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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%, $p < 0.001$).

Table 1
Baseline characteristics stratified for bleeding risk.

	HBR $n = 547$			Non-HBR $n = 1515$		
	CP $n = 245$	TP $n = 302$	p	CP $n = 764$	TP $n = 751$	p
Age (years)	75.4 ± 9.1	76.2 ± 8.7	0.29	58.4 ± 9.3	59.0 ± 9.4	0.75
Male sex	143 (58.4)	172 (57.0)	0.74	559 (72.2)	576 (76.7)	0.11
BMI (kg/m^2)[a]	26.6 ± 4.3	27.1 ± 4.3	0.18	27.6 ± 4.3	27.9 ± 4.3	0.21
Clinical history						
Hypertension	142 (58.0)	156 (51.7)	0.14	286 (37.4)	284 (37.8)	0.88
Hypercholesterolemia	96 (39.2)	104 (34.4)	0.25	264 (34.6)	280 (37.3)	0.27
Diabetes Mellitus	51 (20.8)	76 (25.2)	0.23	107 (14.0)	110 (14.6)	0.72
Peripheral artery disease	40 (16.3)	21 (7.0)	0.001	49 (6.4)	37 (4.9)	0.21
Previous MI	48 (19.6)	54 (17.9)	0.61	98 (12.8)	97 (12.9)	0.96
Previous PCI	49 (20.0)	72 (23.8)	0.28	117 (15.3)	102 (13.6)	0.34
Previous CABG	41 (16.7)	35 (11.6)	0.08	31 (4.1)	28 (3.7)	0.74
Previous stroke	19 (7.8)	20 (6.6)	0.61	13 (1.7)	11 (1.5)	0.71
Clinical presentation						
ST-elevation MI	89 (36.3)	95 (31.5)	0.23	363 (47.5)	339 (45.1)	0.35
Non-ST-elevation MI	78 (31.8)	92 (30.5)	0.73	178 (23.3)	200 (26.6)	0.13
Unstable angina	78 (31.8)	115 (38.1)	0.13	223 (29.2)	212 (28.2)	0.68
HBR criteria						
Age > 75 years	183 (74.7)	226 (74.8)	0.97			
Hemoglobin < 11 g/dl	36 (14.7)	40 (13.2)	0.63			
Platelet count < 100.000/mm^3	5 (2.0)	5 (1.7)	0.74			
Previous GI bleeding < 1 year	1 (0.4)	3 (1.0)	0.42			
Previous stroke < 1 year	3 (1.2)	4 (1.3)	0.92			
Previous intracranial bleeding	1 (0.4)	3 (1.0)	0.42			
Creatinine clearance < 40 ml/min/1.73m^2	24 (9.8)	26 (8.6)	0.63			
Cancer < 3 years	21 (8.6)	43 (14.2)	0.04			
NSAID at discharge	22 (9.0)	18 (6.0)	0.18			
Number of HBR criteria			0.87			
1	202 (82.4)	248 (82.1)				
2	36 (14.7)	43 (14.2)				
≥ 3	7 (2.9)	11 (3.6)				

Values are n (%), or mean ± SD. Abbreviations: BMI = body mass index; CABG = coronary artery bypass grafting; CP = clopidogrel period; GI = gastro-intestinal; HBR = high bleeding risk; MI = myocardial infarction; NSAID = non-steroidal anti-inflammatory drug; PCI = percutaneous coronary intervention; TP = ticagrelor period.
[a] Out of 1921 patients.

Table 2
Procedural characteristics and medication stratified for bleeding risk.

