Effect of Platelet Inhibition by Cangrelor Among Obese Patients Undergoing Coronary Stenting: Insights From CHAMPION

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BACKGROUND: In randomized trials, cangrelor reduced periprocedural ischemic events related to percutaneous coronary intervention without increasing GUSTO severe bleeding. However, some antiplatelet agents have shown a differential treatment effect by body mass index (BMI).

METHODS: Patients from the 3 CHAMPION trials (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) who were randomized to cangrelor versus clopidogrel during percutaneous coronary intervention were stratified by BMI. The primary efficacy end point was a composite of death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis within 48 hours. The principal safety outcome was GUSTO moderate or severe bleeding at 48 hours, although more sensitive bleeding measures such as Thrombolysis in Myocardial Infarction major bleeding were also assessed. We examined obese patients (defined as BMI \( \geq 30 \)) versus nonobese patients.

RESULTS: There were 24,893 patients, with 8,979 (36.1\%) having BMI of \( \geq 30 \). There was no significant difference in the primary efficacy end point among obese versus nonobese patients (4.3\% versus 4.2\%; rate ratio, 1.01 [95\% CI, 0.89–1.15]; \( P=0.82 \)). There was a consistent benefit in the primary efficacy end point in patients who received cangrelor versus placebo who were obese (3.9\% versus 4.7\%, rate ratio, 0.83 [95\% CI, 0.68–1.02]; \( P=0.07 \)) and not obese (3.8\% versus 4.7\%; rate ratio, 0.81 [95\% CI, 0.69–0.94]; \( P=0.0053 \)); interaction \( P=0.77 \). There was no difference in GUSTO moderate or severe bleeding among patients who received cangrelor versus placebo who were obese (0.6\% versus 0.6\%; rate ratio, 0.99 [95\% CI, 0.58–1.67]; \( P=0.96 \)).

CONCLUSIONS: Cangrelor at the time of percutaneous coronary intervention is effective and safe in obese and nonobese patients. There was no difference in short-term efficacy between obese and nonobese patients. Periprocedural cangrelor is an effective and safe antiplatelet agent, irrespective of BMI.

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Key words: clopidogrel ▪ obesity ▪ percutaneous coronary intervention ▪ platelet aggregation inhibitors ▪ thrombosis
WHAT IS KNOWN

• Pharmacological studies have suggested that there may be a difference in platelet reactivity among obese versus nonobese patients who have been treated with P2Y12 inhibitors.
• In spite of a dramatic rise in obesity, obese patients continue to be under-represented in clinical trials.

WHAT THE STUDY ADDS

• In one of the largest prospective studies of anti-thrombotic therapy in patients undergoing percutaneous coronary intervention, we show that there is a consistent benefit to using cangrelor versus clopidogrel at the time of percutaneous coronary intervention, without any excess of bleeding complications, among obese patients (body mass index ≥30).
• Patients with lower body mass index had a higher risk of bleeding regardless of antiplatelet strategy compared with patients with higher body mass index.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Definition                                      |
|--------------|------------------------------------------------|
| BMI          | body mass index                                |
| CHAMPION     | Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition |
| GUSTO        | Global Use of Strategies to Open Occluded Arteries |
| PCI          | percutaneous coronary intervention             |
| TIMI         | Thrombolysis in Myocardial Infarction          |

Cangrelor for Obese Patients Undergoing PCI

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factors, affecting obese patients at a significantly younger age than their peers.2–5 It has been postulated, however, that there is a different prothrombotic milieu among obese versus nonobese patients with coronary artery disease, possibly suggesting that a differential treatment response to antiplatelet therapy may exist.6 Obesity and insulin resistance are known to cause increased platelet count, platelet volume, and oxidative stress.7

