

ORIGINAL INVESTIGATIONS

# Platelet Reactivity in Patients With Acute Coronary Syndromes Awaiting Surgical Revascularization



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## ABSTRACT

**BACKGROUND** Dual antiplatelet therapy is recommended for patients with acute coronary syndromes (ACS).

Approximately 10% to 15% of these patients will undergo coronary artery bypass graft (CABG) surgery for index events, and current guidelines recommend stopping clopidogrel at least 5 days before CABG. This waiting time has clinical and economic implications.

**OBJECTIVES** This study aimed to evaluate if a platelet reactivity-based strategy is noninferior to standard of care for 24-h post-CABG bleeding.

**METHODS** In this randomized, open label noninferiority trial, 190 patients admitted with ACS with indications for CABG and on aspirin and P2Y<sub>12</sub> receptor inhibitors, were assigned to either control group, P2Y<sub>12</sub> receptor inhibitor withdrawn 5 to 7 days before CABG, or intervention group, daily measurements of platelet reactivity by Multiplate analyzer (Roche Diagnostics GmbH, Vienna, Austria) with CABG planned the next working day after platelet reactivity normalization (pre-defined as  $\geq 46$  aggregation units).

**RESULTS** Within the first 24 h of CABG, the median chest tube drainage was 350 ml (interquartile range [IQR]: 250 to 475 ml) and 350 ml (IQR: 255 to 500 ml) in the intervention and control groups, respectively (p for noninferiority <0.001). The median waiting period between the decision to undergo CABG and the procedure was 112 h (IQR: 66 to 142 h) and 136 h (IQR: 112 to 161 h) (p < 0.001), respectively. In the intention-to-treat analysis, a 6.4% decrease in the median in-hospital expenses was observed in the intervention group (p = 0.014), with 11.2% decrease in the analysis per protocol (p = 0.003).

**CONCLUSIONS** A strategy based on platelet reactivity-guided is noninferior to the standard of care in patients with ACS awaiting CABG regarding peri-operative bleeding, significantly shortens the waiting time to CABG, and decreases hospital expenses. (Evaluation of Platelet Aggregability in the Release of CABG in Patients With ACS With DAPT; NCT02516267) (J Am Coll Cardiol 2021;77:1277-86) © 2021 by the American College of Cardiology Foundation.



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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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## ABBREVIATIONS AND ACRONYMS

**ACS** = acute coronary syndromes

**AUC** = area under the curve

**ADP** = adenosine diphosphate

**CABG** = coronary artery bypass grafting

**DAPT** = dual antiplatelet therapy

**MDRD** = modification of diet in renal disease

**NSTEMI** = non-ST-segment elevation myocardial infarction

**STEMI** = ST-segment elevation myocardial infarction

Dual antiplatelet therapy (DAPT) with acetylsalicylic acid and P2Y<sub>12</sub> receptor blockers are recommended for patients with acute coronary syndromes (ACS), based on the demonstration of superiority of DAPTs compared with aspirin alone in reducing ischemic event occurrences such as stent thrombosis, ischemic stroke, and reinfarction (1–3).

Although recommended by guidelines, DAPT initiated at hospital admission can pose some challenges in 16% of patients with ACS who need to undergo coronary artery bypass graft (CABG) surgery for the index event (4). The major concerns are the increased risks of bleeding and the need for

blood transfusions (2,5). Recent exposure to DAPT before CABG surgery has been associated with an increased relative risk of death and reoperation of about 50% and 200%, respectively (6). To avoid excessive bleeding, current guidelines recommend a standardized 5-day pre-operative period of withdrawal for clopidogrel, 3 days for ticagrelor, and 7 days for prasugrel (7–10).

SEE PAGE 1287

It is well established that clopidogrel therapy is associated with highly variable antiplatelet response, with approximately 30% of patients showing inadequate response (11). These findings are explained mainly by suboptimal generation of clopidogrel-active metabolite secondary to genetic polymorphism (12); drug metabolism and interactions; and demographic, cellular, or clinical factors (13,14). Therapy with prasugrel and ticagrelor has been associated with less variability in platelet inhibition than clopidogrel; however, the recovery of platelet function is also variable with these drugs (15–17). Therefore, the one-size-fits-all waiting time may not benefit selected patients and may be associated with increased hospital stay, thus having negative impact on clinical complications and increased hospital expense.

The TARGET-CABG (Time Based Strategy to Reduce Clopidogrel Associated Bleeding Related to Coronary Artery Bypass Graft), a nonrandomized study, found that a strategy of waiting time to CABG based on thromboelastography in clopidogrel-treated patients was associated with the same amount of bleeding as in clopidogrel-naïve patients but with a 50% shorter pre-operative waiting period than recommended by the guidelines (18).

