The limitations and challenges in the study by Hsiang and colleagues[6] do not diminish the relevance of their findings. Challenges with RACD due to high levels of subpatent infections not detected by conventional diagnostic tools have been found elsewhere.[11] Bold but evidence-supported actions are required to accelerate progress towards malaria elimination wherever possible. The presented evidence on rfMDA and RAVC, alone or in combination, should encourage larger scale implementation of these strategies in other settings, accompanied by well designed, long-term evaluations.

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Antiplatelet strategies in ageing patients with acute coronary syndromes

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Older patients who present with a non-ST-segment elevation acute coronary syndrome (NSTE-ACS) are at particular risk of recurrent ischaemic events, but also of bleeding complications.[1] Choosing the optimal dual antiplatelet strategy for the ageing patient with ACS can thus present a dilemma in daily practice. Should dual antiplatelet therapy in an older patient include the less potent P2Y12 inhibitor clopidogrel, thus minimising bleeding risk, or should a more potent P2Y12 inhibitor such as ticagrelor or prasugrel be used to avoid recurrent ischaemic events? In addition, the ideal dual antiplatelet therapy duration for these patients remains unclear. Unfortunately, guidelines do not contain specific age-tailored advice, reflecting the conflicting and suboptimal evidence from primary clinical studies.[1–5]

Additional guidance for treating older NSTE-ACS patients now comes from the POPular AGE trial by Marieke Gimbel and colleagues,[6] reported in *The Lancet*. In this study, 1002 patients with NSTE-ACS, aged 70 years or older (64% male and 36% female), were randomly assigned to either clopidogrel or one of the two more potent P2Y12 inhibitors, ticagrelor or prasugrel, for 1 year after their acute event. 475 (95%) patients received ticagrelor in the ticagrelor or prasugrel group; therefore, the results show a comparison between clopidogrel and ticagrelor. The primary outcome, any bleeding requiring medical intervention, was significantly lower in the clopidogrel group (88 [18%] of 500 patients) than in the ticagrelor group (118 [24%] of 502; hazard ratio [HR] 0·71, 95% CI 0·54–0·94; p=0·02). The reduction in bleeding risk with clopidogrel was not only driven by fewer minor bleedings, but also by a lower risk of major bleeding. There were also five fatal bleedings in the ticagrelor group versus none in the clopidogrel group. Net clinical benefit, a coprimary endpoint, including bleeding and ischaemic outcomes, was similar for both treatment groups (p=0·03 for non-inferiority). Although five stent thromboses occurred with clopidogrel versus none with ticagrelor, there were no differences in myocardial infarction or cardiovascular death. Overall, the study showed that in NSTE-ACS patients, aged 70 years or older, clopidogrel can decrease bleeding risk in a clinically

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meaningful way, probably without exposing them to a higher atherothrombotic risk.

Clinical trials with older patients are notoriously difficult to do because recruitment, adherence, and retention can be low. The authors need to be congratulated for bringing this important study to a successful conclusion. How do their results compare to what we already know? In PLATO,[3] patients older than 75 years (n=2878) had fewer ischaemic events with ticagrelor than with clopidogrel, without an increased bleeding risk. However, in a subanalysis in patients with NSTE-ACS only, ticagrelor improved outcomes in younger patients but not in those older than 65 years ($p_{interaction}$<0·01).[4] The results from POPular AGE appear to confirm this result to some extent,[4] even when the study was underpowered for ischaemic events. Early discontinuation or switching occurred in both treatment groups, but was higher with ticagrelor in this open-label study, and higher than in the double-blind PLATO trial.[3] These data reflect not only a higher frequency of side-effects with ticagrelor, but probably also a more contemporary preference for shorter dual antiplatelet therapy durations in patients with ACS who are at an increased risk of bleeding, as now accommodated for in guidelines.[2]

Although approximately a third of the patients in POPular AGE were older than 80 years, it remains unclear whether the results of the trial can be extended to very old or frail people. Because these patient categories are even more likely to experience bleeding complications, a more conservative approach with clopidogrel as in POPular AGE might be warranted. In addition, most patients were pretreated, many of them with ticagrelor. While this pretreatment with ticagrelor is recommended by guidelines,[2] it remains unclear what the effect of preloading was on the outcomes of patients subsequently randomly assigned to clopidogrel. Indeed, it has become more and more clear that systematically preloading all patients with NSTE-ACS might not necessarily improve outcomes,[7,8] and such an approach might be especially harmful to older patients.

Does POPular AGE now end the discussion about which dual antiplatelet strategy provides the most optimal benefit–risk balance in ageing patients? We think not, because there are several other options that still need to be considered and, ideally, explored in clinical trials on older patients. For instance, a planned short dual antiplatelet treatment duration with any P2Y12 inhibitor might be preferred in frail, elderly patients in the first place, given the safety of current drug-eluting stents.[9] Other valid options not yet explored in older patients include guided therapy or planned de-escalation to clopidogrel after an initial short treatment period with ticagrelor or prasugrel.[10,11] In POPular AGE, patients in the ticagrelor group received the conventional 90 mg twice daily dose, but a lower maintenance dose of ticagrelor 60 mg or prasugrel 5 mg needs to be tested to find out if it preserves the benefit of a more potent P2Y12 inhibitor over clopidogrel in ageing patients while minimising the increased bleeding risk associated with both drugs.[8,12] While the European Society of Cardiology guidelines for ticagrelor or prasugrel undoubtedly remain appropriate for patients with ACS in their seventies, it now seems wise to adhere to a "less is more" approach in the very old or frail patients with a NSTE-ACS: no preloading and preferably clopidogrel either as an initial strategy or after early de-escalation.

