Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data

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Summary

Background Cangrelor is a potent, rapid-acting, reversible intravenous platelet inhibitor that was tested for percutaneous coronary intervention (PCI) in three large, double-blind, randomised trials. We did a pooled analysis of data from three trials that assessed the effectiveness of cangrelor against either clopidogrel or placebo in PCI.

Methods This prespecified, pooled analysis of patient-level data from three trials (CHAMPION-PCI, CHAMPION-PLATFORM, and CHAMPION-PHOENIX) compared cangrelor with control (clopidogrel or placebo) for prevention of thrombotic complications during and after PCI. Trial participants were patients undergoing PCI for ST-elevation myocardial infarction (11·6%), non-ST-elevation acute coronary syndromes (57·4%), and stable coronary artery disease (31·0%). Efficacy was assessed in the modified intention-to-treat population of 24 910 patients, with a prespecified primary efficacy composite of death, myocardial infarction, ischaemia-driven revascularisation, or stent thrombosis at 48 h. The primary safety outcome was non-coronary artery bypass graft-related GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) severe or life-threatening bleeding at 48 h.

Findings Cangrelor reduced the odds of the primary outcome by 19% (3·8% for cangrelor *vs* 4·7% for control; odds ratio [OR] 0·81, 95% CI 0·71–0·91, p=0·0007), and stent thrombosis by 41% (0·5% *vs* 0·8%, OR 0·59, 95% CI 0·43–0·80, p=0·0008). Cangrelor reduced the odds of the secondary triple composite (all-cause death, myocardial infarction, or ischaemia-driven revascularisation at 48 h) by 19% (3·6% *vs* 4·4%, OR 0·81, 95% CI 0·71–0·92, p=0·0014). Efficacy outcomes were consistent across the trials and main patient subsets. These benefits were maintained at 30 days. There was no difference in the primary safety outcome (0·2% in both groups), in GUSTO moderate bleeding (0·6% *vs* 0·4%), or in transfusion (0·7% *vs* 0·6%), but cangrelor increased GUSTO mild bleeding (16·8% *vs* 13·0%, p<0·0001).

Interpretation Compared with control (clopidogrel or placebo), cangrelor reduced PCI periprocedural thrombotic complications, at the expense of increased bleeding.

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Introduction

Percutaneous coronary intervention (PCI) has become the most widely used treatment for myocardial revascularisation. Although PCI is a highly effective therapy across a wide range of clinical presentations, periprocedural thrombotic complications can occur, causing death, myocardial infarction, or stent thrombosis (ST) during or immediately after PCI.[1] Oral platelet $P2Y_{12}$ inhibitors have been shown to reduce the risk of ischaemic events, including death and ST, in patients with acute coronary syndromes (ACS) and in those undergoing PCI.[2–8] These drugs do, however, have several limitations in the acute treatment phase of patients referred for PCI. In the case of clopidogrel and prasugrel, there is a delayed onset of action related to the need for intestinal absorption and metabolic transformation from prodrug to active metabolite. Clopidogrel can also have a variable and often limited efficacy,[9] with irreversible binding to the platelet $P2Y_{12}$ receptor[10] which needs a delay of 5–7 days for washout before coronary artery bypass surgery.[11–14] Additionally, in the setting of acute myocardial infarction, the bioavailability of oral agents might be severely impaired,[15] which reduces the antiplatelet effect at the crucial time when urgent PCI is undertaken.[16–21]

Cangrelor is a novel, intravenous, direct-acting $P2Y_{12}$ receptor antagonist that blocks adenosine diphosphate-induced platelet activation and aggregation. Cangrelor provides fast-onset, potent, and consistent $P2Y_{12}$ inhibition, with reversible binding and a half-life of 3–6 min. The CHAMPION programme consisted of three randomised (1:1), double-blind, double-dummy trials (CHAMPION-PCI,[22] CHAMPION-PLATFORM,[23] and CHAMPION-PHOENIX[24]) designed to test whether a $P2Y_{12}$ treatment strategy of intravenous cangrelor at the time of PCI (30 μg/kg bolus, followed immediately by a 4 μg/kg per min infusion for 2 to 4 h), followed by transition to oral clopidogrel is more effective than control

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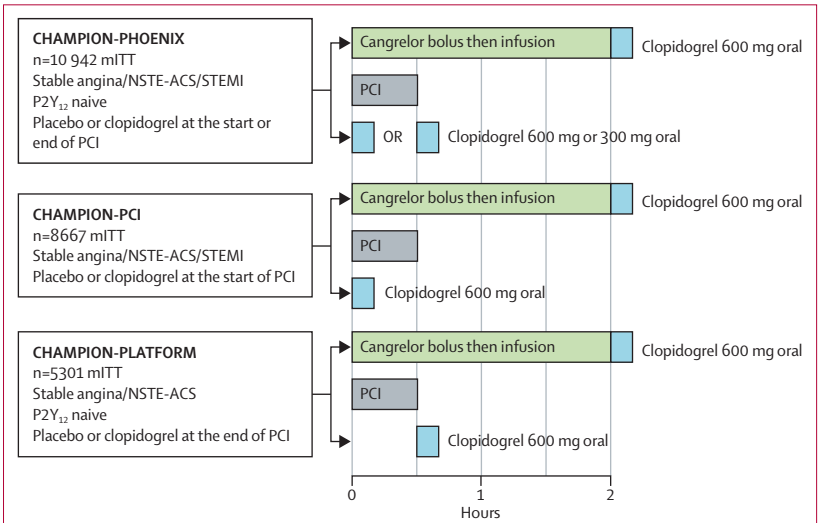

Figure 1: **CHAMPION study designs**
mITT=modified intention-to-treat. NSTE-ACS=non-ST-segment elevation acute coronary syndrome. PCI=percutaneous coronary intervention. STEMI=ST-segment elevation myocardial infarction.

(placebo or oral clopidogrel), given at the beginning or the end of PCI, at reducing the rate of thrombotic events during and immediately after PCI. The individual study results, as well as a retrospective pooled analysis of the CHAMPION-PCI and CHAMPION-PLATFORM studies, have previously been published.[22–25] In this paper, we present the results of a pooled analysis of data from the three trials in the CHAMPION programme, using patient-level data and prespecified event definitions. This analysis was prespecified before the start of the CHAMPION-PHOENIX trial.

Methods

Study design and participants

Our analysis pooled individual patient-level data from three phase 3 trials that compared cangrelor with either clopidogrel or placebo in PCI: CHAMPION-PCI, CHAMPION-PLATFORM, and CHAMPION-PHOENIX. The main differences between the trials related to the timing of clopidogrel administration and the loading dose of clopidogrel, differences in the population (eg,

	CHAMPION-PLATFORM[23]	CHAMPION-PCI[22]	CHAMPION-PHOENIX[24]
Patient population	70% troponin elevated at baseline $P2Y_{12}$ inhibitor naive Placebo or clopidogrel control (all patients received 600 mg) loaded at the end of PCI PCI required with: NSTEMI: troponin elevated UA: ECG changes and pain and age/diabetes Stable angina: capped (15%)	70% troponin elevated at baseline Previous chronic clopidogrel allowed Placebo or clopidogrel control (all patients received 600 mg) loaded at the start of PCI PCI required with: STEMI: ECG changes including persistent (>20 min) ST-segment elevation in ≥2 contiguous leads NSTEMI: troponin elevated UA: ECG changes and pain and age/diabetes Stable angina: capped (15%)	35% troponin elevated at baseline $P2Y_{12}$ inhibitor naive Placebo or clopidogrel (300 mg or 600 mg) loaded at the start (96·5% and 50·5%) or at the end of PCI (3·5% and 49·5%) PCI required (stable angina, NSTE-ACS, STEMI)
Number of patients (mITT)	5301	8667	10 942
Comparator	600 mg clopidogrel Loaded at the end of PCI	600 mg clopidogrel Loaded at the end of PCI	300 or 600 mg (per hospital standard of care) Loaded at the start or at the end of PCI per physician
Endpoint	Primary: death/MI/IDR at 48 h	Primary: death/MI/IDR at 48 h	Primary: death/MI/IDR/ST at 48 h Key secondary: ST at 48 h
MI definition	Not UDMI: reliance on cardiac markers alone to define PCI MI 1 baseline sample Biomarker normal at baseline: MI defined as CK-MB ≥3×ULN post-PCI Biomarker elevated at baseline: elevation in CK-MB ≥3×ULN and 50% increase from baseline sample or ECG changes	Not UDMI: reliance on cardiac markers alone to define PCI MI 1 baseline sample Biomarker normal at baseline: MI defined as CK-MB ≥3×ULN post PCI Biomarker elevated at baseline: elevation in CK-MB ≥3×ULN and 50% increase from baseline sample or ECG changes	UDMI implemented: reliance on cardiac markers and other evidence of ischaemia to define PCI MI 2 baseline samples ≥6 h apart required in NSTE-ACS patients to confirm resolving MI at baseline Baseline normal patients: MI defined as CK-MB ≥3×ULN post PCI Baseline abnormal patients were classified into MI increasing or decreasing at baseline: Increasing: re-elevation in CK-MB post PCI (≥3×ULN and 50% increase from baseline)+additional evidence of ischaemia (2 of 2): ECG changes AND angiographic evidence Decreasing: re-elevation in CK-MB post PCI (≥3×ULN and 50% increase from baseline)+additional evidence of ischaemia (at least 1 of 3): ischaemic symptoms, ECG changes, or angiographic evidence
Stent thrombosis definition	Non-standard definition Angiographic stent thrombosis associated with IDR Confirmed by clinical events committee using angiographic source data	Non-standard definition Angiographic stent thrombosis associated with IDR Confirmed by clinical events committee using angiographic source data	Either definite stent thrombosis as per ARC definition, for post PCI events or intraprocedural stent thrombosis for events occurring within PCI=(any procedural new or worsened thrombus related to the stent, based on angiographic evidence)

