New-generation drug-eluting coronary stents in octogenarians: Patient-level pooled analysis from the TWENTE I-IV trials

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Background Patients aged ≥80 years are often treated with new-generation drug-eluting stents (DES), but data from randomized studies are scarce owing to underrepresentation in most trials. We assessed 1-year clinical outcome of octogenarians treated with new-generation DES versus younger patients.

Methods We pooled patient-level data of 9,204 participants in the TWENTE, DUTCH PEERS, BIO-RESORT, and BIONYX (TWENTE I-IV) randomized trials. The main clinical end point was target vessel failure (TVF), a composite of cardiac death, target vessel–related myocardial infarction (MI), or clinically indicated target vessel revascularization.

Results The 671 octogenarian trial participants had significantly more comorbidities. TVF was higher in octogenarians than in 8,533 patients <80 years (7.3% vs 5.3%, hazard ratio [HR]: 1.36, 95% CI: 1.0-1.83, $P = .04$). The cardiac death rate was higher in octogenarians (3.9% vs 0.8%, $P < .001$). There was no significant between-group difference in target vessel MI (2.3% vs 2.3%, $P = .88$) and repeat target vessel revascularization (1.9% vs 2.8%, $P = .16$). In multivariate analyses, age ≥ 80 years showed no independent association with TVF (adjusted HR: 1.04, 95% CI: 0.76-1.42), whereas the risk of cardiac death remained higher in octogenarians (adjusted HR: 3.38, 95% CI: 2.07-5.52, $P < .001$). In 6,002 trial participants, in whom data on major bleeding were recorded, octogenarians (n = 459) showed a higher major bleeding risk (5.9% vs 1.9%; HR: 3.08, 95% CI: 2.01-4.74, $P < .001$).

Conclusions Octogenarian participants in 4 large-scale randomized DES trials had more comorbidities and a higher incidence of the main end point TVF. Cardiac mortality was higher in octogenarians, whereas there was no increase in MI or target vessel revascularization rates. Treatment of octogenarian patients with new-generation DES appears to be safe and effective. (Am Heart J 2020;228:109-115.)

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In many countries, there is an increase in the proportion of octogenarians, who are known to have a higher prevalence of cardiovascular risk factors and a higher burden of coronary atherosclerosis.[1,2] Octogenarian patients with obstructive coronary artery disease have more diffuse and complex lesions with a higher degree of calcification as compared to younger patients, and they suffer more often from comorbidities such as heart failure, renal insufficiency, and history of stroke.[3-5] In addition, cognitive disorders are increasingly common in older adults[6] and may contribute to their overall increased risk of experiencing adverse clinical events.

Yet, octogenarian patients are underrepresented in most randomized stent trials. They are often directly excluded based on age or, indirectly, based on restraining eligibility criteria concerning major comorbidities and a high all-cause mortality risk.[7] Most previous research on

Table I. Overview of patients per randomized clinical trial and DES used

	All patients (N = 9204)	≥80 y old (n = 671)	Randomized stents
TWENTE I	1391	93 (6.7)	Resolute* versus Xience V†
TWENTE II (DUTCH PEERS)	1811	119 (6.6)	Resolute Integrity* versus Promus Element‡
TWENTE III (BIO-RESORT)	3514	251 (7.1)	Synergy‡/Orsiro§ versus Resolute Integrity
TWENTE IV (BIONYX)	2488	208 (8.4)	Resolute Onyx* versus Orsiro

Data are n (%). The percentages displayed are percentage of octogenarians per TWENTE trial.
* Medtronic, Santa Rosa, CA.
† Abbott Vascular, Santa Clara, CA.
‡ Boston Scientific, Marlborough, MA.
§ Biotronik, Bülach, Switzerland.

octogenarians, who were treated with percutaneous coronary intervention (PCI), focused on bare metal stents or on early-generation drug-eluting stents (DES).[8-11] The TWENTE trials[12-15] exclusively assessed new-generation DES, which in various clinical studies have shown safety profiles that were superior to early-generation DES and target lesion revascularization rates that were lower than in bare metal stents.[16-19] New-generation DES have been studied predominantly in patients aged 60-65 years, whereas less data are available from comparisons between octogenarian and younger patients who were treated with new-generation DES.