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Beware of the second wave of COVID-19

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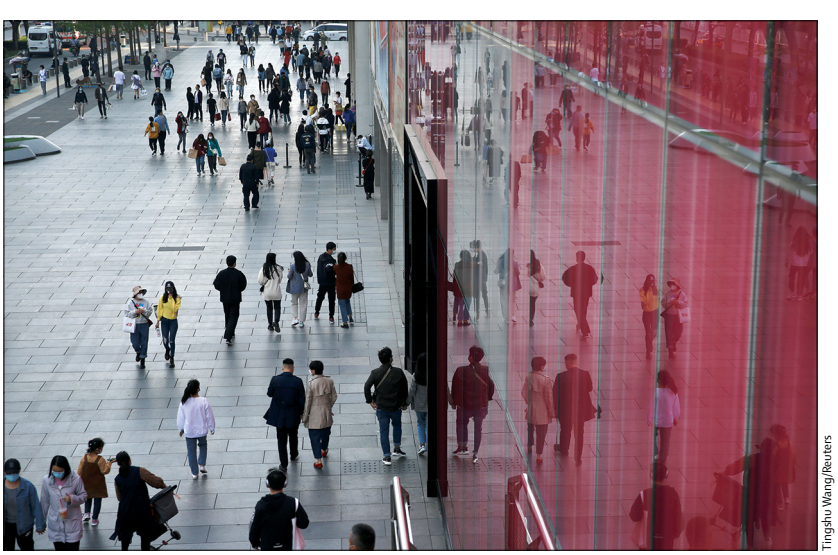
The outbreak of coronavirus disease 2019 (COVID-19), which began in Wuhan, China, in late 2019, has spread to 203 countries as of March 30, 2020, and has been officially declared a global pandemic.[1] With unprecedented public health interventions, local transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appears now to have been contained in China. Multiple countries are now experiencing the first wave of the COVID-19 epidemic; thus, gaining an understanding of how these interventions prevented the transmission of SARS-CoV-2 in China is urgent.

In *The Lancet,* Kathy Leung and colleagues[2] report their assessment of the transmissibility and severity of COVID-19 during the first wave in four cities and ten provinces in China outside Hubei. The study estimated the instantaneous reproduction number in the selected locations decreased substantially after non-pharmaceutical control measures were implemented on Jan 23, 2020, and has since remained lower than 1. The transmission of SARS-CoV-2 in these locations was mainly driven by imported cases from Hubei until late January, which is, to some extent, similar to the transmission in January in several countries. The epidemics in Chinese provinces outside Hubei were believed to be driven by local transmission dynamics after Jan 31;[3] therefore, the findings of Leung and colleagues' study highlight the fact that the package of non-pharmaceutical interventions in China has the ability to contain transmission—not only imported cases, but also local transmission. The epidemic is accelerating rapidly in multiple countries, indicating shortfalls in preparedness. Given that multiple countries imposed travel restrictions against China in late January, there is a need to model whether earlier implementation of interventions such as social distancing, population behavioural change, and contact tracing would have been able to contain or mitigate the epidemic.

Leung and colleagues also modelled the potential adverse consequences of premature relaxation of interventions, and found that such a decision might lead to transmissibility exceeding 1 again—ie, a second wave of infections. The finding is critical to governments globally, because it warns against premature relaxation of strict interventions. However, the effect of each intervention, or which one was the most effective in



Tingshu Wang/Reuters

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

Marieke Gimbel, Khalid Qaderdan, Laura Willemsen, Rik Hermanides, Thomas Bergmeijer, Evelyn de Vrey, Ton Heestermans, Melvyn Tjon Joe Gin, Reinier Waalewijn, Sjoerd Hofma, Frank den Hartog, Wouter Jukema, Clemens von Birgelen, Michiel Voskuil, Johannes Kelder, Vera Deneer, Jurriën ten Berg

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Summary

Background Current guidelines recommend potent platelet inhibition with ticagrelor or prasugrel in patients after an acute coronary syndrome. However, data about optimal platelet inhibition in older patients are scarce. We aimed to investigate the safety and efficacy of clopidogrel compared with ticagrelor or prasugrel in older patients with non-ST-elevation acute coronary syndrome (NSTE-ACS).

Methods We did the open-label, randomised controlled POPular AGE trial in 12 sites (ten hospitals and two university hospitals) in the Netherlands. Patients aged 70 years or older with NSTE-ACS were enrolled and randomly assigned in a 1:1 ratio using an internet-based randomisation procedure with block sizes of six to receive a loading dose of clopidogrel 300 mg or 600 mg, or ticagrelor 180 mg or prasugrel 60 mg, and then a maintenance dose for the duration of 12 months (clopidogrel 75 mg once daily, ticagrelor 90 mg twice daily, or prasugrel 10 mg once daily) on top of standard care. Patient and treating physicians were aware of the allocated treatment strategy, but the outcome assessors were masked to treatment allocation. Primary bleeding outcome consisted of PLATelet inhibition and patient Outcomes (PLATO; major or minor bleeding [superiority hypothesis]). Co-primary net clinical benefit outcome consisted of all-cause death, myocardial infarction, stroke, PLATO major and minor bleeding (non-inferiority hypothesis, margin of 2%). Follow-up duration was 12 months. Analyses were done on intention-to-treat basis. This trial is registered with the Netherlands Trial Register (NL3804), ClinicalTrials.gov (NCT02317198), and EudraCT (2013–001403–37).

Findings Between June 10, 2013, and Oct 17, 2018, 1002 patients were randomly assigned to clopidogrel (n=500) or ticagrelor or prasugrel (n=502). Because 475 (95%) patients received ticagrelor in the ticagrelor or prasugrel group, we will refer to this group as the ticagrelor group. Premature discontinuation of the study drug occurred in 238 (47%) of 502 ticagrelor group patients randomly assigned to ticagrelor, and in 112 (22%) of 500 patients randomly assigned to clopidogrel. Primary bleeding outcome was significantly lower in the clopidogrel group (88 [18%] of 500 patients) than in the ticagrelor group (118 [24%] of 502; hazard ratio 0·71, 95% CI 0·54 to 0·94; p=0·02 for superiority). Co-primary net clinical benefit outcome was non-inferior for the use of clopidogrel (139 [28%]) versus ticagrelor (161 [32%]; absolute risk difference –4%, 95% CI –10·0 to 1·4; p=0·03 for non-inferiority). The most important reasons for discontinuation were occurrence of bleeding (n=38), dyspnoea (n=40), and the need for treatment with oral anticoagulation (n=35).

