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Clopidogrel, prasugrel, and ticagrelor for all-comers with ST-segment elevation myocardial infarction

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ABSTRACT

Background: To compare effectiveness and safety of clopidogrel, prasugrel, and ticagrelor among all-comers with ST-segment elevation myocardial infarction (STEMI) and extend the knowledge from randomized clinical trials.
Methods: All consecutive patients with STEMI admitted to Copenhagen University Hospital, Rigshospitalet, from 2009 to 2016 were identified via the Eastern Danish Heart Registry. By individual linkage to Danish nationwide registries, claimed drugs and end points were obtained. Patients alive a week post-discharge were included, stratified according to clopidogrel, prasugrel, or ticagrelor treatment, and followed for a year. The effectiveness end point (a composite of all-cause mortality, recurrent myocardial infarction, and ischemic stroke) and safety end point (a composite of bleedings leading to hospitalization) were assessed by multivariate Cox proportional-hazards models.
Results: In total, 5123 patients were included (clopidogrel [1245], prasugrel [1902], ticagrelor [1976]) with ≥95% treatment persistency. Concomitant use of aspirin was ≥95%. Females accounted for 24% and elderly for 17%. Compared with clopidogrel, the effectiveness end point occurred less often for ticagrelor (HR 0.50, 95% CI 0.35–0.70) and prasugrel (HR 0.48, 95% CI 0.33–0.68) without differences in bleedings leading to hospitalization. No differences in comparative effectiveness or safety were found between prasugrel and ticagrelor. Sensitivity analyses with time-dependent drug exposure and the period 2011–2015 showed similar results.
Conclusions: Among all-comers with STEMI, ticagrelor and prasugrel were associated with reduced incidence of the composite end point of all-cause mortality, recurrent myocardial infarction, and ischemic stroke without an increase in bleedings leading to hospitalization compared with clopidogrel. No differences were found between prasugrel and ticagrelor.

1. Introduction

Until 2009, recommendations for dual antiplatelet therapy (DAPT) in patients with acute coronary syndromes (ACS) was aspirin and clopidogrel [1]. As randomized clinical trials (RCTs) found ticagrelor and prasugrel to be superior to clopidogrel treatment by reducing cardiovascular mortality and incidence of ischemic events, recommendations were changed to aspirin with ticagrelor or prasugrel among ACS patients without contraindications [2,3]. In 2019, a RCT compared the efficacy of ticagrelor and prasugrel among ACS patients and found prasugrel to be superior to ticagrelor mainly by reducing the incidence of recurrent myocardial infarction (MI) without increasing bleedings [4]. Critique points have been raised: it was unblinded, approximately 85% were treated with PCI, and patients with non-ST-segment elevation myocardial infarction (non-STEMI) had short time from admission to angiography (mean time 1 h).

The recommendations for DAPT among patients with STEMI have been extrapolated from RCTs in which patients with STEMI accounted

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for 26% and 38% [2,3]. Despite this, The European Society of Cardiology and the American College of Cardiology and the American Heart Association make strong recommendations for prasugrel or ticagrelor over clopidogrel treatment for patients with STEMI without contraindications [5,6]. However, a minority was elderly (aged ≥75 years) (13% [2], 15% [3], and 24% [4]) and patients with need of anticoagulants or prior bleeding were excluded [2–4]. Hence, these cohorts are often highly selective and may not be generalizable to an all-comers population.

This study aimed to compare effectiveness and safety of clopidogrel, prasugrel, and ticagrelor treatment among all-comers with STEMI to extend the knowledge from RCTs to a broader population.

2. Methods

2.1. Study design and data sources

This was a single-center cohort study. Patients with STEMI were identified via the Eastern Danish Heart Registry from 2009 to 2016, which holds detailed information on clinical, angiographic, and procedural characteristics on all consecutive patients with STEMI treated with primary percutaneous coronary intervention (PPCI) at the Copenhagen University Hospital, Rigshospitalet. Initially, Rigshospitalet had a catchment area of 30% (1.7 million) extended in 2011 to a catchment area corresponding to 45% (2.5 million) of the entire Danish population [7].

Data from the Eastern Danish Heart Registry were linked on an individual level to nationwide administrative registries via a unique civil registration number. Data on medical treatment was obtained from the Danish National Prescription Registry by use of the Anatomical Therapeutic Chemical System (ATC) codes (Supplemental Table 1). This registry holds information on strength, quantity, and dispensing date of all claimed drug prescriptions from Danish pharmacies. Information on hospital admission, discharge, and diagnosis codes according to the International Classification of Disease, Tenth Revision (ICD-10) were assessed from the Danish National Patient Registry (Supplemental Table 2). Vital status was retrieved from the Danish Civil Registration System. Finally, information on blood levels of creatinine were obtained from an electronic laboratory database.

2.2. Study population

Patients aged ≥18 years with symptoms ≤12 h and acute ST-segment elevation on an electrocardiogram were qualified. All patients underwent angiography and subsequent PPCI. For patients with multiple admissions, only the first admission with STEMI was considered. Details are listed in flow chart (Fig. 1).

Patients were stratified according to first claimed prescription of clopidogrel, prasugrel, or ticagrelor within 7 days from discharge. Patients who did not claim a prescription were excluded, as were patients who died within 7 days from discharge to avoid immortal time-bias. Number of patients shifting treatment during follow up were reported. Treatment persistency was calculated as percentage of days covered (PDC) the first year after treatment as done previously [8]. Treatment with aspirin and anticoagulants within the first year from discharge were reported.