The optimal use of antithrombotic therapy in the obese at the time of percutaneous coronary intervention (PCI) has also been a subject of debate, given the differential pharmacodynamics and physiology associated with obesity. For example, different disciplines may use lean versus actual body mass for dosing of heparin.8 Very obese patients taking edoxaban versus warfarin may have a higher risk of bleeding, while obese patients taking apixaban versus warfarin had lower all-cause mortality and cardiovascular mortality.9,10 In 1 study, when 402 patients were loaded with 600 mg of clopidogrel before PCI, obese patients exhibited significantly higher adenosine diphosphate-induced platelet aggregation than nonobese patients.11 In another study, 1542 consecutive patients who underwent stenting were loaded with clopidogrel versus prasugrel. In both thienopyridine groups, platelet reactivity indices were higher among obese patients with the metabolic syndrome but not obese patients without the metabolic syndrome.12 Then, in a follow-up study, 186 patients undergoing PCI were assigned to prasugrel or ticagrelor; obese patients taking prasugrel had higher platelet reactivity indices, but obese patients taking ticagrelor did not.13 Cangrelor is frequently given in addition to the above-mentioned agents during PCI, especially during treatment of ST-segment–elevation myocardial infarction and thrombotic lesions. Large-scale randomized data, however, have not yet detected a difference in the response to cangrelor or other P2Y12 inhibition among obese versus nonobese patients.14 Although cangrelor has 100% bioavailability and universal dosing, it is not known whether there may be differential treatment effect among the obese, as with the novel oral anticoagulants and other P2Y12 inhibitors—or whether the addition of cangrelor to these agents with variable pharmacological effects in the obese may lead to a differential treatment effect or bleeding risk.

The 3 phase-3 CHAMPION trials (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) were conducted to test the safety and efficacy of cangrelor infusion versus clopidogrel at the time of PCI. In CHAMPION PLATFORM and CHAMPION PCI, there was no difference in the composite efficacy or bleeding safety endpoints among patients who received cangrelor versus clopidogrel at the time of PCI, whereas, in the larger CHAMPION PHOENIX trial, there was a significant reduction in the combined efficacy end point (death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 hours) without an increase in bleeding.15–17

This analysis of the combined CHAMPION trials aims to assess whether there is a differential treatment response with respect to major adverse cardiovascular events (MACE) or bleeding among obese versus nonobese patients who were treated with cangrelor versus placebo at the time of PCI.

METHODS

Study Population

The data that support these findings of the study are available from the corresponding author upon reasonable request. The study designs of the 3 prospective, double-blind, double-dummy CHAMPION trials have been published previously.18,19 Patients ≥18 years of age requiring PCI for stable or acute coronary disease were randomly assigned to receive a cangrelor infusion (30 μg/kg bolus, followed by a 4 μg/kg per
minute infusion for at least 2 hours, or the duration of PCI, whichever was longer) or clopidogrel. Timing of oral clopido- 
grel load (300 or 600 mg) was different in the 3 trials: at the 
beginning of PCI in CHAMPION PCI, at the end of PCI in 
CHAMPION PLATFORM, and according to site-specific stan-
dard of care in CHAMPION PHOENIX. Periprocedural anti-
coagulation, stent selection, and sheath management were 
left to the discretion of the individual clinicians. Subsequent to 
PCI, patients were treated with dual antiplatelet therapy with 
aspirin and clopidogrel at the direction of site investigators. 
Exclusion criteria related to recent P2Y12 inhibitor use, fibrino-
lytic, and glycoprotein IIb/IIIa inhibitor therapy are published 
in the individual trials.15–17 All patients provided written and 
informed consent before enrollment. The trial protocols and 
all subsequent amendments were approved by national regu-
larity agencies in participating countries and by institutional 
review boards or ethics committees at all participating sites. 
Independent data safety and monitoring boards provided reg-
ular oversight of patient data at regular intervals.

End Points and Follow-Up
As in the CHAMPION PHOENIX trial, the primary end point 
for this analysis is the cumulative incidence of a composite 
of death, myocardial infarction, ischemia-driven revascular-
ization, and stent thrombosis at 48 hours. Incidence of the same 
composite end point at 30 days as well as the individual com-
ponents were used as secondary end points. For the pooled 
analysis, the second universal definition of myocardial infarction 
was used and stent thrombosis was defined by the academic 
research consortium.20,21 As specified in the trial protocol, end 
points were adjudicated according to a prespecified modi-
fied intention to treat population, consisting of patients who 
received the study drug and underwent PCI.

The primary safety end point was cumulative incidence of 
GUSTO (Global Use of Strategies to Open Occluded Arteries) 
defined noncoronary artery bypass graft moderate or severe 
bleeding. Secondary bleeding end points included the need 
for any blood transfusion within 48 hours or Thrombolysis in 
Myocardial Infarction defined bleeding.

Statistical Analysis
For the primary analysis, patients were divided into 2 groups 
according to body mass index (BMI): obese patients (BMI≥30), 
and nonobese patients (BMI<30). Baseline characteristics 
were compared between the 2 groups; continuous variables 
expressed as mean (SD) or median (interquartile range) and 
categorical variables expressed as n (%). Between-group com-
parisons were made using T-tests for continuous variables and 
χ² for categorical variables.

