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Outcomes in patients treated with ticagrelor or clopidogrel after acute myocardial infarction: experiences from SWEDEHEART registry

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Aims Ticagrelor reduces ischaemic events and mortality in acute coronary syndrome (ACS) vs. clopidogrel. We wished to study clinical outcomes in a large real-world population post-ACS.

Methods and results We performed a prospective cohort study in 45 073 ACS patients enrolled into Swedish Web system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies who were discharged on ticagrelor ($N = 11\,954$) or clopidogrel ($N = 33\,119$) between 1 January 2010 and 31 December 2013. The primary outcome was a composite of all-cause death, re-admission with myocardial infarction (MI) or stroke, secondary outcomes as the individual components of the primary outcome, and re-admission with bleeding. The risk of the primary outcome with ticagrelor vs. clopidogrel was 11.7 vs. 22.3% (adjusted hazard ratio (HR) 0.85 [95% confidence interval: 0.78–0.93]), risk of death 5.8 vs. 12.9% (adjusted HR 0.83 [0.75–0.92]), and risk of MI 6.1 vs. 10.8% (adjusted HR 0.89 [0.78–1.01]) at 24 months. Re-admission with bleeding with ticagrelor vs. clopidogrel occurred in 5.5 vs. 5.2% (adjusted HR 1.20 [1.04–1.40]). In a subset of patients undergoing percutaneous coronary intervention (PCI) on ticagrelor vs. clopidogrel the PCI-related in-hospital bleeding was 3.7 vs. 2.7% (adjusted odds ratio, OR, 1.57 [1.30–1.90]).

Conclusion Ticagrelor vs. clopidogrel post-ACS was associated with a lower risk of death, MI, or stroke, as well as death alone. Risk of bleeding was higher with ticagrelor. These real-world outcomes are consistent with randomized trial results.

Keywords Acute coronary syndrome • Platelet inhibition • Ticagrelor

Introduction

Platelet inhibition is essential in the treatment of patients with acute coronary syndrome (ACS) and novel antiplatelet agents such as ticagrelor are more potent than clopidogrel.[1,2] The PLATelet inhibition and patient outcomes (PLATO) trial showed that ticagrelor reduced the incidence of vascular death, non-fatal myocardial infarction (MI), or stroke when compared with clopidogrel, although at the expense of an increased risk of major non-CABG-related bleeding.[3] Interestingly, ticagrelor was more strongly recommended in ESC guidelines[4–7] than in those of ACC/AHA[8,9] post-PLATO. This divergence of opinion suggests that more data are required on ticagrelor in ACS patients.

While randomized controlled trials (RCT) are the gold standard for novel therapies, they do have inherent limitations.[10] Post-approval studies in real-world patients may therefore provide valuable complementary data to externally validate RCT findings. We undertook the present observational study to evaluate outcomes in a large population of ACS patients treated with ticagrelor or clopidogrel in Sweden, who were enrolled into the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry.[11]

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Methods

Databases and patient selection

Patients were identified in the national MI registry SWEDEHEART. A full description of SWEDEHEART is available elsewhere.[11,12] In brief, patients admitted to a cardiac unit in Sweden with symptoms suggestive of an ACS are prospectively enrolled into SWEDEHEART (www.ucr.uu.se/swedeheart). Data accuracy is audited by an external monitor annually against source documents (agreement: 96%).[11]

Ticagrelor became available in Sweden in the latter half of 2011. The inclusion period was selected so as to span from a time when clopidogrel dominated until a time when ticagrelor was well established, and chosen *a priori* to achieve adequate statistical power. Baseline characteristics were enriched with data on diagnoses made during hospital admissions in Sweden since 1987 available at the National Patient Registry. Merging of registries was approved by the National Board of Health and Welfare in Sweden, the study complies with the Declaration of Helsinki, the protocol was approved by the regional ethics committee in Stockholm and the requirement for written consent was waived.

