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Original Research

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Comparison of Short-term and Standard Duration Dual Antiplatelet Therapy in Elderly Patients: A Pooled Analysis of Five Korean Randomized Clinical Trials

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AUTHOR'S SUMMARY

The optimal dual antiplatelet therapy (DAPT) strategy in the elderly population remains unclear, given their increased risk of ischemic and bleeding outcomes. This pooled analysis of 5 Korean randomized clinical trials demonstrated that patients aged ≥75 years are at high risk for both outcomes. In the elderly population, standard DAPT offers no additional protective effects against ischemic outcomes, while significantly increasing the bleeding risk. This study provides robust insights into age-specific risks and benefits of short-term versus standard DAPT.

ABSTRACT

Backgrounds and Objectives: Data on the optimal duration of dual antiplatelet therapy (DAPT) by age in patients undergoing percutaneous coronary intervention (PCI) are limited. This study assessed clinical outcomes based on age groups and DAPT duration, focusing on patients aged ≥75 years.
Methods: We analyzed data from 10,487 patients across 5 Korean randomized trials examining the impact of DAPT durations on clinical outcomes after drug-eluting stent implantation. Patients were categorized into 2 groups: ≥75 years (n=1,571) and <75 years (n=8,916). Each group was further stratified into short-term DAPT (1–6 months) and standard DAPT (12 months). The primary outcome was major bleeding within 12 months of PCI. Major adverse cardiovascular and cerebrovascular events (MACCE) and net adverse clinical events (NACE), a composite of MACCE and major bleeding, were also compared.
Results: Patients aged ≥75 had a higher risk of major bleeding and MACCE than those aged <75. In patients aged ≥75, standard DAPT was associated with a higher risk of major bleeding

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Conflict of Interest
The authors have no financial conflicts of interest.

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The data generated in this study is available from the corresponding author upon reasonable request.

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than short-term DAPT (hazard ratio [HR], 2.34; 95% confidence interval [CI], 1.17–4.68; p=0.016). In patients aged <75 years, the risk was comparable (HR, 1.45; 95% CI, 1.00–2.10; p=0.053), with no significant interaction between groups (p=0.207). The risks of MACCE and NACE did not differ significantly between DAPT strategies or age groups.
Conclusions: Standard DAPT strategy may increase bleeding risk in elderly patients without reducing ischemic events, despite no significant age-treatment interaction.

Trial Registration: ClinicalTrials.gov Identifier: NCT01145079 (RESET), NCT01308281 (IVUS-XPL), NCT01752894 (DETECT-OCT), NCT02494895 (TICO), NCT02513810 (One-Month-DAPT)

Keywords: Coronary artery disease; Ticagrelor; Clopidogrel; Platelet aggregation inhibitors; Duration of therapy; Elderly

INTRODUCTION

Dual antiplatelet therapy (DAPT), combining a $P2Y_{12}$ inhibitor with aspirin, is required for a specific period in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) with drug-eluting stents (DES).[1)2)] Current guidelines on antiplatelet strategies for patients with DES implantation recommend specific DAPT durations based on ischemic or bleeding risks.[3-6)] However, the optimal strategy for patients with both ischemic and bleeding risks remains unclear. Elderly patients are known to have increased risks of both ischemic and bleeding events.[7)8)] Therefore, this study aimed to evaluate how ischemic and bleeding risks vary with DAPT strategies in patients undergoing PCI, focusing on those aged ≥75 years, based on 5 previously published randomized clinical trials in Korea.

METHODS

Ethical statement

The ethics committees of each institution reviewed and approved the respective randomized clinical trial protocols (Representative: Severance Hospital). All studies adhered to the Declaration of Helsinki (2013), and patients provided written informed consent to participate.

Study design and population

The study population was drawn from a pooled group of 5 randomized clinical trials investigating the effects of DAPT duration on clinical outcomes following DES implantation. The current study comprised 5 randomized clinical trials, all of which were coordinated by the same lead institution in Korea and conducted under a similar protocol framework between 2009 and 2019: (1) RESET (Real Safety and Efficacy of a 3-month Dual Antiplatelet Therapy Following E-ZES Implantation; NCT01145079),[9)] (2) IVUS-XPL (Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; NCT01308281),[10)] (3) DETECT-OCT (Determination of the Duration of the Dual Antiplatelet Therapy by the Degree of the Coverage of The Struts on Optical Coherence Tomography From the Randomized Comparison Between Everolimus-Eluting Stents Versus Biolimus A9-eluting Stents; NCT01752894),[11)] (4) One-Month-DAPT (A Randomized Controlled Comparison Between One Versus More Than Six Months of Dual Antiplatelet Therapy After Biolimus A9-eluting Stent Implantation; NCT02513810),[12)] and (5) TICO (Ticagrelor Monotherapy After 3 Months in Patients Treated With New-Generation Sirolimus Stent for