ACS=acute coronary syndrome. ARC=Academic Research Consortium. CK-MB=creatine phosphokinase myocardial band. ECG=electrocardiogram. IDR=ischaemia-driven revascularisation. MI=myocardial infarction. mITT=modified intention-to-treat. NSTE-ACS=non-ST-elevation acute coronary syndromes. NSTEMI=non-ST-segment elevation myocardial infarction. PCI=percutaneous coronary intervention. ST=stent thrombosis. STEMI=ST-segment elevation myocardial infarction. UA=unstable angina. UDMI=universal definition of myocardial infarction. ULN=upper limit of normal.

Table 1: **Comparison of design features of the CHAMPION studies**

patients with ST-segment elevation myocardial infarction [STEMI]), and in the outcome definitions.

Eligible patients were men or non-pregnant women 18 years of age or older who required PCI. In CHAMPION-PCI and CHAMPION-PHOENIX, patients with stable angina, non-ST-segment elevation ACS (NSTE-ACS), or STEMI were enrolled, whereas CHAMPION-PLATFORM did not enrol patients with STEMI. Patients provided written informed consent. Major exclusion criteria were receipt of a $P2Y_{12}$ inhibitor or abciximab at any time in the 7 days before randomisation (except for CHAMPION-PCI, in which patients could be taking clopidogrel before randomisation), and receipt of eptifibatide, tirofiban, or fibrinolytic therapy in the 12 h before randomisation.

All three trials were double-blind, double-dummy, and randomised. Therefore, all patients received an intravenous and an oral study drug. In all trials, the intravenous study drug was administered as a bolus (30 μg/kg of cangrelor or matching placebo), followed by an infusion (4 μg/kg per min of cangrelor or matching placebo). The bolus and infusion were to be administered as soon as possible after randomisation after confirmation of suitable anatomy in patients with stable angina or NSTE-ACS. In patients with STEMI, intravenous study drugs could be administered before the coronary anatomy was known. The infusion was to be continued for at least 2 h or until the conclusion of the index PCI, whichever was longer. At the end of the infusion, patients in the cangrelor group received 600 mg of clopidogrel.

The comparator group differed between the three studies. In CHAMPION-PCI, the comparator group was given 600 mg clopidogrel at the start of PCI; in CHAMPION-PLATFORM, clopidogrel 600 mg was given at the end of PCI; and in CHAMPION-PHOENIX clopidogrel 300 mg or 600 mg, as by site standard of care, was to be administered either at the start or at the end of PCI.

Efficacy outcomes

For the purpose of this pooled analysis and as prespecified in CHAMPION-PHOENIX, we used the main composite efficacy outcome of all-cause death, myocardial infarction, ischaemia-driven revascularisation, or stent thrombosis at 48 h. We used the key secondary outcome of stent thrombosis at 48 h. As an additional secondary outcome and as prespecified in CHAMPION-PCI and CHAMPION-PLATFORM, we used the triple composite of all-cause death, myocardial infarction, or ischaemia-driven revascularisation at 48 h. Additional outcomes of interest are each of the individual components of these outcomes and their composites at 48 h and 30 days post-randomisation. In all three trials, the components of the primary efficacy outcome were reviewed and adjudicated by an independent clinical events committee through 30 days after randomisation.

In this pooled analysis, myocardial infarction was defined according to the universal definition, published in 2007,[26] which was the definition used in CHAMPION-PHOENIX, and was prespecified for this pooled analysis. According to this definition, PCI-related myocardial infarction (type 4a) requires categorisation of the patient's baseline status into normal, abnormal, or unknown, based on a combination of ischaemic symptoms, electrocardiogram changes, and biomarker samples, preferably troponin. For patients with normal baseline status, myocardial infarction after PCI is easy to measure (defined as a creatine phosphokinase–myocardial band of mass ≥3×upper limit of normal). For patients with abnormal or unknown baseline (ie, baseline myocardial infarction confirmed or cannot be excluded), more restrictive criteria to define myocardial infarction after PCI were required (defined by a combination of creatine phosphokinase–myocardial band re-elevation with supportive evidence of ischaemia including ECG changes, angiographic evidence, and ischaemic symptoms). For consistency, this definition was applied retrospectively to the adjudicated events from the CHAMPION-PLATFORM and CHAMPION-PCI databases. Specifically, new or recurrent myocardial infarctions as adjudicated by the clinical events committee were considered to meet the universal definition of myocardial infarction when the patient had normal baseline or unknown baseline troponin levels. If baseline troponin levels were abnormal, only Q-wave myocardial infarctions were considered to meet the universal definition of myocardial infarction. In this pooled analysis, PCI-related myocardial infarction was not assessed in patients with STEMI.

Stent thrombosis was categorised using the definition available in each of the trials. In the CHAMPION-PHOENIX trial, stent thrombosis was adjudicated and categorised as either intraprocedural stent thrombosis or,

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	Cangrelor (n=12 475)	Clopidogrel (n=12 435)	Overall (n=24 910)
Age (years)			
Median (IQR)	63·0 (55–71)	63·0 (55–71)	63·0 (55–71)
≥65 years, n (%)	5699/12 475 (45·7%)	5620/12 435 (45·2%)	11 319/24 910 (45·4%)
Men	9035/12 475 (72·4%)	8964/12 435 (72·1%)	17 999/24 910 (72·3%)
Ethnicity*			
White	10 736/12 475 (86·1%)	10 642/12 435 (85·6%)	21 378/24 910 (85·8%)
Asian	952/12 475 (7·6%)	960/12 435 (7·7%)	1912/24 910 (7·7%)
Black/African-American	432/12 475 (3·5%)	448/12 435 (3·6%)	880/24 910 (3·5%)
Hispanic/Latino	279/12 475 (2·2%)	298/12 435 (2·4%)	577/24 910 (2·3%)
Weight, kg			
Median (IQR)	83·0 (72–95)	83·0 (72–95)	83·0 (72–95)
Patient type†			
STEMI	1412/12 475 (11·3%)	1479/12 435 (11·9%)	2891/24 910 (11·6%)
NSTE-ACS	7144/12 475 (57·3%)	7152/12 435 (57·5%)	14 296/24 910 (57·4%)
Stable angina	3919/12 475 (31·4%)	3804/12 435 (30·6%)	7723/24 910 (31·0%)
Baseline cardiac markers >ULN			
Troponin I/T	5783/11 621 (49·8%)	5889/11 565 (50·9%)	11 672/23 186 (50·3%)
CK-MB	3749/11 410 (32·9%)	3791/11 432 (33·2%)	7540/22 842 (33·0%)

