Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial

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Summary

Background Intracoronary stenting can improve procedural success and reduce restenosis compared with balloon angioplasty in patients with acute coronary syndromes, but can also increase the rate of thrombotic complications including stent thrombosis. The TRITON–TIMI 38 trial has shown that prasugrel—a novel, potent thienopyridine—can reduce ischaemic events compared with standard clopidogrel therapy. We assessed the rate, outcomes, and prevention of ischaemic events in patients treated with prasugrel or clopidogrel with stents in the TRITON–TIMI 38 study.

Methods Patients with moderate-risk to high-risk acute coronary syndromes were included in our analysis if they had received at least one coronary stent at the time of the index procedure following randomisation in TRITON-TIMI 38, and were further subdivided by type of stent received. Patients were randomly assigned in a 1 to 1 fashion to receive a loading dose of study drug (prasugrel 60 mg or clopidogrel 300 mg) as soon as possible after randomisation, followed by daily maintenance therapy (prasugrel 10 mg or clopidogrel 75 mg). All patients were to receive aspirin therapy. Treatment was to be continued for a minimum of 6 months and a maximum of 15 months. Randomisation was not stratified by stents used or stent type. The primary endpoint was the composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Stent thrombosis was assessed using Academic Research Consortium definitions, and analysis was by intention to treat. TRITON-TIMI 38 is registered with ClinicalTrials.gov, number NCT00097591.

Findings 12 844 patients received at least one coronary stent; 5743 received only drug-eluting stents, and 6461 received only bare-metal stents. Prasugrel compared with clopidogrel reduced the primary endpoint (9·7 *vs* 11·9%, HR 0·81, p=0·0001) in the stented cohort, in patients with only drug-eluting stents (9·0 *vs* 11·1%, HR 0·82, p=0·019), and in patients with only bare-metal stents (10·0 *vs* 12·2%, HR 0·80, p=0·003). Stent thrombosis was associated with death or myocardial infarction in 89% (186/210) of patients. Stent thrombosis was reduced with prasugrel overall (1·13 *vs* 2·35%, HR 0·48, p<0·0001), in patients with drug-eluting stents only (0·84 *vs* 2·31%, HR 0·36, p<0·0001), and in those with bare-metal stents only (1·27 *vs* 2·41%, HR 0·52, p=0·0009).

Interpretation Intensive antiplatelet therapy with prasugrel resulted in fewer ischaemic outcomes including stent thrombosis than with standard clopidogrel. These findings were statistically robust irrespective of stent type, and the data affirm the importance of intensive platelet inhibition in patients with intracoronary stents.

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Introduction

Intracoronary stents are an important advance in the care of patients with coronary artery disease who undergo percutaneous coronary intervention. Stent use has resulted in greater procedural success and lower rates of post-procedure restenosis than has balloon angioplasty,[1,2] although coronary stents are associated with higher rates of thrombosis. The introduction of dual antiplatelet therapy with aspirin and a thienopyridine has resulted in substantial improvements in reducing stent thrombosis compared with aspirin and an oral anticoagulant.[3–5] These benefits suggest that stent-related ischaemic events might be largely related to platelet activation and aggregation. As such, dual antiplatelet therapy has become a cornerstone of the medical regimen for prevention of ischaemic events in patients undergoing percutaneous coronary intervention with stent placement.[6,7] The subsequent introduction of drug-eluting stents greatly reduced the need for repeated procedures for in-stent restenosis compared with bare-metal stents,[8,9] but also extended the period during which patients are at risk for stent thrombosis.[10] Additionally, dual antiplatelet

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See Comment page 1315

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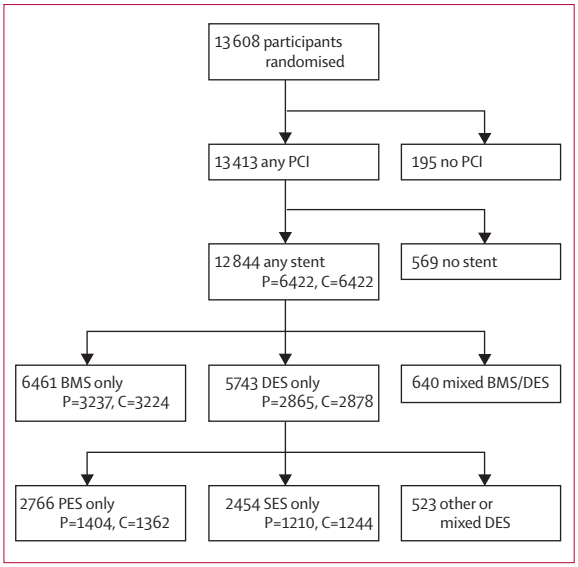

Figure 1: **Distribution of patients in the TRITON–TIMI 38 trial**
PES=paclitaxel-eluting stent. SES=sirolimus-eluting stent. P=prasugrel. C=clopidogrel. 12 844 patients were included in the overall analysis, 6461 patients in the bare-metal stents only analysis, 5743 patients in the drug-eluting stents only analysis, 2766 patients in the paclitaxel-eluting stents only analysis, and 2454 patients in the SES only analysis.

therapy with aspirin and clopidogrel was better than aspirin alone for the reduction of ischaemic events in patients with acute coronary syndromes irrespective of coronary intervention, but seemed particularly beneficial for those with acute coronary syndromes undergoing percutaneous coronary intervention.[11,12]

Despite advances in both devices and pharmacological support for patients with acute coronary syndromes undergoing percutaneous coronary intervention, there remains a persistent risk of ischaemic events. Concerns have arisen about the continued thrombotic risk related to intracoronary stenting, particularly in patients with acute coronary syndromes or those treated outside the indications used in pivotal trials for stent approval.[13–17] Efforts to reduce stent-related thromboses and myocardial infarctions have focused on compliance with dual antiplatelet therapy and on extended durations of therapy.[18] In addition to these concerns, a growing body of evidence suggests that patients have variable responses to clopidogrel[19,20] and that a lesser response to the drug could be a risk factor for ischaemic complications, including myocardial infarction and stent thrombosis after angioplasty.[21–24]

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38 study[25] showed that treatment with prasugrel—a thienopyridine that achieves greater, more rapid, and more consistent platelet inhibition than clopidogrel[26]—resulted in a 19% reduction in the composite primary endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke in patients with acute coronary syndromes with planned percutaneous coronary intervention. This reduction in ischaemic events with prasugrel compared with clopidogrel was at a cost of higher rates of TIMI major bleeding not related to coronary artery bypass grafting,[25] and though rare, higher rates of life-threatening and fatal bleeding. In view of the benefit of aspirin and thienopyridines in preventing thrombotic complications in patients undergoing percutaneous coronary intervention,[27–30] we postulated that prasugrel would show reductions in stent-related thrombotic complications and new ischaemic complications not related to stents. We therefore examined the rates of ischaemic events and stent thrombosis in TRITON–TIMI 38 and the size and timing of the effects of prasugrel compared with clopidogrel in patients receiving different types of intracoronary stents.

