Journal of the Society for Cardiovascular Angiography & Interventions xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of the Society for Cardiovascular Angiography & Interventions

journal homepage: www.jscai.org

Comprehensive Review

Small Vessel Coronary Artery Disease: Rationale for Standardized Definition and Critical Appraisal of the Literature

Jorge Sanz-Sánchez, MD, PhD [a,b], Mauro Chiarito, MD [c,d], Gauravpal S. Gill, MD [e], Liefke C. van der Heijden, MD, PhD [f], Yigal Piña, MD [g], Bernardo Cortese, MD [h], Fernando Alfonso, MD [i], Clemens von Birgelen, MD, PhD [f,j], Jose Luis Diez Gil, MD, PhD [a,b], Ron Waksman, MD [e], Hector M. Garcia-Garcia, MD, PhD [e,*]

[a] *Hospital Universitari i Politecnic La Fe, Valencia, Spain;* [b] *Centro de Investigación Biomedica en Red (CIBERCV), Madrid, Spain;* [c] *Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy;* [d] *IRCCS Humanitas Clinical and Research Center, Milan, Italy;* [e] *Interventional Cardiology, MedStar Washington Hospital Center, Washington, District of Columbia;* [f] *Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, the Netherlands;* [g] *Interventional Cardiology, National Heart Institute, Mexico City, Mexico;* [h] *Department of Interventional Cardiology, ASST Fatebenefratelli-Sacco, Milan, Italy;* [i] *Interventional Cardiology, Hospital La Princesa, Madrid, Spain;* [j] *Department of Health Technology and Services Research, Faculty of Behavioural, Management and Social Sciences, Technical Medical Centre, University of Twente, Enschede, the Netherlands*

A B S T R A C T

Small vessel coronary artery disease (CAD) is present in 30% to 67% of patients undergoing percutaneous coronary intervention according to different series, representing an unmet clinical need in light of an increased risk of technical failure, restenosis, and need for repeated revascularization. The definition of small vessel is inconsistent across trials, and no definite cutoff value has yet been determined. The lack of consensus on the definition of small vessel CAD has contributed to the high degree of heterogeneity in the safety and efficacy of the various revascularization options. Therefore, the aim of this article is to provide a critical appraisal of existing reports and to propose a reference vessel diameter of <2.5 mm definition of small vessel CAD to guide future clinical trials and clinical decision-making.

Introduction

Coronary artery disease (CAD) is the foremost cause of mortality and morbidity worldwide. Myocardial revascularization by percutaneous coronary intervention (PCI) should be considered in patients presenting with acute coronary syndromes and in patients with chronic coronary syndromes for whom medical therapy fails. Of note, small vessel CAD is present in 30% to 67% of patients undergoing PCI according to different series,[1,2] especially in female patients, in patients with diabetes mellitus or chronic renal failure,[3,4] and in specific anatomic subsets, such as distal vessel segments and bifurcation lesions, in which commonly the distal main and side branches fall within this small vessel category. All these patient and lesion characteristics are a recipe for an increased risk of device failure, restenosis, and need for repeated revascularization.[5-7] In addition, the European Society of Cardiology guidelines for myocardial revascularization recommend that complete revascularization may not be required for stenoses located in the small vessels with a small subtended myocardial area (ie, when at least 75% of the length of the segment distal to the lesion has a vessel diameter of <2 mm).[8] For these reasons, it is crucial to carefully evaluate the vessel size before therapeutic decision-making.

The definition of small vessel is inconsistent across trials, and no definite cutoff value has yet been determined. The lack of consensus on the definition of small vessel CAD has certainly contributed to the high degree of heterogeneity in the safety and efficacy of the various revascularization options. Notably, to classify small target vessels, dedicated "small vessel studies" have used different thresholds of maximum lumen size that ranged from 2.25 to 3.0 mm. Consequently, there was substantial overlap with vessel sizes treated in "large vessel trials," of which some used a threshold of 2.75 mm as the minimum vessel size and yielded contradictory results.[9] This discrepancy might have an important impact, contributing to differences in treatment effects. Therefore, the aim of this article is to provide a critical appraisal of existing reports, to find a threshold on the definition of small vessel CAD that maximizes the

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; DCB, drug-coated balloon; DES, drug-eluting stent; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLF, target lesion failure; TLR, target lesion revascularization.

Keywords: Coronary artery disease; small vessel.

* Corresponding author: hector.m.garciagarcia@medstar.net (H.M. Garcia-Garcia).

https://doi.org/10.1016/j.jscai.2022.100403

Received 18 February 2022; Received in revised form 31 May 2022; Accepted 14 June 2022

Available online xxxx

difference in the risk of adverse clinical outcomes, and to propose a standardized definition of small vessel CAD to guide future clinical trials and clinical decision-making.

Clinical impact of small vessel CAD

Despite the high prevalence of small vessel disease among patients undergoing coronary angiography and subsequent PCI or coronary artery bypass grafting (CABG),[3] a number of factors complicate the proper estimation of the prognostic impact of obstructive CAD in small vessels compared with large vessels. First and more importantly, there is a lack of a standardized definition of small vessel.[10-12] Second, only up to 30% of patients with lesions in proximal coronary arteries show concomitant lesions in distal small vessels, whereas in patients with small CAD, proximal segments are virtually always involved.[13] Third, the amount of myocardium tributary of the affected vessel is directly related to the vessel diameter and its length.[14] Fourth, the true vessel diameter of an artery, defined as small by coronary angiography, is often underestimated.[15] In this setting, intravascular imaging, which is able to define both lumen and vessel dimension, reveals nonprotruding lesions and has been shown to recognize the real lumen shape and size of atherosclerotic vessels better than coronary angiography.[16] Indeed, the angiographic lumen area is particularly misleading in the small vessels where positive and negative remodeling phenomena are very common, and these can only be unraveled by "tomographic" imaging techniques.

