Original Article

Transition between ticagrelor and two different doses of clopidogrel at hospital discharge in patients with acute coronary syndrome submitted to percutaneous coronary intervention

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ARTICLE INFO

Article history:
Received 6 January 2016
Accepted 15 February 2016

Keywords:
Acute coronary syndrome
Angioplasty
Platelet aggregation inhibitors

ABSTRACT

Background: The transition from ticagrelor to clopidogrel is not based on pharmacodynamic or clinical studies, but it is a common practice. The aim of the present study was to test, in an exploratory way, the transition to two different doses of clopidogrel at the time of hospital discharge in patients diagnosed with acute coronary syndrome submitted to percutaneous coronary intervention who were initially treated with ticagrelor.
Methods: Patients previously treated with ticagrelor were randomized to receive a loading dose of 300 mg clopidogrel at hospital discharge, or 75 mg without the loading dose. The primary endpoint was the incidence of cardiovascular adverse events or bleeding at 30 days.
Results: Of 348 selected patients, 132 were enrolled and completed the study. The incidence of ischemic and hemorrhagic events at 30 days was similar between the groups, resulting in a rate of cardiac and cerebrovascular events of 6.1% vs. 9.1% (RR: 0.787; 95% CI: 0.361-1.715; $p = 0.74$).
Conclusions: The transition to clopidogrel with a dose of 75 mg at discharge, without a loading dose, appears to be a possible strategy. Studies with greater statistical power are needed to confirm these findings.

Transição entre ticagrelor e duas diferentes doses de clopidogrel na alta hospitalar de pacientes submetidos à intervenção coronária percutânea na vigência de síndrome coronariana aguda

Palavras-chave:
Síndrome coronariana aguda
Angioplastia
Inibidores da agregação de plaquetas

RESUMO

Introdução: A transição do ticagrelor para o clopidogrel não está fundamentada em estudos farmacodinâmicos ou clínicos, mas é uma prática comum. O objetivo do presente estudo foi testar, de forma exploratória, em pacientes com diagnóstico de síndrome coronariana aguda submetidos à intervenção coronariana percutânea, inicialmente tratados com ticagrelor, a transição para duas diferentes doses de clopidogrel no momento da alta hospitalar.
Métodos: Pacientes previamente tratados com ticagrelor foram randomizados para receber uma dose de ataque de 300 mg de clopidogrel no momento da alta hospitalar, ou 75 mg, omitindo-se a dose de ataque. O objetivo primário foi a incidência de eventos adversos cardiovasculares ou sangramento aos 30 dias.
Resultados: Dentre 348 pacientes selecionados, 132 foram incluídos e completaram o estudo. A incidência de eventos isquêmicos e hemorrágicos aos 30 dias foi similar entre os grupos, traduzindo-se em uma taxa de eventos cardíacos e cerebrovasculares de 6,1% vs. 9,1% (RR: 0,787; IC 95%: 0,361-1,715; $p = 0,74$).
Conclusões: A transição para clopidogrel com a dose de 75 mg no momento da alta, omitindo-se uma dose de ataque, aparenta ser uma estratégia possível. Estudos com maior poder estatístico são necessários para confirmar estes achados.

DOI of original article: http://dx.doi.org/10.1016/j.rbci.2017.08.005
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Peer review under the responsibility of Sociedade Brasileira de Hemodinâmica e Cardiologia Intervencionista.

Introduction

In the management of patients with acute coronary syndrome (ACS), the use of a new P2Y12 receptor blocking agent such as ticagrelor, instead of clopidogrel, is the therapy of choice given the reduction observed in the incidence of severe adverse cardiac events, including cardiovascular mortality, without a significant increase in the risk of severe bleeding.[1] Despite the proven cost-effectiveness,[2,3] it is often the case that public healthcare policies or supplemental healthcare plans reimbursement policies do not provide for the supply of ticagrelor after discharge, even for patients to whom this use is indicated.[4]

Although part of the benefit of using ticagrelor in reducing mortality may depend on its possible pleiotropic effects, such as increased adenosine-mediated coronary flow velocity and fewer sudden deaths over 12 months,[5] its rapid onset of action and potent platelet inhibition effect are associated with lower rates of acute complications, such as definitive stent thrombosis.[6] Thus, even in a scenario in which the patient cannot afford long-term use of ticagrelor, this drug is used as the first treatment line for ACS during the in-hospital phase, in order not to deprive the patient of any advantages provided by the drug use during this period.

The transition from ticagrelor to clopidogrel is not based on pharmacodynamic or clinical studies, but it is common in clinical practice.[7,8] Since ticagrelor shows a rapid termination of antiplatelet action (around 48 to 72 hours),[9] and considering that the daily administration of 75 mg clopidogrel, not preceded by a loading dose, may take up to 7 days to reach its full effect,[10] the question about the best transition strategy between the drugs persists, due to a theoretical time gap during which the patient would not be adequately receiving optimal platelet antiaggregation therapy.

