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REVIEW

Fundamentals of percutaneous coronary bifurcation interventions

Tamer Kırat

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Abstract

Coronary bifurcation lesions (CBLs) account for 15%-20% of all percutaneous coronary interventions. The complex nature of these lesions is responsible for poorer procedural, early and late outcomes. This complex lesion subset has received great attention in the interventional cardiac community, and multiple stenting techniques have been developed. Of these, the provisional stenting technique is most often the default strategy; however, the elective double stenting (EDS) technique is preferred in certain subsets of complex CBLs. The double kissing crush technique may be the preferred EDS technique because of its efficacy and safety in comparative trials; however, this technique consists of many steps and requires training. Many new methods have recently been added to the EDS techniques to provide better stent scaffolding and to reduce early and late adverse outcomes. Intravascular imaging is necessary to determine the interventional strategy and postinterventional results. This review discusses the basic concepts, contemporary percutaneous interventional technical approaches, new methods, and controversial treatment issues of CBLs.

Key Words: Percutaneous coronary intervention; Coronary artery disease; Drug-eluting stents; Bifurcation lesion; Stenting technique; Left main intervention

Core Tip: Coronary bifurcation lesions are one of the most challenging subsets in percutaneous interventions. Many different interventional techniques have been used to overcome the relatively poor procedural and long term outcomes of these lesions of great interest. In this review, basic aspects of coronary bifurcation lesions and step-by-step classical stenting techniques, as well as recently introduced techniques, modifications, trials and important issues in the latest guidelines are discussed.

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INTRODUCTION

Percutaneous interventions of coronary bifurcation lesions (CBLs) are not only technically challenging, with lower procedural success and higher complication rates, but also have higher thrombosis and restenosis rates than nonbifurcation lesions[1-3]. The broad anatomical (*i.e.*, bifurcation site and angle, and vessel diameters) and pathological (*i.e.*, severity, locations and lengths of the atherosclerotic plaques) spectrum of CBL, as well as dynamic changes (carina, plaque shift and dissection) during intervention are responsible for the complexity of these lesions[3,4]. Many stenting and other interventional techniques have been developed and are used to provide optimum stent scaffolding, resulting in fewer clinical adverse outcomes. Operators should be familiar with these techniques and the basic aspects of CBLs.

BASIC ASPECTS

Anatomy

In epicardial coronary arteries, bifurcations show a fractal geometry[5] (a fractal is a geometric shape in which every smaller structure is similar to the whole part). This geometry provides minimum energy consumption and the optimum amount of blood required for the underlying myocardium[6]. A coronary bifurcation consists of a flow divider (carina) and three vessel segments: The proximal main vessel (PMV), the distal main vessel (DMV) and the side branch (SB) (Figure 1). There is a constant relationship between these three vessels that was identified by Murray's law 95 years ago[7] as:

$(\text{Diameter of PMV})^3 = (\text{Diameter of DMV})^3 + (\text{Diameter of SB})^3$

Nearly a decade ago, this law was modified in human coronary arteries by the Huo-Kassab law[8] as:

$(\text{Diameter of PMV})^{7/3} = (\text{Diameter of DMV})^{7/3} + (\text{Diameter of SB})^{7/3}$

Nearly at the same time, Finet's formula was created by IVUS measurements in normal human coronary arteries[9] as:

(Diameter of PMV) = 0.678 (*i.e.*, approximately 2/3) × (Diameter of DMV + Diameter of SB)

Huo *et al*[10] compared these 2 Laws and Finet's formula in the epicardial coronary bifurcations of patients and swine in a later study. They found that Huo-Kassab law accurately predicts all size diameters of the epicardial coronary bifurcation vessels whereas Murray's law and Finet's formula can only do so in certain size subsets[10]. However, due to its simplicity, Finet's formula is the most commonly used in clinical practice in most angiography units.

The polygon of confluence (POC) is an independent area between the PMV, DMV and SB whose boundaries are formed by the lines drawn vertically in the ostium of branches and at the end of the PMV (Figure 1)[11,12]. Finally, the bifurcation angle (carinal angle) is important in accessing the SB and in the decision of the stent treatment strategy.

Definition

A bifurcation lesion is a major epicardial coronary artery stenosis next to and/or including the ostium of a significant side branch[13,14]. A significant SB is a branch whose severe narrowing or acute occlusion before or during intervention can cause considerable ischemia or a new infarction area that will worsen the clinical course of a particular patient. To determine the significance of the SB, not only the diameter, length, location and collateral function of the SB but also the symptoms, left ventricular function and viability of the supplied myocardium should be evaluated[13,14].

Pathophysiology of atherosclerosis in CBL

Bifurcations are among the sites most affected by atherosclerotic processes in the coronary tree. *In vitro* and recent *in vivo* studies on the anatomy and flow patterns of coronary bifurcations have shown that local flow disturbances and thus endothelial shear stress (ESS) play the most important role in the localization and progression of atherosclerotic plaques[15]. ESS is the tangential force caused by the friction of the flowing blood on the endothelial surface[16]. The major determinants of ESS are the blood viscosity and the spatial gradient of the blood velocity. Endothelial mechanoreceptors sense ESS; and in response to high ESS, these receptors induce many intracellular signaling pathways resulting in the expression of many atheroprotective genes and suppression of many proatherogenic genes. Conversely, in the case of low or oscillatory ESS, atheroprotective genes are suppressed and proatherogenic genes that promote atherosclerosis are upregulated[15-17]. Indeed, in IVUS and autopsy studies of bifurcation

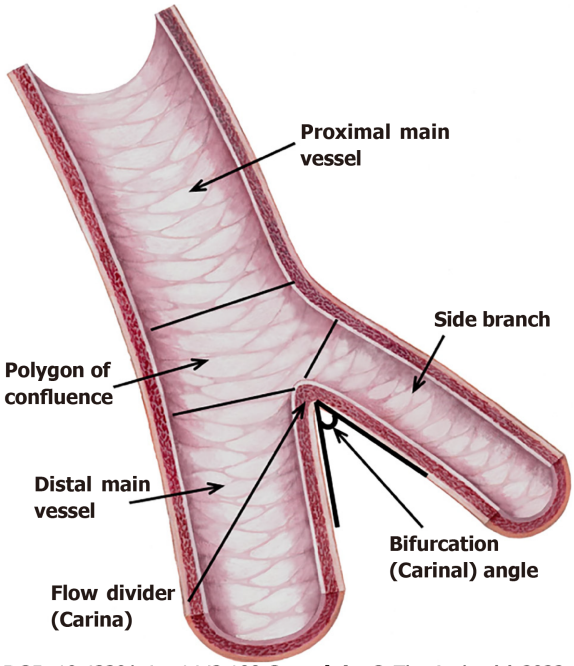

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Figure 1 Coronary bifurcation anatomy.

lesions, atherosclerosis was most frequently demonstrated in the lateral walls of MVs and side branches where ESS was low and oscillatory and uncommon in the carina where ESS was high[18]. Moreover, the carinal angle was found to affect the severity of atherosclerosis as larger angles have been correlated with increased plaque burden[19]. This is again explained by the role of ESS since larger angles produce lower and more oscillatory ESS in the lateral walls of the bifurcation vessels. Finally, in addition to its most important role in plaque initiation and progression, low ESS has also been found to be associated with rupture-prone atherosclerotic plaque formation[19]. Thus, CBLs have an increased tendency for plaque rupture, platelet aggregation and atherothrombosis[20].

Classification

Various angiographic classifications of CBL have been proposed[21]. Because of its simplicity, the easiest to remember and most prevalently used is the Medina classification[22]. This classification is established on the presence ("1") or absence ("0") of significant stenosis (≥ 50%) in the proximal main vessel (MV), distal MV and SB in CBLs, respectively (Figure 2). According to this classification, two different types are described: "true" and "non-true " CBLs. Significant stenosis (≥ 50%) in both vessels (proximal MV and/or distal MV and SB), *i.e.*, Medina 1,1,1/1,0,1 and 0,1,1 classes are defined as "true", while all others are defined as "non-true" CBLs. "True" bifurcation lesions are more complex and more difficult to treat with poorer outcomes than "non-true" types[23]. However, in true bifurcation lesions, Medina 1,1,1 and 0,1,1 lesions were found to have a higher risk of cardiac death, myocardial infarction (MI), and more SB occlusion than Medina 1,0,1 lesions[23]; and only these two classes have been taken as the criterion or one of the criteria of complex true lesions in many bifurcation (especially left main) trials.

Finally, the Medina classification does not consider other important information that may direct treatment strategies, such as lesion size and length, calcification and bifurcation angles. Therefore, additional modalities such as multislice computed tomography (MSCT), intravascular ultrasound (IVUS), optical coherence tomography (OCT) and fractional flow reserve (FFR) or other functional tests may be necessary to clarify the true classification of a bifurcation lesion and to determine the treatment strategy[24].

PERCUTANEOUS CORONARY INTERVENTION (PCI) TECHNIQUES

Classification

Many stenting techniques have been developed and published. For simplicity, these techniques were classified by the European Bifurcation Club (EBC) as "MADS" in 2008. However, some techniques have been abandoned due to adverse outcomes or lack of effectivity. Therefore, an updated new classification called "MADS-2" was created by the EBC in 2020[25]. This classification is based on the location of the

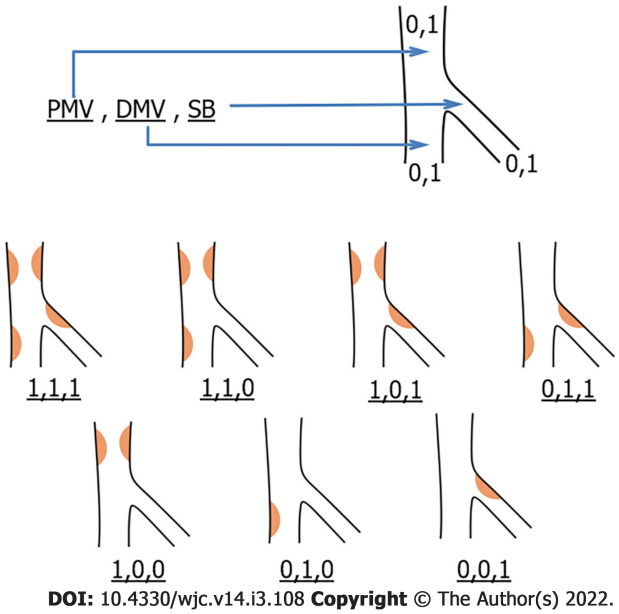

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Figure 2 Medina classification. "1" indicates ≥ 50% stenosis, and "0" indicates < 50% stenosis. Atherosclerosis is most often seen in the lateral walls of vessels where endothelial shear stress is low and oscillatory. DMV: Distal main vessel; PMV: Proximal main vessel; SB: Side branch.

first stent implanted (as Main vessel, Across side branch, Double lumen in proximal MV or Side branch). Balloon applications and dedicated bifurcation stent types are added to the original form in this new classification[25].

Although MADS-2 involves many stenting techniques, the most widely used major bifurcation stenting techniques recommended by the EBC are as follows[25]: (1) One-stent techniques: The provisional stenting technique (PST) and inverted provisional stenting technique; and (2) Two-stent techniques (Elective, or bail-out in PST): (a) T/T and protrusion (TAP) stenting; (b) Culotte/inverted culotte stenting techniques; and (c) Double kissing (DK)-crush technique.

Vascular access and guiding catheter selection

In one-stent techniques, most CBLs can be treated transradially or transfemorally using a 6 Fr guiding catheter (GC). However, if a rotablator with a burr size ≥ 2 mm is used or more than two balloons are used simultaneously in the GC, a 7 Fr or larger GC is required[26]. Although transfemoral is the most preferred route in this situation, an increasing number of operators prefer the transradial route using slender sheaths or sheathless guiding catheters.

Two-stent techniques can also be performed using 6 Fr GC except when there are two stents in the GC at the same time, such as mini-crush, V or simultaneous kissing stenting techniques[27].

Due to the challenging interventional nature of CBLs, guiding catheters with strong support (such as extra back-up guiding catheters for the left coronary artery and AL 0.75, AL1 or AR2 for the right coronary artery (RCA)) should be preferred[28].

Optimal views for bifurcation lesions[28,29]: (1) Left main coronary artery (LMCA) bifurcation: (a) Working view: RAO caudal (0–30°, 25–30°); and (b) Side branch ostium visualization: LAO caudal (30–60°, 25–30°), AP caudal (0, 45-55°); (2) LAD-first diagonal bifurcation: (a) Working view: RAO cranial (10°, 40°); and (b) Side branch ostium visualization: AP/LAO cranial (0–45°, 25–70°); (3) For early diagonals: LAO caudal (45–55°, 25–30°); (4) LCx-first marginal: (a) Working view: RAO caudal (0–15°, 25°); (b) Side branch ostium visualization: AP caudal (0, 25°–40°), LAO caudal (45–55°, 25–30°); and (5) RCA-PDA/PL: (a) Working view: LAO 35–50°; and (b) Side branch ostium visualization: AP/LAO cranial (0–55°, 30-40°).

Which technique should be selected? The PST or the elective double stenting technique?

Most of the randomized comparative trials prior to the mid-2010s showed no difference in major adverse cardiovascular events (MACE) between the PST and elective double stenting (EDS) techniques [26,30,31]. Even, lower mortality rates were found for the PST compared to EDS in two recent meta-analyses[32,33]. As a result, the provisional stenting technique has been recommended as the default strategy for CBLs in the guidelines and consensus statements for more than 15 years. However, it should be noted that the EDS techniques in these trials and meta-analyses were the culotte, T, and crush techniques. After the introduction of the DK-crush technique, in 2011, Chen *et al*[34] showed that there was a significant reduction in target lesion revascularization (TLR) and target vascular revascularization (TVR) rates in favor of the DK-crush technique *vs* the PST with no MACE differences in complex true

bifurcation lesions in the DKCRUSH II trial. Later, the DKCRUSH III trial showed that the culotte stenting technique was worse than the DK-crush technique in terms of MACE in patients with unprotected left main (LMCA) bifurcation lesions[35]. Moreover, the DKCRUSH V study presented in 2017 found a lower rate of target lesion failure (TLF) at 1 year with the DK-crush technique than with the PST in complex true LMCA bifurcation lesions[36].

Recently, the 3-year outcomes of the DKCRUSH V trial were published and confirmed the one-year results and additionally showed a reduction in the stent thrombosis rate in favor of the DK-crush technique[37]. Crimi *et al*[38] found that the DK-crush technique lowered device-oriented clinical events (defined as a composite of cardiac death, target-vessel MI, stent thrombosis and TLR or TVR) *vs* the PST and other EDS techniques in their recent meta-analysis. In another concurrent network meta-analysis, Di Gioia *et al*[39] showed that TLR was significantly lower with the DK-crush technique than with the PST and other EDS techniques with no differences in cardiac death, MI or stent thrombosis rates. In addition, in this meta-analysis, a clinical benefit was observed with EDS techniques over PST in CBL with SB lesion lengths ≥ 10 mm. In the recently published DEFINITION II trial, complex bifurcation lesions were defined by the sum of various criteria, as shown in Table 1. In this trial, the EDS technique (DK-crush 77.8%, culotte 17.9%, and other 4.3%) provided a significant reduction in TLF (mainly driven by target vessel MI and clinically driven TLR) compared to the PST in the defined complex bifurcation lesions at one year[40].

Despite the favorable results of the DK-crush technique in randomized studies and two meta-analyses, the recent guidelines still recommend the PST as the default strategy for complex CBLs and a class IIb indication for the DK-crush technique over the PST in true LMCA bifurcations[25,41-43]. The reason for this may be some reservations that have been described[30]: (1) The DK-crush technique has multiple steps and is a challenging technique; (2) The DKCRUSH trials mostly come from the same group of interventional experts who have performed this procedure for many years; and (3) The PST results in these trials were worse than previously published ones, which might be associated with a high SB stenting rate (29%-47%) due to the high rate of long SB lesions (mean 15-17 mm).

When deciding between the PST and EDS, the high risk of SB occlusion should also be considered, as SB occlusion may result in serious adverse clinical outcomes[44]. SB occlusion predictors by angiography, IVUS and OCT have been described recently[44,45]. Angiographically, plaque on the same side of the SB, SB stenosis > 50%, POC stenosis > 50%, bifurcation angle > 70%, MV/SB diameter ratio (diameter of PMV+DMV/2×diameter of SB) > 1 and a low MV TIMI flow grade were found to be predictors of SB occlusion after MV stenting. A risk score was described based on these predictors[44]. According to this risk score, higher stenosis rates, larger bifurcation angles, larger MV/SB diameter ratios, a lower TIMI flow grade, and more predictors result in higher SB occlusion rates[44].

The recently published EBC-MAIN study, which compared the PST and EDS techniques in LMCA bifurcation lesions, showed that there were fewer MACE in the PST than EDS, although the difference was statistically insignificant. The authors consequently recommended the PST as the default strategy for LMCA bifurcation lesions. However, it should be noted that the DK-crush technique was used in only 5% of the EDS patients in this trial. In addition, the mean lesion lengths of the side vessels were not long: 5.8 cm and 7.9 cm in the PST and EDS patients, respectively[46].

Consequently, for non-true CBL, the default strategy is the PST[47]. In true complex CBL (Medina 1,1,1 or 0,1,1), if the SB is ≥ 2.5 mm and the SB lesion length ≥ 10 mm or the likelihood of SB occlusion is high or SB wiring is difficult, it is better to choose EDS; otherwise, the PST is preferred[38,39,41,45,48]. In true non-complex CBL (Medina 1,0,1), the inverted PST may be an appropriate treatment if there is no large difference between the SB and the PMV diameter[42]; otherwise, and in the case of the above risks, EDS may be preferred[39,45,48,49]. A proposed algorithm for choosing between the PST/inverted PST and the EDS technique is shown in Figure 3.

