Small-vessel treatment with contemporary newer-generation drug-eluting coronary stents in all-comers: Insights from 2-year DUTCH PEERS (TWENTE II) randomized trial

Liefke C. van der Heijden, MD,[a] Marlies M. Kok, MD,[a] Peter W. Danse, MD, PhD,[b] Alexander R. Schramm, MD,[c] Marc Hartmann, MD, PhD,[a] Marije M. Löwik, PhD,[a] Gerard C. M. Linssen, MD, PhD,[d] Martin G. Stoel, MD, PhD,[a] Carine J. M. Doggen, PhD,[e] and Clemens von Birgelen, MD, PhD[a,e] *Enschede, Arnhem, Emmen, and Almelo and Hengelo, the Netherlands*

Background Treatment of lesions in small vessels was associated with worse clinical outcome, and various definitions of "small vessels" have been used. Data with novel drug-eluting stents are scarce.

Methods To compare the outcome of patients with vs without small-vessel treatment, we assessed 2-year follow-up data of the DUTCH PEERS randomized trial (ClinicalTrials.gov: NCT01331707), in which 1,811 all-comers were treated with contemporary zotarolimus-eluting (Resolute Integrity) or everolimus-eluting (Promus Element) stents. Primary end point was target lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction, and target lesion revascularization.

Results The rates of TLF (9.5% vs 5.4%; *P* log rank = .001) and 2 individual components thereof—target vessel myocardial infarction (3.1% vs 1.3%; *P* log rank = .006) and target lesion revascularization (4.8% vs 2.8%; *P* log rank = .02)—were higher among 798 (44.1%) patients treated in at least one small vessel (<2.50 mm by quantitative coronary angiography). Multivariate analysis with propensity score adjustment demonstrated that treatment of small-vessel lesions independently predicted TLF at 2-year follow-up (hazard ratio 1.60, 95% CI 1.09-2.34). Patients with the smallest target vessel being <2.25 mm had TLF rates similar to patients with smallest target vessels of 2.25 to <2.50 mm; however, patients treated in vessels no smaller than 2.50 to <3.00 mm and patients treated in vessels ≥3.00 mm had lower TLF rates (9.3%, 9.8%, 5.0%, and 5.8%, respectively; *P* log rank = .009).

Conclusion Patients treated with novel drug-eluting stents in small-vessel lesions had higher adverse event rates than did patients who had no small-vessel treatment. Our data suggest that with current stents, a vessel diameter <2.50 mm is a suitable threshold to identify small target vessels. (Am Heart J 2016;176:28-35.)

Treatment of lesions in small coronary vessels is a challenge for percutaneous coronary intervention (PCI) and has been associated with an increased risk of adverse clinical events.[1–6] Several studies have shown an impact of the stent type used on clinical outcome after PCI in small vessels, especially on the occurrence of restenosis.[2,7–12] In contrast to bare-metal stents,[2–6] the use of first-generation drug-eluting stents (DESs) in small vessels reduced the need for repeat revascularization due to less in-stent neointimal proliferation.[8,13–16] Nevertheless, early DES still showed a certain neointima-induced late lumen loss during follow-up, which may be related to more unfavorable consequences and adverse clinical events in small target vessels compared with large vessels.[17] Strut thickness, lesion length, and the minimum stent lumen diameter were previously identified as independent predictors of restenosis in DES.[4,6,18,19] Treatment of small-vessel lesions with second-generation durable polymer DES may result in somewhat more favorable results, but data from randomized clinical all-comer trials are scarce.[9–11,20,21] As a consequence, it is of interest to investigate the clinical outcome of patients who were treated with novel DES in small target vessels.[22]

From the [a]Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, the Netherlands, [b]Department of Cardiology, Rijnstate Hospital, Arnhem, the Netherlands, [c]Department of Cardiology, Treant Zorggroep, Location Scheper, Emmen, the Netherlands, [d]Department of Cardiology, Ziekenhuisgroep Twente, Almelo and Hengelo, the Netherlands, and [e]Health Technology and Services Research, MIRA—Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, the Netherlands.

RCT No. NCT01331707

Submitted September 14, 2015; accepted February 27, 2016.

Reprint requests: Clemens von Birgelen, MD, PhD, Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, Koningsplein 1, 7512 KZ Enschede, the Netherlands.

E-mail: c.vonbirgelen@mst.nl

0002-8703

http://dx.doi.org/10.1016/j.ahj.2016.02.020

The randomized DUTCH PEERS trial compares in all-comer patients 2 recent DESs that combine the coating and drug of second-generation DES with modified metallic stent platforms that aim to increase flexibility and deliverability.[23] In this study, the zotarolimus-eluting Resolute Integrity (Medtronic, Santa Rosa, CA) and the everolimus-eluting Promus Element stent (Boston Scientific, Natick, MA) have shown similar and favorable safety and efficacy up to 2 years.[24]

In the present substudy of the DUTCH PEERS trial, we analyzed the 2-year clinical follow-up data of all-comer patients treated for lesions in at least one *small coronary vessel* (<2.50 mm) vs patients with target lesions in larger-sized vessels (≥2.50 mm). In addition, adverse clinical event rates of patients with various different minimum target vessel sizes (ie, previous definitions of small vessels) were compared to further evaluate the impact of target vessel size on clinical outcome.