Comorbidities were defined according to the modified Ontario Acute Myocardial Infarction Mortality Prediction Rules by diagnosis either from hospital admissions or outpatient contacts 1 year prior to STEMI index admission (ICD-10 codes are shown in Supplemental Table 2) [9]. To avoid underestimation, use of antidiabetics, statins, or antihypertensives (at least two antihypertensive prescriptions) combined with corresponding diagnosis were used as a proxy for diabetes, hypercholesterolemia, and hypertension, respectively, as done previously [7,10]. Median level of creatinine during hospitalization was calculated as a measurement of renal function due to few patients with the diagnosis

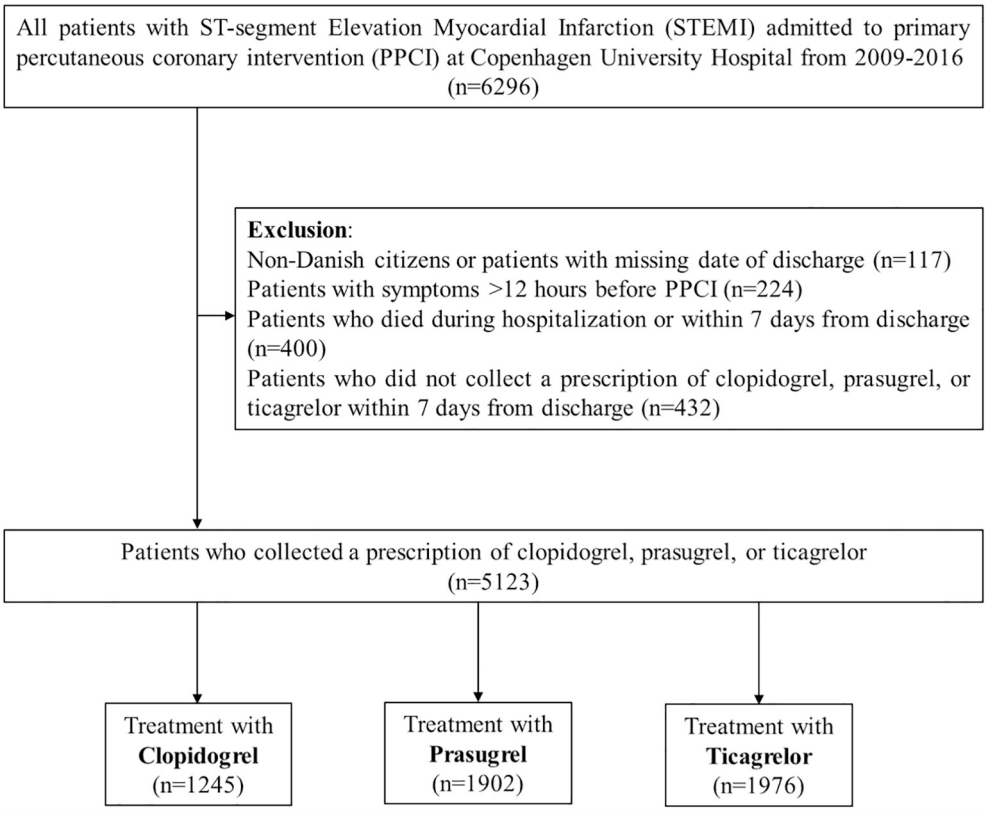

Fig. 1. Flowchart.

codes of acute or chronic renal failure ($n < 10$).

2.3. End points

The primary effectiveness end point was a composite of all-cause mortality, recurrent MI, and ischemic stroke during follow up. Recurrent MI was defined as hospital admission with MI minimum 28 days after the STEMI index admission [11]. The secondary safety end point was a composite of bleedings leading to hospitalization. ICD-10 codes are listed in Supplemental Table 2. The follow up period ran from 7 days after discharge until the outcome of interest, death, or emigration within 1 year after inclusion.

2.4. Statistical analysis

Baseline characteristics are presented as frequencies, means with standard deviations (SD), and medians and ranges (IQR). Differences were calculated using the chi-square test for categorical and the nonparametric Wilcoxon rank-sum test for continuous variables. Missing values are reported. Number of events and incidence rates (IR) per 100 patient years (PY) for the end points were calculated. Univariate and multivariate Cox proportional-hazards models were performed to estimate the comparative effectiveness and safety of ticagrelor vs. clopidogrel, prasugrel vs. clopidogrel, and prasugrel vs. ticagrelor within 1 year. Only covariates with <1% missing was included in the multivariate analyses. The following covariates were included in the models assessing the primary effectiveness end point: sex, age (categorized in <65, 65–74, and ≥ 75 years of age), comorbidities (heart failure, cardiac arrhythmia, cerebrovascular disease, diabetes, and cancer), culprit lesion (left main artery or left anterior descending artery [LM/LAD] vs. non-LM/LAD), median creatinine level during hospitalization (categorized in <50, 50–110, and ≥ 110 μmol/L), use of aspirin and anticoagulants post-discharge, and calendar year. Due to fewer events, models assessing all-cause mortality and ischemic events (a composite of recurrent MI and ischemic stroke) were adjusted for sex, age, comorbidities (diabetes and heart failure), creatinine level, use of aspirin and anticoagulants post-discharge, and calendar year. Adjustments for culprit lesion were added to the models assessing ischemic events. Adjustment for pulmonary edema and shock were not conducted due to low number of events and/or no significant differences between the treatment groups. For the safety end point, the following covariates were considered: sex, age, comorbidities (diabetes, hypertension, and cerebrovascular disease), creatinine level, use of anticoagulants post-discharge, and calendar year (body weight was also included in a sensitivity analysis). Propensity score matching was conducted to reduce possible confounder imbalance. The propensity scores were estimated by logistic regression including relevant differences in characteristics at discharge between clopidogrel vs. ticagrelor, clopidogrel vs. prasugrel, and prasugrel vs. ticagrelor. One-to-one matching with the nearest neighbor method was used. Comparative differences for the effectiveness and safety end points were calculated by multivariate Cox proportional-hazards model adjusting for the same covariates.