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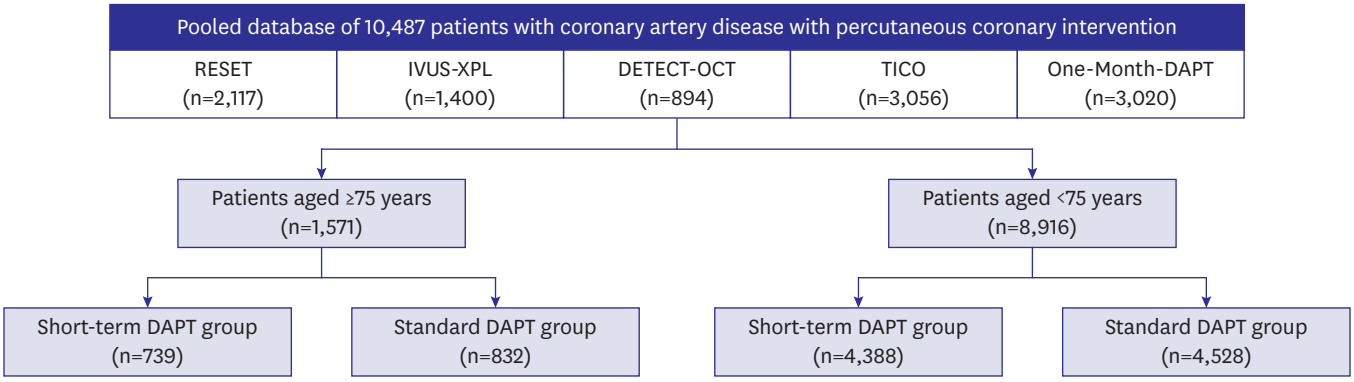

Figure 1. Study flowchart.
DAPT = dual antiplatelet therapy.

Acute Coronary Syndrome; NCT02494895)[13] trials. A brief overview of each trial is presented in **Supplementary Table 1**.

The study flow is shown in **Figure 1**. This pooled database includes 5 randomized clinical trials with a total of 10,487 patients with CAD who underwent PCI with DES between April 2009 and September 2019. Following the Academic Research Consortium for High Bleeding Risk, which defines patients aged ≥75 years as high bleeding risk (HBR),[8] we divided patients into 2 groups: aged ≥75 years (n=1,571) and aged <75 years (n=8,916). Each group was divided into 2 subgroups based on DAPT duration: the short-term DAPT group (1 to 6 months) and the standard DAPT group (12 months).

Study procedures

Detailed explanations of antiplatelet loading and maintenance doses were provided in each clinical trial. The choice of medication and DAPT duration was determined by the individual trial protocols.[9-13] The use of other antithrombotic agents was not allowed. Guideline-directed medical therapy was strongly recommended for other treatments. All procedures were performed using standard interventional techniques. The choice of stent type, size, and length followed the individual trial protocols.

Outcomes and definitions

The primary outcome was major bleeding within 12 months after PCI. According to the Thrombolysis in Myocardial Infarction (TIMI) criteria, major bleeding was defined as intracranial hemorrhage, bleeding with a hemoglobin decrease of at least 5 g/dL, or fatal bleeding leading to death within 7 days.[14] Secondary outcomes included major adverse cardiovascular and cerebrovascular events (MACCE), defined as the composite of all-cause death, myocardial infarction (MI), stent thrombosis, and stroke; net adverse clinical events (NACE), defined as the composite of major bleeding and MACCE; each component of NACE; and cardiovascular death.

Cardiovascular death was defined as death due to MI, cardiac perforation or pericardial tamponade, fatal arrhythmia, stroke within 30 days of the procedure or related to it, death due to a procedural complication, or any death in which a cardiac cause could not be excluded, as adjudicated by the Clinical Endpoints Committee. MI after discharge was defined as the presence of symptoms or evidence of myocardial ischemia, confirmed by

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electrocardiogram or imaging, along with a creatine kinase MB fraction above the upper normal limit or a troponin T or I level greater than the 99th percentile of the upper normal limit. Stent thrombosis was defined as definite or probable, according to the Academic Research Consortium definition. Stroke was defined as an acute cerebrovascular event leading to a neurological deficit lasting more than 24 hours, or imaging evidence of acute infarction.

Statistical analysis

Data were expressed as mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables. Student's t-test was used to compare continuous variables between the 2 groups. Categorical variables were compared using the chi-squared test or Fisher's exact test. Cumulative incidences of clinical events at 12 months were calculated using the Kaplan-Meier method, and the log-rank test assessed comparisons of clinical outcomes between patients aged ≥75 and <75 years, as well as between the short-term and standard DAPT duration groups. Additional age-stratified analyses were performed to evaluate the consistency of the effects of DAPT duration across age groups. We divided patients into 3 groups: Those aged <62 years, 62–74 years, and ≥75 years (median cut-off of 62 years for patients aged <75 years). Cox proportional hazards regression analysis was used to calculate the hazard ratio (HR) with a 95% confidence interval (CI) for each clinical outcome. Variables included in the multivariable adjustment analysis are as follows: age, sex, body mass index (BMI), acute coronary syndrome, hypertension, diabetes, potent $P2Y_{12}$ inhibitor use, previous coronary revascularization, multi-vessel disease, multi-lesion intervention, and total stent length. Cox proportional hazard models with shared gamma frailty were also used to account for heterogeneity in clinical outcomes between the randomized controlled trials.[15] Subgroup analyses were conducted to compare short-term versus standard DAPT for each clinical outcome. Post hoc subgroups included clinical presentation (stable angina vs. acute coronary syndrome) and potent $P2Y_{12}$ inhibitor use (clopidogrel vs. ticagrelor). Effect modification across subgroups was determined by including multiplicative interaction terms in the Cox regression models.

