Journal of the American Heart Association

ORIGINAL RESEARCH

Age-Dependent Effect of Ticagrelor Monotherapy Versus Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events: A Post Hoc Analysis of the TICO Randomized Trial

Byung Gyu Kim, MD*; Sung-Jin Hong, MD*; Byeong-Keuk Kim, MD, PhD; Seung-Jun Lee, MD; Chul-Min Ahn, MD; Dong-Ho Shin, MD, MPH; Jung-Sun Kim, MD; Young-Guk Ko, MD; Donghoon Choi, MD; Myeong-Ki Hong, MD; Yangsoo Jang, MD

BACKGROUND: We aimed to evaluate the age-dependent effect of ticagrelor monotherapy after 3-month dual-antiplatelet therapy (DAPT) versus ticagrelor-based 12-month DAPT on major bleeding and cardiovascular events in patients with acute coronary syndrome.

METHODS AND RESULTS: From the TICO trial (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome), which randomized 3056 patients (median age, 61 years) to the ticagrelor monotherapy after 3-month DAPT group or ticagrelor-based 12-month DAPT group, this post hoc analysis evaluated the age-dependent effect of the treatment strategies on the primary end point (a composite of major bleeding, death, myocardial infarction, stent thrombosis, stroke, or target-vessel revascularization) using the subpopulation treatment effect pattern plot. The cutoff age for distinguishing patients with greater benefit from this strategy was also determined. The risk reduction effect of ticagrelor monotherapy after 3-month DAPT versus ticagrelor-based 12-month DAPT on the primary end point gradually increased with age and was more marked from the subpopulation of age 64 years with the change point. With this cutoff value of 64 years, the occurrence of the primary end point was significantly lower in the ticagrelor monotherapy after 3-month DAPT group than in the ticagrelor-based 12-month DAPT group (4.4% versus 9.0%; *P*=0.002) in patients aged ≥64 years (n=1278), but it was not different in those aged <64 years (n=1778) with a significant interaction (*P*-interaction=0.036).

CONCLUSIONS: The age-dependent increase in the benefit of ticagrelor monotherapy after 3-month DAPT versus ticagrelor-based 12-month DAPT was observed in the patients with acute coronary syndrome. In elderly patients with acute coronary syndrome, ticagrelor monotherapy after short-term DAPT might be more optimal than ticagrelor-based 12-month DAPT.

Key Words: acute coronary syndrome ■ age ■ dual-antiplatelet therapy ■ ticagrelor

Dual-antiplatelet therapy (DAPT) with potent $P2Y_{12}$ inhibitors, such as ticagrelor or prasugrel, for up to 12 months is recommended for patients with acute coronary syndrome (ACS) who undergo percutaneous coronary intervention (PCI) with a drug-eluting stent (DES).[1,2] However, this strategy is associated with some concerns related to increased bleeding risks even in patients with high thrombotic risks.[3,4] Recently, treatment

Correspondence to: Byeong-Keuk Kim, MD, PhD, Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Yonsei-ro 50-1, Seodaemun-gu, 03722 Seoul, South Korea. E-mail: kimbk@yuhs.ac

*B. G. Kim and S.-J. Hong contributed equally.

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.022700

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Although ticagrelor monotherapy after 3-month dual-antiplatelet therapy (DAPT) resulted in a significant reduction in a composite end point of major bleeding and cardiovascular events compared with ticagrelor-based 12-month DAPT in patients with acute coronary syndrome, it remains uncertain whether this effect is dependent according to the ages.
- Our study presents an age-dependent increasing benefit of the ticagrelor monotherapy after 3-month DAPT versus ticagrelor-based 12-month DAPT as for the net adverse clinical outcome. The benefit was more pronounced in elderly patients (aged ≥64 years) than in younger patients (aged <64 years).

What Are the Clinical Implications?

- Our results suggest that ticagrelor monotherapy after short-term DAPT, rather than ticagrelor-based 12-month DAPT, might be an optimal antiplatelet strategy in elderly patients with acute coronary syndrome.

Nonstandard Abbreviations and Acronyms

DAPT	dual-antiplatelet therapy
DES	drug-eluting stent
MACCE	major adverse cardiac and cerebrovascular event

strategies, such as short-term DAPT followed by potent $P2Y_{12}$ inhibitor monotherapy or $P2Y_{12}$ inhibitor deescalation, have been proposed,[5–7] and these strategies have demonstrated a significant reduction in bleeding events without an increase in thrombotic complications. The TICO randomized trial (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome) also showed that early discontinuation of aspirin with switch to ticagrelor monotherapy is effective for balancing both bleeding and ischemic outcomes in patients with ACS who undergo PCI.[5] This aspirin-free strategy with ticagrelor monotherapy is particularly beneficial in older patients, considering that older patients are at a greater risk of bleeding compared with younger patients, and old age is a well-known determinant of poor outcomes after PCI.[8,9] However, whether this aspirin-free strategy used in the TICO trial for ACS treatment is age dependent is unclear.

We evaluated the age-dependent effect of ticagrelor monotherapy after 3-month DAPT versus ticagrelor-based 12-month DAPT on the net adverse clinical events (a composite of major bleeding, death, myocardial infarction, stent thrombosis, stroke, or target-vessel revascularization), the primary end point, in patients with ACS as a post hoc analysis of the TICO trial. In addition, we investigated the cutoff age to distinguish patients with greater benefit from this strategy.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population and Groups

The TICO trial was a multicenter randomized trial and included the 3056 patients with ACS who underwent PCI with ultrathin bioresorbable polymer sirolimus-eluting stents (Orsiro; Biotronik AG, Bülach, Switzerland). More detailed inclusion and exclusion criteria have been previously published.[5] The trial was approved by the institutional review board at each center and was performed in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent before participation in the trial. In the TICO trial, patients were randomly assigned 1:1 to receive either ticagrelor monotherapy after 3-month DAPT or ticagrelor-based 12-month DAPT after DES implantation. Clinical follow-up was completed for all except 78 patients, of whom 48 were lost to follow-up and 30 withdrew consent.

Study Outcomes

The primary end point was the occurrence of a net adverse clinical event, defined as a composite of major bleeding and major adverse cardiac and cerebrovascular events (MACCEs) at 12 months after PCI.[5] Major bleeding was defined according to the TIMI (Thrombolysis in Myocardial Infarction) criteria: intracranial bleeding, hemorrhage with at least 5 g/dL decrease in hemoglobin, or fatal bleeding causing death within 7 days.[5] MACCE was defined as a composite of all-cause death, myocardial infarction, stent thrombosis, stroke, and target-vessel revascularization.[5] Key secondary end points were major bleeding and MACCE. Other clinical end points were as follows: intracranial bleeding, fatal bleeding, all-cause death, cardiac death, noncardiac death, myocardial infarction, stent thrombosis, stroke, or target-vessel revascularization.

