Aspirin responsiveness safely lowers perioperative cardiovascular risk

Daniela Calderaro, MD, PhD,[a] Adriana Feio Pastana, BSBIO,[a] Tania Rubia Flores da Rocha, PharmD,[b] Pai Ching Yu, MD, PhD,[a] Danielle Menosi Gualandro, MD, PhD,[a] Nelson DeLuccia, MD, PhD,[c] Élbio Antônio D`Amico, MD, PhD,[b] and **Bruno Caramelli, MD, PhD,[a]** *São Paulo, Brazil*

Introduction: **Vascular surgeries are related to high cardiac morbidity and mortality, and the maintenance of aspirin in the perioperative period has a protective effect. The purpose of this study was to evaluate the association between preoperative platelet aggregability and perioperative cardiovascular (CV) events.**

Methods: **A preoperative platelet aggregation test was performed on an impedance aggregometer in response to collagen and to arachidonic acid (AA) for 191 vascular surgery patients under chronic use of aspirin. We analyzed the following CV events: acute myocardial infarction, unstable angina, isolated troponin elevation, acute ischemic stroke, reoperation, and cardiac death. Hemorrhagic events were also evaluated and classified according to the Thrombolysis In Myocardial Infarction criteria.**

Results: **The incidence of CV events was 22% (n = 42). Higher platelet response to AA was associated with CV events, so that patients in the fourth quartile (higher than 11Ω) had almost twice the incidence of CV events when compared with the three lower quartiles: 35% vs 19%; $P = .025$. The independent predictors of CV events were hemodynamic instability during anesthesia (odds ratio [OR], 4.12; 95% confidence interval [CI], 1.87-9.06; $P < .001$), dyslipidemia (OR, 3.9; 95% CI, 1.32-11.51; $P = .014$), preoperative anemia (OR, 2.64; 95% CI, 1.19-5.85; $P = .017$), and AA platelet aggregability in the upper quartile (OR, 2.48; 95% CI, 1.07-5.76; $P = .034$). Platelet aggregability was not associated with hemorrhagic events, even when we compared the lowest quartile of AA platelet aggregability (0-1.00 Ω) with the three upper quartiles (>1.00 Ω; OR, 0.77; 95% CI, 0.43-1.37; $P = .377$).**

Conclusions: **The degree of aspirin effect on platelet aggregability maybe important in the management of perioperative CV morbidity, without increment in the bleeding toll. (J Vasc Surg 2013;58:1593-9.)**

Vascular surgeries are related to high morbidity mainly due to acute cardiac events.[1] Recent data unraveled the great debate regarding the underlying mechanism of perioperative myocardial ischemia, and the current concept is that, besides myocardial oxygen supply and demand mismatch, the classical atherothrombosis is a determinant factor.[2]

The perioperative use of beta-blockers attenuates the oxygen mismatch,[3-5] while statins[6-8] and acetylsalicylic acid[9] are targeted for atherothrombosis prevention.

The American Heart Association and American College of Cardiology Guidelines (AHA/ACC),[1] the European Society of Cardiology (ESC) guidelines,[10] and the Brazilian Society of Cardiology guidelines for perioperative evaluation[11] recommend that aspirin should not be discontinued in the perioperative period of vascular surgeries as the benefit of platelet anti-aggregation outweighs the bleeding risk.[12,13] Burger et al have found in their meta-analysis that the discontinuation of aspirin can trigger the occurrence of cardiac, cerebrovascular, and peripheral arterial events, while the continued use of aspirin in the perioperative period of noncardiac surgeries does not increase the mortality and morbidity, despite a 50% increase in the bleeding risk.[12] Oscarsson et al found a reduction in cardiovascular (CV) events 30 days after noncardiac surgery in patients randomized to maintain aspirin perioperatively without a significant increase in the bleeding tendency.[9] The purpose of the present study is to evaluate if the level of platelet aggregation influences the perioperative CV adverse event rate, considering that there is a great variability in individual responsiveness for aspirin therapy.[14-16]

The test to evaluate the effect of aspirin is based on the platelet aggregation response to arachidonic acid (AA), which is the substrate of cyclooxygenase 1 that is inhibited by aspirin. It can be performed with the point-of-care Verify-Now (Accumetrics Inc, San Diego, Calif) system or with optical aggregometry or impedance aggregometry in the whole blood.

METHODS

This protocol was approved by the local Ethics Committee, and patients were enrolled after giving their written informed consent.

