

Dual antiplatelet therapy duration after percutaneous coronary intervention in high bleeding risk: a meta-analysis of randomized trials

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Abstract

Aims

The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) in patients at high bleeding risk (HBR) is still debated. The current study, using the totality of existing evidence, evaluated the impact of an abbreviated DAPT regimen in HBR patients.

Methods and results

A systematic review and meta-analysis was performed to search randomized clinical trials comparing abbreviated [i.e. very-short (1 month) or short (3 months)] with standard (≥ 6 months) DAPT in HBR patients without indication for oral anticoagulation. A total of 11 trials, including 9006 HBR patients, were included. Abbreviated DAPT reduced major or clinically relevant non-major bleeding [risk ratio (RR): 0.76, 95% confidence interval (CI): 0.61–0.94; $I^2 = 28\%$], major bleeding (RR: 0.80, 95% CI: 0.64–0.99, $I^2 = 0\%$), and cardiovascular mortality (RR: 0.79, 95% CI: 0.65–0.95, $I^2 = 0\%$) compared with standard DAPT. No difference in all-cause mortality, major adverse cardiovascular events, myocardial infarction, or stent thrombosis was observed. Results were consistent, irrespective of HBR definition and clinical presentation.

Conclusion

In HBR patients undergoing PCI, a 1- or 3-month abbreviated DAPT regimen was associated with lower bleeding and cardiovascular mortality, without increasing ischaemic events, compared with a ≥ 6 -month DAPT regimen.

Study registration

PROSPERO registration number CRD42021284004

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Structured Graphical Abstract

Key Question

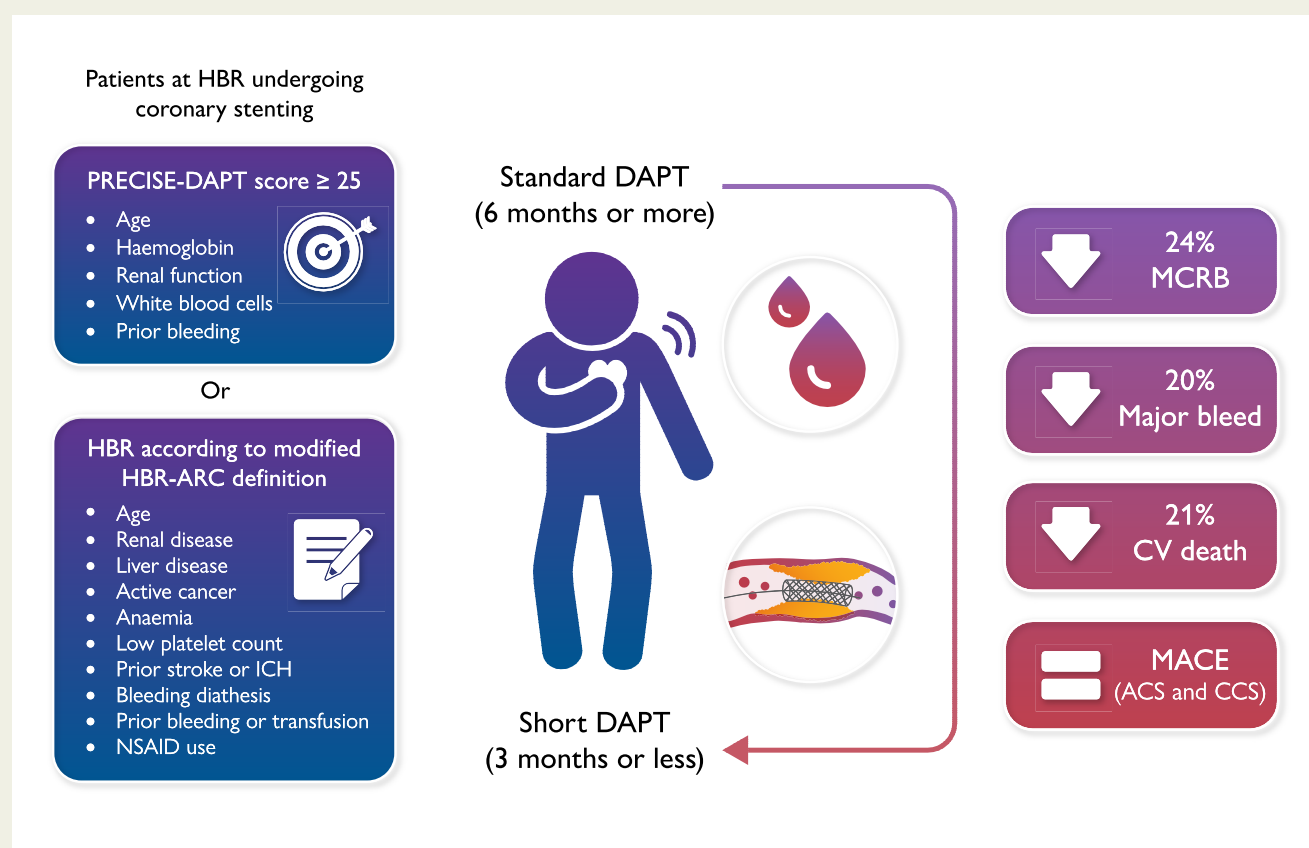
The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) in patients at high bleeding risk (HBR) is still debated. An abbreviated compared with a more prolonged DAPT regimen in this setting by using the totality of existing evidence was appraised.

Key Finding

Abbreviated DAPT for one or three months reduced major or clinically relevant non major bleeding compared to standard DAPT in HBR patients treated with PCI, and was similarly effective for the prevention of ischaemic events, irrespective of clinical presentation and type of antiplatelet agent administered after short DAPT discontinuation.

Take Home Message

Less than 3 months DAPT courses after PCI appears to be an appealing treatment option in HBR patients to optimize outcomes.



Impact of abbreviated vs. standard DAPT in patients at high bleeding risk undergoing coronary stenting.

Keywords

Dual antiplatelet therapy • High bleeding risk • Percutaneous coronary intervention • Aspirin • P2Y12 inhibitor • Monotherapy

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor blocker is the standard antithrombotic treatment after percutaneous coronary intervention (PCI).^{1,2} Yet, the optimal duration of treatment is still a matter of debate. DAPT has a narrow therapeutic window, as it

is associated with a substantial increase in major bleeding (MB) as a function of its duration and composition.^{1,2} It has been known for a decade that bleeding is not merely an inconvenience of antithrombotic therapy but carries important subsequent risks of adverse cardiac outcomes:³ a bleeding complication has been associated with a three- to five-fold increase of subsequent mortality, and could easily offset the

benefit of ischaemic protection from prolonged DAPT. Preserving the balance between ischaemic and bleeding risk during DAPT is even more challenging among patients at high bleeding risk (HBR). Roughly one in three patients undergoing PCI is at HBR, and these can be identified based on clinical features such as older age, lower haemoglobin, thrombocytopenia, renal insufficiency, cancer, a prior stroke, and a bleeding history.⁴ Importantly, HBR features are also associated with an increased ischaemic risk, posing further challenges to the selection of optimal treatment duration.⁵ International guidelines recommend standardized bleeding and ischaemic risk evaluation to inform treatment decisions, favouring a more conservative approach in terms of therapy type or duration in HBR patients.^{1,6,7} Previous studies suggested that shortening DAPT to mainly 6 months in HBR patients may reduce bleeding without significant ischaemic liability.⁸ More recent studies further assessed whether DAPT durations of 1 or 3 month(s) after PCI could improve the ischaemic/bleeding trade-off compared with more prolonged regimens.^{9,10}

The aim of the current study was to estimate the impact of an abbreviated DAPT (≤ 3 months) compared with standard DAPT (≥ 6 months) after PCI in HBR patients, using the totality of available evidence from randomized clinical trials (RCTs).

Methods

Study selection, eligibility criteria and risk of bias

The two authors [Francesco Costa (F.C.), Claudio Montalto (C.M.)] independently searched PubMed, Embase, BioMedCentral, Google Scholar, and the Cochrane Central Register of Controlled Trials for articles published between 1 January 2000 and 31 October 2021, using the following combinations of search keywords: 'percutaneous coronary intervention(PCI)', 'coronary stenting', 'acute coronary syndrome(ACS)', 'dual antiplatelet therapy (DAPT)', 'aspirin', 'clopidogrel', 'prasugrel', 'ticagrelor', 'P2Y12 inhibitor', 'monotherapy', 'DAPT duration', 'HBR', 'academic research consortium high bleeding risk (HBR-ARC)', 'PRECISE-DAPT(PD)', and 'randomized trial'. The full search strategy is reported in [Supplementary material online, Table S1](#). Articles were initially screened by title and abstract content. In addition, the reference lists from all eligible studies were screened to identify any additional citations. RCTs of patients treated with PCI who were randomized to abbreviated (≤ 3 months) or standard (≥ 6 months) DAPT durations, and reporting outcome data for bleeding and ischaemic endpoints at a minimum follow-up of 12 months after enrolment were included. Patients' baseline characteristics and treatment outcomes of the subgroup of patients at HBR were obtained as aggregated data through the published literature or, if not available, upon direct request to the study principal investigators.^{9–20} Studies including patients treated with oral anticoagulants (OAC) were excluded, whereas those that recruited patients with and without OAC (i.e. MASTER-DAPT trial), outcome data were selectively extracted for the latter population only. Events occurring during study phases investigating other treatment strategies than a DAPT duration comparison were censored (i.e. after 12 months from inclusion in the GLOBAL LEADERS/GLASSY study).

