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ORIGINAL ARTICLE
Thrombosis and antithrombotic therapy

Within and beyond 12-month efficacy and safety of antithrombotic strategies in patients with established coronary artery disease: two companion network meta-analyses of the 2022 joint clinical consensus statement of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Association for Acute CardioVascular Care (ACVC), and European Association of Preventive Cardiology (EAPC)

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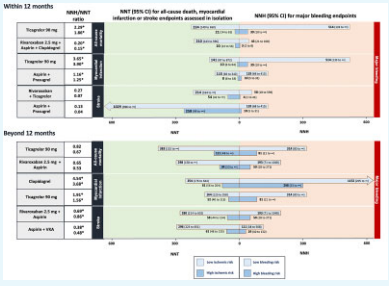
Aims To appraise all available antithrombotic treatments within or after 12 months following coronary revascularization and/or acute coronary syndrome in two network meta-analyses.

Methods and results Forty-three (N = 189 261 patients) trials within 12 months and 19 (N = 139 086 patients) trials beyond 12 months were included for efficacy/safety endpoints appraisal. Within 12 months, ticagrelor 90 mg bis in die (b.i.d.) [hazard ratio (HR), 0.66; 95% confidence interval (CI), 0.49–0.88], aspirin and ticagrelor 90 mg (HR, 0.85; 95% CI, 0.76–0.95), or aspirin, clopidogrel and rivaroxaban 2.5 mg b.i.d. (HR, 0.66; 95% CI, 0.51–0.86) were the only treatments associated with lower cardiovascular mortality, compared with aspirin and clopidogrel, without or with greater bleeding risk for the first and the other treatment options, respectively. Beyond 12 months, no strategy lowered mortality; compared with aspirin; the greatest reductions of myocardial infarction (MI) were found with aspirin and clopidogrel (HR, 0.68; 95% CI, 0.55–0.85) or $P2Y_{12}$ inhibitor monotherapy (HR, 0.76; 95% CI: 0.61–0.95), especially ticagrelor 90 mg (HR, 0.54; 95% CI, 0.32–0.92), and of stroke with VKA (HR, 0.56; 95% CI, 0.44–0.76) or aspirin and rivaroxaban 2.5 mg (HR, 0.58; 95% CI, 0.44–0.76). All treatments increased bleeding except $P2Y_{12}$ monotherapy, compared with aspirin.

Conclusion Within 12 months, ticagrelor 90 mg monotherapy was the only treatment associated with lower mortality, without bleeding risk trade-off compared with aspirin and clopidogrel. Beyond 12 months, $P2Y_{12}$ monotherapy, especially ticagrelor 90 mg, was associated with lower MI without bleeding trade-off; aspirin and rivaroxaban 2.5 mg most effectively reduced stroke, with a more acceptable bleeding risk than VKA, compared with aspirin.
Registration URL: https://www.crd.york.ac.uk/PROSPERO/; Unique identifiers: CRD42021243985 and CRD42021252398.

Graphical Abstract



The two best-in-class treatments for each outcome. Number needed to treat (NNT) and number needed to harm (NNH) with 95% confidence intervals were generated from the within and beyond 12 months network meta-analyses (NMAs) and adjusted according to baseline risk profile (low and high risks). Best-in-class antithrombotic regimens for patients at high and low risk of all-cause mortality, myocardial infarction, stroke, or major bleeding are presented in hierarchical order in terms of net benefit (NNH/NNT ratio). The average follow-up for the within and beyond 12 months NMA was 12 and 30 months, respectively. * denotes statistically significant differences in the NMA.

Keywords Coronary artery disease • Antithrombotics • Network meta-analysis

Introduction

Antithrombotic therapy is the cornerstone of secondary and tertiary prevention among patients with established coronary artery disease (CAD).[1,2] Societal guidelines generally provide different recommendations for oral antithrombotic therapy during the early (i.e. within 1 year) and late (i.e. after 1 year) periods after a cardiovascular event, including myocardial infarction (MI) or coronary revascularization.[1–3] This distinction is principally due to a heightened risk of recurrent ischaemic events in the early period prompting intensification of antithrombotic therapy during this timeframe.[4] Long-term use of aspirin monotherapy remains the most frequently adopted regimen in this clinical setting. Current 2020 European Society of Cardiology (ESC) Guidelines for the management of acute coronary syndrome (ACS) in patients without persistent ST-segment elevation state that treatment intensification with an additional antithrombotic drug, such as a $P2Y_{12}$ inhibitor or rivaroxaban, may or should be considered instead of aspirin monotherapy for a time window up to 12–36 months if the bleeding risk is not high, depending on whether the ischaemic risk is moderate or high, respectively.[3] Due to the lack of head-to-head trials among these treatments, no further guidance is provided on strategy selection among these treatment options in individual patients.

With the aim to inform the 2022 European consensus document on antithrombotic treatment strategies for secondary or tertiary prevention in patients with established CAD, we performed two separate network meta-analyses (NMAs) of the totality of randomized evidence with a focus on acute (within 12 months) and post-acute (>12 months) CAD, including ACS, coronary revascularization, or medically managed chronic coronary syndrome (CCS).

Methods

Established methods recommended by the Cochrane Collaboration were used to conduct the two meta-analyses.[5] The findings were reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[6] The following databases were searched: MEDLINE, EMBASE, TCTMD (https://www.tctmd.com/), and ClinicalTrials.gov, from database inception date through 29 December 2021 (PROSPERO CRD42021243985 and CRD42021252398).

The detailed search algorithms are provided in Supplementary material online, *Tables S1* and *S2*. Additional information on search strategies, detailed inclusion and exclusion criteria, quality assessment, and data extraction is provided in the Supplementary material, including Supplementary material online, *Figures S1–S3* for network flow charts of compared treatments and PRISMA flow diagrams.

Outcome measures at follow-up

Pre-specified efficacy and safety endpoints were separately analysed at 1 year and at the longest available follow-up. A detailed description of efficacy [all-cause and cardiovascular (CV) mortality, MI, or stroke] and safety outcomes (major bleeding and primary bleeding definition according to each trial) is reported in the Supplementary material. The definitions of MI and bleeding across trials are provided in Supplementary material online, *Table S3*.

Statistical analysis

We performed frequentist NMAs to generate direct and indirect evidence among interventions. A detailed description of statistical analysis is provided in the Supplementary material.

The consistency between direct and indirect sources of evidence was examined by the node-splitting method for the within (Supplementary material online, *Figure S4a–e*) and beyond 12-month meta-analysis (Supplementary material online, *Figure S5a–e*). The results were regarded as significant when the 95% CIs of the HRs did not include the unit value.

Publication bias was estimated using funnel plot (Supplementary material online, *Figures S6a–e* and *S7A–F*) and Egger's regression test (Supplementary material online, *Tables S4* and *S5*). Stratified NMAs for all outcomes by type of $P2Y_{12}$ agent given as monotherapy (clopidogrel or ticagrelor 90 mg) were pre-specified. Bias assessment is shown in Supplementary material online, *Table S6*. Meta-regressions with a Bayesian framework were carried out to assess the impact of age, proportion of patients with ACS on outcomes. The goodness-of-fit of the regression models was compared with that of the original model by means of the deviance information criterion (DIC), considering a five-unit DIC reduction suggestive for a goodness-of-fit improvement (Supplementary material online, *Table S7*).

All analyses were performed using R Project version 4.0.3 for statistical computing -'*netmeta*' and '*Bugsnet*' packages and Microsoft Excel.

Results

Within 12-month NMA: study selection and patient population

Of 12 058 articles, 43 trials (189 261 patients) met inclusion criteria (Supplementary material online, *Figure S2*). References of included trials are provided in the Supplementary material. The average follow-up was 12 months. The antithrombotic regimens used in the included trials are shown in *Table 1*. A detailed description of employed drug regimens in the NMA is provided in Supplementary material online, *Table S8*.

Beyond 12-month NMA: study selection and patient population

Of 12 058 articles, 19 trials (139 086 patients) met the inclusion criteria (Supplementary material online, *Figure S3*). References of included trials are provided in the Supplementary material. The data of the THEMIS study were appraised as aspirin and ticagrelor 60 mg bis in die regimen vs. aspirin monotherapy.[7]

Main characteristics of included studies are shown in *Table 2*. Average follow-up was 30 months (*Table 2*). Mean age of study participants was 55 years. Bias assessment is shown in Supplementary material online, *Table S6*. Employed drug regimens of the NMA and events in the RCTs are provided in Supplementary material online, *Table S8*.

All-cause and cardiovascular mortality

Twelve-month treatment effect appraisal

All-cause mortality was available in 43 trials (189 261 patients) with a total of 9357 events (4.94%). CV mortality with 4612 events (2.91%) was obtained from a total of 36 trials (158 319 patients). There was no heterogeneity across treatments ($\tau^2 = 0$), with no publication bias (Supplementary material online, *Table S4*).