The ongoing BBK3 trial will provide more data on the outcomes of the PST or EDS techniques in non-LMCA bifurcation lesions[50].

The choice between the different EDS techniques depends partially on the bifurcation angle. The T technique can only be applied at bifurcation angles very close to 90°[25]. The TAP technique can be performed at bifurcation angles from 70°-90°. Culotte/inverted culotte stenting and the DK-crush techniques (unlike the crush technique) can be implemented regardless of the bifurcation angle[51,52]; however, applying the culotte technique at < 70° angles gives better results[35]. If the bifurcation angle is from 70°-90°, due to simplicity and familiarity, an increasing number of operators are using the T/TAP technique not only when a second stent is required in the PST[53] but also in the EDS technique as the first-line therapy and perform the culotte/inverted culotte or DK-crush techniques if the angle is < 70° [41,54].

In conclusion, in view of recent data, the DK-crush technique may be preferred over the other two-stent techniques regardless of the bifurcation angle; however, it is a complex procedure with many steps, and the operator's familiarity with a particular technique is an important factor in the choice of which EDS technique to perform and in obtaining the best result[45].

Table 1 DEFINITION criteria for a complex coronary bifurcation lesion[40]

Major criteria	Complex lesion definition	Minor criteria
For left main bifurcation (Major 1)	**Major 1 or Major 2 + any 2 minor criteria**	> Mild calcification
SB lesion length ≥10 mm and SB diameter stenosis ≥ 70%		Multiple lesions
		Bifurcation angle < 45° or > 70°
For non-left main bifurcation (Major 2)		MV-RVD < 2.5 mm
SB lesion length ≥ 10 mm and SB diameter stenosis ≥ 90%		MV lesion length ≥ 25 mm
		Thrombus-containing lesions

All bifurcation lesions are in Medina 1,1,1 or 0,1,1. MV: Main vessel; RVD: Reference vessel diameter; SB: Side branch

PST

The step-by-step PST is shown in Figure 4.

Wiring the vessels

In addition to the MV, the SB should also be wired in all CBLs. This wire helps to prevent SB occlusion after MV stenting, serves as a marker in case of SB occlusion, widens the angle between the PMV and SB for easier access, enhances support of the guiding catheter, and finally can be used as a rescue balloon guidewire that will be described later. To prevent the two wires from wrapping, the more difficult vessel (mostly the SB) should be wired first, and the second wire should be inserted without much manipulation.

Wire types and shaping

The types of wires are left to the operator's preference. Any type of wire (hydrophilic with or without polymer coating and hydrophobic) can be used[55,56]. One necessary point is not to jail the radiopaque tip part of the wire in the SB ostium during MV stenting.

Both wires should be ready for the exchange technique if needed after MV stenting. To accomplish this, the MV guidewire tip should be angled so that its length will be longer than the proximal MV reference diameter to reach the SB ostium. A 1-1.5 mm secondary bend can also be added to the tip to hook the struts of the MV stent[57]. The SB wire should be prepared as a sharp angled short tip that will make it easier to create a "U" shape to pass through the MV stent during wire exchange[58]. The MV wire should not be pushed too distally in order to maintain the shape of the tip for exchange and to reduce the risk of distal perforation or dissection that can occur during many maneuvers.

Troubleshooting SB wiring problems

SB wiring may be difficult in the following circumstances: a bifurcation angle greater than 70°-90°, severe ostial SB stenosis, MV stenosis or severe calcifications in the proximal MV and/or ostial SB. In addition, tortuosity before or at the SB take-off may flatten or change the angle of the wire, resulting in difficult SB wiring[58].

Possible solutions for solving the SB wiring problem are the following[52,58]: (1) If the problem is wide angulation, a wide smooth bend or double bend shape given to the tip can help; (2) The workhorse wire can be replaced with a stiffer or hydrophilic polymer-coated wire. Stiffer wires are preferred first because hydrophilic wires can easily go subintimally and cause dissection or perforation; (3) Pull-back wire technique: A wide smooth bent or double bent wire is advanced into the DMV and pulled back to intubate the SB ostium. After intubating, a gentle counterclockwise rotation allows the wire to advance in the SB; (4) Reverse wire technique: When the SB has an excessively angled take-off (greater than 90°), a polymer-jacket wire with a 3-5 cm tip bent 180°, like a hairpin, is used in this technique (Figure 5). The wire is advanced in the DMV and pulled back to the bifurcation, and an attempt is made to enter the SB ostium. After intubation, the wire is gently withdrawn and gently rotated counterclockwise to allow the wire to advance in the SB; (5) A dual lumen microcatheter, a steerable-tip microcatheter (Venture, Teleflex, Wayne, PA, United States) or an angled microcatheter (SuperCross 45-90-120°-XT, Teleflex) can be used to direct the wire to the SB; (6) When there is a large plaque burden that prevents wiring the SB, debulking techniques such as rotational/orbital atherectomy or laser may be used; (7) Balloon dilatation of the MV to modify the plaque is performed by many operators as a last effort. However, it can cause plaque and/or carina shift, resulting in SB occlusion; and (8) Finally, if the SB cannot be wired, the decision to abandon the procedure can be made based on the patient's clinicopathological condition.

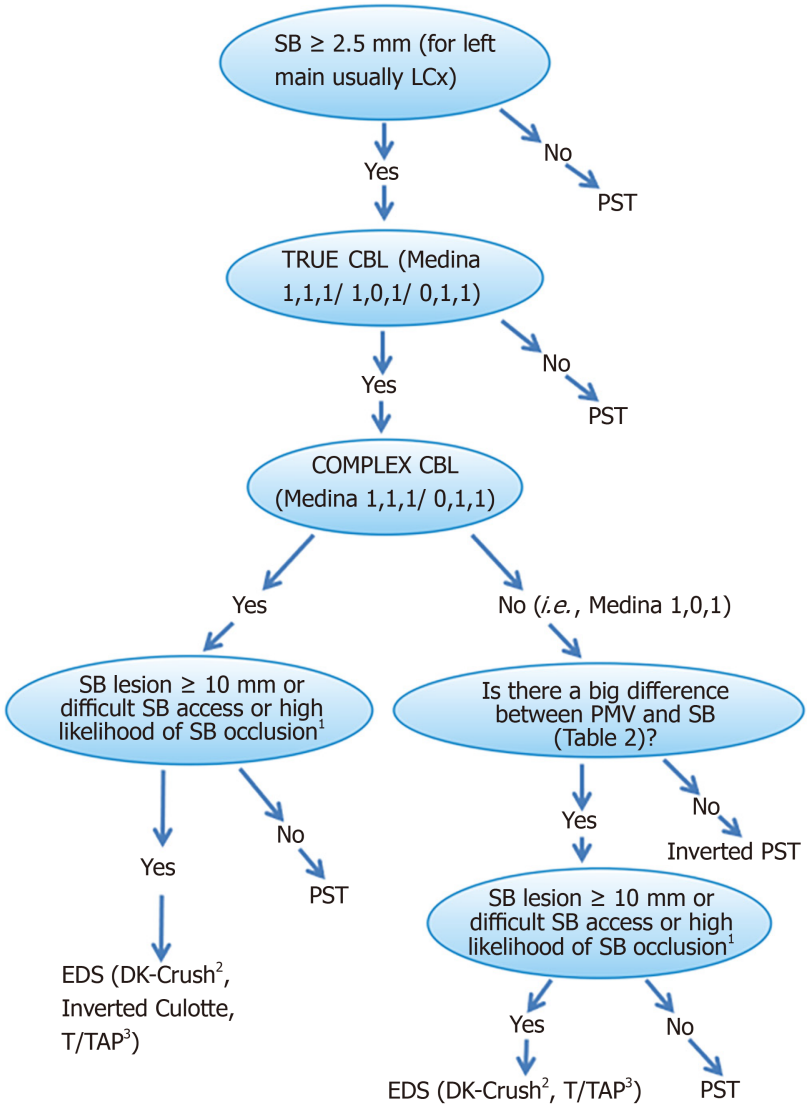

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Figure 3 Proposed algorithm for selecting an optimum percutaneous coronary intervention strategy in both left main coronary artery and non-left main coronary artery bifurcation lesions. [1]Plaque on the same side of SB, SB stenosis > 50%, POC stenosis > 50%, bifurcation angle > 70%, MV/SB diameter ratio (diameter of PMV+DMV/2×diameter of SB) >1 and low MV TIMI flow grade are predictors of a high likelihood of SB occlusion. The larger the size of the numbers and/or the lower the TIMI flow grade and/or the more predictors, the higher the risk of SB occlusion. A recently created SB occlusion risk score may be used[44]. [2]The DK-crush technique seems to be preferable to the other EDS techniques in view of the recent data; however, the operator's experience is decisive in the choice between the EDS technique and is important in obtaining the best result. [3]The TAP technique cannot be considered the upfront technique in cases with difficult SB access and a high risk of SB occlusion because of SB stenting after MV stenting. CBL: Coronary bifurcation lesion; EDS: Elective double stenting; LCx: Left circumflex artery; LMCA: Left main coronary artery; MV: Main vessel; POC: Polygon of confluence; PST: Provisional stenting technique; SB: Side branch.

Predilation of the MV and the SB

Optimal preparation of the MV is necessary before stenting. Therefore, the operator can decide to predilate the MV and/or perform any debulking procedure according to the MV lesion properties.

Routine predilation of the SB has been a controversial issue in the PST. Predilation aims to prevent SB closure after MV stenting; however, it can cause dissection that may prevent guidewire advancement during wire exchange or may require an extra stent in the SB. A prospective randomized study showed that SB predilation resulted in improved flow with less need to treat the SB[59]. However, another double-blind smaller randomized study and a recent meta-analysis of eight trials demonstrated the opposite: SB predilation increased SB intervention rates and made no difference in procedural angiographic and long-term major cardiovascular outcomes[60,61]. Consequently, it seems that routine predilation of the SB cannot be recommended currently. Conditions that favor SB predilation with an undersized non-compliant balloon are severe ostial SB narrowing, extensive SB calcification, difficult SB access or decreased flow after MB predilation and/or debulking[14,49].

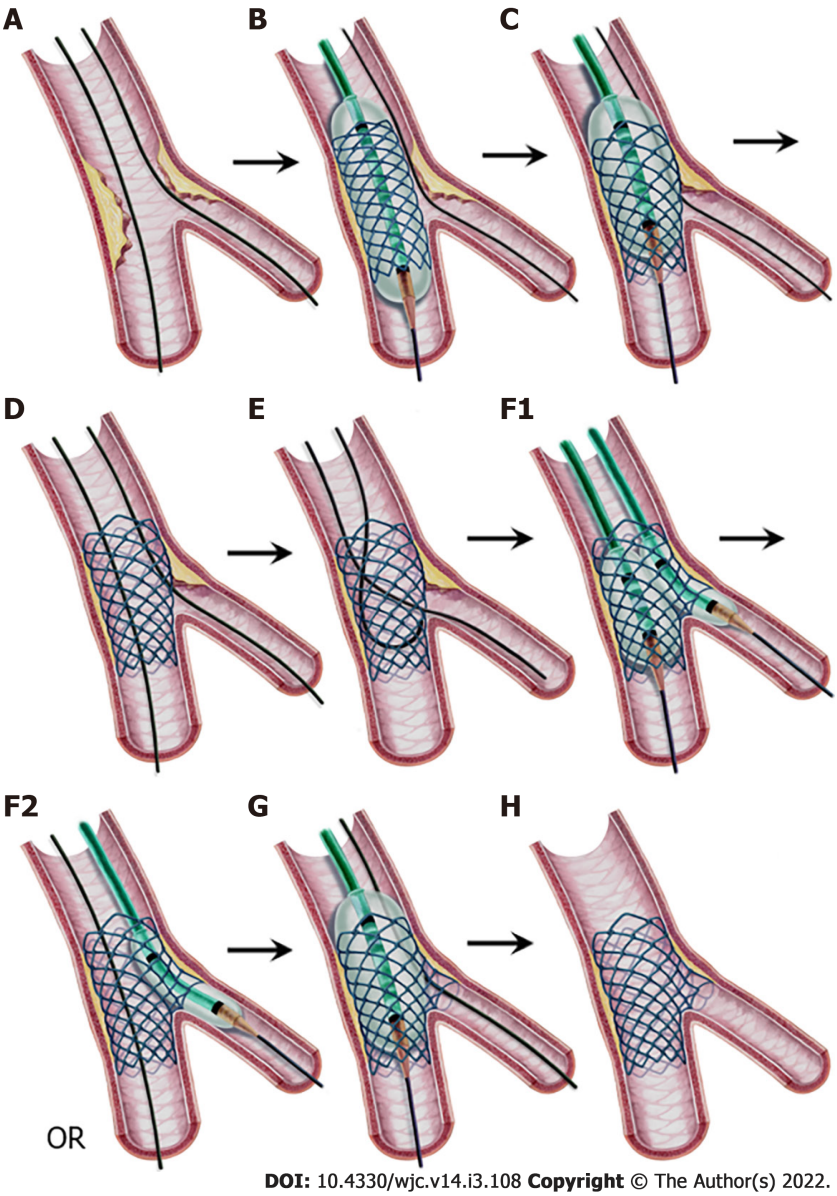

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Figure 4 Provisional stenting technique, step-by-step. A: Both branches are wired; B: A stent sized to the distal MV diameter is implanted in the MV; C: Proximal optimization technique (POT) application with a balloon sized to the proximal MV diameter with its distal shoulder aligned to the carina; D: Stent view after POT. If the result is satisfactory, stop here. If not, proceed to step E; E: Guidewire exchange; First, the SB is wired through the most distal cell. Second, the retracted and released SB wire is advanced into the distal MV as a "U" shape; F1: Kissing balloon inflation sized to branch diameters, or F2: SB ostium ballooning as a part of the POT-side-POT technique; G: Final POT; and H: Final result. MV: Main vessel; POT: Proximal optimization technique; SB: Side branch.

When the SB is predilated, the angiographic result should be carefully evaluated before MV stenting. In situations where the SB is compromised, such as dissection or difficult SB access, the operator should be ready to change the stenting strategy to another strategy, such as the inverted PST or the DK-crush technique[49].

Newer side branch protection techniques

To prevent side branch occlusion during the PST, various novel techniques have been developed recently: the pre-kissing technique, jailed balloon, jailed semi-inflated balloon and modified jailed balloon techniques. The pre-kissing technique involves the simultaneous dilation of two undersized balloons (one in the MV and the other in the SB) whose proximal parts are aligned in the proximal MV before MV stenting. The aim of this technique is to sustain the central position of the carina while moving the atherosclerotic plaques away. Using first-generation drug eluting stents (DESs), this technique was shown to reduce SB-related complications in a small retrospective study[62].

The jailed balloon technique (JBT) and the jailed semi-inflated balloon technique (JSBT) involve implanting an MV stent while a semi-compliant balloon is in the SB protruding to the MV. The proximal marker of the SB balloon is positioned to align or 1-2 mm proximal to the marker of the MV stent (Figure 6). The SB balloon is uninflated (JBT) or inflated to low or moderate pressure (< 3 to 7 atm)

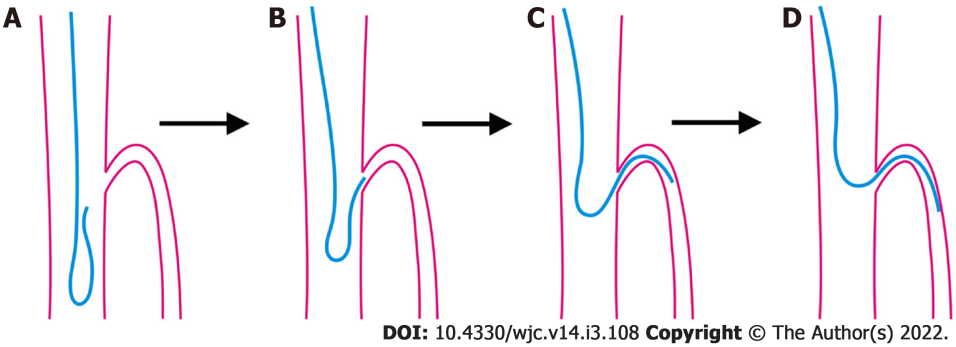

Figure 5 Reverse wire technique. A, B: The wire shaped as a hairpin is advanced into the distal main vessel and withdrawn back to the carina; C, D: When the tip intubates the side branch (SB) ostium, slight withdrawal and gentle counterclockwise rotation allow the wire to advance in the SB.

