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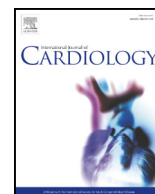
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Clopidogrel in noncarriers of CYP2C19 loss-of-function alleles versus ticagrelor in elderly patients with acute coronary syndrome: A pre-specified sub analysis from the POPular Genetics and POPular Age trials CYP2C19 alleles in elderly patients

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ABSTRACT

Background: Patients with acute coronary syndrome (ACS) who are carrying CYP2C19 loss-of-function alleles derive less benefit from clopidogrel treatment. Despite this, in elderly patients, clopidogrel might be preferred over more potent P2Y₁₂ inhibitors due to a lower bleeding risk. Whether CYP2C19 genotype-guided antiplatelet treatment in the elderly could be of benefit has not been studied specifically.

Methods: Patients aged 70 years and older with known CYP2C19*2 and *3 genotype were identified from the POPular Genetics and POPular Age trials. Noncarriers of loss-of-function alleles treated with clopidogrel were compared to patients, irrespective of CYP2C19 genotype, treated with ticagrelor and to clopidogrel treated carriers of loss-of-function alleles. We assessed net clinical benefit (all-cause death, myocardial infarction, stroke and Platelet Inhibition and Patient Outcomes (PLATO) major bleeding), atherothrombotic outcomes (cardiovascular

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Pharmacogenetics
P2Y₁₂
Older
Genotyping

death, myocardial infarction, stroke) and bleeding outcomes (PLATO major and minor bleeding).

Results: A total of 991 patients were assessed. There was no significant difference in net clinical benefit (17.2% vs. 15.1%, adjusted hazard ratio (adjHR) 1.05, 95% confidence interval (CI) 0.77–1.44), atherothrombotic outcomes (9.7% vs. 9.2%, adjHR 1.00, 95%CI 0.66–1.50), and bleeding outcomes (17.7% vs. 19.8%, adjHR 0.80, 95%CI 0.62–1.12) between clopidogrel in noncarriers of loss-of-function alleles and ticagrelor respectively.

Conclusion: In ACS patients aged 70 years and older, there was no significant difference in net clinical benefit and atherothrombotic outcomes between noncarriers of a loss-of-function allele treated with clopidogrel and patients treated with ticagrelor. The bleeding rate was numerically; though not statistically significant, lower in patients using clopidogrel.

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1. Introduction

In patients with acute coronary syndrome (ACS), dual antiplatelet therapy (DAPT) plays an essential role in preventing recurrent atherothrombotic events [1]. Although clopidogrel is still widely used in combination with aspirin, The Platelet Inhibition and Patient Outcomes (PLATO) [2] and Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction (TRITON TIMI) 38³ trials demonstrated superiority of ticagrelor and prasugrel, respectively, over clopidogrel in preventing atherothrombotic events in patients with ACS. Therefore, current guidelines favor these more potent platelet inhibitors over clopidogrel [4,5]. However, patients treated with ticagrelor or prasugrel are at a higher bleeding risk compared to patients treated with clopidogrel [2,3], which is even more pronounced in elderly patients [6]. The Clopidogrel versus Ticagrelor or Prasugrel in Patients Aged 70 years or older with non-ST-elevation Acute Coronary Syndrome (POPular Age) trial showed that in elderly patients, DAPT with clopidogrel has similar results as DAPT with the more potent platelet inhibitors in terms of ischemic events, while bleeding events were lower [7].

Clopidogrel is a prodrug which is converted to its active metabolite by CYP P450 hepatic enzymes [8]. Approximately 30% of the Caucasian population show an inadequate response to clopidogrel when measured with platelet function tests, which is associated with a worse clinical outcome [9]. At least part of this variation in drug efficacy can be explained by genetic variations, of which the *CYP2C19**2 and *3 loss-of-function alleles are the most important [10]. For ticagrelor and prasugrel no relevant gene-drug interaction have been found [11,12]. Although the correlation of *CYP2C19* genotype and clinical outcome was not assessed in the POPular Age trial so far, it can be hypothesized that also in elderly patients *CYP2C19* genotype influences the balance between benefit and harm when the more potent P2Y₁₂ inhibitors are prescribed in comparison to clopidogrel.

A strategy in which the antiplatelet treatment was chosen based on *CYP2C19* genotype, although in a cohort of patients with ST-segment elevation myocardial infarction (STEMI), was evaluated in the The Genotype-Guided Antiplatelet Therapy in ST-Segment Elevation Myocardial Infarction Patients – Patient Outcome after Primary Percutaneous Coronary Intervention (POPular Genetics) trial [13]. In this trial, a genotype-guided strategy was found to be non-inferior compared to standard treatment with ticagrelor or prasugrel for a net clinical benefit outcome and ischemic events, while bleeding events were lower. While both atherothrombotic and bleeding event rates are higher in elderly patients, and bleeding events have shown to be strongly correlated to a worse clinical outcome [14], the use of genetic testing may improve clinical decision making in selecting patients who benefit most from clopidogrel versus prasugrel or ticagrelor treatment.

In the present analysis, containing ACS patients aged 70 years and older derived from the POPular Age and POPular Genetics trial cohorts, we compare the use of clopidogrel in noncarriers of *CYP2C19* loss-of-function alleles with ticagrelor, irrespective of *CYP2C19* genotype and we assess the effect of *CYP2C19* loss-of-function alleles in clopidogrel treated elderly patients.