Interpretation In patients aged 70 years or older presenting with NSTE-ACS, clopidogrel is a favourable alternative to ticagrelor, because it leads to fewer bleeding events without an increase in the combined endpoint of all-cause death, myocardial infarction, stroke, and bleeding. Clopidogrel could be an alternative P2Y12 inhibitor especially for elderly patients with a higher bleeding risk.

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Introduction

Dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 inhibitor, is essential for the prevention of recurrent thrombotic events in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS). Guidelines recommend the use of the stronger P2Y12 inhibitors, ticagrelor or prasugrel, over clopidogrel in patients with acute coronary syndrome, unless there is an excessive risk of bleeding.[1,2] This advice is based on the results of the TRITON-TIMI 38 trial[3] and the PLATO trial.[4] Both studies showed superiority of prasugrel and ticagrelor versus clopidogrel in reducing cardiovascular death, myocardial infarction, and stroke. With increasing age, patients have higher risks of bleeding and thrombotic events, making

Research in context

Evidence before this study

For patients with acute coronary syndrome, European guidelines recommend potent platelet inhibition with aspirin and ticagrelor or prasugrel, irrespective of age. Therefore, older patients receive potent platelet inhibitors, despite the fact that they are at increased risk of bleeding. To identify the optimal antiplatelet regimen, we did a search in PubMed on Nov 19, 2019, with no language restrictions using the search terms "acute coronary syndrome", "clopidogrel", "ticagrelor" and "prasugrel".

We found two trials that showed prasugrel (TRITON-TIMI 38 trial) and ticagrelor (PLATO trial) are superior to clopidogrel at reducing cardiovascular death and reducing myocardial infarction and stroke. TRITON-TIMI 38 did not show a net clinical benefit of prasugrel in the subgroup of older patients (aged ≥75 years), due to higher rates of bleeding, and therefore the use of prasugrel is not recommended in patients of this age, or with dose adjustment. Although, the superiority of ticagrelor in the PLATO trial was not found to be age dependent, ticagrelor related bleeding (including intracranial and fatal bleeding) occurred more frequently, especially in the older patients, than did clopidogrel related bleeding. Therefore, the preference for ticagrelor in older patients from the guideline seems controversial. The Elderly ACS 2 trial, aimed to show superiority of prasugrel 5 mg over clopidogrel in older patients with acute coronary syndrome; however, was prematurely interrupted because of futility for efficacy. After recruitment of 1443 patients, at 1-year follow-up, the primary outcome of mortality, myocardial infarction, stroke, rehospitalisation for cardiovascular causes, or bleeding occurred equal in both groups.

Added value of this study

The POPular AGE trial is the first randomised trial to investigate clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with a non-ST-elevation acute coronary syndrome. Treatment with clopidogrel on top of standard treatment significantly reduced bleeding risk and did not increase risk of thrombotic events compared with ticagrelor or prasugrel. By showing non-inferiority of clopidogrel in net clinical benefit (all-cause death, myocardial infarction, stroke, and PLATelet inhibition and patient Outcomes; major or minor bleeding), our trial provides important evidence justifying treatment with clopidogrel as an alternative strategy in older patients with non-ST-elevation acute coronary syndrome.

Implications of all the available evidence

Popular AGE has proven the safety and efficacy of a treatment strategy with clopidogrel in older patients with non-ST-elevation acute coronary syndrome, especially when these patients have a higher bleeding risk. Therefore, clopidogrel is a favourable alternative to ticagrelor.

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the optimal choice of antithrombotic therapy challenging.[5,6] These risks are shown in the TRITON-TIMI 38 and the PLATO studies.[3,4] TRITON-TIMI 38 did not show a net clinical benefit of prasugrel in the subgroup of older patients (aged ≥75 years), due to higher rates of bleeding; therefore, the use of prasugrel is not recommended in patients of this age, or with dose adjustment. Although, the superiority of ticagrelor in the PLATO trial was not found to be age dependent, ticagrelor-related bleeding (including fatal bleeding) occurred more frequently, especially in the older patients, than did clopidogrel-related bleeding.[7] Based on these data, the preference for ticagrelor in older patients from the guideline seems controversial. Therefore, we aimed to determine the optimal P2Y12 inhibitor in older patients with NSTE-ACS by assessing the safety and efficacy of clopidogrel compared with ticagrelor or prasugrel in patients aged 70 years or older.

Methods

Trial design and participants

The POPular AGE trial was an open-label, randomised, clinical trial done at 12 sites (ten hospitals and two univeristy hospitals) in the Netherlands, in which clopidogrel was compared with ticagrelor or prasugrel in patients aged 70 years or older with NSTE-ACS.

Details of the rationale and design of this study have been described previously.[8] In short, eligible patients were aged 70 years or older, presenting with a NSTE-ACS (defined according to the third universal definition of myocardial infarction),[9] and randomised within 72 h after admission. Key exclusion criteria were contraindication to one of the P2Y12 inhibitors, NSTE-ACS while on DAPT before admission, clinically significant out of range values for platelet count or haemoglobin, major surgery within 90 days before randomisation, cardiogenic shock, or having a life expectancy less than 1 year at the time of screening. On March 10, 2014, after recruitment of 33 patients, important changes to the eligibility criteria were made to broaden the study population: the age limit was changed from 75 years or older to 70 years or older, patients on oral anticoagulation were no longer excluded from the trial, and the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines (CRUSADE) risk score 31 or higher was waived. The trial protocol, as well as the amendments from March 10, 2014, were approved by an accredited medical research ethics committee and the competent authorities of all study sites. The trial was done in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent before enrolment.