Previous all-comer trials that compared new-generation DES allowed enrollment of patients in all stages of life, but the actual number of octogenarians per individual trial is quite small, and therefore, data from randomized trials on the use of new-generation DES in octogenarians are scarce. As a consequence, it is of great interest to analyze pooled data from several trials. In the current patient-level pooled analysis of 4 large-scale randomized trials,[12-15] we examined the 1-year clinical outcome of octogenarians treated with new-generation DES as compared to younger patients.

Methods

Study participants and design

For the current analysis, we pooled patient-level data of all participants in the TWENTE (TWENTE I, clinicaltrials.gov: NCT01066650), DUTCH PEERS (TWENTE II, NCT01331707), BIO-RESORT (TWENTE III, NCT01674803), and BIONYX (TWENTE IV, NCT02508714) randomized trials, which studied patients with various acute or stable coronary syndromes who were all treated with new-generation DES. In all 4 trials, patients were eligible for participation if they were aged 18 years or older, capable of providing informed consent, and required PCI. The inclusion criteria were broad. There was no limit for lesion type (ie, de novo lesion, restenosis, or graft lesion), lesion length, reference vessel size, and number of lesions or vessels to be treated. TWENTE II-IV enrolled patients with all clinical syndromes. The TWENTE I trial enrolled all clinical syndromes except for ST-segment elevation myocardial infarction within <48 hours. Further details on in- and exclusion criteria and a list of all TWENTE trial investigators are provided in the online supplement (Supplementary Methods).

In the current analysis, we compared the 1-year clinical outcome of octogenarians with patients aged <80 years who were treated in TWENTE I-IV. Detailed description of the individual designs of the 4 randomized trials has been reported.[12-15] All trials are investigator-initiated, assessor- and patient-blinded, randomized studies that included patients treated at Thoraxcentrum Twente (TWENTE I/II/III/IV) or several other centers for coronary revascularization in the Netherlands (TWENTE II/III/IV), Belgium (TWENTE IV), and Israel (TWENTE IV). Table I shows which DES were compared in each trial and the number of participants per trial. The TWENTE I-IV trials demonstrated noninferiority of the respectively compared DES. The trials complied with the Declaration of Helsinki and were approved by the Medical Ethics Committee Twente, as well as the institutional review boards of all participating centers. Written informed consent was provided by all patients.[12-15]

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Procedures

The interventional procedures were performed according to standard techniques. Technical details of the implanted new-generation DES (all with strut thickness ≤ 91 μm) have been reported,[12-15] and an overview is provided in the online supplement (Online Table I). The choice of concomitant medication and the type and duration of dual antiplatelet therapy were based on routine clinical practice and current international guidelines. After PCI, electrocardiographs and cardiac biomarkers were systematically assessed with subsequent serial measurements in case of suspected ischemia. Angiographic analyses and offline

quantitative coronary angiographic measurements were performed by analysts of an angiographic core laboratory, according to current standards, using dedicated software (QAngio XA version 7.1, 7.2, and 7.3, Medis, Leiden, the Netherlands).

Follow-up, monitoring, and event adjudication

Clinical follow-up was obtained at patient visits to the outpatient clinics and by telephone follow-up or questionnaires. There was no routine angiographic follow-up. Trial and data management was coordinated by the clinical research organization Cardiovascular Research and Education Enschede (Enschede, the Netherlands). Data monitoring was performed by an independent clinical research organization (Diagram, Zwolle, the Netherlands). Adverse clinical events were adjudicated by independent, blinded clinical event committees: Cardialysis (Rotterdam, the Netherlands) for TWENTE I, Diagram (Zwolle, the Netherlands) for TWENTE II and III, and a committee of experienced interventional cardiologists of the University of Amsterdam (Amsterdam, the Netherlands) for TWENTE IV.