Patients were considered eligible for the study if they were admitted to the hospital for an elective vascular surgery

From the Interdisciplinary Medicine in Cardiology Unit,[a] the Coagulation Laboratory of the Clinics Hospital,[b] and the Vascular and Endovascular Surgery Clinic of the Clinics Hospital,[c] University of São Paulo Medical School.

Supported by a grant from the Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP), process 2009/160642.

Author conflict of interest: none.

Reprint requests: Daniela Calderaro, MD, PhD, Interdisciplinary Medicine in Cardiology Unit, Heart Institute (InCor), University of São Paulo Medical School, Av Dr Enéas de Carvalho Aguiar, 44, 05403-000 São Paulo, Brazil (e-mail: daniela.calderaro@gmail.com).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214/$36.00

http://dx.doi.org/10.1016/j.jvs.2013.06.061

(carotid/aortic or peripheral revascularization) and if they were under chronic and continuous use of aspirin, regardless of the aspirin dosage. The exclusion criteria were: use of other antiplatelet agent (clopidogrel, prasugrel, or dipyridamole); platelet transfusion; treatment with warfarin; use of nonsteroidal anti-inflammatory drug in the past week; acute coronary syndrome; myocardial revascularization or stroke in the previous 3 months; current malignancy; current infection; and platelet count below 100,000/μL.

Detailed medical history and preoperative medication use were obtained from the patients and relatives. Resting 12-derivation electrocardiogram, chest radiography, creatinine, electrolytes, lipid profile, blood glucose levels, and complete blood count were obtained for all patients. Cardiac risk estimate and myocardial perfusion stress testing indications were based on the current guidelines for perioperative evaluation from the AHA/ACC[1] and from the Brazilian Society of Cardiology.[11] Intraoperative data regarding duration of anesthesia and hemodynamic instability, defined as hypotension or bradycardia requiring vasopressors, necessity of blood transfusion, lowest hemoglobin level, and highest creatinine level were all computed for analysis, and an equal or above 50% increase in the baseline creatinine level was defined as acute kidney injury (AKI).[17]

Platelet aggregation tests

To test platelet aggregation before surgery, we performed whole blood impedance aggregometry (Chronolog Corp, Havertown, Pa) up to 180 minutes after blood collection. The blood samples were obtained by venipuncture, early in the morning after an 8-hour fast period, and were carefully handled in sodium citrate tubes (3.2% concentration). Maximum extent of aggregation, measured in ohms, assesses the amount of platelet aggregates after exposure to each of the following agonists: collagen 1 μg/mL; collagen 2 μg/mL; collagen 5 μg/mL; and AA 0.5 mM. In short, the accumulation of platelet aggregate adds electrical resistance to a circuit inserted into the test sample. Initially, a positive voltage is applied to the circuit to stimulate initial platelet aggregation. After a stable impedance value is obtained, one of the agonists is added to the system, stimulating further platelet aggregation that adds electrical resistance to the circuit. This change in impedance is measured and quantified in ohms, and higher levels mean greater platelet aggregation. The AA agonist is the most important agent in the present study because it is the substrate to cyclooxygenase and is converted to thromboxane A2. Aspirin inhibits this pathway, determining a reduction in aggregation in response to AA. This method is already validated and is a reliable toll for the measurement of aspirin response.[18] The collagen does not specifically evaluate aspirin action, although it is extremely important as a physiological stimulus to platelet aggregation. The different collagen concentrations allows the evaluation of platelet function besides the aspirin effect; it is expected that patients under aspirin therapy could show poor platelet aggregation to lower concentrations, but when high collagen concentration is added, their platelet aggregation should not be inhibited.

CV events

Patients were submitted to CV monitoring for early event detection by daily cardiologist evaluation until hospital discharge and electrocardiogram and troponin-T dosage once a day during the first 72 postoperative hours, repeated as needed.

We defined the following CV events:

Acute myocardial infarction. Detection of a typical rise and fall of biochemical markers of myocardial necrosis (cardiac troponin T) with at least one value above the 99th percentile of the upper reference limit together with ischemic symptoms or development of pathological Q waves on the electrocardiogram (ECG) or ECG changes indicative of ischemia (ST segment elevation or depression) or new regional contractile abnormality in the echocardiography.

Unstable angina. Ischemic symptoms lasting for at least 20 minutes with or without ECG changes, without cardiac troponin elevation.