Methods

Patients

The TRITON–TIMI 38 trial enrolled participants who had a range of acute coronary syndromes.[25,31] Individuals could be enrolled with moderate-risk to high-risk unstable angina or non-ST-elevation myocardial infarction (UA/NSTEMI), or with ST-segment-elevation myocardial infarction (STEMI) after medical therapy with coronary anatomy known to be suitable for percutaneous coronary intervention. Patients could also be enrolled with STEMI and planned primary angioplasty irrespective of whether coronary anatomy was known. Key exclusion criteria included a history of bleeding diathesis or use of a thienopyridine within 5 days of enrolment.[25,31] The choice of vessels on which to intervene, devices used (including stent types), and supporting medications other than thienopyridines were at the discretion of the treating physician. Patients were randomised in a 1 to 1 fashion to prasugrel or clopidogrel. Randomisation was not stratified on the basis of stents used or stent type. Patients were to receive a loading dose of blinded study drug (prasugrel 60 mg or clopidogrel 300 mg) as soon as possible after randomisation, followed by daily maintenance therapy (prasugrel 10 mg or clopidogrel 75 mg). Treatment was to be continued for the total duration of a patient's participation in the trial, a minimum of 6 months and a maximum of 15 months; the median duration of therapy was 14·5 months. Outcomes were assessed on an intention-to-treat basis for the total duration of a patient's participation in the trial.

Participants were included in the present analysis if they received at least one coronary stent at the time of the index (enrolment) angioplasty (figure 1). They were classified as having received only bare-metal stents, only drug-eluting stents, or a combination of stent types at the time of the index percutaneous coronary intervention. Patients with a mix of stent types were infrequent (N=640, <5% of the trial population) and were excluded from the separate analysis of each type of stent, since they did not fit clearly into either group.

Procedures

The primary endpoint of TRITON–TIMI 38 was the composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.[25,31] Net clinical benefit was defined as the composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, and non-fatal TIMI major bleeding not related to coronary artery bypass grafting. All components of the endpoints were adjudicated by a clinical events committee blinded to treatment assignment. Enrolment in TRITON–TIMI 38 began in November, 2004, and ended in January, 2007. The data were unblinded in September, 2007.

Because of concerns about stent thrombosis in other studies, particularly with drug-eluting stents, raised in late 2006, the Operations Committee for the TRITON–TIMI 38 trial, blinded to the results of our study, made the decision before the completion of enrolment to assess this issue prospectively, and prespecified analyses of stent thrombosis used here. All cases of cardiovascular death and cardiac ischaemic events were reviewed to assess the presence of stent thrombosis by adjudicators who were unaware of treatment assignment. Stent thrombosis was assessed based on the Academic Research Consortium (ARC) designations of definite, probable, or possible, with the prespecified key endpoint being definite or probable.[32] Definite stent thrombosis was defined as total occlusion originating in or within 5 mm of the stent, or visible thrombus within the stent or within 5 mm of the stent in the presence of an acute ischaemic clinical syndrome within 48 h. Probable stent thrombosis was defined as any unexplained death within the first 30 days or any myocardial infarction, which was related to documented acute ischaemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause. Possible stent thrombosis was defined as any unexplained death from 30 days after intracoronary stenting until end of study follow-up.

Events were assessed using available event reports, discharge summaries, death certificates, autopsy reports, and cardiac catheterisation reports. Cardiac catheterisation films were not reviewed by a core laboratory for the purpose of identifying stent thrombosis. Early stent thrombosis was defined as any event occurring within 30 days of randomisation. This definition was subdivided into acute (<24 h) and subacute (24 h–30 days). Late stent thrombosis was defined as occurring more than 30 days after randomisation, and was tested by use of landmark analyses that included all patients alive at 30 days irrespective of whether a previous stent thrombosis had occurred.

Statistical analysis

Baseline characteristics of patients by stent type were compared using the χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables.

	Bare-metal stent only (n=6461)			Drug-eluting stent only (n=5743)		
	Pras n=3237	Clop n=3224	p	Pras n=2865	Clop n=2878	p
Age, median (25%–75%)	60 (53–69)	61 (53–70)	0·17	60 (52–69)	60 (52–69)	0·19
Age ≥75 years	13%	14%	0·41	13%	12%	0·35
NSTEMI/unstable angina	68%	67%	0·54	82%	82%	0·44
Sex (men)	74%	73%	0·62	75%	73%	0·018
White	94%	94%	0·45	91%	91%	0·85
Region			0·47			0·37
North America	8%	7%		59%	59%	
South America	7%	7%		1%	1%	
Western Europe	25%	26%		27%	27%	
Eastern Europe	44%	44%		3%	4%	
Africa/Middle East	16%	16%		10%	10%	
History of hypertension	63%	64%	0·69	65%	64%	0·59
History of hypercholesterolaemia	49%	50%	0·74	62%	62%	0·50
History of diabetes	20%	21%	0·63	25%	25%	0·90
Current tobacco use	40%	39%	0·25	37%	38%	0·62
Previous myocardial infarction	16%	16%	0·76	19%	18%	0·19
Previous coronary artery bypass graft	6%	5%	0·19	9%	9%	0·58
Creatinine clearance <60 mL/min*	11%	12%	0·21	10%	10%	0·74
Previous stenosis >50% in past 6 months	2%	1%	0·69	2%	2%	0·88
Antithrombin			0·33			0·51
Unfractionated heparin	67%	68%		61%	60%	
Low molecular weight heparin	8%	7%		9%	9%	
Bivalirudin	1%	1%		6%	6%	
Other/combination	23%	23%		21%	22%	
GPIIb/IIIa inhibitor	45%	45%	0·86	66%	67%	0·53
Multivessel PCI	9%	10%	0·19	16%	14%	0·17
Bifurcation lesion	5%	5%	0·44	7%	8%	0·14
Maximum stent length			<0·01			0·57
≤20 mm	66%	66%		50%	50%	
21–30 mm	25%	23%		29%	30%	
31–40 mm	7%	6%		15%	13%	
>40 mm	3%	4%		6%	7%	
Vessel treated						
Left main	1%	1%	0·99	1%	2%	0·84
Left anterior descending	37%	38%	0·39	46%	46%	0·92
Left circumflex	31%	30%	0·29	31%	29%	0·054
Right coronary artery	38%	39%	0·34	34%	35%	0·36
Saphenous vein graft	3%	3%	0·73	4%	4%	0·28
Arterial grafts	0·4%	0·3%	0·84	0·6%	0·4%	0·33

NSTEMI=non-ST-elevation myocardial infarction. PCI=percutaneous coronary intervention. GP=glycoprotein. *Calculated with the the Cockroft-Gault equation.

