



# Bleeding complications with clopidogrel or ticagrelor in ST-elevation myocardial infarction patients – A real life cohort study of two treatment strategies <sup>☆</sup>

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## ABSTRACT

**Introduction:** Dual antiplatelet therapy (DAPT), including potent P2Y12 inhibition after ST-elevation myocardial infarction (STEMI) is recommended in clinical guidelines. However, bleeding complications are common, and associated with worse outcomes. The aim of this study was to assess incidence of bleeding events with a clopidogrel-based compared to a ticagrelor-based DAPT strategy, in a real world population. Secondary aims were to assess ischemic complications and mortality.

**Methods and Results:** We identified 330 consecutive STEMI patients with a clopidogrel-based and 330 with a ticagrelor-based DAPT strategy. Patients' medical records were searched for bleeding and ischemic complications, over 6 months follow-up.

The two groups were well balanced in baseline characteristics, age (69 years in both groups), sex (31% vs. 32% females), history of diabetes (19% vs. 21%), hypertension (43% in both) and MI (17% vs. 15%). There was no difference in CRUSADE bleeding score (28 vs. 29). After discharge, there were more than twice as many bleeding events with a ticagrelor-based compared with a clopidogrel-based strategy (13.3% vs. 6.5%,  $p = 0.005$ ). Bleeding events included significantly more severe bleeding complications (TIMI major/minor [5.8 vs. 1.0,  $p = 0.001$ ]) during the ticagrelor-based period. There was no significant difference in the composite of death, MI or stroke (7.8% vs. 7.1%,  $p = 0.76$ ).

**Conclusions:** In this observational study, a ticagrelor-based DAPT strategy was associated with significantly more bleeding complications, without any significant change in death, MI or stroke. Larger studies are needed to determine whether bleeding complications off-sets benefits with a more potent DAPT strategy in older and more comorbid real-life patients.

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## 1. Introduction

Dual antiplatelet therapy (DAPT), including aspirin and a P2Y12-inhibitor, is a cornerstone in both acute and long-term treatment of acute coronary syndrome (ACS) [1]. In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor was superior to clopidogrel, reducing cardiovascular death, myocardial infarction (MI) or stroke in ACS patients. There was no difference in overall bleeding complications, but a higher incidence of non-coronary

artery by-pass grafting (CABG) bleeding events was reported with ticagrelor [2]. Based on these data, current clinical guidelines advocate potent DAPT (including ticagrelor or prasugrel) after ACS, and ticagrelor is given a higher recommendation than clopidogrel, especially in ST-elevation MI (STEMI) [1,3]. However, data from real world patients, typically older and with more comorbid conditions than patients included in randomized controlled trials (RCT), have shown contradictory results [4,5]. Bleeding complications are the most common non-ischemic complications in ACS patients. The importance of bleeding complications, and the association with worse outcomes, including increased mortality, has gained increased attention during recent years [6–8].

We hypothesized that a real world population, with STEMI all-comers, i.e. including the oldest, most frail and co-morbid patients,

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would have a substantially larger increase in bleeding risk associated with the more potent platelet inhibition achieved with ticagrelor vs. clopidogrel, as compared to previous RCT data.

The aim of the current study was to assess incidence of bleeding events with a clopidogrel-based strategy compared with a ticagrelor-based strategy, using three established bleeding definitions, in a real world population with STEMI. Secondary aims were to assess ischemic complications and mortality. Tertiary aims were to assess differences in severity and localizations of the observed bleeding complications.

## 2. Methods

### 2.1. Study population

We used a local part of the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry to identify all patients with STEMI in the county of Östergötland, Sweden. Details of the registry have previously been published [9]. Briefly, SWEDEHEART is a national quality register where all coronary care units (CCU) in Sweden register patients, including information on baseline characteristics, comorbidities, symptoms on arrival, ECG-findings, angiographic findings, medication at discharge, and discharge diagnosis.

On Nov 1st 2011, all three hospitals in the county of Östergötland, changed from a clopidogrel-based strategy to a ticagrelor-based DAPT strategy (on top of aspirin), in patients with STEMI/new left bundle branch block (LBBB). According to local guidelines, high bleeding risk patients, could be treated with clopidogrel also during the ticagrelor-based period.

For this analysis, we included 330 consecutive patients from Jun 23rd 2010 to Oct 31st 2011. During Nov 2011 the ticagrelor-based strategy was implemented, and from Dec 1st 2011 to Mar 9th 2013 another 330 consecutive patients were included.

To capture all bleeding complications and ischemic complications we undertook a detailed search of each individual patient's medical records. A template was used to ensure a standardized review of events during hospitalization and six months follow-up. Thereafter, data from the templates were merged with the SWEDEHEART database.

This analysis was performed and presented in accordance with the STROBE statement.

(<http://www.strobe-statement.org/>).