Isolated cardiac troponin elevation. Troponin level above the 99th percentile of the upper reference limit without ischemic symptoms or ECG changes.

Acute ischemic cerebrovascular event. Signs of ischemic stroke confirmed with imaging studies (computed tomography or magnetic resonance).

Reoperation. New vascular procedure due to thrombotic complication of the index operation.

Bleeding events

The postoperative bleeding was classified according to an adapted Thrombolysis In Myocardial Infarction (TIMI) criterion, as minor or major bleeding.[19,20]

Major bleeding. Decrease in hemoglobin >5 g/dL (or 15% in hematocrit).

Minor bleeding. Decrease in hemoglobin: 3.1 to 5 g/dL (or 10% in hematocrit).

Importantly, red blood cell transfusion was computed into the TIMI criteria and each unit of red blood cell accounted for 1 g/dL.

Sample size and statistics

Sample size was calculated based on the incidence of CV events after vascular surgery observed in two previous studies of our group with similar populations: 14.6%[21] and 15.5%.[6,21] Therefore, we calculated a sample size of 200 patients, for detection of 30 CV events. The study was designed to have 80% power to detect a difference in platelet aggregability of 30% or more between patients with and without a CV event, assuming a confidence interval (CI) of 95%, two-sided.

Categorical data are presented as frequencies, and continuous variables are presented as mean and respective standard deviations. Continuous variables that passed in the normality test were compared using an unpaired

t-test, and the categorical data were compared with the χ^2 test. Variables that failed to pass in the normality test were compared with the nonparametric equivalent tests.

Separate logistic regression stepwise models identified the independent predictors of CV and hemorrhagic events. All univariate variables with a *P* value <.2 were selected for the multivariate analysis, and the CV events analysis was adjusted for the cardiac risk level, predicted according to the American College of Physicians Guidelines.[22] The adequacies of the models were tested with the Hosmer-Lemershow goodness-of-fit test. All statistical analysis was performed using the SPSS 17.0 software (IBM, Armonk, NY) and a two-tailed 95% CI was considered significant.

RESULTS

In total, 206 patients were included in the study between June 2010 and January 2012, and 15 were excluded from the analysis because of surgery cancellation. Baseline and vascular procedure characteristics of the patients are displayed in Table I.

From the 191 patients submitted to the elective vascular surgery, 42 (22%) had a CV event during hospitalization: 7 acute myocardial infarctions, 2 unstable anginas, 9 isolated troponin elevations, nine acute cerebrovascular ischemic events, 14 vascular reoperations, and 1 CV death. The incidence of hemorrhagic events was high: 50.97%, with 45 minor and 60 major events.

Regarding antiplatelet therapy, aspirin was maintained for all patients. Patients submitted to endovascular treatment of carotid artery or lower limb arteries received aspirin plus clopidogrel, started in the first hours after surgery. They received a loading dose of 300 mg and continued to receive 75 mg per day.

In the univariate analysis, we found that hemodynamic instability during anesthesia (50% in patients with CV events vs 24.16% in patients without CV events; $P = .001$), AKI (33.33% vs 16.78%; $P = .019$), postoperative significant anemia, defined as the lowest hemoglobin postoperative level below 9 g/dL, (47.62% vs 30.20%; $P = .035$), baseline anemia (42.86% vs 25.5%; $P = .029$), and dyslipidemia (88.1% vs 70.47%; $P = .021$) were all significantly associated with CV events. The operative time was nonsignificantly associated to CV events: 238 minutes for patients with CV events vs 204 minutes for patients without CV events ($P = .292$). Other variables that were not significantly associated with CV events in the univariate analysis, but that qualified for the multivariate model entry, were angina ($P = .10$), heart failure symptoms ($P = .138$), red blood cell transfusion ($P = .138$), and hemorrhagic event ($P = .114$). Platelet aggregation tests results in patients with and without CV events are displayed in Table II. We found significant association between higher platelet response to AA and CV events. There is no definitive cut-off for the platelet aggregability tests to define aspirin resistance. Some authors consider that any value above 0 Ω indicates aspirin resistance,[23] others consider the 3Ω cut-off,[24] but there is no proof until now that these values are the best in screening populations with prognostic implications. We decided to analyze our data according to the distribution of the results in our population and stratified the values in quartiles. Post-hoc analysis of these data was performed categorizing this variable according to quartile distribution: 0-1.00 Ω; 1.01-4.00 Ω; 4.01-11.00 Ω; and higher than 11.00 Ω, corresponding to the first to fourth quartile, respectively. The cut-off of 11 Ω, chosen for analysis, corresponded to the 75th percentile. Patients in the fourth quartile had almost twice the incidence of CV events when compared with the three lower quartiles: 35% vs 18.54%; $P = .025$.

