Dual-Antiplatelet Therapy Cessation and Cardiovascular Risk in Relation to Age: Analysis from the PARIS Registry

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Structured Abstract

Objectives: To examine the association between dual-antiplatelet therapy (DAPT) cessation and cardiovascular risk after percutaneous coronary intervention (PCI) in relation to age.

Background: Examination of outcomes by age after PCI is relevant given the aging population.

Methods: Two-year clinical outcomes, incidence and effect of DAPT cessation on outcomes were compared by ages ≤55, 56-74, and ≥75 years from the PARIS (Patterns of Non-Adherence to Antiplatelet Regimens in Stented Patients) registry. DAPT cessation included physician- recommended discontinuation, interruption for surgery, and disruption (from non-compliance or bleeding). Clinical endpoints were major adverse cardiac events (MACE) (composite of cardiac death, definite or probable stent thrombosis, spontaneous myocardial infarction, or clinically indicated target lesion revascularization), a secondary restrictive definition of MACE (MACE2) excluding target lesion revascularization, and bleeding.

Results: A total of 1,192 (24%) patients were ≤55 years, 2,869 (57%) were 56-74 years, and 957 (19%) were ≥75 years. Patients ≥75 years had higher DAPT cessation rates and increased risk of MACE2, death, cardiac death, and bleeding compared to younger patients. Discontinuation and interruption were not associated with increased cardiovascular risk across age groups, whereas disruption was associated with increased risk for MACE and MACE2 in younger patients, but not in patients ≥75 years (p-for-trend <0.05).

Conclusion: Non-adherence and outcomes vary by age with patients ≥75 years having the highest DAPT cessation rates. We observed no association between outcomes and DAPT cessation in patients ≥75 years, whereas discontinuation was associated with lower MACE rates and disruption with increased MACE rates in patients <75 years.

Keywords: Dual antiplatelet therapy, percutaneous coronary intervention, age

Condensed Abstract

Two-year clinical outcomes, incidence of DAPT cessation, and effect of DAPT cessation on outcomes were compared by ages ≤55, 56-74, and ≥75 years from the PARIS (Patterns of Non- Adherence to Antiplatelet Regimens in Stented Patients) registry. DAPT cessation and incidence of cardiovascular events significantly varied by age with patients ≥75 years having the highest rates of DAPT cessation. Discontinuation and interruption were not associated with increased cardiovascular risk across age groups, whereas risk after disruption attenuated in older versus younger individuals.

Abbreviations

ACS= acute coronary

syndrome(s) CI= confidence

interval

DAPT= dual-antiplatelet

therapy DES= drug-eluting

stent(s)

HR= hazard ratio

MACE= major adverse cardiac event(s)

MI= myocardial infarction

PCI= percutaneous coronary intervention

ST= stent thrombosis

TLR= target lesion revascularization

Introduction

More than 650,000 patients are treated annually with percutaneous coronary intervention (PCI) in the United States alone (1). As the average life expectancy of the population continues to rise, an increasing number of PCI patients are ≥75 years old (2,3). Dual antiplatelet therapy (DAPT) for ≥6 months with aspirin and a $P2Y_{12}$ inhibitor is the standard therapy of care for patients after PCI in the absence of indications for oral anticoagulation, whereas a shortened DAPT duration of 3 months can be considered in patients with high bleeding risk features according to ACC/AHA guidelines(4). Elderly patients are at greater risk of both ischemic and bleeding complications after PCI compared to younger patients (5,6). Given the increasing proportion of elderly patients, understanding patient outcomes by age is relevant. Furthermore, optimal duration of DAPT and net benefit of balancing ischemic and bleeding events warrants systemic investigation with regard to age (7).

Medication adherence to DAPT after PCI is important to optimize clinical outcomes (8,9). Variability in medication adherence in elderly patients has been associated with education level, dosing frequency, explanation of medication, and health-related problems (10-12). Given that premature DAPT cessation is associated with an increased risk of stent thrombosis (ST), myocardial infarction (MI), or death, it is pertinent to understand the effect of DAPT cessations on outcomes with respect to age (13).

To investigate the impact of age on modes of DAPT cessation and its association with major adverse cardiovascular events (MACE), the PARIS (Patterns of Non-Adherence to Antiplatelet Regimens in Stented Patients) registry was analyzed.

Methods

Study design and population

PARIS was a prospective, international, multicenter, observational study of all-comer PCI patients treated with DAPT to assess different modes of DAPT cessation and their association with subsequent adverse cardiovascular events (13). The different modes of DAPT cessation (discontinuation, interruption, and disruption) were assessed in association with clinical events and findings from these results were published previously (13). In this subanalysis, we studied baseline characteristics, procedural characteristics, medication, and clinical outcomes among three different age groups (≤55, 56-74, ≥75 years). Furthermore, we examined the incidence of DAPT cessation mode in each age group, and compared risk of clinical outcomes between uninterrupted DAPT therapy and any DAPT cessations across age groups.