Data manipulation and statistical analysis were performed using R software (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria) with the survival package. All tests were 2-tailed, and statistical significance was defined as a p value less than 0.05.

RESULTS

Baseline characteristics

In the study population 10,487, the mean age was 63.3±10.3 years, and 71.3% were male. The age distribution is shown in **Supplementary Figure 1**.

Baseline characteristics by age (≥75 vs. <75 years) are presented in **Table 1**. Patients aged ≥75 years were more likely to be female and had a lower BMI than those aged <75 years. They had higher rates of comorbidities such as hypertension, diabetes, stroke history, and previous coronary revascularization, along with a higher prevalence of multivessel disease. No significant differences were observed in other variables.

Baseline characteristics by standard DAPT and short-term DAPT strategy are shown in **Supplementary Table 2**. Apart from the type of implanted DES, no significant differences were found between the 2 groups.

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Table 1. Baseline characteristics according to age subgroups

Variables	Crude population				
	Total population (n=10,487)	Age ≥75 years (n=1,571)	Age <75 years (n=8,916)	p value	SMD
Age (years)	63.3±10.3	78.0±2.8	60.7±8.9	<0.001	2.60
Male sex	7,478 (71.3)	831 (52.9)	6,647 (74.6)	<0.001	−0.46
Body mass index	24.8±3.1	24.1±3.2	24.9±3.1	<0.001	−0.28
Clinical presentation				0.420	−0.02
Stable angina	4,043 (38.6)	620 (39.5)	3,423 (38.4)		
Acute coronary syndrome	6,444 (61.4)	951 (60.5)	5,493 (61.6)		
Unstable angina	3,574 (34.2)	575 (36.6)	3,009 (33.7)		
NSTEMI	1,706 (16.3)	265 (16.9)	1,441 (16.2)		
STEMI	1,154 (11.0)	111 (7.1)	1,043 (11.7)		
Hypertension	6,246 (59.6)	1,179 (75.0)	5,067 (56.8)	<0.001	0.39
Diabetes mellitus	3,201 (30.5)	585 (37.2)	2,616 (29.3)	<0.001	0.17
Dyslipidemia	7,080 (67.5)	1,045 (66.5)	6,035 (67.7)	0.362	−0.02
Current smoker	2,684 (25.6)	141 (9.0)	2,543 (28.5)	<0.001	−0.52
Prior MI	339 (3.2)	51 (3.2)	288 (3.2)	0.973	<0.01
Prior revascularization	1,120 (10.7)	231 (14.7)	889 (10.0)	<0.001	0.14
Prior stroke	486 (4.6)	144 (9.2)	342 (3.8)	<0.001	0.22
Use of $P2Y_{12}$ inhibitor				<0.001	0.10
Clopidogrel	7,431 (70.9)	1,170 (74.5)	6,261 (70.2)		
Ticagrelor	3,056 (29.1)	401 (25.5)	2,655 (29.8)		
DAPT duration				0.897	0.00
Short-term DAPT	4,428 (42.2)	910 (57.9)	5,149 (57.8)		
Standard DAPT	6,059 (57.8)	661 (42.1)	3,767 (42.2)		
Multi-vessel disease	5,038 (48.0)	881 (56.1)	4,157 (46.6)	<0.001	0.19
Multi-lesion intervention	2,077 (19.8)	295 (18.8)	1,782 (20.0)	0.268	−0.03
Type of drug-eluting stents				<0.001	0.43
Biolimus	3,470 (33.1)	780 (49.6)	2,690 (30.2)		
Sirolimus	3,396 (32.4)	326 (27.8)	2,960 (33.2)		
Everolimus	2,116 (20.2)	228 (14.5)	1,888 (21.2)		
Zotarolimus	1,505 (14.4)	127 (8.1)	1,378 (15.5)		
Number of lesions treated per patient	1.23±0.49	1.21±0.46	1.23±0.50	0.199	−0.05
Total number of stents per patient	1.4±0.7	1.3±0.6	1.4±0.7	0.112	−0.06
Stent number ≥2	3,039 (29.0)	436 (27.8)	2,603 (29.2)	0.245	−0.03
Total stent length per patient	32.1±19.1	32.1±18.7	32.2±19.1	0.296	<0.01

Data are presented as the mean ± standard deviation or number (%).
DAPT = dual antiplatelet therapy; MI = myocardial infarction; NSTEMI = non-ST-segment-elevation myocardial infarction; SMD = standardized mean difference; STEMI = ST-segment-elevation myocardial infarction.

The baseline characteristics of the groups classified by age and treatment strategies are summarized in **Table 2**. Among patients aged ≥75 years (n=1,571), the standard DAPT group (n=910) had a lower proportion of ticagrelor use and a longer total stent length compared to the short-term DAPT group (n=661). Patients aged <75 years (n=8,916) were also divided into a standard DAPT group (n=5,149) and a short-term DAPT group (n=3,767). No significant differences were found between the standard DAPT and short-term DAPT groups for any variable, except for the type of implanted DES, in both age groups. The standardized mean differences were within ±0.1 for both groups (**Supplementary Figure 2**).

