Effectiveness and Safety of Ticagrelor Implementation in Patients with Acute Coronary Syndrome undergoing Percutaneous Coronary Intervention: A Cohort Study in Western Denmark

Pernille Gro Thrane,[a]* Kevin Kris Warnakula Olesen,[a] Morten Würtz,[a] Christine Gyldenkerne,[a] Morten Madsen,[b,c] Lisette Okkels Jensen,[d] Bent Raungaard,[e] Henrik Toft Sørensen,[b,c] Troels Thim,[a,b] Steen Dalby Kristensen,[a,b] and Michael Maeng[a,b]

[a]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
[b]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[c]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[d]Department of Cardiology, Odense University Hospital, Odense, Denmark
[e]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark

Summary

Background Ticagrelor was introduced in Denmark in 2011 after randomised data showed its superiority over clopidogrel for patients with acute coronary syndrome (ACS). We assessed the effectiveness and safety of ticagrelor implementation in ACS patients undergoing percutaneous coronary intervention (PCI).

Methods We identified PCI-treated ACS patients in Western Denmark who redeemed a P2Y12 inhibitor prescription within 14 days. Using Danish health registries, 1-year outcomes were compared before (2007-2010) and after (2012-2015) introduction of ticagrelor. Outcomes were MACE (death, myocardial infarction, and ischaemic stroke) and hospitalisation for bleeding. Inverse probability of treatment weights were used to estimate weighted incidence rate ratios (wIRRs).

Findings We included 14,450 patients; 7,102 were treated in the earlier time period (99·9% clopidogrel) and 7,348 in the later time period (87·8% ticagrelor). Ticagrelor implementation was not associated with a clinically relevant difference in 1-year risk of MACE with 413 events in the ticagrelor period vs. 424 events in the clopidogrel period (cumulative incidence percentage [CIP] 5·6% vs. 6·0%; wIRR 1·06, 95% CI 0·92-1·22). The 1-year risk of bleeding was also similar between groups with 335 bleedings requiring hospitalisation in the ticagrelor period vs. 309 events in the clopidogrel period (CIP 4·6% vs. 4·4%; wIRR 1·05, 95% CI 0·89-1·23). Results were robust in patients above and below 70 years of age.

Interpretation Implementation of ticagrelor was not associated with changes in risks of ischaemic or bleeding events in Danish PCI-treated ACS patients.

Keywords: Myocardial infarction; Antiplatelet therapy; Percutaneous coronary intervention; Risk-benefit

The Lancet Regional Health - Europe 2022;14: 100301
Published online xxx
https://doi.org/10.1016/j.lanepe.2021.100301

Introduction

Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor is standard care for patients with acute coronary syndrome (ACS) to reduce the risk of ischaemic events.[1,2] In 2009, the Platelet Inhibition and Patient Outcomes (PLATO) trial showed the superiority of ticagrelor over clopidogrel for ACS patients, with absolute risk reductions of 1·9% for major adverse cardiac events (MACE) and 1·4% for all-cause mortality.[3] This came at the cost of increased rates of non-coronary artery bypass grafting (CABG)-related bleedings and dyspnea.[3] Based on the PLATO trial and favourable results with prasugrel,[4] guidelines recommend ticagrelor or prasugrel over clopidogrel in patients with ACS

DOI of original article: http://dx.doi.org/10.1016/j.lanepe.2022.100309.

*Address for correspondence: Pernille Gro Thrane, Department of Cardiology, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark, Phone: +45 26140993.

E-mail address: pethra@rm.dk (P.G. Thrane).Funding: Department of Cardiology, Aarhus University Hospital and Department of Clinical Medicine, Aarhus University.

Research in context

Evidence before this study

We searched PubMed until September 13, 2021, with search terms including "Acute Coronary Syndrome", "ACS", "Myocardial infarction", and "AMI" in combination with "Ticagrelor" and "Clopidogrel". We had a special focus on large observational studies and randomised trials with a proper statistical power (>1,000 patients) comparing ticagrelor vs. clopidogrel in patients with acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI). Two randomised trials were identified. The largest of these, the Platelet Inhibition and Patient Outcomes (PLATO) trial included 18,624 ACS patients and showed that ticagrelor reduced cardiovascular death, myocardial infarction, or ischaemic stroke with an absolute risk reduction of 1·9% compared with clopidogrel. This reduction in ischaemic events came at a 0·7% absolute increase in non-coronary artery bypass graft-related major bleeding. In the smaller randomised POPular AGE trial (clopidogrel vs. ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation ACS), 1,003 Dutch patients with age above 70 years with non-ST-elevation myocardial infarction were randomised to clopidogrel or potent platelet inhibition with prasugrel or ticagrelor with 95% receiving ticagrelor. The study showed a 6·0% absolute risk reduction in terms of major plus minor bleeding favouring clopidogrel (hazard ratio 0·71, 95% confidence interval [CI] 0·54 to 0·94; p=0·02 for superiority) and a 4·3% lower risk (95% CI from 10·0% lower to 1·4% higher risk) of the net clinical benefit outcome of ischaemic and bleeding events.

Several observational studies comparing patients receiving ticagrelor and clopidogrel following the introduction of ticagrelor have been carried out. The largest cohort study was a South Korean and American registry-based study including 189,579 ACS patients treated with PCI from 2011 to 2019, of whom 24% received ticagrelor and 76% received clopidogrel. The study found no difference in the net clinical effect endpoint of ischaemic and bleeding events. Similarly, a Canadian study included 11,185 ACS patients between 2012 and 2016, of whom 37% received ticagrelor and 63% clopidogrel, and found no difference in risk of major adverse cardiac events (MACE) but an increased risk of bleeding with ticagrelor at 12-month follow-up. Other observational studies including studies from Sweden and Germany have reported conflicting results. These observational studies have inherent risk of confounding by indication related to the direct comparison of two treatment strategies in clinical practice where clopidogrel is often given to patients with more frailty. Furthermore, the relatively low proportion of patients treated with ticagrelor increases the risk of such confounding. To the best of our knowledge, only a smaller (n = 2,061 patients) single centre study, the CHANGE DAPT study, assessed the effect of the transition from clopidogrel to ticagrelor, and reported an increased risk of net adverse clinical and cerebral events in the ticagrelor period, driven by an increased risk of bleeding events.

Added value of this study

Our observational study assessed the effectiveness and safety of ticagrelor *implementation* in 14,450 ACS patients undergoing first-time PCI by comparing a four-year period prior to ticagrelor introduction (2007-2010) to a four-year period following ticagrelor introduction (2012-2015). This approach was possible due to a high proportion of ticagrelor-treated patients (88%) in the late period (2012-2015). We found that implementation of ticagrelor was not associated with a clinically relevant difference in one-year risks of MACE or hospitalisations for bleeding. Patients treated in the ticagrelor period had a 5% lower adherence rate and 14% of patients switched to another P2Y12 inhibitor (primarily clopidogrel). Thus, the transition from 99·9% use of clopidogrel in 2007-2010 to 87·8% use of ticagrelor in 2012-2015 did not lead to a measurable clinical benefit in 14,450 Danish ACS patients undergoing first-time PCI.

Implications of all the available evidence

The combined evidence from the smaller randomised POPular AGE trial, from our novel pre-post cohort analysis of ticagrelor implementation in Denmark, and other observational data from countries like Sweden, Canada, and the USA/South Korea cohort question whether the introduction of ticagrelor has led to measurable clinical benefits in daily clinical practice, at least in such countries with high standards of clinical care. Finally, a randomised trial may assess if very early de-escalation, within days from index procedure, from ticagrelor to clopidogrel is safe and cost-effective in low-risk populations.

undergoing percutaneous coronary intervention (PCI).[1,2]

"Real-world" patients often differ from clinical trial populations in terms of age, sex, comorbidity level, comedications, and treatment adherence, creating uncertainty about the applicability of trial findings in routine clinical care.[5] It is imperative to address these differences when balancing benefits and risks of a new treatment. Recent observational studies question whether ticagrelor reduces ischaemic outcomes compared with clopidogrel in the modern era of PCI.[6-8] Especially in elderly ACS patients, this is a topic for debate following the relatively small randomised POPular AGE trial.[9] This trial showed that ticagrelor treatment compared with clopidogrel did not reduce ischaemic events, but increased bleeding events in Dutch patients with non-ST elevation myocardial infarction (non-STEMI) aged ≥70 years.[9]

In Denmark, ticagrelor was introduced in the latter half of 2011 for patients with ACS undergoing PCI. In order to examine the effectiveness and safety of

switching from clopidogrel to ticagrelor, we assessed the risk of ischaemic and bleeding outcomes in a Danish cohort of ACS patients treated with PCI before and after implementation of ticagrelor.