Recommendations for standardized definitions of small vessel CAD

A systematic review, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplemental Table S3), was performed to summarize the available evidence for the treatment of patients with small vessel CAD. We restricted our consideration to randomized clinical trials and prospective single-arm studies evaluating percutaneous treatment with newer-generation drug-eluting stents (DESs) and drug-coated balloons (DCBs) in small vessel CAD. Trials with at least 1 treatment arm that satisfied the inclusion criteria were kept in the analysis after having discarded the arms that did not satisfy the inclusion criteria. Cypher sirolimus-eluting stent (Cordis), the Taxus paclitaxel-eluting stents (Taxus and Taxus Element; Boston Scientific), and the Endeavor zotarolimus-eluting stent (Medtronic) were considered "early-generation" DESs for the purpose of this study; therefore, data obtained with one of these DESs were not

Table 1. Studies evaluating second-generation DESs for the treatment of patients with small vessel CAD.

	Study	Year	Study design	Sample size	Follow-up (mo)	DES	Vessel size inclusion criteria (mm)	Vessel size assessment	Mean VD (mm)	Outcomes			
										TLR	TVR	TLF	MI
≤3.0 mm													
	BASKET-SMALL[17]	2016	RCT	191	12	Endeavor	<3	-	-	-	6.6%	-	1.1%
	BIOSCIENCE[18]	2019	RCT	1234	60	Orsiro	≤3	Stent diameter	2.76	13.6%	15.3%	22.3%	10.1%
						Xience			2.75	10.9%	13.8%	18.3%	11.9%
≤2.75 mm													
	BIOFLOW[19]	2020	RCT	1347	12	Orsiro	≤2.75	Angiographic	-	3.8%	-	8.0%	4.2%
						Xience				4.6%	-	12.4%	7.6%
	LEADERS[20]	2009	RCT	863	12	Biomatrix	≤2.75	Angiographic	2.21	9.6%	10.7%	-	5.6%
	Parikh et al[21]	2016	Pooled analysis	1304	36	Resolute Onyx	>2.25 and ≤2.75	Angiographic	2.6	4.5%	7.6%	9.3%	3.6%
	Oliveira et al[22]	2013	RCT	24	12	Sparrow	<2.75	QCA	2.46	0%	0%	0%	0%
≤2.5 mm													
	BIO-RESORT[23]	2019	RCT	1506	36	Orsiro	<2.5	QCA	2.11	2.9%	4.9%	6.7%	3.8%
						Synergy			2.12	3.3%	5%	7.5%	3.8%
						Resolute Integrity			2.11	3.8%	6.1%	8.3%	4.1%
	BIONYX[24]	2020	RCT	898	36	Resolute Onyx	<2.5	QCA	-	4.7%	6.9%	7.2%	4.5%
						Orsiro				4.6%	6.2%	7.5%	4.5%
	Caputo et al[25]	2014	Pooled analysis	1956	24	Resolute	≤2.5	Visual estimation	2.4	5.3%	7.7%	10.1%	3.9%
	CENTURY II[26]	2016	RCT	525	12	Ultimaster	≤2.5	QCA	2.3	4.0%	6.5%	6.9%	3.3%
						Xience			2.31	5.7%	8.5%	7.7%	3.6%
	Guedeney et al[27]	2018	Pooled analysis	1607	12	Promus	≤2.5	Angiographic	2.5	-	5.7%	-	5.2%
	Hermiller et al[28]	2013	Single-arm prospective	838	12	Xience	≤2.5	Visual estimation	2.55	3.8%	6.2%	5.7%	3.8%
	SPIRIT[29]	2011	Single-arm prospective	150	12	Xience	<2.5	Angiographic	2.13	5.1%	8.8%	8.1%	1.5%
	TWENTE II[30]	2016	RCT	798	24	Resolute/ Promus	≤2.5	QCA	-	4.8%	-	9.5%	3.1%
	ZEUS[31]	2013	Single-arm retrospective	142	12	Resolute Integrity	≤2.5	QCA	2.15	-	4.2%	-	1.4%
≤2.25 mm													
	CENTURY JSV[32]	2016	Single-arm prospective	70	24	Ultimaster	≤2.25	Angiographic	1.95	4.3%	7.1%	5.7%	4.3%
	Parikh et al[21]	2016	Pooled analysis	837	36	Resolute Onyx	≤2.25	Angiographic	2.2	6.9%	11.2%	12.4%	4.4%
	Price et al[33]	2017	Single-arm prospective	101	12	Resolute Onyx	<2.25	Visual estimation	1.91	2.0%	2.0%	5.0%	3.0%

CAD, coronary artery disease; DES, drug-eluting stent; MI, myocardial infarction; QCA, quantitative coronary angiography; RCT, randomized controlled trial; TLF, target lesion failure; TLR, target lesion revascularization; TVR, target vessel revascularization; VD, vessel diameter.

considered for inclusion in the present analysis. A summary of the search strategy and detailed results are shown in the Supplemental Figure S1.

In brief, 1240 studies were screened and 25 were finally included; 18 studies included patients treated with DESs and 7 studies assessed patients treated with DCBs. The high degree of heterogeneity among trials precluded performing a pooled comparison of clinical outcome according to the vessel size. In addition to important differences in both patients' baseline characteristics and treatment strategies, the inclusion of few studies with a threshold of vessel diameter of ≤2.25 or ≤3.0 mm to define small vessels rendered a comparison of the clinical outcome between different vessel sizes hypothesis-generating only. Yet, the different thresholds for defining a small vessel size was not the only source of heterogeneity among the included studies: (1) the reference vessel diameter was assessed in different ways that ranged from visual assessment to quantitative coronary angiographic analysis, (2) the classification of target vessels as small was performed not only based on reference vessel diameter but also according to the nominal diameter of the implanted stent, and (3) the follow-up duration varied substantially among studies, ranging from 12 to 60 months. Tables 1 and 2 report the clinical outcomes according to treatment strategy (ie, DES or DCB) and reference vessel diameter. In addition, Figures 1 and 2 show the median event rates for target lesion revascularization (TLR), target vessel revascularization, target lesion failure (TLF), and myocardial infarction (MI) in patients treated for small vessel CAD with DESs and DCBs, respectively.