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	Cangrelor (n=12 475)	Clopidogrel (n=12 435)	Overall (n=24 910)
(Continued from previous page)			
Medical history			
Diabetes mellitus	3658/12 475 (29·3%)	3711/12 435 (29·8%)	7369/24 910 (29·6%)
Current smoker (within past 30 days)	3575/12 475 (28·7%)	3593/12 435 (28·9%)	7168/24 910 (28·8%)
Hypertension	9468/12 475 (75·9%)	9339/12 435 (75·1%)	18 807/24 910 (75·5%)
Hyperlipidaemia	7458/12 475 (59·8%)	7375/12 435 (59·3%)	14 833/24 910 (59·5%)
Family history of CAD	4799/12 475 (38·5%)	4794/12 435 (38·6%)	9593/24 910 (38·5%)
Stroke/TIA	650/12 475 (5·2%)	620/12 435 (5·0%)	1270/24 910 (5·1%)
Myocardial infarction	2791/12 475 (22·4%)	2908/12 435 (23·4%)	5699/24 910 (22·9%)
Congestive heart failure	1083/12 475 (8·7%)	1101/12 435 (8·9%)	2184/24 910 (8·8%)
Peripheral artery disease	889/12 475 (7·1%)	831/12 435 (6·7%)	1720/24 910 (6·9%)
PTCA/PCI	2889/12 475 (23·2%)	2971/12 435 (23·9%)	5860/24 910 (23·5%)
CABG	1323/12 475 (10·6%)	1258/12 435 (10·1%)	2581/24 910 (10·4%)
Preprocedural medications			
Clopidogrel	1488/12 475 (11·9%)	1472/12 435 (11·8%)	2960/24 910 (11·9%)
Ticlopidine	6/12 475 (0·0%)	8/12 435 (0·1%)	14/24 910 (0·1%)
Periprocedural medications			
Bivalirudin	3135 /12 468 (25·1%)	3175/12 427 (25·5%)	6310/24 895 (25·3%)
Unfractionated heparin	9218 /12 470 (73·9%)	9194/12 421 (74·0%)	18 412/24 891 (74·0%)
LMWH	2865 /12 462 (23·0%)	2901/12 419 (23·4%)	5766/24 881 (23·2%)
Fondaparinux	280 /12 461 (2·2%)	256/12 421 (2·1%)	536/24 882 (2·2%)
Aspirin‡	11 704/12 450 (94·0%)	11 587/12 413 (93·3%)	23 291/24 863 (93·7%)
Glycoprotein IIb/IIIa inhibitor	1542/12 471 (12·4%)	1631/12 431 (13·1%)	3173/24 902 (12·7%)
Bailout IIb/IIIa inhibitor	325/12 471 (2·6%)	420/12 431 (3·4%)	745/24 902 (3·0%)
Routine IIb/IIIa inhibitor	1217/12 471 (9·8%)	1211/12 431 (9·7%)	2428/24 902 (9·8%)
Clopidogrel loading dose§			
300 mg	1405/12 475 (11·3%)	1401/12 435 (11·3%)	2806/24 910 (11·3%)
600 mg	11 070/12 475 (88·7%)	11 034/12 435 (88·7%)	22 104/24 910 (88·7%)
Timing of clopidogrel load§			
Before start of PCI	6914/12 396 (55·8%)	6868/12 359 (55·6%)	13 782/24 755 (55·7%)
During PCI	1659/12 396 (13·4%)	1703/12 358 (13·8%)	3362/24 754 (13·6%)
Within 1 h post PCI	3799/12 396 (30·6%)	3762/12 358 (30·4%)	7561/24 754 (30·5%)
Duration of PCI (min)			
Median (IQR)	20 (11–32)	20 (11–32)	20 (11–32)
Stent type			
Drug-eluting	6666/12 475 (53·4%)	6588/12 435 (53·0%)	13 254/24 910 (53·2%)
Bare-metal	5449/12 475 (43·7%)	5482/12 435 (44·1%)	10 931/24 910 (43·9%)

Data are n (%), n/N (%), or median (IQR). CABG=coronary artery bypass graft. CAD=coronary artery disease. CK-MB=creatine phosphokinase myocardial band. LMWH=low-molecular weight heparin. mITT=modified intention-to-treat population. NSTE-ACS=non-ST-elevation acute coronary syndromes. NSTEMI=non-ST-segment elevation myocardial infarction. PCI=percutaneous coronary intervention. PTCA=percutaneous transluminal coronary angioplasty. STEMI=ST-segment elevation myocardial infarction. TIA= transient ischemic attack. ULN=upper limit of normal. Glycoprotein IIb/IIIa inhibitor used (PCI/platform only), 1473/7025 (21·0%) 1488/6998 (21·3%). *Ethnicity was self-reported. †As determined by statistical analysis, taking into account clinical study data available after time of randomisation. ‡Prior or procedural. §Figures pertain to clopidogrel placebo.

***Table 2*: Patient baseline characteristics and procedure characteristics, according to treatment group in the mITT population**

for events occurring after PCI was completed, as definite stent thrombosis according to the Academic Research Consortium.[27] Intraprocedural stent thrombosis was defined as the development of occlusive or non-occlusive new thrombus in or adjacent to a recently implanted stent before completion of the PCI procedure, and was consistently measured by a blinded angiographic core laboratory who reviewed the index and revascularisation films of all patients. In CHAMPION-PHOENIX, the combination of intraprocedural stent thrombosis and definite stent thrombosis at 48 h was the key secondary outcome. In the CHAMPION-PLATFORM and CHAMPION-PCI trials, stent thrombosis was only assessed in patients with ischaemia-driven revascularisation and had to be confirmed by the clinical events committee using angiographic source data. Stent thrombosis as adjudicated at 48 h and 30 days within each study is included in the pooled efficacy analysis.

Site-reported angiographic complications were collected in all three trials and are pooled for this analysis. These events were adjudicated by an angiographic core laboratory in CHAMPION-PHOENIX only.

Safety outcomes

The primary safety outcome for this pooled analysis was defined as severe bleeding not related to CABG according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria, at 48 h after PCI,[26,28] which was the primary safety outcome of CHAMPION-PHOENIX, while no specific primary safety outcome was defined in the two other trials. In the three trials, bleeding was also assessed using the Thrombolysis In Myocardial Infarction (TIMI) and Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) bleeding scales.[29,30] Bleeding outcomes were not independently adjudicated. Adverse events (serious or not) were also analysed, including dyspnoea (one of the most common adverse events previously reported with cangrelor) and fatal bleeding.

Statistical analyses

All analyses used individual patient-level data. The primary efficacy analysis was conducted in the modified intention-to-treat (mITT) population from pooled data from the three CHAMPION trials, while the safety analyses were performed in the pooled safety population. The mITT population was defined as all patients randomised into the trials who underwent the index PCI and received at least one dose of study drug. The safety population was defined as all patients who were randomised and received any study drug. Treatment classification was based on treatment actually received for the safety analysis.

This pooled analysis was prespecified in the statistical analysis plan of the CHAMPION-PHOENIX trial (section 7.0), which stated that the universal definition of myocardial infarction would be applied for the efficacy outcome. All statistical tests were two-tailed using a level of significance of 0·05.

Heterogeneity between trials was examined using the Breslow–Day test. The primary outcome comparisons were done as event proportions by calculating odds

ratios (ORs) with accompanying 95% CIs according to binomial distribution, which were also used to analyse the secondary outcomes. The χ^2 test was used for calculating p values for comparing proportions and Fisher's exact test was used for sparse data. Heterogeneity of the ORs within subgroup interactions was examined using the Breslow-Day test. Kaplan-Meier curves were generated to compare time-to-event profiles and estimate event rate accounting for censored data for the primary and the key secondary composite outcomes between treatment groups, with the log-rank test used for calculating p values. For the secondary efficacy outcomes and safety analyses, adjustment for multiple comparisons was not done.

Role of the funding source

The studies were designed and undertaken by academic executive committees in conjunction with the sponsor. The corresponding, second, and last authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The study design of the three trials is shown in figure 1, and the main features are summarised in table 1. The pooled mITT population used for the efficacy analysis included 24910 patients (n=12475 cangrelor; n=12435 control), whereas the population used for the safety analysis included 25107 patients (n=12565 cangrelor; n=12542 control). A summary of patient baseline data and procedural characteristics for the mITT population is shown in table 2. 14296 (57·4%) patients had NSTE-ACS, whereas 7723 (31·0%) had stable angina and 2891 (11·6%) had STEMI. Baseline characteristics were balanced between the cangrelor and control arms. Overall, the mean age was 63·0 (IQR 55–71) years: 45·4% of patients were at least 65 years of age, 72·3% were men, and 85·8% were white. The median weight was 83·0 kg. Overall, 29·6% of patients presented with diabetes mellitus, 22·9% had a history of myocardial infarction, and 23·5% had a history of PCI. The median duration of PCI was 20 (IQR 11–32) min, and 53·2% of the patients received drug-eluting stents.