Methods

Data sources

Since 1999, all patients treated with PCI in the Southern, Northern, and Central Danish regions have been registered in the Western Denmark Heart Registry.[10] This registry contains detailed prospectively recorded information on patient, procedure, and lesion characteristics. All Danish residents are assigned a 10-digit unique personal identifier at birth or immigration, which enables cross-linkage at the individual level of several national health registries. This allowed us to obtain and link information on vital status, hospital admissions, and prescribed medications, with long-term clinical follow-up and minimal loss to follow-up.

The national health registries have previously been described in detail.[10] In brief, we used the following health registries: The Danish Civil Registration system, which contains information on age, sex, and vital status including date of death; the Danish National Patient Registry, which contains information on hospital contacts since 1977; and the Danish National Prescription Registry, which contains information on prescriptions (including dosage and number of pills) redeemed from Danish pharmacies since 1995.

Setting

We identified all ACS patients who underwent PCI (index PCI) in Western Denmark between Jan 1, 2007 and Dec 31, 2015. To avoid inclusion of the same patient (s), the cohort was restricted to first-time PCI patients. We compared two different time periods, before (2007-2010) and after (2012-2015) the introduction of ticagrelor, excluding patients in 2011, where ticagrelor was introduced (Figure 1). The clopidogrel period (2007-2010) and ticagrelor period (2012-2015) were compared overall and according to age (above or below 70 years). Patients were included in the analysis if they were aged ≥18 years and redeemed a prescription for clopidogrel, ticagrelor, or prasugrel within 14 days after PCI. Follow-up started on day 14. Patients were excluded if they died or emigrated between the date of their PCI and start of follow-up, or if they redeemed a prescription for any

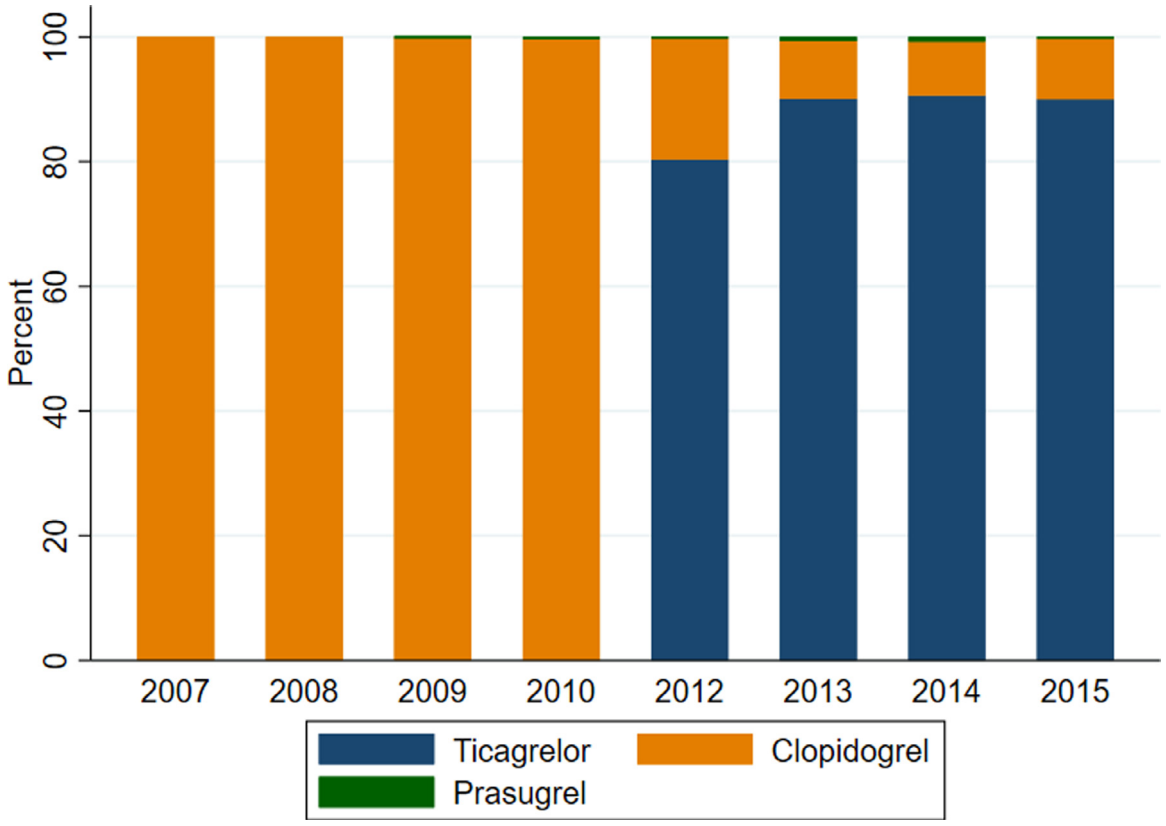

Figure 1. Implementation of ticagrelor.
Temporal use of clopidogrel, ticagrelor, and prasugrel among patients with acute coronary syndrome treated with first-time percutaneous coronary intervention in Western Denmark.

oral anticoagulant drug from six months before to 14 days after PCI, or any P2Y12 inhibitor from six months to one week before PCI. Throughout the study period, low-dose aspirin (75 mg daily) was part of the dual antiplatelet regimen. Since aspirin is available over-the-counter in Denmark and patients could have had pills left from a previous supply at study start, we assumed that all patients received concomitant treatment with aspirin.

Comorbidity and comedication

The Western Denmark Heart Registry provided information on demography, comorbidities, procedures, and treated lesions. These data were enriched with information on comorbidities from the Danish National Patient Registry, based on diagnoses coded according to the *International Classification of Diseases, Tenth Revision (ICD-10)*. Medication use was defined as redemption of ≥1 prescription(s) six months before to 14 days after PCI, ascertained from the Danish National Prescription Registry.

Outcomes

The main effectiveness outcome was MACE, defined as a composite of death from any cause, myocardial infarction, and ischaemic stroke. Each outcome was also assessed individually. In validation studies, the diagnoses of myocardial infarction and ischaemic stroke have shown positive predictive values of up to 97% for both.[11-13] The safety outcome was any bleeding event requiring hospitalisation.[14]

Statistical analyses

All patients were followed until one year after start of follow-up or until death, emigration, or an outcome event. We defined baseline treatment as the first redemption of a P2Y12 inhibitor prescription within 14 days after the index PCI. We estimated the 1-year cumulative incidence as a measure of absolute risk. For non-fatal outcomes, a competing risk model was used to estimate the cause-specific cumulative incidence accounting for the competing risk of death.[15] Groups were compared using crude incidence rate ratios (IRRs) and weighted IRRs (wIRRs) by fitting a Poisson regression model using the event as the outcome and the natural log of person-years as the offset.[16] We applied robust variance estimators. In all analyses, the clopidogrel period was used as reference.

We assessed adherence to P2Y12 inhibitor treatment by calculation of the medication possession ratio (MPR), which was defined as the percentage of days within the first year after PCI on which a P2Y12 inhibitor supply was available based on redeemed prescriptions and pill count. Consistent with previous studies,[7] we defined treatment adherence as an MPR ≥80%. We defined medication switch as the proportion of patients who switched from their first P2Y12 inhibitor prescription redeemed to any other P2Y12 inhibitor within the first year after PCI. We estimated the absolute difference in adherence and switch. All diagnosis and medication codes used in the study are provided in Supplemental Tables S1 and S2. Patients remained in the analysis if they discontinued treatment with a given drug or switched to another.