Since many patients shifted treatment during follow up, sensitivity analyses were performed in which clopidogrel, prasugrel, and ticagrelor treatment were defined as time-dependent covariates. A separate analysis of the period 2011–2015 and of patients without concomitant use of anticoagulants post-discharge was performed. Similar multivariable Cox proportional-hazards models adjusted for the same covariates and assessing the same end points as stated above were performed. All models were tested for the proportional hazard assumption and lack of relevant interactions and found valid.

Statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA) and R [12]. The corresponding author had access to all the data and takes full responsibility for its integrity.

2.5. Ethics approval

Approval from the Danish Data Protection Agency (2007-58-0015/GEH-2014-014 and I-suite number: 02732) was received. Since the civil registration numbers were encrypted, individual patients were not identifiable. Due to the retrospective nature of the study, informed consent could not be retrieved. Ethical approval is not required for register-based studies in Denmark.

3. Results

Of all 5123 patients with STEMI, 1245 (24%) were treated with clopidogrel, 1902 (37%) with prasugrel, and 1976 (39%) with ticagrelor (Fig. 1). Concomitant use of aspirin was ≥95% for all. The yearly distribution of treatments is illustrated in Fig. 2.

3.1. Characteristics

Baseline characteristics are summarized in Table 1. The elderly population (≥75 years of age) accounted for 17% and females for 24% of the population. Patients treated with clopidogrel were older with more comorbidities, less often treated with drug eluting stent, and more often treated with anticoagulants. The median time from discharge to claimed prescription was 1 day [0,2] and treatment persistency during the first year after discharge was high (PDC values of ≥95% for all) (Table 2). A total of 493 patients (10%) shifted treatment during follow up, of whom 25 (5%) shifted from clopidogrel, 161 (33%) from prasugrel, and 307 (62%) from ticagrelor (data not shown).

3.2. End points

Number of events and IRs per 100 PY for the primary effectiveness end point at 1 year were 133 (IR 11.4) for clopidogrel, 88 (IR 4.8) for prasugrel, and 114 (IR 6.0) for ticagrelor treatment (Fig. 3 and Supplemental Table 3). Unadjusted analyses are presented in Supplemental Table 4. The adjusted analysis showed a reduction in the primary effectiveness end point at 1 year for patients treated with both ticagrelor (HR 0.50, 95% CI 0.35–0.70, $p < 0.001$) and prasugrel (HR 0.48, 95% CI 0.33–0.68, $p < 0.001$) compared with clopidogrel (Fig. 3A). The increased effectiveness of ticagrelor treatment was mainly driven by a reduction in all-cause mortality (HR 0.32, 95% CI 0.21–0.51, $p < 0.001$) (Table 3). Prasugrel treated patients had reduced risk of both all-cause mortality (HR 0.30, 95% CI 0.17–0.51, $p < 0.001$) and ischemic events (HR 0.63, 95% CI 0.40–1.00, $p = 0.0498$) (Table 3). No difference was found between prasugrel and ticagrelor treatment for the primary

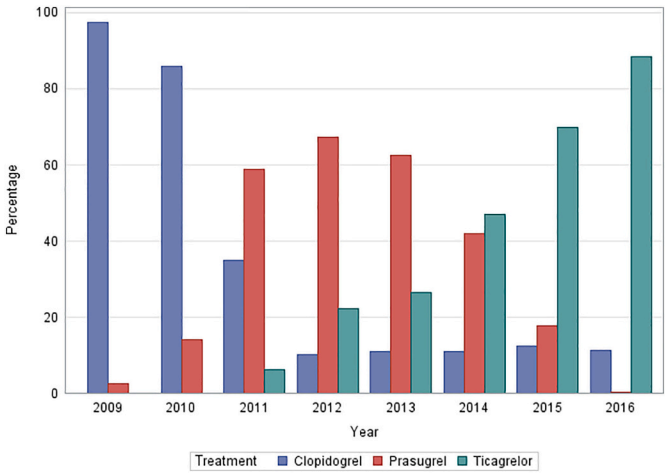

Fig. 2. Yearly distribution of treatment with clopidogrel, prasugrel, and ticagrelor among patients with ST-segment elevation myocardial infarction.

Table 1
Baseline.

