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High bleeding risk patients with acute coronary syndromes treated with contemporary drug-eluting stents and Clopidogrel or Ticagrelor: Insights from CHANGE DAPT☆

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ABSTRACT

Background: The prospective observational CHANGE DAPT study compared clopidogrel versus ticagrelor-based dual antiplatelet (DAPT) regimens in consecutive patients with acute coronary syndrome (ACS), treated with percutaneous coronary intervention (PCI) with contemporary drug-eluting stents (DES). During the ticagrelor period (TP, May 2014–August 2015) there were more major bleedings than during the clopidogrel period (CP, December 2012–April 2014).

Methods and results: To evaluate whether the excess of major bleedings during TP may be limited to high bleeding risk (HBR) patients, we performed an explorative analysis of all 2062 CHANGE DAPT participants, of whom 547 (26.5%) were classified as HBR (CP, $n = 245$; TP, $n = 302$). In HBR and non-HBR patients, we assessed the impact of CP versus TP on propensity score-adjusted rates of major bleeding and a pre-defined ischemic endpoint (composite of cardiac death, myocardial infarction, or stroke) at 1-year follow-up. Among HBR patients, the rate of major bleeding was significantly higher during TP (1.7% vs. 5.0%; $HR_{adjusted}$ 3.70 [95% CI 1.18–11.67], $p = 0.03$), while there was no significant difference in the ischemic endpoint (6.6% vs. 8.0%, $HR_{adjusted}$ 1.23 [95% CI 0.63–2.42], $p = 0.54$). In non-HBR patients, the rates of major bleeding (1.1% vs. 1.7%; $HR_{adjusted}$ 2.13 [95% CI 0.84–5.43], $p = 0.11$) and the ischemic endpoint (2.8% vs. 3.4%, $HR_{adjusted}$ 1.38 [95% CI 0.74–2.57], $p = 0.32$) were similar between both periods.

Conclusions: Among consecutive ACS patients, the increased risk of major bleeding during ticagrelor-based DAPT was limited to HBR patients. In both HBR and non-HBR patients, ticagrelor-based DAPT did not reduce ischemic outcomes following treatment with contemporary DES implantation.

1. Introduction

Ticagrelor, a more potent antiplatelet agent, is recommended over clopidogrel as part of dual antiplatelet therapy (DAPT) in patients with acute coronary syndromes (ACS) treated with percutaneous coronary intervention (PCI) [1,2]. This recommendation is based on the large-scale randomized PLATO trial, in which ticagrelor-treated moderate-to-high risk ACS patients who underwent PCI, surgical, or non-invasive treatment showed a reduction of a composite ischemic endpoint (cardiovascular death, myocardial infarction [MI], or stroke) [3]. However, this benefit in ischemic outcomes came at the cost of more major bleedings [3,4]. A more recent prospective real-world registry – the CHANGE DAPT study – compared clopidogrel versus ticagrelor-based DAPT regimens in consecutive low-to-high risk ACS patients who were treated by PCI with contemporary drug-eluting stents (DES), and observed no reduction in ischemic endpoints during the ticagrelor period, but significantly more major bleedings [5].

Abbreviations: ACS, Acute coronary syndrome; CP, Clopidogrel period; DAPT, Dual antiplatelet therapy; DES, Drug-eluting stent; HBR, High bleeding risk; MI, Myocardial infarction; NACCE, Net adverse clinical and cerebral events; PCI, Percutaneous coronary intervention; TP, Ticagrelor period.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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The excess in major bleedings in ticagrelor-treated patients may be of particular concern in patients at high bleeding risk (HBR). While the most recent focused update on DAPT from the European Society of Cardiology does not favor clopidogrel over ticagrelor in HBR patients undergoing PCI [5], multiple real-world observational studies have shown that complex high-risk ACS patients are more frequently treated with clopidogrel instead of the more potent antiplatelet agents prasugrel and ticagrelor [6–8].

