



Ticagrelor in patients with heart failure after acute coronary syndromes—Insights from the PLATelet inhibition and patient Outcomes (PLATO) trial

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Background Heart failure (HF) following acute coronary syndromes (ACS) is associated with worse prognosis; however, the efficacy and safety of ticagrelor in patients with HF and if ticagrelor influences the risk of new-onset HF are unknown.

Methods We examined the efficacy and safety of ticagrelor compared to clopidogrel in patients with ACS in the randomized PLATelet inhibition and patient Outcomes (PLATO) trial subdivided by strata: (1) previous HF and/or clinical signs of HF on admission or (2) no HF on admission.

The primary outcome was the combination of cardiovascular death, myocardial infarction, or stroke evaluated by multivariable Cox regression models. The safety outcome was major bleeding. *New-onset HF* was defined as an HF event after discharge in patients without previous HF.

Results Data were available in 18,556 patients, whom 2,862 (15.4%) patients had HF, including 1,584 (8.5%) patients with previous HF.

Patients randomized to ticagrelor had lower risk of the composite end point regardless of HF status: hazard ratio (HR) 0.87 (95% CI: 0.73-1.03) in patients with HF and HR 0.84 (95% CI: 0.75-0.93) in patients with no HF ($P = .76$). Corresponding HR for major bleeding were HR 1.08 (95% CI: 0.87-1.34) and HR 1.03 (95% CI: 0.94-1.14) ($P = .71$). There was no difference in new-onset HF at 12 months between patients randomized to ticagrelor (4.1%, $n = 278$) or clopidogrel (4.0%, $n = 276$).

Conclusions In patients with ACS, ticagrelor is more efficacious in protecting against new ischemic events and mortality than clopidogrel irrespective of the presence of HF. There is no difference between ticagrelor or clopidogrel treatment in new-onset HF post-ACS. (Am Heart J 2019;213:57-65.)

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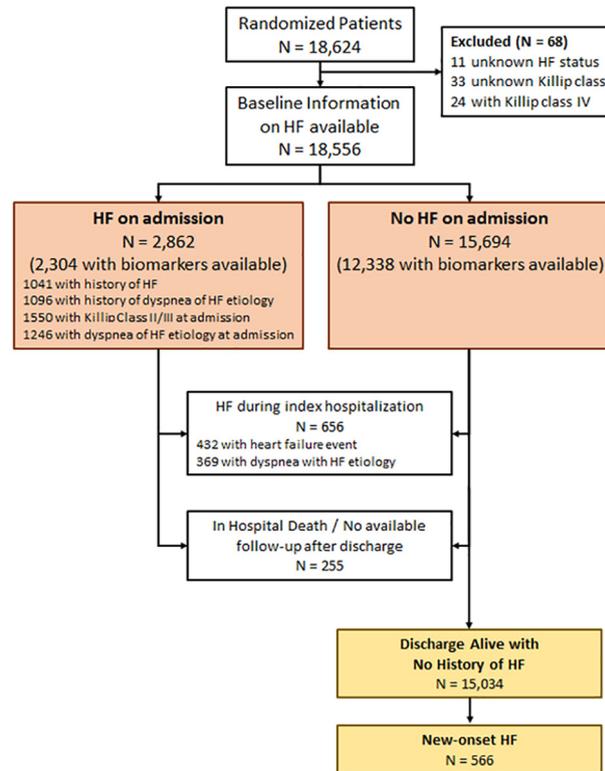
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Heart failure (HF) is a common complication in patients during or after acute coronary syndromes (ACS) and is associated with worse prognosis.¹⁻³ The prognosis for patients with ACS has remarkably improved over the last decades^{4,5} partly due to revascularization therapy and evidence-based secondary prevention.^{6,7} The incidence of HF however remains high and will likely continue to play a major role in the future regarding health care resources and individual morbidity and mortality partly due to a generally older population but also due to the increased survival after ACS.^{1,4,6}

In the PLATelet inhibition and patient Outcomes (PLATO) trial (NCT00391872), direct intense P2Y12 inhibition with ticagrelor, as compared with indirect, irreversible less intense P2Y12 inhibition with clopidogrel, reduced cardiovascular (CV) mortality and morbidity in patients with non-ST-elevation ACS (NSTEMI) and ST-elevation myocardial infarction (STEMI).^{8,9} Although