Table I. Baseline characteristics of the study population

Characteristic	
Clinical parameters	
Age, years	67.10 ± 9.73
Male gender	137 (71.7)
Hypertension	163 (85.3)
Dyslipidemia	142 (74.3)
Diabetes mellitus	54 (28.3)
Smoking status	
Current	42 (22.0)
Previous	113 (59.2)
Non-smoker	36 (18.8)
Previous myocardial infarction	44 (23.0)
Angina pectoris	19 (9.9)
Heart failure	43 (22.5)
Preoperative anemia	56 (29.3)
Cardiac risk (American College of Physicians)	
Low	77 (40.3)
Intermediate	101 (52.9)
High	13 (6.8)
Medication	
Beta-blocker	133 (69.6)
Statin	188 (98.4)
ACE inhibitor	116 (60.7)
Aspirin dosage	
100 mg	170 (89)
200 mg	20 (10.5)
300 mg	1 (0.5)
Laboratory parameters	
Platelet count, × 10^3/μL	234 ± 82.33
Hemoglobin, g/dL	13.30 ± 1.58
White blood cell, /μL	7918 ± 2033
Creatinine, mg/dL	1.33 ± 0.88
LDL-cholesterol, mg/dL	99.89 ± 41.47
HDL-cholesterol, mg/dL	42.05 ± 13.22
Triglycerides, mg/dL	146.74 ± 89.25
Vascular surgical parameters	
Endovascular procedure	95 (49.7)
Conventional procedure	96 (50.3)
Vascular disease	
Peripheral arterial obstructive disease	57 (29.8)
Carotid disease	44 (23.0)
Abdominal aortic aneurysm	61 (31.9)
Descending thoracic aortic aneurysm/dissection	9 (4.7)
Other	20 (10.5)

ACE, Angiotensin-converting enzyme; *HDL*, high density lipoprotein; *LDL*, low density lipoprotein.
Continuous data are presented as mean ± standard deviation and categoric data as number (%).

Table II. Platelet aggregation parameters in patients with and without cardiovascular (*CV*) events

Test	*Total*	*CV events +*	*CV events −*	P
Impedance aggregometry				
Collagen 1 μL/mL (Ω)	5.48 ± 4.28	5.79 ± 4.21	5.39 ± 4.31	.606
Collagen 2 μL/mL (Ω)	10.48 ± 5.27	11.31 ± 5.60	10.25 ± 5.17	.250
Collagen 5 μL/mL (Ω)	16.96 ± 5.69	17.95 ± 5.41	16.68 ± 5.75	.203
AA 0.5 mM/mL (Ω)	5.83 ± 5.90	7.40 ± 6.39	5.39 ± 5.70	.050

AA, Arachidonic acid.
Data are presented as mean ± standard deviation.

There was no significant impact of the variable dose of aspirin on platelet aggregation level. When we compared the quartiles of platelet aggregation in response to AA in patients receiving 100 mg vs higher dosages, we did not find significant difference: 38.8% vs 47.6% were in the first quartile, 15.3% vs 9.5% in the second quartile, 24.1% vs 28.6% in the third quartile, and 21.8% of the patients receiving aspirin 100 mg vs 14.3% of the patients receiving higher dosages were in the fourth quartile ($P = .697$), respectively.

The independent predictors of CV events identified in the logistic regression model, adjusted for the predicted risk according to the American College of Physicians algorithm,[22] were AA platelet aggregability in the upper quartile, dyslipidemia, preoperative anemia, and hemodynamic instability during anesthesia (Table III).

The incidence of hemorrhagic events was 50.97%, with 45 minor and 60 major events, and the variables significantly correlated to this complication identified in the univariate analysis were smoking, heart failure, normal preoperative hemoglobin level, conventional open vascular surgery, absence of clopidogrel prescription in the postoperative period, and hemodynamic instability. Diabetes and male gender qualified for the multivariate model although were not significantly associated to hemorrhagic events ($P = .076$ and $P = .148$, respectively). The platelet aggregability in response to collagen and AA was not associated to hemorrhagic events (Table IV). Not even the lowest AA platelet aggregability quartile was associated to hemorrhagic events, when compared with the three other quartiles: 58.41% vs 51.32%; $P = .336$.