2. Methods

2.1. Study design

The detailed design and results of the POPular Age and POPular Genetics trials have been published previously [15,16]. In brief, the POPular Genetics trial was an open label, assessor blinded, randomized controlled trial performed in 10 centers in the Netherlands, Belgium and Italy. Between 2012 and 2018, 2488 patients with STEMI undergoing primary PCI aged 21 years and older were included. Patients were randomized within 48 h of primary PCI to either a standard treatment arm (treatment with ticagrelor or prasugrel for one year), or to the genotype-guided arm (treatment adjustment after rapid *CYP2C19* genetic testing). In the genotype-guided arm, patients carrying a *CYP2C19**2 or *3 loss-of-function allele were treated with ticagrelor or prasugrel, while noncarriers (*1/*1) were treated with clopidogrel. The POPular Age trial was an open label, assessor blinded, randomized controlled trial performed in 12 centers in the Netherlands. Between 2013 and 2018, 1002 patients with non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina aged 70 years and older were included. Within 72 h after hospital admission, patients were randomized to either treatment with clopidogrel, or to treatment with ticagrelor or prasugrel. In both trials, follow-up duration was 12 months. An institutional review board at all study sites approved the trials and all patients provided written informed consent.

In both trials, blood samples were collected for genotyping purposes, although only the samples derived from patients in the genotyping arm of the POPular Genetics trial were genotyped prospectively. All other samples were genotyped after study completion for the *CYP2C19**2 and *3 loss-of-function alleles. In the POPular Age trial, blood samples were not collected in all participating hospitals and are therefore not available for all patients. Genotyping was performed by LGC Biosearch Technologies (Hoddesdon, United Kingdom) using a KASP genotyping assay.

2.2. Statistical analysis

The current analysis was pre-specified in both trials, although this sub-analysis was not prospectively powered. Therefore, the number of patients is based on the available patients of 70 years and older in whom *CYP2C19* genotype was available in the study cohorts. The following outcome parameters were assessed: (1) a net clinical benefit outcome, consisting of all-cause death, myocardial infarction, stroke and PLATO major bleeding; (2) an atherothrombotic outcome, consisting of cardiovascular death, myocardial infarction and stroke; and (3) a bleeding outcome, consisting of PLATO major and minor bleeding. Other outcomes were the individual components of the composite outcomes. The outcome definitions were identical to the definitions used in both main trials, in which a blinded event committee adjudicated all adverse clinical events.

The current analysis compared noncarriers of the *CYP2C19**2 and *3 alleles treated with clopidogrel to patients treated with ticagrelor. A small number of prasugrel treated patients was therefore excluded. A modified intention-to-treat analysis was performed in which patients

were divided in a clopidogrel or a ticagrelor treated group, based on the drug that was prescribed at discharge after the index hospital admission. Two additional analyses were performed. An on-treatment analysis, in which patients were censored if they discontinued or switched P2Y₁₂ inhibitor therapy and an analysis in which patients treated with oral anticoagulation were excluded. Additionally, outcomes in clopidogrel treated patients were assessed according to *CYP2C19* loss-of-function allele carrier status and we assessed outcomes in the subgroups of the POPular Age and POPular Genetics trial separately.

Variables are presented as number (percentages) and mean \pm standard deviation, or median with an interquartile range. Missing data was not imputed. Time-to-event curves were constructed using the Kaplan-Meier method. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox proportional-hazard models. To adjust for possible confounders, all baseline characteristics with a *p*-value <0.10 were selected for univariate regression analysis. If there was a significant interaction (*p* < 0.05) in the univariate analysis, they were selected for multivariable regression analysis. The final model included only those characteristics with a significant interaction in the multivariable analysis. *P*-values <0.05 were considered statistically significant. Data were analyzed using 'R' (version 3.6.0 or later).

3. Results

Fig. 1 shows how the different subgroups were selected from the two trials. For 1084 patients aged 70 years and older (548 patients from the POPular Genetics trial and 536 patients from the POPular Age trial) the *CYP2C19* genotype was available. Of those, 401 were noncarriers of loss-of-function alleles treated with clopidogrel, 82 were carriers of loss-of-function alleles treated with clopidogrel and 590 were treated

with ticagrelor. Baseline characteristics are presented in Table 1. The mean age was 77 years. In noncarriers of loss-of-function alleles treated with clopidogrel, more female patients and a lower baseline hemoglobin level were observed, compared to patients treated with ticagrelor. Almost 10% of the elderly patients in this study received medical treatment only, without coronary angiography, even though it was suspected they had obstructive coronary artery disease. In 11% of patients who underwent coronary angiography, coronary artery disease was found, but there was no clear target lesion, while another 10% of patients who underwent coronary angiography, but not a PCI, either received coronary artery bypass surgery or they were deemed unsuitable for PCI, (e.g. due to the location or type of lesion and/or due to comorbidities). The sensitivity analysis excluding patients with oral anticoagulation included 345 clopidogrel and 530 ticagrelor treated patients. Baseline differences were similar to that of the main analysis. Between clopidogrel treated carriers and noncarriers of loss-of-function alleles there were many different baseline characteristics, like higher rates of dyslipidemia, prior PCI and prior stroke, in addition to the more frequent diagnosis of NSTEMI and unstable angina at discharge in the *CYP2C19* loss-of-function allele carrier group and the less frequent use of drug eluting stents and PCI in this group.

In the POPular Genetics subgroup, 616 patients aged 70 years and older were available for analysis. Of those, 306 patients were in the genotype-guided cohort and 310 patients were in the standard treatment arm. Both groups were well balanced with regards to baseline and procedural characteristics. In the POPular Age subgroup, *CYP2C19* genotype was available in 536 patients. Of those, 199 patients were noncarriers of a *CYP2C19* loss-of-function allele treated with clopidogrel, and 265 patients were treated with ticagrelor. Groups were well balanced, except for more peripheral arterial disease in the ticagrelor treated patients.