Figure 1



Graphic illustration of the subgroups by HF. A total of 255 patients died during the index hospitalization or had no follow-up after discharge and were consequently not part of the analyses.

ticagrelor provided more pronounced platelet inhibition and less recurrent ischemic events, the exact cause to the reduction in CV mortality is still debated. A possible contributing explanation may include the increased extracellular adenosine concentrations observed during ticagrelor treatment causing increased coronary blood flow and reduced myocardial infarction size,¹⁰⁻¹³ whose effects might lead to a lower risk of HF. The occurrence of HF has not been investigated in detail, although we previously reported that the mortality rates attributed to HF did not differ between patients randomized to ticagrelor ($n = 31$, 0.3%) or clopidogrel ($n = 42$, 0.5%).¹⁴

In the current ancillary study, we examined the efficacy and safety of ticagrelor in comparison with clopidogrel concerning CV mortality, ischemic, bleeding, and HF events in patients with ACS stratified for history of HF on admission.

Methods

Study population and outcomes

The PLATO trial enrolled 18,624 patients with ACS who were randomized to either clopidogrel or ticagrelor treatment in addition to optimal medical therapy,

including aspirin, and optional invasive strategy.^{9,15} The primary end point was the time to any component of the composite of CV death, myocardial infarction (MI), or stroke. The time to postdischarge new-onset HF was a secondary outcome. The main safety end point was major bleeding. All patients were evaluated for HF at baseline, in-hospital, and at outpatient visits during follow-up as a part of the safety protocol. The details of the study have previously been published.^{9,15}

Definitions of HF

At baseline, patients with a history of clinical HF or dyspnea regarded to be of HF origin, based on interviews, were considered to have previous HF (Figure 1). *HF at the time of randomization* was defined as Killip class II/III on admission or with dyspnea judged by the investigator to have a probable HF etiology. *HF on admission* was defined as previous HF and/or HF at the time of randomization. *No HF on admission* was consequently defined as patients without previous or ongoing HF at the time of randomization. Patients with missing HF status, missing Killip class, or Killip class IV were excluded (Figure 1).

HF during the index hospitalization was defined as HF events recorded as adverse events or dyspnea suspected to be of HF origin by the attending physician in-hospital. HF after discharge was based upon reported events judged by the investigator to have a probable HF etiology. *New-onset HF* during follow-up, after discharge for the index event, was defined as rehospitalization for HF in patients without a history of HF, without HF on admission, and without HF during the index hospitalization (Figure 1). Any hospitalization during follow-up was collected as safety data in the trial, and if the primary reason for the hospitalization was due to HF, it was considered an HF hospitalization. Importantly, neither new-onset HF nor hospitalizations due to HF were prespecified end points of the PLATO trial, and they were not adjudicated. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was collected at randomization, however not at hospital admission, and was not used for HF classification either on admission or during follow-up.

Laboratory analysis

Venous blood samples were collected at randomization prior to administration of study medication (within 24 hours of symptom onset). Plasma aliquots were kept frozen at -80°C until analyzed at a central laboratory (QUEST laboratories), including NT-proBNP and troponin I and serum creatinine levels. Estimated creatinine clearance was calculated with the Cockcroft-Gault equation.¹⁶

Statistical analysis

Baseline characteristics are presented in 2 subgroups: history of HF on admission and no history of HF, each summarized overall and by treatment group. Categorical variables are presented as frequencies and percentages and continuous variables as medians with interquartile intervals. χ^2 and Wilcoxon tests were used to compare the HF on admission subgroup with the no HF on admission subgroup. The significance level was set to $\alpha = .05$.

Efficacy and safety end points in patients with and without HF on admission were compared using Cox regression models. Adjustment variables included age; gender; smoking status; type of ACS (STEMI or NSTEMI); and history of angina, MI, hypercholesterolemia, diabetes, chronic obstructive pulmonary disease (COPD), (chronic kidney disease) CKD, previous percutaneous coronary intervention (PCI), previous coronary artery bypass grafting (CABG), stroke, transient ischemic attack (TIA), or hypertension; heart rate; β -blockers during index hospitalization; estimated creatinine clearance; hemoglobin; NT-proBNP (log-transformed); and troponin I (dichotomized at $>0.08 \mu\text{g/L}$). In the assessment of bleeding, variables with possible association with bleeding risk, including glycoprotein IIb/IIIa inhibitors and previous gastrointestinal bleeding, were evaluated as

possible adjustment variables. Continuous variables were tested for linearity and transformed when needed.