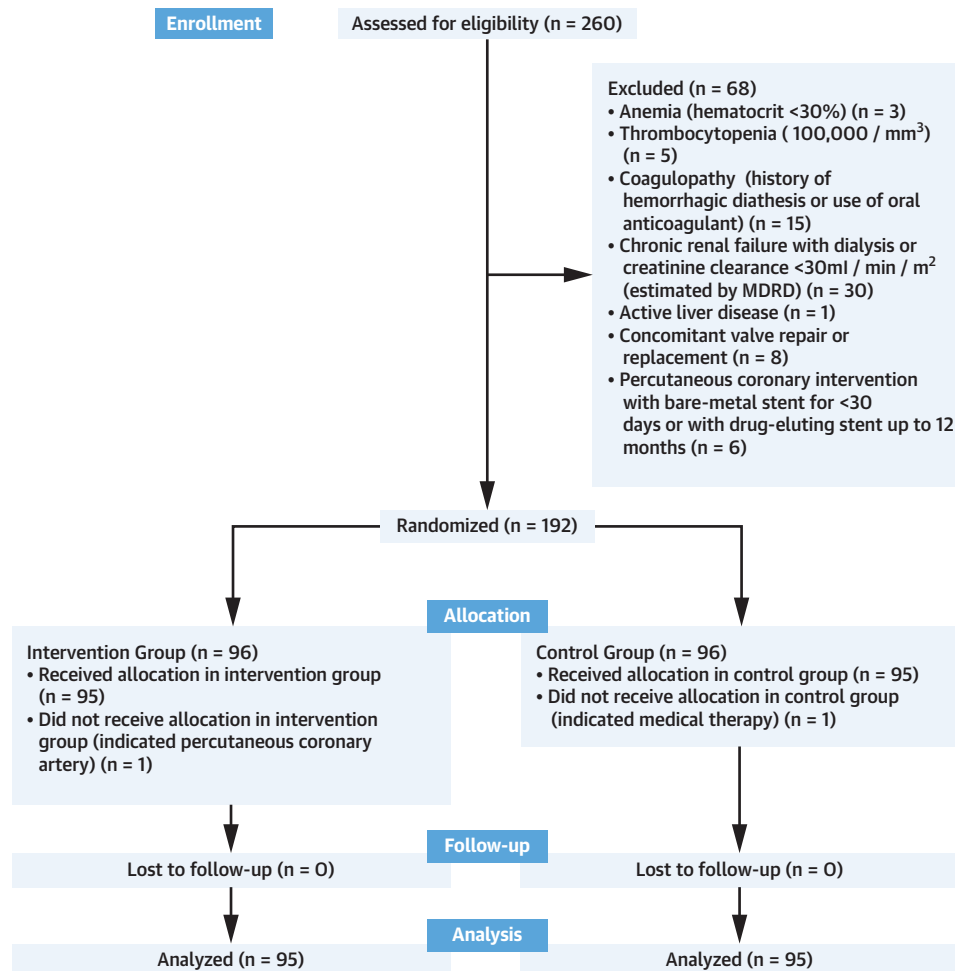
The Multiplate analyzer (Roche Diagnostics GmbH, Vienna, Austria) is an alternative to

thromboelastography to assess antiplatelet response to P2Y<sub>12</sub> receptor blockers. Previous reports showed a good correlation between the results of Multiplate analyzer and the need for platelet transfusion in the post-operative period after heart surgery (19,20). A recent North American statement preferentially recommends the use of “point of care” tests (e.g., Multiplate, VerifyNow [Accumetrics, Depew, New York], thromboelastography) over the traditional ones (20). In addition, North American and European guidelines recommend the use of platelet function tests to determine the timing of cardiac surgery in patients on P2Y<sub>12</sub> receptor-blocker therapy (8,21,22). However, no prospective randomized study using the Multiplate analyzer has been performed to determine the optimal timing of CABG surgery in patients treated with DAPT. The current study evaluated the strategy of timing of CABG surgery based on an assessment of antiplatelet effect of P2Y<sub>12</sub> receptor blockers using the Multiplate analyzer versus standard-of-care therapy in patients with ACS scheduled for CABG for the index event, aiming mainly to analyze its impact in bleeding, time to surgery, and hospital costs.

## METHODS

**PATIENT SELECTION.** PLAT-CABG (Platelet Reactivity in Patients with Acute Coronary Syndromes Awaiting Surgical Revascularization) was a randomized, single-center, open label, noninferiority study. Randomization was performed in blocks by an electronic system, and the surgeons and post-operative intensive care unit staff were blinded to the strategy allocation. All consecutive patients hospitalized in the Coronary Care Unit of the Heart Institute of the University of São Paulo Medical School, presenting with ACS with indication for CABG, were consented to participate in the study. The patients were on DAPT according to the guidelines (9,10). ACS clinical presentation consisted of unstable angina, ST-segment elevation myocardial infarction (STEMI) (type 1) and non-ST-segment elevation myocardial infarction (NSTEMI) (type 1). Unstable angina was defined as ischemic symptoms with unstable pattern associated with an electrocardiogram compatible with ischemia fulfilling 1 of the following criteria: new or presumably new ST-segment depression >0.5 mm in 2 contiguous leads or inversion of new or presumably new T-wave >1 mm in leads with wide R wave in 2 contiguous leads. The third universal definition of myocardial infarction (23) was applied to patients with STEMI and NSTEMI. The patient’s attending physician had the final decision regarding indication for CABG. The main inclusion criteria were age >18

**FIGURE 1** Study Flow Chart Diagram Showing the Number of Patients Screened, Excluded, and Analyzed



Modified with permission from Schulz et al. (27). MDRD = modification of diet in renal disease.

years, ACS as diagnosis, use of DAPT, and willingness to participate and sign the informed consent form. The main exclusion criteria were anemia (hematocrit <30%); thrombocytopenia (<100,000/mm<sup>3</sup>); coagulopathy (history of bleeding diathesis or use of oral anticoagulants); chronic renal failure dialysis or creatinine clearance <30 ml/min/m<sup>2</sup> (estimated by modification of diet in renal disease [MDRD] formula); active liver disease (alanine aminotransferase >3 times the upper limit of normal and total bilirubin >2 times the upper limit of normal); concomitant valve repair or replacement; percutaneous coronary intervention with bare-metal stent for fewer than 30 days or with drug-eluting stent up to 12 months; considering the randomization time,

use of streptokinase in the previous 48 h, or fibrin-specific fibrinolytic in the previous 24 h.