Aspirin comparator: All-cause mortality was lower with ticagrelor 90 mg monotherapy [HR, 0.68 (95% CI, 0.52–0.89)], aspirin and ticagrelor 90 mg dual therapy [HR, 0.84 (95% CI, 0.71–1.00)], and rivaroxaban 2.5 mg, aspirin, and clopidogrel triple therapy [HR, 0.66 (95% CI, 0.50–0.88)] (Supplementary material online, *Figure S8a*). Results were consistent for CV mortality (*Figure 1a*). Ticagrelor 90 mg and triple therapy with rivaroxaban 2.5 mg, aspirin and clopidogrel ranked as the two best strategies for reducing CV (*P* score = 0.89 for both, Supplementary material online, *Figure 9a*) and all-cause mortality (Supplementary material online, *Figure S9b*) (*P* score = 0.89 and *P* score = 0.91, respectively).

Aspirin and clopidogrel for 12-month comparator: All-cause mortality was lower with ticagrelor 90 mg monotherapy [HR, 0.70 (95% CI, 0.55–0.89)], aspirin and ticagrelor 90 mg dual therapy [HR, 0.87 (95% CI, 0.79–0.96)] and rivaroxaban 2.5 mg, aspirin and clopidogrel triple therapy [HR, 0.68 (95% CI, 0.53–0.87)] (Supplementary material online, *Figure S8a*). Results were consistent for CV mortality (*Figure 1a*).

Beyond 12-month treatment effect appraisal

A total of 16 trials (128 047 patients) contributed to CV mortality with 4064 cardiovascular deaths (3.17%). There was low-to-moderate heterogeneity among treatments ($\tau^2 = 0.02$), with no publication bias (Supplementary material online, *Table S5*).

Placebo comparator: None of the investigated treatments affected all-cause or CV mortality (Supplementary material online, *Figure S8b* and *Figure 1b*).

Aspirin comparator: None of the investigated treatments affected all-cause or CV mortality (Supplementary material online, *Figure S8b* and *Figure 1b*).

Myocardial infarction

Twelve-month treatment effect appraisal

Forty trials (169 548 patients) reported 7822 (4.61%) MI events. There was low heterogeneity across treatments ($\tau^2 = 0.01$) and no evidence of publication bias (Supplementary material online, *Table S4*).

Aspirin comparator: Several combination strategies including antiplatelet and anticoagulant medications yielded a significant reduction of MI risk, including aspirin and prasugrel [HR, 0.62 (95% CI, 0.47–0.82)], with ticagrelor 90 mg [HR, 0.69 (95% CI, 0.50–0.95)], triple therapy with rivaroxaban 2.5 mg, aspirin and clopidogrel [HR, 0.69 (95% CI, 0.48–1.00)], aspirin and ticagrelor 90 mg [HR, 0.75 (95% CI, 0.57–0.99)] or aspirin and clopidogrel for 12 months [HR, 0.77 (95% CI, 0.60–0.97)], but not for 6 or 3 months (*Figure 2a*). DAPT with

Table 1 Main characteristics of studies included in the within 12-month network meta-analysis

Study name	Year	Total patients	Clinical settings	First strategy (type and dose)	Second strategy (type and dose)	Primary efficacy endpoint	% patients undergoing PCI or CABG	% patients with ACS
APPRAISE-2	2011	7392	Patients with ACS with at least two high-risk features	Apixaban 5 mg b.i.d. (2.5 mg b.i.d. if eGFR < 40 mL/min) combined with standard antiplatelet therapy (ASA +/− P2Y12i)	Standard antiplatelet therapy (ASA +/− P2Y12i)	Cardiovascular death, MI, or ischaemic stroke	• PCI: 3255 pts, 44% • CABG: 55 pts, 0.7%	100%
ATLAS ACS 2-TIMI 51	2012	15526	Patients with ACS	• Rivaroxaban 5 mg b.i.d. combined with standard antiplatelet therapy (ASA +/− P2Y12i) • Rivaroxaban 2.5 mg b.i.d. combined with standard antiplatelet therapy (ASA +/− P2Y12i)	Standard antiplatelet therapy (ASA +/− P2Y12i)	Cardiovascular death, MI, or any stroke	• PCI: 9631 pts, 62% • CABG: 10 pts, 0.1%	100%
CARDIFF-I	1979	1705	Patients with AMI	Aspirin 300 mg	Placebo	All-cause death	NA	100%
CARDIFF-II	1979	1682	Patients with AMI	Aspirin 300 mg three times daily	Placebo	All-cause death, cardiovascular death, non-fatal MI	NA	100%
CARS	1997	8803	Patients with AMI	• Warfarin 1 mg and aspirin 80 mg • Warfarin 3 mg and aspirin 80 mg	Aspirin 160 mg	Cardiovascular death, non-fatal MI, non-fatal ischaemic stroke	NA	100%
CHAMP	2002	5059	Patients with AMI	Warfarin (INR 1.5–2.5) and aspirin 81 mg	Aspirin 162 mg	All-cause death	NA	100%
CREDO	2002	2116	Patients with stable CAD, unstable angina or recent MI	12-month DAPT (clopidogrel 75 mg and aspirin 381–25 mg)	1-month DAPT (clopidogrel 75 mg and aspirin 81–325 mg) followed by aspirin alone	All-cause death, MI, or stroke	• PCI: 1818 pts, 85.9% • CABG: 83 pts, 3.9%	67%
CURE	2001	12562	Patients with ACS without ST-segment elevation	Clopidogrel 75 mg and aspirin 75–325 mg	Aspirin 75–325 mg	Cardiovascular death, non-fatal MI, or non-fatal stroke	• PCI: 2658 pts, 21.2% • CABG: 2072 pts, 16.5%	100%
Elderly-ACS 2	2018	1443	Patients >74 years old with ACS undergoing PCI	Prasugrel 5 mg and aspirin 75–100 mg	Clopidogrel 75 mg and aspirin 75–100 mg	All-cause mortality, MI, disabling stroke, or rehospitalization for cardiovascular causes or bleeding	PCI: 1433 pts, 99%	100%
EXCELLENT	2012	1443	Patients undergoing PCI	6-month DAPT (aspirin 100–200 mg and clopidogrel 75 mg) followed by aspirin alone	12-month DAPT (aspirin 100–200 mg and clopidogrel 75 mg)	Cardiac death, MI, or TVR	PCI: 100%	52%

Table 1 Continued

Study name	Year	Total patients	Clinical settings	First strategy (type and dose)	Second strategy (type and dose)	Primary efficacy endpoint	% patients undergoing PCI or CABG	% patients with ACS
GEMINI-ACS	2017	3037	Patients with ACS	Rivaroxaban 2.5 mg b.i.d. and P2Y12i (clopidogrel 75 mg or ticagrelor 90 mg b.i.d.)	Aspirin 100 mg and P2Y12i (clopidogrel 75 mg or ticagrelor 90 mg b.i.d.)	Cardiovascular death, MI, stroke, or definite ST	• PCI: 2647 pts, 87% • CABG: 9 pts, 0.01%	100%
GLASSY	2020	7585	Patients with stable CAD or ACS undergoing PCI	1-month DAPT (aspirin 75–100 mg and 90 ticagrelor mg b.i.d.) followed by 23-month ticagrelor 90 mg b.i.d. monotherapy	12-month DAPT (aspirin 75–100 mg and clopidogrel in stable CAD or ticagrelor 90 mg b.i.d. in ACS) followed by aspirin alone for 12 months	All-cause mortality, non-fatal MI, non-fatal stroke, or urgent TVR	PCI: 100%	51%
I-LOVE-IT 2	2016	1829	Patients with stable CAD or ACS undergoing PCI	6-month DAPT (aspirin 100 mg and clopidogrel 75 mg) followed by aspirin alone	12-month DAPT (aspirin 100 mg and clopidogrel 75 mg)	Cardiac death, target vessel MI, or clinically indicated TLR	PCI: 100%	86%
ISAR-REACT5	2019	4018	Patients with ACS	Aspirin 75–100 mg and ticagrelor 75 mg b.i.d.	Aspirin 75–100 mg and prasugrel 10 mg (5 mg in patients >75 years old or <60 kg)	All-cause mortality, MI, or stroke	• PCI: 3377 pts, 84% • CABG: 93 pts, 2%	100%
ISAR-SAFE	2015	4000	Patients on DAPT (aspirin and clopidogrel) 6 month after PCI for both stable CAD and ACS	6-month of aspirin 81–200 mg and clopidogrel 75 mg (a total length of 12-month DAPT)	6-month of aspirin 81–200 mg and placebo (a total length of 6-month DAPT)	All-cause death, MI, definite or probable ST, stroke, or TIMI major bleeding	PCI: 100%	40%
ISIS-2	1988	17187	Patients with suspected AMI	Aspirin 162.5 mg	Placebo	All-cause death	NA	100%
ITALIC	2015	1894	Patients undergoing PCI	6-month DAPT (aspirin 100 mg and clopidogrel 75 mg) followed by aspirin alone	24-month DAPT (aspirin 100 mg and clopidogrel 75 mg)	All-cause death, MI, repeat emergency TVR, stroke, or TIMI major bleeding	PCI: 100%	23%
IVUS-XPL	2016	1400	Patients with stable CAD or ACS undergoing PCI	6-month DAPT (aspirin 100 mg and clopidogrel 75 mg) followed by aspirin alone	12-month DAPT (aspirin 100 mg and clopidogrel 75 mg)	All-cause death, MI, stroke, or TIMI major bleeding	PCI: 100%	49%
MASTER-DAPT	2021	4579	HBR patients with stable CAD or ACS undergoing PCI	Abbreviated therapy (immediate discontinuation of DAPT one month after PCI)	Standard therapy (at one month after PCI: continuation of DAPT for at least two additional months)	Death from any cause, MI, stroke, or major bleeding, and death from any cause, MI, or stroke	PCI:100%	48%