As there is a lack of studies comparing DAPT regimens based on different antiplatelet drugs in ACS patients *with HBR*, we evaluated in the present analysis whether the excess of major bleedings during the ticagrelor-period of CHANGE DAPT was a universal finding or limited to HBR patients only. In addition, as most ACS patients with increased bleeding risk also have an increased risk of ischemic events [9], we assessed whether the use of ticagrelor reduced the rates of ischemic events within the HBR population of the CHANGE DAPT study.

2. Methods

2.1. Study population and design

The study population and design of the CHANGE DAPT study (NCT03197298) has been published before [10]. Briefly, CHANGE DAPT was an investigator-initiated, prospective observational study of 2062 consecutive ACS patients, who were treated with PCI with contemporary DES. The study was performed at the tertiary PCI center Thoraxcentrum Twente in the Netherlands and assessed two successive treatment periods with different primary DAPT regimens (i.e., the clopidogrel period [CP; December 2012 – April 2014], and the ticagrelor period [TP; May 2014 – August 2015]). Generally, the intended DAPT duration was 1 year. The study did not include patients who were on oral anticoagulation therapy, as international guidelines discourage ticagrelor-based DAPT in such patients [1]. The study complied with the Declaration of Helsinki and was performed by the contract research organization Cardio Research Enschede (Enschede, the Netherlands). Clinical events were adjudicated by a clinical endpoint committee consisting of three members of the research team, and an experienced neurologist assessed all strokes.

Although several specific risk factors for major bleeding have previously been reported and multiple bleeding risk scores have been suggested [11–13], a generally accepted definition of HBR in ACS patients is currently not available. In the present explorative analysis of the CHANGE DAPT data, we used HBR criteria that followed the criteria of the LEADERS FREE trial [14]. CHANGE DAPT participants were classified at HBR if they fulfilled at least one of the following criteria: 1) age ≥ 75 years; 2) hemoglobin <11 g/dl; 3) platelet count < 100.000/mm^3; 4) hospital admission for gastro-intestinal bleeding in the previous 12 months; 5) stroke during the previous 12 months; 6) any previous intracranial hemorrhage; 7) creatinine clearance <40 ml/min/1.73 m^2 (calculated from serum creatinine, using the Modification of Diet in Renal Disease [MDRD] equation); 8) cancer (except skin) diagnosed in the previous 3 years; and 9) non-steroidal anti-inflammatory drug use at discharge. As 10) the use of oral anticoagulation at baseline and 11) planned major surgery in the next 6 months after the index PCI had been exclusion criteria of the CHANGE DAPT study [10], none of the CHANGE DAPT patients fulfilled HBR criteria 10 or 11. In contrast to the LEADERS FREE trial, we did not have information about severe liver disease (e.g. cirrhosis) available in our database and therefore we might have missed some of these HBR patients. However, if patients with severe liver disease had reduced levels of hemoglobin or platelet count, they anyway were classified as HBR.

2.2. Definitions of clinical endpoints

The main clinical endpoints of the present study were the 1-year rates of major bleeding and a composite ischemic endpoint of cardiac death, any MI, or stroke. Major bleeding was defined as any Bleeding Academic Research Consortium (BARC) class 3 or 5 bleeding and/or all Thrombolysis in Myocardial Infarction (TIMI) major bleedings (i.e., including CABG-related major bleeding) [15,16]. MI was defined according to the modified Academic Research Consortium criteria, in which creatine kinase with additional creatine kinase myocardial band or troponin were used [17,18]. Laboratory measurements and definitions of MI did not change during the study. Strokes were defined as a focal loss of neurologic function by an ischemic or hemorrhagic event, with residual symptoms after ≥24 h or leading to death.

Secondary endpoints were Net Adverse Clinical and Cerebral Events (NACCE; a composite of all-cause death, any MI, stroke, or major bleeding); any clinically indicated revascularization, and definite or probable stent thrombosis according to the Academic Research Consortium criteria [17].

2.3. Statistical analysis

Patients treated during the CP were compared to patients treated during the TP and stratified for HBR. Additional sensitivity analyses were performed, comparing patients who were actually treated with clopidogrel during the CP versus patients actually treated with ticagrelor during the TP. Treatment with either clopidogrel or ticagrelor was assessed at discharge or, if a NACCE occurred before discharge, at the time of that in-hospital event.