Clinical outcomes by age groups or by the dual antiplatelet therapy strategies

During the follow-up period (median, 365 days; interquartile range, 365 to 365 days), 1-year follow-up was completed in 93.0% (9,752/10,487) of patients, and clinical outcomes of patients aged ≥75 and <75 years are presented in **Figure 2**. The elderly population aged ≥ 75 years had a significantly higher risk of TIMI major bleeding (HR, 1.71; 95% CI, 1.18–2.46; p=0.004) and MACCE (HR, 1.83; 95% CI, 1.44–2.34; p<0.001), leading to a higher risk of NACE (HR, 1.75; 95% CI, 1.42–2.17; p<0.001) compared to patients aged <75 years. These results remained consistent after multivariable adjustment (**Supplementary Table 3**).

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Table 2. Baseline characteristics by age and treatment strategies

	Age ≥75 years (n=1,571)			Age <75 years (n=8,916)		
	Standard DAPT (n=832)	Short-term DAPT (n=739)	p value	Standard DAPT (n=4,528)	Short-term DAPT (n=4,388)	p value
Age (years)	77.9±2.8	78.0±2.9	0.615	60.8±8.9	60.7±8.8	0.432
Male sex	453 (54.4)	378 (51.2)	0.191	3,396 (75.0)	3,251 (74.1)	0.323
Body mass index	24.0±3.1	24.1±3.3	0.238	24.9±3.1	25.0±3.1	0.445
Clinical presentation			0.511			0.369
Stable angina	322 (38.7)	298 (40.3)		1,759 (38.8)	1,664 (37.9)	
Acute coronary syndrome	510 (61.3)	441 (59.7)		2,769 (61.2)	2,724 (62.1)	
Unstable angina	313 (37.6)	262 (35.5)		1,538 (34.0)	1,471 (33.5)	
NSTEMI	140 (16.8)	125 (16.9)		709 (15.7)	732 (16.7)	
STEMI	57 (6.9)	54 (7.3)		522 (11.5)	521 (11.9)	
Hypertension	621 (74.6)	558 (75.5)	0.691	2,580 (57.0)	2,487 (56.7)	0.774
Diabetes mellitus	316 (38.0)	269 (36.4)	0.518	1,318 (29.1)	1,298 (29.6)	0.624
Dyslipidemia	560 (67.3)	485 (65.6)	0.482	3,053 (67.4)	2,982 (68.0)	0.590
Current smoker	66 (7.9)	75 (10.1)	0.125	1,285 (28.4)	1,258 (28.7)	0.762
Prior MI	29 (3.5)	22 (3.0)	0.570	132 (2.9)	156 (3.6)	0.088
Prior revascularization	132 (15.9)	99 (13.4)	0.168	441 (9.7)	448 (10.2)	0.459
Prior stroke	82 (9.9)	62 (8.4)	0.315	186 (4.1)	156 (3.6)	0.174
Use of $P2Y_{12}$ inhibitor			0.696			0.189
Clopidogrel	623 (74.9)	547 (74.0)		3,208 (70.8)	3,053 (69.6)	
Ticagrelor	209 (25.1)	192 (26.0)		1,320 (29.2)	1,335 (30.4)	
Type of antiplatelet after DAPT discontinuation			0.696			0.189
Aspirin	623 (74.9)	547 (74.0)		3,208 (70.8)	3,053 (69.6)	
Ticagrelor	209 (25.1)	192 (26.0)		1,320 (29.2)	1,335 (30.4)	
Multi-vessel disease	470 (56.5)	411 (55.6)	0.727	2,106 (46.5)	2,051 (46.7)	0.827
Multi-lesion intervention	154 (18.5)	141 (19.1)	0.773	881 (19.5)	901 (20.5)	0.204
Type of drug-eluting stents			<0.001			<0.001
Biolimus	412 (49.5)	368 (49.8)		1,372 (30.3)	1,318 (30.0)	
Sirolimus	244 (29.3)	192 (26.0)		1,625 (35.9)	1,335 (30.4)	
Everolimus	135 (16.2)	93 (12.6)		1,126 (24.9)	762 (17.4)	
Zotarolimus	41 (4.9)	86 (11.6)		405 (8.9)	973 (22.2)	
Number of lesions treated per patient	1.2±0.5	1.2±0.5	0.741	1.2±0.5	1.2±0.5	0.293
Total number of stents per patient	1.3±0.6	1.3±0.6	0.750	1.4±0.7	1.4±0.7	0.920
Stent number ≥2	234 (28.1)	202 (27.3)	0.727	1,314 (29.0)	1,289 (29.4)	0.712
Total stent length per patient	31.5±18.1	32.7±19.4	0.123	32.3±19.4	32.0±18.9	0.781

Data are presented as the mean ± standard deviation or number (%).
DAPT = dual antiplatelet therapy; MI = myocardial infarction; NSTEMI = non-ST-segment-elevation myocardial infarction; STEMI = ST-segment-elevation myocardial infarction.

Additional age-stratified analyses revealed progressively increasing risks of TIMI major bleeding, MACCE, and NACE across the 3 age groups (p for trend=0.042, 0.032, and 0.028, respectively) (**Supplementary Figure 3**).