Table 1 **Continued**

Study name	Year	Total patients	Clinical settings	First strategy (type and dose)	Second strategy (type and dose)	Primary efficacy endpoint	% patients undergoing PCI or CABG	% patients with ACS
NIPPON	2017	3773	Patients with stable CAD or ACS undergoing PCI	6-month DAPT (aspirin 81–162 mg and clopidogrel 75 mg) followed by aspirin alone	18-month DAPT (aspirin 81–162 mg and clopidogrel 75 mg)	All-cause death, MI, cerebrovascular events, or major bleeding	PCI: 100%	33%
ONE-MONTH DAPT	2021	3020	Patients with stable CAD or ACS undergoing PCI	1-month DAPT (aspirin 100 mg and clopidogrel 75 mg) followed by aspirin alone	6–12 months DAPT (aspirin 100 mg and clopidogrel 75 mg) followed by aspirin alone	Cardiac death, nonfatal MI, TVR, stroke, or major bleeding	PCI:100%	40%
OPTIMA-C	2017	1368	Patients undergoing PCI	6-month DAPT (aspirin 100 mg and clopidogrel 75 mg) followed by aspirin alone	12-month DAPT (aspirin 100 mg and clopidogrel 75 mg)	Cardiac death, target vessel-related, MI, ischaemia-driven TLR	PCI: 100%	51%
OPTIMIZE	2013	3119	Patients with stable CAD or low-risk ACS undergoing PCI	3-month DAPT (aspirin 100–200 mg and clopidogrel 75 mg) followed by aspirin alone	12-month DAPT (aspirin 100–200 mg and clopidogrel 75 mg)	All-cause death, MI, stroke, or major bleeding	PCI: 100%	32%
PLATO	2010	13408	Patients with ACS with planned invasive strategy	Aspirin 75–100 mg and ticagrelor 90 mg b.i.d.	Aspirin 75–100 mg and clopidogrel 75 mg b.i.d.	Cardiovascular death, MI, or stroke	• PCI: 10298 pts, 77% • CABG: 782 pts, 6%	100%
POPULAR AGE	2020	1002	Patients >70 years old with NSTE-ACS	Clopidogrel 75 mg combined with local antithrombotic therapy (aspirin 86%)	Ticagrelor 90 mg b.i.d. on top of local antithrombotic therapy (Aspirin 86%)	All-cause death, MI, stroke, major, or minor bleeding	• PCI: 474 pts, 47% • CABG: 165 pts, 16%	100%
PRAGUE-18	2016	1230	Patients with AMI undergoing primary-PCI	Prasugrel 10 mg (5 mg in patients >75 years old or <60 kg) and aspirin 100 mg	Ticagrelor 90 mg b.i.d. and aspirin 100 mg	All-cause death, MI, stroke, major bleeding, or urgent TVR	PCI: 1220 pts, 99%	100%
PRASFIT-ACS	2014	1363	Patients with ACS undergoing PCI	Prasugrel 3.75 mg and aspirin 81–100 mg	Clopidogrel 75 mg and aspirin 81–100 mg	Cardiovascular death, non-fatal MI, or non-fatal ischaemic stroke	PCI: 100%	100%
PRODIGY	2012	1970	Patients with stable CAD or ACS at 1-month after PCI	6-month DAPT (clopidogrel 75 mg and aspirin 80–160 mg) followed by aspirin alone	24-month DAPT (clopidogrel 75 mg and aspirin 80–160 mg)	All-cause death, non-fatal MI, cerebrovascular accident	PCI: 100%	74%
RACS	2007	1004	Patients with ACS undergoing PCI	1-month DAPT (clopidogrel 75 mg and aspirin 75–325 mg) followed by aspirin alone	6-month DAPT (clopidogrel 75 mg and aspirin 75–325 mg)	All-cause death, MI, or stroke	PCI: 100%	100%

Table 1 Continued

Study name	Year	Total patients	Clinical settings	First strategy (type and dose)	Second strategy (type and dose)	Primary efficacy endpoint	% patients undergoing PCI or CABG	% patients with ACS
RESET	2012	2117	Patients undergoing PCI	3-month DAPT (clopidogrel 75 mg and aspirin 100 mg) followed by aspirin alone	12-month DAPT (clopidogrel 75 mg and aspirin 100 mg)	Cardiovascular death, MI, ST, ischaemia-driven TVR, or bleeding	PCI: 100%	55%
SECURITY	2014	1399	Patients with stable or unstable angina undergoing PCI	6-month DAPT (clopidogrel 75 mg and aspirin) followed by aspirin alone	12-month DAPT (clopidogrel 75 mg and aspirin)	All-cause death, MI, stroke, definite or probable ST, BARC 3 or 5 bleeding	PCI: 100%	38%
SMART-CHOICE	2019	2993	Patients with stable CAD or ACS undergoing PCI	Aspirin and a P2Y12i for 3 months followed by P2Y12i monotherapy	12-month DAPT (aspirin and P2Y12i)	All-cause death, MI, or stroke	PCI: 100%	58%
SMART-DATE	2018	2712	Patients with ACS undergoing PCI	6-month DAPT (aspirin 100 mg and P2Y12i; clopidogrel 75 mg in 80% of patients) followed by aspirin alone	12-month DAPT (aspirin 100 mg and P2Y12i; clopidogrel 75 mg in 80% of patients)	All-cause death, MI, or stroke	PCI: 100%	100%
STOPDAPT-2 ACS	2021	4136	Patients with ACS undergoing PCI	1-month DAPT (aspirin and clopidogrel 75 mg or prasugrel 3.75 mg) followed by clopidogrel 75 mg monotherapy	12-month DAPT (aspirin and clopidogrel 75 mg)	Cardiovascular death, MI, definite ST, any stroke, TIMI major or minor bleeding	PCI: 100%	100%
TALOS AMI	2021	2697	AMI patients without adverse events one month after successful PCI treated with aspirin and ticagrelor	Aspirin 100 mg and ticagrelor 90 mg twice daily	Aspirin 100 mg and clopidogrel 75 mg daily	Cardiovascular death, MI, stroke, or BARC type 2, 3, or 5 bleeding	PCI: 100%	100%
TenBerg et al.	2000	1058	Patients with symptomatic CAD with planned PCI	VKA (INR 2.1–4.8) and aspirin 100 mg	Aspirin 100 mg	All-cause death, MI, TLR, or stroke	PCI: 100%	0%
TICAB	2019	1893	Patients with stable CAD or ACS undergoing CABG	Ticagrelor 90 mg b.i.d.	Aspirin 100 mg	Cardiovascular death, MI, stroke, or repeat revascularization	CABG: 100%	31%
TICO	2020	3056	Patients with ACS undergoing PCI	3-month DAPT (clopidogrel 90 mg b.i.d. and aspirin 100 mg) followed by ticagrelor alone	12-month DAPT (clopidogrel 90 mg b.i.d. and aspirin 100 mg)	All-cause death, MI, ST, stroke, TVR, or TIMI major bleeding	PCI: 100%	100%

Table 1 Continued

Study name	Year	Total patients	Clinical settings	First strategy (type and dose)	Second strategy (type and dose)	Primary efficacy endpoint	% patients undergoing PCI or CABG	% patients with ACS
TREAT	2019	3799	Patients with STEMI receiving fibrinolytic therapy	Ticagrelor 90 mg b.i.d. and aspirin 75–100 mg	Clopidogrel 75 mg and aspirin 75–100 mg	Cardiovascular death, MI, or stroke	• PCI: 2132 pts, 56% • CABG: 71 pts, 1.9%	100%
TRILOGY ACS	2012	7243	Patients with ACS managed conservatively	Prasugrel 10 mg (5 mg in patients >75 years old or <60 kg) and aspirin 100 mg	Clopidogrel 75 mg and aspirin 100 mg	Cardiovascular death, non-fatal MI, or non-fatal stroke	Among 7243 patients <75 years old: • PCI: 427 pts, 5.9% • CABG: 170 pts, 2.3%	100%
TRITON-TIMI 38	2007	13608	Patients with ACS undergoing PCI	Prasugrel 10 mg and aspirin 75–162 mg	Clopidogrel 75 mg and aspirin 75–162 mg	Cardiovascular death, non-fatal MI, or non-fatal stroke	• PCI: 99% • CABG: 1%	100%
TWILIGHT	2019	7119	High-risk patients undergoing PCI	3-month DAPT (ticagrelor 90 mg b.i.d. and aspirin 81–100 mg) followed by 12-month of ticagrelor monotherapy	3-month DAPT (ticagrelor 90 mg b.i.d. and aspirin 81–100 mg) followed by 12-month of ticagrelor and aspirin	All-cause death, non-fatal MI, non-fatal stroke	PCI: 100%	65%
VACS	1983	1266	Patients with unstable angina	Aspirin 324 mg	Placebo	All-cause death or acute MI	NA	100%

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; ASA, aspirin; BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; INR, international normalized ratio; MI, myocardial infarction; NSTE-ACS, non-ST segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; P2Y12i, P2Y12 inhibitor; ST, stent thrombosis; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; VKA, vitamin-K antagonist.