After obtaining written informed consent, patients were enrolled and randomly assigned to 2 groups. The control group comprised patients who had discontinued P2Y<sub>12</sub> receptor-blocker therapy 5 to 7 days before CABG. The intervention group included patients who underwent daily measurements of platelet reactivity to adenosine diphosphate (ADP), using the Multiplate analyzer; patients were eligible for CABG when platelet reactivity reached ≥46 area under the curve (AUC). Aspirin 100 mg/day was maintained, and CABG was performed in the next day.

CABG surgery was performed according to local practices, with the surgical technique following the

**TABLE 1** Baseline Characteristics of the Population\*

	Intervention (n = 95)	Control (n = 95)
Age, yrs	61.26 ± 8.15	61.63 ± 9.58
Male	69 (72.6)	71 (74.7)
BMI, kg/m <sup>2</sup>	27 (25-30)	27 (25-30)
ACS		
STEMI	28 (29.5)	31 (32.6)
NSTEMI	62 (65.2)	63 (66.3)
Unstable angina	5 (5.3)	1 (1.1)
Ejection fraction, %	60 (45-61)	56.5 (45.75-60)
Creatinine, mg/dl	1.03 (0.85-1.17)	0.98 (0.85-1.19)
Hypertension	72 (75.8)	71 (74.7)
Diabetes	47 (49.5)	47 (49.5)
Dyslipidemia	49 (51.6)	52 (54.7)
History of MI	23 (24.2)	23 (24.2)
History of stent	11(11.6)	16 (16.8)
Number of diseased vessels		
1	3 (3.1)	1 (1.1)
2	17 (17.9)	24 (25.2)
≥3	75 (79)	70 (73.7)
Left main disease	21 (24.9)	15 (16.5)
Killip class		
I	92 (96.8)	92 (96.8)
II	3 (3.2)	3 (3.2)
EuroSCORE II	1.32 (0.99-1.68)	1.24 (0.97-1.78)
Bleeding risk score	13 (8-18)	13 (9-17)
Morphine in admission	2 (2.1)	2 (2.1)
Previous use of medications		
Aspirin	33 (34.7)	35 (37.2)
β-blockers	35 (36.8)	32 (34.0)
ACE inhibitors/ARBs	35 (36.8)	30 (31.9)
Statins	64 (67.4)	54 (56.8)
Oral hypoglycemic	32 (34.0)	35 (37.2)
Insulin	7 (7.4)	7 (7.4)

Values are mean ± SD, n (%), or median (interquartile range). \*All p = NS.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; BMI = body mass index; EuroSCORE = European system for cardiac operative risk evaluation; IQR = interquartile range; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

surgeon's preference, with or without the use of cardiopulmonary bypass. This study was conducted according to the protocol approved by the Scientific Committee of InCor, by the Research Ethics Committee of HC/FMUSP.

**PLATELET FUNCTION TESTING.** In the intervention group, blood samples were obtained by venipuncture daily at 8:00 AM to 9:00 AM and on the immediate post-operative day; in the control group, blood samples were obtained immediately before and after CABG. Platelet reactivity was assessed by the Multiplate analyzer, using the ADP test.

The Multiplate analyzer measures the aggregometry of whole blood by the electrical impedance between 2 electrodes immersed in whole blood, 6 min after the addition of an agonist. The increase in impedance correlates with the amount of platelet

aggregates that are deposited on the electrodes after the addition of the agonist. The agonist used was ADP to specifically assess the effect of P2Y<sub>12</sub> receptor blockers. The graph of electrical impedance is drawn according to the reaction time, so that the aggregometry is evaluated by the AUC (24).

**STUDY ENDPOINTS.** The primary endpoint was the volume (in ml) of chest-tube drainage in the first 24 h post-CABG. The main secondary endpoints were need for blood transfusion, waiting time to CABG, in-hospital all-cause mortality, and hospital expenses from the perspective of the Brazilian Government Health System.

**ANALYSIS OF HOSPITAL EXPENSES.** Hospital expenses (expressed in Brazilian currency: Reais) were estimated in an economic evaluation proposed by Silva et al. (25). We analyzed the costs related to interventions and expenses according to the values contained from the perspective of the Brazilian Government Health System (Supplemental Table 1) and the cost of the platelet function test by the Multiplate analyzer.

**STATISTICAL ANALYSIS.** Details of the statistical analysis and sample size calculations are provided in the Supplemental Appendix (Statistical Methods on page 1). Briefly, the analysis of the primary endpoint was performed by the Mann-Whitney *U* Test for noninferiority (1-tailed). Variance was estimated from the interquartile range using the Hozo method (26) and confidence intervals (CIs) obtained to calculate *p* for noninferiority under the null hypothesis of more bleeding (24-h chest-tube output) in the intervention group. For this hypothesis, a pre-specified noninferiority margin of 25% increase in bleeding in the intervention group was considered, based on previous literature data (18). This means that noninferiority would be met if 95% upper boundary of the CI for difference in the primary endpoint between both groups did not cross a value, in ml, of 25% the actual 24-h chest-tube output observed in the control group (i.e., ruling out an 25% increase in 24-h chest-tube output with the intervention platelet function-based strategy). Post hoc per-protocol analyses were performed in patients who followed the specified protocol and underwent CABG on the day after the authorization for the CABG to be performed.

For the noninferiority hypothesis tests, a *p* < 0.025 (1-tailed) was considered statistically significant. For other tests, a 2-tailed *p* < 0.05 was considered, unless otherwise specified. The statistical software package used for statistical analysis was

the SPSS 24.0 (Microsoft, Chicago, Illinois). All the statistical analyses, including the sample size calculation, were developed by an independent statistician.

