Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis

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Summary

Background Whether guided selection of antiplatelet therapy in patients undergoing percutaneous coronary intervention (PCI) is effective in improving outcomes compared with standard antiplatelet therapy remains controversial. We assessed the safety and efficacy of guided versus standard selection of antiplatelet therapy in patients undergoing PCI.

Methods For this systematic review and meta-analysis, from Aug 20 to Oct 25, 2020, we searched MEDLINE (via PubMed), Cochrane, Embase, and Web of Science databases for randomised controlled trials and observational studies published in any language that compared guided antiplatelet therapy, by means of platelet function testing or genetic testing, versus standard antiplatelet therapy in patients undergoing PCI. Two reviewers independently assessed study eligibility, extracted the data, and assessed risk of bias. Risk ratios (RRs) and 95% CIs were used with random-effects or fixed-effect models according to the estimated heterogeneity among studies assessed by the I^2 index. Coprimary endpoints were trial-defined primary major adverse cardiovascular events and any bleeding. Key secondary endpoints were all-cause death, cardiovascular death, myocardial infarction, stroke, definite or probable stent thrombosis, and major and minor bleeding. This study is registered with PROSPERO (CRD42021215901).

Findings 3656 potentially relevant articles were screened. Our analysis included 11 randomised controlled trials and three observational studies with data for 20 743 patients. Compared with standard therapy, guided selection of antiplatelet therapy was associated with a reduction in major adverse cardiovascular events (RR 0·78, 95% CI 0·63–0·95, p=0·015) and reduced bleeding, although not statistically significant (RR 0·88, 0·77–1·01, p=0·069). Cardiovascular death (RR 0·77, 95% CI 0·59–1·00, p=0·049), myocardial infarction (RR 0·76, 0·60–0·96, p=0·021), stent thrombosis (RR 0·64, 0·46–0·89, p=0·011), stroke (RR 0·66, 0·48–0·91, p=0·010), and minor bleeding (RR 0·78, 0·67–0·92, p=0·0030) were reduced with guided therapy compared with standard therapy. Risks of all-cause death and major bleeding did not differ between guided and standard approaches. Outcomes varied according to the strategy used, with an escalation approach associated with a significant reduction in ischaemic events without any trade-off in safety, and a de-escalation approach associated with a significant reduction in bleeding, without any trade-off in efficacy.

Interpretation Guided selection of antiplatelet therapy improved both composite and individual efficacy outcomes with a favourable safety profile, driven by a reduction in minor bleeding, supporting the use of platelet function or genetic testing to optimise the choice of agent in patients undergoing PCI.

Funding None.

Introduction

Dual antiplatelet therapy, consisting of aspirin and a $P2Y_{12}$ inhibitor, represents the standard of care for the prevention of thrombotic complications in patients undergoing percutaneous coronary intervention (PCI).[1,2] Clopidogrel is the most commonly used $P2Y_{12}$ inhibitor.[3] However, the pharmacodynamic effects of clopidogrel are characterised by interindividual variability and a considerable number of patients persist with high on-treatment platelet reactivity (HPR).[4,5] Importantly, the presence of HPR in clopidogrel-treated patients undergoing PCI is associated with increased thrombotic risk.[4,5] Multiple mechanisms have been shown to contribute to clopidogrel HPR. Among these, genetic polymorphisms of the hepatic cytochrome P450 2C19 (CYP2C19) enzyme, required to transform clopidogrel into its active metabolite, have an important role, with carriers of loss-of-function alleles characterised by reduced active metabolite generation, increased HPR rates, and enhanced thrombotic risk.[4,6–9]

Prasugrel and ticagrelor are $P2Y_{12}$ inhibitors with more potent and predictable pharmacodynamic effects compared with clopidogrel and are not modulated by *CYP2C19* genes.[4,7,10–12] In turn, HPR is uncommon with prasugrel and ticagrelor and, in patients with an acute coronary syndrome, these drugs are associated with

Research in context

Evidence before this study

The use of platelet function testing and genetic testing in patients undergoing percutaneous coronary intervention (PCI) has aimed to improve outcomes by tailoring antiplatelet treatment to the individual patient. However, early randomised controlled trials did not find any benefit with a guided approach. Pitfalls in trial designs, such as the inclusion of low-risk patients, inadequate identification of patients with impaired clopidogrel-induced platelet inhibition, and infrequent use of potent $P2Y_{12}$ inhibitors, could have contributed to these findings. These considerations, as well as the broader availability of rapid bedside assays and more potent $P2Y_{12}$ inhibitors, have led to the design of investigations better suited to define the potential benefits of a guided selection of antiplatelet therapy. Despite these advancements and the availability of new studies designed to investigate the use of platelet function or genetic testing as a strategy (ie, to test or not to test), these studies were not powered for efficacy endpoints composed of hard ischaemic events and have not provided unequivocal results. Meta-analyses are useful to overcome these limitations.

From Aug 20 to Oct 25, 2020, we searched MEDLINE (via PubMed), Cochrane, Embase, and Web of Science databases in addition to abstracts and presentations of international cardiology meetings published in any language. Randomised controlled trials as well as observational studies comparing guided (ie, platelet function testing or genetic testing) versus standard antiplatelet therapies in patients with acute or chronic coronary syndromes undergoing PCI with stent implantation were included.

Added value of this study

This comprehensive meta-analysis pooling data from the available evidence and including more than 20 000 patients showed that a strategy of guided selection of antiplatelet therapy significantly reduced the risk of major adverse cardiovascular events compared with standard antiplatelet therapy. Moreover, hard individual efficacy outcomes including cardiovascular death, myocardial infarction, stent thrombosis, and stroke were also reduced. Such efficacy findings occurred with a non-significant reduction in bleeding driven by a reduction in minor bleeding. Outcomes varied according to the strategy used for guided therapy: escalation (ie, switching from clopidogrel to prasugrel, ticagrelor, or double-dose clopidogrel, or adding cilostazol) or de-escalation (ie, switching from prasugrel or ticagrelor to clopidogrel). An escalation approach was associated with a reduction in ischaemic events without any increase in bleeding, and a de-escalation approach was associated with a reduction in bleeding, without any increase in ischaemic events.

Implications of all the available evidence

This meta-analysis helps overcome some of the many limitations of thus far available studies investigating the role of platelet function testing and genetic testing to guide the selection of antiplatelet therapy. Our findings support the use of these assays to aid with the selection of the antiplatelet treatment regimen in patients undergoing PCI. Furthermore, outcomes vary according to whether an escalation or de-escalation approach is used, with an escalation approach reducing ischaemic events without trade-off in bleeding and a de-escalation approach reducing bleeding without trade-off in ischaemic events.

reduced thrombotic risk compared with clopidogrel, but at the expense of increased bleeding.[10,12] The availability of potent $P2Y_{12}$ inhibitors and other strategies associated with enhanced platelet inhibition (eg, double-dose clopidogrel or adjunctive use of cilostazol) have prompted investigations aimed at tailoring the selection of antiplatelet regimens under the guidance of platelet function testing or genetic testing with the goal of improving outcomes in patients undergoing PCI.[4,7,13,14] Previous studies and meta-analyses comparing guided versus standard antiplatelet therapy were selectively done in patients with HPR or carriers of *CYP2C19* loss-of-function alleles.[4,5,15–18] More recent studies investigated the use of platelet function testing or genetic testing as a strategy (ie, to test or not to test). Nevertheless, studies thus far were not powered for hard efficacy outcomes (ie, death, cardiovascular death, myocardial infarction, stent thrombosis, or stroke) and have not provided unequivocal results.[19–24] We did a systematic review and meta-analysis to determine the safety and efficacy of guided versus standard selection of antiplatelet therapy in patients undergoing PCI.

