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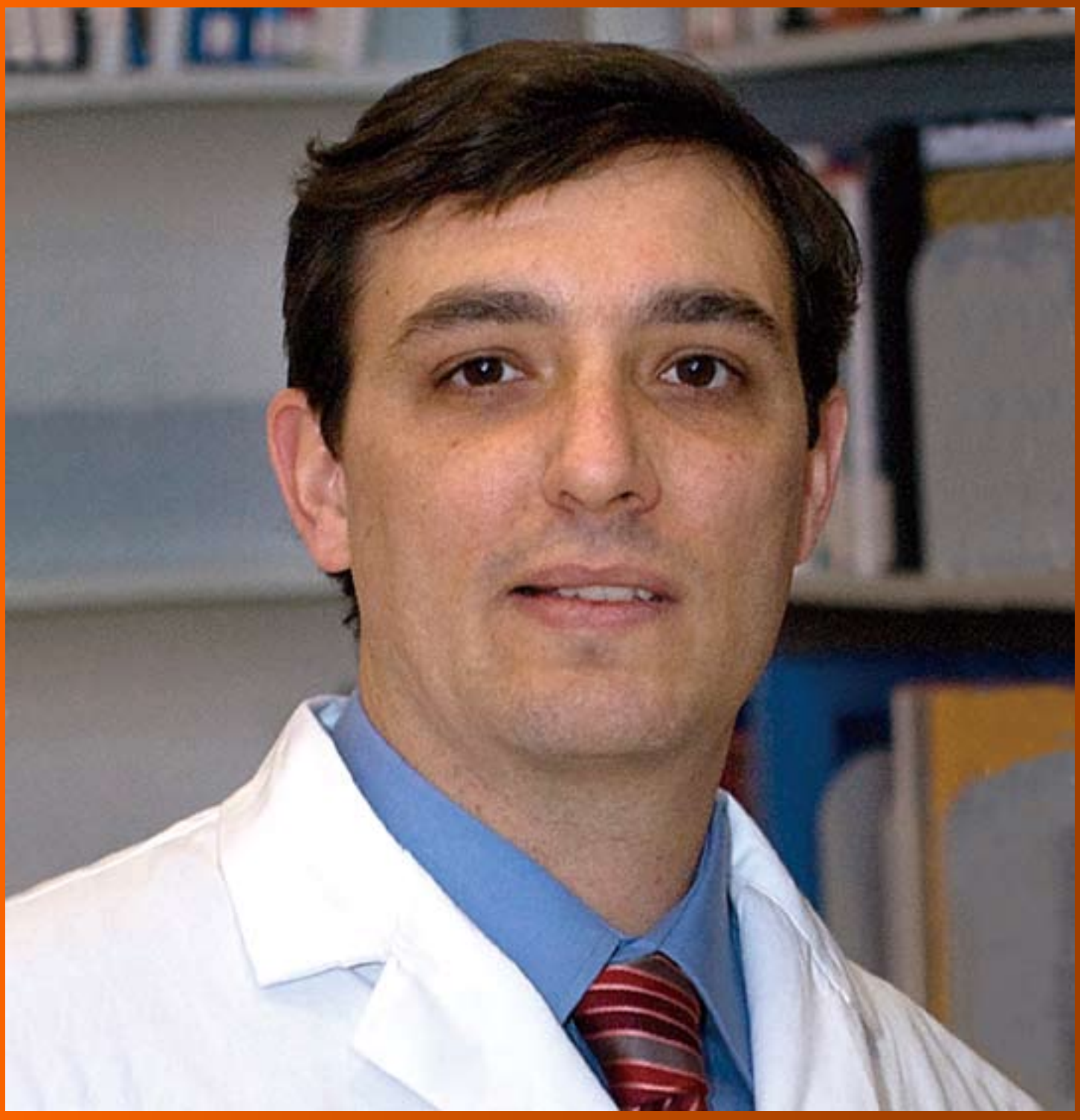

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EDITORIAL

Thin and crush: The new mantra in left main stenting?

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Abstract

Complex bifurcations have been suggested to be better approached by a planned double stent technique; however, recent randomized trials have shown better outcomes of provisional compared to planned two-stent strategy, in terms of both short-term efficacy and safety. In left main (LM) bifurcations, double kissing (DK)-Crush has demonstrated its superiority over Culotte and provisional-T in terms of restenosis and stent thrombosis, gaining respect as one of the most performant techniques for bifurcations stenting. On the other hand, the Nano-Crush technique has recently become part of the repertoire of double stenting techniques, providing evidence that the use of ultrathin strut stents and very minimal crush would be beneficial for both the physiological and rheological properties of the complex bifurcations, even in LM scenario, leading to a lower rate of thrombosis and restenosis at both side branch and true carina. Finally, the newest generation of ultrathin strut stents are gaining a re-putation for its safe and effective use in LM treatment thanks to improved design with increased expansion rate capable of LM treatment up to 5-6 mm diameter. The modern crush techniques, such as DK-Crush and Nano-Crush, are providing excellent results on mid and long-term follow up, suggesting that minimal crushing obtained using ultra-thin stents is a good way to obtain surgical-like outcomes in the treatment of complex LM bifurcation disease.

Key words: Stent; Crush; Interventional cardiology; Percutaneous coronary intervention; Percutaneous coronary intervention; Coronary bifurcation

Core tip: Modern crush techniques such as DK-Crush and Nano-Crush are providing excellent results on mid and

long-term follow-up, suggesting that minimal crushing obtained using ultra-thin stents is a good way to obtain surgical-like outcomes in the treatment of complex left main bifurcation disease.

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INTRODUCTION

Complex bifurcations have been suggested to be better approached by a planned double stent technique[1-2], although recent randomized trials have shown better outcomes of provisional compared to planned two-stent strategy in terms of both short-term efficacy and safety[3-4].The total amount of metal layers at both the carina and bifurcation angle after double stenting techniques[5-6] appeared to be important issues to achieve favorable short- and long-term outcomes.

Left main (LM) bifurcation disease is probably the only real important bifurcation in the human vascular tree. The DEFINITION trial[7] has given a practical definition of what is complex and what it is not in the treatment of coronary artery bifurcation disease. Indeed, a length of the left circumflex coronary artery (LCx) > 10 mm has already been identified as a predictor of complex LM bifurcation probably requiring a double stenting strategy.

To achieve similar or better post-procedural results guaranteed by surgical treatment from a rheolytic point of view, the use of intravenous ultrasound is mandatory[8] to properly assess the size and length of the disease in both branches and in the LM body, allowing an accurate selection of the most appropriate stenting technique and stents.

Culotte, mini-Culotte, DK-Crush, T-stent and Protrusion (TAP) are currently the most used double stenting techniques (Table 1)[9]. Recently, DK-Crush has demonstrated its superiority over Culotte[10] and provisional-T[11] techniques in terms of restenosis and stent thrombosis, gaining respect as one of the most performant techniques for bifurcation stenting.

Even more recently, the Nano-Crush technique[12-13] has become part of the repertoire of double stenting techniques, providing evidence that the use of ultrathin strut stents and very minimal crush is beneficial for both the physiological and rheological properties of the complex bifurcations, leading to a lower rate of thrombosis and restenosis at both side branch (SB) and true carina[14].

TECHNICAL COMPARISON AMONG NANO-CRUSH, DK-CRUSH AND OTHERS

Compared to the classical Crush technique introduced by Colombo *et al*[15], both the Nano- and DK–Crush

Table 1 Available techniques for left main interventions

Single stent	Double stent
Cross over-provisional	T-stenting
	T and protrusion
	Mini-Crush
	Culotte and Mini-culotte
	DK crush
	Nano-Crush

represent a further modern development of the former. Both these latter techniques require wiring and pre-dilation of both branches and in both SB stenting before main branch (MB) stenting. A different strand is represented by the entity of the SB stent protrusion, which is minimal, with only one ring if possible, in the Nano-Crush, while it appears greater, with at least 3-4 mm of protrusion, in the DK-Crush technique.

Protrusion length of the SB stent explains why kissing is required when DK-Crush is adopted. In the classical DK-Crush, rewiring of the SB generally represented the next step after MB stenting. However, more recently, the use of proximal optimization technique (POT) has been recommended, as in Nano-Crush, where POT facilitates LCx rewiring. Subsequently, both techniques included a type of kissing balloon: Classical for the DK and with snuggle configuration in Nano-Crush. Moreover, the classical DK-Crush technique has been modified introducing a POT as the final step, as in Nano-Crush (Figure 1).

Different from DK-Crush, in which the ostium circumference is completely covered by the SB stent, in the Nano-Crush, the ostium is covered at the carina by the SB stent strut and at the opposite site of the carina by the MB struts opened by the POT into the SB ostium, providing complete circumferential coverage, especially in the case of tight angles, in which the ostium coverage might be incomplete at the carina.

Among these two stenting techniques, one significant difference is represented by the most appropriate stent to implant. In DK-Crush, virtually every kind of stent can be used, while the Nano-Crush has been created to fit with the concept of less metal in the carina, so the ideal stent should have the thinnest struts possible, at least 60 to 80 microns.

TAP or standard T usually leave the SB stent strut floating into the MB; this causes a non-physiologic flow, which may induce lower wall shear stress and turbulent flow, leading to thrombosis and in-stent restenosis[16]. On the other hand, the Culotte usually leaves two or three metal layers into the carina for a length ranging from 5 to 15 mm, even in the "Mini" version.

AMOUNT OF METAL INTO THE CARINA: DOES IT REALLY MATTER?

The lack or excess amount of metal layers at the carina has been suggested to be a potential cause of

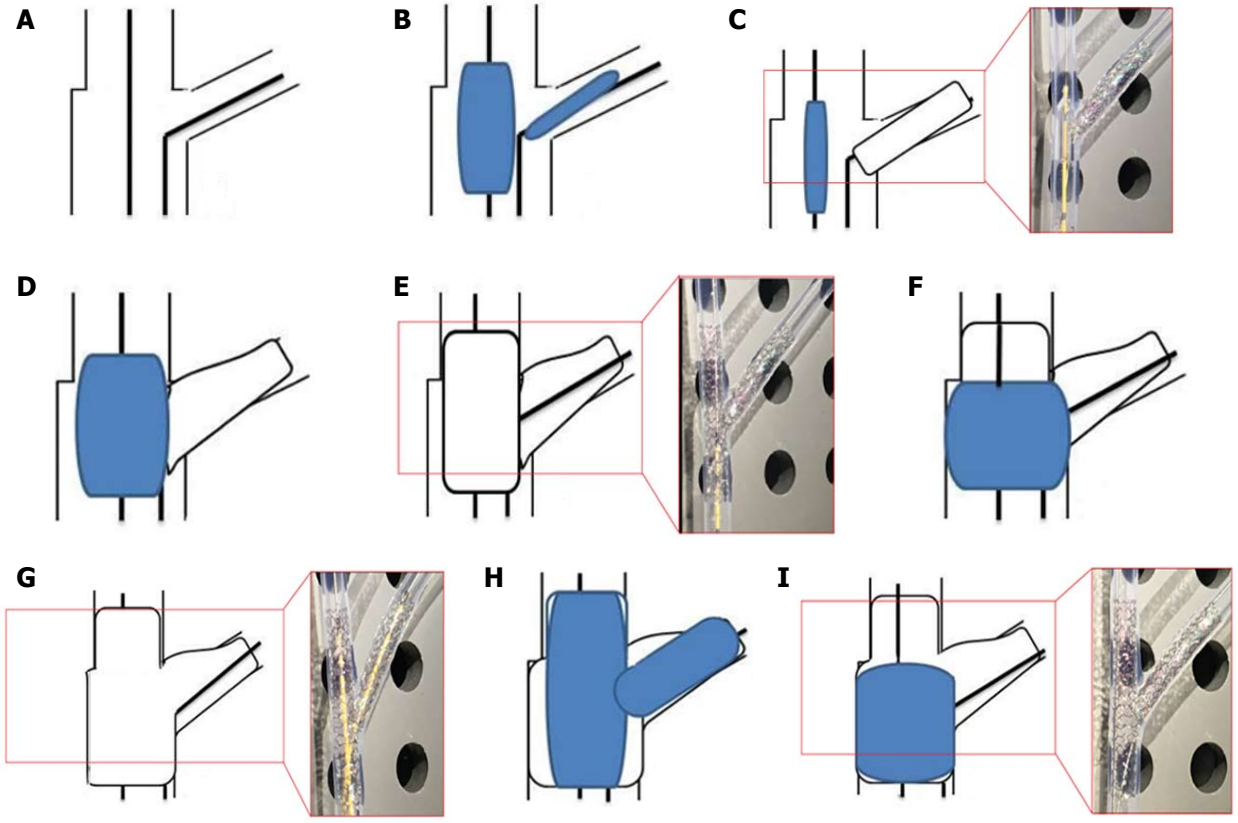

Figure 1 Key steps in the Nano-Crush stenting technique. As both branches are wired (A), both branches are predicated with non-compliant balloons (B) and the stent is deployed at the side branch (C: bench test correlate image). The balloon of the deployed stent is withdrawn and the main branch balloon is inflated in the main branch (MB) at high atmosphere (D); The MB stent of the diameter of the distal reference diameter (3.0 mm) is placed in position and deployed (E: bench test correlate image); Proximal optimization technique (POT) with non-compliant balloon of the same diameter of the MB is performed at high atmosphere (F) and after rewiring of the side branch (G: bench test correlate image), a snuggle kiss is performed with non-compliant balloons (H); Finally, a re-POT is performed with a non-compliant balloon at high atmosphere atm (I: bench test correlate image).

stent restenosis and thrombosis, respectively[17]. As recently suggested by our group, using computed fluid dynamics, the Culotte and other techniques that leave large amounts of metal at the carina unfavorably impacted the bifurcation rheology, causing an increase in lower wall shear stress (WSS) and in the SB. Indeed, low WSS is a potential substrate for restenosis and thrombosis (Figure 2).

To achieve a more physiological flow profile, there should ideally be less metal coverage in the carina side and full metal coverage in the area opposite of the carina and the ostium of the SB. DK-Crush and Nano-Crush are likely to work differently in terms of lowering WSS areas depending on the LM bifurcation. The distribution of metal and the coverage of the carina by the struts strictly depends on the angles: Sharp angles tend to increase the amount of metal at the carina, especially when a generous portion of the SB stent is protruding and should be crushed, whereas if the portion of the stent to be crushed is shorter and the angle is wider, the amount of the metal would be less and coverage might be even incomplete. Obviously, the use of ultra-thin stent struts in DK-Crush or other techniques would potentially improve both safety and long-term outcomes.

STENT ENGINEERING CONSIDERATIONS

The Orsiro (Biotronic AG, BÜlach, Switzerland) stent is considered to have the thinnest struts commercially available. In the most recent European randomized trials, this stent demonstrated a very good safety and efficacy profile. Indeed, its low rate of stent thrombosis reached the non-inferiority statistical significance compared to Xience Prime stent (Abbott Inc., United States)[18-19] with a faster strut endothelium coverage evaluated by optical coherence tomography in respect to the competitors[20]. These results could be achieved even after overcoming the major intrinsic structural limitation to the stent's design, such as longitudinal shortening[21]. Nowadays, other stents have been designed with similar ultra-thin struts, such as the Resolute Onyx stent by Medtronic Inc. or the Ultimaster by Terumo Inc., which are currently being evaluated in real-world scenarios but promise to maintain the line of their predecessor or do even better in terms of strut neointima coverage.

Nowadays, stent working size in most LMs should not be less than 4.5 mm, and all modern techniques imply the use of POT at high pressure. All of these issues

Table 2 Thinnest struts stents and their maximum expansion for left main interventions

Stent type	Strut thickness (μ)	Max size achievable (mm)
Orsiro Biotronik, Sui	60-80	5.3 (3.5 stent)
Onyx Medtronic, United States	70	6 (4.0 stent)
Ultimaster Terumo, Japan	80	5.8 (3.5 stent)
Biomime Meril	65	5.3 (4.5 stent)[1]
Synergy Boston Scientific, United States	74	5.7 (4.0 stent)

Data of maximum expansion retrieved from Sawaya FJ *et al*[24]. [1]Not verified in bench test.

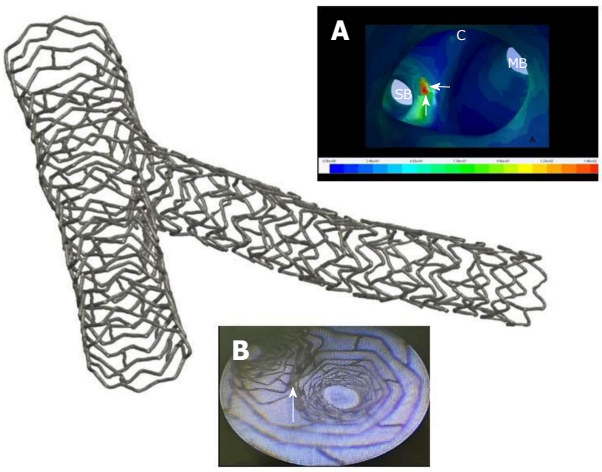

Figure 2 Microcomputed tomography picture of a bifurcation treated by the Nano-Crush technique. A: Region of the carina investigated by computed fluid dynamic showing from the inside of a vessel with high wall shear stress (red zone, white arrows) located at the side branch portion of the carina, which should potentially be in favor of less restenosis and thrombosis at that site; B: Angioscopic image of the same region showing a very smooth transition of the wall at the bifurcation with a very minimal (Nano) apposition of two stent layers. SB: Side branch; MB: Main branch.

could contribute to stent deformation and polymer rupture, both of which can influence thrombosis and restenosis rates. The availability of thin struts and different sized stents useful to treat LM bifurcation, maintaining a good radial force and minimal shortening will represent a mandatory goal to be accomplished by companies in the market in the near future (Table 2).

THE NEW MANTRA OF LM STENTING

Nowadays, LM stenting has gaining respect as an alternative to surgical treatment[22-24], but the treatment of complex LM disease distal/bifurcation disease remains a significant obstacle to overcome to achieve satisfactory results. In such disease, the double stenting technique would provide a more reliable strategy as supported by the evidence coming from both clinical and virtual studies about the benefits provided by thin strut stent technology.

The modern crush techniques such as DK-Crush and Nano-Crush are providing excellent results on mid and long-term follow up, suggesting that minimal crushing obtained using ultra-thin stents is a good way to obtain surgical-like outcomes in the treatment of complex LM bifurcation disease.

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EDITORIAL

Revisiting endovascular treatment in below-the-knee disease. Are drug-eluting stents the best option?

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Abstract

Patients with below-the-knee arterial disease are primarily individuals suffering from critical limb ischemia (CLI), while a large percentage of these patients are also suffering from diabetes or chronic renal failure or both. Available data from randomized controlled trials and their meta-analysis demonstrated that the use of infrapopliteal drug-eluting stents (DES), in short- to medium- length lesions, obtains significantly better results compared to plain balloon angioplasty and bare metal stenting with regards to vascular restenosis, target lesion revascularization, wound healing and amputations. Nonetheless, the use of this technology in every-day clinical practice remains limited mainly due to concerns regarding the deployment of a permanent metallic scaffold and the possibility of valid future therapeutic perspectives. However, in the majority of the cases, these concerns are not scientifically justified. Large-scale, multicenter randomized controlled trials, investigating a significantly larger number of patients than those already published, would provide more solid evidence and consolidate the use of infrapopliteal DES in CLI patients. Moreover, there is still little evidence on whether this technology can be as effective for longer below-the-knee lesions, where a considerable number of DES is required. The development and investigation of new, longer balloon-expanding or perhaps self-expanding DES could be the answer to this problem.

Key words: Critical limb ischemia; Infrapopliteal arterial disease; Drug-eluting stents; Peripheral arterial disease; Balloon angioplasty

Core tip: The use of infrapopliteal drug-eluting stents

(DES) remains limited in clinical practice mainly due to concerns regarding the deployment of a permanent metallic scaffold and the possibility of valid future therapeutic perspectives. However, these concerns are not scientifically justified. Large-scale, multicenter randomized controlled trials investigating a significantly larger number of patients would consolidate the use of infrapopliteal DES in critical limb ischemia patients. Moreover, there is still little evidence on whether this technology can be as effective for longer lesions, where a considerable number of DES is required. The development and investigation of longer balloon-expanding or self-expanding DES could solve this problem.

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INTRODUCTION

Patients with below-the-knee (BTK) arterial disease are mainly suffering from critical limb ischemia (CLI), the malignant expression of peripheral arterial disease[1]. Additionally, a large percentage of CLI patients with BTK disease are suffering from diabetes or chronic renal failure or both[2]. Specifically, patients with diabetes and CLI should undergo prompt revascularization, as the 5-year survival rate in such patients has been reported to be as low as 25%, while diabetes has been correlated with increased risk of limb amputation and repeat revascularization procedures[2]. These fundamental characteristics of BTK disease demarcate the therapeutic approach. More specifically, CLI sets the goal of treatment, which is limb salvage, rather than increasing walking distance, as in cases of intermittent claudication. Limb salvage is strongly related to direct, immediate and acute flow restoration to the foot, also described as immediate lumen gain.

The traditional endovascular treatment algorithm suggests the use of balloon angioplasty or bare metal stenting (BMS) as a bail-out option in cases of residual stenosis or flow-limiting dissection. However, diabetes and chronic renal failure contribute to the formation of an aggressive, hard, atherosclerotic plaque with marked calcifications that are resistant to balloon dilation, reducing the possibility of achieving an adequate acute luminal gain with the use of plain balloon angioplasty[2]. Therefore, in this specific population, the use of stents is, in many occasions, mandatory to obtain an acceptable immediate outcome. As outcomes of BMS in infrapopliteal arteries have been similar to those attained by balloon angioplasty and because short-term patency was not warranted, several studies, including multicenter randomized controlled trials (RCTs), investigated the use of infrapopliteal drug-eluting stents (DES) and the evidence in favor of this technology, which is widely used in coronary disease, began to accumulate[3,4].

Table 1 Endovascular devices for infrapopliteal arterial disease

Balloon angioplasty
Bare metal stents (balloon- or self-expandable)
Drug-eluting stents
Bioabsorbable stents
Bioabsorbable drug-eluting stents
Drug-coated balloons
Drug-infusion devices
Atherectomy devices
Lithotripsy

As a result, a significant volume of high-level evidence supporting the safety and effectiveness of infrapopliteal DES has emerged in the literature, motivating the Trans-Atlantic Society Consensus Ⅱ update to endorse the use of DES in the treatment algorithm of CLI and establish endovascular treatment as a valid and successful alternative to surgery. Notably, the specific consensus document supports the use of DES in short-length infrapopliteal lesions[1]. The endovascular devices currently available for the treatment of infrapopliteal arterial disease are summarized in Table 1.

In a 2013 meta-analysis of five RCTs (611 patients), Fusaro *et al*[5] found that infrapopliteal DES use significantly decreased major amputations and reinterventions compared to plain balloon angioplasty or BMS.