The primary analysis was based on treatment allocation at discharge and included all patients in the country of Sweden who were enrolled into SWEDEHEART between 1 January 2010 and 31 December 2013 for cardiac biomarker-verified acute MI (ICD code I21), were aged ≥18 years and discharged alive on dual antiplatelet therapy (DAPT) with aspirin (almost exclusively 75 mg daily) and ticagrelor or clopidogrel. Exclusion criteria were previous admission for MI, treatment with oral anticoagulant, revascularization by CABG during the index hospitalization.

In a separate analysis based on treatment allocation defined prior to or during percutaneous coronary intervention (PCI), we included patients who were enrolled during the same period for cardiac biomarker-verified acute MI (ICD code I21), aged ≥18 years, had PCI during the admission, and received DAPT with aspirin and either clopidogrel or ticagrelor prior to or during PCI, excluding previous admissions for MI and patients on oral anticoagulation. In this population, we evaluated PCI-related in-hospital bleeding (second bleeding outcome) and mortality (sensitivity analysis).

Definition of outcomes

The primary outcome was evaluated in the main population as the time from discharge to the first occurrence of a combination of death, readmission for MI, or stroke (see Supplementary material online) at 24 months. The secondary outcomes were evaluated as the time from discharge to each of the individual components of the primary outcome. In the analysis of MI, an initial 28-day blanking period was applied at discharge as early events may be either due to transfers between hospitals, causing the index event to be counted twice, or due to a clinical coding practice where any early readmission post-AMI deemed to be attributable to the index event by the managing team is given the same diagnosis.[13,14]

Risk of bleeding was evaluated using two outcomes: the primary bleeding outcome (analysed in the main population) was time from discharge to hospitalization with bleeding (bleeding definitions available online). The second bleeding outcome (analysed in the PCI population) was the probability of PCI-related in-hospital bleeding defined as any of the following: puncture site haematoma or pseudoaneurysm, drop in haemoglobin or requirement for prolonged compression, transfusion or surgical intervention.

Statistical analyses

Cox proportional hazard analysis with mixed effects was used to study primary and secondary outcomes, as well as the first bleeding outcome, entering hospital as a random effect and other covariates (determined using directed acyclic graphs[15]) as fixed effects. Covariates were ticagrelor treatment, hospital, calendar time, sex, age, history of diabetes, hypertension, MI, congestive heart failure, renal dysfunction (estimated glomerular filtration rate [eGFR] calculated using the Chronic Kidney Disease Epidemiology Collaboration equation),[16] peripheral vascular disease, ischemic stroke, chronic obstructive pulmonary disease, cancer within 3 years, bleeding (defined as above), Killip class on admission >1, ACS type (NSTEMI vs. STEMI), PCI during admission, bleeding during admission and drugs on discharge including β-blockers, angiotensin-converting enzyme inhibitors (ACEi), and statins. Proportional hazard was plotted from cox regression models as adjusted 1-survival (cumulative incidence) curves using mean value for continuous covariates and modal value for categorical.

A second model was built using logistic regression to study the secondary bleeding outcome of PCI-related in-hospital bleeding in patients undergoing PCI: covariates were antiplatelet treatment with ticagrelor, calendar time, sex, age, history of diabetes, eGFR, hypertension, MI, congestive heart failure, peripheral vascular disease, ischaemic stroke, chronic obstructive airways disease, cancer, bleeding, Killip class on admission >1, ACS type (STEMI vs. NSTEMI), concomitant use of unfractionated heparin, low-molecular-weight heparin, bivalirudin, glycoprotein IIb/IIIa inhibitor, radial vs. femoral access, and use of a vascular closure device.

Pre-specified subgroup analyses were performed after dichotomizing by ACS type (STEMI vs. NSTEMI) and by invasive strategy (PCI vs. non-PCI). Missing data were imputed using multiple imputation (see Supplementary material online). Sensitivity analyses were: (i) events at 12 months were used as outcome variables, (ii) complete cases were used (91.3% of the study population), (iii) patients with ticagrelor were matched pair-wise to patients with clopidogrel based on propensity scores calculated by logistic regression, (iv) patients were excluded with a diagnosis of dialysis-dependent renal failure, major bleeding, or intracranial haemorrhage, (v) patients were censored based on intended treatment duration as documented at time of discharge in SWEDEHEART, (vi) data on stent type (older vs. newer generation drug-eluting stent vs. bare metal stent) were included, (vii) relation of ticagrelor vs. clopidogrel to in-hospital mortality (analysed using the same model and population as PCI-related in-hospital bleeding), (viii) angiographic and haemodynamic data (LV ejection fraction, cardiogenic shock) were included. Analyses were performed with R (version 3.2.0; cox regression package: coxme).