Efficacy and safety end points were compared between 
BMI categories and by cangrelor versus clopidogrel arms 
within BMI categories using Poisson regression analysis to 
estimate event rates ratio (RR) and 95% CIs. Kaplan-Meier 
curves were constructed for the primary efficacy end point 
and compared using the log-rank test. Between-group com-
parisons of treatment effect were performed using Poisson 
regression, adjusting for age, sex, and diabetes. In a separate 
analysis, BMI was also considered as a continuous variable 
against the efficacy and safety end points, adjusted for age, 
sex, and diabetes.

In an exploratory analysis, efficacy and safety end points 
were compared by cangrelor versus clopidogrel within different 
BMI categories: (BMI, <25, BMI, 25 to <30, BMI 30 to <35, 
and BMI ≥35). There was no statistical adjustment for multiple 
comparisons. All statistical analyses were performed using SAS 
9.4 (SAS institute, Cary, NC).

RESULTS
Of the 25384 patients randomized in the CHAMPION 
trials, 474 (1.9%) did not receive the study drug or did 
not have a PCI and were not included in the modified 
intention-to-treat analysis. An additional 17 patients did 
not have a BMI available for calculation. Thus, there were 
24893 patients included for this analysis; 8979 (36.1%) 
with a BMI≥30 and 15914 (63.9%) with a BMI<30.

Baseline Characteristics
There were notable and expected differences among 
patients who were obese versus nonobese included in 
this analysis. Compared with nonobese patients, obese 
patients were younger (61 versus 64 years), more likely to 
be female (29.6% versus 26.7%), from the United States 
(54.3% versus 37.5%), and less likely to be smokers than 
nonobese patients (26.6% versus 30.0%). Obese patients 
were more likely to have comorbid conditions than non-
obese patients: diabetes (40.2% versus 23.6%), hyper-
tension (82.4% versus 71.6%), hyperlipidemia (67.7% 
versus 54.9%), prior stroke (5.3% versus 5.0%), prior MI 
(24.4% versus 22.0%). Obese patients were more likely 
than nonobese patients to present with stable angina 
(35.0% versus 28.8%) and less likely to present with elevated 
cardiac biomarker (46.6% versus 52.0%), non–ST-segment–elevation myocardial infarction (55.1% versus 
58.7%), or ST-segment–elevation myocardial infarction 
(9.9% versus 12.5%), and more likely than nonobese 
patients to be treated with a drug-eluting stent (56.7% 
versus 51.2%). Among patients for whom arterial access 
site was known, there were similar rates of radial access 
among obese versus nonobese patients (26.8% versus 
25.7%; Table 1). While there were important demographic 
differences between obese and nonobese patients, base-
line characteristics were evenly balanced among patients 
who were randomized to receive cangrelor versus clopido-
grel in both obese and nonobese patients (Table 1).

There were some notable differences in antithrombotic 
thepathies given to obese versus nonobese patients. Obese 
patients were somewhat more likely to be loaded with 600 
mg of clopidogrel and less likely to be loaded with 300 
mg of clopidogrel. Obese patients were also more likely 
to receive bivalirudin and less likely to received unfraction-
ated heparin or low molecular weight heparin (Table 1). 
After adjusting for geographic region, the differences in 
clopidogrel loading dose and unfractionated heparin were 
similar, but there was no difference in frequency of bivali-
rudin or low molecular weight heparin use.
Table 1. Baseline Characteristics of Patients Undergoing PCI in the CHAMPION Trials by BMI Cutoff of 30