Studies defining small vessels based on a reference vessel diameter of ≤2.25, ≤2.5, ≤2.75, and ≤3.0 mm showed substantial dissimilarities in adverse event rates across vessel sizes, confirming that most studies that aimed at evaluating the optimal threshold to define small vessels in patients undergoing PCI provided conflicting and spurious results to date. Nevertheless, despite the fact that 2.5 mm was the most often used threshold to define small vessel CAD, this diameter referred to highly dissimilar parameters, that is, the angiography-based reference vessel diameter or the smallest nominal diameter of the implanted stents.

Of note, none of these studies used intracoronary imaging to determine vessel size before study inclusion, which might have contributed to the important observed differences between the vessel size–based inclusion criteria and actual reference vessel diameters (Tables 1[17-33] and 2[10-12,34-37]).

The DUTCH PEERS (DUrable polymer-based sTent CHallenge of Promus ElemEnt versus ReSolute integrity) trial, a DES study in all-comers that compared the Resolute Integrity cobalt-chromium durable polymer–coated zotarolimus-eluting stent (Medtronic) and the Promus Element platinum-chromium durable polymer–coated everolimus-eluting stent (Boston Scientific), is one of the few studies that evaluated the outcomes of patients treated for lesions in at least 1 small coronary vessel (<2.50 mm) vs patients with target lesions in larger sized vessels (≥2.50 mm). At the 2-year follow-up, the rates of TLF (9.5% vs 5.4%, $P = .001$) and 2 of its individual components—target vessel MI (3.1% vs 1.3%, $P = .006$) and TLR (4.8% vs 2.8%; $P = .02$)—were higher among patients treated in at least 1 small vessel. Of note, patients with a target vessel diameter of <2.25 mm had TLF rates similar to those with a target vessel diameter of 2.25 to <2.50 mm; however, patients with vessel diameters >2.50 to <3.00 mm and those with vessel diameters of ≥3.00 mm who underwent treatment had lower TLF rates (9.3%, 9.8%, 5.0%, 5.8%, respectively; Plogrank = .009). These findings suggest a target vessel diameter of <2.50 mm to be the threshold associated with increased adverse event risk. However, some limitations of the aforementioned post hoc analysis should be taken into account. First, the definition of the subgroup of small vessel size did not exclude patients with lesions treated in larger vessels. Second, some differences in the baseline and lesion characteristics among groups (ie, diabetes mellitus, previous MI, multivessel intervention, the presence of chronic total occlusion, bifurcation and stented length) might have contributed to the less favorable outcomes in patients presenting with small vessel CAD.

Accurate assessment of the vessel size depends on achieving a state of adequate vasodilation, and in this regard, intracoronary nitroglycerin should always be administered before evaluating the vessel size. Despite the fact that visual estimation is the most widespread technique to estimate the reference vessel diameter, the use of intracoronary imaging (eg, intracoronary ultrasound and optical coherence tomography) is highly encouraged in future studies to quantitatively assess the true vessel size and to reduce both between-operator variability and potential operator bias in identifying small target vessels. Coronary computed tomography angiography plays the potential role to accurately evaluate vessel size and guide PCI. However, its clinical benefit still needs demonstration in large-scale clinical trials.[38]

Therefore, we suggest that with current DES and DCB technology, a reference vessel diameter of <2.50 mm measured with intracoronary imaging should be used as the cutoff value for classifying small coronary vessels (Central Illustration). Notwithstanding, other modalities, such as visual estimation or quantitative coronary angiography might be used if

Table 2. Studies evaluating DCBs for the treatment of patients with small vessel CAD.

	Study	Year	Study design	Sample size	Follow-up (mo)	DCB	Vessel size inclusion criteria (mm)	Vessel size assessment	Mean RVD (mm)	Outcomes			
										TLR	TVR	TLF	MI
≤3.0 mm													
	BASKET-SMALL 2[10]	2018	RCT	758	36	SeQuent Please	<3	Angiographic	-	-	9%	-	6%
	BELLO[34]	2017	RCT	182	12	IN.PACT	<2.8	Visual estimation	2.41	6.7%	10.1%	-	1.1%
	Unverdorben et al[35]	2010	Single-arm prospective	118	12	SeQuent Please	>2.25 and <2.8	Visual estimation	2.35	4.9%	-	-	1.3%
≤2.75 mm													
	PICCOLETO I[12]	2010	RCT	57	9	Dior	≤2.75	Angiographic	2.45	32.1%	32.1%	-	3.6%
	PICCOLETO II[11]	2020	RCT	232	12	Elutax	>2.0 and ≤2.75	Visual estimation	2.23	5.6%	-	-	1.9%
	RESTORE SVD China[36]	2018	RCT	230	12	Restore	≥2.25 and ≤2.75	Visual estimation	2.42	4.4%	5.3%	4.4%	0.9%
≤2.5 mm													
	Vaquerizo et al[37]	2015	Single-arm prospective	104	12	Dior	≤2.5	Angiographic	1.95	2.9%	-	-	1.0%

CAD, coronary artery disease; DCB, drug-coated balloon; MI, myocardial infarction; RCT, randomized controlled trial; RVD, reference vessel diameter; TLF, target lesion failure; TLR, target lesion revascularization; TVR, target vessel revascularization.