Table 1: **Comparison of baseline characteristics of participants randomised to prasugrel compared with clopidogrel, stratified by stent type**

Since randomisation was not stratified by stent type, baseline characteristics were compared between patients by stent type and treatment assignment; statistical testing for differences in outcomes by stent types was not done in this analysis. Survival analyses were used to

	Prasugrel n=6422	Clopidogrel n=6422	Hazard ratio (95% CI)	p
Primary endpoint (CV death/ non-fatal MI/non-fatal stroke)	10%	12%	0·81 (0·72–0·90)	0·0001
CV death/non-fatal MI/UTVR	10%	12%	0·80 (0·72–0·89)	0·0001
CV death/non-fatal MI	9%	11%	0·79 (0·71–0·89)	0·0001
CV death	2%	2%	0·84 (0·66–1·08)	0·17
MI*	7%	10%	0·76 (0·67–0·86)	<0·0001
UTVR	2%	4%	0·68 (0·55–0·84)	0·0003
Revascularisation	4%	6%	0·77 (0·65–0·90)	0·001
TIMI major bleeding†	2%	2%	1·27 (0·99–1·63)	0·06
Death/non-fatal MI/non-fatal stroke/non-fatal TIMI major bleed†	12%	14%	0·86 (0·77–0·95)	0·002

Endpoint rates have been rounded. CV=cardiovascular. MI=myocardial infarction. UTVR=urgent target vessel revascularisation. TIMI=thrombolysis in myocardial infarction. *Fatal or non-fatal. †Not related to coronary bypass surgery.

Table 2: **Clinical events for prasugrel versus clopidogrel in patients with at least one stent**

compare outcomes by treatment assignment (prasugrel *vs* clopidogrel) overall and among different subgroups of patients stratified by stent type. Event rates are reported with Kaplan-Meier failure estimates at 450 days and were compared by the log-rank test. Comparisons are expressed as univariate hazard ratios and 95% CIs including the entire duration of follow-up. To assess for the effect of any differences in baseline characteristics between randomised groups, multivariable analyses were done for the primary clinical endpoint and for stent thrombosis, including any variable which tended to be different between prasugrel and clopidogrel ($p<0·2$) within all stented patient, bare-metal stents only, and drug-eluting stents only. All analyses were done with STATA/SE 9.2 (College Station, TX, USA).

Role of the funding source

The sponsors supported the design and implementation of the main trial from which these results are obtained. All analyses were done by the TIMI Study Group using an independent copy of the complete clinical trial database. The authors wrote all drafts of the manuscript and take responsibility for its content. The sponsors had the opportunity to review and comment on this manuscript, but had no editorial authority. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 13 608 patients enrolled in the TRITON–TIMI 38 trial, 12 844 (94%) received at least one stent. This subset included 6461 who received bare-metal stents only, 5743 who received drug-eluting stents only, and 640 who received both bare-metal stents and drug-eluting stents at the time of the index procedure. Patients who received drug-eluting stents only were more likely to have been enrolled in North America, to have presented with UA/NSTEMI, and to have had previous coronary artery disease, myocardial infarction, or coronary artery bypass grafting surgery than those receiving bare-metal stents only. They were also more likely to have longer stent lengths (>20 mm), multivessel percutaneous coronary intervention, left main or left anterior descending percutaneous coronary intervention, or bifurcation lesions. Patients with drug-eluting stents only were more likely to have used glycoprotein IIb/IIIa antagonists during the index hospitalisation, and to have received the loading dose of study drug during percutaneous coronary intervention than those receiving bare-metal stents only. Baseline characteristics were well balanced between patients randomly assigned prasugrel or clopidogrel within the separate bare-metal stents and drug-eluting stents only groups (table 1).

Overall, a 19% reduction in the primary endpoint was recorded with prasugrel compared with clopidogrel in

	Bare-metal stent only				Drug-eluting stent only			
	Prasugrel n=3237	Clopidogrel n=3224	Hazard ratio (95% CI)	p	Prasugrel n=2865	Clopidogrel n=2878	Hazard ratio (95% CI)	p
Primary endpoint (CV death/non-fatal MI/non-fatal stroke)	10%	12%	0·80 (0·69–0·93)	0·003	9%	11%	0·82 (0·69–0·97)	0·019
CV death/non-fatal MI/UTVR	10%	12%	0·82 (0·71–0·95)	0·009	9%	11%	0·78 (0·66–0·92)	0·004
CV death/non-fatal MI	9%	11%	0·79 (0·68–0·92)	0·003	8%	10%	0·80 (0·67–0·95)	0·012
CV death	2%	3%	0·83 (0·60–1·14)	0·25	1%	2%	0·74 (0·49–1·13)	0·16
MI*	8%	10%	0·77 (0·65–0·91)	0·003	7%	9%	0·77 (0·64–0·93)	0·006
UTVR	3%	3%	0·79 (0·59–1·05)	0·10	2%	4%	0·54 (0·38–0·76)	0·0003
Revascularisation	5%	6%	0·80 (0·64–1·00)	0·045	4%	6%	0·73 (0·57–0·94)	0·014
TIMI major bleeding†	2%	2%	1·37 (0·95–1·99)	0·09	2%	2%	1·19 (0·83–1·72)	0·34
Death/non-fatal MI/non-fatal stroke/ non-fatal TIMI major bleed†	12%	14%	0·88 (0·77–1·01)	0·07	11%	13%	0·84 (0·72–0·98)	0·025

Endpoint rates have been rounded. CV=cardiovascular. MI=myocardial infarction. UTVR=urgent target vessel revascularisation. TIMI=thrombolysis in myocardial infarction. *Fatal or non-fatal. †Not related to coronary bypass surgery.