Categorical data are reported as numbers and percentages, continuous data as mean ± standard deviation. Differences are compared using the chi-square test (or Fisher's exact test when appropriate) and Student's *t*-test, respectively. Time to clinical endpoints was calculated using Kaplan-Meier analyses and the log-rank test was applied for between-group comparisons. Hazard ratios were computed using Cox proportional hazards regression analyses. To adjust for potential confounders, propensity scores were estimated using multiple logistic regression analysis. All baseline and procedural variables of the CHANGE DAPT study were used to calculate the propensity score for treatment during the TP; a multivariate Cox regression model was then used to adjust for the propensity score. All *p*-values were two-sided and p-values <0.05 were considered significant. Data analysis was performed with SPSS, Version 22.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Study population

Between December 21, 2012, and August 25, 2015, a total of 2062 patients were included in the CHANGE DAPT study; 1009 (48.9%) during the CP, and 1053 (51.1%) during the TP (Supplementary Fig. A.1). Of all participants, 547/2062 (26.5%) were at HBR, of which 245 (44.8%) underwent PCI during the CP and 302 (55.2%) during the TP. Of all 1515/2062 (73.5%) non-HBR patients, 764 (50.4%) were treated during the CP and 751 (49.6%) during the TP. HBR patients were significantly older than non-HBR patients, had significantly more comorbidities, presented more often with non-ST-elevation ACS, were more often diagnosed with multivessel disease, and were more often treated with clopidogrel-based DAPT at discharge (Supplementary Tables A.1 and A.2).

3.2. High bleeding risk patients: characteristics and clinical outcomes

Baseline demographics and HBR criteria are presented in Table 1. Age and comorbidities for HBR patients treated during the CP and TP were similar except for a more frequent diagnosis of peripheral artery disease during the CP (16.3% vs. 7.0%, $p = 0.001$). HBR criteria were comparable between both treatment periods except for more previous cancer in the TP patients (8.6% vs. 14.2%, $p = 0.04$). This difference was mainly driven by the proportion of TP patients with previously diagnosed breast cancer (0.8% vs. 4.3%). Interventional procedural characteristics and medication are presented in Table 2. During the course of the study, i.e., from CP to TP, trans-radial procedures were more often performed (16.3% vs. 37.7%, $p < 0.001$) while the use of glycoprotein IIb/IIIa-inhibitors decreased (33.5% vs. 15.2%, $p < 0.001$).

Table 3 and Fig. 1 show the various 1-year clinical outcomes including propensity score-adjusted hazard ratios. Among HBR patients, the rate of major bleeding was significantly higher during the TP (1.7% vs. 5.0%, adjusted HR 3.70 [95% CI 1.18–11.67], $p = 0.03$), while there was no statistically significant difference in the composite ischemic endpoint (6.6% vs. 8.0%, adjusted HR 1.23 [95% CI 0.63–2.42], $p = 0.54$). This resulted in a significantly higher NACCE rate for TP patients (8.2% vs. 13.4%, adjusted HR 1.80 [95% CI 1.02–3.17], $p = 0.04$), while there were no statistically significant between-group differences in all other secondary clinical endpoints.

All HBR patients (i.e. HBR patients treated during CP plus during TP) had significantly higher 1-year rates of major bleeding and a composite ischemic endpoint (cardiac death, MI, or stroke) as compared to all non-HBR patients (Supplementary Table A.3).

3.3. Non-high bleeding risk patients: characteristics and clinical outcomes

In non-HBR patients, most baseline demographics, interventional procedural characteristics and medications were similar for patients treated during the CP and TP (Tables 1 and 2). However, TP patients underwent more often trans-radial procedures (18.2% vs. 47.4%, $p < 0.001$), received less glycoprotein IIb/IIIa-inhibitors (47.0% vs. 28.5%, $p < 0.001$), and were more often treated with proton pump inhibitors (37.0% vs. 50.5%, $p < 0.001$).

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