### 2.2. Outcomes

All non-CABG related bleeding events were characterized according to three established bleeding definitions; Thrombolysis in Myocardial Infarction (TIMI), PLATO, and Bleeding Academic Research Consortium (BARC) [10,11]. Bleeding localizations, defined as gastrointestinal, intracranial, urogenital, procedural or other, are presented. We assessed nonfatal MI, stroke and mortality, and the association with bleeding. MI diagnoses were made according to current guidelines at the time of inclusion [12]. Major adverse cardiovascular event (MACE) was defined as death, MI or stroke. There was no loss to follow-up.

### 2.3. Risk calculations

Risk of bleeding was estimated using the Can Rapid risk stratification of Unstable angina Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE score) [13]. Risk of 6 months mortality was estimated using the Global Registry of Acute Coronary Events (GRACE) score [14].

### 2.4. Ethics

In accordance with the ethical regulations for National Swedish quality registries, all patients were informed about their participation in the registry and the right to deny registration. For the current study, we obtained approval from the Ethical review board in Linköping (Dnr. 2013/152-31, April 24, 2013).

### 2.5. Statistics

Continuous variables are presented as mean and standard deviation or median and interquartile range, depending on whether the variable was normally distributed or not. Categorical variables are presented as counts and percentages. Comparisons between groups were performed using chi-square tests for categorical variables and Students' *t*-test or Mann Whitney test for continuous variables, depending on whether the variable was normally distributed or not. We present short (during hospital stay) and long-term (from discharge to six months follow-up) events separately to minimize bias from changes in PCI-routines (such as radial/femoral approach at PCI and concomitant use of GPIIb/IIIa inhibitors). We also performed a sensitivity analysis restricted to patients discharged on DAPT, including aspirin and clopidogrel or ticagrelor. In a second sensitivity analysis we compared patients discharged with clopidogrel and ticagrelor (as treated). Due to large differences in baseline characteristics between these two groups, we calculated a propensity score for probability of being discharged with clopidogrel or ticagrelor. Data are presented as odds ratio (OR) and 95% confidence interval (CI). A *p*-value <0.05 was considered statistically significant.

All statistical analyses were performed with the SPSS Version 23.0 (PASW Statistics 23) software (SPSS, Inc, Chicago, Ill).

## 3. Results

### 3.1. Baseline characteristics on arrival and hospital care.

There were minimal differences between the two groups in baseline characteristics, including age (69 years in both groups), proportion of females (31% vs. 32%), BMI (27 vs. 26 kg/m<sup>2</sup>), medical history, (such as history of hypertension, diabetes, stroke/TIA, MI, revascularisation, or a history of bleeding) and medication on arrival. Importantly, we found no difference in the level of the CRUSADE bleeding score (28 vs. 26), the level of the GRACE six months mortality score (103 vs. 104), history of anemia, hemoglobin (Hb) on arrival, last in-hospital Hb or estimated Glomerular filtration rate (eGFR). The only statistically significant difference observed was a higher mean platelet count during the ticagrelor-based period ( $267 \times 10^9 /L$  vs.  $251 \times 10^9 /L$ , *p* = 0.02) (Table 1).

All but 5 patients in each group (98.5%) underwent coronary angiography, and 96% in each group were treated with PCI. There was no difference in number of diseased vessels or stent use. General PCI success was reported in 91% of patients in both groups. We found significant differences in adjunctive medical therapy during PCI, with more abciximab during the clopidogrel-based period and more tirofiban and bivalirudin during the ticagrelor-based period. At discharge both groups were well treated with aspirin (98% vs. 97%) betablocker (94% vs. 92%), statin (94% vs 95%) and angiotensin receptor blocker (ARB) / angiotensin-converting enzyme inhibitor (ACE-I) (79% vs. 87%, *p* = 0.010) in the clopidogrel and ticagrelor-based group respectively. There was a clear difference in use of clopidogrel (90% vs. 21%, *p* < 0.001) and ticagrelor (0.7% vs. 74%, *p* < 0.001) between the clopidogrel-based and ticagrelor-based time periods (Table 1).

