Factors Associated with Inadequate Management of Antiplatelet Agents in Perioperative Period of Non-Cardiac Surgeries

Juliana Maria Dantas Mendonça Borges,1,2 Pamella de Assis Almeida,1 Mariana Martins Gonzaga do Nascimento,1 José Augusto Soares Barreto Filho,1,4,5 Mario Borges Rosa,3 Antonio Carlos Sobral Sousa1,4,5

Universidade Federal de Sergipe,1 Aracaju, SE – Brazil
Universidade Tiradentes,2 Aracaju, SE - Brazil
Instituto Para Práticas Seguras no Uso de Medicamentos,3 Belo Horizonte, MG – Brazil
Centro de Ensino e Pesquisa da Fundação São Lucas,4 Aracaju, SE – Brazil
Departamento de Medicina da Universidade Federal de Sergipe (UFS),5 Aracaju, SE - Brazil

Abstract

Background: The current guidelines dispose recommendations to manage antiplatelet agents in the perioperative period; however, the daily medical practices lack standardization.

Objectives: To assess factors associated with inadequate management of antiplatelet agents in the perioperative period of non-cardiac surgeries.

Methods: Cross-sectional Study conducted in hospital from October 2014 to October 2016. The study dependent variable was a therapy that did not comply with the recommendations in the Brazilian Association of Cardiology (SBC) guidelines. The independent variables included some characteristics, the people in charge of the management and causes of lack of adherence to those guidelines. Variables were included in the multivariate model. Analysis was based on the odds ratio (OR) value and its respective 95% confidence interval (CI) estimated by means of logistic regression with 5% significance level.

Results: The sample was composed of adult patients submitted to non-cardiac surgeries and who would use acetylsalicylic acid (aspirin) or clopidogrel (n = 161). The management failed to comply with the recommendations in the guidelines in 80.75% of the sample. Surgeons had the highest number of noncomplying orientations (n = 63). After multivariate analysis it was observed that patients with a higher level of schooling (OR = 0.24; CI95% 0.07-0.78) and those with a previous episode of acute myocardial infarction (AMI) (OR = 0.18; CI95% 0.04-0.95) had a higher probability of using a therapy complying with the guidelines.

Conclusion: Positive association between patients’ schooling level, or those with a history of previous AMI, with management of the use of aspirin and clopidogrel in the perioperative period of non-cardiac surgeries. However, diverging conducts stress the need of having internal protocol defined. (Arq Bras Cardiol. 2018; 111(4):596-604)

Keywords: Surgery/perioperative care; Intraoperative Care; Platelet Aggregation; Adults; Myocardial Infarction; Educational Status.

Introduction

A study published in 2018 by the World Health Organization (WHO) informed that in 2012 313 million surgeries had been performed worldwide, thus evidencing a 38% increase in eight years. During that period in Brazil approximately 6 thousand surgeries per 100,000 inhabitants were performed, summing up about 10 to 13 million surgical procedures in 2012, and the rate of non-cardiac surgeries was estimated at 3 million per year. These figures still are bound to increase due to several factors, such as the growing and ageing population.5

In 2014, Botto et al.,4 stated that cardiac complications are the main cause of post-operation deaths of patients submitted to non-cardiac surgeries. These are alarming data once in the world over 10 million adults every year have at least one cardiac complication in the first 30 days following a non-cardiac surgical procedure.4,5 Among the cardiac complications arising from these types of procedure the most common is acute myocardial infarction (AMI),4,6,7 which is also associated with long-term mortality, although often enough it is detected earlier during clinical screening.8

Due to the key role performed by platelets in pathogenesis of atherothrombotic events, using antiplatelet agents is of the essence for primary and secondary prevention of cardiovascular events.9 However, although the use of antiplatelet agents has increased cardiovascular safety of many
patients, 10 when they need a non-cardiac surgery, surgeons and anesthesiologists frequently have to face the decision of whether to interrupt or not antiplatelet therapy in those patients during the perioperative period considering the risks of the occurrence of thrombi or bleedings, respectively. 11-13

Thus, in order to help physicians make decisions in the perioperative period referring to antiplatelet therapy, the recommendations of the American association of thorax physicians (2012) and of the Brazilian (2013), European and American cardiology societies of cardiology (2014) are supposed to serve as basis of clinical evidence to help perioperative conducts and, consequently, to guarantee more safety to patients. 5,14-16

In this sense, this study is an attempt to assess the factors associated with inadequate management of antiplatelet agents in the perioperative period of non-cardiac surgeries based on the existing Brazilian guidelines.