## RESULTS

**STUDY POPULATION.** As shown in [Figure 1](#) (27), a total of 260 patients were assessed for eligibility; 68 patients were excluded for different reasons. In addition, 2 patients (1 intervention group and 1 control group) were excluded because of a failure to undergo surgery. In the end, 190 patients taking DAPT with aspirin and clopidogrel (n = 188), or ticagrelor (n = 2) were randomized and included in the study.

Baseline characteristics are presented in [Table 1](#). As expected, the intervention group and the control group were well balanced. The majority of patients were male, with mean age of 61 years, presenting with NSTEMI and Killip 1. In general, patients had high cardiovascular risk profiles (approximately 50% had diabetes, two-thirds had coronary obstruction in 3 or more vessels, and approximately 20% had left main coronary disease obstruction). On the other hand, the population showed a relatively low EuroSCORE II and bleeding scores.

Importantly, there were no significant differences in baseline characteristics between the control group and intervention groups both, for the whole population and for the population included in the per-protocol analyses ([Supplemental Table 2](#)).

**PERI-OPERATIVE PATIENT CHARACTERISTICS.** The intraoperative characteristics of patients are presented in [Table 2](#). Intervention and control groups had similar characteristics, such as cardiopulmonary bypass time (91 vs. 95 min, respectively) and cross-clamp time (68 vs. 73 min, respectively). In addition, no significant differences in peri-operative patient characteristics were observed between the intervention and control groups, both for the general population and for patients included in the per-protocol analyses ([Supplemental Table 3](#)).

**PERI-OPERATIVE LABORATORY MEASUREMENTS.** Fibrinogen, D-dimer, platelet count, and platelet reactivity to ADP measured at immediate post-operative time were similar between intervention and control groups ([Table 2](#)). On the other hand, international normalized ratio (INR) (1.2 vs. 1.28, p = 0.019) and activated partial thromboplastin time (aPTT) (28.8 vs. 30.9, p = 0.02) levels were significantly higher in the control group, despite the fact that the absolute differences were small and probably not clinically relevant.

**TABLE 2** Intraoperative and Immediate Post-Operative Characteristics

	Intervention (n = 95)	Control (n = 95)
Duration of surgery, min	360 (300-420)	360 (360-420)
CPB time, min	91 (71-105)	95 (80-111)
Cross-clamp, min	68.39 ± 26.56	73.38 ± 29.1
Venous grafts		
0	10 (10.5)	11 (11.6)
1	25 (26.3)	13 (13.7)
2	43 (45.3)	52 (54.7)
3	17 (17.9)	18 (18.95)
4	0 (0.0)	1 (1.05)
Arterial grafts		
0	8 (8.4)	2 (2.1)
1 (left internal mammary)	74 (77.9)	80 (84.2)
2 (left and right internal mammary)	11 (11.6)	10 (10.5)
2 (left internal mammary and radial)	2 (2.1)	2 (2.1)
3 (left and right internal mammary and radial)	0 (0.0)	1 (1.1)
INR at ICU arrival	1.20 (1.1-1.3)	1.22 (1.2-1.3)*
aPTT at ICU arrival, s	29 (27-32)	31(28-33)†
Fibrinogen at ICU arrival, mg/dl	289 (240-360)	304 (251-346)
D-dimer at ICU arrival, µg/dl	0.59 (0.4-0.81)	0.63 (0.37-1.13)
Platelets at ICU arrival, platelet/µl	172,000 (146,750-218,000)	174,000 (132,000-215,000)
Mean platelet volume at ICU arrival, fl	10 (8-11)	10 (7-11)
Platelet reactivity at ICU arrival, AUC	64.64 ± 29.34	65.98 ± 31.44

Values are median (interquartile range), mean ± SD, or n (%). \*p = 0.014; †p = 0.020; all other p = NS.  
aPTT = activated partial thrombotic time; AUC = area under the curve; CPB = cardiopulmonary bypass; fl = femtoliter; ICU = intensive care unit; INR = international normalization ratio.