Statistical Analysis

Continuous variables are expressed as mean±SD, and categorical variables are expressed as numbers and frequencies. Group comparisons were performed

using the Student *t* test, Mann-Whitney *U* test, χ^2 test, or Fisher exact test. To potential nonlinear relationship between age (a continuous variable) and clinical outcomes, restricted cubic spline curves were plotted. Age-dependent analyses were performed on an intention-to-treat basis, and graphically visualized using a subpopulation treatment effect pattern plot.[10] To determine the cutoff age for distinguishing patients with greater benefit from this strategy, the change point of the subpopulation age, marking the beginning of greater divergence, was selected, and serial interactions between treatment group factor and age (a continuous variable) were explored. Time-to-event data were presented using Kaplan-Meier curves, and the differences between groups were examined using the log-rank test. The treatment effect of ticagrelor monotherapy after 3-month DAPT versus ticagrelor-based 12-month DAPT between the 2 age subgroups was evaluated using an unadjusted Cox regression model. The interaction term (treatment-by-age category) was assessed using Cox regression models for the outcomes of interest. Univariate and multivariate Cox regression analyses were performed to determine predictors of primary and key secondary end points. Variables found to be significant ($P<0.10$) in univariate analysis for ticagrelor monotherapy after 3-month DAPT were included in multivariate analysis. There were no missing data for the baseline medical conditions, and the patients with missing outcome data were censored at the time of loss to follow-up. All tests were 2 sided. $P<0.05$ was considered statistically significant. Statistical analyses were performed using R Statistical Software (version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Age-Dependent Effect of Ticagrelor Monotherapy After 3-Month DAPT

The age distribution of the 3056 patients is presented in Figure 1. The median age was 61 years (interquartile range, 53–69 years). No significant differences were observed in age distribution between the 2 antiplatelet strategy groups ($P=0.256$). The cubic spline curves revealed that the risks of net adverse clinical events (primary end point), major bleeding, and MACCE increased with patient age (Figure 2). In the subpopulation treatment effect pattern plot, the event rate curve of the primary end point in the ticagrelor monotherapy after 3-month DAPT group and that in the ticagrelor-based 12-month DAPT group gradually diverged with age. Notably, this divergence was markedly pronounced from the subpopulation of age 64 years (Figure 3A, upper panel). Consequently, an age-dependent gradual increasing benefit of ticagrelor monotherapy after 3-month DAPT versus ticagrelor-based 12-month DAPT for primary end point was observed, and it was more marked from the subpopulation aged 64 years with the change point (Figure 3A, lower panel). An additional exploratory analysis for interaction testing also revealed the age of 64 years as an optimal cutoff for separating age categories for the primary end point from ticagrelor monotherapy after 3-month DAPT versus ticagrelor-based 12-month DAPT. Subpopulation treatment effect pattern plots for the major bleeding and MACCE showed the similar pattern with primary end point (Figure 3B and 3C).

Interaction Between Age and Treatment Strategy for the Primary End Point

When the patients were categorized on the basis of the cutoff age of 64 years, 1278 (42%) patients were aged ≥64 years and 1778 (58%) patients were aged <64 years. The baseline characteristics according to the age groups and antiplatelet strategies are summarized in Table 1. No differences were found in the baseline characteristics of the ticagrelor monotherapy after 3-month DAPT and ticagrelor-based 12-month DAPT groups according to patient age. A comparison of the baseline characteristics according to age subgroups is summarized in Table S1.

Table 2 summarizes all relevant outcome data and interaction terms for ischemic and bleeding events, according to age subgroups. In patients aged ≥64 years, ticagrelor monotherapy after 3-month DAPT resulted in a significant reduction in the primary end point compared with ticagrelor-based 12-month DAPT (4.4% versus 9.0%; hazard ratio [HR], 0.49; 95% CI, 0.31–0.76; $P=0.002$) (Table 2 and Figure 4A). However, the incidence of primary end point was not different in patients aged <64 years (Figure 4B). Moreover, a significant interaction was observed between age and treatment group ($P=0.036$) (Table 2). Three-month landmark analyses revealed that among patients aged ≥64 years, the incidence of primary end point was significantly lower in the ticagrelor monotherapy after 3-month DAPT group than in the ticagrelor-based 12-month DAPT group (HR, 0.30; 95% CI, 0.15–0.56; $P<0.001$) (Figure 4C). Among patients aged <64 years, no significant differences were found between the 2 groups for the incidence of primary end point (HR, 0.41; 95% CI, 0.32–1.60) (Figure 4D).

Interaction Between Age and Treatment Strategy for the Secondary End Points

For major bleeding, the incidence was significantly lower in the ticagrelor monotherapy after 3-month DAPT group than in the ticagrelor-based 12-month DAPT group among patients aged ≥64 years ($P=0.016$). However, among patients aged <64 years, it was not significantly higher in the ticagrelor monotherapy after