The randomized treatment effect (ticagrelor vs clopidogrel) in patients with and without HF on admission was estimated using Cox regression models including main effects for HF and randomized treatment and its interaction. Results are presented as hazard ratios (HRs) with 95% CIs and *P* value to test the interaction.

Factors associated with new-onset HF were evaluated in the subgroup of patients free of HF at discharge with available follow-up. Variables included in the final multivariate model were selected using a backward selection algorithm with α level for retention in the model set to .05. Candidate variables included age, gender, smoking status, history of angina, MI, PCI, CABG, stroke/TIA, hypertension, hypercholesterolemia, diabetes, COPD, CKD, blood pressure, heart rate, β -blockers during index admission, estimated creatinine clearance, NT-proBNP, troponin I, revascularization during index admission, and type of ACS. Missing values were few ($<1\%$) or null for all the variables except troponin I (4%), estimated creatinine clearance (18%), and NT-proBNP (21%). Twenty-five imputed data sets were created using multiple imputations. Variable selection was performed in each imputed data set, and variables selected in most data sets were included in the final model. The proportional-hazard assumption was tested by adding interactions of each variable selected in the final model with the logarithm of time to new-onset HF or censoring. All the variables included in the final model satisfied the proportional-hazard assumption. All analyses were done with SAS software, version 9.3 (SAS Institute, Cary, NC).

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

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Results

Patient population

Data on HF at the time of randomization were available for 18,556 (99.6%) patients (Figure 1). The background characteristics are presented by subgroups—no HF on admission and HF on admission—and subdivided by randomized treatment (Table D). The background characteristics for the entire study population have previously been reported.^{9,18}

Heart failure

On admission, 1,584 patients (8.5%), with available HF data, had a history of previous HF or history of dyspnea

Table I. Baseline characteristics in subgroups of (1) no previous HF and (2) previous HF and/or HF on admission (n = 18,556)