Results

The main study population comprised 45 073 patients of whom 11 954 discharged on ticagrelor and 33 119 on clopidogrel (*Figure 1*). As shown in *Figure 2*, ticagrelor captured almost 50% of the market for DAPT within 9 months of its introduction (uptake across geographic regions of Sweden shown as Supplementary material online). Differences between patients discharged on ticagrelor vs. clopidogrel (see *Table 1*) included age (67 vs. 71 years), sex (71.5 vs. 65.2% males), ACS type (46.7 vs. 31.4% STEMI), and intended duration of DAPT (tabulated by year online).

Combined and individual outcomes of death, MI, and stroke

The cumulative probability of the combined outcome of death, MI, and stroke at 24 months was 11.7% (95% CI 10.6–12.8) with ticagrelor and 22.3% (95% CI 21.8–22.7) with clopidogrel. As for

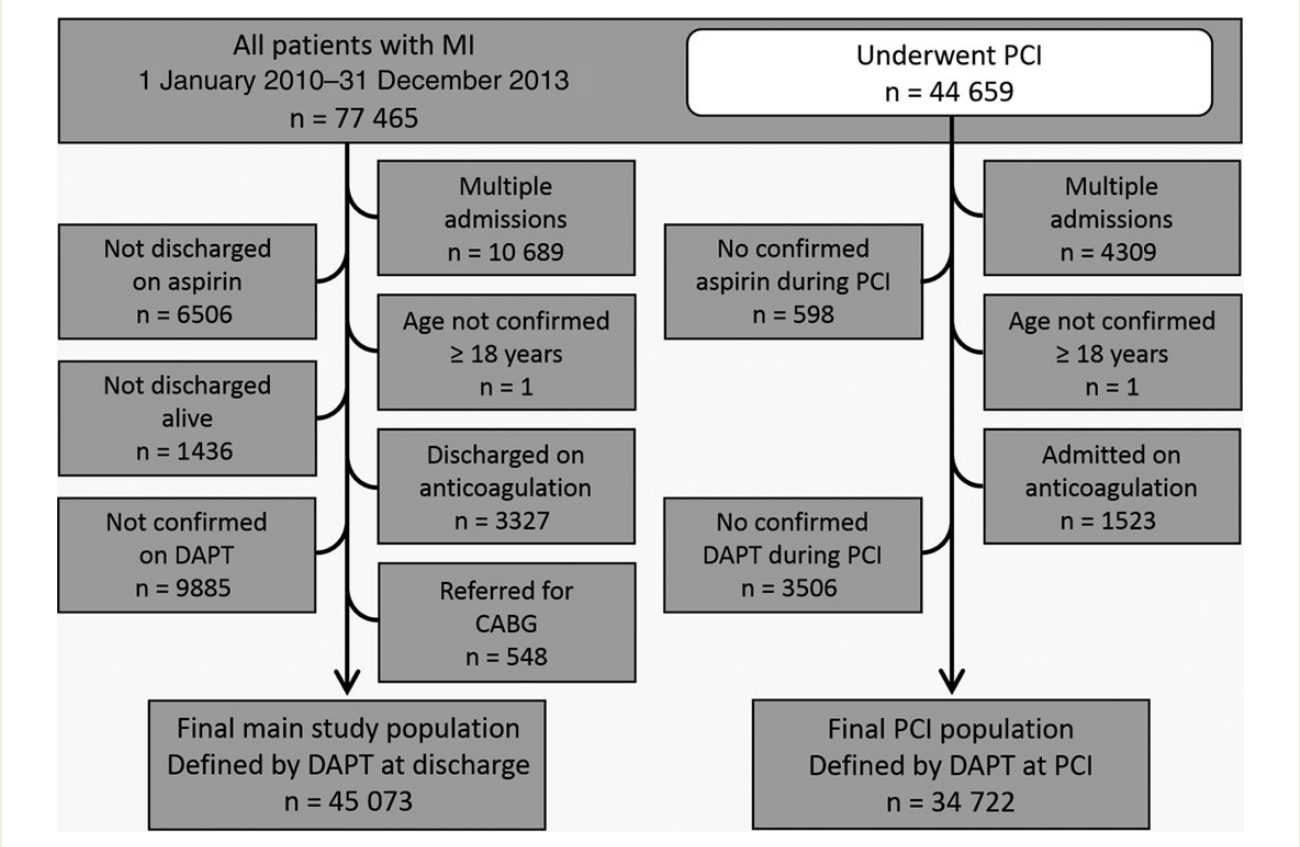

