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Concomitant use of warfarin and ticagrelor as an alternative to triple antithrombotic therapy after an acute coronary syndrome

Oscar Ö. Braun [a], Besim Bico [a], Uzma Chaudhry [b], Henrik Wagner [b], Sasha Koul [a], Patrik Tydén [a], Fredrik Scherstén [a], Stefan Jovinge [a], Peter J. Svensson [c], J. Gustav Smith [a], Jesper van der Pals [a,*]

[a] Department of Cardiology, Skåne University Hospital, Lund University, Lund and Malmö, Sweden
[b] Department of Internal Medicine, Helsingborg Hospital, Lund University, Lund and Helsingborg, Sweden
[c] Department for Coagulation Disorders, Skåne University Hospital, Lund University, Lund and Malmö, Sweden

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ABSTRACT

Introduction: Treatment with warfarin in combination with clopidogrel has been shown to reduce the incidence of major bleeding as compared to triple antithrombotic therapy (TT; warfarin, clopidogrel and aspirin). However, there are uncertainties regarding the risk for thrombosis since poor-responsiveness to clopidogrel is common. Ticagrelor is a more potent platelet inhibitor, but data supporting concurrent use of ticagrelor and warfarin (dual antithrombotic therapy, DT) is limited. This study therefore sought to evaluate the risk of bleeding and thrombosis associated with DT after an acute coronary syndrome (ACS).

Materials and methods: We identified all ACS patients on DT upon discharge from Helsingborg Hospital and Skåne University Hospital in Malmö and Lund, Sweden, during 2013. Patients on DT were compared with historical controls discharged with TT. Major bleeding was defined in accordance with the HAS-BLED derivation study. Patients were retrospectively followed for three months.

Results: In total, 107 DT patients were identified and compared with 159 controls on TT. Mean HAS-BLED bleeding risk score and duration of treatment were similar between the groups (HAS-BLED 2.2 +/− 0.8 vs 2.2 +/− 1.0 units, p = NS; duration 2.7 +/− 0.8 vs 2.5 +/− 0.9 months, p = NS; DT vs TT). The incidence of spontaneous major bleeding was similar between the groups, as was a composite of all thrombotic events, i.e. peripheral embolism, stroke/TIA and acute coronary syndrome (bleeding 8/106 (7.5%) vs 11/157 (7.0%), p = NS; thrombosis 5/106 (4.7%) vs 5/157 (3.2%), p = NS; DT vs TT).

Conclusions: Rates of thrombotic and bleeding events were similar in patients with TT and patients with ticagrelor and warfarin.

Introduction

A currently unresolved clinical problem centers on patients with an indication for oral anticoagulation but who also have an indication for antiplatelet treatment due to intercurrent coronary disease [1]. Oral anticoagulation is necessary in patients with venous thromboembolism, mechanical heart valves and most patients with atrial fibrillation. Warfarin has been the mainstay of such treatment and the efficacy in preventing and treating thromboembolic complications is well established, as is the risk of bleeding complications [2].

Aspirin has been widely used since the 1980s for secondary prevention in coronary disease patients, and has received a class 1 recommendation in clinical practice guidelines [3–5]. The major risk with aspirin is bleeding [6], and bleeding risks have become more prominent with the advent of dual antiplatelet therapy (aspirin in combination with clopidogrel) [7,8]. Triple antithrombotic therapy (TT) with warfarin, aspirin and clopidogrel carries a substantially higher bleeding risk than dual antiplatelet therapy [9]. However, patients with dual antiplatelet therapy and prolonged warfarin interruption in this setting have a threefold increased risk of stroke or thromboembolic events [1,10], and dual antiplatelet therapy is associated with lower rates of death and myocardial infarction compared to aspirin and warfarin alone [8,11].

In an attempt to reduce bleeding complications in this context, the WOEST trial investigated the treatment efficacy of warfarin in combination with clopidogrel as an alternative to TT [12]. A significantly reduced incidence of major bleeding was reported along with a similar incidence

Abbreviations: ACS, Acute coronary syndrome; COPD, Chronic obstructive pulmonary disease; DT, Dual antithrombotic therapy; INR, International normalized ratio; PPI, Proton pump inhibitor; STEMI, ST-elevation myocardial infarction; TIA, Transitory ischemic attack; TT, Triple antithrombotic therapy.