Characteristic	No HF on admission			HF on admission			P value
	Overall (n = 15,694)	Ticagrelor (n = 7890)	Clopidogrel (n = 7804)	Overall (n = 2862)	Ticagrelor (n = 1411)	Clopidogrel (n = 1451)	
Gender							<.001
Male	11,436 (72.9%)	5734 (72.7%)	5702 (73.1%)	1846 (64.5%)	915 (64.8%)	931 (64.2%)	
Female	4258 (27.1%)	2156 (27.3%)	2102 (26.9%)	1016 (35.5%)	496 (35.2%)	520 (35.8%)	
Age, y	61, 53-70	61, 53-70	61, 53-70	67, 58-75	67, 59-75	67, 58-75	<.001
Habitual smoker	5898 (37.6%)	2975 (37.7%)	2923 (37.5%)	755 (26.4%)	376 (26.6%)	379 (26.1%)	<.001
Systolic blood pressure	133, 120-150	134, 120-150	133, 120-150	130, 120-150	130, 120-150	130, 120-150	.003
Diastolic blood pressure	80, 70-90	80, 70-90	80, 70-90	80, 70-87	80, 70-89	80, 70-86	<.001
Heartrate, beat/min	72, 64-82	72, 64-82	73, 64-82	77, 68-90	77, 67-88	77, 68-90	<.001
Medical history							
Angina pectoris	6594 (42.0%)	3346 (42.4%)	3248 (41.6%)	1746 (61.0%)	867 (61.4%)	879 (60.6%)	<.001
MI	2782 (17.7%)	1384 (17.5%)	1398 (17.9%)	1030 (36.0%)	511 (36.2%)	519 (35.8%)	<.001
PCI	1980 (12.6%)	1017 (12.9%)	963 (12.3%)	499 (17.4%)	248 (17.6%)	251 (17.3%)	<.001
CABG	842 (5.4%)	412 (5.2%)	430 (5.5%)	264 (9.2%)	120 (8.5%)	144 (9.9%)	<.001
TIA	403 (2.6%)	201 (2.5%)	202 (2.6%)	96 (3.4%)	45 (3.2%)	51 (3.5%)	.017
Nonhemorrhagic stroke	516 (3.3%)	255 (3.2%)	261 (3.3%)	203 (7.1%)	98 (6.9%)	105 (7.2%)	<.001
Hypertension	9950 (63.4%)	5021 (63.6%)	4929 (63.2%)	2194 (76.7%)	1103 (78.2%)	1091 (75.2%)	<.001
Dyslipidemia	7172 (45.7%)	3609 (45.7%)	3563 (45.7%)	1489 (52.0%)	728 (51.6%)	761 (52.4%)	<.001
Diabetes mellitus	3563 (22.7%)	1785 (22.6%)	1778 (22.8%)	1081 (37.8%)	535 (37.9%)	546 (37.6%)	<.001
Asthma	442 (2.8%)	223 (2.8%)	219 (2.8%)	86 (3.0%)	44 (3.1%)	42 (2.9%)	.577
COPD	781 (5.0%)	408 (5.2%)	373 (4.8%)	297 (10.4%)	144 (10.2%)	153 (10.5%)	<.001
CKD	482 (3.1%)	229 (2.9%)	253 (3.2%)	294 (10.3%)	146 (10.3%)	148 (10.2%)	<.001
Treatment approach	11,771 (75.0%)	5920 (75.0%)	5851 (75.0%)	1582 (55.3%)	783 (55.5%)	799 (55.1%)	<.001
invasive							
Medications at randomization							
Aspirin	14,712 (93.8%)	7407 (93.9%)	7305 (93.7%)	2661 (93.1%)	1320 (93.6%)	1341 (92.5%)	.131
Unfractionated heparin	8033 (51.2%)	4032 (51.1%)	4001 (51.3%)	1400 (49.0%)	706 (50.1%)	694 (47.9%)	.026
Low-molecular weight heparin	6112 (39.0%)	3068 (38.9%)	3044 (39.1%)	1181 (41.3%)	587 (41.6%)	594 (41.0%)	.019
Glycoprotein IIb/IIIa inhibitors	4109 (26.2%)	2045 (25.9%)	2064 (26.5%)	459 (16.1%)	229 (16.2%)	230 (15.9%)	<.001
β-Blockers	11,110 (70.9%)	5577 (70.7%)	5533 (71.0%)	1856 (64.9%)	926 (65.7%)	930 (64.2%)	<.001
ACE inhibitors	8674 (55.3%)	4367 (55.4%)	4307 (55.3%)	1815 (63.5%)	906 (64.3%)	909 (62.7%)	<.001
Angiotensin II receptor blockers	1335 (8.5%)	662 (8.4%)	673 (8.6%)	305 (10.7%)	165 (11.7%)	140 (9.7%)	<.001
Biochemistry							
Creatinine clearance (mL/min)	82.5, 65.8-100.6	82.7, 66.2-100.8	82.2, 65.3-100.3	67.4, 51.4-87.2	67.4, 51.0-87.1	67.4, 51.6-87.2	<.001
Creatinine (μmol/L)	80.0, 71.0-97.0	80.0, 71.0-97.0	80.0, 71.0-97.0	88.0, 79.6-115.0	88.0, 79.6-115.0	88.0, 79.6-114.9	<.001
Glucose (mmol/L)	6.8, 5.7-8.6	6.8, 5.7-8.7	6.8, 5.7-8.6	7.3, 5.9-9.9	7.2, 5.9-9.8	7.4, 5.9-10.0	<.001
HbA1c (%)	5.9, 5.6-6.5	5.9, 5.6-6.5	6.0, 5.6-6.5	6.2, 5.8-7.3	6.2, 5.7-7.3	6.2, 5.8-7.2	<.001
NT-proBNP (ng/L)	49.4, 17.0-144.4	48.5, 16.8-140.3	49.8, 17.3-149.0	184.6, 51.3-594.8	182.9, 50.5-590.9	185.4, 52.0-595.2	<.001

P values comparing no HF with HF (ignoring randomized treatment).

considered to be of HF etiology (Figure 1). A total of 2,862 patients had a history of HF and/or experienced HF on admission and constituted the HF on admission subgroup. A total of 255 patients died during the index hospitalization or had no follow-up after discharge and were excluded.