The clinical efficacy outcomes are shown in table 3. At 48 h, cangrelor reduced the odds of the primary composite quadruple outcome by 19% (3·8% for cangrelor *vs* 4·7% for control; OR 0·81, 95% CI 0·71–0·91, p=0·0007). The reduction in thrombotic events was seen early with cangrelor and maintained through transition to oral $P2Y_{12}$ inhibition (figure 2A). Cangrelor reduced the odds of the key secondary outcome of stent thrombosis by 41% (0·5% for cangrelor *vs* 0·8% for control; OR 0·59, 95% CI 0·43–0·80, p=0·0008; figure 2B) and also reduced the odds of the secondary triple composite outcome (death, myocardial infarction, ischaemia-driven revascularisation) by 19% (3·6% in the cangrelor arm *vs* 4·4% in the control arm; OR 0·81, 95% CI 0·71–0·92, p=0·0014; figure 2C) as well as the composite of death, Q-wave myocardial infarction, and stent thrombosis (0·8% *vs* 1·3%, 0·63, 95% CI 0·49–0·81, p=0·0002; figure 2D). When the 48-h primary composite outcome was restricted to death, Q-wave myocardial infarction, and ischaemia-driven revascularisation, the benefit of cangrelor remained, with a 32% reduction (0·8% in the cangrelor arm *vs* 1·2% in the control arm; OR 0·68, 95% CI 0·52–0·87, p=0·0022). Cangrelor also reduced the odds of ischaemia-driven revascularisation by 29% (0·5% *vs* 0·7%; OR 0·71, 95% CI 0·52–0·98, p=0·0363) and myocardial infarction by 15% (3·1% *vs* 3·6%; OR 0·85, 95% CI 0·74–0·97, p=0·0182) at 48 h. There was no significant reduction in death at 48 h, although the number of deaths was lower in patients who received cangrelor (0·3% *vs* 0·4%; OR 0·73, 95% CI 0·47–1·15, p=0·1694).

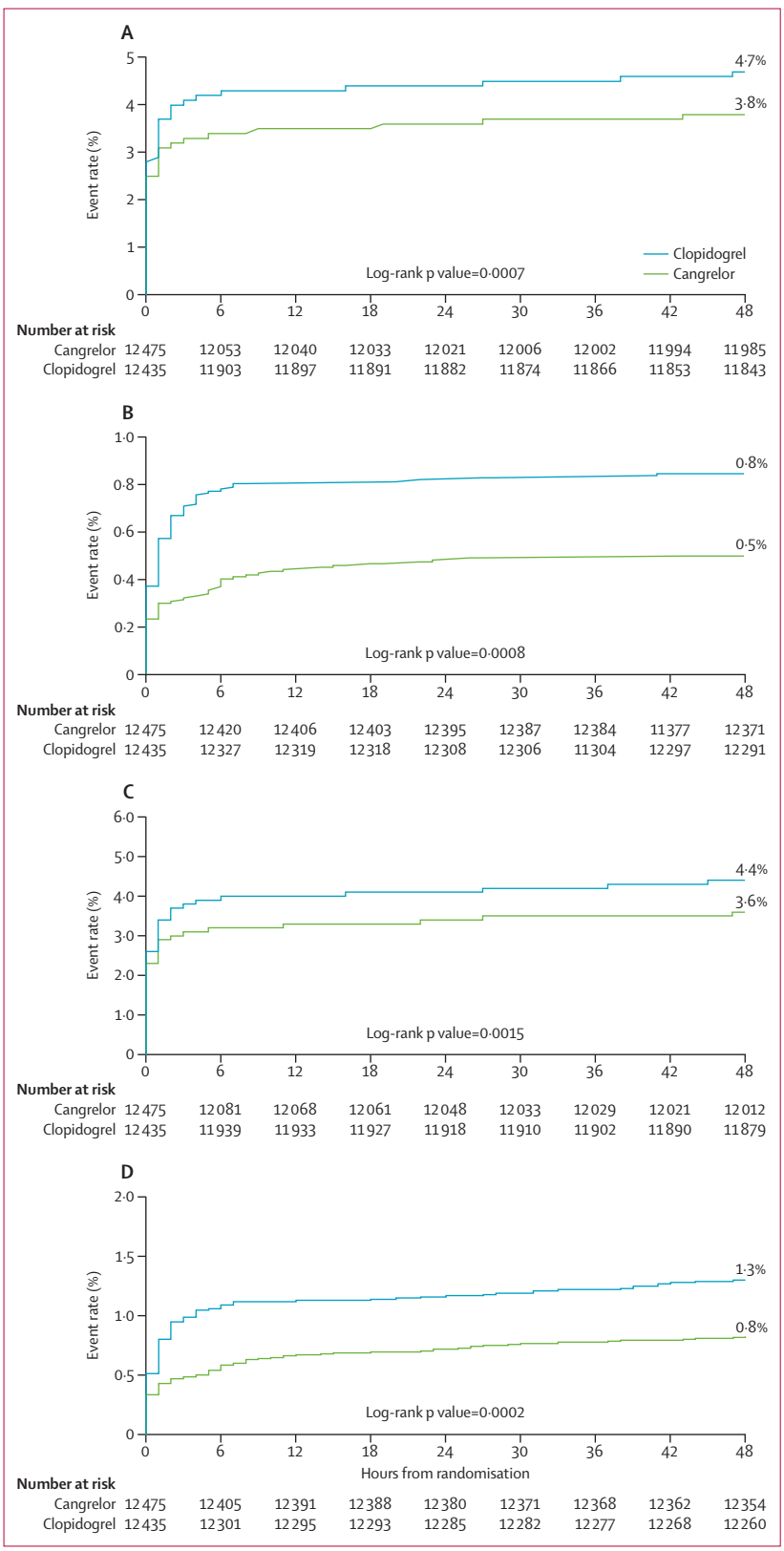
Analysis of the efficacy outcomes at 30 days post-randomisation was consistent with the primary efficacy results (table 3, figure 3). The reductions seen at 48 h

	n/N (%) of patients		Cangrelor *vs* clopidogrel	
	Cangrelor (n=12475)	Clopidogrel (n=12435)	OR (95% CI)	p*
48 h (primary)				
Death/MI/IDR/ST	473/12459 (3·8%)	579/12422 (4·7%)	0·81 (0·71–0·91)	0·0007
ST	62/12459 (0·5%)	105/12422 (0·8%)	0·59 (0·43–0·80)	0·0008
Death/MI/IDR	446/12459 (3·6%)	543/12422 (4·4%)	0·81 (0·71–0·92)	0·0014
Death/Q-wave MI/IDR	102/12459 (0·8%)	150/12422 (1·2%)	0·68 (0·52–0·87)	0·0022
Death	33/12459 (0·3%)	45/12422 (0·4%)	0·73 (0·47–1·15)	0·1694
MI	387/12459 (3·1%)	453/12422 (3·6%)	0·85 (0·74–0·97)	0·0182
IDR	66/12459 (0·5%)	92/12422 (0·7%)	0·71 (0·52–0·98)	0·0363
Q-wave MI	19/12459 (0·2%)	36/12422 (0·3%)	0·53 (0·30–0·92)	0·0211
Death/MI/ST	450/12459 (3·6%)	550/12422 (4·4%)	0·81 (0·71–0·92)	0·0011
Death/Q-wave MI/ST	103/12459 (0·8%)	162/12422 (1·3%)	0·63 (0·49–0·81)	0·0002
Death/MI	414/12459 (3·3%)	495/12422 (4·0%)	0·83 (0·73–0·95)	0·0054
Death/IDR	92/12459 (0·7%)	130/12422 (1·0%)	0·70 (0·54–0·92)	0·0098
Death/ST	89/12459 (0·7%)	140/12422 (1·1%)	0·63 (0·48–0·82)	0·0007
30 days				
Death/MI/IDR/ST	657/12407 (5·3%)	748/12357 (6·1%)	0·87 (0·78–0·97)	0·0099
ST	113/12407 (0·9%)	162/12357 (1·3%)	0·69 (0·54–0·88)	0·0027
Death/MI/IDR	631/12407 (5·1%)	710/12357 (5·7%)	0·88 (0·79–0·98)	0·0218
Death/Q-wave MI/IDR	287/12407 (2·3%)	323/12357 (2·6%)	0·88 (0·75–1·04)	0·1269
Death	137/12407 (1·1%)	141/12357 (1·1%)	0·97 (0·76–1·23)	0·7832
MI	418/12407 (3·4%)	487/12357 (3·9%)	0·85 (0·74–0·97)	0·0165
IDR	153/12407 (1·2%)	178/12357 (1·4%)	0·85 (0·69–1·06)	0·1555
Q-wave MI	31/12407 (0·2%)	51/12357 (0·4%)	0·60 (0·39–0·95)	0·0257
Death/MI/ST	586/12407 (4·7%)	681/12357 (5·5%)	0·85 (0·76–0·95)	0·0049
Death/Q-wave MI/ST	238/12407 (1·9%)	293/12357 (2·4%)	0·81 (0·68–0·96)	0·0139
Death/MI	538/12407 (4·3%)	609/12357 (4·9%)	0·87 (0·78–0·98)	0·0266
Death/IDR	277/12407 (2·2%)	301/12357 (2·4%)	0·91 (0·78–1·08)	0·2895
Death/ST	224/12407 (1·8%)	268/12357 (2·2%)	0·83 (0·69–0·99)	0·0405