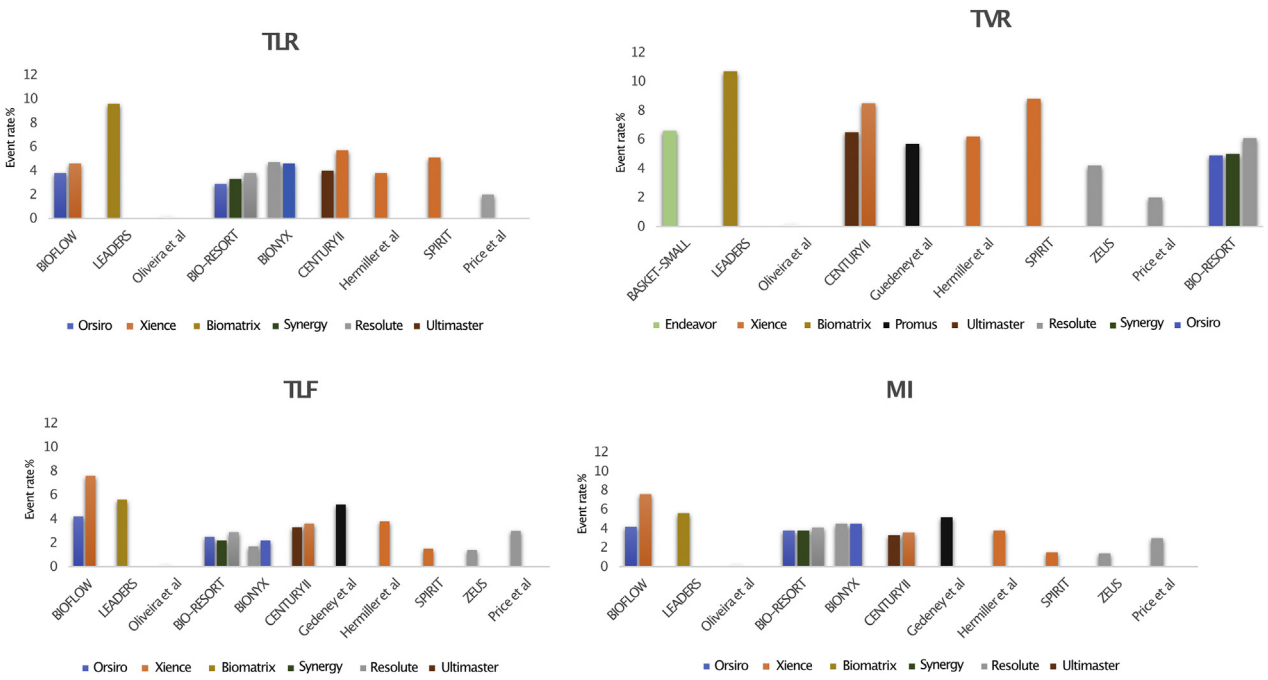


Figure. 1. Median event rates for TLR, TVR, TLF, and MI in patients treated for small vessel coronary artery disease with drug-eluting stent. Only trials with follow-ups at 9 to 12 months were included. MI, myocardial infarction; TLF, target lesion failure; TLR, target lesion revascularization; TVR, target vessel revascularization.

intracoronary imaging is not available. The threshold is supposed to guide future clinical trials and clinical decision-making.

Therapeutic strategies in patients with small vessel CAD

In daily clinical practice, the management of patients with small vessel CAD represents a great challenge because of an increased rate of technical failure during CABG and an increased risk of restenosis and repeat revascularization after PCI.

DESs

Contemporary second-generation DESs showed an outstanding performance in patients with small vessel CAD, assessed in a great number of dedicated studies and subgroup analysis of large randomized clinical trials (Table 1). New-generation DESs reduced both late lumen loss and (clinical) restenosis. This was seen even in small vessels that tolerate lumen loss less well than large vessels, which proves the efficacy of new-generation DESs in this challenging setting. In addition, the rates of death, MI, and stent thrombosis were low, which underline the safety of these devices.[39]

Impact of strut thickness. One of the main features that differentiates early- and new-generation DESs is related to a reduction in strut thickness that is likely to play a role in improving the outcome of patients with small vessel CAD, as reduced strut thickness has been associated with a lower rate of both angiographic restenosis and clinically driven revascularization.[40] Indeed, thick struts induce intense alterations in blood flow and shear stress that result in delayed or limited strut endothelialization and, subsequently, in a higher risk of stent thrombosis.[41] Nevertheless, evidence in favor of DESs with particularly thin struts in the setting of small vessel CAD is conflicting and mainly limited to subgroup analyses from randomized studies that evaluated an ultrathin-strut biodegradable polymer–coated sirolimus-eluting stent (Orsiro, Biotronik).

In a pooled analysis of patients enrolled in the BIOFLOW (ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable

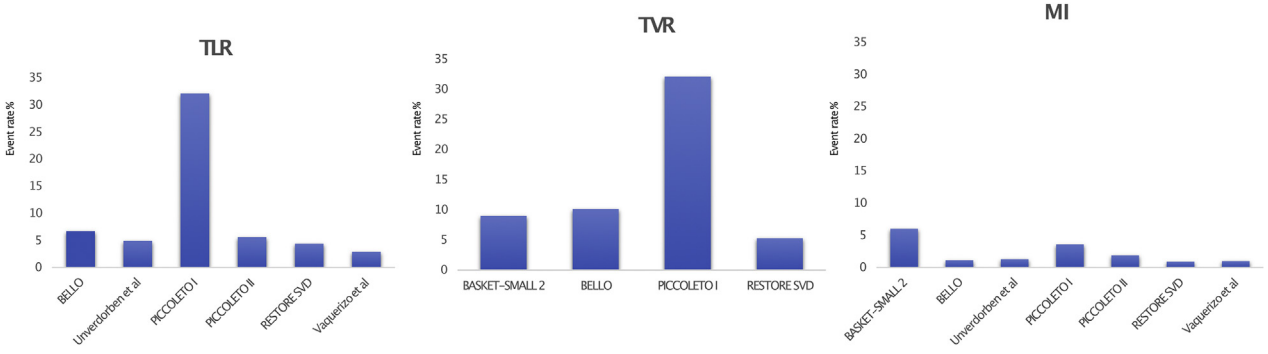
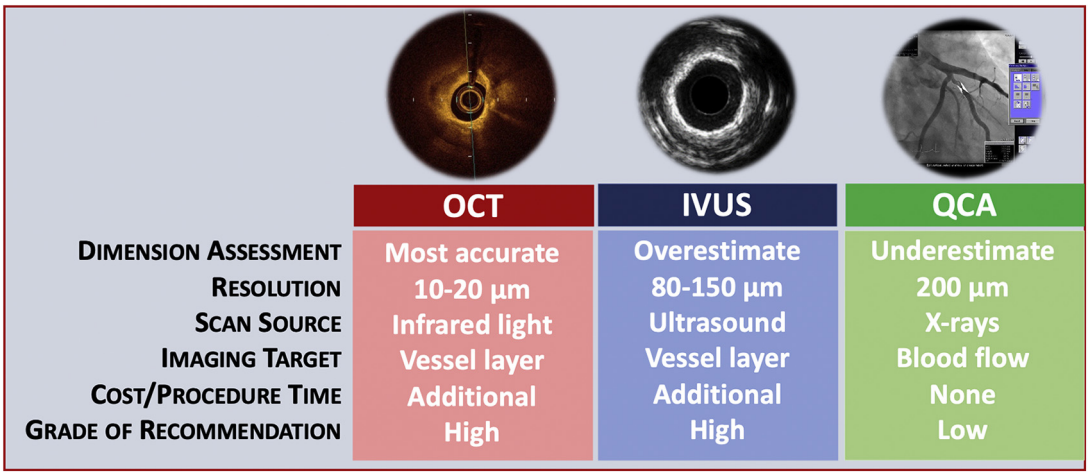