The comparison of clinical outcomes between the standard and short-term DAPT groups was depicted in **Supplementary Figure 4** and **Supplementary Table 4**. The risk of TIMI major bleeding was higher in the standard DAPT group. The risks of MACCE and NACE were not significantly different between the 2 groups. These results were consistent after multivariable adjustment. When the short-term DAPT group was further divided into the aspirin monotherapy and ticagrelor monotherapy groups based on the type of antiplatelets used after DAPT discontinuation, outcomes were calculated from the time of study enrollment. No significant differences in clinical outcomes were observed when comparing antiplatelet monotherapy strategies for aspirin versus ticagrelor in the short-term DAPT group and in patients aged ≥75 and <75 years (**Supplementary Tables 5** and **6**).

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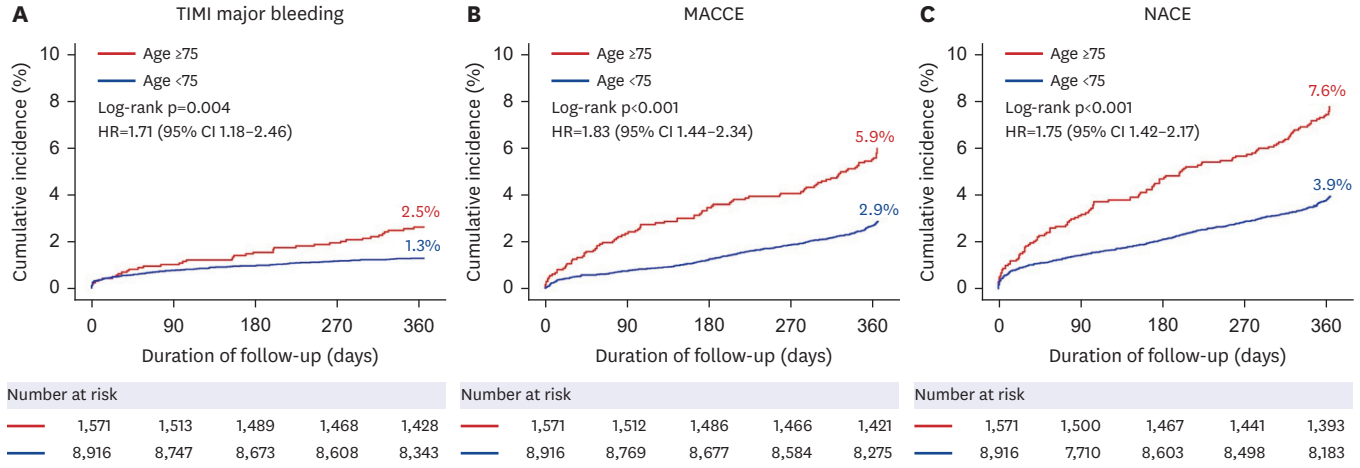

Figure 2. Time-to-event curves for TIMI major bleeding, MACCE, and NACE according to age. Kaplan-Meier estimate for (A) TIMI major bleeding, (B) MACCE, (C) and NACE according to age.
CI = confidential interval; HR = hazard ratio; MACCE = major adverse cardiovascular and cerebrovascular events; NACE = net adverse clinical events; TIMI = thrombolysis in myocardial infarction.

Subgroup analyses comparing short-term versus standard DAPT for clinical outcomes are shown in **Supplementary Figure 5**. While none of the interaction terms achieved statistical significance, directionally consistent trends favoring short-term DAPT were observed across most subgroups.

Clinical outcomes according to the age groups and dual antiplatelet therapy strategies

The comparisons of clinical outcomes in the crude populations among groups stratified by age (≥75 vs. <75 years) and DAPT strategy (standard vs. short-term DAPT) are presented in **Figure 3** and **Table 3**. The occurrence of TIMI major bleeding was significantly different among the stratified groups. In patients aged ≥75 years, the standard DAPT strategy was significantly