Data are n/N (%) unless stated otherwise. A patient who did not complete the scheduled follow-up and had no event was not counted in the denominator. IDR=ischaemia-driven revascularisation. MI=myocardial infarction. OR=odds ratio. ST=stent thrombosis. *p values for OR based on the χ^2 test.

Table 3: **Clinical efficacy outcomes at 48 h and at 30 days**

See Online for appendix



were maintained at 30 days for the primary composite quadruple outcome (5·3% *vs* 6·1%; OR 0·87, 95% CI 0·78–0·97, p=0·0099; figure 3A), for stent thrombosis (0·9% *vs* 1·3%; 0·69, 0·54–0·88, p=0·0027; figure 3B), and the secondary triple composite efficacy outcome (5·1% *vs* 5·7%; 0·88, 0·79–0·98, p=0·0218; figure 3C) as well as for the composite of death, Q-wave myocardial infarction and stent thrombosis (1·9% *vs* 2·4%; OR 0·81, 95% CI 0·68–0·96, p=0·0139; figure 3D). The overall effect of cangrelor versus control and the effect within each of the three trials at 48 h is shown in figure 4. There was no heterogeneity between trials, and none of the interaction p values were significant. The detailed efficacy results by trial and by component of the composite primary outcome are shown in the appendix.

Data for all-cause death at 1 year were collected for the CHAMPION-PCI and CHAMPION-PLATFORM studies only: rates at 1 year did not differ between the cangrelor (3·3%) and control groups (3·7%; OR 0·89, 95% CI 0·75–1·07, p=0·2200).

The benefit of cangrelor on the primary efficacy outcome at 48 h was consistent across all of the prespecified subgroups, including patients with biomarker elevations at baseline, diabetes mellitus, and age 75 years or older (figure 5). The benefits were consistent irrespective of the clinical presentation as STEMI, NSTE-ACS, or stable angina; cangrelor was associated with a consistent reduction in the primary efficacy composite at 48 h in patients undergoing PCI for STEMI (OR 0·84, 95% CI 0·55–1·27, p=0·4104), NSTE-ACS (0·82, 0·68–0·99, p=0·0421), or stable angina (0·77, 0·64–0·93, p=0·0053), with no interaction between treatment effect and clinical presentation (interaction p=0·8663). Analysis of clopidogrel loading dose and timing indicated that cangrelor also reduced the primary quadruple outcome at 48 h in patients treated with a clopidogrel 600 mg loading dose (3·5% *vs* 4·4%; OR 0·80; 95% CI 0·70–0·92, p=0·0013) or in those who received clopidogrel at the start of PCI (4·1% *vs* 4·9%; 0·83, 0·70–0·97, p=0·0212). The benefit of cangrelor on the key secondary outcome of stent thrombosis at 48 h was also consistent across all of the prespecified subgroups (appendix).

The most common angiographic complications across the three trials as reported by the investigators are shown in table 4. Overall, angiographic procedural complications were reduced by cangrelor (OR 0·81, 95% CI 0·71–0·92, p=0·0014), with a marked reduction in new or suspected thrombus, in acute stent thrombosis, and in the need for bailout glycoprotein IIb/IIIa inhibitor.

Figure 2: **Kaplan-Meier curves of the primary, key secondary, and secondary efficacy outcomes at 48 h**
(A) Time to first occurrence of death/MI/IDR/ST. (B) Time to first occurrence of stent thrombosis. (C) Time to death/MI/IDR. (D) Time to first occurrence of death/Q-wave MI/ST. IDR=ischaemia-driven revascularisation. MI=myocardial infarction. ST=stent thrombosis.

Non-CABG-related bleeding events measured at 48 h are shown in table 5. There was no increase in the primary safety outcome of GUSTO severe or life-threatening bleeding with cangrelor. There was also no increase in GUSTO moderate bleeding, in TIMI major bleeding, or in blood transfusions. Cangrelor increased the rate of less severe bleeding events such as GUSTO mild bleeding, TIMI minor bleeding, or ACUITY major or minor bleeding. The increase in ACUITY major bleeding was in part due to increased number of haematomas larger than 5 cm but persisted after exclusion of these haematomas. Although not pre-specified, we analysed the more frequent safety outcome of non-CABG-related GUSTO severe or moderate bleeding, because of the limited number of primary safety outcome events. The results of the subset safety analysis are presented in the appendix. Overall, the safety results seemed consistent across the various subsets, with the exception of a significant interaction suggesting a divergent effect according to number of vessels treated with PCI (with cangrelor reducing the rate of bleeding in patients undergoing multivessel PCI) and periprocedural glycoprotein IIb/IIIa inhibitor use (with cangrelor reducing the rate of bleeding in patients who did receive such agents).

Serious treatment-emergent adverse events were equally frequent in both groups (2·2% in each), but any treatment-emergent adverse events were more frequent with cangrelor (table 6), with an increase in dyspnoea. Treatment discontinuation due to an adverse event was rare in both groups. Dyspnoea-related treatment discontinuations were rare, but more frequent with cangrelor (n=8 [0·1%] *vs* n=0, p=0·0078 by Fisher's exact test). Fatal bleeding occurred in 0·1% of patients in each group.

Discussion

Intravenous cangrelor given at the time of PCI significantly reduced the risk of periprocedural events at 48 h and at 30 days compared with oral clopidogrel or placebo (with deferred clopidogrel given at the end of PCI), including a reduction in the rate of stent thrombosis. This benefit was clear and consistent across the main patient subsets of the trials, including presentation as STEMI, NSTE-ACS, or stable angina. Cangrelor also reduced the risk of procedural angiographic complications. Treatment with cangrelor did not increase the risk of severe bleeding events, as measured by GUSTO severe or life-threatening bleeding, GUSTO moderate rates, or TIMI major bleeding