| Baseline characteristics by BMI cutoff | BMI≥30 (n=8979) | BMI<30 (n=15 914) | P value |
|---------------------------------------|-----------------|-------------------|---------|
| Age, y                                | 61.0 (54–68)    | 64.0 (56–73)      | <0.0001*|
| Female                                | 2661 (29.6%)    | 4243 (26.7%)      | <0.0001 |
| White race                            | 8025 (89.5%)    | 13339 (83.9%)     | <0.0001 |
| Weight, kg                            | 100.0 (90–110)  | 76.0 (68–84)      | <0.0001*|
| Diagnosis at presentation             |                 |                   | <0.0001 |
| Stable angina                         | 3142 (35%)      | 4578 (28.8%)      |         |
| NSTE-ACS                              | 4946 (55.1%)    | 9340 (58.7%)      |         |
| STEMI                                 | 891 (9.9%)      | 1996 (12.5%)      |         |
| Region                                |                 |                   | <0.0001 |
| United States                         | 4872 (54.3%)    | 5966 (37.5%)      |         |
| Other countries                       | 4107 (45.7%)    | 9948 (62.5%)      |         |
| Elevation of cardiac biomarker        | 4103 (46.6%)    | 8173 (52.0%)      | <0.0001 |
| Medical history                       |                 |                   |         |
| Diabetes                              | 3608 (40.2%)    | 3761 (23.7%)      | <0.0001 |
| Current smoker                        | 2390 (26.6%)    | 4773 (30.0%)      | <0.0001 |
| Hypertension                          | 7403 (82.7%)    | 11 391 (71.9%)    | <0.0001 |
| Hyperlipidemia                        | 6081 (73.4%)    | 8742 (59.9%)      | <0.0001 |
| Prior stroke or TIA                   | 473 (5.3%)      | 797 (5.0%)        | 0.37    |
| Prior MI                              | 2195 (24.7%)    | 3499 (22.2%)      | <0.0001 |
| Prior PTCA or PCI                     | 2449 (27.3%)    | 3407 (21.5%)      | <0.0001 |
| CABG                                  | 1020 (11.4%)    | 1560 (9.8%)       | <0.0001 |
| CHF                                   | 910 (10.2%)     | 1274 (8.0%)       | <0.0001 |
| PAD                                   | 621 (7.0%)      | 1099 (7.0%)       | 0.89    |
| Periprocedural medications            |                 |                   |         |
| Clopidogrel 300 mg                    | 927 (10.3%)     | 1878 (11.8%)      | 0.0004  |
| Clopidogrel 600 mg                    | 8052 (89.7%)    | 14 036 (88.2%)    | 0.0004  |
| Bivalirudin                           | 2761 (30.8%)    | 3443 (33.2%)      | <0.0001 |
| Unfractionated heparin                | 5370 (59.8%)    | 10 346 (85.0%)    | <0.0001 |
| LMWH                                  | 663 (7.4%)      | 1523 (9.6%)       | <0.0001 |
| Fondaparinux                          | 56 (0.6%)       | 109 (0.7%)        | 0.57    |
| Aspirin                               | 8378 (93.5%)    | 14 896 (83.8%)    | 0.38    |
| Duration of PCI, min                  | 20 (11–33)      | 20 (11–32)        | 0.36*   |
| DES                                   | 5093 (60.2%)    | 8150 (54.2%)      | <0.0001 |
| BMS                                   | 3367 (39.8%)    | 6876 (45.8%)      | <0.0001 |
| Balloon angioplasty                   | 4193 (46.7%)    | 7200 (45.2%)      | 0.03    |

BMI indicates body mass index; BMS, bare metal stent; CABG, coronary artery bypass grafting; CHAMPION, Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition; CHF, congestive heart failure; DES, drug-eluting stent; HLD, hyperlipidemia; HTN, hypertension; LMWH low-molecular weight heparin; MI, myocardial infarction; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; STEMI, ST-segment–elevation myocardial infarction; and TIA, transient ischemic attack.

*F-test, all other P value are χ². Baseline characteristics stratified by BMI cutoff and by treatment allocation.
**End Points by BMI Category**

There was no significant difference in the primary end point among obese versus nonobese patients (4.3% versus 4.2%; RR, 1.01 [95% CI, 0.89–1.15]; P=0.82). There was a lower rate all-cause mortality among all patients who were obese versus nonobese at 48 hours (0.2% versus 0.4%, RR, 0.49 [95% CI, 0.29–0.85]; P=0.01) and at 30 days (0.9% versus 1.2%, RR 0.77 [95% CI, 0.60–1.00]; P=0.048). However, these associations were nonsignificant, when adjusted for age, sex, and diabetes (P=0.63 and 0.65, respectively). Obese patients were more likely than nonobese patients to experience stent thrombosis at 30 days (1.3% versus 1.0%, RR 1.27 [95% CI, 1.00–1.62]; P=0.047). There was no difference in any of the bleeding end points among obese versus nonobese patients (Table 2). In continuous models, there was also no significant association between BMI and the primary efficacy end point at 48 hours (P=0.81) or at 30 days (P=0.91) by treatment group, adjusted for age, sex, and diabetes.