Variables	Level	Clopidogrel (*n* = 1245)	Prasugrel (*n* = 1902)	Ticagrelor (*n* = 1976)	p (prasugrel vs. clopidogrel)	p (ticagrelor vs. clopidogrel)	p (prasugrel vs. ticagrelor)
Sex, n (%)	Male	889 (71.4)	1532 (80.5)	1463 (74.0)	<0.001	0.11	<0.001
	Female	356 (28.6)	370 (19.5)	513 (26.0)			
Age, years	median [IQR]	66 [57, 76]	59 [51, 67]	64 [54, 73]	<0.001	<0.001	<0.001
<65	n (%)	597 (48.0)	1325 (69.7)	1027 (52.0)	<0.001	0.005	<0.001
65–74		318 (25.5)	470 (24.7)	522 (26.4)			
≥75		330 (26.5)	107 (5.6)	427 (21.6)			
Body weight	median [IQR]	80 [70, 90]	83 [74, 94]	80 [72, 92]	<0.001	0.007	<0.001
Comorbidities							
Hypertension	n (%)	503 (40.4)	599 (31.5)	636 (32.2)	<0.001	<0.001	0.67
Hypercholesterolemia		350 (28.1)	514 (27.0)	507 (25.7)	0.53	0.14	0.35
Diabetes		159 (12.8)	194 (10.2)	224 (11.3)	0.029	0.24	0.28
Heart Failure		98 (7.9)	146 (7.7)	105 (5.3)	0.89	0.005	0.003
Cardiac arrhythmias		153 (12.3)	155 (8.1)	127 (6.4)	<0.001	<0.001	0.045
Cerebrovascular disease		19 (1.5)	8 (0.4)	14 (0.7)	0.002	0.039	0.33
Cancer		25 (2.0)	19 (1.0)	30 (1.5)	0.028	0.37	0.19
Acute renal failure		8 (0.6)	4 (0.2)	12 (0.6)	0.10	1.00	0.09
Chronic renal failure		12 (1.0)	7 (0.4)	19 (1.0)	0.06	1.00	0.039
Shock		17 (1.4)	13 (0.7)	14 (0.7)	0.08	0.09	1.00
Pulmonary edema		6 (0.5)	≤3 (≤0.2)	≤3 (≤0.2)	0.19	0.030	0.59
Blood levels during hospitalization							
Creatinine, μmol/L	median [IQR]	79 [68, 96]	79 [69, 90]	83 [72, 96]	0.019	0.003	<0.001
<50	n (%)	39 (3.2)	33 (1.7)	26 (1.3)	<0.001	<0.001	<0.001
50–110		1006 (81.6)	1742 (91.7)	1732 (88.0)			
≥110		188 (15.2)	124 (6.5)	210 (10.7)			
Procedural variables							
Minutes from symptom onset to PCI	median [IQR]	190 [135, 277]	154 [115, 236]	169 [124, 258]	<0.001	<0.001	<0.001
Infarct location, n (%)	Anterior	517 (45.6)	747 (41.6)	822 (44.5)	0.035	0.58	0.08
	Non-anterior	616 (54.4)	1049 (58.4)	1024 (55.5)			
Culprit lesion, n (%)	LM	7 (0.6)	9 (0.5)	13 (0.7)	0.31	0.78	0.10
	LAD	549 (44.3)	785 (41.4)	853 (43.3)			
	RCA	502 (40.5)	831 (43.8)	788 (40.1)			
	CX	181 (14.6)	271 (14.3)	312 (15.9)			
Killip Class, n (%)	I-II	1147 (97.5)	1826 (99.0)	1863 (98.6)	0.001	0.027	0.33
	>II	30 (2.5)	18 (1.0)	26 (1.4)			
Medication during procedure, n (%)	Aspirin	1191 (95.7)	1844 (97.0)	1897 (96.0)	0.07	0.70	0.13
	Heparin	1170 (94.0)	1796 (94.4)	1872 (94.7)	0.65	0.40	0.72
	Glycoprotein IIB/IIIa receptor inhibitor	581 (46.7)	384 (20.2)	159 (8.0)	<0.001	<0.001	<0.001
	Bivalirudin	250 (20.1)	1319 (69.3)	807 (40.8)	<0.001	<0.001	<0.001
Pre-TIMI, n (%)	0-I	805 (65.5)	1166 (62.1)	1194 (61.0)	0.06	0.012	0.53
	II-III	424 (34.5)	713 (37.9)	763 (39.0)			
Post-TIMI, n (%)	0-I	33 (2.7)	22 (1.2)	27 (1.4)	0.003	0.012	0.67
	II-III	1195 (97.3)	1851 (98.8)	1926 (98.6)			
Intervention, n (%)	DE stent	621 (50.3)	1462 (77.4)	1660 (84.7)	<0.001	<0.001	<0.001
	BM stent	158 (12.8)	43 (2.3)	19 (1.0)			
	Stent unknown	2012 (17.2)	9 (0.5)	≤3 (≤0.2)			
	No stent or	37 (3.0)	60 (3.2)	59 (3.0)			
	POBA only	206 (16.7)	315 (16.7)	220 (11.2)			
Medication after discharge							
Aspirin	n (%)	1176 (94.5)	1875 (98.6)	1944 (98.4)	<0.001	<0.001	0.71
Anticoagulants		249 (20.0)	88 (4.6)	80 (4.0)	<0.001	<0.001	0.42
Vitamin K-antagonist		169 (13.6)	65 (3.4)	38 (1.9)	<0.001	<0.001	0.001
Direct oral anticoagulants (Dabigatran, Rivaroxaban, or Apixaban)		80 (6.4)	23 (1.2)	42 (2.1)			

The daily dose of the first claimed prescription was 75 mg for patients treated with clopidogrel, 180 mg for patients treated with ticagrelor, and 5 mg (5%) or 10 mg (95%) for patients treated with prasugrel.
Missing values: Body weight (2%) Creatinine level (<1%), Minutes from symptom onset to PCI (3%), Infarct location (7%), Culprit lesion (<1%), Killip class (4%), Pre- and Post-TIMI (1%), and Intervention (1%).
Abbreviations: BM (bare metal stent); CX (circumflex artery); DE (drug eluting stent); LAD (left descending artery); LM (left main artery); PCI (percutaneous coronary intervention); POBA (plain old balloon angioplasty); RCA (right coronary artery); TIMI (thrombolysis in myocardial infarction).

effectiveness end point (Fig. 3B).