In a recent network meta-analysis of 16 RCTs (1805 patients), Katsanos *et al*[6] demonstrated that both DES and drug-coated balloons (DCBs) had significantly better results compared to plain balloon angioplasty and BMS with regards to vascular restenosis, target lesion revascularization and wound healing. Moreover, DES had also significantly better results when compared with DCB for the most important, strong clinical endpoint of amputations. The Infrapopliteal Drug-Eluting Angioplasty Versus Stenting (commonly known as IDEAS) trial by Siablis *et al*[7] is the only study so far that directly compares these state-of-the-art technologies in BTK disease. Despite the fact that DES demonstrated significantly less binary restenosis at six months follow-up, late lumen loss was similar between the two technologies. An in-depth analysis revealed that this was attributed to the superior acute luminal gain obtained by DES compared to balloon dilation. In the case of small-caliber BTK arteries, even a few millimeters of initial gain are significant, as a larger initial vessel diameter requires superior volume of hyperplasia to reach the critical point of clinically significant restenosis. Therefore, the current data demonstrate the superiority of DES technology for the management of BTK disease (Table 2). Nonetheless, the penetration of this technology in everyday clinical practice has been poorer than expected, due to several issues that remain to be addressed.

First of all, the implementation of a permanent metallic scaffold in such small-caliber vessels as the

Table 2 Randomized controlled trials for infrapopliteal drug-eluting technologies

Study	Yr of publication
Falkowski *et al*[22]	2009
BELOW. Tepe *et al*[23]	2010
ACHILLES. Scheinert *et al*[24]	2012
YUKON-BTX Rastan *et al*[25]	2012
DESTINY Bosiers *et al*[26]	2012
DEBATE-BTK. Liistro *et al*[27]	2013
IN.PACT DEEP. Zeller *et al*[28]	2014
IDEAS. Siablis *et al*[7]	2014
BIOLUX P-II. Zeller *et al*[29]	2015
PADI. Spreen *et al*[30]	2017

tibial arteries raises the issue of whether an occlusion would be re-accessible. Spiliopoulos *et al*[8] performed a retrospective analysis on the recanalization of occluded DES in BTK vessels. Within a period of seven years, a total 367 patients were treated with infrapopliteal DES and the re-occlusion rate was 11.4%. Notably, the success rate of endovascular recanalization of DES occlusions was 90.7% (49/54 cases), while endovascular recanalization was rarely technically demanding. Failure to recanalize the occluded stent(s) was associated with tandem popliteal stent occlusion and stent fractures. This concern of fracture or deformation that compromises patency and re-intervention options has been addressed in another retrospective analysis by Karnabatidis *et al*[9] in which the incidence and clinical implications of DES fracture was evaluated. In 63 CLI patients and 191 lesions, 369 stents were deployed. The follow-up period was 15 ± 11 mo. Only one (0.3%) severe stent fracture and eleven (3.0%) stent compressions were noted. The authors concluded that stent fracture or severe compression is rare and occurs in specific anatomical locations, mainly the distal anterior tibial artery. The authors recommended avoiding stenting in the specific anatomical location, as fractures lead to patency loss and inability to recanalize the occlusion[9]. The cost-effectiveness of DES was also a concern considering their higher price compared to plain balloon angioplasty and their short length, which leads to the deployment of a significant number of stents for the treatment of the characteristically long BTK lesions. This was also addressed in a cost-effectiveness study by Katsanos *et al*[10], where they concluded that the higher DES direct cost is counter-balanced by the smaller number of re-interventions required for limb salvage. Considering that the price of DES has decreased, longer stents could further diminish the direct cost and optimize the cost-effectiveness of infrapopliteal DES use. Finally, some physicians advocate that the deployment of infrapopliteal DES could compromise future surgical options. According to the authors' opinion, stenosed or occluded BTK arterial segments are not a suitable target for surgical reconstruction. Nevertheless, stent placement should always be performed with a view to future treatment options and should certainly respect non-diseased arterial segments that could be used for bypass surgery.

DCBs have been successfully used for the treatment of superficial femoral artery lesions and granted themselves an established role in the treatment algorithm, while there is already increasing evidence for their role in the treatment of dysfunctional dialysis access[11-16]. The use of this technology transformed treatment into a two-step procedure, with an initial step of mechanical treatment required to treat the immediate problem of vascular stenosis, while DCBs are implemented to slow down the process of restenosis using the cytotoxic drug paclitaxel. Several up-to-date tools are available in both the superficial femoral artery and dialysis access to perform vessel preparation[17,18]. However, in BTK vascular disease, the evidence supporting the use of DCB is rather controversial, as two large multicenter RCTs studies have failed to demonstrate the superiority of these devices over standard percutaneous transluminal angioplasty[19]. It is the authors' opinion that this disadvantage in BTK vessels is due to the deficient initial treatment vessel preparation step, which is not required when using balloon-expandable DES. Hence, it remains to be tested whether new technologies dedicated to vessel preparation and minimization of dissection will improve outcomes of infrapopliteal DCB angioplasty.

To conclude, although available data support the use of infrapopliteal DES for short- to medium-length lesions, the use of this technology in everyday clinical practice remains limited, mainly due to concerns regarding the deployment of a permanent metallic scaffold and the possibility of valid future therapeutic perspectives. However, in the majority of the cases, these concerns are not scientifically justified. Large-scale, multicenter RCTs investigating a significantly larger number of patients than those already published would provide solid evidence and would strengthen the use of infrapopliteal DES in CLI patients. Moreover, there is still little evidence on whether this technology can be as effective for longer BTK lesions, where a considerable number of DES is required[20,21]. The development and investigation of new, longer balloon-expanding or perhaps self-expanding DES could be the answer to this problem.

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EDITORIAL

Coronary spasm: It's common, but it's still unsolved

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Abstract

Coronary spasm is caused by a transient coronary narrowing due to the constriction of epicardial coronary artery, which leads to myocardial ischemia. More than 50 years have passed since the first recognition of coronary spasm, and many findings on coronary spasm have been reported. Coronary spasm has been considered as having pivotal roles in the cause of not only rest angina but also exertional angina, acute coronary syndrome, and heart failure. In addition, several new findings of the mechanism of coronary spasm have emerged recently. The diagnosis based mainly on coronary angiography and spasm provocation test and the mainstream treatment with a focus on a calcium-channel blocker have been established. At a glance, coronary spasm or vasospastic angina (VSA) has become a common disease. On the contrary, there are several uncertain or unsolved problems regarding coronary spasm, including the presence of medically refractory coronary spasm (intractable VSA), or an appropriate use of implantable cardioverter defibrillator in patients with cardiac arrest who have been confirmed as having coronary spasm. This editorial focused on coronary spasm, including recent topics and unsolved problems.

Key words: Vasospastic angina; Medically refractory coronary spasm; Variant angina; Coronary vasospasm

Core tip: Coronary spasm is the transient vasoconstriction of epicardial coronary artery, leading to myocardial ischemia. Recently, coronary spasm has become widely accepted as one of the important pathophysiologies of coronary artery disease. However, even at present, there are several unsolved problems regarding coronary spasm.

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INTRODUCTION

More than several decades have passed since the first recognition of coronary spasm[1-3]. Since then, numerous studies have been conducted, and many findings regarding coronary spasm have been clarified. Coronary spasm is caused by transient narrowing due to the vasoconstriction of the epicardial coronary arteries, leading to myocardial ischemia, and it plays pivotal roles in the cause of not only rest angina but also exertional angina, acute coronary syndrome, including unstable angina, acute myocardial infarction, and ischemic sudden death[4-9]. Recently, coronary spasm has been considered one of the causes of heart failure with reduced ejection fraction[10-12]. Mechanisms responsible for coronary spasm were reported to be the abnormal response of the autonomic nervous system[13], endothelial dysfunction[14-17], abnormal or hyper-reaction of vascular smooth muscles[18-20], and other factors, such as magnesium deficiency[21,22], inheritance[23], or specific anatomy of the coronary artery[24-27]. In addition, the diagnosis and treatment of coronary spasm were based on the guidelines of coronary spasm[28,29]. Its diagnosis has been based on several examinations on the presence of coronary spasm; however, coronary angiography and spasm provocation test (SPT) have been recognized as the standard and final tests[28,30]. It is mainly treated with coronary vasodilators particularly with calcium-channel blocker (CCB)[28,31]. According to the accumulations of experiences, numerous studies, and recent guidelines[6,7,28,29], recently, many physicians roughly know "coronary spasm" or "vasospastic angina" (VSA). However, even at present, there have been undoubtedly several uncertain or unsolved problems on coronary spasm, such as management of medically refractory coronary spasm (intractable VSA) and coronary microvascular angina or appropriate use of implantable cardioverter defibrillator (ICD) for patients with cardiac arrest, who were confirmed as having coronary spasm[28,32,33]. Therefore, this paper focuses on the mechanisms, diagnosis, and treatment of coronary spasm, including recent topics and uncertain or unsolved problems.

MECHANISM OF CORONARY SPASM

Several mechanisms have reported the causes of coronary spasm, such as the abnormal response of the autonomic nervous system[13], endothelial dysfunction of the coronary artery or systemic peripheral vasculature[14-17], abnormal or hyper-reaction of vascular smooth muscles[18-20], and other factors such as a magnesium deficiency[21,22], inheritance[23], or specific anatomy of the coronary artery[24-27]. Naturally, the mechanism of coronary spasm may not be always simple, but may be also multi-factorial. We have come to strongly recognize the multi-factorial mechanisms responsible for coronary spasm when we consider sex differences in the clinical characteristics of VSA patients. Smoking, presence of atherosclerosis of the coronary artery, and morphology of coronary spasm during the SPT differ in male and female VSA patients[8,34,35], indicating the presence of multi-factorial mechanisms of coronary spasm. Findings that the presence of family history of coronary artery disease is higher in women than in men or that younger female VSA patients had higher incidence of smoking than older female VSA patients did, despite the lower incidence of smoking among the whole of female VSA patients[8], are of great interest, taking into consideration the mechanisms of coronary spasm in female patients (Table 1).

Among the mechanisms of coronary spasm shown above, Ohyama *et al*[20,36] have recently reported the relationship between coronary spasm and perivascular components, such as perivascular adipose tissue and adventitial vasa vasorum (Table 1). They showed that such perivascular components play an important role as a source of various inflammatory mediators and showed that inflammatory changes of such perivascular components caused increased the formation of adventitial vasa vasorum and increased the activity of Rho-kinase, leading to the occurrence of coronary spasm[20,36]. These findings appeared to be novel and noteworthy. These findings may account for the presence of focal spasm, because it appears quite difficult to consider the presence of focal spasm based solely on endothelial dysfunction of the coronary artery. On the contrary, the studied VSA patients had coronary spasm of the left anterior descending coronary artery (LAD)[20,36]. Moreover, coronary spasm occurs more frequently in the LAD and right coronary artery (RCA) than in the left circumflex coronary artery (LCX)[37], and it remains unclear whether the findings reported by Ohyama *et al*[20,36] may also account for coronary spasm in the RCA or differences in the frequency of coronary spasm according to the territory of coronary arteries.

Recently, some interest has also focused on the specific coronary anatomy in VSA patients (Table 1): The presence of myocardial bridge (MB), which is characterized by the systolic narrowing of the epicardial coronary artery because of myocardial compression during systole[24-27]. Furthermore, coronary spasm occurs more frequently at the MB, which is in part mediated by coronary vascular dysfunction, including endothelium-dependent and endothelium-independent dysfunctions, at the MB segments. Further observation regarding the occurrence of coronary spasm at MB segments is needed in the international registry of VSA.

Previously, the prevalence of coronary spasm had been considered higher in Asians than in Caucasians[38,39], showing the presence of racial difference in the occurrence of VSA. However, recently, the presence of VSA is more frequent in Caucasians when SPT is aggressively performed[40,41]. In addition, coronary spasm is considered as playing some roles in the cause of acute coronary syndrome with plaque rupture[42] or myocardial infarction with non-obstructive coronary artery[43]. The aggressive effort of making a diagnosis of VSA may clarify the real presence of VSA worldwide (Table 1).

Table 1 Recent topics and unsolved problems regarding coronary spasm

	Previously reported or established	Recent topics	Unsolved problems
Mechanism	Abnormal autonomic nervous system		
	Endothelial dysfunction		
	Hyperreactivity of the coronary smooth muscle	Inflammation of perivascular components	
	Others	Specific anatomy of the coronary artery (myocardial bridge)	Different mechanisms in men and women
	Inheritance		Is there a racial difference in coronary spasm?
	Magnesium deficiency		
Diagnosis	Non-invasive:	Malondialdehyde-modified low-density lipoprotein	Is a biochemical marker for coronary spasm present?
	Holter ECG	Exercise ECG	
	Invasive:	Higher doses of ACh infusions	Detailed SPT protocol using EM
	SPT	Sequential SPT	Are higher doses of ACh for SPT being used?
		SPT using a pressure wire	
		Second SPT despite of negative results of first SPT	Does SPT positivity continue for decades?
Treatment	Life style		
	Stop smoking		
	Pharmacological		
	Calcium-channel blockers	Cilostazol	Treatment of intractable VSA
	Sublingual nitroglycerin during attacks	Statin	Which combinations of coronary vasodilator are the most effective?
	Combination of coronary vasodilators	Aspirin	
	Non-pharmacological	Use of ICD in VSA patients with cardiac arrest	Which is effective in preventing adverse events in VSA patients with cardiac arrest: use of ICD or aggressive medical therapy?
		Cardiac rehabilitation	Treatment of accompanying microvascular angina

ACh: Acetylcholine; ECG: Electrocardiogram; EM: Ergonovine maleate; ICD: Implantable cardioverter defibrillator; SPT: Spasm provocation test; VSA: Vasospastic angina; SPT: Spasm provocation test.

DIAGNOSIS OF CORONARY SPASM

According to the guideline on coronary spasm[28,29], the recognition of transient changes in ST-T segments on electrocardiogram (ECG) during chest symptoms, as well as the presence of chest symptoms derived from coronary spasm, including the good responses to sublingual nitroglycerin and timing of occurrence of coronary spasm at rest, during sleep, or early in the morning, is very important in the diagnosis of VSA. Thus, needless to say, Holter ECG monitoring is important in the diagnosis of VSA[28]; however, Sueda *et al*[44] reported that approximately half of VSA patients had pathologic exercise tests, showing the importance of exercise ECG testing in the clinical setting. Exercise ECG testing may be also useful in patients suspected of coronary spasm (Table 1). As a biochemical index, which has been eagerly longed for but has not been detected until now (Table 1), the level of malondialdehyde-modified low-density lipoprotein (MDA-LDL) was increased in VSA patients[45]. However, this biochemical marker is reported elevated in patients with other unstable coronary diseases[46,47]. An elevated MDA-LDL level may be carefully interpreted in the diagnosis of VSA. In general, using coronary computed tomography (CT) angiography alone, the diagnosis of VSA itself cannot be obtained, and we doubt the presence of VSA when no significant coronary stenosis is detected on coronary CT angiography. We have sometimes experienced patients with coexistence of coronary spasm and organic coronary stenosis (Figure 1), and the assessment of or exclusion for organic coronary stenosis using a coronary CT angiography may be also needed even in patients, whose diagnosis of VSA was made based on the typical chest symptoms and transient ST-T changes in ECG. Furthermore, as shown above, coronary spasm sometimes occurs at the MB segments[24-27], and the presence of MB on a coronary CT angiography[48] may be a useful clue of the possibility of VSA in patients with chest pain when atherosclerosis was absent on a coronary CT angiography. According to Ohyama *et al*[20], positron-emission tomography, which has been adopted in the assessment of inflammatory perivascular components, cannot be performed widely in the clinical setting.

Thus, SPT is considered the gold standard examination and actually has been performed frequently because transient ST-T changes on ECG during chest symptoms cannot always be obtained in the clinical setting. Furthermore, SPT may be useful not only in the diagnosis of VSA but also in providing some information in the activity of coronary spasm and prognosis; presence of organic stenosis, multi-vessel spasm, focal spasm, coronary spasm induced by a low dose of acetylcholine (ACh), and total occlusion due to coronary spasm[49-51]. The provocative drugs in SPT are ACh and ergonovine maleate (EM). The methodology of SPT using ACh infusions has been almost established[28-30,52,53], except for the use of transient pacing catheter or the maximal doses of ACh. In general, during SPT using ACh infusions, an insertion of transient pacing catheter *via* an internal

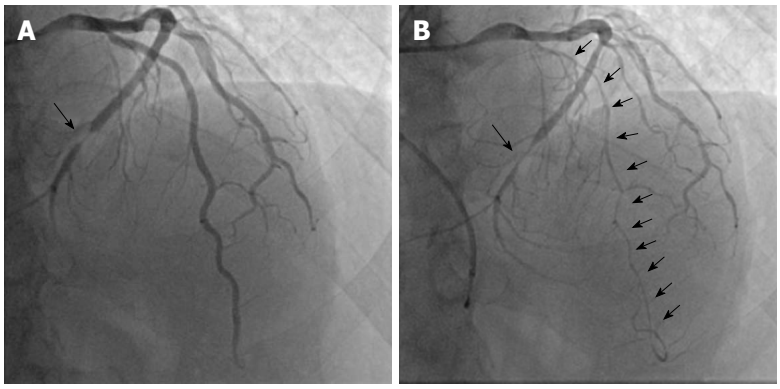

Figure 1 A representative case with coronary spasm and coronary stenosis. The patient, who had chest symptoms for 20 min at rest, accompanied with cold sweating, was admitted to our institution for the evaluation of his chest symptoms. A: Coronary angiography showed coronary stenosis at the distal segment of the left circumflex coronary artery, which cannot be considered as the cause of his chest symptoms; B: The spasm provocation test using 100 μg of acetylcholine showed diffuse coronary spasm throughout the left anterior descending coronary artery, accompanied with usual chest pain, which had been restored after nitroglycerin injection. Coronary stenosis and spastic segments were indicated by bold arrow and plain arrows, respectively.

jugular vein or a medial cubital vein may be safer to avoid ACh-induced bradycardia despite the duration of ACh infusion into the coronary artery[54]. The recommended maximal doses of ACh is 100 μg for the left coronary artery (LCA) and 50 μg for the RCA[28]; however, such maximal doses of ACh were determined based on the doses of ACh adopted for the provocation of coronary spasm in patients with variant angina[55], which involved increased coronary spasm activity[49,56]. Thus, the higher maximal doses of ACh in patients with stable VSA are reasonable. Recently, some adopt the maximal doses of ACh as 200 μg for the LCA and 80 μg for the RCA, showing the higher induction of coronary spasm without a significant increase in complications[40,57]. However, it remains unclear whether the higher doses of ACh than the above-mentioned doses are useful or harmful in the SPT (Table 1). On the contrary, the methodology of SPT using EM infusion has not been established sufficiently, compared with that of using ACh (Table 1). The total doses of EM, which are described as the doses of EM with 20-60 μg for 2-5 min for each coronary artery in the guideline[28], vary. In addition, the method of EM infusion, which was infused continuously or with a stepwise incremental dose, has still not been determined. In general, the insertion of transient pacing catheter is unnecessary, and this appears to be advantageous.

Moreover, the experienced method of SPT using ACh or EM at each institution may be performed safely; however, several tips regarding SPT using these provocative drugs have been known. Female VSA patients have more sensitivity to ACh provocation[8,34,35], and the SPT using ACh infusion may be recommended in female patients who undergo SPT. In addition, some patients have positive SPT using EM infusions despite the negative results in SPT using ACh infusions[30]. Furthermore, Sueda *et al*[58] have reported the sequential SPT, which was induced by infusions of first ACh, then EM, and finally ACh, showing the high provocative rate without a significant increase in complications[53]. Naturally, the ACh or EM working receptors are different[59], and the use of different provocative drugs for a short duration is reasonable. The sequential SPT may stimulate both receptors simultaneously, leading to a higher provocation of coronary spasm. To our knowledge, the sequential SPT may be the strongest until now. Sueda *et al*[53,58] showed no difference in complications including major ones or atrial fibrillation between the sequential and standard SPTs. On the contrary, further verification on the presence of false-positive cases will be needed using the sequential SPT. Furthermore, younger patients have a tendency of negative induction of coronary spasm in response to standard provocation[60] due to the not-severe coronary vascular dysfunction, and the sequential SPT may be useful in such patients. In addition, we have experienced some patients who showed no significant coronary stenosis on coronary angiography despite the fact that significant coronary stenosis was suspicious based on the results of examinations and patients' symptoms. In such cases, the diagnosis of VSA was possible; however, performing an SPT was difficult because an intracoronary nitroglycerin infusion had been administered or taking vasodilators before coronary angiography were continued. Under such circumstances, the sequential SPT may also be useful (Figure 2).

According to the length of coronary spasm induced by the SPT, there have been a subclassification with "focal spasm", which is defined as vasoconstriction within the confines of one isolated coronary segment, and "diffuse spasm", which is defined as the vasoconstriction of $\geqslant$ 2 adjacent coronary segments[29,50]. Sato *et al*[50] have shown poorer prognosis in focal spasm than in diffuse spasm. On the contrary, Sueda *et al*[61] have shown the importance of diffuse spasm as one of causes of medically refractory VSA. Thus, it may be an unsolved problem which "focal spasm" or "diffuse spasm" is worse in the clinical setting[50,61] (Table 1).

The positive criteria of SPT is defined as "transient, total, or sub-total occlusion (> 90% stenosis) of a coronary artery with signs/symptoms of myocardial

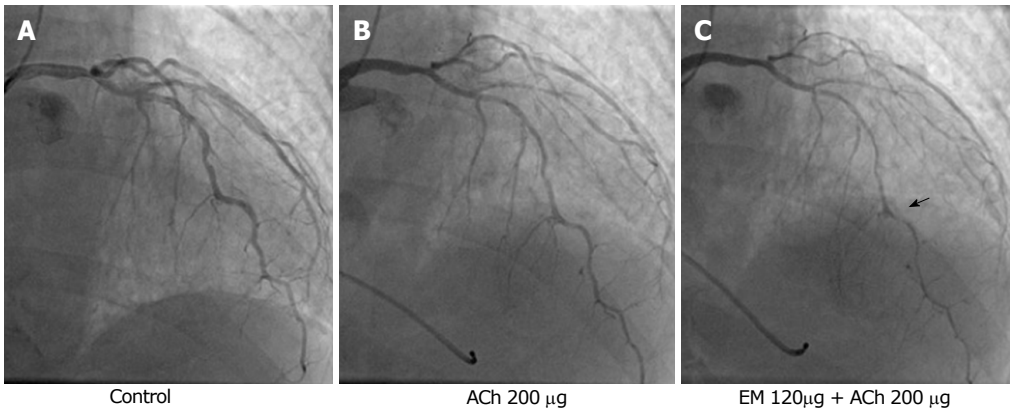

Figure 2 A case of coronary spasm, which was documented by sequential spasm provocation test, which was performed after the routine coronary angiography, vasodilator administration, and preprocedural infusion of nitroglycerin. A: The patient had chest symptoms at exercise early in the morning. Coronary computed tomography angiography showed stenosis of the left anterior descending coronary artery. However, the coronary angiography showed no significant coronary stenosis; B: Because the presence of vasospastic angina was suspicious, the spasm provocation test was performed despite the intracoronary infusion of nitroglycerin and calcium channel blocker intake. The standard doses of acetylcholine (ACh, up to maximal 200 μg) did not cause coronary spasm; C: Consequently, we performed the sequential spasm provocation test: 120 μg of ergonovine maleate was infused first followed by 200 μg of ACh, showing the presence of coronary spasm (right panel) and obtained the diagnosis of vasospastic angina. The spastic site was indicated by an arrow. Ach: Acetylcholine; EM: Ergonovine maleate.

ischemia (anginal pain and ischemic ST changes)"[28]. However, some patients have significant narrowing induced by provocative drugs despite the chest symptoms and ST-T changes on ECG. Sueda *et al*[37] showed that such patients were detected in 6.8% of studied patients who underwent an SPT. In addition, we have also experienced some patients with moderate vasoconstriction diffused with chest symptoms and/or ECG changes. Under such circumstances, the diagnosis of VSA may be difficult. At that time, other supportive index for the diagnosis of VSA may be needed. We have shown that the use of pressure wire may help in the diagnosis of VSA[62-64], showing the sudden drop of intracoronary pressure in response to ACh infusions in SPT-positive vessels and less frequency of major complications related to SPT. The validity of SPT using a pressure wire should be verified (Table 1); however, this method may be useful in the following situations: (1) when hemodynamic instability may be precipitated by coronary spasm, such as when patients have hypertrophic cardiomyopathy or left ventricular dysfunction; (2) when patients have chronic kidney disease; and (3) when cardiologists seek to clarify the disease status through a second SPT. SPT has been considered the final examination; however, the results of SPT is not absolute, and we have to make a diagnosis of VSA comprehensively, taking other conditions as well as the results of SPT into consideration. The second session of SPT may be needed in patients who had repeated chest symptoms despite the negative results of the first SPT[64].