Clinical Endpoint Definitions

In the present analysis, major adverse cardiac events (MACE) were defined as the composite of cardiac death, definite or probable ST, spontaneous MI, or clinically indicated target lesion revascularization (TLR) (13). A secondary restrictive definition of MACE (MACE2) included cardiac death, definite or probable ST, and spontaneous MI. Death and ST were classified as specified by Academic Research Consortium (ARC) criteria (14). TLR was defined as any repeat percutaneous or surgical intervention of the target lesion and further classified as clinically indicated or not clinically indicated. Spontaneous MI was defined as the presence of clinical or electrocardiographic changes consistent with myocardial ischemia in the setting of increased cardiac biomarkers above the upper limit of normal (15). Bleeding was classified using the Bleeding Academic Research Consortium (BARC) criteria (16). A bleeding event, unless otherwise specified, was defined as one that met criteria for BARC type ≥3. In addition to the BARC criteria, all bleeding events were also adjudicated using the TIMI

(Thrombolysis In Myocardial Infarction) and ACUITY (Acuity Catheterization and Urgent Intervention Triage Strategy) definitions (17,18). The modes of cessations were classified according to PARIS definitions as discontinuation, interruption, or disruption. Discontinuation included physician-directed and recommended withdrawal of the antiplatelet agent. Interruption was defined as temporary cessation of the antiplatelet agent due to surgery, but reinstituting DAPT within 14 days. Lastly, disruption was defined to include physician-recommended antiplatelet cessation due to bleeding or non-physician guided non-compliance. These DAPT classifications were not mutually exclusive, as patients could experience more than one mode of cessation during their 2-year follow-up period. All DAPT cessations and clinical endpoints were adjudicated by an external committee. DAPT cessations were adjudicated according to the following hierarchical order: disruption was prioritized over interruption, which in turn was prioritized over recommended discontinuation.

Statistical Analysis

Categorical variables are shown as frequencies and percentages and were compared between groups using chi-square tests. Continuous variables are expressed as mean ± SD and were compared using one-way ANOVA. The cumulative incidence rates for DAPT cessation were calculated using Kaplan-Meier estimates of time to the first cessation and were compared between groups using a Log-Rank test. Incidence rates for DAPT cessation were also represented by locally weighted regressions over continuous age (19,20). Risk for outcomes due to different modes of DAPT cessation was examined using a Cox regression analysis with DAPT cessation as a time-updated categorical variable, using uninterrupted DAPT over 2 years of age ≤55 years as a common reference (13). A test for trend was performed across age groups and mode of cessation on risk for outcomes. A test for

interaction was also performed for each age group using uninterrupted DAPT as the reference group. We presented results as hazard ratios (HRs) and 95% confidence interval (CI). We adjusted for the following baseline covariates: sex, diabetes, location (USA vs. Europe), stent type (bare metal stent vs. first-generation drug-eluting stent [DES] vs. second-generation DES), and the number of stents implanted. Statistical analyses were performed with Stata version 15.1 (StataCorp, College Station, Texas). A p-value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

Of the 5,018 patients in the final study population of the PARIS registry, 1,192 were ≤55 years (24%), 2,869 were 56-74 years (57%), and 957 were ≥75 years (19%). Given that follow-up was fixed at 2 years, the median follow-up duration was 730 days with 9% of patients lost prior to the 2-year study visit. Table 1 shows the baseline characteristics of patients of the PARIS registry who continued DAPT for 2 years according to age group. Patients ≤55 years more often were current smokers, more often had a family history of coronary artery disease (CAD), had a higher body mass index (BMI), and more often presented with acute coronary syndrome (ACS) upon admission compared to the older age groups. Patients 56- 74 years were more often diabetic, and presented more frequently with silent ischemia compared to patients ≤55 and ≥75 years. Lastly, patients ≥75 years were more frequently female, more often had an ischemic event history, and were more likely to have presented with stable angina at time of admission compared to younger age groups.

Procedural Characteristics and Medication

At time of admission, patients ≥75 years were more often treated for left main CAD,

whereas patients ≤55 years were more often treated for a thrombotic lesion. Furthermore, patients ≤55 years more often received glycoprotein IIb/IIIa inhibitors during PCI. Patients ≥75 years more often received bare metal stents during PCI compared to the other age groups. Overall, patients most frequently received a second-generation DES, with patients 56-74 years more frequently receiving a second-generation DES compared to the other age groups. At discharge, younger patients were more frequently prescribed prasugrel compared to older age groups, whereas clopidogrel, warfarin, and a proton pump inhibitor were more often prescribed with increasing age (Table 2).

DAPT Cessation

Of the different modes of DAPT cessation, the cumulative incidence at 2 years for discontinuation ($p<0.0001$) and interruption ($p=0.003$) increased significantly with age (Figure 1). The incidence of disruption was highest among patients ≥75 years, although there was a higher incidence in patients ≤55 years compared to patients 56-74 years (18.1 % vs. 14.3% vs. 13.0%; $p=0.0003$, Figure 1). Discontinuation was the most frequent mode of cessation, and disruption was more frequent than interruption (Figure 1). Using age as a continuous variable, the frequency of discontinuation increased until 80 years, and then decreased in frequency as age increased beyond 80 years. Contrastingly, the frequency of disruption decreased with increasing age until 60 years, and then increased with age from 60-90 years. Interruption increased with age, but plateaued after 60 years (Figure 2).

Outcomes

The incidence of death, cardiac death, BARC major bleeding, TIMI major bleeding, and MACE2 at 2 years was significantly higher in patients ≥75 years, and increased with increasing age (Table 3). When adjusted for sex, diabetes, location (USA vs. Europe), stent

type (bare metal stent vs. first-generation DES vs. second-generation DES), and the number of stents implanted, patients ≥75 years had higher rates of death, cardiac death, BARC major bleeding, and MACE2 ($p<0.0001$, $p=0.003$, $p<0.0001$, $p=0.04$ respectively) (Table 4). Contrarily, the adjusted incidence of clinically indicated TLR was lower in patients ≥75 years compared to younger patients ($p=0.02$).

Age-associated Risks of DAPT Cessation

Figure 3 shows the time-adjusted risk of adverse events through comparison of different DAPT cessation modes to uninterrupted DAPT. Physician-recommended discontinuation was associated with lower rates of adverse events in younger patients and was not associated with an increased risk for MACE in patients ≥75 years ($p_{trend}=0.01$). Discontinuation was also not associated with increased risk for MACE2 without a significant trend according to age groups ($p_{trend}=0.51$). The risk for MACE or MACE2 after interruption was not modified by age (MACE $p_{trend}=0.29$; MACE2 $p_{trend}=0.97$). Contrastingly, disruption of DAPT was associated with increased risk of MACE and MACE2 in patients ages ≤55 years and 56-74 years, but cardiovascular risk was attenuated in patients ≥75 years (MACE $p_{trend}=0.03$; MACE2 $p_{trend}<0.0001$). The test for interaction between DAPT cessation and cardiovascular risk in each age group was not significant for MACE or MACE2.