Methods

Search strategy and selection criteria

This meta-analysis was done according to the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (appendix pp 3–4).[25] We included randomised controlled trials and observational studies comparing guided antiplatelet therapy (ie, platelet function testing or genetic testing) versus standard antiplatelet therapy in patients with acute coronary syndrome or chronic coronary syndromes undergoing PCI with stent implantation. We included platelet function testing or genetic testing because they represent the most common tools to guide antiplatelet therapy.[4] Guided therapy could have included a strategy of either escalation (ie, switching from clopidogrel to prasugrel, ticagrelor, or double-dose clopidogrel, or adding cilostazol) or de-escalation (ie, switching from prasugrel or ticagrelor to clopidogrel).[4,13] Studies reporting clinical outcomes at a follow-up shorter than 6 months were excluded because this duration was considered inadequate to assess a difference in hard endpoints between groups.

See Online for appendix

From Aug 20 to Oct 25, 2020, we did a systematic digital search using the MEDLINE (via PubMed), Cochrane, Embase, and Web of Science databases. Additionally, we searched abstracts and presentations from annual meetings of the following societies: European Society of Cardiology, European Association of Percutaneous Cardiovascular Interventions, American Heart Association, American College of Cardiology, Transcatheter Cardiovascular Therapeutics, and Society of Cardiovascular Angiography and Interventions. Search terms were "guided", "percutaneous coronary intervention", "CYP2C19", "antiplatelet", "genotype", "clopidogrel resistance", "personalized", "platelet function", "phenotype", "pharmacogenomics", in addition to combinations of these terms (see appendix p 5 for the full search strategy). Literature search terms were reviewed by an experienced medical librarian. Two investigators (MG, SB) independently screened titles and abstracts for eligibility as well as the full text, supplementary material, online appendices, and reference lists of each eligible study, to confirm the inclusion criteria and to identify further published studies. The same two investigators independently performed data extraction. There were no restrictions with respect to the language used, publication status, or publication date. Disagreements were solved by consensus.

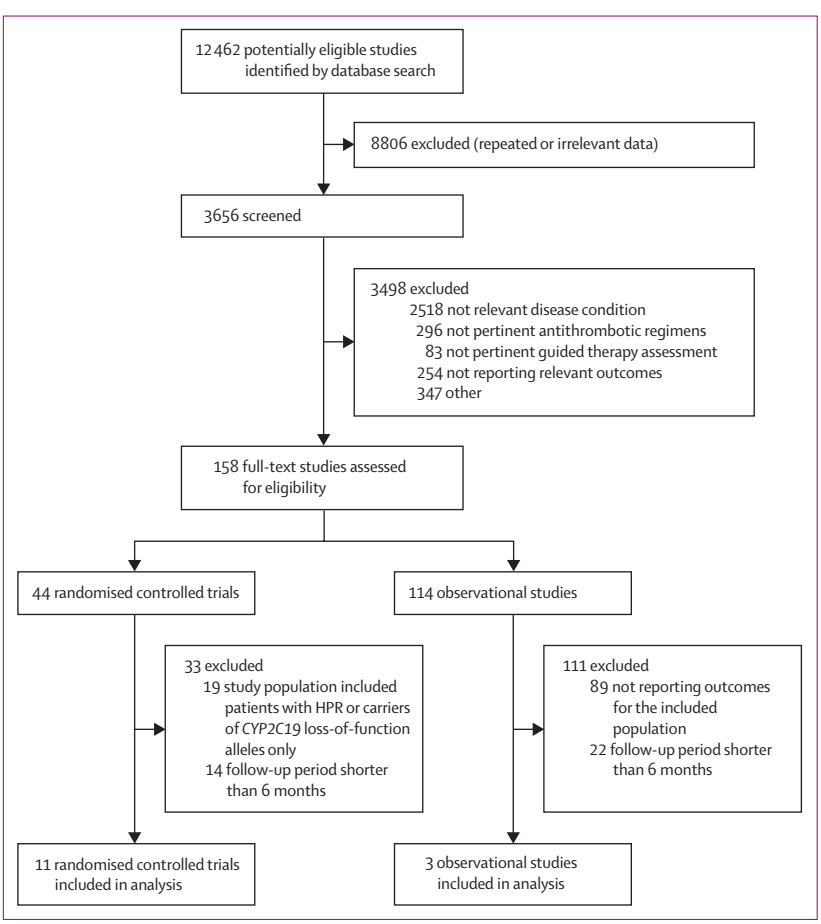

Figure 1: **Study selection**
HPR=high on-treatment platelet reactivity.

Data analysis

The risk of bias assessment was independently assessed by two investigators (MG, SB) according to the Cochrane Collaboration risk-of-bias-tool 2 (RoB 2) for randomised studies and Risk of Bias in Non-randomized Studies of Interventions (ROBINS-1) for non-randomised studies.[26,27] The primary efficacy outcome was trial-defined primary major adverse cardiovascular events according to the definition of this outcome in the respective trials (appendix pp 6–10). Secondary efficacy endpoints were all-cause death, cardiovascular death, myocardial infarction, stroke, and definite or probable stent thrombosis. The primary safety endpoint was any bleeding. Secondary safety endpoints were major bleeding and minor bleeding. Major, minor, or any bleeding were defined according to trial definitions. We prioritised the Bleeding Academic Research Consortium definition when available. If not reported, we chose the Thrombolysis in Myocardial Infarction criteria or Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria. Details on endpoint definitions are provided in the appendix (pp 6–10).

Risk ratios (RRs) with 95% CIs were calculated with R version 3.3.3 to facilitate a consistent interpretation of effect estimates. The Cochran's *Q* test and Higgins' I^2 statistics were used to estimate heterogeneity among studies, with I^2 less than 25% indicating low heterogeneity, 25–50% indicating moderate heterogeneity, and more than 50% indicating high heterogeneity.[26] For moderate-to-high heterogeneity, the random-effects model with inverse variance weighting was used, whereas the Mantel-Haenszel fixed-effect model was used for low heterogeneity. p values less than 0·05 were considered significant.