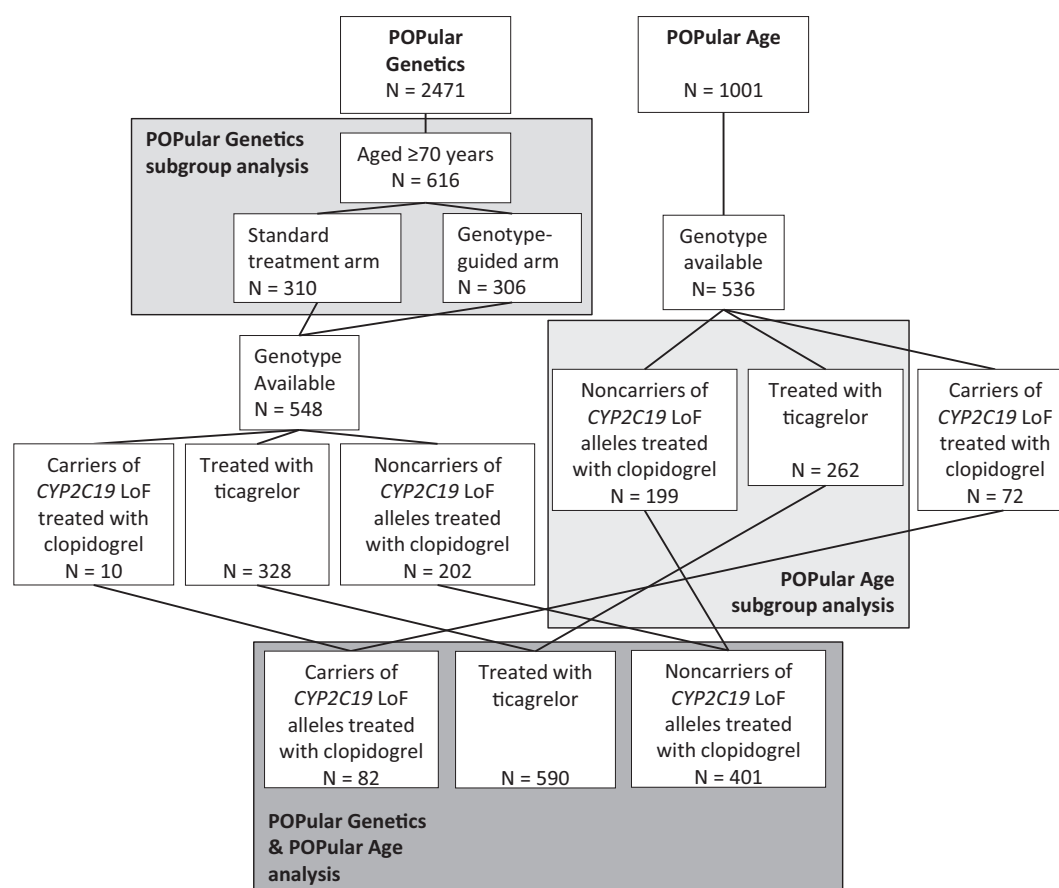


Fig. 1. Flowchart. Flowchart of patient selection for the different subgroup analyses. LoF: Loss-of-function.

Table 1
Baseline characteristics.

Characteristics	Clopidogrel noncarrier N = 401	Ticagrelor N = 590	P value	Clopidogrel LoF allele carriers N = 82	P value
Age (years, mean \pm SD)	77.0 \pm 5.4	77.0 \pm 5.4	0.84	78.0 \pm 5.1	0.09
Female sex	161 (40.1)	189 (32.0)	0.01	32 (39.0)	0.95
BMI (kg/m ² , mean \pm SD)	26.3 \pm 3.98	26.5 \pm 3.77	0.54	26.4 \pm 3.55	0.87
Creatinine clearance (eGFR CKD-EPI) <60 ml/min/1.73 m ²	127 (31.8)	165 (28.2)	0.25	24 (29.3)	0.76
Hemoglobin at admission (mmol/l, mean \pm SD)	8.40 \pm 0.83)	8.54 \pm 0.92)	0.02	8.51 \pm 0.98	0.34
Medical history					
Current smoker	64 (16.1)	112 (19.2)	0.24	10 (12.3)	0.50
Hypertension	250 (62.3)	357 (60.5)	0.61	56 (69.1)	0.30
Dyslipidemia	143 (35.8)	234 (39.8)	0.22	41 (50.0)	0.02
Diabetes Mellitus	81 (20.2)	128 (21.7)	0.63	25 (30.5)	0.06
Myocardial infarction	73 (18.2)	107 (18.2)	1.0	21 (25.6)	0.16
PCI	52 (13.0)	95 (16.1)	0.22	19 (23.2)	0.03
CABG	40 (10.0)	56 (9.5)	0.89	13 (15.9)	0.17
Stroke	10 (2.5)	20 (3.4)	0.54	7 (8.5)	0.02
Peripheral arterial disease	27 (6.8)	54 (9.2)	0.21	8 (9.8)	0.47
Bleeding	16 (4.0)	20 (3.4)	0.74	5 (6.1)	0.38
CYP2C19 genotype					
Normal metabolizer	402 (100)	375 (63.6)		0 (0)	
Intermediate metabolizer	0 (0)	189 (32.0)		75 (91.5)	
Poor metabolizer	0 (0)	17 (3.9)		7 (8.5)	
At discharge					
Diagnosis			0.13		<0.001
Unstable angina	17 (4.3)	22 (3.8)		9 (11.1)	
NSTEMI	177 (44.4)	225 (38.4)		56 (69.1)	
STEMI	202 (50.6)	328 (56.0)		10 (12.3)	
Aspirin	349 (88.4)	529 (90.7)	0.27	70 (86.4)	0.76
P2Y ₁₂ inhibitor					
Clopidogrel	383 (100)	0 (0)		69 (100)	
Ticagrelor	0 (0)	554 (100)		0 (0)	
Oral anticoagulation	56 (14.0)	60 (10.2)	0.09	14 (17.1)	0.58
Beta blocker	304 (77.0)	451 (77.4)	0.95	62 (76.5)	1.00
Ace inhibitor	241 (61.0)	372 (63.8)	0.41	52 (64.2)	0.68
ARB	73 (18.5)	109 (18.7)	1.0	13 (16.0)	0.72
Statin	375 (93.8)	553 (94.2)	0.87	72 (87.8)	0.10
Procedural characteristics					
CAG performed	365 (91.0)	557 (94.4)	0.17	71 (86.6)	0.35
Femoral access site	125 (34.2)	184 (33.0)		29 (40.8)	
Radial access site	240 (65.8)	366 (65.7)		42 (59.2)	
Multivessel disease	213 (53.2)	330 (56.1)	0.41	41 (50.0)	0.68
POBA	10 (2.5)	9 (1.5)	0.39	2 (2.4)	1.00
Bare metal stent	12 (3.0)	20 (3.4)	0.87	0 (0)	0.23
Drug eluting stent	267 (66.6)	419 (71.0)	0.16	44 (53.7)	0.04

Baseline characteristics of patients aged 70 years and older from both the POPular Age and POPular Genetics trial with acute coronary syndrome in whom the CYP2C19 genotype was known, stratified according to P2Y₁₂ inhibitor treatment and LoF carrier status.

