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

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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 \( \geq 64 \) 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
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

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

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 biolrosorbable polymer sirolimus-eluting stents (Orsiro; Biotronik AG, Bülach, Switzerland). More detailed inclusion and exclusion criteria have been previously published. 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. 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. MACCE was defined as a composite of all-cause death, myocardial infarction, stent thrombosis, stroke, and target-vessel revascularization. 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, χ² 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. 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
Kim et al Age-Dependent Effect of Ticagrelor Monotherapy

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 $\geq 64$ 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 $\geq 64$ 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
Kim et al. Age-Dependent Effect of Ticagrelor Monotherapy

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 P2Y₁₂ 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 P2Y₁₂ 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, 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 P2Y₁₂ 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 P2Y₁₂ 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.
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 antiplatelet 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) |
|----------------------------------|-------------------------------|-------------------------------|
|                                 | Ticagrelor monotherapy after 3-mo DAPT (n=639) | P value | Ticagrelor monotherapy after 3-mo DAPT (n=892) | P value | P value* |
| Age, y                           | 71.2±4.8                      | 0.477                           | 53.2±6.9                      | 0.150   | <0.001   |
| Body mass index, kg/m²           | 24.1±3.1                      | 0.860                           | 25.5±3.1                      | 0.938   | <0.001   |
| Women                            | 209 (32.9)                    | 0.843                           | 114 (12.8)                    | 0.082   | <0.001   |
| Hypertension                     | 383 (60.3)                    | 0.487                           | 377 (42.3)                    | 0.827   | <0.001   |
| Dyslipidemia                     | 359 (56.5)                    | 0.449                           | 565 (63.3)                    | 0.426   | 0.010    |
| Diabetes                         | 203 (32.0)                    | 0.332                           | 215 (24.1)                    | 0.294   | <0.001   |
| Current smoker                   | 122 (19.2)                    | 0.143                           | 433 (48.5)                    | 0.637   | <0.001   |
| Chronic kidney disease           | 166 (26.1)                    | 0.050                           | 126 (14.1)                    | 1.054   | <0.001   |
| Prior PCI                        | 72 (11.3)                     | 0.994                           | 63 (7.1)                      | 0.253   | <0.001   |
| Prior stroke                     | 43 (6.8)                      | 1.000                           | 17 (1.9)                      | 0.504   | <0.001   |
| Prior myocardial infarction      | 29 (4.6)                      | 1.000                           | 35 (3.9)                      | 0.058   | 0.046    |
| Prior CABG                       | 6 (0.9)                       | 0.621                           | 2 (0.2)                       | 1.000   | 0.001    |
| Clinical presentation            | 215 (33.9)                    | 0.555                           | 227 (25.4)                    | 0.015   | <0.001   |
| Unstable angina                  | 218 (34.3)                    | 0.644                           | 262 (29.6)                    | 1.365   | 0.055    |
| NSTEMI                            | 226 (35.1)                    | 0.370                           | 370 (41.8)                    | 0.858   | 0.118    |
| Ejection fraction, %             | 54.6±12.1                     | 0.972                           | 54.5±11.6                     | 0.790   | 0.900    |
| Transradial approach             | 352 (55.4)                    | 0.554                           | 485 (54.4)                    | 0.623   | 0.488    |
| Multivessel diseases             | 395 (62.2)                    | 0.564                           | 447 (50.1)                    | 0.812   | <0.001   |
| Multilesion intervention         | 132 (20.8)                    | 0.370                           | 174 (19.5)                    | 1.365   | 0.055    |
| Total no. of stents per patients | 1.4±0.7                       | 0.844                           | 1.4±0.7                       | 1.3±0.6 | 0.858    |
| Total stent length per patient, mm | 35.3±20.5                    | 0.901                           | 34.0±20.5                     | 0.550   | 0.174    |
| Stent diameter, mm               | 3.1±0.4                       | 0.427                           | 3.2±0.5                       | 3.2±0.4 | 0.501    |

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) | 1.99 (0.18–21.97) | 0.574 | 0.429 |
|                       | ≥64 | 0 | 1 (0.2) | 0.51 (0.05–5.60) | 0.580 |         |
| 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 (0.8) | 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) | 0.660 | 0.864 |
|                       | ≥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.
should be 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**

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**Disclosures**

None.

**Supplemental Material**

Tables S1–S3

**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.
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/m²              | 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.

| Predictors of net adverse clinical event | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | Hazard ratio (95% CI) | P value | Hazard ratio (95% CI) | P value |
| **Patients age ≥64 years** | | | | | | |
| 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** | | | | | | |
| 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.

| Patients Age ≥64 years | Univariate | Multivariate |
|------------------------|------------|--------------|
|                        | Hazard ratio (95% CI) | P value | Hazard ratio (95% CI) | P value |
| 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 3-month 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 |
|                      | CI             | p-value | CI             | p-value |
|----------------------|----------------|---------|----------------|---------|
| 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