All analyses were done according to the prespecified subgroups of randomised controlled trials versus observational studies to assess the weight of non-randomised studies on each analysis. Two further subgroup analyses were run according to the type of test used to guide the selection of therapy (platelet function testing *vs* genetic testing) and the type of strategy used (de-escalation *vs* escalation). A difference between the estimates of these subgroups was considered significant for $p_{interaction}<0·10$.[28]

To explore whether a single study significantly affected the robustness of our findings, we did a sensitivity analysis by sequentially removing each single study from the pooled effect estimates. We did a further sensitivity analysis for all the included outcomes by excluding studies that used the addition of cilostazol or double-dose clopidogrel in the guided therapy group, to assess the use of the potent $P2Y_{12}$ inhibitors (ie, ticagrelor and prasugrel). Random-effects meta-regression analyses with the empirical Bayes (Paule-Mandel) method to

	Number of patients in each group		Clinical presentation (%)				Average proportion of patients treated with drug-eluting stent (%)	Type of test and targets or cutoffs	Antiplatelet drugs (%)		Strategy	Follow-up duration (months)
	Guided therapy	Standard therapy	STEMI	NSTEMI	UA	CCS			Guided therapy group	Standard therapy group		
Claassens et al, 2019 (POPular Genetics)[19]	1242	1246	100%	..	..	..	100%	Genotype-guided; *CYP2C19*2* or *CYP2C19*3* loss-of-function alleles	Clopidogrel 61%; ticagrelor 38%; prasugrel 1%	Ticagrelor 90%	De-escalation	12
Pereira et al, 2020 (TAILOR-PCI)[20]	2641	2635	22%	29%	18%	31%	NA	Genotype-guided; *CYP2C19*2* or *CYP2C19*3* loss-of-function alleles	Clopidogrel 68%; ticagrelor 31%; prasugrel 1%; cilostazol 1%	Clopidogrel 98%; ticagrelor 1%; prasugrel 1%	Escalation	12
Collet et al, 2012 (ARCTIC)[21]	1213	1227	..	27%	..	73%	97%	Platelet function testing (Verify Now); HPR if PRU ≥235, ≤15% inhibition, or both	Clopidogrel 150 mg 28%; clopidogrel 75 mg 60%; prasugrel 12%	Clopidogrel 86%; prasugrel 6%	Escalation	12
Cayla et al, 2016 (ANTARCTIC)[22]	435	442	35%	48%	18%	..	80%	Platelet function testing (Verify Now); HPR if PRU ≥208, LPR if PRU ≤85	Clopidogrel 39%; prasugrel 59%	Clopidogrel 4%; prasugrel 94%	De-escalation	12
Sibbing et al, 2017 (TROPICAL-ACS)[23]	1304	1306	55%	45%	..	..	77%	Platelet function testing (Multiplate Analyzer); HPR if ≥46 U by ADP test	Clopidogrel 39%; prasugrel 61%	Prasugrel 100%	De-escalation	12
Notarangelo et al, 2018 (PHARMCLO)[24]	448	440	28%	68%	2%	2%	100%	Genotype-guided; *ABCB1* 3435, *CYP2C19*2*, and *CYP2C19*17*	Clopidogrel 43%; prasugrel 8%; ticagrelor 43%	Clopidogrel 51%; prasugrel 8%; ticagrelor 33%	Escalation	12
Xie et al, 2013 (IAC-PCI)[29]	301	299	NA	NA	NA	NA	100%	Genotype-guided; *CYP2C19*2* or *CYP2C19*3*	Clopidogrel 90%; cilostazol 10%	Clopidogrel 100%	Escalation	6
Zhu et al, 2015[30]	154	151	NA	NA	NA	NA	69%	Platelet function testing (PACKS-4 Aggregometer); low clopidogrel response: <10% IPA	Clopidogrel 82%; cilostazol 18%	Clopidogrel 100%	Escalation	12
Zheng et al, 2020 (PATH-PCI)[31]	1146	1139	..	..	..	100%	100%	Platelet function testing (PL-12); HPR: MAR >55%	Clopidogrel 37%; ticagrelor 63%	Clopidogrel 100%	Escalation	6
Tuteja et al, 2020[32]	249	255	14%	21%	15%	50%	94%	Genotype-guided; *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* alleles	Clopidogrel 71%; ticagrelor 12%; prasugrel 17%	Clopidogrel 79%; ticagrelor 9%; prasugrel 12%	Escalation	16

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	Number of patients in each group		Clinical presentation (%)				Average proportion of patients treated with drug-eluting stent (%)	Type of test and targets or cutoffs	Antiplatelet drugs (%)		Strategy	Follow-up duration (months)
	Guided therapy	Standard therapy	STEMI	NSTEMI	UA	CCS			Guided therapy group	Standard therapy group		
(Continued from previous page)												
Hazarbasanov et al, 2012[33]	97	95	24%	33%	..	43%	18%	Platelet function testing (Multiplate Analyzer); HPR if ≥46 U by ADP test	Clopidogrel 150 mg 18%; clopidogrel 75 mg 81%	Clopidogrel 100%	De-escalation	6
Shen et al, 2016[24]	309	319	NA	NA	NA	NA	98%	Genotype-guided; *CYP2C19*2* and *CYP2C19*3*	Clopidogrel 150 mg 45%; clopidogrel 75 mg 43%; ticagrelor 12%	Clopidogrel 100%	Escalation	12
Sánchez-Ramos et al, 2016[35]	317	402	42%	27%	20%	11%	66%	Genotype-guided; *CYP2C19*2*, *CYP2C19*3*, and *ABCB1*	Clopidogrel 59%; ticagrelor 3%; prasugrel 38%	Clopidogrel 93%; prasugrel 7%	Escalation	12
Lee et al, 2018[36]	683	248	NA	NA	NA	NA	84%	Genotype-guided; *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17*	Clopidogrel 53%; ticagrelor or prasugrel 47%	Clopidogrel 88%; ticagrelor or prasugrel 12%	Escalation	12

ADP=adenosine diphosphate. CCS=chronic coronary syndrome. CYP=cytochrome P450. HPR=high platelet reactivity. IPA=inhibition of platelet aggregation. LPR=low platelet reactivity. MAR=maximal aggregation ratio. NA=not available. NSTEMI=non-ST-segment elevation myocardial infarction. PRU=$P2Y_{12}$ reaction units. STEMI=ST-segment elevation myocardial infarction. UA=unstable angina.

Table: **Key study characteristics and clinical presentation of patients included in the meta-analysis**

estimate the between-study variance τ^2 and the Hartung-Knapp-Sidik-Jonkman adjustment were done to evaluate the relation of covariates (year of trial, proportion of patients with acute coronary syndrome, proportion of patients with drug-eluting stents, and duration of follow-up) on all the included outcomes. The presence of publication bias was investigated with Harbord and Egger tests, and by visual estimation of funnel plots. This study is registered with PROSPERO (CRD42021215901).

Role of the funding source

There was no funding source for this study.