Figure. 2. Median event rates for TLR, TVR, and MI in patients treated for small vessel coronary artery disease with drug-coated balloon. MI, myocardial infarction, TLR, target lesion revascularization; TVR, target vessel revascularization.



Central Illustration. Imaging techniques to evaluate small-vessel coronary artery disease. A reference vessel diameter <2.50 mm by intracoronary imaging is proposed as the cutoff value for classifying small coronary vessels. An overview of the different imaging techniques to evaluate small vessel coronary artery disease is depicted. IVUS, intravascular ultrasound; OCT, optical coherence tomography; QCA, quantitative coronary angiography.

polymer everolimus-eluting stents in patients undergoing coronary revascularisation) RCTs, which compared the Orsiro biodegradable polymer sirolimus-eluting stent with the Xience durable polymer everolimus-eluting stent (Abbott Vascular), a reduced TLF rate was observed with the former DES in patients treated for small vessel lesions, defined as reference vessel diameter <2.5 mm, mainly driven by reduced risk of target-vessel MI[42] Nevertheless, this finding was not confirmed in the BIO-RESORT (very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease) trial, which reported only a numerically lower TLF rate after PCI with the Orsiro stent vs a thin strut durable polymer zotarolimus-eluting stent (Resolute Integrity) at the 3-year follow-up, yet there was a significant difference in the TLR in favor of the ultrathin-strut Orsiro stent.[23] Conversely, even a numerically higher 5-year TLF rate was observed with the ultrathin-strut Orsiro stent vs the thin strut Xience stent in the BIOSCIENCE trial.[18] Therefore, further data confirming the potential benefits of the ultrathin-strut DESs in patients with small vessel CAD—probably extended to other ultrathin stent platforms[43]—are necessary before definitely supporting its preferred use in this setting.

Diabetes mellitus. Among patients with small vessel disease, patients with diabetes represent a very high-risk subset. Recently reported substudies of large randomized stent trials showed reasonable event rates after PCI with several contemporary DESs in diabetic all-comers,[44,45] but dedicated studies to compare the performance of different DESs in this specific setting are limited. However, a number of studies suggest that patients with diabetes with small vessel disease could benefit the most from the use of DCBs instead of DESs,[34,46] reinforcing the hypothesis that in this setting the permanent presence of an implanted metal stent increases the risk of target vessel MI and restenosis.

DCBs

DCBs have emerged as an alternative to DESs for the treatment of patients with small vessel CAD. This approach provides a fast and high-dose delivery of antiproliferative drugs to the vessel wall and carries several anticipated benefits over DES, such as the lack of permanent scaffold—extremely relevant in small coronary vessels—and the need for only a short prescription of dual antiplatelet therapy. Actually, the use of DCBs in *de novo* lesions, which are not appealing for the implantation of stents (including small vessels with diffuse disease), represents a growing indication for these devices, as it follows a strategy of "leaving nothing behind." In fact, the use of DCBs in anatomic settings adverse for treatment with DESs was not only shown to be similarly efficacious but also safer, as shown by the reduced risk of vessel thrombosis with DCBs than with DESs in patients with small vessel CAD.[47,48]

Two early randomized clinical trials have reported conflicting results about the effects of DCBs compared with early-generation DESs on angiographic outcomes in patients with native small vessel CAD.[12,49] More recently, larger randomized trials with the use of second-generation DESs and novel DCB devices provided new evidence about the clinical and angiographic effects of these treatments.[10,11,36] Differences in study results might not only be explained by variations in DCB technology and lesion preparation but also by discrepancies in the definition of a small vessel size, which varied from <3 mm[10] and <2.8 mm[49] to even ≤2.75 mm.[11,12,36] A recent meta-analysis has shown that the use of paclitaxel-releasing DCB is associated with risks of target vessel revascularization and restenosis that are similar to DES (odds ratio [OR], 0.97; 95% CI, 0.56-1.68; $P = .92$ and OR, 1.12; 95% CI, 0.69-1.84; $P = .64$, respectively), whereas DCB yielded to a significant reduction in the risk of vessel thrombosis (OR, 0.12; 95% CI, 0.01-0.94; $P = .04$) and DES implantation resulted in slightly better angiographic surrogate end points at the mid-term follow-up.[47]

However, a recent observational study that included a nationwide cohort of 14,788 patients who underwent PCI with DCBs or DESs for small vessel CAD (defined as ≤2.5 mm, but inferred by the size of the implanted device) showed that treatment with DCBs compared with DESs was associated with a significantly higher risk for restenosis (hazard ratio, 2.02; 95% CI, 1.54-2.67; $P < .001$) and a similar risk of target lesion thrombosis, MI, and all-cause death.[50]