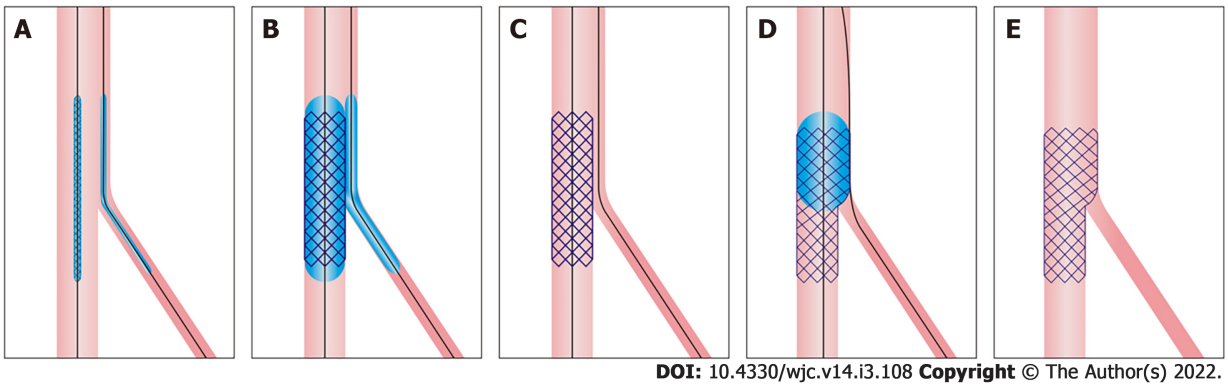

Figure 6 Jailed balloon technique and jailed semi-inflated balloon technique. A: A balloon is positioned in the side branch (SB) to align or 1-2 mm proximal to the main vessel (MV) stent in the proximal MV; B: The stent is deployed while the SB balloon is kept inflated at a low or moderate pressure (in the jailed semi-inflated balloon technique) or uninflated (in the jailed balloon technique); C: Both balloons are removed; D: Proximal optimization technique sized to the proximal MV diameter; and E: Final result.

(JSBT) during MV stent balloon inflation at nominal pressure. After MV stent implantation, if the SB flow is not compromised (*i.e.*, TIMI-3 flow), the uninflated SB balloon is inflated at low (< 3 atm) pressure in the JBT (not shown in Figure 6). If less than TIMI-3 flow in the SB is observed, the SB balloon is inflated at nominal pressure. After the balloons are removed, the proximal optimization technique (POT) is performed in the PMV[63,64].

In the modified jailed balloon technique (M-JBT), the MV stent is positioned across the SB, and a balloon is placed in the SB with its proximal end touching the MB stent (Figure 7). Both the MV stent and SB balloon are inflated at the same nominal pressure (*e.g.*, 12 atm) simultaneously. After deflation and removal of the balloons, the POT is performed in the PMV[65].

All three JBTs, the jailed semi-inflated balloon technique and the M-JBT were investigated in small-sized trials and found to have low SB loss, SB dissection and MACE rates[66,67]; however, larger randomized controlled trials are required for the routine use of these new techniques in the PST.

MV stenting

The preferred type of stent is new-generation DESs which reduce the risk of restenosis and repeat interventions compared to bare metal stents and early-generation DESs[68,69]. The diameter of the MV stent should be chosen at a 1:1 ratio according to the reference distal MV size (Figure 4B). The implantation of a larger stent can cause distal dissection and carinal shift, which can result in severe narrowing or even occlusion of the SB. The length of the stent should be selected so that its PMV part will be equal to or longer than the shortest balloon available (usually 6-8 mm) for the subsequent POT [25,48]. The stent should be implanted at nominal pressures, avoiding overexpansion, which is called the "distal optimization technique" (called "DOT" in the literature)[53].

POT

Since the diameter of the MV stent is chosen according to the diameter of the DMV, a semi-compliant or non-compliant balloon sized to the PMV diameter should be inflated in the PMV stent part to correct malapposition[25] (Figures 4B and 4C). The distal shoulder of the balloon (the point where balloon parallelism ends) should be aligned to the level of the carina so as to avoid stent underexpansion at the

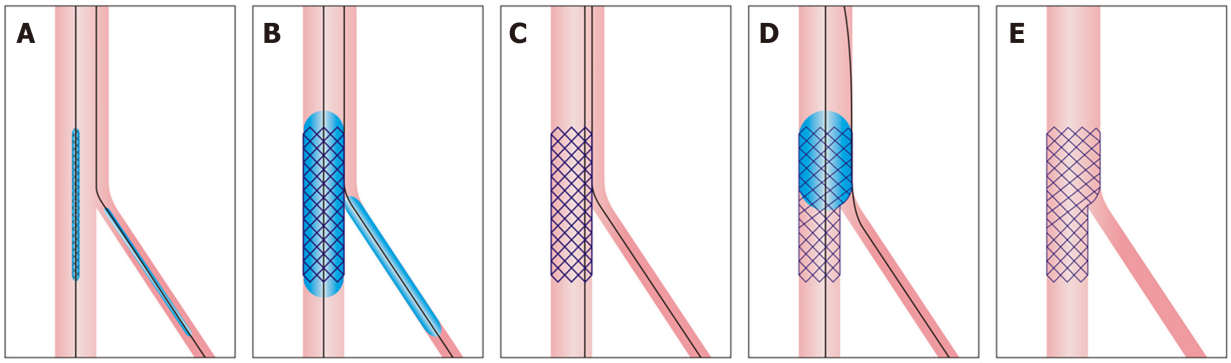

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Figure 7 Modified jailed balloon technique. A: Semicompliant balloon in the side branch is positioned with its proximal end touching the main vessel (MV) stent; B: Both the MV stent and balloon are inflated at the same nominal pressure; C: Both balloons are removed; D: Proximal optimization technique sized to proximal MV diameter; E: Final result.

polygon of confluence (occurs when placed more proximally) and carinal shift (occurs when placed more distally)[70]. Many operators use the distal balloon marker as the distal shoulder; however, as the location of this marker varies between manufacturers, the operator should be familiar with the design of the balloon used to avoid misplacement[49,71]. The POT corrects the malapposition of the stent in the PMV, prevents understrut passing of subsequent wires, provides strut protrusion into the SB and widens the distance between struts in the SB ostium which facilitates subsequent wire and balloon passing into the SB.

When the POT balloon is shorter than the PMV stent part, the POT must be applied to the entire PMV stent part. Furthermore, the POT balloon should not be longer than the PMV part of the stent; otherwise, it can cause proximal stent edge dissection.

Finally, the overexpansion capacity of the available stent types should be known to select the correct stent in order to provide natural fractal anatomy of the coronary bifurcation with the POT [72] (Table 2).

Is routine kissing balloon inflation or POT-side-POT technique necessary after the first POT?

KBI involves the inflation of two non-compliant balloons (one in the MV and the other in the SB) whose proximal parts are aligned in the proximal MV. The aim of this procedure after MV stenting is to remove the stent struts at the SB ostium, to eliminate the stenosis in the SB, and to maintain the carina in its central position.

In a recent meta-analysis, routine final KBI resulted in a significant reduction in SB restenosis, but an increase in MV restenosis rates with no significant differences in clinical outcomes[73]. Another recent larger meta-analysis of final KBI *vs* no-final KBI in PST trials also showed similar results in that there was no difference in terms of MACEs and other outcomes[74].

SB dilatation to open the struts at the ostium of the SB after MV stent implantation was shown to cause stent distortion with malapposition of struts at the opposite side of the SB ostium in bench studies [75,76]. Therefore, the POT or KBI should be performed to correct this distortion[71,75,76]. POT-side-POT is a new technique that involves initial POT + SB balloon dilatation + final POT (or re-POT) and will be described later.

Presently, there are no convincing data for KBI and insufficient data for the POT-side-POT technique to recommend either of them for routine use after the first POT in PST.

When should we treat the SB after the POT?

After the POT, if the SB flow is TIMI-3 and there is < 75% stenosis in the ostium, or no dissection, then the operation is completed.

After MV stenting, the MV plaque and/or carina shift can create an angiographic image of SB ostial narrowing. However, angiography is unreliable with regard to the functional significance of SB stenosis in this situation. It was shown in a study that none of the < 75% and only 27% of the SB stenoses ≥ 75% were found to be significant with the FFR[77]. This situation can be explained by the oval shape of the SB ostium (the narrower the carinal angle, the more oval the ostium) (Figure 8), the edge effect originating from angiography[57] and the recently shown elliptical stretch of the SB ostium after MV stenting[78].

Consequently, severe stenosis (≥ 75%) in the SB ostium, FFR ≤ 0.8, less than TIMI-3 flow or dissection in the SB requires SB intervention.

Technical steps of SB intervention after the POT

If the SB requires intervention after MV stenting and the POT, the sequential techniques and technical steps are as follows:

Table 2 Maximum-expansion capacity of stents

Manufacturer	Stent type	Stent size (mm)	Balloon[1] (bench test) (mm)	Maximum expansion (bench test) (mm)[72]	Maximum expansion (mm) (manufacturer recommendation)
Biosensors	Biomatrix A	3	5	4.1	-
		4	6	5.9	5.8
Medtronic	Resolute Onyx	2.5	4	3.3	-
		3	5	4.4	-
		4	6	5.6	-
		5	6	6	6
Biotronik	Orsiro	3	5	4	-
		4	6	5.3	4.4
Abbott	Xience	3	5	4.1	3.75
		4	6	5.6	5.5
Terumo	Ultimaster	3	5	4.3	-
		4	6	5.8	5.5
Boston Scientific	Synergy	2.75	5	3.6	3.5
		3.5	5	4.2	4.25
		4	6	5.7	5.75

[1]In the bench test, all balloons are inflated at 14 *atm*[72].

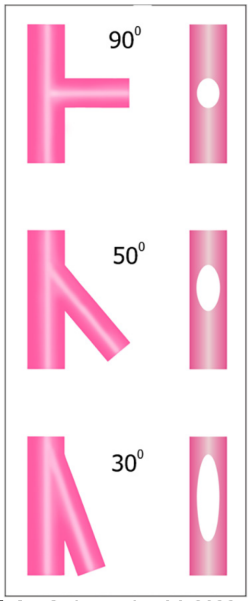

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Figure 8 Effect of bifurcation angle on side branch ostium ellipticity. Narrower angles result in more oval ostium shapes.

Guidewire exchange technique: The MV wire tip is pulled to the level of the carina and tried to pass into the SB through the most distal cell of the MV stent (carinal cell) at the SB ostium (Figure 4E). The passing of the wire through the distal cell is very important in the PST as subsequent balloon inflation will direct the struts to the non-carinal ostial segment of the SB, providing better scaffolding[26]. The jailed SB wire should not be retracted until the MV wire passes into the SB, since this wire indicates the SB ostium location and can be used when a rescue balloon is required as described next.

If the wire cannot be passed through the stent struts into the SB, the following options are available: (1) It can be reshaped; (2) The POT with a larger balloon can be performed again to open the cells and remove the struts at the SB ostium; (3) A hydrophilic polymer-coated or a stiffer wire can be used; (4) A

steerable-tip microcatheter (Venture, Teleflex), an angled microcatheter (SuperCross, Teleflex) or a dual lumen microcatheter can be used; and (5) Finally, a small balloon (1-1.5 mm) can be passed through the jailed wire under the stent struts and dilated at the ostium of the SB, which not only rescues the SB in case of occlusion but also allows the MV wire to enter the SB[26]. In extreme cases, the inverted crush technique can be implemented as a last effort to rescue the occluded SB.

After the MV wire is inserted in the SB, the jailed SB wire is withdrawn until it comes out under the stent struts and is then pushed forward into the stent. At this time, the tip should be formed into a "U" shape to easily cross the MV stent, avoiding passing under the struts (Figure 4E). While the jailed SB wire is being retracted, the guiding catheter may intubate deeply into the vessel, which can cause dissection and longitudinal stent deformation in the case of LMCA stenting[26]. Therefore, the guiding catheter tip should be withdrawn a few mm into the aorta beforehand; and while retracting the wire with right hand, the operator should control the guiding catheter with left hand while closely monitoring its tip[26].

Rarely, the jailed wire cannot be easily removed under the struts. In this case, a small balloon passed over the jailed wire with or without inflation at the jailed site may help.

Instead of the wire exchange technique, a third wire can be used to pass into the SB while the jailed wire is in place. The third wire is advanced into the DMV and then retracted back, and an attempt is made to enter through the most distal cell.

Kissing balloon inflation technique: After exchanging the wires, a non-compliant balloon sized to the SB diameter is inserted into the SB, and another non-compliant balloon sized to the DMV diameter is inserted into the MV. The balloons should be sufficiently short to prevent inflation outside the MV stent and disease-free regions in the SB. Moreover, minimal balloon overlap is recommended to keep elliptical stent deformation in the PMV to a minimum (Figure 4F1)[25,79]. First, the SB balloon is inflated at a high pressure to open the struts and eliminate the stenosis; and after deflation, the MV balloon is inflated to a high pressure. Subsequently, to maintain the carina in its central position, simultaneous inflation and deflation of both balloons is conducted using moderate pressures (at approximately 8-10 atm) as high pressures cause more oval distortion in the PMV segment of the stent[25].

A modified kissing balloon inflation (KBI) technique investigated in a bench test study was described by Mortier *et al*[80]. In this technique, the SB balloon is inflated to 12 atm and deflated to 4 atm. Then, the MB balloon is inflated to 12 atm; and finally, both balloons are deflated simultaneously. This technique was found to cause less elliptical stent deformation of the PMV segment with optimization of SB access compared to KBI with 12 atm inflation and deflation of both balloons simultaneously.

After KBI, to correct the oval (elliptical) stent deformation in the PMV segment, the POT should be performed again, which is termed the re-POT or final POT. In a recent bench test study, the position of the re-POT balloon was found to be an important factor in the alteration of the SB cell area size of the MV stent. The distal shoulder of the balloon positioned across the SB takeoff caused a reduction in the SB cell area whereas the distal shoulder positioned proximal to the SB takeoff did not[71]. The results of future *in vivo* tests and clinical studies of this approach are needed.

Balloon crossing problem to the SB: If the balloon does not cross to the SB through the stent struts, the following steps are performed[26,51]: (1) The first step is to check the position of the guiding catheter to determine whether it is at the ostium and coaxial to the vessel; (2) The second step is to use a smaller or the smallest balloon (1-1.5 mm) available; (3) It is suspected that the two wires are wrapped if the balloon cannot be forwarded to the SB ostium or if the MV wire is observed coming back while pushing the balloon. In this case, the MV wire is withdrawn back to the GC and inserted again into the DMV; (4) The next step is to inflate a balloon in the DMV stent part to increase the support of the GC (the anchor-balloon technique); (5) Performing the re-POT with a larger balloon to open the cells at the ostium of the SB is another choice; (6) Some operators advance a small balloon until it stops at the SB ostium, inflate it at high pressure with the objective of opening the struts, and then try to advance the balloon while deflating it[81]; and (7) As a last effort, the SB can be rewired from a different stent cell.

POT-Side-POT technique: After the first POT and exchanging wires, instead of the KBI, the POT-Side-(re)POT technique was proposed as an alternative and is increasingly used[82-84]. Technically, after the first POT, a balloon sized to the SB diameter is dilated in the SB to eliminate stenosis and remove the struts at the ostium, followed by the re-POT (Figures 4F2 and 4G). Because only one balloon is inserted and inflated at a time, this technique can be performed with 5 Fr guiding catheters, requires only one indeflator, and permits more proper balloon positioning. In a small recent clinical prospective registry using optical coherence tomography (OCT), the global strut malapposition, ellipticity index and SB occlusion rates were significantly reduced with a good sixth-month safety outcome[83].

Inverted PST

In Medina 0,0,1 bifurcation lesions with a very large SB (for ex., ostial circumflex or ostial diagonal lesion), a stent from the PMV to the SB may be implanted. This is called the "inverted PST"[25]. In addition, if there is no large difference between the PMV and the SB, this technique can also be performed in Medina 1,0,1 Lesions (Figure 3). The technical steps are the same as for the PST. The only difference is that the DMV is considered the SB and the SB is considered the DMV.

SIDE BRANCH STENTING FOLLOWING THE PST

After KBI or POT-side-POT techniques, if there is dissection, TIMI flow grade < 3 or FFR ≤ 0.8 in the SB, a second stent is required. Since there is a poor correlation between angiography and FFR measurements, when there is a suspicion of severe stenosis in the SB ostium after PST, it is better to use FFR to decide on SB stent implantation[14].

T/TAP stenting techniques

These stenting techniques are the simplest methods of second stent implantation in the PST. If the bifurcation angle is very close to 90°, then implanting a second stent in the SB as a "T form" is suitable. Technically, optimal angiographic views of the SB ostium should be obtained and stent augmentation tools should be used for successful T stenting[25].

Bench test studies and clinical practice have demonstrated that the bifurcation angle is usually not 90°; thus, the second stent may not completely cover the SB ostium with the T stenting technique, resulting in increased restenosis rates[25]. Therefore, the TAP stenting technique was developed. The TAP technique allows complete coverage of the SB ostium at the cost of creating a metallic neocarina. The length of the metallic neocarina depends on the bifurcation angle; the narrower the bifurcation angle is, the longer the length of the neocarina. For this reason, the TAP technique is generally not recommended at bifurcation angles < 70°.

The technical steps of the TAP technique in the PST are as follows[25] (Figure 9): (1) After the MV stenting and exchanging wires, the SB ostium is dilated with a balloon; (2) A DES of the SB diameter and appropriate length is positioned in the SB; (3) A balloon sized to DMV diameter is placed uninflated in the MV for use in subsequent KBI; (4) The SB stent is implanted with great care so that the non-carinal ostium is completely covered with minimal protrusion in the carinal segment (Figure 9B); (5) After the implantation of the SB stent, the stent balloon is slightly withdrawn and inflated at high pressure to provide optimum stent expansion in the SB ostium and postdilation of the stent (Figure 9C); (6) The uninflated, parked MV balloon and SB stent balloon are aligned in the PMV. Simultaneous KBI at moderate pressure and deflation are implemented to hold the neocarina in a central position; and (7) As a last step, the re-POT is performed to correct the oval shape if KBI has been implemented in a long segment in the PMV; otherwise, this step is not mandatory. It is of upmost importance that the re-POT balloon should not reach the metallic neocarina (Figure 9E). If this happens, the neocarina can bend to the SB side, which can result in rejailing and reduction in the SB ostial cell area[71].