Table 2 Main characteristics of studies included in the beyond 12-month network meta-analysis

Study, year of publication	Study design	Key inclusion criteria	Time to randomization	Arms	No. of patients (ITT)	Follow-up (mo.)
AMIS, 1980	Double-blind RCT	29–70-years-old patients with previous MI (8 weeks to 5 years before randomization), NYHA class I or II	8 weeks to 5 years after the qualifying MI	Aspirin	2267	38.2 (mean follow-up)
				Placebo	2257	
ASCET, 2012	Open label, RCT	18–80-years-old patients, with angiographically documented CAD, on long-term aspirin therapy (160 mg/d, ≥2 years)	At any time in aspirin-treated (≥2 years) stable CAD patients	Clopidogrel 75 mg	499	24 (max. follow-up)
				Aspirin 75 mg	502	
CAPRIE, 1996	Blinded RCT	Atherosclerotic vascular disease manifested as either recent ischaemic stroke (onset ≥1 week and ≤6 months, neurological signs persisting ≥1 week from stroke onset), myocardial infarction (onset ≤35 days before randomization), or symptomatic PAD	Different temporal window according to sub-groups	Clopidogrel 75 mg	9599	22.8 (mean follow-up)
				Aspirin 325 mg	9586	
CDPA, 1976	Double-blind RCT	At least one ECG-documented MI, NYHA functional classes I, II, or III	At any time	Aspirin	758	22 (mean follow-up)
				Placebo	771	
CHARISMA, 2006	Double-blind RCT	Patients ≥45 years old and one of the following conditions: multiple atherothrombotic risk factors, documented CAD, cerebrovascular disease, or symptomatic PAD	At any time	Aspirin + clopidogrel	1903	28 (median follow-up)
				Aspirin	1943	
COMPASS, 2017	Double-blind RCT	CAD (defined as MI within the last 20 years, or multi-vessel CAD with symptoms or with history of stable or unstable angina, or multi-vessel PCI, or multi-vessel CABG) and/or PAD. Subjects with CAD must also meet at least one of the following criteria: age ≥65 years, or age <65 years and documented atherosclerosis or revascularization involving at least two vascular beds or at least two additional risk factors: current smoker, diabetes mellitus, renal dysfunction, HF, and non-lacunar ischaemic stroke (≥1 month)	At any time, following a run-in phase	Rivaroxaban 2.5 mg b.i.d. + aspirin 100 mg o.d.	9152	23 (mean follow-up)
				Rivaroxaban 5 mg b.i.d.	9117	
				Aspirin 100 mg once daily	9126	

Table 2 **Continued**

Study, year of publication	Study design	Key inclusion criteria	Time to randomization	Arms	No. of patients (ITT)	Follow-up (mo.)
DAPT study, 2014	RCT	Subjects >18 years old undergoing PCI with stent deployment (or had within 3 calendar days) and without known contraindication to DAPT for at least 30 months after enrolment and stent implantation. Randomization inclusion criterion at 12 months: subjects treated with 12 months of DAPT post index procedure and who were event free during that time	12 months after index PCI	Aspirin + clopidogrel 75 mg	3187	21 (max. follow-up)
				Aspirin + prasugrel 10 mg	1742	
				Aspirin (75–162 mg)	4941	
DES-LATE, 2013	Open-label, RCT	Patients undergoing DES implantation at least 12 months before enrolment, in absence of MACE (myocardial infarction, stroke, or repeat re-vascularization) or major bleeding and receiving dual antiplatelet therapy at the time of enrolment	At least 12 months after index PCI	Aspirin	2514	42 (median follow-up)
				Aspirin + clopidogrel	2531	
GLASSY, 2019	GLOBAL-LEADERS sub-study	Age ≥18 years. Patients with any clinical indication for PCI. Presence of one or more coronary artery stenosis ≥50% in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation in a vessel with a RVD of at least 2.25 mm	After index coronary angiography but before PCI	Ticagrelor 90 mg	3794	12 (max. follow-up)
				Aspirin	3791	
HOST-EXAM, 2021	Open-label, RCT	Patients aged 20 years or older who underwent PCI with DES and maintained DAPT without any ischaemic and major bleeding complications (i.e. non-fatal MI, any repeat revascularization, readmission due to a CV, and major bleeding) within 6–18 months after PCI	At 6 up to 18 months after PCI (at the end of intended time of DAPT)	Clopidogrel 75 mg	2710	24 (max. follow-up)
				Aspirin 100 mg	2728	
ITALIC, 2017	Open-label, RCT	Patients aged 18 years or older, eligible for PCI, implanted with at least 1 Xience V DES. All clinical situations were deemed eligible excluding primary PCI for acute MI and LMCA treatment	At index PCI	Aspirin + clopidogrel	903	12 (max. follow-up)
				Aspirin	904	

Table 2 Continued

Study, year of publication	Study design	Key inclusion criteria	Time to randomization	Arms	No. of patients (ITT)	Follow-up (mo.)
LoWASA, 2004	Open-label RCT	Previous hospitalization for AMI, fulfiling at least two of the following criteria: pain suggesting AMI, elevated enzyme activity more than twice the upper normal limit, development of Q-waves in at least two leads on a 12-lead standard ECG	Up to 42 days after qualifying MI	Aspirin 75 mg + VKA 1.25 mg	1659	60 (median follow-up)
				Aspirin 75 mg	1641	
OPTIDUAL, 2016	Open-label RCT	Patients with symptoms of stable angina, silent ischaemia, or ACS with ≥1 lesion with stenosis >50% located in a native vessel ≥2.25 mm in diameter and who were implanted with ≥ 1 DES of any type	At 12 ± 3 months after index PCI	Aspirin (75– 160 mg) + clopidogrel 75 mg	695	36 (max. follow-up)
				Aspirin (75–160 mg)	690	
PEGASUS-TIMI 54, 2015	Double-blind RCT	Patients with at least 50 years of age and previous spontaneous MI (1–3 years before enrolment). One of the following additional high-risk features: age ≥65 years, diabetes mellitus requiring medication, a second prior spontaneous MI, multivessel CAD, or CKD	1–3 years after a spontaneous MI	Aspirin + ticagrelor 90 mg b.i.d.	7050	33 (median follow-up)
				Aspirin + ticagrelor 60 mg b.i.d.	7045	
				Aspirin	7067	
PRODIGY, 2012	Open-label RCT	Patients ≥18 years of age with chronic stable CAD or ACS, with at least one lesion with a diameter stenosis of ≥50% that was suitable for coronary stent implantation (in a vessel with a RVD of ≥2.25 mm)	1 month after index PCI	Aspirin + clopidogrel	947	12 (max. follow-up)
				Aspirin	943	
REAL ZEST-LATE, 2010	Open-label RCT	Patients undergoing DES implantation at least 12 months before enrolment, with no major adverse CV event (MI, stroke, or repeat revascularization) or major bleeding since implantation, and receiving DAPT at the time of enrolment	At least 12 months after index PCI	Aspirin (100–200 mg) + clopidogrel 75 mg	1357	19.2 (median follow-up)
				Aspirin (100–200 mg)	1344	

Table 2 **Continued**

Study, year of publication	Study design	Key inclusion criteria	Time to randomization	Arms	No. of patients (ITT)	Follow-up (mo.)
SAPAT, 1992	Double-blind RCT	History of exertional chest pain for at least one month in patients aged 30–80	At any time	Aspirin 75 mg	1099	50 (median follow-up)
				Placebo	1026	
THEMIS, 2019	Double-blind RCT	Patients (≥50 years of age) with stable CAD and type 2 diabetes mellitus. The presence of stable CAD was determined by any one of the following criteria: a history of previous PCI or CABG, or documentation of angiographic stenosis of at least 50% in at least one coronary artery. The presence of type 2 DM was determined by the receipt of an antihyperglycemic medication for at least 6 months	At any time	Aspirin (75—150 mg/day) + ticagrelor 60 mg	9619	40 (median follow-up)
				Aspirin (75—150 mg/day)	9601	
WARIS-II, 2002	Open-label RCT	Adult patients (<75 years of age) who were hospitalized for acute MI according to the presence of two or more of the following criteria: a history of typical chest pain; ECG changes typical of MI; and a creatine kinase level >250 U per liter, an aspartate aminotransferase level >50 U per liter, or both, of probable cardiac origin.	At any time	Aspirin 75 mg + VKA	1208	48 (mean follow-up)
				VKA	1216	
				Aspirin 160 mg	1206	

Abbreviations: ACS, acute coronary syndrome; BMS, bare-metal stent; CAD, coronary artery disease; CEC, clinical event committee; CNS, central nervous system; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; EF, ejection fraction; HF, heart failure; HR, heart rate; LMCA, left main coronary artery; MACE, major adverse cardiovascular event; MI, myocardial infarction; NYHA, New York Heart Association; NSAIDs, non-steroid antiinflammatory drugs; OAC, oral anticoagulation; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; RVD, reference vessel diameter; ST, stent thrombosis.