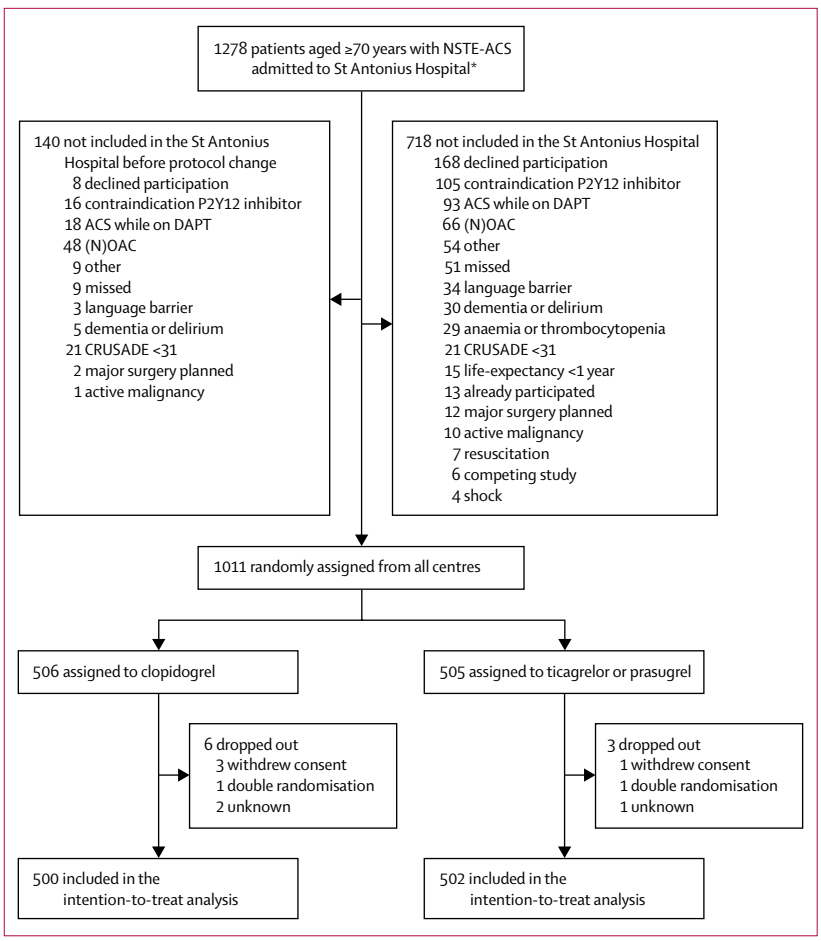


Figure 1: **Trial profile**
ACS=acute coronary syndrome. DAPT=dual antiplatelet therapy. NOAC=non-vitamin K antagonist oral anticoagulants. CRUSADE=Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines. *Only St Antoniuos Hospital was able to keep a screenings log.

Randomisation and masking

Eligible participants were randomly assigned in a 1:1 ratio to receive clopidogrel, or ticagrelor or prasugrel on top of standard of care. Blocked randomisation was done by participating phycician investigators after careful instruction in REDCap,[10,11] a customisable informatics browser-based software system, with block sizes of six, stratified by study site. Treatment was open label, with both patient and treating physicians being aware of the allocated treatment strategy. Two independent members of the clinical event committee, who assessed and confirmed all outcomes, were masked for the treatment assignment.

Procedures

After admission and before randomisation, patients were given a P2Y12 inhibitor according to local protocol. Patients without a P2Y12 inhibitor before randomisation received a loading dose of the study drug (clopidogrel 300 mg or 600 mg, ticagrelor 180 mg, or prasugrel 60 mg), after which a maintenance dose was prescribed for the duration of 1 year (clopidogrel 75 mg once daily, ticagrelor 90 mg twice daily, or prasugrel 10 mg once daily). In patients given prasugrel, a 5 mg once daily maintenance dose was used in patients aged 75 years or older or with a bodyweight less than 60 kg. Prasugrel was not prescribed to patients who have had a stroke or transient ischaemic attack; therefore, if those patients were randomly assigned to ticagrelor or prasugrel they could be given only ticagrelor. If the P2Y12 inhibitor had to be switched after randomisation according to study protocol, a loading dose of the newly started drug was given at the discretion of the treating physician. Pretreatment with the P2Y12 inhibitor, before coronary angiography, was also at the discretion of the treating physician. Additional antithrombotic treatment was given in accordance to local standards. From a subgroup of patients, a blood sample was collected for analysis of *CYP2C19* gene polymorphisms, which was done after study completion. For all patients, the hospital medical files, and, if necessary, the medical records of the general practitioner or pharmacy records were screened for outcomes and adverse events until 1-year follow-up. To enhance accuracy of data, patients were sent a questionnaire at 1 month and 1 year after admittance, inquiring about therapy adherence, hospital readmissions, and bleedings.

An independent data safety monitoring board evaluated safety and efficacy in the study population after recruitment and 1-year follow-up of the first 500 patients.

Outcomes

There were two primary outcomes. The first primary outcome was a bleeding outcome, consisting of any bleeding requiring medical intervention, defined as PLATO major or minor bleeding.[4] The second primary outcome was the net clinical benefit of all-cause death, myocardial infarction (defined according to the third universal definition of myocardial infarction),[9] stroke (defined as an acute new neurological deficit ending in death or lasting >24 h not due to another readily identifiable cause such as trauma), and PLATO major or minor bleeding. Secondary outcomes were the individual components from net clinical benefit outcome, and cardiovascular death, definite stent thrombosis (defined according to the Academic Research Consortium),[12] urgent revascularisation, unstable angina, and transient ischaemic attack (defined as an acute new neurological deficit lasting <24 h not due to another readily identifiable cause such as trauma). Bleeding was also classified according to the Bleeding Academic Research Consortium and thrombolysis in myocardial infarction definitions.[13]

Statistical analysis

The incidence of the primary bleeding outcome was estimated to be 17% in the ticagrelor or prasugrel group and 10% in the clopidogrel group. These assumptions