Discussion

Our findings show that the incidence of each mode of DAPT cessation differed significantly with age. Whereas older age was associated with a higher incidence of DAPT cessation due to discontinuation or interruption, disruption displayed a bimodal pattern occurring more frequently in both younger and older patients. Furthermore, age ≥75 years was associated with significantly higher adverse event rates compared to younger patients. Finally, we observed

a significant trend for risk of MACE and MACE2 among age groups after DAPT disruption, indicating an association with increased cardiovascular risk in the younger patient groups, but not in patients ≥75 years.

Given the ongoing debate on the optimal duration of DAPT, the consideration of potential beneficial effects of long-term DAPT must be compared to the increased risk of bleeding and subsequent increased risk of mortality (21-24). Many randomized trials comparing a shortened duration to a prolonged duration of DAPT showed shortened DAPT duration was associated with lower risk of bleeding and lower mortality with the increased use of second generation DES (23-26). The results from the current analysis show higher incidences of all modes of DAPT cessation in age ≥75 years compared to other age groups. Furthermore, the highest incidences of adverse events were among the oldest age group. Such findings are expected given that older patient populations are typically burdened with more comorbidity (3,6). Physicians treating these elderly patients likely considered the greater risk for the harmful effects of bleeding from DAPT compared to the protective effects from thrombotic events in duration of DAPT. The current analysis suggests that age is not a modifier of risk of adverse cardiovascular events after discontinuation or interruption. Discontinuation in particular was associated with lower rates of MACE in younger patient groups and was not associated with increased risk in patients ≥75 years. Such findings support the use of physician-recommended discontinuation and interruption as safe clinical practices.

The incidence of disruption differed from those of interruption and discontinuation with respect to age. Whereas the incidence of discontinuation and interruption increased with increasing age, disruption was highest in the elderly group, but also higher in the youngest patient population compared to ages 56-74 years. Although a relatively high rate of disruption

in patients ≥75 years can be expected as a result of an expected higher rate of bleeding, the seemingly paradoxical increase of noncompliance in younger patients is consistent with the Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention (FOCUS) study (27). Medication noncompliance is a common and clinically important problem, yet complicated by its often multifaceted nature (11). Many factors that affect medication adherence include socio-economic, health system-related, condition-related, therapy/medication-related, and patient- related factors (11,12) . FOCUS showed that age <50 years, as well as depression, lack of social support, and complexity of treatment contributed independently to non-compliance (27). Moreover, in TRANSLATE-ACS (Treatment With Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome) DAPT disruption was associated with younger patient age and socio-economic factors such as lack of health insurance (28). It is difficult to interpret increased disruption in younger patient populations given the array of factors that impact medication adherence. However, one possible explanation may be that these young patients with early cardiovascular events differ from young people in the general population in such factors that impact medication adherence.

The risk for cardiovascular events after disruption was also significantly modified by age group. We observed a significant trend showing an attenuation of risk after DAPT disruption with increasing age. The current analysis showed significantly increased rates of MACE and MACE2 in patients ≤55 years and 56-74 years, but not in patients ≥75 years. These findings suggest that the risk of adverse clinical outcomes after DAPT disruption may not be as severe in older patients, thereby rendering them suitable candidates for a shortened DAPT duration after PCI with stent implantation. Future adequately-powered clinical trials

should therefore be conducted to investigate the safety and efficacy of shortened DAPT duration in older patients. Indeed, the efficacy and safety of potent P2Y12 inhibitors versus clopidogrel is not modified by age (29). In contrast, medication noncompliance and risk for cardiovascular events after disruption remain as major concerns when treating younger patients. Given that medication cost is often an important socio-economic factor that can affect medication adherence, ARTEMIS (The Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study) showed an increased persistence with P2Y12 inhibitors when patients were provided vouchers to cover medication co-payments (30). Furthermore, guided DAPT de-escalation strategies have been shown to significantly benefit younger patients in decreasing cardiovascular risk (31). Younger patients may therefore benefit from strategies such as co-pay reduction or DAPT de-escalation to improve medication adherence and lower risk for adverse clinical outcomes.

Limitations

This PARIS subanalysis was performed in an observational study, thus precluding causal inferences. DAPT cessation information collected was also self-reported, which may have caused potential bias. Despite the known effect on the adherence, socio-economic status and psychosocial parameters such as mental health were not collected. Information on bleeding history was also not available, although ischemic history was assessed. Additionally, the age group cutoff utilized did not result in an even distribution of the numbers of patients. However, this was done with consideration to the preference of clinical applicability, and cutoffs used in the Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk (LEADERS FREE) and FOCUS trials (27,32). Furthermore, only 6% of patients were prescribed prasugrel although

≥40% of patients enrolled presented with an ACS, and ticagrelor had not yet been approved during the time of enrollment. Given that current guidelines recommend prasugrel and ticagrelor in patients presenting with ACS, our findings warrant confirmation in larger samples treated with potent P2Y12 inhibitors (4,21). Lastly, the low number of events reported per group of this subanalysis limited the power of analyses investigating associations between DAPT cessation and clinical outcomes, especially in patients ≥75 years.

Conclusion

Patterns of non-adherence to DAPT and incidence of cardiovascular events significantly vary by age with patients ≥75 years having the highest rates of DAPT cessation. We observed no association between clinical outcomes and DAPT cessation in patients ≥75 years, whereas discontinuation was associated with lower MACE rates and disruption with increased MACE rates in patients <75 years.