Methods

Study outline, sample and data collection

This is a cross-sectional study conducted in a high-complexity hospital, which is reference in cardiology and has internal hospital accreditation. That hospital unit contains 150 beds and, during the study period, 650 non-cardiac surgeries per month were performed on average.

In the study patients submitted to non-cardiac surgeries and who previously and regularly used at least one platelet agent for primary or secondary prevention were included, which composed a sample obtained by convenience instead of probabilistic, composed of adult patients (18 years old or older).

Data were collected from October 2014 to October 2016 by means of interviews with patients, or with their companions, before they were submitted to surgical procedures, using a questionnaire specific to obtain data. The interviews were held by a team of professionals and academics previously trained who attended the Departments of Pharmacy and Medicine of a public university and the Department of Pharmacy of a private university.

Variables and data analysis

Descriptive analysis of the variables was done by determining absolute and relative frequencies for qualitative variables, and the means for quantitative variables. In the univariate and multivariate analyses the preoperative therapy with aspirin or clopidogrel was defined the dependent variable, which is inadequate according to the SBC recommendations (yes or no), once the study was conducted in Brazil. For this variable firstly was determined whether the patients had used antiplatelet agent for primary and secondary prevention, and then whether the recommendations disposed in the SBC guidelines referring to antiplatelet agents and anticoagulants in cardiology had been met, those adopted by the institution as reference at the time of the study, as presented in Box 1.

Independent variables are described in Table 1. Patients were deemed to have a history of revascularization procedure if they had already been submitted to percutaneous coronary intervention or surgical revascularization. Patients were deemed dyslipidemic when they used medicines such as statins, resins, ezetimibe or fibrates, which the V Brazilian Guideline of Dyslipidemia and Atherosclerosis Prevention (2013) deems treatments of choice for dyslipidemia, 17 additionally, patients were deemed hypertensive when at their medical records there was this information and because they used anti-hypertensive medicines, as described in the 7th Brazilian Guideline of Arterial Hypertension (2016). 18 For the Body Mass Index (BMI), patients who had 18.5-24.9 Kg/m² BMI19 were considered having normal weight. As to a surgery’ intrinsic risk of cardiac complications, the 3rd SBC Guideline of Perioperative Cardiovascular Assessment20 was adopted as reference20.

We conducted univariate analyses using the Pearson chi-square test or Fisher exact test with expected frequency equal or lower than five. All variables were included in the multivariate model which, on its turn, was done with logistic regression. Multivariate analysis was based on the odds ratio (OR) value and its respective 95% confidence interval (CI95%), estimated by logistic regression. A 5% level of statistical significance was the criterion adopted to identify characteristics independently associated with the dependent variable. The likelihood-ratio test was used to compare the models, and the final models’ properness was assessed with the Hosmer-Lemeshow test. All statistical analyses were done with the Stata® statistic software package, version 12.

Ethical aspects

This investigation was registered in the National Council of Ethics in Research – CONEP with the Certificate of Submission for Ethical Appreciation – CAAE no. 3389914.2.0000.5546,
Table 1 – Sample characteristics (n = 161). High-complexity hospital, Aracaju, Sergipe, Brazil, 2014-2016