TREATMENT OF CORONAY SPASM

Needless to say, smoking cessation is an important treatment of VSA[28]. As a pharmacological treatment for VSA, CCB as prevention and sublingual nitroglycerin during anginal attacks are the first-line therapies for VSA[28,29,31,65]. The monotherapy of β-blockers is class Ⅲ in VSA patients with organic stenosis[28]. However, VSA is accompanied with many cardiovascular diseases, in which β blockers are effective, such as left ventricular dysfunction[10-12], hypertrophic cardiomyopathy[66], and myocardial bridging[24,26,27,62,67]. Under such conditions, coronary vasodilators should be administered first, and then β blockers should be administered from small doses, observing carefully for the worsening of chest symptoms and hemodynamics.

In addition, the sudden cessation of coronary vasodilators while chest symptoms disappeared under long-term intake of coronary vasodilators may cause severe conditions due to coronary spasm[68]. Avoidance of sudden cessation of coronary vasodilators should be repeated to VSA patients, although the duration of continued coronary spasm activity has not been clarified (Table 1).

Some patients have angina attacks even while under CCB medications. In such conditions, several countermeasures should be followed. First, we must consider the type of CCB, because CCBs may differ in their ability to prevent angina attacks[31,65]. Second, the dosing regimen should be considered, such as whether a submaximal or maximal dose or medication once or twice a day would be appropriate. There are patients on a once-a-day CCB regimen who have had angina attacks just before the dosage time. Third, dosage-timing should be considered. In general, angina attacks often occur between midnight and early morning[5-7,28]. Thus, taking CCB at bedtime is usually recommended. However, for some VSA patients, taking CCB at the time of rising may be effective. Fourth, we must check whether the vasodilators prescribed are branded vasodilators. In VSA patients with high coronary spasm activities, switching from branded vasodilators to generic ones may worsen their chest symptoms[69]. Finally, another vasodilator must be added such as long-acting nitrates, nicorandil, and other type of CCBs (dihydropyridine CCB *vs* non-dihydropyridine CCB).

The combination of more than one and two kinds of coronary vasodilators varies and dependent mainly on each primary doctors' experience. However, which combination of coronary vasodilators was more useful in preventing coronary spasm is still unclear[70] (Table 1).

Recently, in a randomized, multicenter, double-blind, placebo-controlled study, Shin *et al*[71] have shown that an addition of cilostazol, which was a selective inhibitor of phosphodiesterase 3, to a CCB decreased the frequency and severity of chest symptoms in VSA patients. Moreover, they showed that an additional of cilostazol may be promising, although the finding that the CCB adopted in the present study was amlodipine, which was not the standard CCB for the prevention of coronary spasm in VSA patients, was a slightly controversial. The usefulness of other drugs such as statins[72,73] and a low-dose aspirin[74,75] on clinical outcomes has been accumulated, and these drugs may be considered to improve the clinical outcomes in VSA patients (Table 1).

UNCERTAIN OR UNSOLVED PROBLEMS REGARDING CORONARY SPASM

First, one of the unsolved problems related to coronary spasm is the presence of intractable VSA, which was defined as angina that cannot be controlled even with the administration of two types of coronary vasodilators. A study revealed that 13.7% of VSA patients had intractable VSA with a younger age at the time of onset and included higher proportions of tobacco smokers and normotensive patients[28]. Our previous report has shown that the presence of SPT-related angiographic findings, such as provocation induced by a low-dose ACh, total occlusion due to coronary spasm, and multivessel coronary spasm, were predictors for the presence of intractable VSA[51], showing the importance of performing SPT. When we have controlled the condition of taking several kinds of coronary vasodilators, as shown above, there have been many patients who were refractory to the administrations of several kinds of coronary vasodilators. Among the VSA patients, there have been some VSA patients with microvascular dysfunction[76,77]. Standard coronary vasodilators are less effective in patients with microvascular dysfunction or microvascular angina[33]. Therefore, the comorbid of VSA and microvascular dysfunction may contribute to the presence of intractable VSA. Thus, additional novel drugs may be anticipated. Cardiac rehabilitation has been reportedly effective in preventing coronary spasm in VSA patients[78], and non-pharmacological treatment may be also anticipated.

Second, the need for ICD in VSA patients with cardiac arrest has been one of the unsolved problems of coronary spasm[28,32,56,79,80]. Recently, Sueda *et al*[32] have summarized the results that appropriate ICD shocks were observed in 24.1% of VSA patients with aborted ICD. Rodríguez-Mañero *et al*[80] have shown that ICD was effective when insufficient medications were administered in VSA patients. In the clinical setting, whether sufficient medications without ICD can prevent such malignant arrhythmia due to coronary spasm is still undetermined. The physicians-in-chief of the heart team should carefully determine the ICD by taking patient background such as taking coronary vasodilators sufficiently and the results of SPT under sufficient medications[81] into consideration (Table 1).

CONCLUSION

Given the accumulation of studies on coronary spasm for more than half a century, coronary spasm is the key player and main cause in the pathophysiology of heart diseases. At present, its mechanisms, diagnosis, and treatments have been understood. Nonetheless, some unsolved problems on coronary spasm are still present, and we have to make efforts in obtaining clues to these unsolved problems.

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REVIEW

Clinical applications of feature-tracking cardiac magnetic resonance imaging

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Abstract

Cardiovascular diseases represent the leading cause of mortality and morbidity in the western world. Assessment of cardiac function is pivotal for early diagnosis of primitive myocardial disorders, identification of cardiac involvement in systemic diseases, detection of drug-related cardiac toxicity as well as risk stratification and monitor of treatment effects in patients with heart failure of various etiology. Determination of ejection fraction with different imaging modalities currently represents the gold standard for evaluation of cardiac function. However, in the last few years, cardiovascular magnetic resonance feature tracking techniques has emerged as a more accurate tool for quantitative evaluation of cardiovascular function with several parameters including strain, strain-rate, torsion and mechanical dispersion. This imaging modality allows precise quantification of ventricular and atrial mechanics by directly evaluating myocardial fiber deformation. The purpose of this article is to review the basic principles, current clinical applications and future perspectives of cardiovascular magnetic resonance myocardial feature tracking, highlighting its prognostic implications.

Key words: Left ventricular ejection fraction; Cardiac magnetic resonance; Cardiovascular disease; Strain; Feature-tracking

Core tip: Cardiac magnetic resonance feature tracking analysis is progressively establishing its role as an

accurate tool to for quantitative evaluation of cardiovascular function by directly evaluating myocardial fiber deformation. Feature-tracking derived strain parameters are able to identify subtle myocardial abnormalities before overt clinical manifestation thus allowing early diagnosis of primitive cardiomyopathies, identification of cardiac involvement in systemic diseases, detection of drug-related cardiac toxicity as well as risk stratification and monitor of treatment effects in patients with heart failure of various etiology. The present article summarizes the basic principles, current applications and future perspectives of cardiovascular magnetic resonance myocardial feature tracking.

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INTRODUCTION

The evaluation of cardiac function has a pivotal role in diagnosis, risk stratification and assessment of treatment response in several cardiac disorders. Traditionally, left ventricular ejection fraction (LVEF) defined as the ratio between systolic output and end diastolic volume, assessed by various techniques including ventricular angiography, 2D- and 3D- echocardiography, cardiac single proton emission tomography, computed tomography and cardiac magnetic resonance (CMR), has represented the gold standard for evaluating cardiac function. Current international guidelines recommend the use of LVEF to assess the risk of sudden cardiac death (SCD) in patients with ischemic and non-ischemic cardiomyopathies, being patients with LVEF $\leqslant$ 35% at particular high risk and therefore referred for primary prevention implantable cardioverter defibrillator (ICD)[1]. Assessment of LVEF is also routinely recommended for familiar screening in patients affected by cardiomyopathies as well as to early detect cardiac involvement in systemic immune-mediated diseases or cardiac toxicity in patients undergoing cancer treatments[2-4]. However, in the last decade, new imaging modalities such as echo and CMR myocardial strain have progressively emerged as superior tools to evaluate global and regional myocardial mechanics, pointing out the limitations of LVEF especially in evaluating regional myocardial function and detecting early stage subclinical cardiac disorders[5]. In the present review we will focus on CMR feature tracking (CMR-FT) imaging of myocardial strain summarizing its basic principles, current clinical applications and future perspectives.

GENERAL PRINCIPLES

Myocardial strain is a deformation index defined as the percentage change in dimension from a resting state (end-diastole) to the one achieved after contraction (end-systole)[6]. Considering a myocardial fiber, and being L0 its initial length in end-diastole and L1 its final length in end-systole, myocardial strain (S) can be defined as follow:

S = (L1 - L0)/L0 (Figure 1)

Due to the complex 3D architecture of the left ventricular (LV) musculature, systolic deformation takes place along several different directions. The evaluation of strain along each of these axes leads to the definition of different types of strain: (1) longitudinal strain (LS) represents the longitudinal shortening of the cardiac muscle, from the base to the apex, it is mostly determined by the longitudinally oriented muscle fibers in the subendocardial layer and is conventionally represented by a negative value due to systolic shortening; (2) circumferential strain (CS) is an expression of cardiomyocytes shortening along the LV circular perimeter, it is calculated in a short-axis view, it is mostly influenced by circumferentially oriented muscle fibers in the mid-wall and as well as LS it has a negative value due to systolic shortening; and (3) radial strain (RS) represents myocardial deformation toward the center of the ventricular cavity, and it is a measure of the LV thickening during systole and therefore is conventionally represented by a positive value.

Several other mechanical deformation parameters can be derived from strain analysis, of note: (1) Strain rate representing the "velocity" or rate at which the deformation occurs; and (2) LV torsion defined by the angle generated by the clockwise rotation of the basal segments and the counterclockwise rotation of the apex relatively to a stationary reference point conventionally located at a mid-ventricular level.

Myocardial CMR strain was initially investigated using tagging techniques in which magnetic labels (tags) are superimposed to the LV during cine imaging acquisition by radiofrequency spatial modulation of magnetization able to saturate parallel planes throughout the image, allowing the analysis of deformation of those lines throughout the cardiac cycle by post-processing semi-automated methods[7,8]. Soon after those initial experiences, new methods to evaluate myocardial strain based upon post-processing tracking of myocardial "features" overcame the need for prospective time-consuming image acquisition protocols. Cardiac CMR-FT is able to detect and follow over time myocardial boundaries leading to a more automatized quantification of strain parameters[9]. From a technical point of view, the features tracked by CMR-FT are anatomic elements typically identified along the cavity-myocardial interface due to the high contrast resolution between blood pool and myocardium. Every feature is tracked across the cardiac cycle by specific algorithms searching the most similar image pattern on the following frame within a small window centered around the feature[10]. The endocardial and epicardial borders are usually manually traced in the end-diastolic phase, then the CMR-FT software automatically tracks the border across the

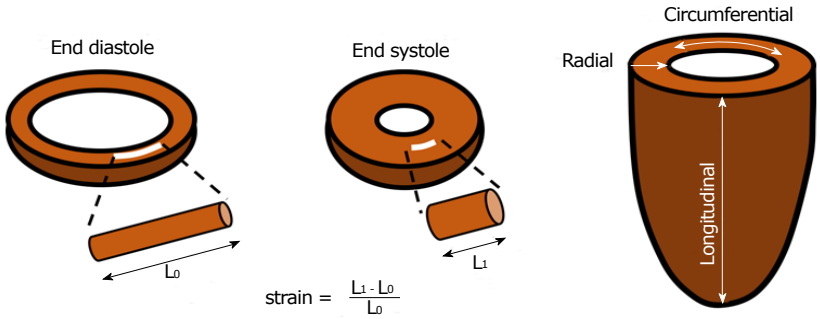


Figure 1 Schematic representation illustrating the physics principle beyond strain as well as the 3 main axes along which myocardial strain is calculated.

whole cardiac cycle. Global longitudinal strain (GLS) is derived by 2 or 3 long-axis steady state free precession (SSFP) cine images while global circumferential strain (GCS) and global radial strain (GRS) are derived from the short axis cine image stack. Several CMR-FT softwares are commercially available and can be directly applied to all CMR routine scans, as they work on standard SSFP cine images[11].

FEATURE TRACKING NORMAL VALUES

Studies investigating CMR-FT strain values in healthy subjects have repeatedly demonstrated that global measurements are more reproducible compared to regional ones that are limited by partial volume effect with features fading/leaving the image plane between end diastole and end systole[12]. In particular, GCS seems to be less affected by inter-observer and inter-vendor variability compared to GRS and GLS in which the complex anatomy of the atrio-ventricular annular region may lead to poor tracking[11]. Strain values are affected by both gender and age but in general terms, values of circumferential and LS < -17% to -20% as well as values of RS > 25%-30% are considered within normal range[12-15].

CLINICAL APPLICATIONS

Ischemic heart disease

Both global and regional strain parameters as well as dyssynchrony indices have been widely investigated in patients with ischemic heart disease. The main areas of interest include the correlation between regional strain parameters and infarct characteristics, the impact of strain parameters on long-term LV remodeling and the ability of strain to predict long-term clinical outcomes and to identify inducible ischemia[16].

All strain parameters are impaired in infarcted territories with strain values inversely related to the infarct size and infarct transmurality[17,18]. Compared to wall motion abnormalities, segmental strain values allows a more accurate discrimination between areas of subendocardial from transmural infarction and non-infarcted remote zones with only certain limitations in the early post-infarct phase due to the coexistence of edema, inflammatory cells, hemorrhage and viable and necrotic myocardial fibers[17,19-21]. Among all strain parameters, CS has shown to be the more accurate in assessing infarct extension and has also demonstrated its superiority to conventional LVEF determination in identifying subtle impairments of LV contractile function[19,22,23].

Data concerning the capability of strain analysis to predict adverse LV remodeling after acute myocardial infarction are debating[24-26]. In a study including 74 patients who underwent CMR within 4 d after successfully reperfused ST-elevation myocardial infarction (STEMI), a cut-off value of -19.3% for GCS appeared as accurate as late gadolinium enhancement (LGE) extension to identify patients with recovered LVEF ($\geqslant$ 50%) at 6-mo follow-up while no significant correlation was determined using GLS[24]. In another study including 164 STEMI who underwent CMR a median of 3 d after the acute event, CS was not inferior to the area of LGE in predicting segmental functional improvement/normalization after a median of 9-mo[25]. Conversely, Shetye *et al*[26] have recently failed to demonstrate a correlation between baseline strain parameters and the development of adverse LV remodeling after 4-mo follow-up among 65 patients with STEMI who underwent CMR within 3 d post-reperfusion, even though a good correlation was found between strain parameters, baseline LVEF and infarct size.

The correlation between scar extent determined by LGE imaging and long-term risk of major adverse cardiac events (MACE) after myocardial infarction is well known[27]. However, it has been recently pointed out how various CMR-FT derived parameters maybe able to accurately predict long-term clinical outcomes (Table 1). In a large study by Gavara *et al*[28], the prognostic value of CMR-FT was investigated among 323 patients who underwent CMR one week after a STEMI. During a median follow-up of 36-mo, all strain parameters were correlated to the incidence of a composite endpoint including cardiac death, readmission for heart failure and reinfarction. However, after adjustment for baseline and CMR variables, GLS (HR 1.21; 95%CI: 1.11-1.32; P < 0.001) was the only independent predictor of MACE. In

Table 1 Principal studies analyzing the prognostic role of cardiac magnetic resonance-feature tracking in patients with ischemic and non-ischemic cardiomyopathy

Reference	No. of patients	Herat disease	Parameters analyzed	Outcome	Occurrence of outcome, %	Independent predictors of the outcome event (HR)	Follow-up duration
Gavara *et al*[28], 2017	323	IHD (recent STEMI)	GLS GCS GRS n. segments with altered LS n. segments with altered CS n. segments with altered RS LVEF LGE MVO	Cardiac death, readmission for heart failure and reinfarction	17	GLS (1.21)	36 mo (median)
Nucifora *et al*[29], 2018	180	IHD (recent STEMI)	GCS LVEF LGE MVO	Cardiovascular death, aborted SCD and hospitalization for heart failure	22	GCS (1.16)	95 mo (median)
Muser *et al*[30], 2017	130	IHD (recent STEMI)	Mechanical dispersion LVEF LGE MVO	Cardiovascular death, aborted SCD and hospitalization for heart failure	20	Mechanical dispersion (1.39)	95 mo (median)
Buss *et al*[35], 2015	210	IDCM	GLS GCS GRS Mean LS Mean CS Mean RS LVEF LGE	Composite of cardiac death, heart transplant and aborted SCD	12	GLS (1.27) Mean LS (5.44)	5.3 yr (median)
Riffel *et al*[36], 2016	146	IDCM	Long axis strain LVEF LVEDV LGE	Composite of cardiac death, heart transplant and aborted SCD	16	Long axis strain (1.28) LVEDV/BSA (1.01) LGE (2.51)	4.3 ± 2.0 yr
Romano *et al*[37], 2017	470	IHD + IDCM	GLS LVEF LGE	All-cause death	20	GLS (2.35) LVEF (0.95)	4 yr (median)
Romano *et al*[38], 2018	1012	IHD + NICM	GLS LVEF LGE	All-cause death	13	GLS (1.89)	4.4 yr (median)
Pi *et al*[39], 2018	172	IDCM	GLS GCS GRS LVEF LGE	Composite of cardiac death and heart transplant	25	LGE (4.73)	47 mo (median)

IHD: Ischemic heart disease; STEMI: ST-elevation myocardial infarction; GLS: Global longitudinal strain; GCS: Global circumferential strain; GRS: Global radial strain; LVEF: Left ventricular ejection fraction; LGE: Late gadolinium enhancement; MVO: Microvascular obstruction; SCD: Sudden cardiac death; IDCM: Idiopathic dilated cardiomyopathy; LVEDV: Left ventricular end diastolic volume; BSA: Body surface area.

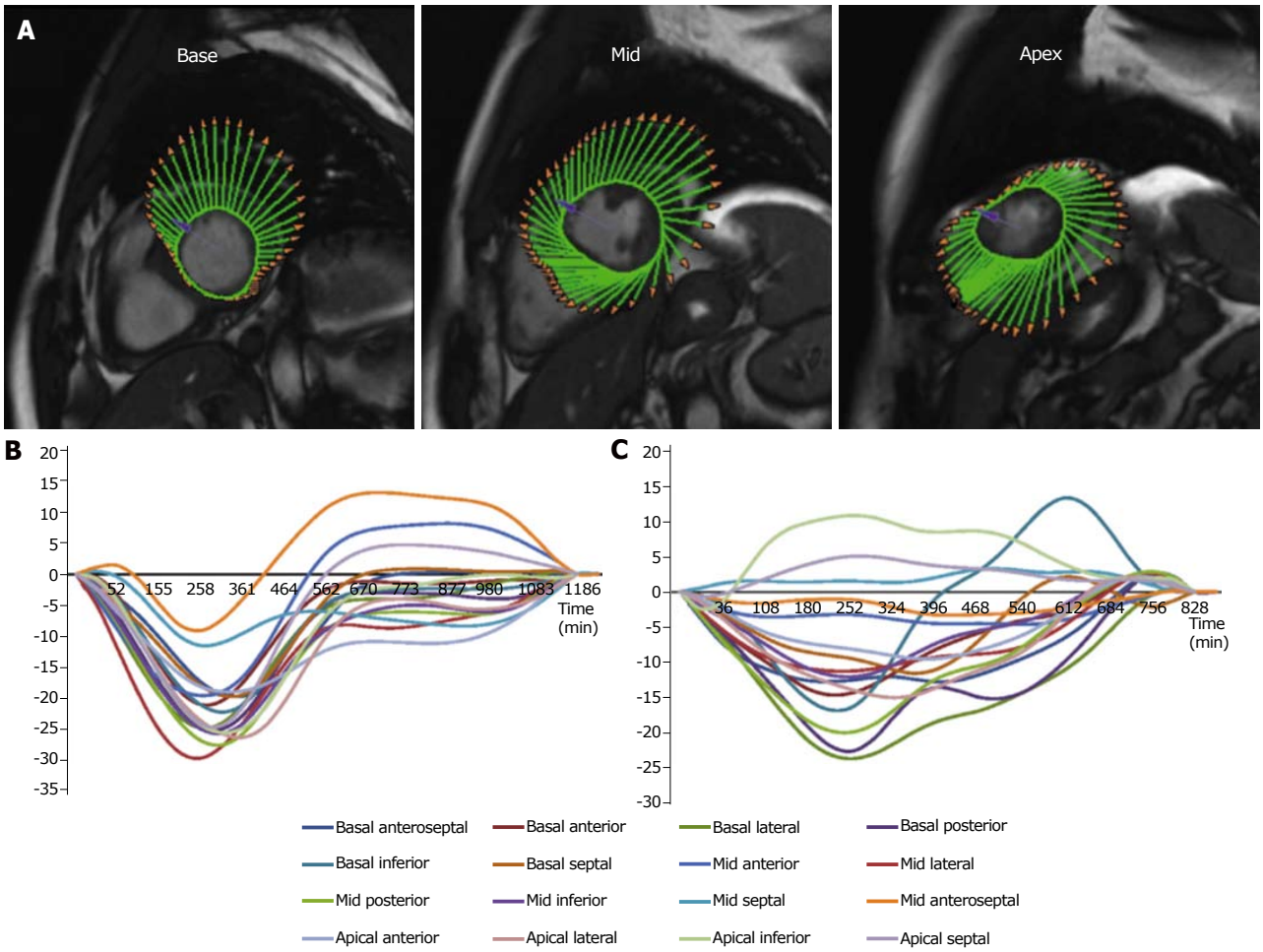


Figure 2 Example of left ventricular endocardial feature tracking. A: Example of tracking of the endocardial border of the left ventricle (LV) on basal, mid, and apical short-axis, steady-state free-precession images using an dedicated feature-tracking software. The software automatically calculates the circumferential strain of each myocardial segment; B: Example of a patient with homogenous LV contraction; C: Example of a patient with extreme regional heterogeneity of myocardial contraction. Reprinted with permission from Muser *et al*[30].

particular, MACE rate was higher in patients with a GLS $\geqslant$ -11% (22% *vs* 9%; P = 0.001). In the same study, those results were also validated in an external cohort of 190 STEMI patients confirming both the higher incidence of MACE in patients with a GLS $\geqslant$ -11% (34% *vs* 9%; $P < 0.001$) and the independent predictive value of GLS (HR 1.18; 95%CI: 1.04-1.33; P = 0.008)[28]. These findings were subsequently confirmed and extended by our group. We have reported GCS to be significantly and independently associated to the occurrence of a composite endpoint including cardiovascular death, aborted SCD and hospitalization for heart failure (HR 1.16; 95%CI: 1.07-1.25; $P < 0.001$) during a median follow-up of 95 mo in a population of 180 patients admitted for a first STEMI and who underwent CMR imaging a median of 8 d following the index event[29]. We have also reported how early assessment (median of 7 d after STEMI) of LV mechanical dispersion defined as the standard deviation of the time-to-peak CS of the LV segments, is significantly and independently related to the occurrence of MACE (HR 1.39, 95%CI: 1.20-1.62, $P < 0.001$) (Figure 2)[30].