Clinical Perspectives

What's known? Risk for cardiovascular events after DAPT cessation in PCI-treated patients can vary according to duration and reason for cessation. It is well known that elderly patients are at greater risk of both ischemic and bleeding complications after PCI compared to younger patients. However, patterns of DAPT cessation and subsequent risks for adverse outcomes according to age are unknown.

What is new? Elderly patients had higher rates of DAPT cessation compared to younger age groups in the 2 years after PCI. The impact of each mode of DAPT cessation varied significantly by age. Discontinuation and interruption were not associated with increased cardiovascular risk across age groups, whereas disruption was associated with increased cardiovascular risk in younger patients but not in patients ≥75 years.

What is next? Future prospective studies should be conducted to investigate the safety and efficacy of shortened DAPT in older patients. In younger patients, strategies should be developed to optimize medication adherence and mitigate risk for adverse cardiovascular events after disruption. Younger patients may benefit from DAPT de-escalation strategies, as well as strategies that account for socio-economic and patient-centered factors.

Figure Titles and Legends

Figure 1. Title: Cumulative Incidences of Mode of Dual-Antiplatelet Therapy Cessation Across Follow-up Time Points. Legend: (A) The cumulative incidence of any DAPT cessation through 2 years after PCI in patients ages ≤55 vs. ages 56-74 vs. ages ≥75 years. The cumulative incidence of DAPT discontinuation, interruption, and disruption are represented in B, C, and D, respectively. DAPT=dual-antiplatelet therapy.

Figure 2. Title: Incidence of Dual-Antiplatelet Therapy Cessation Mode According to Age as a Continuous Variable. Legend: Central Figure. Incidence rates (%) at 2 years are represented by locally weighted regression over continuous age.

Figure 3. Title: Adjusted Risk for Adverse Cardiovascular Events at 2 years by Dual-Antiplatelet Therapy Cessation Mode According to Age Group. Legend: Patients age ≤55 years on dual-antiplatelet therapy (DAPT) were used as the reference group. All modes included the following variables: sex, diabetes, location (USA vs. Europe), stent type (bare metal stent vs. first-generation drug-eluting stent [DES] vs. second-generation DES), and the number of stents implanted. CI= confidence interval; DAPT= dual-antiplatelet therapy; HR= hazard ratio with 95% confidence interval; MACE= major adverse cardiac event(s) (cardiac death, myocardial infarction, clinically indicated target lesion revascularization, or definite or probable stent thrombosis); MACE2= major adverse cardiac event(s) 2 (cardiac death, myocardial infarction, or definite or probable stent thrombosis).

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Table 1. Baseline Characteristics

	Age ≤55 (n=1192 [24.0%])	55<Age<75 (n=2869 [57.0%])	Age ≥75 (n=957 [19.0%])	p Value
Female	215 (18.0%)	698 (24.3%)	366 (38.2%)	<0.0001
BMI, kg/m ^{2}	30.3 ± 6.1	29.4 ± 5.6	27.7 ± 4.8	<0.0001
Dyslipidemia requiring medication	818 (68.6%)	2225 (77.6%)	758(79.2%)	<0.0001
Hypertension requiring medication	811 (68.0%)	2356 (82.1%)	842(88.0%)	<0.0001
Family History of CAD	483 (40.5%)	909 (31.7%)	214 (22.4%)	<0.0001
Current Smoker	458 (38.4%)	481 (16.8%)	42 (4.4%)	<0.0001
Diabetes	321 (26.9%)	1020 (35.6%)	313 (32.7%)	<0.0001
On Insulin	113 (9.5%)	341 (11.9%)	91 (9.5%)	0.46
Education Level				<0.0001
Less than Secondary School	128 (10.7%)	313 (10.9%)	152 (15.9%)	
Secondary School	604 (50.7%)	1395 (48.6%)	484 (50.6%)	
Tertiary University Degree	345 (28.9%)	780 (27.2%)	222 (23.2%)	
Advanced degree	88 (7.4%)	312 (10.9%)	85 (8.9%)	
Ischemic history				
Previous MI	289 (24.2%)	702 (24.5%)	223 (23.3%)	0.77
Previous CABG	83 (7.0%)	405 (14.1%)	197 (20.6%)	<0.0001
Stroke (CVA)	18 (1.5%)	106 (3.7%)	49 (5.1%)	<0.0001
TIA	21 (1.8%)	75 (2.6%)	41 (4.3%)	0.002
PVD	65 (5.5%)	222 (7.7%)	105 (11.0%)	<0.0001
Previous CAD (Prior PCI, CABG, or MI)	493 (41.4%)	1460 (50.9%)	536 (56.0%)	<0.0001
Cardiac status at admission				
Silent Ischemia	96 (8.1%)	336 (11.8%)	90 (9.5%)	0.001
Stable Angina	487 (40.9%)	1454 (50.7%)	500 (52.2%)	<0.0001
Acute Coronary Syndrome	608 (51.0%)	1081 (37.7%)	367 (38.3%)	<0.0001

Values are n (%) or mean ± SD.

BMI= body mass index; CABG= coronary artery bypass grafting; CAD= coronary artery disease including myocardial infarction, PCI, and CABG; CVA= cerebrovascular accident; MI= myocardial infarction; PCI= percutaneous coronary intervention; PVD= peripheral vascular disease; TIA= transient ischemic attack.