	HBR $n = 547$			Non-HBR $n = 1515$		
	CP $n = 245$	TP $n = 302$	p	CP $n = 764$	TP $n = 751$	p
Procedural characteristics						
Vascular access			<0.001			<0.001
Radial	40 (16.3)	114 (37.7)		139 (18.2)	356 (47.4)	
Femoral	205 (83.7)	188 (62.3)		625 (81.8)	395 (52.6)	
Multivessel treatment	52 (21.2)	52 (17.2)	0.24	124 (16.2)	129 (17.2)	0.62
Glycoprotein IIb/IIIa-inhibitor	82 (33.5)	46 (15.2)	<0.001	359 (47.0)	214 (28.5)	<0.001
Stent type			0.52			0.42
Co-Cr SES	56 (22.9)	77 (25.5)		212 (27.7)	213 (28.4)	
Co-Cr ZES	112 (45.7)	142 (47.0)		314 (41.1)	313 (41.7)	
Pt-Cr EES	76 (31.0)	83 (27.5)		231 (30.2)	223 (29.7)	
Other DES	1 (0.4)	0 (0.0)		7 (0.9)	2 (0.3)	
Medication at discharge						
Aspirin	100 (100)	100 (100)	–	100 (100)	100 (100)	–
Clopidogrel	215 (87.8)	83 (27.5)	–	662 (86.6)	76 (10.1)	–
Ticagrelor	30 (12.2)	219 (72.5)	–	102 (13.4)	675 (89.9)	–
PPI	147 (60.0)	201 (66.6)	0.11	283 (37.0)	379 (50.5)	<0.001
Medication at 1-year						
Aspirin	212 (86.5)	263 (87.1)	0.53	732 (95.8)	719 (92.5)	0.99
DAPT	204 (83.3)	252 (83.4)	0.69	712 (93.2)	695 (92.5)	0.87
with Clopidogrel	179 (73.1)	79 (26.2)	–	615 (80.5)	105 (14.0)	–
with Ticagrelor	25 (10.2)	173 (57.3)	–	97 (12.7)	590 (78.6)	–
OAC + $P2Y_{12}$ inhibitor	19 (7.8)	15 (5.0)	0.35	23 (3.0)	15 (2.0)	0.45

Values are n (%), or mean ± SD. Abbreviations: Co-Cr SES = cobalt chromium sirolimus-eluting stent; Co-Cr ZES = cobalt chromium zotarolimus-eluting stent; CP = clopidogrel period; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; HBR = high bleeding risk; OAC = oral anticoagulant; PPI = proton pump inhibitor; Pt-Cr EES = platinum chromium everolimus-eluting stent; TP = ticagrelor period.

Table 3
One-year clinical outcome stratified for bleeding risk.

1-year	HBR $n = 547$					Non-HBR $n = 1515$				
	CP $n = 245$	TP $n = 302$	Unadjusted HR (95% CI)	p	Propensity score-adjusted HR (95% CI)	p	CP $n = 764$	TP $n = 751$	Unadjusted HR (95% CI)	p	Propensity score-adjusted HR (95% CI)	p
Major bleeding	4 (1.7)	15 (5.0)	3.09 (1.02–9.30)	0.04	3.70 (1.18–11.67)	0.03	8 (1.1)	13 (1.7)	1.65 (0.68–3.98)	0.26	2.13 (0.84–5.43)	0.11
Cardiac death, any MI or stroke	16 (6.6)	24 (8.0)	1.21 (0.65–2.29)	0.55	1.23 (0.63–2.42)	0.54	21 (2.8)	25 (3.4)	1.21 (0.68–2.16)	0.52	1.38 (0.74–2.57)	0.32
NACCE	20 (8.2)	40 (13.4)	1.65 (0.97–2.83)	0.06	1.80 (1.02–3.17)	0.04	31 (4.1)	41 (5.5)	1.35 (0.84–2.15)	0.21	1.67 (1.01–2.75)	0.04
All-cause death	14 (5.8)	23 (7.6)	1.33 (0.69–2.59)	0.40	1.38 (0.68–2.79)	0.38	6 (0.8)	7 (0.9)	1.19 (0.40–3.53)	0.76	1.20 (0.65–6.24)	0.23
Cardiac death	10 (4.1)	11 (3.7)	0.89 (0.38–2.09)	0.79	0.76 (0.30–1.91)	0.56	2 (0.3)	1 (0.1)	0.51 (0.05–5.62)	0.57	0.49 (0.04–6.64)	0.59
Any MI	6 (2.5)	9 (3.0)	1.21 (0.43–3.39)	0.72	1.60 (0.54–4.76)	0.40	18 (2.4)	20 (2.7)	1.13 (0.60–2.13)	0.71	1.30 (0.66–2.59)	0.45
Stroke	1 (0.4)	5 (1.7)	4.06 (0.47–34.74)	0.17	3.33 (0.36–31.20)	0.29	2 (0.3)	6 (0.8)	3.06 (0.62–15.15)	0.15	2.62 (0.47–14.54)	0.27
Any clinically indicated revascularization	12 (5.1)	14 (4.8)	0.94 (0.44–2.03)	0.88	0.82 (0.36–1.87)	0.63	29 (3.9)	42 (5.7)	1.49 (0.93–2.39)	0.10	1.57 (0.94–2.61)	0.09
Definite-or-probable ST	3 (1.2)	4 (1.3)	1.08 (0.24–4.82)	0.92	0.72 (0.14–3.60)	0.69	3 (0.4)	4 (0.5)	1.36 (0.31–6.08)	0.69	1.44 (0.29–7.25)	0.66
Definite ST	2 (0.8)	2 (0.7)	0.81 (0.11–5.75)	0.83	0.45 (0.06–3.65)	0.45	1 (0.1)	4 (0.5)	4.08 (0.46–36.50)	0.17	5.11 (0.52–50.03)	0.16

