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REVIEW ARTICLE

Optimizing the Use of Cangrelor in the Real World

Arman Qamar[1] · **Deepak L. Bhatt**[1]

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Abstract Thrombotic events such as myocardial infarction or stent thrombosis are the major cause of adverse outcomes in patients undergoing percutaneous coronary intervention (PCI). While current antiplatelet agents, anticoagulants, and PCI techniques have reduced the risk of thrombotic events in PCI-treated patients, a considerable hazard still remains. Cangrelor is an intravenous P2Y12 receptor antagonist that provides a rapid onset and maximal platelet inhibition, which is quickly reversible. In the large-scale CHAMPION PHOENIX trial, cangrelor was shown to reduce ischemic events significantly, including myocardial infarction and stent thrombosis, without increasing the risk of severe bleeding across the full spectrum of patients undergoing PCI, with substantial benefits in all patient subgroups examined. The pharmacologic profile of cangrelor makes it a valuable addition to the armamentarium of physicians providing care to a broad range of patients with coronary artery disease. Cangrelor is currently approved for reducing thrombotic events in patients undergoing PCI who have not been pretreated with a P2Y12 receptor inhibitor and are not receiving a glycoprotein IIb/IIIa inhibitor. Future studies are needed to determine the role of cangrelor in other clinical settings, such as upstream therapy in ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndrome (NSTE-ACS), and as a bridge to coronary artery bypass graft (CABG) or other non-cardiac surgeries in patients who require ongoing adenosine diphosphate receptor blockade.

Key Points

Intravenous cangrelor, a potent platelet P2Y12 receptor inhibitor, provides fast-onset and rapidly reversible platelet inhibition.

Cangrelor reduces periprocedural thrombotic events in patients undergoing percutaneous coronary intervention (PCI).

Cangrelor is approved for use in patients undergoing PCI who have not received a P2Y12 receptor blocker and are not being treated with a glycoprotein IIb/IIIa inhibitor.

1 Background

Platelet activation and aggregation plays a crucial role in atherothrombosis and subsequent ischemic events [1]. Indeed, platelets are a pivotal therapeutic target in the management of patients across the full spectrum of acute coronary syndromes (ACS) and those undergoing percutaneous coronary intervention (PCI). The last decade has witnessed significant progress in the development of new antiplatelet agents [2]. These advances have revolutionized the treatment of patients in the settings of ACS and PCI. Currently, dual antiplatelet therapy with aspirin in addition to P2Y12 receptor inhibitors is the standard of care for

✉ Deepak L. Bhatt
dlbhattmd@post.harvard.edu

[1] Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA

patients with ACS as well as those treated with PCI [3–6]. In patients undergoing PCI, thrombotic events such as myocardial infarction (MI) or stent thrombosis are the major cause of death and adverse events. Although periprocedural antithrombotic therapy with platelet inhibitors has reduced ischemic events in patients undergoing PCI, a substantial risk still remains.

Clopidogrel, the most widely used P2Y12 receptor inhibitor, has been shown to reduce ischemic events in stable coronary artery disease (CAD) and ACS patients undergoing PCI [7–9]. However, despite its efficacy, clopidogrel has several limitations, including slower onset and offset of action, interindividual variability and only modest platelet inhibition [10–13]. More potent oral P2Y12 receptor inhibitors such as prasugrel and ticagrelor have faster onset of effect and less variable response than clopidogrel. In ACS patients, treatment with prasugrel or ticagrelor as compared with clopidogrel has proved to be more effective in preventing ischemic events, including stent thrombosis [14–17]. However, consistent with increased platelet inhibition, this benefit is associated with a significant increase in the rates of bleeding. Similar to clopidogrel, prasugrel and ticagrelor can only be administered orally. Many patients with ACS have conditions such as nausea, vomiting, impaired gut perfusion, therapeutic hypothermia, or use of narcotics that reduce the absorption of oral antiplatelet agents [18–21]. As a result, these patients are at an increased risk of stent thrombosis and adverse ischemic events in the vulnerable peri-PCI period.

Furthermore, as management of ACS has evolved, the time from hospital admission to PCI has continued to shorten in all settings [22]. Accordingly, there is a need for a faster-onset antiplatelet therapy. Although quicker than clopidogrel, both prasugrel and ticagrelor may take several hours to achieve optimal platelet inhibition even following a loading dose in patients with ACS, particularly in those with ST-segment elevation myocardial infarction (STEMI) [23–25]. Use of a high loading dose regimen or crushing tablets has been tried to enhance the bioavailability of oral P2Y12 receptor inhibitors in STEMI patients undergoing PCI [26, 27]. However, to date, none of these strategies have resulted in the desired immediate platelet inhibition, warranting the need for intravenous therapies such as cangrelor. Thus far, randomized trials have shown uncertain benefit and possible harm with oral P2Y12 receptor inhibitor preloading before coronary angiography with intent to perform PCI [28–31]. This equipoise has led to marked practice variation in the timing of oral P2Y12 receptor inhibitor loading in patients undergoing PCI [32, 33]. Notably, less than one-third of patients undergoing coronary angiography with the goal of revascularization are pretreated with an oral P2Y12 receptor inhibitor [34]. Many physicians are concerned that coronary angiography could show an indication for coronary artery bypass graft (CABG) surgery, and refrain from administering P2Y12 receptor inhibitors until coronary anatomy is delineated. Approximately 10–15 % of ACS patients require CABG. It takes 5–7 days for platelet function to recover in patients treated with clopidogrel, prasugrel, or ticagrelor; consequently, CABG is often delayed, causing inconvenience to patients, families and prolongation of hospitalizations. Current guidelines recommend stopping oral P2Y12 receptor inhibitors at least 5 days before CABG. Discontinuing antiplatelet therapy in patients with ACS increases thrombotic risk, and continuing through surgery increases surgical bleeding risk [35]. While intravenous antiplatelet therapy with glycoprotein IIb/IIIa receptor inhibitors such as abciximab, eptifibatide, and tirofiban reduces thrombotic events in ACS patients receiving PCI, it also increases bleeding, and platelet function may take hours to days to normalize after discontinuation [36]. A parenteral antiplatelet agent with a rapid onset of action to achieve an early desirable level of platelet inhibition that is quickly reversible if an urgent CABG is needed would address these concerns.