| Characteristics                              | Total n(%) | Noncomplying with recommendations* | Value p_i |
|----------------------------------------------|------------|------------------------------------|-----------|
|                                              |            | No(%)  | Yes (%)               |           |
| Gender                                       |            |        |                      |           |
| Male                                         | 73(45.3)   | 23.3   | 76.7                 | 0.237     |
| Female                                       | 88(54.7)   | 15.9   | 84.1                 |           |
| Age                                          |            |        |                      |           |
| 40-69 years                                  | 85(52.8)   | 15.3   | 84.7                 | 0.178     |
| 70-99 years                                  | 76(47.2)   | 23.7   | 76.3                 |           |
| Schooling                                    |            |        |                      |           |
| Up to high-school                            | 65(40.4)   | 12.3   | 87.7                 | 0.180     |
| Primary School – complete – incomplete       | 40(24.8)   | 25.0   | 75.0                 |           |
| University – complete or incomplete          | 56(34.8)   | 23.2   | 76.8                 |           |
| Married                                      |            |        |                      |           |
| No                                           | 63(39.1)   | 20.6   | 79.4                 | 0.722     |
| Yes                                          | 98(60.9)   | 18.4   | 81.6                 |           |
| Works                                        |            |        |                      |           |
| No                                           | 126(78.3)  | 23.0   | 77.0                 | 0.022     |
| Yes                                          | 35(21.7)   | 5.7    | 94.3                 |           |
| Has children                                 |            |        |                      |           |
| No                                           | 10(6.2)    | 10.0   | 90.0                 | 0.443     |
| Yes                                          | 151(93.8)  | 19.9   | 80.1                 |           |
| Body Mass Index†                             |            |        |                      |           |
| Up to 29                                     | 115(71.3)  | 20.2   | 79.8                 | 0.687     |
| 30 or more                                   | 46(28.7)   | 17.4   | 82.6                 |           |
| Number of diseases‡                          |            |        |                      |           |
| 0-2                                          | 120(74.5)  | 20.8   | 79.2                 | 0.385     |
| 3-4                                          | 41(25.5)   | 14.6   | 85.4                 |           |
| Previous revascularization procedure*        |            |        |                      |           |
| No                                           | 124(77.6)  | 19.4   | 80.6                 | 0.953     |
| Yes                                          | 37(23.0)   | 18.9   | 81.1                 |           |
| Acute Myocardial Infarct                     |            |        |                      |           |
| No                                           | 132(82.0)  | 15.9   | 84.1                 | 0.022     |
| Yes                                          | 29(18.0)   | 34.5   | 65.5                 |           |
| Stroke                                       |            |        |                      |           |
| No                                           | 152(94.4)  | 18.4   | 81.6                 | 0.270     |
| Yes                                          | 9(5.6)     | 33.3   | 66.7                 |           |
| Dyslipidemia                                 |            |        |                      |           |
| No                                           | 94(58.4)   | 25.5   | 74.5                 | 0.017     |
| Yes                                          | 67(41.6)   | 10.5   | 89.5                 |           |
| Systemic Arterial Hypertension               |            |        |                      |           |
| No                                           | 43(26.7)   | 16.3   | 83.7                 | 0.563     |
| Yes                                          | 118(73.3)  | 20.3   | 79.7                 |           |
Continuation

Time using aspirin or clopidogrel

|          | 1-4 years | 5 years or more |
|----------|-----------|-----------------|
| Aspirin  | 72(44.7)  | 89(55.3)        |
| Clopidogrel | 19.4 | 19.1            |
|           | 80.6      | 80.9            |

Surgeon expertise

| System                | Frequency | Percentage |
|-----------------------|-----------|------------|
| General or digestive  | 67(41.6)  | 80.6       |
| Orthopedist           | 24(14.9)  | 83.3       |
| Other                 | 59(36.7)  | 78.0       |
| Urologist             | 11(6.8)   | 16.1       |
| Orthopedist           | 24(14.9)  | 83.3       |

Discussion

The rather expressive frequency of therapies with aspirin and clopidogrel lacking compliance with the SBC guidelines’ recommendations (2013) in the perioperative period of non-cardiac surgeries was not observed in other studies once, as far as we are aware, this is the first one conducted in Brazil on this subject. However, the lack of organization of standardization of medical conducts in the management of antiplatelet agents is well known, i.e., there are groups of physicians who advocate the suspension of those medicines before surgeries in order to avoid bleedings, while others advocate their maintenance in order to avoid thrombotic events.11-13,21-24

The Brazilian guidelines say that in cases where aspirin or clopidogrel is used for primary prevention of cardiovascular diseases, they should be suspended, respectively seven and five days before a non-cardiac surgical procedure. However, in this study, the majority of the noncompliance with the Brazilian guidelines happened due to their suspension for periods longer than those disposed for aspirin and clopidogrel. This conduct can potentially expose patients to cardiac complications in the perioperative period once the literature evidences that those medicines, after being introduced to the market, have shown to not have their own assistance protocols focused
on this matter, and, as such, diverging conducts strengthen the need of defining internal conducts, more divulgence of the guidelines used as reference at that institution, and continued education. Double checking conducts according to internal protocols of an institution can also be an important choice to ensure patients’ safety.