**Table 1**  
Baseline characteristics and Treatments.

	Clopidogrel-based group (n = 330)	Ticagrelor-based group (n = 330)	p-value
<b>Demographics</b>			
Age, year (mean ± SD)	68.6 ± 13	69.3 ± 13	0.46
Female sex, n (%)	103 (31.2)	105 (31.8)	0.87
Body weight, kg (mean ± SD)	79 ± 16	78 ± 16	0.28
BMI kg/m <sup>2</sup> (mean ± SD)	27 ± 4	26 ± 4	0.48
<b>Medical History, n (%)</b>			
Hypertension	142 (43.0)	141 (42.7)	0.90
Diabetes Mellitus	63 (19.1)	68 (20.6)	0.70
Stroke	32 (9.7)	26 (7.9)	0.49
TIA	6 (1.8)	6 (1.8)	1.00
Renal failure (dialysis)	6 (1.8)	8 (2.4)	0.60
Previous history of MI	55 (16.7)	50 (15.2)	0.60
Previous history of PCI	34 (10.3)	33 (10.0)	0.57
Previous history of CABG	11 (3.3)	14 (4.2)	0.54
Known left ventricular dysfunction	24 (7.3)	21 (6.4)	0.64
Bleeding history	17 (5.2)	15 (4.5)	0.70
Anemia last 2 years	76 (23.1)	89 (27.0)	0.25
Previous ulcer	3 (0.9)	8 (2.4)	0.13
Current smoker	86 (26.1)	101 (30.6)	0.48
Former smoker	114 (34.5)	103 (31.2)	
<b>Risk Scores, (mean ± SD)</b>			
CRUSADE Bleeding Score	28 ± 15	29 ± 16	0.29
GRACE score	103 ± 29	104 ± 31	0.79
<b>Medication at arrival to CCU, n (%)</b>			
Aspirin	88 (26.7)	85 (25.8)	0.97
P2Y <sub>12</sub> -receptor blocker	15 (4.5)	7 (2.1)	0.06
Warfarin	15 (4.5)	20 (6.1)	0.69
β-blocker	99 (30.0)	96 (29.1)	0.97
ACE-I	68 (20.6)	53 (16.1)	0.32
ARB	25 (7.6)	46 (13.9)	0.03
Statin	88 (26.7)	69 (20.9)	0.22
Diuretics	63 (19.1)	64 (19.4)	1.00
NSAIDs	4 (1.2)	8 (2.4)	0.41
PPI	39 (12)	52 (16)	0.07
<b>Laboratory data index (mean ± SD)</b>			
Hb on arrival, g/L	139 ± 15	140 ± 17	0.19
Platelet count, x10 <sup>9</sup> /L	251 ± 91	267 ± 84	0.02
Last Hb during hospital stay, g/L	128 ± 18	129 ± 20	0.67
eGFR, ml/min	79 ± 34	74 ± 34	0.08
<b>Interventions, n (%)</b>			
No Catheterisation	5 (1.5)	5 (1.5)	0.62
Catheterisation only	23 (7.0)	17 (5.2)	
PCI	302 (91.5)	308 (93.3)	
Radial access*	199 (61.2)	209 (64.3)	0.42
<b>Severity of coronary disease*</b>			
1 vessel disease	157 (48.3)	159 (48.9)	0.88
2 vessel disease	92 (28.3)	94 (28.9)	
3 vessel disease	52 (16.0)	49 (15.1)	
Left main stenosis	8 (2.5)	10 (3.1)	
<b>Procedure details<sup>†</sup></b>			
Stent deployed <sup>†</sup>	236 (78.1)	236 (76.6)	0.52
DES	131 (43.4)	153 (49.7)	0.12
<b>Number of stents</b>			
1 stent	196 (65.1)	192 (62.3)	0.29
2 stents	33 (11.0)	41 (13.3)	
3 or more stents	7 (2.3)	3 (0.9)	
General success <sup>†</sup>	286 (94.7)	288 (93.5)	0.64
<b>Medication during hospital stay, n (%)</b>			
LMWH	90 (27.3)	114 (34.5)	0.04
Abciximab	237 (71.8)	62 (18.8)	<0.001
Tirofiban	0	113 (34.2)	<0.001
Bivalirudin	0	82 (24.8)	<0.001
<b>Medication at discharge</b>			
	<b>Clopidogrel-based group (n = 308)</b>	<b>Ticagrelor-based group (n = 308)</b>	
Aspirin	303 (98)	299 (97)	<0.001
Clopidogrel	276 (90)	63 (20)	0.08
Prasugrel	4 (1.3)	1 (0.3)	0.25
Ticagrelor	2 (0.7)	228 (74)	0.15
Warfarin	35 (11.4)	27 (8.8)	0.41
LMWH	4 (1.3)	1 (0.3)	0.33
DAPT only	254 (82.5)	269 (87.3)	0.99
TAT	22 (7.1)	17 (5.5)	0.66
DAT	16 (5.2)	11 (3.6)	<0.001
β-blocker	290 (94.2)	283 (91.9)	0.86

(continued on next page)

Table 1 (continued)

	Clopidogrel-based group (n = 330)	Ticagrelor-based group (n = 330)	p-value
ACE-I	217 (70.5)	212 (68.8)	0.63
ARB	27 (8.8)	57 (18.5)	0.03
Statin	290 (94.2)	291 (94.5)	1.00
PPI	68 (22.1)	75 (24.4)	
Steroids	11 (4.4)	4 (1.3)	
NSAID	1 (0.3)	1 (0.3)	

Results are presented as numbers and percentages unless otherwise indicated.

\* Of patients undergoing catheterization.

† Of patients undergoing PCI. Abbreviations (in order of appearance): SD, standard deviation; BMI, body mass index; TIA, transient ischemic attack; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; CRUSADE, Can Rapid risk stratification of Unstable angina Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines; GRACE, Global Registry of Acute Coronary Events; ARB, angiotensin receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; NSAID, non-steroid anti-inflammatory drugs; PPI, proton pump inhibitor; Hb, Hemoglobin; eGFR, estimated glomerular filtration rate, calculated with the Cockcroft Gault equation; DES, drug eluting stent; LMWH, low molecular weight heparin; DAPT, dual antiplatelet therapy; TAT, triple antithrombotic therapy; DAT, dual antithrombotic therapy.