There was a consistent benefit with respect to the primary end point at 48 hours in patients who received cangrelor versus clopidogrel who were obese (3.87% versus 4.66%, RR, 0.83 [95% CI, 0.68–1.02]; P=0.07) and not obese (3.75% versus 4.66%; RR, 0.81 [95% CI, 0.69–0.94]; P=0.0053); interaction P=0.77. There was also a similar reduction in the rate of the composite thromboembolic end point at 30 days in patients who received cangrelor versus clopidogrel who were obese (5.27% versus 6.02%; RR, 0.87 [95% CI, 0.73–1.03]; P=0.11) and not obese (5.09% versus 5.86%; RR, 0.88 [95% CI, 0.77–1.00]; P=0.056); interaction P=0.98 (Figure 1). When stratified by BMI and clinical trial (PLATFORM versus PCI versus PHOENIX), there were similar or better rates of efficacy with respect to the primary thrombotic end point at 48 hours. In CHAMPION PHOENIX, the most recent and largest of the trials, there was a significant benefit to using cangrelor in patients with a BMI ≥30 (OR, 0.70 [95% CI, 0.53–0.92]; Figure 2A).

At 48 hours, there was a similar reduction in stent thrombosis in patients who received cangrelor versus clopidogrel in patients who were obese (0.5% versus 0.9%; RR, 0.61 [95% CI, 0.37–1.01]; P=0.054) and nonobese (0.5 versus 0.8%; RR, 0.58 [95% CI, 0.39–0.86]; P=0.0069); interaction P=0.87. There was also a consistent reduction in stent thrombosis at 30 days in patients who received cangrelor versus clopidogrel who were obese (1.0% versus 1.5%; RR, 0.68 [95% CI, 0.47–0.99]; P=0.04) and nonobese (0.8% versus 1.2%; RR, 0.70 [95% CI, 0.51–0.96]; P=0.03); interaction P=0.90.

Among obese patients, there was no difference in any of the bleeding end points in patients who received cangrelor versus clopidogrel. However, among nonobese patients, there was a consistent benefit with respect to the primary end point at 48 hours (P=0.81) or at 30 days (P=0.91) by treatment group, adjusted for age, sex, and diabetes.

### Table 2. Summary of End Points Among Obese (BMI ≥30) Versus Nonobese (BMI <30) in the Combined CHAMPION Trials

| End point       | Event rate ratio (95% CI) | P value | Adjusted P value* | Adjusted interaction P value* |
|-----------------|--------------------------|---------|-------------------|------------------------------|
| **48-h efficacy end points** |             |         |                   |                              |
| Death/MI/IDR/ST | 1.01 (0.89–1.15)         | 0.82    | 0.2975            | 0.77                         |
| Death           | 0.49 (0.29–0.86)         | 0.01    | 0.0111            | 0.63                         |
| MI              | 1.08 (0.94–1.24)         | 0.28    | 0.0588            | 1.00                         |
| IDR             | 1.14 (0.83–1.57)         | 0.41    | 0.4275            | 0.10                         |
| ST              | 1.07 (0.78–1.47)         | 0.66    | 0.8946            | 0.87                         |
| Death/ST        | 0.88 (0.67–1.16)         | 0.36    | 0.3217            | 0.90                         |
| **30-d efficacy end points** |             |         |                   |                              |
| Death/MI/IDR/ST | 1.02 (0.92–1.14)         | 0.66    | 0.2163            | 0.98                         |
| Death           | 0.77 (0.60–1.00)         | 0.047   | 0.2542            | 0.66                         |
| MI              | 1.08 (0.95–1.24)         | 0.25    | 0.0643            | 0.57                         |
| IDR             | 1.15 (0.92–1.43)         | 0.22    | 0.3320            | 0.31                         |
| ST              | 1.27 (1.00–1.62)         | 0.047   | 0.1020            | 0.90                         |
| Death/ST        | 0.98 (0.82–1.18)         | 0.85    | 0.9394            | 0.74                         |
| **48-h bleeding** |             |         |                   |                              |
| GUSTO moderate/severe | 0.79 (0.57–1.08)         | 0.14    | 0.2613            | 0.26                         |
| Any TIMI bleeding | 0.83 (0.61–1.13)         | 0.24    | 0.3283            | 0.68                         |
| TIMI major      | 0.89 (0.52–1.52)         | 0.66    | 0.8984            | 0.46                         |
| TIMI minor      | 0.81 (0.55–1.17)         | 0.26    | 0.2893            | 1.00                         |
| Any blood transfusion | 0.81 (0.58–1.13)         | 0.21    | 0.2820            | 0.51                         |

BMI indicates body mass index; CHAMPION, Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition; GUSTO, Global Strategies for Opening Occluded Coronary Arteries; IDR, ischemia-driven revascularization; MI, myocardial infarction; ST, stent thrombosis; and TIMI, Thrombolysis in Myocardial Infarction.