Table 2. Procedural Characteristics

	Age ≤55 (n=1192 [24.0%])	55<Age<75 (n=2869 [57.0%])	Age ≥75 (n=957 [19.0%])	p Value
PCI vessel				
Left main	22 (1.8%)	81 (2.8%)	55 (5.7%)	<0.0001
Left anterior descending	576 (48.3%)	1302 (45.4%)	446 (46.6%)	0.23
Proximal left anterior descending	267 (22.4%)	631 (22.0%)	219 (22.9%)	0.84
Left circumflex	340 (28.5%)	896 (31.2%)	314 (32.8%)	0.08
Right coronary artery	429 (36.0%)	1007 (35.1%)	324 (33.9%)	0.59
Number of vessels treated				0.03
One	1026 (86.1%)	2479 (86.4%)	787 (82.2%)	
Two	157 (13.2%)	363 (12.7%)	158 (16.5%)	
Three	9 (0.8%)	27 (0.9%)	12 (1.3%)	
Bifurcation lesion	132 (11.1%)	340 (11.9%)	123 (12.9%)	0.45
Chronic total occlusion	49 (4.1%)	119 (4.1%)	24 (2.5%)	0.06
Thrombotic lesion	163 (13.7%)	207 (7.2%)	45 (4.7%)	<0.0001
Stent type				
Bare metal stent	228 (19.1%)	432 (15.1%)	224 (23.4%)	<0.0001
First-generation DES	151 (12.7%)	406 (14.2%)	117 (12.2%)	0.22
Second-generation DES	861 (72.2%)	2137 (74.5%)	671 (70.1%)	0.02
Number of stents implanted				0.17
1	681 (57.1%)	1595 (55.6%)	506 (52.9%)	
2	336 (28.2%)	804 (28.0%)	275 (28.7%)	
>2	175 (14.7%)	470 (16.4%)	176 (18.4%)	
Total stent length				0.42
≤20 mm	471 (39.5%)	1075 (37.5%)	373 (39.0%)	
>20 mm	721 (60.5%)	1794 (62.5%)	584 (61.0%)	
GP inhibitor	221 (18.5%)	391 (13.6%)	72(7.5%)	<0.0001
Discharge medication				
Aspirin	1192 (100.0%)	2869 (100.0%)	957 (100.0%)	
Thienopyridine	1192 (100.0%)	2869 (100.0%)	957 (100.0%)	
Warfarin	42 (3.5%)	163 (5.7%)	109 (11.4%)	<0.0001
Thienopyridine Type				<0.0001
Clopidogrel	1060 (88.9%)	2641 (92.1%)	934 (97.6%)	
Prasugrel	119 (10.0%)	179 (6.2%)	16 (1.7%)	
Ticlopidine	13 (1.1%)	49 (1.7%)	7 (0.7%)	
Proton Pump Inhibitor	246 (20.6%)	679 (23.7%)	249 (26.0%)	0.012

Values are n (%)

DES= drug-eluting stent(s); GP= glycoprotein

Table 3. Incidence of Clinical Outcomes at 12 and 24 Months by Age

	Age ≤55 (n=1192 [24.0%])	55<Age<75 (n=2869 [57.0%])	Age ≥75 (n=957 [19.0%])	p Value*
Death				
12 Months	18 (1.6%)	59 (2.1%)	36 (3.8%)	<0.0001
24 Months	30 (2.7%)	115 (4.2%)	82 (8.8%)	<0.0001
Cardiac death				
12 Months	18 (1.6%)	44 (1.6%)	23 (2.4%)	0.14
24 Months	25 (2.2%)	74 (2.7%)	49 (5.4%)	<0.0001
Probable or definite stent thrombosis				
12 Months	14 (1.2%)	36 (1.3%)	5 (0.5%)	0.18
24 Months	19 (1.7%)	45 (1.6%)	7 (0.8%)	0.11
Clinically indicated TLR				
12 Months	61 (5.3%)	151 (5.4%)	37 (4.0%)	0.21
24 Months	91 (8.1%)	212 (7.7%)	53 (5.9%)	0.07
Spontaneous MI				
12 Months	23 (2.0%)	64 (2.3%)	21 (2.3%)	0.65
24 Months	43 (3.9%)	100 (3.6%)	37 (4.1%)	0.78
TIMI major				
12 Months	10 (0.9%)	41 (1.5%)	19 (2.0%)	0.02
24 Months	11 (1.0%)	59 (2.1%)	31 (3.4%)	0.0001
BARC major (BARC ≥ 2)				
12 Months	40 (3.4%)	160 (5.7%)	90 (9.6%)	<0.0001
24 Months	56 (4.9%)	218 (7.9%)	127 (13.9%)	<0.0001
BARC major (BARC ≥ 3)				
12 Months	17 (1.5%)	79 (2.8%)	40 (4.3%)	<0.0001
24 Months	21 (1.8%)	114 (4.1%)	61 (6.7%)	<0.0001
MACE				
12 Months	82 (7.0%)	211 (7.5%)	70 (7.4%)	0.71
24 Months	130 (11.4%)	311 (11.2%)	117 (12.7%)	0.42
MACE2				
12 Months	38 (3.3%)	108 (3.8%)	46 (4.9%)	0.59
24 Months	64 (5.7%)	170 (6.1%)	81 (8.8%)	0.006

Values are n (%)

*P-values are for a test for trend in % across age groups

BARC= Bleeding Academic Research Consortium; MACE= major adverse cardiac event(s) (cardiac death, myocardial infarction, clinically indicated target lesion revascularization, or definite or probable stent thrombosis); MACE2= major adverse cardiac event(s) 2 (cardiac death, myocardial infarction, or definite or probable stent thrombosis); MI= myocardial infarction; TIMI=thrombolysis in myocardial infarction; TLR= target lesion revascularization.