Table 3: **Clinical events for prasugrel versus clopidogrel stratified by stent type**

the cohort of patients who had a stent (9·7% *vs* 11·9%, HR 0·81, p=0·0001). Additional clinical outcomes for all patients with stents are shown in table 2. Significantly lower rates of the composite of cardiovascular death, non-fatal myocardial infarction, or urgent target vessel revascularisation, myocardial infarction alone, and urgent target vessel revascularisation alone, were seen in patients receiving prasugrel than those receiving clopidogrel. Overall, a higher rate of TIMI major bleeding not related to coronary artery bypass grafting was seen for prasugrel than for clopidogrel, but this difference was not significant (2·4 *vs* 1·9%, HR 1·27, p=0·06). The net benefit, defined as the composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, and non-fatal TIMI major bleeding not related to coronary artery bypass grafting, significantly favoured prasugrel treatment in this cohort (12·0 *vs* 13·7%, HR 0·86, p=0·002).

When patients were divided into those who received either bare-metal stents only or drug-eluting stents only (table 3) the benefits of prasugrel compared with clopidogrel were similar to those for the all stent cohort. For patients in the bare-metal stents only group, a 20% relative reduction (10·0 *vs* 12·2%, HR 0·80, p=0·003) was reported in the primary endpoint favouring prasugrel. Similarly, in patients receiving only drug-eluting stents, an 18% relative reduction (9·0 *vs* 11·1%, HR 0·82, p=0·019) was noted in the primary endpoint favouring prasugrel. Analyses of the primary endpoint remained significant after multivariable adjustment for imbalances in baseline characteristics between randomised treatment groups. In each stent group, myocardial infarction was reduced by 23%. A similar net clinical benefit was seen with prasugrel for each stent group. Major bleeding was directionally, but not significantly, increased in both the drug-eluting stents and bare-metal stents groups with prasugrel. No significant interaction between treatment and stent type (drug-eluting stents only or bare-metal stents only) was observed for clinical endpoints. When patients in the drug-eluting stents only group were further divided into those receiving only sirolimus-eluting stents and those receiving only paclitaxel-eluting stents, similar magnitudes of event reduction with prasugrel were recorded. The rate of cardiovascular death, non-fatal myocardial infarction, or nonfatal stroke in patients assigned prasugrel was reduced by 25% (8.9 *vs* 11.9%, HR 0.75, p=0.02) in those treated with paclitaxel-eluting stents only, and by 21% (8.2 *vs* 10.5%, HR 0.79, p=0.08) in those treated with sirolimus-eluting stents only.

Stent thrombosis was markedly and significantly reduced by prasugrel in patients with stents, irrespective of the ARC definition used (table 4). When the analysis was limited to definite stent thrombosis, a 58% reduction was seen (0·88 *vs* 2·03%, HR 0·42, p<0·0001) with prasugrel compared with clopidogrel. The endpoint of definite or probable stent thrombosis was reduced by 52% (1·13 *vs* 2·35%, HR 0·48, p<0·0001), and definite, probable, or possible stent thrombosis was reduced by 44% (1·54 *vs* 2·75%, HR 0·56, p<0·0001).

	Prasugrel	Clopidogrel	Hazard ratio (95% CI)	p
Any stent (n=12 844)				
Definite ST	0·88%	2·03%	0·42 (0·31–0·59)	<0·0001
Definite/probable ST	1·13%	2·35%	0·48 (0·36–0·64)	<0·0001
Definite/probable/possible ST	1·54%	2·75%	0·56 (0·43–0·73)	<0·0001
Bare-metal stent only (n=6461)				
Definite ST	0·96%	2·13%	0·44 (0·29–0·69)	0·0002
Definite/probable ST	1·27%	2·41%	0·52 (0·35–0·77)	0·0009
Definite/probable/possible ST	1·77%	2·84%	0·63 (0·45–0·89)	0·007
Drug-eluting stent only (n=5743)				
Definite ST	0·70%	1·92%	0·35 (0·21–0·61)	0·0001
Definite/probable ST	0·84%	2·31%	0·36 (0·22–0·58)	<0·0001
Definite/probable/possible ST	1·13%	2·68%	0·41 (0·27–0·63)	<0·0001
Sirolimus-eluting stent only (n=2454)				
Definite ST	0·42%	1·69%	0·26 (0·10–0·69)	0·004
Definite/probable ST	0·68%	2·10%	0·33 (0·15–0·73)	0·004
Definite/probable/possible ST	0·95%	2·57%	0·38 (0·19–0·76)	0·004
Paclitaxel-eluting stent only (n=2766)				
Definite ST	0·82%	1·95%	0·40 (0·19–0·84)	0·012
Definite/probable ST	0·82%	2·32%	0·33 (0·16–0·68)	0·002
Definite/probable/possible ST	1·16%	2·67%	0·41 (0·22–0·76)	0·004

ST=stent thrombosis. p for interaction=0·23.

Table 4: **Stent thrombosis rates for prasugrel compared with clopidogrel using Academic Research Consortium definitions and stratified by stent type**

Reduction in stent thrombosis with prasugrel was consistent and significant for patients treated with bare-metal stents only or drug-eluting stents only (table 4). Analyses of stent thrombosis remained significant after multivariable adjustment for imbalances in baseline characteristics between randomised groups. Of 210 patients with stent thrombosis (definite or probable), 186 (89%) either died or had a myocardial infarction associated with the stent thrombosis event, including 47 (22%) who died as a result of the stent thrombosis; 26 with bare-metal stents only (23%), and 19 (23%) with drug-eluting stents only. Death resulting from stent thrombosis was reported in 18 (0·28%) patients treated with prasugrel and 29 (0·46%) patients treated with clopidogrel (HR 0·62, p=0·11).

Most stent thrombosis events happened while patients were still receiving treatment or within 7 days of discontinuation or interruption of treatment. After more than 7 days after interruption or discontinuation, there were ten definite or probable stent thrombosis events in patients treated with prasugrel and 11 in those treated with clopidogrel. If events that occurred off of the study drug for more than 7 days were excluded from the analysis, a 55% reduction in stent thrombosis in favour of prasugrel was recorded (0·98 *vs* 2·14%, HR 0·45, p<0·0001).