Other important datum in this study, and one that draws attention, is that a significant number of noncomplying therapies occurred resulting from having patients oriented to suspend antiplatelet agents when the Brazilian guidelines state the opposite for cases where patients use aspirin and clopidogrel for secondary prevention of cardiovascular diseases, except for clopidogrel, which depends of the procedure’s bleeding risk; but in this case, all 5 patients who had been using this drug were submitted to low bleeding-risk surgeries. According to some authors, an increased bleeding risk related to the effect of the antiplatelet action of those drugs is well known, mainly in the ageing population, which stands for the majority in this study.

However, other studies, as much as the SBC orientations (2013), except for neurosurgeries and transurethral resection of the prostate, advocate that the benefits of secondary prevention substantially exceeds the bleeding risks those drugs may cause once the AMI is the main cause of death in old patients after non-cardiac surgeries.

A successful surgery depends on the aptitude and technical skills of the surgeon, on the indication and previous preparation, on the perioperative period management and care dimensioning the risks, on preventing and treating complications. In other words, a surgeon operates trying to avoid surgical complications during the procedure as much as possible, and among them one can be highlighted among general complications, whose universal example is hemorrhage. Those statements can justify the results of this study because the medical expertise representing the majority of the results noncomplying with the guidelines was surgery.

As to the association with patients’ characteristics, it was observed that patients with more schooling and those who at some moment had an AMI episode have more chance of using antiplatelet therapy in the preoperative period of non-cardiac surgeries according to the SBC (2013). No studies with this type of association were found in the literature.

However, on this matter, in a research done in the United States, its findings strongly suggest that the level of schooling is able to affect the risk of an individual developing cardiovascular diseases, regardless of any cardiovascular risk factor defined, i.e., patients with less than 12-year schooling ran significantly higher risk of AMI than those with 12-year or more schooling. As much as other authors, we understand that a higher schooling level enables patients to understand better the doctor’s orientations as to managing medicines and their health condition, as much as to have more access to information, once nowadays patients would rather participate more and more in the decision-making process with their doctors.

As to patients who already had an AMI episode and are in the group where the antiplatelet therapy complies more with the guidelines in the perioperative period, one can understand that surgeons and doctors in charge of this medicine management look for avoiding reinfarction, and so they instruct their patients not to suspend aspirin or clopidogrel in the preoperative period of non-cardiac surgeries, thus abiding by the recommendations in the guidelines and advocated by other authors.

This study has some limitations since the information obtained about management of antiplatelet therapy was rendered by the very patients, or by their companions, who in some situations said that opinions diverged between surgeon and cardiologist, or between surgeon and anesthetist, for instance, which would lead the very patients, or their companions, to decide which orientations should be followed. Additionally, the answers were written down on the patients’ reports, and physicians did not have the opportunity of confirming them. In addition, the study is limited to assessing simultaneously the two types of revascularization procedures (angioplasty and coronary revascularization) referring to the management of the antiplatelet agents, and it just does not assess the clinical impact of the antiplatelet therapy after the preoperative period. Therefore, we suggest that future studies address this prospective approach in order to size up the occurrence of thrombotic or hemorrhagic events during and after surgery.