	Clopidogrel (n=500)	Ticagrelor (n=502)
Age, years	77 (73–81)	77 (73–82)
≥75 years	327 (65%)	326 (65%)
≥80 years	181 (36%)	178 (36%)
Sex		
Male	313 (63%)	325 (65%)
Female	187 (37%)	177 (35%)
Body-mass index, kg/m²	26·7 (4·0)	26·9 (4·2)
Bodyweight <60 kg	35 (7%)	30 (6%)
Previous medical history		
Myocardial infarction	121 (24%)	136 (27%)
Percutaneous coronary intervention	98 (20%)	122 (24%)
CABG	84 (17%)	86 (17%)
Ischaemic stroke*	22 (4%)	25 (5%)
Transient ischaemic attack*	37 (7%)	38 (8%)
Peripheral arterial disease	49 (10%)	62 (12%)
COPD	61 (12%)	49 (10%)
Risk factors		
Hypertension	362 (73%)	365 (73%)
Dyslipidaemia	323 (65%)	325 (65%)
Diabetes	146 (29%)	150 (30%)
Current smoker	67 (14%)	62 (13%)
Family history for cardiovascular disease	133 (29%)	146 (31%)
Characteristic at admission		
Haemoglobin, mmol/L	8·6 (8·0–9·1)	8·5 (7·9–9·1)
eGFR <60 mL/min per 1·73 m²	181 (36%)	186 (37%)
Killip class II–IV	50 (10%)	44 (9%)
$P2Y_{12}$ inhibitor after admittance		
Clopidogrel	132 (27%)	153 (31%)
Ticagrelor	354 (71%)	337 (67%)
(Table 1 continues in next column)		

	Clopidogrel (n=500)	Ticagrelor (n=502)
(Continued from previous column)		
During hospital stay		
Coronary angiography	439 (88%)	452 (90%)
Radial access	319 (74%)	340 (77%)
Multivessel disease	267 (61%)	267 (59%)
Percutaneous coronary intervention	232 (46%)	242 (48%)
Drug-eluting stent	219 (94%)	224 (93%)
Bare metal stent	2 (1%)	6 (3%)
CABG	78 (16%)	87 (17%)
At discharge		
Aspirin	422 (86%)	423 (86%)
Clopidogrel	434 (96%)	51 (12%)
Ticagrelor	19 (4%)	387 (88%)
Prasugrel	1 (<1%)	2 (<1%)
Non-vitamin K oral anticoagulant	21 (4%)	36 (7%)
Vitamin K antagonist	62 (12%)	65 (13%)
Proton pump inhibitor	446 (91%)	446 (90%)
Diagnosis at discharge		
NSTEMI	424 (86%)	423 (86%)
Unstable angina	54 (11%)	52 (11%)
Other	13 (3%)	17 (4%)

Data are n (%), median (IQR), or mean (SD). CABG=coronary artery bypass grafting. COPD=chronic obstructive pulmonary disease. eGFR=estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration formula). NSTEMI=non-ST-elevation myocardial infarction. *These patients randomly assigned to ticagrelor or prasugrel received only ticagrelor.

Table 1: **Baseline characteristics**

were based on data from the PLATO,[4] TRITON TIMI-38,[3] and WOEST trial.[14] Using a power of 80% and an α level of 0·05 we calculated that 821 patients would be needed to show superiority of clopidogrel. For the primary net clinical benefit outcome, the incidence was assumed to be 36·0% in the ticagrelor or prasugrel group and 30·8% in the clopidogrel group. The non-inferiority threshold for the absolute difference between the two groups in the incidence of the primary outcome was set at 2% points. We calculated that 1000 patients were needed to show non-inferiority (power 80%, α 2·5% one sided). The primary safety analysis and net clinical benefit analysis were done on an intention-to-treat basis as a time-to-event analysis from randomisation to the first occurrence of an event. Follow-up was 1 year. In addition, a per-protocol analysis was done. Per-protocol analysis included all patients who took the at least one dose of study drug they were randomly assigned to. In case of premature discontinuation, they were included until discontinuation of study drug. The net clinical benefit outcome was first assessed in an analysis of non-inferiority of clopidogrel versus ticagrelor or prasugrel. If non-inferiority was proven, superiority was tested. The trial was powered for both primary outcomes. Correction for multiple testing was not indicated.[15] Both primary outcomes were also assessed in 27 prespecified subgroups. Secondary outcomes were done on an intention-to-treat basis. We used Kaplan-Meier estimates with log-rank test to test for significant differences in outcomes between clopidogrel and ticagrelor or prasugrel. Hazard ratios and 95% CIs were generated with the use of a Cox proportional-hazards models. We tested the proportional hazards assumption for a Cox regression model fit with Schoenfeld residuals test. All tests were two-tailed and used a p value less than 0·05 to show statistical significance. All calculations were made in IBM SPSS Statistics (version 24). This trial is registered with the Netherlands Trial Register (NL3804), ClinicalTrials.gov (NCT02317198), and EudraCT (2013–001403–37).

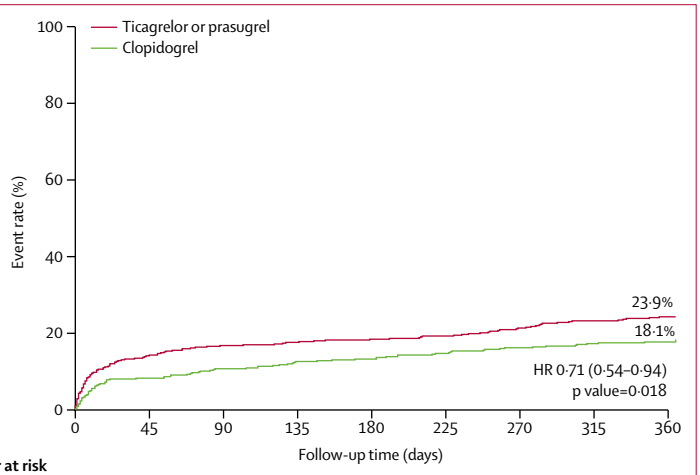
Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MG and JtB had full access to all the data in