*The adjusted group and interaction P value are produced by Poisson regression. The model is: logit(value)~treatment BMI(≥30) treatment*BMI(≥30) age sex diabetes.
Figure 1. Cumulative incidence of the primary end point (death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis).
Panel A represents events at 48 hours, and panel B at 30 d in obese (BMI ≥ 30) vs non-obese (BMI < 30) patients randomized to cangrelor vs clopidogrel. BMI indicates body mass index.
there was an increased risk of GUSTO moderate to severe bleeding among patients who received cangrelor versus clopidogrel (0.9% versus 0.6%; RR, 1.48 [95% CI, 1.03–2.11]; \(P=0.03\); Table 3). Of note, there was a significantly higher rate of GUSTO moderate bleeding (\(P=0.03\)) and of GUSTO moderate to severe bleeding (\(P=0.02\)) among all patients with lower BMI, when assessed continuously. There was a similar trend with bleeding when stratified by BMI cutoff and by individual trial—similar bleeding risk among patients with BMI≥30 and increase in bleeding risk with cangrelor among patients with BMI<30 (Figure 2b).

**Figure 2.** Forest plots of the treatment effect (patients randomized to cangrelor or clopidogrel) for the 48 h primary efficacy and safety end points, stratified by obesity (BMI≥30, BMI<30) and clinical trial (CHAMPION PHOENIX, CHAMPION PCI, CHAMPION PLATFORM). Panel A represents the primary composite end point (death, myocardial infarction [MI], ischemia-driven revascularization [IDR], and stent thrombosis [ST]). Panel B represents GUSTO (Global Use of Strategies to Open Occluded Arteries) severe/moderate bleeding. CHAMPION indicates Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition.

**Exploratory Analysis**

There were 5688 patients with a BMI<25, 10523 patients with a BMI 25 to <30, 6134 patients with a BMI 30 to <35, and 3017 patients with a BMI≥35. There was a similar reduction in the risk of having the primary end point among patients who received cangrelor versus clopidogrel who were obese (0.1% versus 0.2%; \(P=0.30\)) or nonobese (0.2% versus 0.2%; \(P=0.86\)).

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**CANGRELOR FOR OBESE PATIENTS UNDERGOING PCI**

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**Table 3. Summary of End Points Among Obese and Nonobese Patients Who Were Randomized to Cangrelor Versus Clopidogrel in the Combined CHAMPION Trials**