Figure 1 Patient flow diagram: Shown are criteria used to identify patients eligible for inclusion into the main study as well as the percutaneous coronary intervention population subset. DAPT, dual antiplatelet therapy; CABG, coronary artery bypass grafting.

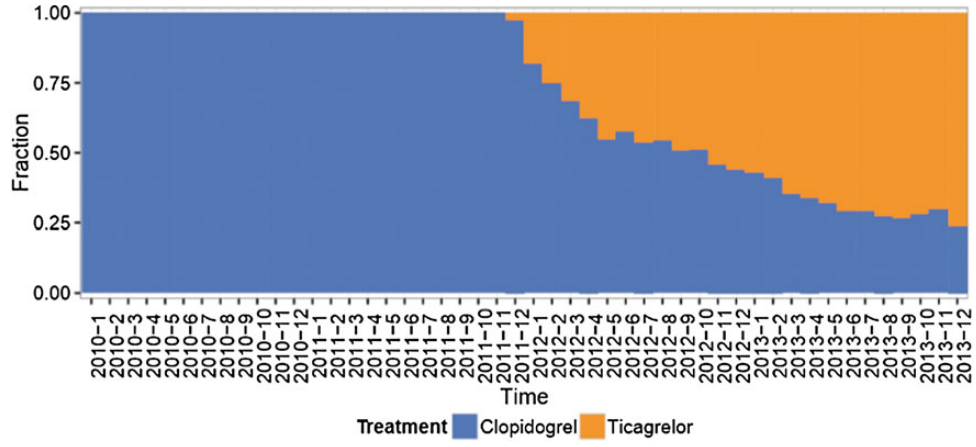

Figure 2 Proportion of patients discharged on ticagrelor per month between January 2010 and December 2013. Bars show the proportion of patients with acute coronary syndrome discharged on clopidogrel (blue) vs. ticagrelor (yellow) between 1 January 2010 and 31 December 2013.

secondary outcomes, the cumulative probability of death was 5.8% (95% CI 5.3–6.3) with ticagrelor and 12.9% (95% CI 12.5–13.3) with clopidogrel. The corresponding figures for MI were 6.1% (95% CI 5.2–7.0) with ticagrelor and 10.8% (95% CI 10.4–11.1) with clopidogrel, and for stroke 1.8% (95% CI 1.4–2.2) with ticagrelor and 3.8% (95% CI 3.6–4.1) with clopidogrel. *Table 2* shows crude number of events per 100 patient-years as well as unadjusted and adjusted hazard ratios for the two treatments. *Figure 3* shows