The independent predictors of the 105 hemorrhagic events were current smoking status (odds ratio [OR], 5.05; 95% CI, 1.74-14.67; $P = .003$), hemodynamic instability (OR, 3.41; 95% CI, 1.53-7.59; $P = .003$), conventional open vascular surgery (OR, 1.56; 95% CI, 1.14-1.77; $P = .016$), acute kidney injury (OR, 3.28; 95% CI, 1.23-8.77; $P = .018$), and preoperative anemia (OR, 0.43; 95% CI, 0.20-0.89; $P = .024$). We have also analyzed exclusively the need for red blood cell transfusion, and 20.4% of our patients received at least one unit of red blood cells in the postoperative period, ranging from 2.3% of the patients submitted to carotid surgery and 15.8% of the patients submitted to peripheral revascularization to 34.3% of the patients submitted to aortic aneurysm repair.

DISCUSSION

For the first time, the present study shows that higher level of platelet aggregation despite aspirin therapy before vascular surgery is associated with CV complications. It is well known that platelet activation and adherence to damaged endothelium starts thrombus formation that is very important for hemostasis in the surgical wound but is also responsible for acute cardiac events. Even in the surgical wound, sometimes the intensity of the process can be inappropriate and cause graft or stent thrombosis. The perfect balance between antithrombotic effect and no prejudice in hemostasis is very difficult to achieve, and in our study, we found that greater response to aspirin was protective against CV complications and, on the other hand, was not related to increased risk of hemorrhagic events.

Although higher platelet aggregation level is considered by many authors a marker of cardiac risk in the context of chronic coronary disease, mainly after percutaneous revascularization,[25-27] there are few reports of platelet aggregation and perioperative cardiac risk. Burdess et al[28] found higher platelet activation in the perioperative period of vascular surgery in patients with critical limb ischemia when compared with patients submitted to surgery because of intermittent claudication, but differently from our study, they did not report the incidence of cardiac events and their correlation with platelet function. Other authors had already shown that platelet status correlates positively with the severity of the peripheral vascular disease even in a clinical context.[29,30]

Rajagopalan et al[31] have previously observed, in 136 patients undergoing vascular surgery, that the platelet response to 75-mg aspirin therapy was variable, and at baseline, 16% of the patients presented aspirin reaction units above 550, which is considered by some authors a nonresponsiveness parameter according to the VerifyNow assay.[32] Differently from our study, they have not found significant association between the preoperative AA-stimulated platelet aggregation level and CV events,[31] but they reported a significant association between postoperative AA-stimulated platelet aggregation and troponin elevation.[31] Although the definition of cardiac events in ours and Rajagapalan's study were different, as they have analyzed exclusively postoperative troponin elevation, the incidence was quite similar: 21%[31] and 22% in the present study. It is

Table III. Results of the multivariate analysis of cardiovascular (CV) events risk predictors

Variable	*Category*	*OR*	$OR_{adjusted}$	*95% CI* $OR_{adjusted}$	P
Hemodynamic instability	No	1.00	1.00	Ref.	<.001
	Yes	3.14	4.12	1.87-9.06	
Dyslipidemia	No	1.00	1.00	Ref.	.014
	Yes	3.10	3.90	1.32-11.51	
Preoperative anemia	No	1.00	1.00	Ref.	.017
	Yes	2.19	2.64	1.19-5.85	
AA platelet aggregability	≤11 Ω	1.00	1.00	Ref.	.034
	>11 Ω	2.36	2.48	1.07-5.76	

AA platelet aggregability, Platelet aggregability in response to arachidonic acid; *CI,* confidence interval; *OR,* odds ratio; *OR adjusted,* odds ratio adjusted for the predicted risk according to the American College of Physicians algorithm; *Ref,* reference.