At discharge, 15,034 patients were alive, were free of HF so far during the study (no previous, ongoing, or index hospitalization HF), and had available follow-up (Figure 1). In this cohort, we observed 566 (3.8%) patients with new-onset

HF after the index hospitalization. The Kaplan-Meier rates of any HF event (with or without hospitalization) were 2.3% (338) at 3 months, 3.0% (450) at 6 months, and 3.6% (517) at 9 months.

HF in relation to outcomes

The associations between HF on admission and CV outcomes are presented in Table II (n = 18,556). The combined end point of CV death, MI, or stroke occurred in 529 (20.0%) of the patients in the HF group and 1,328

Table II. Comparison of patients with HF on admission to patients without HF on admission in relation to prespecified clinical end points (n = 18,556)

End point	HF on admission (n = 2862)	No HF on admission (n = 15,694)	HR 95% CI HF on admission vs no HF on admission	
	KM% (n)	KM% (n)	Unadjusted	Adjusted
CV death/MI/stroke	20.0 (529)	9.1 (1328)	2.32 (2.10-2.57)	1.31 (1.10-1.56) ¹
All-cause death	13.5 (350)	3.7 (541)	3.74 (3.27-4.28)	1.87 (1.48-2.37) ²
CV death	12.4 (320)	3.1 (462)	3.99 (3.46-4.60)	2.07 (1.62-2.65) ²
MI	9.6 (245)	5.9 (847)	1.68 (1.46-1.94)	1.30 (1.10-1.54) ³
Stroke	2.4 (60)	1.2 (167)	2.10 (1.56-2.81)	1.02 (0.59-1.76) ¹
Major bleeding	13.4 (334)	11.0 (1538)	1.26 (1.12-1.42)	1.02 (0.84-1.24) ⁴
Non-CABG major bleeding	6.1 (148)	3.8 (508)	1.69 (1.40-2.03)	1.20 (0.96-1.49) ⁵

1 Adjusted by prior MI, prior non-hemorrhagic stroke, heart rate, Killip class at entry, age, white blood cells, PAD, prior CABG, time from onset of symptoms to randomization, diabetes, hemoglobin, region, changes in ECG at entry, final diagnosis, prior TIA, randomized treatment and creatinine.

2 Adjusted by age, heart rate, white blood cells, hemoglobin, region, prior non-hemorrhagic stroke, systolic blood pressure, final diagnosis, Killip class at entry, changes in ECG at entry, PAD, time from onset of symptoms to randomization and prior MI.

3 Adjusted by age, final diagnosis, prior MI, prior CABG, prior TIA, prior non-hemorrhagic stroke, PAD, diabetes, cardiac markers (troponin/CKMB), hemoglobin and time from onset of symptoms to randomization.

4 Adjusted by prior CABG, final diagnosis, diabetes, smoking status, dyslipidemia, ECG depression, white blood cells, age, angina pectoris, Killip class at entry, and hemoglobin.

5 Adjusted by age, hemoglobin, GP IIb/IIIa inhibitors at randomization, randomized treatment, white blood cells, creatinine clearance, PAD, and prior GI bleeding.

Table III. Efficacy and safety end points in subgroups of (1) patients with no HF on admission and (2) patients with previous and/or HF on admission, as well as subgrouped by randomized treatment (n = 18,556)