Due to its high sensitivity in identifying contractile function compared to visual assessment of wall motion abnormalities or determination of changes in LVEF, CMR-FT has recently been proposed to evaluate inducible ischemia and establishing contractile reserve in patients with chronic ischemic heart disease[31,32]. Schneeweis *et al*[33] have demonstrated how in 25 patients with suspected or known coronary artery disease, undergoing dobutamine stress CMR, CS during high doses of dobutamine, was able to identify segments supplied by a vessel of > 70% narrowing with a sensitivity of 75% and specificity of 67% using a strain threshold of -33.2%[33]. In the same study, the authors also showed how impairment of CS already occurred at intermediate-doses of dobutamine allowing an earlier detection of inducible ischemia compared to visual assessment[33]. In another study including 15 patients undergoing viability assessment by low-dose dobutamine stress, there was no response to dobutamine in dysfunctional segments with scar transmurality > 75% while dysfunctional segments without scar showed improvement either in subendocardial and subepicardial GCS as well as in GRS. In particular, GCS improved in all segments up to a transmurality of 75% while GRS improved in

segments with < 50% transmurality and remained unchanged above 50% transmurality[32].

Idiopathic dilated cardiomyopathy

The presence and extension of scar represents a negative prognostic factor in patients with idiopathic dilated cardiomyopathy (IDCM), as well[27]. Unfortunately, no clear evidence of LGE can be found in up to 60% of these patients making extremely important to identify new potential predictors to further stratify individual risk beyond simple LVEF[34]. A study including 210 patients with IDCM found GLS to be an independent predictor of MACE including cardiac death, heart transplantation and aborted SCD (HR 1.27, 95%CI: 1.06-1.52, $P < 0.02$) during a median follow-up of 5.3-years regardless to the baseline LVEF and the presence of LGE, while no significant association was found with GCS and GRS[35]. Another study including 146 patients affected by IDCM, investigated the value of "long axis strain" defined as the distance between the epicardial border of the LV apex and the midpoint of a line connecting the origins of the mitral valve leaflets in end-systole and end-diastole in predicting a combination of cardiac death, heart transplantation and aborted SCD and found that the ratio between LV end-diastolic volume/body surface area (HR 1.01, 95%CI: 1.00-1.02, $P = 0.04$), the presence of LGE (HR 2.51, 95%CI: 1.02–6.19, $P = 0.04$) as well as long axis strain (HR 1.28, 95%CI: 1.07-1.52, $P < 0.01$) were all independent predictors of MACE[36]. The incremental value of CMR-FT strain was subsequently confirmed in a series of 470 patients of whom 140 with IDCM, in which was described an independent correlation of GLS (HR 2.35, 95%CI: 1.81-3.06, $P < 0.001$) and LVEF (HR 0.95, 95%CI: 0.91-0.99, $P = 0.038$) with the risk of death during a median follow-up of 4-years regardless to the presence and extension of LGE[37]. In a large multicenter study including 1012 patients with both ischemic heart disease and non-ischemic cardiomyopathy, GLS was an independent predictor of all-cause mortality over LVEF and presence of LGE in the all cohort (HR 1.89, 95%CI: 1.55-2.07, $P < 0.001$) as well as in the ischemic (HR 1.95, 95%CI: 1.48-2.58, $P < 0.001$) and non-ischemic (HR 2.14, 95%CI: 1.56-2.91, $P < 0.001$) subgroups[38]. The above results have not been confirmed by a recent study including 172 patients with IDCM and moderately to severely reduced LVEF (<40%). In this study, neither GLS, GCS or GRS were correlated with the risk of death or heart transplant during a median follow-up of 47-mo, while presence of LGE and serum sodium were the only independent predictors of the outcome event (Table 1)[39].

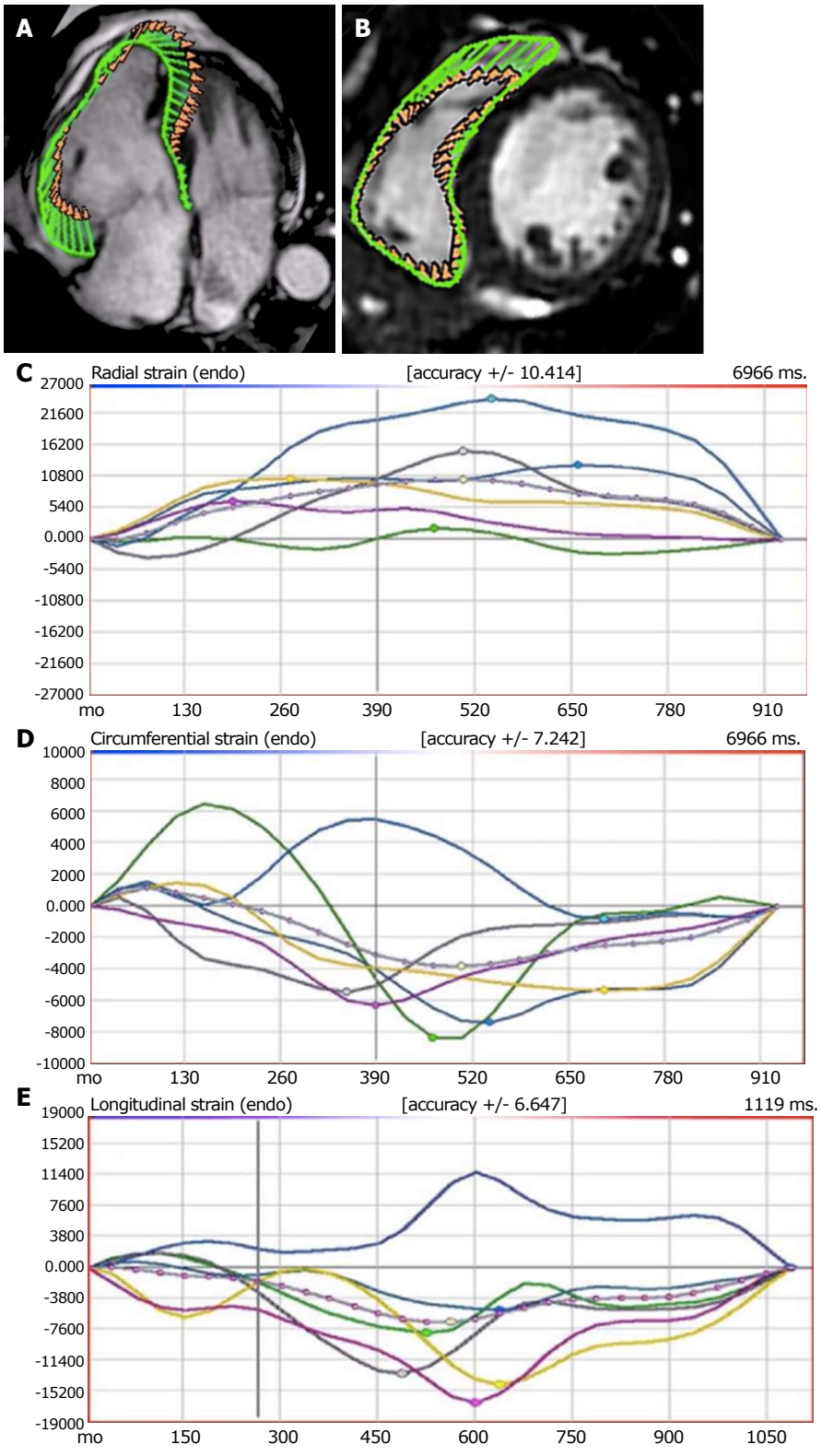
Other forms of non-ischemic cardiomyopathy

Myocardial strain has proven to be a valuable tool in early identification, staging and risk stratification of several forms of non-ischemic cardiomyopathy. In patients with hypertrophic cardiomyopathy (HCM), a direct correlation between strain parameters and the presence of LGE has been repeatedly proven, being the presence of replacement fibrosis associated to a reduction in CS[40,41]. However, intramural strain has demonstrated to be reduced in more hypertrophied segments compared to the non-hypertrophied ones regardless to the presence of LGE, proving myocardial scarring not to be the only determinant of regional contractile dysfunction[42].

Global and regional right ventricular (RV) strain parameters have shown to be impaired in patients with overt arrhythmogenic right ventricular cardiomyopathy (ARVC) regardless to RV dimensions and function[43,44]. In a study comparing RV strain parameters in 32 patients matching the task force criteria for ARVC but with no or only minor CMR criteria, to 32 patients with idiopathic RV outflow tract premature ventricular contractions and 32 healthy volunteers, we found that RV GLS, GCS and GRS were all significantly reduced in the ARVC group. In particular, a RV GLS > -23.2% was able to identify 88% of ARVC patients without definite CMR criteria showing the incremental value of CMR-FT over conventional CMR imaging in early detection of the disease (Figure 3)[45].

In the same direction, strain parameters have shown to be impaired in patients with acute or previous myocarditis and preserved LVEF regardless to the presence of LGE confirming the higher sensitivity of CMR-FT in identifying contractile impairment at a subclinical stage[46,47]. In patients affected by LV non-compaction, we have found that subclinical impairment of myocardial deformation, occurs early in the natural history of the disease, being noticeable since the pediatric age with e reduction in all global strain parameters while overt LVEF reduction tends to manifest only later in adulthood[48]. In this regard, CMR-FT may be used to early detect cardiac involvement in systemic diseases or during administration of drugs with potential cardiotoxic effects. Monitoring of cardiotoxicity during cancer therapies is currently recommended by echocardiographic evaluation of LVEF and a decline in the LVEF is needed in order to decide to suspend/modify therapy[3]. Nakano *et al*[49] have demonstrated how both GLS and GCS were significantly reduced after 6 mo of therapy with trastuzumab in 9 women treated for breast cancer. Changes in global strain parameters were correlated with changes in LVEF, however their predictive value on the development of heart failure needs to be proven[49].

Some preliminary data have shown that parameters derived from CMR-FT such as LV rotational indices are disease specific and therefore maybe be used to differentiate between cardiomyopathies. We compared LV twist and untwist rates between 20 patients with cardiac amyloidosis (CA) to 20 patients with HCM and 20 healthy controls showing how both peak LV twist and peak LV untwist rates were significantly impaired in patients with CA while peak LV twist rate was significantly increased in patients with HCM compared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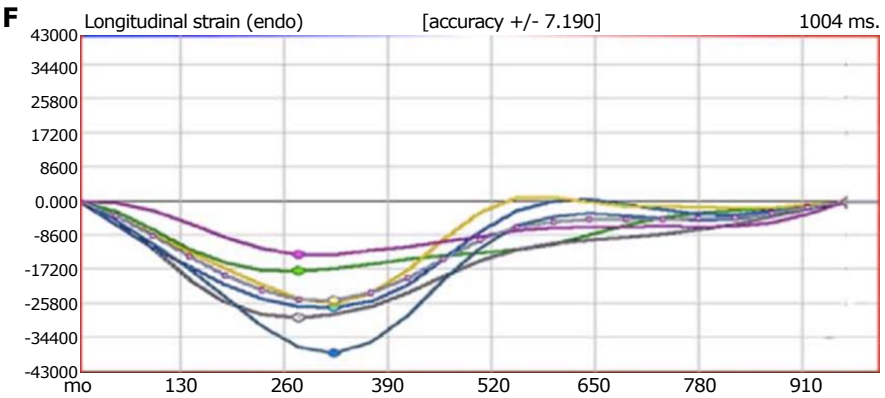

Figure 3 Example of endocardial feature tracking of the right ventricle. A: Tracking of the endocardial border of the right ventricle (RV) on a 4-chamber steady-state free precession image using a dedicated feature-tracking software; B: Example of tracking on the mid-section of a short-axis view; C: Radial; D: Circumferential; E: Longitudinal strain patterns of a patient with arrhythmogenic RV cardiomyopathy; F: Example of the RV longitudinal strain pattern of a healthy subject. Reprinted with permission from Prati *et al*[45].

to controls. Patients with HCM also presented a preserved peak LV untwist rate. The time to peak LV untwist rate was significantly prolonged both in CA and HCM compared to healthy subjects[50].

Congenital heart diseases

The follow-up of grown-up patients with congenital heart diseases (CHD) is usually based upon echocardiography, however, the poor acoustic window due to previous multiple surgical procedures or coexistence of other anatomical deformities as well the complex anatomy of repaired congenital defects represents some major limitations. For this reason, CMR imaging is increasingly becoming the imaging modality of choice for evaluation of CHD. In these terms CMR-FT derived parameters may have important clinical implications in evaluating surgical results and in early detection of complications. In patients with repaired tetralogy of Fallot (TOF), for example, a significant impairment of all global strain parameters has been described in those patients who experienced death or sustained ventricular tachycardia compared to those of similar age who did not experienced outcome events[51]. An improvement in LV GCS and GLS within 6 mo after transcatheter implantation of a pulmonic valve has also been documented in patients with repaired TOF and clinically relevant residual pulmonary regurgitation/stenosis after initial corrective surgery[52]. Moreover, RV GLS has been related to clinically relevant variables such as exercise capacity and oxygen consumption in 28 patients with repaired TOF[53]. Those findings have been further confirmed in a recent large prospective series of 372 repaired TOF patients, in which LV GCS and RV GLS independently predicted death, aborted SCD or documented ventricular tachycardia during a median follow-up of 7.4 years[54]. Similar findings have been found in 15 patients who underwent Fontan palliative intervention; GCS and GLS of the single ventricle both correlated with New York Heart Association class and peak oxygen uptake on cardiopulmonary exercise test[55]. Among patients with successful repaired coarctation of the aorta and preserved LVEF, impairment of GLS but not GCS or GRS has been associate to coexistence of LV hypertrophy[56].

Cardiac resynchronization therapy

A significant proportion of cardiac resynchronization therapy (CRT) patients may fail to reach an adequate response in terms of LVEF and HF status improvement and those patients are commonly addressed as "non-responders". Increasing efforts have been made in the last years to better select optimal candidates to CRT but also to identify the best site for LV lead implantation in order to maximize the chances of response[57,58]. For this reason, CMR has emerged as a valuable technique been able to noninvasively evaluate LV activation patterns and dyssynchrony[30,45,59]. Taylor *et al*[60] have demonstrated that CRT implantation guided by determination of segments with latest mechanical activation (defined by time to peak systolic CS) and absence of LGE is able to improve LV reverse remodeling as well as long term survival and reduce the risk of hospitalizations for heart failure. From a practical point of view, CMR derived information on scar, dyssynchrony and coronary venous anatomy maybe integrated with fluoroscopy or 3D-electroanatomical mapping systems to real-time guide LV lead placement during interventional procedures[61,62].

Atrial physiology

The application of CMR-FT techniques to the left atrium (LA) have shown to accurately characterize LA physiology compared to simple global measures such as atrial volume, area and atrial ejection fraction[63]. It has been advocated that changes in LA function precede the development of heart failure in several cardiac disorders. The development of LA dysfunction due to increased LV stiffness associated to the presence of replacement or diffuse ventricular fibrosis has been described as a potential marker of early diastolic disfunction[64].

Recent findings highlighted how there may be disease specific patterns of LA dysfunction. Patients with HCM, for example, present an increased contractile function compared with healthy controls. On the other side, patients with diastolic dysfunction and preserved LVEF have reduced atrial contractility[65]. There is some evidence that quantitative measurement of LA function may also have prognostic implications as impairment in LA strain has shown to precede development of heart failure in the general population and to improve risk stratification for cerebrovascular events in patients with atrial fibrillation[66,67].

Special populations

Analysis of CMR-FT strain parameters has been applied to patients with isolated bicuspid aortic valve (BAV) (*i.e.*, without aortic stenosis, aortic regurgitation or aortic dilatation)[68]. Interestingly, patients with "clinically normal" BAV have significant impairment of LV systolic and diastolic myocardial mechanics; furthermore, the impairment of LV systolic mechanics observed in BAV patients is independently related to the congenital abnormality of aortic valve itself. The authors postulated that the observed intrinsic impairment of LV contractility may accelerate the ominous LV remodeling pathways occurring after the development of significant aortic valve dysfunction, possibly explaining the described premature occurrence of congestive heart failure in BAV patients compared with the general population[69].

CMR-FT strain analysis has been also applied to study the adult consequences of pre-term birth. Pre-term birth interferes with the normal in-utero development of the heart, potentially leading to abnormally remodeled left ventricles. In a large study, 102 subjects have been prospectively followed since pre-term birth (gestational age = 30.3 ± 2.5 wk) to the age of 20-39 years when they underwent a CMR study. Compared to 132 subjects born at term of similar age, preterm individuals had increased LV mass proportional to the degree of prematurity and short LVs with small internal diameters and a displaced apex. Interestingly, even if LVEF was similar to subjects born at term, both longitudinal systolic (peak strain, strain rate, and velocity) and diastolic (peak strain rate and velocity) function as well as rotational (apical and basal peak systolic rotation rate, net twist angle) parameters were significantly lower[70]. Similar findings have been described by the same group affecting the RV. Pre-term subjects had smaller RV with bigger RV mass with the severity of differences proportional to gestational age. Moreover, differences in RV function were greater than those reported for the LV as subjects born pre-term had significantly lower RV ejection fraction (RVEF) with 6% of them having clear RV systolic dysfunction. In agreement with the lower RVEF, RV GLS and peak systolic strain rate were also significantly lower compared to subjects born at term[71]. The clinical implications of these findings on the potential development of overt cardiomyopathies need further prospective evaluation.

CONCLUSION

In the last years a growing amount of evidence suggests that study of cardiac function by strain analysis can accurately detect cardiac disorders at a subclinical level, improve risk stratification of patients with various cardiac conditions and potentially monitor treatment effect. In this setting, the use of CMR-FT may represent an easy and fast tool due to its applicability to routinely acquired SSFP cine images by dedicated software without need for upfront use of specific protocols. Further technical improvements able to achieve a higher level of accuracy and reproducibility in the assessment of measures and more standardization between different vendors are still required to make CMR-FT ready to use in routine clinical practice.

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ORIGINAL ARTICLE

Clinical Trials Study

Safety and efficacy of frequency-domain optical coherence tomography in evaluating and treating intermediate coronary lesions

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Abstract

AIM

To establish whether frequency-domain optical coherence tomography (FD-OCT) is safe and effective in the evaluation and treatment of angiographically-intermediate coronary lesions (ICL)

METHODS

Sixty-four patients with 2-dimensional quantitative

coronary angiography (2D-QCA) demonstrating ICL were included. OCT imaging was performed. According to predetermined OCT criteria, patients were assigned to either of 2 groups: OCT-guided percutaneous coronary intervention (PCI) or OCT-guided optimal medical therapy (OMT). The primary efficacy endpoint was to demonstrate the superiority and higher accuracy of FD-OCT compared to 2D-QCA in evaluating stenosis severity in patients with ICL. The primary safety endpoint was the incidence of 30-d major adverse cardiac events (MACE). Secondary endpoints included MACE at 12 mo and other clinical events.

RESULTS

Analysis of the primary efficacy endpoint demonstrates that 2D-QCA overestimates the stenosis severity of ICL in both the OCT-guided PCI and OMT groups, proving FD-OCT to be superior to and more precise than 2D-QCA in treating this subset of lesions. The primary safety endpoint was fully met with the incidence of 30-d MACE being nil in both the OCT-guided PCI and OCT-guided OMT groups. Incidences of secondary endpoints were found to be low in both arms, the only exception being the relatively high incidence of recurrent episodes of angina which was, however, very similar in the 2 groups.

CONCLUSION

FD-OCT is safe and effective in the evaluation and treatment of ICL. Larger studies are needed to firmly establish the efficacy and safety of FD-OCT in treating ICL across all coronary artery disease population subgroups.

Key words: Percutaneous coronary intervention; 2-dimensional quantitative coronary angiography; Frequency-domain optical coherence tomography; Intermediate coronary lesions; Optical coherence tomography

Core tip: The management of intermediate coronary lesions (ICL), defined as a diameter stenosis of 40% to 70%, remains a therapeutic dilemma. The 2-dimensional representation of the arterial lesion by angiography is limited in guiding therapy. Frequency-domain optical coherence tomography (FD-OCT) is an ultra-high resolution imaging technique that enables a detailed evaluation of the coronary lumen. Despite its undebatable superiority over angiography and other intravascular imaging techniques, the benefit of FD-OCT over its procedural risks in clinical practice is uncertain. The current study is the first to date to investigate whether FD-OCT is safe and effective in the evaluation of ICL, in guiding treatment, and optimizing procedural outcomes.

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INTRODUCTION

An intermediate coronary lesion (ICL) on angiography is defined as a luminal narrowing with a diameter stenosis ⩾ 40% but ⩽ 70%. Cardiac catheterisation laboratory assessment of a coronary lesion with intermediate severity continues to be a challenge for cardiologists both from a diagnostic and therapeutic perspective. Selective coronary angiography (CAG) is accepted as the standard for determining the presence and extent of epicardial coronary artery disease (CAD), but has obvious limitations given that it provides only a two-dimensional projection of the three-dimensional geometry of the coronary artery lumen[1,2]. Although there is little controversy regarding the usefulness of CAG in separating patients with entirely normal coronary arteries from those with severe high-grade stenotic lesions, the potential of the coronary arteriogram in predicting the hemodynamic significance of lesions that appear angiographically moderate remains controversial[3]. For this subset of obstructions, a number of adjunctive, invasive techniques have been proposed to improve the diagnostic accuracy of the coronary angiogram. Fractional-flow-reserve (FFR) represents the gold standard to evaluate ICL. Three randomized trials (DEFER, FAME-Ⅰ and FAME-Ⅱ) established FFR as the gold standard for assessing the significance of non-left main coronary artery intermediate lesions[4]. Intracoronary FD-OCT, on the other hand, is a novel, advanced imaging technique that allows ultra-high resolution evaluation of the coronary artery lumen, 10-20 times higher than the resolution obtained by intravascular ultrasound (IVUS)[5]. The superior spatial resolution of OCT could thus very well translate into meaningful clinical benefits in patients with ICL. However, while the superiority of OCT in comparison to any other available intravascular imaging modality in terms of spatial resolution is unchallenged, there is uncertainty in its risk-benefit role in routine extensive clinical practice compared to IVUS or angiography alone[6,7]. In the setting of ICL, no interventional study has to date investigated whether FD-OCT, as an invasive intracoronary imaging technique, is safe and effective in the evaluation of ICL, in guiding their treatment, and in optimizing procedural outcomes. Furthermore, the efficacy and safety of OCT in evaluating and treating ICL in patients presenting with acute coronary syndromes (ACS) as opposed to stable angina (SA) alone is unknown. We therefore designed this study aiming to explore the safety and efficacy of FD-OCT in dealing with angiographically-borderline coronary artery lesions in the

cardiac catheterisation laboratory.