Table IV. Platelet aggregation in patients with and without hemorrhagic events

Test	*Total*	*Hemorrhagic event +*	*Hemorrhagic event −*	P
Impedance aggregometry				
Collagen 1 μL/mL (Ω)	5.48 ± 4.28	4.97 ± 3.78	6.11 ± 4.80	.079
Collagen 2 μL/mL (Ω)	10.48 ± 5.27	10.17 ± 5.43	10.88 ± 5.10	.358
Collagen 5 μL/mL (Ω)	16.96 ± 5.69	17.02 ± 5.91	16.92 ± 5.47	.914
AA 0.5 mM/mL (Ω)	5.83 ± 5.90	5.98 ± 5.89	5.60 ± 5.96	.660

AA, Arachidonic acid.
Data are presented as mean ± standard deviation.

possible that the smaller sample size of Rajagapalan's study explains the different results. Another possibility relies on the method applied for platelet aggregation measurement; the VerifyNow is considered the best point of care method but the comparison of results from different tests may be a limitation.[24]

Regarding the other predictors of CV events, it was not surprising that preoperative anemia increased the risk of CV events after vascular surgery, as anemia is a recognized risk marker for noncardiac surgery,[33] and it is less well tolerated in the presence of CV disease.[34] The finding of dyslipidemia as a perioperative risk marker was intriguing, as every patient had high atherosclerotic disease burden and almost 100% received statin therapy because of its perioperative indication. There is a clear recommendation in various perioperative care guidelines to administer statin to vascular surgery patients, regardless of the cholesterol levels.[1,2,10] It is possible that patients who informed the diagnosis of dyslipidemia were patients with known coronary artery disease at higher cardiac risk. We have already shown in a previous study that coronary artery disease patients are much more aware of their disease, and the importance of risk factor control, than vascular surgery patients.[35]

The presence of hemodynamic instability during anesthesia indicates a four-fold risk increase. We believe that more than a clinical sign of the CV event, patients who experience hemodynamic instability due to bleeding, vasoplegia, hypovolemia, or anesthetic effect experience uncontrolled myocardial oxygen supply demand mismatch that can cause sudden ischemia (type II myocardial infarction) or trigger further plaque disruption (type I myocardial infarction). Actually, for our 21 patients with a CV event, we found a delay between hemodynamic instability and the CV event; 76.2% of the events occurred in the first 48 hours after surgery, but only 38% were concentrated in the first 24 hours.

We did expect that the degree of platelet aggregation would be inversely correlated to hemorrhagic events, but fortunately, even when we analyzed the lowest quartile of platelet aggregation in response to AA, there was no increase in the rate of bleeding, reinforcing the security of aspirin maintenance throughout the perioperative period.

The high incidence of hemorrhagic events (50.97%) was a disturbing finding, but we believe that the TIMI criteria oversized the magnitude of the problem in this very specific perioperative context. We decided to adopt the TIMI criteria for an objective classification of events considering the lack of a specific perioperative criterion for hemorrhagic events. In the perioperative setting, there is always some degree of acute blood loss, different than what is expected for acute coronary syndromes, the setting where the TIMI criteria were validated.[19] When we analyze exclusively the need for red blood cell transfusion of the patients submitted to aortic aneurysm repair, the 34.3% rate found in our study is in accordance with the transfusion rate reported in the literature. In the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial, 39.13% of the 345 patients submitted to aortic aneurysm repair received blood transfusion (6% for the endovascular group and 72% for the open repair group).[36] In the 429 open aneurysm repair patients enrolled in the Open Versus Endovascular Repair (OVER) trial, the authors observed a median of 1.000 mL of blood loss during

surgery.[37] Even considering the limitations of the absolute information of the TIMI criteria for the perioperative context, in our study, we decided to maintain it for statistical analysis because it is more complete and less subject to bias than the transfusion requirement, as the transfusion decision was at the discretion of the attending physicians, without uniform criteria.

Although it is very tempting to consider that the current results indicate that therapeutic adjustment of platelet aggregation could possibly interfere with perioperative CV morbidity and mortality, it is important to remember that this study was not designed to test any intervention.

There are some study limitations. We did not obtain the thromboxane B2 serum levels that could provide additive information about aspirin effect. But we believe that the results from the impedance aggregometry test indicating association of the platelet response exclusively to AA agonist and CV events already indicate the prognostic importance of individual aspirin response. The heterogeneity of the vascular procedures in the study population could be considered another limitation, but considering that the primary end point was CV events, that the mechanisms involved in the pathogenesis of CV complications in the perioperative setting of these different surgical interventions is similar,[1,2,13] and that previous studies have included the same population as a whole group,[8,9,22,30] we do not believe that it could affect the conclusions of the study. Data regarding platelet aggregation after AA stimuli allowed the identification of different reference ranges. Despite being the result of post-hoc analysis, we found that this finding is very important as it is more representative from the clinical standpoint. Future studies including an increased number of patients must strongly consider the reference ranges and cut-offs proposed in the present study.