	Clopidogrel (n=500)	Ticagrelor (n=502)	HR (95% CI)	p value
PLATO major and minor bleeding	88 (18%)	118 (24%)	0·71 (0·54–0·94)	0·018
PLATO minor bleeding	57 (12%)	74 (15%)	0·74 (0·52–1·04)	0·09
PLATO other major bleeding	25 (5%)	28 (6%)	0·89 (0·52–1·52)	0·69
PLATO major life threatening bleeding	15 (3%)	27 (6%)	0·56 (0·30–1·05)	0·06
PLATO major bleeding	38 (8%)	53 (11%)	0·71 (0·47–1·08)	0·11
PLATO non-CABG-related major bleeding	23 (5%)	43 (9%)	0·53 (0·32–0·88)	0·013
TIMI non-CABG-related major bleeding	6 (1%)	18 (4%)	0·33 (0·13–0·83)	0·014
TIMI major or minor bleeding	27 (6%)	45 (9%)	0·59 (0·37–0·95)	0·032
TIMI major bleeding	9 (2%)	21 (4%)	0·42 (0·19–0·93)	0·028
TIMI minor bleeding	20 (4%)	25 (5%)	0·79 (0·44–1·43)	0·46
TIMI minimal bleeding	86 (18%)	117 (24%)	0·69 (0·52–0·91)	0·010
Intracranial haemorrhage	2 (<1%)	5 (1%)	0·41 (0·08–2·09)	0·26
Fatal bleeding	0	5 (1%)	0·02 (0·00–20·79)	0·026
BARC 2 bleeding	66 (14%)	95 (19%)	0·65 (0·48–0·89)	0·009
BARC 3 bleeding	28 (6%)	41 (8%)	0·68 (0·42–1·10)	0·11
BARC 4 bleeding	16 (3%)	12 (2%)	1·32 (0·63–2·79)	0·44
BARC 5 bleeding	0	5 (1%)	0·02 (0·00–20·79)	0·026
BARC 3 and 5 bleeding	28 (6%)	46 (9%)	0·61 (0·38–0·98)	0·034

Data are n (%), unless otherwise stated. BARC=Bleeding Academic Research Consortium. CABG=coronary artery bypass grafting. HR=hazard ratio. PLATO=PLATelet inhibition and patient Outcomes. TIMI=thrombolysis in myocardial infarction.

Table 2: **Bleeding outcomes**



Number at risk									
Ticagrelor or prasugrel	502	422	408	404	398	394	383	372	366
Clopidogrel	500	452	438	422	419	408	399	391	387
Ticagrelor or prasugrel discontinuation	502	346	312	295	285	276	264	253	242
Clopidogrel discontinuation	500	424	402	392	388	379	369	362	356

Figure 2: **Kaplan-Meier curve for the primary bleeding outcome**
HR=hazard ratio.

See Online for appendix

the study and had final responsibility for the decision to submit for publication.

Results

Between June 10, 2013, and Oct 17, 2018, patients were screened for eligibility. A total of 1011 patients were enrolled and randomly assigned to clopidogrel or ticagrelor or prasugrel. There were no patients lost to follow-up, although nine patients dropped out (figure 1). Subsequently, 1002 patients entered the intention-to-treat analysis (500 in the clopidogrel group and 502 in the ticagrelor or prasugrel group). The baseline characteristics were well balanced between both treatment groups (table 1). Median age of patients was 77 years, 64% were male and 36% were female, and 36% had an impaired renal function, defined as an estimated glomerular filtration rate of less than 60 mL/min per 1·73 m². 977 (98%) of 1002 patients received a P2Y12 inhibitor after admittance and before randomisation. Median duration from admittance until randomisation was 26 h (IQR 18–48). In total 891 (89%) of 1002 patients underwent coronary angiography, of which 460 (52%) of 891 after randomisation. At discharge, 845 (86%) of 986 patients were prescribed aspirin and 184 (18%) of 993 had oral anticoagulation in addition to the P2Y12 inhibitor. 475 (95%) of 502 patients randomly assigned to ticagrelor or prasugrel were prescribed ticagrelor, therefore from here on, we will refer to the ticagrelor or prasugrel group as the ticagrelor group. During follow-up, premature discontinuation or switching of the study drug occurred in 238 (47%) of 502 of the patients randomised to ticagrelor, as compared with 112 (22%) of 500 of the patients randomised to clopidogrel. The most important reasons for discontinuation or switching of ticagrelor were dyspnoea, concomitant use of non-vitamin K oral anticoagulants, and bleeding (appendix p 15). The most important reasons for discontinuation or switching of clopidogrel were revision of diagnosis, bleeding, and undergoing coronary artery bypass grafting (CABG). Of the 78 patients randomly assigned to clopidogrel undergoing CABG during hospital stay, 56 (72%) patients were discharged on clopidogrel and 52 (67%) were on clopidogrel at 1-year follow-up. Of the 87 patients in the ticagrelor group, 49 (56%) patients undergoing CABG were discharged on ticagrelor and 35 (40%) were on ticagrelor at 1-year follow-up. The median duration of exposure to the study drug in the clopidogrel group was 365 days (IQR 247–365), and 324 days (22–365) in the ticagrelor group.

The primary bleeding outcome, consisting of PLATO major or minor bleeding after 12 months, occurred significantly less often in the clopidogrel group (in 88 [18%] of 500 patients) than in the ticagrelor group (in 118 [24%] of 502; hazard ratio 0·71, 95% CI 0·54 to 0·94, p=0·02 for superiority; table 2, figure 2). The composite net clinical benefit outcome, consisting of all-cause death, myocardial infarction, stroke, PLATO major and minor bleeding after 12 months, occurred in 139 (28%) patients receiving clopidogrel versus 161 (32%) patients receiving ticagrelor. The clopidogrel strategy met the prespecified criterion for non-inferiority (absolute risk difference –4% [95% CI –10·0 to 1·4]; p=0·03) for non-inferiority but not for superiority (0·82 [0·66 to 1·03];

p=0·11; table 3, figure 3). The results of the per-protocol analysis were consistent with those of the primary analysis (appendix p 16).