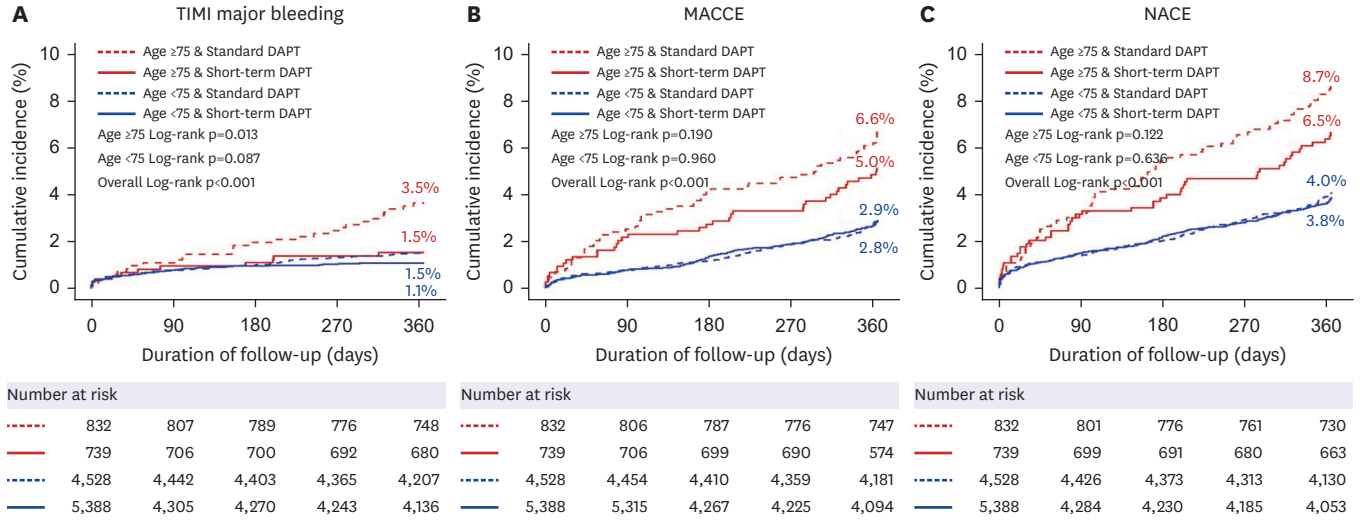

Figure 3. Time-to-event curves for TIMI major bleeding, MACCE, and NACE according to age and DAPT strategies. Kaplan-Meier estimate for (A) TIMI major bleeding, (B) MACCE, (C) and NACE according to age and DAPT strategies.
DAPT = dual antiplatelet therapy; MACCE = major adverse cardiovascular and cerebrovascular events; NACE = net adverse clinical events; TIMI = thrombolysis in myocardial infarction.

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Table 3. Clinical outcomes by age and DAPT strategies

	Age ≥75 years (n=1,571)				Age <75 years (n=8,916)				
	Standard DAPT (n=832)	Short-term DAPT (n=739)	HR (95% CI)	p value	Standard DAPT (n=4,528)	Short-term DAPT (n=4,388)	HR (95% CI)	p value	p value for interaction
Primary outcomes									
TIMI major bleeding	29 (3.5)	11 (1.5)	2.34 (1.17–4.68)	0.016	67 (1.5)	47 (1.1)	1.45 (1.00–2.10)	0.053	0.207
Secondary outcomes									
MACCE*	55 (6.6)	37 (5.0)	1.32 (0.87–2.00)	0.192	129 (2.8)	126 (2.9)	1.04 (0.81–1.33)	0.766	0.291
NACE†	72 (8.7)	48 (6.5)	1.33 (0.93–1.92)	0.123	167 (3.8)	181 (4.0)	1.10 (0.89–1.36)	0.372	0.320
Composite of all-cause death, MI, stent thrombosis, or TVR	47 (5.6)	29 (3.9)	1.45 (0.91–2.30)	0.119	106 (2.3)	103 (2.3)	1.04 (0.79–1.37)	0.769	0.206
All-cause death	30 (3.6)	16 (2.2)	1.67 (0.91–3.06)	0.098	32 (0.7)	23 (0.5)	1.35 (0.79–2.31)	0.273	0.635
Cardiovascular death	16 (1.9)	6 (0.8)	2.36 (0.92–6.03)	0.073	17 (0.4)	12 (0.3)	1.37 (0.66–2.88)	0.400	0.375
MI	10 (1.2)	5 (0.7)	1.79 (0.61–5.24)	0.287	27 (0.6)	21 (0.5)	1.31 (0.74–2.31)	0.359	0.582
Stent thrombosis	7 (0.8)	6 (0.8)	1.04 (0.35–3.08)	0.950	14 (0.3)	16 (0.4)	0.87 (0.43–1.79)	0.706	0.767
TVR	14 (1.7)	10 (1.4)	1.24 (0.55–2.79)	0.607	59 (1.3)	69 (1.6)	0.87 (0.62–1.23)	0.440	0.409
Stroke	10 (1.2)	8 (1.1)	1.10 (0.44–2.79)	0.837	25 (0.6)	25 (0.6)	0.97 (0.56–1.69)	0.916	0.828

Data are presented as the number (%).
CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; MACCE = major adverse cardiovascular and cerebrovascular events; MI = myocardial infarction; NACE = net adverse clinical events; TIMI = thrombolysis in myocardial infarction; TVR = target vessel revascularization.
*Includes all-cause death, MI, stent thrombosis, TVR, or stroke.
†Includes TIMI major bleeding and MACCE.