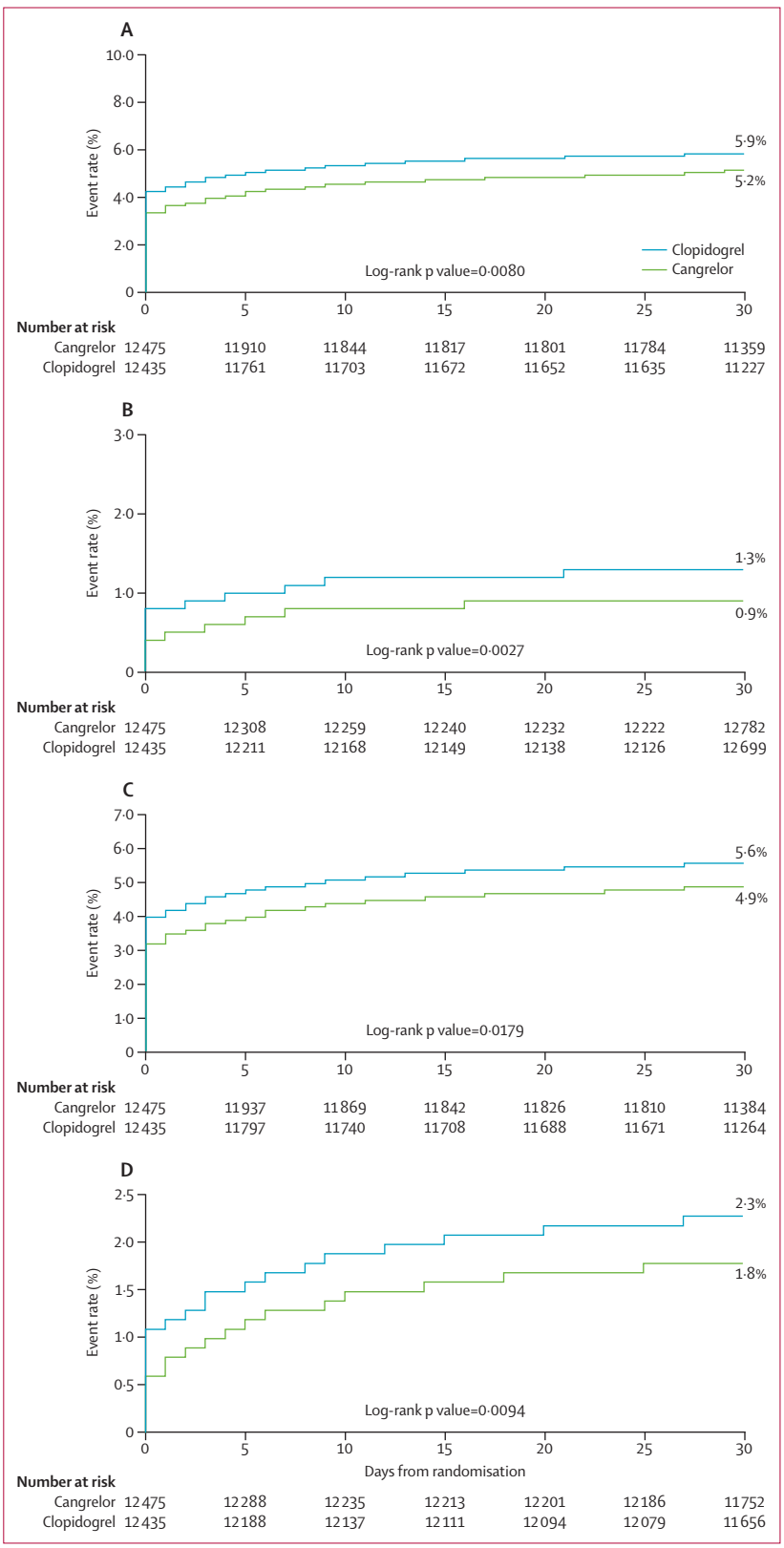


Figure 3: **Kaplan-Meier curves of the primary, key secondary, and secondary efficacy outcomes at 30 days**
(A) Time to first occurrence of death/MI/IDR/ST. (B) Time to first occurrence of stent thrombosis. (C) Time to first occurrence of death/MI/IDR. (D) Time to first occurrence of death/Q-wave MI/ST. MI=myocardial infarction. IDR=ischaemia-driven revascularisation. ST=stent thrombosis.

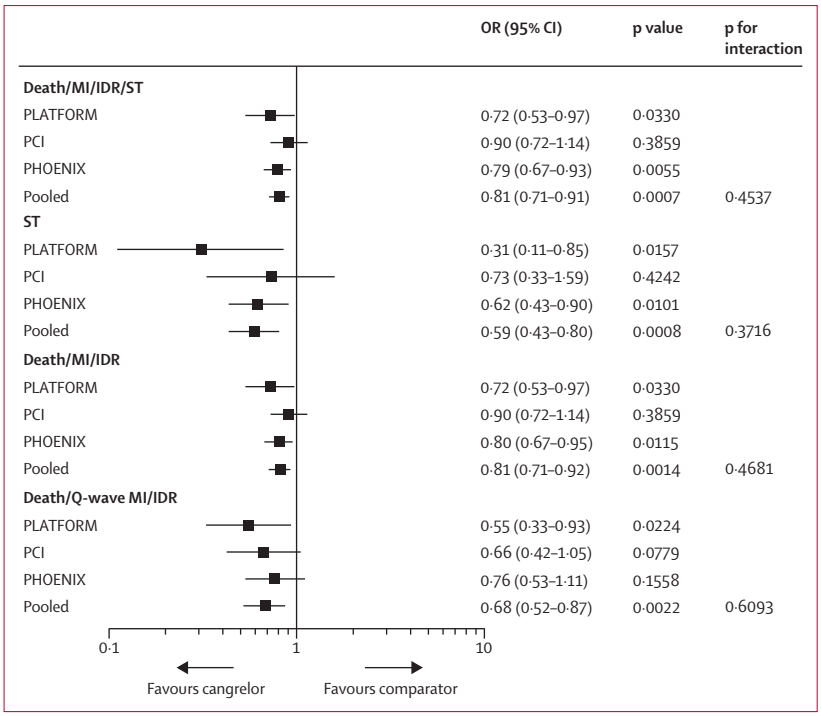


Figure 4: **Forest plot of the primary, key secondary, and secondary outcomes at 48 h, overall and in each of the three trials**
IDR=iscaemia-driven revascularisation. MI=myocardial infarction. ST=stent thrombosis.

rates. It also did not increase the rate of transfusions, but it did increase the rate of less severe bleeding events such as GUSTO mild, TIMI minor, or ACUITY bleeds. The risk of transient dyspnoea was increased with cangrelor, and led to more cases of drug cessation, although in only 0·1% of patients.

Patients with ACS receiving oral platelet $P2Y_{12}$ inhibitors might have several bioavailability issues due to nausea, use of opiates, or impaired perfusion resulting in reduced absorption, and therefore might not derive sufficient antiplatelet effect.[9,15–21] Additionally, multiple sources of variation in clopidogrel pharmacokinetics and pharmacodynamics have been described, resulting in an unpredictable patient response to oral loading doses, especially in an acute setting.[9] Novel oral $P2Y_{12}$ antagonists such as prasugrel or ticagrelor provide more rapid and consistent platelet inhibition than clopidogrel, although recent reports highlight that in the setting of ACS, particularly STEMI, even these agents may require several hours to achieve effective platelet inhibition.[16–21] Lastly, in patients in whom an antiplatelet effect is no longer desirable, such as in patients with bleeding complications after PCI or those needing urgent surgery, the antiplatelet effect is not reversible, or, in the case of ticagrelor, will need several days for reversibility to translate into recovery of platelet function (5 days recommended).[10]

The CHAMPION trials did not test cangrelor against prasugrel or ticagrelor, and the outcome of this comparison is therefore unknown. They also did not test cangrelor against clopidogrel pre-treatment with loading given several hours before PCI, although the clinical benefit of pre-treatment has been questioned.[31] However, cangrelor offers an alternative to loading with oral $P2Y_{12}$ receptor blockers in the acute phase of PCI, with greater potency than clopidogrel, increased speed of onset compared with all oral $P2Y_{12}$ receptor blockers, and the added benefit of flexibility due to its rapidly reversible effect. This flexibility might be of particular interest for ACS or stable patients undergoing coronary angiography but who have not been preloaded with oral agents, either because that is not feasible (as in STEMI) or because clinicians are concerned that angiography could identify an indication for CABG. With cangrelor, CABG can be scheduled without delay given the rapid reversibility of cangrelor, as opposed to the need to wait for 5–7 days with oral agents. Conversely, should there be an indication for PCI, the procedure can be done straight away with immediate effective adenosine diphosphate receptor blockade.

When examining the more frequent GUSTO severe or moderate bleeding events, two subgroups stood out with significant interactions between treatment used and safety: patients with multivessel intervention and patients receiving glycoprotein IIb/IIIa inhibitors. However, these interactions should be interpreted conservatively given the post-hoc definition of the outcome, the large number of subgroups examined without statistical adjustment for multiple comparisons, and the lack of a clear biological explanation, which suggests possible confounding or a chance finding. Irrespective of these points, cangrelor clearly increased bleeding compared with control, although this increase was only apparent when analysing fairly sensitive measures of bleeding, which correspond to less clinically severe events than the predefined primary safety outcome of GUSTO severe or life-threatening bleeding. There was also no increase in the need for transfusions. Although use of transfusions can vary according to geography and practice settings, it is a costly therapy, potentially hazardous, and an important index of clinically important bleeding events. Therefore, the fact that the transfusion requirements were not increased in this pooled analysis is reassuring.