In order to provide a homogenized definition for HBR patients, this was set in all studies according to a PD score ≥ 25 , in keeping with current guideline recommendations.^{1,6,8} The present work was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology guidelines.^{21,22} PRISMA checklist is reported in [Supplementary material online, Table S2](#). The two authors (F.C., C.M.) independently assessed the quality of studies and risk of bias according to the RoB-2 tool.²³ All clinical trials were approved by the ethics committees

at each study centre, and all patients provided written informed consent. The study protocol is submitted to PROSPERO (CRD42021284004).

Study outcomes

The co-primary safety and efficacy endpoints of this analysis were the occurrence of major or clinically relevant non-major bleeding (MCRB) and major adverse cardiovascular events (MACE) up to 12 months after PCI. MCRB were analysed as reported by each individual study (see [Supplementary material online, Table S3](#)). The two different composite endpoints of MACE for all-cause death, myocardial infarction (MI) or stroke (i.e. MACE 1), and cardiovascular (CV) death, MI, or stroke (i.e. MACE 2), have been reported. Other safety endpoints of MB as per the study definition as well as individual endpoints according to the Bleeding Academic Research Consortium (BARC) and thrombolysis in MI bleeding definitions were also collected and analysed.²⁴ Other efficacy endpoints, including Net Adverse Clinical Events (NACE), all-cause death, CV death, MI, stroke, and stent thrombosis, were also separately appraised.

Statistical analysis

For descriptive purposes, the incidence rate from individual studies was log transformed and then pooled using a random-effects model with corresponding 95% confidence intervals (CI) adjusted according to the truncated Hartung–Knapp method with *ad-hoc* variance correction. Risk ratios (RRs) were used as summary statistics for outcomes of interest and were calculated using a random-effects model with 95% CI adjusted according to the truncated Hartung–Knapp method with *ad-hoc* variance correction.²⁵ Statistical heterogeneity of exposure was assessed by calculating the I^2 index, which summarizes the amount of variance between studies beyond chance. Heterogeneity was considered to be low if $I^2 < 25\%$, moderate if $I^2 < 75\%$ and high if $I^2 > 75\%$.²⁶ Publication bias was assessed for primary endpoints by visual inspection of funnel plots and by Egger's and Begg's test.²⁷

Several additional analyses were also planned and performed. First, considering the different designs of the studies included, which performed randomization and started follow-up immediately after index PCI (i.e. treatment was similar in the two study arms in the first study period) or at the time of treatment divergence (see [Supplementary material online, Table S3](#)), a landmark analysis including only events occurring after treatment divergence in the two study arms was performed. Second, we explored treatment outcomes in studies with centrally adjudicated events only. For this analysis, we excluded the GLOBAL LEADERS and included the GLASSY trial, which is a pre-specified sub-study of the larger GLOBAL LEADERS trial, implementing independent central event adjudication, instead of investigator-reported outcomes.¹⁶ Third, we performed *ad-hoc* subgroup analysis for the type of drug-eluting stent (DES) (durable vs. biodegradable/no-polymer) used in the short DAPT arm, and post-hoc analyses according to clinical presentation, separately reporting treatment outcomes for patients presenting with ACS or chronic coronary syndrome (CCS), and for the type of continuation therapy with either aspirin or a P2Y12 inhibitor after short DAPT interruption. Subgroup analyses were performed using a fixed-effect plural model estimating subgroup difference with a Q-test. *Ad-hoc* sensitivity analysis using an alternative definition of HBR according to the originally proposed or adapted ARC–HBR consensus criteria was also performed.^{4,10}

Statistical significance was set at a *P*-value < 0.05 (two-sided). Data analysis was performed in the R environment (R Foundation for Statistical Computing, Vienna, Austria; packages meta, metafor).

Results

Search strategy and a study flow diagram are presented in [Supplementary material online, Tables S1, S2](#) and [Figure S1](#), respectively. A total of 11 RCTs, including 9006 HBR patients (abbreviated DAPT, $n = 4476$ vs. standard DAPT, $n = 4530$) undergoing PCI with coronary

stenting, were identified and included. An alternative definition for HBR according to the ARC-HBR definition was available in seven of the 11 RCTs, with a total of 6545 HBR patients (abbreviated DAPT, $n = 3212$ vs. standard DAPT, $n = 3333$). The main characteristics of the included studies are shown in [Table 1](#). Further details on study inclusion/exclusion criteria and clinical endpoints are reported in [Supplementary material online, Tables S3 and S4](#). Baseline characteristics are presented in [Table 2](#): 40% of patients were women, and 58% presented with ACS; DES was used in all patients; complex PCI characteristics such as multi-vessel PCI and left main PCI were present in 26% and 3.9% of patients, respectively. Study quality was high across all included studies (see [Supplementary material online, Table S5](#)).

Bleeding endpoints

The rates of MCRB and MB at 12 months in the control group were 6.07% (95% CI: 4.58% to 8.03%) and 3.63% (95% CI: 2.40% to 5.49%), respectively, in the PD identified HBR population. Abbreviated DAPT significantly reduced both MCRB (RR: 0.76, 95% CI: 0.61–0.94; $I^2 = 28\%$) ([Figs 1 and 2A](#)), and MB (RR: 0.80, 95% CI: 0.64–0.99; $I^2 = 0\%$) ([Figs 1 and 2B](#)) compared with the standard DAPT regimen.

These results were consistent when using the TIMI or BARC bleeding definitions (see [Supplementary material online, Figs S2 and S3](#)). The risk of fatal bleeding did not differ (RR: 0.63, 95% CI: 0.24–1.70; $I^2 = 0\%$) ([Figure 1](#)). Funnel plots for bleeding endpoints are presented in [Supplementary material online, Figure S4A and B](#).

At landmark analysis accounting only for events occurring after treatment divergence in the two study arms, MCRB (RR: 0.69, 95% CI: 0.57–0.85; $I^2 = 0\%$) and MB (RR: 0.73, 95% CI: 0.53–1.01; $I^2 = 6\%$) were lower with abbreviated compared with standard DAPT ([Figure 3](#)).

The rates of MCRB and MB at 12 months in the control group were 5.32% (95% CI: 3.54% to 7.98%) and 3.10% (95% CI: 2.23% to 4.30%), respectively, in the ARC-HBR identified HBR population. Abbreviated DAPT significantly reduced both MCRB (RR: 0.52, 95% CI: 0.35–0.77; $I^2 = 18\%$) and MB (RR: 0.47, 95% CI: 0.24–0.91; $I^2 = 32\%$) compared with a standard DAPT regimen in the ARC-HBR identified HBR population ([Figure 4A and B](#)).

Ischaemic endpoints

No significant difference for the composite efficacy endpoints of all-cause death, MI and stroke (i.e. MACE 1) (RR: 0.97, 95% CI: 0.74–1.26; $I^2 = 38\%$) or CV death, MI, and stroke (i.e. MACE 2) (RR: 0.92, 95% CI: 0.77–1.10; $I^2 = 0\%$) was observed between abbreviated and standard DAPT regimens ([Figs 1 and 2C, D](#)). Cardiovascular mortality was significantly lower in HBR patients with abbreviated DAPT compared with standard DAPT regimens (RR: 0.79, 95% CI: 0.65–0.95; $I^2 = 0\%$), whereas all-cause mortality did not differ (RR: 0.91, 95% CI: 0.68–1.23; $I^2 = 24\%$) ([Figs 1 and 2E, F](#)). Similarly, definite stent thrombosis, definite or probable stent thrombosis, MI, or stroke rates were similar with abbreviated compared with standard DAPT ([Figure 1 and Supplementary material online, Figure S5](#)). Funnel plots for ischaemic endpoints are presented in [Supplementary material online, Figure S4C and D](#).

At landmark analysis, accounting only for events that occurred during the single antiplatelet therapy vs. DAPT phases of the included studies, MACE 1 and MACE 2 were similar in the two treatment arms ([Figure 3](#)). Consistent results for the ischaemic endpoints were observed in the ARC-HBR identified HBR population ([Figure 4](#)).

Sensitivity analyses

Leave-one-out study analyses for MCRB, MB, and MACE are presented in [Supplementary material online, Table S6](#). When only studies with central events adjudication were included, results remained consistent to the main analysis, confirming lower MCRB (RR: 0.73, 95% CI: 0.61–0.87; $I^2 = 0\%$), MB (RR: 0.79, 95% CI: 0.62–0.99; $I^2 = 0\%$), and CV mortality (RR: 0.81, 95% CI: 0.66–0.99; $I^2 = 0\%$) with abbreviated DAPT, and no difference in MACE according to multiple definitions (see [Supplementary material online, Figure S6](#)).

Subgroup analyses

Subgroup analyses according to clinical presentation, type of antiplatelet therapy continuation after short DAPT discontinuation, and type of DES implanted were performed.

Abbreviated DAPT was associated with a reduction of MCRB and MB irrespective of clinical presentation (test for subgroup differences in MCRB: $p_{int} = 0.62$;—test for subgroup differences in MB: $p_{int} = 0.17$) ([Figure 5](#)). No difference was observed between abbreviated and standard DAPT irrespective of clinical presentation with respect to MACE 1 ($p_{int} = 0.70$) or MACE 2 ($p_{int} = 0.91$) definitions ([Figure 5](#)). The treatment effect was similar, irrespective of clinical presentation, and also for the other reported endpoints.

With respect to type of antiplatelet therapy administered after short DAPT discontinuation, abbreviated DAPT was consistently associated with lower MCRB and MB in patients who continued aspirin or a P2Y₁₂ inhibitor after DAPT discontinuation (test for subgroup differences in MCRB: $p_{int} = 0.43$ —test for subgroup differences in MB: $p_{int} = 0.83$), with no difference for MACE 1 ($p_{int} = 0.55$), MACE 2 ($p_{int} = 0.59$), or other explored endpoints (see [Supplementary material online, Figure S7](#)).