Culotte stenting technique in the PST (classical culotte technique)

TAP is the most often used technique in the PST due to its simplicity; however, when the bifurcation angle is less than 70°, some operators prefer to use the culotte technique first introduced by Chevalier *et al*[85]. The culotte technique provides full coverage of the bifurcation; however, two layers of struts in the PMV are the disadvantage of this technique. Furthermore, before deciding to perform this technique, the overexpansion capacity of the available stent types should be known (Table 2)[72]. If the maximum expanded diameter of the available SB stent is less than the diameter of the PMV according to the table, then the culotte technique cannot be performed. This is especially the case when there is a large difference between the PMV and SB diameters.

The technical steps of culotte stenting in PST are the following[25] (Figure 10): (1) After the stages of the PST are completed (Figures 10A-C), wire exchange and balloon dilatation of the SB ostium is performed (Figures 10D and E); (2) A DES with the same diameter as the SB and an appropriate length that extends from the SB to overlap the proximal part of the MV stent is implanted while the MV wire is in place. The overlap part is long in the classical culotte technique but is kept at 1-3 mm in the "mini-culotte" technique (Figure 10F); (3) A new POT is performed through the SB wire with a non-compliant balloon sized to the PMV. The balloon distal shoulder should be aligned to the carinal level (Figure 10G); (4) Wire exchange should be performed for the second time. It should be noted that the SB wire must be passed from the cell closest to the carina into the DMV (Figure 10H). This allows the deployed SB stent struts to move to the lateral walls of the MV rather than the carina and the SB ostium during the next balloon inflation. The MV wire is retracted under the SB stent and advanced into the SB as a "U" shape; (5) A non-compliant balloon sized to the DMV and another non-compliant balloon sized to the SB are advanced into the relevant vessels, and the proximal balloon markers are aligned in the PMV. Each balloon is inflated at high pressure and deflated sequentially, followed by KBI at moderate pressures (Figure 10I); and (6) A last POT should be performed for correcting the oval shape created by previous KBI (Figure 10J).

ELECTIVE DOUBLE STENTING TECHNIQUES

Inverted culotte stenting technique

To maintain access to the SB during the procedure, the culotte stenting technique was modified to the "inverted culotte stenting technique" in elective double-stent implantation. Similar to the culotte

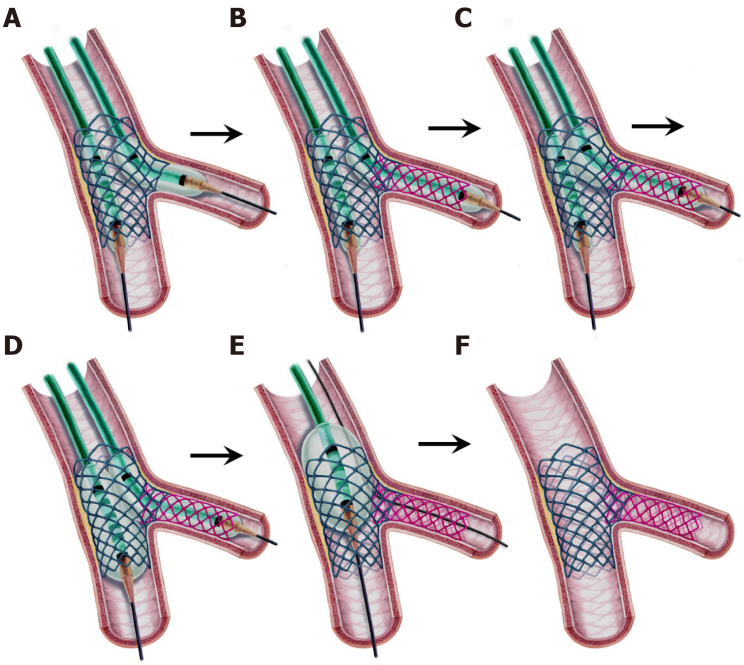

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Figure 9 Step-by-step T and protrusion technique. A: After main vessel (MV) stenting, an uninflated balloon is positioned in the MV, and the side branch (SB) ostium is dilated by a balloon; B: The SB stent is deployed with minimal protrusion and covers the ostium completely; C: The stent balloon is withdrawn slightly and inflated at high pressure; D: Kissing balloon inflation; E: Proximal optimization technique with a short balloon not reaching the neocarina. (This step is not mandatory if the kissing balloon inflation area in the proximal MV is not long.); F: Final result.

technique, the inverted culotte technique provides full coverage of the bifurcation at the expense of two layers of struts in the PMV, and it cannot be performed when there is a large difference between the PMV and SB diameters.

The technical steps of inverted culotte stenting are as follows (Figure 11): (1) Both branches are wired, and MV predilation and/or debulking is performed with predilation of the SB; (2) A stent sized 1:1 to the SB diameter is deployed in the SB protruding into the PMV. The length of the stent is selected so that the PMV part is sufficiently long enough for the subsequent POT. In the "mini-culotte technique" introduced a decade ago, the PMV part of the SB stent is kept as short as 1-3 mm to reduce the length of the two stent layers[86,87] (Figure 11B). This technique was found to be associated with high procedural success and very good 9-month outcomes in a pilot study[88]. Randomized, controlled, larger comparative studies are needed to confirm the favorable outcomes of this method; (3) The PMV part of the stent is dilated with a non-compliant or semicompliant balloon sized to 1:1 to the PMV diameter. This is the first POT (Figure 11C); (4) Wire exchange (or a third wire advancement) should then be performed. The DMV should be wired from the closest cell to the carina for the reasons described above (Figure 11D); (5) Stent struts are opened by a DMV balloon. Instead, KBI, which is part of the recently introduced "DK-culotte technique", can be performed[89,90] (Figure 11E). This technique was found to achieve better morphological properties than classical culotte stenting in a bench test study[89], and it reduced the total procedural time with better strut apposition than the culotte and even the DK-crush techniques in another study[90]; (6) An MV stent sized 1:1 to the DMV diameter is advanced and implanted. The length of the PMV part should be sufficient to cover the PMV part of the SB and be at least equal to the shortest POT balloon (Figure 11F); (7) A second POT is performed in the PMV (Figure 11G); (8) A second wire exchange is performed by passing the MV wire through the closest cell to the carina into the SB and the U-shaped SB wire into the DMV (Figure 11H); (9) KBI is performed with short non-compliant balloons sized 1:1 to the branches. Before KBI, sequential balloon inflation is recommended. The SB balloon is first inflated to a high pressure; and after deflation, the MV balloon is inflated to a high pressure. Then, both balloons are inflated at moderate pressures (at approximately 8-10 atm) and deflated simultaneously (Figure 11I). A recent mini-KBI in culotte stenting was described in a bench test study[91]. In this technique, the SB balloon only protrudes into the MV at the upper edge of the SB, and the KBI is performed. Compared to classical KBI, this modification significantly prevented stent deformation and overexpansion in the MV stent and provided better apposition of the MV stent and better expansion of the SB stent[91]; and (10) A final POT is performed in the PMV (Figure 11J).

Double-kissing crush technique

The crush technique was first introduced by Colombo *et al*[92]. The aim of this technique was to provide full coverage of the ostium to lessen SB restenosis with immediate patency of both branches. However,

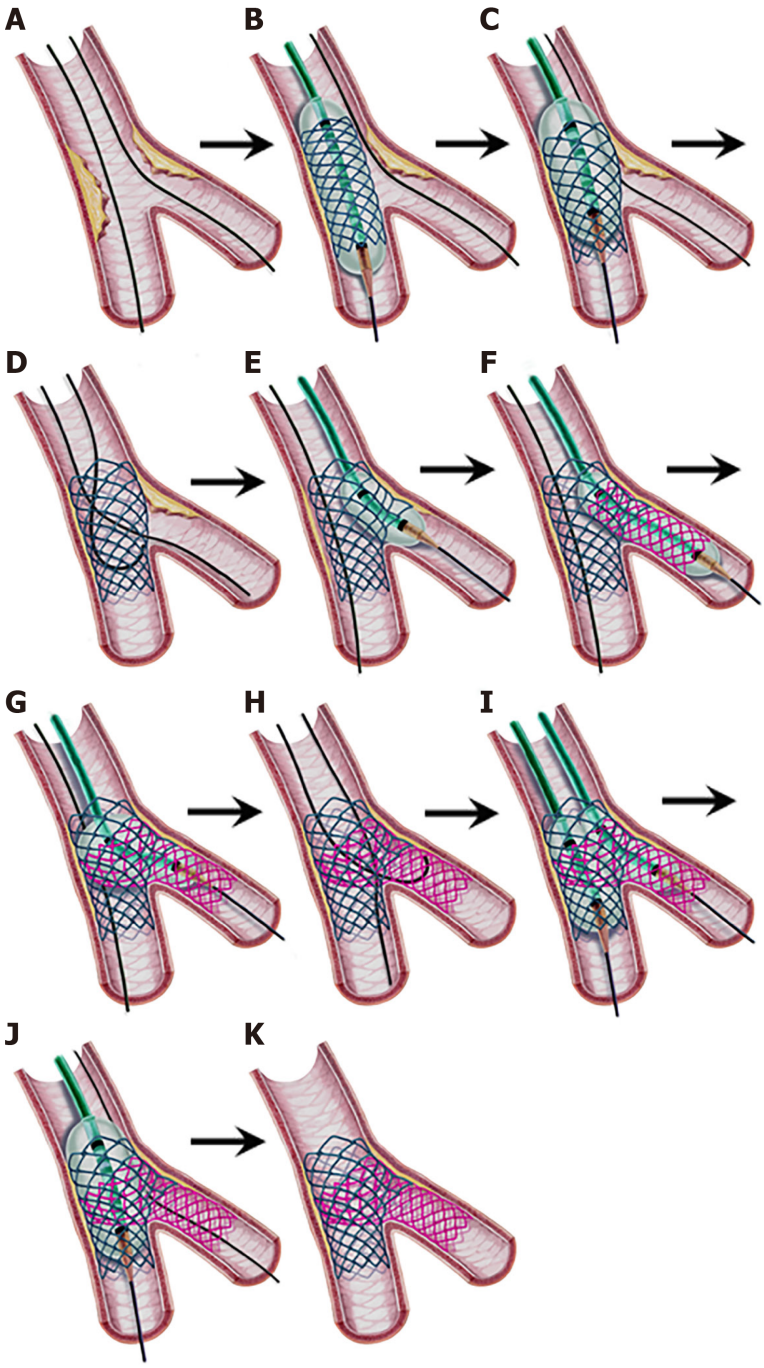

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Figure 10 Step-by-step classical (provisional) culotte stenting. A: Both vessels are wired; B: After predilatation, the main vessel (MV) stent sized to the distal MV is deployed; C: First proximal optimization technique (POT); D: Wire exchange; E: Balloon dilatation of the side branch (SB) ostium; F: Deployment of the SB stent protruding into the proximal MV (1-3 mm in "mini-culotte"(shown) or more in classical culotte technique); G: POT for the SB stent; H: Second wire exchange with wiring the distal MV through the closest cell to the carina, and the other wire tip is "U" shaped to cross the SB stent; I: Kissing balloon inflation; J: Final POT; K: Final result.

in clinical practice and in trials, the rate of achievable KBI was found to be low, leading to suboptimal long-term outcomes. Thus, this technique is no longer recommended[49]. Some modifications of this technique, such as "mini-crush"[93], "step-crush"[94], and "double-kissing (DK) crush"[95] were described. As described before, the DK crush technique has received great attention due to its high final KBI success rate and its efficacy with long-term safety in complex bifurcation lesions in a series of trials [25,34-36,96]. Nonetheless, this technique is complex with many steps that require proper training and experience.

The technical steps of the contemporary DK-crush technique are as follows[25] (Figure 12): (1) After wiring the two branches, optimal preparation of the MV with balloon inflation and/or debulking with predilatation of the SB is performed; (2) A DES, sized to the SB diameter and with a length to ensure full coverage of the SB lesion, is advanced into the SB. The stent is positioned protruding 2-3 mm into the

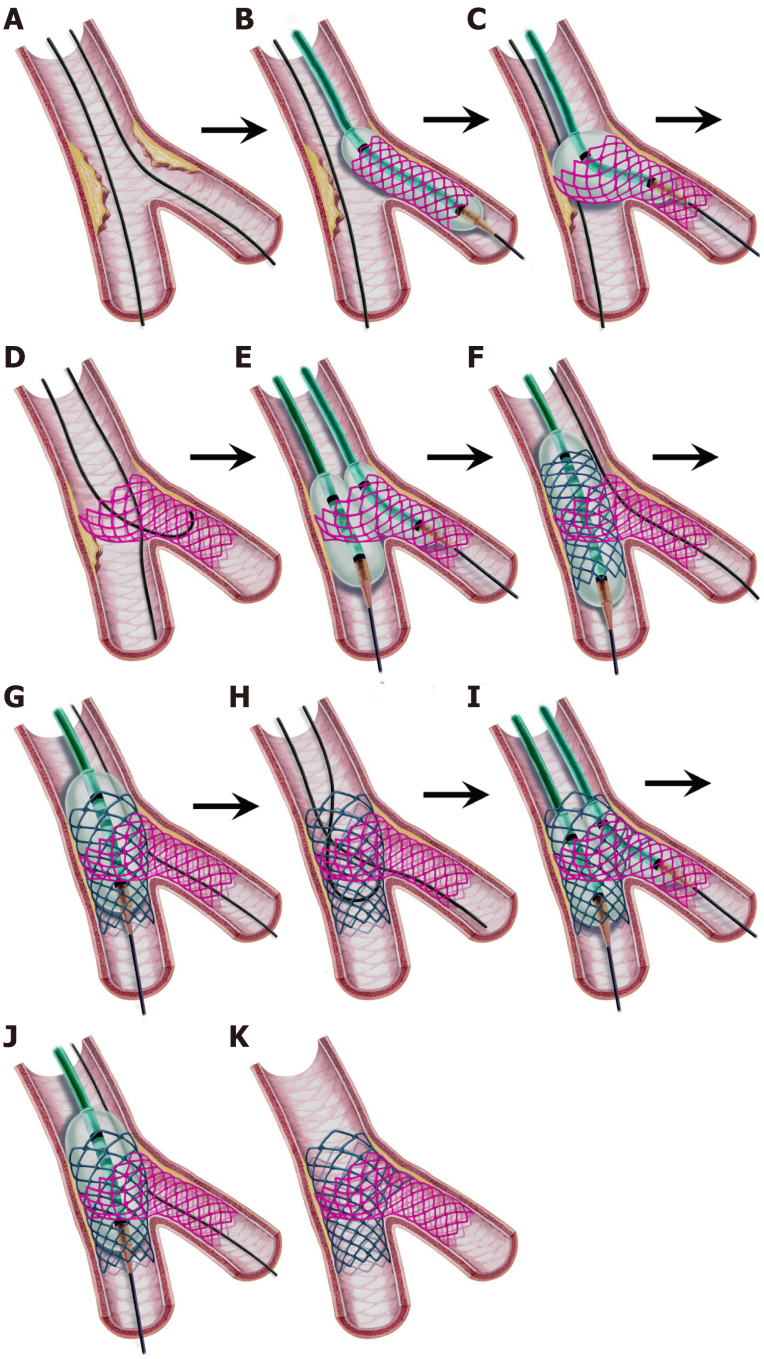

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Figure 11 Step-by-step inverted culotte stenting. A: Both vessels are wired; B: The side branch (SB) stent protruding in the proximal main vessel is deployed (protrusion part is 1-3 mm in the "Mini-culotte technique"); C: Proximal optimization technique (POT) for the SB stent; D: Wire exchange. The distal main vessel (MV) wiring from the closest cell to the carina and the "U" shaped wire is advanced into the SB; E: Kissing balloon inflation (KBI) (in the "double kissing mini-culotte "technique) or classical balloon dilatation only in the distal MV ostium may be performed; F: MV stenting; G: POT for the MV stent; H: Second wire exchange. Wiring the SB through the closest cell to the carina and the "U" shaped wire crossing the MV stent; I: KBI; J: Final POT; K: Final result.