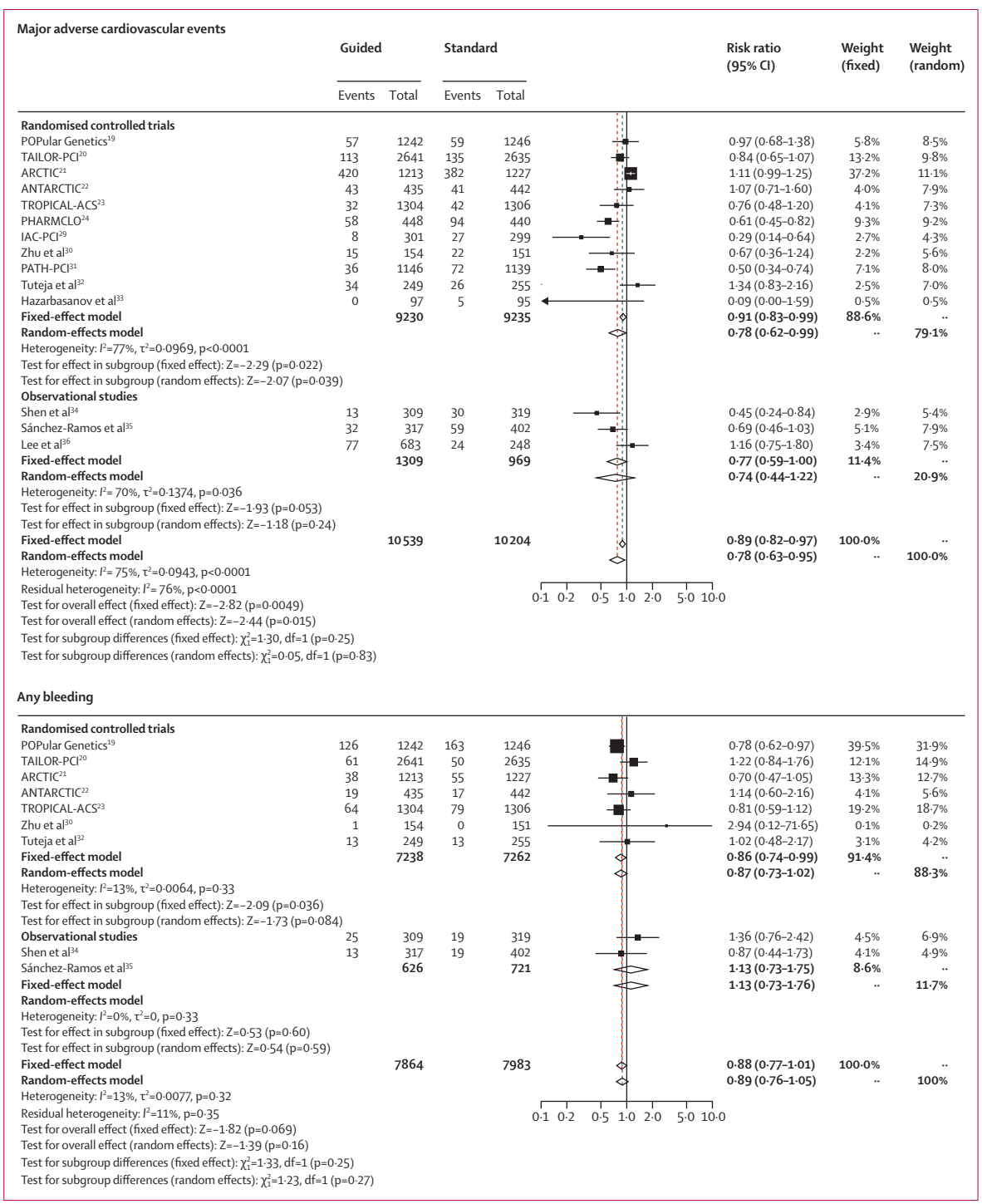
Results

3656 potentially relevant articles were screened (figure 1). 14 studies with a total of 20743 patients and a mean follow-up of 11 months were included in the analysis. Of these, 11 were randomised controlled trials[19–24,29–33] and three were observational studies.[34–36] Duration of follow-up was 6 months in three studies, 16 months in one study, and 12 months in ten studies (table). Platelet function testing was used in six studies and genetic testing was used in eight studies. Regimens used in patients undergoing guided therapy were cilostazol in adjunct to dual antiplatelet therapy in two studies, double-dose clopidogrel in three studies, and ticagrelor or prasugrel in the remaining nine studies. De-escalation was used in four studies and escalation in ten studies. Detailed descriptions of the main features of each trial are given in the table and the appendix (pp 11–17). The proportion of patients with acute coronary syndrome ranged from 0% in PATH-PCI[31] to 100% in POPular Genetics[19] and TROPICAL-ACS;[23] drug-eluting stent use ranged from 18% in the study by Hazarbasanov and colleagues[33] to 100% in POPular Genetics,[19] PHARMCLO,[24] IAC-PCI,[29] and PATH-PCI;[31] year of publication ranged from 2012 (Hazarbasanov and colleagues[33] and ARCTIC[21]) to 2020 (TAILOR-PCI[20]). Within each trial, baseline characteristics were similar between the guided and standard therapy groups. Detailed baseline clinical features are shown in the appendix (pp 18–20). Five of 11 randomised controlled trials and one of three observational studies were considered at low risk for bias;[20–24,34] the other studies were at increased risk of bias (see appendix pp 21–23 for risk of bias for each study, estimate of overall risk of bias, and publication bias by visual inspection of funnel plots).

The primary efficacy endpoint of major adverse cardiovascular events was significantly reduced with guided selection of antiplatelet therapy compared with standard antiplatelet therapy (RR 0·78, 95% CI 0·63–0·95, p=0·015, I^2=75%; figure 2). The benefit in favour of a guided strategy was significant in the subgroup of randomised controlled trials (RR 0·78, 95% CI 0·62–0·99, p=0·039, I^2=77%) but not in the subgroup of observational studies (RR 0·74, 0·44–1·22, p=0·24, I^2=70%), although

no significant difference was seen between these subgroups (p=0·83).

The primary safety endpoint of any bleeding with guided selection of antiplatelet therapy compared with standard antiplatelet therapy was RR 0·88 (95% CI 0·77–1·01, p=0·069, I^2=13%; figure 2). Any bleeding was reduced with guided therapy in the subgroup of randomised controlled trials (RR 0·86, 95% CI 0·74–0·99, p=0·036, I^2=13%) but not in the subgroup of observational studies (RR 1·13, 0·73–1·75, p=0·60, I^2=0%), although no significant difference was seen between these subgroups (p=0·25).



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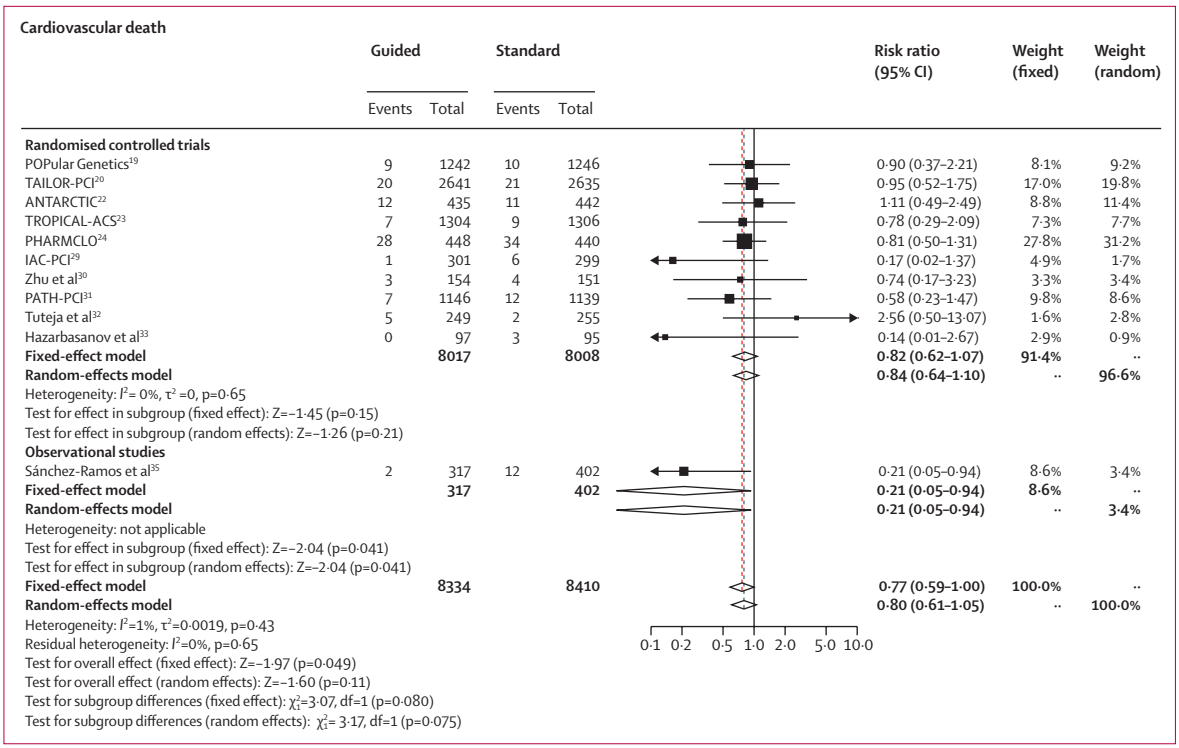