## 3.2. Outcomes

### 3.2.1. In-hospital outcome events

During hospital stay there was no statistical difference in overall bleeding complications (8.8% vs. 7.0%,  $p = 0.39$ ) or severe bleeding complications (TIMI major [0.3% vs. 0.9%,  $p = 0.62$ ] PLATO major/other major [3.0% vs. 3.0%,  $p = 1.00$ ] or BARC type  $\geq 3$  [2.7% vs.

2.7%,  $p = 1.00$ ]). The majority of observed bleeding events were defined as TIMI minimal, PLATO minor/minimal or BARC type 2.

We observed 22 deaths in each group (6.7%) during hospital stay and no significant difference in reinfarction (3.0% vs. 2.4%,  $p = 0.54$ ) between the two strategies (Table 2).

Table 2  
Outcomes.

In-hospital events	Clopidogrel-based group (n = 330)	Ticagrelor-based group (n = 330)	p-value
<b>Any Bleeding</b>	29 (8.8)	23 (7.0)	0.39
TIMI (major/minor/minimal)	1/9/19	3/7/13	0.49
TIMI (major/minor)	10 (3.0)	10 (3.0)	1.00
TIMI (major)	1 (0.3)	3 (0.9)	0.62
PLATO (major/other major/minor/minimal)	2/8/11/8	4/6/7/6	0.70
PLATO (major/other major/minor)	21 (6.4)	17 (5.2)	0.62
PLATO (major/other major)	10 (3.0)	10 (3.0)	1.00
BARC (type1/2/3a/3b/3c/5b)	5/15/4/4/1/0	3/11/3/5/0/1	0.75
BARC type 2 or more	24 (7.3)	20 (6.1)	0.53
BARC type 3 or more	9 (2.7)	9 (2.7)	1.00
BARC type 3b or more	5 (1.5)	6 (1.8)	1.00
<b>Death</b>	22 (6.7)	22 (6.7)	1.00
<b>Reinfarction</b>	10 (3.0)	8 (2.4)	0.54
<b>Blood transfusions</b>	6 (1.8)	7 (2.1)	0.78
<b>From discharge to end of follow-up</b>	<b>N = 308</b>	<b>N = 308</b>	
<b>Any Bleeding</b>	20 (6.5)	41 (13.3)	0.005
TIMI (major/minor/minimal)	0/3/17	6/12/23	0.004
TIMI (major or minor)	3 (1.0)	18 (5.8)	0.001
TIMI (major)	0	6 (1.9)	0.03
PLATO (major/other major/minor/minimal)	0/1/6/13	6/4/12/19	0.02
PLATO (major, other major or minor)	7 (2.3)	22 (7.1)	0.004
PLATO (major or other major)	1 (0.3)	10 (3.2)	0.01
BARC (type1/type2/type3a/type3b/type3c)	9/9/1/1/0	10/23/2/3/3	0.046
BARC type 2 or more	11 (3.6)	31 (10.1)	0.001
BARC type 3 or more	2 (0.6)	8 (2.6)	0.12
BARC type 3b or more	1 (0.3)	6 (1.9)	0.12
<b>Non-bleeding Outcomes</b>			
<b>MACE</b>	24 (7.8)	22 (7.1)	0.76
Myocardial infarction	6 (1.9)	5 (1.6)	0.77
Stroke	5 (1.6)	6 (1.9)	0.76
Death	15 (4.9)	13 (4.2)	0.70

Results are presented as numbers and (percentages). Abbreviations (in order of appearance): Bleeding definitions: TIMI, Thrombolysis in Myocardial Infarction; PLATO, Platelet Inhibition and Patient Outcomes; BARC, Bleeding Academic Research Consortium; MACE, Major adverse cardiovascular event (includes death, myocardial infarction and stroke).

### 3.2.2. Follow-up outcome events (from discharge to six months follow-up)

In patients discharged alive, there were more than twice as many bleeding events during the ticagrelor-based period as compared with the clopidogrel-based period (13.3% vs. 6.5%,  $p = 0.005$ ). (Fig. 1) Bleeding events included significantly more severe bleeding complications (TIMI major/minor [5.8% vs. 1.0%,  $p = 0.001$ ], PLATO major/other major/minor [7.1% vs. 2.3%,  $p = 0.004$ ] and BARC type  $\geq 2$  [10.1% vs. 3.6%,  $p = 0.001$ ]) during the ticagrelor-based period compared to the clopidogrel-based period. If the comparison was restricted to the most severe bleeding events, the difference persisted, with more bleeding events during the ticagrelor-period (TIMI major [1.9% vs. 0%,  $p = 0.03$ ] or PLATO major/other major [3.2% vs. 0.2%,  $p = 0.01$ ], with a nonsignificant trend in the same direction for BARC type  $\geq 3$  [2.6% vs. 0.6%,  $p = 0.107$ ]) (Table 2).