We used a marginal structural model to adjust for confounders related to the year of treatment.[17] We fitted a logistic regression and calculated the propensity score (*i.e.* the predicted probability of being treated in 2012-2015) based on all covariates shown in Supplemental Figures S1-S3. Inverse probability weights were calculated using the propensity score and was subsequently used to create a pseudo population in which the distribution of measured covariates were standardised to the distribution in the entire study population.[17] Weights were stabilised by multiplying the weight by the probability of being treated in the contrary study period. Stabilisation reduces variability of weights and preserves the sample size.[18] Balance in propensity score distributions of patients treated in the ticagrelor and clopidogrel period showed a high degree of overlap (Supplemental Figure S4). We estimated standardised differences to assess balance in covariates after applying standardised weights. No extreme weights were found (standardised weights <10). Weighted cumulative incidence curves were constructed for MACE and hospitalisation for bleeding based on the stabilised inverse probability of treatment weights.

Three confounders had missing data: body mass index category, smoking status, and multivessel disease at the last coronary angiography prior to PCI. The frequencies of missing values are reported in Table 1. To address missingness, we used multiple imputations with chained equations to generate ten imputed datasets using variables outlined in Supplemental Table S3.[19] Weighted estimates from the ten imputed datasets were pooled according to the combination rules of Rubin.[20]

We conducted multiple sensitivity analyses to assess robustness in subgroups and of the chosen standardised model. First, we performed several subgroup analyses presented as forest plots. Second, we compared results with another propensity score weighting method (*i.e.*, standardized mortality ratio weights) in which covariates were standardised to the clopidogrel period. Third, the analysis was performed using multivariable regression analysis with inclusion of clinically important confounders. Finally, we performed asymmetrical trimming in order to trim patients with very small and very large weights. In all analyses p values <0·05 were considered significant. Data management and statistical analyses were performed using STATA® statistical software version 16.1 (StataCorp LP, College Station, TX).

	Overall		≥70 years		<70 years	
	2012-2015 Ticagrelor period n=7,348	2007-2010 Clopidogrel period n=7,102	2012-2015 Ticagrelor period n=2,397	2007-2010 Clopidogrel period n=2,316	2012-2015 Ticagrelor period n=4,951	2007-2010 Clopidogrel period n=4,786
Clopidogrel	862 (11·7)	7,095 (99·9)	414 (17·3)	2,313 (99·9)	448 (9·0)	4,782 (99·9)
Ticagrelor	6,451 (87·8)	..	1,973 (82·3)	..	4,478 (90·4)	..
Prasugrel	35 (0·5)	7 (0·1)	10 (0·4)	3 (0·1)	25 (0·5)	4 (0·1)
Demographics						
Male sex	5,390 (73·4)	5,206 (73·3)	1,507 (62·9)	1,435 (62·0)	3,771 (78·4)	3,883 (78·8)
Age, median (Q1-Q3)	64 (55-73)	63 (55-72)	77 (73-81)	76 (73-81)	58 (51-64)	58 (51-64)
BMI group						
Underweight	93 (1·3)	69 (1·0)	45 (1·9)	48 (2·1)	48 (1·0)	21 (0·4)
Normal	1,861 (25·3)	1,436 (20·2)	767 (32·0)	559 (24·1)	1,094 (22·1)	877 (18·3)
Overweight	3,209 (43·7)	2,290 (32·2)	1,023 (42·7)	712 (30·7)	2,186 (44·2)	1,578 (33·0)
Obese	1,743 (23·8)	1,169 (16·5)	411 (17·1)	258 (11·1)	1,341 (27·1)	911 (19·0)
Missing	433 (5·9)	2,138 (30·1)	151 (6·3)	739 (31·9)	282 (5·7)	1,399 (29·2)
Smoking						
Active (vs. former/never)	2,906 (39·5)	2,398 (33·8)	498 (20·8)	460 (19·9)	2,408 (48·6)	1,938 (40·5)
Missing	438 (6·0)	1989 (28·0)	208 (8·7)	704 (30·4)	230 (4·6)	1,287 (26·9)
Procedure information						
PCI year						
2007	..	1,755 (24·7)	..	573 (24·7)	..	1,182 (24·7)
2008	..	1,796 (25·3)	..	574 (24·8)	..	1,222 (25·5)
2009	..	1,773 (25·0)	..	566 (24·4)	..	1,207 (25·2)
2010	..	1,778 (25·0)	..	603 (26·0)	..	1,175 (24·6)
2011	..	..	..	..	..	..
2012	1,810 (24·6)	..	586 (24·4)	..	1,224 (24·7)	..
2013	1,760 (23·9)	..	565 (23·6)	..	1,195 (24·1)	..
2014	1,856 (25·3)	..	619 (25·8)	..	1,237 (25·0)	..
2015	1,922 (26·2)	..	627 (26·2)	..	1,295 (26·2)	..
PCI indication						
STEMI (vs. non-STEMI/UAP)	3,658 (49·8)	3,967 (55·9)	1,063 (44·3)	1,216 (52·5)	2,595 (52·4)	2,751 (57·5)
Multivessel disease	2,709 (36·9)	2,829 (39·8)	1,115 (46·6)	1,185 (51·2)	1,594 (32·2)	1,644 (34·4)
Missing	11 (0·1)	19 (0·3)	8 (0·3)	8 (0·3)	3 (0·1)	11 (0·2)
Drug-eluting stent (at least one)	6,510 (88·7)	5,417 (76·3)	2,055 (85·7)	1,614 (69·7)	4,464 (90·2)	3,803 (79·5)
New generation drug-eluting stent	6,393 (87·0)	4,241 (59·7)	2,007 (83·7)	1,279 (55·2)	4,386 (88·6)	2,962 (61·9)

Table 1 *(Continued)*

	Overall		≥70 years		<70 years	
	2012-2015 Ticagrelor period n=7,348	2007-2010 Clopidogrel period n=7,102	2012-2015 Ticagrelor period n=2,397	2007-2010 Clopidogrel period n=2,316	2012-2015 Ticagrelor period n=4,951	2007-2010 Clopidogrel period n=4,786
Glycoprotein IIb/IIIa inhibitor	520 (7·1)	3,072 (43·3)	134 (5·6)	851 (36·7)	386 (7·8)	2,221 (46·4)
Bivalirudin	2,623 (35·7)	302 (4·3)	700 (29·2)	91 (3·9)	1,911 (38·7)	209 (4·4)
EMT call to cath lab	129 (1·8)	128 (1·8)	40 (1·7)	43 (1·9)	89 (1·8)	85 (1·8)
No. of treated lesions						
1	5,995 (81·6)	5,601 (78·9)	1,891 (78·9)	1,740 (75·1)	4,104 (82·9)	3,861 (80·7)
≥2	1,331 (18·1)	1,478 (20·8)	500 (20·9)	562 (24·3)	831 (16·9)	916 (19·1)
Lesions type B2 or C (at least one)	4,859 (66·1)	4,674 (65·8)	1,661 (69·3)	1,556 (67·2)	3,198 (64·6)	3,118 (65·1)
Radial arterial access	765 (10·4)	381 (5·4)	250 (10·4)	131 (5·7)	515 (10·4)	250 (5·2)
Comorbidity						
Hypertension	3,514 (47·8)	3,262 (45·9)	1,504 (62·7)	1,328 (57·3)	2,010 (40·6)	1,934 (40·4)
Heart failure	868 (11·8)	752 (10·6)	393 (16·4)	366 (15·8)	475 (9·6)	386 (8·1)
Diabetes	1,013 (13·8)	787 (11·1)	388 (16·2)	262 (11·3)	625 (12·6)	525 (11·0)
Renal disease	217 (3·0)	170 (2·4)	115 (4·8)	82 (3·5)	102 (2·1)	88 (1·8)
Atrial fibrillation	284 (3·9)	311 (4·4)	147 (6·1)	186 (8·0)	137 (2·8)	125 (2·6)
Peripheral artery disease	369 (5·0)	375 (5·3)	209 (8·7)	200 (8·6)	160 (3·2)	175 (3·7)
Previous MI	304 (4·1)	470 (6·6)	195 (8·1)	266 (11·5)	109 (2·2)	204 (4·3)
Chronic obstructive pulmonary disease	456 (6·2)	512 (7·2)	270 (11·3)	290 (12·5)	186 (3·8)	222 (4·6)
Cancer within last year	102 (1·4)	91 (1·3)	52 (2·2)	56 (2·4)	50 (1·0)	35 (0·7)
Ischaemic stroke	212 (2·9)	273 (3·8)	124 (5·2)	159 (6·9)	88 (1·8)	114 (2·4)
Transient ischaemic attack	120 (1·6)	145 (2·0)	70 (2·9)	85 (3·7)	50 (1·0)	60 (1·3)
Comedication						
Statin	6,996 (95·2)	6,713 (94·5)	2,192 (91·4)	2,146 (92·7)	4,804 (97·0)	4,567 (95·4)
High-intensity statin	4,615 (62·8)	280 (3·9)	1,259 (52·5)	67 (2·9)	3,356 (67·8)	213 (4·5)
Other lipid-lowering drugs	65 (0·9)	35 (0·5)	20 (0·8)	12 (0·5)	45 (0·9)	23 (0·5)
Betablocker	5,809 (79·1)	6,153 (86·6)	1,804 (75·5)	1,931 (83·6)	3,999 (80·8)	4,219 (88·2)
Calcium-channel blocker	1,532 (20·8)	1,416 (19·9)	718 (30·0)	667 (28·8)	814 (16·4)	749 (15·6)
Thiazide	741 (10·1)	985 (13·9)	397 (16·6)	493 (21·3)	344 (6·9)	492 (10·3)
Loop diuretics	899 (12·2)	967 (13·6)	542 (22·6)	570 (24·6)	357 (7·2)	397 (8·3)
ACE-inhibitor or ATII-receptor-blocker	3,648 (49·6)	3,698 (52·1)	1,381 (57·6)	1,340 (57·9)	2,267 (45·8)	2,358 (49·3)