PMV (Figure 12A); (3) A balloon sized to the PMV is positioned in the MV to crush the stent later. This balloon will be kept uninflated until the crushing procedure (Figure 12A); (4) After the SB stent is implanted, a new method called the "proximal side optimization" described by Lavarra[97,98] and considered useful by the EBC[25] may be performed. In this method, the stent balloon is slightly withdrawn and inflated at 4-6 atm higher than the nominal pressure (Figure 12B); and after removing this balloon, a new NC balloon (0.25-0.5 mm larger than the SB stent) is again inflated in the protruding part of the stent and the SB ostium (Figure 12C). The purpose of this method is to achieve adequate expansion and apposition of the SB stent in the ostium and to provide a larger stent cell area for rewiring; (5) After the SB balloon is removed, angiography should be performed to evaluate the results of SB stent implantation, such as the stent expansion, flow pattern, distal dissection or new lesion development. If an additional stent is required, it should be implanted at this time as the SB wire will be

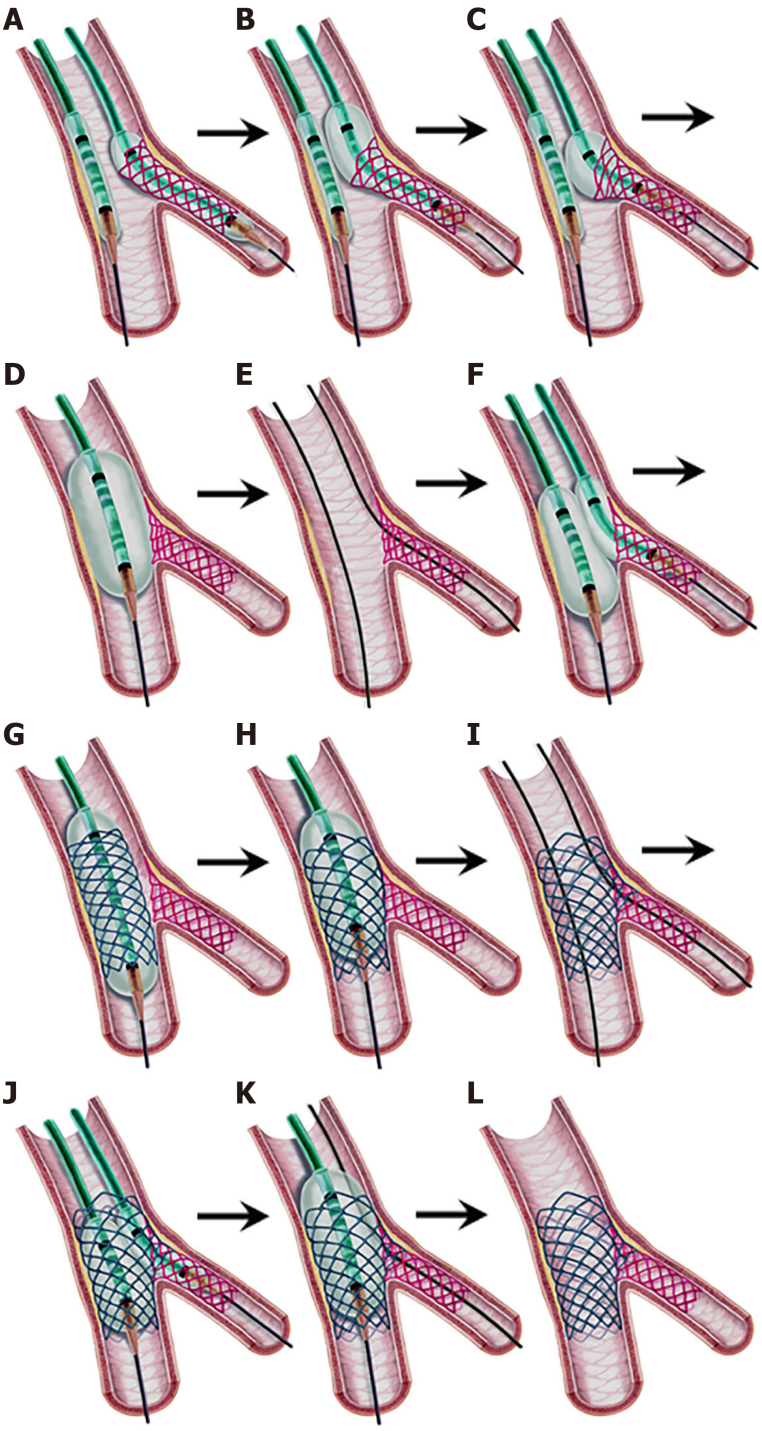

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Figure 12 Step-by-step double kissing-crush technique. A: After the preparation of the vessels, the side branch (SB) stent protruding 2-3 mm into the proximal main vessel (MV) is deployed while an uninflated proximal optimization technique (POT) balloon is positioned in the MV; B, C: "Proximal side optimization". A slightly withdrawn stent balloon is inflated at a higher pressure. Then, a new larger NC balloon is inflated in the protruding stent part to further open the struts; D: Crushing the stent by POT after the SB balloon and wire are removed; E: Wiring the SB through a non-distal cell; F: First kissing balloon inflation (KBI) after sequential inflation of the two balloons; G: MV stenting after the SB balloon and wire are removed; H: Second POT; I: Wiring the SB through a non-distal cell for the second time; J: Second KBI; K: Final POT; L: Final result.

removed in the next step and rewiring and stent advancement may be challenging in later steps[99]; (6) The SB wire is removed (some operators leave it in), and the pending uninflated MV balloon is positioned with its distal shoulder aligned to the carina. High-pressure inflation (POT) is performed to crush the protruding part of the SB stent, which is called "balloon crushing"[25]. It was demonstrated in bench tests that the POT is required to achieve total crushing. (Figure 12D); (7) The SB is rewired through a *non-distal* cell of the crushed stent (Figure 12E). Non-distal cell rewiring, the opposite of distal rewiring in the PST, is important because more frequent suboptimal KBI results and higher SB stent restenosis were found with distal wiring[100]. The mechanism of this is explained by the fact that the

KBI in the distal cell pushes the stent struts to the proximal side, causing incomplete coverage of the distal 1/3 of the SB ostium[100]. How to overcome wiring problems is explained in the relevant section of the PST; (8) An SB balloon sized 1:1 to the SB diameter and an MV balloon sized 1:1 to the DMV diameter are advanced. To perform the first KBI, the SB balloon is inflated at high pressure to open the struts; and after deflation, the MV balloon is inflated at high pressure. Eventually, simultaneous inflation and deflation of both balloons with moderate pressures (at approximately 8-10 atm) is conducted (Figure 12F). How to overcome balloon crossing problems is explained in the relevant section of the PST; (9) The two balloons and the SB wire are removed. A DES sized 1:1 to the DMV diameter is positioned across the SB covering all the distal and proximal MV lesions and deployed (Figure 12G). The PMV part of the DES should be at least equal to the shortest POT balloon; (10) After removing the stent balloon, a repeat POT with a balloon sized 1:1 to the PMV diameter should be performed (Figure 12H); (11) The SB is rewired again through a non-distal cell (Figure 12I); (12) A second KBI is performed (Figure 12J); (13) A final POT is performed to correct the oval shape of the PMV created by the previous KBI (Figure 12K).

Nano-crush technique

The "nano-crush" technique was first presented by Ray *et al*[101,102] at the 12th EBC meeting in 2016. Later, in 2017, Rigatelli *et al*[103] published a bench test and clinical outcome study of a technique with the same name. Although both procedures use a tiny SB stent part for crushing, the techniques are somewhat different from each other. Rigatelli *et al*[104] recently changed the name of their technique to the "nano inverted T stenting technique".

In the nano-crush technique described by Ray *et al*[105], the SB stent is positioned uninflated in the SB, and a non-compliant MV balloon is positioned across the carina and then inflated at a nominal pressure. While the MV balloon is inflated, the SB stent is pulled back until a small part protrudes into the MV and is deployed. However, in the nano-crush technique described by Rigatelli *et al*[103,104], 0.5-1 mm protrusion of the proximal part of the SB stent for crushing is adjusted visually by angiography. Moreover, the KBI numbers and techniques are also different. Where Ray *et al*[102] perform double "classical" KBI at high pressures without a final POT, Rigatelli *et al*[103-105] perform only one "snuggle" KBI, then a final POT. The other steps are similar to the DK-crush stenting technique described before. Finally, Rigatelli *et al*[103-105] use only ultrathin strut stents in their technique.

Both techniques provided complete coverage of the SB ostium with a tiny amount of metal at the carina in bench tests[106,107]. In a clinical study with a small number of patients, Ray *et al*[102] demonstrated short procedural times and no procedural complications with acceptable clinical outcomes with their technique. Rigatelli *et al*[104,108] showed a low incidence of TLF, no stent thrombosis and a good survival rate in left main bifurcation lesions in a small registry study and less contrast use and less procedural and radiation exposure time in comparison to the culotte technique in left main bifurcation lesions in an observational study.

Further controlled, randomized, larger studies are needed to confirm the favorable procedural and long-term clinical outcomes of these techniques in left main and non-left main bifurcation lesions.

OTHER DOUBLE STENTING TECHNIQUES

Mini-crush and step-crush techniques

The mini-crush technique is a version of the crush technique in which the crushed part of the SB stent is 1-2 mm instead of 3-4 mm. The main advantage of the crush and mini-crush techniques is that instant patency of both branches is secured[52]. However, the main disadvantage of these techniques is that a 7 Fr guiding catheter is required because two stents are positioned in the coronary arteries at the same time. After the SB stent is deployed, the stent balloon and wire are withdrawn, and the prepositioned MV stent is inflated while the SB stent is crushed. The SB is rewired followed by balloon dilatation of the ostial struts, KBI and a final POT, sequentially. Rewiring the SB and balloon passing can be challenging due to three layers of stent struts, which is the reason for the low KBI rate in classical crush trials resulting in more adverse outcomes.

The step-crush technique is the same as the DK-crush technique except that the first KBI is not implemented in this technique.

Reverse (internal) crush technique

When a second stent is required in the PST, some operators use the reverse (internal) crush technique [48]. A stent is positioned in the SB, and a balloon is placed in the MV. The stent is pulled back prolapsing 2-3 mm into the MV and implanted. After the stent balloon and wire is removed, the MV balloon is inflated at a high pressure to crush the SB stent. After rewiring, KBI and the POT are subsequently performed. In this technique, the crushed SB part is on the MV stent facing the lumen, unlike the other crushing techniques where it is under the stent and adheres to the vessel wall. There is no large study investigating the safety and efficacy of this technique.

Inverted DK-crush technique

When the SB is larger than the DMV, the inverted DK-crush technique may be performed. The technical steps are the same as those of the DK-crush technique with the only difference being that the DMV is considered the SB and the SB is considered the DMV.

In addition, in very rare PST cases, when the SB is occluded after MV stenting and cannot be rewired, this technique can be used to rescue the SB. The PMV stent part is crushed with a balloon passed through the jailed wire, followed by the DK-crush technique steps.

V and simultaneous kissing stent techniques

The V and simultaneous kissing stent (SKS) techniques consist of the simultaneous implantation of the MV and SB stents. The two stents are positioned so their proximal parts overlap in the PMV to form a neocarina. If the neocarina is ≤ 2 mm, the technique is called "V stenting"; however, if it is ≥ 3 mm, it is called "SKS"[28,109]. Due to the simultaneous implantation of two stents, at least a 7 Fr guiding catheter is required. The main advantage of these two techniques is that access to both branches is maintained throughout the procedure without the need to rewire any branches. Therefore, these techniques are easy and fast and may be preferable to the more complex double stenting procedures in emergencies such as acute LMCA occlusion.

There are also disadvantages of these techniques[52]: (1) The possibility of PMV dissection is relatively higher because of barotrauma during two-stent implantation or postdilation; (2) If a proximal dissection occurs during the procedure or proximal restenosis develops on follow-up, a stent cannot be implanted simply proximal to the stents since a gap between the new stent and the others is inevitable. In this situation, one of the branch stents (mostly the SB) should be crushed by the new stent, but this results in four strut layers in the ostium of the branch causing difficulty for rewiring; (3) If restenosis or lesions occur distal to the stents during follow-up, wiring can be difficult as the wire can pass under or between the struts in the neocarina; and (4) Finally, SKS causes a long neocarina that has been shown to transform into a thin diaphragmatic membranous structure over time; however, the long-term adverse outcomes of this structure are unknown.

The main application of the V stenting technique is Medina 0,1,1 Lesions where the PMV is free of disease and the carinal angle is < 90°. Although many authors recommend this technique in this situation[28,48,52], there is no large study investigating the acute and long-term clinical outcomes of this technique. Due to the long carina and the above disadvantages, the SKS technique is not approved by the interventional community for use in nonemergent bifurcation interventions[48,51].

PROCEDURAL COMPLICATIONS AND OUTCOMES OF CBL INTERVENTIONS

The PCI of CBLs has more procedural risks and higher rates of adverse outcomes and restenosis than non-CBLs[99,110]. In addition to classical PCI risks such as dissection, no-reflow and perforation, the procedural risks specific to CBL interventions include acute side branch closure (2.8%-5.2%), the fracture of a jailed wire, and SB stent embolism while passing or withdrawing it through the implanted MV stent [99,110]. Early (< 30 d) (especially more in the EDS techniques) and late stent thrombosis rates are higher than those for non-CBLs[111-113]. This may be due to higher rates of stent underexpansion and malapposition and more metallic and polymer burdens, which may provide stimuli for hypersensitivity and acute thrombogenicity reactions[99,111].

Long-term MACEs are also higher after successful DES implantation for CBLs compared to non-CBLs. Finally, distal LMCA interventions compared to non-LMCA bifurcations are associated with higher MACE (death and TVR) rates[2,99].

INTRAVASCULAR IMAGING IN CBLs

Since coronary angiography is two-dimensional lumenography, it has some limitations in evaluating lesion characteristics and post-intervention results. The intravascular imaging techniques IVUS and OCT provide accurate tomographic images and essential information that guides planning and optimizing PCI treatment[114,115]. OCT provides much higher resolution images of the luminal surface, calcifications, wire positions and SB ostium than IVUS[43]. On the other hand, IVUS has been used more, needs no extra contrast or vessel flushing and is better in evaluating the plaque burden[43].

Compared to angiography, better visualization of the location and extension of plaques using these imaging techniques before PCI can assist in selecting an appropriate stenting strategy and avoid unnecessary two-stent implantation[26]. In addition, proximal and distal vessel sizes and plaque locations can be determined more accurately to determine the stent size, and calcifications that require debulking before stenting can also be identified[47]. In patients without ostial side branch involvement (*i.e.*, Medina 1,1,0/1,0,0/0,1,0), the "eyebrow" sign identified by IVUS was found to be a strong predictor of SB narrowing or occlusion after MV stent implantation[116], in which case the intervention strategy

can be changed. After stenting, OCT can help rewire through the distal cell, which is required for optimal stent scaffolding by subsequent balloon or KBI[115]. Stent expansion and apposition status, distal or proximal stent edge dissection, or residual stenosis can be well identified by both IVUS and OCT[43].

The MAIN-COMPARE registry trial, comparing the use of IVUS in LMCA bifurcation lesions to angiography alone, showed a lower 3-year mortality rate; and the other registry trial SCAAR showed a significantly lower primary endpoint (all-cause mortality, restenosis, or definitive stent thrombosis)[117,118]. In addition, a recently published analysis of the British Cardiovascular Intervention Society Database has shown lower in-hospital MACE and lower 1-year death rates with the use of IVUS in LMCA interventions[119]. Finally, the results were found to be similar in two recent meta-analyses[120,121]. In view of these data, IVUS is recommended as the gold standard for PCI of LMCA bifurcation lesions; and although there are no large data, it has been reported that OCT is feasible in LMCA bifurcation lesions in recent guidelines[41,47].

In non-LMCA lesions, an observational PCI study found a lower 7-year cardiac death, MI and MACE rates in the IVUS guided compared to angiography alone in true bifurcation lesions[122]. There are no randomized trials confirming the clinical benefits of routine IVUS use in non-LMCA bifurcation lesions, but the EBC emphasizes the benefit of intravascular imaging in all CBLs in the latest guidelines[20,47].

Although OCT provides superior images compared to IVUS, there are limited clinical data that only come from observational trials with a small number of bifurcation patients[115]. The results of ongoing large randomized trials OCTOBER (comparing two-year MACE between OCT guided or angiography alone interventions in CBLs) and OPTIMUM (comparing 3D OCT guided *vs* angiography alone provisional stenting in terms of malapposed struts in bifurcation lesions) will shed more light on the benefits of OCT use in CBL interventions[123,124].

LEFT MAIN BIFURCATION LESIONS

LMCA stenosis is detected in 5-8% of patients undergoing diagnostic angiography[125], and left main bifurcation lesions (LM-BLs) account for approximately 80% of LMCA lesions[125,126]. The LMCA with its bifurcation has specific properties and requires some different technical approaches[26,42,43,126]: (1) The LMCA supplies > 75% of the blood of the myocardium in a right dominant coronary system, so any complication may result in catastrophic outcomes; (2) The LMCA diameter is between 3.5-6.5 mm with a mean of 4.75-5 mm, so the overexpansion capacity of the stent to be used should be known (Table 2); (3) The left circumflex artery (LCx) is usually the side branch and supplies > 10% of the blood of the myocardium in > 95% of cases, so its loss during PCI is unacceptable; (4) The bifurcation angle is wider than the other bifurcations with a mean value of 70°-80°, so LCx rewiring may be more difficult, and it should be noted that worse outcomes were found with culotte stenting than with the DK-crush technique in patients with bifurcation angles > 70° in LM-BLs[35]; (5) The guiding catheter is close to the LMCA stent, so wires can go behind the struts. In addition, during the withdrawal of jailed wires or balloons, the guiding catheter can enter the LMCA and cause longitudinal compression of the LMCA stent, which is associated with adverse outcomes if untreated[26,57,127]; (6) Diffuse LMCA disease can be overlooked when using angiography due to the lack of a reference segment. Due to the physical laws of coronary bifurcation, LMCA diffuse disease should be considered when the LMCA reference diameter is similar to that of the LAD; and (7) A total of 10%-15% of patients have trifurcation with the addition of an intermediate (ramus) branch, so the complexity of PCI increases, and larger guides are required for triple kissing inflations.