**Conclusion**

General surgeons stand for a group of physicians which follows the least the guidelines for managing antiplatelet agents in perioperative periods of non-cardiac surgeries.
| Characteristic                                           | OR (CI<sup>95%</sup>)<sup>†</sup> | Value p<sup>†</sup> |
|--------------------------------------------------------|----------------------------------|------------------|
| Gender                                                 |                                  |                  |
| Male                                                   | 1.00                             | -                |
| Female                                                 | 2.22(0.74-6.68)                 | 0.155            |
| Age                                                    |                                  |                  |
| 40-69 years                                            | 1.00                             | -                |
| 70-99 years                                            | 0.63(0.24-1.65)                 | 0.354            |
| Schooling                                              |                                  |                  |
| Up to high school                                      | 1.00                             | -                |
| Primary school complete or incomplete                  | 0.46(0.13-1.66)                 | 0.237            |
| University complete incomplete                         | 0.24(0.07-0.78)                 | 0.018            |
| Married                                                |                                  |                  |
| No                                                     | 1.00                             | -                |
| Yes                                                    | 1.28(0.47-3.48)                 | 0.631            |
| Work outside the home                                  |                                  |                  |
| No                                                     | 1.00                             | -                |
| Yes                                                    | 4.80(0.92-25.11)                | 0.063            |
| Has children                                           |                                  |                  |
| No                                                     | 1.00                             | -                |
| Yes                                                    | 0.60(0.06-5.73)                 | 0.655            |
| Body Mass Index<sup>‡</sup>                            |                                  |                  |
| Up to 29                                                | 1.00                             | -                |
| 30 or more                                             | 1.24(0.43-3.54)                 | 0.689            |
| Number of diseases<sup>§</sup>                        | 1.72(0.65-4.56)                 | 0.279            |
| Previous revascularization procedure<sup>#</sup>       |                                  |                  |
| No                                                     | 1.00                             | -                |
| Yes                                                    | 2.08(0.58-7.49)                 | 0.261            |
| Acute Myocardial Infarction                            |                                  |                  |
| No                                                     | 1.00                             | -                |
| Yes                                                    | 0.18(0.04-0.95)                 | 0.043            |
| Stroke                                                 |                                  |                  |
| No                                                     | 1.00                             | -                |
| Yes                                                    | 0.21(0.03-1.66)                 | 0.138            |
| Dyslipidemia                                           |                                  |                  |
| No                                                     | 1.00                             | -                |
| Yes                                                    | 1.00(0.24-4.17)                 | 0.999            |
| Systemic Arterial Hypertension                         |                                  |                  |
| No                                                     | 1.00                             | -                |
| Yes                                                    | 0.22(0.04-1.27)                 | 0.090            |
| Time using aspirin or clopidogrel                      |                                  |                  |
| 1-4 years                                              | 1.00                             | -                |
| 5 years or more                                        | 0.90(0.35-2.36)                 | 0.837            |
| Surgeon expertise                                      |                                  |                  |
| General or digestive system                            | 1.00                             | -                |
| Urologist                                              | 3.30(0.33-33.09)                | 0.310            |
| Orthopedist                                            | 1.38(0.32-5.88)                 | 0.665            |
| Other                                                  | 0.75(0.28-2.03)                 | 0.578            |

ASPIRIN: acetylsalicylic acid; SBC: Brazilian Society of Cardiology; (*) Odds Ratio (CI<sup>95%</sup>) estimated with the logistic regression method; (†) Logistic regression significant when < 0.05; (‡) Body Mass Index = (weight in Kgs) / (height in meters)²; (#) History of Percutaneous Coronary Intervention or surgical revascularization; (§) Number of diseases documented in medical records and confirmed by patient on the date they were admitted for surgery – continuous variable.
Divergences in conducts seem to stress the need of defining internal protocols, to divulge guidelines and continued education to ensure patients’ safety. Additionally, it was concluded that patients with more schooling, or a previous history of AMI, agree more with the cardiology guidelines, i.e., patients who have less schooling should be better accompanied in the management of the medicine therapy, and also to have more access to information about their health condition. However, fear of the possibility of a new infarction in a patient leads physicians no to hesitate to suspend the antiplatelet agent in non-cardiac surgical procedures when they are not neurosurgeries or transurethral resection of the prostate.