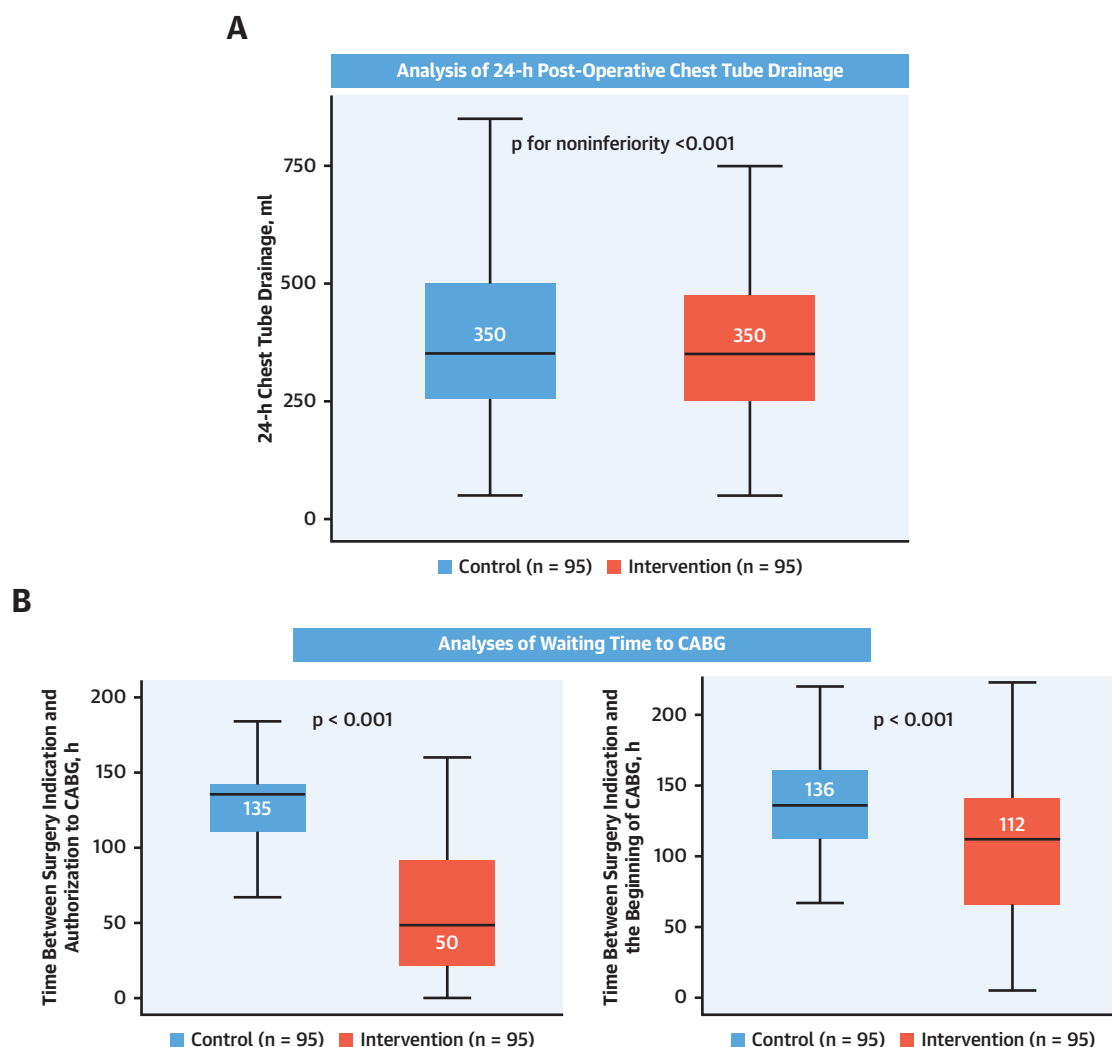
**PRIMARY ENDPOINT.** The median chest tube drainage was 350 ml (interquartile range [IQR]: 250 to 475 ml) and 350 ml (IQR: 255 to 500 ml), respectively, in the intervention and control groups. Considering a noninferiority margin of 25% increase in bleeding with the intervention arm—that is, 88 ml more bleeding—a significant p value for noninferiority was met (<0.001) ([Central Illustration](#)). The 95% CI for the difference between medians was -50 to 70 ml.

In per-protocol analyses, the median chest-tube drainage was numerically smaller in the intervention compared with the control group 345 ml (IQR: 215 to 525 ml) versus 350 ml (IQR: 250 to 500 ml), respectively (p for noninferiority <0.001).

**BLOOD TRANSFUSIONS.** There were no differences in red blood cell (23.5% vs. 23.5%), platelets (5.3% vs. 4.3%), and fresh plasma (3.3% vs. 1.1%) transfused in the intervention group versus control group (p = 0.452, p = 0.733, and p = 0.642, respectively).

**WAITING TIME TO CABG.** Evaluation of waiting time to CABG is depicted in [Central Illustration and Table 3](#). The waiting time between the indication for surgery and the authorization for the surgeon to proceed with the procedure was reduced by 85 h in the intervention group versus control group (50 h vs. 135 h;

# CENTRAL ILLUSTRATION Main results of the PLAT-CABG Study



Nakashima, C.A.K. et al. J Am Coll Cardiol. 2021;77(10):1277-86.

Analyses of (A) 24-h post-operative chest-tube drainage and (B) waiting time to CABG in patients with acute coronary syndromes. CABG = coronary artery bypass graft; PLAT-CABG = Platelet Reactivity in Patients with Acute Coronary Syndromes Awaiting Surgical Revascularization.

$p < 0.001$ ), and the time between the indication for surgery and the beginning of the procedure was 24 h shorter in the intervention group (112 h vs. 136 h;  $p < 0.001$ ). The median length of hospital stay was similar with 356.3 h (IQR: 283.5 to 427 h) in the intervention group compared with 367.3 h (IQR: 324 to 459 h) in the control group ( $p = 0.10$ ).

The analyzed times obtained in the per-protocol analyses are shown in Table 4. There was a significant reduction of 81 h between the indication for surgery and the authorization for the surgeon to proceed ( $p < 0.001$ ), and of 55 h between the

indication for surgery and the beginning of the procedure ( $p < 0.001$ ). The total length of hospital stay was 58 h shorter in the intervention group compared with the control group (297 h [IQR: 236 to 412 h] vs. 355 h [IQR: 307 to 447 h];  $p = 0.009$ ).

**IN-HOSPITAL ALL-CAUSE MORTALITY.** There were 3 deaths in each group. In the intervention group, the cause of death was sepsis in all cases; in the control group, the causes of death were cardiogenic shock in 1 case, hemorrhagic shock in another case, and sepsis in the third case. There were 5 and 3 patients



**TABLE 3** Evaluation of Waiting Time to CABG

	Intervention (n = 95)	Control (n = 95)	p Value
Time between surgery indication and authorization to CABG, h	50 (22-92)	135 (111-142)	<0.001
Time between the surgery indication and the beginning of CABG, h	112 (66-142)	136 (112-161)	<0.001

Values are median (interquartile range). p values indicate differences between intervention group and control group.  
CABG = coronary artery bypass graft.

with major adverse cardiac events (MACE) (CV deaths, myocardial infarction, stroke, or new revascularization) in the intervention and control groups, respectively.