***Table 1*: Baseline characteristics in patients treated before (2007-2010) versus after (2012-2015) the introduction of ticagrelor (before weighting and imputation of missing data). Data presented for the cohort overall and stratified by age (≥70 and <70 years).**

Abbreviations: ACE, angiotension converting enzyme; ATII, angiotensin II; BMI, body mass index; EMT, emergency medical team; MI, myocardial infarction; non-STEMI/UAP, non-ST-elevation myocardial infarction/ unstable angina pectoris; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Role of the funding source
This work was supported the Department of Cardiology, Aarhus University Hospital and the Department of Clinical Medicine, Aarhus University, Denmark. The funding sources had no role in study design, data collection, data analysis, interpretation, or writing of the report.

Ethical considerations
The study was approved by the Danish Data Protection Agency (record number 1-16-02-625-18). Danish registry-based research does not require ethical approval or informed consent from participants. All patient data were handled confidentially and pseudonymised prior to analysis.

Results

Patient characteristics
The study cohorts comprised of 14,450 patients. Of these, 7,348 were treated in 2012-2015 after introduction of ticagrelor (ticagrelor period) and 7,102 were treated in 2007-2010 before introduction ticagrelor (clopidogrel period) (Figure 2). In the ticagrelor period, 6,451 (87·8%) patients were treated with ticagrelor, 862 (11·7%) with clopidogrel, and 35 (0·5%) with prasugrel. In the clopidogrel period, 7,095 (99·9%) patients were treated with clopidogrel and the remaining patients with prasugrel. The implementation of ticagrelor in Denmark was fast and effective, with almost 80% of all first-time PCI-treated ACS patients redeeming a prescription for ticagrelor within 14 days of their procedure in 2012, reaching approximately 90% in the following years (Figure 1).

Baseline characteristics of patients in the ticagrelor and clopidogrel periods are provided in Table 1. In general, baseline characteristics were similar in the two periods in terms of age, sex, comorbidity, and comedication. Median age was 64 years in the ticagrelor period and 63 years in the clopidogrel period, with men comprising 73% of each cohort. Compared to patients treated in the clopidogrel period, those treated in the ticagrelor period presented more often with non-STEMI or unstable angina pectoris, had less multivessel disease, while a higher proportion were treated with drug-eluting stents (DES) including newer generation DES with increased procedural use of bivalirudin and decreased use of glycoprotein IIb/IIIa inhibitors. Diabetes, hypertension, heart failure, and use of high-intensity statins were slightly more frequent in the ticagrelor period, while prior ischaemic stroke and use of beta-blockers and thiazide diuretics were more frequent in the clopidogrel period.

In the ticagrelor period, the proportion of ticagrelor users was lower among patients ≥70 years (1,973/2,397, 82%) than among patients <70 years (4,478/4,951, 90%). Elderly patients were more likely to be women, to have comorbidities, and to have non-STEMI or unstable angina pectoris, while active smoking and obesity were more frequent among younger patients. All covariates were balanced adequately in weighted analyses with standardised mean differences <0·10 (Supplemental Figures S1-S3).

Overall outcomes
The 1-year risk of MACE was similar between the two treatment periods with 413 events in the ticagrelor period vs. 424 events in the clopidogrel period (cumulative incidence percentage [CIP] 5·6% vs. 6·0% in the clopidogrel period; wIRR 1·06, 95% confidence interval [CI] 0·92-1·22). The 1-year risk of hospitalisation for bleeding was also similar between the two periods (335 vs. 309 events; CIP 4·6% vs. 4·4%; wIRR 1·05, 95% CI 0·89-1·23). The individual risks of all-cause death, myocardial infarction, and ischaemic stroke were comparable in the two cohorts (Table 2 and Figure 3). Overall, the main results were robust in subgroup and sensitivity analyses including the propensity score weighting method using standardised mortality ratio weights (Figures 4-5, Supplemental Table S6). However, the risk of hospitalisation for bleeding tended to be higher in the ticagrelor period among women (Figure 5).

Outcomes in patients aged above and below 70 years
In patients aged ≥70 years, 1-year MACE occurred in 224 patients in the ticagrelor period and 247 patients in the clopidogrel period (CIP 9·4% vs. 10·7%; wIRR 0·98, 95% CI 0·81-1·19). In patients aged <70 years, risks of MACE were also similar with 189 events in the ticagrelor period and 177 events in the clopidogrel period (CIP 3·8% vs. 3·7%; wIRR 1·12, 95% CI 0·90-1·38). Risks of bleeding were similar between treatment periods for patients above and below 70 years with 167 events in the ticagrelor period vs. 163 events in the clopidogrel period in patients aged ≥70 years (CIP 7·0% vs. 7·0%; wIRR 0·94, 95% CI 0·75-1·19) and 168 vs. 146 events in patients aged <70 years (CIP 3·4% vs. 3·1%; wIRR 1·15, 95% CI 0·92-1·45). Results remained robust in sensitivity analyses (Supplemental Table S6).

Treatment adherence and drug switching
The number of patients adherent to any P2Y12 inhibitor was 6,188 (84·2%) in the ticagrelor period and 6,336 (89·2%) in the clopidogrel period (Supplemental Table S4). The absolute difference in adherence was -6·3% in the subgroup aged <70 years (ticagrelor period 83·2% vs. clopidogrel period 89·5%) and -2·4% in the subgroup aged ≥70 years (ticagrelor period 86·3% vs. clopidogrel period 88·6%). In the ticagrelor period, 1,002 (13·6%) patients switched to another P2Y12 inhibitor