Table I Basic characteristics of the study population

	All (*N* = 45 073)	Ticagrelor (*N* = 11 954)	Clopidogrel (*N* = 33 119)
Age (years); median (IQR)	70.0 (61.0–79.0)	67.0 (59.0–75.0)	71.0 (62.0–80.0)
Male	66.9% (30 133)	71.5% (8550)	65.2% (21 583)
ST-elevation ACS	35.5% (15 973)	46.7% (5578)	31.4% (10 395)
Diabetes	22.5% (10 144)	20.5% (2446)	23.2% (7698)
Hypertension	54.4% (24 365)	49.9% (5939)	56.1% (18 426)
Current smoker	24.5% (10 417)	27.6% (3202)	23.3% (7215)
Past medical history			
MI	22.2% (9963)	15.1% (1796)	24.8% (8167)
PCI	13.8% (6176)	10.8% (1285)	14.9% (4891)
CABG surgery	6.9% (3098)	4.6% (545)	7.7% (2553)
Congestive heart failure	10.3% (4628)	5.5% (660)	12.0% (3968)
Peripheral vascular disease	4.8% (2154)	3.3% (396)	5.3% (1758)
Ischaemic stroke	8.3% (3750)	5.4% (649)	9.4% (3101)
Bleeding hospitalization	4.9% (2202)	3.7% (437)	5.3% (1765)
COPD	6.6% (2966)	5.2% (616)	7.1% (2350)
Cancer within last 3 years	2.7% (1239)	2.0% (244)	3.0% (995)
Killip class >1 on admission	8.5% (3765)	5.4% (636)	9.7% (3129)
Medication on admission			
Aspirin	36.1% (16 155)	27.0% (3207)	39.3% (12 948)
Antiplatelet therapy			
Clopidogrel	4.4% (1977)	1.7% (197)	5.4% (1780)
Prasugrel	0.0% (4)	0.0% (1)	0.0% (3)
Ticagrelor	0.3% (114)	0.9% (106)	0.0% (8)
Ticlopidine	0.0% (5)	0.0% (0)	0.0% (5)
Other	0.6% (279)	0.3% (35)	0.7% (244)
β-Blocker	33.4% (14 898)	26.3% (3113)	35.9% (11 785)
Calcium antagonist	18.4% (8240)	17.3% (2044)	18.9% (6196)
Digoxin	0.9% (424)	0.4% (45)	1.2% (379)
ACEi/ARB	17.7% (6260)	16.8% (1651)	18.0% (4609)
Diuretic	19.7% (8816)	13.9% (1649)	21.8% (7167)
Statin	28.0% (12 564)	22.9% (2723)	29.9% (9841)
In-hospital course			
Inotropic support	1.8% (803)	2.0% (239)	1.7% (564)
Diuretic therapy	14.2% (6383)	11.5% (1377)	15.1% (5006)
Coronary angiography	85.8% (38 670)	96.1% (11 486)	82.1% (27 184)
PCI	73.4% (33 072)	88.5% (10 585)	67.9% (22 487)
New-onset AF	2.9% (1294)	2.7% (326)	3.0% (968)
Medication at discharge			
Aspirin	100% (45 073)	100% (11 954)	100% (33 119)
Intended DAPT duration			
3 months	7.7% (799)	3.3% (233)	17.6% (566)
6 months	4.8% (499)	3.8% (272)	7.0% (227)
12 months	73.6% (7634)	83.8% (5995)	50.9% (1639)
Permanent	5.8% (598)	3.7% (267)	10.3% (331)
Not determined at discharge	5.8% (605)	4.3% (307)	9.2% (298)
β-Blocker	90.5% (40 765)	91.1% (10 889)	90.2% (29 876)
Calcium antagonist	16.2% (7290)	14.0% (1672)	17.0% (5618)
Digoxin	1.1% (508)	0.5% (61)	1.3% (447)
ACEi/ARB inhibitor	80.3% (36 076)	84.4% (10 084)	78.8% (25 992)
Diuretic	24.4% (11 001)	16.8% (2011)	27.1% (8990)
Statin	92.1% (41 508)	96.2% (11 501)	90.6% (30 007)

Continued

Table 1 *Continued*

	All (N = 45 073)	Ticagrelor (N = 11 954)	Clopidogrel (N = 33 119)
Serum creatinine (mg/dL), median (IQR)[a]	0.93 (0.78–1.11)	0.90 (0.78–1.06)	0.93 (0.78–1.12)
Dialysis-dependent renal failure	0.5% (244)	0.3% (36)	0.6% (208)
eGFR, mL/min/1.73 m^2, median (IQR)	78.1 (60.4–91.1)	81.9 (66.0–93.2)	76.6 (58.3–90.1)

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CABG, coronary artery by-pass grafting; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; IQR, inter-quartile range.
[a]To convert creatinine levels from mg/dL to mmol/L, multiply by 88.4. Data are shown as per cent (n) unless otherwise stated. All between-subgroup differences were statistically significant except new-onset AF (P = 0.18).