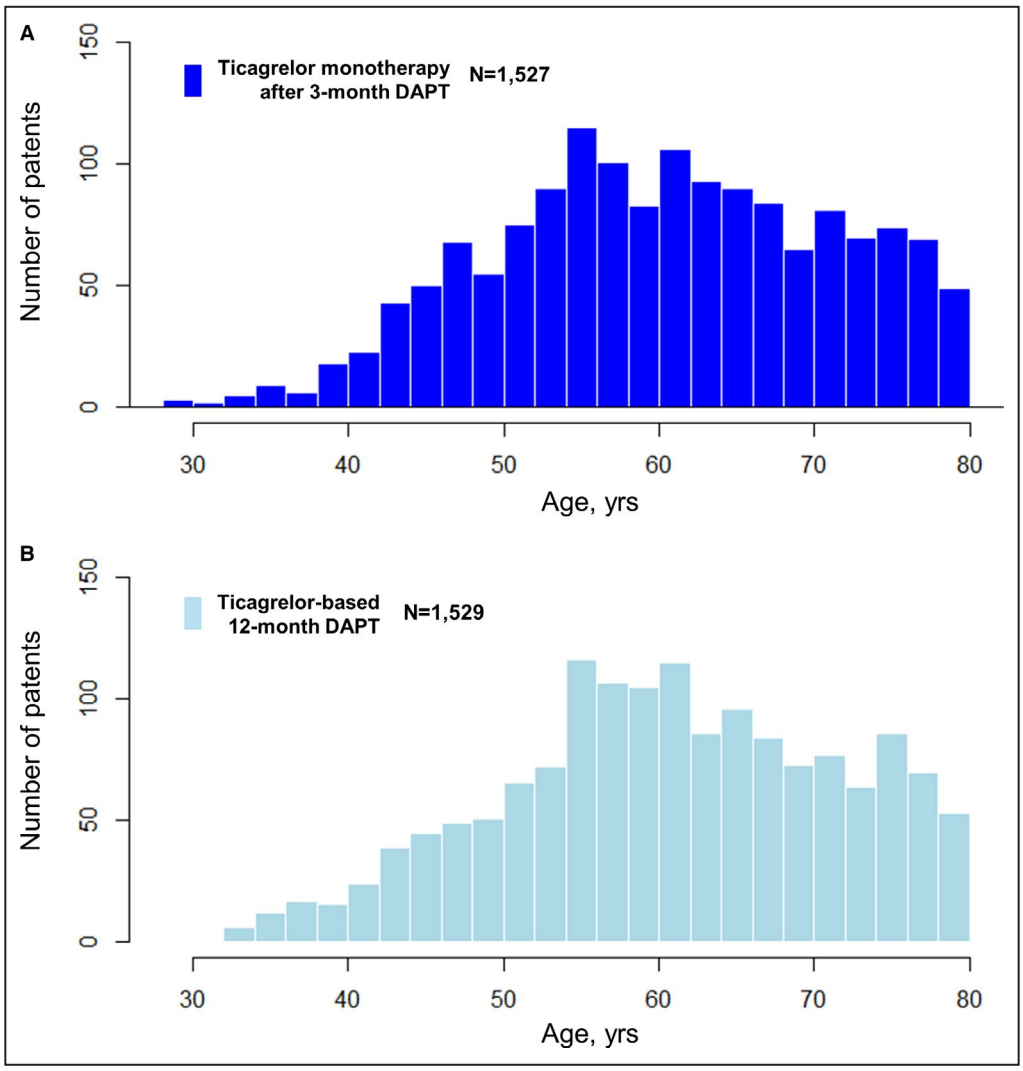

Figure 1. Distribution of age stratified by antiplatelet therapy strategies.
Histogram of ticagrelor monotherapy after 3-month dual-antiplatelet therapy (DAPT) (**A**) and ticagrelor-based 12-month DAPT group (**B**).

3-month DAPT group than in the ticagrelor-based 12-month DAPT group (P=0.456). For MACCE, it was significantly lower in the ticagrelor monotherapy after 3-month DAPT group than in the ticagrelor-based 12-month DAPT group among patients aged ≥64 years (P=0.022). However, among patients aged <64 years, it did not differ between the 2 groups (P=0.878). For major bleeding or MACCE, no significant interactions were found between age and treatment strategies (P=0.268 and P=0.103, respectively).

Predictors of Clinical Outcomes According to the Age Subgroups

Predictors of clinical outcomes according to age subgroups are shown in Tables S2 and S3. Among patients aged ≥64 years, ticagrelor monotherapy after 3-month DAPT was found to be an independent predictor of reduced risk of primary end point (HR, 0.58; 95% CI, 0.36–0.93; P=0.024) and major bleeding (HR, 0.49; 95% CI, 0.24–0.99; P=0.047). However, ticagrelor monotherapy after 3-month DAPT did not have a significant effect on either primary or key secondary end points in patients aged <64 years.

DISCUSSION

The present analysis of the TICO trial is the first dedicated analysis demonstrating the age-dependent effects of ticagrelor monotherapy after 3-month DAPT versus ticagrelor-based 12-month DAPT in patients with ACS after PCI with new-generation DES. Considering the general significant effect of patient age on clinical outcomes after PCI, our research to determine the effect of the new DAPT strategy according to age is

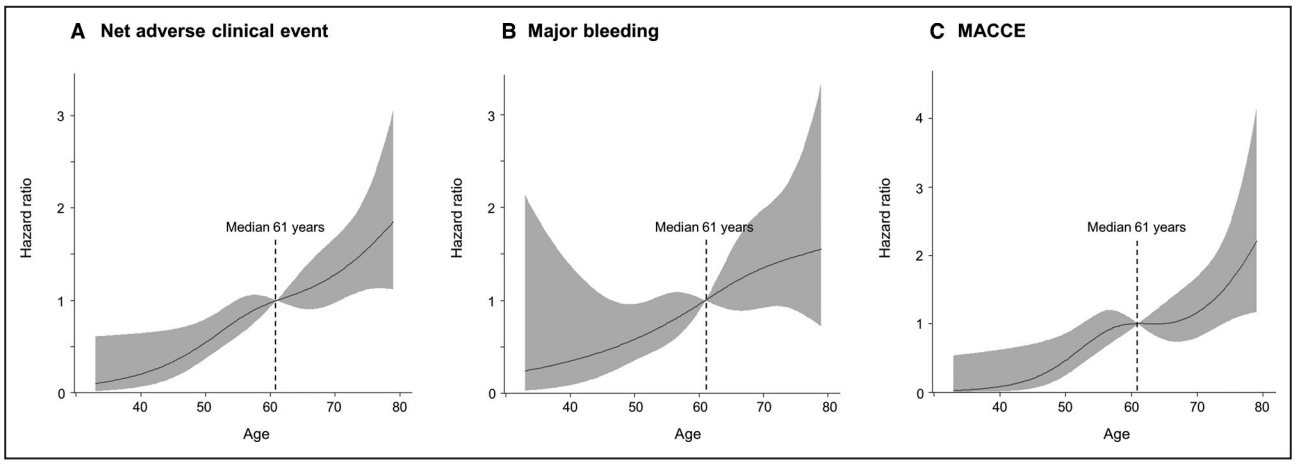

Figure 2. Relationship between age and clinical outcomes.
Black curve with gray area indicates unadjusted hazard ratio with 95% CI for net adverse clinical events (**A**), major bleeding (**B**), and major adverse cardiac and cerebrovascular events (MACCEs) (**C**).

an important study that can help establish a patient-tailored DAPT strategy. The main findings of our study are as follows: (1) the incidence of net adverse clinical event, major bleeding, and MACCE increases with the age of patients with ACS; (2) the beneficial effect of reduction in a composite end point of major bleeding and cardiovascular events attributable to ticagrelor monotherapy after 3-month DAPT versus ticagrelor-based 12-month DAPT increased with patient age; (3) the net clinical benefit of ticagrelor monotherapy after 3-month DAPT was more pronounced in elderly patients (aged ≥64 years) than in younger patients (aged <64 years); and (4) multivariate analysis revealed that ticagrelor monotherapy after 3-month DAPT is an independent predictor of reduced risk of net adverse clinical event and major bleeding in elderly patients aged ≥64 years.