The ticagrelor-period appeared to be similarly associated with increased bleeds in patients above 75 years of age (18.4% vs. 9.6%,  $p = 0.10$ ) and under (10.3% vs. 5.1%,  $p = 0.05$ ), compared to the clopidogrel-based period. Significantly more patients were hospitalized due to bleeding complications during the ticagrelor-based period (6.8% vs. 1.9%,  $p = 0.003$ ). A second bleeding event during follow-up occurred in few patients, without any difference between the two groups (1.9% vs. 1.6%,  $p = 0.761$ ). Treatment with a P2Y12 inhibitor was stopped prematurely because of bleeding more often during the ticagrelor-based period (5.2% vs. 1.6%,  $p = 0.015$ ), but there was no difference in overall rate of discontinuation (14.3% vs. 10.9%,  $p = 0.206$ ).

The bleeding rates appeared higher with OAC + DAPT (TAT) (12.8%) and OAC + single antiplatelet inhibitor (DAT) (14.8%) than with DAPT only (9.2%), but the majority of the bleeding events after discharge occurred in patients treated with DAPT only (48 [78.7% of all bleeds]) and relatively few inpatients treated with DAT (4 [6.6%]) or TAT (5 [8.2%]). There were no significant differences in MACE (7.8% vs. 7.1%,  $p = 0.76$ ) or the individual components, all-cause death (4.2% vs. 4.9%,  $p = 0.70$ ), new MI (1.6% vs. 1.9%,  $p = 0.77$ ) or stroke (1.9% vs. 1.6%,  $p = 0.76$ ) with a ticagrelor vs a clopidogrel-based strategy (Table 2).

There was no significant difference in stent thrombosis over the complete study period, (2.1% vs. 1.2%,  $p = 0.356$ ) in the ticagrelor-based and the clopidogrel-based period respectively.

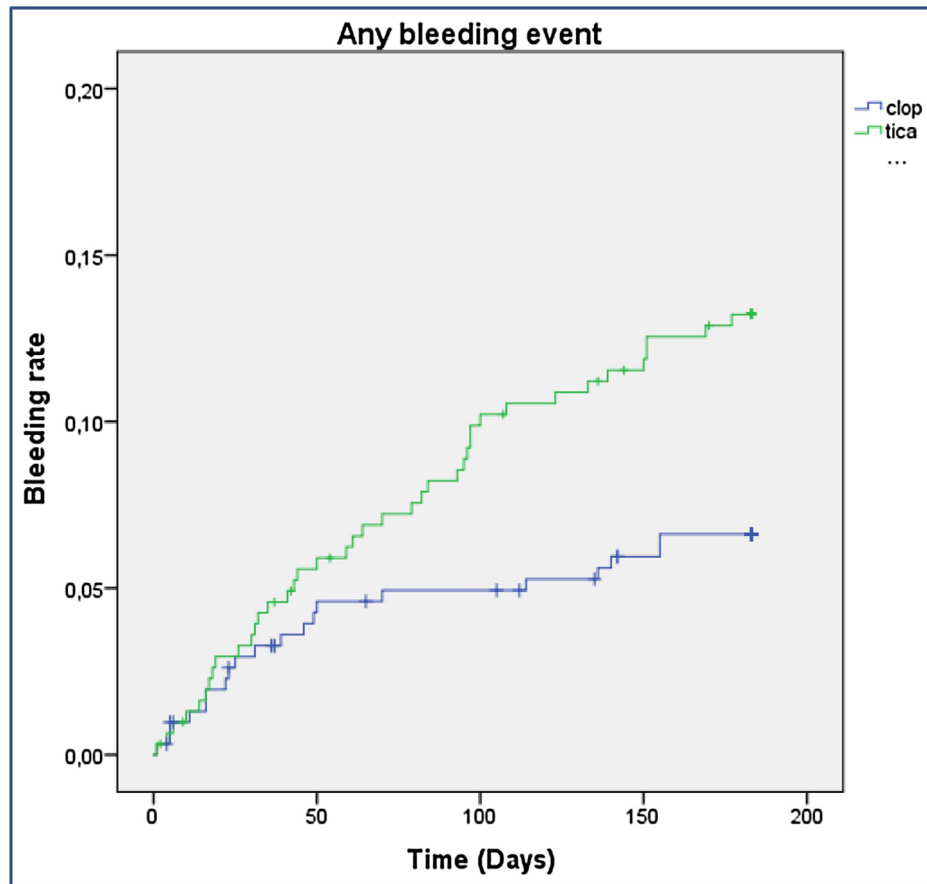


Fig. 1. Any bleeding complication from discharge to end of follow-up with a clopidogrel-based compared to a ticagrelor-based strategy. Log Rank test:  $p = 0.008$ .