Figure 2: **Pooled analyses of guided versus standard antiplatelet therapy for the primary efficacy and safety endpoints and the secondary outcome of cardiovascular death**

Compared with standard therapy, a guided approach was associated with a reduction in cardiovascular death, myocardial infarction, stent thrombosis, and stroke; there was no difference between guided and standard strategies in all-cause death (figures 2, 3). Compared with standard therapy, a guided approach was associated with a reduction in minor bleeding but not major bleeding (figure 3). No significant differences were seen between subgroups of randomised controlled trials and observational studies, except for all-cause death and cardiovascular death, for which a benefit in favour of guided therapy compared with standard therapy was found in observational studies but not among randomised controlled trials.

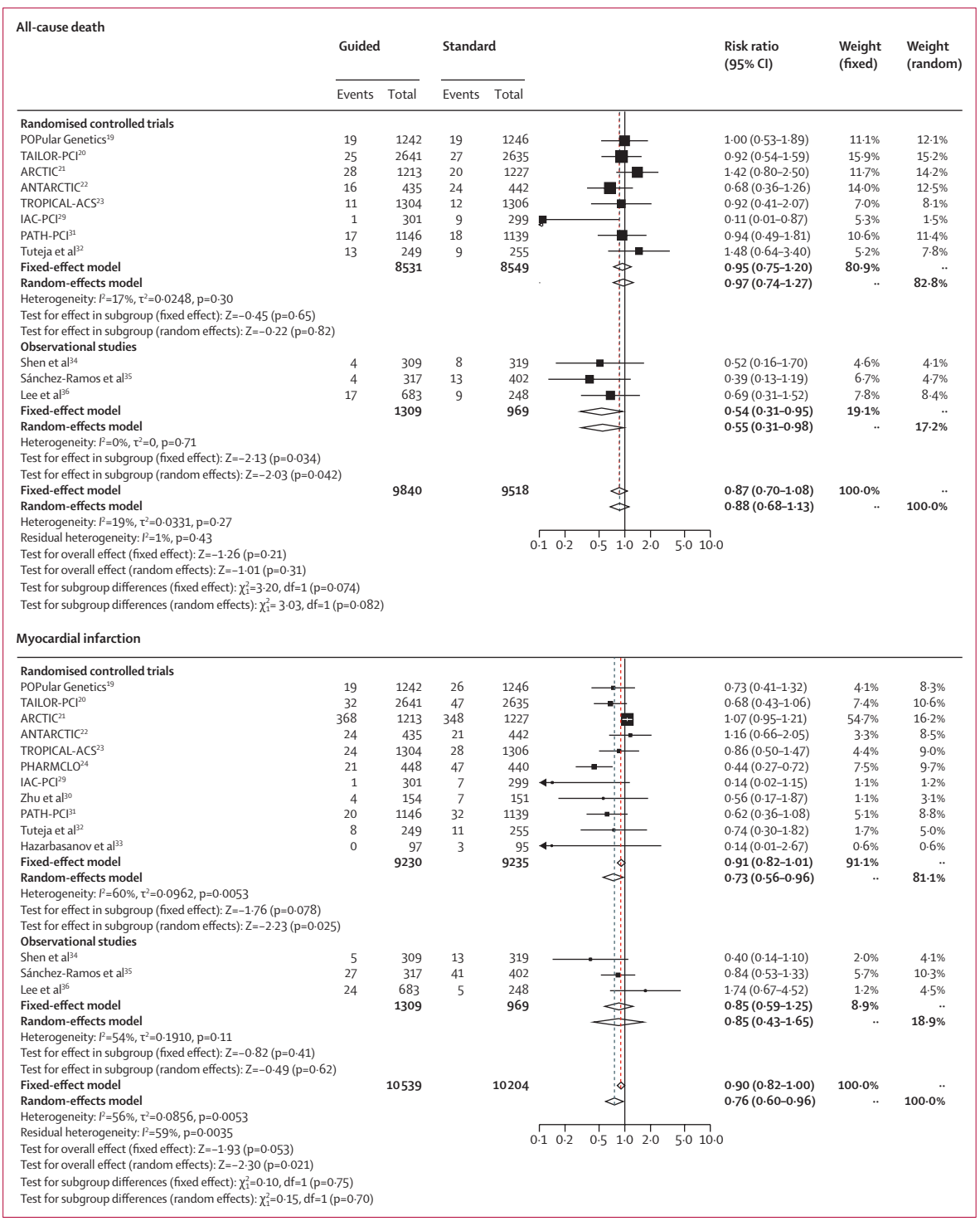
The exclusion of each single study from the pooled effect estimates affected the outcome of cardiovascular death, whereas the exclusion of very few studies affected the outcome of myocardial infarction (PHARMCLO[24]), stent thrombosis (IAC-PCI[29] and PATH-PCI[31]), stroke (PATH-PCI[31]), and minor bleeding (POPular Genetics;[19] appendix pp 24–25). After exclusion of studies with use of cilostazol[29,30] or double-dose clopidogrel[21,33,34] in the guided therapy group, the RR for major adverse cardiovascular events compared with standard therapy was 0·83 (95% CI 0·68–1·01, p=0·058); myocardial infarction, stent thrombosis, stroke, and minor bleeding were not affected by exclusion of these studies, and were reduced with guided therapy compared with standard therapy, but cardiovascular death was not (appendix pp 26–27).

Meta-regression analysis based on year of the study, proportion of patients with acute coronary syndrome, and proportion of patients with drug-eluting stents showed no significant relation between the covariates and all included outcomes (appendix pp 28–33). There was a significant interaction between duration of follow-up and the outcomes of major adverse cardiovascular events and stent thrombosis (appendix pp 34–35).

There were no differences between subgroups according to the type of test used to guide selection of therapy (platelet function testing *vs* genetic testing; appendix pp 36–37) or strategy (de-escalation *vs* escalation; appendix pp 38–39). In the subgroup of patients undergoing an escalation strategy, guided therapy was associated with reductions in major adverse cardiovascular events (RR 0·74, 95% CI 0·57–0·95, p=0·020, I^2=82%), cardiovascular death (RR 0·73, 0·54–1·00, p=0·052, I^2=24%), myocardial infarction (RR 0·71, 0·52–0·97, p=0·031, I^2=66%), stent thrombosis (RR 0·62, 0·42–0·91, p=0·020, I^2=5%), and stroke (RR 0·66, 0·45–0·97, p=0·034, I^2=0%) compared with standard therapy (figure 4, appendix pp 38–39). In the subgroup of patients undergoing a de-escalation strategy, guided therapy was associated with reductions in any bleeding (RR 0·81, 0·68–0·96, p=0·018, I^2=0%) and minor bleeding (RR 0·77, 0·64–0·91, p=0·0031, I^2=0%) compared with standard therapy (figure 4, appendix pp 38–39).