Methods

Study design and patient population

The randomized, patient-blinded, multicenter DUTCH PEERS (TWENTE II) trial compares the Resolute Integrity zotarolimus-eluting cobalt-chromium stent (Medtronic Vascular) and the Promus Element everolimus-eluting platinum-chromium stent (Boston Scientific). The study design and procedures of this investigator-initiated trial (ClinicalTrials.gov: NCT01331707) have been described in detail[23,25] and 2-year clinical outcome has been reported.[24] In brief, 1,811 all-comer patients who were treated by PCI for de novo or restenotic lesions in coronary arteries or bypass grafts were enrolled. There was no limit for lesion length, reference size, or number of lesions or diseased vessels to be treated. Both Resolute Integrity stents as Promus Element stents were available, with nominal sizes ranging from 2.25 to 4.00 mm. The trial complied with the Declaration of Helsinki and was approved by the independent Medical Ethics Committee Twente and the institutional review boards of all participating centers. All patients provided written informed consent. Study enrollment was performed between November 2010 and May 2012.

In the present substudy, patients who were treated for at least one small-vessel lesion were compared with patients treated for lesions in larger vessels only. A *small vessel* was defined as a coronary artery with a reference vessel diameter less than 2.50 mm, as measured by quantitative coronary angiography.

Clinical follow-up, monitoring, event adjudication, and angiographic analysis

Interventional procedures and application of concomitant medication were performed in accordance with medical guidelines, clinical standards, and the physician's judgment. Lesion predilation, direct stenting, stent postdilation, and use of glycoprotein IIb/IIIa receptor antagonists were left at the operator's discretion. In general, dual antiplatelet therapy was prescribed for 12 months.[23]

Research nurses, blinded to the treatment arm, obtained information on clinical events through a medical questionnaire or, in the absence of a response, a telephone interview that was based on the same questions. Data monitoring was performed by the independent contract research organization Diagram (Zwolle, the Netherlands). The independent contract research organization Cardialysis (Rotterdam, the Netherlands) performed the processing of clinical outcome data and clinical event adjudication.

For all patients, offline quantitative coronary angiographic analysis was performed according to current standards by angiographic analysts from Thoraxcentrum Twente, who were blinded for the stent-type and clinical outcome (Qangio XA 7.2; Medis, Leiden, the Netherlands).

Clinical end points

Definitions of all predefined clinical end points have previously been described in detail[23,25] and follow the suggestions from the Academic Research Consortium, including the addendum on myocardial infarction (MI).[26,27] Death was considered cardiac, unless an evident noncardiac cause could be established. *Myocardial infarction* was defined by any creatine kinase concentration of more than double the upper limit of normal with elevated values of a confirmatory cardiac biomarker. A target vessel–related MI was related to the target vessel or could not be related to another vessel. Side branches of bifurcated target lesions were only classified as target vessel when being stented. *Periprocedural MI* (PMI) was defined as target vessel–related MI within 48 hours after PCI. Both clinical outcomes and enzyme elevation as reported by the extended historical MI definition were used for defining PMI in case of elevated creatine kinase (or creatine kinase MB) from index MI that has not yet reached its maximum level.[27] Stent thrombosis was classified according to the Academic Research Consortium definitions.[26,27]

The composite end point *target lesion failure* (TLF) was defined as cardiac death, target vessel–related MI, or clinically indicated target lesion revascularization (TLR). Target lesion failure, which is based on these 3 individual event components with different mechanisms and time courses, reflects the device and lesion-related part of the entire spectrum of adverse events that may occur during the years of follow-up. Target lesion revascularization is considered clinically indicated if the angiographic diameter stenosis was ≥70%, or ≥50% in the presence of ischemic signs or symptoms. The use of FFR was left to the operator's discretion. *Major adverse cardiac event* (MACE) was defined as a composite of all-cause death, any MI, emergent coronary artery bypass surgery, or clinically indicated TLR.