So, we conclude that the degree of aspirin effect is important in the management of perioperative morbidity and mortality, reinforcing the putative importance of atherothrombosis in the physiopathology of CV complications after vascular surgery.[2] Aspirin dose titration is a potential tool for perioperative risk management, but confirmation of the optimal platelet aggregation level and targeted aspirin dose titration studies are still needed.

The authors wish to acknowledge Dr Karina de Cássia Ribeiro for the statistical analysis, Prof Pedro Puech-Leão, Dr Gabriel Assis Lopes do Carmo, and Dr Ivan Casella for the important suggestions for the analysis of the results, and Miss Valeria Oliveira and Mrs Maria Luiza Silva Alves for the technical support in the coagulation laboratory.

AUTHOR CONTRIBUTIONS

Conception and design: DC, AP, TR, PY, DG, NL, EA, BC
Analysis and interpretation: DC, AP, TR, PY, DG, NL, EA, BC
Data collection: DC, AP, TR, PY, DG, EA, BC
Writing the article: DC, DG, NL, BC
Critical revision of the article: DC, TR, DG, GC, BC
Final approval of the article: DC, AP, TR, PY, DG, NL, EA, BC
Statistical analysis: DC, DG, BC
Obtained funding: DC, BC
Overall responsibility: DC

REFERENCES

1. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation 2007;116:e418-99.
2. Gualandro DM, Campos CA, Calderaro D, Yu PC, Marques AC, Pastana AF, et al. Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: frequent and dangerous. Atherosclerosis 2012;222:191-5.
3. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999;341:1789-94.
4. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. N Engl J Med 2005;353:349-61.
5. Hoeks SE, Scholte Op Reimer WJ, van Urk H, Jörning PJ, Boersma E, Simoons ML, et al. Increase of 1-year mortality after perioperative beta-blocker withdrawal in endovascular and vascular surgery patients. Eur J Vasc Endovasc Surg 2007;33:13-9.
6. Durazzo AES, Machado FS, Ikeoka DT, De Bernoche C, Monachini MC, Puech-Leao P, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. J Vasc Surg 2004;39:967-75.
7. Schouten O, Boersma E, Hoeks SE, Benner R, van Urk H, van Sambeek MR, et al. Fluvastatin and perioperative events in patients undergoing vascular surgery. N Engl J Med 2009;361:980-9.
8. Schouten O, Hoeks SE, Welten GM, Davignon J, Kastelein JJ, Vidakovic R, et al. Effect of statin withdrawal on frequency of cardiac events after vascular surgery. Am J Cardiol 2007;100:316-20.
9. Oscarsson A, Gupta A, Fredrikson M, Järhult J, Nyström M, Pettersson E, et al. To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial. Br J Anaesth 2010;104:305-12.
10. Poldermans D, Bax JJ, Boersma E, De Hert S, Eeckhout E, Fowkes G, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. Eur Heart J 2009;30:2769-812.
11. Gualandro DM, Yu PC, Calderaro D, Marques AC, Pinho C, Caramelli B, et al. II Guidelines for perioperative evaluation of the Brazilian Society of Cardiology. Arq Bras Cardiol 2011;96(3 Suppl 1):1-68.
12. Burger W, Chemnitius JM, Kneissl GD, Rücker G. Low-dose aspirin for secondary cardiovascular prevention - cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation - review and meta-analysis. J Intern Med 2005;257:399-414.
13. Lotrionte M, Biondi-Zoccai GG. The hazards of discontinuing acetylsalicylic acid therapy in those at risk of coronary artery disease. Curr Opin Cardiol 2008;23:487-93.
14. Rocca B, Santilli F, Pitocco D, Mucci L, Petrucci G, Vitacolonna E, et al. The recovery of platelet cyclooxygenase activity explains interindividual variability in responsiveness to low-dose aspirin in patients with and without diabetes. J Thromb Haemost 2012;10:1220-30.