MATERIALS AND METHODS

Ethics and organization

This was a single center, prospective, interventional study to investigate the safety and efficacy of FD-OCT in the evaluation and treatment of patients with ICL. The study protocol was approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University (Ethics Approval ID: 2017-SR-328). The study conforms to the Declaration of Helsinki. Each patient gave written informed consent prior to the procedure.

Study population

From August 2016 to August 2017, diagnostic CAG was performed at the interventional cardiology center of the First Affiliated Hospital of Nanjing Medical University, Nanjing, China, on patients presenting with one of the following: SA, defined as chest discomfort and associated symptoms precipitated by some form of physical activity, with minimal or non-existent symptoms at rest or after administration of sublingual nitroglycerin, unstable angina (UA, defined as chest pain occurring at rest or minimal exertion and generally lasting more than 20 min, or severe and new-onset chest pain, or chest pain manifesting in a crescendo pattern, with no biochemical evidence of myocardial damage), non ST-elevation myocardial infarction [NSTEMI, biochemical evidence of myocardial damage with no ST-elevation on electrocardiography (ECG)], or ST-elevation myocardial infarction (STEMI, biochemical evidence of myocardial damage with ST-elevation on ECG). Most of these patients had initial non-invasive testing for CAD with either Exercise Stress Test or Coronary Computed Tomography Angiography. Patients of all ages in whom assessment by 2D-QCA demonstrated ICL (considered as lesions with an angiographic stenosis severity of $\geqslant$ 45% but < 75%), and who consented to undergo further assessment with OCT, were enrolled in the study to determine whether they would benefit from PCI or OMT. Sixty-four patients with angiographically-demonstrated ICL consented to proceed with imaging. Based on the OCT findings, the patients were assigned to one of 2 arms: OCT-Guided PCI or OCT-Guided OMT. Predetermined OCT criteria used to decide which patient to assign to which arm were as follows: patients with an ICL atherosclerotic plaque burden > 76%, or a minimum luminal area (MLA) < 2.6 mm^2, or in whom unstable plaque factors existed (endocardial discontinuity, or a fibrous cap thickness < 65 μm, or a large lipid core > 180 degrees, or evidence of macrophage aggregation) were assigned to the PCI arm. On the other hand, patients with a plaque burden $\leqslant$ 76%, and with a MLA $\geqslant$ 2.6 mm^2, and in whom OCT showed no features of plaque instability were assigned to the OMT group. The inclusion criteria for this study were only those participants in whom diagnostic CAG and 2D-QCA demonstrated ICL and who consented to undergo further evaluation with OCT imaging. Exclusion criteria were subjects presenting with cardiogenic shock, acute stroke, renal dysfunction, left main stem ICL, and acute or chronic total occlusion coronary lesions.

Study endpoints

The primary efficacy endpoint of the study was to demonstrate that FD-OCT is superior to and more accurate than 2D-QCA alone in evaluating the degree of stenosis in patients with ICL. The primary safety endpoint was defined as the incidence of 30-d MACE composed of cardiac death, peri-procedural myocardial infarction (MI), acute stent thrombosis, emergency coronary artery bypass graft, significant vessel dissection or perforation, cerebrovascular accident and major vascular complications in both the OCT-guided PCI and OCT-guided OMT groups. Secondary end points were the incidence of MACE at 12 mo, plus recurrent episodes of angina, repeat hospitalisation, major bleeding events, minor bleeding episodes (defined as minimal amount of bleeding, for example bruising, bleeding gums and oozing from injection sites, not requiring intervention or treatment), stroke and heart failure. All outcomes were defined in keeping with the Academic Research Consortium recommendations[8].

Quantitative coronary angiography imaging

2D-QCA measurements of the ICL were performed offline using an automated software. These were done on image sequences adequately filled with contrast and when the vessel was not foreshortened. Calibration was performed on the contrast filled segment of the guiding catheter.

OCT image acquisition and analysis

OCT imaging was performed using a FD-OCT system (C7-XR OCT Intravascular Imaging System, St. Jude Medical, St. Paul, MN, United States). The radial approach was used in most patients (87%) for CAG and OCT imaging. Weight-adjusted, unfractionated heparin or bivalirudin was administered for anticoagulation. After placement of the guiding catheter (6 Fr) into the coronary ostium, a standard percutaneous transluminal coronary angioplasty guide wire was advanced into the coronary artery and the lesion was crossed. The C7 Dragonfly™ OCT catheter was then advanced over the wire. Once the catheter was positioned distal to the lesion, it was pulled backed manually at a speed of 15 mm/s. All images were acquired using a non-occlusive technique with manual injection of iso-osmolar iodixanol (Visipaque™ by GE Healthcare) contrast to clear the vessel of blood. OCT image analysis scrutinized serial cross-sectional images of the vessel at 1 mm intervals using the Light Lab Imaging offline software.

Measurements

Coronary artery parameters measured by 2D-QCA

Table 1 Baseline characteristics of the optical coherence tomography study population

Variable	Overall (n = 64)	OCT-guided PCI (n = 38)	OCT-guided OMT (n = 26)	P-value
Age (yr)	63.17 ± 9.68	63.42 ± 9.88	62.81 ± 9.56	0.806
Male (%)	43 (67.2)	25 (65.8)	18 (69.2)	0.773
Diabetes mellitus (%)	10 (15.6)	7 (18.4)	3 (11.5)	0.693
Hypertension (%)	39 (60.9)	22 (57.9)	17 (65.4)	0.546
Discharge treatment				
Aspirin (%)	64 (100)	38 (100)	26 (100)	1
P2Y12 inhibitor (%)	59 (92.2)	38 (100)	25 (96.1)	0.406
Statin (%)	64 (100)	38 (100)	26 (100)	1
Beta-blocker (%)	29 (45.3)	19 (50)	10 (38.5)	0.362
ACE- I /ARB (%)	33 (51.6)	23 (60.5)	10 (38.5)	0.083
CCB (%)	24 (37.5)	13 (34.2)	11 (42.3)	0.511
Nitrates (%)	36 (56.2)	21 (55.3)	15 (57.7)	0.847
Admission diagnosis				0.068
Stable angina (%)	7 (10.9)	4 (10.5)	3 (11.5)	
Unstable angina (%)	53 (82.8)	34 (89.5)	19 (73.1)	
NSTEMI (%)	2 (3.1)	0 (0)	2 (7.7)	
STEMI (%)	2 (3.1)	0 (0)	2 (7.7)	
ICL vessel				0.671
LAD (%)	37 (57.8)	21 (55.3)	16 (61.5)	
LCX (%)	12 (18.8)	6 (15.8)	6 (23.1)	
RCA (%)	15 (23.4)	10 (26.3)	5 (19.2)	

Data are expressed as mean ± SD and n (%), or median and 25th and 75th percentiles, for non-normal distribution. OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention; OMT: Optimal medical therapy; ACE: Adverse cardiac events; ARB: Angiotensin receptor blockers; NSTEMI: Non ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; ICL: Intermediate coronary lesions; LAD: Left anterior descending; LCX: Left circumflex; RCA: Right coronary artery.

and FD-OCT in the OCT-guided PCI and OCT-guided OMT groups were the following: Reference area (RA), Minimum Luminal Area (MLA) and % Area Stenosis (AS), from which appropriate statistical analysis was performed.

Statistical analysis

No statistical sample-size calculation was undertaken in this study as this was a pioneering experience of our center in terms of use of intracoronary OCT imaging to assess ICL leading to several patients not consenting to the OCT procedure, hence automatically reducing our sample size, and given the time restriction of the current study to 1 year duration which further limits the number of subjects that could be included in the study, statistical calculation of sample size to achieve a reasonable statistical power would have been futile. Furthermore, no recently published findings from studies with a similar clinical design could be found to enable statistical determination of what sample size of subjects per group is needed to answer the research question. An independent statistician performed the statistical analysis. Continuous variables were expressed as mean ± SD and categorical variables as percentage and counts. Calculations and statistical analyses were performed by using the SPSS 19.0 software (SPSS, Statistics, IBM, United States). The Chi-square or Fisher exact test or χ^2 correction test for continuity performed on categorical variables. Continuous variables were tested using the Mann-Whitney U test, student's t test and Wilcoxon rank-sum test. A P-value of < 0.05 was considered as statistically significant.

12-mo follow-up

All patients were individually followed up for a total period of 12 mo to record the incidence of MACE, defined as the occurrence of any one or more of the following: death, recurrent MI, stent thrombosis or repeat revascularization of the target lesion. Other clinical events recorded during this 12-mo period were the incidences of recurrent episodes of angina, repeat hospitalisation, stroke, heart failure and bleeding events if any. All clinical events were recorded using a clinical report form and evaluated independently by a blinded clinical events committee.

RESULTS

Baseline characteristics

A total of 64 patients were included in the study to proceed with OCT after diagnostic angiography and 2D-QCA demonstrated an angiographically-intermediate coronary lesion. Following OCT imaging and in accordance with the predetermined OCT criteria mentioned above, 38 patients (59.4%) were assigned to the PCI arm, and the other 26 patients (40.6%) to the OMT arm (Table 1). Our study population comprised 43 males (67.2%) and 21 females (32.8%), with an overall mean age of 63.17 ± 9.68 years. 39 patients (60.9%) suffered from hypertension, 10 patients (15.6%) from diabetes, and none reported any bleeding disorder. 53 patients (82.8%) presented with UA, 7 (10.9%) with stable angina (SA), while the NSTEMI and STEMI presentations comprised only 2 patients each (3.1%). The left anterior descending artery comprised

Table 2 Two-dimensional quantitative coronary angiography findings pre-optical coherence tomography in the percutaneous coronary intervention and optimal medical therapy groups

Variable	OCT-guided PCI (n = 38)	OCT-guided OMT (n = 26)	P-value
Reference area, mm^2	7.91 (5.61-10.45)	7.97 (6.01-11.16)	0.538
Minimum luminal area, mm^2	1.97 (1.37-2.80)	2.40 (1.73-3.82)	0.029
Area stenosis %	74.02 ± 6.43	67.77 ± 6.44	0.001

Data are expressed as mean ± SD and n (%), or median and 25th and 75th. Percentiles for non-normal distribution. OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention; OMT: Optimal medical therapy.

Table 3 Frequency-domain optical coherence tomography findings in the percutaneous coronary intervention and optimal medical therapy groups

Variable	OCT-guided PCI (n = 38)	OCT-guided OMT (n = 26)	P-value
Reference area mm^2	9.00 (7.56-11.21)	9.32 (7.73-12.14)	0.507
Minimum luminal area mm^2	2.44 (1.93-3.15)	3.43 (2.61-4.72)	0.001
Area stenosis %	72.22 ± 7.39	61.87 ± 7.51	< 0.001

Data are expressed as mean ± SD and n (%), or median and 25th and 75th. Percentiles for non-normal distribution. OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention; OMT: Optimal medical therapy.

most of the ICL (57.8%), followed by the right coronary artery (23.4%) and circumflex artery (18.8%). The mean post-procedural in-hospital stay was 3.0 ± 0.7 d. Discharge treatment was similar in both arms with 100% prescription of aspirin, and 100% and 96.1% prescription of P2Y12 inhibitors in the PCI and OMT groups respectively.

Correlation of admission diagnosis with OCT findings and treatment modality

Of the 38 patients in the PCI group, the vast majority of them (34, 89.5%) presented with UA, only 4 (10.5%) with SA, and none with NSTEMI or STEMI (Table 1). On the other hand, out of the 26 patients treated with OMT, most of them (19, 73.1%) were also admitted with UA, while the rest were divided between SA (3, 11.5%), NSTEMI (2, 7.7%) and STEMI (2, 7.7%). UA was therefore, by far the most common admission diagnosis in both the PCI and OMT groups. Furthermore, from the UA admission subgroup of 53 patients, 34 (64.1%) were treated with PCI while the rest (19, 35.9%) were treated with OMT, while in the SA subgroup of 7 patients, 4 (57.1%) were managed interventionally, and the rest (3, 42.9%) medically. On the other hand, the 4 (6.2%) patients presenting with NSTEMI and STEMI combined were all treated with OMT after OCT imaging was performed.

2D-QCA findings

Pre-OCT 2D-QCA findings are summarized in Table 2. Retrospective analysis of parameters measured by 2D-QCA showed the following: The median RA as obtained from 2D-QCA was 7.97 (6.01-11.16) mm^2 in the OMT arm compared to 7.91 (5.6-10.45) mm^2 in the PCI arm (P = 0.538). Similarly, the median MLA measured by 2D-QCA was also comparatively larger in the OMT [2.40 (1.73-3.82) mm^2] *vs* the PCI group [1.97 (1.37-2.80) mm^2] (P = 0.029). The mean % AS was less severe (67.77% ± 6.44%) in the OMT as opposed to 74.02% ± 6.43% in the PCI arm (P = 0.001).

FD-OCT findings

These findings are summarized in Table 3. All lesions were suitable for OCT imaging analysis, which revealed a higher mean stenosis severity (mean % AS) of the ICL in the PCI group (72.22% ± 7.39%) compared to the OMT group (61.87% ± 7.51%) (P < 0.001). The median MLA measured by OCT was also smaller in the PCI [2.44 (1.93-3.15) mm^2] compared to the OMT arm [3.43 (2.61-4.72) mm^2] (P = 0.001), while there was no significant difference between the median RA obtained in the PCI *vs* the OMT arm (P = 0.507). Furthermore, the ICL in all the patients comprising the PCI group demonstrated either features of plaque instability, or a plaque burden exceeding 76%.

Efficacy assessment

OCT was successfully performed and well-tolerated in all of the intervened patients. The primary efficacy endpoint was met by comparing the mean RA, MLA and AS values obtained by 2D-QCA analysis with similar parameter values from OCT imaging (Table 4). Our results clearly demonstrate that 2D-QCA overestimates the stenosis severity of the ICL both in the OCT-guided PCI and OMT groups. In the PCI group, the mean AS was 72.22% ± 7.39% as assessed by OCT, compared to 74.02% ± 6.44% by 2D-QCA (P = 0.027). In the same group, the mean MLA was found to be 2.58 ± 1.04 mm^2 by OCT as opposed to 2.14 ± 1.00 mm^2 by 2D-QCA analysis (P < 0.001). Similarly, the mean RA was 9.39 ± 3.28 mm^2 by OCT compared to 8.16 ± 3.24 mm^2 by 2D-QCA evaluation (P < 0.001). In the OMT group, similar results were obtained in that 2D-QCA assessment demonstrated a comparatively smaller

Table 4 Two-dimensional quantitative coronary angiography vs frequency-domain optical coherence tomography findings

Group	2D-QCA	FD-OCT	*P*-value
Reference area, mm^2			
OCT-guided PCI	8.16 ± 3.24	9.39 ± 3.28	< 0.001
OCT-guided OMT	7.97 (6.01-11.16)	9.32 (7.73-12.14)	0.005
Minimum luminal area mm^2			
OCT-guided PCI	2.14 ± 1.00	2.58 ± 1.04	< 0.001
OCT-guided OMT	2.40 (1.73-3.82)	3.43 (2.61- 4.72)	< 0.001
Area stenosis %			
OCT-guided PCI	74.02 ± 6.44	72.22 ± 7.39	0.027
OCT-guided OMT	67.77 ± 7.31	61.87 ± 7.51	< 0.001

Data are expressed as mean ± SD and *n* (%), or median and 25th and 75th. Percentiles for non-normal distribution. 2D-QCA: Two-dimensional quantitative coronary angiography; FD-OCT: Frequency-domain optical coherence tomography; PCI: Percutaneous coronary intervention; OMT: Optimal medical therapy.

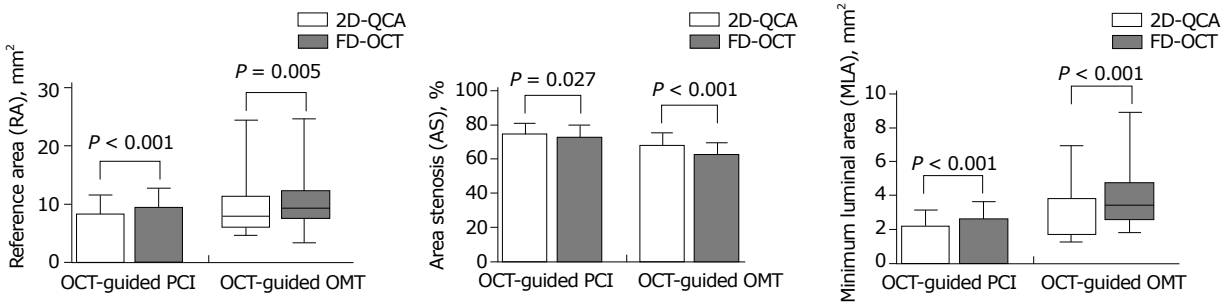

Figure 1 Box plot diagrams comparing reference area, minimum luminal area and % area stenosis parameters obtained from two-dimensional quantitative coronary angiography and frequency-domain optical coherence tomography imaging in the optical coherence tomography-guided percutaneous coronary intervention and optical coherence tomography-guided optimal medical therapy groups. 2D-QCA: Two-dimensional quantitative coronary angiography; FD-OCT: Frequency-domain optical coherence tomography; PCI: Percutaneous coronary intervention; OMT: Optimal medical therapy.

mean RA (P = 0.005) and mean MLA (P < 0.001), thereby leading to an overestimation of the mean % AS by 2D-QCA in comparison with FD-OCT (67.77% ± 7.31% *vs* 61.87% ± 7.51%), (P < 0.001). The results of the efficacy assessment of OCT compared to 2D-QCA in evaluating the stenosis severity of ICL were therefore statistically significant as illustrated by the box plot diagrams in Figure 1.

Safety assessment

No procedural complications were observed, including the no-reflow phenomenon, acute vessel occlusions, coronary vasospasm, angiographically-detectable dissections, thrombi formation or embolic phenomena. Transient chest discomfort during the procedure was rare, with no significant ECG changes. Furthermore, none of the patients in the 2 groups developed acute kidney injury following the procedure. There were also no serious in-hospital post-procedural adverse events noted. The primary safety end-point (incidence of MACE at 30 d post-procedure) was fully met in both groups, with none of the 64 patients experiencing any of the following: Cardiac death, post-procedure MI, acute stent thrombosis, significant vessel perforation or dissection, emergent revascularization, major vascular complications or cerebrovascular accidents. However, given the relatively small sample size of this study, the above results pertaining to the 30-d MACE primary safety end-point should be interpreted with caution in the current context of this study.

Clinical outcomes at 12-mo follow-up

Follow-up was undertaken in person so as to achieve optimal subjective evaluation, after each of the 64 patients was telephonically informed of his/her follow-up date. None of the patients were lost to follow up. At 12 mo, no death, thrombosis, heart failure, cerebrovascular accidents and major bleeding events was observed in either group. Only 1 recurrent MI (2.6%) was noted in the OCT-guided PCI group that had no relation with the target vessel (Table 5), while none was recorded in the OCT-guided OMT group. With regards to the rates of target lesion revascularization, no significant difference (2.6% *vs* 0%) was noted between the 2 groups. Repeat episodes of angina was the only most frequent event observed, with 13 (34.2%) patients in the PCI arm reporting recurrent chest pain, compared to 8 (30.1%) patients in the OMT arm. The incidences of the remaining 2 secondary endpoints (repeat hospitalization and minor bleeding events) were also low and similar in both groups, making the overall comparison of safety clinical outcomes between the OCT-Guided PCI and OCT-Guided OMT groups not statistically significant (P = 0.634) (Figure 2).

Table 5 Clinical outcomes at 12 mo follow-up *n* (%)

Variable	OCT-guided PCI (*n* = 38)	OCT-guided OMT (*n* = 26)	*P*-value, overall = 0.634
Myocardial infarction	1 (2.6)	0	1
Target lesion revascularisation	1 (2.6)	0	1
Re-angina	13 (34.2)	8 (30.8)	0.603
Re-hospitalisation	3 (7.9)	2 (7.7)	0.920
Minor bleeding events	5 (13.2)	1 (3.8)	0.427

Data are expressed as mean ± SD and *n* (%), or median and 25th and 75th. Percentiles for non-normal distribution. OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention; OMT: Optimal medical therapy.

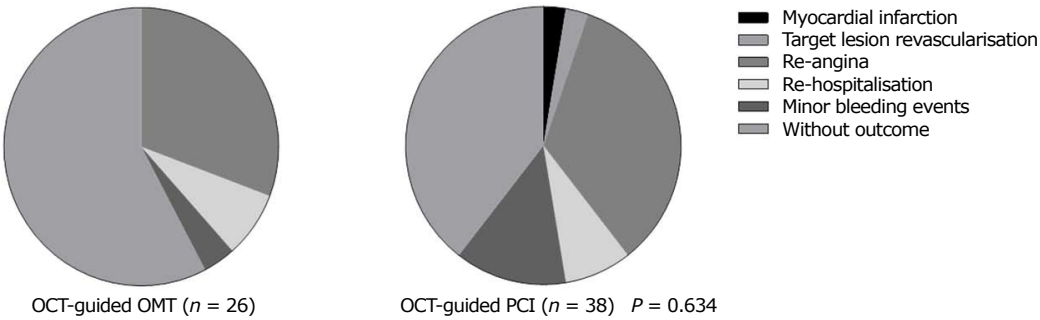

Figure 2 Pie charts comparing outcome at 12 mo between the optical coherence tomography-guided percutaneous coronary intervention and optical coherence tomography-guided optimal medical therapy groups. OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention; OMT: Optimal medical therapy.

DISCUSSION

The present study is the first to date to explore the safety and efficacy of FD-OCT in evaluating and guiding the treatment of patients with ICL. Several studies have analyzed the role of OCT in guiding PCI and evaluating post-PCI results. However, none has thus far investigated the efficacy and safety of OCT in the evaluation and optimal treatment of angiographically-borderline coronary artery lesions.