Although a potent $P2Y_{12}$ inhibitor-based DAPT is currently recommended for up to 12 months in patients with ACS treated with DES, the increased bleeding risks because of prolonged DAPT and the related worse long-term outcomes raise the concerns about the use of DAPT after DES implantation for ACS.[1,2] Especially, elderly patients with coexisting risk factors for bleeding who undergo PCI tend to be at a greater risk of bleeding complications.[11] Advanced age has been found to be an independent predictor of bleeding and ischemic events.[12–17] A recent randomized trial comparing the use of clopidogrel versus a potent $P2Y_{12}$ inhibitor in patients aged ≥70 years with non–ST-segment–elevation ACS revealed that clopidogrel leads to fewer bleeding events without an increase in net clinical outcome compared with ticagrelor, indicating that elderly patients with ACS are particularly at great risk for bleeding.[15] In accordance with the previous studies in patients with ACS,[16] the current study demonstrated that the overall rates of bleeding and ischemic events were high in elderly patients aged ≥64 years and twice those in patients aged <64 years. In these elderly patients, although new DAPT strategies, such as aspirin-free ticagrelor monotherapy after the short-term phase that promotes the balance between bleeding and ischemic events, may be more appropriate for reducing adverse events, clinical evidence is lacking. Furthermore, investigating age-dependent effects of new DAPT strategies is necessary, considering the high prevalence of early termination of DAPT or switching of $P2Y_{12}$ inhibitors in elderly patients in the real world.[17]

Although it still remains uncertain which single antiplatelet therapy is most effective and safe after short-term DAPT, short-term DAPT followed by aspirin monotherapy had a higher incidence of myocardial infarction driven by spurt of events just after DAPT cessation, as indicated in the SMART-DATE trial (6-Versus 12-Month or Longer Dual Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients With Acute Coronary Syndrome) among the patients with ACS.[18] In the STOPDAPT-2 trial (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent), clopidogrel monotherapy after short-term DAPT increased the tendency, although not statistically significant, of myocardial infarction.[19] For clopidogrel monotherapy after short-term DAPT, there was a decreased response to clopidogrel attributable to genetic polymorphisms, particularly in patients with ACS.[20] Meanwhile, ticagrelor has superior pharmacodynamic effects over clopidogrel, regardless of the differences in genotype. The ticagrelor monotherapy after short-term DAPT improved bleeding outcomes without increasing the risk of ischemic events after DAPT termination in recent trials.[5,6,21] Hence, potent $P2Y_{12}$ inhibitor-based monotherapy after short-term DAPT may be a good option without increasing both bleeding and ischemic risks in patients with ACS and high bleeding risk, such as elderly patients.

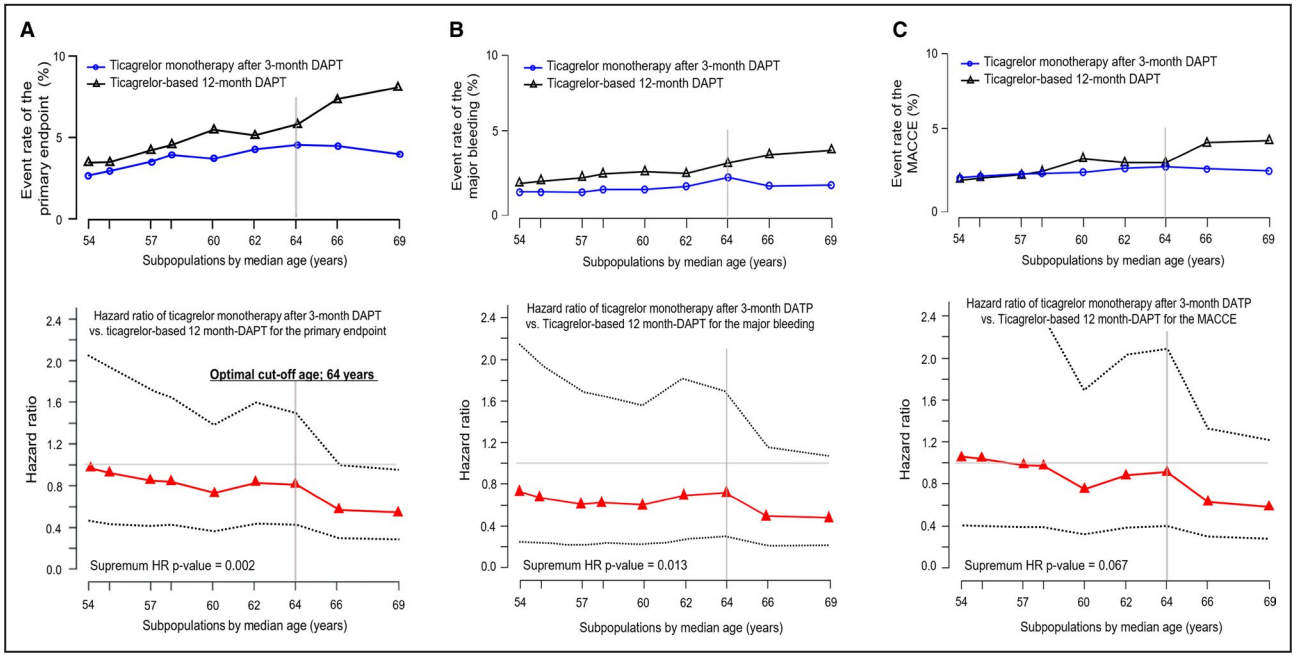

Figure 3. Subpopulation treatment effect pattern plot for treatment group and age.
Event rate of the clinical end points of the 2 treatment groups and subpopulation treatment effect pattern plot hazard ratio (HR) for net adverse clinical events (**A**), major bleeding (**B**), and major adverse cardiac and cerebrovascular events (MACCEs) (**C**). The red line represents the HRs, and the dotted lines represent the 95% CI. The supremum *P* value denotes the interaction term derived from subpopulation treatment effect pattern plot analysis. DAPT indicates dual-antiplatelet therapy.

In the present post hoc analysis of the TICO trial, although ticagrelor monotherapy after 3-month DAPT was found to be an effective and safe strategy that could replace ticagrelor-based 12-month DAPT in all age groups, the potential benefits of ticagrelor monotherapy were not uniform in all age groups. The effect of ticagrelor monotherapy on net clinical benefit tended to increase with patient age, and it was more pronounced in elderly patients aged ≥64 years. In particular, among the patients aged ≥64 years, the ticagrelor monotherapy after 3-month DAPT group showed lower occurrence of MACCE as well as bleeding events than the ticagrelor-based 12-month DAPT group. Although the precise mechanism of simultaneous reduction of both bleeding and ischemic events is unclear, it is postulated that ischemia can also be promoted by both overt and covert bleeding events because of a decrease in relative oxygen-carrying capacity, which causes hypotension and induces ischemia and severe arrhythmias, and discontinuation of antithrombotic drugs to manage bleeding.[22,23] According to other studies evaluating the optimal antiplatelet or antithrombotic strategies, a similar trend of simultaneous reduction of both bleeding and ischemic event was also observed.[24–27] Therefore, although direct association with overt bleeding-related events and MACCE was not observed because of relatively small event numbers in our data, bleeding reduction strategy of ticagrelor monotherapy versus ticagrelor-based DAPT may be an optimal strategy for both bleeding and ischemic event, especially in fragile elderly patients. Elderly patients have high risks of both bleeding and ischemia and, therefore, it could be more important to achieve a balance between bleeding and ischemic risks than to focus on either side. Given the fact that elderly patients represent the fast-growing patient subgroup undergoing PCI these days, our results show the evidence of the efficacy of the novel ticagrelor monotherapy, especially for high-risk patients of advanced age. Furthermore, a large-scale long-term clinical trial in elderly patients is required to definitively address and generalize the efficacy of ticagrelor monotherapy with short-term DAPT in these patients.