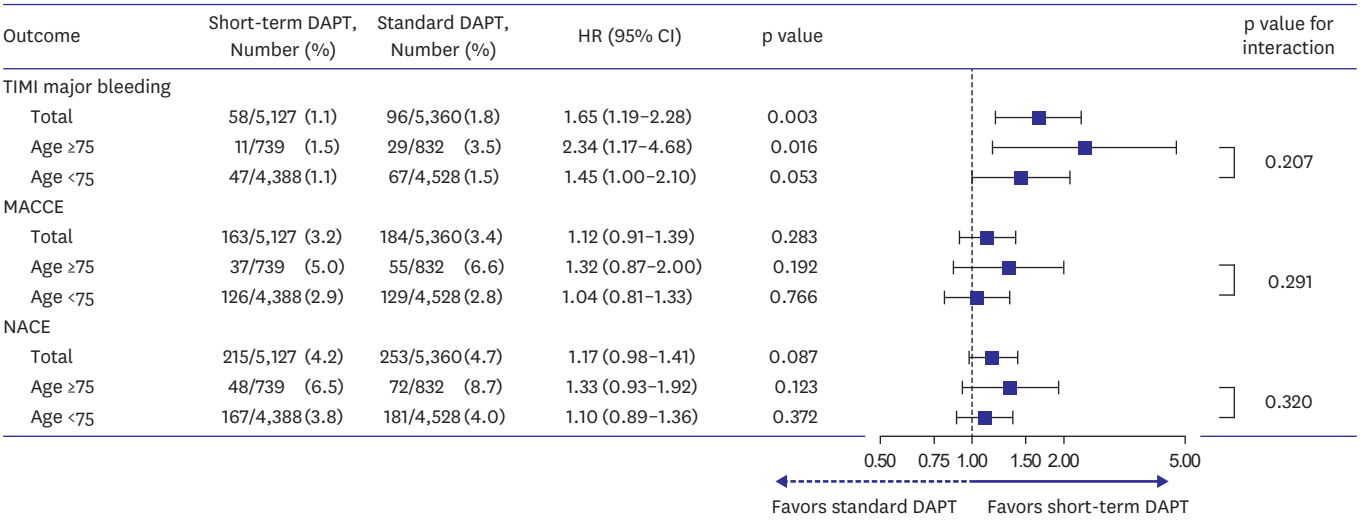

Figure 4. Relative risk for TIMI major bleeding, MACCE, and NACE according to age and DAPT strategies. Relative risk for (A) TIMI major bleeding, (B) MACCE, (C) and NACE according to age and DAPT strategies. The difference in treatment effect between treatment strategies in elderly and young patients was calculated using the Cox regression model.
CI = confidential interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; MACCE = major adverse cardiovascular and cerebrovascular events; NACE = net adverse clinical events; TIMI = thrombolysis in myocardial infarction.

associated with a higher risk of major bleeding compared to the short-term DAPT strategy (HR, 2.34; 95% CI, 1.17–4.68; p=0.016), while no significant difference was observed between the 2 treatment groups in patients aged <75 years (HR, 1.45; 95% CI, 1.00–2.10; p=0.053) (**Figures 3A** and **4**, **Table 3**). The results remained robust after multivariable adjustment analysis (multivariable-adjusted HR, 2.31; 95% CI, 1.15–4.63; p=0.019). In elderly patients (≥75 years), major bleeding was observed at a significantly higher rate with standard DAPT use without statistical interactions, but the risk of MACCE or NACE was not reduced significantly compared to the other 3 groups. (**Supplementary Figure 6**, **Supplementary Table 7**). However, no significant interaction was found between age and DAPT strategies for major bleeding (p for interaction=0.207). Additionally, the occurrences of MACCE and NACE significantly differed

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among the 4 groups. However, there was no significant difference between the standard and short-term DAPT groups in both age groups (**Figures 3B**, **3C**, and **4**, **Table 3**). In patients aged <75 years, no significant difference was observed in TIMI major bleeding, MACCEs, and NACEs between the standard and short-term DAPT groups before and after adjustment (**Table 3**, **Supplementary Figure 6**).

DISCUSSION

The main findings of this pooled analysis of 5 randomized clinical trials evaluating the effect of DAPT duration by age group on clinical outcomes after DES implantation are as follows: (1) The elderly population (≥75 years) is at bi-risk, being vulnerable to both bleeding and ischemic events; and (2) In elderly patients (≥75 years), major bleeding was observed at a significantly higher rate with standard DAPT use without statistical interactions, but the risk of MACCE or NACE was not reduced significantly compared to the other 3 groups. These findings remained consistent after multivariable adjustment.

Although DAPT is known to reduce fatal ischemic events, bleeding complications associated with its use can worsen clinical outcomes, diminishing its overall benefits.[3)4)16)] Based on these situations, the concept of reducing DAPT intensity has been suggested within the new Academic Research Consortium definitions of antiplatelet therapy modulation,[17)] and various short-term DAPT strategies have been explored to reduce DAPT duration. The RESET trial demonstrated that 3-month DAPT was non-inferior to 12-month DAPT in reducing major cardiovascular events.[9)] The One-Month-DAPT trial recently showed that a One-Month-DAPT duration achieved outcomes comparable to standard DAPT in terms of net clinical outcomes for ischemic and bleeding events.[12)] Short-term DAPT proved particularly effective in patients with HBR without high ischemic risk, supporting contemporary European guidelines advocating short-term DAPT based on this evidence.[3)4)]

However, limited evidence exists on DAPT strategies for elderly patients, and contemporary guidelines lack specific recommendations for this population. Our study showed that patients aged ≥75 years represent a bi-risk group with elevated risks of both ischemic and bleeding events. This is primarily due to the prevalence of multiple comorbidities in this age group. Hemostatic imbalance from endothelial dysfunction, blood stasis, and increased platelet reactivity contribute to ischemic events, while age-related amyloid deposits in small vessels heighten susceptibility to bleeding events.[18)] The results of age-specific analysis further revealed that the risk of ischemic and bleeding events gradually increased with age, suggesting that the elderly population may indeed be considered a bi-risk group. Recent studies have supported short-term DAPT strategies for HBR patients, including those aged ≥75 years.[19)20)] A prospective, multicenter, single-arm study, with two-thirds of participants aged 75 or older, demonstrated the safety of 1-month DAPT in mitigating both ischemic and bleeding risks.[20)] The s-DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen) trial demonstrated that a 1-month DAPT regimen was non-inferior to at least 6-month DAPT regarding overall clinical outcomes and superior in reducing bleeding outcomes among patients with HBR.[21)] Our study found that standard DAPT did not reduce ischemic risks but increased bleeding risks compared to short-term DAPT, particularly in patients aged ≥75 years. These results suggest that a tailored short-term DAPT strategy for elderly patients, rather than routine use of standard DAPT, may be more beneficial in

managing these risks.