15. Li C, Hirsh J, Sloane D, Liang Y, Bai J, Paikin J, et al. Aspirin response variability after major orthopedic surgery. Thromb Res 2012;130: 216-20.
16. Angiolillo DJ. Variability in responsiveness to oral antiplatelet therapy. Am J Cardiol 2009;103(3 Suppl):27A-34A.
17. Kellum JA, Lameire N; for the KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care 2013;17:204.
18. Ivandic BT, Giannitsis E, Schlick P, Staritz P, Katus HA, Hohlfeld T. Determination of aspirin responsiveness by use of whole blood platelet aggregometry. Clin Chem 2007;53:614-9.
19. Cannon CP, Battler A, Brindis RG, Cox JL, Ellis SG, Every NR, et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. A report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). J Am Coll Cardiol 2001;38:2114-30.
20. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial—phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988;11:1-11.
21. Calderaro D, Monachini MC, Vieira CL, Yu PC, Gualandro DM, Marques AC, et al. Reactive hyperemia revisited. Arterioscler Thromb Vasc Biol 2008;28:e23-4; author reply: e25.
22. Guidelines for assessing and managing the perioperative risk from coronary artery disease associated with major noncardiac surgery. Ann Intern Med 1997;127:309-12.
23. Kuliczkowski W, Witkowski A, Polonski L, Watala C, Filipiak K, Budaj A, et al. Interindividual variability in the response to oral antiplatelet drugs: a position paper of the Working Group on antiplatelet drugs resistance appointed by the Section of Cardiovascular Interventions of the Polish Cardiac Society, endorsed by the Working Group on Thrombosis of the European Society of Cardiology. Eur Heart J 2009;30:426-35.
24. Lordkipanidzé M, Pharand C, Schampaert E, Turgeon J, Palisaitis DA, Diodati JG. A comparison of six major platelet function tests to determine the prevalence of aspirin resistance in patients with stable coronary artery disease. Eur Heart J 2007;28:1702-8.
25. Frelinger AL, Li Y, Linden MD, Barnard MR, Fox ML, Christie DJ, et al. Association of cyclooxygenase-1-dependent and -independent platelet function assays with adverse clinical outcomes in aspirin-treated patients presenting for cardiac catheterization. Circulation 2009;120: 2586-96.
26. Brar SS, ten Berg J, Marcucci R, Price MJ, Valgimigli M, Kim HS, et al. Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention. A collaborative meta-analysis of individual participant data. J Am Coll Cardiol 2011;58:1945-54.
27. Snoep JD, Hovens MM, Eikenboom JC, van der Bom JG, Huisman MV. Association of laboratory-defined aspirin resistance with a higher risk of recurrent cardiovascular events: a systematic review and meta-analysis. Arch Intern Med 2007;167:1593-9.
28. Burdess A, Nimmo AF, Campbell N, Harding SA, Garden OJ, Dawson AR, et al. Perioperative platelet and monocyte activation in patients with critical limb ischemia. J Vasc Surg 2010;52:697-703.
29. Rajagopalan S, Mckay I, Ford I, Bachoo P, Greaves M, Brittenden J. Platelet activation increases with the severity of peripheral arterial disease: implications for clinical management. J Vasc Surg 2007;46: 485-90.
30. Robless PA, Okonko D, Lintott P, Mansfield AO, Mikhailidis DP, Stansby GP. Increased platelet aggregation and activation in peripheral arterial disease. Eur J Vasc Endovasc Surg 2003;25:16-22.
31. Rajagopalan S, Ford I, Bachoo P, Hillis GS, Croal B, Greaves M, et al. Platelet activation, myocardial ischemic events and postoperative non-response to aspirin in patients undergoing major vascular surgery. J Thromb Haemost 2007;5:2028-35.
32. Coleman J, Wang J, Simon D. Determination of an individuals response to aspirin therapy using the accumetrics Ultragras PRFA-ASA system. Point of Care: The Journal of Near-Patient Testing & Technology 2004;3:77-82.
33. Wu WC, Schifftner TL, Henderson WG, Eaton CB, Poses RM, Uttley G, et al. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. JAMA 2007;297:2481-8.
34. Carson JL, Duff A, Poses RM, Berlin JA, Spence RK, Trout R, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet 1996;348:1055-60.
35. Chang VY, Handa KK, Fernandes M, Yacoub C, Pastana A, Caramelli B, et al. Improving cardiovascular prevention through patient awareness. Rev Assoc Med Bras 2012;58:550-6.
36. Prinssen M, Verhoeven EL, Buth J, Cuypers PW, van Sambeek MR, Balm R, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med 2004;351:1607-18.
37. Lederle FA, Freischlag JA, Kyriakides TC, Padberg FT, Matsumura JS, Kohler TR, et al. Outcomes following endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. JAMA 2009;302: 1535-42.

Submitted Apr 19, 2013; accepted Jun 16, 2013.