All variables were expressed as number (%), unless specified.

ACS: Acute coronary syndrome, ARB: Angiotensin II receptor blocker, BMI: Body mass index, CABG: Coronary artery bypass surgery, CAG: Coronary angiography, LoF: Loss-of-function, NSTEMI: Non-ST elevation myocardial infarction, PCI: Percutaneous coronary intervention, POBA: Plain old balloon angioplasty, STEMI: ST-elevation myocardial infarction.

Results are presented in Table 2, Fig. 2 and Fig. 3. The variables included in the multivariable regression analysis to adjust for baseline differences are presented in Table S1 in the supplementary appendix. After adjustment for differences in baseline characteristics between the groups, there was no statistically significant difference in the net clinical benefit outcome (17.2% vs. 15.1%, adjusted hazard ratio (adjHR) 1.05, 95%CI, 0.77–1.44, $p = 0.76$) (Fig. 2A), thrombotic outcome (9.7% vs. 9.2%, adjHR 1.00, 95%CI, 0.66–1.50, $p = 0.98$) (Fig. 2B), and bleeding outcome (17.7% vs. 19.8%, adjHR 0.83, 95%CI, 0.62–1.12, $p = 0.23$) (Fig. 2C), in noncarriers of loss-of-function alleles treated with clopidogrel compared to patients treated with ticagrelor irrespective of CYP2C19 genotype. Results for the on-treatment analysis and the analysis excluding patients treated with oral anticoagulation are presented in Fig. 3 and in Table S2 in the supplementary appendix.

There were no significant differences between the clopidogrel treated noncarriers group and the small clopidogrel treated carriers of loss-of-function alleles group (Table 2) in the net clinical benefit outcome (17.2% vs. 20.7%, HR 0.96, 95%CI, 0.56–1.63, $p = 0.87$), thrombotic

outcome (9.7% vs. 13.4%, HR 0.83, 95%CI, 0.42–1.64, $p = 0.60$) and bleeding outcome (17.7% vs. 22.0%, HR 0.80, 95%CI 0.47–1.33, $p = 0.39$).

Results for the subgroup analysis of the POPular Age and POPular Genetics trial cohorts are presented in Fig. 3 and in Table S3 in the supplementary appendix. In both analyses, there are no significant differences in any of the outcomes.

4. Discussion

In this pre-specified sub analysis from the POPular Genetics and POPular Age trials, we compared the use of clopidogrel in noncarriers of CYP2C19 loss-of-function alleles with the use of ticagrelor in patients with ACS aged 70 years and older. No statistically significant differences were found for both atherothrombotic and bleeding outcomes. Nevertheless, the finding of a comparable atherothrombotic event rate (adjHR 1.00) combined with a numerically, though not statistically significant, lower number of bleeding events in the clopidogrel treated patients without CYP2C19 loss-of-function allele (adjHR 0.83) is clinically

Table 2

Main outcomes.

Outcome	Clopidogrel noncarrier (N = 401)	Ticagrelor (N = 590)	Hazard ratio ^a (95% CI)	P value ^a	Clopidogrel LoF allele carrier (N = 82)	Hazard ratio (CI)	P value
Net clinical benefit outcome							
All-cause death, MI, stroke, PLATO major bleeding	69 (17.2)	89 (15.1)	1.05 (0.77–1.44)	0.76	17 (20.7)	0.96 (0.56–1.63)	0.87
Thrombotic outcomes							
Combined outcome (cardiovascular death, MI, stroke)	39 (9.7)	54 (9.2)	1.00 (0.66–1.50)	0.98	11 (13.4)	0.83 (0.42–1.64)	0.60
Cardiovascular death	14 (3.5)	12 (2.0)	1.58 (0.73–3.42)	0.25	3 (3.7)	0.96 (0.28–3.35)	0.95
Stroke	5 (1.2)	16 (2.7)	0.44 (0.16–1.20)	0.11	3 (3.7)	0.34 (0.08–1.42)	0.14
Myocardial infarction	25 (6.2)	31 (5.3)	1.14 (0.67–1.93)	0.64	6 (7.3)	1.04 (0.43–2.56)	0.93
Stent thrombosis	1 (0.2)	1 (0.2)	1.48 (0.09–23.6)	0.78	0 (0)	–	–
Bleeding outcomes							
PLATO major & minor bleeding	71 (17.7)	117 (19.8)	0.83 (0.62–1.12)	0.23	18 (22.0)	0.80 (0.47–1.33)	0.39
PLATO major	28 (7.0)	37 (6.3)	1.04 (0.64–1.70)	0.88	8 (9.8)	0.71 (0.32–1.56)	0.39
PLATO minor	48 (12.0)	86 (14.6)	0.79 (0.56–1.13)	0.20	10 (12.2)	0.92 (0.47–1.83)	0.81

The combined subgroup analysis of the POPular Genetics and POPular Age compares clopidogrel in noncarriers of CYP2C19 LoF alleles with with ticagrelor treated patients. Additionally, they were compared to clopidogrel treated carriers of LoF alleles. All patients are aged 70 years and older.

LoF: Loss-of-function, MI: Myocardial infarction, PLATO: Platelet Inhibition and Patient Outcomes.