The secondary safety end point occurred among 44 patients (IR 3.7) for clopidogrel, 53 patients (IR 2.9) for prasugrel, and 61 patients (IR 3.2) for ticagrelor treatment at 1 year (Fig. 4 and Supplemental Table 3). No differences in bleedings leading to hospitalization were found between all treatments (Fig. 4). Similar results were found after adding body weight to the adjusted analysis for the safety endpoint (data not shown).

Results from the propensity score matching are presented in supplementary with a few remaining differences in the baseline characteristics (Supplemental Tables 5.1–5.3, 6.1–6.3). Overall, similar results were observed for the effectiveness and safety end points after

Table 2
Initiation of treatment and treatment persistency.

Variables	Level	Clopidogrel	Prasugrel	Ticagrelor
Days to collection of first prescription	median [IQR]	1 [0, 2]	1 [0, 2]	1 [0, 2]
Treatment persistency (percentage of days covered [PDC[a]])	mean (±SD)	0.99 (±0.08)	0.97 (±0.12)	0.95 (±0.14)
	median [IQR]	1 [1,1]	1 [1, 1]	1 [1, 1]

[a] If treated 360 days/year PDC = 1.0.

propensity score matching (Table 4).

3.3. Sensitivity analysis

The sensitivity analysis with time-dependent drug exposure, and the separate sensitivity analysis of the period 2011–2015 both demonstrated similar results (Supplemental Fig. 1–2 and Supplemental Table 7). After exclusion of patients with concomitant use of anticoagulants post-discharge (8%), similar results were found (Supplemental Table 8).

4. Discussion

We compared effectiveness and safety of clopidogrel, prasugrel, and ticagrelor treatment among >5000 all-comers with STEMI who underwent PPCI. Median time from discharge to claimed prescription was 1 day and treatment persistency was almost complete for clopidogrel, prasugrel, and ticagrelor treatment. Overall, we observed reduced incidence of the composite end point of all-cause mortality, recurrent MI, and ischemic stroke at 1 year for treatment with ticagrelor and prasugrel without increase in bleedings leading to hospitalization compared with clopidogrel. No differences in effectiveness or safety were found between prasugrel and ticagrelor.

4.1. Ticagrelor vs. clopidogrel

Compared with a sub-study of the PLATO trial (Platelet Inhibition and Patient Outcomes) on patients with STEMI, the unadjusted IR of the primary effectiveness end point was lower for ticagrelor treated patients in our cohort, both due to lower mortality and incidence of ischemic events [13]. This may be explained the design of our study as patients had to survive until 7 days post-discharge. Our patients also had shorter time from symptom onset to PPCI, which could reduce the risk of long-term outcomes. The lower incidence of recurrent MIs for ticagrelor and clopidogrel treatment in our cohort compared with the STEMI cohort of the PLATO trial, may be due to different definitions of recurrent MI. Also, the revascularization therapy differed. All patients were treated with PPCI and 72% with a drug eluting stents in our cohort and only 72% and 21%, respectively, in the subgroup study of the PLATO trial [13]. Number of bleedings leading to hospitalization in our study was comparable with non-CABG related major bleedings in the sub-study of the PLATO trial [13].

In line with our findings, another single-center cohort study including elderly (≥75 years of age) all-comers with STEMI treated with ticagrelor and clopidogrel found reduced rates of the efficacy outcome (a