The incidence of PLATO non-CABG-related major bleeding and fatal bleeding was also significantly lower in the clopidogrel group than in the ticagrelor group (table 2). There were no significant differences in the composite thrombotic outcome consisting of cardiovascular death, myocardial infarction, and stroke, or in other secondary thrombotic outcomes, except for definite stent thrombosis, which occurred more frequently in patients randomly assigned to clopidogrel (table 3).

The prespecified subgroup analyses of the primary outcomes are shown in appendix pp 10,11. The results were generally consistent with the main findings of the study.

	Clopidogrel (n=500)	Ticagrelor (n=502)	ARD (95% CI)	HR (95% CI)	p value
Primary net clinical benefit outcome					
Non-inferiority analysis	139 (27%)	161 (32%)	−4·3 (−10·0 to 1·4)	..	0·025*
Superiority analysis	139 (28%)	161 (32%)	..	0·82 (0·66 to 1·03)	0·11
Secondary net clinical benefit outcome					
Cardiovascular death, myocardial infarction, stroke, PLATO major bleeding	85 (17%)	97 (20%)	..	0·87 (0·65 to 1·16)	0·37
Secondary thrombotic outcomes					
Cardiovascular death, myocardial infarction, stroke	53 (11%)	57 (12%)	..	0·92 (0·64 to 1·34)	0·71
All-cause death	37 (7%)	34 (7%)	..	1·08 (0·68 to 1·72)	0·72
Cardiovascular death	18 (4%)	15 (3%)	..	1·19 (0·60 to 2·37)	0·60
Myocardial infarction	37 (8%)	37 (8%)	..	1·00 (0·63 to 1·57)	0·99
Unstable angina	11 (2%)	10 (2%)	..	1·08 (0·46 to 2·55)	0·83
Ischaemic stroke	5 (1%)	10 (2%)	..	0·50 (0·17 to 1·46)	0·20
Transient ischaemic attack	7 (1%)	8 (2%)	..	0·87 (0·32 to 2·40)	0·80
Stent thrombosis	5 (1%)	0	..	..	0·03
Urgent revascularisation	12 (3%)	9 (2%)	..	1·33 (0·56 to 3·15)	0·50

Data are n (%), unless otherwise stated. ARD=absolute risk difference. HR=hazard ratio. PLATO=PLATelet inhibition and patient Outcomes. *p value for non-inferiority.

Table 3: **Primary net clinical benefit outcome and secondary thrombotic outcomes**

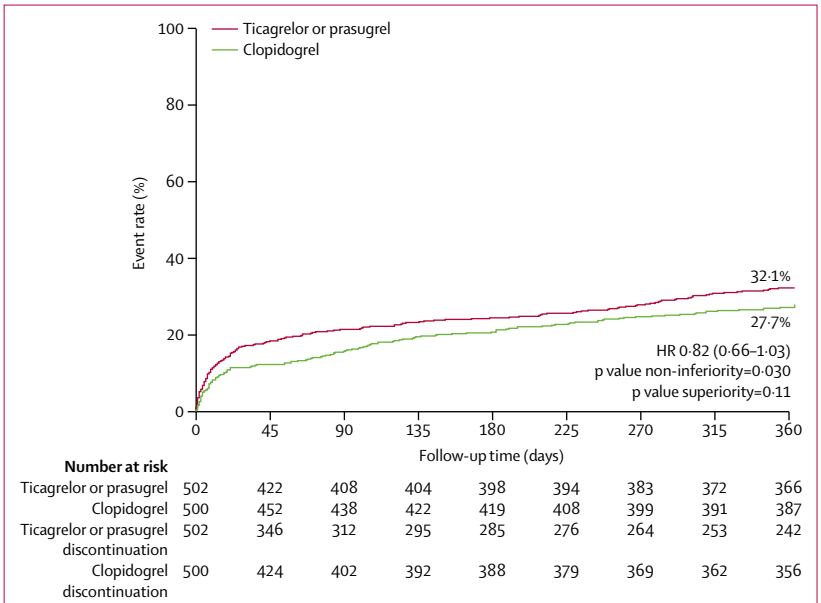


Figure 3: **Kaplan-Meier curve for the primary net clinical benefit outcome**
HR=hazard ratio.

Discussion

The POPular AGE trial, done in patients aged 70 years or older presenting with NSTE-ACS, showed that treatment with clopidogrel results in a significantly lower bleeding rate compared with treatment with ticagrelor, not only for the composite major and minor bleeding outcome, but also for PLATO non-CABG related major bleeding and fatal bleeding. These benefits of clopidogrel were not counterbalanced by an increase in thrombotic events, although the overall net clinical benefit outcome was non-inferior.

Previous trials have shown the benefit of adding clopidogrel to aspirin in patients with acute coronary syndrome to reduce the risk of death, myocardial infarction, and stroke.[16,17] Studies with the stronger P2Y12 inhibitors prasugrel and ticagrelor showed a further reduction of thrombotic risk compared with clopidogrel.[3,4,18,19] However, these benefits were in part counterbalanced by an increased risk for major bleeding. In these trials,[3,4,18,19] older patients with acute coronary syndrome were at increased risk for bleeding compared with younger patients.[3,7] This higher risk of bleeding poses an important concern, because bleeding is strongly associated with increased mortality.[20] Even nuisance bleeding frequently leads to premature discontinuation of the P2Y12 inhibitor, which puts the patient at risk for thrombotic events.[21,22] Therefore, it is important to weigh the benefit of a stronger antiplatelet strategy to the associated bleeding risk. Our study shows that the risk can be significantly reduced by using clopidogrel instead of ticagrelor in older patients.