Limitations

Our study has several limitations. First, because this was a post hoc analysis to determine the effect of age on treatment efficacy, the age group obtained by post hoc analysis was not specifically powered for the primary or key secondary outcomes. Therefore, our findings need to be interpreted only in the context of hypothesis generation. Second, because the TICO trial was an open-label study in which the investigator and patient were not masked, there might be some possibility that residual bias and confounding factors have influenced the conclusion. Third, the TICO trial excluded patients aged >80 years. Elderly patients in this study included only those aged 64 to 80 years; generalization of findings to very elderly patients (aged >80 years)

Table 1. Baseline Characteristics of the Patients According to Age Subgroups

Characteristics	Patients aged ≥64 y (n=1278)			Patients aged <64 y (n=1778)			*P* value*
	Ticagrelor monotherapy after 3-mo DAPT (n=635)	Ticagrelor-based 12-mo DAPT (n=643)	*P* value	Ticagrelor monotherapy after 3-mo DAPT (n=892)	Ticagrelor-based 12-mo DAPT (n=886)	*P* value	
Age, y	71.2±4.8	71.4±4.8	0.477	53.2±6.9	53.7±7.1	0.150	<0.001
Body mass index, kg/m^2	24.1±3.1	24.2±3.1	0.860	25.5±3.1	25.5±3.4	0.938	<0.001
Women	209 (32.9)	216 (33.6)	0.843	114 (12.8)	89 (10.0)	0.082	<0.001
Hypertension	383 (60.3)	401 (62.4)	0.487	377 (42.3)	380 (42.9)	0.827	<0.001
Dyslipidemia	359 (56.5)	378 (58.8)	0.449	565 (63.3)	544 (61.4)	0.426	0.010
Diabetes	203 (32.0)	223 (34.7)	0.332	215 (24.1)	194 (21.9)	0.294	<0.001
Current smoker	122 (19.2)	146 (22.7)	0.143	433 (48.5)	441 (49.8)	0.637	<0.001
Chronic kidney disease	166 (26.1)	201 (31.3)	0.050	126 (14.1)	127 (14.3)	0.954	<0.001
Prior PCI	72 (11.3)	74 (11.5)	0.994	63 (7.1)	53 (6.0)	0.408	<0.001
Prior stroke	43 (6.8)	44 (6.8)	1.000	17 (1.9)	22 (2.5)	0.504	<0.001
Prior myocardial infarction	29 (4.6)	29 (4.5)	1.000	35 (3.9)	20 (2.3)	0.058	0.046
Prior CABG	6 (0.9)	9 (1.4)	0.621	2 (0.2)	1 (0.1)	1.000	0.001
Clinical presentation			0.555			0.015	<0.001
Unstable angina	215 (33.9)	230 (35.8)		227 (25.4)	254 (28.7)		
NSTEMI	218 (34.3)	226 (35.1)		321 (36.0)	262 (29.6)		
STEMI	202 (31.8)	187 (29.1)		344 (38.6)	370 (41.8)		
Ejection fraction, %	54.6±12.1	54.5±13.1	0.972	54.7±11.6	54.5±11.6	0.790	0.900
Transradial approach	352 (55.4)	368 (57.2)	0.554	485 (54.4)	493 (55.6)	0.623	0.488
Multivessel diseases	395 (62.2)	411 (63.9)	0.564	447 (50.1)	450 (50.8)	0.812	<0.001
Multilesion intervention	132 (20.8)	148 (23.0)	0.370	174 (19.5)	164 (18.5)	0.635	0.055
Total no. of stents per patients	1.4±0.7	1.4±0.7	0.844	1.4±0.7	1.3±0.6	0.858	0.118
Total stent length per patient, mm	35.3±20.5	35.4±21.6	0.901	34.0±20.5	34.6±19.9	0.550	0.174
Stent diameter, mm	3.1±0.4	3.1±0.4	0.427	3.2±0.5	3.2±0.4	0.501	<0.001

Data are presented as mean±SD or number (percentage). CABG indicates coronary artery bypass grafting; DAPT, dual-antiplatelet therapy; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*Comparison between patients aged ≥64 years and those aged <64 years.

Table 2. Clinical Outcomes at 1 Year According to Age Subgroups

Clinical outcomes	Subgroups of ages, y	Ticagrelor monotherapy after 3-mo DAPT (n=1527)	Ticagrelor-based 12-mo DAPT (n=1529)	Hazard ratio (95% CI)	*P* value	*P* value for interaction
Primary end point						
Net adverse clinical event	<64	31 (3.5)	31 (3.5)	1.00 (0.61–1.64)	0.985	0.036
	≥64	28 (4.4)	58 (9.0)	0.49 (0.31–0.76)	0.002	
Key secondary end points						
Major bleeding	<64	13 (1.5)	17 (1.9)	0.76 (0.37–1.56)	0.456	0.268
	≥64	12 (1.9)	28 (4.4)	0.43 (0.22–0.85)	0.016	
Major adverse cardiac and cerebrovascular events	<64	18 (2.0)	17 (1.9)	1.05 (0.54–2.04)	0.878	0.103
	≥64	17 (2.7)	34 (5.3)	0.51 (0.28–0.91)	0.022	
Other clinical end points						
Intracranial bleeding	<64	2 (0.2)	1 (0.1)	1.99 (0.18–21.97)	0.574	0.429
	≥64	1 (0.2)	2 (0.3)	0.51 (0.05–5.60)	0.580	
Fatal bleeding	<64	0	1 (0.1)	…		
	≥64	0	1 (0.2)	…		
All-cause death	<64	6 (0.7)	6 (0.7)	1.00 (0.32–3.09)	0.995	0.467
	≥64	10 (1.6)	17 (2.6)	0.60 (0.27–1.31)	0.197	
Cardiac death	<64	2 (0.2)	3 (0.3)	0.66 (0.11–3.98)	0.654	0.878
	≥64	5 (0.8)	9 (1.4)	0.56 (0.19–1.68)	0.304	
Noncardiac death	<64	4 (0.5)	3 (0.3)	1.33 (0.30–5.93)	0.711	0.441
	≥64	5 (0.8)	8 (1.2)	0.64 (0.21–1.95)	0.428	
Myocardial infarction	<64	3 (0.3)	5 (0.6)	0.60 (0.14–2.49)	0.479	0.877
	≥64	3 (0.5)	6 (0.9)	0.51 (0.13–2.04)	0.340	
Stent thrombosis, definite or probable	<64	2 (0.2)	2 (0.2)	1.00 (0.14–7.07)	0.997	0.590
	≥64	4 (0.6)	2 (0.3)	2.03 (0.37–11.09)	0.413	
Stroke	<64	6 (0.7)	4 (0.5)	1.49 (0.42–5.29)	0.535	0.111
	≥64	2 (0.3)	7 (1.1)	0.29 (0.06–1.39)	0.122	
Target-vessel revascularization	<64	2 (0.2)	3 (0.3)	0.66 (0.11–3.96)	0.650	0.984
	≥64	2 (0.3)	3 (0.5)	0.68 (0.11–4.06)	0.672	

Data are presented as numbers (event rates, %). Event rates were calculated using Kaplan-Meier estimates. The cutoff age of 64 years was derived from the subpopulation treatment effect pattern plot where the effect of ticagrelor monotherapy after 3-month DAPT vs ticagrelor-based 12-month DAPT on the net adverse clinical event was markedly pronounced with the change point. DAPT indicates dual-antiplatelet therapy.