Discussion

The results of this meta-analysis of data from 20743 patients showed that, compared with standard antiplatelet therapy, the use of platelet function testing or genetic testing to guide the selection of antiplatelet therapy in patients undergoing PCI reduced the risk of major adverse cardiovascular events. Moreover, in addition to the composite ischaemic outcome of major adverse cardiovascular events, hard individual efficacy outcomes, including cardiovascular death, myocardial



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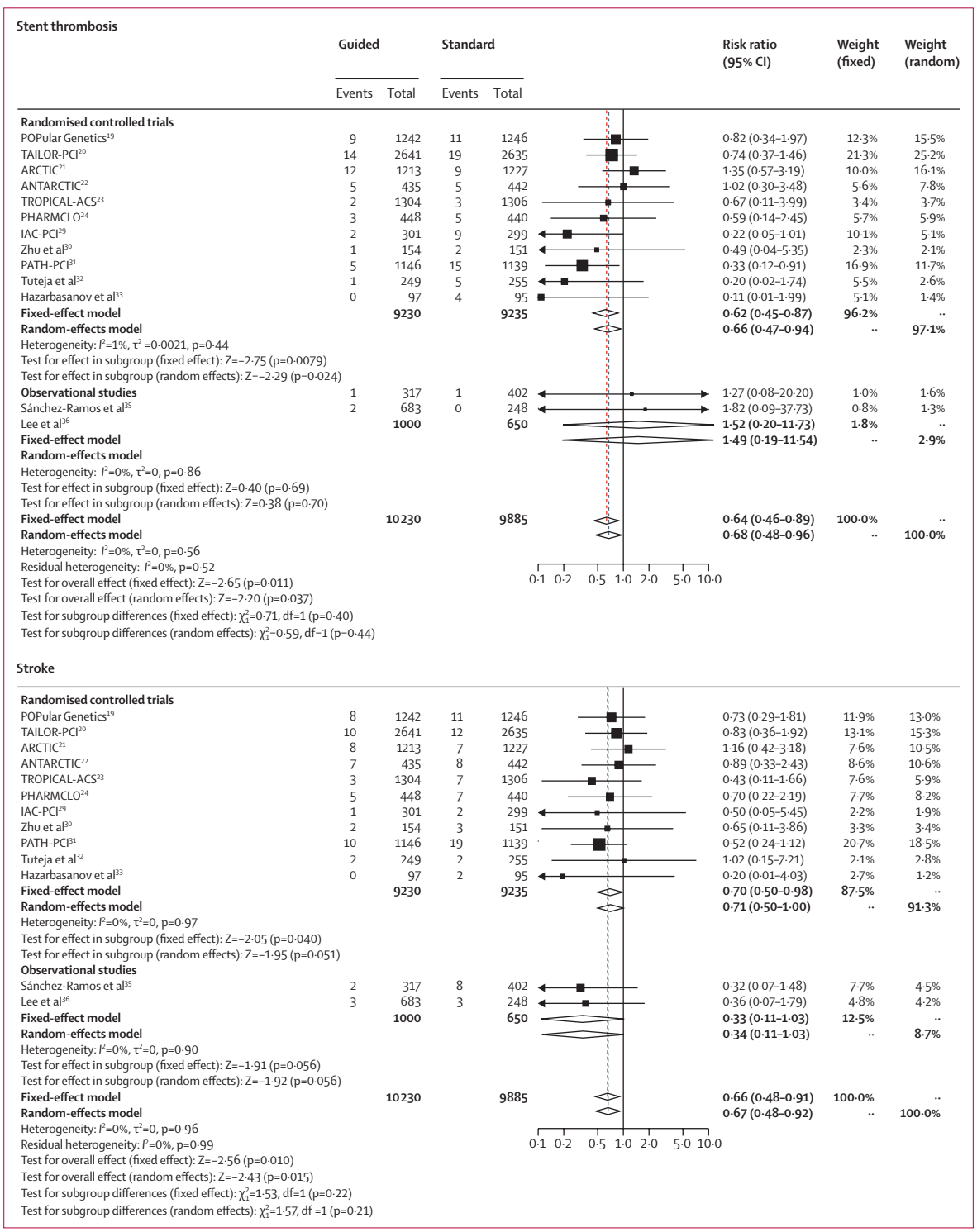
infarction, stent thrombosis, and stroke, were also reduced. Guided selection of therapy was also associated with a non-significant reduction in the endpoint of any bleeding, which became significant when randomised controlled trials only were included in the analysis, driven by a reduction in minor bleeding but no difference in the incidence of major bleeding. Outcomes of guided selection of antiplatelet therapy varied according to the



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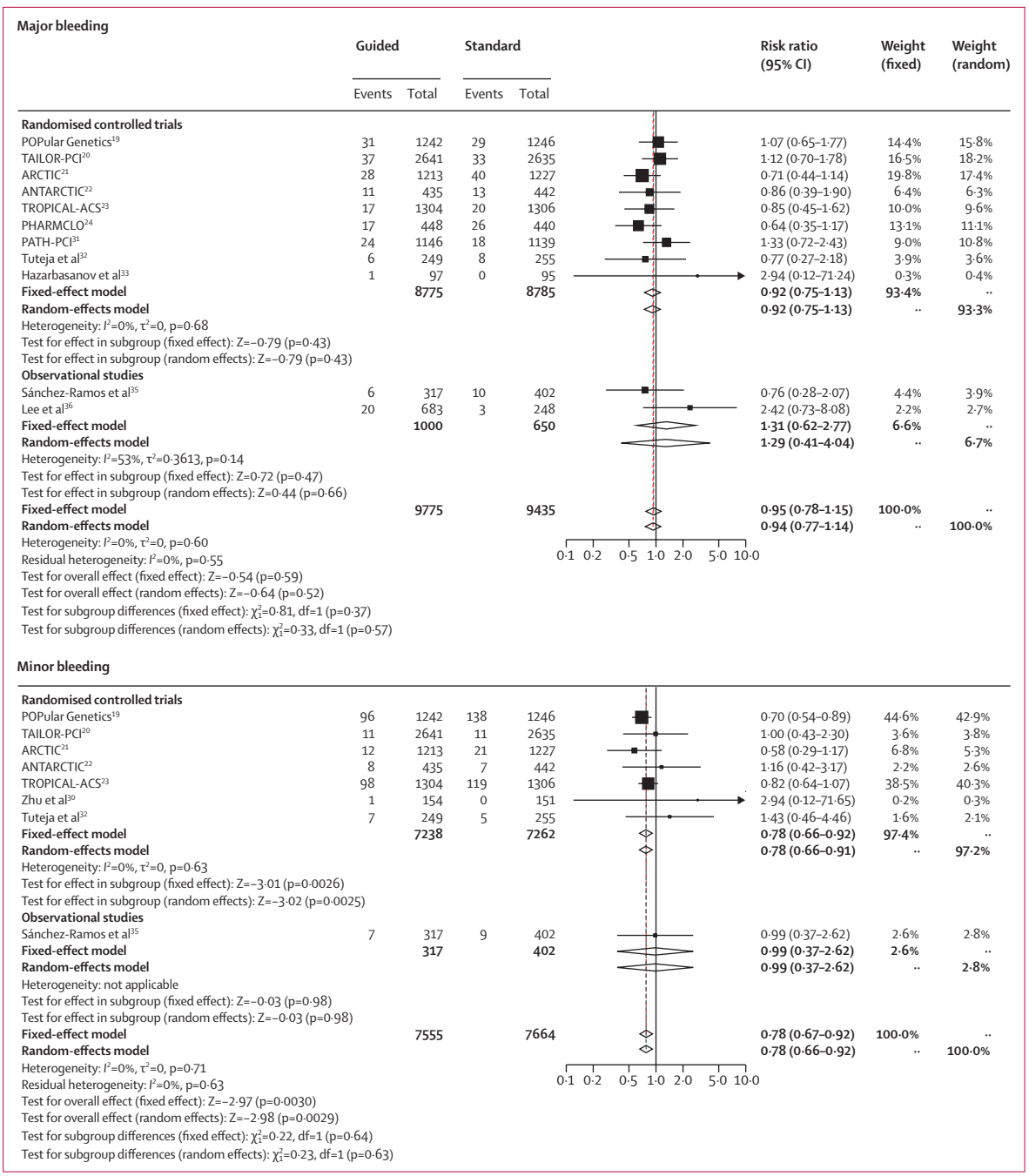