Table 2 Association between use of ticagrelor vs. clopidogrel and outcomes

Event	Ticagrelor	Clopidogrel	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Primary outcome				
Death, MI, or stroke	11.7	22.3	0.49 (0.46–0.53)	0.85 (0.78–0.93)
Secondary outcomes				
Death	5.8	12.9	0.43 (0.39–0.47)	0.83 (0.75–0.92)
MI	6.1	10.8	0.52 (0.47–0.58)	0.89 (0.78–1.01)
Stroke	1.8	3.8	0.53 (0.44–0.63)	0.81 (0.65–1.01)
Risk of bleeding				
Admission with bleeding	5.5	5.2	1.0 (0.92–1.20)	1.20 (1.04–1.40)

Data shown as cumulative probability of events per 100 patient-years at 24 months.
CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

adjusted cumulative incidence of outcomes (unadjusted incidence curves and trends in outcomes over time included as Supplementary material online).

Bleeding outcomes

The cumulative probability of bleeding requiring admission was similar between patients treated with ticagrelor and clopidogrel: 5.5% (95% CI 4.7–6.3) vs. 5.2% (95% CI 5.0–5.5), respectively (unadjusted hazard ratio 1.0; *Table 2*, *Figure 3*). The adjusted HR was 1.20 (95% CI 1.04–1.40), indicating a higher risk of bleeding associated with ticagrelor after correcting for confounders.

Percutaneous coronary intervention-related in-hospital bleeding (*Figure 1*; basic characteristics included as Supplementary material online) occurred in 413 of 11 221 patients on ticagrelor vs. 634 of 23 501 patients on clopidogrel (3.7 vs. 2.7%; unadjusted odds ratio (OR) 1.40 [95% CI 1.20–1.60], adjusted OR 1.57 [95% CI 1.30–1.90]).

Subgroup analyses

Acute coronary syndrome type (STEMI vs. NSTEMI) did not interact with the association between ticagrelor treatment and patient outcomes. Invasive strategy (PCI vs. non-PCI) did not interact with regards to the primary outcome (P = 0.08), but an interaction was noted between invasive strategy and type of antiplatelet therapy with regards to death (P = 0.03): the association between ticagrelor treatment and a lower risk of death was more pronounced in patients undergoing PCI (adjusted hazard ratio 0.74 [95% CI 0.63–0.86] vs. 0.93 [95% CI 0.78–1.10] in non-PCI patients; forest plot included as Supplementary material online).

Sensitivity analyses

All sensitivity analyses showed similar results to main analyses in direction and magnitude including in-hospital mortality which did not differ between patients undergoing PCI on ticagrelor vs. clopidogrel (see Supplementary material online).

Discussion

The main finding of this study was that real-world outcomes in patients with ACS treated with ticagrelor vs. clopidogrel appeared similar to the benefit achieved in the PLATO trial: patients discharged on ticagrelor had lower incidence of the composite of death, MI, or stroke, as well as lower mortality alone. Patients prescribed ticagrelor were also at higher risk of bleeding, as evidenced both by more re-admissions with bleeding and more PCI-related in-hospital bleeding events.

Ticagrelor is recommended by current ACS guidelines based on the PLATO trial.[4–9] An RCT is carried out under strictly controlled conditions: the target population is well characterized and often highly selected, follow-up is complete, and non-compliance and attrition are identified. As such, the population in which the drug is ultimately licensed for use may to some extent differ from that of the original trial population. This makes real-world registry