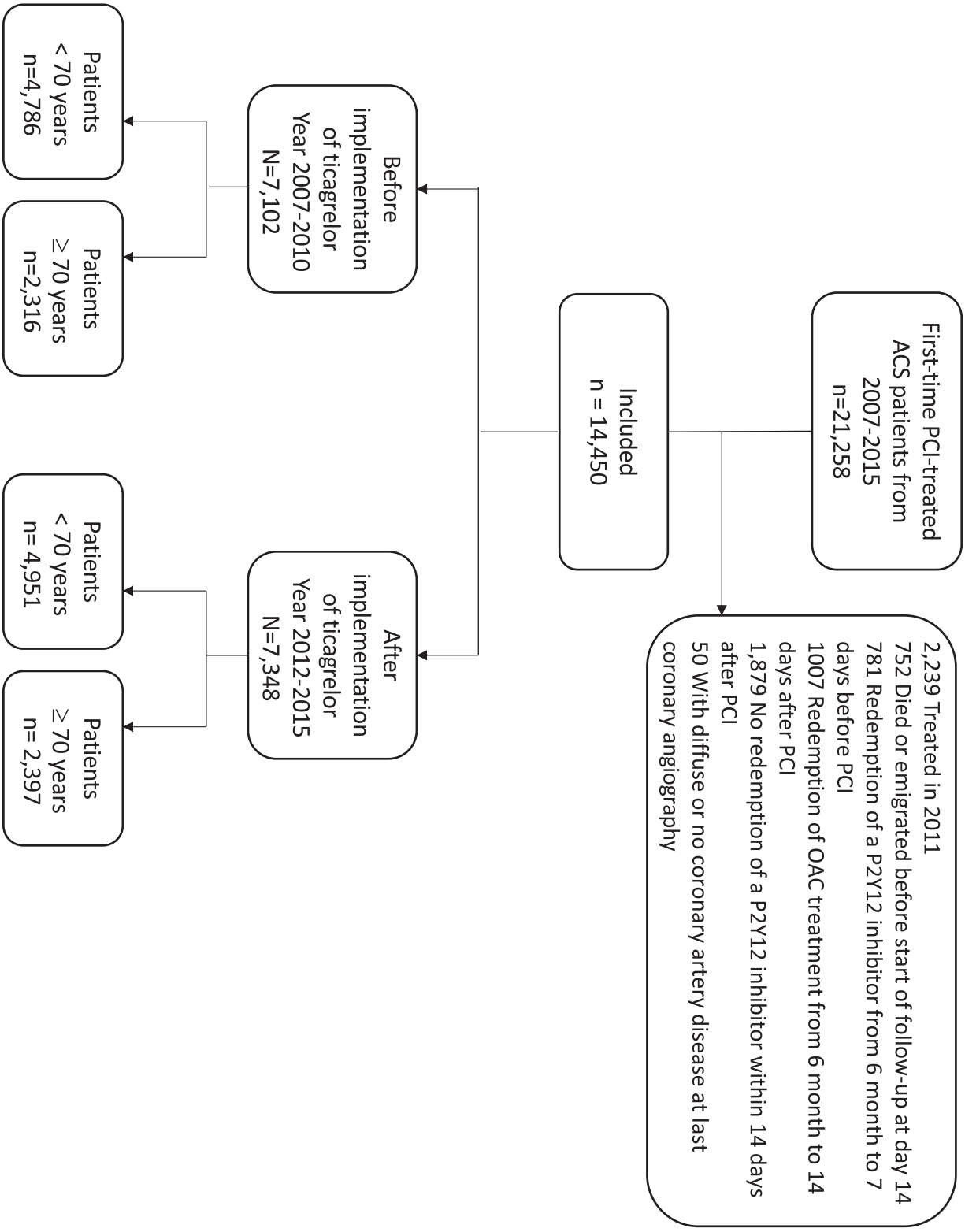

Figure 2. Patient selection.
Abbreviations: ACS, acute coronary syndrome; OAC, oral anticoagulant treatment; PCI, percutaneous coronary intervention.

	2012-2015 Ticagrelor period n=7,348		2007-2010 Clopidogrel period (reference) n=7,102			
	Events, n	CIP (95% CI)	Events, n	CIP (95% CI)	Crude IRR (95% CI)	IPTW IRR (95% CI)
Overall cohort						
MACE	413	5·62 (5·12-6·17)	424	5·97 (5·44-6·55)	0·94 (0·82-1·08)	1·06 (0·92-1·22)
Myocardial infarction	211	2·87 (2·51-3·27)	218	3·07 (2·69-3·49)	0·93 (0·77-1·13)	1·04 (0·85-1·27)
Death	190	2·59 (2·25-2·98)	203	2·86 (2·50-3·27)	0·90 (0·74-1·10)	1·05 (0·85-1·29)
Ischaemic stroke	38	0·52 (0·37-0·70)	57	0·80 (0·62-1·03)	0·64 (0·43-0·97)	0·75 (0·49-1·16)
Hospitalisation for bleeding	335	4·56 (4·10-5·05)	309	4·35 (3·89-4·84)	1·05 (0·90-1·22)	1·05 (0·89-1·23)
≥70 years	n=2,397		n=2,316			
MACE	224	9·35 (8·25-10·58)	247	10·66 (9·48-11·99)	0·87 (0·72-1·04)	0·98 (0·81-1·19)
Myocardial infarction	91	3·80 (3·08-4·62)	102	4·40 (3·62-5·29)	0·86 (0·64-1·14)	1·00 (0·75-1·41)
Death	136	5·67 (4·82-6·68)	148	6·39 (5·47-7·47)	0·88 (0·70-1·12)	1·00 (0·78-1·28)
Ischaemic stroke	18	0·75 (0·46-1·17)	40	1·73 (1·26-2·32)	0·43 (0·25-0·75)	0·47 (0·26-0·84
Hospitalisation for bleeding	167	6·97 (5·99-8·03)	163	7·04 (5·99-8·03)	0·98 (0·79-1·21)	0·94 (0·75-1·19)
< 70 years	n=4,951		n=4,786			
MACE	189	3·82 (3·32-4·39)	177	3·70 (3·20-4·27)	1·03 (0·84-1·27)	1·12 (0·90-1·38)
Myocardial infarction	120	2·42 (2·02-2·88)	116	2·42 (2·02-2·89)	1·00 (0·77-1·29)	1·08 (0·83-1·41)
Death	54	1·09 (0·84-1··42)	55	1·15 (0·88-1·49)	0·95 (0·65-1·38)	1·00 (0·66-1·49)
Ischaemic stroke	20	0·40 (0·26-0·62)	17	0·36 (0·22-0·56)	1·14 (0·60-2·17)	1·41 (0·71-2·79)
Hospitalisation for bleeding	168	3·40 (2·92-3·93)	146	3·05 (2·59-3·57)	1·12 (0·89-1·39)	1·15 (0·92-1·45)

***Table 2*: Crude and weighted analyses of treatment before (2007-2010) versus after (2012-2015) the introduction of ticagrelor in the overall cohort.**

MACE is a composite of death, myocardial infarction, and ischaemic stroke.

Abbreviations: CI, confidence interval; CIP, cumulative incidence percentages; IPTW, inverse probability treatment weights; IRR, incidence rate ratio; MACE, major adverse cardiac events.

during 1-year follow-up. The rate of switching in the clopidogrel period was low (0·3%) but at that time no other P2Y12 inhibitor was available. Among patients switching drugs in the ticagrelor period, 96% switched from ticagrelor to clopidogrel (Supplemental Tables S4 and S5).

Discussion

We examined the effectiveness and safety of the implementation of ticagrelor during the transition from clopidogrel to ticagrelor as standard care for patients with ACS undergoing first-time PCI in Western Denmark. Overall, when comparing the clopidogrel and ticagrelor periods, risks of adverse ischaemic outcomes and hospitalisation for bleeding remained practically unchanged, indicating that the implementation of ticagrelor was not associated with substantial clinical improvements. Results were consistent in patients aged above and below 70 years, as well as in a number of subgroups and sensitivity analyses. A unique feature of our study is that we examined the *implementation* of ticagrelor by comparing two four-year periods separated by the widespread initiation of ticagrelor in 2011. In contrast, previous studies compared outcomes in patients treated with either ticagrelor or clopidogrel and subsequently adjusted for potential confounding factors.[6,8,21,23] Our study design was possible due to the effective implementation of ticagrelor of 87·8% in the ticagrelor period. This is substantially higher than the 24%-49% treatment rates reported in previous studies.[6,7,22,23] While our study did not find the expected improvements in ischaemic outcomes following the results of the PLATO trial,[3] our findings concur with most previously published observational data,[6,8,21,23] and the recently published randomised POPular AGE trial focusing on non-STEMI patients above 70 years.[9]

We acknowledge the principle that randomised trials provide the highest level of evidence. Still, it is generally accepted that most randomised trials may have limitations in terms of the external validity due to strict inclusion and exclusion criteria, as well as a tendency to include patients who are likely to be compliant with the study protocol.[5] Thus, phase IV studies assessing the effect of implementation of evidence-based treatments in unselected cohorts are of interest. Based on the large relative difference of 16% in MACE in the PLATO trial, we had expected that the implementation of ticagrelor in PCI-treated ACS patients in a non-randomized setting would translate into an ischaemic benefit in the ticagrelor period.