Clinical end points

The 4 TWENTE trials applied the same clinical end points which were defined according to the Academic Research Consortium and were previously described.[20,21] The main clinical end point of the current pooled analysis was target vessel failure (TVF), a composite of cardiac death, target vessel–related myocardial infarction (MI), or clinically indicated target vessel revascularization, which also was the primary end point of all 4 TWENTE trials. Death was considered to be cardiac unless an unequivocal noncardiac cause could be determined. A target vessel–related MI was related to the target vessel or could not be related to another vessel. Secondary end points included target lesion revascularization, definite or probable stent thrombosis, and the composite end point of major adverse cardiac events (all-cause death, any MI, emergent coronary bypass surgery, or repeat clinically indicated target lesion revascularization). Independently adjudicated data on bleeding events were only available for TWENTE III and IV. *Major bleeding* was defined as Bleeding Academic Research Consortium class 3-5 (3a, 3b, 3c, 4, 5a, 5b) and/or all Thrombolysis in Myocardial Infarction major bleedings (including coronary artery bypass graft [CABG]–related major bleeding).

Statistical analysis

Between-group differences in categorical variables were assessed with the Pearson χ^2 test or Fisher exact test, as appropriate, and in continuous variables with the Student *t* test. The time to end points was assessed according to the Kaplan-Meier method, and the log-rank test was applied for between-group comparisons. Hazard ratios (HRs) were computed using the Cox proportional hazards analysis. *P* values < .05 were considered significant. *P* values and CIs were 2-sided.

The multivariate model was constructed using stepwise backward selection. Variables with a nonsignificant association with the main outcome were excluded from the model. The variables that were included in the model are arterial hypertension, hypercholesterolemia, current smoker, chronic renal insufficiency, previous MI, acute coronary syndrome, left main treated, graft treated, at least 1 complex lesion, at least 1 severe calcification, at least 1 chronic total occlusion, and number of lesions treated. Because of the large number of confounders, we used a propensity score (including all confounders previously

Table II. Baseline patient, lesion, and procedural characteristics

	≥80 y old (n = 671)	<80 y old (n = 8533)	*P* value
Age (y)	82.70 ± 2.55	62.53 ± 9.80	
Female sex	289 (43.1)	2143 (25.1)	<.001
BMI (kg/m^2)	26.5 ± 3.9	27.8 ± 4.3	<.001
Diabetes mellitus	159 (23.7)	1600 (18.8)	.002
Arterial hypertension	412 (61.8)	4231 (49.8)	<.001
Hypercholesterolemia	254 (38.4)	3846 (45.5)	<.001
Current smoker	47 (7.2)	2509 (29.9)	<.001
Chronic renal insufficiency*	83 (12.4)	292 (3.4)	<.001
Previous MI	179 (26.7)	1717 (20.1)	<.001
Previous PCI	160 (23.8)	1643 (19.3)	.004
Previous CABG	88 (13.1)	676 (7.9)	<.001
Left ventricular ejection fraction < 30%	19 (2.9)	129 (1.6)	.01
Clinical presentation at admission			<.001
Acute coronary syndrome	459 (68.4)	5534 (64.9)	.06
STEMI	115 (17.1)	1949 (22.8)	
NSTEMI	209 (31.1)	2040 (23.9)	
Unstable angina	135 (20.1)	1545 (18.1)	
Stable angina	212 (31.6)	2999 (35.1)	.06
Multivessel treatment	146 (21.8)	1567 (18.4)	.03
Left main treated	27 (4.0)	188 (2.2)	.01
Graft treated	36 (5.4)	170 (2.0)	<.001
At least 1 complex lesion	551 (82.1)	6497 (76.1)	<.001
At least 1 severe calcification	201 (30.0)	1687 (19.8)	<.001
At least 1 CTO	20 (3.0)	402 (4.7)	.04
At least 1 bifurcation	222 (33.1)	2822 (33.1)	.51
No. of lesions treated	1.5 ± 0.67	1.3 ± 0.58	<.001
Total stent length	38.9 ± 26.7	38.8 ± 26.8	.90
Postdilation	528 (78.7)	6651 (77.9)	.65
DES used			.18
Resolute	46 (6.9)	651 (7.6)	
Xience V	47 (7.0)	647 (7.6)	
Promus Element	62 (9.2)	843 (9.9)	
Resolute Integrity	137 (20.4)	1942 (22.8)	
Orsiro	195 (29.1)	2219 (26.0)	
Synergy	77 (11.5)	1095 (12.8)	
Resolute Onyx	107 (15.9)	1136 (13.3)	

Data are n (%) or mean ± SD.
BMI, body mass index; *STEMI*, ST-segment elevation myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; *CTO*, chronic total occlusion.
**Chronic renal insufficiency* defined as creatinine level ≥ 130 μmol/L, an estimated glomerular filtration rate of less than 30 mL/min/1.73 m^2 of body surface area, or the need for dialysis.