Table I. Baseline characteristics of study population, comparing patients with vs without small-vessel treatment

	All patients (n = 1811)		
Patient characteristics	Small vessel (n = 798)	No small vessel (n = 1013)	*P*
Age (y)	64.2 ± 10.7	63.8 ± 10.8	.40
Female	228 (28.6)	261 (25.8)	.18
Diabetes mellitus	163 (20.4)	161 (15.9)	.01
Current smoker	167 (20.9)	277 (27.3)	.002
Arterial hypertension	430 (53.9)	554 (54.7)	.73
Hypercholesterolaemia	381 (47.7)	467 (46.1)	.49
Family history of coronary artery disease	404 (50.6)	499 (49.3)	.56
Previous MI	208 (26.1)	189 (18.7)	<.001
Previous PCI	159 (19.9)	190 (18.8)	.53
Previous CABG	84 (10.5)	89 (8.8)	.21
Stable angina pectoris	384 (48.1)	365 (36.0)	<.001
Lesion/procedural characteristics			
Stent type used			.14
Zotarolimus-eluting stent	415 (52.0)	491 (48.5)	
Everolimus-eluting stent	383 (48.0)	522 (51.5)	
Multivessel treatment	196 (24.6)	100 (9.9)	<.001
Treated coronary vessels			
Right coronary artery	240 (30.1)	429 (42.3)	<.001
Left anterior artery	423 (53.0)	431 (42.5)	<.001
Circumflex artery	315 (39.5)	208 (20.5)	<.001
De novo lesions	706 (88.5)	921 (90.9)	.09
At least one chronic total occlusion	54 (6.8)	22 (2.2)	<.001
At least one in-stent restenosis	17 (2.1)	38 (3.8)	.05
At least one severe calcification	175 (21.9)	232 (22.9)	.62
At least one bifurcation	225 (28.2)	240 (23.7)	.03
At least one lesion length >27 mm	161 (20.2)	157 (15.5)	.009
Total stent length	44.9 ± 30.2	32.5 ± 21.4	<.001
No. of stents per patient	2.1 ± 1.2	1.5 ± 0.8	<.001
Postdilation	602 (75.4)	801 (79.1)	.07
Degree of stenosis pre PCI	71.4 ± 18.4	70.4 ± 17.5	.24
Degree of stenosis post PCI	18.5 ± 8.7	16.6 ± 7.8	<.001

Values are n (%) or mean ± SD. A small vessel was defined by a reference vessel diameter <2.5 mm by quantitative coronary angiography.
Abbreviation: *CABG*, Coronary artery bypass grafting.

Statistical analysis

Data were reported as frequencies and percentages for dichotomous and categorical variables, and as mean ± SD for continuous variables. Categorical variables were assessed with the χ^2 test or Fisher exact test as appropriate, whereas continuous variables were assessed with the Student *t* test or Wilcoxon rank sum test as appropriate. The Kaplan-Meier analysis was used to calculate the time to clinical end point, and the log-rank test was applied to compare between-group differences. A 2-sided *P* value less than .05 was considered significant. Variables were considered as potential confounders if associations were found with a *P* value <.15 in univariate analysis. For adjustment of potential confounders, propensity score analysis was used. The propensity score was estimated using multiple logistic regression analysis. Diabetes mellitus, current smoker, previous acute MI, clinical syndrome at presentation, multivessel treatment, total number of stents implanted, treatment of at least one chronic total occlusion treatment, left anterior descending artery treatment, ramus circumflexus treatment, bifurcation treatment, percentage diameter stenosis post-PCI, Syntax score, and postdilatation were used to calculate the propensity score for treatment of small-vessel lesions. Subsequently, a Cox regression analysis was performed using small-vessel treatment and the propensity score as independent variables. Statistical analyses were performed with SPSS (version 22.0; SPSS Inc, Chicago, IL).

The investigator-initiated DUTCH PEERS (TWENTE II) study is equally funded by Boston Scientific and Medtronic; there are no other sponsors than indicated. The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript.

Table II. Two-year clinical outcome, comparing patients with vs without small-vessel treatment

	All patients (n = 1810)		Unadjusted *P* log rank	HR (95% CI)	Adjusted *P* log rank
	Small vessel (n = 798)	No small vessel (n = 1012)			
Death	28 (3.5)	29 (2.9)	.44	1.33 (0.75-2.36)	.33
Cardiac death	20 (2.5)	19 (1.9)	.36	1.37 (0.69-2.74)	.37
Target vessel MI	25 (3.1)	13 (1.3)	.006	1.40 (0.67-2.93)	.37
PMI	19 (2.4)	11 (1.1)	.03	1.05 (0.46-2.38)	.90
Clinically indicated TLR	38 (4.8)	28 (2.8)	.03	1.83 (1.07-3.13)	.03
TLF	76 (9.5)	55 (5.4)	.001	1.60 (1.05-2.10)	.02
MACEs	86 (10.8)	69 (6.8)	.003	1.48 (1.05-2.10)	.03
Definite or probable stent thrombosis	12 (1.5)	8 (0.8)	.15	1.54 (0.57-4.13)	.39

Values are n (%). A small vessel was defined by a reference vessel diameter <2.5 mm by quantitative coronary angiography. Two-year follow-up was available for 1,810 of all 1,811 patients (99.9%)

Results

Characteristics of patients, lesions, and PCI procedures

A total of 798 (44.1%) of all 1,811 randomized trial participants were treated in at least one small vessel (diameter <2.50 mm). 1,013 (55.9%) patients were treated for larger vessels only. Patients treated for small-vessel lesions more often had a history of diabetes mellitus (20.4% vs 15.9%; P = .01) and a previous MI, more often presented with stable angina, and more often underwent treatment of multiple vessels (Table I). Treatment was more frequently performed in bifurcation lesions (28.2% vs 23.7%; P = .03) and lesions longer than 27 mm (20.2% vs 15.5%; P = .009), and thereby, as expected, the total number of stents implanted and the total stent length was higher in patients with small-vessel lesions (Table I).