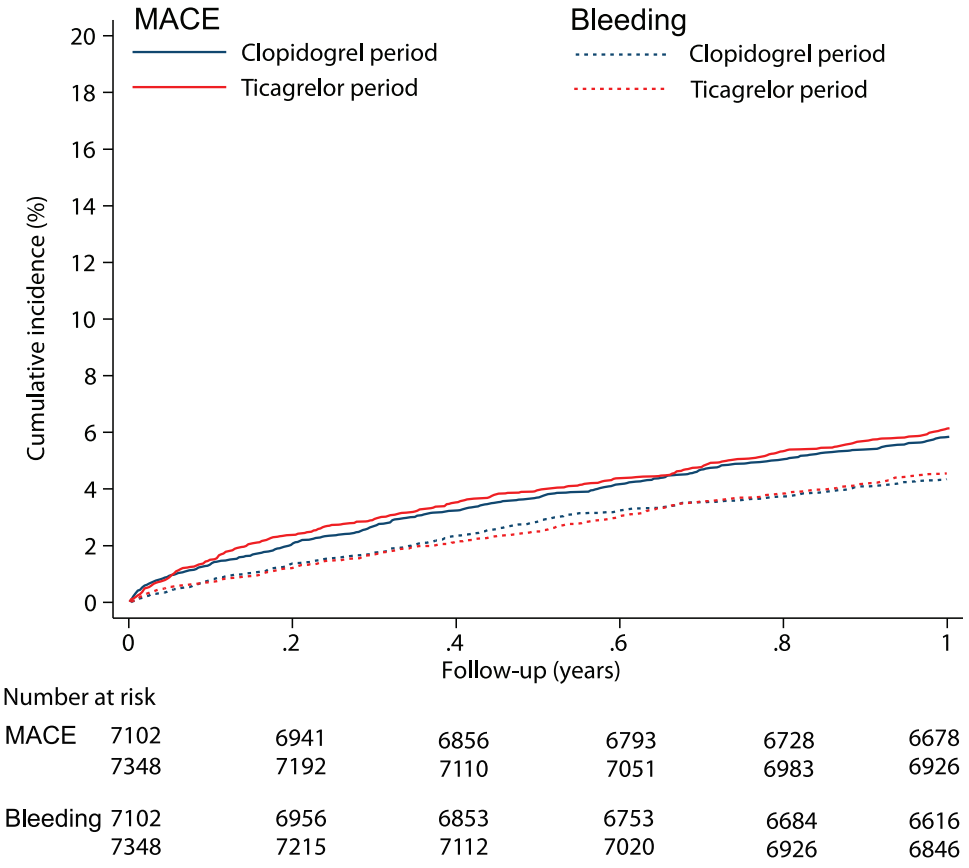

Figure 3. Weighted cumulative incidence curves of MACE and hospitalisation for bleeding in patients treated with PCI in the clopidogrel period (2007-2010) and ticagrelor period (2012-2015).

Weighted cumulative incidence curves using stabilised inverse propability of treatment weights. MACE is a composite of all-cause death, myocardial infarction, or ischaemic stroke.

Abbreviation: MACE, major adverse cardiac events.

However, there are several differences between the PLATO trial and our observational study, which may explain why we could not translate the ischaemic benefit of the PLATO trial into a reduced risk of ischaemic outcomes in our pre-post observational study. The PLATO trial included patients from all major continents,[3,24] while our study was undertaken in Denmark. The standards of care and cardiovascular mortality rates differ between countries and continents, which might impact clinical outcomes. A subgroup analysis of North American participants in the PLATO trial did not indicate a benefit of ticagrelor in this subgroup.[3,24] Western Europe was in these subgroup analyses not singled out but combined with Eastern Europe, the Middle East, and Africa. However, since the standards of care and cardiovascular mortality rates in Western Europe (*i.e.*, including Denmark) and North America are considered comparable and may differ in many aspects from other parts of the world, stronger platelet inhibition may be of less benefit in these lower-risk countries.[7-9]

We studied a large population-based cohort of ACS patients undergoing first-time PCI. In PLATO, 64% of participants underwent PCI and only 18% of PLATO participants received DES as compared to 76% use of DES in our clopidogrel period.[3] While a PLATO substudy showed comparable results in patients intended for non-invasive and invasive management,[25] we cannot exclude the possibility that the increasing use of DES after the PLATO trial may have diminished the effect of ticagrelor treatment in patients undergoing PCI. The 1-year event rates were substantially higher in the PLATO trial than in our study (PLATO: ticagrelor 10·2% vs. clopidogrel 12·3%; our study: ticagrelor period 5·6% vs. clopidogrel period 6·0%). This difference might reflect that our patients were first-time PCI-treated patients and included 14 days after PCI – as compared to five hours after hospitalisation in PLATO[3] – to allow for redemption of a prescription for a P2Y12 inhibitor. In this regard, it is important that the event rates in PLATO gradually diverged *after* the first ≈14 days,[3] an observation that we could not reproduce in our cohort.