Values are n (%). Analyses based on Kaplan-Meier method, implying that patients who died, withdrew consent or were lost were censored at exact moments of dropout. Therefore, percentages may differ slightly from results of straightforward calculations. Abbreviations: CI = confidence interval; CP = clopidogrel period; HBR = high bleeding risk; HR = hazard ratio; MI = myocardial infarction; NACCE = net adverse clinical and cerebral events; ST = stent thrombosis; TP = ticagrelor period.

At 1-year follow-up, non-HBR patients treated during the CP and during the TP had rates of major bleeding (1.1% vs. 1.7%, adjusted HR 2.13 [95% CI 0.84–5.43], $p = 0.11$) and the composite ischemic endpoint (2.8% vs. 3.4%, adjusted HR 1.38 [95% CI 0.74–2.57], $p = 0.32$) that did not differ significantly (Table 3, Fig. 1).

3.4. Sensitivity analyses for high bleeding risk and non-high bleeding risk patients

Of the *HBR patients*, 215/547 (87.8%) were actually treated with clopidogrel during the CP and 219/302 (72.5%) were actually treated with ticagrelor during the TP. Clopidogrel-treated HBR patients during the CP had significantly more comorbidities than ticagrelor-treated HBR patients during the TP (Supplementary Table B.1). In addition, ticagrelor-treated HBR patients during the TP were more often treated via the trans-radial approach (15.3% vs. 38.4%, $p < 0.001$) and less often with glycoprotein IIb/IIIa-inhibitors (34.9% vs. 18.3%, $p < 0.001$) (Supplementary Table B.2). There were no significant between-group differences in HBR criteria, except for more previous cancer in the ticagrelor-treated patients during the TP (7.9% vs. 14.2%, $p = 0.04$). At 1-year follow-up, clopidogrel-treated HBR patients during CP had significantly fewer major bleedings than ticagrelor-treated HBR patients during the TP (1.4% vs. 5.5%, adjusted HR 5.28 [95% CI 1.38–20.29], $p = 0.02$) while the rates of the composite ischemic endpoint were similar (6.6% vs. 7.4%, adjusted HR 1.45 [95% CI 0.66–3.19], $p = 0.35$) (Supplementary Table B.3).

Of the *non-HBR patients*, 662/764 (86.6%) were treated with clopidogrel during the CP, and 675/751 (89.9%) were treated with ticagrelor during the TP (Supplementary Table B.1). *Trans*-Radial procedures (16.9% vs. 48.0%, $p < 0.001$) and proton pump inhibitors (36.0% vs. 50.4%, $p < 0.001$) were more often used in ticagrelor-treated non-HBR patients during the TP, while glycoprotein IIb/IIIa inhibitor use was lower in these patients (47.9% vs. 30.4%, $p < 0.001$) (Supplementary Table B.2). There were no statistically significant differences in major bleeding (1.1% vs. 1.8%, adjusted HR 2.56 [95% CI 0.95–6.87], $p = 0.06$) and the composite ischemic endpoint (2.9% vs. 3.3%, adjusted HR 1.25 [95% CI 0.64–2.46], $p = 0.51$) (Supplementary Table B.3). Furthermore, there were no statistically significant between-group differences in other clinical endpoints.