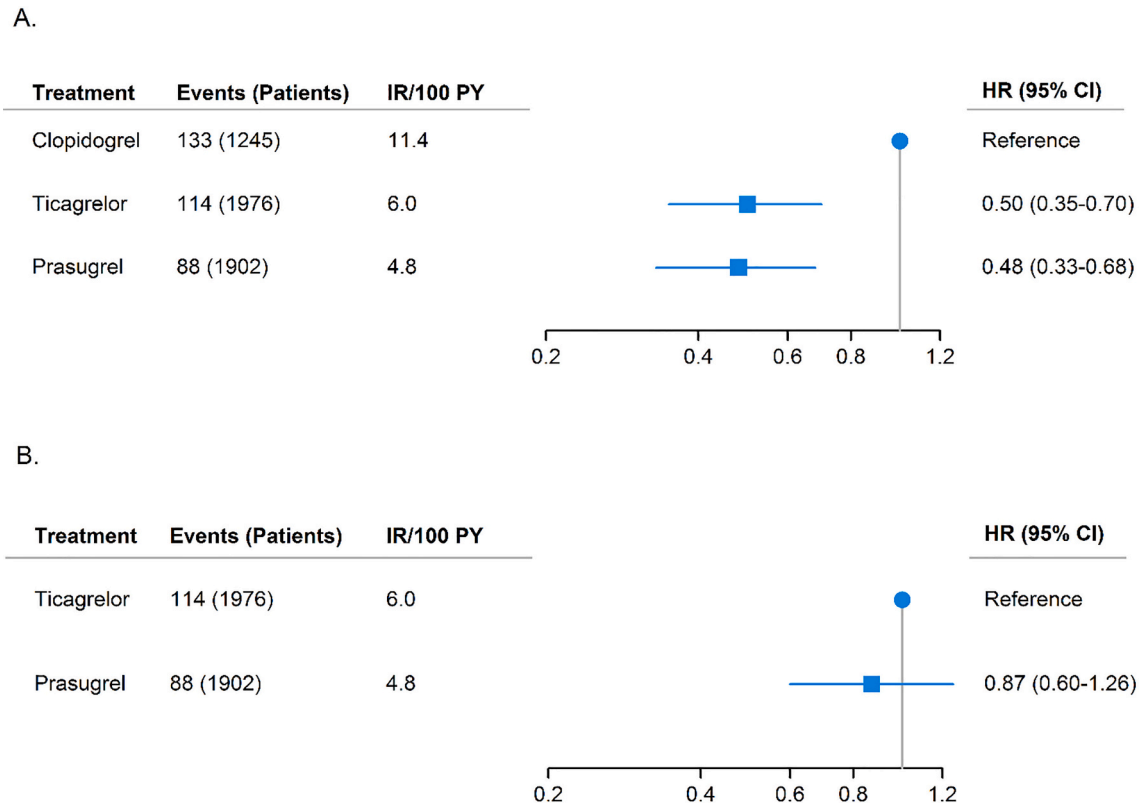

Fig. 3. A+B: The primary effectiveness end points (a composite of all-cause mortality, recurrent myocardial infarction, and ischemic stroke) at 1 year.
Number of events and patients and incidence rates (IR) per 100 patient years (PY) in each treatment group are illustrated for the primary effectiveness end point (a composite of all-cause mortality, recurrent myocardial infarction, and ischemic stroke) at 1 year. Adjusted hazard ratios (HR) and the corresponding 95% confidence interval (CI) calculated from multivariate Cox proportional-hazards models are presented, which were adjusted for sex, age (categorized in <65, 65–74, and ≥ 75 years of age), comorbidities (heart failure, cardiac arrhythmia, cerebrovascular disease, diabetes, and cancer), culprit lesion (left main artery or left anterior descending artery [LM/LAD] vs. non-LM/LAD), median creatinine level during hospitalization (categorized in <50, 50–110, and ≥ 110 μmol/L), use of aspirin and anticoagulants post-discharge, and calendar year. Only ≤1% of patients were excluded due to missing values for creatinine level and culprit lesion. HR (blue squares) and 95% CI (blues lines associated with the use of ticagrelor compared with clopidogrel (Fig. 3A) and prasugrel compared with ticagrelor (Fig. 3B) are shown.

Table 3
Number of events, incidence rates (IR) per 100 patient years (PY), and adjusted hazard ratios (HR) for all-cause mortality and ischemic events (a composite of recurrent myocardial infarction and ischemic stroke) at 1 year.

End points	No. of events (IR/100 PY)		Hazard ratio		
	Ticagrelor (n = 1976)	Clopidogrel (n = 1245)	Ticagrelor vs. Clopidogrel	95% CI	p
All-cause mortality	48 (2.5)	79 (6.6)	0.32	0.21–0.51	<0.001
Ischemic events	69 (3.6)	65 (5.4)	0.75	0.46–1.23	0.25
	Prasugrel (n = 1902)	Clopidogrel (n = 1245)	Prasugrel vs. Clopidogrel	95% CI	p
All-cause mortality	26 (1.4)	79 (6.6)	0.30	0.17–0.51	<0.001
Ischemic events	66 (3.5)	65 (5.4)	0.63	0.40–1.00	0.0498
	Prasugrel (n = 1902)	Ticagrelor (n = 1976)	Prasugrel vs. Ticagrelor	95% CI	p
All-cause mortality[a]	26 (1.4)	48 (2.5)	0.98	0.54–1.79	0.94
Ischemic events	66 (3.5)	69 (3.6)	0.81	0.52–1.28	0.37

Patients could have had more than one type of end point event. Adjusted hazard ratios (HR) and the corresponding 95% confidence interval (CI) calculated from multivariate Cox proportional-hazards models assessing all-cause mortality and ischemic events (a composite of recurrent myocardial infarction and ischemic stroke) at 1 year are presented. All models were adjusted for sex, age (categorized in <65, 65–74, and ≥75 years of age), comorbidities, (diabetes and heart failure), median creatinine level during hospitalization (categorized in <50, 50–110, and ≥110 μmol/L), aspirin and anticoagulants post-discharge, and calendar year. Adjustments for culprit lesion (left main artery or left anterior descending artery [LM/LAD] vs. non-LM/LAD) were added to the models assessing ischemic events. Less than 1% of patients were excluded due to missing values for creatinine level and/or culprit lesion.

[a] Diabetes was excluded from this model due to a fewer number of events.