Table III. Patient outcome at 1-year follow-up

	≥80 y old (n = 671)	<80 y old (n = 8533)	*P* log-rank	HR (95% CI)
Any death	40 (6.0)	127 (1.5)	<.001	4.10 (2.87-5.85)
Cardiac death	26 (3.9)	66 (0.8)	<.001	5.12 (3.25-8.05)
Any MI	17 (2.6)	205 (2.4)	.83	1.06 (0.64-1.73)
Target vessel MI	15 (2.3)	199 (2.3)	.88	0.96 (0.57-1.62)
Periprocedural MI	10 (1.5)	167 (2.0)	.40	0.76 (0.40-1.44)
Any revascularization	22 (3.4)	420 (5.0)	.07	0.68 (0.44-1.04)
Target vessel revascularization	12 (1.9)	236 (2.8)	.16	0.66 (0.37-1.18)
Target lesion revascularization	12 (1.9)	164 (1.9)	.87	0.95 (0.53-1.71)
Target vessel failure*	48 (7.3)	454 (5.3)	.04	1.36 (1.01-1.83)
MACE†	63 (9.4)	468 (5.3)	<.001	1.74 (1.34-2.26)
Definite or probable stent thrombosis	4 (0.6)	49 (0.5)	.93	1.05 (0.38-2.90)
Definite stent thrombosis	3 (0.4)	29 (0.3)	.64	1.33 (0.41-4.36)
Any bleeding‡	34/459 (7.6)	155/5543 (2.8)	<.001	2.75 (1.90-3.99)
Major bleeding§	26/459 (5.8)	106/5543 (1.9)	<.001	3.07 (2.00-4.72)

Data are n (%).
*The main end point of target vessel failure consists of cardiac death, target vessel MI, or target vessel revascularization.
† MACE consists of any death, any MI, emergent coronary artery bypass surgery, or clinically indicated target lesion revascularization.
‡ Bleeding data were only available for participants of TWENTE III and IV.
§ *Major bleeding* is defined as Bleeding Academic Research Consortium class 3-5 and/or all Thrombolysis in Myocardial Infarction major bleedings (including CABG-related major bleeding).

mentioned) in the logistic regression analysis. Finally, a Cox regression analysis was performed that adjusted for this propensity score. Statistical analyses were performed with SPSS, version 24.0 (IBM, Armonk, NY).