This study has several limitations. First, there was disparity between the control groups across the trials, and in the definition of some outcome events (myocardial infarction and stent thrombosis). The comparator group (with different timings and loading dose of clopidogrel) and the population studied (clopidogrel naive or clopidogrel pretreated; type of ACS) also differed. Specifically, in CHAMPION-PCI, the comparator was clopidogrel, whereas in CHAMPION-PLATFORM and CHAMPION-PHOENIX (for some patients), the comparator was placebo, with deferred administration of clopidogrel given at the end of PCI in the control arm.

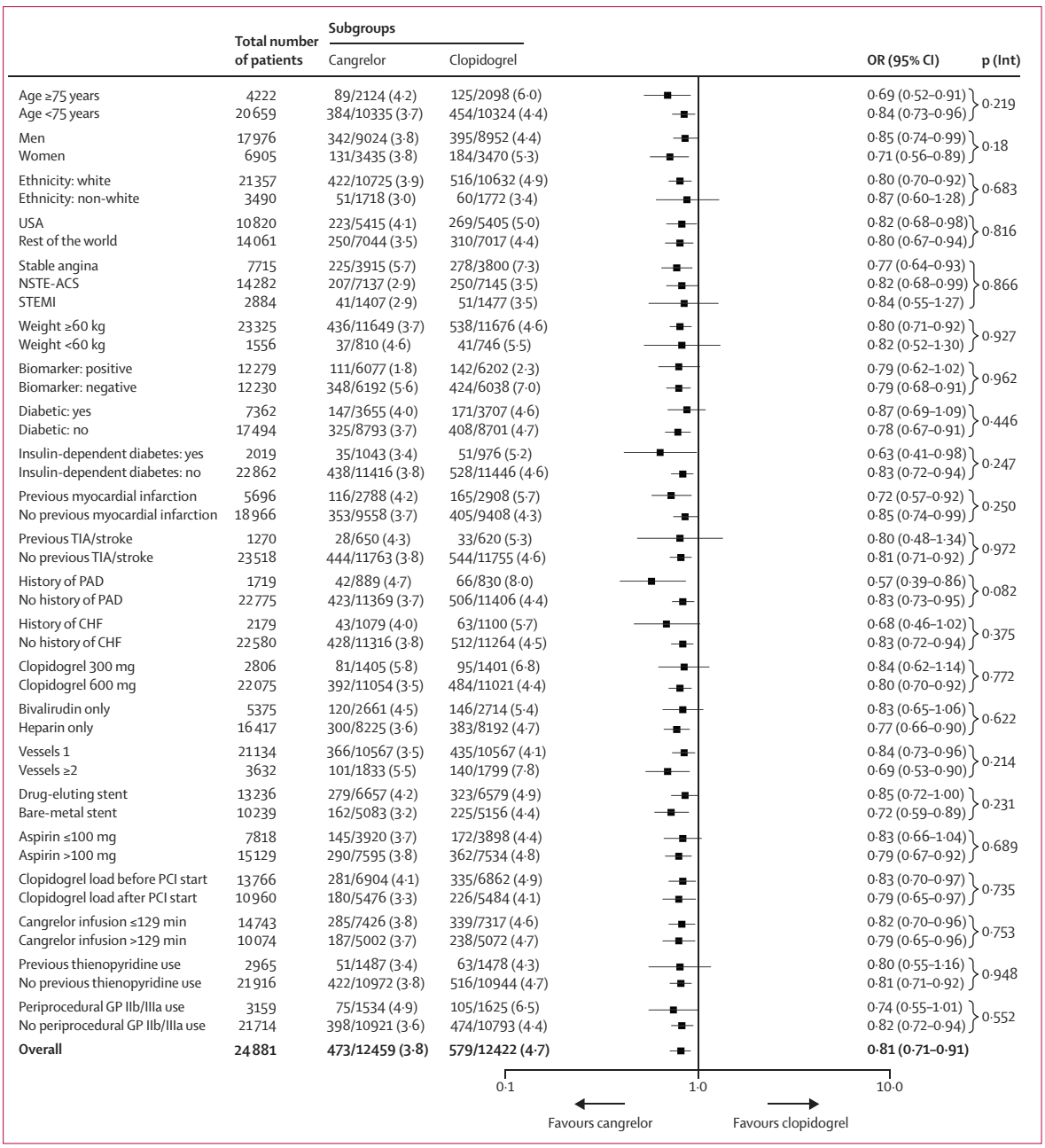


Figure 5: **Forest plot of the primary efficacy outcome in subgroups**
Primary composite outcome of death/myocardial infarction/iscaemia-driven revascularisation/stent thrombosis at 48 h in subgroups. CHF=congestive heart failure. GP=glycoprotein. NSTE-ACS=non-ST-elevation acute coronary syndromes. PAD=peripheral arterial disease. PCI=percutaneous coronary intervention. STEMI=ST-segment elevation myocardial infarction. TIA=transient ischemic attack.

The deferred administration of clopidogrel could have magnified the difference in platelet inhibition between study arms. However, in all three trials, the control arm received a loading dose of clopidogrel at the end of PCI or soon after, and the effect of cangrelor seemed consistent across trials and patient subsets, including timing and dose used for clopidogrel loading, without significant heterogeneity (ie, no interaction was significant). The myocardial infarction component used in the primary analysis also differed among trials: it was the clinical events committee-adjudicated, protocol-specified definition for CHAMPION-PHOENIX,[32] whereas the universal definition of myocardial infarction was used for CHAMPION-PCI and CHAMPION-PLATFORM, defined post-hoc.[26] As clinical practice has evolved, time from admission to angiography has shortened

	n/N (%) of patients		Cangrelor *vs* clopidogrel	
	Cangrelor (n=12 565)	Clopidogrel (n=12 542)	OR (95% CI)	p*
Any procedural event	445/12 465 (3·6%)	542/12 428 (4·4%)	0·81 (0·71–0·92)	0·0014
Threatened abrupt closure	23/6993 (0·3%)	21/6958 (0·3%)	1·09 (0·60–1·97)	0·7754
Abrupt vessel closure	61/12 465 (0·5%)	67/12 428 (0·5%)	0·91 (0·64–1·28)	0·5833
New or suspected thrombus	85/12 465 (0·7%)	116/12 428 (0·9%)	0·73 (0·55–0·97)	0·0267
Acute stent thrombosis	12/12 465 (0·1%)	25/12 428 (0·2%)	0·48 (0·24–0·95)	0·0317
Need for bailout GPI	326/12 561 (2·6%)	422/12 537 (3·4%)	0·76 (0·66–0·89)	0·0003

Data are n/N (%). GPI=glycoprotein IIb/IIIa inhibitor. OR=odds ratio. *p values for OR based on the χ^2 test.

Table 4: **Site-reported angiographic complications**

	Cangrelor (n=12 565)	Clopidogrel (n=12 542)	OR (95% CI)	p*
GUSTO bleeding				
Severe/life threatening	28 (0·2%)	23 (0·2%)	1·22 (0·70–2·11)	0·4875
Moderate	76 (0·6%)	56 (0·4%)	1·36 (0·96–1·92)	0·0828
Severe/moderate	103 (0·8%)	79 (0·6%)	1·30 (0·97–1·75)	0·0762
Mild	2109 (16·8%)	1627 (13·0%)	1·35 (1·26–1·45)	<0·0001
Mild, excluding ecchymosis, oozing, and <5 cm haematoma	707 (5·6%)	515 (4·1%)	1·39 (1·24–1·56)	<0·0001
Any GUSTO bleed	2196 (17·5%)	1696 (13·5%)	1·35 (1·26–1·45)	<0·0001
TIMI bleeding				
Major	32 (0·3%)	28 (0·2%)	1·14 (0·69–1·90)	0·6101
Minor	77 (0·6%)	51 (0·4%)	1·51 (1·06–2·15)	0·0218
TIMI major/minor	109 (0·9%)	79 (0·6%)	1·38 (1·03–1·85)	0·0290
ACUITY bleeding				
Major	534 (4·2%)	353 (2·8%)	1·53 (1·34–1·76)	<0·0001
Major excluding haematoma ≥5 cm	169 (1·3%)	123 (1·0%)	1·38 (1·09–1·74)	0·0071
Minor	1738 (13·8%)	1381 (11·0%)	1·30 (1·20–1·40)	<0·0001
Minor excluding ecchymosis, oozing, and <5 cm haematoma	293 (2·3%)	255 (2·0%)	1·15 (0·97–1·36)	0·1053
ACUITY major/minor	2196 (17·5%)	1696 (13·5%)	1·35 (1·26–1·45)	<0·0001
Any blood transfusion	90 (0·7%)	70 (0·6%)	1·29 (0·94–1·76)	0·1154

ACUITY=Acute Catheterization and Urgent Intervention Triage Strategy. CABG=coronary artery bypass graft. GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. TIMI=Thrombolysis In Myocardial Infarction. *p value for OR based on the χ^2 test.