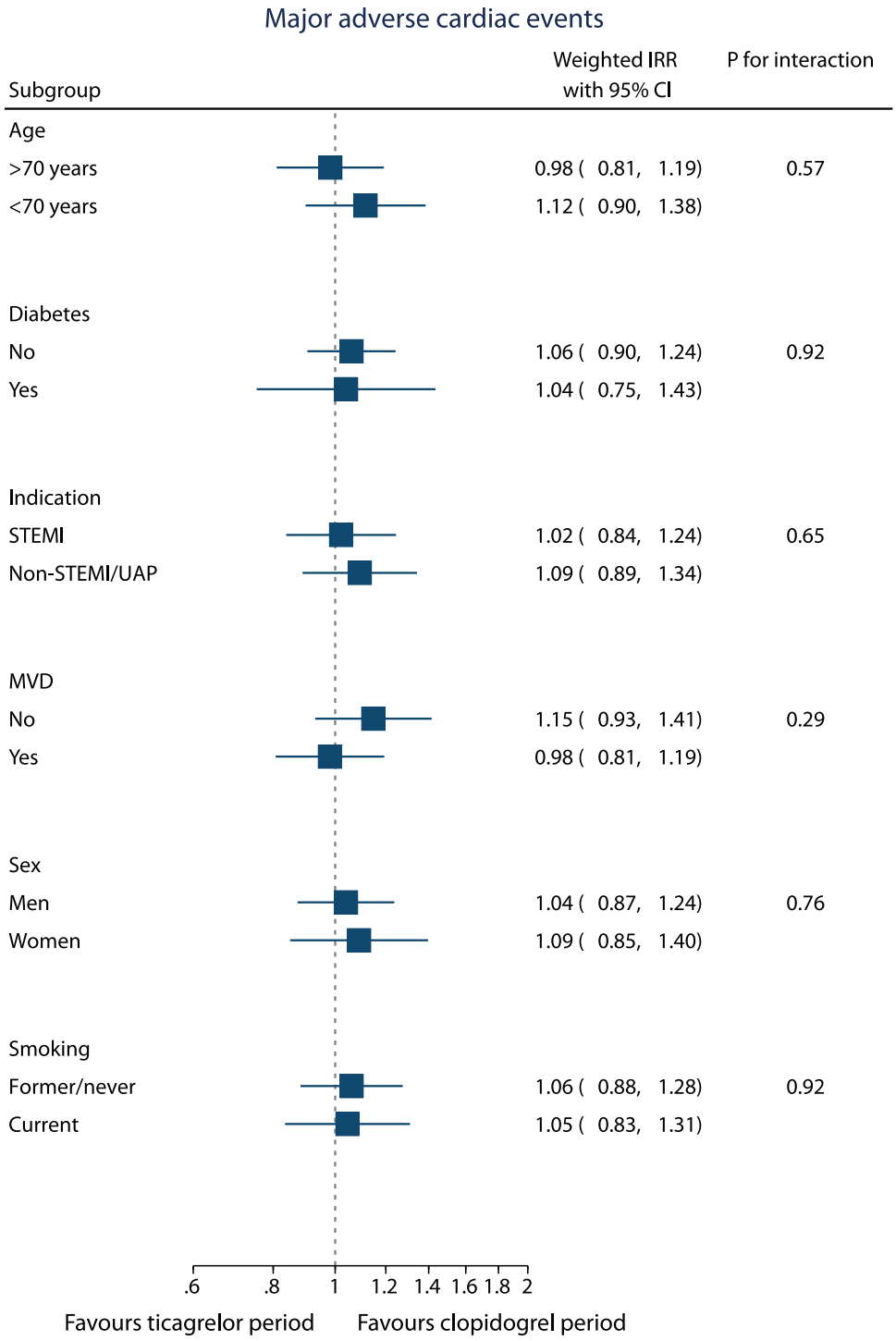

Figure 4. Subgroup analysis forMACE.

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; MVD, multi-vessel disease; Non-STEMI/UAP, non-ST-elevation myocardial infarction/ unstable angina pectoris; STEMI, ST-elevation myocardial infarction.

Moreover, considering differences in cardiovascular mortality between countries, a lower event rate in Denmark would be expected compared to the average event rate reported in PLATO.[26]

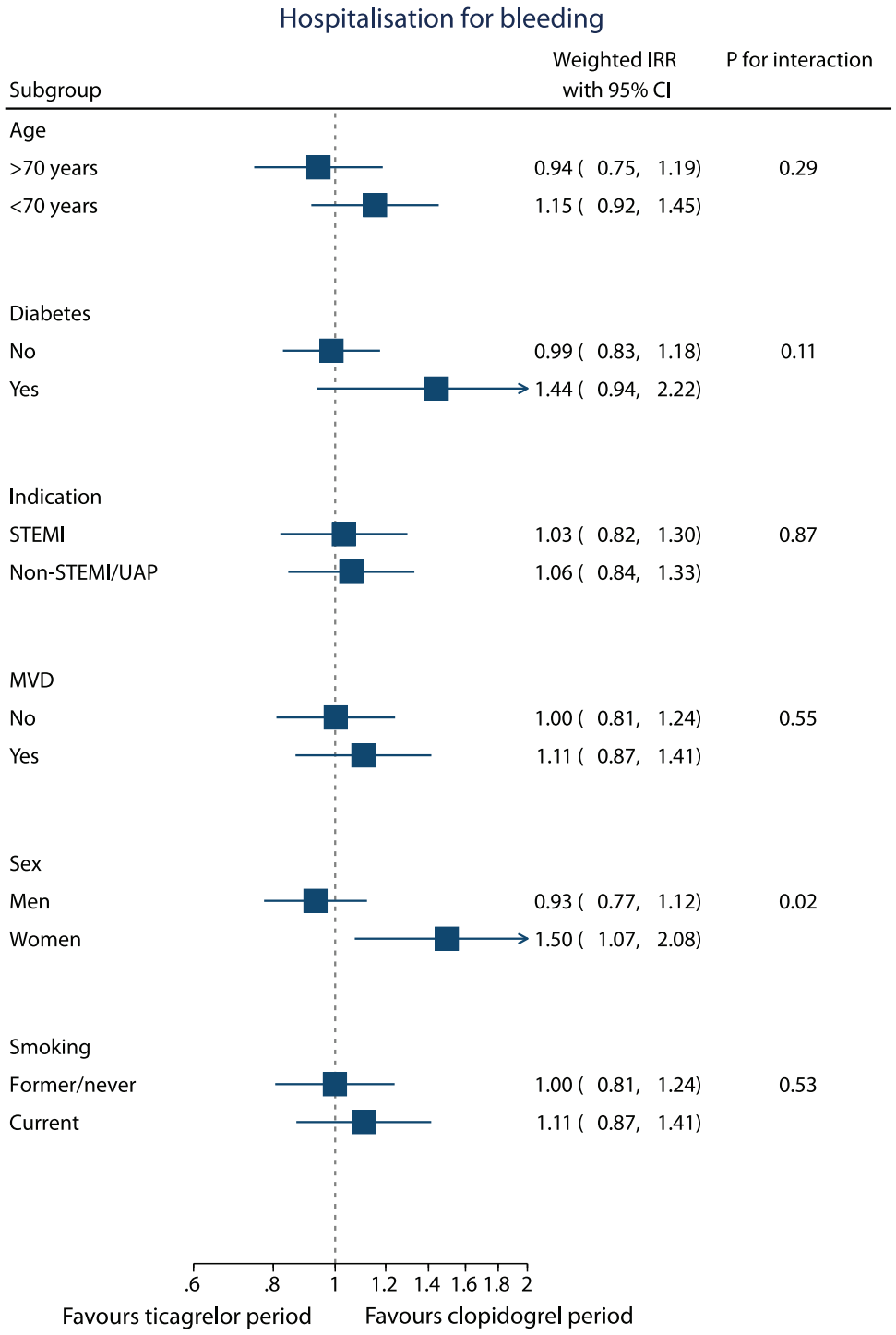

Figure 5. Subgroup analysis for hospitalisation for bleeding.

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; MVD, multi-vessel disease; Non-STEMI/UAP, non-ST-elevation myocardial infarction/ unstable angina pectoris; STEMI, ST-elevation myocardial infarction.

Patients in our study were older, with 20% of patients aged ≥75 years compared to approximately 15% in the PLATO trial. Still, the lack of benefit with ticagrelor was present even when we restricted our analysis to patients aged <70 years. Other differences might be explained by increased rates of drug switching and non-adherence. In our study, treatment adherence was high in general, but nonetheless declined by 5% after

introduction of ticagrelor. In daily clinical practice non-adherence is multifactorial and may be related to several factors such as ticagrelor being more expensive than clopidogrel, twice-daily vs. single dosing regimens, and risk of minor bleeds and adverse effects such as dyspnoea.[3,9] It is noteworthy that 13·6% of patients in the ticagrelor period switched to another P2Y12 inhibitor (96% to clopidogrel), which matches the rate of dyspnoea in the ticagrelor group in the PLATO trial as well as the switch rate in the ISAR-REACT 5 trial.[3,27]

We cannot rule out that the 12% of patients receiving clopidogrel in our ticagrelor period counterbalanced a potential benefit of ticagrelor. Although the 87·8% uptake rate in our cohort is by far the highest reported so far,[6,7,21,22] we conclude that this high-level implementation did not improve clinical outcomes.

Other changes in treatment have evolved during the time period from 2007 to 2015, including implementation of newer-generation DESs and high-intensity statin treatment. Despite these improvements, which in general would favour the patients included in the late period in our study (i.e. the ticagrelor period), we were unable to identify a risk reduction following the implementation of ticagrelor, which questions the benefit of ticagrelor treatment in Danish patients. The overall benefit has also been questioned in recent observational studies.[6-8] The largest of these, a registry-based study using South Korean and American data on 189,579 ACS patients treated with PCI from 2011-2019, showed no difference in the combined outcome of ischemia and bleeding at 12-month follow-up.[6] In secondary analyses, the risks of bleeding and dyspnoea were increased with ticagrelor. Similarly, a Canadian cohort study including ACS patients from 2012-2016 showed no difference in adjusted MACE risk, but an increased bleeding risk with ticagrelor at 12-month follow-up.[7] None of these studies assessed *implementation* of ticagrelor, but rather compared ticagrelor-treated vs. clopidogrel-treated patients following availability of ticagrelor. Since physicians tend to prescribe clopidogrel to patients with increased age, comorbidity, and frailty, confounding by indication may be a problem in these studies, especially since the proportions of ticagrelor-treated patients were low (24%[6] and 37% [7]) and clopidogrel-treated patients were older and had more comorbidities than ticagrelor-treated patients.[6,7] The risk of confounding by indication is avoided in a pre-post study design like ours. Only one smaller (n=2,062) single centre study has previously used a similar study design to assess implementation of ticagrelor in ACS patients, and reported an increased risk of net adverse clinical and cerebral events in the ticagrelor period, driven by an increased risk of major bleeding while rates of myocardial infarction and death did not differ.[28] The pre-post design implies that we cannot exclude the possibility that more complex patients were treated in the 2012-2015 period than the former period. However, our data do not support this possibility as we found a higher prevalence of patients with STEMI and multivessel disease in the 2007-2010 period and comparable rates of multivessel PCI and complex (type B2/C) lesions. Furthermore, we used a propensity score weighting method to account for the differences in patients' characteristics.