### 3.2.3. Sensitivity analysis

In a sensitivity analysis restricted to patients discharged on DAPT with ticagrelor or clopidogrel in addition to aspirin during the clopidogrel ( $n = 251$ ) and ticagrelor-based period ( $n = 268$ ), the observed difference in bleeding complications between the two groups remained. For baseline characteristics see supplementary Table S1. We found significantly higher incidence of any bleeding complication during the ticagrelor-based period (11.9% vs. 6.3%,  $p = 0.029$ ), including significantly more bleeding events defined as TIMI major/minor (4.5% vs. 0.8%,  $p = 0.010$ ) and BARC type  $\geq 2$  (8.2% vs. 3.2%,  $p = 0.014$ ). Numerically there were also more PLATO major/other major and BARC type  $\geq 3$  events, but the difference did not reach statistical significance.

There were numerically more MACE during the clopidogrel period, but it did not reach statistical significance (8.4% vs. 5.2%,  $p = 0.154$ ) (Table S2).

In addition, we performed a second sensitivity analysis based on actual treatment at discharge, 339 with clopidogrel and with 229 ticagrelor. Clopidogrel treated patients were older (69 vs. 65 years,  $p = 0.016$ ), more often women (32% vs. 24%,  $p = 0.043$ ), more often discharged with an oral anticoagulant (10.9% vs. 0.4%,  $p < 0.001$ ). Moreover, clopidogrel patients had more co-morbid conditions as reflected in a higher CRUSADE score (28 vs. 24,  $p = 0.001$ ) and higher GRACE score (103 vs. 92,  $p < 0.001$ ). Ticagrelor was significantly associated with any bleeding event (12.7% vs. 7.7%,  $p = 0.048$ ) compared to clopidogrel (OR 1.75, 95% CI; 1.0–3.05,  $p = 0.05$ ). After adjustment with propensity score the association was strengthened (adjusted OR 2.06, 95% CI; 1.07–3.96,  $p = 0.03$ ). Also TIMI major/minor were associated with ticagrelor treatment (adjusted OR 6.14, 95% CI; 1.79–21.00,

$p = 0.004$ . In contrast, ticagrelor was associated with fewer MACE (3.1% vs. 9.7%,  $p = 0.002$ ), which was non-significant after adjustment (OR 0.46, 95% CI; 0.18–1.15,  $p = 0.10$ ).