End point	No HF on Admission (n = 15,694)			HF on Admission (n = 2862)			Interaction P value
	Ticagrelor KM rate (n)*	Clopidogrel KM rate (n)*	HR (95% CI) (ticagrelor vs clopidogrel)	Ticagrelor KM rate (n)*	Clopidogrel KM rate (n)*	HR (95% CI) (ticagrelor vs clopidogrel)	
Efficacy end points							
Death from vascular cause, MI, or stroke	8.3 (609)	9.8 (719)	0.84 (0.75-0.93)	18.3 (243)	21.7 (286)	0.87 (0.73-1.03)	.758
Death from any cause	3.2 (236)	4.3 (305)	0.77 (0.65-0.91)	11.8 (155)	15.3 (195)	0.81 (0.66-1.00)	.705
Death from vascular causes	2.7 (201)	3.6 (261)	0.77 (0.64-0.92)	11.0 (145)	13.9 (175)	0.84 (0.68-1.05)	.495
MI	5.3 (385)	6.4 (462)	0.83 (0.72-0.94)	9.2 (116)	10.0 (129)	0.92 (0.71-1.18)	.469
Stroke	1.3 (90)	1.1 (77)	1.16 (0.86-1.57)	2.6 (32)	2.3 (28)	1.19 (0.72-1.97)	.921
Safety end points							
Major bleeding, study criteria	11.2 (783)	10.8 (755)	1.03 (0.94-1.14)	14.0 (171)	12.8 (163)	1.08 (0.87-1.34)	.709
Life-threatening or fatal bleeding, study criteria	5.6 (401)	5.7 (393)	1.02 (0.89-1.17)	7.1 (86)	6.2 (81)	1.10 (0.82-1.49)	.635
Non-CABG-related major bleeding, study criteria	4.1 (281)	3.4 (227)	1.23 (1.04-1.47)	6.4 (76)	5.8 (72)	1.08 (0.78-1.49)	.479

* KM rate = Kaplan-Meier estimate at 365 days (n = the cumulative number of events at 365 days).

(9.1%) of the patients in the no HF group: HR after multivariable adjustment 1.31 (95% CI 1.10-1.56). This difference was mainly driven by a higher rate of CV death: multivariable adjusted HR of 2.07 (95% CI 1.62-2.65) (Table II).

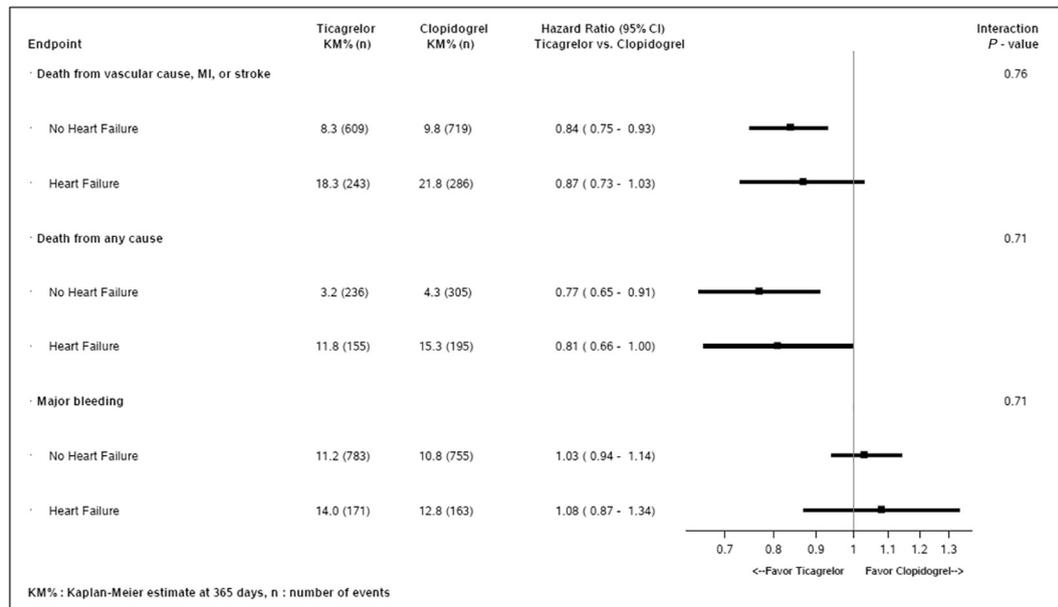
Effects of ticagrelor versus clopidogrel on CV events according to HF

Patients randomized to ticagrelor, compared to clopidogrel, had results consistent with the overall PLATO cohort concerning the primary composite of CV death, MI, and

stroke irrespective of HF on admission (HR 0.87, 95% CI: 0.73-1.03) or no HF on admission (HR 0.84, 95% CI: 0.75-0.93) (P value for interaction .76). The results were similar for CV death alone and MI alone (Table III, Figure 2).