CABG is the gold standard treatment for LMCA lesions according to both recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) and American Heart Association/American College of Cardiology (AHA/ACC) guidelines[41,128]. However, there are some differences in PCI implementation between these guidelines. The ESC/EACTS recommends PCI as a Class I indication for LMCA patients with SYNTAX scores < 22 (low risk), Class IIa with SYNTAX scores between 23-32 (intermediate risk), and Class III with higher scores. On the other hand, the AHA/ACC classifies LMCA lesions as ostial, trunk and bifurcation. LMCA bifurcation lesions with an increased risk of surgical outcomes (Society of Thoracic Surgeons (STS) score > 2) are Class IIb indications whereas ostial and trunk lesions with a very high risk of surgical outcomes (STS score ≥ 5) are recommended as Class IIa indications for PCI. After these guidelines, 5-year results of two important EXCEL and NOBLE trials have been published, which have caused intense debate about the treatment of LMCA disease with PCI *vs* CABG[129,130]. Repeat revascularization rates were higher in the PCI arms of both trials. Although mortality rates were similar between the CABG and PCI arms, PCI was inferior in terms of the nonprocedural MI in the NOBLE trial. On the other hand, no significant difference between CABG and PCI was found in the primary outcome (composite of death, stroke or MI) in the EXCEL trial. However, the primary outcome definition that does not include repeat revascularization and the MI definition that differs from the second or third universal definition of MI have been criticized[131]. Moreover, although the cardiac death rates were not different, a higher total mortality rate in the PCI arm was noted[47]. A meta-analysis of five randomized trials involving EXCEL

and NOBLE was recently published and found that individual total mortality, cardiac death, stroke and MI rates were not different between the CABG and PCI arms, and unplanned revascularization rates were significantly higher in the PCI arm, as expected[132]. Finally, the multidisciplinary heart team approach, which considers the anatomical and clinicopathological status of each patient and the experience of the operators, is required in the LMCA treatment decision[45,47].

LM-BLs that involves only one branch (*i.e.*, Medina 1,1,0 or 1,0,1) are considered non-complex lesions, and the default strategy is the PST[42]. Two-branch involvement (*i.e.*, Medina 1,1,1 or 0,1,1) in LM-BLs is a complex true lesion. The EBC still recommends the PST for the vast majority of these complex lesions [42], and recommends the EDS techniques in the case of long SB (usually LCx) lesions (≥ 10 mm) or difficult SB access[49]. Furthermore, EDS is preferred in cases where there is a high risk of SB occlusion [48]. Finally, as described before, preferring the DK-crush technique over the PST in complex-true LMCA lesions is a Class IIb indication in the 2018 ESC/EACTS myocardial revascularization guidelines [40].

As described before, the EBC-MAIN trial was recently published and showed that there was no statistically significant difference between the PST and EDS techniques in LM-BL interventions in short SB lesions. The DK-crush technique was used in only 5% of EDS patients in this trial[46].

In light of the latest data and expert opinions, the PST is most often the default strategy[37-39,46,48]. However, it is better to prefer EDS if the SB (usually LCx) is ≥ 2.5 mm and the lesion length is ≥ 10 mm or the likelihood of SB occlusion is high or SB wiring is difficult in complex-true (Medina 1,1,1; 0,1,1) LM-BLs; furthermore, if the operator is familiar with the technique, the DK-crush technique may be preferred over other EDS techniques (Figure 3).

Angiographical LMCA stenosis > 50% is considered significant; however, there are many cases of ambiguous lesions. FFR and/or IVUS should be used to decide on revascularization for these lesions. Collected data showed that if FFR > 0.8, then it is safe to defer revascularization; and if FFR ≤ 0.8, then revascularization of the LMCA is indicated[42,133]. On the other hand, an IVUS-derived minimum lumen area (MLA) of 6 mm^2 is usually considered to be the cut-off value of significant LMCA lesions [42]; however, this value was determined in Western populations who typically have larger body and vessel sizes, and an IVUS-derived MLA of 4.5 mm^2 was found to be the cut-off value in an Asian population study[134]. Consequently, in LMCA lesions, it is recommended to defer revascularization if the MLA > 6 mm^2, to revascularize if the MLA < 4.5 mm^2 and to evaluate with FFR measurement if the MLA is between 4.5 and 6 mm^2[135]. There is no defined cut-off value for OCT yet[42].

After LMCA stenting, IVUS-derived minimum stent area cut-off values for predicting angiographic restenosis were 5 mm^2 for the ostial LCx, 6.3 mm^2 for the ostial left anterior descending artery (LAD), 7.2 mm^2 for the polygon of confluence, and 8.2 mm^2 for the LMCA above the polygon of confluence (the so-called 5-6-7-8 rule) in a study[136]. However, this trial was conducted in Asian patients and it appears that larger LMCA cut-off values should be targeted in other populations and large body size patients [127]. Indeed, in an IVUS substudy of the EXCEL trial, the minimum LMCA stent area cut-off value for predicting angiographic restenosis was 9.8 mm^2; and in the NOBLE trial substudy, this value was found to be 13.4 mm^2[137,138].

After crossover stenting in the LMCA during the PST, whether the nonobstructed SB (usually LCx) ostium should be opened is a matter of debate[47]. A recent large registry, however, showed that there was no significant difference between the KBI and non-KBI arms in terms of TLR in patients with crossover stenting from the LMCA to the LAD[139].

The optimal PCI strategy for isolated ostial LAD lesions and ostial LCx lesions (Medina 0,1,0 and 0,0,1) is uncertain[25]. The extension of LMCA bifurcation plaques may not be detected by angiography, so IVUS/OCT is preferred for isolated ostial LAD or LCx lesions. Indeed, angiographic assessment was found to underestimate the extension and severity of lesions. Distal LMCA atherosclerotic plaques extended 90% to the LAD, 66% to the LCx, and 62% to both whereas isolated ostial plaque involvement of the LAD and LCx was only 9% and 17%, respectively, in an IVUS study[140]. In conclusion, if the anatomy is appropriate according to IVUS/OCT (the carinal angle is approximately 90°, the LMCA is free of plaque and there is certain visualization of the ostium of the other branch), then ostial stenting may be preferred to avoid LMCA stenting. Otherwise, the PST (from LMCA to LAD stenting) for isolated ostial LAD and the inverted PST (from LMCA to LCx stenting) for isolated ostial LCx seem to be the preferred options[25,47].

Finally, after successful LMCA stenting, late (3-12 mo) control angiography may be considered regardless of symptoms according to recent guidelines (Class IIb, level of evidence C)[41].

DRUG–COATED BALLOONS IN CBLs

Drug–coated balloons (DCBs) are a new technology intended for the prevention of restenosis as an alternative option to DESs[26]. The use of DCBs in CBL is attractive due to the high rate of restenosis after CBL intervention. Observational studies using a DES in the MB and a DCB in the SB showed good SB results[141]. The PEPCAD-BIF trial showed that DCBs provided very acceptable late lumen loss in SB lesions without both major dissections and significant early vessel recoil[142]. In the BABILON trial,

a DCB in the SB plus a bare metal stent in the MV was found to be worse than the provisional DES strategy in terms of MACE and TLR[26]. It should be noted that these and all the other studies to date on the use of DCBs in de novo CBLs are heterogeneous and include a small number of patients[47]. A recent meta-analysis that included four studies with 349 patients treated with DCBs *vs* standard balloon angioplasty, showed that the DCB reduced the SB late lumen loss, but the SB binary restenosis rates and the clinical outcomes (MACE and TLR) were not different[143]. Consequently, there still is insufficient conclusive data on the use of DCBs in de novo CBLs[48]. A new "POT-side DCB-POT" method was recently described in a case report[144], and more research is expected on the clinical consequences of this technique.

DCBs have been tested in in-stent restenosis (especially after two-stent implantation) and have been found to provide a good clinical outcome without requiring extra stent implantation[145]. Therefore, the method was reported as "feasible" in this case in the latest EBC guidelines[47].

DEDICATED BIFURCATION STENTS

The difficulties in accessing the SB after MV stenting, or vice versa, resulted in the development of dedicated bifurcation stents (DBSs). Although many types are available, 4 DBSs were studied in randomized trials: BiOSS Expert and BiOSS LIM (Balton, Warsaw, Poland), the Tryton stent (Tryton Medical, Durham, North Carolina) and the Axxess bifurcation stent (Biosensors International, Singapore).

The BiOSS Expert is a paclitaxel-eluting balloon-expandable dedicated bifurcation stent that is implanted in the MV and has an open side to the ostium of the SB. In the Polbos I trial, the BiOSS Expert was compared with many types of DESs using the PST. Although the MACE rates were similar, the TLR rate was higher in the BiOSS Expert group[146]. The BiOSS LIM is a sirolimus-eluting balloon-expandable dedicated stent. In the Polbos II trial, no difference was found between the BiOSS LIM and provisional DES techniques in terms of the MACE and TLR rates[147].

The Tryton stent is a balloon expandable dedicated cobalt chromium non-DES. This stent is implanted in the SB, and a DES is implanted in the MV through the open struts of this dedicated stent. A pooled analysis of the Tryton pivotal randomized controlled trial and post-approval confirmatory study comparing this stent with the PST with a DES showed that the Tryton stent was clinically non-inferior to the PST with good angiographic outcomes at 1 year[148].

The Axxess stent is a self-expandable biolimus-eluting dedicated stent that is designed for EDS. It is implanted in the proximal MV with its distal end aligned to the carina, allowing easy access to both the distal MV and the SB[149]. In the COBRA study, Axxess with two biolimus-eluting stents (in the distal MV and the SB) was compared to the culotte stenting technique with two everolimus-eluting stents and found no difference in stent coverage at 9 mo and similar favorable clinical outcomes at 5 years[150].

Consequently, DBSs have not yet been found to be superior to conventional bifurcation stenting strategies for routine use in CBLs[151].

ANTITHROMBOTIC THERAPY

Since the periprocedural and long-term risk of stent thrombosis (ST) of coronary bifurcation PCI is high [112], antithrombotic therapy is an important part of CBL treatment. The anatomical properties of bifurcations lead to a relatively high rate of strut malapposition, stent underexpansion and isolated strut noncoverage, resulting in thrombosis[113]. EDS, except for the DK-crush technique, has been found to cause higher ST risk than one-stent implantation. In addition, the ST rate of "bail-out" second stent implantation in the PST was shown to be higher than that in EDS[152]. Therefore, careful preselection of the stenting strategy is required. ST most often occurs acutely or in the first 30 d postprocedure rather than later[20].

Unfractioned heparin is the standard anticoagulant agent for every PCI procedure. Given the complex and time-consuming nature of bifurcation intervention, close monitoring of ACT values is required. In order to prevent ST in the acute and early phases, IV cangrelor may be preferred in $P2Y_{12}$ inhibitor-naïve patients (ESC Class IIb, LOE A recommendation)[40].

Dual antiplatelet therapy (DAPT) with $P2Y_{12}$ inhibitors and aspirin is the standard treatment after every coronary stent implantation. In acute coronary syndrome (ACS), the potent $P2Y_{12}$ inhibitors prasugrel and ticagrelor are preferred over clopidogrel. Due to the results of the recent ISAR–REACT 5 trial, prasugrel is preferred over ticagrelor in the latest ESC guidelines (Class IIa)[153]. In stable coronary artery disease (CAD), although they have not been documented to be more efficient than clopidogrel, the potent $P2Y_{12}$ inhibitors prasugrel or ticagrelor may be considered in high ST risk situations, such as LMCA interventions, according to the ESC guidelines (Class IIb, LOE C recommendation)[41].

The duration of DAPT depends on the clinical presentation (stable CAD or ACS) and the ST and bleeding risk. In both stable CAD and ACS interventions, high ST risk patients such as bifurcation PCI ≥ 2 stents and LMCA PCI, the duration of DAPT may be prolonged beyond 12 mo if the bleeding risk is not high (Class IIb indication for stable CAD and class IIa indication for ACS)[41,154]. However, in the case of high bleeding risk (*e.g.*, PRECISE-DAPT score ≥ 25), DAPT duration may be considered as 3 mo for stable CAD and 3-6 mo for ACS patients with the cessation of $P2Y_{12}$ inhibitor (Class IIa indication according to ESC and Class IIb indication according to the latest AHA/ACC guidelines, for both stable CAD and ACS)[41,154-156]. Finally, after the recent publication of 5 large trials that also included CBLs, the AHA/ACC recommends a class IIa indication for a shorter DAPT duration (1-3 months) followed by $P2Y_{12}$ inhibitor monotherapy to reduce the risk of bleeding events in selected patients [156].

CONCLUSION

Coronary bifurcation lesions are complex and require meticulous preplanning of the stenting strategy. The provisional stenting technique is the default strategy in most cases. However, two-stent techniques, especially the DK-crush technique, may be the upfront-stenting strategy in some patients with complex lesions. Multiple consecutive steps are required to perform a successful stenting procedure. During the procedure, intravascular imaging is an essential tool since it is not only helpful in the selection of the stenting technique but also necessary for optimization of the result. The results of ongoing and anticipated future trials are awaited to clarify various unresolved issues in percutaneous coronary bifurcation interventions.

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REVIEW

Arrhythmic risk stratification in ischemic, non-ischemic and hypertrophic cardiomyopathy: A two-step multifactorial, electrophysiology study inclusive approach

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Abstract

Annual arrhythmic sudden cardiac death ranges from 0.6% to 4% in ischemic cardiomyopathy (ICM), 1% to 2% in non-ischemic cardiomyopathy (NICM), and 1% in hypertrophic cardiomyopathy (HCM). Towards a more effective arrhythmic risk stratification (ARS) we hereby present a two-step ARS with the usage of seven non-invasive risk factors: Late potentials presence (≥ 2/3 positive criteria), premature ventricular contractions (≥ 30/h), non-sustained ventricular tachycardia (≥ 1episode/24 h), abnormal heart rate turbulence (onset ≥ 0% and slope ≤ 2.5 ms) and reduced deceleration capacity (≤ 4.5 ms), abnormal T wave alternans (≥ 65μV), decreased heart rate variability (SDNN < 70ms), and prolonged QT_c interval (> 440 ms in males and > 450 ms in females) which reflect the arrhythmogenic mechanisms for the selection of the intermediate arrhythmic risk patients in the first step. In the second step, these intermediate-risk patients undergo a programmed ventricular stimulation (PVS) for the detection of inducible, truly high-risk ICM and NICM patients, who will benefit from an implantable cardioverter defibrillator. For HCM patients, we also suggest the

incorporation of the PVS either for the low HCM Risk-score patients or for the patients with one traditional risk factor in order to improve the inadequate sensitivity of the former and the low specificity of the latter.

Key Words: Arrhythmic sudden cardiac death; Risk stratification; Non-invasive risk factors; Electrophysiology study; Two-step approach; Arrhythmias in cardiomyopathy

Core Tip: An effective arrhythmic risk stratification approach based on two steps is proposed for the detection of truly high arrhythmic risk patients among ischemic and non-ischemic cardiomyopathy groups: In the first step, patients are screened for several non-invasive risk factors (NIRFs). When even one of these NIRFs is present, patients proceed to the second step, *i.e.*, an electrophysiological study with programmed ventricular stimulation. An implantable cardiac defibrillator is offered to the inducible patients. We also suggest the incorporation of an electrophysiological study in the arrhythmic risk stratification approach among low-risk groups of hypertrophic cardiomyopathy patients.

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INTRODUCTION

Arrhythmic sudden cardiac death (SCD) could potentially pose a threat to patients with ischemic[1] (ICM), non-ischemic[2] (NICM), and hypertrophic[3] (HCM) cardiomyopathy. It occurs by a sudden heart rhythm disorder caused by either an abrupt shift of the normal rhythm to ventricular tachycardia (VT), which degenerates into ventricular fibrillation (VF), or rarely by direct VF[4]. One of the common substrates for this rhythm disturbance in ICM as well as in NICM and HCM is myocardial fibrosis[5]. Arrhythmogenic fibrotic areas are ubiquitous in the post-infarcted myocardial segments in ICM[5], in the left ventricular septum or left ventricular free wall in NICM[6], and interstitially in the left ventricular wall in HCM[7]. The annual SCD rate may range from 0.6% to 4% in ICM[8,9], 1% to 2% in NICM[6] and 1% in HCM[3]. Nevertheless, patients may be protected from arrhythmic SCD thanks to Dr. Mirowski, who conceived the idea, invented and implanted the first cardioverter defibrillator (ICD) back in 1980. However, prior to an ICD implantation, an effective arrhythmic risk stratification (ARS) of a large number of patients at potential arrhythmic risk is required in order to identify those at truly high risk[9] thus, avoiding unnecessary implantations with undue exposure to complications and health system resources exhaustion.

Current status of arrhythmic risk stratification and its limitations

Current European[10] and American Guidelines for SCD prevention are based on previous studies[1,2] with significant inherent design limitations. For the primary prevention of SCD in post-myocardial infarction (post-MI) patients, an ICD implantation is recommended in all patients with left ventricular ejection fraction (LVEF) ≤ 35% based on the MADIT II[1] study results, published 19 years ago. While 18 devices have to be implanted, to save one life during a 2-year follow-up with this strategy[11], a rather significant post-MI subpopulation demonstrating preserved left ventricular systolic function and LVEF > 35%, will be still exposed to SCD with an annual prevalence of malignant arrhythmias ranging between 0.6% to 1%[8]. Similarly, according to the results of SCD-HeFT and DEFINITE[2] studies, an ICD implantation for primary prevention of SCD is recommended for NICM patients with a reduced left ventricular systolic function (LVEF ≤ 35%)[10]. The usage of the LVEF ≤ 35% criterion for non-ischemic dilated cardiomyopathy patients' selection for ICD implantation bears two limitations: first, as the LVEF ≤ 35% criterion fails to identify the truly arrhythmic risk patients, the majority of the implanted ICDs within this spectrum are not expected to be activated, and, as the recent DANISH study has shown, survival may not be improved. Secondly, in a significant proportion of NICM patients with an LVEF>35%, fatal arrhythmic events may occur[6].