^a Hazard ratio is adjusted for sex, baseline hemoglobin level and the use of oral anticoagulation at discharge (See Table S1 in the supplementary appendix for more details).

relevant. Additionally, we identified numerically less atherothrombotic events and bleeding events in noncarriers of CYP2C19 loss-of-function alleles treated with clopidogrel compared to carriers of loss-of-function alleles, though, in this very small subgroup with many baseline differences, these differences were not statistically significant. Therefore, any real conclusions cannot be made based on this data.

These results are in accordance with the elderly subgroup analysis of the TRITON-TIMI 38 trial ($n = 1809$), comparing prasugrel with

clopidogrel, which found a lower bleeding risk in clopidogrel treated patients of 75 years and older [3]. In contrast, the subgroup analysis of the PLATO trial, studying the use of ticagrelor in the elderly population ($n = 2878$), showed a benefit of ticagrelor in reducing ischemic events, without significantly increasing the risk of bleeding, although fatal bleeding and non-CABG related major bleeding were higher in the elderly treated with ticagrelor [17]. These results were confirmed in the Bremen STEMI registry, which included 1087 STEMI patients aged 75 years older

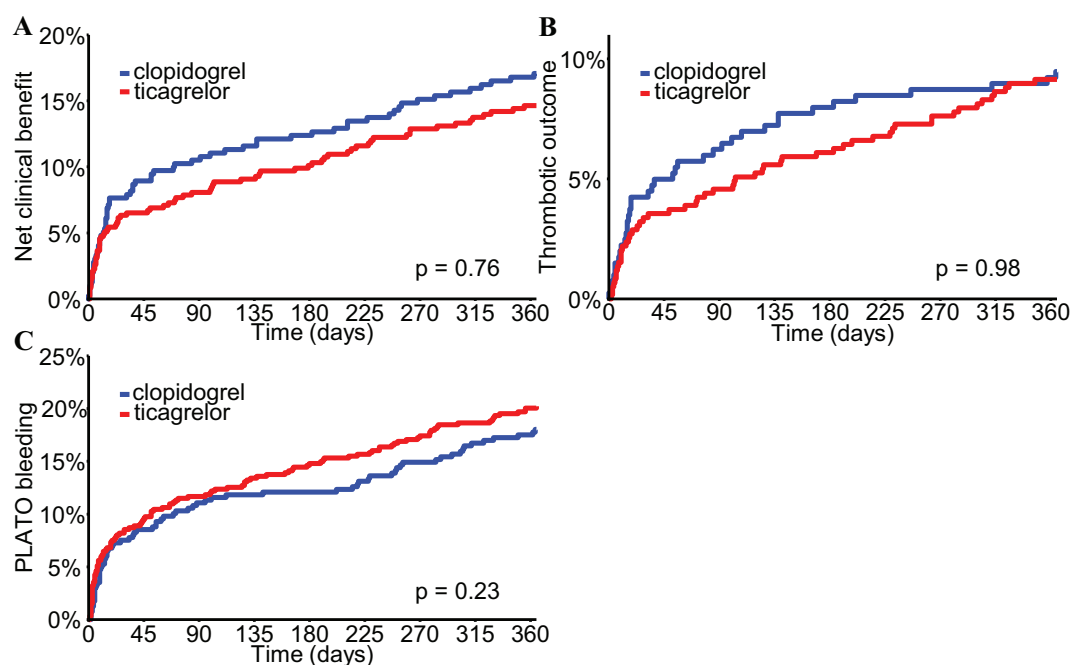


Fig. 2. Time to event curves. Cumulative event rates of the net clinical benefit outcome (defined as all-cause death, myocardial infarction, stroke and PLATO major bleeding; 2A), the thrombotic outcome (defined as cardiovascular death, myocardial infarction and stroke; 2B) and the bleeding outcome (defined as PLATO major and minor bleeding; 2C). ACS: acute coronary syndrome, PLATO: platelet inhibition and patient outcomes.