Clinical outcome and multivariate analysis

Two-year follow-up data were available in 1,810 (99.9%) patients (Table II).[25] A Kaplan-Meier analysis for TLF is presented in Figure 1 (9.5% vs 5.4%; P log rank = .003, unadjusted hazard ratio [HR] 1.79, 95% CI 1.27-2.54). These time-to-event curves reflect a higher incidence of target vessel MI (3.1% vs 1.3%; P log rank = .006) and clinically indicated TLR (4.8% vs 2.8%; P log rank = .02) in patients treated for small-vessel lesions. Landmark analysis revealed that during the first 48 hours from stenting, the rate of target vessel MI was significantly higher among patients treated for small-vessel lesions vs patients treated for lesions in vessels ≥2.50 mm (2.4% vs 1.1%; P log rank = .03). From 48 hours until 2 years of follow-up, the rate of target vessel MI was numerically, but not significantly higher in patients treated for small-vessel lesions (0.8% vs 0.2%; P log rank = .07). In patients with multivessel PCI and small-vessel lesions, all but 3 target vessel MIs were related to a small-vessel lesion. Multivariate analysis with propensity score adjustment demonstrated that after adjustment for all potential confounders, treatment of small-vessel lesions was an independent predictor of TLF at 2-year follow-up (HR 1.60, 95% CI 1.09-2.34). Patients treated with Resolute Integrity vs Promus Element stents had similar rates of the composite main clinical end point TLF (9.9% vs 9.1%; P = .72). In patients with single-vessel treatment, the TLF rate was higher in patients, with the smallest target vessel being <2.50 mm vs ≥2.50 mm (8.6% vs 5.4%; P = .01). The rates of target vessel MI were 2.7% vs 1.2% (P = .04).

Vessel sizes

A total of 493 (61.8%) patients were treated for at least one lesion in a very small vessel (<2.25 mm); in these patients, the rates of the composite end point TLF and various other clinical end points were comparable to those of 305 (38.2%) patients with the smallest target vessel diameter being 2.25 to <2.50 mm (Table III; Figure 2). Both patients treated in vessels no smaller than 2.50 to <3.00 mm and patients treated in vessels ≥3.00 mm had lower TLF rates (P log rank = .009) (Figure 2).