* Corresponding author at: Department of Cardiology, Skåne University Hospital, Lund University, 221 85 Lund, Sweden. Tel.: +46 46 17 13 64, +46 704 674 773; fax: +46 46 17 60 11.

E-mail addresses: oscar.braun@med.lu.se (O.Ö. Braun), besim.bico@med.lu.se (B. Bico), uzma9c@hotmail.com (U. Chaudhry), henrik.wagner@med.lu.se (H. Wagner), sasha.koul@med.lu.se (S. Koul), patrik.tyden@skane.se (P. Tydén), fredrik.schersten@skane.se (F. Scherstén), stefan.jovinge@med.lu.se (S. Jovinge), peter.svensson@med.lu.se (P.J. Svensson), gustav.smith@med.lu.se (J. Gustav Smith), jesper.vanderpals@med.lu.se (J. van der Pals).

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of thrombotic events as compared to TT, even though the trial was not adequately powered to study the latter endpoint [13].

Thus, the optimal treatment remains unclear when both risks for bleeding and thrombosis are taken into account and clinical practice patterns vary as a consequence. The fact that 20-25% of the population is not adequately responsive to clopidogrel has caused concerns over a potentially increased risk of stent thrombosis with the combination of clopidogrel and warfarin [14]. Since ticagrelor is an alternative to clopidogrel but with very low rates of non-responding patients [15], the combination of ticagrelor and warfarin has emerged as an attractive albeit unstudied treatment option in clinical pratice.

The aim of the present study was therefore to evaluate the safety and efficacy of concurrent medication with warfarin and ticagrelor (dual antithrombotic therapy, DT) in comparison to TT after an acute coronary syndrome (ACS).

Material and Methods

Study Sample

All patients over 18 years of age treated for an ACS at the Coronary Care Units at Helsingborg Hospital and Skåne University Hospital during 2013 were retrospectively screened for ticagrelor and warfarin at discharge. In 2013, this treatment combination was introduced as a preferred alternative to TT by local consensus and guidelines at the participating hospitals. All patients discharged on triple therapy from Skane University Hospital in Lund after an ACS between 2005 and 2010, during which time TT was the recommended regimen by local consensus and guidelines, were used as a control group [9]. Eligible patients were identified from the RIKS-HIA registry (Register of Information and Knowledge About Swedish Heart Intensive Care Admissions), which includes detailed information on all patients treated at Swedish Coronary Care Units as described previously [16]. The study was part of an ethically approved quality control and assurance program aiming to follow up the introduction of this new therapeutic strategy.

Study Definitions

Mortality data was extracted from the Swedish National Registry. All other data was gathered from patients' electronic medical records, including baseline characteristics and follow-up data. Patients were followed for three months by retrospective review of records, for bleeding events, thromboembolic events and medication changes. Spontaneous major bleeding during follow-up was defined according to the HAS-BLED derivation study: any bleeding requiring hospital care and/or causing a decrease in hemoglobin level of more than 20 g/L and/or requiring blood transfusion and/or with intracranial location [17]. In addition, the bleeding events were classified according to TIMI, GUSTO and BARC criteria [18]. Thromboembolic events were defined as a physician's diagnosis of stroke, transient ischemic attack (TIA), ACS or peripheral arterial embolism.

The HAS-BLED score was calculated for each individual: one point was assigned for each of hypertension, abnormal hepatic or renal function (maximum two points), stroke, bleeding history or predisposition, labile INR, elderly (>65) and drugs/alcohol concomitantly (antiplatelet agents or non-steroidal anti-inflammatory drugs; 1 point for drugs plus 1 point for alcohol excess, maximum 2 points) [17]. $CHADS_2VA_2Sc$ was used for thromboembolic risk stratification in atrial fibrillation patients [19].