**ECONOMIC ANALYSES.** The economic analyses are depicted in [Figure 2](#). Considering the intention-to-treat analyses, the median hospital expenses for the intervention and control groups were, respectively, R\$15,202.33 (IQR: R\$13,609.12 to R\$17,647.32) and R\$16,251.37 (IQR: R\$14,838.51 to R\$18,178.82) (difference of R\$1,049.04, or 6.4%;  $p = 0.014$ ). By per-protocol analyses, the median hospital expenses for the intervention group were R\$14,248.41 (IQR: R\$12,954.77 to R\$16,444.48) and for the control group R\$16,039.55 (IQR: R\$14,561.30 to R\$17,993.93) (difference of R\$1,791.14 or 11.2%;  $p = 0.003$ ).

## DISCUSSION

**BLEEDING POST-CABG.** To the best of our knowledge, this is the first prospective randomized study analyzing the safety of a platelet function analysis-based strategy in patients with ACS undergoing CABG. We demonstrated that personalized strategy based on platelet-function measurement is safe with similar median chest-tube drainage in the first 24 h after surgery (350 ml in both groups) with a significant p value for noninferiority ( $<0.001$ ). Our chest-tube drainage values are smaller than those obtained in previous studies, in which values ranging from 540 ml to 680 ml were reported ([4,18,28,29](#)). These differences could be related to the fact that we selected only highly experienced surgeons to perform the surgery in our patients, or the fact that, with only 1 exception, the other studies did not use the platelet-reactivity evaluation to authorize the clearance for surgery.

During the last decade, several studies have demonstrated a good correlation between platelet-reactivity measurement before surgery and the amount of bleeding in the peri- and post-operative period. Most of these studies were observational, with retrospective information from medical records ([30,31](#)), or even prospective, but without randomization ([18,32-34](#)). Agarwal et al. ([35](#)) performed a randomized study with 249 patients (173 had used anti-ADP in the 5 days before the intervention) to evaluate platelet reactivity tests as a guide for the use blood transfusion in patients undergoing CABG and demonstrated a significant reduction in the need for blood transfusion and lower hospital cost. However, as already mentioned, these researchers used the platelet-reactivity tests as part of an algorithm to determine the need for transfusions and not as a tool for clinical decision making to determine timing of the surgical intervention.

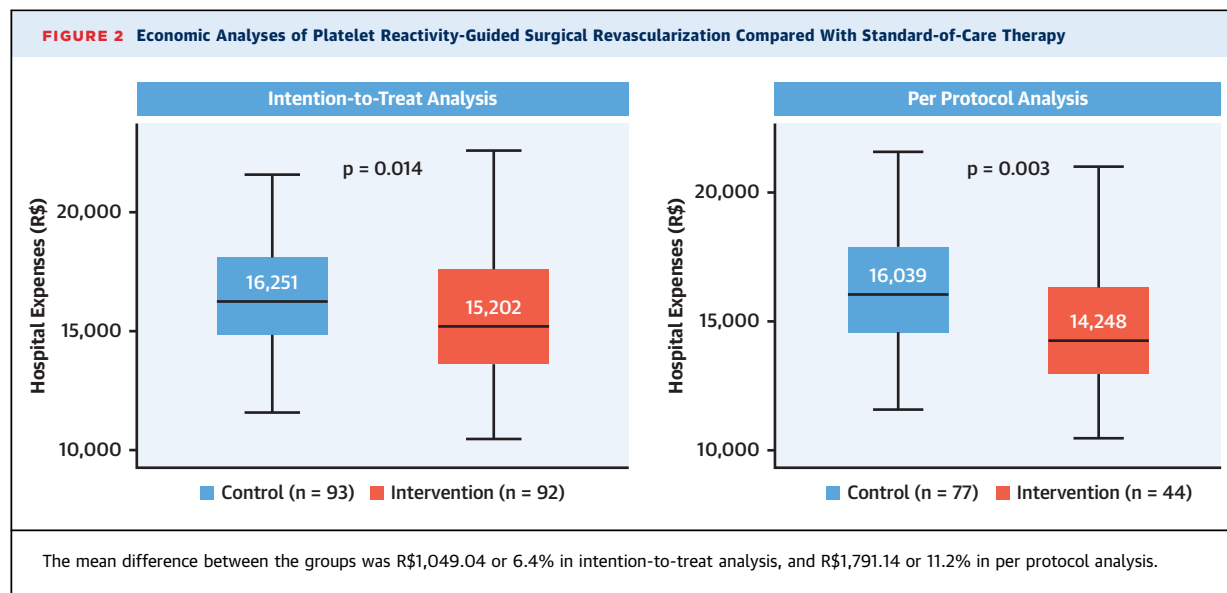
**BLOOD TRANSFUSIONS.** We analyzed the incidence of blood transfusion during the intraoperative period, the first 24 h post-CABG, and the total hospitalization period; there were no statistically significant differences between the groups in any of the performed analyses. Chen et al. ([36](#)) performed a prospective study with 90 patients, using an algorithm that evaluated clinical information of the patient and platelet reactivity measured before CABG and found a significant correlation between the number of transfusions with low platelet reactivity before CABG.