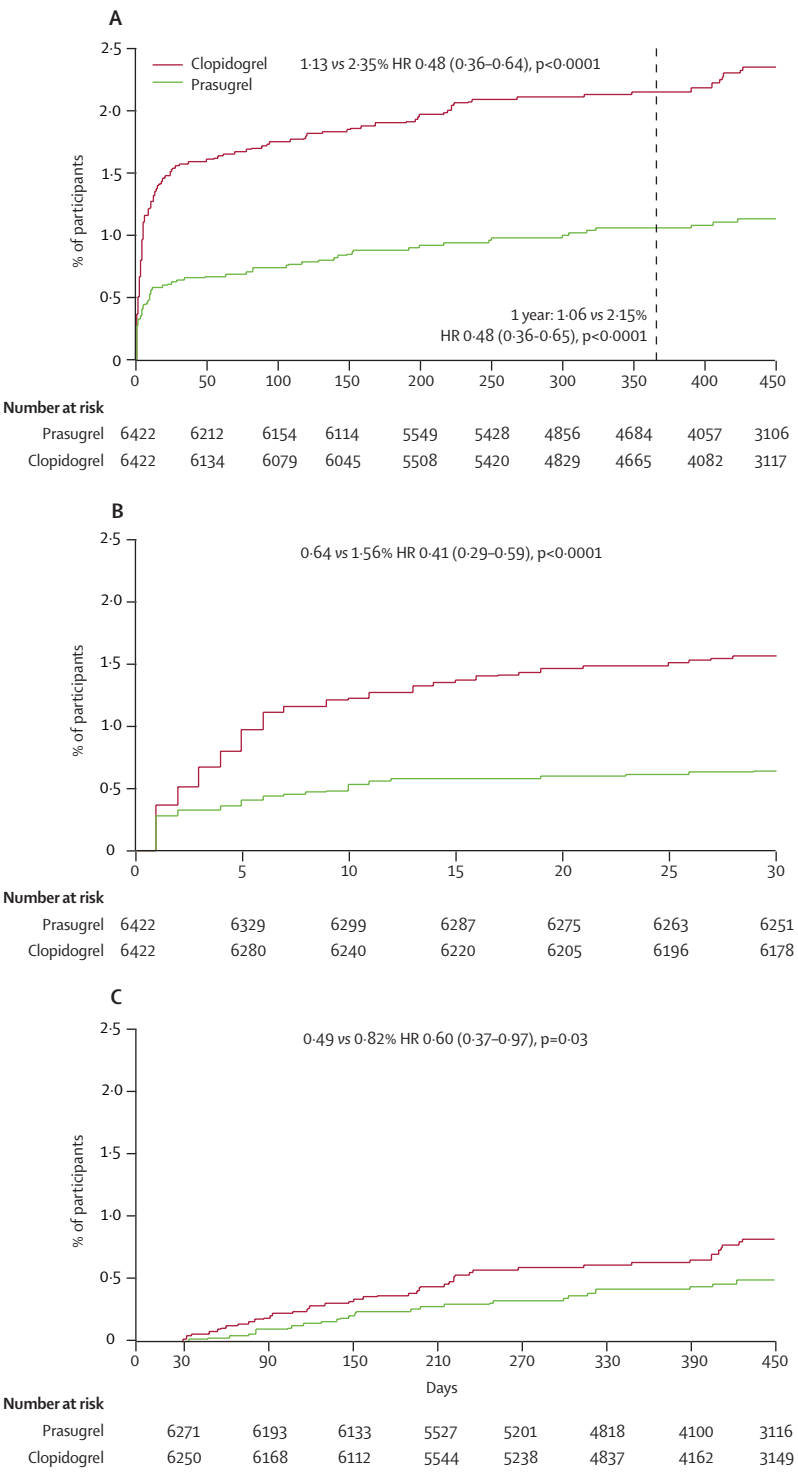

Figure 2: **Kaplan–Meier curves of Academic Research Consortium definite or probable stent thrombosis for all patients receiving at least one intracoronary stent**

(A) Kaplan–Meier curves of stent thrombosis from randomisation (day 0) to day 450 after randomisation. (B) Kaplan–Meier curves of early stent thrombosis from 0–30 days. (C) Kaplan–Meier curves for late stent thrombosis using landmark analysis for all patients alive at 30 days, with events occurring from 0–30 days censored from the analysis.

Stent thrombosis was reduced both early and late after stent placement with prasugrel compared with clopidogrel (figure 2). Within 30 days of stent placement, definite or probable stent thrombosis was reduced by 59% (p<0·0001) and after 30 days by 40% (p=0·03). Early stent thrombosis was significantly reduced in patients with drug-eluting stents only (figure 3B, HR 0·29, p=0·0001) and bare-metal stents only (figure 4B, HR 0·45, p=0·0009). Acute stent thrombosis (<24 h) was infrequent, with limited statistical power to detect a difference, but was numerically but not statistically lower in patients treated with prasugrel than with clopidogrel. Between day 0 and day 3, there was a significant reduction in stent thrombosis with prasugrel in the overall cohort (0·33 *vs* 0·67%, HR 0·49, p=0·006), with significant benefit in the group with drug-eluting stents only (0·14 *vs* 0·63%, HR 0·22, p=0·003), but was not significant for the group with bare-metal stents only (0·40 *vs* 0·72%, HR 0·57, p=0·10). Subacute stent thrombosis (24 h–30 days) was lowered (0·36 *vs* 1·19%, HR 0·30, p<0·0001) with prasugrel for the entire cohort, including for drug-eluting stents only (0·32 *vs* 1·16%, HR 0·27, p=0·0002) and bare-metal stents only (0·38 *vs* 1·24%, HR 0·31, p=0·0001). Reductions for late stent thrombosis (after 30 days) were noted overall (0·49 *vs* 0·82% HR 0·60, p=0·03) for both groups. However, this reduction was significant for patients with drug-eluting stents only (0·42 *vs* 0·91%, HR 0·46, p=0·04), but was not significant for those with bare-metal stents only (0·53 *vs* 0·78%, HR 0·68, p=0·24).

The reduction in stent thrombosis favouring prasugrel was consistent across multiple subgroups (figure 5) with respect to baseline characteristics (age, sex, acute coronary syndromes presentation, creatinine clearance, diabetes, or previous myocardial infarction) and treatment characteristics (glycoprotein IIb/IIIa use, stent length, and presence of bifurcation stenting). As a result of similar relative benefits, the greatest absolute benefits were seen in patients at higher risk for stent thrombosis, such as those with longer stents, bifurcation stents, impaired kidney function, and diabetes. Similar benefit of prasugrel was also seen in patients who received the study drug before percutaneous coronary intervention (0·83 *vs* 2·23%, HR 0·37, p=0·002) or after coronary angioplasty was started (1·24 *vs* 2·39%, HR 0·51, p<0·0001, p for interaction=0·39).

For ischaemic events not related to stent thrombosis (with all stent thrombosis-related events censored from the analysis), a significant reduction in the primary endpoint was still seen with prasugrel compared with clopidogrel (8·7 *vs* 10·3%, HR 0·85, p=0·005).