Figure 3: **Pooled analyses of guided versus standard antiplatelet therapy for the secondary efficacy and safety endpoints**

strategy used, with an escalation approach associated with a reduction in ischaemic events without any trade-off in safety, and a de-escalation approach associated with a reduction in bleeding, without any trade-off in efficacy.

Studies showing that the potent $P2Y_{12}$ inhibitors have enhanced ischaemic benefit compared with clopidogrel in patients with HPR or *CYP2C19* loss-of-function alleles, and that clopidogrel is associated with a low risk of ischaemic events and a lower risk of bleeding compared with potent $P2Y_{12}$ inhibitors in patients without HPR or *CYP2C19* loss-of-function alleles support the rationale for implementation of platelet function testing and genetic testing to tailor the selection of antiplatelet agent with the goal of optimising safety and efficacy outcomes.[4,5,7,9,11,14,16] However, results of early randomised controlled trials, such as TRIGGER-PCI and GRAVITAS, which selectively enrolled patients with HPR while receiving clopidogrel, did not show any benefit with a guided approach.[17,18]

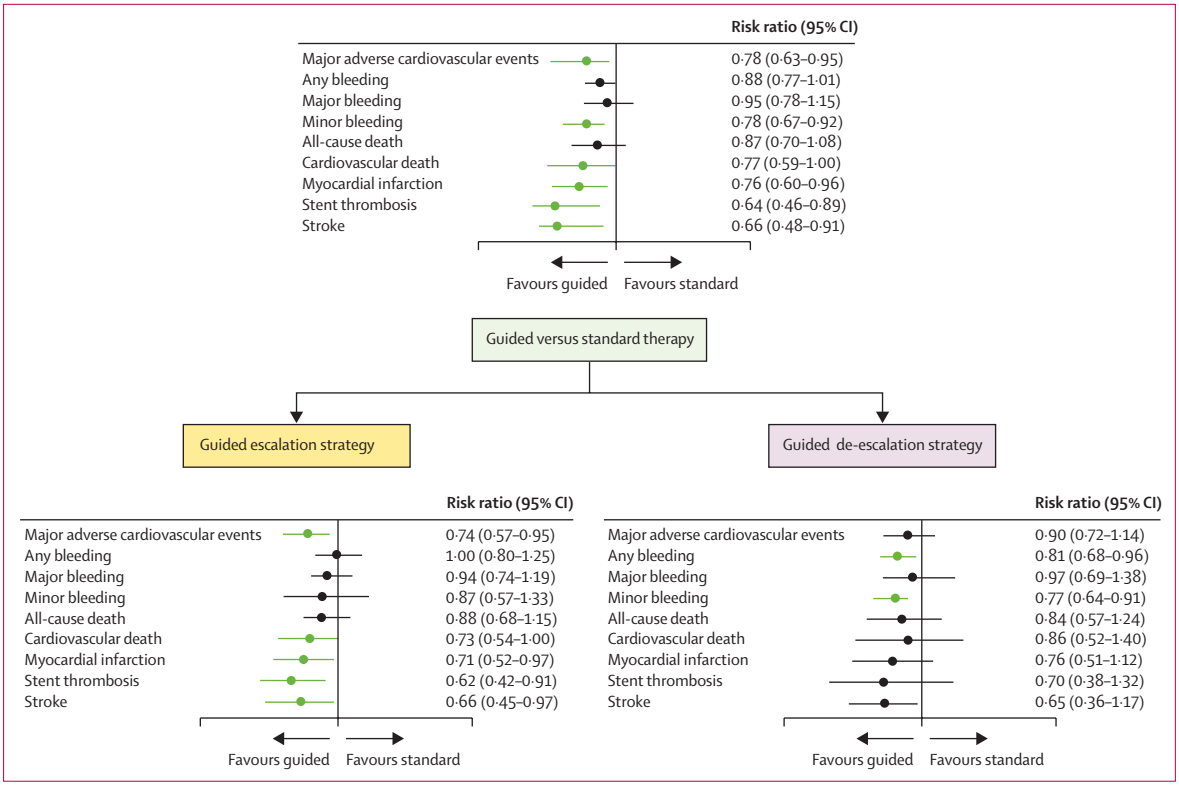

Figure 4: **Summary effect estimates for overall guided versus standard therapy, guided de-escalation strategy versus standard therapy, and guided escalation strategy versus standard therapy**
Significant risk ratios (95% CIs) are shown in green.

Indeed, major pitfalls of these early trials, including the low risk profile of the patient population, inadequate identification of patients with impaired clopidogrel-induced platelet inhibition, and infrequent use of potent $P2Y_{12}$ inhibitors, inevitably did not allow observation of a treatment effect with a guided approach.[4,37] An understanding of the limitations of these earlier studies led to the design of investigations better suited to define the potential benefits of guided selection of antiplatelet therapy.[4]

Following studies investigating a guided approach in patients with HPR or *CYP2C19* loss-of-function alleles, a subsequent line of research investigated the use of platelet function testing or genetic testing as a strategy (ie, to test or not to test) for overall patients undergoing PCI.[4] This latter objective, specifically evaluated in this meta-analysis, is of key clinical relevance because it answers the practical question of whether guided selection of antiplatelet therapy in all patients undergoing PCI is advantageous compared with the current standard of care of an unguided approach. The result of testing guided selection of antiplatelet therapy as a strategy can therefore lead to escalation or de-escalation of $P2Y_{12}$ inhibitor therapy, which may vary according to the clinical setting given that the default antithrombotic approaches in acute coronary syndrome and chronic coronary syndromes are different. In particular, while in acute coronary syndrome the default approach is, in the absence of contraindications, the use of a potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), in chronic coronary syndromes the default approach is clopidogrel. Therefore, in acute coronary syndrome a guided approach would result in de-escalation, the objective of which is to reduce bleeding without compromising efficacy, whereas in chronic coronary syndromes the approach would result in escalation, the objective of which is to reduce thrombotic complications.[4]