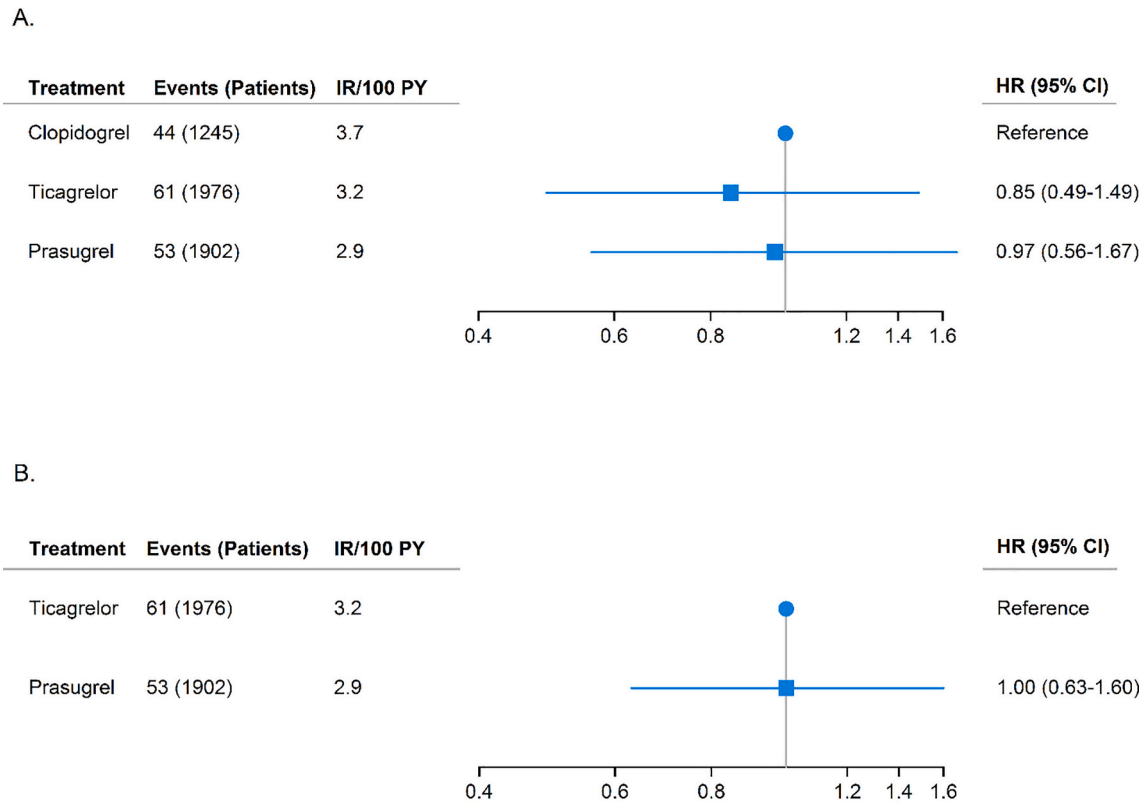

Fig. 4. A+B: The safety end point (a composite of bleedings leading to hospitalization) at 1 year.
Number of events and patients and incidence rates (IR) per 100 patient years (PY) in each treatment group are illustrated for the safety end point (a composite of bleedings leading to hospitalization) at 1 year. Adjusted hazard ratios (HR) and the corresponding 95% confidence intervals (CI) calculated from multivariate Cox proportional-hazards models are presented, which were adjusted for sex, age (categorized in <65, 65–74, and ≥ 75 years of age), comorbidities (diabetes, hypertension, and heart failure), median creatinine level during hospitalization (categorized in <50, 50–110, and ≥110 μmol/L), use of aspirin and anticoagulants post-discharge, and calendar year. Less than 1% of patients was excluded due to missing values for creatinine level. HR (blue squares) and 95% CI (blues lines associated with the use of ticagrelor compared with clopidogrel (Fig. 4A) and prasugrel compared with ticagrelor (Fig. 4B) are shown.

composite of all-cause mortality, recurrent MI, and stroke) and all-cause mortality alone with no difference in bleedings [14].

4.2. Prasugrel vs. clopidogrel

The unadjusted IRs of the effectiveness end points for prasugrel and clopidogrel treatment in our study differed from that of a sub-study of the TRITON-TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–-Thrombolysis in Myocardial Infarction) evaluating patients with STEMI [15]. In our cohort, a lower rate of the primary effectiveness end point was found for prasugrel treatment mainly due to fewer recurrent MIs (different definitions of recurrent MI). In our study, prasugrel treated patients were younger with fewer comorbidities, thus healthy survivors

Table 4
Number of events, incidence rates (IR) per 100 patient years (PY), and adjusted hazard ratios (HR) for the primary effectiveness end points (a composite of all-cause mortality, recurrent myocardial infarction, and ischemic stroke) and the safety end point (bleedings leading to hospitalization) at 1 year after propensity score matching.

End points	No. of events (IR/100 PY)		Hazard ratio		
	Clopidogrel (n = 1027)	Ticagrelor (n = 1027)	Clopidogrel vs. Ticagrelor	95% CI	p
Primary effectiveness end point	100 (10.4)	60 (6.1)	2.05	1.37–3.07	0.001
Bleedings	32 (3.3)	35 (3.5)	1.18	0.64–2.18	0.60
	Clopidogrel (n = 854)	Prasugrel (n = 854)	Clopidogrel vs. Prasugrel	95% CI	p
Primary effectiveness end point	58 (7.1)	34 (4.1)	2.29	1.37–3.83	0.002
Bleedings	24 (2.9)	33 (4.0)	1.23	0.65–2.32	0.52
	Prasugrel (n = 1459)	Ticagrelor (n = 1459)	Prasugrel vs. Ticagrelor	95% CI	p
Primary effectiveness end point	62 (4.4)	68 (4.8)	0.80	0.51–1.23	0.31
Bleedings	41 (2.9)	33 (2.3)	0.79	0.45–1.36	0.39

Patients could have had more than one type of event. Propensity scores were estimated by logistic regression and included age, sex, heart failure, median creatinine level during hospitalization (categorized in <50, 50–110, and ≥ 110 μmol/L), intervention (categorized as stent vs. no stent), and anticoagulants at discharge. One-to-one matching with the nearest neighbor method was used. Adjusted hazard ratios (HR) and the corresponding 95% confidence interval (CI) calculated from multivariate Cox proportional-hazards models assessing the primary effectiveness end point were adjusted for sex, age (categorized in <65, 65–74, and ≥ 75 years of age), comorbidities (cardiac arrhythmia, cerebrovascular disease, diabetes, and cancer), culprit lesion (left main artery or left anterior descending artery [LM/LAD] vs. non-LM/LAD), use of aspirin at discharge, and calendar year. Models assessing the safety end point (a composite of bleedings leading to hospitalization) where adjusted for sex, age, comorbidities (diabetes, hypertension, and cerebrovascular disease), and calendar year. Less than 1% of patients were excluded from the models assessing the primary effectiveness end point due to missing levels of culprit lesion.

may have been selected. For clopidogrel treated patients, the primary effectiveness end point occurred more frequently in our study mainly due to increased mortality, which could be due to higher age [15]. Overall, comparable IRs of bleedings were found in both studies [15].