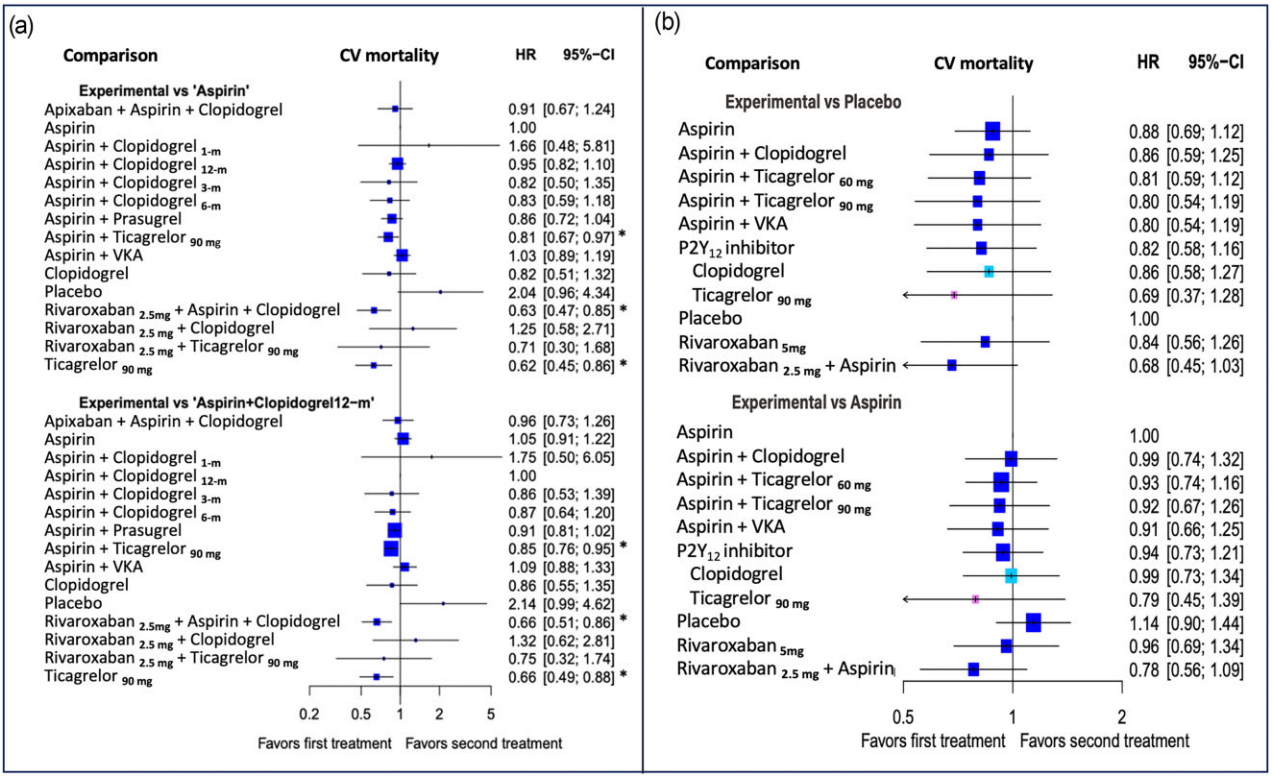


Figure 1 Within (*a*) and beyond (*b*) 12 months treatment effects for cardiovascular mortality. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) are determined by network meta-analysis. *denotes statistically significant differences.

aspirin and prasugrel ranked the most effective treatment to reduce MI (*P* score = 0.92), followed by ticagrelor 90 mg monotherapy (*P* score = 0.79)

Aspirin and clopidogrel for 12-month comparator: Only aspirin and prasugrel [HR, 0.81 (95% CI, 0.70–0.94)] (*Figure 2a*) yielded a significant MI reduction.

Beyond 12-month treatment effect appraisal

Nineteen trials (139 086 patients) reported 4746 (3.41%) MI events. There was low heterogeneity among treatments ($\tau^2 = 0.015$) and no evidence of publication bias (Egger's test $P = 0.36$, Supplementary material online, *Table S5*).

Placebo comparator. All investigated strategies yielded a significant reduction of MI rates, except vitamin K antagonist (VKA) [HR, 0.68 (95% CI, 0.45–1.02)] and rivaroxaban 5 mg [HR, 0.68 (95% CI, 0.46–1.00)] monotherapies. The treatment effects varied among the treatment options and were highest with aspirin and clopidogrel dual therapy [HR, 0.51 (95% CI, 0.37–0.71)], and $P2Y_{12}$ inhibitor monotherapy [HR, 0.58 (95% CI, 0.42–0.80)], especially ticagrelor [HR, 0.41 (95% CI, 0.23–0.73)] and lowest with aspirin monotherapy [HR, 0.76 (95% CI, 0.60–0.96)] (*Figure 2b*).

Aspirin comparator. A significant MI risk reduction was found with aspirin and clopidogrel dual therapy [HR, 0.68 (95% CI, 0.55–0.85)] and $P2Y_{12}$ monotherapy [HR, 0.76 (95% CI, 0.61–0.95)], which was more pronounced with ticagrelor [HR, 0.54 (95% CI, 0.32–0.92)] than with clopidogrel monotherapy [HR, 0.81 (95% CI, 0.65–1.01)]. No significant differences in MI risk occurred with the other strategies in comparison with aspirin (*Figure 2b*). Ticagrelor 90 mg monotherapy had the highest ranking in preventing MI (*P* score = 0.92, *Figure 3a*), followed by aspirin and clopidogrel dual therapy (*P* score = 0.90) and aspirin and ticagrelor 90 mg dual therapy (*P* score = 0.62). Bayesian probability curves of individual treatments showed that ticagrelor 90 mg monotherapy had a 75.2% probability to be the first treatment in the hierarchy, followed by dual antiplatelet therapy with aspirin and clopidogrel with a probability of 20.1% (*Figure 3b*).

Stroke

Twelve-month treatment effect appraisal

A total of 40 trials assessed stroke ($N = 169\,266$). A total of 1625 stroke episodes occurred (1.00%). Heterogeneity across trials was absent ($\tau^2 = 0$).

Aspirin comparator. No treatment decreased the risk of stroke compared with aspirin (*Figure 4a*).

Aspirin and clopidogrel for 12-month comparator. No treatment decreased the risk of stroke compared with 12-month aspirin and clopidogrel (*Figure 4a*).

Beyond 12-month treatment effect appraisal

Eighteen trials (132 620 patients) reported 2877 (2.17%) strokes. Heterogeneity was low-to-moderate ($\tau^2 = 0.026$). No publication bias was observed (Egger's test $P = 0.35$, Supplementary material online, *Table S5*).