The subgroup analysis according to the type of DES implanted in the experimental arm showed that abbreviated DAPT was associated with a borderline interaction for MCRB ($p_{int} = 0.06$) and a significant quantitative interaction for MB ($p_{int} = 0.02$), whereas a borderline qualitative interaction for MACE 1 ($p_{int} = 0.12$) and all-cause mortality ($p_{int} = 0.08$), but not for MACE 2 ($p_{int} = 0.23$) and CV mortality ($p_{int} = 0.85$) was observed (see [Supplementary material online, Figure S8](#)).

Discussion

The main findings of the present analysis are summarized as follows: (i) abbreviated DAPT for 1 or 3 months was associated with lower MCRB, MB and CV mortality compared with standard DAPT in HBR patients treated with PCI; (ii) abbreviated DAPT was similarly effective compared with standard DAPT for the prevention of MACE, stent thrombosis, and other ischaemic events, irrespective of clinical presentation and type of antiplatelet agent administered after short DAPT discontinuation; (iii) these findings remained consistent irrespective of the HBR definition, either based on PD score or the ARC-HBR framework, as endorsed by guidelines ([Structured Graphical Abstract](#)).

The present collaborative meta-analysis, which includes data from all randomized trials available in the field, is the largest source of information to date for HBR patients, enabling greater statistical power to assess the safety, and effectiveness of an abbreviated DAPT course compared with a standard DAPT regimen for this selected patient population. Compared with prior studies, the current analysis has the strength of exclusively including data from RCTs, avoiding potential biases introduced by observational data. In addition, data on relevant subgroups were obtained, which allowed for assessing the effect of

Table 1 Main characteristics of the HBR subgroups from included studies

Trial	Enrolment	Study population	Primary HBR definition	Alternative HBR Definition	Abbreviated DAPT	Standard DAPT	HBR Population Sample Size	DOI
RESET	2009–2010	PCI for CCS or ACS	PD score ≥25	ARC-HBR	3m DAPT (aspirin + clopidogrel) followed by aspirin	12m DAPT (aspirin + clopidogrel)	490	10.1016/S0140-6736(17)30397-5
OPTIMIZE	2009–2010	PCI for CCS or low-risk ACS	PD score ≥25	N/A	3m DAPT (aspirin + clopidogrel) followed by aspirin	12m DAPT (aspirin + clopidogrel)	414	10.1016/S0140-6736(17)30397-5
GLOBAL LEADERS	2013–2015	PCI for CCS or ACS	PD score ≥25	N/A	1m DAPT (aspirin + ticagrelor) followed by aspirin	12m DAPT (aspirin + clopidogrel/ticagrelor) followed by aspirin	2483	10.1093/ehjcvp/pvaa106
GLASSY	2013–2015	PCI for CCS or ACS	PD score ≥25	N/A	1m DAPT (aspirin + ticagrelor) followed by aspirin	12m DAPT (aspirin + clopidogrel/ticagrelor) followed by aspirin	1180	10.1093/ehjcvp/pvaa106
REDUCE	2014–2016	PCI for ACS	PD score ≥25	ARC-HBR	3m DAPT (aspirin + prasugrel, ticagrelor or clopidogrel) followed by aspirin	12m DAPT (aspirin + prasugrel, ticagrelor or clopidogrel)	151	10.4244/EJ-D-19-00539
SMART CHOICE	2014–2018	PCI for CCS or ACS	PD score ≥25	N/A	3m DAPT (aspirin + prasugrel, ticagrelor or clopidogrel) followed by P2Y12i	12m DAPT (aspirin + prasugrel, ticagrelor or clopidogrel)	578	10.1001/jama.2019.8146
STOPDAPT-2	2015–2017	PCI for CCS or ACS	PD score ≥25	ARC-HBR	1m DAPT (aspirin + prasugrel/clopidogrel) followed by clopidogrel	12m DAPT (aspirin + prasugrel/clopidogrel for 1 m, then aspirin + clopidogrel for 11m)	568	10.1007/s12928-020-00651-9
TWILIGHT	2015–2017	PCI for CCS or ACS	PD score ≥25	ARC-HBR	3m DAPT (aspirin + ticagrelor) followed by ticagrelor	15m DAPT (aspirin + ticagrelor)	1087	10.1093/eurheartj/ehab702
TICO	2015–2018	PCI for ACS	PD score ≥25	ARC-HBR	3m DAPT (aspirin + ticagrelor) followed by ticagrelor	12m DAPT (aspirin + ticagrelor)	399	10.4070/kcj.2021.0321
ONE-MONTH DAPT	2015–2019	PCI for CCS or ACS	PD score ≥25	ARC-HBR	1m DAPT (aspirin + clopidogrel) followed by aspirin	6 to 12m DAPT (aspirin + clopidogrel)	590	10.1016/ijcin.2021.06.003
STOPDAPT-2-ACS	2015–2020	PCI for ACS	PD score ≥25	N/A	1–2m DAPT (aspirin + prasugrel/clopidogrel) followed by clopidogrel	12m DAPT (aspirin + prasugrel/clopidogrel for 1 m, then aspirin + clopidogrel for 11m)	534	10.1001/jamacardio.2021.5244
MASTER-DAPT	2016–2019	PCI for CCS or ACS	PD score ≥25	Modified ARC-HBR	1m DAPT (aspirin + P2Y12- ^a) followed by SAPT ^a	6 to 12m DAPT (aspirin + P2Y12- ^a) followed by SAPT ^a	1712	10.1056/NEJMoa2108749

ACS, acute coronary syndrome; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; PCI, percutaneous coronary intervention; PD, PRECISE-DAPT; N/A, not available; SAPT, single antiplatelet therapy
^aChoice at the physician's discretion.