2 Cangrelor: Pharmacologic Characteristics

Cangrelor is a highly potent, intravenously administered, platelet P2Y12 receptor inhibitor that directly blocks adenosine diphosphate (ADP)-induced platelet aggregation and activation. It provides rapid onset and sustained platelet inhibition that is quickly reversible following discontinuation of cangrelor infusion [37, 38]. For example, in healthy volunteers, a 30-μg/kg bolus followed by a 4-μg/kg/min continuous infusion achieved at least over 90 % inhibition of platelet aggregation within 2 min of bolus administration, and this was maintained throughout the infusion [39]. Following termination of the infusion, platelet function returned to baseline in approximately 60 min. Unlike clopidogrel and prasugrel, cangrelor is not a prodrug and does not require metabolic activation for antiplatelet effect. The plasma half-life of cangrelor is 3–5 min, and platelet function returns to normal within 1 h after stopping the infusion. In contrast to intravenous antiplatelet therapy with glycoprotein IIb/IIIa receptor inhibitors, cangrelor overdosing is not associated with increased bleeding, a favorable effect attributed to its very short half-life and rapid offset of action [40]. Similar to other P2Y12 receptor inhibitors, the most common side effect associated with cangrelor is bleeding. The other reported adverse effect of cangrelor is dyspnea, though very uncommon and rarely leads to discontinuation. Transient dyspnea is a well known side effect of reversible platelet ADP-receptor antagonists that may influence other

adenosine-mediated pathways, and has previously been reported with ticagrelor. In phase I and phase II studies, cangrelor safety, pharmacokinetics, and pharmacodynamics were not affected by age, hepatic, or renal function. Thus, no dose adjustments are needed in older patients or in patients with liver or kidney disease. Given its favorable pharmacologic profile, cangrelor can fill the gaps in the antithrombotic therapy of patients with ACS and those undergoing PCI.

Thus far, the use of cangrelor as a periprocedural antiplatelet agent in patients undergoing PCI has been investigated in three phase III clinical trials: Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PCI, CHAMPION PLATFORM, and CHAMPION PHOENIX [41–44] (Table 1). The CHAMPION PCI and PLATFORM trials examined the role of cangrelor compared with clopidogrel in patients with stable angina or ACS who were treated with PCI. Both trials were prematurely terminated for their futility regarding reducing their primary composite end point of death from any cause, MI, or ischemia-driven revascularization (IDR) at 48 h. However, in a prespecified pooled analysis of the CHAMPION PCI and CHAMPION PLATFORM data using the universal definition of MI instead of the trial definition, treatment with cangrelor compared with clopidogrel significantly reduced the rates of periprocedural ischemic events, including stent thrombosis, with no increase in severe bleeding [45]. These findings were further investigated in the CHAMPION PHOENIX trial.

3 CHAMPION PHOENIX Trial

In this double-blind, placebo-controlled trial, cangrelor was compared with clopidogrel in 11,145 patients who were undergoing either elective or urgent PCI [43, 44]. The indication for PCI was stable angina in 56 % of the patients, non-ST-segment elevation acute coronary syndrome (NSTE-ACS) in 26 %, and STEMI in 18 %. Overall, the median time from hospital admission to PCI was approximately 4 h. Patients were randomized to receive either cangrelor (30-μg/kg/min bolus followed by a 4-μg/kg/min infusion for at least 2 h or the duration of the procedure, whichever was longer) or to receive a loading dose of 600 or 300 mg of clopidogrel before PCI. The investigators excluded patients who had received a P2Y12 receptor inhibitor or abciximab at any time in the 7 days before randomization and those who received other glycoprotein IIb/IIIa inhibitors or fibrinolytic therapy in the 12 h before randomization. All patients were treated with aspirin (75–325 mg) and clopidogrel 75 mg during the first 48 h; thereafter, patients received either clopidogrel or another P2Y12 receptor inhibitor at the discretion of the investigator. Three-fourths of the trial patients were anticoagulated with unfractionated heparin, and in the remainder, operators chose to use bivalirudin, low-molecular weight heparin, or fondaparinux.