| BMI | End point        | Cangrelor (N=4601) | Clopidogrel (N=4550) | Event rate ratio (95% CI) | P value |
|-----|------------------|--------------------|----------------------|---------------------------|---------|
| ≥30 | 48-h efficacy end points |                    |                      |                           |         |
|     | Death/MI/IDR/ST  | 175/4514 (3.9)     | 208/4456 (4.7)       | 0.83 (0.68–1.02)          | 0.07    |
|     | Death            | 8/4514 (0.2)       | 9/4456 (0.2)         | 0.88 (0.34–2.27)          | 0.79    |
|     | MI               | 147/4514 (3.3)     | 171/4456 (3.8)       | 0.85 (0.68–1.06)          | 0.14    |
|     | IDR              | 31/4514 (0.7)      | 31/4456 (0.7)        | 0.99 (0.60–1.62)          | 0.96    |
|     | ST               | 24/4514 (0.5)      | 39/4456 (0.9)        | 0.61 (0.37–1.01)          | 0.05    |
|     | Death/ST         | 30/4514 (0.7)      | 46/4456 (1.0)        | 0.64 (0.41–1.02)          | 0.06    |
| <30 | 30-d efficacy end point |                |                      |                           |         |
|     | Death/MI/IDR/ST  | 241/4496 (5.4)     | 273/4426 (6.2)       | 0.87 (0.73–1.03)          | 0.11    |
|     | Death            | 43/4496 (1.0)      | 41/4426 (0.9)        | 1.03 (0.67–1.58)          | 0.88    |
|     | MI               | 155/4496 (3.4)     | 188/4426 (4.2)       | 0.81 (0.66–1.00)          | 0.05    |
|     | IDR              | 65/4496 (1.4)      | 65/4426 (1.5)        | 0.98 (0.70–1.39)          | 0.93    |
|     | ST               | 47/4496 (1.0)      | 68/4426 (1.5)        | 0.68 (0.47–0.99)          | 0.04    |
|     | Death/ST         | 78/4496 (1.7)      | 97/4426 (2.2)        | 0.79 (0.59–1.07)          | 0.12    |
|     | 48-h bleeding    |                    |                      |                           |         |
|     | GUSTO moderate/severe | 28/4555 (0.6)    | 28/4495 (0.6)        | 0.99 (0.58–1.67)          | 0.96    |
|     | Any TIMI bleeding | 36/4555 (0.8)     | 24/4495 (0.5)        | 1.48 (0.88–2.48)          | 0.14    |
|     | TIMI major       | 12/4555 (0.3)     | 8/4495 (0.2)         | 1.48 (0.61–3.62)          | 0.39    |
|     | TIMI minor       | 24/4555 (0.5)     | 16/4495 (0.4)        | 1.48 (0.79–2.79)          | 0.22    |
|     | Any blood transfusion | 26/4555 (0.6)  | 24/4495 (0.5)        | 1.07 (0.61–1.86)          | 0.81    |
| <30 | 30-d efficacy end points |            |                      |                           |         |
|     | Death/MI/IDR/ST  | 416/7904 (5.3)     | 474/7921 (6.0)       | 0.88 (0.77–1.00)          | 0.06    |
|     | Death            | 94/7904 (1.2)      | 99/7921 (1.2)        | 0.95 (0.72–1.26)          | 0.73    |
|     | MI               | 263/7904 (3.3)     | 299/7921 (3.8)       | 0.88 (0.75–1.04)          | 0.14    |
|     | IDR              | 88/7904 (1.1)      | 113/7921 (1.4)       | 0.78 (0.59–1.03)          | 0.08    |
|     | ST               | 66/7904 (0.8)      | 94/7921 (1.2)        | 0.70 (0.51–0.96)          | 0.03    |
|     | Death/ST         | 146/7904 (1.8)     | 170/7921 (2.1)       | 0.86 (0.69–1.07)          | 0.18    |
|     | 48-h bleeding    |                    |                      |                           |         |
|     | GUSTO moderate/severe | 75/8003 (0.9)   | 51/8037 (0.6)        | 1.48 (1.03–2.11)          | 0.03    |
|     | Any TIMI bleeding | 73/8003 (0.9)     | 55/8037 (0.7)        | 1.33 (0.94–1.89)          | 0.11    |
|     | TIMI major       | 20/8003 (0.2)     | 20/8037 (0.2)        | 1.00 (0.54–1.87)          | 0.99    |
|     | TIMI minor       | 53/8003 (0.7)     | 35/8037 (0.4)        | 1.52 (0.99–2.34)          | 0.06    |
|     | Any blood transfusion | 64/8003 (0.8)   | 46/8037 (0.6)        | 1.40 (0.96–2.04)          | 0.08    |

BMI indicates body mass index; CHAMPION, Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition; GUSTO, Global Strategies for Opening Occluded Coronary Arteries; IDR, ischemia-driven revascularization; MI, myocardial infarction; ST, stent thrombosis; and TIMI, Thrombolysis in Myocardial Infarction.
DISCUSSION

This large-scale analysis of the 3 CHAMPION trials reveals that cangrelor has a consistent benefit over clopidogrel with respect to ischemic events and stent thrombosis at 48 hours and at 30 days in obese and nonobese patients. There was no difference in any of the bleeding end points examined among obese patients who received cangrelor versus clopidogrel. The increasing global rates of obesity and concomitant complications of obesity such as coronary artery disease highlight the importance of these findings.

Understanding the subtleties of pharmacodynamics among obese and very obese patients has become increasingly relevant—in addition to the technical obstacles of performing PCI in this challenging patient population. It is interesting and encouraging to note that there were no differences in procedure length, rates of radial versus femoral arterial access or of successful PCI. Also, the rates of receiving a full 600 mg clopidogrel load were similar among obese and nonobese patients.

The distribution and characteristics of the patients in this study mimicked the so-called obesity paradox, in which obese patients have lower mortality from myocardial infarction, likely because of younger age and more stable presentation of coronary disease. As expected, there was lower unadjusted all-cause mortality among the obese patients when compared with the nonobese patients. As evidenced in the adjusted models, the lower all-cause mortality of the obese group is likely in large part due to an obesity paradox.