Surgery

The presence of diffuse disease with the involvement of small coronary arteries was consistently shown to be a very detrimental factor that lead to poor outcome after PCI.[51] Consequently, surgical myocardial revascularization is usually recommended in patients who would require extensive and small vessel stenting.[8] However, diffuse and small vessel CAD also pose relevant challenges to surgical treatment with CABG. Although the definition of a small vessel is different in the context of CABG (commonly a vessel diameter of <1.25 mm),[14] the detrimental impact of small vessel disease is as relevant in CABG as in PCI.[52] In patients undergoing CABG, small vessel disease is an independent predictor of several adverse events, such as a reduced graft patency and both short- and long-term mortality.[52-54] Similarly, a small vessel diameter is a poor

prognostic factor in both female and male sexes and in both venous and arterial bypass grafts, although its detrimental impact is higher in female sex and venous grafts.[55] Proposed explanations of the impact of vessel diameter on prognosis among patients undergoing CABG were an increased risk of poor anastomosis quality with higher turbulence and wall shear stress,[56] a graft-vessel mismatch (ie, oversized graft-host diameter ratio) that could induce adverse rheologic conditions and might impair graft patency,[57] and a poor run-off.[58]

Conclusions

Over the past 3 decades, research on small vessel CAD has been exhaustive and inconclusive. Indeed, patients with small vessel CAD still represent an unmet clinical need, and there is an urgent need for a definite cutoff value that defines a small vessel size. Based on previous research, we propose that a reference vessel diameter of <2.5 mm should be considered a cutoff for defining a small vessel both in future clinical trials and in clinical decision-making. Iterations in DES and DCB technologies will hopefully help to further improve the results of PCI in these complex coronary lesions. This will require future trials that should use the recommended definition of small vessels to permit a reliable comparison of clinical outcomes between the studies.

Declaration of competing interest

Dr von Birgelen receives institutional grant support from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. Dr Garcia-Garcia receives institutional grant support from Biotronik, Boston Scientific, Medtronic, Abbott, Neovasc, Shockwave, Phillips, and Corflow. Drs Sanz-Sánchez, Chiarito, Gill, Piña, Cortese, Alfonso, von Birgelen, Gil, and Waksman reported no financial interests.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics statement

The research reported has adhered to the relevant ethical guidelines.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2022.100403.

References

1. Colombo A, Chieffo A. Drug-eluting stent update 2007: part III: technique and unapproved/unsettled indications (left main, bifurcations, chronic total occlusions, small vessels and long lesions, saphenous vein grafts, acute myocardial infarctions, and multivessel disease). *Circulation*. 2007;116(12):1424–1432. https://doi.org/10.1161/CIRCULATIONAHA.106.621359
2. Morice MC. Stenting for small coronary vessels. *J Invasive Cardiol*. 2003;15(7):377–379.
3. 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(6):1610–1618. https://doi.org/10.1016/s0735-1097(98)00444-6
4. Ito H, Hermiller JB. Percutaneous coronary intervention for small-vessel coronary disease: highlight on the everolimus-eluting stent. *Expert Rev Cardiovasc Ther*. 2010;8(9):1239–1245. https://doi.org/10.1586/erc.10.88
5. Cassese S, Byrne RA, Tada T, et al. Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. *Heart*. 2014;100(2):153–159. https://doi.org/10.1136/heartjnl-2013-304933
6. Mehilli J, Dibra A, Kastrati A, et al. Randomized trial of paclitaxel- and sirolimus-eluting stents in small coronary vessels. *Eur Heart J*. 2006;27(3):260–266. https://doi.org/10.1093/eurheartj/ehi721
7. Godino C, Furuichi S, Latib A, et al. Clinical and angiographic follow-up of small vessel lesions treated with paclitaxel-eluting stents (from the TRUE registry). *Am J Cardiol*. 2008;102(8):1002–1008. https://doi.org/10.1016/j.amjcard.2008.05.052
8. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *EuroIntervention*. 2019;14(14):1435–1534. https://doi.org/10.4244/EIJY19M01_01
9. Tsai ML, Chen CC, Chen DY, et al. Review: the outcomes of different vessel diameter in patients receiving coronary artery stenting. *Int J Cardiol*. 2016;224:317–322. https://doi.org/10.1016/j.ijcard.2016.09.061