Discussion

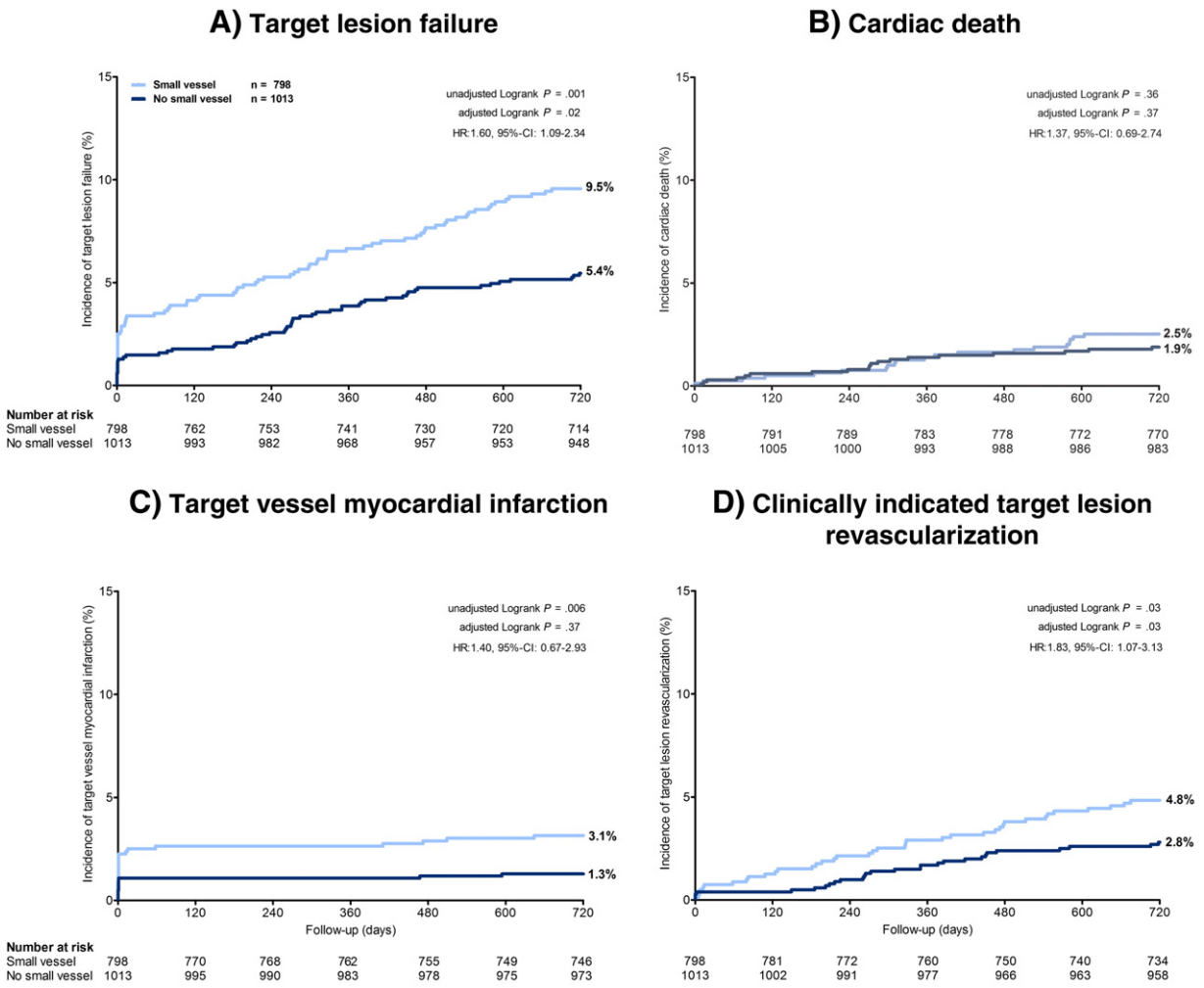
Major findings

All-comer patients treated for at least one small-vessel lesion had a significantly higher incidence of TLF at 2-year follow-up, after adjustment for any potential confounders (HR 1.60, 95% CI 1.09-2.34). This difference resulted mostly from a higher rate of target vessel MI and clinically indicated TLR. Within the subgroup of patients treated for lesions in small vessels, there was no difference in clinical end points between patients treated for very small vessel (<2.25 mm) lesions and patients who underwent stenting of vessels with a minimum diameter of 2.25 mm to less than 2.50 mm. Patients with target vessels no smaller than 2.50 to <3.00 mm as well as patients treated for lesions in vessels ≥3.00 mm only had lower TLF rates than did patients with small-vessel lesions.

Outcome of PCI in small-vessel lesions in previous trials with DES

The treatment of lesions in small vessels has always been associated with a higher incidence of restenosis as

Figure 1



Two-year cumulative event rates of TLF and its components, comparing patients with vs without small-vessel treatment. The rates of TLF, target vessel MI, and TLR were significantly higher in patients with small-vessel (<2.50 mm) treatment.

compared with the treatment of larger-vessel lesions.[2,6,28] In a study in which 2,058 patients were treated with either sirolimus-eluting or a paclitaxel-eluting early-generation DES, higher restenosis rates at angiographic follow-up were seen in patients treated in vessels with a diameter smaller than 2.41 mm, as compared with patients treated in larger vessels (>2.41 mm). The restenosis rates in the subgroups of patients treated in larger vessels (vessel diameter of 2.41-2.84 and >2.84 mm) were similar (8.4% vs 8.0%).[28]

A recent substudy of the LEADERS trial, in which 1,707 patients were treated with either a biolimus-eluting or sirolimus-eluting stent, revealed comparable findings. A significantly higher rate of TLR (9.6% vs 2.6%) and MACE (12.1% vs 7.1%) was seen in patients treated in small vessels (<2.75 mm).[29]

It has been hypothesized that the difference in restenosis rates is mainly caused by late lumen loss.[3,4,12] In small vessels, a relatively higher loss of lumen diameter will occur, resulting in a higher risk of restenosis when vessel sizes get smaller.[2,17] Apart from the higher risk caused by late lumen loss, patients with lesions in smaller vessels differ significantly on baseline characteristics from patients with lesions in larger vessels. Female gender[30] and diabetes[8,31] are often associated with smaller vessel diameters. Furthermore, patients with smaller vessels were more often treated for longer lesions,[32] multiple vessels,[1,2,7] and had more often a history of PCI.[1,2]

Table III. Two-year clinical outcome of all patients treated in small target vessels, comparing patients treated in very small-vessel lesions (<2.25 mm) vs patients treated in target vessels being 2.25 to <2.50 mm