The statistically significant results demonstrated by our study as reported in Table 4 and Figure 1 prove that FD-OCT is superior to and more accurate than 2D-QCA in evaluating stenosis severity in ICL owing to its superior spatial resolution, thus meeting our primary efficacy end-point. FD-OCT provides a more accurate evaluation of stenosis severity in ICL, and hence positively influences physician decision-making regarding whether to proceed with PCI or to treat the lesion medically. In addition, other parameters such as % plaque burden and unstable plaque morphology can be clearly delineated and measured by FD-OCT, crucial in influencing physician decision-making in the setting of ICL. From our results of % mean AS by OCT in Table 3 (72.22% ± 7.39% in the PCI and 61.87 ± 7.51 in the OMT group), we may conclude that it is beneficial to proceed with OMT as opposed to PCI in any ICL with an average % AS of less than 62% on FD-OCT imaging, provided that plaque stability is not compromised and the plaque burden is ⩽ 76%. These results also lead us to conclude that lesions with an average % AS greater than 72%, or demonstrating unstable plaque morphology features, or a plaque burden exceeding 76% are likely to benefit more from PCI than OMT. For ICL with a % AS between 62% and 72%, the decision whether to proceed with OMT or PCI should be taken on an individual basis, taking into account whether unstable plaque factors exist and the % of atherosclerotic plaque burden. To the best of our knowledge, the only study that compared 2D-QCA directly with OCT in the assessment of coronary artery lesion dimensions was conducted by Mazhar *et al*[9]. It showed there is a good correlation between QCA and OCT for measurement of proximal and distal reference diameters of a lesion, but the MLD was underestimated by QCA. The latter findings are in keeping with the results of our study. However, the aim of this study did not set its focus on the ICL subset of narrowings, but instead considered a whole range of coronary stenoses from moderate to severe.

The results of our study also demonstrate that the primary safety end-point (incidence of 30-d MACE) was fully met, with none of the 64 subjects experiencing any serious post-procedural adverse events such as cardiac death, post-procedure MI, acute stent thrombosis, significant vessel perforation or dissection, emergent revascularization, major vascular complications or cerebrovascular accidents. Therefore, major complications following intracoronary OCT study of ICL are highly unlikely, which can be minimized using a careful procedural scheme. Furthermore, no patients developed acute kidney injury during their in-hospital stay despite the additional amount of contrast media used during the FD-OCT procedure. However, these

results evaluating safety end-points of the current study should be interpreted with appropriate caution, given the relatively small sample size. In addition, other safety end-points such as duration of the procedure, fluoroscopy time, amount of contrast media used, and radiation dose delivered were not formally evaluated by our study.

Evaluation of the secondary end-points showed that at 12 mo, up to one-third of patients in each group experienced recurrent episodes of chest pain, the most frequent event of the secondary end-points (Table 5). Whether repeat episodes of angina has any relation to the intervened or non-intervened ICL is a difficult question to answer, and therefore cannot be used on its own as a measure to evaluate success or failure of the FD-OCT procedure. Factors such as the patient' s subjective interpretation of angina, progression of disease, de novo coronary lesions, poor compliance to anti-platelet therapy are factors that could account for recurrence of angina episodes in these patients. However, with the exception of the relatively high incidence of repeat episodes of angina in both the OCT-guided PCI and OCT-guided OMT groups, incidence of the other secondary end-points such as MACE at 12 mo and other adverse clinical events during that time period were nil or similarly very low (Figure 2), leading to the comparison of safety clinical outcomes between the 2 groups being statistically not significant. This proves that FD-OCT is a safe technique as it did not itself contribute to a worse clinical outcome whether the patient was treated with PCI or OMT following intracoronary OCT imaging.

Further deductions can be made from the results of our study. 53 of the 64 patients (82.8%) presented with UA, only 7 (10.9%) patients presented with SA, while NSTEMI and STEMI presentations accounted for 2 patients each (6.2% combined) (Table 1). From these findings, it can be inferred that patients with ICL have a high likelihood of presenting with symptoms of UA and are at increased risk of acute coronary events. OCT thus presents as a crucial investigative tool to decide whether to treat the ICL in these patients interventionally or conservatively, depending on the OCT findings of % AS, plaque instability and % plaque burden. Out of the 53 patients who presented with UA, there was a significant difference between the percentage of subjects treated with PCI (64.1%) compared to OMT (35.9%), showing that OCT is determinant in guiding optimal therapy of the ICL found in this subset of ACS patients. With regards to the SA subgroup of 7 patients, 4 (57.1%) were treated with PCI, while the remaining 3 (42.9%) were managed medically; however, the number of patients comprising this subgroup was too small to draw any definitive conclusions.

On the other hand, only 4 (6.2%) patients in our study presented with either a STEMI or NSTEMI, all of whom were treated with OMT post-OCT. In this minority of patients, no indications were found to proceed with PCI based on the predetermined OCT criteria or, the pathological hallmark in these patients comprised the entity of myocardial infarction with non-obstructive coronary arteries (MINOCA)[10]. The small number of patients comprising this subgroup limits our ability to conclude whether OCT is safe and effective in the setting of an acute myocardial infarction (AMI). However, it does importantly demonstrate that patients with AMI not always require PCI, but can be managed conservatively should OCT demonstrate no features of plaque instability or no significant stenosis. These deductions can potentially be linked to the findings of the recently published landmark ORBITA trial[11]. The latter indicated that among SA patients with anatomically and functionally significant coronary stenoses ($\geqslant$ 70% severity), PCI did not result in greater improvements in exercise times or anginal frequency compared with a placebo procedure, though it did resolve ischemia more effectively as ascertained by follow-up stress echocardiography, these findings requiring however to be validated in a larger randomized controlled trial. Even though the ORBITA trial did not involve the use of OCT as an imaging tool to evaluate the degree of stenosis on the coronary lesions and its aim was, in fact, to evaluate the efficacy of PCI compared with a placebo procedure for angina relief among patients with SA, it did however show that SA patients with severe coronary stenoses are not automatically candidates for PCI, as many of them can have an equally good outcome with OMT. In this setting, OCT can be of utmost value in guiding the interventionist to decide as to which of these patients will benefit more from PCI than OMT and vice-versa, based on accurate OCT assessment of stenosis severity, and other crucial parameters such as plaque instability and % of atherosclerotic plaque burden obtained from the OCT study.

Whether OCT is effective and safe in evaluating and treating ICL in patients presenting with an AMI, in whom emergency CAG shows no obstructive lesions, but instead borderline or even minimal coronary stenosis in accordance with the MINOCA entity, is an important issue. In the setting of an unstable patient with an AMI undergoing emergency CAG, the efficacy and safety of FD-OCT with regards to the optimal outcome for the patient is debatable. FD-OCT can be time-consuming in less experienced hands, requires additional instrumentation and increased doses of contrast agent and anticoagulants. On the other hand, it does provide vital information on plaque stability or instability of the ICL suspected to be the infarct-related lesion, crucial in aiding decision whether to proceed with PCI or OMT in the AMI setting. In their study on the OCT evaluation of intermediate coronary lesions in patients with NSTEMI, Bogale *et al*[12] showed that OCT imaging confirmed the lack of severe anatomical stenosis in most patients but also identified coronary lesions with unstable features. On the other hand, Takahashi *et al*[13] showed in their case report on an OCT-based diagnosis

in a patient with STEMI and non-obstructive coronary arteries that OCT may provide a clue to identifying the underlying pathophysiological process especially in patients with MINOCA caused by coronary disorders. Another case report by Shah and Ing on the role of OCT in managing patients with STEMI demonstrated that OCT offers significantly improved resolution over IVUS, and hence should be used for assessment of the infarct-related lesion, especially in cases where the underlying pathophysiology is not clearly evident. The authors however pointed out that performing such an investigation requires additional vessel instrumentation and increased contrast use[14]. Both of these case reports and the clinical study by Bogale *et al*[12] did not shed any light though on how safe and effective OCT is in dealing with the ICL subset of lesions in a patient presenting with an AMI.

The only 3 efficacy clinical studies conducted so far on the OCT evaluation and treatment of patients with angiographically-borderline coronary lesions mostly focused on comparing OCT with FFR, but none investigated how effective OCT is as a stand-alone technique in dealing with ICL in the cardiac catheterization laboratory[15-17]. Furthermore, the OPUS-CLASS, CLI-OPCI and ILUMIEN Ⅰ studies clearly show the advantages conferred by OCT in providing reliable quantitative measurements of coronary artery dimensions, improving clinical outcomes of patients undergoing PCI, and positively influencing both physician decision-making and procedural strategy pre and post-PCI respectively[18-20], while the ILUMIEN Ⅱ, OPINION and CLI-OPCI Ⅱ studies all investigated the efficacy of OCT in assessing stent deployment and expansion[21-23]. Despite highlighting the clinical and interventional benefits of OCT, none of these trials however explored the efficacy of this ultra-high resolution intracoronary imaging procedure in the ICL subset of stenosis alone.

On the other hand, whether the theoretical advantages of OCT also translate into safety benefits has been evaluated by only a limited number of clinical trials to date. A pioneering experience by Imola *et al*[24] on the safety of FD-OCT to guide decision making in PCI, showed OCT guidance to be safe. Furthermore, a multicenter study by Yoon *et al*[25] demonstrated that FD-OCT provides fast and reliable resolution images of the coronary artery, and the pullback can be safely performed over long segments of the artery without serious adverse events. The only 2 published randomised trials to have compared OCT-guided PCI with angiography-guided PCI (ILUMIEN Ⅲ and DOCTORS) both showed that OCT-guided PCI was safe and did not increase peri-procedural complications[26,27]. Three other studies successfully demonstrated the safety and also the efficacy of intravascular OCT for coronary artery evaluation in the clinical setting, none of which however focused on the ICL subset of coronary narrowings[28-30]. So despite demonstrating intracoronary OCT to be a safe procedure, the question as to whether the above studies would have reached similar conclusions in dealing with ICL alone cannot be answered. Therefore, in our opinion, the present study is of significant value as it is the first one ever to investigate both the efficacy and safety of FD-OCT in evaluating and guiding the optimal treatment of patients with angiographically-borderline coronary artery lesions.

Study limitations

The present study has certain noteworthy limitations. First, it was a single-center study conducted over a 1 year period with a relatively sample size which was nevertheless reasonable considering the time duration of the study and the selection criteria of the patient population being studied. Because of the small sample size, the study lacked statistical power to determine whether the more accurate mean % AS measurement obtained by FD-OCT contrasted significantly with that obtained by 2D-QCA, even though a statistically significant difference was actually observed. In addition, as explained in the methodology section, no statistical sample-size calculation was undertaken in this study. Second, this was a non-randomized study as the subjects were assigned to either arm based on specific predetermined OCT criteria. Confounding and bias resulting from non-randomization could potentially affect the results of the study. In view of the favorable experience of this study, we intend to conduct a multicenter clinical trial which is registered in ClinicalTrials.gov (NCT03229993), with a larger sample size and a longer clinical study and follow-up time duration.

CONCLUSION

Our study clearly demonstrates that in evaluating and treating patients with angiographically-intermediate coronary lesions, OCT is a safe and effective ultra-high resolution imaging technique. It is superior to and more accurate than visual diagnostic CAG and 2D-QCA, hence allowing better evaluation and treatment of the ICL subset of coronary narrowings. In experienced hands, major procedural complications are rare, as are short to medium-term MACE. The data from our study warrant a large-scale randomized controlled trial to establish if OCT is equally safe and effective in the evaluation and treatment of ICL in patients presenting with the whole spectrum of ACS and SA, and whether proceeding with OCT imaging in these subjects does actually improve clinical outcomes in comparison with decisions based on angiographic guidance alone.

ARTICLE HIGHLIGHTS

Research background

Conventional angiography and other adjunct coronary imaging techniques such as fractional flow reserve and intravascular ultrasound have in the past been used to evaluate the anatomical and physiological significance of coronary lesions considered to fall in the intermediate category (40%-70%). However, to this date, no study has been conducted to assess the safety and efficacy of

frequency-domain optical coherence tomography (FD-OCT) in the evaluation and treatment of angiographically-intermediate coronary lesions (ICL). Our interventional team wanted to explore if FD-OCT could assist us in our daily practice to better evaluate and treat this subset of coronary lesions, compared to when angiographic-guidance alone is used to guide decision making in this clinical setting.

Research motivation

The current study addresses a very important topic in interventional cardiology, as it focuses specifically on the management of ICL. Cases of coronary lesions considered to be borderline are frequently under- or over-treated, hence providing a reliable tool for the accurate assessment of these lesions is of great importance to their appropriate management. Coronary angiography has several known limitations, including a lack of correlation between the percentage of stenosis and the lesion's physiologic importance, and considerable inter-observer variability in classifying the lesion's severity. On the other hand, percutaneous coronary intervention (PCI) has inherent risks even in the most experienced hands. The possibility of procedural complications with PCI such as coronary dissection, no reflow phenomenon, in-stent restenosis, and stent thrombosis requires accurate stratification of patients with intermediate coronary lesions to appropriate therapy. The present study explores the use of FD-OCT as an ultra-high resolution intracoronary imaging tool with regards to its safety and efficacy to accurately assess and manage intermediate coronary lesions interventionally or medically, and will spark interest for further research in this specific setting to reinforce the concept being explores.

Research objectives

Our aim in designing this study was to demonstrate that FD-OCT is a safe and effective procedure to be performed when faced with intermediate coronary artery lesions during coronary angiography in the cardiac catheterization laboratory. As this is the first study to investigate the safety and efficacy of OCT in the setting of ICL, it will pave the way for further studies (multi-center, larger sample size, longer follow-up times) to be conducted to confirm our findings, and reinforce our conclusions and recommendations. In particular, these studies are expected to have higher statistical power, with a larger sample size and a more equal representation of patients from the different coronary artery disease (CAD) population subgroups. This paper will provide investigators from across the world a platform to improve on the study design, methodology in conducting studies with similar objectives, taking into account the difficulties we encountered in this study, and the related limitations that ensued.

Research methods

With the aim in mind of elucidating whether FD-OCT was safe and effective in treating ICL, we decided to conduct the study by including patients found to have borderline lesions on angiography in our cardiac catheterization laboratory, and who consented to the OCT procedure. Patients who presented with cardiogenic shock, acute stroke, renal dysfunction, left main stem ICL, and acute or chronic total occlusion coronary lesions were excluded from the study. Patients were assigned to either of the 2 arms of the study based on specific predetermined OCT criteria. Focusing importantly on the specific aim of our study, we clearly defined our primary efficacy endpoint (demonstration of the superiority and higher accuracy of FD-OCT compared to 2D-QCA in evaluating stenosis severity in patients with ICL), primary safety endpoint [incidence of 30-d major adverse cardiac events (MACE)] and secondary endpoints (MACE at 12 mo and other clinical events), and obtained the necessary 2D-QCA and FD-OCT measurements, as well as the follow-up statistical results on MACE and other clinical outcomes. These results generated enabled an in-depth discussion and appropriate conclusions to be made. We hope that the methodology and study design used in our study will be useful in assisting investigators to design further studies with similar objectives.

Research results

The primary efficacy endpoint of our study was fully met, with statistically significant results clearly demonstrating that 2D-QCA overestimates the stenosis severity of the ICL in both the OCT-guided PCI and OMT groups. Our primary safety endpoint was also fully met, with none of the patients in the study experiencing any MACE at 30 d post-procedure. Incidences of secondary endpoints were also found to be low in both arms, the only exception being the relatively high incidence of recurrent episodes of angina which was, however, very similar in the 2 groups. Analysis of the above results gives a clear insight into the superiority of FD-OCT compared to 2D-QCA in evaluating stenosis severity of ICL, and lays a foundation on which further studies to further reinforce this finding and implement its application in clinical practice in managing patients with angiographically-borderline lesions, owing to the efficacy of the FD-OCT in this setting. The findings of the present study also highlighted the safety of this intracoronary-imaging technique in the same setting. However, these results should be interpreted with appropriate caution, given the relatively small sample size of the study, which resulted in the study lacking statistical power. In addition, patients across the different CAD population subgroups are not equally represented in this study, especially patients presenting with an AMI. Further studies are required to address these limitations from our present study, so that the safety and efficacy of FD-OCT can be extrapolated to the management of ICL in patients presenting with different categories of CAD.

Research conclusions

To this date, the efficacy and safety of FD-OCT when specifically faced with an ICL in the cardiac catheterization laboratory irrespective of the clinical presentation of the patient, was unknown. The present study provides significant insight into the topic and successfully meets the objectives laid out by its investigators. It shows that in evaluating and treating an ICL, performing FD-OCT following coronary angiography adds significant value to the assessment and management of that lesion, and is found to be a safe and effective procedure in this setting. However, further studies are required with larger sample size and higher statistical power to determine whether this statement can be applicable to patients with ICL across the different CAD population subgroups, and if OCT is equally safe and effective in treating ICL in patients presenting with an AMI, compared to those presenting with UA or SA. It is expected that this pioneering study sparks further interest amongst researchers in the field of CAD and amongst interventional cardiologists in practice to design and conduct large, multicenter clinical trials in order to obtain more reliable data that can be used to implement guidelines and positively change clinical practice, as well as provide direction for future research in this field and in the clinical setting of ICL.

Research perspectives

This study shows that 2D-QCA leads to an overestimation of lesion severity in comparison to FD-OCT, which is a prerequisite for overtreatment. On the other hand, the results show that OCT-guided decision making seems to be safe. The population with intermediate coronary lesions is largely underrepresented across different randomized trials. Therefore, despite its relatively small sample size, this prospective single center interventional study adds a lot of important data to the topic and provides a good platform for future larger multicenter clinical trials to be conducted to further reinforce the utility of FD-OCT in evaluating and treating ICL with regards to its safety and efficacy in this specific clinical setting.

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ORIGINAL ARTICLE

Observational Study

Incidence and risk factors for potentially suboptimal serum concentrations of vancomycin during cardiac surgery

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Author contributions: Cotogni P designed the study and drafted the manuscript; Barbero C participated in the study design, carried out the study and helped to draft the manuscript; Rinaldi M participated in the study design and coordination and revised it critically for important intellectual content; all authors read and approved the final manuscript.

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Abstract

AIM

To investigate the incidence and risk factors for vancomycin concentrations less than 10 mg/L during cardiac surgery.

METHODS

In this prospective study, patients undergoing cardiac surgery received a single dose of 1000 mg of vancomycin. Multiple arterial samples were drawn during surgery. Exclusion criteria were hepatic dysfunction; renal dysfunction; ongoing infectious diseases; solid or hematologic tumors; severe insulin-dependent diabetes; body mass index of < 17 or > 40 kg/m^2; pregnancy or lactation; antibiotic, corticosteroid, or other immunosuppressive therapy; vancomycin or non-steroidal anti-inflammatory drug therapy in the previous

2 wk; chemotherapy or radiation therapy in the previous 6 mo; allergy to vancomycin or cefazolin; drug abuse; cardiac surgery in the previous 6 mo; previous or scheduled organ transplantation; preoperative stay in the intensive care unit for more than 24 h; emergency procedure or lack of adequate preparation for surgery; and participation in another trial.

RESULTS

Over a 1-year period, 236 patients were enrolled, and a total of 1682 serum vancomycin concentrations (median 7/patient) were measured. No vancomycin levels under 10 mg/L were recorded in 122 out of 236 patients (52%), and 114 out of 236 patients (48%) were found to have at least 1 serum sample with a vancomycin level < 10 mg/L; 54 out of 236 patients (22.9%) had at least 5 serum samples with a vancomycin level lower than 10 mg/L. Vancomycin infusion was administered for 60 min in 97 out of 236 patients (41%). In 47 patients (20%), the duration of infusion was longer than 60 min, and in 92 patients (39%) the duration of infusion was shorter than 60 min. The maximum concentration and area under the concentration-time curve were significantly higher in patients with no vancomycin levels less than 10 mg/L ($P < 0.001$). The multivariate analysis identified female gender, body mass index (BMI) > 25 kg/m^2, and creatinine clearance above 70 mL/min as risk factors for vancomycin levels less than 10 mg/L.

CONCLUSION

Results of this study identified female gender, BMI > 25 kg/m^2, and creatinine clearance above 70 mL/min as risk factors for suboptimal vancomycin serum concentration during cardiac surgery; no relationship was found between infusion duration and vancomycin levels less than 10 mg/L. These findings call attention to the risk of facilitating the emergence of vancomycin-resistant methicillin-resistant Staphylococcus aureus strains.

Key words: Cardiopulmonary; Bypass; Surgical site infections; Vancomycin pharmacokinetics; Antibiotic therapy; Methicillin-resistant *Staphylococcus aureus*

Core tip: The aim of this study was to investigate the incidence and risk factors for vancomycin concentrations less than 10 mg/L during cardiac surgery. Over a 1-year period, 236 patients were enrolled, and a total of 1682 serum vancomycin concentrations were measured. A total of 48% of patients were found to have ⩾ 1 sample with a vancomycin level < 10 mg/L. The maximum concentration and area under the concentration-time curve were significantly higher in patients with no vancomycin levels less than 10 mg/L ($P < 0.001$). The multivariate analysis identified female gender, body mass index > 25 kg/m^2, and creatinine clearance above 70 mL/min as risk factors for vancomycin levels less than 10 mg/L.

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INTRODUCTION

Surgical site infections (SSIs) related to methicillin-resistant Staphylococcus aureus (MRSA) after cardiac surgery continue to cause substantial morbidity and mortality[1-3]. Therefore, the prevention of this feared complication, particularly in terms of antimicrobial prophylaxis, is a matter of discussion in the literature. The practice guidelines from the Society of Thoracic Surgeons on antibiotic prophylaxis in patients undergoing cardiac surgery suggests combining a β-lactam (cefazolin) with a glycopeptide (vancomycin) for antimicrobial prophylaxis in the scenario of an established "high incidence" of MRSA; a dose of 1 to 1.5 g or a weight-adjusted dose of 15 mg/kg of vancomycin administered intravenously over 1 h, with the infusion ending within 1 h from the incision of the skin, is recommended[4,5]. Likewise, the 2011 guidelines of the American College of Cardiology and the American Heart Association recommend that vancomycin should be initiated 2 h before cardiac surgery and administered by a slow infusion[6]. However, a detailed protocol of administration with dose and levels of vancomycin to reach and maintain during the surgical procedure is still not reported.

In addition, evidence highlights that in the current practice there is often a gap between the duration of administration or timing of antimicrobial prophylaxis recommended in the guidelines and what is practiced[7,8]; this may increase the risk of potentially suboptimal serum vancomycin levels during surgery, jeopardizing the efficacy of antimicrobial prophylaxis. Indeed, low serum vancomycin concentrations-lower than 10 mg/L - seem to be related with the emergence of vancomycin-resistant MRSA strains: vancomycin-resistant Staphylococcus aureus (VRSA), vancomycin-intermediate Staphylococcus aureus (VISA), and heteroresistant VISA (hVISA)[9-11]. To date, strains of VRSA, VISA, and hVISA have been reported from many countries, including the United States, Japan, Australia, France, Scotland, Brazil, Korea, Hong Kong, and others[10-12].

Our group has already analyzed intraoperative vancomycin pharmacokinetics (PK) in 236 patients undergoing cardiac surgery over a 1-year period[13]. In this study, and in the same study population, the incidence of potentially suboptimal vancomycin levels during cardiac surgery was investigated.

The primary objective of the present study was to investigate the incidence of vancomycin levels less than 10 mg/L during cardiac surgery. The secondary objective was to identify risk factors for intraoperative vancomycin levels less than 10 mg/L.