Author contributions
Conception and design of the research: Borges JMDM, Almeida PA, Nascimento MMG, Barreto Filho JAS, Rosa MB, Sousa ACS; Acquisition of data: Borges JMDM, Almeida PA; Analysis and interpretation of the data: Borges JMDM, Nascimento MMG, Barreto Filho JAS, Rosa MB, Sousa ACS; Statistical analysis: Borges JMDM, Nascimento MMG, Barreto Filho JAS, Sousa ACS; Obtaining financing: Borges JMDM, Sousa ACS; Writing of the manuscript: Borges JMDM, Nascimento MMG, Rosa MB, Sousa ACS; Critical revision of the manuscript for intellectual content: Borges JMDM, Nascimento MMG, Barreto Filho JAS, Rosa MB, Sousa ACS.

Potential Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Sources of Funding
This study was funded by FAPITEC.

Study Association
This article is part of the thesis of Doctoral submitted by Juliana Maria Dantas Mendonça, from Núcleo de Pós-graduação em Ciências da Saúde da Universidade Federal de Sergipe.

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Universidade Federal de Sergipe under the protocol number 33899914.2.0000.5546. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References
1. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, et al; Size and distribution of the global volume of surgery in 2012. Bull World Health Organ. 2016;94(3):201-9F.
2. Yu PC, Calderaro D, Guandalino DM, Marques AC, Pastana AF, Prandini JC, et al. Non-cardiac surgery in developing countries: epidemiological aspects and economical opportunities—the case of Brazil. PLoS One. 2010;5(5):e10607.
3. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet. 2008;372(9633):139-44.
4. Botto F, Alonso-Coello P, Chan MT, Villar JC, Xavier D, Srirathan S, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. Anesthesiology. 2014;120(3):564-78.
5. Kristensen SD, Knautz J, Saraste A, Anker S, Batker HE, De Hert S, et al. [Brazilian guidelines on platelet antiaggregants and anticoagulants in noncardiac surgery: cardiovascular assessment and management]. Kardiol Pol. 2014;72(11):857-918.
6. Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Benwanger O, Villar JC, et al; Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA. 2012;307(21):2295-304. Erratum in: JAMA. 2012;307(24):2590.
7. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, et al; POISE (PeriOperative ISchemic Evaluation) Investigators. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. Ann Intern Med. 2011;154(8):523-8.
8. Puelacher C, Lurati Buse G, Seебeherger D, Sazgany L, Marbot S, Lampart A, et al; BASEL-PMI Investigators. Perioperative myocardial injury after noncardiac surgery: incidence, mortality, and characterization. Circulation. 2018;137(12):1221-32.
9. Silva MV, Dusse LM, Vieira LM, Carvalho Md. Platelet antiaggregants in primary and secondary prevention of atherothrombotic events. Arq Bras Cardiol. 2013;100(6):e78-84.
10. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345(7):494-502. Erratum in: N Engl J Med. 2001;345(20):1506; N Engl J Med. 2001;345(23):1716.
11. Columbo JA, Lambour AJ, Sundling RA, Chauhan NB, Bessen SY, Linshaw DL, et al. A meta-analysis of the impact of aspirin, clopidogrel, and dual antiplatelet therapy on bleeding complications in noncardiac surgery. Ann Surg. 2018;267(1):1-10.
12. Eikelboom JW, Hirsh J, Spencer FA, Baglin TP, Weitz JI. Antiplatelet drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e89S-119S.
13. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al; Antithrombotic Trials’ (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373(9678):1849-60.
14. Fleisher LA, Fleischmann KE, Austen WG, Barnett SA, Beckman JA, Bozkurt B, et al; American College of Cardiology; American Heart Association. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014;64(22):e77-137.
15. Lorga Filho AM, Azmus AD, Soeiro AM, Quadros AS, Avezum Junior A, Marques AC, et al. [Brazilian guidelines on platelet antiaggregants and anticoagulants in cardiology]. Arq Bras Cardiol. 2013;101(3 Suppl 3):1-93.
16. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaifer AK, Eckman MH, et al. Perioperative management of antithrombotic agents: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e326S-e50S.

17. Xavier HT, Izzar MC, Faria Neto JR, Assad MH, Rocha VZ, Sposito AC, et al. Sociedade Brasileira de Cardiologia. [V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis]. Arq Bras Cardiol. 2013;101(4 Suppl 1):1-20.