Factors associated with postdischarge new-onset HF

Baseline factors associated with new-onset postdischarge HF included STEMI, higher NT-proBNP, higher heart rate, COPD, hypertension, age, diabetes, and lower estimated creatinine clearance (Table IV). Overall C-index for prediction of new-onset HF by these factors was 0.71.

Figure 2

Efficacy and safety of ticagrelor compared with clopidogrel, by subgroups of HF, during up to 1 year of follow-up.

Table IV. Multiple regression analysis to assess factors on admission associated with new-onset HF postdischarge

Variable	DF	χ^2	P value	HR represents...	HR (95%CI)
Type of ACS	1	47.71	<.0001	STEMI vs NSTEMACS	1.84 (1.55-2.19)
NT-proBNP (log)	1	29.25	<.0001	Doubling NT-proBNP	1.15 (1.10-1.22)
Heart rate	1	27.41	<.0001	10 bpm in crease	1.15 (1.09-1.21)
Troponin I (3linear splines, log)	3	16.73	<.0001	Doubling troponin I under 0.5 $\mu\text{g/L}$	1.18 (1.08-1.31)
				Doubling troponin I between 0.5 and 8 $\mu\text{g/L}$	0.85 (0.79-0.92)
				Doubling troponin I above 8 $\mu\text{g/L}$	1.18 (1.07-1.30)
COPD	1	13.90	.0002	Yes vs no	1.72 (1.29-2.28)
Hypertension	1	10.89	.0010	Yes vs no	1.39 (1.14-1.69)
Age	1	8.51	.0035	5-y increase	1.08 (1.03-1.14)
Diabetes	1	6.92	.0085	Yes vs no	1.28 (1.07-1.54)
Creatinine clearance (truncated)	1	6.88	.0087	10-U increase (below 115)	0.93 (0.88-0.98)
Systolic blood pressure	1	6.51	.0107	10-mm Hg increase	0.95 (0.92-0.99)
History of CABG	1	6.04	.0140	Yes vs no	1.46 (1.08-1.98)
History of nonhemorrhagic stroke/TIA	1	5.52	.0188	Yes vs no	1.42 (1.06-1.91)

Overall C-index for prediction of new-onset HF was 0.71.

Effects of ticagrelor versus clopidogrel on new-onset HF

The number of patients with new-onset HF, by strata of randomized treatment, at 12 months after randomization were ticagrelor: 278 (4.1%) and clopidogrel: 276 (4.0%), with an HR of 1.01 (95% CI 0.85-1.19) (Table V). Of the 278 HF events in the patients randomized to ticagrelor, 140 (50%) originated from dyspnea considered to have HF etiology, 68 (25%) were from HF events only (reported adverse event), and 70 (25%) were from both dyspnea and HF events. The 276 events in patients randomized to clopidogrel originated from dyspnea: 114

(41%), HF events: 101 (37%), and both dyspnea and HF events: 61 (22%).

Discussion

In the current study of patients with ACS, ticagrelor was more efficacious than clopidogrel in preventing the combination of CV mortality and morbidity in patients without HF. Similarly, ticagrelor was more efficacious than clopidogrel in patients with HF. Thus, there was no significant interaction between HF and the benefits of

Table V. Association between randomized treatment and new-onset HF in patients free of HF at discharge (n = 15,034)

	Any HF		Hospitalization due to HF	
	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel
	Events (%)	Events (%)	Events (%)	Events/n (%)
3 m	171 (2.30)	167 (2.24)	48 (0.65)	54 (0.73)
6 m	229 (3.09)	221 (2.98)	64 (0.86)	64 (0.86)
9 m	256 (3.55)	261 (3.65)	76 (1.06)	76 (1.07)
12 m	278 (4.05)	276 (3.99)	82 (1.20)	81 (1.18)

Any HF after discharge was based upon reported HF events or dyspnea judged by the investigator to have a probable HF etiology. Hospitalization due to HF was obtained from safety data.

%. Kaplan-Meier estimate,

HR (ticagrelor vs clopidogrel) for any HF: 1.01 (0.85-1.19), *P* value = .9242.