Table 4. Adjusted Outcomes at 24 Months by Age

	Unadjusted		Adjusted	
Event	**HR [CI%]**	**p Value**	**HR [CI%]**	**p Value**
Death				
≤55	Ref.			
56-74	1.57 [1.05,2.34]	0.03	1.56 [1.04,2.33]	0.03
≥75	3.40 [2.24,5.16]	<.0001	2.93 [1.92,4.47]	<0.0001
Cardiac death				
≤55	Ref.			
56-74	1.21 [0.77,1.90]	0.41	1.17 [0.75,1.86]	0.48
≥75	2.44 [1.51,3.94]	0.0003	2.11 [1.30,3.44]	0.003
Spontaneous MI				
≤55	Ref.		Ref.	
56-74	0.95 [0.67,1.37]	0.80	0.95 [0.66,1.36]	0.79
≥75	1.07 [0.69,1.67]	0.75	0.97[0.61,1.51]	0.88
Clinically indicated TLR				
≤55	Ref.		Ref.	
56-74	0.96 [0.75,1.22]	0.73	0.92 [0.72,1.18]	0.53
≥75	0.72 [0.51,1.01]	0.06	0.67 [0.47,0.94]	0.02
Definite/probable ST				
≤55	Ref.		Ref.	
56-74	0.98 [0.57,1.67]	0.93	0.98 [0.57,1.68]	0.93
≥75	0.46 [0.19,1.09]	0.08	0.42 [0.18,1.02]	0.06
BARC major (BARC ≥2)				
≤55	Ref.		Ref.	
56-74	1.62 [1.21-2.17]	0.001	1.61 [1.20-2.17]	0.001
≥75	2.94 [2.15-4.03]	<0.0001	2.60 [1.89-2.17]	<0.0001
BARC major (BARC≥3)				
≤55	Ref.		Ref.	
56-74	2.24 [1.40-3.58]	0.001	2.23 [1.40-3.57]	0.001
≥75	3.68 [2.24-6.05]	<0.0001	3.21 [1.94-5.31]	<0.0001
MACE				

≤55	Ref.		Ref.	
56-74	0.98 [0.80,1.21]	0.87	0.96 [0.78,1.18]	0.70
≥75	1.11 [0.87,1.43]	0.39	1.03 [0.78,1.32]	0.83
MACE 2				
≤55	Ref.		Ref.	
56-74	1.09 [0.82,1.46]	0.55	1.07 [0.80,1.43]	0.63
≥75	1.58 [1.14,2.19]	0.006	1.42 [1.02,1.98]	0.04

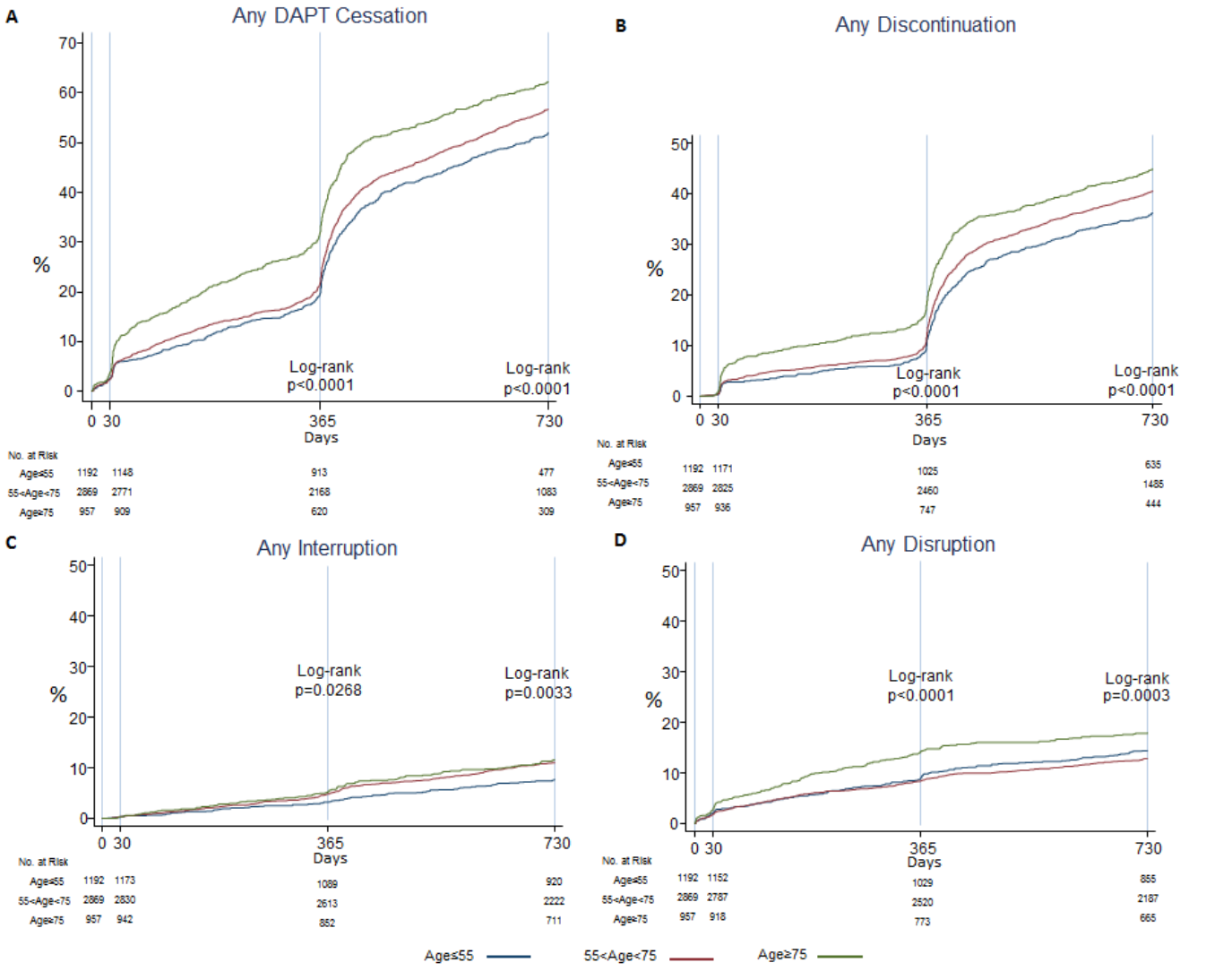
Table 4. Adjusted Outcomes at 24 Months by Age