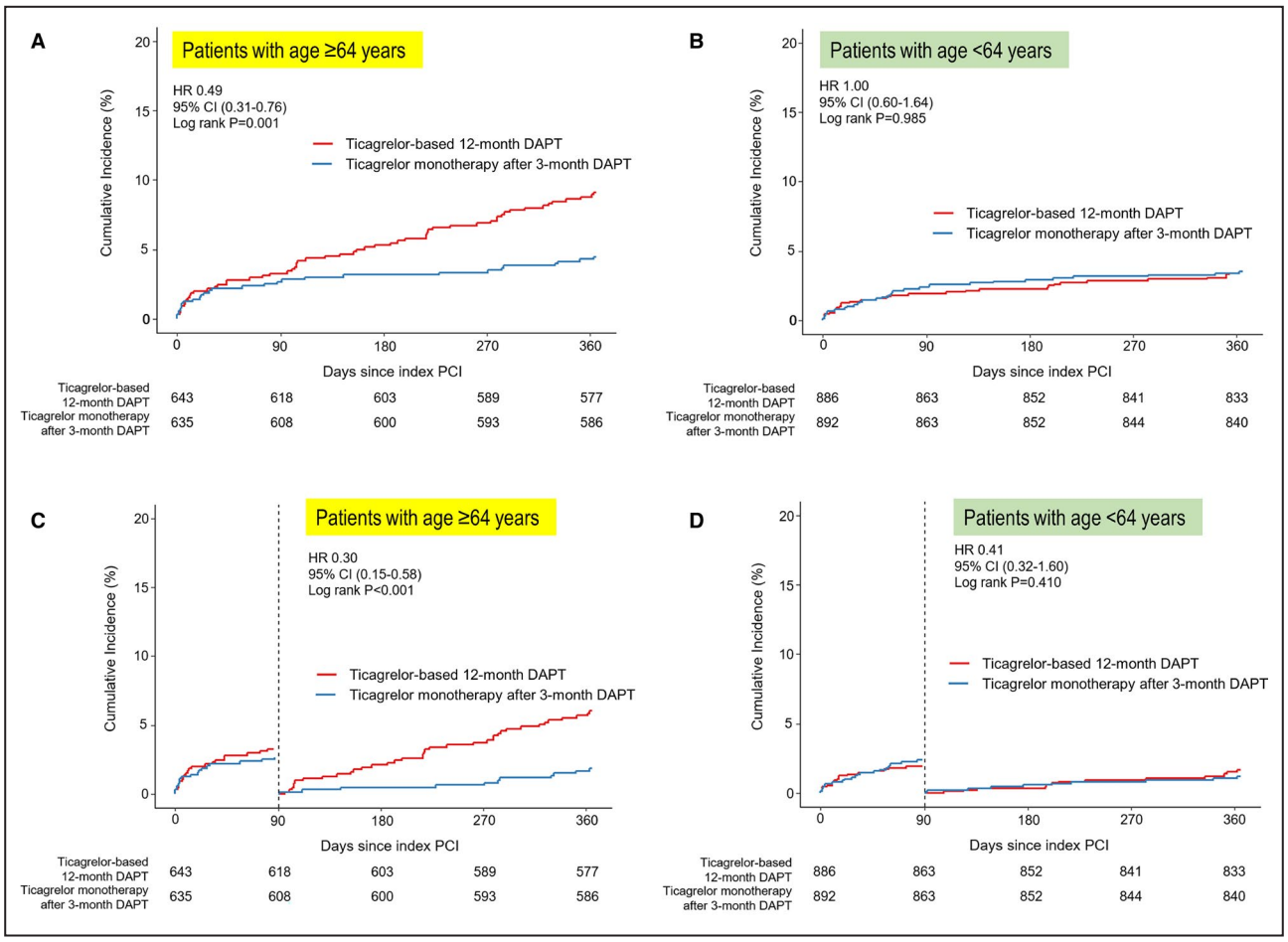

Figure 4. Kaplan-Meier curves for the primary end point according to age groups.
Ticagrelor monotherapy after 3-month dual-antiplatelet therapy (DAPT) significantly reduced the incidence of primary end point compared with ticagrelor-based 12 month-DAPT in patients aged ≥64 years (**A**), unlike in patients aged <64 years (**B**). These findings are consistent with those of landmark analyses in patients aged ≥64 years (**C**) and those aged <64 years (**D**). HR indicates hazard ratio; and PCI, percutaneous coronary intervention.

should made with caution. Fourth, some patients with high bleeding risk strongly associated with old age were excluded from the study, which might have affected the overall results. Further large-scale studies, including patients of various age groups with minimal limitations, are required. Finally, because the TICO trial was performed exclusively in patients who underwent ultrathin sirolimus-eluting stent implantation, our results should be interpreted cautiously for the general population treated with other DESs.

CONCLUSIONS

The age-dependent increase in the benefit of ticagrelor monotherapy after 3-month DAPT versus ticagrelor-based 12-month DAPT was observed, and the beneficial treatment effect of this strategy tends to be remarkable in elderly patients aged ≥64 years. These results suggest that ticagrelor monotherapy after short-term DAPT, rather than ticagrelor-based 12-month DAPT, might be a more suitable antiplatelet strategy in elderly patients with ACS who implanted bioabsorbable polymer sirolimus-eluting stents.

ARTICLE INFORMATION

Received June 1, 2021; accepted November 8, 2021.

Affiliations

Division of Cardiology, Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea (B.G.K.); and Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Korea (S.H., B.K., S.L., C.A., D.S., J.K., Y.K., D.C., M.H., Y.J.).

Sources of Funding

This work was supported by the Cardiovascular Research Center, Seoul, South Korea.

Disclosures

None.