10. Jeger RV, Farah A, Ohlow MA, et al. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet*. 2018;392(10150):849–856. https://doi.org/10.1016/S0140-6736(18)31719-7
11. Cortese B, Di Palma G, Guimaraes MG, et al. Drug-coated balloon versus drug-eluting stent for small coronary vessel disease: PICCOLETO II randomized clinical trial. *JACC Cardiovasc Interv*. 2020;13(24):2840–2849. https://doi.org/10.1016/j.jcin.2020.08.035
12. Cortese B, Micheli A, Picchi A, et al. Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial. The PICCOLETO study. *Heart*. 2010;96(16):1291–1296. https://doi.org/10.1136/hrt.2010.195057
13. Hochman JS, Phillips WJ, Ruggieri D, Ryan SF. The distribution of atherosclerotic lesions in the coronary arterial tree: relation to cardiac risk factors. *Am Heart J*. 1988;116(5 Pt 1):1217–1222. https://doi.org/10.1016/0002-8703(88)90443-7
14. Ngaage DL, Hashmi I, Griffin S, Cowen ME, Cale AR, Guvendik L. To graft or not to graft? Do coronary artery characteristics influence early outcomes of coronary artery bypass surgery? Analysis of coronary anastomoses of 5171 patients. *J Thorac Cardiovasc Surg*. 2010;140(1):66–72.e1. https://doi.org/10.1016/j.jtcvs.2009.09.029
15. Briguori C, Tobis J, Nishida T, et al. Discrepancy between angiography and intravascular ultrasound when analysing small coronary arteries. *Eur Heart J*. 2002;23(3):247–254. https://doi.org/10.1053/euhj.2001.2730
16. Kawasaki M, Takatsu H, Noda T, et al. In vivo quantitative tissue characterization of human coronary arterial plaques by use of integrated backscatter intravascular ultrasound and comparison with angioscopic findings. *Circulation*. 2002;105(21):2487–2492. https://doi.org/10.1161/01.CIR.0000017200.47342.10
17. Jeger R, Pfisterer M, Pfister O, et al. First-generation paclitaxel- vs. second-generation zotarolimus-eluting stents in small coronary arteries: the BASKET-SMALL Pilot Study. *Adv Interv Cardiol*. 2016;12(4):314–320.
18. Iglesias JF, Heg D, Roffi M, et al. Long-term effect of ultrathin-strut versus thin-strut drug-eluting stents in patients with small vessel coronary artery disease undergoing percutaneous coronary intervention: a subgroup analysis of the BIOSCIENCE randomized trial. *Circ Cardiovasc Interv*. 2019;12(8):e008024. https://doi.org/10.1161/CIRCINTERVENTIONS.119.008024
19. Kandzari DE, Mauri L, Koolen JJ, et al. Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a randomised trial. *Lancet*. 2017;390(10105):1843–1852. Erratum in: *Lancet*. 2017;390(10105):1832.
20. 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. *JACC Cardiovasc Interv*. 2009;2(9):861–870.
21. Parikh MA, Soverow J, Leon MB, et al. Outcomes of stenting extra-small (≤2.25 mm) vessels using the Resolute zotarolimus-eluting stent (R-ZES). *EuroIntervention*. 2016;12:1215–1221.
22. Oliveira FR, Mattos LA, Abizaid A, et al. Miniaturized self-expanding drug-eluting stent in small coronary arteries: late effectiveness. *Arq Bras Cardiol*. 2013;101(5):379–387.
23. Buiten RA, Ploumen EH, Zocca P, et al. Outcomes in patients treated with thin-strut, very thin-strut, or ultrathin-strut drug-eluting stents in small coronary vessels: a prespecified analysis of the randomized BIO-RESORT trial. *JAMA Cardiol*. 2019;4(7):659–669. https://doi.org/10.1001/JAMACARDIO.2019.1776
24. Ploumen EH, Buiten RA, Zocca P, et al. First report of 3-year clinical outcome after treatment with novel Resolute Onyx stents in the randomized BIONYX trial. *Circ J*. 2021;85(11):1983–1990.
25. Caputo R, Leon M, Serruys P, et al. Performance of the resolute zotarolimus-eluting stent in small vessels. *Catheter Cardiovasc Interv*. 2014;84(1):17–23.
26. Wöhrle J, Markovic S, Rottbauer W, et al. Bioresorbable polymer sirolimus-eluting coronary stent compared with permanent polymer everolimus-eluting coronary stent implantation for treatment of small vessel coronary artery disease: CENTURY II trial. *EuroIntervention*. 2016;12(2):e167–e174.
27. Guedeney P, Claessen BE, Mehran R, et al. Small-vessel PCI outcomes in men, women, and minorities following platinum chromium everolimus-eluting stents: insights from the pooled PLATINUM Diversity and PROMUS Element Plus Post-Approval studies. *Catheter Cardiovasc Interv*. 2019;94:82–90.
28. 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(1):7–16.
29. Cannon LA, Simon DI, Kereiakes D, et al. The XIENCE nano everolimus eluting coronary stent system for the treatment of small coronary arteries: the SPIRIT small vessel trial. *Catheter Cardiovasc Interv*. 2012;80(4):546–553.