In our study, we observed no benefit of ticagrelor implementation in patients ≥70 years, consistent with results from the randomized POPular AGE trial focusing on non-STEMI patients, which was limited by its size (n=1,002) and a substantial rate of discontinuation or switching in the ticagrelor group (47%).[9] Further, Swedish registry data on elderly patients aged ≥80 years showed no difference in 1-year risk of ischaemic outcomes when comparing ticagrelor with clopidogrel, but did find an increased risk of bleeding and all-cause death among ticagrelor-treated patients.[21] Bleeding rates in the POPular AGE study were strikingly higher than in our study (POPular AGE: ticagrelor 24% vs. clopidogrel 18%; our study: ticagrelor period 7% vs. clopidogrel period 7%). This likely reflects inclusion of patients on oral anticoagulant treatment in the POPular AGE trial, differing definitions of bleeding, and the start of follow-up 14 days after PCI in our study. Further, our bleeding endpoint is defined as bleedings leading to hospitalisation which thereby reflects a more severe type of bleeding and does not capture minor bleeds. This definition may be comparable to the definition of major bleeding in the PLATO trial and the PLATO substudy in patients above and below 75 years of age by Husted et al., where no difference in bleeding between ticagrelor and clopidogrel was found.[29,30] In contrast, minor bleeds leading to contacts with primary care were included in the POPular AGE trial.[9] We had expected a benefit of ticagrelor in patients below 70 years given their lower bleeding risk, but even among younger patients, ticagrelor use was not associated with improved outcomes despite higher treatment adherence and fewer switches from ticagrelor to clopidogrel compared to the elderly.

Finally, although our study did not include a formal cost-benefit analysis, the lack of improved clinical outcome, combined with an approximately 20-30 times higher price for ticagrelor compared to clopidogrel, suggest that the change in P2Y12 inhibitor strategy was not cost-effective in Denmark.

Conclusion

Ticagrelor was rapidly and effectively implemented in Denmark as the standard of care for ACS patients treated with first-time PCI. However, the implementation of ticagrelor was not associated with improved clinical outcomes which questions the superiority of ticagrelor over clopidogrel in these patients. Future randomised clinical trials may assess if very early de-escalation, i.e. within days from PCI, from ticagrelor to clopidogrel is safe and cost-effective.

Declaration of interests

MW reports lecture fees from BMS/Pfizer. MiM has received lecture and/or advisory board fees from Novo Nordisk. SDK reports lecture fees from Astra/Zeneca. All remaining authors have no conflicts to report.

Contributors

PGT took part in study planning, analysed the data, and wrote the first draft of the manuscript. MiM designed the study, supervised data processing, and critically reviewed the manuscript. SDK, TT, and KKWO took part in study design and interpretation, supervised data processing, and critically reviewed the manuscript. MoM provided statistical advice and critically reviewed the manuscript. KKWO verified the data reported. MW, CG, BR, LOJ, and HTS took part in interpretation of data and critically reviewed the manuscript.

Data availability statement

Open access to data is not allowed by the Danish Data Protection Agency. However, given a reasonable request, additional analyses can be conducted after contacting the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanepe.2021.100301.

References

1 Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology. *(ESC)* 2017: 119–77. https://doi.org/10.1093/eurheartj/ehx393.

2 Collet J-P, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2020.

3 Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**(11):1045–57.

4 Wiviott SD, Antman EM, Gibson CM, et al. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). *Am Heart J* 2006;**152**(4):627–35.

5 Sørensen HT, Lash TL, Rothman KJ. Beyond randomized controlled trials: a critical comparison of trials with nonrandomized studies. *Hepatology* 2006;**44**(5):1075–82.

6 You SC, Rho Y, Bikdeli B, et al. Association of Ticagrelor vs Clopidogrel With Net Adverse Clinical Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. *JAMA* 2020;**324**(16):1640.

7 Turgeon RD, Koshman SL, Youngson E, et al. Association of Ticagrelor vs Clopidogrel With Major Adverse Coronary Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. *JAMA Intern Med* 2020;**180**(3):420–8.

8 Völz S, Petursson P, Odenstedt J, et al. Ticagrelor is Not Superior to Clopidogrel in Patients With Acute Coronary Syndromes Undergoing PCI: A Report from Swedish Coronary Angiography and Angioplasty Registry. *J Am Heart Assoc* 2020;**9**(14):e015990.

9 Gimbel M, Qaderdan K, Willemsen L, et al. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. *Lancet* 2020;**395**(10233):1374–81.

10 Schmidt M, Maeng M, Madsen M, Sorensen HT, Jensen LO, Jakobsen CJ. The Western Denmark Heart Registry: Its Influence on Cardiovascular Patient Care. *J Am Coll Cardiol* 2018;**71**(11):1259–72.

11 Egholm G, Madsen M, Thim T, et al. Evaluation of algorithms for registry-based detection of acute myocardial infarction following percutaneous coronary intervention. *Clin Epidemiol* 2016;**8**:415–23.

12 Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology* 2007;**28**(3):150–4.

13 Sundboll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016;**6**(11):e012832.

14 Sørensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet* 2009;**374**(9706):1967–74.

15 Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol* 2012;**41**(3):861–70.

16 Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;**159**(7):702–6.

17 Sato T, Matsuyama Y. Marginal structural models as a tool for standardization. *Epidemiology* 2003;**14**(6):680–6.

18 Stürmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. *J Intern Med* 2014;**275**(6):570–80.

19 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;**30**(4):377–99.

20 Leyrat C, Seaman SR, White IR, et al. Propensity score analysis with partially observed covariates: How should multiple imputation be used? *Stat Methods Med Res* 2019;**28**(1):3–19.

21 Szummer K, Montez-Rath ME, Alfredsson J, et al. Comparison Between Ticagrelor and Clopidogrel in Elderly Patients With an Acute Coronary Syndrome. *Circulation* 2020;**142**(18):1700–8.

22 Schmucker J, Fach A, Mata Marin LA, et al. Efficacy and Safety of Ticagrelor in Comparison to Clopidogrel in Elderly Patients With ST-Segment-Elevation Myocardial Infarctions. *J Am Heart Assoc* 2019;**8**(18):e012530.

23 Sahlén A, Varenhorst C, Lagerqvist B, et al. Outcomes in patients treated with ticagrelor or clopidogrel after acute myocardial infarction: experiences from SWEDEHEART registry. *Eur Heart J* 2016;**37**(44):3335–42.

24 Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation* 2011;**124**(5):544–54.

25 James SK, Roe MT, Cannon CP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. *Bmj* 2011;**342**:d3527.

26 Thim T, Maeng M, Kaltoft A, et al. Zotarolimus-eluting vs. sirolimus-eluting coronary stents in patients with and without acute coronary syndromes: a SORT OUT III substudy. *Eur J Clin Invest* 2012;**42**(10):1047–54.

27 Schüpke S, Neumann FJ, Menichelli M, et al. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. *N Engl J Med* 2019;**381**(16):1524–34.

28 Zocca P, van der Heijden LC, Kok MM, et al. Clopidogrel or ticagrelor in acute coronary syndrome patients treated with newer-generation drug-eluting stents: CHANGE DAPT. *EuroIntervention* 2017;**13**(10):1168–76.

29 Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**(11):1045–57.

30 Husted S, James S, Becker RC, et al. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes. *Circ Cardiovasc Qual Outcomes* 2012;**5**(5):680–8.