Supplemental Material

Tables S1–S3

REFERENCES

1. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:2354–2394. doi: 10.1161/CIR.0000000000000133
2. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: 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*. 2016;37:267–315. doi: 10.1093/eurheartj/ehv320
3. Antman EM, Wiviott SD, Murphy SA, Voitk J, Hasin Y, Widimsky P, Chandna H, Macias W, McCabe CH, Braunwald E. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRION-TIMI 38 (trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction) analysis. *J Am Coll Cardiol*. 2008;51:2028–2033. doi: 10.1016/j.jacc.2008.04.002
4. Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, French J, Held C, Horrow J, Husted S, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the platelet inhibition and patient outcomes (PLATO) trial. *Eur Heart J*. 2011;32:2933–2944. doi: 10.1093/eurheartj/ehr422
5. Kim B-K, Hong S-J, Cho Y-H, Yun KH, Kim YH, Suh Y, Cho JY, Her A-Y, Cho S, Jeon DW, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA*. 2020;323:2407–2416. doi: 10.1001/jama.2020.7580
6. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet*. 2018;392:940–949. doi: 10.1016/S0140-6736(18)31858-0
7. Kim H-S, Kang J, Hwang D, Han J-K, Yang H-M, Kang H-J, Koo B-K, Rhew JY, Chun K-J, Lim Y-H, et al. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. *Lancet*. 2020;396:1079–1089. doi: 10.1016/S0140-6736(20)31791-8
8. Yan RT, Yan AT, Tan M, Chow CM, Fitchett DH, Ervin FL, Cha JY, Langer A, Goodman SG; Canadian Acute Coronary Syndromes Registry Investigators. Age-related differences in the management and outcome of patients with acute coronary syndromes. *Am Heart J*. 2006;151:352–359. doi: 10.1016/j.ahj.2005.03.039
9. Lopes RD, Alexander KP, Manoukian SV, Bertrand ME, Feit F, White HD, Pollack CV Jr, Hoekstra J, Gersh BJ, Stone GW, et al. Advanced age, antithrombotic strategy, and bleeding in non-ST-segment elevation acute coronary syndromes: results from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *J Am Coll Cardiol*. 2009;53:1021–1030. doi: 10.1016/j.jacc.2008.12.021
10. Bonetti M, Gelber RD. Patterns of treatment effects in subsets of patients in clinical trials. *Biostatistics*. 2004;5:465–481. doi: 10.1093/biostatistics/kxh002
11. Feldman DN, Gade CL, Slotwiner AJ, Parikh M, Bergman G, Wong SC, Minutello RM; New York State Angioplasty Registry. Comparison of outcomes of percutaneous coronary interventions in patients of three age groups (<60, 60 to 80, and >80 years) (from the New York State Angioplasty Registry). *Am J Cardiol*. 2006;98:1334–1339.
12. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, Pilgrim T, Hong M-K, Kim H-S, Colombo A, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet*. 2017;389:1025–1034. doi: 10.1016/S0140-6736(17)30397-5
13. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, Ariti C, Litherland C, Dangas G, Gibson CM, et al. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. *J Am Coll Cardiol*. 2016;67:2224–2234. doi: 10.1016/j.jacc.2016.02.064
14. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003;163:2345–2353. doi: 10.1001/archinte.163.19.2345
15. Gimbel M, Qaderdan K, Willemsen L, Hermanides R, Bergmeijer T, de Vrey E, Heestermans T, Tjon Joe Gin M, Waalewijn R, Hofma S, 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;395:1374–1381. doi: 10.1016/S0140-6736(20)30325-1
16. Sibbing D, Gross L, Trenk D, Jacobshagen C, Geisler T, Hadamitzky M, Merkely B, Kiss RG, Komócsi A, Parma R, et al. Age and outcomes following guided de-escalation of antiplatelet treatment in acute coronary syndrome patients undergoing percutaneous coronary intervention: results from the randomized TROPICAL-ACS trial. *Eur Heart J*. 2018;39:2749–2758. doi: 10.1093/eurheartj/ehy332
17. De Luca L, D'Ascenzo F, Musumeci G, Saia F, Parodi G, Varbella F, Marchese A, De Servi S, Berti S, Bolognese L. Incidence and outcome of switching of oral platelet P2Y12 receptor inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention: the SCOPE registry. *EuroIntervention*. 2017;13:459–466. doi: 10.4244/EIJ-D-17-00092
18. Hahn J-Y, Song YB, Oh J-H, Cho D-K, Lee JB, Doh J-H, Kim S-H, Jeong J-O, Bae J-H, Kim B-O, et al. 6-Month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. *Lancet*. 2018;391:1274–1284. doi: 10.1016/S0140-6736(18)30493-8
19. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA*. 2019;321:2414–2427. doi: 10.1001/jama.2019.8145
20. Hasan MS, Basri HB, Hin LP, Stanslas J. Genetic polymorphisms and drug interactions leading to clopidogrel resistance: why the Asian population requires special attention. *Int J Neurosci*. 2013;123:143–154. doi: 10.3109/00207454.2012.744308
21. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381:2032–2042. doi: 10.1056/NEJMoa1908419
22. Kawakami S, Yasuda S, Ogawa H. Antithrombotic therapy in atrial fibrillation patients with coronary artery disease: shifting paradigm to a "less is more" concept regimen. *J Cardiol*. 2020;76:35–43. doi: 10.1016/j.jjcc.2020.03.001
23. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *Lancet*. 2013;382:1714–1722. doi: 10.1016/S0140-6736(13)61720-1
24. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N Engl J Med*. 2019;381:1103–1113. doi: 10.1056/NEJMoa1904143
25. Koo B-K, Kang J, Park KW, Rhee T-M, Yang H-M, Won K-B, Rha S-W, Bae J-W, Lee NH, Hur S-H, et al. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. *Lancet*. 2021;397:2487–2496. doi: 10.1016/S0140-6736(21)01063-1
26. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med*. 2019;380:1509–1524. doi: 10.1056/NEJMoa1817083
27. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, et al. Very short dual antiplatelet therapy after drug-eluting stent implantation in patients with high bleeding risk: insight from the STOPDAPT-2 trial. *Circulation*. 2019;140:1957–1959. doi: 10.1161/CIRCULATIONAHA.119.043613

Supplemental Material

Table S1. Comparison of baseline characteristics between patients with ≥64 years of age and <64 years.

Characteristics	Age ≥64 years (n=1,278)	Age <64 years (n=1,778)	P value
Age, y	71.3±4.8	53.5±7.0	<0.001
Body mass index, kg/m^2	24.1±3.1	25.5±3.3	<0.001
Female	425 (33.3)	203 (11.4)	<0.001
Comorbidities, n (%)			
Hypertension	784 (61.3)	757 (42.6)	<0.001
Dyslipidemia	737 (57.7)	1,109 (62.4)	0.010
Diabetes	426 (33.3)	409 (23.0)	<0.001
Current smoker	268 (21.0)	874 (49.2)	<0.001
Chronic kidney disease	367 (28.7)	253 (14.2)	<0.001
Prior PCI	146 (11.4)	116 (6.5)	<0.001
Prior stroke	87 (6.8)	39 (2.2)	<0.001
Prior MI	58 (4.5)	55 (3.1)	0.046
Prior CABG	15 (1.2)	3 (0.2)	0.001
Clinical presentation, n (%)			<0.001
Unstable angina	445 (34.8)	481 (27.1)	
NSTEMI	444 (34.7)	583 (32.8)	
STEMI	389 (30.4)	714 (40.2)	
Laboratory findings			
Hemoglobin, g/dL	13.5±1.7	14.8±1.6	<0.001
Creatinine, mg/dL	1.1±1.0	1.0±0.7	0.015
Ejection Fraction, %	54.5±12.6	54.6±11.6	0.900
Transradial approach, n (%)	720 (56.3)	978 (55.0)	0.488
Multi-vessel diseases, n (%)	806 (63.1)	897 (50.4)	<0.001
Multi-lesion intervention, n (%)	280 (21.9)	338 (19.0)	0.055
Total No. of stents per patients	1.4±0.7	1.4±0.6	0.118
Total stent length per patient, mm	35.4±21.1	34.3±20.2	0.174
Mean stent diameter, mm	3.1±0.4	3.2±0.4	<0.001

Data are presented as mean ± SD or n (%).