Table 2 Baseline characteristics

	RESET		OPTIMIZE		GLOBAL LEADERS		REDUCE		SMART CHOICE		STOP-DAPT2		TWILIGHT		TICO		One-month DAPT		STOP-DAPT2-ACS		MASTER DAPT	
	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std
	DAPT	n	DAPT	n	DAPT	n	DAPT	n	DAPT	n	DAPT	n	DAPT	n	DAPT	n	DAPT	n	DAPT	n	DAPT	n
Age (years)	71.9 ± 5.2	73.5 ± 5.2	73.6 ± 1.0	73.6 ± 1.0	74.9 ± 8.0	75.0 ± 7.9	80 ± 6	79 ± 7	73.3 ± 9.1	73.3 ± 9.1	76.7 ± 9.0	76.6 ± 9.1	74.3 ± 9.0	74.5 ± 8.5	70.7 ± 8.4	70.9 ± 8.6	740 ± 1.8	740 ± 1.8	784 ± 8.2	784 ± 8.6	784 ± 8.8	784 ± 8.1
Female sex	84 (33.2)	95 (40.1)	157 (62.6)	153 (71.2)	499 (40)	470 (38)	62 (78)	43 (61)	124 (43)	132 (46)	93 (34)	99 (33)	173 (33)	210 (38)	77 (40)	75 (36)	166 (60.0)	168 (54.0)	99 (35)	88 (35)	321 (37)	330 (39)
BMI (kg/m ²)	n.a.	n.a.	n.a.	n.a.	28.0 ± 4.5	27.9 ± 4.7	n.a.	n.a.	24.1 ± 3.4	24.2 ± 3.2	23.4 ± 3.4	23.1 ± 3.8	28.6 ± 6.0	28.9 ± 5.7	24.3 ± 3.5	24.3 ± 3.1	24.6 ± 3.3	24.2 ± 3.3	22.7 ± 3.7	22.5 ± 3.2	26.5 ± 4.4	27.0 ± 4.8
Hypertension	181 (71.5)	170 (71.7)	167 (67.9)	197 (91.6)	1092 (88)	1019 (83)	58 (73)	48 (68)	223 (77)	230 (80)	225 (83)	252 (85)	427 (80)	448 (81)	130 (68)	139 (67)	223 (81.0)	269 (86.0)	203 (73)	206 (81)	691 (80)	691 (81)
Diabetes	75 (29.6)	71 (30.0)	70 (28.8)	63 (29.3)	465 (37)	432 (35)	80 (34)	22 (31)	156 (54)	154 (54)	127 (47)	129 (44)	226 (43)	253 (46)	100 (52)	100 (48)	149 (54.0)	176 (56.0)	83 (30)	96 (38)	310 (36)	324 (38)
CKD	44 (75.8)	41 (70.6)	n.a.	n.a.	721 (58)	694 (56)	64 (80)	58 (82)	35 (12)	46 (16)	236 (87)	239 (81)	340 (64)	361 (65)	147 (77)	166 (80)	149 (54)	170 (54)	235 (84)	213 (84)	253 (29)	295 (35)
Dyslipidemia	141 (55.7)	134 (56.5)	121 (63.7)	100 (46.5)	n.a.	n.a.	36 (45)	41 (58)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	213 (77.0)	259 (83.0)	n.a.	n.a.	n.a.	n.a.
Smoking	31 (12.3)	24 (10.1)	23 (12.1)	12 (5.6)	160 (13)	154 (12)	11 (14)	14 (18)	58 (20)	38 (13)	50 (18)	30 (10)	57 (11)	72 (13)	47 (24)	49 (24)	24 (9.0)	24 (8.0)	64 (23)	47 (19)	80 (9)	67 (8)
COPD	n.a.	n.a.	n.a.	n.a.	104 (8)	103 (8)	n.a.	n.a.	n.a.	n.a.	12 (4)	13 (4)	33 (6)	50 (9)	n.a.	n.a.	n.a.	n.a.	10 (4)	10 (4)	94 (11)	106 (12)
PAD	n.a.	n.a.	n.a.	n.a.	125 (10)	130 (11)	n.a.	n.a.	8 (3)	12 (4)	42 (15)	42 (14)	66 (12)	70 (13)	n.a.	n.a.	n.a.	n.a.	8 (3)	7 (3)	83 (10)	113 (13)
Previous PCI	8 (3.2)	6 (2.5)	37 (19.5)	37 (17.2)	433 (35)	461 (37)	21 (25)	12 (17)	31 (11)	40 (14)	117 (43)	131 (44)	224 (42)	235 (42)	23 (12)	26 (13)	54 (20.0)	62 (20.0)	34 (12)	37 (15)	219 (25)	244 (29)
Previous CABG	0 (0)	0 (0)	9 (4.7)	18 (8.4)	107 (9)	127 (10)	9 (11)	8 (11)	10 (3)	4 (1)	5 (2)	13 (4)	82 (15)	81 (15)	1 (1)	4 (2)	7 (3.0)	7 (2.0)	3 (1)	7 (3)	51 (6)	67 (8)
Previous MI	6 (2.4)	0 (0)	51 (26.8)	60 (27.9)	309 (25)	332 (27)	n.a.	n.a.	11 (4)	18 (6)	44 (16)	46 (16)	143 (27.0)	163 (29)	11 (6)	13 (6)	14 (5.0)	12 (4.0)	23 (8)	19 (7)	160 (19)	170 (20)
Previous cerebrovascular accident	12 (4.7)	17 (7.2)	7 (3.7)	7 (3.3)	57 (5)	60 (5)	2 (3)	5 (7)	29 (10)	38 (13)	29 (11)	32 (11)	0 (0)	0 (0)	15 (8)	13 (6)	29 (11.0)	41 (13.0)	22 (8)	20 (8)	57 (7)	62 (7)
Previous bleeding	0 (0)	0 (0)	0 (0)	43 (3)	47 (4)	47 (4)	0 (0)	0 (0)	61 (21)	53 (19)	19 (7)	28 (9)	25 (5)	27 (5)	2 (1)	2 (1.0)	0 (0.0)	0 (0.0)	14 (5)	8 (3)	104 (12)	98 (12)
PD score (pts)	30.9 ± 5.8	31.1 ± 5.5	29.8 ± 4.7	29.4 ± 4.3	31.4 ± 6.6	31.0 ± 6.3	31 ± 5	30 ± 5	36.0 ± 10.6	35.9 ± 10.4	34.5 ± 9.2	35.0 ± 9.4	31.3 ± 6.6	31.6 ± 7.3	31.6 ± 6.3	32.7 ± 7.8	33 ± 7	34 ± 8	33.4 ± 8.4	33.3 ± 7.8	34.0 ± 9.3	34.3 ± 9.2
Stable presentation	105 (41.5)	108 (45.6)	119 (62.6)	144 (67.0)	619 (50)	637 (52)	0 (0)	0 (0)	101 (35)	110 (38)	180 (66)	201 (68)	192 (36)	200 (36)	0 (0)	0 (0)	131 (43.0)	183 (58.0)	0 (0)	0 (0)	374 (43)	368 (43)
ACS presentation	148 (58.5)	129 (54.4)	71 (27.4)	71 (33.0)	629 (50)	598 (48)	80 (100)	71 (100)	190 (65)	176 (62)	92 (34)	95 (32)	339 (64)	356 (64)	192 (100)	207 (100)	103 (37.0)	131 (42.0)	280 (100)	254 (100)	488 (57)	482 (57)
UA	108 (39.5)	94 (39.7)	34 (17.9)	33 (15.3)	161 (13)	148 (12)	0 (0)	0 (0)	86 (30)	84 (29)	35 (13)	33 (11)	185 (35)	193 (35)	42 (22)	55 (27)	98 (36.0)	116 (37.0)	34 (12)	40 (16)	92 (11)	91 (11)
NSTEMI	36 (14.2)	28 (11.8)	11 (5.8)	4 (1.9)	272 (22)	301 (24)	52 (65)	47 (66)	63 (22)	61 (21)	11 (4)	18 (6)	154 (29)	163 (29)	71 (37)	75 (36)	5 (2.0)	15 (5.0)	60 (21)	52 (20)	250 (29)	263 (31)
STEMI	12 (4.7)	7 (3.0)	1 (0.5)	1 (0.5)	196 (16)	149 (12)	28 (35)	24 (34)	41 (14)	31 (11)	46 (17)	44 (15)	0 (0)	0 (0)	79 (41)	77 (37)	0 (0)	0 (0)	186 (66)	162 (64)	146 (17)	128 (15)
Procedural Characteristics																						
DES	253 (100)	237 (100)	190 (100)	215 (100)	1231 (100)	1219 (100)	80 (100)	71 (100)	291 (100)	287 (100)	272 (100)	296 (100)	529 (100)	553 (99.9)	192 (100)	207 (100)	276 (100)	313 (99.9)	280 (100)	254 (100)	862 (100)	850 (100)
Railroad Access	n.a.	n.a.	n.a.	n.a.	824 (66)	827 (67)	53 (64)	50 (70)	172 (59)	163 (57)	167 (61)	201 (68)	360 (68)	368 (66)	89 (46)	90 (43)	182 (64.0)	201 (64.0)	226 (81)	207 (81)	702 (81)	715 (84)
Femoral Access	n.a.	n.a.	n.a.	n.a.	430 (35)	405 (33)	28 (35)	21 (30)	119 (41)	124 (43)	69 (25)	56 (19)	167 (31)	187 (34)	103 (54)	117 (57)	94 (34.0)	113 (36.0)	53 (19)	51 (20)	157 (18)	132 (16)
Multi-vessel PCI	121 (47.8)	119 (50.2)	40 (21.0)	46 (21.4)	193 (16)	202 (16)	0 (0)	0 (0)	73 (25)	73 (25)	20 (7)	30 (10)	147 (27)	138 (25)	38 (20)	39 (18)	186 (67.0)	197 (63.0)	70 (25)	68 (27)	219 (26)	251 (29)
Left Main treated	0 (0)	0 (0)	7 (3.7)	2 (2.5)	46 (4)	41 (3)	2 (3)	1 (1)	3 (1)	9 (3)	14 (5)	6 (2)	31 (6)	34 (6)	10 (5)	6 (3)	0 (0)	0 (0)	17 (6)	17 (7)	45 (5)	59 (7)
LAD treated	163 (64.4)	153 (64.6)	142 (63.7)	142 (63.7)	557 (45)	587 (48)	26 (32)	32 (45)	182 (62)	183 (64)	134 (49)	168 (57)	296 (56)	305 (55)	104 (54)	111 (54)	181 (64.0)	180 (57.0)	149 (53)	146 (57)	439 (51)	462 (54)
LCX treated	66 (26.1)	57 (24.1)	57 (29.8)	60 (26.9)	346 (28)	363 (29)	21 (26)	15 (21)	84 (29)	62 (22)	45 (17)	64 (22)	189 (36)	169 (30)	38 (20)	44 (21)	64 (23)	57 (18)	54 (19)	47 (19)	246 (29)	262 (31)
RCA treated	80 (31.6)	82 (34.6)	55 (28.8)	67 (30)	446 (36)	392 (32)	31 (39)	23 (32)	101 (35)	111 (39)	98 (36)	88 (30)	175 (33)	204 (37)	84 (44)	86 (42)	71 (26)	109 (35)	128 (46)	113 (44)	345 (40)	315 (37)
Total stent length (mm)	32.2 ± 19.0	33.5 ± 19.0	n.a.	n.a.	36.2 ± 25.9	37.5 ± 26.6	27 ± 14	23 ± 11	40.4 ± 22.4	38.1 ± 22.0	31.8 ± 18.2	30.9 ± 16.3	37.8 ± 23.0	38.1 ± 22.7	37.8 ± 22.0	38.2 ± 22.4	33.0 ± 18.0	31.0 ± 18.0	40.0 ± 28.8	36.6 ± 23.6	38.8 ± 28.3	40.7 ± 28.7
No. of implanted stents	1.5 ± 0.7	1.6 ± 0.8	1.5 ± 0.7	1.5 ± 0.7	1.8 ± 1.1	1.8 ± 1.2	1.3 ± 0.6	1.2 ± 0.5	1.5 ± 0.7	1.5 ± 0.7	1.3 ± 0.6	1.3 ± 0.5	n.a.	n.a.	1.4 ± 0.7	1.3 ± 0.7	1.36 ± 0.64	1.31 ± 0.60	1.6 ± 1.0	1.5 ± 0.8	1.7 ± 1.1	1.8 ± 1.1
DAPT at discharge																						
Aspirin	253 (100)	237 (100)	190 (100)	215 (100)	0 (0)	1218 (100)	80 (100)	71 (100)	0 (0)	287 (100)	0 (0)	296 (100)	0 (0)	556 (100)	0 (0)	207 (100)	271 (98)	298 (95)	0 (0)	254 (100)	0 (0)	850 (100)

