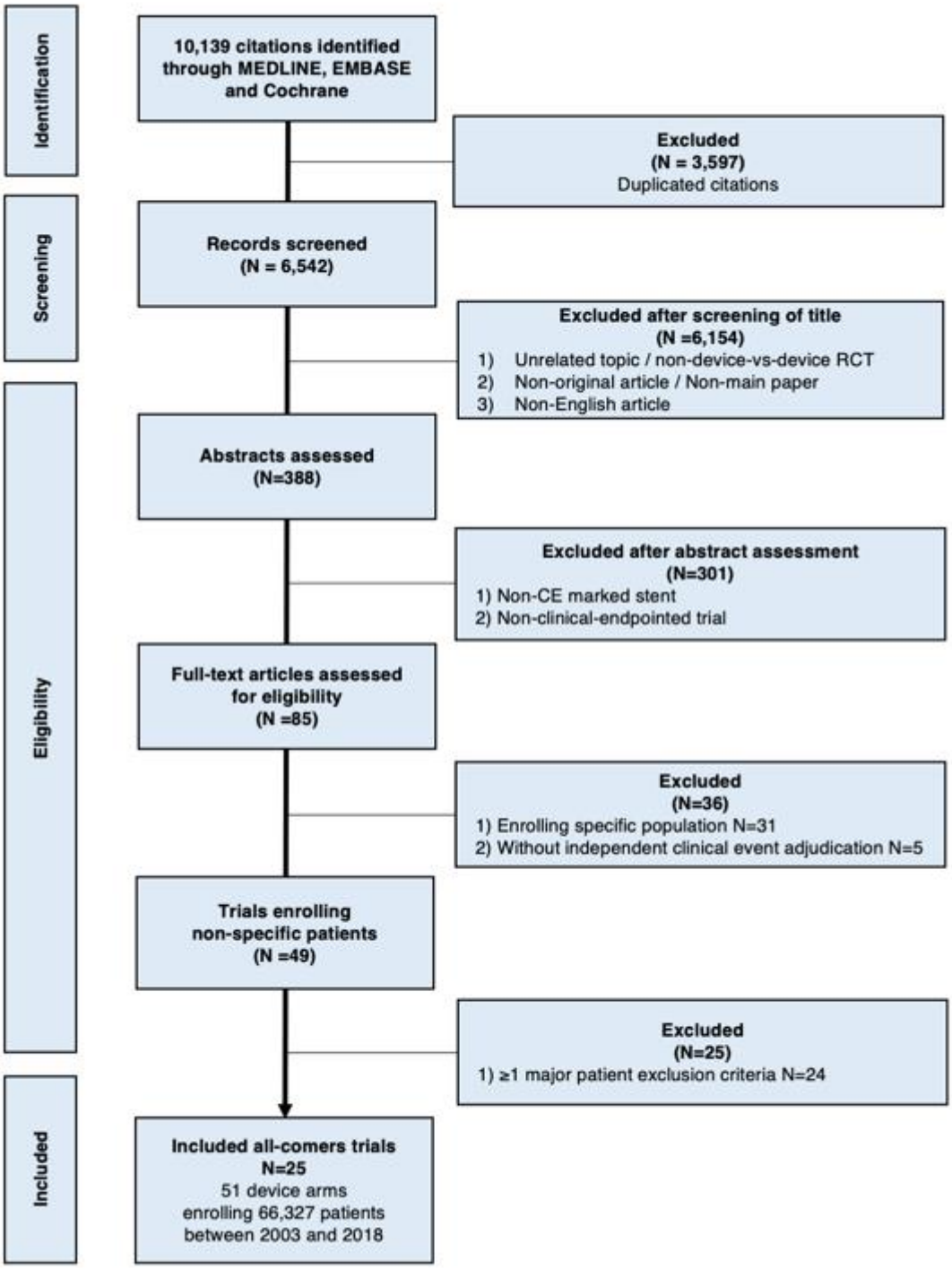
Supplementary Table 9. List of antiplatelet therapy regimens and bleeding event rates in the included trials.