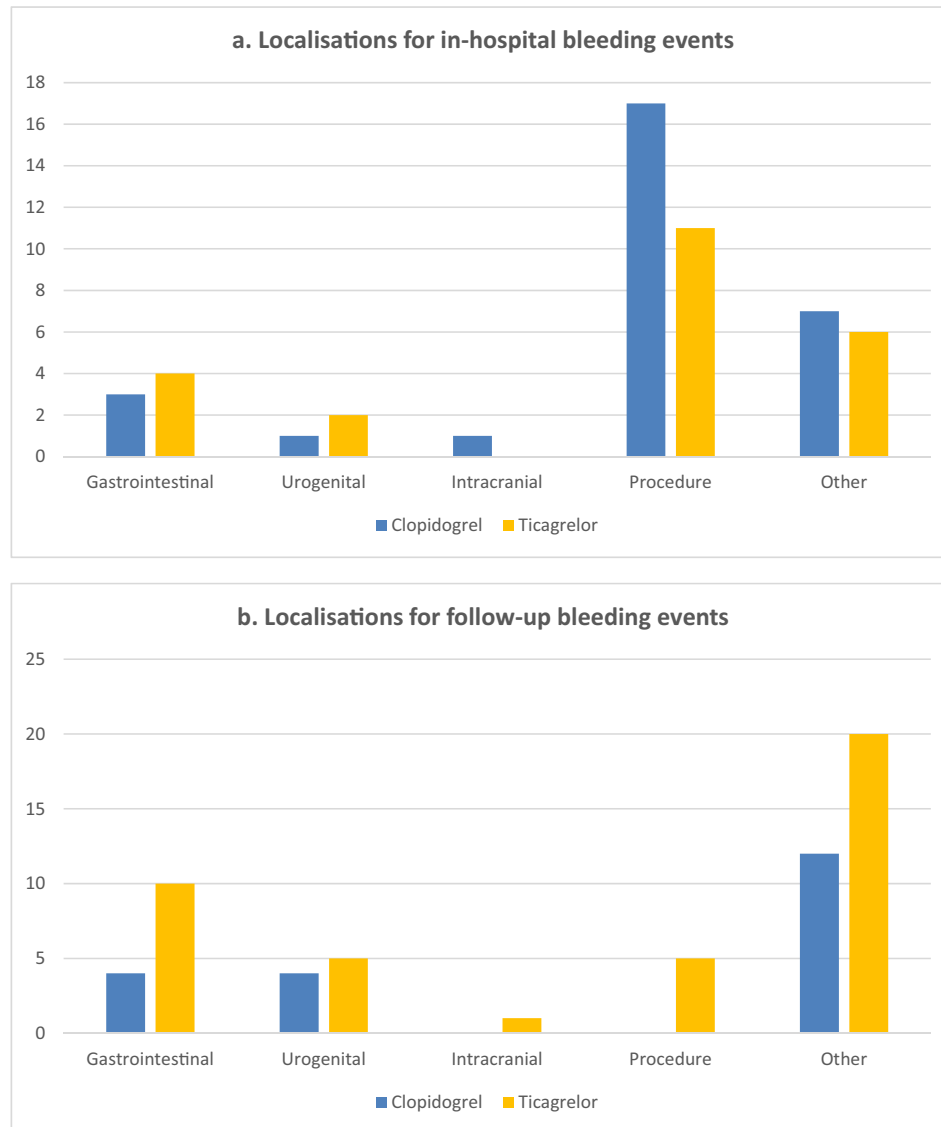
### 3.2.4. Bleeding localizations

During hospital stay, procedure related bleeding events were most frequent. After discharge, GI bleeding complications and bleeds other than GI/Urogenital/intracranial/procedure-related predominated. Other bleeding events consisted mainly of hematomas and epistaxes (Fig. 2).

## 4. Discussion

The main finding of this real-life study of consecutive STEMI patients, was a doubled bleeding complication rate with a ticagrelor-based strategy as compared to a clopidogrel-based strategy from discharge, over 6 months follow-up. Even though the majority of the bleeding complications were less severe, we observed more TIMI major, PLATO major or BARC  $\geq 2$  bleeding events with a more potent strategy. There were no significant differences in death, new MI or stroke.

The PLATO trial, in which ticagrelor was compared to clopidogrel in high risk ACS patients, showed a decreased incidence of the primary composite endpoint CV death/MI/stroke with ticagrelor. No significant difference in overall major bleeding was reported. However, ticagrelor was associated with an 18% higher rate of non-CABG major bleeding events [2]. The subgroup analysis on STEMI patients produced similar results regarding the primary endpoint but no difference in non-CABG major/minor bleeding



**Fig. 2.** a. Localisations of bleeding events during hospital stay. Other localisations included mainly hematomas and epistaxis. b. Localisations of bleeding events from discharge to end of follow-up. Other localisations included mainly hematomas and epistaxis.

rates [15]. Based on these results, clinical practice guidelines from the European Society of Cardiology recommend ticagrelor over clopidogrel [3]. A smaller trial on Asian patients could not reproduce the results from PLATO regarding efficacy but confirmed increased bleeding with ticagrelor. However, the trial was not powered to assess efficacy outcomes [16].

Randomized controlled trials are the gold standard in clinical research, but limited external validity has been discussed, as patients receiving a treatment in real-life cohorts differ substantially from patients in RCT cohorts, in which the drug was originally tested [17]. Increased awareness of the described differences in study populations has led to an increased interest from care-givers and authorities in real-life data. The latter was exemplified in the 21st Century Cures Act, signed by former President Obama in 2016, which mandates the American Food and Drug Administration to use “real world evidence” in regulatory decisions [18]. In two previous observational studies, on STEMI patients [4] 2017 and on ACS patients, [5] ticagrelor was associated with a reduced risk of MI/stroke and CV death similar to the PLATO trial, also after adjustment for differences in baseline characteristics. In a large study from the SWEDEHEART registry a 20% increase

in readmissions for bleeding was reported. Substantial differences in baseline characteristics between the study arms, for example 8 years younger patients with significantly lower CRUSADE score and GRACE score associated with ticagrelor treatment, illustrate the previously reported risk-treatment paradox, with the newest and most effective treatments initially being used in lower risk patients [19–21]. Adjustment for differences was performed using statistical methods, but with large differences between the groups, unknown confounders may have been important for the observed outcome. In contrast, in the present analysis the study groups were similar, without any significant differences in age, sex or medical history (including history of bleeding and anemia), and almost identical measures of ischemic risk according to the GRACE score and bleeding risk according to the CRUSADE score. In addition there were no differences in PCI use, stent use or PCI success. Importantly, there were no major changes in long-term treatments during follow-up, except for angiotensin receptor blocker and, by design, type of P2Y12-inhibitor included in the DAPT regime (but no difference in proportion treated with DAPT).

During the study period, two changes in in-hospital treatment were introduced. Radial access and bivalirudin (instead of a GP

IIb/IIIa-inhibitor) was significantly more often used during the ticagrelor-based period. We therefore analysed in-hospital events and follow-up events separately. Compared to RCTs we had a very different population; for example patients included in the present analysis were about 10 years older (which inevitably means more comorbidity) and more often female (32% vs. 24% women), compared to patients included in the PLATO STEMI substudy, both factors associated with bleeding. During hospital stay there was no difference in bleeding events (8.8% vs 7.9%,  $p = 0.39$ ) with an over-all low rate of major bleeding events between the two treatment strategies. Use of LMWH and bivalirudin was higher during the ticagrelor period, but due increased use of radial access [22] and decreased use of GPIIb/IIIa-inhibitors, [23] one would have expected a decrease in bleeding events associated with the later time period. Lack of difference in bleeding events may be due to a more potent oral platelet inhibition. We did not observe any differences between the groups in death, MI or stroke.