Discussion

The TRITON–TIMI 38 trial showed that treatment with prasugrel—a thienopyridine that achieves greater, more rapid, and more consistent platelet inhibition than standard dose clopidogrel—resulted in a significant reduction in ischaemic events compared with

clopidogrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention with more bleeding.[25] The present analysis compared prasugrel to clopidogrel in patients receiving coronary stents as part of their index percutaneous coronary intervention and provides information about contemporary outcomes in patients with stents. Stent thrombosis, although infrequent, has severe consequences with high rates of death and myocardial infarction. The present data indicate a consistent reduction in clinical ischaemic events with prasugrel compared with clopidogrel in patients treated with bare-metal stents or drug-eluting stents, and in patients treated with paclitaxel-eluting stents and sirolimus-eluting stents. Additionally, a consistent and significant reduction in stent thrombosis, irrespective of stent type and stent thrombosis definition, and across a broad range of baseline and procedural characteristics shows a robust effect of prasugrel compared with clopidogrel on stent thrombosis. However, a highly significant reduction of ischaemic events remained when events related to stent thrombosis were excluded. Therefore, our data indicate a benefit for intensive antiplatelet therapy in patients with coronary angioplasty for acute coronary syndromes both at the site of and at sites distinct from the coronary stent placement (ischaemic clinical events related to and exclusive of stent thrombosis). As expected, TIMI major bleeding tended to be more frequent in patients assigned to prasugrel than to clopidogrel. Differences in the relative risk of bleeding and rates of bleeding when patients were subdivided by stent type are more likely to represent differences in baseline characteristics and adjunctive medication usage than a direct relation between stent types and bleeding.

Since the minimum duration of therapy in TRITON–TIMI 38 was 6 months, all patients were to be treated with dual antiplatelet therapy for at least the duration of time recommended by the package inserts of all approved stents. As would be expected from the study enrolling moderate-to-high-risk patients with acute coronary syndromes, rates of clinical ischaemic events (including myocardial infarction and stent thrombosis) were higher for patients treated with clopidogrel than in previous reports from pivotal trials for stent approval (largely elective stenting), including analyses that used ARC definitions.[8,32–35] In view of the patient population, a large proportion of stent implantations would be considered as off-label for currently approved drug-eluting stents. The safety and efficacy of off-label stent usage is an area of intense clinical and regulatory interest.[13] The rates of stent thrombosis in TRITON–TIMI 38 were similar to reports of off-label stent use from registries[15–17] or clinical trials using predominantly or exclusively patient populations with acute coronary syndromes.[36–38] Stents were used according to physician preference and no randomisation

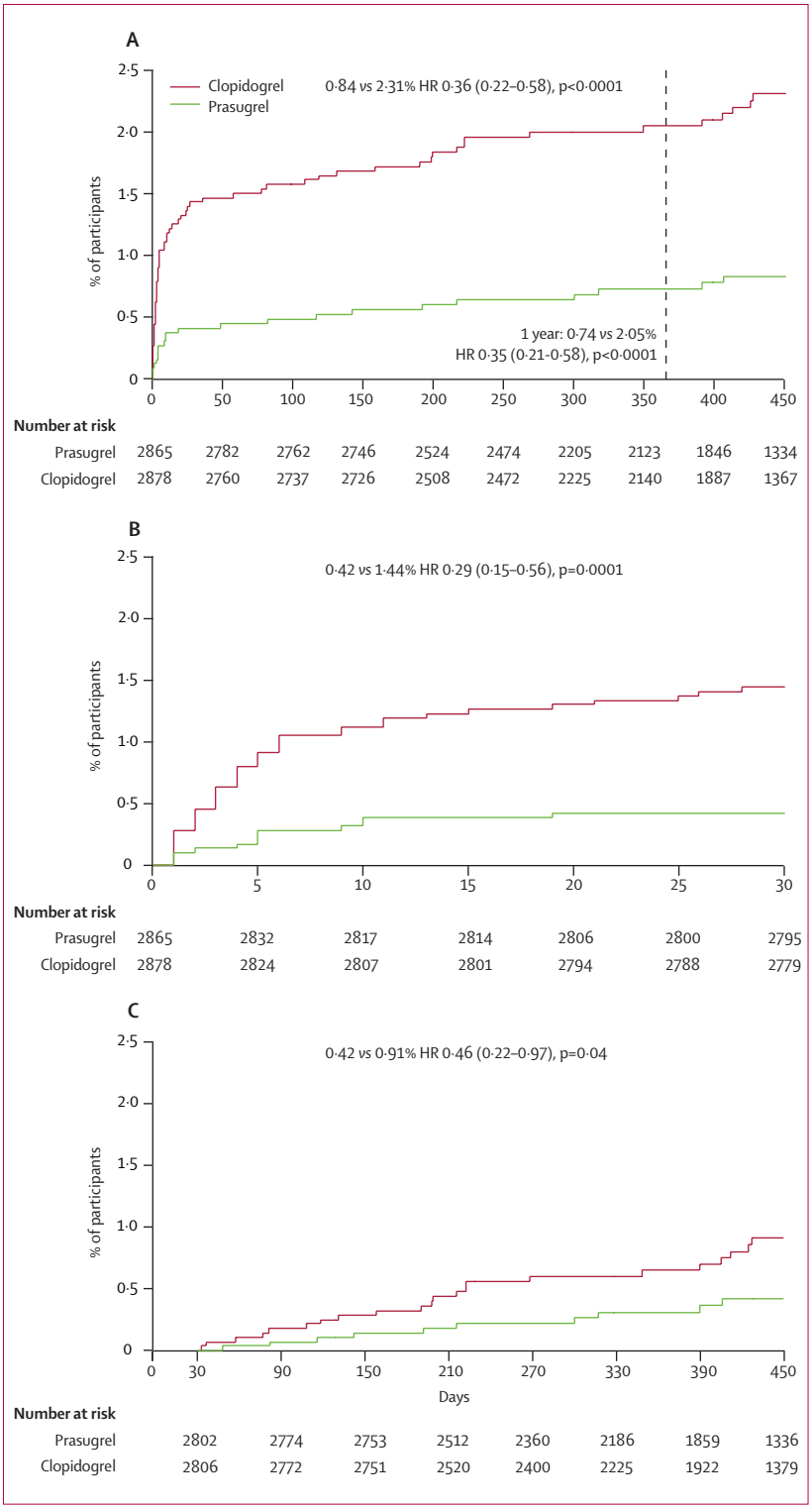

***Figure 3*: Kaplan–Meier curves of Academic Research Consortium definite or probable stent thrombosis for all patients receiving only drug-eluting stents**
(A) Kaplan–Meier curves of stent thrombosis from randomisation (day 0) to day 450 after randomisation. (B) Kaplan–Meier curves of early stent thrombosis from 0–30 days. (C) Kaplan–Meier curves for late stent thrombosis using landmark analysis for all patients alive at 30 days, with events occurring from 0–30 days censored from the analysis.