Study name	Study start year	Device	N of patients	Recommended DAPT duration (months)	Recommended $P2Y_{12}$ inhibitor	Percent of patients on DAPT at 1 year	Percent of patients with major bleeding at 1 year	Definition for bleeding event
SIRTAX	2003	CYPHER	503	12	Clopidogrel	Not reported	**Not reported**	NA
		TAXUS Express	509			Not reported	**Not reported**	NA
LEADERS	2006	BioMatrix	857	12	Clopidogrel	Not reported	**Not reported**	NA
		CYPHER	850			Not reported	**Not reported**	NA
SORT OUT III	2006	Endeavor	1,162	12	Clopidogrel	Not reported	**Not reported**	NA
		CYPHER	1,170			Not reported	**Not reported**	NA
COMPARE	2007	XIENCE	897	12	Clopidogrel	70.0	**Not reported**	NA
		TAXUS Liberté	903			70.0	**Not reported**	NA
PROTECT	2007	Endeavor	4,357	3 to 12	Ticlopidine or clopidogrel	87.0	**Not reported (only 2-year incidence reported)**	TIMI
		CYPHER	4,352			88.0	**Not reported (only 2-year incidence reported)**	TIMI
SORT OUT IV	2007	XIENCE / PROMUS	1,390	12	Clopidogrel or prasugrel	Not reported	**Not reported**	NA
		CYPHER	1,384			Not reported	**Not reported**	NA
Resolute All Comer	2008	Resolute	1,140	At least 6	Clopidogrel	Not reported	**Not reported**	NA
		XIENCE	1,152			Not reported	**Not reported**	NA
COMPARE II	2009	Nobori	1,795	12	Clopidogrel	67.0	**Not reported**	NA
		XIENCE	912			66.6	**Not reported**	NA
SORT OUT V	2009	Nobori	1,229	12	Clopidogrel or prasugrel	Not reported	**Not reported**	NA
		CYPHER	1,239			Not reported	**Not reported**	NA
DUTCH PEERS	2010	Resolute	906	12	Clopidogrel	Not reported	**Not reported**	NA
		XIENCE	905			Not reported	**Not reported**	NA
HOST–ASSURE	2010	PROMUS	2,503	Not reported	Double dose of clopidogrel or normal dose of clopidogrel plus cilostazol	91.1	**1.1**	PLATO
		Resolute	1,252			92.6	**1.3**	PLATO
PLATINUM PLUS	2010	PROMUS Element	1,952	At least 6	Clopidogrel or prasugrel	59.4	**Not reported**	NA
		XIENCE	1,028			61.2	**Not reported**	NA
RESET	2010	XIENCE	1,597	At least 3	Ticlopidine or clopidogrel	89.0	**1.0**	TIMI
		CYPHER	1,600			90.0	**1.3**	TIMI
NEXT	2011	Nobori	1,617	At least 3	Ticlopidine or clopidogrel	86.7	**1.1**	TIMI
		XIENCE / PROMUS	1,618			87.5	**0.9**	TIMI
SORT OUT VI	2011	Resolute	1,502	12	Clopidogrel, ticagrelor or prasugrel	Not reported	**Not reported**	NA
		BioMatrix	1,497			Not reported	**Not reported**	NA
BIO-RESORT	2012	SYNERGY	1,172	6 to 12	Clopidogrel, ticagrelor or prasugrel	85.5	**Not reported**	NA
		Resolute	1,173			86.3	**Not reported**	NA
		Orsiro	1,169			85.1	**Not reported**	NA
BIOSCIENCE	2012	Orsiro	1,063	12	Clopidogrel, ticagrelor or prasugrel	83.4	**2.9**	BARC 3-5
		XIENCE	1,056			82.1	**2.6**	BARC3-5
SORT OUT VII	2012	Orsiro	1,261	12	Clopidogrel, ticagrelor or prasugrel	Not reported	**Not reported**	NA