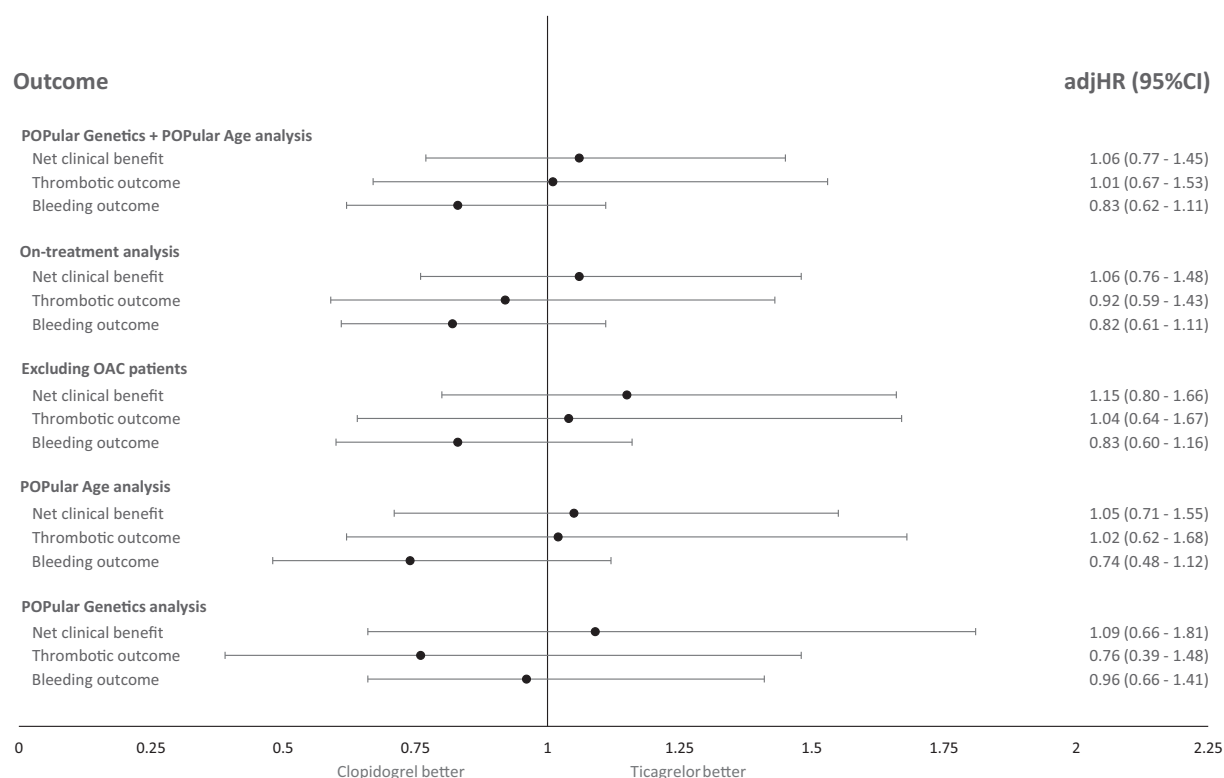


Fig. 3. Outcomes of all analyses. A forest plot displaying all the main outcomes from the different sub analyses from the POPular Genetics and POPular Age trials. adjHR: adjusted Hazard ratio.

treated with primary PCI, comparing ticagrelor to clopidogrel [18]. This benefit with ticagrelor was not found in the POPular Age trial ($n = 1002$), studying patients of 70 years or older with non-ST elevation ACS [7]. While thrombotic risk was not statistically different with the use of ticagrelor or clopidogrel, the bleeding rate was lower in the clopidogrel treated patients. These results are strengthened by the large ($n = 14,005$), nationwide SWEDEHEART registry including patients of 80 years and older with ACS [19]. Although the evidence is conflicting, which for some part might be due to differences in patient selection, selection of different age groups and development and improvement of drug-eluting stents, enhanced secondary prevention and improved intervention techniques in the past decade decreasing ischemic risk, it might be concluded that the more potent P2Y₁₂ inhibitors are not superior for all elderly patients with ACS regarding net clinical benefit outcomes, and clopidogrel is a reasonable alternative.

The POPular Genetics trial found lower bleeding rates without increasing atherothrombotic rates when using *CYP2C19* genetic testing compared to standard treatment with ticagrelor. These results also applied to the elderly subgroup, where no significant interaction was found. The results from the combined POPular Genetics and POPular Age subgroup analysis confirm the main results of the POPular Genetics trial in this elderly subgroup, with similar atherothrombotic and lower bleeding event rates in the clopidogrel group compared to the ticagrelor group. This was not statistically significant due to the limited sample size of this subgroup. The TAILOR PCI trial also investigated *CYP2C19* genetic testing and included patients who underwent PCI (82% because of ACS, 18% with stable coronary artery disease) and randomized them to the control arm or genotype-guided therapy arm. In the control arm patients received clopidogrel, and in the genotype-guided arm patients received clopidogrel if they were noncarriers of the *CYP2C19**2 and *3 loss-of-function alleles or ticagrelor if they were carriers of these alleles [20]. A numeric reduction was found in thrombotic events in carriers of *CYP2C19* loss-of-function alleles when treated with ticagrelor as compared to clopidogrel, though this difference was not statistically

significant ($p = 0.056$), which is in agreement with the results of this subanalysis [20]. However, there was also no significant benefit of the genotype guided strategy in regard to the safety outcome, probably because they compared with clopidogrel in the control arm instead of ticagrelor. The elderly subgroup analysis of patients aged 75 years and older of the TAILOR PCI trial ($n = 261$) showed no significant interaction [20]. Combining the results of the TAILOR PCI with this subgroup analysis, specifying antiplatelet therapy by means of *CYP2C19* genotyping might be promising for improving clinical outcomes in the elderly ACS patient, however further research is needed.

To this day, clopidogrel remains the most widely used platelet inhibitor in elderly patients with ACS [21–23]. Although most evidence regarding elderly patients is based on subgroup analysis and is underpowered, it might be concluded that the more potent P2Y₁₂ inhibitors prasugrel and ticagrelor are not superior in all elderly patients with ACS regarding net clinical benefit outcomes, and clopidogrel could be a reasonable alternative. This effect might be the strongest in patients without *CYP2C19* loss-of-function allele, who are expected to have optimal clopidogrel efficacy. A *CYP2C19* genotype guided strategy might be promising for improving clinical outcome in the elderly ACS patient.

Several limitations to this study need to be mentioned. Although this is one of the largest analyses comparing clopidogrel with ticagrelor in elderly patients with ACS and known *CYP2C19* genotype, it was not powered to find statistical differences between both treatment strategies. In addition, both trials had an open-label design and the POPular Age trial was not designed to compare a genotype-guided strategy with standard treatment. Therefore, our results are hypothesis generating and should be interpreted with caution. Furthermore, since our main analysis only included clopidogrel treated noncarriers of loss-of-function alleles, results cannot be extrapolated to all clopidogrel treated patients. Lastly, since we compared our data to ticagrelor treated patients only, it is unknown how outcomes compare to prasugrel treated patients.

5. Conclusion

In patients with ACS aged 70 years and older, there were no significant differences in atherothrombotic or bleeding event rates between noncarriers of a *CYP2C19* loss-of-function allele treated with clopidogrel, and patients treated with ticagrelor irrespective of *CYP2C19* genotype. Nevertheless, the bleeding rate was numerically, though not statistically significant, lower in clopidogrel treated patients. Further research focusing on the value of *CYP2C19* genotyping in this specific and vulnerable group of patients might help to find an optimal antiplatelet treatment for the elderly.