**WAITING TIME TO CABG.** As pointed out earlier, the antiplatelet response to clopidogrel varies widely ([11-17](#)), and this may affect the incidence of bleeding during surgery. Actually, approximately 30% of the population taking clopidogrel has inadequate or no antiplatelet response ([37](#)). In this context, the

**TABLE 4** Evaluation of Waiting Time to CABG in Per-Protocol Analysis

	Intervention (n = 45)	Control (n = 78)	p Value
Time between surgery indication and authorization to CABG, h	40 (21-92)	121 (109-142)	<0.001
Time between the surgery indication and the beginning of CABG, h	66 (43-104)	121 (109-142)	<0.001

Values are median (interquartile range). p values indicate differences between intervention group and control group.  
CABG = coronary artery bypass graft.



guideline recommendation to wait at least 5 days before major surgery after withdrawing the clopidogrel is relatively arbitrary, as it does not consider the variable antiplatelet response to P2Y<sub>12</sub> receptor blockers. As a consequence, more than needed waiting periods in some patients may increase the risk of ischemic complications and infections.

This study demonstrated that a strategy based on platelet-function measurement by Multiplate analyzer shortened by 60% the waiting period between the decision for CABG and the authorization for the surgeon to proceed with the intervention, without increasing CABG-related bleeding. Other studies reported similar results; in a case-control study in which platelet reactivity was analyzed with the PFA-100 system in patients treated with DAPT, Mannacio et al. (32) showed a reduction of 3.6 ± 1.7 days in the waiting time to CABG. Using thromboelastography to assess platelet function in patients treated with DAPT, the TARGET-CABG study (18) found a 46% reduction in the waiting time to surgery. In our study we showed a 60% decrease in the waiting time using the Multiplate analyzer, which is less expensive.

**ECONOMIC ANALYSES.** Cardiovascular diseases are ranked first among hospital costs in Brazil, North America, or Europe (38-40). It has been reported that efficiency in the management of health services should address initiatives aimed at reducing pre-operative time (41). In 2015, the average length of hospital stay for surgical revascularizations covered by Brazilian Government Health System was 12.8 days (42), and a significant reduction in waiting will lead to a great impact on expenses by public and private

health insurers. The current study reduced hospital expenses per patient by 6.4% (p = 0.014) by intention-to-treat analysis and 11.2% according to per protocol analysis (p = 0.003). For an estimated 70,000 CABG procedures per year in Brazil (43), we estimate that the implementation of this routine would save up to R\$125,370,000.00 per year.

Moreover, the in-hospital expenditures of the Brazilian government health system are much lower compared with European and North American countries. According to the World Health Organization (44), the gross national income per capita is approximately 3 to 4 times higher in the United States (\$53,960), Sweden (\$44,760), and United Kingdom (\$35,760) compared with Brazil (\$14,750). As expected, the government expenditures on health per capita are also much higher in the United States (\$9,403), Sweden (\$5,219), and the United Kingdom (\$3,377), in comparison with Brazil (\$1,318). The United States spends an estimated \$6.5 billion per year on CABG procedures (45); the implementation of the strategy tested in the current study could save between \$416,000,000 (6.4% decrease obtained in the intention to treat analyses) and \$728,000,000 (11.2% obtained in the as-protocol analyses).

**STUDY LIMITATIONS.** This study was in a single center with quaternary characteristics, a high surgical volume (730 CABG procedures in 2019). Also, only patients with ACS undergoing CABG in the same hospitalization were included; therefore, our findings may not be applicable to other populations (such as stable patients with CAD post-percutaneous coronary intervention on DAPT). Finally, the pre-specified



interim analyses developed for safety purposes led to a recalculation of the trial sample size during the study.

## CONCLUSIONS

A strategy based on platelet reactivity measurement is noninferior to standard of care in patients with ACS awaiting CABG with respect to peri-operative bleeding and is associated with significantly shorter waiting periods and lower hospital expenses.

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## PERSPECTIVES

### COMPETENCY IN PATIENT CARE AND PROCEDURAL

**SKILLS:** In patients with acute coronary syndromes awaiting coronary artery bypass surgery, management based on measurements of platelet reactivity can facilitate earlier surgery while avoiding excess peri-operative bleeding.

**TRANSLATIONAL OUTLOOK:** Further research is needed to determine whether measurement of platelet reactivity can improve the safety and efficiency of revascularization-care pathways in other clinical settings.

## REFERENCES

1. Mehta SR, Yusuf S. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. *Eur Heart J* 2000;21:2033-41.
2. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1607-21.
3. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.
4. Gimbel M, Qaderdan K, Willemsen L, et al. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. *Lancet* 2020;395:1374-81.
5. Nicolau JC, Moreira HG, Baracioli LM, et al. The bleeding risk score as a mortality predictor in patients with acute coronary syndrome. *Arq Bras Cardiol* 2013;101:511-8.
6. Nijjer SS, Watson G, Athanasios T, et al. Safety of clopidogrel being continued until the time of coronary artery bypass grafting in patients with acute coronary syndrome: a meta-analysis of 34 studies. *Eur Heart J* 2011;32:2970-88.
7. Ferraris VA, Saha SP, Oestreich JH, et al. 2012 update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations. *Ann Thorac Surg* 2012;94:1761-81.
8. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61:78-140.
9. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;64:139-228.
10. Neuman F-J, Sousa- Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2018;40:87-165.
11. Stone GW, Witzensichler B, Weisz G, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet* 2013;382:614-23.
12. Aradi D, Storey RF, Komocsi A, et al. Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. *Eur Heart J* 2014;35:209-15.
13. Aradi D, Kirtane A, Bonello L, et al. Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. *Eur Heart J* 2015;36:1762-71.
14. Furtado RH, Giugliano RP, Strunz CM, et al. Drug interaction between clopidogrel and ranitidine or omeprazole in stable coronary artery disease: a double-blind, double dummy, randomized study. *Am J Cardiovasc Drugs* 2016;16:275-84.
15. Nicolau JC, Bhatt DL, Roe MT, et al. Concomitant proton-pump inhibitor use, platelet activity, and clinical outcomes in patients with acute coronary syndromes treated with prasugrel versus clopidogrel and managed without revascularization: insights from the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes trial. *Am Heart J* 2015;170:680-94.