	Unadjusted		Adjusted	
Event	**HR [CI%]**	**p Value**	**HR [CI%]**	**p Value**
Death				
≤55	Ref.			
56-74	1.57 [1.05,2.34]	0.03	1.56 [1.04,2.33]	0.03
≥75	3.40 [2.24,5.16]	<.0001	2.93 [1.92,4.47]	<0.0001
Cardiac death				
≤55	Ref.			
56-74	1.21 [0.77,1.90]	0.41	1.17 [0.75,1.86]	0.48
≥75	2.44 [1.51,3.94]	0.0003	2.11 [1.30,3.44]	0.003
Spontaneous MI				
≤55	Ref.		Ref.	
56-74	0.95 [0.67,1.37]	0.80	0.95 [0.66,1.36]	0.79
≥75	1.07 [0.69,1.67]	0.75	0.97[0.61,1.51]	0.88
Clinically indicated TLR				
≤55	Ref.		Ref.	
56-74	0.96 [0.75,1.22]	0.73	0.92 [0.72,1.18]	0.53
≥75	0.72 [0.51,1.01]	0.06	0.67 [0.47,0.94]	0.02
Definite/probable ST				
≤55	Ref.		Ref.	
56-74	0.98 [0.57,1.67]	0.93	0.98 [0.57,1.68]	0.93
≥75	0.46 [0.19,1.09]	0.08	0.42 [0.18,1.02]	0.06
BARC major (BARC ≥2)				
≤55	Ref.		Ref.	
56-74	1.62 [1.21-2.17]	0.001	1.61 [1.20-2.17]	0.001
≥75	2.94 [2.15-4.03]	<0.0001	2.60 [1.89-2.17]	<0.0001
BARC major (BARC≥3)				
≤55	Ref.		Ref.	
56-74	2.24 [1.40-3.58]	0.001	2.23 [1.40-3.57]	0.001
≥75	3.68 [2.24-6.05]	<0.0001	3.21 [1.94-5.31]	<0.0001
MACE				
≤55	Ref.		Ref.	
56-74	0.98 [0.80,1.21]	0.87	0.96 [0.78,1.18]	0.70
≥75	1.11 [0.87,1.43]	0.39	1.03 [0.78,1.32]	0.83
MACE 2				

≤55	Ref.		Ref.	
56-74	1.09 [0.82,1.46]	0.55	1.07 [0.80,1.43]	0.63
≥75	1.58 [1.14,2.19]	0.006	1.42 [1.02,1.98]	0.04

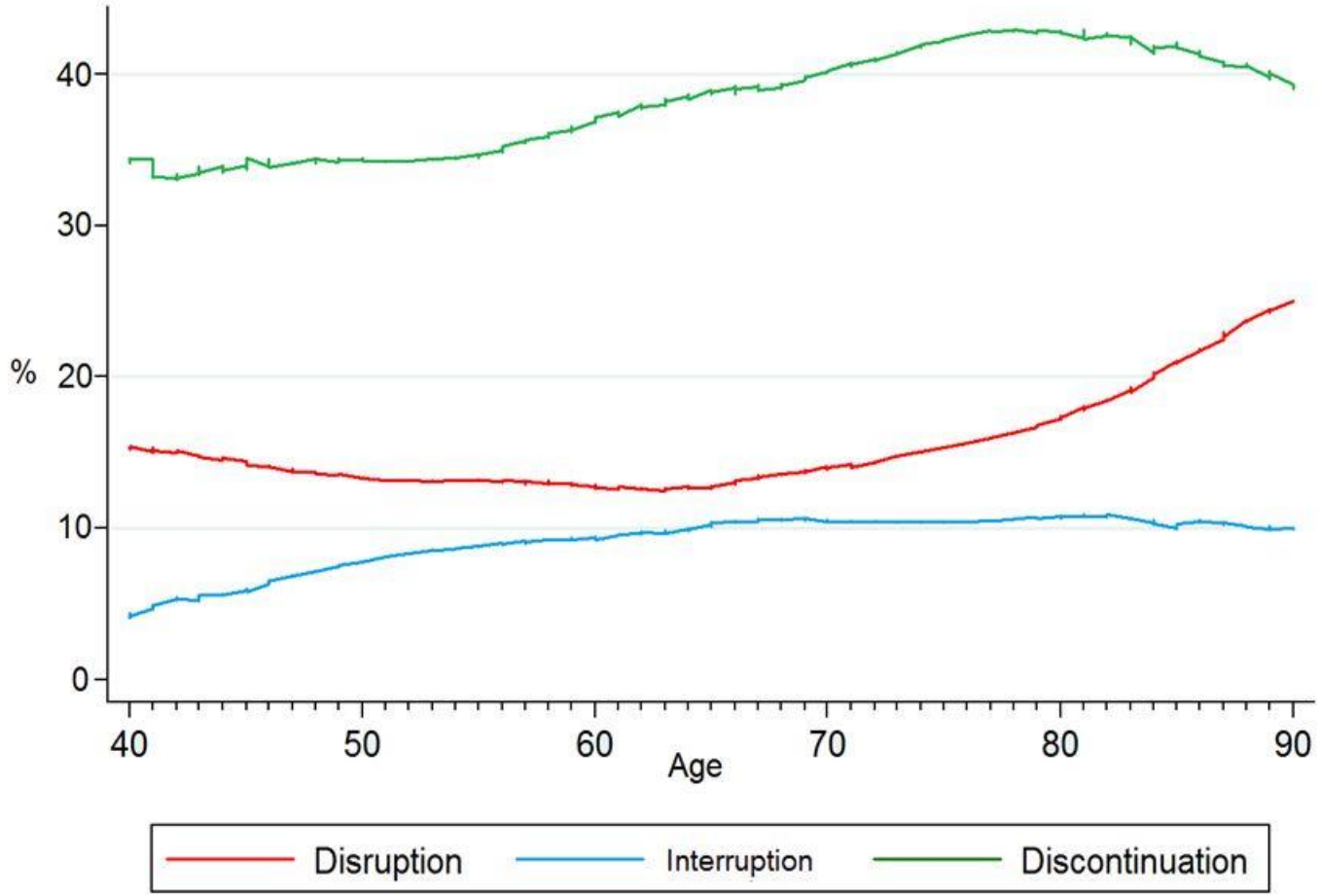
DAPT Cessation Outcomes by Age After PCI