MATERIALS AND METHODS

Study design

Over a 1-year period, a prospective study was carried out in the Department of Cardiovascular Surgery of a 1200-bed tertiary care university hospital, where approximately 850 cardiac operations are performed every year. The study design has been described previously[13]. The inclusion criteria included adult patients undergoing cardiac surgery, who were receiving a single 1000 mg vancomycin dose as prophylaxis, diluted in 100 mL 0.9% NaCl solution and administered by intravenous infusion over 60 min, with a skin incision made between 16 and 120 min after the end of the vancomycin infusion, as recommended by Garey *et al*[14]. The exclusion criteria included hepatic dysfunction (bilirubin $\geqslant$ 2 mg/dL); renal dysfunction [creatinine > 1.5 mg/dL or creatinine clearance (CrCl) $\leqslant$ 30 mL/min, estimated by the Cockcroft-Gault formula]; infectious diseases that required antibiotic therapy 2 wk prior to the procedure; solid or hematologic tumors; severe insulin-dependent diabetes; a body mass index (BMI) < 17 or > 40 kg/m^2; pregnancy or lactation; antibiotic, corticosteroid, or other immunosuppressive therapy; vancomycin or non-steroidal anti-inflammatory drug therapy 2 wk prior to the procedure; chemotherapy or radiation therapy in the previous 6 mo; allergy to vancomycin or cefazolin; drug abuse; cardiac surgery in the previous 6 mo; previous or scheduled organ transplantation; a preoperative stay in the intensive care unit for more than 24 h; an emergency procedure or lack of adequate preparation for surgery; and participation in another trial.

Our protocol of antimicrobial prophylaxis is also designed for a single 1000 mg cefazolin dose, diluted in a 20 mL 0.9% NaCl solution, initiated 30 to 60 min before surgery and administered as a slow intravenous bolus. Three further doses of 1000 mg of cefazolin at 8-h intervals were given postoperatively, while no further doses of vancomycin were administered postoperatively. Since 2005, our protocol has allowed the choice to combine cefazolin with vancomycin for antimicrobial prophylaxis in patients undergoing cardiac surgery[13,15]. The rationale for using vancomycin was due to an increased prevalence of MRSA infections, which exceeded 60% hospital-wide, and to the identification of isolates in cardiac surgery patients with SSIs. The vancomycin protocol and timing of administration were chosen based upon recommendations of our Hospital Infection Control Committee and guidelines from the Society of Thoracic Surgeons[5,13,15].

A healthcare provider (*i.e.,* physician, nurse or cardiovascular technician) was required to document the exact time the antibiotic infusion was initiated, as well as anesthesiologists or cardiac surgeons who recorded the exact time of the first skin incision and skin closure.

The study protocol was reviewed and approved by our Institutional Ethics Committee (approval No. 0078553), and patients provided written informed consent before their enrollment. The work was conducted in compliance with the Institutional Review Board/Human Subjects Research Committee requirements.

Vancomycin assay and pharmacokinetic analysis

The vancomycin assay and PK analysis have been reported previously[13].Briefly, for the on-pump group, arterial samples were drawn from the arterial catheter before cardiopulmonary bypass (CPB) [end of infusion maximum concentration (C_{max}) and skin incision ($C_{incision}$)], during CPB (5, 30, 60 min after the CPB start, and subsequently every 60 min to the CPB end: C_5, C_{30}, C_{60}, C_{120}, C_{180}, and C_{240}), and after CPB [wound closure ($C_{closure}$)]. For the off-pump group, some arterial samples (*i.e.,* C_5, C_{30}, C_{60}, C_{120}, C_{180}, and C_{240}) were drawn and time-matched to the CPB period of the on-pump group.

According to the Centers for Disease Control and Prevention guidelines, the definition of SSI requires positive culture results of surgical sites or drainage from the mediastinal area or evidence of infection during surgical re-exploration or fever, sternal instability, and positive blood culture results[16]. SSIs were classified as (1) superficial (infection above the sternum with no bone involvement); (2) deep (infection involving the sternum and organ/space such as mediastinitis); and (3) leg donor site infections[16].

Statistical analysis

The receiver operator characteristic (ROC) curve analysis was used to investigate the relationship between the duration of drug infusion and the occurrence of vancomycin concentrations under 10 mg/L. PK characteristics were compared between patients with vancomycin levels constantly above 10 mg/L and patients with at least 1 vancomycin level lower than 10 mg/L using the Fisher's exact test for categorical variables and the Mann-Whitney test for continuous ones. All reported *P*-values were obtained by the 2-sided exact method, at the conventional 5% significance level. A multivariate binary logistic model was used to predict risk factors for vancomycin levels less than 10 mg/L. Data were analyzed using R 3.4.0 (The R Foundation for Statistical Computing, Vienna, Austria http://www.R-project.org). The statistical methods of this study were reviewed by R Passera, a biomedical statistician.

RESULTS

Two hundred thirty-six cardiac surgery patients were enrolled in this study. The patients' characteristics are shown in Table 1. During the study, 1682 serum vancomycin concentrations were measured, and 7 (median; range 6-9) blood samples per patient were collected. Vancomycin PK during cardiac surgery has been reported previously[13]. Out of the 1682 serum samples, vancomycin levels were lower than 10 mg/L in 443 cases, between 10 and 20 mg/L in 821 cases, between 20 and 30 mg/L in 192 cases, between 30 and

Table 1 Patients' characteristics *n* (%)

Characteristics	
Patients	236
Age, median (range)	70 (25-86)
Male gender	149 (63)
BMI, kg/m^2, median (range)	26 (18-40)
Diabetes	46 (19)
COPD	0
Hypertension	151 (64)
Smoke	28 (12)
Surgical time, min, median (range)	249 (119-593)
Surgical procedure	
CABG	72 (30.5)
Valve	113 (47.9)
CABG+Valve	34 (14.4)
Other[1]	17 (7.2)
Off-pump CABG	21 (8.9)
Left IMA	53 (22.4)
Both IMA	17 (7.2)
EUROscore add, median (range)	5 (1-6)
EUROscore log, median (range)	4.8 (1-7.74)
Mechanical ventilation, d, median (range)	7 (2-912)
ICU stay, d, median (range)	1 (1-24)
RBC transfusions, *n*, median (range)	2 (0-9)

[1]Aortic, atrial or ventricular septal defect repair, and congenital surgery. BMI: Body mass index; CABG: Coronary artery bypass grafting; COPD: Chronic obstructive pulmonary disease; EUROscore: European System for Cardiac Operative Risk Evaluation; add: Additive; log: Logistic; ICU: Intensive care unit; IMA: Internal mammary artery; RBC: Red blood cell.

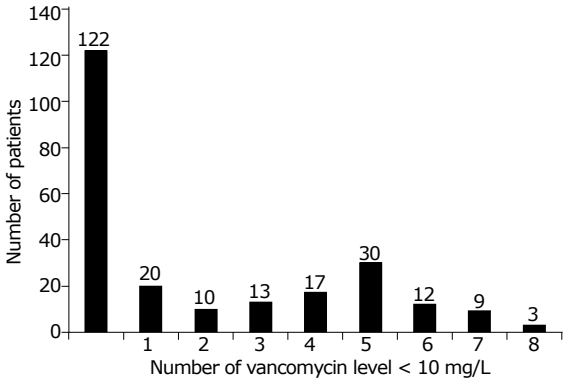

Figure 1 Distribution of patients without serum samples with a vancomycin level < 10 mg/L and of those with 1 or more serum samples with a vancomycin level < 10 mg/L during cardiac surgery.

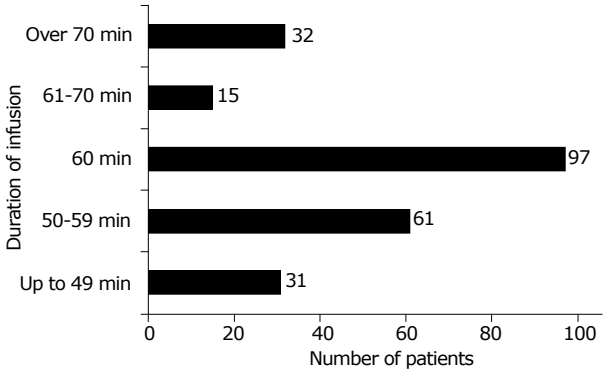

Figure 2 Distribution of patients according to the duration of vancomycin infusion. The target time for the duration of vancomycin infusion is 60 min.

40 mg/L in 73 cases, between 40 and 50 mg/L in 50 cases, and higher than 50 mg/L in 103 cases.

Three SSIs were recorded (1.3%): one was a superficial wound infection, and 2 were deep wound infections; no SSIs were detected at the donor site. Pathogens isolated in SSIs included two gram-negative bacteria or fungi and one methicillin-sensitive Staphylococcus aureus.

Figure 1 shows that, between the C_{max} time and C_{close} time, no vancomycin levels less than 10 mg/L were recorded in 122 out of 236 patients (52%) and that 114 out of 236 patients (48%) were found to have at least 1 sample with a vancomycin level < 10 mg/L. Fifty-four out of 236 patients (22.9%) had at least 5 serum samples with vancomycin levels lower than 10 mg/L.

Vancomycin infusion was administered for 60 min in 97 out of 236 patients (41%). In 47 patients (20%), the duration of infusion was longer than 60 min, and in 92 patients (39%) the duration of infusion was shorter than 60 min (Figure 2).

The ROC curve analysis showed no influences of duration of drug infusion on the occurrence of vancomycin concentrations less than 10 mg/L. No significant relationships were found between the number of episodes of vancomycin levels less than 10 mg/L and the clusters of duration of infusion ($P = 0.089$).

No significant differences were observed in terms of the SSI rate between patients with vancomycin levels constantly above 10 mg/L (2 out of 3 cases) and patients with at least 1 level less than 10 mg/L (1 out of 3 cases).

Vancomycin PK parameters were estimated and compared between above versus under 10 mg/L patient groups (Table 2): C_{max} and the area under the concentration-time (AUC) curve were significantly higher in patients with no vancomycin level under 10 mg/L, while the apparent total body clearance (Cl) and the apparent volume of distribution during the terminal phase (V_d) were significantly higher in patients with at least 1 episode of vancomycin concentration under 10 mg/L.

The multivariate binary logistic model identified female gender, BMI higher than 25, and creatinine clearance above 70 mL/min as risk factors for vancomycin levels less than 10 mg/L (Tables 3 and 4).

DISCUSSION

SSI is still one of the most serious complications after cardiac surgery, and one of the main strategies for prevention is the use of an appropriate antibiotic prophylaxis[17]. The spectrum of microorganisms related to SSIs varies among institutions; however, in the literature, MRSA and methicillin-resistant *S. Epidermidis* are the leading pathogens, and this brings attention to vancomycin as the prophylactic drug of choice[1-3].

Vancomycin has been one of the most investigated antimicrobial drugs as well as one of the most used antibiotics for the prevention and treatment of infections

Table 2 Pharmacokinetic comparison between patients with at least 1 serum sample with a vancomycin concentration < 10 mg/L (in the left column) and patients without serum samples with a vancomycin concentration < 10 mg/L (in the right column)

	Vancomycin levels < 10 mg/L (*n* = 114)	Vancomycin levels ⩾ 10 mg/L (*n* = 122)	*P*-value
C_{max} (mg/L)	33.2 (6.2-122.0)	57.9 (14.6-210.0)	<0.001
AUC (mg*h/L)	119.2 (28.3-247.7)	191.7 (95.8-467.8)	<0.001
$t_{1/2}$ (h)	3.9 (1.6-9.2)	4.0 (1.3-9.8)	0.437
CL (L/h)	8.4 (4.0-35.3)	5.2 (2.1-10.4)	<0.001
V_d (L)	47.2 (16.5-195.2)	29.8 (12.4-63.3)	<0.001

AUC: Area under the curve; CL: Total body clearance; C_{max}: Maximum concentration; $t_{½}$: Elimination half-life; V_d: Volume of distribution.

Table 3 Risk factors for vancomycin levels under 10 mg/L - univariate binary logistic model

	OR	95%CI	*P*-value
CPB (off-pump *vs* on-pump)	0.51	0.20-1.30	0.156
Vancomycin infusion (stopped *vs* non-stopped)	0.6	0.17-2.10	0.421
Age at surgery (> 70 yr *vs* ⩽ 70 yr)	0.54	0.32-0.92	0.021
Gender (Female *vs* male)	0.44	0.26-0.76	0.003
BMI (> 25 *vs* ⩽ 25)	2.3	1.36-3.88	0.002
Fluid balance (> 2000 mL *vs* ⩽ 2000 mL)	1.44	0.86-2.41	0.163
CrCl (> 70 mL/min *vs* ⩽ 70 mL/min)	2.56	1.51-4.34	<0.001
Vancomycin dosage (> 15 mg/kg *vs* ⩽ 15 mg/kg)	0.38	0.21-0.66	0.001
Vancomycin infusion duration			0.237
50-59 min *vs* < 50 min	0.5	0.21-1.21	0.123
60 min *vs* < 50 min	0.63	0.28-1.42	0.26
61-70 min *vs* < 50 min	0.48	0.14-1.69	0.254
> 70 min *vs* < 50 min	1.2	0.44-3.31	0.719

BMI: Body mass index; CPB: Cardiopulmonary bypass; CrCl: Creatinine clearance.

Table 4 Risk factors for vancomycin levels under 10 mg/L - multivariate binary logistic model

	OR	95%CI	*P*-value
Age at surgery (>70 yr *vs* ⩽ 70 yr)	0.69	0.36-1.28	0.245
Gender (Female *vs* male)	0.54	0.30-0.97	0.039
BMI (> 25 *vs* ⩽ 25)	1.99	1.15-3.45	0.015
CrCl (> 70 mL/min *vs* ⩽ 70 mL/min)	1.92	1.09-3.40	0.024
Vancomycin dosage (>15 mg/kg *vs* ⩽ 15 mg/kg)	0.75	0.36-1.57	0.451

BMI: Body mass index; CrCl: Creatinine clearance.

in cardiac surgery[10]. Several studies have investigated the association between vancomycin use as an antimicrobial prophylactic drug and the rate of SSIs in this surgical population. Different studies have analyzed vancomycin PK during cardiac surgery and the effects of CPB on serum vancomycin concentrations[13,18-20]. Other studies were carried out examining the timing of antibiotic prophylaxis, and in particular, the relationship between the end of vancomycin infusion and the first skin incision[14,15].

However, to date, no general agreement exists regarding guidelines for the dose and duration of antimicrobial prophylaxis administration, and, particularly, the level of vancomycin to reach and maintain during the surgical procedure for effective antimicrobial prophylaxis. Moreover, whether or not suboptimal intraoperative vancomycin levels are a cause of postoperative SSIs is still controversial. Studies have suggested that vancomycin operates in a concentration-independent fashion in which AUC is more effective than the drug level[10]. PK results of our study are in line with reports in the literature, even when administering vancomycin in the case of treating infections rather than antibiotic prophylaxis[10,21]; in particular, in our study, AUC was wider in the group of patients with no vancomycin levels less than 10 mg/L.

Larsson *et al*[22] simulated an *in vitro* model in which free vancomycin peak concentrations of 40, 20, 10, and 5 mg/L reported no significant difference in the corresponding bacterial kill curves for Staphylococcus aureus. On the other hand, to date, increasing evidence supports that Staphylococcus aureus exposure to trough serum concentrations of vancomycin lower than 10 mg/L can generate MRSA strains with vancomycin-resistant characteristics[5,10,11,23]. Sakoulas *et al*[24] have determined that the emergence of hVISA or VISA occurred when MRSA was exposed to suboptimal vancomycin concentrations (<10 mg/L); in this *in*

vitro study the minimal inhibitory concentration (MIC) increased from 1 to 8 mg/L. Tsuji *et al*[25] evaluated Staphylococcus aureus accessory gene regulator groups Ⅰ - Ⅳ exposed both to suboptimal and optimal vancomycin doses (1.5-10 mg/L) and reported that exposure to low vancomycin doses produced increases in the MIC to that of the VISA range.

In the present study, 114 out of 236 patients were found to have at least 1 value of vancomycin level lower than 10 mg/L between the C_{max} time and C_{close} time. The relatively small sample size and the low incidence of SSIs in this surgical population (1.3%, 3 out of 236 cases) make it difficult to obtain a significant relationship between vancomycin concentrations during surgery and the incidence of SSIs. However, this finding may be considered an indicator of the risk of selection of MRSA strains with vancomycin-resistant characteristics.

The multivariate analysis showed that female gender, BMI higher than 25, and creatinine clearance above 70 mL/min were risk factors for potentially suboptimal vancomycin concentrations. Regarding the BMI as a risk factor, our results are in line with other reports that highlight the efficacy of weight-based vancomycin dosing[26,27]. Recently, the European Medicines Agency claimed that the starting dose of vancomycin by infusion should be calculated according to the age and weight of the patient[28].

Strengths and limitations of the study

The study has many important characteristics. First of all, the results were obtained through a clinical trial and not from an analysis of a registry or database. Second, it was a prospective study. Third, only patients undergoing cardiac surgery were included. Fourth, information regarding antibiotic timing was gathered in "real-time" in the operating theater and not from the patient chart. Finally, the same protocol of antimicrobial prophylaxis was administered to all patients. Moreover, to the best of our knowledge, this is the first study investigating the incidence and risk factors for potentially suboptimal serum concentrations of vancomycin during cardiac surgery with such a large number of measured serum vancomycin concentrations (*i.e.,* 1682).

This study has some limitations. First, no statistical analysis was performed on the number of patients enrolled since the study was planned by our statistician to be continuous over 12 mo. Second, it was a single-center trial. Third, we considered vancomycin levels of 10 mg/L as an arbitrary cut-off for potentially suboptimal serum concentrations when an antimicrobial prophylaxis has been administered, referring to the level reported in the literature in the case of antimicrobial therapy. Finally, a larger study should be carried out to investigate clinical variables; indeed, the number of subjects was appropriate for a pharmacokinetic study but insufficient to find statistically significant differences in the SSI rate between patient groups with vancomycin levels above or under 10 mg/L.

In conclusion, evidence in the literature suggests that the exposure to low vancomycin levels should be considered a risk factor in the selection of MRSA strains with vancomycin-resistant characteristics. The present study on vancomycin PK in cardiac surgery patients has reported an incidence of intraoperative potentially suboptimal concentrations of vancomycin in almost 50% of patients. Our data analysis shows that female gender, BMI higher than 25, and creatinine clearance above 70 mL/min were risk factors for potentially suboptimal concentrations of vancomycin. Overall, these findings call attention to the risk of potentially suboptimal serum concentrations of vancomycin during cardiac surgery. However, further studies are needed to better define the threshold level of serum intraoperative vancomycin concentration associated with the risk for the emergence of vancomycin resistance.

ARTICLE HIGHLIGHTS

Research background

Based on evidence suggesting that Staphylococcus aureus exposure to low vancomycin concentrations can produce vancomycin-resistant strains, it is recommended that trough therapeutic serum concentrations of vancomycin are maintained above 10 mg/L.

Research motivation

There are no recommendations in the literature indicating target vancomycin concentrations to maintain intraoperatively for effective antimicrobial prophylaxis.

Research objectives

The aim of this prospective study was to evaluate the incidence and risk factors for vancomycin concentrations under 10 mg/L in adult patients undergoing cardiac surgery.

Research methods

In this study, the frequency of suboptimal vancomycin levels intraoperatively was investigated in samples collected from cardiac surgery patients receiving a single 1000 mg vancomycin dose.

Research results

We found an incidence of intraoperative potentially suboptimal concentrations of vancomycin in almost 50% of these patients. The multivariate analysis identified female gender, body mass index > 25, and creatinine clearance above 70 mL/min as risk factors for vancomycin levels less than 10 mg/L.

Research conclusions

Although we arbitrarily considered vancomycin levels of 10 mg/L as a cut-off, the findings of our study are interesting because they suggest a high incidence of potentially suboptimal serum concentrations in the case of antimicrobial prophylaxis.

Research perspectives

Further studies will be necessary to define the cut-off of intraoperative vancomycin levels representing the optimal concentration of vancomycin for appropriate antimicrobial prophylaxis in patients undergoing cardiac surgery.

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META-ANALYSIS

Surgical left atrial appendage occlusion during cardiac surgery: A systematic review and meta-analysis

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Abstract

AIM

To evaluate the safety and efficacy of surgical left atrial appendage occlusion (s-LAAO) during concomitant cardiac surgery.

METHODS
We performed a comprehensive literature search through May 31st 2018 for all eligible studies comparing s-LAAO *vs* no occlusion in patients undergoing cardiac surgery. Clinical outcomes during follow-up included: embolic events, stroke, all-cause mortality, atrial fibrillation (AF), reoperation for bleeding and postoperative complications. We further stratified the analysis based on propensity matched studies and AF predominance.

RESULTS
Twelve studies (n = 40107) met the inclusion criteria. s-LAAO was associated with lower risk of embolic events (OR: 0.63, 95%CI: 0.53-0.76; P < 0.001) and stroke (OR: 0.68, 95%CI: 0.57-0.82; P < 0.0001). Stratified analysis demonstrated this association was more prominent in the AF predominant strata. There was no significant difference in the incidence risk of all-cause mortality, AF, and reoperation for bleeding and postoperative complications.

CONCLUSION
Concomitant s-LAAO during cardiac surgery was associated with lower risk of follow-up thromboembolic events and stroke, especially in those with AF without significant increase in adverse events. Further randomized trials to evaluate long-term benefits of s-LAAO are warranted.

Key words: Left atrial appendage; Left atrial appendage occlusion; Embolic events; Stroke; Adverse events

Core tip: Surgical left atrial appendage occlusion (s-LAAO) is performed during cardiac surgeries in patients with atrial fibrillation. However, evidence to perform routinely during cardiac surgeries is conflicting and contrasting. It is currently given a class Ⅱb recommendation in the professional medical society guidelines. We sought to perform a meta-analysis of all the studies published to date to evaluate the safety and efficacy of s-LAAO.

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INTRODUCTION

The left atrial appendage (LAA) is considered to be the dominant source of embolism (> 90%) in patients with non-valvular atrial fibrillation (AF)[1]. Occlusion or resection of the left atrial appendage occlusion (LAAO) remains an important intervention for prevention of recurrent emboli in patients who are at risk of stroke. LAAO provides an opportunity to avoid systemic anti-coagulation, thereby minimizing the risk of bleeding.

Surgical LAAO (s-LAAO) usually involves LAA closure while performing other cardiac surgeries. With the increasing prevalence of AF[2], there is a growing interest in the surgical community for s-LAAO. Prior studies assessing the clinical impact of surgical occlusion of the LAA during cardiac surgery have shown contradictory results[3-14]. Furthermore, there are no large scale randomized controlled trials evaluating routine s-LAAO during cardiac surgery. Therefore s-LAAO remains a class IIb recommendation in professional medical society guidelines[15,16]. Despite this recommendation, s-LAAO is routinely performed in patients with AF undergoing cardiac surgery. Therefore, we sought to perform a meta-analysis of the available studies published to date to evaluate the safety and efficacy of concomitant s-LAAO *vs* no occlusion during cardiac surgery[3,4,6-14].