Placebo comparator. Aspirin and ticagrelor 60 mg dual therapy, aspirin and VKA dual therapy, $P2Y_{12}$ monotherapy, aspirin and rivaroxaban 2.5 dual therapy, and VKA monotherapy reduced stroke. The treatment effects varied among the treatment options and were highest with VKA monotherapy [HR, 0.40 (95% CI, 0.19–0.84)] or aspirin and rivaroxaban 2.5 mg dual therapy [HR, 0.42 (95% CI,

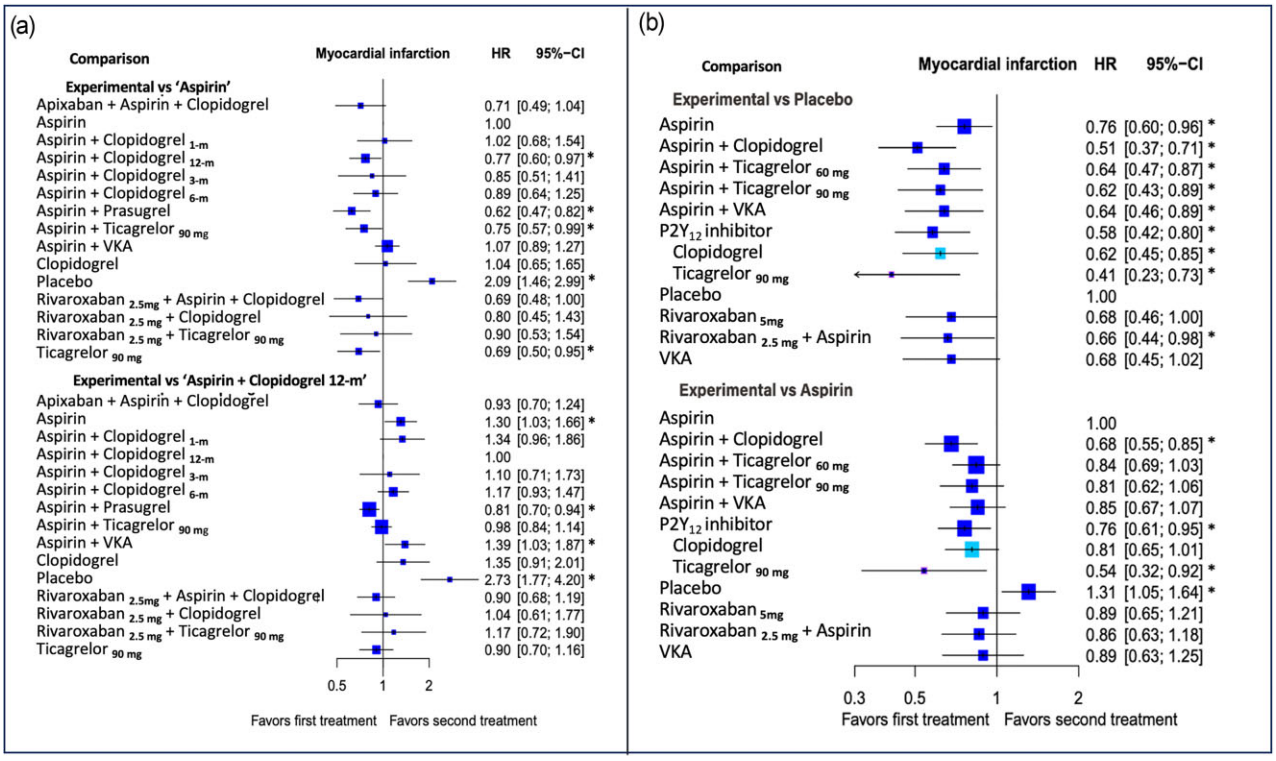


Figure 2 Within (*a*) and beyond (*b*) 12 months treatment effects for myocardial infarction. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) are determined by network meta-analysis. * denotes statistically significant differences.

0.24–0.73)], and lowest with aspirin monotherapy [HR, 0.72 (95% CI, 0.50–1.04)] (*Figure 4b*).

Aspirin comparator: The lowest stroke risk was observed with VKA monotherapy [HR, 0.56 (95% CI, 0.44–0.76)] or aspirin and an anticoagulant dual therapy, consisting of either rivaroxaban 2.5 mg [HR, 0.58 (95% CI, 0.44–0.76)] or VKA [HR, 0.64 (95% CI, 0.49–0.83)] (*Figure 4b*).

Treatment with aspirin and rivaroxaban 2.5 mg dual therapy was the highest-ranked treatment option (*P* score = 0.84, *Figure 3e*), immediately followed by VKA monotherapy (*P* score = 0.82). Bayesian probability curves of individual treatments showed VKA monotherapy (*Figure 3f*) to be the first treatment in the hierarchy, with a probability of 53%, followed by aspirin and rivaroxaban 2.5 mg dual therapy.

Bleeding endpoints

Twelve-month treatment effect appraisal

Thirty-eight trials (166 740 patients) were included in the analysis of major bleeding (4553 events, 2.73%). Heterogeneity was low ($\tau^2 = 0.02$). There was no evidence of publication bias (Egger's test $P = 0.27$, Supplementary material online, *Table S4*).

Aspirin comparator: Major bleeding risk was more than three-fold higher with triple therapies, either in the form of apixaban, aspirin and clopidogrel [HR, 3.92 (95% CI, 2.15–7.13)] or rivaroxaban 2.5 mg, aspirin and clopidogrel [HR, 3.50 (95% CI, 1.99–6.15)]; more than two-fold higher with rivaroxaban in combination with ticagrelor [HR, 2.86 (95% CI, 1.20–6.85)] or clopidogrel [HR, 2.09 (95% CI, 0.78–5.57)]; less than two-fold higher with aspirin and prasugrel [HR, 1.81 (95% CI, 1.26–2.59)], aspirin and ticagrelor 90 mg [HR, 1.84 (95% CI, 1.30–2.59)], or VKA and aspirin [HR, 1.56 (95% CI, 1.14–2.14)]; similar with monotherapies with clopidogrel or ticagrelor or dual therapy with aspirin and clopidogrel (*Figure 5a*).

Aspirin and clopidogrel for 12-month comparator: Clopidogrel monotherapy [HR, 0.62 (95% CI, 0.40–0.96)], aspirin monotherapy [HR, 0.71 (95% CI, 0.53–0.96)], and 6-month aspirin and clopidogrel [HR, 0.73 (95% CI, 0.53–0.99)] were associated with a significant reduction of major bleeding. Apixaban, aspirin and clopidogrel [HR, 2.79 (95% CI, 1.66–4.70)], rivaroxaban 2.5 mg, aspirin and clopidogrel [HR, 2.49 (95% CI, 1.54–4.03)], aspirin and prasugrel [HR, 1.29 (95% CI, 1.05–1.58)], or aspirin and ticagrelor 90 mg [HR, 1.31 (95% CI, 1.08–1.58)] resulted in a significant increase in the risk of major bleeding (*Figure 5a*). Results on study-defined bleeding were consistent (Supplementary material online, *Figure S10A*).

Beyond 12-month treatment effect appraisal

Seventeen trials with 133 033 patients were analysed for major bleeding with a total of 2204 events (1.66%). Heterogeneity was absent ($\tau^2 = 0.0014$). There was no evidence of publication bias (Egger's test p = 0.54, Supplementary material online, *Table S5*).

Placebo comparator: Aspirin monotherapy or $P2Y_{12}$ inhibitor monotherapy, either clopidogrel or ticagrelor, were the only treatment options that were not associated with statistically significant increased bleeding risk. The bleeding risk was highest with VKA [HR, 5.12 (95% CI, 2.03–12.91)] (*Figure 5b*).

Aspirin comparator: Major bleeding was greater with all treatment combinations and with VKA or rivaroxaban 5 mg monotherapies. The bleeding risk did not differ with placebo or $P2Y_{12}$ monotherapy, albeit it was numerically lower with clopidogrel [HR, 0.83 (95% CI, 0.68–1.02)] and higher with ticagrelor [HR, 1.34 (95% CI, 0.73–2.46)]