The rate of the primary composite efficacy end point of death from any cause, MI defined according to the universal definition, IDR, or stent thrombosis at 48 h after randomization was significantly lower in patients receiving cangrelor compared with those receiving clopidogrel (4.7 vs. 5.9 %) [odds ratio 0.78; 95 % confidence interval (CI) 0.66–0.93; $P = 0.005$] (Fig. 1). The beneficial effect of cangrelor in reducing the primary efficacy end point was not influenced by the clopidogrel loading dose (600 vs. 300 mg) or the timing of administration of the loading dose (immediately before PCI vs. during or after the procedure). Moreover, there was no heterogeneity in the favorable effect of cangrelor between patients presenting with stable angina, NSTE-ACS, and STEMI. At 48 h, the rate of the key secondary efficacy end point of stent thrombosis occurred in fewer patients in the cangrelor group than in the clopidogrel group (0.8 vs. 1.4 %) (odds ratio 0.62; 95 % CI 0.43–0.90; $P = 0.01$) (Fig. 2). Similarly, at 30 days, the frequency of the primary composite efficacy end point and the rate of stent thrombosis remained significantly lower in the cangrelor group than in the clopidogrel group. Glycoprotein IIb/IIIa inhibitors were only used as rescue therapy during PCI to treat new or persistent thrombus formation, slow or no reflow, side branch compromise, dissection, or distal embolization. The need for rescue therapy during PCI was significantly lower with cangrelor than with clopidogrel.

The primary safety end point, Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe bleeding, did not significantly differ in the cangrelor and clopidogrel groups (0.16 vs. 0.11 %) (odds ratio 1.50; 95 % CI 0.53–4.22; $P = 0.44$). A composite end point termed net adverse clinical events, comprising the primary efficacy and the primary safety end points, occurred in 4.8 % patients in the cangrelor group and 6.0 % of patients in the clopidogrel group (odds ratio 0.80; 95 % CI 0.68–0.94; $P = 0.008$). The rate of adverse events related to treatment was similar in both the groups, though there was a higher incidence of transient dyspnea with cangrelor compared with clopidogrel (1.2 vs. 0.3 %; $P < 0.001$). However, most dyspnea events in the cangrelor group were mild in severity, and only four patients discontinued therapy due to dyspnea. Overall, intravenous platelet inhibition with cangrelor in the CHAMPION PHOENIX trial reduced ischemic events without a significant increase in severe bleeding or in transfusions across entire spectrum of CAD patients undergoing PCI, with consistent benefit across all major patient subsets.

Table 1 Comparison of design features of the CHAMPION trials. Reprinted with permission from Steg et al. [46]

	CHAMPION PLATFORM	CHAMPION PCI	CHAMPION PHOENIX
Patient population	70 % troponin elevated at baseline	70 % troponin elevated at baseline	35 % troponin elevated at baseline
	P2Y12 inhibitor naive	Previous chronic clopidogrel allowed	P2Y12 inhibitor naive
	Placebo or clopidogrel control (all patients received 600 mg) loaded at the end of PCI	Placebo or clopidogrel control (all patients received 600 mg) loaded at the start of PCI	Placebo or clopidogrel (300 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 with:	PCI required with:	PCI required (stable angina, NSTE-ACS, STEMI)
	NSTEMI: troponin elevated	STEMI: ECG changes including persistent (>20 min) ST-segment elevation in ≥2 contiguous leads	
	UA: ECG changes and pain and age/diabetes	NSTEMI: troponin elevated	
	Stable angina: capped (15 %)	UA: ECG changes and pain and age/diabetes	
		Stable angina: capped (15 %)	
Number of patients (mITT)	5301	8667	10,942
Comparator	600 mg clopidogrel	600 mg clopidogrel	300 or 600 mg (per hospital standard of care)
	Loaded at the end of PCI	Loaded at the end of PCI	Loaded at the start or at the end of PCI per physician
End point	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	Not UDMI: reliance on cardiac markers alone to define PCI MI	UDMI implemented: reliance on cardiac markers and other evidence of ischemia to define PCI MI
	1 baseline sample	1 baseline sample	
	Biomarker normal at baseline: MI defined as CK-MB ≥3× ULN post PCI	Biomarker normal at baseline: MI defined as CK-MB ≥3× ULN post PCI	2 baseline samples ≥6 h apart required in NSTE-ACS patients to confirm resolving MI at baseline
	Biomarker elevated at baseline: elevation in CK-MB ≥3× ULN and 50 % increase from baseline sample or ECG changes	Biomarker elevated at baseline: elevation in CK-MB ≥3× ULN and 50 % increase from baseline sample or ECG changes	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 ischemia (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 ischemia (at least 1 of 3): ischemic symptoms, ECG changes, or angiographic evidence
Stent thrombosis definition	Non-standard definition	Non-standard definition	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)
	Angiographic stent thrombosis associated with IDR	Angiographic stent thrombosis associated with IDR	
	Confirmed by clinical events committee using angiographic source data	Confirmed by clinical events committee using angiographic source data	

ARC Academic Research Consortium, *CHAMPION* Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition, *CK-MB* creatine phosphokinase myocardial band, *ECG* electrocardiogram, *IDR* ischemia-driven revascularization, *MI* myocardial infarction, *mITT* modified intent-to-treat, *NSTE-ACS* non-ST-segment elevation acute coronary syndrome, *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