In HCM, the current European guidelines recommend the HCM Risk-SCD score calculation and an ICD implantation for patients with an estimated 5-year SCD risk > 6% (Class IIa)[10]. The HCM Risk-

SCD score, as a screening tool, also has inherent limitations. Since its dawn in the development study among 2082 patients (derivation cohort) and the subsequent application in the evaluation study of 1593 patients[12] (validation cohort), 84 SCD cases occurred during follow-up. An HCM Risk-SCD score > 4% was able to detect 60 out of these 84 SCD cases (71%) but failed to detect the rest (29%, *i.e.*, one out of three patients). This limited performance of the current arrhythmic risk stratification approaches in ischemic and non-ischemic cardiomyopathy is of no surprise because of their inability to estimate the underlying arrhythmic substrate by ignoring significant information from already existing and promising non-invasive[9] and invasive electrophysiology (EP) related techniques[13,14]. MADIT II[1] and SCD-HeFT studies were endeavors for proving the post-ICD implantation survival benefit based on an oversimplistic, rather hemodynamic than EP oriented approach, in coronary artery disease (CAD) and NICM populations, in whom an increased incidence of cardiac mortality was anticipated. In HCM, the development of a multivariate scoring system[12], with the inclusion of clinical, echocardiographic, and electrocardiographic markers, although it achieved some degree of satisfactory performance among patients with several risk factors as recommended in both the European and American guidelines, it failed to detect relatively low-risk patients exhibiting one either strong or rather loose traditional risk factor, and who are still at risk for SCD[15,16]. Furthermore, there is a significant discrepancy between the European and American guidelines, with the former being more specific but less sensitive[17].

Value of the left ventricular ejection fraction in arrhythmic risk stratification and the role of the non-invasive risk factors

Arrhythmic mortality is known to have an inverse correlation with the left ventricular systolic function [9,18]. The more LVEF declines, the more mortality increases: in relatively preserved LVEF > 30% the annual mortality is 3.2%, while in diminished LVEF 21%-30% it raises to 7.7%, and in seriously depressed left ventricular systolic function (LVEF < 20%) it launches, to 9.4%[9]. This inverse correlation between left ventricular systolic function and arrhythmic event rates was known and well described before the MADIT II[1] trial. In this study design, the cutoff point of LVEF ≤ 30% was selected as an enrolment criterion for the recruitment of post-MI patients with moderate to serious heart failure and highly-expected future arrhythmic events[18]. Indeed, the main hypothesis (*i.e.*, ICDs improve survival in post-MI patients) was confirmed within the next 20 mo of follow-up. Thereafter, guideline recommendations[10] for patient selection and ICD implantation were dominated by the enrolment criteria for the CAD patients of the MADIT II study[1], *i.e.*, impaired LVEF ≤ 30% and for the NICM patients by the enrolment criteria of the SCDHeFT study, *i.e.*, diminished LVEF ≤ 35%. It must be emphasized the significant limitations of the LVEF screening tool[9] considering the calculation of left ventricular systolic function may be affected by the intra- and interobserver variability during measurements and may also be affected by the temporal variability arousing from the natural evolution of the disease as well as from therapeutic interventions such as coronary artery bypass, percutaneous coronary intervention, and pharmacological treatment. Furthermore, the LVEF is more correlated with total mortality rather than with arrhythmic sudden cardiac death and it has low sensitivity, as only one-third of SCDs occur in patients with LVEF < 35%, while two-thirds of SCDs occur in patients with an LVEF > 35%.

It should also be noted that, despite the guideline recommendations for primary prevention of SCD, ICD implantation rates in patients with LVEF ≤ 35% seem to be below, both in the United States[19] and Europe[20]. Therefore, a reasonable question arouses: why does LVEF, an anatomic-functional index per se, also predicts future arrhythmic events[9]? Impaired left ventricular systolic function is the consequence of post-MI ischemia, myocardial cell necrosis, and myocardial tissue fibrosis. After the infarction of the left ventricle, both anatomic and electric remodelings are evolving. At the anatomic-functional tissue level, the fibrotic scar formation reduces the left ventricular systolic function, while at the molecular scale, the action potential is prolonged, the intracellular calcium homeostasis is affected, and the dispersion of repolarization is increased. Accumulation of connective tissue into the cellular gap junctions occurs in parallel with systemic neurohormonal activation and increased tone of the sympathetic limp of the autonomic nervous system[21]. As a consequence, the LVEF that quantifies the impaired left ventricular functionality also reflects the subsequent electrical instability, predisposing to VT/VF[9]. The more this anatomic-functional index LVEF decreases, the more it encapsulates hidden electric information occurring in electrophysiological and myocardial cell levels. This information is of some prognostic value but the LVEF criterion is raw, modest, and remote from a personalized estimation of the active presence of the arrhythmogenic mechanisms[9]. The need for effective ARS prior to an ICD implantation constitutes a great challenge; in addition to using LVEF, which is of limited sensitivity and specificity, our research group proposes that this hidden electric information should be discriminated and extracted from the impaired anatomic-functional performance of the left ventricle for personalized prognostic ARS by applying the appropriate methods[9]. Arrhythmic SCD is electric in its origin and the most appropriate ARS approach is the usage of conventional and advanced electrocardiography through recording the electric function of the myocardium and detecting the presence and activity of different arrhythmogenic mechanisms[9,22]. Conventional electrocardiographic (ECG) indices, such as late potentials from signal-averaged ECG[23], QTc interval duration[24], number of ventricular premature beats[24], and non-sustained VT episodes[24] per 24 h, as well as advanced ECG

indices such as standard deviation of normal to normal beats from heart rate variability (SDNN)[25], deceleration capacity of heart rate (DC)[26], heart rate turbulence (HRT)[27,28], and T-wave alternans (TWA)[29], may reveal this prognostic information that is related to different arrhythmogenic mechanisms[22]. The above ECG indices were named "non-invasive risk factors" (NIRFs) when applied during the first step in the PRESERVE-EF[24] study for the selection of patients who were further investigated with programmed ventricular stimulation (PVS) in the second step. The main limitation of NIRFs for SCD prediction is solely that each of these risk factors has low positive predictive accuracy by achieving low odds or hazard ratios**.** To support a decision for an ICD implantation with an acceptable number needed to treat, it has been advocated that a risk stratification index is required to achieve an odds ratio of 25-30. This limitation was effectively addressed in the PRESERVE-EF study[24], through the implementation of PVS in the second step which essentially augmented the performance of the total algorithm after the seven NIRFs had been investigated in the first step.

Cardiac magnetic resonance imaging

Assessment of the arrhythmogenic substrate of the myocardium can be also conducted through cardiac magnetic resonance (CMR). Magnetic resonance diagnostic imaging is based on the contrast between tissues created by the signal generated from the response of hydrogen atoms to the magnetic field. T1 relaxation is the recovery of the longitudinal net magnetization vector and T2 relaxation time is the recovery of the transverse net magnetization vector[30]. T1 mapping does not separate extracellular from cellular segments[31,32]. CMR imaging enhanced with intravenous contrast agents *e.g.*, Gadolinium-based contrast agents (GBCAs), multiplies the extracted information[33]. GBCAs cannot enter the intracellular compartment and are distributed only to the extracellular and interstitial space. After the first distribution, a progressive washout of CBCA is observed in the normal myocardium but this washout is delayed in abnormal fibrotic areas. While late gadolinium enhancement (LGE) expresses the difference between two areas, the extracellular volume (ECV) is reflecting histological changes early in the cardiomyopathies' course, independently of their cause. In CAD, the scar tissue following an acute coronary syndrome forms the arrhythmogenic substrate[34]. LGE detects focal myocardial fibrosis predisposing to arrhythmic risk[35,36]. While in the dense core of the scar the fibrotic areas are interrupted by viable fibers serving as slow conduction pathways, in the "grey zone" that surrounds the core of the scar, the hypoperfused myocardium conceals arrhythmogenic properties[37,38]. CMR by assessing and quantifying the heterogeneity of the scar and size of the border zone predicts malignant arrhythmias and appropriate ICD activations[39]. T1 mapping and ECV abnormal measurements are also correlated with an increased arrhythmic burden[40].

In NICM, both the existence and localization of LGE are independent predictors for arrhythmic SCD and hospitalization in all ranges of LVEF[6,41,42]. Septal LGE carries the worst prognosis, even if the fibrotic area is restricted, while the coexistence of septal with free wall LGE, as well as a subepicardial pattern of LGE, are all additive risk factors for fatal arrhythmias[6,41-43]. ECV reveals the early stages of the disease and represents an independent prognostic factor for cardiovascular death and appropriate ICD activations[44,45].

In HCM, the presence of scar, imaged by LGE, is considered to be a strong independent predictor for ventricular arrhythmias, ventricular remodeling, all-cause mortality, and cardiac death[46]. The extent of myocardial LGE involvement has been proposed as a better risk stratifier, with cutoffs oscillating from as low as 10% to as high as 20%, with the mean value of 15% attaining wider acceptance. The pattern of LGE distribution, patchy with multiple foci or diffuse, does not carry additional risk. Nevertheless, we are not aware of whether the decision for an ICD implantation for primary protection against SCD can be exclusively made based on the cardiac MRI; the specific criteria for such a decision are unknown, and we lack prospective information relevant to the rate of appropriate defibrillator activations among all the implanted devices at follow-up time to evaluate such kind of strategy[47]. The results of the ongoing GUIDE-CMR multicenter study[48] in Australia, a study randomizing both post-MI and NICM patients with relatively preserved LVEF 35%-50% upon CMR findings to ICD *vs* ILR, may provide the initial answers to these questions. In the electrophysiology perspective, CMR characterizes the cardiac tissue and detects the substrate that may be arrhythmogenic. This is a necessary condition for arrhythmogenicity, however, it is considered insufficient. The potential arrhythmogenic function of this scar substrate with the usage of CMR solely remains unknown. In order for this predictive information to be extracted, it is necessary that non-invasive and invasive electrocardiography with VPBs, NSVT, LPs, and inducibility upon PVS in electrophysiology (EP) lab is included in the ARS. CMR may classify an extended number of patients with a scar presence[6,47], and convert all of them to ICD candidates. Following such a strategy, a large number needed to treat may not be avoided, and as it happened with the devices implanted for two decades according to the LVEF criterion, only a small portion will be appropriately activated. While mere CMR is probably insufficient to staunchly support the decision for appropriate patient selection before an ICD implantation, it represents an excellent NIRF for the first initial screening of a two-step, EP inclusive approach.

Electrophysiology study with PVS

Ventricular arrhythmias leading to SCD can be studied in the EP Lab and can be triggered or reproduced in patients prone to arrhythmia. Since 1971, when Wellens *et al*[49] introduced the PVS in

the investigation of arrhythmias, it has been known that malignant VT and VF may be triggered in the EP Lab, with the patient being fully conscious in the supine position. This triggering procedure involves an intracardiac catheter, which has been percutaneously inserted and intravenously advanced into the right ventricle, to contact the myocardium. After the external connection of the catheter to a suitable pulse generator, and the assessment of the effective refractory period of that point of the myocardium, PVS with a specific protocol follows. To increase the sensitivity and specificity of the study, the procedure is usually performed and repeated at two different sites, *i.e.*, at the apex and the right ventricle outflow tract, while NICM patients additionally receive intravenously b-agonists. Myocardial fibrosis forms the substrate for a reentrant mechanism which, during programmed ventricular stimulation with the extra stimuli addition, may be activated and generate monomorphic ventricular tachycardia. Multiple programmed ventricular stimuli may act on the triggering mechanism and they may also cause ventricular tachycardia. The laboratory result of an induced or non-induced sustained ventricular tachyarrhythmia provides unique and valuable information for the management of such patients. This information cannot be extracted through other modalities and requires patients to be subjected to this specific protocol, which in the controlled EP Lab setting, is absolutely safe. Given the importance of the question and the risk of possible future exposure to SCD, there is not a single doubt that a patient's subjection to this invasive procedure is worthwhile. Inducible sustained monomorphic VT has been repeatedly proved to be a predictor of SCD in prospective trials[50]. In contrast, the existing data for polymorphic VT or VF induction are conflicting.

Some studies conclude that the induced polymorphic VT or VF are not associated with a high risk for SCD[50,51] but this point is conflicting, as other data support the aspect that such an arrhythmic response to PVS is also of prognostic value[13,14,52].

In addition, previous studies suggest a low risk of SCD in patients with relatively preserved left ventricular systolic function and LVEF > 40%, even in the presence of inducible VT[53], however, primary protection from major arrhythmic events was recently confirmed for these patients, when the implanted ICDs with the improved two-step, EP inclusive approach in PRESERVE EF study where appropriately activated[24]. In CAD, the ARS may be discerned at three different periods, considering the time pass after the myocardial infarction (MI): (1) the early phase (first 40 d); (2) the subacute phase (40 d–6 mo after the MI); and (3) the remote phase (> 6 mo after the MI).

Acute MI phase (< 40 d): Animal studies have shown that within two weeks after MI, the substrate for reentrant ventricular arrhythmias was formed in the myocardium. In terms of pathophysiology, the experimental results justify an early post-MI PVS investigation[54].

The BEST-ICD study[55] enrolled 143 survivors with left ventricular ejection fraction ≤ 35% and either frequent VPBs > 10/h or depressed SDNN < 70 ms from heart rate variability or abnormal signal-averaged ECG within a month after an acute MI. Of these, 138 were randomized, in a 2:3 ratio, to conventional strategy (n = 59) or PVS guided/ICD strategy (n = 79), with 24 ICDs implanted in the inducible patients. A nonsignificant survival benefit of this early PVS-guided strategy of ICD implantation was shown, but the study was underpowered to provide a definite conclusion for the performance of such an approach. It must be noted that this was a two-step ARS study, with the preselected patients exhibiting a combination of a depressed LVEF ≤ 35% and/or three basic NIRFS, while the PVS was performed after total sample randomization.

Two observational ICD studies found that a positive response on PVS is an efficient arrhythmia predictor. In the first one[56], which included ST-elevation MI patients who had received a primary percutaneous coronary intervention, a benefit from an early ICD implantation for the patients with an impaired LVEF and positive PVS was shown, while in the second one[57], which enrolled post-MI patients with a depressed left ventricular systolic function, the PVS study effectively discriminated - in the long term - patients with a protective ICD implantation (PVS positives) from the vast majority of those at significantly lower risk of arrhythmic events without a defibrillator (PVS negatives).

Furthermore, a negative PVS predicted survival in the absence of an ICD implantation[56]. Despite the negative results produced by IRIS and DINAMIT studies, whose design failed to detect the truly early post-MI high arrhythmic risk patients and, thus, failed to prove a survival benefit for the ICD recipients', consequently withholding such patients from an ICD implantation with a class III recommendation[10], the arrhythmic SCD risk in early post-MI phase exists and this is well known and described. The acknowledgment of this risk explains the paradox: while guidelines that are based on the IRIS and DINAMIT studies reject ICD implantation in early post-MI patients with a Class III recommendation[10], the same guidelines, propose screening these early post-MI patients at potential arrhythmic risk with PVS with a Class IIb recommendation. This specific clinical issue questioning the most appropriate ARS strategy is under investigation by the PROTECT-ICD trial[58], which recruits early post-MI patients with LVEF ≤ 40% and randomizes them to either PVS-guided early ICD implantation or a control standard care arm.

Subacute and remote phases after MI phase (≥ 40 d): Data for the utility of PVS in remote phases after an MI comes from both randomized and observational studies. MADIT I study, 1996, included 196 post-MI patients at increased risk for ventricular tachyarrhythmias. Enrollment was focused on patients fulfilling the inclusion criteria of LVEF < 35%, non-sustained VT, and the inducibility of VT in PVS.

These patients were randomly assigned to receive either an implanted defibrillator (n = 95) or conventional medical therapy (n = 101). A 54% reduction in overall mortality was observed for the ICD treatment arm with a 27-mo follow-up. The MUSTT study[59], 1999, investigated a population at relatively increased arrhythmic risk consisting of patients with a prior MI, LVEF% < 40%, and non-sustained VT that was inducible in PVS (n = 704). After randomization, 351 of them were assigned to EP-guided therapy and 353 were assigned to no antiarrhythmic therapy. The five-year estimates of the incidence of the primary endpoint of cardiac arrest or death from arrhythmia were 25% for the EP guided therapy receivers and 32% for the patients assigned to no antiarrhythmic therapy with a relative risk: 0.73, representing a 27% risk reduction. In this study, a combination of LVEF<40% and inducibility in the PVS resulted in a greater reduction in mortality than the one observed in the MADIT II trial[1], which used the LVEF as the sole criterion for selecting patients for ICD implantation. These two randomized trials have demonstrated the utility of PVS in combination with a reduced LVEF and other variables in the appropriate selection of the candidates before an ICD implantation. MADIT II study[1] in 2002, extended the prophylactic use of an ICD to a broader post-MI patients spectrum under a less arrhythmic risk compared to the MUSST[59] population with an LVEF < 30% as the only pre-implantation criterion. In the MADIT II trial[1], a PVS was not considered necessary for the initial study. These 1232 post-MI patients with significant heart failure were randomly assigned in a 3:2 ratio to receive either an ICD (n = 742) or conventional medical therapy (n = 490). An improvement in survival was observed in the ICD group during an average follow-up of 20 mo with a 0.69 hazard ratio. Although a PVS was not an inclusion criterion for patient selection in the initial study, its performance was examined in a MADIT II sub-study[51] and inducibility was found to be related to subsequent ICD-detected arrhythmias. In that study, while an inducible monomorphic VT predicted future arrhythmic episodes, the induction of polymorphic VT or VF appeared less relevant. These data were retrospectively acquired, with many study-centers contributing only 2–4 cases and without having used a standardized PVS protocol. On the other hand, high PVS predictive accuracy was consistently shown when the EP study was performed in dedicated centers in the context of single-center studies, using standardized protocols[13,14,52]. The prospective observational Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction - CARISMA trial in 2009, investigated 312 post-MI phase patients with a mean LVEF of 31% ± 6% with application of NIRFs (Heart rate variability/turbulence, ambient arrhythmias, signal-averaged electrocardiogram, T-wave alternans) and PVS, applying the NIRFs and the PVS rather independently in a parallel screening than in a two-step sequential approach. Induction of sustained monomorphic VT predicted the future occurrence of VT/VF (adjusted HR = 4.8, P = 0.003).