4. Discussion

4.1. Main results

In the present analysis of 2062 consecutive ACS patients, treated with contemporary DES in the CHANGE DAPT study, approximately one in every four patients was considered to be at HBR, although our study did not assess patients on oral anticoagulation therapy. The main findings were: 1) that treatment during the ticagrelor period was associated with a higher major bleeding risk which was significant in HBR patients only; and 2) that in both HBR and non-HBR patients, ticagrelor-based DAPT was not associated with a benefit in ischemic outcomes.

4.2. Treatment of high bleeding risk patients

Major bleeding in ACS patients is associated with an increased mortality and a reduced quality of life, and therefore it is an essential endpoint to account for in studies that evaluate DAPT [19–22]. Although several bleeding risk scores have been developed to identify patients at HBR and to tailor DAPT, there is no consensus on the standard use of a particular bleeding risk score. In the present study, when applying criteria based on the LEADERS FREE trial [14], more than a quarter of all ACS patients (26.5%) was at HBR. This proportion may seem relatively low when compared to the 41.6% HBR patients in another study, using similar HBR criteria in consecutive, percutaneously treated ACS

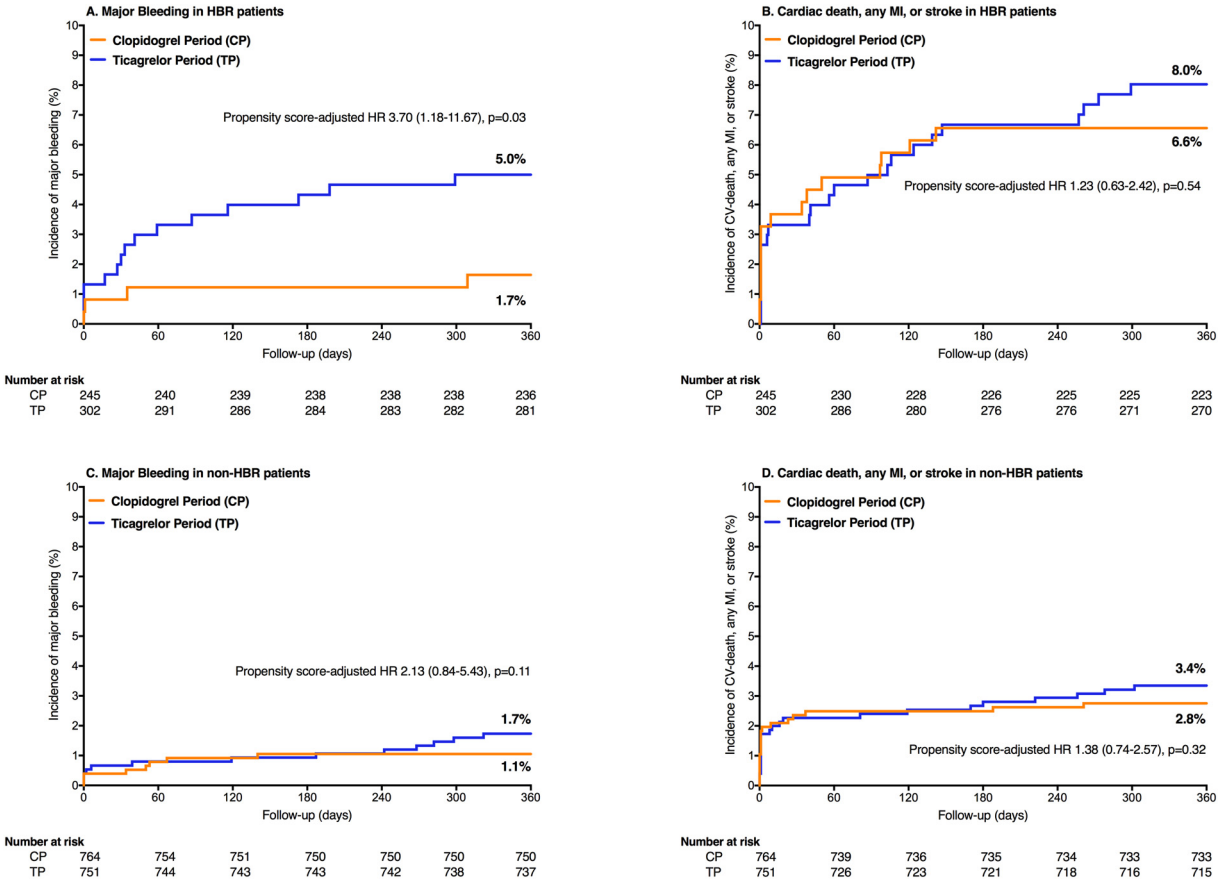

Fig. 1. One-year major bleeding and ischemic events for HBR and non-HBR patients. Kaplan Meier curves for major bleeding and a composite ischemic endpoint consisting of cardiac death, any MI, or stroke in HBR (A, B) and non-HBR (C, D) patients treated during the clopidogrel period (orange) and the ticagrelor period (blue). Abbreviations: CP = clopidogrel period; HBR = high bleeding risk; MI = myocardial infarction; TP = ticagrelor period.

patients [23], but the difference may be largely explained by the exclusion of patients on oral anticoagulation therapy in CHANGE DAPT [10]. These patients were not assessed since guidelines discourage treatment with ticagrelor in patients on oral anticoagulation therapy due to an excessive bleeding risk [1].

The recently published focused update on DAPT from the European Society of Cardiology is the first guideline to include specific recommendations on which $P2Y_{12}$ inhibitor to use in HBR patients: both clopidogrel and ticagrelor received a class IIa recommendation [5]. Since HBR patients, such as the elderly, are frequently under-represented in clinical trials and, therefore, comparative studies assessing different DAPT regimens in these patients are lacking, the recommendation is partly based on expert