To provide robust evidence for the short-term DAPT strategy, it must be based on the strong performance of DES. New-generation DES has been shown to enable more rapid re-endothelialization due to improvements in the drug, drug delivery, and the mechanical and biological design of the stent backbone, compared to first-generation DES.[22] Advancements in new-generation DES have allowed the short-term DAPT strategy to deliver excellent performance without increasing ischemic risk. Each of the 5 randomized trials that comprised our study included new-generation DES, which may not increase ischemic risk with short-term DAPT, particularly in elderly patients, who represent a bi-risk population. Therefore, a short-term DAPT strategy could help minimize ischemic and bleeding risks in elderly patients in the future DES era.

In addition to shortening DAPT duration, the use of mono-antiplatelet therapy after DAPT is emerging, with the choice of monotherapy playing an important role.[4] A short-term DAPT strategy, such as ticagrelor monotherapy after one to 3 months of DAPT, showed better net clinical outcomes without increasing ischemic risks than standard-duration DAPT.[13][23] As ischemic and bleeding risks increase, the short-term DAPT strategy may offer particular advantages to the elderly population by reducing bleeding risk and providing net clinical benefits.[24] Our study compared aspirin and ticagrelor monotherapy after DAPT to explore these potential benefits. There was no significant difference in ischemic and bleeding risks for patients aged ≥75 or <75 years and no group interactions were observed. However, these results may be due to the small sample sizes, and further research is needed to establish more robust evidence.

The study has several limitations. First, the study population may have potential heterogeneity due to slight differences in eligibility criteria despite similar inclusion and exclusion criteria across the 5 randomized clinical trials. For example, the clinical presentation of patients included in each trial was not completely consistent; some trials excluded patients with ST-segment-elevation myocardial infarction, while others excluded those with chronic coronary syndrome. Also, there is heterogeneity in DAPT regimens across the trials, including variations in the use of clopidogrel or ticagrelor and differences in DAPT duration. Second, the included trials were not selected through a formal systematic review process, which may limit generalizability and raise concerns about potential selection bias. In addition, since each included trial was conducted based on Korean cohorts, generalizing these findings to other ethnic populations should be interpreted with caution. Nevertheless, inclusion of each trial was based on the availability of high-quality individual patient-level data and uniformity in study coordination and design, which enhance internal consistency of the pooled dataset. Third, intravascular imaging guidance was only investigated in the DETECT-OCT and IVUS-XPL trials; therefore, data were unavailable for the entire patient population. Fourth, although guideline-recommended durations of standard DAPT differ according to clinical presentation, our analysis applied a uniform classification of DAPT strategies without adjusting for these presentation-specific recommendations. Fifth, although elderly patients were defined as those aged ≥75, octogenarians were excluded due to the original trials' criteria.

This pooled analysis of 5 randomized clinical trials based on Korean cohorts comparing short-term and standard DAPT found that elderly patients (≥75 years) had a higher risk of both ischemic and bleeding events. Short-term DAPT was associated with a lower risk of

major bleeding without an increase in ischemic events, and the reduction in major bleeding with short-term DAPT was more pronounced in elderly patients.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Summary of analyzed studies

Supplementary Table 2
Baseline characteristics by DAPT strategy subgroups

Supplementary Table 3
Clinical outcomes by age before and after multivariable adjustment

Supplementary Table 4
Clinical outcomes by DAPT strategies before and after multivariable adjustment

Supplementary Table 5
Clinical outcomes by type of antiplatelets used after DAPT discontinuation in short-term DAPT group before and after multivariable adjustment

Supplementary Table 6
Clinical outcomes at 1 year by age and type of antiplatelets used after dual antiplatelet therapy discontinuation in short-term DAPT group

Supplementary Table 7
Clinical outcomes at 1 year by age and DAPT strategies after multivariable adjustment*

Supplementary Figure 1
Age distribution of the total population.

Supplementary Figure 2
Covariate balance between short-term DAPT and standard DAPT in the age ≥75 years and age <75 years groups. (A) Age ≥75 years; (B) Age <75 years.

Supplementary Figure 3
Kaplan-Meier curves for TIMI major bleeding, MACCE, and NACE according to age strata. (A) TIMI major bleeding; (B) MACCE; (C) NACE. Log-rank tests for trend were used to evaluate differences in cumulative incidence across age strata (p for trend).

Supplementary Figure 4

Kaplan-Meier curves for TIMI major bleeding, MACCE, and NACE according to DAPT strategies. (A) TIMI major bleeding; (B) MACCE; (C) NACE.

Supplementary Figure 5

Subgroup analyses of short-term versus standard DAPT for clinical outcomes. HRs and interaction p values for TIMI major bleeding, MACCE, and NACE across subgroups stratified by clinical presentation and $P2Y_{12}$ inhibitor use.

Supplementary Figure 6

Cox proportional hazard analysis for TIMI major bleeding, MACCE, and NACE according to age after multivariable adjustment. Clinical outcomes at 1 year by age and dual antiplatelet strategies after multivariable adjustment analysis.

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