		Nobori	1,264			Not reported	**Not reported**	NA
ReCre8	2014	Resolute	751	1 for Tn negative / 12 Tn positive	Clopidogrel, ticagrelor or prasugrel	40.1	**1.7**	BARC 3-5
		Cre8	751			39.4	**1.6**	BARC 3-5
SORT OUT VIII	2014	SYNERGY	1,385	12	Clopidogrel, ticagrelor or prasugrel	Not reported	**Not reported**	NA
		BioMatrix	1,379			Not reported	**Not reported**	NA
BIONYX	2015	Resolute Onyx	1,243	At least 6 for stable coronary disease / 12 for ACS	Clopidogrel, ticagrelor or prasugrel	83.9	**2.5**	BARC 3 or 5 or any TIMI
		Orsiro	1,245			82.2	**2.7**	BARC 3 or 5 or any TIMI
DESSOLVE III	2015	MiStent	703	At least 6	Clopidogrel, ticagrelor or prasugrel	Not reported	**Not reported**	NA
		XIENCE	695			Not reported	**Not reported**	NA
SORT OUT IX	2015	BioFreedm	1,572	6 for stable coronary disease / 12 for ACS	Clopidogrel, ticagrelor or prasugrel	Not reported	**Not reported**	NA
		Orsiro	1,579			Not reported	**Not reported**	NA
TARGET All Comers	2015	FIREHAWK	823	At least 6 for stable coronary disease / 12 for ACS	Clopidogrel, ticagrelor or prasugrel	Not reported	**Not reported**	NA
		XIENCE	830			Not reported	**Not reported**	NA
TALENT	2016	Supraflex	720	At least 6 for stable coronary disease / 12 for ACS	Clopidogrel, ticagrelor or prasugrel	Not reported	**Not reported**	NA
		XIENCE	715			Not reported	**Not reported**	NA

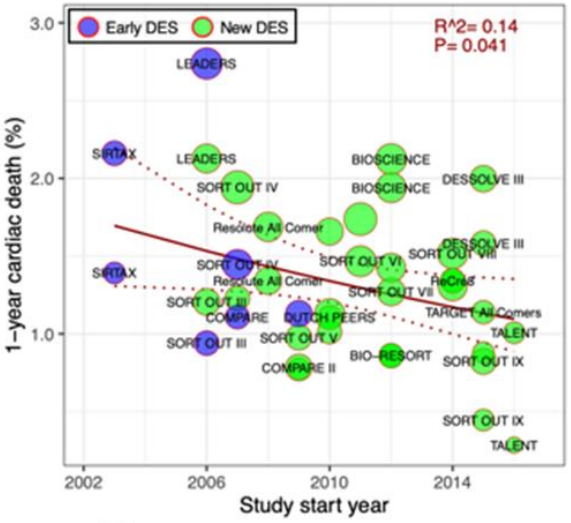
ACS: acute coronary syndrome; DAPT: dual antiplatelet therapy; N: number; NA: not applicable; TIMI: Thrombolysis In Myocardial Infarction; Tn: troponin

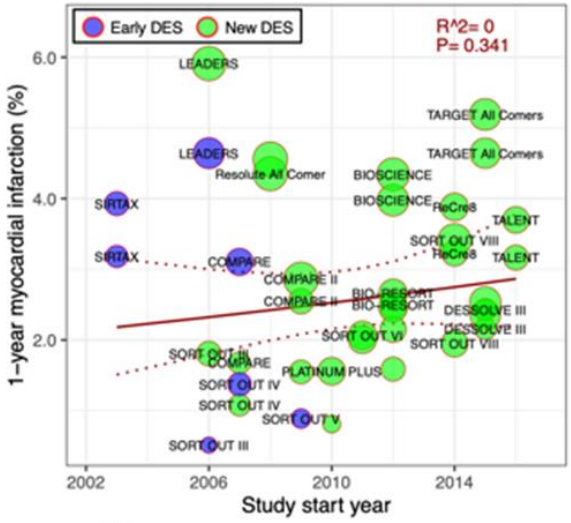
BioFreedom™ (Biosensors, Singapore)
BioMatrix ™ (Biosensors, Singapore)
Cre8™ (Alvimedica, Istanbul, Turkey)
CYPHER® (Cordis Santa Clara, CA, USA)
Endeavor® (Medtronic, Minneapolis, MN, USA)
FIREHAWK® (MicroPort, Shanghai, China)
MiStent® (Micell Technologies, Durham, NC, USA)
Nobori® (Terumo Corp., Tokyo, Japan)
Osiro (Biotronik, Berlin Germany)
PROMUS™ (Boston Scientific, Marlborough, MA, USA)
Resolute™ (Medtronic, Minneapolis, MN, USA)
Resolute Onyx™ (Medtronic, Minneapolis, MN, USA)
Supraflex™ (Sahajanand Medical Technologies, Mumbai, India)
SYNERGY™ (Boston Scientific, Marlborough, MA, USA)
TAXUS Express (Boston Scientific, Marlborough, MA, USA)
TAXUS™ Liberté™ (Boston Scientific, Marlborough, MA, USA)
XIENCE® (Abbott Laboratories, Abbott Park, IL, USA)