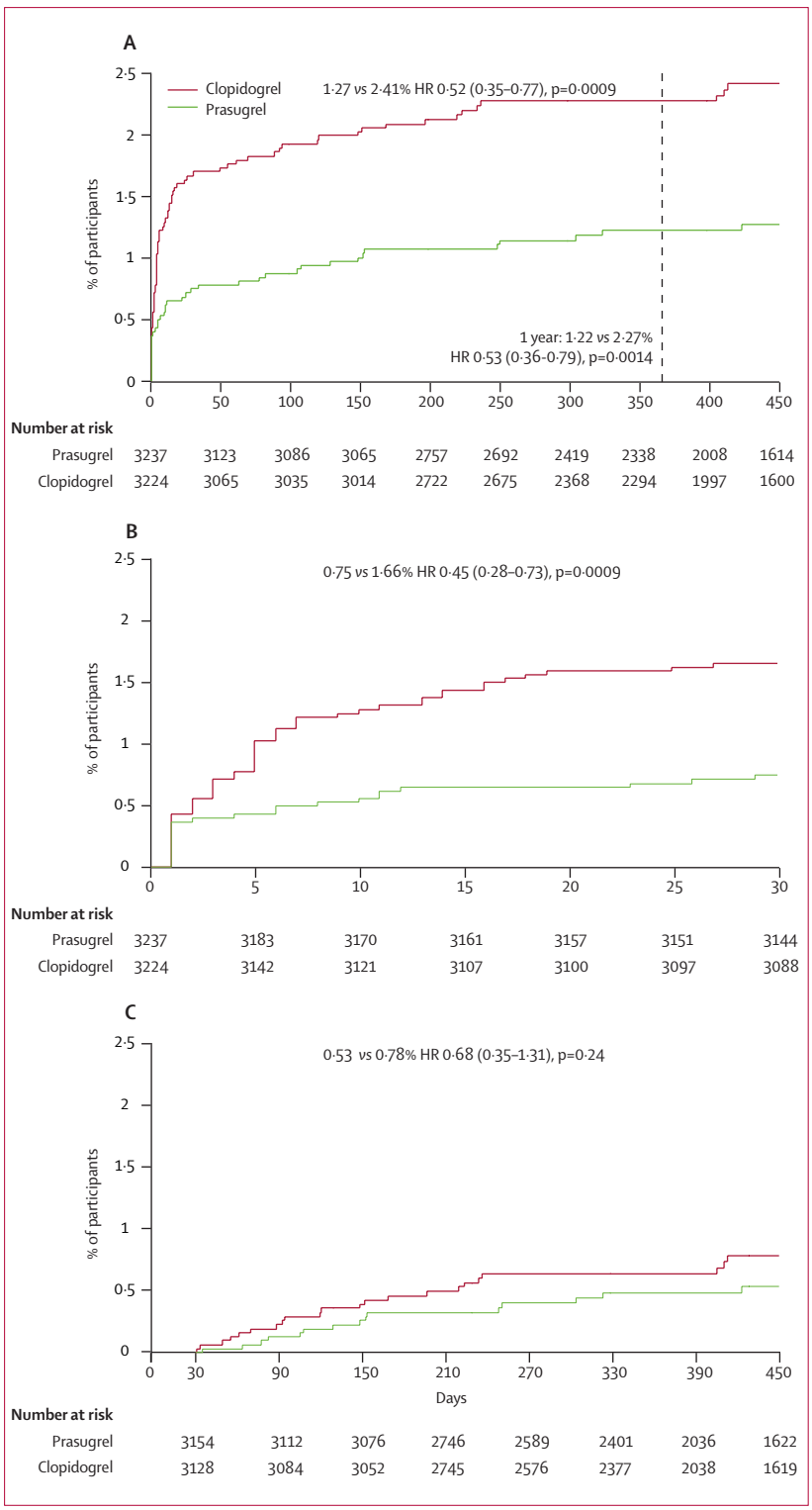

Figure 4: **Kaplan–Meier curves of Academic Research Consortium definite or probable stent thrombosis for all patients receiving only bare-metal stents**

(A) Kaplan–Meier curves of stent thrombosis from randomisation (day 0) to day 450 after randomisation. (B) Kaplan–Meier curves of early stent thrombosis from 0–30 days. (C) Kaplan–Meier curves for late stent thrombosis using landmark analysis for all patients alive at 30 days, with events occurring from 0–30 days censored from the analysis.

between types of stent was done. Although not the focus of this analysis, no clear difference in stent thrombosis events between bare-metal stents and drug-eluting stents was noted. Our analysis of more than 200 cases of ARC definite or probable stent thrombosis also reinforces the severity of stent thrombosis events, with a 22% rate of death and a 89% rate of death or myocardial infarction associated with these events. These findings are similar to those in previously published reports,[32,39] which highlights the importance of strategies to reduce the incidence of such events.

The main goal of our analysis was to compare the two randomised treatments (prasugrel and clopidogrel) on the incidence of thrombotic complications including stent thrombosis. Early discontinuation of clopidogrel in patients with acute coronary syndromes and with stents is a major risk factor for adverse events including stent thrombosis.[40–42] Decisions about stent type[13] and clinical guidelines for antithrombotic therapy have focused on clopidogrel compliance for longer periods than recommended by the stent package inserts.[18] Our analysis, however, indicates that improved outcomes, particularly lower rates of stent thrombosis, can be achieved both early and late with prasugrel than with the studied doses of clopidogrel. More intensive inhibition of platelets with prasugrel resulted in lower rates of stent thrombosis. Although relative reductions were consistent across several subgroups of patients, the absolute benefit in specific groups of patients at higher risk for stent thrombosis was notable. These groups include people with diabetes (1·6% absolute reduction), stents of more than 20 mm in length (1·5% absolute reduction), bifurcation stents (3·2% absolute reduction), and those with myocardial infarction before presentation (2·6% absolute reduction). Our findings suggest that the risk of stent thrombosis can be mitigated by greater intensity of antiplatelet therapy. As would be expected, bleeding rates were not closely related to type of stent used. Clinicians should weigh the absolute and relative risks of ischaemic events and bleeding with long-term antiplatelet therapy when choosing stent types. The potential use of dual antiplatelet therapy with prasugrel, which increases bleeding and improves stent-related ischaemic outcomes to a greater extent than standard therapy, could affect this decision.