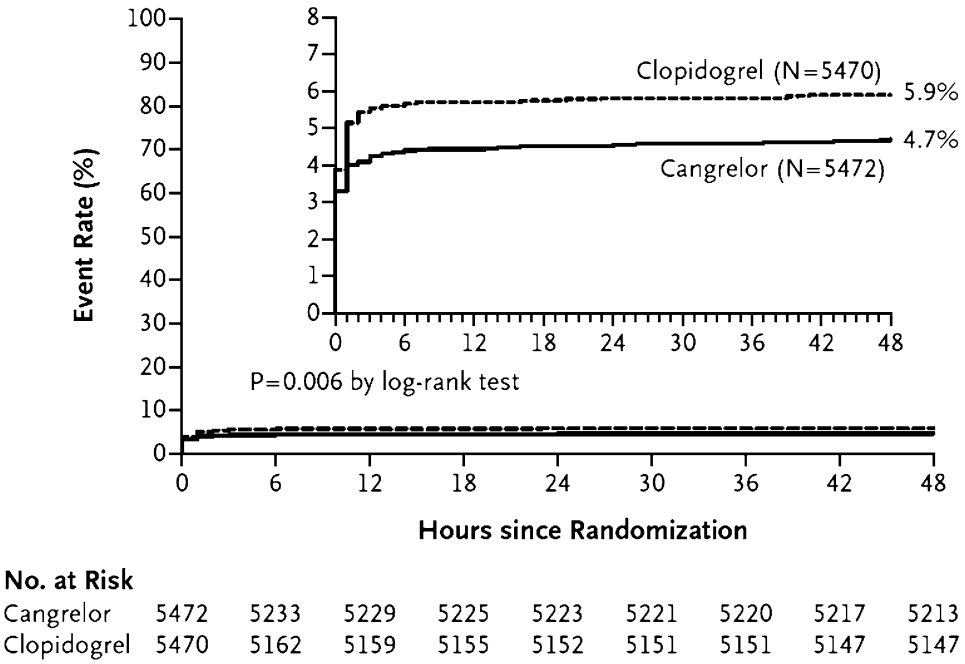

Fig. 1 Kaplan–Meier curves for the primary efficacy end point in the CHAMPION PHOENIX trial. The primary efficacy end point was a composite of death from any cause, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 h after randomization. The inset shows the same data on an enlarged *y*-axis. Reprinted with permission from Bhatt et al. [44]. *CHAMPION* Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition

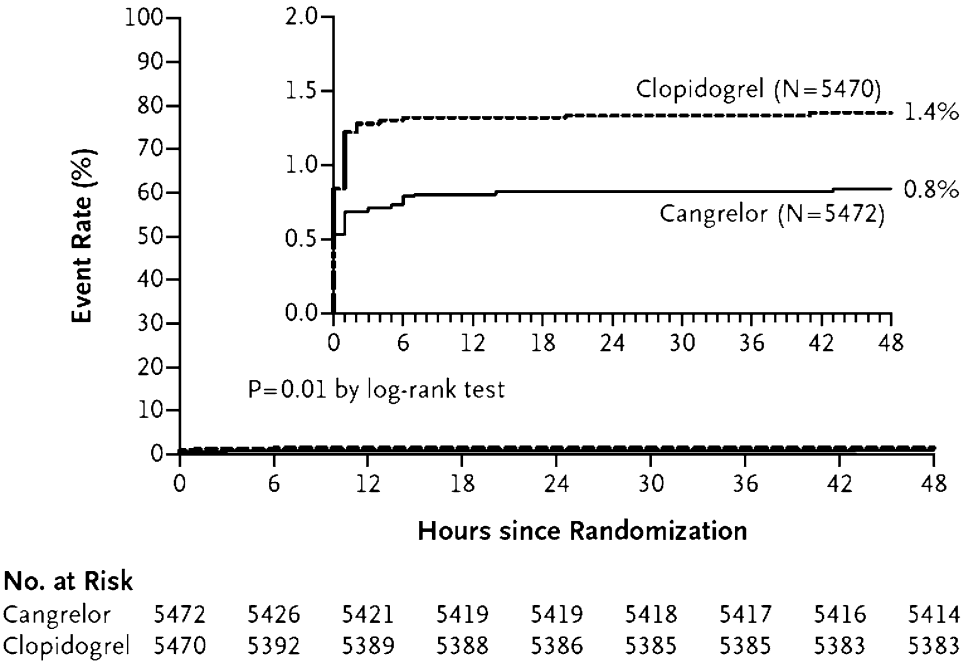

Fig. 2 Kaplan–Meier curves for the secondary end point in the CHAMPION PHOENIX trial. The secondary end point was stent thrombosis at 48 h after randomization. The inset shows the same data on an enlarged *y*-axis. Reprinted with permission from Bhatt et al. [44]. *CHAMPION* Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition

A pooled analysis of the data from the three CHAMPION trials (PCI, PLATFORM, and PHOENIX) explored the efficacy and safety of cangrelor compared with clopidogrel in reducing periprocedural thrombotic events in 24,910 patients undergoing PCI [46]. The prespecified primary efficacy end point of death from any cause, MI defined by universal definition of PCI-related MI, IDR, or stent thrombosis at 48 h occurred in 3.8 % of patients receiving cangrelor and 4.7 % of patients receiving clopidogrel (odds ratio 0.81; 95 % CI 0.71–0.91; $P = 0.007$) (Fig. 3). Furthermore, the rate of the secondary outcome of stent thrombosis at 48 h was also lower in the cangrelor group than in the clopidogrel group (0.5 vs. 0.8 %) (odds ratio 0.59; 95 % CI 0.43–0.81; $P = 0.0008$). These benefits were also significant at 30 days after randomization. The reduction in the primary efficacy end point with cangrelor was consistent across all major subgroups, defined according to the indication for PCI (STEMI, NSTE-ACS, or stable angina), patient characteristics (for example, age, sex, history of diabetes, or MI), and the loading dose or

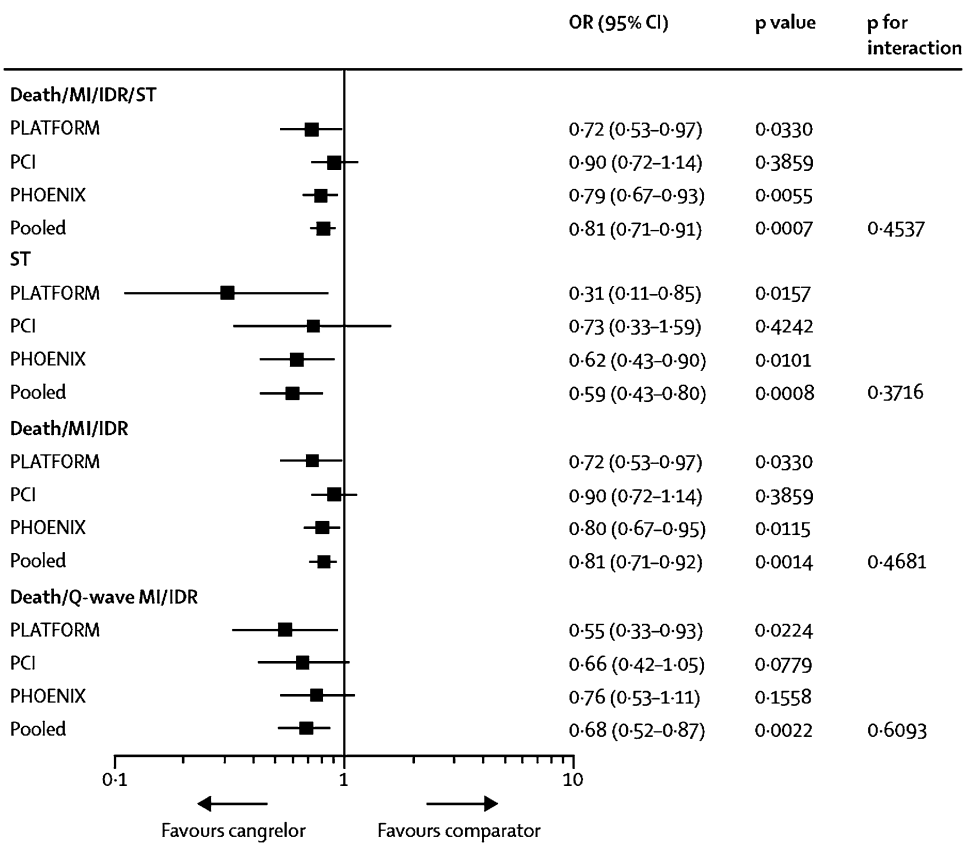

Fig. 3 Forest plot of the primary, key secondary, and secondary outcomes at 48 h, overall and in each of the three CHAMPION trials. Reprinted with permission from Steg et al. [46]. *CHAMPION* Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition, *CI* confidence interval, *IDR* ischemia-driven revascularization, *MI* myocardial infarction, *OR* odds ratio, *PCI* percutaneous coronary intervention, *ST* stent thrombosis

timing of administration of clopidogrel. At 48 h, the rate of the primary safety end point of non-CABG-related GUSTO severe or life threatening bleeding, or thrombolysis in myocardial infarction (TIMI) major bleeding, or the need for transfusions did not differ significantly between the two groups. However, cangrelor compared with clopidogrel significantly increased the incidence of less severe bleeding events and transient dyspnea.

The CHAMPION PHOENIX trial provided the primary evidence of efficacy for cangrelor that resulted in its regulatory approval for clinical use. In June 2015, the US Food and Drug Administration (FDA) approved the use of cangrelor as an adjunct to PCI for reducing periprocedural thrombotic events in patients who have not been treated with a P2Y12 receptor inhibitor or are not receiving a glycoprotein IIb/IIIa inhibitor. Similarly, the European Medicines Agency (EMA) approved the use of cangrelor in patients undergoing PCI who have not been preloaded with an oral P2Y12 receptor inhibitor before PCI, and in clinical settings were treatment with oral P2Y12 inhibitors is not feasible or desirable. Since the publication of the original trial results, several prespecified subgroup analyses in CHAMPION PHOENIX have confirmed the beneficial effect of cangrelor in reducing ischemic events in patients undergoing PCI.