opinion [5]. Several studies address the issue of abbreviated DAPT duration in PCI-treated ACS patients at HBR, but to the best of our knowledge the current analysis is the first to evaluate DAPT based on clopidogrel and ticagrelor in this patient population. Our results suggest that the increase in major bleeding in ticagrelor-treated patients can mainly be found in those at HBR. While one may tend to reconsider the use of ticagrelor-based DAPT to avoid major bleedings in HBR patients, just these patients have a higher risk of ischemic events [9,24]. This was also seen in the present study and is probably related to corresponding risk factors, such as an advanced age. Physicians in both our and other real-world studies tend to treat complex high-risk ACS patients less often with DAPT based on ticagrelor or prasugrel [6–8,25]. This phenomenon is sometimes called a risk-treatment paradox, since the more potent antiplatelet agents are being withheld from patients at the highest risk of ischemic events. Nevertheless, the results of the present study, which observed an increased rate of major bleedings in ticagrelor-treated patients without a benefit in ischemic outcomes, might reassure clinicians who tend to prefer such a "conservative approach". In addition, spontaneous ischemic and bleeding events seem equally related to clinical prognosis [26,27], and procedure-related bleedings (also assessed in the current study) were previously found to be independently associated with an increased mortality [28]. Nevertheless, the optimal approach to balance ischemic and bleeding risks might be a personalized choice of DAPT regimen in individual patients, based on their specific characteristics [29]; the use of dedicated risk scores may be very useful in this context [11–13].

4.3. Treatment with contemporary DES

Several factors may contribute to the lack of benefit in ischemic outcome for ticagrelor-treated HBR and non-HBR patients in CHANGE DAPT. Firstly, in compliance with European guidelines, our study included low-to-high risk ACS patients, while in the PLATO trial moderate-to-high-risk patients were assessed [1,3,10,30]. Secondly, the side-effect profile of ticagrelor may have affected patient compliance [31] and might have resulted in a somewhat higher risk of interruption of DAPT. Thirdly, all patients were treated with PCI with use of contemporary DES, which has shown to improve clinical outcome with lower ischemic event rates (i.e., target-vessel MI and stent thrombosis), as compared to bare metal, and first-generation drug-eluting stents, which were both used in the PLATO trial [3,32].