Previous studies examined the relation between clinical ischaemic events and platelet inhibition after clopidogrel therapy, and the results have suggested that a limited response to clopidogrel is a risk-factor for adverse outcomes,[22,23,43] particularly stent thrombosis.[21] Prasugrel is a thienopyridine antiplatelet agent that, like clopidogrel, binds to and inhibits the $P2Y_{12}$ receptor, but because of metabolic differences in the generation of the active metabolite, this inhibition occurs more rapidly, consistently, and to a greater extent with prasugrel than with standard or even high-dose

clopidogrel.[44–47] Our data, showing a reduction of stent thrombosis compared with an active control, strongly suggest that increased platelet inhibition results in decreased rates of stent thrombosis irrespective of stent type, and highlight the importance of platelet activation and aggregation as the key components in the development of stent thrombosis.

These data also underscore the importance of long-term intensive antiplatelet therapy in patients with drug-eluting stents. In our analysis, stent thrombosis continued to be seen beyond 3–6 months in patients with both bare-metal stents and drug-eluting stents. The greatest overall reduction in stent thrombosis occurred in the first 30 days; however, a significant reduction in late stent thrombosis (beyond 30 days) was seen for the entire cohort, and for those with drug-eluting stents. This observation supports pathological and mechanistic framework around the risks associated with delayed endothelial healing,[48,49] platelet thrombus adhesion,[50] and suggests that protracted intensive antiplatelet therapy is of continued benefit at the stented site, especially in patients treated with drug-eluting stents. These data could have implications for the long-term management of patients with stents.

TRITON–TIMI 38 was a clinical trial of antiplatelet therapy in patients undergoing percutaneous coronary intervention, not a percutaneous coronary intervention or device trial. Therefore, the amount of information obtained about lesion type and procedural details, although robust, is less than would be expected for a trial of a new stent, and as such we cannot fully exclude subtle procedural differences between treatment groups. The size of the trial and lack of difference in other baseline characteristics between the prasugrel and clopidogrel groups makes any unexpected imbalance unlikely. Stent thrombosis was assessed with clinical information provided by sites and source documentation including catheterisation reports without independent review of catheterisation films. Since the entire process was done by all participants blinded to treatment assignment, including clinical investigators and clinical events committee members, systematic bias is unlikely. The effect of misclassification based on clinical information rather than film review would be to bias results toward the null, suggesting that if any difference would have been seen with full angiogram review, a greater relative effect in favour of intensive antiplatelet therapy would be expected. The design of the TRITON–TIMI 38 trial included a comparison of the approved 300 mg loading dose of clopidogrel and 60 mg of prasugrel administered after the coronary anatomy was known to be suitable for percutaneous coronary intervention. Therefore these data cannot directly address the effects of prasugrel compared with higher-dose clopidogrel or the effects of substantial pretreatment with either agent. However, the full effect of 300 mg clopidogrel would be expected to be present by 6–8 h. Since acute (<24 h) stent thrombosis was infrequent, and substantial reductions in subacute stent thrombosis (24 h–30 days) and consistent reductions after this period were recorded, this finding suggests that speed of onset alone would not account for the reduction of stent thrombosis with prasugrel.

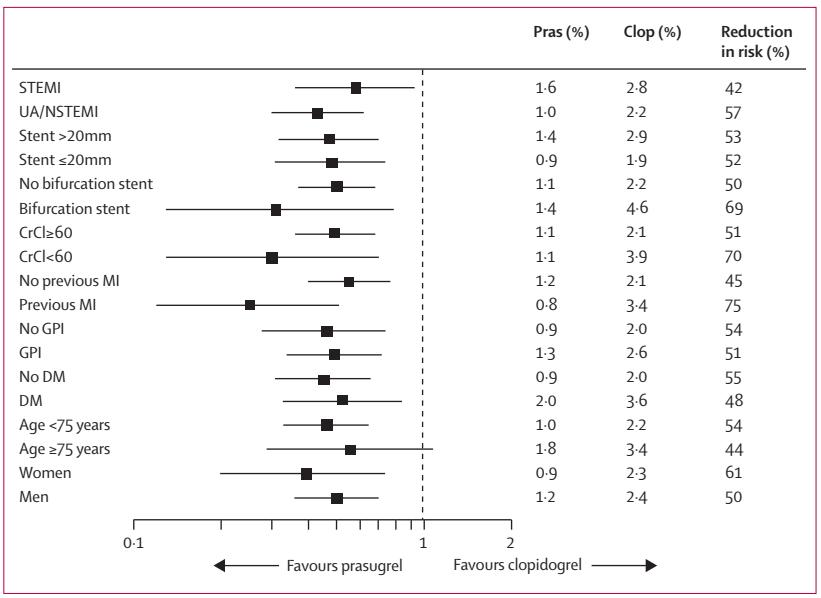

Figure 5: **Effect of prasugrel versus clopidogrel on Academic Research Consortium definite or probable stent thrombosis in key subgroups**

Represents point estimate and 95% CIs for the relative risk of stent thrombosis in patients assigned to prasugrel compared with those assigned to clopidogrel. There was no significant interaction between treatment assignment and subgroup except in patients with previous myocardial infarction (p=0·047). Pras=prasugrel. Clop=clopidogrel. STEMI=ST-segment elevation myocardial infarction. UA/NSTEMI=unstable angina/non-ST-segment elevation myocardial infarction. CrCl=creatinine clearance calculated using the Cockroft-Gault equation, in mL/min. GPI=glycoprotein IIb/IIIa receptor antagonist. DM=diabetes mellitus.

Compared with standard antiplatelet therapy with clopidogrel and aspirin, more intensive antiplatelet therapy with prasugrel and aspirin resulted in lower rates of ischaemic events in patients with acute coronary syndromes receiving coronary stents irrespective of stent type. Stent thrombosis, although infrequent, resulted in serious outcomes including death or myocardial infarction in most patients. Stent thrombosis was reduced substantially and consistently, irrespective of stent type, stent thrombosis definition, or clinical characteristics. Stent thrombosis was reduced both early and late after stent placement in patients randomly assigned prasugrel. Additionally, for patients with stents, significant reductions both in stent thrombosis and in new ischaemic events not related to stent thrombosis were noted. These data highlight the importance of aggressive antiplatelet therapy to reduce ischaemic events in patients with acute coronary syndromes undergoing percutaneous coronary intervention. When balancing risks and benefits of strategies to prevent ischaemic events, consideration should be given to patient characteristics including risk of bleeding and ischaemic events as well as stent and procedural characteristics.

Conflict of interest statement

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