The comparable thrombotic event rates between both treatment groups, as found in this trial, are in contrast with findings from the PLATO trial, which showed superiority of ticagrelor in reducing the risk of the composite of cardiovascular death, myocardial infarction, and stroke. In addition, our trial could not confirm the significant survival benefit of ticagrelor over clopidogrel, as was observed in the PLATO trial. Although, in our trial survival on ticagrelor was numerically better than on clopidogrel, the trial was not powered to find statistical differences in all-cause death between both treatment groups. However, in PLATO, superiority of ticagrelor was not shown in all patients; a subgroup analysis of older patients receiving revascularisation for NSTE-ACS showed similar results for clopidogrel versus ticagrelor.[23] Another

reason for the discrepancy in efficacy of ticagrelor could be that in the PLATO trial bare-metal stents and first-generation drug-eluting stents were used, whereas in our trial almost all patients undergoing percutaneous coronary intervention were stented with second-generation drug-eluting stents. The use of these safer second-generation drug-eluting stents might have reduced the need of the stronger platelet inhibitor ticagrelor. Similar to our trial, both the TOPIC trial,[24] comparing ticagrelor with clopidogrel after 1 month of standard treatment with stronger P2Y12 inhibitors, and the Dutch CHANGE DAPT ACS cohort study,[25] showed no significant difference in thrombotic event rates in patients given clopidogrel or ticagrelor.[25,26] Also in these trials,[24,25] second-generation drug-eluting stents were used.

In our study, the adherence to ticagrelor was much lower than to clopidogrel, with only 53% of patients continuing the more potent P2Y12 inhibitors compared with 78% for clopidogrel during 12-month follow-up. The most important reasons for discontinuation were occurrence of bleeding, other side-effects (mostly dyspnoea), and the need for treatment with oral anticoagulants, for which most patients were switched to clopidogrel, according to local treatment protocol. We nevertheless decided to allow patients on oral anticoagulants to be included in all analyses. We felt that the research question of optimal P2Y12 inhibition was even more relevant in these patients because this group of patients was increasing in non-trial settings; dual therapy (oral anticoagulants plus clopidogrel) was shown to be safe for this group in our WOEST trial;[14] and the atrial fibrillation-percutaneous coronary intervention trials,[26,27] PIONEER trial,[26] and RE-DUAL trial[27] allowed the use of the stronger P2Y12 inhibitor ticagrelor in dual therapy and even in triple therapy (oral anticoagulants, aspirin, and P2Y12 inhibitor) in these patients.

On the one hand, the higher discontinuation rate in the ticagrelor group of our study compared with that observed in other randomised controlled trials might partly be explained by the open label design of the study, because increased bleeding risk and dyspnoea are known side-effects of ticagrelor. On the other hand, this higher discontinuation rate resembles issues of maintaining potent antiplatelet therapy after acute coronary syndrome in a real-life scenario as we, and others, have reported on.[28]

This study has limitations inherent to the open-label design, because knowledge of treatment allocation could have influenced treatment decisions after randomisation. Additionally, because only less than 1% of patients were given prasugrel, the results of this trial cannot be translated to patients given this drug. This can especially be relevant for those study patients between 70 and 75 years of age with acute coronary syndrome, because the ISAR-REACT 5 study[29] showed superiority of prasugrel over ticagrelor in the reduction of death, myocardial infarction, and stroke. Further, the study was not powered to show significant differences between clopidogrel and ticagrelor for the thrombotic endpoint or mortality, making interpretation of the these results of our trial only hypothesis generating. Although, the POPular AGE trial was designed to include an all-comers population with NSTE-ACS, recruitment was slow, which was partly explained by the high number of excluded patients relative to the number of excluded patients from other trials, which could have caused selection bias in the study population. However, the high number of excluded patients also shows the difficulty of doing randomised controlled trials in older patients as was also seen in the After Eighty trial.[30] Finally, premature discontinuation of study medication was high in the POPular AGE trial, especially in the ticagrelor group, which might have affected the results in this group. The high discontinuation rate resembles issues of maintaining potent antiplatelet therapy after acute coronary syndrome in a real-life scenario as we, and others, have reported on.[28,31]

The POPular AGE trial is the largest, completed, randomised trial investigating antiplatelet therapy in older patients with NSTE-ACS published to date, showing favourable results of clopidogrel compared with ticagrelor. These results need confirmation from future trials to change guidelines regarding antiplatelet therapy in older patients. In the meantime, for older patients especially at an increased risk of bleeding, clopidogrel can be used as first choice therapy. Personalised antiplatelet therapy by means of platelet function testing or genotyping, studied in the TROPICAL-ACS trial[32] and POPular Genetics trial[33] respectively, might further optimise antiplatelet therapy in older patients.

In conclusion, in patients aged 70 years or older presenting with NSTE-ACS, clopidogrel is a favourable alternative to ticagrelor, because it leads to fewer bleeding events without an increase in the combined endpoint of all-cause death, myocardial infarction, stroke, and bleeding.

Contributors

JtB, VD, KQ, and TB designed the study. MG, JtB, VD, JK, and KQ participated in the steering committee and contributed to implementation of the study. MG, KQ, LW, TB, RH, EdV, TH, MTJG, RW, SH, FdH, WJ, CvB, and MV contributed to the implementation of the study and did the enrolment of patients in the study. MG collected all the follow-up data of patients. MG and JK did all statistical analyses. MG, JB, VD, and JK analysed and interpreted the data. MG and JB wrote the paper. All authors critically reviewed the manuscript.

Declaration of interests

MG, KQ, LW, TB, VD, and JtB report grants from the Netherlands Organization for Health Research and Development, a Dutch government institution called ZonMw, during the conduct of the study. JB reports grants from AstraZeneca; and personal fees from AstraZeneca, Boehinger Ingelheim, Bayer, Ferrer, Pfizer, and Merck, outside the submitted work. 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. 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. All other authors declare no competing interests.

Data sharing

No individual participant data will be available. The study protocol will be available in the appendix.

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