We report superior effectiveness of prasugrel compared with clopidogrel treatment at 1 year driven by a reduction in all-cause mortality and incidence of ischemic events. The TRITON-TIMI 38 trial and its subgroup study of patients with STEMI also found reduced cardiovascular mortality and incidence of recurrent MI [2,15]. In the TRITON-TIMI 38 trial, the superiority of prasugrel came at the expense of increased bleedings among ACS patients with prior stroke, aged ≥75 years, and body weight ≤ 60 kg [2], hence, was not recommended to these high-risk patients. In our study, allocation to the treatment was done at the discretion of the doctor and according to guidelines [6]. Hence, prasugrel treated patients were less often female possibly due to lower body weight compared with men, and only 6% of patients were ≥ 75 years of age. No increase in bleedings leading to hospitalization was demonstrated for prasugrel compared with clopidogrel in our study.

4.3. Prasugrel vs. ticagrelor

Compared with an observational study evaluating efficacy and safety of prasugrel vs. ticagrelor at 1 year among real-life ACS patients (68% STEMI), all-cause mortality among prasugrel treated patients was slightly lower in our study [16]. This could be due to the study design (inclusion of patients alive >7 days after discharge) and since prasugrel treated patients had fewer comorbidities and more often received drug eluting stents (81% compared with 56%) [16]. Mortality rates were comparable for ticagrelor treated patients, possibly due to higher age in our cohort. Similar incidences of recurrent MI and major bleedings were found for both prasugrel and ticagrelor treated patients [16].

Our study showed no difference in comparative effectiveness or safety at 1 year between prasugrel and ticagrelor treatment. Prior observational studies have shown deviating results in comparison of prasugrel and ticagrelor [16,17]. One RCT comparing ticagrelor and prasugrel among mostly patients with STEMI treated with PPCI evaluated early efficacy and safety (7 days post discharge) but was stopped prematurely [18]. Superiority of prasugrel over ticagrelor has been demonstrated [4,19]. In the ISAR-REACT 5 trial (The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment), increased efficacy of prasugrel compared with ticagrelor treatment was demonstrated among patients with ACS, mainly due to fewer recurrent MIs [4]. Our population differed from that of the ISAR-REACT 5 trial by being younger and all patients with STEMI treated with PPCI. In the ISAR-REACT 5 trial, 41% presented with STEMI and 84% were treated with PCI [4].

4.4. Strengths and limitations

We enrolled >5000 consecutive, all-comers with STEMI from one of the largest PCI centers in Europe treated with clopidogrel, prasugrel, or ticagrelor from 2009 to 2016. Completeness of data was high and the quality of the Danish nationwide registries is known to be high [20].

Our study has several limitations. The study was non-randomized with risk of residual confounding despite relevant statistical adjustments including comorbidities and concomitant use of medication, and propensity score matching. Adjustment for left ventricular ejection fraction was not conducted due to a substantial amount of missing values (72%). Treatment with clopidogrel, prasugrel, and ticagrelor were allocated at the discretion of the operator. Persistence was calculated as proportion of days covered and was ≥95% which is higher compared with previous reports of 85% adherence after a year [21]. Treatment persistency might be overestimated since it was calculated as purchased tablets and not actual intake, and some patients may have received a single prescription for the entire treatment period of a year. Clopidogrel treated patients were older with more comorbidities and less often treated with drug eluting stents. This may be due to difference in treatment strategy over the study period. In 2009, 98% of patients were treated with clopidogrel. This declined and reached a level of approximately 10% in 2012–2016, possibly due to changes in guidelines. To account for yearly difference and differences in age and comorbidities, we adjusted all analysis for calendar year, age, and comorbidities. Furthermore, we conducted a sensitivity analysis of the period 2011–2015 and found comparable results.

The IRs of the outcomes may be underestimated. If patients were not assigned a diagnosis code during hospitalization, these events were unaccounted for. Some events such as minor bleedings may not have been registered since a diagnosis of bleeding demanded hospital admission to be considered. Lastly, we did not have information on cause of death. Since death was included in the primary effectiveness end point, bleeding leading to death could be misclassified as a thrombotic event.

5. Conclusions

Among all-comers with STEMI, both ticagrelor and prasugrel were

associated with reduced all-cause mortality and prasugrel with fewer ischemic events at 1 year without increase in bleedings leading to hospitalization compared with clopidogrel treatment. No differences in effectiveness or safety were found between prasugrel and ticagrelor treatment.

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Declaration of Competing Interest

Dr. Engstrøm reports personal fees from Abbott, Bayer, and Novo Nordisk; Dr. Køber reports personal fees from Novartis, Novo, and Boehringer; Dr. Torp-Pedersen reports grants from Bayer and Novo Nordisk outside the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.07.047.

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