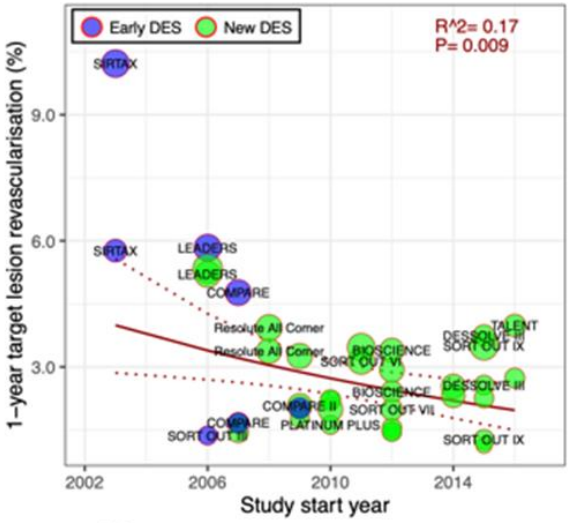


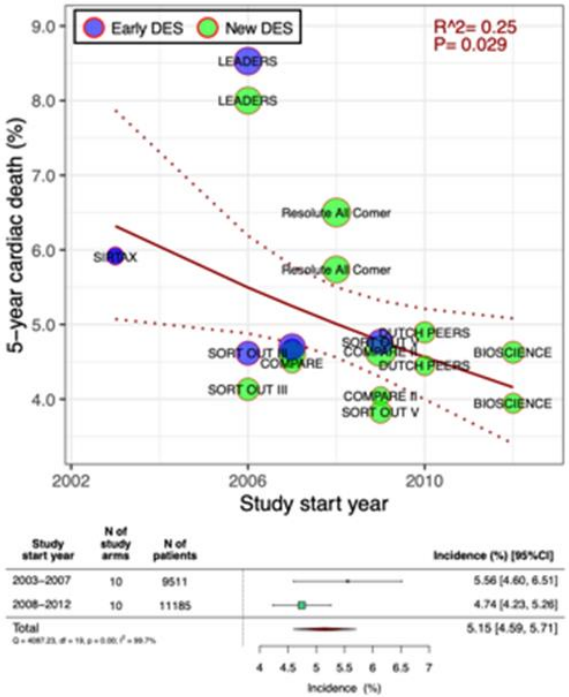
Supplementary Figure 1. Study selection process.

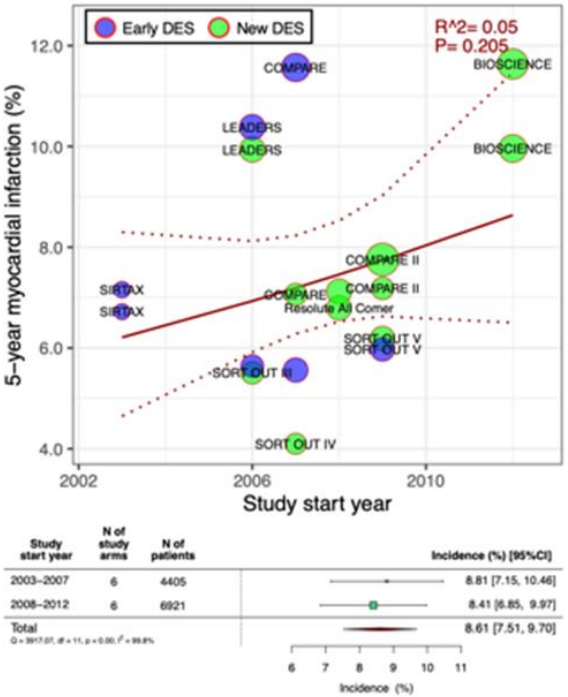
N: number; RCT: randomised controlled trial