Evidence from studies of platelet function testing or genetic testing, taken individually, does not support their routine use to guide the selection of antiplatelet therapy in patients undergoing PCI and such assays are recommended only in selected scenarios in recent guidelines and consensus statements.[2,4] These recommendations stem from the fact that the available studies lacked statistical power to assess an efficacy endpoint composed of hard ischaemic events. Moreover, the primary endpoints of many studies often combined both safety and efficacy outcomes (ie, net adverse events) or included soft ischaemic outcomes (eg, revascularisation) in order to justify their statistical power assumptions, and some studies had a non-inferiority design.[19–23] Meta-analyses are useful to overcome these limitations. This comprehensive meta-analysis,

which pooled data from all the available evidence, showed that guided selection of antiplatelet therapy improved outcomes compared with non-guided selection of antiplatelet therapy. Furthermore, we did additional analyses to distinguish outcomes according to whether a de-escalation or escalation approach was used. This distinction is of clinical importance because each approach aims to achieve different effects on ischaemic and bleeding outcomes; de-escalation aims to reduce bleeding without a trade-off in ischaemic events and escalation aims to reduce ischaemic events without a trade-off in bleeding.[4] Overall, the results of our meta-analysis provide support for the use of guided selection of antiplatelet therapy, by means of platelet function testing or genetic testing, in patients undergoing PCI. Indeed, the use of these tests as an aid to guide therapy should be integrated with other important clinical and procedural variables to enhance the efficacy and safety of the antiplatelet treatment regimen selected for the individual patient.[4,38] The implementation of this strategy could also have a relevant economic impact, by not only improving outcomes but also by reducing costs, especially when guided antiplatelet therapy results in a greater use of clopidogrel or prasugrel, which are currently available in generic formulations.

The optimal choice of test to use, platelet function testing versus genetic testing, represents a topic of debate as each has its advantages and disadvantages.[4] Platelet function testing as a tool to guide therapy has the advantage that it defines the platelet phenotype that is more related to thrombosis.[14] However, platelet function testing has inherent limitations given that it requires patients to be on treatment to define responsiveness and the variability in assay results; also, patients who have HPR after de-escalation would need to escalate to more potent $P2Y_{12}$ inhibitor therapy.[4,14] Indeed, these considerations could represent a challenge for implementation of platelet function testing monitoring in non-specialised centres.[37] Genetic testing for *CYP2C19* loss-of-function alleles, now possible through rapid bedside assays, can overcome some of the above-mentioned limitations given that the genetic make-up of an individual remains unchanged.[4,7] However, multiple factors can contribute to impaired antiplatelet drug response (ie, clopidogrel) and assessment of genetic polymorphisms alone might thus be of limited accuracy to identify patients with HPR status.[4] Integration of clinical variables (eg, age, body-mass index, chronic kidney disease, diabetes) with genotypes to predict HPR status have been proposed to have greater accuracy than the individual components alone.[38] Indeed, integrating platelet function testing and genetic testing may increase the precision of assessing the pharmacological efficacy of an antiplatelet regimen. However, when considering a guided selection of $P2Y_{12}$ inhibitor therapy, guidelines and consensus documents indicate that the choice between platelet function testing and genetic testing depends on assay availability and local site experience.[2,4] These recommendations are in line with the results of our subgroup analysis that found no differences between platelet function testing and genetic testing.

Our meta-analysis has some limitations. First, the absence of patient-level data prevents assessment of many baseline characteristics related to safety and efficacy outcomes. Second, different cohorts of patients (ie, acute coronary syndrome *vs* chronic coronary syndromes) and procedural characteristics (ie, use of drug-eluting stents) were present among studies. Nevertheless, meta-regression analyses based on year of publication, proportion of patients with acute coronary syndrome, and proportion of patients with drug-eluting stents showed no significant relation between the covariates for all outcomes. Third, two of the included studies used cilostazol[29,30] and three included double-dose clopidogrel[21,33,34] in the guided therapy group. It could be argued that these approaches are not recommended by guidelines in patients undergoing PCI.[1–3] Nevertheless, to overcome this limitation, we did a sensitivity analysis that excluded these strategies. Fourth, an estimated high degree of heterogeneity among studies was found for two of nine included outcomes (ie, major adverse cardiovascular events and myocardial infarction). However, the more conservative random-effects model with inverse variance weighting and our secondary analyses including sensitivity analysis with exclusion of one trial at a time were used to at least partly overcome this limitation. Fifth, in sensitivity analysis with exclusion of one trial at a time or exclusion of studies in which cilostazol or double-dose clopidogrel were used in the guided therapy group, the statistical significance of the result was lost for some of the included outcomes. Nevertheless, this effect largely stems from the relatively low number of events available for hard individual endpoints and from the inclusion of soft ischaemic endpoints (ie, revascularisation) in the trial-defined primary major adverse cardiovascular events. However, the benefit of guided selection compared with standard selection of antiplatelet therapy on hard individual ischaemic endpoints such as myocardial infarction, stent thrombosis, and stroke was consistent in most of the sensitivity, subgroup, and meta-regression analyses. Future umbrella reviews could be useful to provide a more comprehensive synthesis of evidence on this topic.

In summary, in patients undergoing PCI, guided selection of oral antiplatelet therapy by means of platelet function testing or genetic testing significantly improves both composite and hard individual efficacy outcomes including cardiovascular death, myocardial infarction, stent thrombosis, and stroke, with a non-significant reduction in any bleeding driven by a significant reduction in minor bleeding but no difference in major bleeding. Efficacy and safety outcomes varied according to the strategy used, with a de-escalation approach more effective in reducing bleeding risk without any trade-off in efficacy and an escalation approach more effective in reducing ischaemic events without any increase in bleeding

compared with standard therapy. These observations provide support for the use of platelet function testing or genetic testing as tools to guide the selection of antiplatelet therapy in patients undergoing PCI.

Contributors

MG and DJA conceived and designed the study. MG, SB, and DJA independently assessed studies for possible inclusion and collected the data. MG and SB analysed the data. MG, DJA, and DC drafted the manuscript. All authors revised and approved the final version of the manuscript. All authors had full access to all the data in the study. MG and DJA accessed and verified the data and had final responsibility for the decision to submit for publication.

Declaration of interests

DC declares that he has received consulting and speaker's fees from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, and Sanofi, outside the present work. FF declares that he has received consulting fees or honoraria from AstraZeneca, Bayer, and Sanofi. FR declares that he has received honoraria from Chiesi. IP reports consulting and speaker's fees from Abiomed, Amgen, AstraZeneca, Bayer, Biotronik, Daiichi Sankyo, Philips, Sanofi, Stentys, and Terumo, outside the present work. DJA declares that he has received consulting fees or honoraria from Abbott, Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company, and has received payments for participation in review activities from CeloNova and St Jude Medical, outside the present work. DJA also declares that his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi Sankyo, Eisai, Eli Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry, Merck, Novartis, Osprey Medical, RenalGuard Solutions, and Scott R MacKenzie Foundation. All other authors declare no competing interests.

Data sharing

Extracted data are available on request to the corresponding author.

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