Results

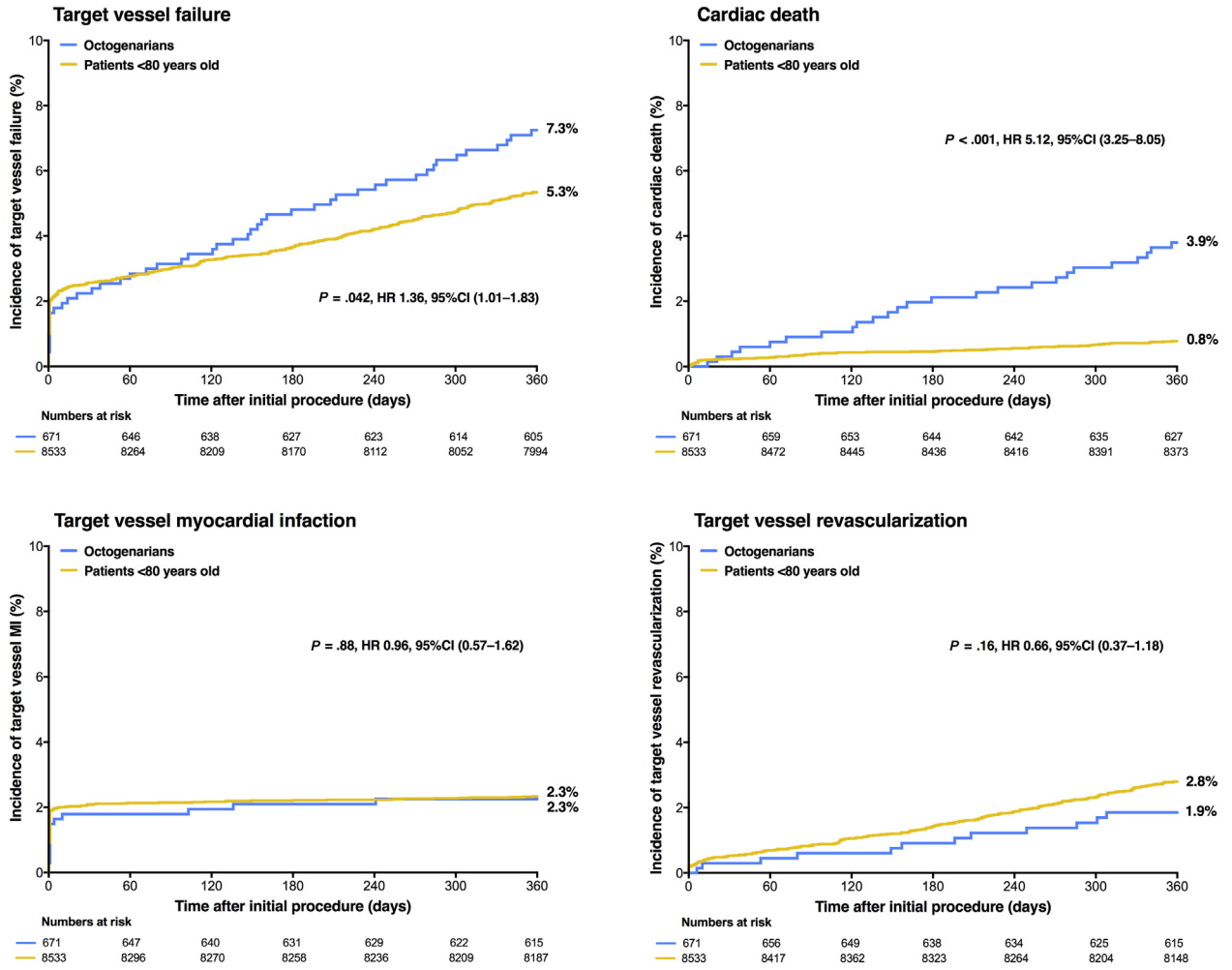
Of the 9,204 patients who were enrolled in the TWENTE trials, a total of 671 (7.3%) were octogenarians. Over time, we noted a slight increase in the proportion of octogenarian trial participants from an average of 6.6% in TWENTE I and II to 8.4% in TWENTE IV(Table I). Patients of the study population were 21 to 96 years old. Between octogenarians and patients aged <80 years, there were significant differences in baseline patient and lesion characteristics. Octogenarians were more often female (43.1% vs 25.1%, $P < .001$), and they had more often diabetes (23.7% vs 18.8%, $P = .002$) and hypertension (61.8% vs 49.8%, $P < .001$). But octogenarians were less often current smokers (7.2% vs 29.9%, $P < .001$) and had a lower body mass index (26.5 ± 3.9 vs 27.8 ± 4.3 kg/m^2, $P < .001$). Furthermore, octogenarians presented more frequently with non–ST-segment elevation MI (31.1%) than patients aged <80 years (23.9%), and their target lesions were more often complex (82.1% vs 76.1%, $P < .001$) and severely calcified (30% vs 19.8%, $P < .001$). Other patient, lesion, and procedural characteristics at baseline are presented in Table II.