Contrasting lack of differences in in-hospital events, we found significantly more bleeding events from discharge to end of follow-up during the ticagrelor-based period. Bleeding complications during follow-up included more TIMI major, PLATO major and BARC  $\geq 2$  bleeding events and three times more hospitalizations due to bleeding during the ticagrelor-based period. Again, there was no significant difference in death/MI or stroke. Our finding is in agreement with a recently published study of PCI-treated ACS patients, before and after introduction of ticagrelor [24]. Zocca et al reported significantly increased major bleeding events of the same magnitude as in our study, without any difference in death, MI or stroke during 1 year follow-up, in ACS patients treated with newer generation drug eluting stent (DES). We confirm previous findings with substantially increased bleeding with a ticagrelor-based treatment strategy, compared to a clopidogrel-based strategy. We also report severity of bleeding complications using three established bleeding definitions and conclude that they show similar result. Even if there were significant differences in major bleeding events between the two treatment strategies, the majority of the bleeding complications were defined as TIMI minimal, PLATO minimal or BARC 1 or 2. While several studies have reported worse outcome associated with major bleeding [7,8,25] there is less firm evidence related to non-major bleeding, which may explain lack of difference in non-bleeding outcomes, in spite of high bleeding rates (6.5% vs 13.3%). Anyhow, less severe bleeding complications may obviously have an impact on the proportion of prematurely stopped treatment [26,27] which was also shown in this study, and quality of life and health expenditures [28]. Better prediction of individual risk for both ischemic and bleeding events, to better inform clinical decision making, which is also recommended in clinical guidelines, may be a way to increase benefit with newer and more potent platelet inhibitors [29–31].

In order to reflect real world clinical practice, our primary study population had no exclusion criteria. Therefore, we included patients treated with oral anticoagulants. However, we performed a sensitivity analysis based on patients discharged with DAPT only (with aspirin plus clopidogrel or ticagrelor). The sensitivity analysis confirmed our findings in the overall study population, with significantly more bleeding complications during the ticagrelor-based period. However, notwithstanding increased bleeding complications and in contrast to some previous observational studies, we observed a non-significant trend towards lower MACE rate during the ticagrelor-based strategy.

In a secondary sensitivity analysis comparing patients discharged with clopidogrel to patients discharged with ticagrelor irrespective of study period, we observed major differences in age and co-morbidity, as expected and previously described as the risk-treatment paradox. Still, ticagrelor was associated with bleeding complication, and the association was strengthened after

propensity score adjustment. Again, we observed a non-significant trend towards lower MACE rate associated with ticagrelor. As pointed out previously, these groups differed substantially in baseline characteristics and unmeasured confounders may have impacted on the result. However, a benefit associated with ticagrelor regarding ischemic events, for which this analysis did not have power, is possible.

In accordance with previous data, GI bleeds were the most frequent bleeding complications during follow-up. Most of these bleeding complications were less severe, and in addition, to a large part probably preventable. Unfortunately, there are no well validated tools for prediction of GI-bleeds, but a more frequent use of proton pump inhibitors than in our study would probably decrease bleeding rates associated with more potent DAPT [32].

Higher bleeding risk in an all-comer population and contemporary stents (associated with less stent thromboses than previous) may off-set some of the advantages with a more potent platelet inhibition. Larger studies on real-life patients are warranted to disentangle whether bleeding complications counter-balance the previously shown lowered MACE rate with ticagrelor in older and more co-morbid patients, and if individual risk prediction may help to adopt a more tailored approach to DAPT.

## 5. Limitations and strengths

There are some limitations to this study. First, the relatively small study population may have obscured a difference in ischemic events, in spite of higher bleeding risk. Second, this was an observational real-life study, with its inherent limitation. Group allocation was based on the advocated strategy during a certain time period and therefore none of the groups were treated exclusively with one P2Y12 receptor inhibitor. However, there was a large difference in use of ticagrelor and clopidogrel between the groups. Moreover, since clopidogrel was more often given to high risk patients during the second period and the well known difficulties to adjust for unmeasured confounders, a strategy comparing two time periods was judged better. The two treatment strategy arms were very similar in baseline characteristics. But unidentified confounding can still not be excluded. Third, we did not have information regarding prevalence of helicobacter pylori, a major risk factor for gastrointestinal bleeding. There is limited data on best management of helicobacter pylori infection in the setting of dual antiplatelet treatment [33]. Future studies should look into the importance of helicobacter pylori infection as a mean to reduce bleeding risk.

Finally, the fact that we included consecutive patients with STEMI/LBBB should be regarded as a strength, increasing external validity.

## 6. Conclusion

In this observational study, a ticagrelor-based strategy was associated with significantly more bleeding complications, including major bleeding, without any significant change in death, MI or stroke.

Higher bleeding risk with a ticagrelor-based strategy was confirmed in a sensitivity analysis on patients discharged on DAPT only. Larger studies are needed to determine whether bleeding complications off-set benefits with a more potent DAPT strategy in older and more comorbid real-life patients.

## Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2020.100495>.

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