16. Malm CJ, Hansson EC, Akesson J, et al. Preoperative platelet function predicts perioperative bleeding complications in ticagrelor-treated cardiac surgery patients: a prospective observational study. *Br J Anaesth* 2016;117:309-15.
17. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009;120:2577-85.
18. Mahla E, Suarez TA, Bliden KP, et al. Platelet function measurement-based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing coronary artery bypass graft surgery: the timing based on platelet function strategy to reduce clopidogrel-associated bleeding related to CABG (TARGET-CABG) study. *Circ Cardiovasc Interv* 2012;5:261-9.
19. Kong R, Trimmings A, Hutchinson N, et al. Consensus recommendations for using the Multiplate for platelet function monitoring before cardiac surgery. *Int J Lab Hematol* 2015;37:143-7.
20. Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y<sub>12</sub> receptor inhibitor treatment in percutaneous coronary intervention. *J Am Coll Cardiol* 2019;12:1521-37.
21. Boer C, Meesters MI, Milojevic M, et al. 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. *J Cardiothorac Vasc Anesth* 2018;32:88-120.
22. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;39:213-60.
23. Thygesen K, Alpert SA, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation* 2012;126:2020-35.
24. Ltd RDI. Multiplate analyzer: cut-off-values ADPtest and ASPItest. Available at: <https://diagnostics.roche.com/global/en/products/instruments/multiplate-6-analyzer.html>. Accessed January 25, 2015.
25. Silva EN, Silva MT, Pereira MG. Identifying, measuring and valuing health costs. *Epidemiol Serv Saude* 2016;25:437-9.
26. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13.
27. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
28. Held C, Asenblad N, Bassand JP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO. *J Am Coll Cardiol* 2011;57:672-84.
29. Kacar SM, Mikic A, Kacar MB. Postoperative bleeding following preoperative clopidogrel administration in patients with haemoglobin level above 110 g/L undergoing urgent CABG. *Braz J Cardiovasc Surg* 2018;33:59-63.
30. Chowdhury M, Shore-Lesserson L, Mais AM, et al. Thromboelastograph with platelet mapping (TM) predicts postoperative chest tube drainage in patients undergoing coronary artery bypass grafting. *J Cardiothorac Vasc Anesth* 2014;28:217-23.
31. Ranucci M, Colella D, Baryshnikova E, et al. Effect of preoperative P2Y<sub>12</sub> and thrombin platelet receptor inhibition on bleeding after cardiac surgery. *Br J Anaesth* 2014;113:970-6.
32. Mannacio V, Meier P, Antignano A, et al. Individualized strategy for clopidogrel suspension in patients undergoing off-pump coronary surgery for acute coronary syndrome: a case-control study. *J Thorac Cardiovasc Surg* 2014;148:1299-306.
33. Della Corte A, Bancone C, Spadafora A, et al. Postoperative bleeding in coronary artery bypass patients on double antiplatelet therapy: predictive value of preoperative aggregometry. *Eur J Cardiothorac Surg* 2017;52:901-8.
34. Mahla E, Prueller F, Farzi S, et al. Does platelet reactivity predict bleeding in patients needing urgent coronary artery bypass grafting during dual antiplatelet therapy? *Ann Thorac Surg* 2016;102:2010-7.
35. Agarwal S, Johnson RI, Shaw M. Preoperative point-of-care platelet function testing in cardiac surgery. *J Cardiothorac Vasc Anesth* 2015;29:333-41.
36. Chen L, Bracey AW, Radovancevic R, et al. Clopidogrel and bleeding in patients undergoing elective coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2004;128:425-31.
37. Gurbel PA, Bliden KP, Hiatt BL, et al. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003;107:2908-13.
38. Ribeiro AL, Duncan BB, Brandt LCC, et al. Cardiovascular health in Brazil. *Circulation* 2016;133:422-43.
39. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation* 2019;139:e56-529.
40. Wilkins E, Wilson L, Wickramasinghe K, et al. European Cardiovascular Disease Statistics 2017. Brussels, Belgium: European Heart Network, 2017.
41. Silva GS, Sousa AG, Soares D, et al. Evaluation of the length of hospital stay in cases of coronary artery bypass graft by payer. *Rev Assoc Med Bras* 2013;59:248-53.
42. Bienert IRC, Rodrigues A, Harada EA, et al. Temporal evaluation of coronary revascularization procedures performed through the Unified Health System (SUS) in Brazil: a 20-year overview. *Int J Cardiovasc Sci* 2017;30:380-90.
43. da Ministério Saúde. DATASUS. (Departamento de Informática do SUS). Available at: <http://tabnet.datasus.gov.br/>. Accessed January 15, 2020.
44. World Health Organization Country Statistics. Available at: <http://www.who.int/countries/en/>. Accessed June 12, 2020.
45. Guduguntla V, Syjamaki JD, Ellimoottil C, et al. Drivers of payment variation in 90-day coronary artery bypass grafting episodes. *JAMA Surg* 2018;153:14-9.

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**KEY WORDS** acute coronary syndrome, myocardial revascularization, platelet reactivity

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**APPENDIX** For supplemental material and tables, please see the online version of this paper.