HR (ticagrelor vs clopidogrel) for HF requiring hospitalization: 1.01 (0.75-1.38), *P* value = .9316.

ticagrelor in comparison to clopidogrel. Irrespective of the randomized treatment, the study confirmed previous knowledge that HF in the context of ACS is associated with worse outcomes, including higher mortality.

Although dyspnea was more common in patients receiving ticagrelor than clopidogrel, this finding did not correspond to elevated risk of new-onset HF. There were no significant differences between the randomized treatments concerning new-onset HF or hospitalizations for HF, thereby indicating that ticagrelor is not associated with any changed risk of HF in patients with ACS. Finally, we verified baseline factors associated with development of new-onset HF after a hospitalization with ACS, including STEMI, higher heart rate, hypertension, older age, and higher NT-proBNP level at entry.

Ticagrelor compared to clopidogrel was associated with a lower risk of CV death in the PLATO trial.⁹ Patients in the ticagrelor group also had a numerically lower proportion of deaths attributed to HF (n = 31, 0.3%) than patients in the clopidogrel group (n = 42, 0.5%).¹⁴ The exact reason for the reduction in CV mortality in the PLATO trial has been debated. It has been questioned if it can be fully explained by the differences in platelet inhibition and lower rate of new ischemic events.¹⁹ It might be speculated that ticagrelor treatment might be associated with less HF, as ticagrelor treatment is associated with increased concentrations of extracellular adenosine that improves coronary blood flow and myocardial perfusion and thereby limits infarct size.¹⁰⁻¹³ However, there are to date no prospective investigations on the effect of ticagrelor on the development of HF as a predefined end point.

In the current study, ticagrelor was confirmed to be more efficacious than clopidogrel irrespective of HF with respect to CV outcomes. However, both randomized treatments exhibited similar rates of new-onset HF. Patients on ticagrelor were, however, more commonly suspected to have HF because of dyspnea events compared to the clopidogrel group (140 events vs 114). This finding was verified by reviewing safety data from the trial, that is,

hospitalizations due to HF, to avoid ticagrelor-associated dyspnea being misclassified as HF.^{17,20}

The increased risk for adverse CV events in patients with HF has previously been reported.^{2,3} In the current study, we confirmed that previous HF or HF on admission was associated with adverse CV outcomes, that is, with an elevated risk of mortality and an elevated risk of MI, but with no significant difference in the risk of stroke. There was no significant association between HF and the risk of bleeding regardless of treatment with ticagrelor or clopidogrel.

Finally, we identified several baseline variables that may contribute to predict the development of new-onset postdischarge HF in patients with ACS treated with P2Y12 inhibition including type of ACS, higher NT-proBNP, higher heart rate, troponin I > 0.08 µg/L, COPD, and older age. Except for COPD, which likely influenced the incidence of dyspnea but not with certainty new-onset HF, our results confirm previous findings on short-term outcomes in clinical data registries and trials from 1994 to 2008.² Our results however emphasize that these factors are prognostically important also when ticagrelor is the preferred antiplatelet drug in ACS and when used in a setting with high rates of revascularization therapy.⁷ Our findings thereby expand the knowledge base concerning which patients with ACS that today are at risk for developing new-onset HF and may help to identify patients at risk for HF.

Limitations

As the overall survival was statistically different between the 2 randomized treatments, there is a risk that a survival bias may lead to an underestimation of an eventual effect of ticagrelor in preventing HF. In the PLATO trial, HF was a clinical diagnosis and not per protocol supported by either echocardiographic assessment of LV function or NT-proBNP. The presence of Killip class II or III in the setting of ACS may not always imply chronic HF; instead, an acute left ventricular dysfunction may be present, which may or may not be

reversible. Furthermore, as HF was not centrally adjudicated, the current study may consequently have resulted in erroneous assignment of the clinical HF diagnosis both at baseline and during follow-up. Again, we emphasize that HF was a part of the safety program and not a part of the prespecified end points in the PLATO trial.

Conclusion

In patients with ACS, ticagrelor is more efficacious than clopidogrel for protection against ischemic events and mortality, irrespective of the presence of HF. There is, however, no difference in the development of new-onset HF during 1-year treatment with ticagrelor or clopidogrel post-ACS.

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