FIGURE 1 Cumulative Incidences of Mode of Dual-Antiplatelet Therapy Cessation Across Follow-up Time Points



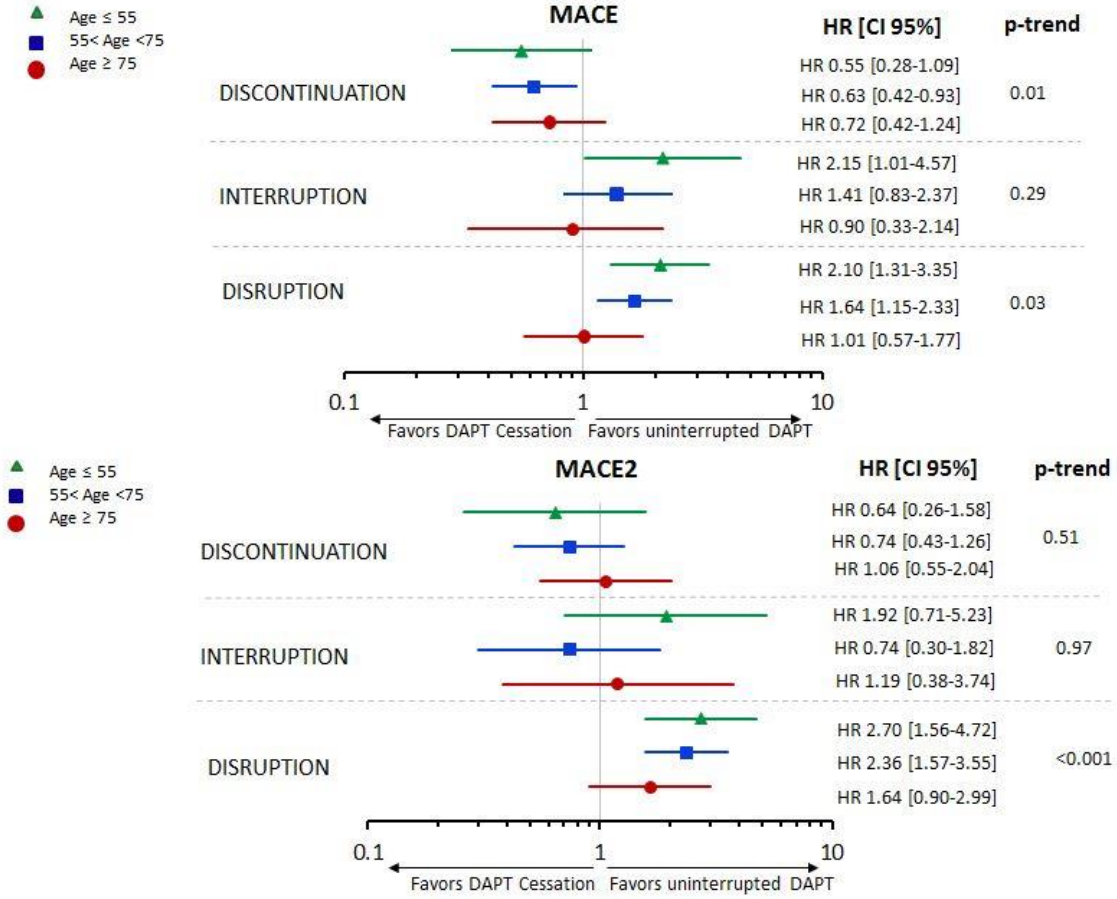
(A) The cumulative incidence of any DAPT cessation through 2 years after PCI in patients ages ≤55 vs. ages 56-74 vs. ages ≥75 years. The cumulative incidence of DAPT discontinuation, interruption, and disruption are represented in B, C, and D, respectively. DAPT=dual-antiplatelet therapy.

FIGURE 2 Incidence of Dual Antiplatelet Therapy Cessation Mode According to Age as a Continuous Variable



Incidence rates(%) at 2-years are represented by locally weighted regression over continuous age.

FIGURE 3 Adjusted Risk for Adverse Cardiac Events at 2 Years by Dual Antiplatelet Therapy Cessation Mode According to Age Group



Patients age ≤55 years on dual-antiplatelet therapy (DAPT) were used as the reference group. All modes included the following variables: sex, diabetes, location (USA vs. Europe), stent type (bare metal stent vs. first-generation drug-eluting stent [DES] vs. second-generation DES), and the number of stents implanted. CI= confidence interval; DAPT= dual-antiplatelet therapy; HR= hazard radio with 95% confidence interval; MACE= major adverse cardiac event(s) (cardiac death, myocardial infarction, clinically indicated target lesion revascularization, or definite or probable stent thrombosis); MACE2=major adverse cardiac event(s) 2 (cardiac death, myocardial infarction, or definite or probable stent thrombosis).