Continued

Table 2 Continued

	RESET		OPTIMIZE		GLOBAL LEADERS		REDUCE		SMART CHOICE		STOP-DAPT2		TWILIGHT		TICO		One-month DAPT		STOP-DAPT2-ACS		MASTER DAPT																	
	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std	Abbr.	Std																
	DAPT	n = 237	DAPT	n = 191	DAPT	n = 223	DAPT	n = 1248	DAPT	n = 71	DAPT	n = 291	DAPT	n = 287	DAPT	n = 272	DAPT	n = 296	DAPT	n = 531	DAPT	n = 556	DAPT	n = 192	DAPT	n = 207	DAPT	n = 276	DAPT	n = 314	DAPT	n = 280	DAPT	n = 254	DAPT	n = 862	DAPT	n = 850
Clopidogrel	253 (100)	237 (100)	190 (100)	215 (100)	12 (1)	581 (47)	48 (60)	23 (29)	22 (31)	9 (13)	9 (13)	37 (13)	245 (84)	246 (86)	269 (99)	281 (95)	0 (0)	531 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	261 (95)	290 (93)	272 (97)	245 (96)	366 (42)	184 (21)	230 (27)	593 (70)				
Ticagrelor	0 (0)	0 (0)	0 (0)	0 (0)	1219 (98)	637 (52)	23 (29)	9 (11)	9 (13)	36 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	13 (5)	16 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	13 (5)	16 (5)	0 (0)	0 (0)	0 (0)	0 (0)	184 (21)	230 (27)				
Prasugrel	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (11)	9 (11)	5 (2)	9 (3)	3 (1)	15 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (3)	9 (4)	11 (1)	27 (3)				

Abbr, abbreviated; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; HBR, high bleeding risk; MI, myocardial infarction; NSTEMI, non ST-elevation myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; PD, PRECISE-DAPT; UA, unstable angina; Std, standard; STEMI, ST-elevation myocardial infarction; RCA, right coronary artery; LCX, left circumflex artery; LAD, left anterior descending artery; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease BMI, body mass index.

an abbreviated DAPT with respect to clinical presentation. Finally, a landmark analysis was performed, censoring all events occurring during the initial DAPT phase and accounting only for events occurring after the treatment differed in the two study groups, which confirms the robustness of the observations in the main analysis.

Current guidelines recommend 3 or 6 months of DAPT in HBR patients undergoing PCI for ACS or CCS, based on prior RCTs, or even shorter treatment courses, based on consensus opinion.^{1,6}

Recently, MASTER-DAPT was the first randomized trial to demonstrate that among HBR patients undergoing coronary stenting with a bioresorbable polymer-based sirolimus-eluting stent, abbreviating DAPT to 1 month was non-inferior to a standard DAPT for 6 months or more in terms of NACE, or major adverse cardiac or cerebral events, and superior in terms of MCRB.¹⁰ Another recent analysis of the XIENCE 28 and XIENCE 90 studies, compared, through propensity-stratified analyses, the outcomes of HBR patients treated with 1- or 3-month DAPT after PCI with a durable polymer everolimus-eluting stent. No difference in any of the ischaemic end-points explored was observed, including stent thrombosis, which was low in both DAPT treatment arms.²⁸ In line with these studies, the current meta-analysis confirmed, with a higher level of precision, that an abbreviated DAPT reduces bleeding, has a favourable impact on CV mortality, and is not associated with a higher risk of ischaemic events. Hence, the current study reinforces the position held by guidelines that DAPT duration should be minimized to 1 and up to 3 months in HBR patients.^{1,6}

An important clinical conundrum is the optimal DAPT duration in patients who are both HBR and at high ischaemic risk, such as those presenting with ACS. The recent STOPDAPT-2 ACS study which randomized 4136 patients to 1–2 month DAPT or a longer DAPT course for 12 months after PCI for ACS, and who were not selected based on HBR criteria, failed to demonstrate the non-inferiority of the abbreviated DAPT regimen for the primary endpoint of NACE.¹⁸ While a significant reduction of bleeding events was observed in the shorter DAPT arm, a numerical increase of ischaemic events raised concern about the feasibility of a very-short DAPT in ACS patients, followed by clopidogrel monotherapy.¹⁸ Whether HBR status modify these outcomes, and what should be the best strategy in patients both at high risk of ischaemic and bleeding events was an important gap in evidence. A prior analysis suggested that despite the concomitant presence of high ischaemic risk features, such as complex PCI or ACS, a shorter treatment with DAPT for 3–6 months was associated with superior net clinical benefit in HBR.⁵ Current meta-analysis extends these findings showing that further reducing DAPT to 1 or 3 months after coronary stenting in HBR patients is beneficial, with a reduction of adverse events and no additional ischaemic liability in the ACS subgroup. This finding reinforces the concept that DAPT duration should be adjusted based on patients' characteristics, and that bleeding rather than ischaemic risk should be prioritized in HBR patients.⁵

Major bleeding is associated with an immediate and sustained increased risk of mortality, similar or greater than recurrent MI, and this is of even greater relevance among HBR patients, in whom these complications are more frequent.²⁹ We observed that abbreviated DAPT was associated with lower CV mortality. This is in line with prior results of the CHARISMA trial in which a prolonged DAPT course in asymptomatic patients was associated with more than a three-fold increased MI risk and CV death.³⁰ Apart from the direct fatal consequences of bleeding in critical organs, such as intracranial haemorrhage, qualifying for CV death adjudication, multiple indirect pathways affecting the CV system could justify bleeding related

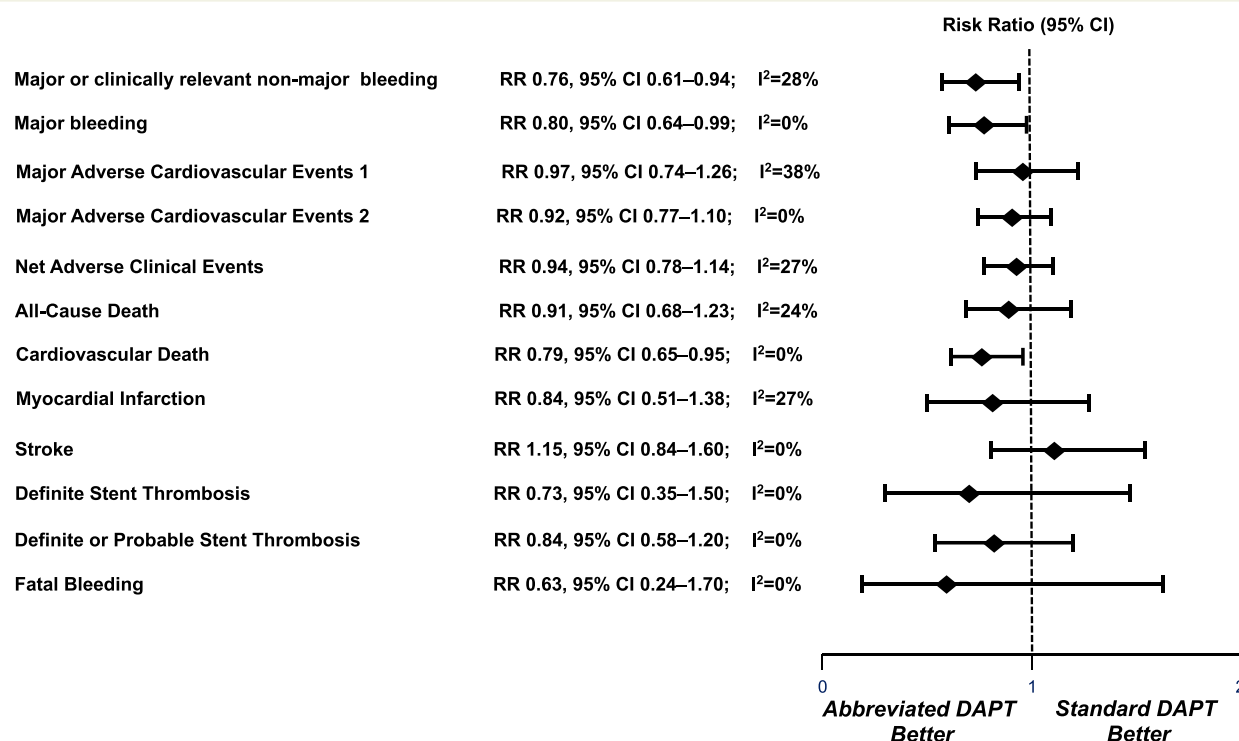


Figure 1 Forest plot for the explored clinical endpoints comparing abbreviated vs. standard dual antiplatelet therapy duration. Relative risks for the random-effects model are presented.

mortality. Bleeding reduces blood oxygen carrying/delivery capacity, leading to myocardial hypoperfusion, precipitating myocardial ischaemia, and is also associated with increased platelet activation and aggregability, which may predispose to coronary thrombotic events.³¹ In addition, blood transfusion could further worsen these conditions, as stored red blood cells have reduced deformability, reduced nitrous oxide delivery, which may promote vasoconstriction and microvascular plugging, worsening myocardial ischaemia.³² Importantly, bleeding events could have a negative impact on drug adherence, with the sudden disruption of key treatments such as antiplatelet agents, β -blockers, and statin which may result in ischaemic complications.³³ The PARIS study showed that an early discontinuation of antiplatelet agents was not associated with an excess of ischaemic events when the decision was co-ordinated by the treating physician.³⁴ Instead, when DAPT was suddenly disrupted, as in the case of MB, there was a dramatic increase of coronary ischaemic events.³⁴ Interestingly, this pattern was evident in both HBR or non-HBR patients.³⁵ Finally, excessive antithrombotic treatment in HBR patients may potentially trigger CV events in multiple districts through atherosclerotic plaque haemorrhage.³⁶

Antiplatelet therapy has a key role in preventing both stent thrombosis and spontaneous atherothrombotic events in other non-stented coronary segments.¹ The introduction of refined DES platforms with thinner struts and more biocompatible polymers drastically reduced the risk of stent thrombosis, allowing progressively shorter DAPT treatment. Contemporary generation DES with either durable or bioresorbable polymers or no-polymer have demonstrated low rates of ischaemic MACE in HBR patients despite very-short DAPT, with consistently improved outcomes compared with bare metal stents.^{37–39} Whether DES efficacy in an abbreviated DAPT setting

is device- or class-specific remains unclear, and confirmation of each device's performance is warranted. In the current meta-analysis, we observed a trend towards better response to abbreviated DAPT for all-cause death and ischaemic events in the subgroup of patients treated with bioresorbable or no-polymer DES. While this limited evidence for a possible stent type and DAPT duration interaction is merely hypothesis generating, it may suggest that biodegradable/non-polymer stents, with a reduced time exposure to the potentially thrombogenic polymer material, might be safer in an abbreviated DAPT environment. Yet, this observation needs confirmation in dedicated randomized studies.