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Conflict of interests

AvtH reports grants from Medtronic, Astra Zeneca and Sanofi and personal fees from Astra Zeneca and AMGEN; CvB reports institutional research grants provided by the research department of Thoraxcentrum Twente, from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic, outside the submitted work; EB reports personal fees from BOSTON SCIENTIFIC, ABBOTT VASCULAR and GE; JtB reports grants from Astra Zeneca and personal fees from AstraZeneca, Daiichi Sankyo, Eli Lilly, the Medicines Company, Accumetrics, Boehringer-Ingelheim, Bayer, BMS, Pfizer and Ferrer; WJ and his department have received research grants from Amgen, Athera, AstraZeneca, Biotronik, Boston Scientific, Daiichi Sankyo, Lilly, Medtronic, Merck-Schering-Plough, Pfizer, Roche, Sanofi Aventis, The Medicine Company, the Netherlands Heart Foundation, Netherlands CardioVascular Research, the Netherlands Heart Institute, and the European Community Framework KP7 Programme; and was a speaker (with and without lecture fees) on amongst others (Continuing Medical Education accredited) meetings sponsored by Amgen, Athera, AstraZeneca, Biotronik, Boston Scientific, Daiichi Sankyo, Lilly, Medtronic, Merck-Schering-Plough, Pfizer, Roche, Sanofi Aventis, The Medicine Company, the Netherlands Heart Foundation, CardioVascular Research the Netherlands, the Netherlands Heart Institute, and the European Community Framework KP7 Programme, during the conduct of the study. All other authors declare no conflicts of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2021.04.029>.

References

- [1] S. Yusuf, F. Zhao, S.R. Mehta, S. Chrolavicius, G. Tognoni, K.K. Fox, Clopidogrel in unstable angina to prevent recurrent events trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation, *N. Engl. J. Med.* 345 (2001) 494–502.
- [2] L. Wallentin, R.C. Becker, A. Budaj, C.P. Cannon, H. Emanuelsson, C. Held, J. Morrow, S. Husted, S. James, H. Katus, K.W. Mahaffey, B.M. Scirica, A. Skene, P.G. Steg, R.F. Storey, R.A. Harrington, P.L.A.T.O. Investigators, A. Freij, M. Thorsén, Ticagrelor versus clopidogrel in patients with acute coronary syndromes, *N. Engl. J. Med.* 361 (2009) 1045–1057.
- [3] S.D. Wiviott, E. Braunwald, C.H. McCabe, G. Montalescot, W. Ruzyllo, S. Gottlieb, F.-J. Neumann, D. Ardissino, Servi S. De, S.A. Murphy, J. Riesmeyer, G. Weerakkody, C.M. Gibson, E.M. Antman, TRITON-TIMI 38 investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes, *N. Engl. J. Med.* 357 (2007) 2001–2015.
- [4] J.-P. Collet, H. Thiele, E. Barbato, O. Barthélémy, J. Bauersachs, D.L. Bhatt, P. Dendale, M. Dorobantu, T. Edvardsen, T. Fogliuati, C.P. Gale, M. Gilard, A. Jobs, P. Jüni, E. Lambrinou, B.S. Lewis, J. Mehili, E. Meliga, B. Merkely, C. Mueller, M. Roffi, F.H. Rutten, D. Sibbing, G.C.M. Siontis, A. Kastrati, M.A. Mamas, V. Aboyans, D.J. Angiolillo, H. Bueno, R. Bugiardini, et al., ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, *Eur. Heart J.* 42 (2021) 1289–1367.
- [5] M. Valgimigli, H. Bueno, R.A. Byrne, J.-P. Collet, F. Costa, A. Jeppsson, P. Jüni, A. Kastrati, P. Kolh, L. Mauri, G. Montalescot, F.-J. Neumann, M. Petricevic, M. Roffi, P.G. Steg, S. Windecker, J.L. Zamorano, G.N. Levine, L. Badimon, P. Vranckx, S. Agewall, F. Andreotti, E. Antman, E. Barbato, J.-P. Bassand, R. Bugiardini, M. Cikirikcioglu, T. Cuisset, M. De Bonis, V. Delgado, et al., 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS, *Eur. Heart J.* 39 (2018) 213–260.
- [6] R.W. Yeh, E.A. Secemsky, D.J. Kereiakes, S.-L.T. Normand, A.H. Gershlick, D.J. Cohen, J.A. Spertus, P.G. Steg, D.E. Cutlip, M.J. Rinaldi, E. Camenzind, W. Wijns, P.K. Apruzzese, Y. Song, J.M. Massaro, L. Mauri, D.A.P.T. Study Investigators, Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention, *JAMA* 315 (2016) 1735–1749.
- [7] M. Gimbel, K. Qaderdan, L. Willemsen, R. Hermanides, T. Bergmeijer, Vrey E. De, T. Heestermans, M. Tjon Joe Gin, R. Waalewijn, S. Hofma, Hartog F. Den, W. Jukema, Birgelen C. Von, M. Voskuil, J. Kelder, V. Deneer, Berg J. Ten, 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* 395 (2020) 1374–1381.
- [8] P. Savi, J.M. Perreillo, M.F. Uzabiaga, J. Combalbert, C. Picard, J.P. Maffrand, M. Pascal, J.M. Herbert, Identification and biological activity of the active metabolite of clopidogrel, *Thromb. Haemost.* 84 (2000) 891–896.
- [9] N.J. Breet, J.W. van Werkum, H.J. Bouman, J.C. Kelder, H.J.T. Ruven, E.T. Bal, V.H. Deneer, A.M. Harmsze, Van Der Heyden JAS, B.J.W.M. Rensing, M.J. Suttorp, C.M. Hackeng, Berg J.M. Ten, Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation, *JAMA* 303 (2010) 754–762.
- [10] A.M. Harmsze, Werkum J.W. Van, Berg J.M. Ten, B. Zwart, H.J. Bouman, N.J. Breet, T. Hof AWJ Van, Ruven HJT, C.M. Hackeng, O.H. Klungel, Boer A. De, Deneer VHM, CYP2C19*2 and CYP2C9*3 alleles are associated with stent thrombosis: a case-control study, *Eur. Heart J.* 31 (2010) 3046–3053.
- [11] L. Wallentin, S. James, R.F. Storey, M. Armstrong, B.J. Barratt, J. Morrow, S. Husted, H. Katus, P.G. Steg, S.H. Shah, R.C. Becker, Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial, *Lancet* 376 (2010) 1320–1328.
- [12] J.L. Mega, S.L. Close, S.D. Wiviott, L. Shen, J.R. Walker, T. Simon, E.M. Antman, E. Braunwald, M.S. Sabatine, Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis, *Lancet* 376 (2010) 1312–1319.
- [13] D.M.F. Claassens, G.J.A. Vos, Bergmeijer TO, R.S. Hermanides, 't Hof AWJ van, Harst P. Van Der, E. Barbato, C. Morisco, R.M. Tjon Joe Gin, F.W. Asselbergs, A. Mosterd, Herrman J. PR, Dewilde WJM, Janssen PWA, J.C. Kelder, M.J. Postma, Boer A. De, C. Boersma, Deneer VHM, Berg J.M. Ten, A genotype-guided strategy for Oral P2Y₁₂ inhibitors in primary PCI, *N. Engl. J. Med.* 381 (2019) 1621–1631.
- [14] J.W. Eikelboom, S.R. Mehta, S.S. Anand, C. Xie, K.A.A. Fox, S. Yusuf, Adverse impact of bleeding on prognosis in patients with acute coronary syndromes, *Circulation* 114 (2006) 774–782.
- [15] Bergmeijer TO, P.W.A. Janssen, J.C. Schipper, K. Qaderdan, M. Ishak, R.S. Ruitenbeek, F.W. Asselbergs, A.W.J. Van't Hof, W.J.M. Dewilde, F. Spanó, J.P.R. Herrman, J.C. Kelder, M.J. Postma, Boer A. De, Deneer VHM, Berg J.M. Ten, CYP2C19 genotype-guided antiplatelet therapy in ST-segment elevation myocardial infarction patients – Rationale and design of the Patient Outcome after primary PCI (POPular) Genetics study, *Am. Heart J.* 168 (2014) 16–22 e1.
- [16] K. Qaderdan, M. Ishak, Heestermans AACM, Vrey E. De, J.W. Jukema, M. Voskuil, Boer M.-J. De, van't Hof AWJ, B.E. Groenemeijer, Vos G. JA, Janssen PWA, Bergmeijer TO, J.C. Kelder, Deneer VHM, Berg J.M. Ten, Ticagrelor or prasugrel versus clopidogrel in elderly patients with an acute coronary syndrome: Optimization of antiplatelet treatment in patients 70years and older—rationale and design of the POPular AGE study, *Am. Heart J.* 170 (2015) 981–985 e1.
- [17] S. Husted, S. James, R.C. Becker, J. Morrow, H. Katus, R.F. Storey, C.P. Cannon, M. Heras, R.D. Lopes, J. Morais, K.W. Mahaffey, R.G. Bach, D. Wojdyla, L. Wallentin, PLATO study group, Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes, *Circ. Cardiovasc. Qual. Outcome* 5 (2012) 680–688.
- [18] J. Schmucker, A. Fach, L.A. Mata Marin, T. Retzlaff, R. Osteresch, B. Kollhorst, R. Hambrecht, H. Pohlmann, H. Wienbergen, Efficacy and safety of ticagrelor in comparison to clopidogrel in elderly patients With ST-segment-elevation myocardial infarctions, *J. Am. Heart Assoc.* 8 (2019) e012530.
- [19] K. Szummer, M.E. Montez-Rath, J. Alfredsson, D. Erlinge, B. Lindahl, R. Hofmann, A. Ravn-Fischer, P. Svensson, T. Jernberg, Comparison between ticagrelor and clopidogrel in elderly patients with an acute coronary syndrome: insights from the SWEDEHEART registry, *Circulation* 142 (2020) 1700–1708.
- [20] N.L. Pereira, M.E. Farkouh, D. So, R. Lennon, N. Geller, V. Mathew, M. Bell, J.H. Bae, M.H. Jeong, I. Chavez, P. Gordon, J.D. Abbott, C. Cagin, L. Baudhuin, Y.P. Fu, S.G. Goodman, A. Hasan, E. Iturriaga, A. Lerman, M. Sidhu, J.F. Tanguay, L. Wang, R.