The aim of the present study was to test, in an exploratory way, the transition to two different doses of clopidogrel at the time of hospital discharge and its impact on the rate of severe adverse cardiac events at 30 days in patients with a diagnosis of ACS submitted to percutaneous coronary intervention (PCI) and initially treated with ticagrelor.

Methods

Study design and population

This was a single-center exploratory study, which included patients with a diagnosis of non-ST elevation ACS (unstable angina or non-ST elevation myocardial infarction) submitted to invasive stratification and PCI with stent implantation, or ST-elevation acute myocardial infarction submitted to primary PCI; previously treated with ticagrelor with a loading dose of 180 mg followed by a maintenance dose of 90 mg every 12 hours and acetylsalicylic acid with a loading dose of 300 mg and maintenance dose of 100 mg daily; and who could not afford ticagrelor after hospital discharge, requiring the transition to clopidogrel. The main exclusion criterion was the possibility of maintaining ticagrelor therapy for 12 months, constituting a representative sample of clinical practice.

Patients were randomized to receive a loading dose of 300 mg of clopidogrel at hospital discharge, followed by 75 mg for 12 months, or 75 mg at discharge and for the next 12 months, without a loading dose. For randomization, a random sequence obtained from computational algorithms was used, kept in individual, sealed opaque envelopes, allowing concealment of the allocation process.

Objectives and definitions

The primary efficacy endpoint of the study was the incidence of severe adverse cardiac events, defined as a combined outcome of cardiovascular mortality, acute myocardial infarction, stent thrombosis, or new target-vessel revascularization at 30 days. The primary safety objective was the incidence of severe bleeding at 30 days. Severe bleeding was defined as bleeding type 3 – (3a) bleeding with hemoglobin decrease ≥ 3 and < 5 g/dL, or packed red blood cell transfusion; (3b) bleeding with hemoglobin decrease ≥ 5 g/dL, or cardiac tamponade, or bleeding requiring surgical intervention, or bleeding requiring intravenous vasoactive drugs; (3c) intracranial hemorrhage, or subcategories confirmed by autopsy, imaging test or lumbar puncture, or intraocular bleeding with impaired vision; or type 5 – (5a) probable fatal bleeding, (5b) definitive fatal bleeding, as defined by the Bleeding Academic Research Consortium.[11]

Procedures

In cases of non-ST elevation ACS, fondaparinux was the anticoagulant agent of choice in the pre-intervention management, except in patients with creatinine clearance < 20 mL/min. During the PCI, supplementation with intravenous unfractionated heparin was implemented at the dose of 85 U/kg or 60 U/kg, when the use of glycoprotein IIb/IIIa inhibitors was planned. Anticoagulation of patients with ST-elevation acute myocardial infarction was obtained with intravenous unfractionated heparin at a dose of 100 U/kg in the interventional laboratory.

The PCI procedures followed the recommendations and practices established by the current guidelines.[12] The radial approach was the first option for vascular access. Manual thrombus aspiration and use of glycoprotein IIb/IIIa inhibitors were performed at the interventionist's discretion. The 12-lead electrocardiogram was performed on admission, and at 30 to 60 minutes after the end of the procedure. Creatinine kinase MB (CK-MB) isoenzyme and troponin measurements were performed every 6 hours, until a decrease in levels of markers was observed; hemoglobin and hematocrit levels were measured between 12 and 24 hours after the end of the procedure. Except when contraindicated, patient prescription included a statin, beta-blocker, and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, in addition to antithrombotic agents. The study was approved by the local Research Ethics Committee and, prior to any procedure, the Free and Informed Consent form was signed.

Statistical analysis

Qualitative variables were shown as absolute frequencies and percentages. Quantitative data were described as means ± standard deviations or medians (25^{th}–75^{th} percentiles), according to each variable distribution. For the comparison of groups, the Chi-squared test or Fisher's exact test were used for the qualitative variables, and Student's *t*-test or the Mann-Whitney test were used for quantitative variables. The results with *p*-value < 0.05 were considered statistically significant. Estimates of event-free probability at 30 days were determined according to the Kaplan-Meier method.

Results

From July 2013 to January 2015, 348 patients diagnosed with ACS submitted to PCI received ticagrelor at hospital admission. Among those who were discharged, 132 could not afford outpatient drug maintenance, and were included in the present study (Fig.1). The mean age of the patients was 60 years, with 27% females and 30% with diabetes mellitus, with no differences between groups (Table 1). Approximately three-quarters of the patients were submitted to primary PCI and, except for the longer hospital length of stay in the group that received 300 mg clopidogrel, no difference was observed in the characteristics of procedures and concomitant medication at