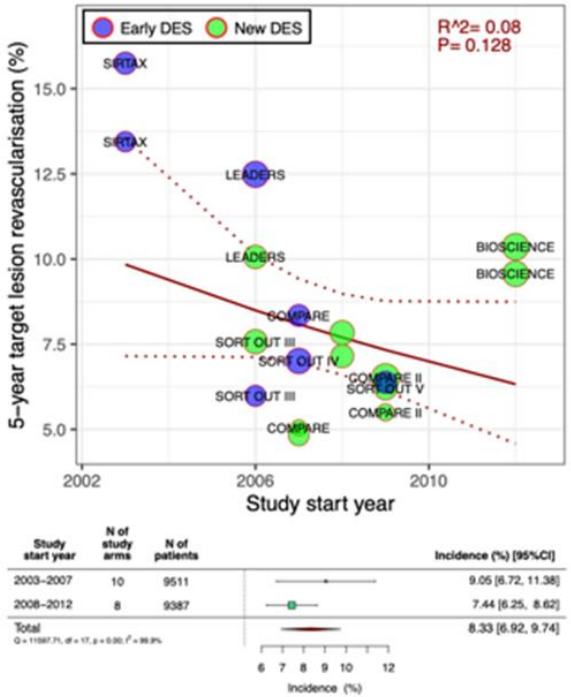

Early DES
New DES
R^2= 0.14
P= 0.041
1−year cardiac death (%)
3.0
2.0
1.0
LEADERS
SIRTAX
LEADERS
SORT OUT IV
BIOSCIENCE
BIOSCIENCE
DESSOLVE III
Resolute All Comer
DESSOLVE III
SORT OUT VIII
SORT OUT VI
SORT OUT IV
SIRTAX
Resolute All Comer
ReCre8
SORT OUT VII
SORT OUT III
COMPARE
DUTCH PEERS
TARGET All Comers
SORT OUT III
SORT OUT V
TALENT
COMPARE II
BIO−RESORT
SORT OUT IX
SORT OUT IX
TALENT
2002
2006
2010
2014
Study start year
Study start year
N of study arms
N of patients
Incidence (%) [95%CI]
2003−2007 10 9600 1.63 [1.27, 1.99]
2008−2012 19 23135 1.27 [1.09, 1.45]
2013−2016 12 11787 1.14 [0.86, 1.41]
Total 1.32 [1.17, 1.47]
0.5
1
1.5
2
Incidence (%)