Follow-up at 1 year was available in 9165 (99.6%) patients. Ten patients were lost to follow-up (all <80 years old), and 29 patients withdrew their consent (4 age ≥ 80 years, 25 age < 80 years); all were censored at moment of dropout. The main composite end point TVF occurred in 7.3% of the octogenarian patients versus 5.3% of patients aged <80 years (HR: 1.36, 95% CI: 1.01-1.83, $P = .04$) (Table III). This difference was driven by a higher cardiac death rate in octogenarians (3.9% vs 0.8%, HR: 5.12, 95% CI: 3.25-8.05, $P < .001$). There was no between-group difference in the rate of target vessel MI (2.3% vs 2.3%, HR: 0.96, 95% CI: 0.57-1.62, $P = .88$). The incidence of target vessel revascularization did not differ significantly between groups (1.9% vs 2.8%, HR: 0.66, 95% CI: 0.37-1.18, $P = .16$). Figure 1 displays the Kaplan-Meier curves of TVF and its components. The 1-year rates of any death (6.0% vs 1.5%, HR: 4.10, 95% CI: 2.87-5.85, $P < .001$) and major adverse cardiac events (9.4% vs 5.3%, HR: 1.74, 95% CI: 1.34-2.26, $P < .001$) were higher in octogenarians. There was no between-group difference in the incidence of definite or probable stent thrombosis (0.6% vs 0.5%, HR: 1.05, 95% CI: 0.38-2.90, $P = .93$). At 1-year follow-up, there was a difference in the rates of dual antiplatelet therapy use between groups; 72.7% of octogenarians versus 87.5% of patients aged <80 years were on dual antiplatelet therapy ($P < .001$) (Table IV).

In a multivariate analysis, age ≥ 80 years showed no independent association with TVF (adjusted HR: 1.04, 95% CI: 0.76-1.42, $P = .81$). The higher cardiac death risk in octogenarians remained significant after adjustment for confounders (adjusted HR: 3.38, 95% CI: 2.07-5.52, $P < .001$). In addition, the adjusted risk of repeat target vessel revascularization was significantly lower in octogenarians (adjusted HR: 0.50, 95% CI: 0.27-0.92, $P = .027$).

Data on bleeding and use of oral anticoagulants were only available for participants of TWENTE III and IV (n = 6,002). The 459 octogenarians more frequently used oral anticoagulants (23.8%) than the 5,543 patients aged <80 years (10.0%, $P < .001$) (Table IV). In addition, the

Figure 1



Kaplan-Meier cumulative event curves for target vessel failure and components at 1-year follow-up.Of all 671 octogenarians, 48 (7.3%) experienced target vessel failure at 1 year after percutaneous coronary intervention with new-generation DES as compared to 454 of 8,533 (5.3%) patients aged <80 years. This significantly higher rate of target vessel failure among octogenarians was driven by a higher rate of cardiac death. The incidence of target vessel myocardial infarction was equal and the incidence of target vessel revascularization was numerically lower in octogenarians versus patients <80 years of age.

octogenarians had a 3 times higher risk of major bleeding (5.8% vs 1.9%, HR: 3.07, 95% CI: 2.00-4.72, $P < .001$).

Discussion

Main findings

In the present pooled analysis of patient-level data from 4 large-scale randomized clinical trials that compared new-generation DES, octogenarians showed 1 year after coronary PCI a higher rate of the main composite end point TVF than patients aged <80 years. Cardiac mortality was higher in octogenarians, whereas there was no increase in MI or target vessel revascularization rates. In addition, the rate of death by any cause was higher in octogenarians, as could be expected from the higher prevalence of comorbidities and from the more advanced age itself. Treatment of octogenarian patients with new-generation DES appears to be safe and effective.

Previous studies

Only 2 randomized trials specifically investigated octogenarians or patients ≥75 years of age treated with new-generation DES. In the XIMA trial, octogenarians were randomized to PCI with durable polymer-coated everolimus-eluting stents (Xience, Abbott Vascular) versus bare metal stents.[8] The 399 XIMA trial participants who received DES showed rates of cardiac death (3.3%) and repeat target vessel revascularization (2.0%) that

Table IV. DAPT regimens and use of oral anticoagulants at 1-year follow-up

	Total (n = 8998)	≥80 y old (n = 627)	<80 y old (n = 8371)	*P* value
Aspirin	7998 (88.9)	478 (76.2)	7520 (89.8)	<.001
DAPT	7784 (86.5)	456 (72.7)	7328 (87.5)	<.001
With clopidogrel	5153 (66.2)	327 (71.7)	4826 (65.9)	.01
With ticagrelor or prasugrel	2631 (33.8)	129 (28.3)	2502 (34.1)	<.001
Oral anticoagulants*	645/6002 (10.7)	102/459 (23.8)	543/5543 (10.0)	<.001

Data are n (%).
* Data on use of oral anticoagulants were only available for participants of TWENTE III and IV.

were similar to our current analysis (3.9% and 1.9%, respectively).[8] The second trial is the SENIOR randomized trial, which was not restricted to assessing octogenarians but studied patients ≥75 years of age (mean age 81.4 years) who were treated with biodegradable polymer-coated everolimus-eluting stents (Synergy, Boston Scientific) versus bare metal stents and were prescribed a short duration of dual antiplatelet therapy in both stent groups.[9] The rates of cardiac death (3.7%) and target lesion revascularization (1.7%) in the 596 DES-treated SENIOR patients[9] were also similar to the corresponding event rates in our current analysis (3.9% and 1.9%, respectively). Hence, both randomized studies corroborated the event rates that were found in the present analysis.