The type of antiplatelet drug to be maintained after DAPT discontinuation is also a matter of debate. While aspirin was traditionally the treatment of choice after DAPT discontinuation and was recommended indefinitely for secondary prevention, several studies have challenged this practice by testing a P2Y12 inhibitor monotherapy after a short course of DAPT.^{9,15} Abbreviated DAPT followed by P2Y12 inhibitor monotherapy was associated with a reduction in MB compared with prolonged DAPT.⁴⁰ In the current meta-analysis, no difference in bleeding and ischaemic protection by continuing single antiplatelet therapy with either aspirin or a P2Y12 receptor blocker was observed, confirming the feasibility of both strategies in HBR patients after an abbreviated DAPT course. These results are in line with prior studies that showed no difference in bleeding between aspirin and a P2Y12 inhibitor during single antiplatelet therapy.^{41,42} However, given the short follow-up in the current study, the ability to observe a longer-term difference between the two single antiplatelet therapy treatment strategies is limited. The CAPRIE trial showed a modest 8.7% relative reduction of ischaemic events with clopidogrel monotherapy

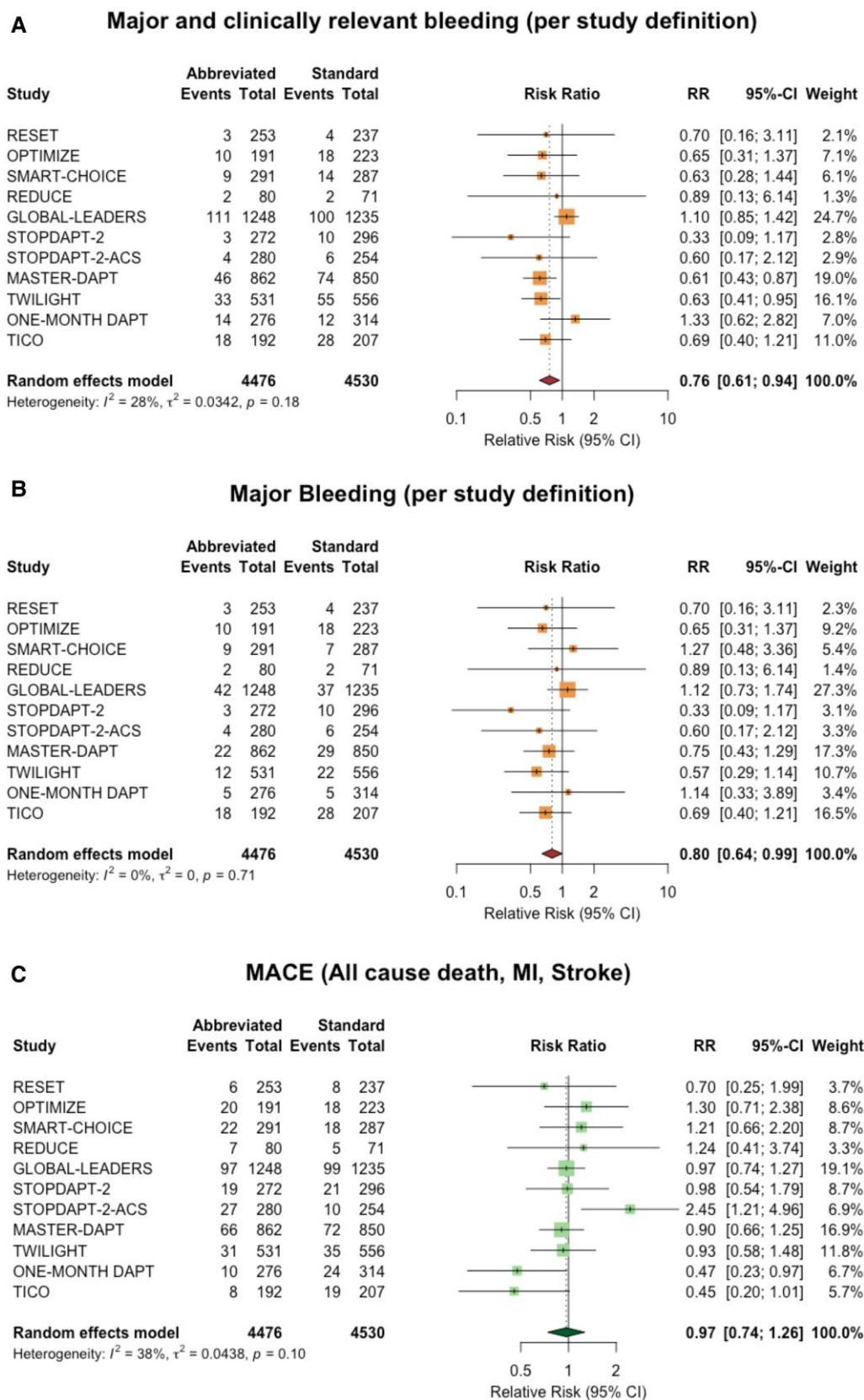


Figure 2 Forest plot for individual endpoints. Major or clinically relevant non-major bleeding (A); major bleeding (B); all-cause death, myocardial infarction or stroke (MACE 1) (C); cardiovascular death, myocardial infarction or stroke (MACE 2) (D); all-cause death (E); and cardiovascular death (F).

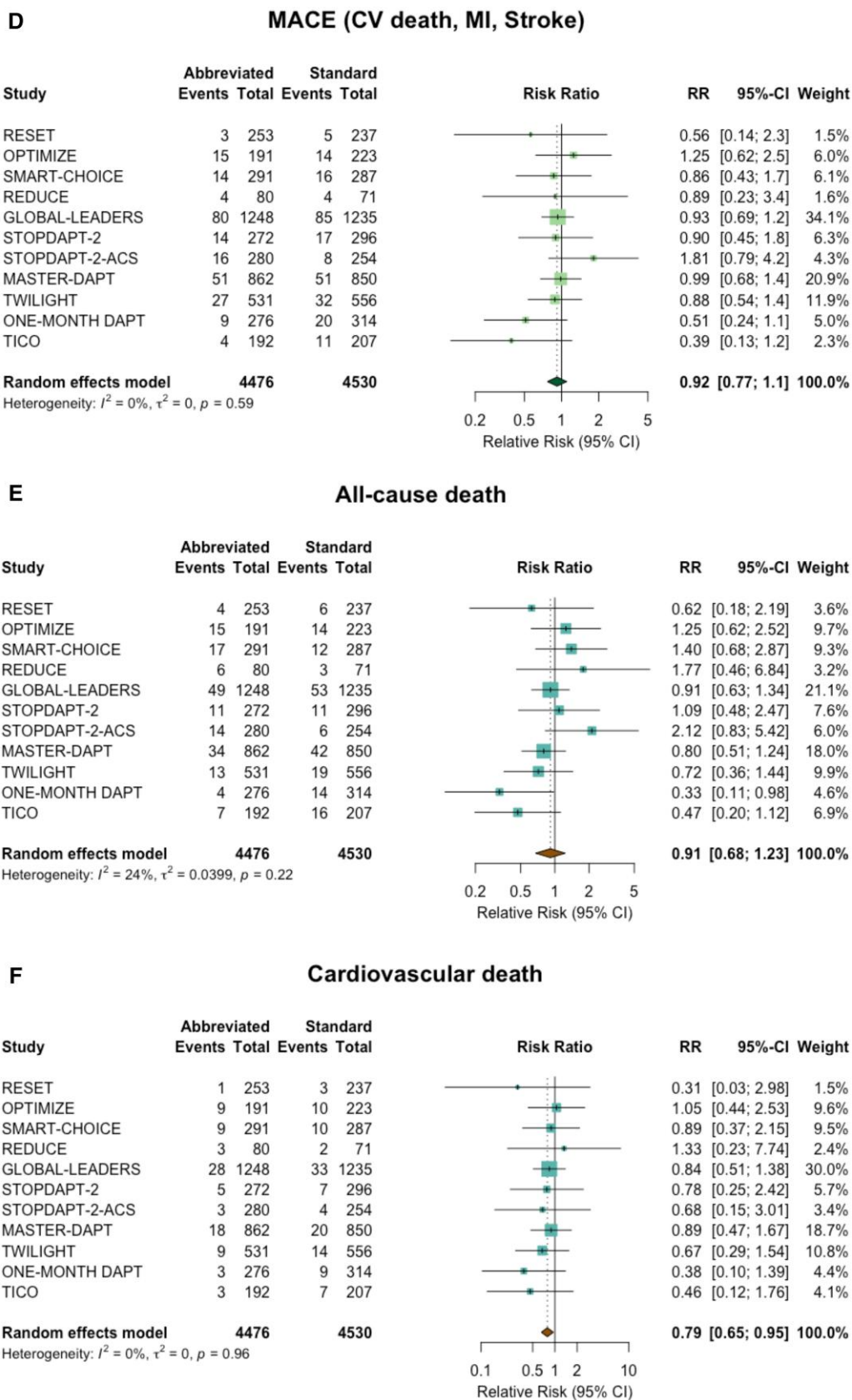
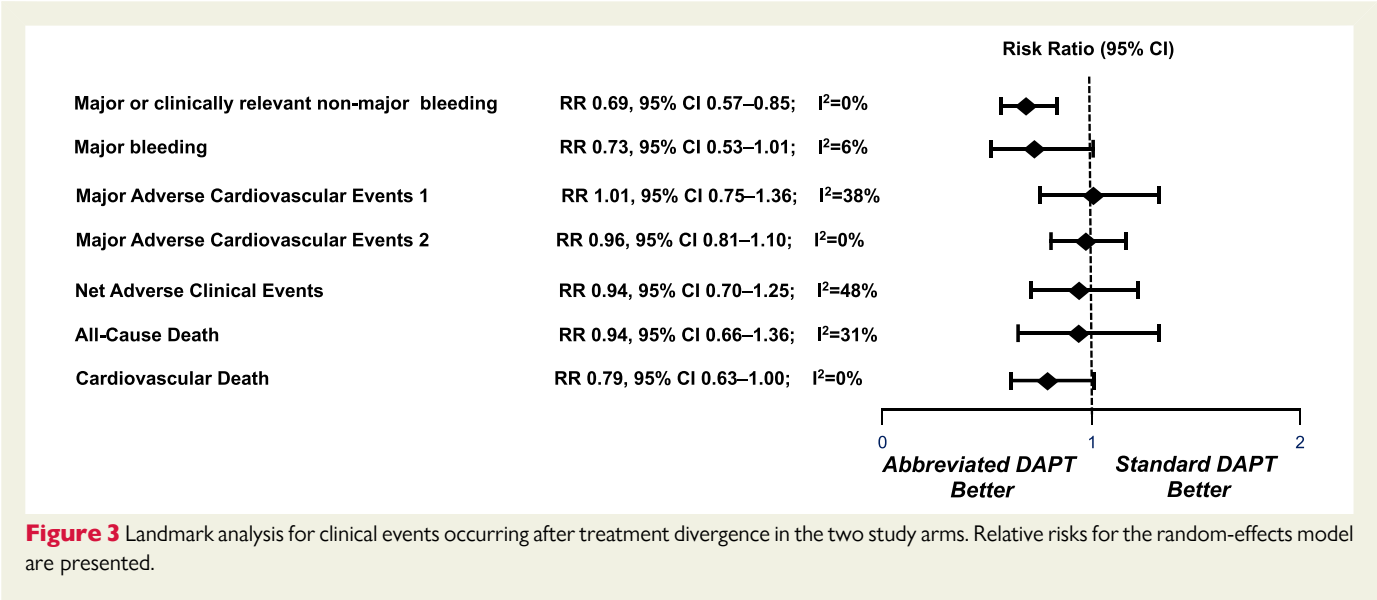