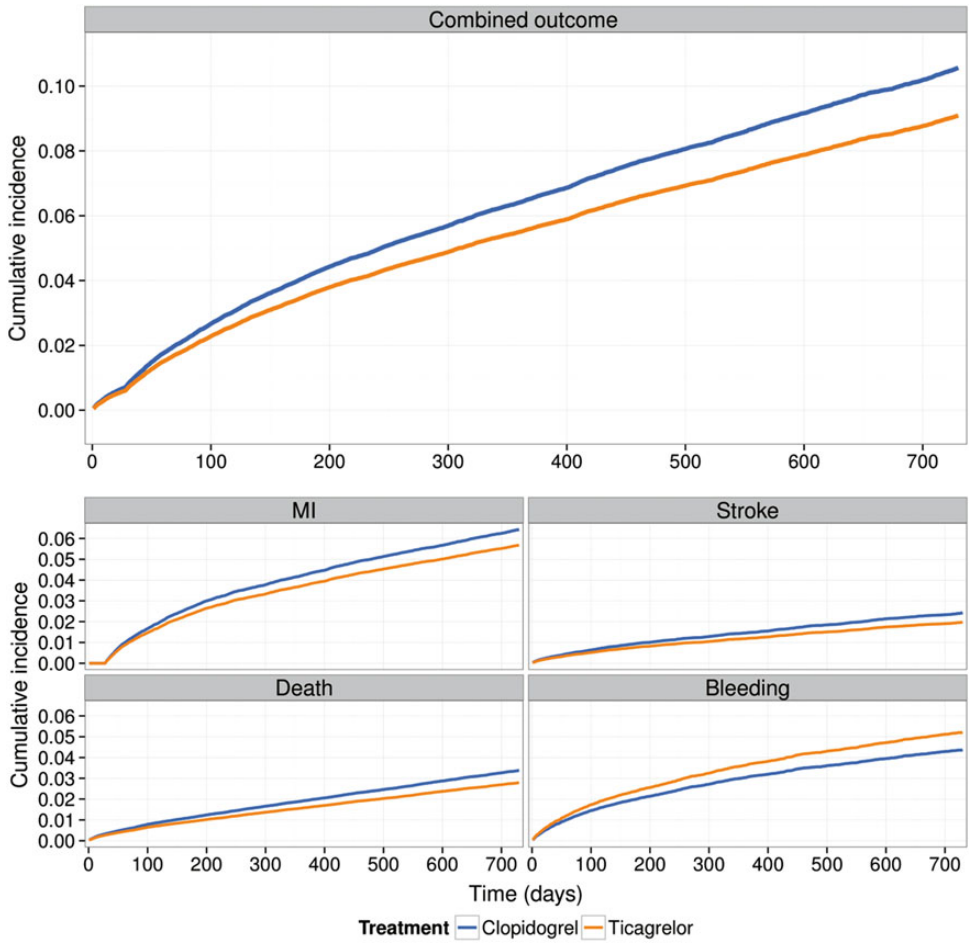

Figure 3 Adjusted cumulative incidence curves for primary and secondary outcomes in patients discharged on ticagrelor and clopidogrel. Top panel shows adjusted cumulative incidence for the primary combined outcome of death, myocardial infarction, or stroke. Bottom panels show the individual components of the primary outcome, as well as the primary bleeding outcome of hospitalization with bleeding (bottom right). Treatment with clopidogrel is shown in blue and ticagrelor in yellow.

experience an important complement that may confirm and externally validate RCT findings. To our knowledge, the present study is the first large-scale evaluation of clinical outcomes of ticagrelor and clopidogrel in real-world ACS patients since the publication of PLATO.

PLATO was designed to study a broad population of patients presenting with ACS. Important risk factors such as diabetes and previous MI were similar in prevalence between PLATO and the present study. Major differences were nonetheless present as evidenced by the mean age of patients in the present study being 8 years higher (70 vs. 62 years) and a higher proportion with a past history of stroke (10.8 vs. 3.9%) and heart failure (10.3 vs. 5.6%).

It may be noted that the present study used all-cause mortality and not vascular mortality as in PLATO. However, there was considerable overlap between vascular and all-cause mortality in PLATO: only 12% of deaths were non-vascular in origin (46 of 399). In our study, ticagrelor was associated with a numerically lower incidence of MI. While the confidence interval in the post-multiple imputation analysis did straddle zero, analysis of complete cases (see Supplementary material online) did achieve numerical statistical significance.