CABG, coronary artery bypass graft; DAPT, dual antiplatelet therapy; MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction

Table S2. Independent Predictors of primary outcome according to age subgroups.

	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Patients age ≥64 years				
Predictors of net adverse clinical event				
Ticagrelor monotherapy after 3-month DAPT	0.49 (0.31–0.76)	0.002	0.53 (0.33–0.84)	0.007
Body mass index	0.88 (0.82–0.95)	<0.001	0.90 (0.83–0.97)	0.009
Diabetes	1.54 (1.00–2.36)	0.048	1.16 (0.73–1.86)	0.524
Current smoker	1.49 (0.93–2.38)	0.099	1.41 (0.85–2.35)	0.180
Chronic kidney disease	2.29 (1.50–3.50)	<0.001	1.72 (1.08–2.76)	0.023
Prior MI	1.93 (0.89–4.18)	0.095	1.46 (0.66–3.22)	0.350
Ejection fraction <40%	2.25 (1.34–3.80)	0.002	1.36 (0.78–2.37)	0.284
Hemoglobin	0.82 (0.72–0.91)	<0.001	0.89 (0.78–1.02)	0.092
Transfemoral approach	1.92 (1.25–2.95)	0.003	1.49 (0.94–2.35)	0.090
Total stent length ≥30mm	1.53 (0.99–2.36)	0.057	1.45 (0.92–2.27)	0.109
Patients age <64 years				
Predictors of net adverse clinical event				
Ticagrelor monotherapy after 3-month DAPT	1.00 (0.60–1.64)	0.985	1.00 (0.59–1.69)	0.999
Female	1.88 (1.00–3.54)	0.049	1.43 (0.71–2.91)	0.319
Body mass index	0.90 (0.83–0.98)	0.019	0.91 (0.84–1.00)	0.041
Hypertension	1.54 (0.94–2.54)	0.088	1.30 (0.75–2.25)	0.354
Diabetes	2.30 (1.38–3.81)	0.001	1.91 (1.09–3.33)	0.024
Chronic kidney disease	2.54 (1.47–4.39)	<0.001	1.56 (0.82–2.97)	0.176
Ejection fraction <40%	3.79 (2.07–6.92)	<0.001	2.53 (1.33–4.81)	0.005
Hemoglobin	0.77 (0.67–0.88)	<0.001	0.93 (0.79–1.09)	0.352
Transfemoral approach	1.60 (0.97–2.65)	0.065	1.36 (0.80–2.31)	0.252
Multi-vessel disease	1.56 (0.94–2.60)	0.088	1.23 (0.69–2.21)	0.478
Total stent length ≥30mm	1.62 (0.97–2.69)	0.063	1.42 (0.80–2.53)	0.228

CI, confidence interval; DAPT, dual antiplatelet therapy; MI, myocardial infarction

Table S3. Independent predictors of key secondary outcomes according to the age subgroups.

	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Patients Age ≥64 years				
Predictors of major bleeding				
Ticagrelor monotherapy after 3-month DAPT	0.43 (0.22–0.85)	0.016	0.44 (0.22–0.88)	0.020
Chronic kidney disease	3.20 (1.72–5.97)	<0.001	2.25 (1.15–4.42)	0.018
Ejection fraction <40%	2.06 (0.95–4.49)	0.068	1.21 (0.54–2.69)	0.644
Hemoglobin	0.76 (0.64–0.90)	0.001	0.82 (0.69–0.98)	0.030
Transfemoral approach	3.05 (1.55–6.00)	0.001	2.41 (1.20–4.84)	0.013
Predictors of major adverse cardiac and cerebrovascular event				
Ticagrelor monotherapy after 3m DAPT	0.51 (0.28–0.91)	0.022	0.60 (0.33–1.08)	0.089
Body mass index	0.88 (0.80–0.97)	0.009	0.88 (0.79–0.97)	0.011
Chronic kidney disease	2.11 (1.22–3.70)	0.008	1.69 (0.93–3.10)	0.087
Prior MI	2.90 (1.24–6.79)	0.014	2.46 (1.02–5.90)	0.044
Ejection fraction <40%	2.35 (1.20–4.60)	0.013	1.68 (0.83–3.39)	0.146
Hemoglobin	0.85 (0.73–0.99)	0.035	0.95 (0.81–1.12)	0.559
Patients Age <64 years				
Predictors of major bleeding				
Ticagrelor monotherapy after 3-month DAPT	0.76 (0.37–1.56)	0.456	0.75 (0.35–1.61)	0.466
Female	3.36 (1.54–7.35)	0.002	2.36 (0.96–5.80)	0.061
Body mass index	0.87 (0.76–0.98)	0.027	0.90 (0.80–1.02)	0.093
Diabetes	2.59 (1.26–5.32)	0.010	2.16 (0.98–4.80)	0.058
Chronic kidney disease	2.63 (1.21–5.75)	0.015	1.25 (0.47–3.32)	0.650
Ejection fraction <40%	4.03 (1.70–9.52)	0.002	2.67 (1.07–6.66)	0.035
Hemoglobin	0.70 (0.59–0.84)	<0.001	0.85 (0.66–1.09)	0.202
Predictors of major adverse cardiac and cerebrovascular event				
Ticagrelor monotherapy after 3-month DAPT	1.05 (0.54–2.04)	0.878	0.96 (0.48–1.92)	0.912
Hypertension	1.81 (0.92–3.53)	0.084	1.33 (0.65–2.73)	0.433
Diabetes	2.25 (1.14–4.41)	0.019	1.82 (0.87–3.80)	0.112
Chronic kidney disease	2.83 (1.39–5.78)	0.004	2.29 (1.04–5.02)	0.039

Prior MI	3.02 (0.93–9.87)	0.067	2.54 (0.75–8.58)	0.135
Ejection fraction <40%	3.62 (1.63–8.03)	0.002	2.72 (1.19–6.22)	0.018
Hemoglobin	0.79 (0.66–0.95)	0.013	0.94 (0.77–1.13)	0.495

CI, confidence interval; DAPT, dual antiplatelet therapy; MI, myocardial infarction