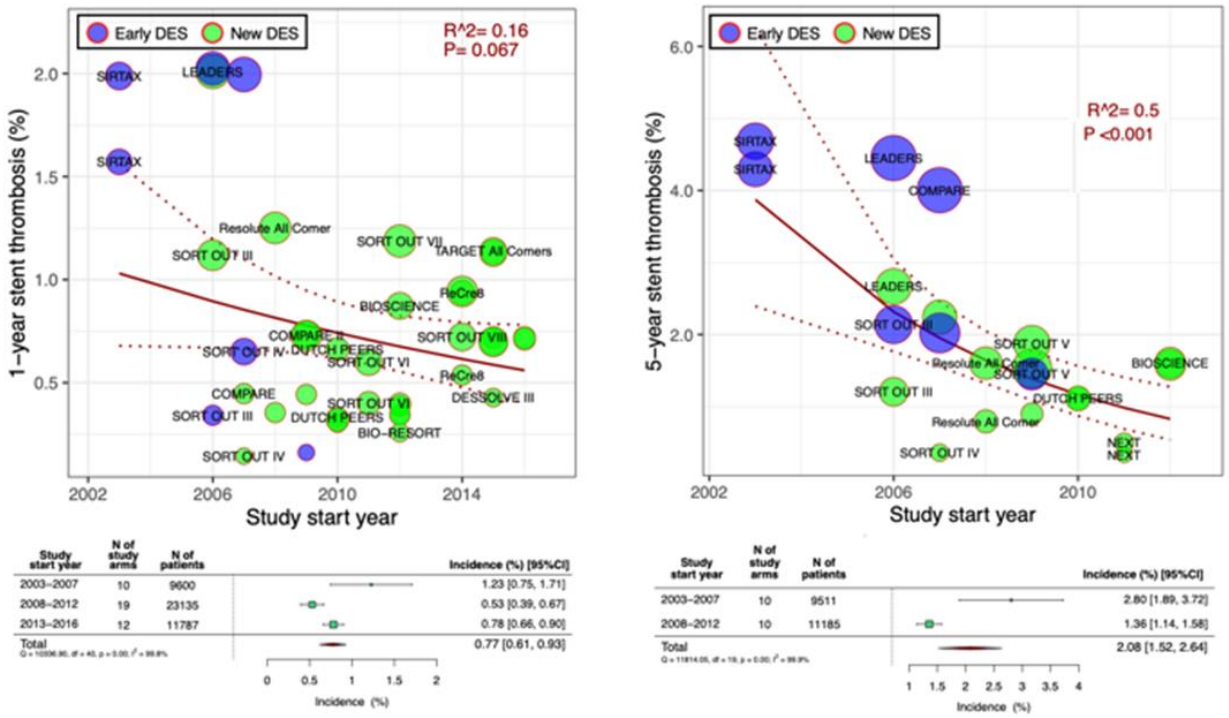

Early DES
New DES
R^2= 0
P= 0.341
1−year myocardial infarction (%)
6.0
4.0
2.0
LEADERS
TARGET All Comers
LEADERS
Resolute All Comer
TARGET All Comers
BIOSCIENCE
SIRTAX
BIOSCIENCE
ReCre8
TALENT
SORT OUT VIII
SIRTAX
COMPARE
ReCre8
TALENT
COMPARE II
BIO−RESORT
COMPARE II
BIO−RESORT
DESSOLVE III
SORT OUT VI
DESSOLVE III
SORT OUT VIII
SORT OUT II
COMPARE
PLATINUM PLUS
SORT OUT IV
SORT OUT IV
SORT OUT V
SORT OUT III
2002
2006
2010
2014
Study start year
Study start year
N of study arms
N of patients
Incidence (%) [95%CI]
2003−2007 6 4495 3.74 [2.58, 4.90]
2008−2012 11 13339 2.94 [2.21, 3.66]
2013−2016 8 5872 3.55 [2.83, 4.26]
Total 3.32 [2.84, 3.81]
2
2.5
3
3.5
4
4.5
5
Incidence (%)


Early DES
New DES
R^2= 0.17
P= 0.009
1−year target lesion revascularisation (%)
9.0
6.0
3.0
SIRTAX
SIRTAX
LEADERS
LEADERS
COMPARE
Resolute All Comer
TALENT
Resolute All Comer
BIOSCIENCE
DESSOLVE III
SORT OUT IX
SORT OUT VI
DESSOLVE III
BIOSCIENCE
COMPARE II
SORT OUT VII
COMPARE
PLATINUM PLUS
SORT OUT II
SORT OUT IX
2002
2006
2010
2014
Study start year
Study start year
N of study arms
N of patients
Incidence (%) [95%CI]
2003−2007 10 9600 4.32 [2.57, 6.08]
2008−2012 19 23135 2.43 [2.08, 2.79]
2013−2016 10 10296 2.60 [2.01, 3.19]
Total 2.96 [2.41, 3.51]
2
3
4
5
6
7
Incidence (%)