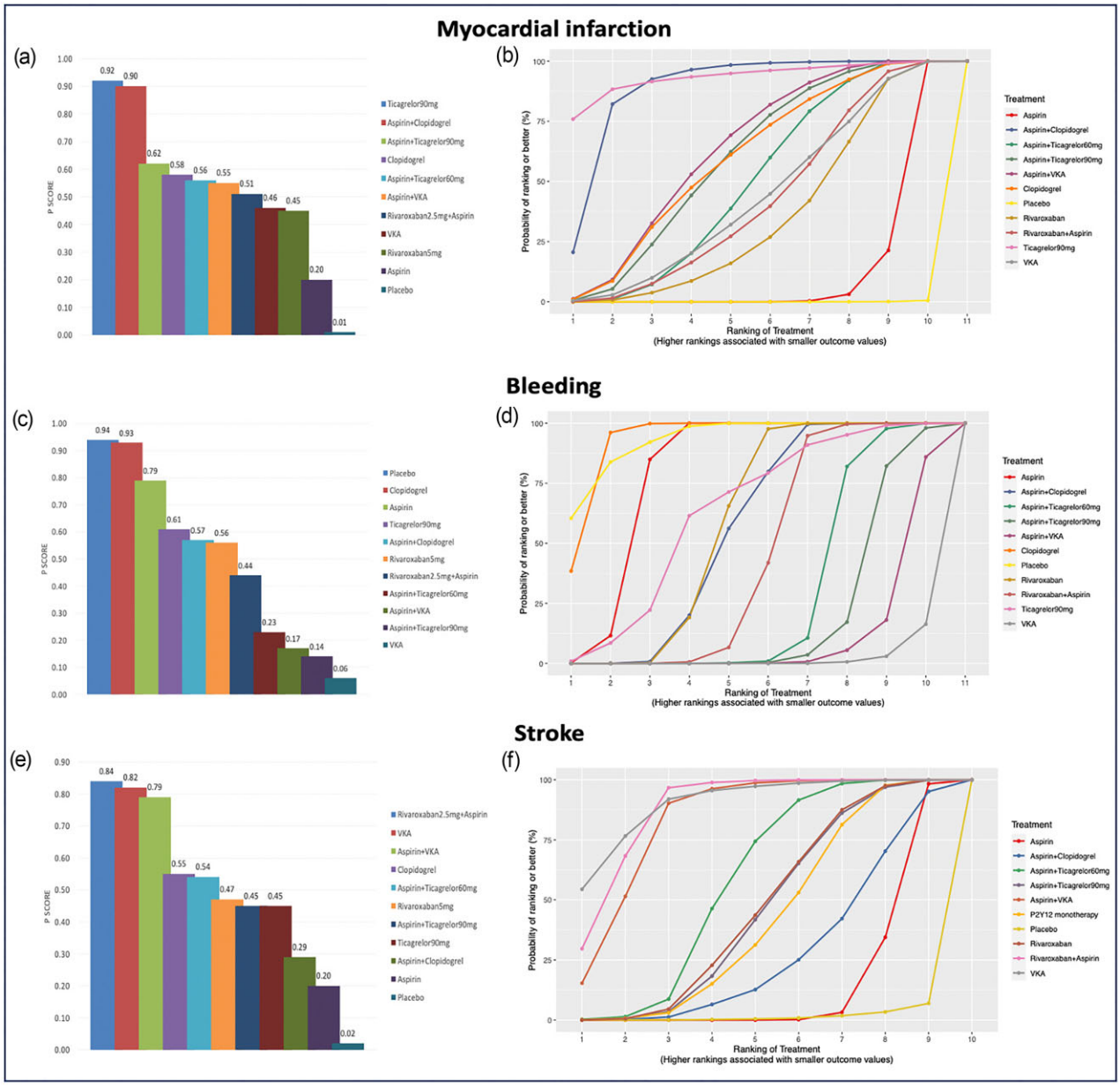


Figure 3 Standard and Bayesian ranking for myocardial infarction (MI), bleeding, and stroke. In the beyond 12-month network meta-analysis, *P* score values for each intervention for MI (*a*), bleeding (*c*), and stroke (e). Corresponding Bayesian probability inferences to be the most effective treatment for MI (*b*), the safest agent for bleeding (*d*), and the most effective agent for stroke (*f*). The value of *P* score varies from 0 to 1, i.e. higher the value, higher the likelihood that a therapy is highly effective or safe, and lower value demonstrates that a therapy is ineffective.

monotherapies (*Figure 5b*). Results on study-defined bleeding were consistent (Supplementary material online, *Figure S10B*).

Network consistency and additional analyses

By node-splitting, both NMAs showed consistency between direct and indirect estimates (Supplementary material online, *Figures S4a–E* and *S5A–E*). Among the included antithrombotic strategies, the two best-in-class agents for each explored outcome expressed in terms of net benefit (number needed to treat for all-cause mortality, MI, or stroke with corresponding number needed to harm for major bleeding) derived from the NMAs are depicted in the Graphical abstract. Bayesian meta-regression analyses did not show any significant impact of age or percentage of patients with ACS with less than five-unit DIC changes in comparison to the original model (Supplementary material online, *Table S7*).

Discussion

To the best of our knowledge, for the first time all available treatment options for secondary and tertiary prevention in CAD patients are

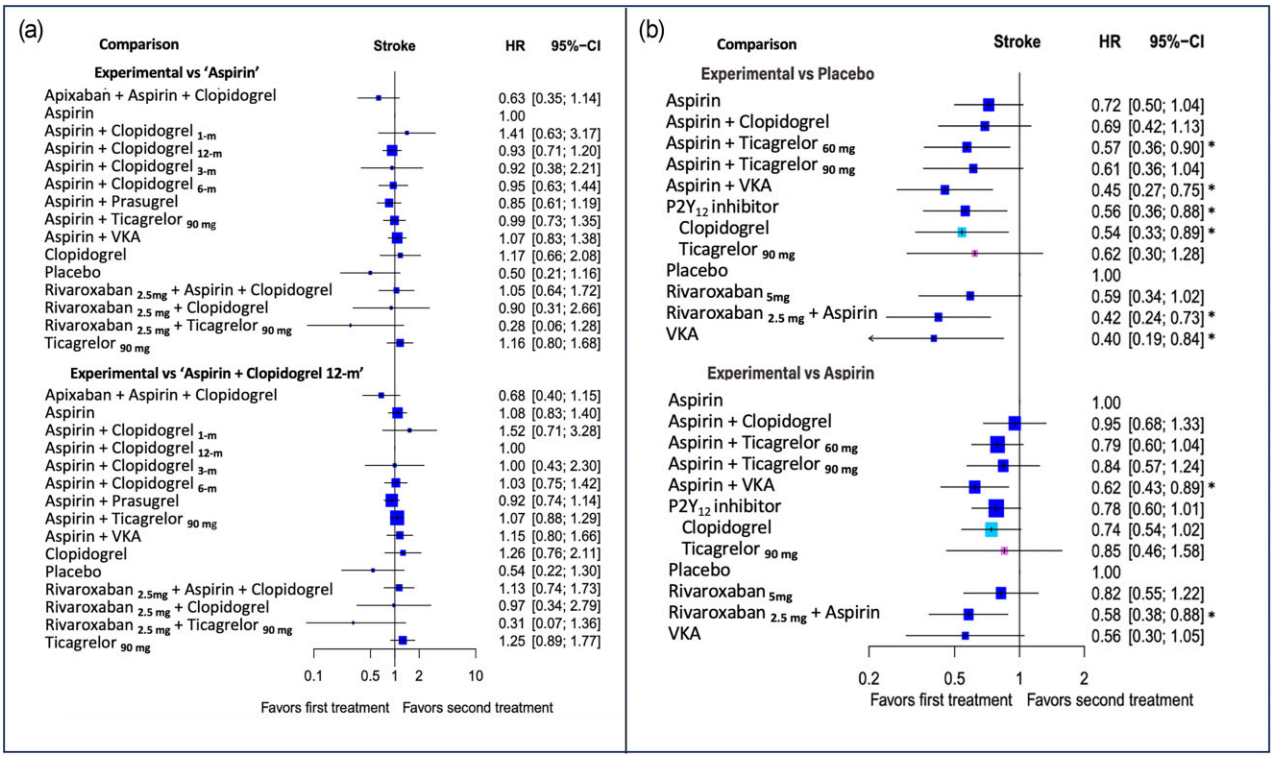


Figure 4 Within (*a*) and beyond (*b*) 12 months treatment effects for stroke. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) are determined by network meta-analysis. * denotes statistically significant differences.

compared by NMAs, with a distinct focus on within and beyond 12 months treatment effects.

In within 12-month NMA, including randomized trials and 189 261 patients, we addressed the efficacy and safety of 14 antithrombotic treatments within 1 year after ACS and/or coronary revascularization. The main findings are the following:

- Compared with aspirin or 12-month aspirin and clopidogrel, ticagrelor 90 mg monotherapy, aspirin and ticagrelor 90 mg dual therapy, and rivaroxaban 2.5 mg, aspirin and clopidogrel triple therapy reduced CV and all-cause death. No other treatment, in isolation or combination, affected mortality.
- Compared with aspirin, several antithrombotic treatment combinations, including triple therapies (rivaroxaban 2.5 mg, aspirin and clopidogrel or apixaban, aspirin and clopidogrel), dual therapies (aspirin and ticagrelor 90 mg or aspirin and clopidogrel for 12 months but not for 3 or 6 months), and a single monotherapy option (ticagrelor 90 mg) reduced the risk of MI. Only aspirin and prasugrel dual therapy reduced the risk of MI compared with 12-month aspirin and clopidogrel.
- No antithrombotic treatment reduced stroke risk either compared with aspirin or 12-month aspirin and clopidogrel.
- Bleeding risk increased progressively from single, through dual to triple antithrombotic treatments. Monotherapies with clopidogrel or ticagrelor were not associated with greater bleeding than aspirin. Compared with 12-month aspirin and clopidogrel, clopidogrel or ticagrelor 90 mg monotherapies were associated with lower and similar bleeding risks, respectively.

Over the years, current practice of antithrombotic therapy has been shifting from ischaemia prevention only to a net clinical benefit perspective, including the estimation of the bleeding risk trade-off, which is associated with increased mortality.[8] Mortality is, therefore, the most solid endpoint in assessing the balance between benefits and risks when considering antithrombotic treatments. Ticagrelor 90 mg monotherapy and rivaroxaban 2.5 mg, aspirin and clopidogrel triple therapy were ranked as the best strategies for reducing all-cause and cardiovascular mortality. A considerable bleeding risk trade-off was noted, however, for rivaroxaban 2.5 mg, aspirin and clopidogrel, which explains why it is infrequently implemented in practice. Our findings suggest that ticagrelor 90 mg monotherapy provides a mortality benefit without increasing the bleeding risk compared with aspirin and clopidogrel. Combining ticagrelor 90 mg with aspirin did not improve protection from fatal or non-fatal ischaemic events, as shown in prior meta-analyses[9,10] and was associated with greater bleeding compared with ticagrelor 90 mg monotherapy.[10]

Clopidogrel monotherapy is an attractive treatment especially in patients at high risk for bleeding, whereas aspirin and prasugrel may be selected in patients in whom the bleeding risk is low and concerns over the MI risk prevail.