We also noted that the difference in outcomes was similar between the main analysis at 24 months, as specified *a priori*, and the sensitivity analysis at 12 months. This is interesting and has several potential explanations, relating to differences in the 2 populations or to effects of ticagrelor on the longer-term clinical course of patients beyond the initial treatment period, possibly owing to non-antiplatelet properties such as restoration of endothelial function or tissue perfusion.[17] Alternatively, treatment length may conceivably have been extended beyond the originally intended duration.

A higher risk of bleeding was seen in ticagrelor-treated patients in the present study. While the PLATO trial found no increase in the primary safety endpoint of major bleeding with ticagrelor, the secondary safety endpoint of major bleeding events after removing CABG-related bleeding was significantly higher with ticagrelor. As bleeding is very common in patients undergoing CABG on

antiplatelet therapy,[18,19] the inclusion of CABG-related bleeding events in trials of anti-thrombotic agents may cause non-CABG bleeding events to be overwhelmed by CABG-related bleeding.[20] Importantly, detailed analyses have shown that the increase in non-CABG bleeding in PLATO was driven chiefly by spontaneous bleeding,[21] which has been linked to an increased risk of death.[22] Indeed, haemorrhagic complications in ACS patients are an independent risk factor for poor outcome.[23,24] It is therefore reassuring to note that while bleeding leading to readmission was indeed more frequently observed in real-world patients discharged on ticagrelor, the risk of death was lower.

We identified a statistically significant effect of managing patients with an invasive vs. non-invasive strategy on the association between ticagrelor treatment and death. Two subgroup analyses from PLATO have been performed to evaluate this particular issue: a consistent benefit of ticagrelor was shown both in a pre-specified study of patients originally intended for a conservative vs. invasive approach at the time of randomization[25] as well as in a second study based on patients' final revascularization status.[26] While the interaction we found between PCI and the association between ticagrelor and death may thus be due to the play of chance, it may also be noted that conservatively treated patients in our study differed in several important ways from non-PCI patients in PLATO: they were substantially older (median age 78 vs. 65 years) and more commonly female (47.5 vs. 36.5%), and a higher proportion had a past history of both CABG (12 vs. 7.4%) and stroke (18.6 vs. $<$10%). Any effect of ticagrelor may therefore have been influenced both by the disease burden of this subgroup and by selection bias.

Limitations

Key limitations include (i) the observational study design which opens up the possibility of residual confounding which is a known potential source of error in registry studies. Accordingly, results should not be construed as providing a precise measure of treatment effect. Nonetheless, data used for this report are based on a very large number of variables where a majority of essential co-morbidities and treatments are characterized and few data missing, results were supported by multiple sensitivity analyses and in line with RCT data from PLATO. (ii) The absolute risk of bleeding is lower in the registry than the risk seen in clinical trials. It is conceivable that this relates to underreporting of bleeding events in the registry. However, this should affect the absolute number of bleeds and not the relative risk with ticagrelor. (iii) Actual treatment duration, attrition, and cross-over are unavailable in the present analysis which is based on intention to treat. However, as more patients in the ticagrelor arm of PLATO discontinued their study drug than in the clopidogrel arm, non-compliance should favour a type II error which cannot explain the findings of the present study. (iv) While SWEDEHEART registers the fact that a patient was discharged on a statin, the actual drug and dose are not available. Nonetheless, statistical models should have been able to control for changes in treatment over time. (v) Early, non-fatal stent thromboses would be undetected owing to the 28-day rule.

Conclusions

In this large observational study, ticagrelor vs. clopidogrel treatment at discharge in patients with ACS was associated with a lower adjusted risk of death, MI, or stroke, as well as death alone. Ticagrelor was also associated with a higher risk of PCI-related in-hospital bleeds as well as bleeding requiring re-admission. These real-world outcomes are consistent with the benefit of ticagrelor in PLATO.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

H.R. performed statistical analysis. S.K.J., L.W., T.J. handled funding and supervision. A.S., C.V., B.L., E.O., D.E., L.W., S.K.J., T.J. acquired the data. A.S., C.V., B.L., H.R., L.W., S.K.J., T.J. conceived and designed the research. A.S., T.J. drafted the manuscript. AS., C.V., B.L., H.R., E.O., D.E., L.W., S.K.J., T.J. made critical revision of the manuscript for key intellectual content.

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