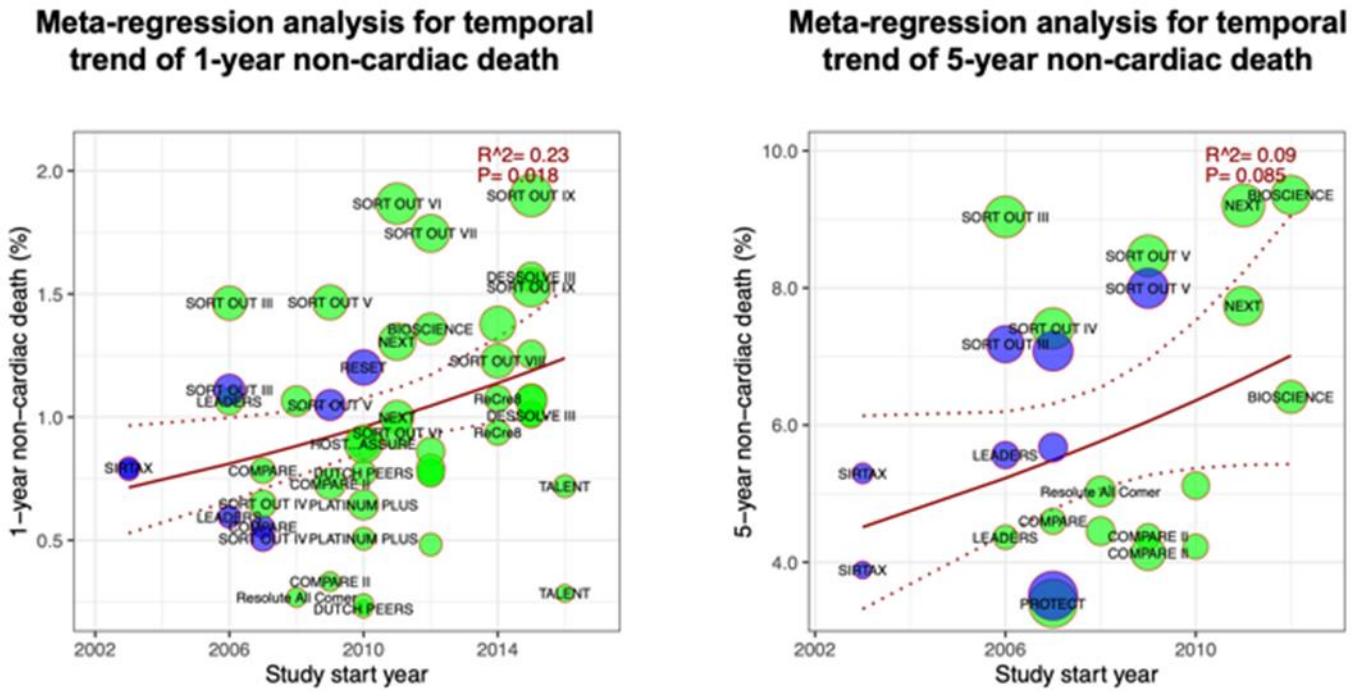

Early DES
New DES
R^2= 0.25
P= 0.029
5−year cardiac death (%)
Study start year
LEADERS
LEADERS
Resolute All Comer
Resolute All Comer
SIRTAX
DUTCH PEERS
SORT OUT V
COMPARE II
DUTCH PEERS
BIOSCIENCE
SORT OUT III
COMPARE II
SORT OUT V
BIOSCIENCE
Study start year
N of study arms
N of patients
Incidence (%) [95%CI]
2003–2007 10 9511 5.56 [4.60, 6.51]
2008–2012 10 11185 4.74 [4.23, 5.26]
Total 5.15 [4.59, 5.71]
Incidence (%)


Early DES
New DES
R^2= 0.05
P= 0.205
5−year myocardial infarction (%)
Study start year
COMPARE
BIOSCIENCE
LEADERS
LEADERS
BIOSCIENCE
COMPARE II
SIRTAX
SIRTAX
COMPARE
COMPARE II
Resolute All Comer
SORT OUT V
SORT OUT V
SORT OUT III
SORT OUT IV
Study start year
N of study arms
N of patients
Incidence (%) [95%CI]
2003–2007 6 4405 8.81 [7.15, 10.46]
2008–2012 6 6921 8.41 [6.85, 9.97]
Total 8.61 [7.51, 9.70]
Incidence (%)


Early DES
New DES
R^2= 0.08
P= 0.128
5−year target lesion revascularisation (%)
Study start year
SIRTAX
SIRTAX
LEADERS
BIOSCIENCE
LEADERS
BIOSCIENCE
COMPARE
SORT OUT III
SORT OUT IV
COMPARE II
SORT OUT V
SORT OUT III
COMPARE II
COMPARE
Study start year
N of study arms
N of patients
Incidence (%) [95%CI]
2003–2007 10 9511 9.05 [6.72, 11.38]
2008–2012 8 9387 7.44 [6.25, 8.62]
Total 8.33 [6.92, 9.74]
Incidence (%)



Supplementary Figure 2. The results of sensitivity analysis**.**



Supplementary Figure 3. Temporal trends of all-cause death and non-cardiac death**.**