	Small vessel (n = 798)		Unadjusted *P* log rank	HR (95% CI)	Adjusted *P* log rank
	<2.25 mm (n = 493)	≥2.25 mm (n = 305)			
Death	17 (3.4)	11 (3.6)	.91	1.03 (0.47-2.24)	.94
Cardiac death	13 (2.6)	7 (2.3)	.76	0.88 (0.34-2.25)	.79
Target vessel MI	13 (2.6)	12 (3.9)	.31	1.90 (0.84-4.28)	.12
PMI	9 (1.8)	10 (3.3)	.19	2.50 (0.98-6.38)	.06
Clinically indicated TLR	24 (4.9)	14 (4.6)	.76	1.02 (0.52-2.01)	.95
TLF	46 (9.3)	30 (9.8)	.81	1.20 (0.75-1.93)	.45
MACEs	51 (10.3)	35 (11.5)	.62	1.24 (0.80-1.93)	.34
Definite or probable stent thrombosis	8 (1.6)	4 (1.3)	1.00	1.02 (0.30-3.53)	.97

Values are n (%). A small vessel was defined by a reference vessel diameter <2.50 mm by quantitative coronary angiography.

Drug-coated balloons have been suggested as an alternative to DES in order to avoid luminal obstruction by the stent struts, which is most important in small target vessels. Although studies with early drug-coated balloons showed inconsistent results in small vessels,[33] a recent, prospective registry revealed encouraging results with a paclitaxel-coated balloon in de novo lesions in small vessels.[34]

Differences in definitions and cutoff points

In previous trials, the reference vessel diameter has been assessed in various ways, ranging from visual assessment to quantitative coronary angiography analysis.[4,21] Consequently, this has led to different definitions of "small vessels," being based on either reference vessel diameter or stent diameter,[20,21] which renders a comparison of studies difficult. With bare-metal stents and early DES, a reference vessel diameter of less than 3.00 mm was most often used to define a small vessel.[5,13,16,19] However, with the development of smaller stent diameters, the cutoff value changed to 2.50 mm.[20,21] With the ongoing trend toward the development of DES with an increasingly smaller minimum stent size, even smaller vessels will become part of the treatable range of coronary vessel dimensions.

Implications

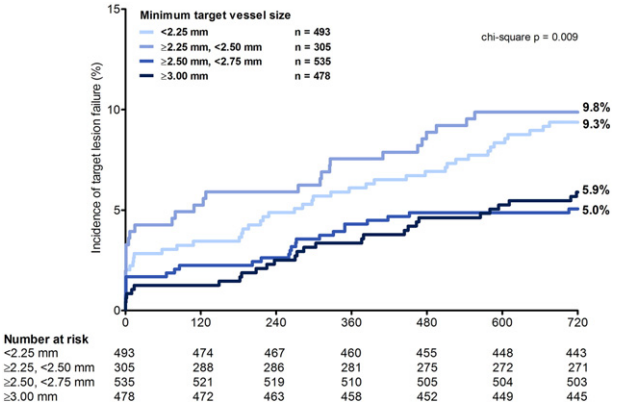
The evolution of the definition of small vessels has paralleled the development of devices with increasingly smaller minimum sizes. So what is currently the most appropriate definition of a small vessel with the use of contemporary newer-generation DES? The results of the present study suggest that the risk of TLF (1) is larger in patients treated in vessels smaller than 2.50 mm, (2) remains similar even for smaller minimum target vessels (<2.25 mm), and (3) is lower in patients with minimum target vessel sizes of more than 2.50 mm (with no difference between medium- and larger-sized vessels). Thus, a cutoff value of 2.50 mm is a legitimate threshold to distinguish between small and larger target vessels in the setting of PCI with contemporary DES as used in the DUTCH PEERS trial and should be considered as a cutoff value in future studies on small-vessel treatment. In addition, in clinical practice, knowledge of the fact that adverse events may be higher after treatment of coronary vessels <2.50 mm may help taking therapeutic decisions in patients with coronary disease that involves small vessels.

Considering the recent enlargement of the interventional armamentarium by ultrasmall DES (2.00 mm), the findings of the present study may be of particular interest and of clinical relevance. Our data suggest that clinical follow-up of interventions with such devices in very small coronary arteries deserves attention, as the event risk after such procedures might be increased.

Limitations

Because of the post hoc nature of the present analysis, the results should be considered hypothesis generating. Based on the data presented, we cannot rule out that a threshold of 2.75 mm might also have been suitable to define small vessels. In future studies, it may be of interest to evaluate the optimal cutoff value, based on smaller increments in vessel size, and to validate the derived threshold in a separate patient cohort. The use of the cutoff value of 2.25 mm in the absence of smaller stents might be considered a limitation. Because patients did not receive a routine angiographic follow-up, there are no data on potential differences in *angiographic* restenosis rate. We did not apply angiographic exclusion criteria; therefore, quantitative coronary angiographic analysis was challenging in some cases. Angiography is limited in its capacity to distinguish between true small vessel size and apparently small vessels in patients with diffuse coronary disease. Intravascular ultrasound is superior to angiography in assessing true vessel size and coronary remodeling.[35,36] In diabetic patients, the lack of angiographic follow-up may be associated with some underestimation of events. Nevertheless, we obtained relevant data on clinically indicated TLR rates without