Figure 2 Continued



compared with a single antiplatelet therapy with aspirin for secondary prevention in patients with established vascular disease, with greater benefit in higher risk subgroups, such as those with diabetes.⁴³ These results were also confirmed in a meta-analysis of 42 108 patients that observed a 19% risk reduction of MI with P2Y12 inhibitor monotherapy compared with aspirin, with similar odds for stroke, all-cause and vascular death.⁴² The HOST-EXAM trial showed that clopidogrel, compared with aspirin monotherapy, during the maintenance period after PCI, reduced the risk of the composite of all-cause death, non-fatal MI, stroke, readmission due to ACS, or BARC type 3 or greater bleeding by 27%, with a positive impact on both ischaemic and bleeding risk.⁴⁴ Therefore, P2Y12 inhibitor monotherapy appears to be a promising alternative to a long-term treatment strategy after PCI. Based on the present analysis, the optimal antiplatelet monotherapy type for long-term risk prevention, that maximizes ischaemic and bleeding risk in HBR patients after an initial short course of DAPT, remains unclear, and further studies are needed in this field.

Limitations

Several important limitations of this analysis should be acknowledged. First, the present aggregated-study meta-analysis cannot overcome the limitations of each individual trial, as, for instance, shown by the lack of a placebo-controlled design in the majority of studies included. Nevertheless, study quality was high, with blinded adjudication of events by an independent clinical event committee assuring a low probability of performance bias. Second, abbreviated DAPT entailed different types of single antiplatelet therapy upon DAPT withdrawal (i.e. aspirin, clopidogrel, prasugrel, or ticagrelor monotherapy), which in some instances were based on physician preference.^{10,13} We tried to overcome this limitation with a dedicated subgroup analysis that explored statistical heterogeneity for a continuation with aspirin or a P2Y12 inhibitor. A more granular evaluation based on the type of P2Y12 inhibitor used (i.e. clopidogrel, prasugrel, or ticagrelor) would have been desirable but not applicable in our case. As the choice of the P2Y12 inhibitor type was not randomized and was based on physician

preference, the impact of unmeasured confounders would bias this comparison. However, in the current study, which entailed a randomized DAPT duration, P2Y12 inhibitor type was balanced between the two treatment arms, limiting the potential of this element to bias the study results. A prior analysis showed that P2Y12 inhibitor monotherapy continuation with either ticagrelor or clopidogrel after short DAPT provided consistent results vs. DAPT continuation up to 15 months.⁴⁵ Yet, dedicated RCTs to test the impact of different antiplatelet monotherapy types in this setting will be useful in the future. Third, specific HBR features (e.g. history of prior intracranial bleeding, recent prior stroke, active bleeding, or bleeding within 1–2 months of study inclusion) were exclusion criteria in many of the included studies. Yet, the application of two standardized and guideline-endorsed bleeding definitions for HBR identification yielded consistent results.^{4,8} The need for urgent surgery, another element proposed in the HBR-ARC definition, was also an exclusion criterion in many of these trials, therefore our results cannot be extended to this patient population. Patients on OAC were also excluded from the current analysis despite being a recognized HBR criterion.⁴ While concurrent treatment with OAC is frequent, presenting in up to 10% of patients undergoing PCI, OAC *per se* is different from other HBR criteria.⁴ OAC drives a higher risk for bleeding due to its biological effect on systemic coagulation, but it also affects the ischaemic risk, reducing the risk of stent-related and non-stent related ischaemic events.⁴⁶ In this regard, current treatment recommendation for OAC patients undergoing PCI diverge from those in the general PCI population: in the European guidelines peri-procedural treatment with DAPT followed immediately after by P2Y12 inhibitor monotherapy is recommended for OAC patients whereas such an approach has not been tested in randomized studies in patients without indication for OAC;⁴⁷ in addition, while PCI patients generally are treated with single antiplatelet therapy indefinitely after stenting, lifelong antiplatelet therapy is not recommended in most OAC patients due to the HBR from this combination.⁴⁸ Thus, DAPT duration recommendations for OAC-treated patients should be derived from separate study meta-analyses.

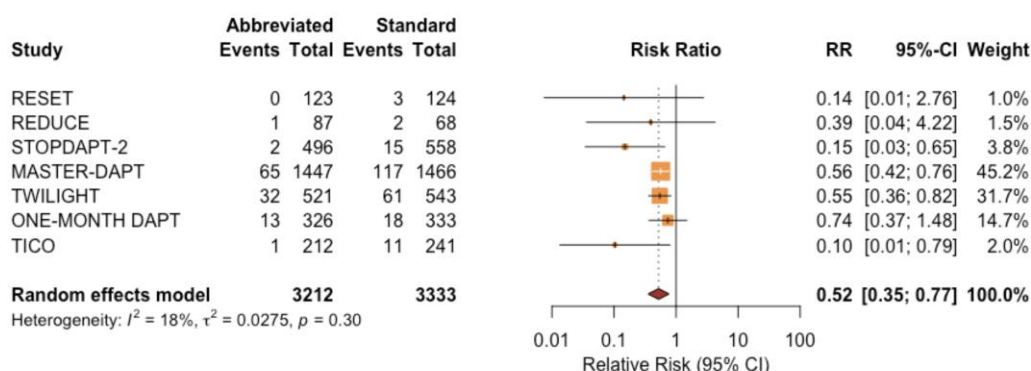
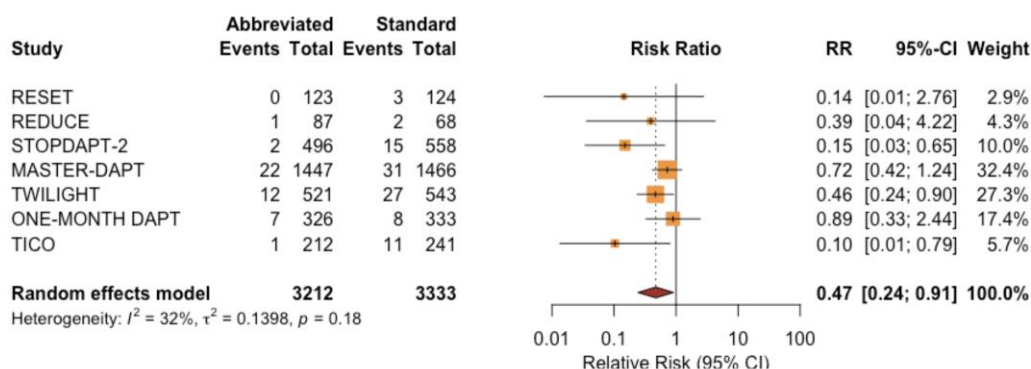
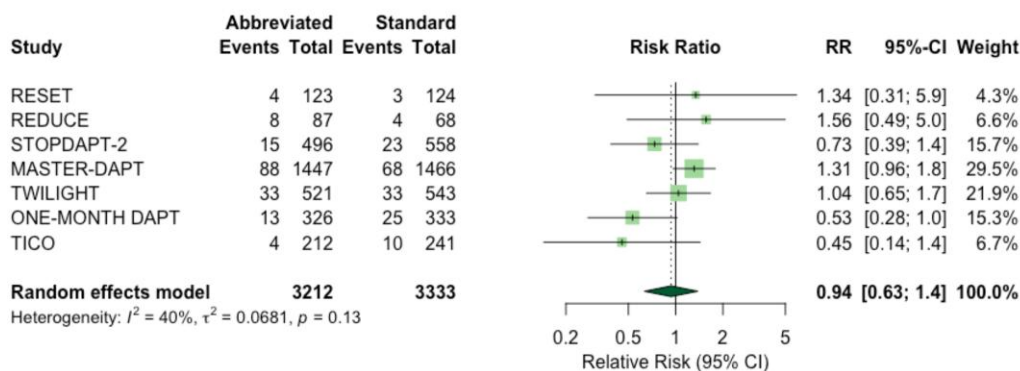
A Major and clinically relevant bleeding (per study definition)**B Major Bleeding (per study definition)****C MACE (per study definition)**

Figure 4 Forest plot for individual endpoints in the academic research consortium high bleeding risk identified high bleeding risk population. Major or clinically relevant non-major bleeding (A); major bleeding (B); major adverse cardiovascular events (C); net adverse clinical events (D); all-cause death (E); and cardiovascular death (F).