MATERIALS AND METHODS

Search strategy

The systematic review and meta-analysis was done in compliance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines[17]. The PRISMA checklist is presented in Supplementary Table 1. The initial search strategy was developed by two authors (V.A and M.A.N). We performed a systematic search, without language restriction, using PubMed, EMBASE, SCOPUS, Google Scholar, and ClinicalTrials.gov from inception to May 31st, 2018 for studies comparing s-LAAO *vs* no occlusion- only in patients undergoing concomitant cardiac surgery. We used the following keywords and medical subject heading: "Cardiac surgeries" OR "Heart surgeries" OR "Cardiac surgical procedures" AND "Left atrial appendage" OR "occlusion" OR "ligation" OR "resection" OR "excision" OR "amputation".

Study selection and data extraction

Only studies comparing s-LAAO *vs* no occlusion during any cardiac surgery were included in our analysis. The reference lists of original studies, conference abstracts and relevant review articles were further reviewed. Two investigators (V.A and M.A.N) independently performed the literature search, reviewed the originally identified titles and abstracts and selected studies for pooled analysis based on the inclusion criteria. Any divergence was resolved through discussion with a third independent reviewer (M.K.T). The quality of observational studies was assessed using the Newcastle Ottawa scale, Supplementary Table 2.

Clinical outcomes

We evaluated the following clinical outcomes during follow-up in each report: (1) embolic events; (2) stroke; (3) all-cause mortality; (4) AF; (5) postoperative

complications; and (6) reoperation for bleeding. We further performed stratified meta-analysis to evaluate the potential source of heterogeneity across the included studies. Stratification factors are inclusion of only propensity matched studies and studies with AF predominant cohort (> 50% of study population having AF). The ischemic events attributed to embolic causes in the included studies were included in the embolic events. Complications included in the analysis are appendage tears, myocardial infarction, major bleeding, septicemia, pacemaker implants, renal failure, pericardial effusion, cardiac tamponade, and stroke.

Statistical analysis

The meta-analysis was done using Review Manager (RevMan), Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014. Due to methodological and clinical heterogeneity between the included studies, a random-effects model estimating the odds ratio (OR) and the estimated 95% confidence interval (CI) of the above-mentioned outcomes were used. The OR estimate of each study was calculated by the random-effects model obtained by the DerSimonian-Lariad method[18].

Heterogeneity was assessed using Higgins' and Thompson's I2 statistic, with I2 values of > 50% was considered significant. Publication bias was visually estimated by funnel plots. A 2-tailed $P < 0.05$ was considered statistically significant for all analyses.

RESULTS

Search results

A total of 1328 reports were retrieved during the initial search (Supplementary figure 1). 1049 reports were selected after removing 279 duplicates. 387 reports were screened and 354 were excluded. 33 reports were assessed for eligibility. Finally, after excluding 21 reports (no comparison groups-14, others-7) 12 studies were included. Among these 12 studies, three were randomized controlled trials (RCTs) and nine were observational studies. Among these nine observational studies, four were propensity matching studies[5,6,10,13]. one was case matching study[12]. The inter-reviewer agreement on study eligibility was 100%.

Study characteristics

The characteristics of the included studies are presented in Table 1 and Table 2. Out of 40107 patients included, 13535 patients received s-LAAO during cardiac surgery while the remaining 26572 patients did not receive s-LAAO. The mean (SD) age of the study population ranged from 50.7 (12.4) years to 77.4 (6.8) years. The primary cardiac operation varied widely. The surgical procedures were primarily valve surgery in the studies by Garcia-Fernandez, Nagpal, Lee and Elbadawi[3,5,8,12], while they were primarily coronary artery bypass grafting (CABG) in the studies by Healey, and Elbadawi[7,11]. Remaining studies included a combination of valve surgery and CABG. Lee *et al*[5] also performed ablation of AF together with mitral valve surgery. The prevalence of AF varied in the study cohorts. The s-LAAO techniques varied; the methods variously included double suturing, exclusion, amputation, resection and stapling (Table 2). The follow-up period ranged from in-hospital only to 109.2 mo.

Clinical outcomes

s-LAAO was associated with lower risk of embolic events (OR: 0.63, 95%CI: 0.53-0.76; $P < 0.001$) and a lower risk of stroke (OR: 0.68, 95%CI: 0.57-0.82; $P < 0.0001$) (Figure 1A and 1B). There was no significant difference in all-cause mortality between the two groups (OR: 0.83, 95%CI: 0.51-1.36; $P = 0.46$) (Figure 1C). There was no significant difference in the incidence of follow-up AF between the two groups (OR: 1.41, 95%CI: 0.79-2.52, $P = 0.24$) (Figure 1D).

With regard to postoperative complications, there was no significant difference between the groups (OR: 1.44, 95%CI: 0.91-2.25; $P = 0.12$) (Figure 1F). Similarly, there was no significant difference in the incidence of reoperation for bleeding between the two groups (OR: 0.98, 95%CI: 0.57-1.69; $P = 0.94$) (Figure 1G).

Test of heterogeneity and publication bias

Test of heterogeneity was not significant for follow-up embolic events (P heterogeneity = 0.60, I2 = 0%) and stroke ($P = 0.84$, I2 = 0%), while it was significant for all-cause mortality ($P < 0.001$, I2 = 92%), AF ($P < 0.001$, I2 = 95%), postoperative complications ($P = 0.004$, I2 = 66%) and reoperation for bleeding ($P = 0.20$, I2 = 36%).

Subgroup analysis

In subgroup analysis including only propensity matched studies, s-LAAO group had a trend towards lower risk of stroke (OR: 0.78, 95%CI: 0.60-1.00; $P = 0.05$), Supplementary Figure 2A. Test of heterogeneity was not significant ($P = 0.63$, I2 = 0%). There was no significant difference in the incidence of all-cause mortality (OR: 1.10, 95%CI: 0.34-3.60; $P = 0.87$), Supplementary Figure 2B**.** In subgroup analysis including only AF predominant studies (> 50%), s-LAAO was associated with lower risk of stroke (OR: 0.60, 95%CI: 0.46-0.78; $P = 0.0002$) (Supplementary Figure 3A). There was no significant difference in all-cause mortality (OR: 0.87, 95%CI: 0.11-7.12; $P = 0.89$) (Supplementary Figure 3B). Test of heterogeneity was not significant for stroke ($P = 0.86$, I2 = 0%) while it was significant for all-cause mortality ($P < 0.001$, I2 = 94%).

Funnel plot for visual inspection of publication bias is shown in Supplementary Figure 4.

DISCUSSION

The main findings of our meta-analysis of patients un-

Table 1 Characteristics of the included studies

Study, yr	Country	Study period	Study design	Sample size		Cardiac surgery type	Follow up period (mo)
				s-LAAO	No occlusion		
García-Fernández *et al*, 2003[3]	Spain	2003	retrospective	58	147	MVS	69.4 ± 67
Healey *et al*, 2005[7]	Germany	2001-2002	RCT	52	25	CABG	13 ± 7
Nagpal *et al*, 2009[8]	Canada	2007-2007	RCT	22	21	MVS	<1
Whitlock *et al*, 2013[9]	Canada	2009-2010	RCT	26	25	CABG and VS	1
Zapolanski *et al*, 2013[4]	United States	2005-2012	retrospective	808	969	CABG and VS	NR
Kim *et al*, 2013[6]	United States	2001-2010	retrospective	631	631	CABG and MVS	1
Lee *et al*, 2014[1][5]	Korea	1999-2011	retrospective	119	119	MVS with AF ablation	63 ± 44
Melduni *et al*, 2017[1][10]	United States	2000-2005	prospective	461	461	CABG and VS	109.2
Elbadawi *et al*, 2017[2][11]	United States	1998-2013	retrospective	652	652	VS	In-hospital
Elbadawi *et al*, 2017[12]	United States	2004-2013	retrospective	2519	12595	CABG	In-hospital
Friedman *et al*, 2018[14]	United States	2011-2012	retrospective	3892	6632	CABG, MVS, AVS	31.2
Yao *et al*, 2018[1][13]	United States	2009-2017	retrospective	4295	4295	CABG, VS	25.2 ± 22.8

RCT: Randomized controlled trial; CABG: Coronary artery bypass grafting; VS: Valvular surgery; MVS: Mitral valve surgery; AVS: Aortic valve surgery; AF: Atrial fibrillation. [1]Propensity match studies. [2]Case matching study.

Table 2 Baseline and procedural characteristics of included studies

Study	Age (mean ± SD)		Hypertension		AF (%)		Technique of s-LAAO
	s-LAAO	No occlusion	s-LAAO	No occlusion	s-LAAO	No occlusion	
García-Fernández *et al*, 2003[3]	63 ± 12	62 ± 10	NR	NR	NR		Double suturing
Healey *et al*, 2005[7]	72 ± 6	71 ± 5	75	92	17	8	Suture or stapler
Nagpal *et al*, 2009[8]	57.8 ± 13.3	59.2 ± 11.9	NR	NR	18	29	Resection
Whitlock *et al*, 2013[9]	77.4 ± 6.8	74.6 ± 7.6	92.3	92	100	100	Amputation and closure or stapler
Zapolanski *et al*, 2013[4]	70.52 ± 11.83		83.9	80.6	19.9	10.7	Double ligation
Kim *et al*, 2013[6]	66.6 ± 11.4	65.8 ± 11.6	80.9	73.1	NR	NR	Ligation and excision
Lee *et al*, 2014[5]	55.9 ± 12.2	50.7 ± 12.4	19.8	14.5	100	100	Amputation
Melduni *et al*, 2017[10]	67.4 ± 12.7	67.6 ± 13.5	59	61	47	45	Amputation, suturing or stapler
Elbadawi *et al*, 2017[11]	70.8 ± 10.2	71.2 ± 11.1	70.6	52.8	100	100	NR
Elbadawi *et al*, 2017[12]	71.3 ± 9	70.6 ± 8.7	78.5	76.1	100	100	NR
Friedman *et al*, 2018[14]	75 ± 5.9	76.4 ± 6.4	14.5	12.7	50.5	43.4	Any technique
Yao *et al*, 2018[13]	68.2 ± 10.6	65.8 ± 11.3	88.6	90.4	75.4	31.4	

dergoing s-LAAO during concomitant cardiac surgery are the following: (1) s-LAAO was associated with lower rates of embolic events and stroke; and (2) there was no significant difference in the incidence of all-cause mortality, postoperative complications or reoperations for bleeding between the two groups. The reduced risk of embolic events and stroke with s-LAAO was retained in the subgroup analysis including only studies with AF predominant population (Table 3).

The estimated global prevalence of AF is on the rise due to a demographic shift with more prevalent ageing population carrying a higher burden of comorbidities[19]. About 25% of the strokes in the United States are related to AF and about 90% of the strokes in non-valvular AF are caused by thrombi originating in LAA[20]. Anticoagulants, both warfarin and direct acting oral anticoagulants (DOACs) reduce the incidence of stroke by more than 60%[21,22] but they are associated with increasing risk of bleeding, and significant drug-drug interactions[16]. The benefits of anticoagulants are also limited by other issues including underutilization, poor compliance and cost[16].

The higher risk of stroke in the ageing population with AF has led to the increased adoption of LAA occlusion in clinical practice[23]. The two largest RCTs - PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) and PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) showed percutaneous LAAO being non-inferior to warfarin with respect to stroke rates and embolic events[24,25]. Following the success with percutaneous LAAO, there has been a resurgence of interest in s-LAAO within the surgical community, especially with increase in the aging population and rising prevalence of AF[6,10,14].

Our findings show that s-LAAO was associated with lower risk of follow-up embolic events and stroke. The association of lower risk of stroke was more prominent in subgroup with AF predominant population. S-LAAO theoretically prevents formation of thrombus in LAA. However, successful s-LAAO is largely influenced by LAA morphology, occlusion technique and also operator

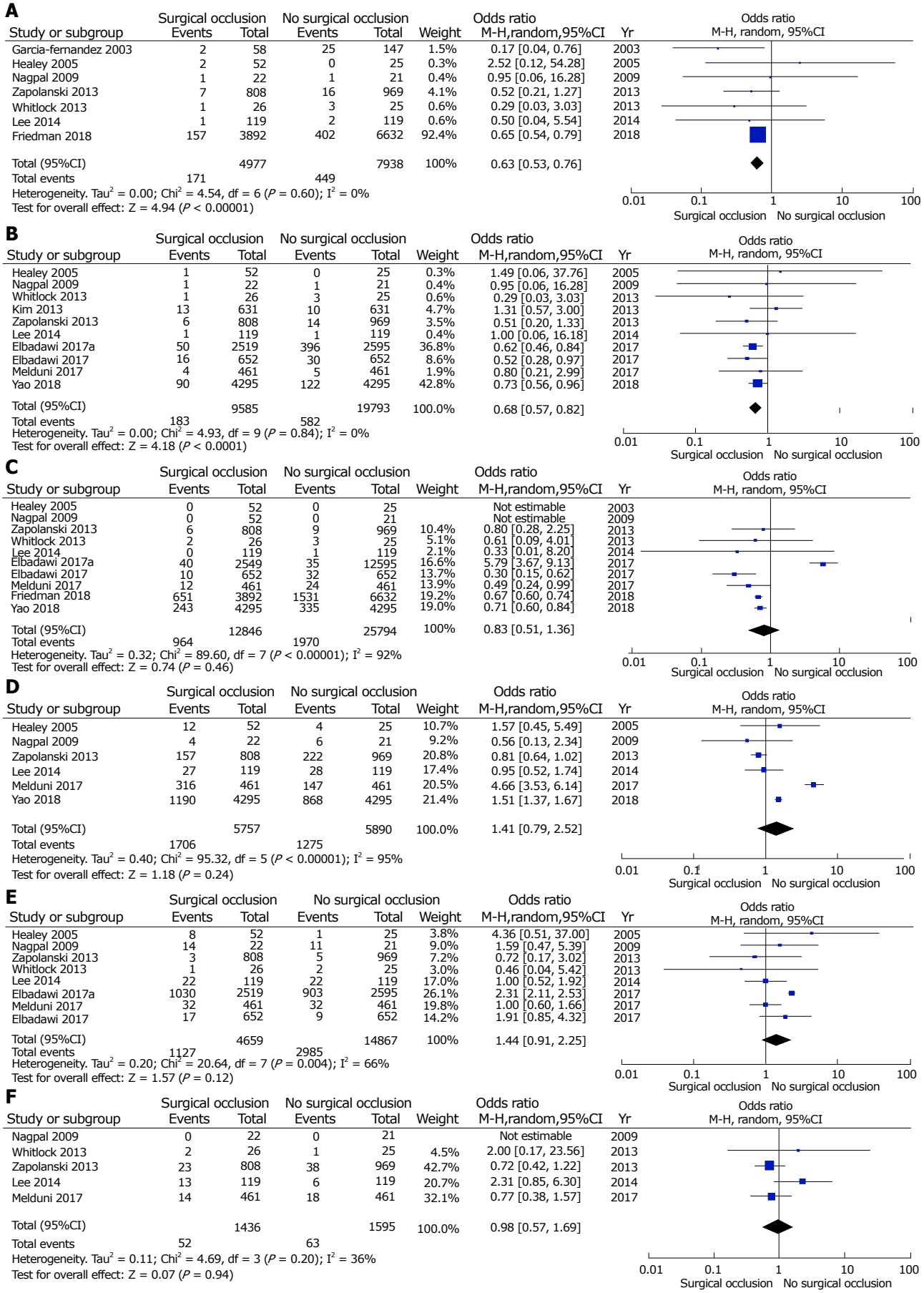

Figure 1 Forest plots for study outcomes. A: Embolic events; B: Stroke; C: All-cause mortality; D: Atrial fibrillation; E: Postoperative complications; F: Reoperation for bleeding.

Table 3 Complications reported in the individual studies

Study	Total complications	Type of complications	
	s-LAAO (%) *vs* No occlusion (%)	s-LAAO	No occlusion
Healey *et al*, 2005[7]	8 (52) *vs* 1 (4)	8- intraoperative LAA tears	1- LAA tear
Nagpal *et al*, 2009[8]	14 (63.6) *vs* 11 (52.3)	1- septicemia	1- RBC transfusion
		1- myocardial infarction	7- temporary pacemaker
		2- RBC transfusion	3- permanent pacemaker
		8- temporary pacemaker	
		2- permanent pacemaker	
Whitlock *et al*, 2013[9]	1 (3.8) *vs* 2 (25)	1- major bleeding	2- major bleeding
Zapolonski *et al*, 2013[4]	3 (0.3) *vs* 5 (0.6)	3- myocardial infarction	5- myocardial infarction
Lee *et al*, 2014[5]	22 (18.4) *vs* 22 (18.4)	9- requirement of dialysis	1- low cardiac output syndrome
		4- permanent pacemaker insertion	10- dialysis
		1- wound revision	2- permanent pacemaker insertion
		8- pericardial effusion	1- mediastinitis
			2- wound revision
			6- pericardial effusion
Melduni *et al*, 2017[10]	32 (6.9) *vs* 32 (6.9)	14- pneumonia	14- pneumonia
		18- acute renal failure	18- acute renal failure
Elbadawi *et al*, 2017[11]	17 (3.1) *vs* 9 (1.6)	17- pericardial effusion	7- pericardial effusion
			2- hemorrhage
Elbadawi *et al*, 2017[12]	1030 (40.8) *vs* 2903 (23)	16- cardiac tamponade	19- cardiac tamponade
		68- pericardial effusion	151- pericardial effusion
		917- hemorrhage	2687- hemorrhage
		29- postoperative shock	46- postoperative shock

RBC: Red blood cell; LAA: Left atrial appendage.

skill. A previous study showed that a complete LAA occlusion was achieved in only 40%-50% of the patient population[10,26]. The techniques of s-LAAO varied widely amongst the included studies as summarized in Table 2. The excision technique to exclude LAA has been shown to have a higher success rate than the other modalities of s-LAAO[24]. Currently, concomitant LAA closure is given a Class Ⅱb (level of evidence B) by the European Society of Cardiology (ESC)/European Society for Cardio-Thoracic Surgery (EACTS) guidelines and a Class IIb (level of evidence C) by the 2017 Society of Thoracic Surgeons guidelines (STS)[16]. Therefore, there is a wide practice level variation in the utilization of s-LAAO during cardiac surgery. The number of studies with a particular technique is inadequate to perform individual technique based meta-analysis so we combined all different techniques of s-LAAO in our meta-analysis. It should be noted that none of the other studies except the study from Friedman *et al*[14] reported long-term benefits. However, Friedman *et al*[14] showed a remarkable reduction in postoperative embolism at follow up. Further studies with long-term follow up of embolic events are essential. Our results are similar to a previous meta-analysis comparing s-LAAO vs no occlusion[27,28]. However, we included additional studies by Friedman *et al*[14], Elbadawi *et al*[11] and Yao *et al*[13] yielding a larger sample size. In addition, we performed a subgroup analysis of the included studies to identify the patient population that is most likely to benefit from this procedure.

In the current study, we found no significant difference in the risk of postoperative complications and reoperation for bleeding. s-LAAO is associated with inherent risk of procedural complications including LAA tears as observed in the study by Healey *et al*[7] and so learning curve plays an essential role in success of the procedure. Hypothetically, avoidance of aggressive anticoagulation after s-LAAO might have contributed to some of the benefits observed with s-LAAO. However, only few studies reported the long-term details of anticoagulation. Lee *et al*[5] reported no difference in the utilization of anticoagulation between the two groups (62.2% *vs* 55.4%). In the study by Friedman *et al*[14], anticoagulation was prescribed to 68.9% of the patients in the s-LAAO group compared to only 60.3% in the group without s-LAAO. In contrast to percutaneous LAAO, evidence regarding the utilization of anticoagulation after s-LAAO is not clear. The 2016 ESC/EACTS guidelines still recommend therapeutic anti-coagulation in all patients despite s-LAAO (Class Ⅰ, level of evidence B)[15]. With lack of long term data, there is need for prospective trials to address this issue. The ongoing LAAOS-Ⅲ (left atrial appendage occlusion study Ⅲ) and the ATLAS (AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures) trials should be able to provide further insights into the benefits of s-LAAO.

LIMITATIONS

Our study should be viewed in the context of following limitations. First, due to the small number of studies with small sample sizes, except the study by Friedman *et al*[14], the results might be underpowered to detect the true clinical benefits of certain clinical outcomes. Second, there was a wide variation of surgical techniques of LAAO, so we were not able to address the effect of individual techniques. Third, only Friedman *et*

al[14] reported long-term embolic events, whereas the other studies did not report long term outcomes. The study by Friedman *et al*[14] reported readmissions for embolic events, so some of the events which did not require hospitalization were not included. The effect of anticoagulation on postoperative outcomes remains unclear due to inadequate reporting in the included studies. Fourth, it is unclear if s-LAAO increases the duration of the surgical procedure as it was only reported in two studies. Fifth, the burden of AF varied among the included studies, thus carrying risk of a selection bias. Finally, publication bias is an inherent limitation of any meta-analysis.

CONCLUSION

In conclusion, our results support the safety of s-LAAO and favor its continued use in conjunction with concomitant cardiac surgery, especially in patients with AF. Randomized controlled trials are essential to evaluate the long-term benefits of s-LAAO.

ARTICLE HIGHLIGHTS

Research background

The left atrial appendage (LAA) is a common site for intracardiac thrombus formation in patients with atrial fibrillation (AF). Surgical left atrial appendage occlusion (s-LAAO) during concomitant cardiac surgery has been evaluated as an effective treatment approach to reduce the risk of stroke and embolic events.

Research motivation

Percutaneous LAAO has been shown to be non-inferior compared with warfarin in reducing the risk of stroke and embolic events in two large randomized controlled trials, PROTECT-AF and PREVAIL. However, data regarding s-LAAO is conflicting and contrasting. So, we performed a systematic review and meta-analysis of all the studies published to date to evaluate if concomitant s-LAAO during cardiac surgery is safe and effective.

Research objectives

The purpose of this study is to evaluate the safety and efficacy of concomitant s-LAAO during cardiac surgery.

Research methods

We searched five databases for studies comparing concomitant s-LAAO with no occlusion during cardiac surgery. We obtained a total of 12 studies for inclusion and performed a meta-analysis. The outcomes of interest were embolic events, stroke, all-cause mortality, AF, postoperative complications and reoperation for bleeding.

Research results

Concomitant s-LAAO during cardiac surgery was associated with lower risk of embolic events and stroke. This was evident in the AF predominant strata as well. There was no significant difference in the risk of all-cause mortality, AF, postoperative complications and reoperation for bleeding.

Research conclusions

Our meta-analysis including all the studies published to date comparing concomitant s-LAAO against no occlusion during cardiac surgery supports the use of concomitant s-LAAO during cardiac surgeries. It was associated with lower risk of stroke and embolic events.

Research perspectives

From this meta-analysis, it could be seen that concomitant s-LAAO during cardiac surgeries was associated with lower risk of stroke and embolic events compared with no occlusion. This association was prominent amongst the AF predominant strata as well. These beneficial effects could be seen due to the occlusion of LAA which is the source of 90% thrombi in non-valvular AF. Future randomized trials are needed to evaluate the long term benefits of s-LAAO.

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