4 Effect of Cangrelor on Intraprocedural Stent Thrombosis

Intraprocedural stent thrombosis (IPST) is a rare but potentially fatal complication of PCI. IPST is independently associated with subsequent ischemic events and mortality in patients undergoing PCI [47]. Moreover, IPST correlates with development of stent thrombosis according to the Academic Research Consortium (ARC) definition and carries a significant adverse risk, justifying the need to prevent it. In the CHAMPION PHOENIX trial, IPST occurred in approximately 1 % ($n = 89$) of the study participants [48]. IPST was associated with a significant increase in the risk of adverse ischemic events including, death, MI, IDR, or stent thrombosis at 48 h and at 30 days. In addition, development of IPST resulted in more frequent use of rescue therapy with glycoprotein IIb/IIIa inhibitors, bleeding, and prolongation of hospitalization. In a prespecified angiographic core lab analysis of 10,939 patients—the largest such angiographic analysis to date—treatment with cangrelor reduced the odds of IPST by 35 % (odds ratio 0.65; 95 % CI 0.42–0.99; $P = 0.04$) compared with clopidogrel at 48 h after randomization. The benefit of cangrelor in reducing IPST was evident irrespective of the clinical presentation as stable angina, NSTE-ACS, or

STEMI. Importantly, the use of cangrelor in comparison to clopidogrel at randomization was independently associated with freedom from IPST during PCI.

5 Effect of Cangrelor Using Various Definitions of Myocardial Infarction

Various definitions of periprocedural MI exist. A sensitivity analysis examined the effect of cangrelor versus clopidogrel in CHAMPION PHOENIX using several definitions of MI [49]. Of the 11,145 patients in CHAMPION PHOENIX, 4.2 % ($n = 421$) had an MI as defined by the second universal definition, and 1.2 % had an MI ($n = 134$) when the Society of Coronary Angiography and Intervention (SCAI) definition of periprocedural MI was used. Occurrence of MI in patients undergoing PCI, irrespective of the definition, was associated with an increased risk of death at 30 days. Treatment with cangrelor resulted in consistent reduction in periprocedural MI regardless of the definition used. At 48 h, MI as defined by the universal definition occurred in fewer patients in the cangrelor group than in the clopidogrel group (3.8 vs. 4.7 %) (odds ratio 0.80; 95 % CI 0.67–0.97; $P = 0.02$). Similarly, the incidence of MI using the SCAI definition for periprocedural MI was lower in patients receiving cangrelor compared with those receiving clopidogrel (1.0 vs. 1.5 %) (odds ratio 0.65; 95 % CI 0.46–0.92; $P = 0.01$). In addition, cangrelor also reduced MIs defined by several other definitions, including peak creatine phosphokinase myocardial band (CK-MB) that was $\geq$10 times the upper limit normal (ULN), CK-MB $\geq$10 times ULN with ischemic symptoms or electrocardiogram (ECG) changes, and those with ischemic symptoms or ECG changes alone. These findings further validate the beneficial effect of cangrelor in reducing ischemic events in patients undergoing PCI.

6 Net Clinical Benefit of Cangrelor in Women

Women are underrepresented in cardiovascular clinical trials relative to their disease prevalence [50]. Because of the paucity of data, the impact of antiplatelet therapy on thrombotic and bleeding risks in women treated with PCI remains uncertain. In particular, concerns have been raised about the heterogeneity in net clinical benefit of antiplatelet therapy between men and women [51–53]. As a result, many physicians may withhold evidence-based antithrombotic therapies in women. In a prespecified subgroup analysis of the CHAMPION PHOENIX trial, cangrelor showed consistent reductions in periprocedural and 30-day ischemic events in both men and women [54]. Of the 11,145 patients enrolled in the CHAMPION PHOENIX trial, 28 % ($n = 3051$) were women. In women, cangrelor compared with clopidogrel reduced the rate of the primary efficacy end point by 35 % (odds ratio 0.65; 95 % CI 0.48–0.89; $P = 0.01$) and decreased the incidence of stent thrombosis by 61 % (odds ratio 0.39; 95 % CI 0.20–0.77; $P = 0.01$). In men, treatment with cangrelor resulted in a 14 % reduction in the odds of the primary efficacy end point (odds ratio 0.86; 95 % CI 0.70–1.05; $P = 0.014$; P interaction = 0.23) and a 16 % reduction in the odds of stent thrombosis (odds ratio 0.84; 95 % CI 0.53–1.33; $P = 0.44$; P interaction = 0.11). In addition, cangrelor compared with clopidogrel did not increase the rate of the primary safety end point, GUSTO severe or life threatening bleeding, in either women or men. Importantly, net clinical benefit, a composite of the primary efficacy and safety end points, favored cangrelor over clopidogrel in both women and men. These findings provide reassurance regarding the efficacy and safety of cangrelor in women undergoing PCI.

7 Cangrelor in Older Patients

Advancing age is one of the most important predictors of mortality and morbidity in patients with ACS. Older patients ($\geq$75 years) have more complex coronary anatomy, more comorbidities and are at an increased risk of periprocedural thrombotic and bleeding events after PCI than younger patients (<75 years) [55, 56]. Improved PCI techniques and advances in antithrombotic therapy have improved outcomes in older patients [57]. However, there is a paucity of evidence to direct treatment in this patient population, as older patients have been excluded in most clinical trials. Consequently, older patients who present with ACS are less likely to receive guideline-directed therapies, including PCI, particularly because of concerns for bleeding [58, 59]. Periprocedural bleeding in older patients is well known to increase the risk of adverse events, including death, MI, stroke, and prolonged hospitalization.