30. van der Heijden LC, Kok MM, Danse PW, et al. Small-vessel treatment with contemporary newer-generation drug-eluting coronary stents in all-comers: insights from 2-year DUTCH PEERS (TWENTE II) randomized trial. *Am Heart J*. 2016;176:28–35. https://doi.org/10.1016/j.ahj.2016.02.020
31. Jim MH, Yiu KH, Fung RC, et al. Zotarolimus-eluting stent utilization in small-vessel coronary artery disease (ZEUS). *Heart Vessels*. 2014;29(1):29–34.
32. Saito S, Ando K, Ito Y, et al. Two-year results after coronary stenting of small vessels in Japanese population using 2.25-mm diameter sirolimus-eluting stent with bioresorbable polymer: primary and long-term outcomes of CENTURY JSV study. *Cardiovasc Interv Ther*. 2019;34(1):25–33.
33. Price MJ, Saito S, Shlofmitz RA, et al. First report of the Resolute Onyx 2.0-mm zotarolimus-eluting stent for the treatment of coronary lesions with very small reference vessel diameter. *JACC Cardiovasc Interv*. 2017;10(14):1381–1388.
34. Giannini F, Latib A, Jabbour RJ, et al. Comparison of paclitaxel drug-eluting balloon and paclitaxel-eluting stent in small coronary vessels in diabetic and nondiabetic patients—results from the BELLO (balloon elution and late loss optimization) trial. *Cardiovasc Revasc Med*. 2017;18(1):4–9. https://doi.org/10.1016/J.CARREV.2016.12.008
35. Unverdorben M, Kleber FX, Heuer H, et al. Treatment of small coronary arteries with a paclitaxel-coated balloon catheter. *Clin Res Cardiol*. 2010;99(3):165–174.
36. Tang Y, Qiao S, Su X, et al. Drug-coated balloon versus drug-eluting stent for small-vessel disease: the RESTORE SVD China randomized trial. *JACC Cardiovasc Interv*. 2018;11(23):2381–2392. https://doi.org/10.1016/j.jcin.2018.09.009
37. Vaquerizo B, Miranda-Guardiola F, Fernández E, et al. Treatment of small vessel disease with the paclitaxel drug-eluting balloon: 6-month angiographic and 1-year clinical outcomes of the Spanish multicenter registry. *J Interv Cardiol*. 2015;28:430–438.
38. Collet C, Sonck J, Leipsic J, et al. Implementing coronary computed tomography angiography in the catheterization laboratory. *JACC Cardiovasc Imaging*. 2021;14(9):1846–1855. https://doi.org/10.1016/j.jcmg.2020.07.048
39. Stefanini GG, Alfonso F, Barbato E, et al. Management of myocardial revascularisation failure: an expert consensus document of the EAPCI. *EuroIntervention*. 2020;16(11):e875–e890. https://doi.org/10.4244/EIJ-D-20-00487
40. Kolandaivelu K, Swaminathan R, Gibson WJ, et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. *Circulation*. 2011;123(13):1400–1409. https://doi.org/10.1161/CIRCULATIONAHA.110.003210
41. Chiarito M, Cao D, Cannata F, Panico C, Reimers B, Stefanini GG. The synergy stent in high-bleeding risk patients: why design matters. *Minerva Cardioangiol*. 2018;66(5):646–658. https://doi.org/10.23736/S0026-4725.18.04673-X
42. Dan K, Garcia-Garcia HM, Kolm P, et al. Comparison of ultrathin, bioresorbable-polymer sirolimus-eluting stents and thin, durable-polymer everolimus-eluting stents in calcified or small vessel lesions. *Circ Cardiovasc Interv*. 2020;13(9):e009189. https://doi.org/10.1161/CIRCINTERVENTIONS.120.009189
43. Zaman A, de Winter RJ, Kogame N, et al. Safety and efficacy of a sirolimus-eluting coronary stent with ultra-thin strut for treatment of atherosclerotic lesions (TALENT): a prospective multicentre randomised controlled trial. *Lancet*. 2019;393(10175):987–997. https://doi.org/10.1016/S0140-6736(18)32467-X
44. Kereiakes DJ, Meredith IT, Masotti M, et al. Safety and efficacy of a bioabsorbable polymer-coated, everolimus-eluting coronary stent in patients with diabetes: the EVOLVE II diabetes substudy. *EuroIntervention*. 2017;12(16):1987–1994. https://doi.org/10.4244/EIJ-D-16-00643
45. Ploumen EH, Buiten RA, Kok MM, et al. Treating diabetic all-comers with contemporary drug-eluting stents: prespecified comparisons from the BIO-RESORT and the BIONYX randomized trials. *Int J Cardiol*. 2021;325:37–44. https://doi.org/10.1016/j.ijcard.2020.10.051
46. Wöhrle J, Scheller B, Seeger J, et al. Impact of diabetes on outcome with drug-coated balloons versus drug-eluting stents: the BASKET-SMALL 2 trial. *JACC Cardiovasc Interv*. 2021;14(16):1789–1798. https://doi.org/10.1016/j.jcin.2021.06.025
47. Sanz Sánchez J, Chiarito M, Cortese B, et al. Drug-coated balloons vs drug-eluting stents for the treatment of small coronary artery disease: a meta-analysis of randomized trials. *Catheter Cardiovasc Interv*. 2021;98(1):66–75. https://doi.org/10.1002/ccd.29111
48. Elgendy IY, Gad MM, Elgendy AY, et al. Clinical and angiographic outcomes with drug-coated balloons for de novo coronary lesions: a meta-analysis of randomized clinical trials. *J Am Heart Assoc*. 2020;9(10):e016224. https://doi.org/10.1161/JAHA.120.016224
49. Latib A, Colombo A, Castriota F, et al. A randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels: the BELLO (Balloon Elution and Late Loss Optimization) study. *J Am Coll Cardiol*. 2012;60(24):2473–2480. https://doi.org/10.1016/j.jacc.2012.09.020
50. Silverio A, Buccheri S, Venetsanos D, et al. Percutaneous treatment and outcomes of small coronary vessels: a SCAAR report. *JACC Cardiovasc Interv*. 2020;13(7):793–804. https://doi.org/10.1016/j.jcin.2019.10.062
51. Hara H, Ono M, Kawashima H, et al. Impact of stent length and diameter on 10-year mortality in the SYNTAXES trial. *Catheter Cardiovasc Interv*. 2021;98(3):E379–E387. https://doi.org/10.1002/ccd.29721
52. Shah PJ, Gordon I, Fuller J, et al. Factors affecting saphenous vein graft patency: clinical and angiographic study in 1402 symptomatic patients operated on between 1977 and 1999. *J Thorac Cardiovasc Surg*. 2003;126(6):1972–1977. https://doi.org/10.1016/S0022-5223(03)01276-5
53. O'Connor NJ, Morton JR, Birkmeyer JD, Olmstead EM, O'Connor GT. Effect of coronary artery diameter in patients undergoing coronary bypass surgery. Northern New England Cardiovascular Disease Study Group. *Circulation*. 1996;93(4):652–655. https://doi.org/10.1161/01.CIR.93.4.652
54. Limanto DH, Chang HW, Kim DJ, Kim JS, Park KH, Lim C. Coronary artery size as a predictor of Y-graft patency following coronary artery bypass surgery. *Medicine (Baltimore)*. 2021;100(2):e24063. https://doi.org/10.1097/MD.0000000000024063
55. Ramström J, Lund O, Cadavid E, Thuren J, Oxelbark S, Henze A. Multiarterial coronary artery bypass grafting with special reference to small vessel disease and results in women. *Eur Heart J*. 1993;14(5):634–639. https://doi.org/10.1093/eurheartj/14.5.634
56. Li H, Xie B, Gu C, et al. Distal end side-to-side anastomoses of sequential vein graft to small target coronary arteries improve intraoperative graft flow. *BMC Cardiovasc Disord*. 2014;14:65. https://doi.org/10.1186/1471-2261-14-65
57. Keynton RS, Evancho MM, Sims RL, Rittgers SE. The effect of graft caliber upon wall shear within in vivo distal vascular anastomoses. *J Biomech Eng*. 1999;121(1):79–88. https://doi.org/10.1115/1.2798047
58. Vural KM, Şener E, Taşdemir O. Long-term patency of sequential and individual saphenous vein coronary bypass grafts. *Eur J Cardiothorac Surg*. 2001;19(2):140–144. https://doi.org/10.1016/S1010-7940(00)00629-1