18. Malaquias MV, Souza WK, Plavnik FL, Rodrigues CI, Brandão AA, Neves MF, et al; Sociedade Brasileira de Cardiologia. 7ª diretriz brasileira de hipertensão arterial. Arq Bras Cardiol. 2016;107(3 Suppl 3):1-83.

19. World Health Organization. (WHO). Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. (Technical Report Series 894).

20. Gualandro DM, Yu PC, Caramelli B, Marques AC, Caldeireo D, Fornari LS, et al. 3rd Guideline for Perioperative Cardiovascular Evaluation of the Brazilian Society of Cardiology. Arq Bras Cardiol. 2017;109(3 Suppl 1):1-104.

21. Joseph B, Rawashdeh B, Aziz H, Kulvatunyou N, Pandit V, Jehangir Q, et al. An acute care surgery dilemma: emergent laparoscopic cholecystectomy in patients on aspirin therapy. Am J Surg. 2015;209(4):689-94.

22. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, et al; POISE-2 Investigators. Aspirin in patients undergoing noncardiac surgery. N Engl J Med. 2014;370(16):1494-503.

23. Wolf AM, Pucci MJ, Gabale SD, McIntyre CA, Irizarry AM, Kennedy EP, et al. Safety of perioperative aspirin therapy in pancreatic operations. Surgery. 2014:155(1):39-46.

24. Oscarsson A, Gupta A, Fredrikson M, Jrhult 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(3):305-12.

25. Ozao-Choy J, Tammaro Y, Fradis M, Weber K, Divino CM. Clopidogrel and bleeding after general surgery procedures. Am Surg. 2008;74(8):721-5.

26. Patrano C, Coller B, FitzGerald GA, Hirsh J, Ruth C. Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):2345-64S.

27. Burger W, Chemnitius JM, Kneissl GD, Rocker 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(5):399-414.

28. Collyer TC, Reynolds HC, Truyen E, Kilshaw L, Corcoran T. Perioperative management of clopidogrel therapy: the effects on in-hospital cardiac morbidity in older patients with hip fractures. Br J Anaesth. 2011;107(6):911-5.

29. Bollati M, Gaia F, Anselmino M. Antiplatelet combinations for prevention of atherothrombotic events. Vasc Health Risk Manag. 2011;7 Jan 12:23-30.

30. Mehta SR, Tanguay JF, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, et al; CURRENT-OASIS 7 trial investigators. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. Lancet. 2010;376(9748):1233-43.

31. Li L, Gorajhcy OC, Mehta Z, Rothwell PM, Study OV. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after various vascular events: a population-based cohort study. Lancet. 2017;390(10093):490-9.

32. Olivetti G, Melissari M, Capasso JM, Anversa P. Cardiomyopathy of the aging human heart: myocyte loss and reactive cellular hypertrophy. Cir Res.1991;68(6):1560-8.

33. Fernandes EO, Guerra EE, Pitrez FA, Fernandes FM, Rosito GB, González HE, et al. Avaliação pré-operatória e cuidados em cirurgia eletriva: recomendações baseadas em evidências. Revista da AMRIGS, Porto Alegre. 2010;54(2):240-56.

34. Stracieri LD. Cuidados e complicações pós-operatórias. Medicina (Ribeirão Preto). 2008;41(4):465-8.

35. Qureshi AI, Suri MF, Saad M, Hopkins LN. Educational attainment and risk of stroke and myocardial infarction. Med Sci Monit. 2003;9(11):CR466-73.

36. Samal D, Greisenegger S, Auff E, Lang W, Lalouschek W. The relation between knowledge about hypertension and education in hospitalized patients with stroke in Vienna. Stroke. 2007;38(4):1304-8.

37. Skowron KB, Angelos P. Surgical informed consent revisited: time to revise the routine? World J Surg. 2017;41(1):1-4.

38. Gerstein NS, Schulman PA, Gerstein WH, Petersen TR, Tawill I. Should more patients continue aspirin therapy perioperatively?: clinical impact of aspirin withdrawal syndrome. Ann Surg, 2012;255(5):811-9.