Further insights were obtained from 2 Japanese observational studies in octogenarians treated with new-generation DES.[3,22] In these registries, assessing 54 and 200 octogenarians, respectively, overall adverse event rates were somewhat higher than in our current analysis, which may be partly related to the fact that these registries did not apply formal exclusion criteria. Nevertheless, both registries do support our findings of a higher incidence of cardiac death and a lower repeat revascularization risk in octogenarians treated with new-generation DES.

Stent thrombosis and bleeding

The rates of target vessel MI and definite or probable stent thrombosis were low and similar in octogenarians and younger patients despite the lower rate of dual antiplatelet therapy use among octogenarians at 1-year follow-up. This can be interpreted as an important signal of safety for treatment with new-generation DES in octogenarians. Nevertheless, the risk of major bleeding was 3 times higher for octogenarians in the TWENTE III and IV trials, which can be partly explained by the rate of oral anticoagulant use. The balance between bleeding and thrombosis appears to be delicate, as a reduction in thrombosis rates may be traded off against an increase in bleeding rates.

Target vessel revascularization

Multivariate analysis showed, after adjustment for confounders, that the risk of clinically indicated target vessel revascularization was significantly lower in octogenarians than in patients aged <80 years (adjusted HR: 0.50). Some possible explanations may be considered. First, a substantial proportion of the octogenarians may not reach the ischemic threshold because of a more sedentary lifestyle or noncardiac physical complaints that may limit their activities. Second, when considering the comorbidities and life expectancy of octogenarians, physicians might be less inclined to perform (non) invasive imaging or to treat them with a repeat PCI (rather than medical therapy), in particular if octogenarians present with stable angina or a limited non–ST-elevation MI. Finally, cognitive impairment, which has an increasing prevalence with advancing age, may hinder recognition of symptoms of myocardial ischemia.

Strengths and limitations

The present analysis of pooled patient-level data from 4 large-scale randomized stent trials with minimal exclusion criteria assesses a relatively large population of octogenarian patients. Analyses include various details of patients, lesions, and treatment characteristics based on the same definitions in the 4 trials. Outcome data were obtained from prospective clinical trials with very high follow up and independent clinical event adjudication.

Nevertheless, this study has limitations. The findings of this analysis should be considered hypothesis generating, and it is not adequately powered to assess infrequent adverse events (eg, stent thrombosis). Life expectancy <1 year was an exclusion criterion in the randomized TWENTE trials. Therefore, the findings should not be generalized toward the group of extremely frail patients, and the inclusion rate of octogenarian patients may have been lower than in some registries that did not use this exclusion criterion.[3,22] Furthermore, the findings of the multivariate analysis should be interpreted with some caution, as we cannot completely exclude the presence of a potential undetected confounder. Follow-up beyond 1 year would also be of interest, as most patients have not yet stopped DAPT at 12-month follow-up. Moreover, adjudicated bleeding data were not available from all trials and were only reported for participants of the TWENTE III and IV trials. In the octogenarian study participants, it would have been informative to also assess frailty as it is associated with mortality. As functional capacity and physical ability were not assessed, we could not determine frailty as a distinct parameter.[23] Nevertheless, the baseline characteristics show in octogenarians a higher incidence of comorbidities which are related to frailty.

Conclusions

Octogenarian participants in 4 large-scale randomized drug-eluting stent trials had more comorbidities and a higher incidence of the main composite clinical end point TVF. Cardiac mortality was higher in octogenarians, whereas there was no increase in MI or target vessel revascularization rates. Treatment of octogenarian patients with new-generation DES appears to be safe and effective.

Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2020.07.003.

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