In a prespecified subgroup of 2010 older patients ($\geq$75 years; $\sim$20 % of study participants) in CHAMPION PHOENIX, cangrelor compared with clopidogrel was shown to reduce ischemic events without increasing severe bleeding events; consistent with the effect in younger patients (<75 years) [60]. In older patients, the primary end point of death, MI, IDR, or stent thrombosis occurred in 5.4 % of patients in the cangrelor group versus 7.4 % in the clopidogrel group (odds ratio 0.71; 95 % CI 0.50–1.02). There was no significant difference in the rates of GUSTO severe bleeding between the two groups (odds ratio 0.58; 95 % CI 0.14–2.44). Furthermore, the frequency of the net composite end point of death, MI, IDR, stent thrombosis, or GUSTO severe bleeding was lower in older patients

treated with cangrelor than clopidogrel (odds ratio 0.71; 95 % CI 0.50–1.01; $P = 0.06$). These data provide strong evidence for the potential role of cangrelor in safely optimizing antiplatelet therapy in older patients undergoing PCI.

8 Cangrelor on a Background of Bivalirudin

The use of bivalirudin in patients undergoing PCI is associated with similar ischemic outcomes and lower bleeding risk than those with heparin plus glycoprotein IIb/IIIa inhibitors. However, bivalirudin is associated with a higher risk of early stent thrombosis [61]. In CHAMPION PHOENIX, the periprocedural anticoagulant choice was at the operator's discretion. Bivalirudin was used in approximately 20 % of the patients ($n = 2059$). A prespecified subgroup analysis investigated the effect of cangrelor versus clopidogrel in patients in whom physicians chose to use bivalirudin during PCI [62]. In this analysis, cangrelor significantly reduced the risk of the primary efficacy end point of death, MI, IDR, or stent thrombosis at 48 h by 32 %, as compared with clopidogrel, with rates of 4.7 and 6.7 %, respectively (odds ratio 0.68; 95 % CI 0.47–0.99; $P = 0.047$). This benefit was consistent across multiple subgroups, including patients with stable angina, NSTE-ACS, or STEMI. In addition, the need for rescue glycoprotein IIb/IIIa inhibitors was also lower in patients receiving cangrelor than in those given clopidogrel (1.4 vs. 3.1 %) (odds ratio 0.44; 95 % CI 0.24–0.84; $P = 0.01$). Cangrelor also reduced the risk of stent thrombosis by 50 % at 48 h. Notably, this beneficial effect was evident as early as 2 h after randomization. Reassuringly, there was no significant difference in the rate of GUSTO severe or moderate bleeding, TIMI major or minor bleeding, or the need for blood transfusions between the two groups. Taken together, these findings suggest that the attractive antiplatelet profile of cangrelor when combined with bivalirudin has the potential to safely lower ischemic events without increasing the risk of early stent thrombosis in patients undergoing PCI.

9 Effect of Cangrelor According to Access Site

Bleeding has been associated with an increased risk of subsequent ischemic events including, death, MI, stroke, and stent thrombosis in patients treated with PCI [63, 64]. Vascular access site complications are the most common cause of bleeding in patients undergoing PCI. Compared with the femoral approach, the radial artery approach reduces bleeding, adverse cardiac events, and the cost of hospitalization [65]. Of the 11,145 patients randomized in CHAMPION PHOENIX, 74 % underwent PCI via femoral access and 26 % through the radial approach. In a prespecified subgroup analysis, Gutierrez et al. explored the benefit of cangrelor according to the access site (femoral vs. radial) used for PCI [66]. In the radial group, the rate of the primary efficacy end point of death, MI, IDR, or stent thrombosis at 48 h was lower in patients receiving cangrelor than clopidogrel (4.4 vs. 5.7 %) (odds ratio 0.76; 95 % CI 0.54–1.06). Similarly, in the femoral group, the use of cangrelor was associated with a reduction in the rate of the primary efficacy end point compared with clopidogrel (4.8 vs. 6.0 %) (odds ratio 0.79; 95 % CI 0.65–0.96; P interaction = 0.83). In both radial and femoral groups, there was no significant difference in the risk of GUSTO severe bleeding, TIMI major bleeding, or blood transfusions in patients treated with cangrelor versus clopidogrel. However, the absolute rates of GUSTO severe bleeding, TIMI major bleeding, or blood transfusions were higher in the femoral group than in the radial group, irrespective of treatment with cangrelor or clopidogrel.