In beyond 12-month NMA, encompassing 139 086 patients from 19 trials, we examined the efficacy and safety profile of nine available antithrombotic strategies in CCS patients.

In comparison with aspirin:

(1) Aspirin and clopidogrel dual therapy or $P2Y_{12}$ inhibitor monotherapy, especially ticagrelor, were associated with lower MI risk.
(2) VKA monotherapy, aspirin and VKA, aspirin and rivaroxaban 2.5 mg dual therapies were associated with a lower risk of stroke.

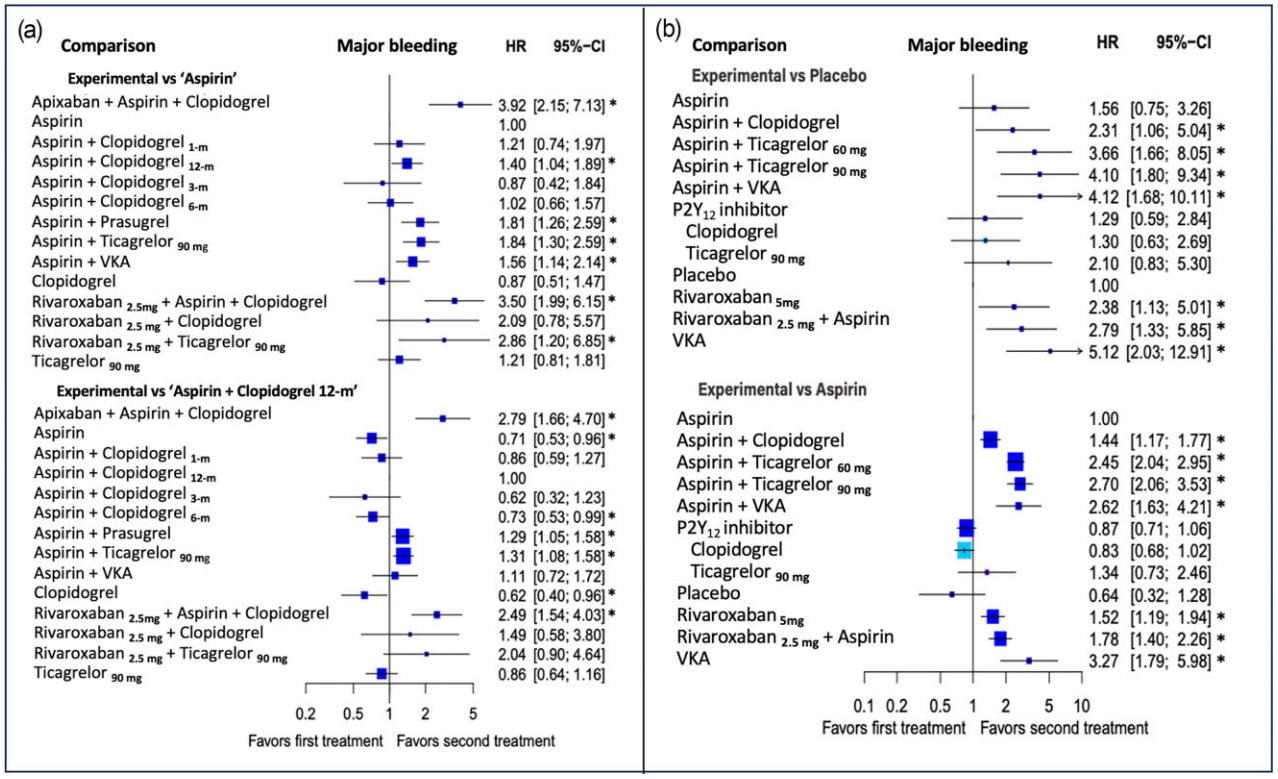


Figure 5 Within (*a*) and beyond (*b*) 12 months treatment effects for major bleeding. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) are determined by network meta-analysis. * denotes statistically significant differences.

(3) All treatment options except $P2Y_{12}$ inhibitor monotherapy were associated with enhanced bleeding risk, with a gradient of risk that was highest for VKA.

Patients with CAD remain at risk over long-term for recurrent cardiovascular and cerebrovascular events, which prompted the endorsement of the CCS terminology in preference to *stable* CAD, to highlight the dynamic nature of the disease and the continuous risk of recurrent events.[11] While aspirin is perceived as the standard antithrombotic long-term treatment for CCS patients, our study findings reinforce the notion that this strategy offers the lowest protection for MI and stroke risks when compared with alternative treatments in CCS patients.[12,13] Yet, the bleeding risk with alternative treatments is also generally higher than with aspirin alone. Our results confirm this prior knowledge with all tested alternative antithrombotic regimens except $P2Y_{12}$ monotherapy, which offers overall greater MI protection without concomitant higher bleeding risk than aspirin. $P2Y_{12}$ monotherapy may therefore be preferred to aspirin as beyond 12-month treatment in both patients with or without high bleeding risk features. When the type of $P2Y_{12}$ inhibitor was separately appraised, the MI risk trended but was not significantly lower with clopidogrel than aspirin, whereas the bleeding risk also was numerically but not significantly lower in favour of clopidogrel. Therefore, clopidogrel is likely to provide a net benefit compared with aspirin, although this composite endpoint was not appraised in our analysis. Ticagrelor monotherapy was associated with a significant MI reduction compared with aspirin. On the other hand, ticagrelor was associated with numerically, albeit not significantly, greater bleeding than aspirin. Hence, the individual bleeding risk profile and the need for protection from recurrent MI (i.e. in patients with prior MI) may inform the selection of the specific $P2Y_{12}$ inhibitor type for monotherapy. Our data do not suggest that the combination of aspirin and a $P2Y_{12}$ inhibitor provides greater ischaemic protection than the $P2Y_{12}$ inhibitor alone. This finding was generally consistent when clopidogrel or ticagrelor monotherapies were separately appraised compared with their combination with aspirin dual therapies and has been replicated in recent individual patient data meta-analyses.[9,10] Bayesian probability curves of individual treatments by providing a ranking of treatments showed that ticagrelor 90 mg monotherapy had greater probability than ticagrelor 90 mg and aspirin dual therapy of being the best treatment for MI prevention. This finding may reflect the different experimental settings, in which these two treatment options were tested and is consistent with a post-hoc analysis from the PLATO trial, suggesting that aspirin may diminish rather than potentiate ticagrelor treatment effect towards ischaemic risk protection.[14]

Unlike previous direct or NMAs,[9,10,15,16] our study is unique on the fact that it did not only address DAPT duration or type therefore, rather appraised all available treatment options that have been tested in the setting of at least one medium-to-large size randomized clinical trial with two distinct time frames (i.e. within and beyond 12 months).

Limitations

The current NMA has limitations. As for study-level meta-analyses, the results are derived from pooled patient data as no individual patient data were collected for this analysis. The absence of direct comparisons for some of the examined treatment options due to the

limited number of available trials precluded a more robust assessment of network coherence in some instances. On the other hand, the consistency of results in the main and sensitivity analyses suggests robustness of findings. Some of the investigated treatment options were investigated in single trial, which limits the precision and the generalizability of the results. However, the consistency between direct and indirect estimates corroborated the findings. We did not perform multiplicity adjustments; therefore, the chance of type I error inflation cannot be dismissed. We included studies conducted decades ago, which no longer reflect current practice, especially for the aspirin vs. no aspirin/placebo and VKA treatment effects. The definition of MI evolved over time with the use of more sensitive biomarkers. Similarly, despite our attempts to homogenize the bleeding metrics, the bleeding definitions were not consistent across trials. This NMA was not designed to investigate separately the clinical effect in patients with or without an ACS that could be addressed with large-scale individual patient data. On the other hand, by Bayesian meta-regressions, the percentage of ACS across trials did not have a significant impact on outcomes.

Conclusions

Within 12 months after coronary revascularization and/or ACS, ticagrelor 90 mg monotherapy was the only treatment associated with lower mortality, without increased bleeding risk compared with aspirin and clopidogrel. Beyond 12 months, $P2Y_{12}$ monotherapy, especially ticagrelor 90 mg, was associated with lower MI without a bleeding risk trade-off; rivaroxaban 2.5 mg and aspirin most effectively reduced stroke risk, with a more acceptable bleeding risk than VKA, compared with aspirin. The use of aspirin monotherapy as routine beyond 12-month antithrombotic treatment in patients with established CAD does not appear justifiable based on the cardiovascular and cerebrovascular ischaemic risks, nor the bleeding risk.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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