Figure 2



Target lesion failure in subgroups of patients with increasingly smaller minimum target vessel size. Patients with the smallest target vessel being <2.25 mm had TLF rates similar to patients with a smallest target vessels being 2.25 to <2.50 mm, whereas patients treated in vessels no smaller than 2.50 to <3.00 mm as well as patients treated in vessels ≥3.00 mm only had lower TLF rates.

amplification by routine angiographic follow-up, which most hospitals do not consider a routine procedure. In addition, due to systematic assessment of post-PCI cardiac markers and electrocardiogram changes, rigorous monitoring, and the availability of follow-up data in as much as 99.9% of the patients, potential underreporting of TLR or other major adverse events is very unlikely, whereas due to the lack of angiographic follow-up, some cases with clinically "silent" obstruction or occlusion of the target vessel may not have been observed. Because of the various cutoff values used to define small vessels in previous trials, it is difficult to compare studies. Nevertheless, the current analysis of the different thresholds shows that we used a legitimate cutoff value to examine the effect of small-vessel treatment.

Conclusion

Patients treated with novel DES in small-vessel lesions had higher adverse event rates than did patients who had no small-vessel treatment. Our data suggest that with current stents, a diameter of 2.50 mm is a suitable threshold value to identify small target vessels.

Disclosures

C.v.B. has been consultant to and has received lecture fees or travel expenses from Boston Scientific and Medtronic; he received lecture fees from MSD and AstraZeneca. The institution has received research grants, provided by Abbott Vascular, Biotronik, Boston Scientific, Medtronic, and AstraZeneca. All other authors reported no conflicts of interest.

References

1. Schunkert H, Harrell L, Palacios IF. Implications of small reference vessel diameter in patients undergoing percutaneous coronary revascularization. J Am Coll Cardiol 1999;34:40-8.
2. Elezi S, Kastratie A, Neumann FJ, et al. Vessel size and long-term outcome after coronary stent placement. Circulation 1998;98: 1875-80.
3. Biondi-Zoccai G, Moretti C, Abbate A, et al. Percutaneous coronary intervention for small vessel coronary artery disease. Cardiovasc Revasc Med 2010;11:189-98.
4. Akiyama T, Moussa I, Reimers B, et al. Angiographic and clinical outcome following coronary stenting of small vessels: a comparison with coronary stenting of large vessels. J Am Coll Cardiol 1998;32: 1610-8.
5. Agostoni P, Biondi-Zoccai GG, Gasparini GL, et al. Is bare-metal stenting superior to balloon angioplasty for small vessel coronary artery disease? Evidence from a meta-analysis of randomized trials. Eur Heart J 2005;26:881-9.
6. Kasaoka S, Tobis JM, Akiyama T, et al. Angiographic and intravascular ultrasound predictors of in-stent restenosis. J Am Coll Cardiol 1998;32:1630-5.
7. Tanimoto S, Daemen J, Tsuchida K, et al. Two-year clinical outcome after coronary stenting of small vessels using 2.25-mm sirolimus- and paclitaxel-eluting stents: insight into the RESEARCH end T-SEARCH registries. Catheter Cardiovasc Interv 2007;69:94-103.
8. Claessen BE, Smits PC, Kereiakes DJ, et al. Impact of lesion length and vessel size on clinical outcomes after percutaneous coronary intervention with everolimus- versus paclitaxel-eluting stents: pooled analysis from the SPIRIT (clinical evaluation of the XIENCE V everolimus eluting coronary stent system) and COMPARE (second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) randomized trials. J Am Coll Cardiol Intv 2011;11: 1209-15.
9. Teirstein PS, Meredith IT, Feldman RL, et al. Two-year safety and effectiveness of the platinum chromium everolimus-eluting stent for the treatment of small vessels and longer lesions. Catheter Cardiovasc Interv 2015;85:207-15.
10. Bartorelli AL, Serruys PW, Miquel-Hébert K, et al. An everolimus-eluting stent versus a paclitaxel-eluting stent in small vessel coronary artery disease: a pooled analysis from the SPIRIT II and SPIRIT III trials. Catheter Cardiovasc Interv 2010;76:60-6.
11. Cho SC, Jeong MH, Kim W, et al. Clinical outcomes of everolimus- and zotarolimus eluting stents in patients with acute myocardial infarction for small coronary artery disease. J Cardiol 2014;63:409-17.
12. Togni M, Eber S, Widmer J, et al. Impact of vessel size on outcome after implantation of sirolimus-eluting and paclitaxel-eluting stents. J Am Coll Cardiol 2007;50:1123-31.
13. Schampaert E, Cohen EA, Schlüter M, et al. The Canadian study of sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). J Am Coll Cardiol 2004;43:1110-5.
14. Puyrimat E, Mangiacapra F, Peace A, et al. Long-term clinical outcome in patients with small vessel disease treated with drug-eluting versus bare-metal stenting. Am Heart J 2011;162:907-13.
15. Ardissino D, Cavallini C, Bramucci E, et al. Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. JAMA 2004;292:2727-34.
16. Parikh SV, Luna M, Selzer F, et al. Outcomes of small coronary artery stenting with bare-metal stents versus drug-eluting stents: results from