Table 5: **Non-CABG-related bleeding events at 48 h**

	Cangrelor (N=12 565)	Clopidogrel (N=12 542)	p*
Patients with any adverse event	2900 (23·1%)	2745 (21·9%)	0·0235
Patients with any serious adverse event	281 (2·2%)	270 (2·2%)	0·6512
Patients discontinuing due to adverse event	74 (0·6%)	51 (0·4%)	0·0402
Dyspnoea	143 (1·1%)	48 (0·4%)	<0·0001
Patients who died	298 (2·4%)	323 (2·6%)	0·2988
Fatal bleeding†	8 (0·1%)	9 (0·1%)	0·8054

Data are n (%). *p value based on the χ^2 test. †Includes patients who died within 30 days from dosing start time.

Table 6: **Numbers and rates of treatment-emergent and serious adverse events in CHAMPION pooled safety population**

substantially, creating important challenges in the definition of recurrent myocardial infarction in the setting of very early PCI for ACS, which were addressed by the universal definition. These challenges might have confounded the myocardial infarction outcome adjudication and potentially obscured the detection of treatment effects in CHAMPION-PCI and CHAMPION-PLATFORM,[25] prompting the design of CHAMPION-PHOENIX. The universal definition of myocardial infarction was therefore used in the primary analysis. Additionally, the first two trials did not use the Academic Research Consortium definition, which was not available when the trials were initiated, and the collection of intraprocedural stent thrombosis was not done in those trials. Finally, follow-up is limited to 30 days, since this was the only data available for CHAMPION-PHOENIX, even though 1-year data were obtained in CHAMPION-PCI and CHAMPION-PLATFORM. However, the effect of a short-term infusion (typically 2 h) extending beyond 30 days seems unlikely. Indeed, most of the effect in the three trials seems to emerge in the first 6 h. Yet, there

Panel: **Research in context**

Systematic review

The three phase 3 trials analysed here represent the totality of evidence available on the use of cangrelor in patients undergoing percutaneous coronary intervention. Other trials with cangrelor either pertain to healthy volunteers, pharmacokinetic/pharmacodynamic studies, or to periprocedural bridging of antiplatelet therapy. Thus far, the results of each individual trial have been published, as well as a pooled analysis of CHAMPION-PCI and CHAMPION-PLATFORM, focusing on the effect of the universal definition of myocardial infarction on the trial outcomes. That hypothesis-generating post-hoc analysis suggested a clinical benefit of cangrelor compared with clopidogrel in the prevention of periprocedural myocardial infarction.

Interpretation

This study shows the clinical benefit of cangrelor in preventing adverse cardiac events such as stent thrombosis or the composite of death, myocardial infarction, ischaemia-driven revascularisation, and stent thrombosis up to 30 days after percutaneous coronary intervention. The size of this pooled analysis also showed the consistency of the effect on major patient subsets, defined according to the clinical indication (ST-segment elevation myocardial infarction, non-ST-segment elevation acute coronary syndromes, or stable angina), the patients' characteristics (eg, age, sex, history of diabetes), and the dose or timing of clopidogrel administration. Although cangrelor did not increase the primary safety outcome of non-coronary artery bypass graft-related GUSTO severe or life-threatening bleeding measured at 48 h, or in TIMI major bleeding, or in the use of transfusions, it did increase the frequency of less severe bleeding events and also increased the frequency of dyspnoea.

are several strengths to this analysis: it was prespecified before the start of the CHAMPION-PHOENIX trial, it used patient-level data, and it provides a comprehensive analysis of the effects of cangrelor for PCI in a large population, with effects that are clear and consistent across a wide array of patient subgroups and clinical presentations. The data represent the totality of evidence regarding clinical outcomes after use of cangrelor for PCI (panel).

Contributors

PGS conceived and designed the experiments and wrote the paper (including the first draft). DLB conceived and designed the experiments and revised the manuscript critically for important intellectual content. CWH, GWS, CMG, and KWM revised the manuscript critically for important intellectual content. SL contributed to the first draft and revised the manuscript critically for important intellectual content. TL analysed the data. SS participated in the conduct of the studies, revised the manuscript critically for important intellectual content. JRD participated in the conduct of the studies and revised the manuscript critically for important intellectual content. RSI, TDS, HSG, LG, and WJF collected data and critically reviewed the manuscript. HDW revised the manuscript critically for important intellectual content. RAH conceived and designed the experiments and revised the manuscript critically for important intellectual content.

Conflicts of interest

PGS has received personal fees from Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Lilly, Merck-Sharpe-Dohme, Novartis, Otsuka, Pfizer, Roche, Sanofi, Servier, The Medicines Company, and Vivus. DLB has been on the advisory or directors board for the American Heart Association Get With The Guidelines Steering Committee, Boston VA Research Institute, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences, and Society of Chest Pain Centers, and received honoraria or research grants from the American College of Cardiology, Amarin, AstraZeneca, Belvoir Publications, Bristol-Myers Squibb, Duke Clinical Research Institute, Eisai, Ethicon, Medtronic, Population Health Research Institute, Slack Publications, Sanofi-Aventis, The Medicines Company (served as CHAMPION programme co-Chair), and WebMD. CWH has received honoraria from Abbott, AstraZeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Merck-Sharpe-Dohme, Bristol-Myers Squibb, BRAHMS, Daiichi Sankyo, Essex, GlaxoSmithKline, Medtronic, Lilly, Sanofi-Aventis, Correvio, Pfizer, Roche, The Medicines Company, Boston Scientific, and Gilead. GWS has been a consultant to Boston Scientific, Eli Lilly, Daiichi Sankyo, and AstraZeneca. CMG has received funding from or been a consultant to Angel Medical Corporation, AstraZeneca, Atrium Medical Systems, Baxter Healthcare, Bayer, Cardiovascular Research Foundation, Consensus Medical Communications, CSL Behring, Cytori Therapeutics, Daiichi Sankyo Company, Eli Lilly and Company, Exeter Group, Genentech, GlaxoSmithKline, Ikaria, Janssen Pharmaceuticals, Johnson & Johnson, Lantheus Medical Imaging, Merck, Ortho-McNeil, Portola Pharmaceuticals, Roche Diagnostics, Sanofi-Aventis, Stealth Peptides, St Jude Medical, The Medicines Company, UpToDate in Cardiovascular Medicine Volcano Corp, and Walk Vascular. KWM has received research grants or consulting fees from Abbott Vascular, Adolor, American College of Cardiology, Amgen, Amylin/BMS, AstraZeneca, Baxter, Bayer, Biotronik, Boehringer Ingelheim, Bristol-Myers Squibb, Cordis, Cubist, Daiichi Sankyo, Dialouges, Duke Center for Educational Excellence, Edwards Lifesciences, Eli Lilly, Elsevier, Forest, Genentech, Gilead Science, GlaxoSmithKline, Guidant, Haemonetics, Ikaria, Janssen, Johns Hopkins University, Johnson & Johnson, Luitpold, Medtronic, Merck, Novartis, Ortho-McNeill, Pfizer, Polymedix, Portola, Pozen, Regado, Regeneron, Roche, Sanofi, Schering-Plough, St Jude Medical, The Medicines Company, South East Area Health Education Center, Springer Publishing, Sun Pharma, and University of British Columbia. TL, SS, and JRD are employees of The Medicines Company. TDS is on the Medical Advisory Board for Boston Scientific, and has received speaker fees and honoraria from Eli Lilly and Daiichi Sankyo. LG is on the speaker's bureau for Janssen and AstraZeneca. RAH has received research grants from Astra Zeneca, Bristol-Myers Squibb, Sanofi, The Medicines Company, Lilly, Daiichi Sankyo, GlaxoSmithKline, Johnson & Johnson, Portola, Merck, and Regado, and has been a consultant for Sanofi, Bristol-Myers Squibb, Merck, Johnson & Johnson, and Gilead. The other authors declare that they have no conflicts of interest.

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