Table 4. Exploratory Analysis of Efficacy and Safety End Points by BMI Cutoffs

| BMI Cutoff | Cangrelor (N) | Clopidogrel (N) | Event rate ratio and 95% CI | P value |
|------------|---------------|----------------|-----------------------------|---------|
| BMI < 25   |               |                |                             |         |
| 48-h: death/MI/IDR/ST | 110/2818 (3.9) | 127/2748 (4.6) | 0.84 (0.65–1.09) | 0.19    |
| 30-d: death/MI/IDR/ST | 162/2804 (5.8) | 174/2731 (6.4) | 0.91 (0.73–1.12) | 0.37    |
| 48-h: GUSTO moderate/severe bleeding | 39/2844 (1.4) | 23/2776 (0.8) | 1.66 (0.99–2.77) | 0.05    |
| BMI 25 to < 30 |               |                |                             |         |
| 48-h: death/MI/IDR/ST | 188/5120 (3.7) | 244/5208 (4.7) | 0.78 (0.65–0.95) | 0.01    |
| 30-d: death/MI/IDR/ST | 254/5100 (5.0) | 300/5190 (5.8) | 0.86 (0.73–1.02) | 0.08    |
| 48-h: GUSTO moderate/severe bleeding | 36/5159 (0.7) | 28/5261 (0.5) | 1.31 (0.80–2.15) | 0.28    |
| BMI 30 to < 35 |               |                |                             |         |
| 48-h: death/MI/IDR/ST | 110/3034 (3.6) | 143/2986 (4.8) | 0.76 (0.59–0.97) | 0.03    |
| 30-d: death/MI/IDR/ST | 155/3021 (5.1) | 180/2968 (6.1) | 0.85 (0.68–1.05) | 0.13    |
| 48-h: GUSTO moderate/severe bleeding | 15/3058 (0.5) | 18/3012 (0.6) | 0.82 (0.41–1.63) | 0.57    |
| BMI ≥ 35    |               |                |                             |         |
| 48-h: death/MI/IDR/ST | 65/1480 (4.4) | 65/1470 (4.4) | 0.99 (0.70–1.40) | 0.97    |
| 30-d: death/MI/IDR/ST | 86/1475 (5.8) | 93/1458 (6.4) | 0.91 (0.68–1.23) | 0.55    |
| 48-h: GUSTO moderate/severe bleeding | 13/1497 (0.9) | 10/1483 (0.7) | 1.29 (0.56–2.94) | 0.52    |

BMI indicates body mass index; GUSTO, Global Strategies for Opening Occluded Coronary Arteries; IDR, ischemia-driven revascularization; MI, myocardial infarction; and ST, stent thrombosis.
measure due to comparing obese patients with older, frailer patients in the lowest BMI categories.4

Despite these differences, there was a similar benefit to receiving cangrelor versus clopidogrel in the obese and nonobese patients, suggesting against a differential treatment response among obese versus nonobese patients. The rates of both efficacy and bleeding among obese patients were very similar to those of the combined primary trials. There was an increased risk of GUSTO moderate to severe bleeding among nonobese patients who received cangrelor versus clopidogrel, and an increase with decreasing BMI analyzed continuously. Some other measures of serious bleeding trended in this direction among the nonobese group, but none reached significance. This trend toward an excess of bleeding seems to be driven by those in the lowest weight categories, as evidenced in the exploratory analysis and as has been described previously in other antiplatelet agents.22,23 After adjustment for age, sex, and geographic location, the increased bleeding was seen for all patients with a BMI ≤25, irrespective of treatment assignment.

Limitations of this study include the fact that this was not a prespecified analysis of the CHAMPION trials, and thus all P should be considered exploratory. Thus, we do not adjust for multiple comparisons. The 3 trials occurred over an extended time period, in which there were significant advances in clinical practice and stent technology as well as in prevalent pharmacological practices associated with PCI, potentially limiting the generalizability of the data from the earlier trials to current practice. However, when stratified by clinical trial, the benefit of cangrelor in obese patients was the most prominent in the most recent of the 3 trials, CHAMPION PHOENIX, which would be the most generalizable in terms of recent stent technology, medical therapy practices, and patient characteristics. Furthermore, the treatment allocation was randomized, and there appears to be even distribution of potential confounders among both obese and nonobese patients randomized to cangrelor versus clopidogrel. In addition, the very large sample size likely allows for the introduction of these new comparisons without introducing additional confounders.

CONCLUSIONS

There was a consistent benefit of cangrelor versus clopidogrel in obese and nonobese patients undergoing PCI, with respect to short-term efficacy. Also, there was no significant increase in periprocedural bleeding among obese patients undergoing PCI. Periprocedural cangrelor is a safe and effective antiplatelet option in obese patients.

ARTICLE INFORMATION

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