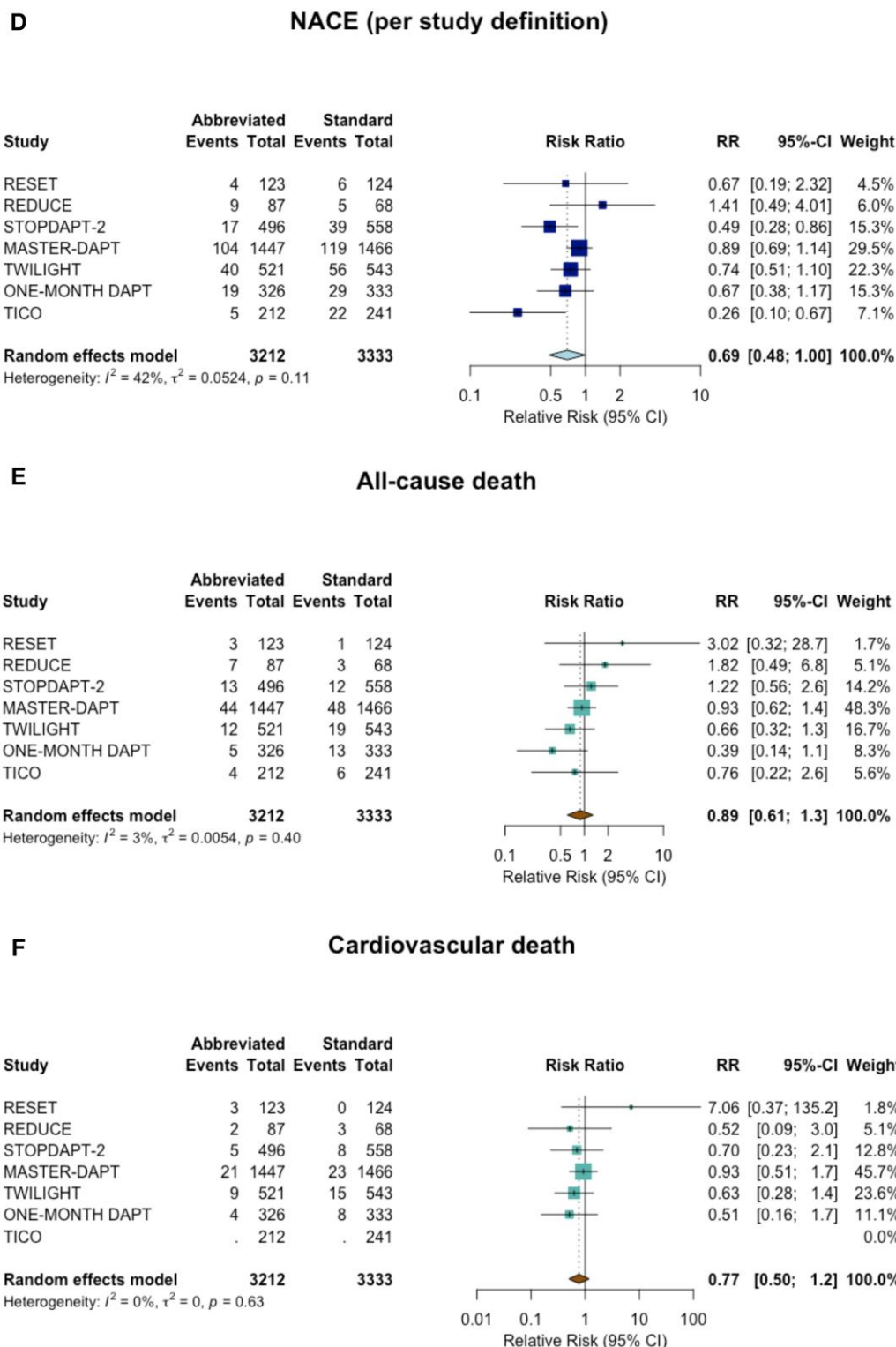


Figure 4 Continued

Fourth, RCTs, with their inherent higher selection based on protocol inclusion/exclusion criteria, tend to select a lower-risk population compared with real-world patients. Yet, a conclusion derived from observational data are limited by unmeasured confounders, hence, in order

to evaluate the impact of DAPT duration, randomized trials are needed for unbiased estimates.

Fifth, the treatment decision of DAPT duration in patients with prior stent thrombosis is currently a clinical conundrum. Stent thrombosis

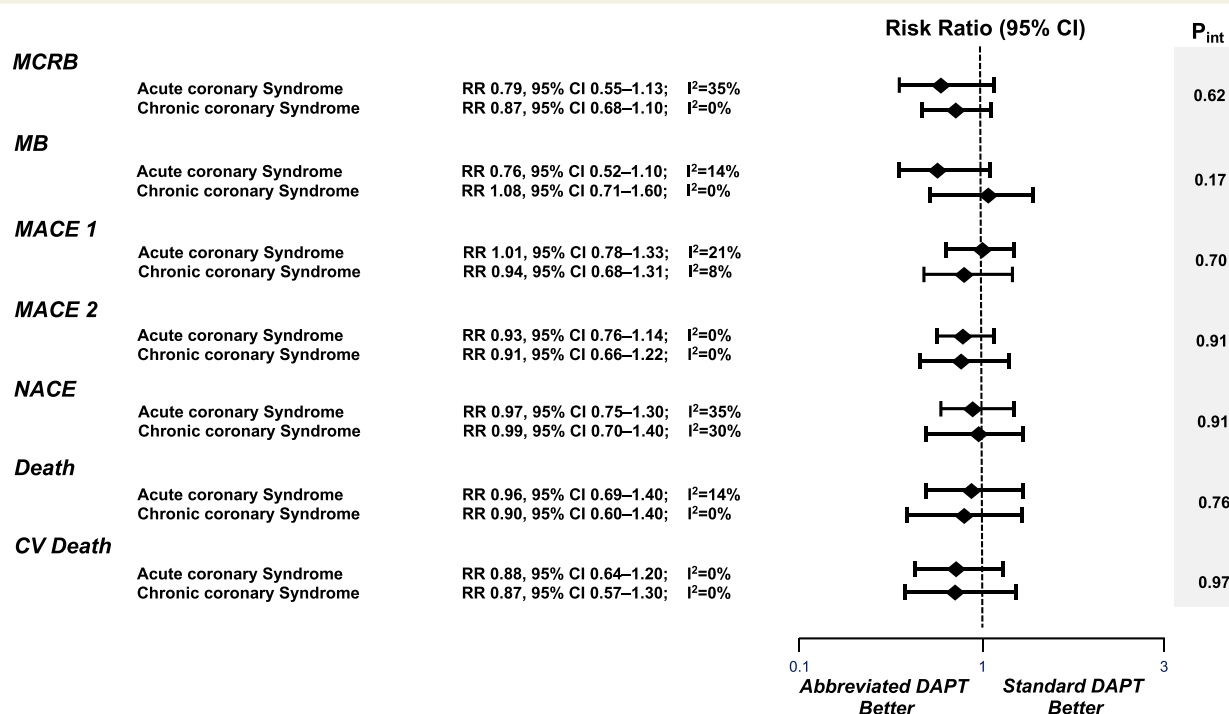


Figure 5 Subgroup analysis based on clinical presentation at the time of percutaneous coronary intervention. Treatment effects and interactions *P*-values are presented for subgroups of patients with acute coronary syndrome and chronic coronary syndrome. Relative risks and interaction testing for the random-effects model are presented.

was an exclusion criterion in many PCI trials, and since these events are rare, especially with modern DES, clinical decisions in this setting are uncertain.

Finally, we did not pre-specify how we would assess the consistency of the treatment effects of a short vs. standard DAPT regimen in patients who underwent complex PCI. However, subgroup analyses from some of the included studies yielded reassuring results.^{49,50}

Conclusions

In the present large-scale, collaborative meta-analysis based on the totality of the available evidence for HBR patients undergoing PCI, an abbreviated DAPT regimen of either 1 or 3 months, followed by single antiplatelet therapy, was associated with lower bleeding, with a favourable effect on CV mortality, without increasing ischaemic events or stent thrombosis. A one-month or 3-month DAPT courses after PCI appears an appealing treatment option in HBR patients to optimize outcomes. Further studies are warranted to determine how to individualize the decision between 1- and 3-month DAPT and the role of single antiplatelet therapy after DAPT.

Supplementary Data

Supplementary data is available at *European Heart Journal* online.

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Data Availability

The novel data underlying this article were provided by each study Principal investigator under permission. Data will be shared on reasonable request to the corresponding author with permission of the data owners.

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