Previously, patients with HBR were often treated with bare metal stents, as the possibility to shorten DAPT duration was effective in lowering the incidence of bleeding. However, two recent trials showed superior outcomes for PCI with contemporary DES versus bare metal stents in ACS patients at HBR [24,33,34]. Based on these results, DES are currently recommended over bare metal stents irrespective of the

intended DAPT duration [5]. Since the widespread availability of contemporary DES, there has been an increase in the proportion of patients with HBR who are treated with DES [23]. A significant benefit of ticagrelor over clopidogrel has not been demonstrated in an ACS patient population that was exclusively treated with contemporary DES. Thus, in such patients the need for a more potent $P2Y_{12}$ inhibitor-based DAPT remains to be demonstrated. The findings of the observational CHANGE DAPT study raise some doubts, but a definite answer will require data from large randomized clinical trials. These future trials should not only assess the optimal duration of DAPT in relation to HBR status, but also evaluate which patient groups truly benefit from a more potent DAPT regimen after PCI with contemporary DES. Such patient groups may be diabetics or patients treated with stenting in left main stems, very long lesions, or small vessels. In addition, it remains to be confirmed whether genotyping [35] might play a role in choosing the type of DAPT prior to PCI procedures or downgrading potent DAPT to clopidogrel-based DAPT in ACS patients who underwent PCI [36,37].

4.4. Minimizing bleeding risk

The impact of different DAPT regimens on the outcome of patients with HBR are currently being assessed by several randomized clinical trials. Studies that randomize clopidogrel versus ticagrelor or prasugrel in the elderly (i.e., the most common HBR criterion) [38], and ticagrelor-based DAPT versus ticagrelor single antiplatelet therapy in high-risk ACS patients [39], will provide information that may help optimize antiplatelet therapy in the future.

Until the results of these studies are available, the risk of HBR could be lowered by adjusting several factors, as compared to the clinical practice that we observed in CHANGE DAPT: 1) while the CHANGE DAPT patients were treated with an intended DAPT duration of 12 months, an abbreviated treatment with DAPT may be more appropriate and is currently recommended in the presence of HBR by international guidelines [5,22]; 2) from today's perspective, the use of the trans-radial access was relatively low in our study (28.2%, most likely because the inclusion period was some years ago and the operators then had a large experience in trans-femoral PCI); which could be increased to reduce procedure-related bleedings [40,41]; 3) the proportion of HBR patients treated with proton pump inhibitors for gastric protection was reasonable (63.6%) but could be further improved. Although during CHANGE DAPT there was a significant improvement from the CP to the TP in the rates of trans-radial access and gastric protection, which theoretically had a lowering effect upon the bleeding risk, a significantly higher incidence of major bleedings was observed during the TP [10].

An alternative approach to lower bleeding risk is to downgrade from DAPT with a more potent $P2Y_{12}$ inhibitor to clopidogrel-based DAPT. Two recent trials assessed such a step-down approach and showed that switching DAPT 1 or 4 weeks after PCI may lower the bleeding risk without increasing ischemic events [36,37].

4.5. Limitations

The results of this exploratory study, in particular the findings of the subgroup analysis, should be considered hypothesis generating. Although there are no expected differences between the treatment periods in underreporting events, we cannot exclude that the relatively low adverse event rates may be partly related to ascertainment bias. We performed propensity score-adjusted analyses, but residual confounding cannot be excluded. This could explain the higher rate of previously diagnosed cancer in the TP patients. In the present study, no data of liver disease or expected noncompliance to DAPT were available; nevertheless, both HBR characteristics applied only to few participants in a previous large-scale HBR trial [33]. Other classifications of HBR are valuable alternatives but may require data that were not available for all patients. The present findings cannot be generalized to ACS patients on oral anticoagulation therapy or treated without PCI.

5. Conclusions

Among the consecutive ACS patients included in the observational CHANGE DAPT study, the increased major bleeding risk during treatment with ticagrelor-based DAPT was limited to HBR patients. In both HBR and non-HBR patients, ticagrelor-based DAPT did not reduce ischemic events after treatment with contemporary DES as compared to clopidogrel-based DAPT. Further randomized trials are warranted to optimize antiplatelet therapy in ACS patients at HBR who are treated with PCI.

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Conflicts of interest

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