Statistical Analysis

Data analysis was performed with SPSS Statistics (Version 21; SPSS Inc, IBM Corporation, NY, USA). Treatment groups were compared for differences in baseline characteristics by the Chi square test for categorical variables and by Student's t-test for continuous variables. The incidence of major bleeding was calculated using the Kaplan-Meier estimator, and differences between treatment groups examined with the log rank test. Two-sided p-values <0.05 were considered statistically significant.

Results

A total of 2148 patients were screened for dual antithrombotic therapy upon discharge. Of those, 107 (5.0%) DT patients were identified. Out of a total of 2423 patients screened for triple antithrombotic therapy, 159 (6.6%) TT patients were found.

All TT patients were treated with 75 mg aspirin and 75 mg clopidogrel once daily, and DT patients with 90 mg ticagrelor twice daily. For patients on warfarin treatment, target international normalized ratio (INR) was between 2.0 and 3.0 unless otherwise specified (Table 1). The duration of treatment was decided by the attending physician, after which the drug considered least important with regard to the indication for treatment, was discontinued. In general, if warfarin was terminated the patients continued with a $P2Y_{12}$ inhibitor and aspirin. If a $P2Y_{12}$ inhibitor was terminated, the patients continued with warfarin and aspirin.

Baseline Characteristics

The clinical characteristics at the study baseline are presented in Table 1. The mean HAS-BLED bleeding risk score was found to be equal between the groups but we observed significant differences between the groups with higher age and more hypertension but less heart failure in DT treated patients. Also, target INR was less often reduced but treatment with a proton pump inhibitor was more common in this group.

The most common indication for oral anticoagulation in the TT group was atrial fibrillation (n = 63, 39.6%) followed by apical akinesia (n = 60, 37.8%), left ventricular thrombus (n = 17, 10.7%), presence of a mechanical valve (n = 6, 3.8%), venous thromboembolism (n = 11, 6.9%) and other causes (n = 2, 1.3%). The most common indication for oral anticoagulation in the DT group was also atrial fibrillation (n = 83, 77.6%) followed by venous thromboembolism (n = 10, 9.3%), apical akinesia (n = 5, 4.7%), presence of a mechanical valve

Table 1
Baseline patient characteristics.

Characteristic, n (%)	TT (n = 159)	DT (n = 107)	p-value
Mean age, years (SD)	67 (+/−11)	74 (+/−9)	<0.001
Female sex	35 (22.0)	26 (24.3)	NS
STEMI[a]	83 (52.2)	56 (52.3)	NS
Mean HAS-BLED, score (SD)	2.2 (+/−1.0)	2.2 (+/−0.8)	NS
Medical history, n (%)			
Heart failure	119 (75.8)	52 (48.6)	<0.001
Stroke/TIA[b]	25 (15.7)	15 (14.0)	NS
Diabetes mellitus	29 (18.2)	37 (34.6)	0.003
Hypertension	67 (42.1)	80 (74.8)	<0.001
Abnormal renal function[c]	3 (1.9)	4 (3.7)	NS
Valvular disease	12 (7.5)	12 (11.2)	NS
COPD[d]	12 (7.5)	11 (10.3)	NS
Thyroid disease	10 (6.3)	11 (10.3)	NS
Malignancy[e]	19 (11.9)	19 (17.8)	NS
Pharmacological treatment, n (%)			
Prior warfarin	53 (33.3)	55 (51.4)	0.004
Reduced INR target[f]	76 (47.8)	2 (1.9)	<0.001
Concomitant PPI[g]	49 (30.8)	49 (45.9)	0.01

TT = Triple antithrombotic therapy (warfarin, clopidogrel and aspirin), DT = Dual antithrombotic therapy (warfarin and ticagrelor). [a]ST-elevation myocardial infarction, [b]Transient ischemic attack, [c]According to the definition used in the HAS-BLED score (presence of chronic dialysis, renal transplantation or serum creatinine ≥200 μmol/L), [d]Chronic obstructive pulmonary disease, [e]Prior or current, [f]International normalized ratio, target range reduced from 2.0 – 3.0 to 2.0 – 2.5. [g]Proton pump inhibitor.