- Weinshilboum, R. Welsh, Y. Rosenberg, K. Bailey, C. Rihal, Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial, *JAMA* 324 (2020) 761–771.
- [21] M.B. Yudi, D.J. Clark, O. Farouque, D. Eccleston, N. Andrianopoulos, S.J. Duffy, A. Brennan, J. Lefkovits, J. Ramchand, T. Yip, E. Oqueli, C.M. Reid, A.E. Ajani, C. Reid, A. Ajani, S. Duffy, D. Clark, G. New, C. Hiew, J.A. Shaw, A. Walton, A. Dart, A. Broughton, J. Federman, C. Keighley, C. Hengel, K.H. Peter, J. O'Brien, H. Bala, L. Selkrig, et al., Clopidogrel, prasugrel or ticagrelor in patients with acute coronary syndromes undergoing percutaneous coronary intervention, *Intern. Med. J.* 46 (2016) 559–565.
- [22] S. Sheikh Rezaei, A. Geroldinger, G. Heinze, B. Reichardt, M. Wolzt, Clopidogrel, prasugrel, or ticagrelor use and clinical outcome in patients with acute coronary syndrome: a nationwide long-term registry analysis from 2009 to 2014, *Int. J. Cardiol.* 235 (2017) 61–66.
- [23] U. Baber, S. Sartori, M. Aquino, A. Kini, S. Kapadia, S. Weiss, C. Strauss, J.B. Muhlestein, C. Toma, S.V. Rao, A. DeFranco, K.L. Poddar, J. Chandrasekhar, W. Weintraub, T.D. Henry, S. Bansilal, B.A. Baker, E. Marrett, S. Keller, M. Effron, S. Pocock, R. Mehran, Use of prasugrel vs clopidogrel and outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention in contemporary clinical practice: results from the PROMETHEUS study, *Am. Heart J.* 188 (2017) 73–81.