10 Geographic Region and Outcomes in CHAMPION PHOENIX

Globalization of clinical trials has led to enrollment of patients from different regions of the world. Regional variation in patient characteristics, race, ethnicity, lifestyle, health-care delivery, and practice patterns may preclude the generalizability of the trial results to all geographic regions [67, 68]. CHAMPION PHOENIX included 11,145 patients from 153 sites from 12 countries, with approximately 40 % of the patients from the USA. In a prespecified subgroup analysis in CHAMPION PHOENIX, Vaduganathan et al. examined the effect of cangrelor on efficacy and safety end points in patients enrolled in US and non-US sites [69]. There was significant heterogeneity in demographics, patient characteristics, periprocedural medication therapy, and indications for PCI among patients enrolled in US versus non-US sites. However, despite these differences, the beneficial effect of cangrelor on efficacy and safety end points did not differ significantly by geographic regions. In patients enrolled in the USA, the rate of the primary efficacy end point of death, MI, IDR, or stent thrombosis was lower in the cangrelor group compared with the clopidogrel group (4.5 vs. 6.4 %) (odds ratio 0.70; 95 % CI 0.53–0.92). Likewise, the rate of the primary end point was lower in patients treated with cangrelor than clopidogrel in patients outside the USA (4.8 vs. 5.6 %) (odds ratio 0.85; 95 % CI 0.69–1.05; P interaction = 0.26). In addition, cangrelor reduced the rates of stent thrombosis in both US (0.5 vs. 1.3 %) (odds ratio 0.38; 95 % CI 0.18–0.79) and non-US cohorts (1.1 vs.

1.4 %) (odds ratio 0.75; 95 % CI 0.48–1.15; P interaction = 0.12). Consistent with the overall trial results, there were no significant differences in the rates of the primary safety end points between the cangrelor and clopidogrel treatment arms in the US and non-US cohorts.

11 Cangrelor in Patients Undergoing Coronary Artery Bypass Graft

Current guidelines recommend discontinuing P2Y12 receptor inhibitors 5–7 days prior to CABG to minimize bleeding. Premature interruption in P2Y12 receptor blockade in ACS patients who were treated medically or with PCI is associated with an increase in the risk of thrombotic events [70]. On the contrary, continuation of P2Y12 receptor inhibitor during CABG increases the risk of bleeding complications. In the BRIDGE trial, 210 patients with ACS or with stents on clopidogrel or prasugrel awaiting CABG were randomized to receive either cangrelor (0.75 μg/kg/min infusion without a bolus) or placebo [71]. Clopidogrel or prasugrel were discontinued, and patients received either cangrelor or placebo for at least 48 h. Cangrelor was stopped 1–6 h before CABG. Patients treated with cangrelor maintained a higher rate of optimal platelet inhibition compared with placebo. The primary efficacy end point of percentage of patients with platelet reactivity less than 240 P2Y12 reaction units (PRU) was higher in patients treated with cangrelor than placebo (98.8 vs. 19.0 %) (relative risk 5.2; 95 % CI 3.3–8.1; $P < 0.001$). Bridging with cangrelor did not result in a significant increase in major bleeding prior to CABG. While this study was not powered to answer if this approach would reduce ischemic events, these findings suggest a possible role of a bridging strategy with cangrelor to maintain optimal platelet inhibition after oral P2Y12 receptor inhibition is stopped in patients awaiting CABG (or potentially other surgeries). Currently, cangrelor is not approved for this indication. However, if a bridging strategy with an intravenous antiplatelet agent is chosen, cangrelor offers a more attractive profile than intravenous glycoprotein IIb/IIIa inhibitors [72].

12 Integrating Cangrelor into Clinical Practice

Cangrelor with its intravenous availability, potent platelet inhibition, and rapid onset and offset of action fulfills an unmet need for an ideal antiplatelet agent in patients receiving PCI. Patients treated with cangrelor require switching to oral P2Y12 inhibitors [73–75]. Consistent with the practice in CHAMPION PHOENIX, clopidogrel 600 mg should be administered immediately after stopping the cangrelor infusion. Pharmacodynamic studies have examined transition strategies from cangrelor to prasugrel or ticagrelor. Accordingly, a 60-mg loading dose of prasugrel should be administered immediately after discontinuing cangrelor. On the other hand, ticagrelor 180 mg can be given before, during, or after cangrelor infusion. To date, clinical trials have only compared cangrelor with clopidogrel. No randomized or observational study has compared clinical outcomes between cangrelor and prasugrel or ticagrelor, though pharmacodynamic data suggest additional antiplatelet effect with cangrelor. Real-world evaluation of cangrelor in comparison to all oral P2Y12 inhibitors (clopidogrel, prasugrel, and ticagrelor) will provide clinicians with further insights in optimizing the use of cangrelor in reducing ischemic events in routine practice [76].

There are several clinical scenarios where cangrelor could be advantageous [77]. The intravenous route of administration is ideal for patients who cannot take oral medications because of vomiting, mechanical ventilation, cardiac arrest, shock, therapeutic hypothermia, morphine use, unconsciousness, or sedation. The fast onset and offset of effect with cangrelor mitigates preloading concerns before coronary angiography. Hence, if PCI is indicated, cangrelor immediately achieves maximal platelet inhibition during the procedure. Alternatively, if the coronary anatomy shows surgical disease, CABG can be performed without delay. Cangrelor may also be valuable in clinical situations where patients need to prematurely interrupt oral P2Y12 inhibition, such as before an urgent surgery.

13 Conclusion

Taken together, cangrelor reduces the risk of ischemic events across the full spectrum of PCI patients, with significant benefits in all major patient subsets. Cangrelor, with an attractive pharmacologic profile and beneficial effect, will play a major role in optimizing periprocedural thrombotic risk in patients treated with PCI. Future studies are needed to determine a role of cangrelor as upstream therapy in STEMI and NSTE-ACS, and as a bridge to cardiac and non-cardiac surgeries. Potential applications in other areas such as ischemic stroke also merit exploration.

Compliance with Ethical Standards

Source of funding None.

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