the NHLBI Dynamic Registry. Catheter Cardiovasc Interv 2014;83: 192-200.
17. Mauri L, Orav EJ, Kuntz RE. Late loss in lumen diameter and binary restenosis for drug-eluting stent comparison. Circulation 2005;111: 3435-42.
18. Kastrati A, Mehilli J, Dirschinger J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. Circulation 2001;103:2816-21.
19. Briguori C, Sarais C, Pagnotta P, et al. In-stent restenosis in small coronary arteries: impact of strut thickness. J Am Coll Cardiol 2002;40:403-9.
20. Hermiller JB, Rutledge DR, Mao VW, et al. Clinical outcomes in real-world patients with small vessel disease treated with Xience V everolimus-eluting stents: one year results from the Xience V USA condition of approval post-market study. Catheter Cardiovasc Interv 2014;84:7-16.
21. Caputo R, Leon M, Serruys P, et al. Performance of the Resolute Zotarolimus–eluting stent in small vessels. Catheter Cardiovasc Interv 2014;84:17-23.
22. Srour JF, Abbott JD. Small vessel and long lesions: changing label indications for drug eluting stents. Catheter Cardiovasc Interv 2015;85:216-7.
23. von Birgelen C, Sen H, Lam MK, et al. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. Lancet 2014;383:413-23.
24. Sen H, Lam MK, Löwik MM, et al. Clinical events and patient-reported chest pain in all-comers treated with Resolute Integrity and Promus Element stents: two-year follow-up of the randomized DUTCH PEERS (TWENTE II) trial. J Am Coll Cardiol Intv 2015;8:889-99.
25. Tandjung K, Basalus MW, Sen H, et al. Durable polymer-based sTent Challenge of promus ElemEnt versus ReSolute integrity (DUTCH PEERS): rationale and study design of a randomized multicenter trial in a Dutch all-comers population. Am Heart J 2012;163:557-62.
26. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
27. Vranckx P, Cutlip DE, Mehran R, et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. EuroIntervention 2010;5:871-4.
28. Elezi S, Dibra A, Mehilli J, et al. Vessel size and outcome after coronary drug-eluting stent placement: results from a large cohort of patients treated with sirolimus- or pacliaxel-eluting stents. J Am Coll Cardiol 2006;48:1304-9.
29. Wykrzykowska JJ, Serruys PW, Onuma Y, et al. Impact of vessel size on angiographic and clinical outcomes of revascularization with biolimus-eluting stent with biodegradable polymer and sirolimus-eluting stent with durable polymer: the LEADERS trial substudy. J Am Coll Cardiol Intv 2009;2:861-70.
30. Dodge JT, Brown BG, Bolson EL, et al. Lumen diameter of normal human coronary arteries: influence of age, sex, anatomic variation, and left ventricular hypertrophy or dilation. Circulation 1992;86: 232-46.
31. Nicholls SJ, Murat Tuzcu E, Kalidindi S, et al. Effect of diabetes on progression of coronary atherosclerosis and arterial remodeling: a pooled analysis of 5 intravascular ultrasound trials. J Am Coll Cardiol 2008;52:255-62.
32. Hsieh I-C, Chien C-C, Chang H-J, et al. Acute and long-term outcomes of stenting in coronary vessel >3.0 mm, 3.0-2.5 mm, and <2.5 mm. Catheter Cardiovasc Interv 2001;53:341-22.
33. Loh JP, Waksman R. Paclitaxel drug-coated balloons: a review of current status and emerging applications in native coronary artery de novo lesions. J Am Coll Cardiol Intv 2012;5:1001-12.
34. Zeymer U, Waliszewski M, Spiecker M, et al. Prospective 'real world' registry for the use of the 'PCB only' strategy in small vessel de novo lesions. Heart 2014;100:311-6.
35. von Birgelen C, Mintz GS, de Vrey EA, et al. Atherosclerotic coronary lesions with inadequate compensatory enlargement have smaller plaque and vessel volumes: observations with three dimensional intravascular ultrasound in vivo. Heart 1998;79:137-42.
36. von Birgelen C, Kutryk MJB, Gil R, et al. Quantification of the minimal luminal cross-sectional area after coronary stenting by two- and three-dimensional intravascular ultrasound versus edge detection and vidodensitometry. Am J Cardiol 1996;78:520-5.