PVS in NICM and HCM

In NICM, the role of PVS has been disputed[60] for years. However, this view was recently challenged by a prospective study of 157 NICM patients[13,61,62], who were evaluated with PVS for primary prevention; during long-term follow-up, appropriate ICD intervention or SCD occurred significantly more frequently among PVS positive NICM patients. This PVS-guided approach was incorporated for the first time in current ESC guidelines[10], albeit at a class IIb recommendation. In HCM, the ESC guidelines[10] for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, following ESC HCM guidelines that are based on an expert opinion level of evidence, do not recommend a PVS for ARS. However, recent results[15] support its use in a study that investigated 203 HCM patients with ≥ 1 NIRFs who were submitted to PVS and received an ICD. During a median follow-up period of 60 mo, the primary endpoint was observed in 20 patients, of whom 19 were inducible in a procedure that was proven safe and they had an ICD implanted. Inducibility at PVS predicted SCD or appropriate device therapy while non-inducibility was associated with prolonged event-free survival. The addition of an EP/PVS risk estimation[15], among HCM patients demonstrating one traditional risk factor, may improve the frequently observed rather poor performance[15,63] of either the American or the European guidelines in this subgroup of HCM patients. Considering the time course for the evolution of research in the field of SCD ARS, one could say that data from previous studies have now dried up, leaving significant gaps in the management of such patients[60], gaps that we do not know if and how they will be filled in by methods such as MRI [17] or Virtual PVS[64] in the future. Nevertheless, the latest results published[24] describe a two-step SCD ARS strategy: in the first step of this strategy, if the included bloodless non-invasive ECG markers (NIRFs) are positive, we proceed with the second step of PVS for the patient selection before an ICD implantation. Similar results based on a two-step, EP inclusive approach, were documented in patients across the entire spectrum of ischemic and organic cardiomyopathy, in post-MI patients with preserved LVEF[24], in patients with heart failure and moderately impaired left ventricular systolic function[65], in NICM[13], and HCM[15] patients, noteworthy with correct ICDs activation of the devices implanted. This strategy has been applied in sudden cardiac death ARS by the First Department of Cardiology and EP Lab, National and Kapodistrian University of Athens at Hippocration Hospital of Athens, Attica, Greece[66], over the last twenty years, thus contributing to the final decision for the appropriate patient selection for ICD implantation across all the ICM[24,65] and NICM[13] and HCM[15] patients' spectrum.

Table 1 Abnormal values and connection of every non-invasive risk factors with the arrhythmogenic mechanisms

Non-invasive risk factors	Abnormal values	Mechanisms
SAECG, LPs	2/3 positive criteria	Fibrotic areas, slow conduction, reentry
QTc	≥ 440 ms (♂), ≥ 450 ms (♀)	Prolonged repolarization, EAD, DAD
TWA	≥ 65 μV (2-channels)	APD and Ca^{2+} alternans, steep APDR and CVR, steep FSRCR
VPBs	≥ 30/24 h	Automaticity (Ca^{2+}oscillations), reentry
NSVT	≥ 1 episode/24 h	Automaticity (Ca^{2+}oscillations), reentry
SDNN/HRV	≤ 75 ms	Enhanced sympathetic tone, autonomic imbalance
DC/HRT	DC ≤ 4.5 ms	Vagal and sympathetic ANS dysfunction
	HRT onset ≥ 0%	
	HRT slope ≤ 2.5ms	

ANS: Autonomic nervous system; APD: Action potential duration; APDR: Action potential duration restitution; CVR: Conduction velocity restitution; DAD: Delayed afterdepolarization; DC: Deceleration capacity from heart rate dynamics; EAD: Early afterdepolarization; FSRCR: Fractional sarcoplasmic reticulum Ca^{2+} release; HRT: Heart rate turbulence; LPs: Late potentials from signal-averaged electrocardiogram; NSVT: Non-sustained ventricular tachycardia; QTc: Corrected according to Fridericia formula QT interval; SAECG: Signal-averaged electrocardiogram; SDNN: Standard deviation of normal to normal beats from heart rate variability analysis; TWA: T wave alternans; VPBs: Ventricular premature beats.

TWO-STEP, NON-INVASIVE RISK FACTORS ELECTROPHYSIOLOGY STUDY INCLUSIVE, RISK STRATIFICATION ALGORITHM

Initially, the concept of the two-step multifactorial, EP inclusive approach had been successfully introduced for the risk stratification and management of post-MI patients, incorporating NIRFs such as heart rate variability, LVEF, late potentials, and complex ventricular arrhythmias[67,68]. Indeed, such studies identified a high-risk group of post-MI patients, predominantly among those with reduced LVEF that are usually offered an ICD, based on current guidelines. This strategy was further refined and improved in the PRESERVE EF study[24] applying an accurate algorithm with multiple advanced ECG markers[9] that reflect the presence and activity of diverse arrhythmic mechanisms to detect high-risk post-MI patients after a limited myocardial injury without any evidence of ongoing myocardial ischemia or significant left ventricular dysfunction. In the first step, the advanced form of the algorithm [24] determined the presence of seven NIRFs, while in its simplified, yet equally effective form[65], it appears to be working well even in the simple presence of only three fundamental NIRFs. Upon detecting the presence of at least one of the NIRFs, patients are referred for PVS. The advantage of ARS using multiple NIRFs during the first step is that they reflect the presence and activity of multiple different arrhythmogenic mechanisms, such as fibrotic areas with late conduction properties predisposing for re-entry (SAECG late potentials)[23], prolonged action potential repolarization duration (QTc)[24], electrical instability with T wave alternations during repolarization (TWA)[29], increased sympathetic tone (SDNN)[25], decreased parasympathetic tone (DC[26] and HRT[27,28]), triggered activity on a substrate that predisposes to and maintains ventricular arrhythmias (VPBs and NSVT)[24]. The pathophysiological connection for every NIRF with the arrhythmogenic mechanisms[22] is presented in Table 1, while its prevalence in the total sample, in the truly high-risk group that was detected after the two-step, EP inclusive approach, and in the 9 patient subgroup with SCD equivalent major arrhythmic events during a 32 mo of follow-up, as investigated in the PRESERVE EF study[24], are presented in Table 2. The results of the implementation of this two-step risk stratification strategy were described in this study in 575 post-MI, relatively not aged (mean age = 57 years) with preserved left ventricular systolic function (LVEF = 50.8%) patients. In this study, 9 major arrhythmic events (MAEs) were observed during a 32 mo follow-up. The MAE prevalence in the total sample of 575 patients was 1.5%. The implementation of the first step of the algorithm determined an intermediate risk subpopulation of 204 patients out of 575 patients in total, with at least one NIRF present. In this intermediate-risk subpopulation with positive NIRFs, who were risk-stratified using the first step, the MAE prevalence increased from 1.5% to 4.4%. When this subpopulation underwent PVS as per the second step, 41 out of 152 patients developed arrhythmia (out of the 204 patients of the intermediate-risk group who gave their informed consent to participate in the EP study). This third group of 41 PVS-positive patients represented the subpopulation at actual high risk with the MAE prevalence accounting for 22% (Figure 1). It is realistically feasible that by this approach, out of the general population of the ischemic, the NICM and the HCM patients, the subpopulation at actual high risk for SCD who could undergo ICD implantation can be defined in 2 steps, whereas the rest of the patients can safely be excluded from implantation[24,60,69]. This approach will be tested in NICM patients in the

Table 2 Prevalence of non-invasive risk factors in the total sample, in the truly high-risk group, detected after the two-step, electrophysiology inclusive approach, and in patients with major arrhythmic events during a 32-mo follow-up, as investigated in the PRESERVE EF study[24]

NIRF	Prevalence in the total preserve-EF study (*n* = 577)	Prevalence in the high-risk group (*n* = 41)	Prevalence in 9 MAE/SCD patients
LPs (%)	13.8	51.2	78 (7/9)
NSVT (%)	8.6	46.3	66 (6/9)
QTc (%)	13.6	36.6	55 (5/9)
VPBs (%)	10.8	39	33 (3/9)
TWA (%)	6.8	24.4	11 (1/9)
SDNN (%)	2.8	9.8	0 (0/9)
HRT and DC (%)	2.8	9.8	0 (0/9)

DC: Deceleration capacity from heart rate dynamics; HRT: Heart rate turbulence from heart rate dynamics; LPs: Late potentials from signal-averaged electrocardiogram; MAE: Major arrhythmic event; NIRF: Non-invasive risk factor; NSVT: Non-sustained ventricular tachycardia; QTc: Corrected according to Fridericia formula QT interval; SDNN: Standard deviation of normal to normal beats from heart rate variability analysis; TWA: T wave alternans; VPBs: Ventricular premature beats.

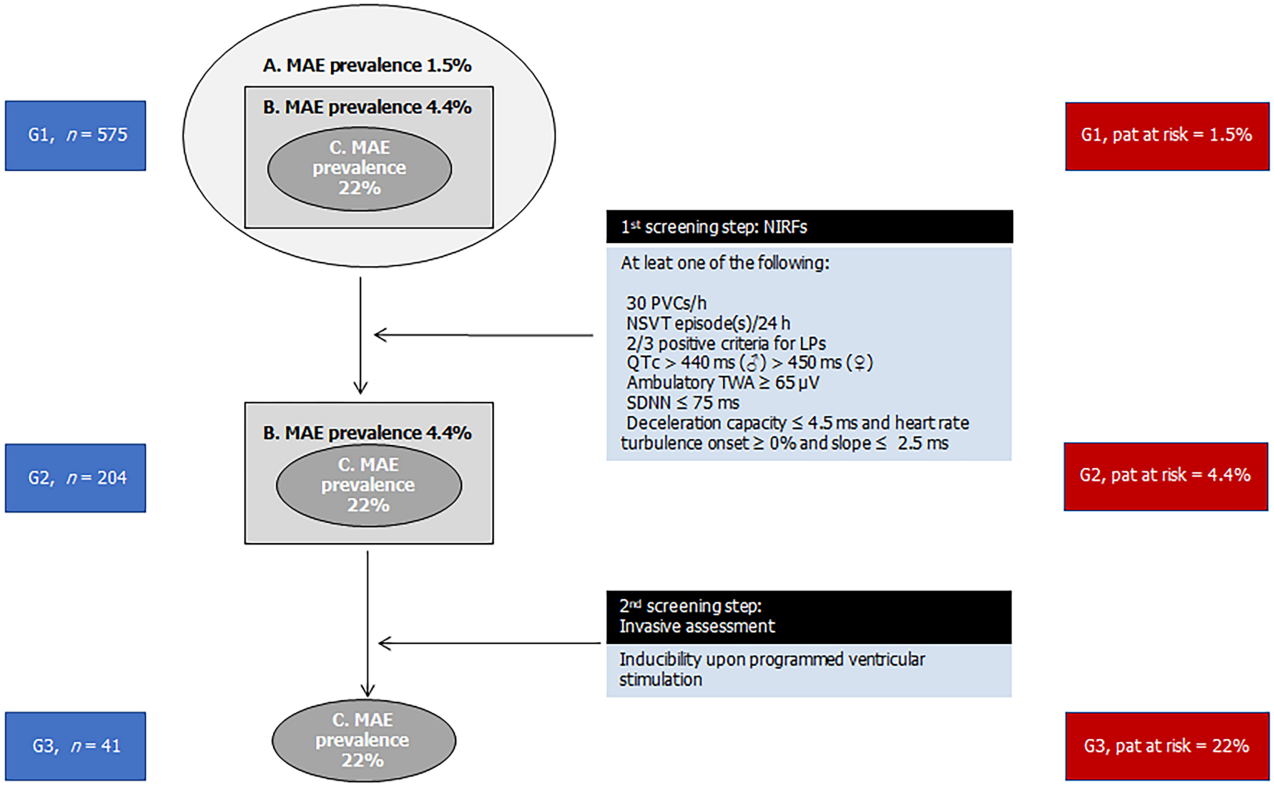

Figure 1 The PRESERVE EF[24] study's two-step arrhythmic risk stratification algorithm. In the total sample of patients the estimated prevalence of major arrhythmic events (MAE) during the 32-mo follow-up was 1.5%. Implementation of the algorithm with the detection of the NIRFs in the first step determines the intermediate-risk subpopulation, with the MAE prevalence accounting for 4.4%. In the second step, the Programmed Ventricular Stimulation determines the actual high-risk subpopulation, with a prevalence reaching 22%. Of the 37 patients with implantable cardioverter defibrillator, there were 9 true activations during the 32-mo follow-up. Neither sudden cardiac death(SCD) nor inappropriate ICD activations were observed during follow-up. (Modified with permission from EHJ[24]).

ReCONSIDER study[70]. An overview of a two-step, non-invasive, EP inclusive ARS approach, for ICM, NICM, and HCM is depicted in Figure 2.

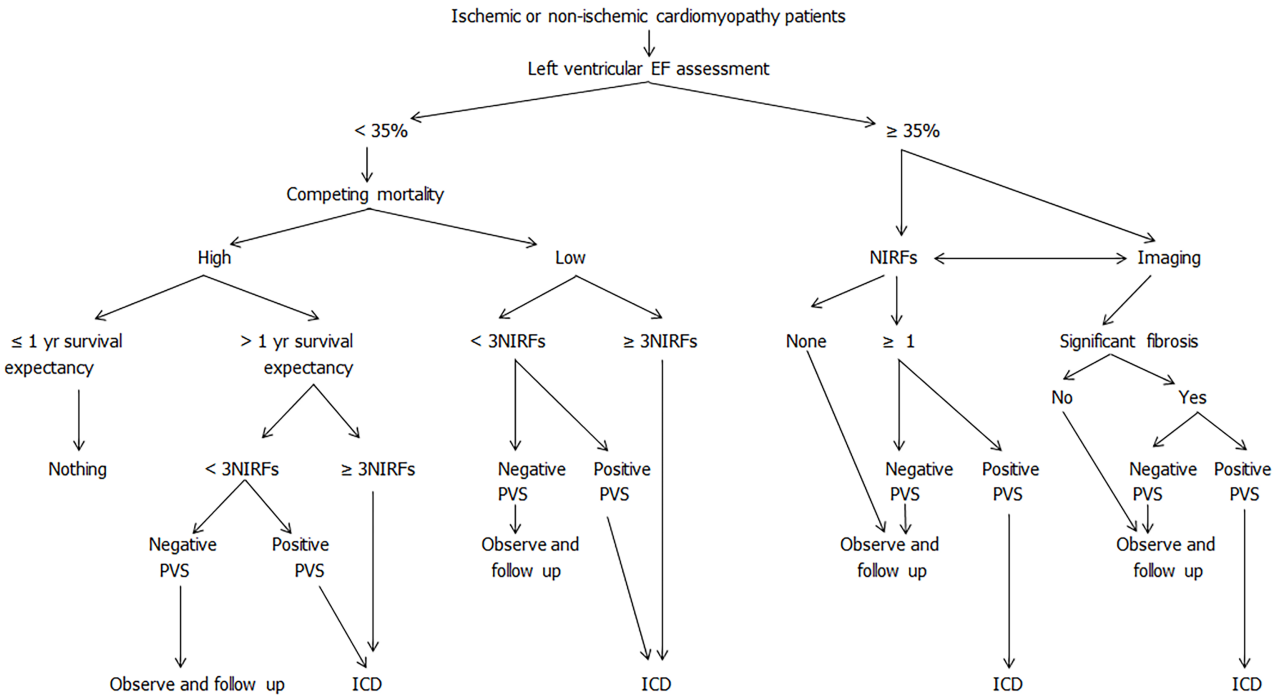

Figure 2 Emerging new sudden cardiac death risk stratification paradigm. It is based on newer evidence, incorporating competing mortality assessments, as well as non-invasive and invasive tests. Non-invasive tests are performed before programmed ventricular stimulation (PVS) to assess the likelihood of functional circuit formation. PVS is pivotal in determining the potential for arrhythmia sustainability and guiding treatment, especially in intermediate and low-risk patients. "Observe and Follow-up" involves repeating tests for NIRF annually and PVS every 3–5 yr. NIRFs (noninvasive ECG risk factors) including the presence of late potentials (≥ 2/3 criteria), frequent premature ventricular contractions (≥ 30/h), non-sustained VT (≥ 1/24 h), abnormal heart rate turbulence (onset ≥ 0% and slope ≤ 2.5ms) and reduced deceleration capacity (≤ 4.5 ms), positive T wave alternans (≥ 65 μV), decreased heart rate variability (SDNN < 70ms), prolonged QT_c interval (> 440 ms in males and > 450 ms in females). (Modified after permission from ANE[60]).

CONCLUSION

The arrhythmic risk stratification for SCD in Ischemic, Non-Ischemic, and Hypertrophic cardiomyopathy for ICD implantation patient selection may be improved with the proposed two-step algorithm. This broad spectrum of patients shares arrhythmogenic mechanisms. Appropriate screening of all these patients with basic and advanced electrocardiographic indices in the first step may detect the subpopulation of intermediate SCD risk. When this subpopulation is subjected to programmed ventricular stimulation in the second step, the truly high SCD risk patients may be detected and effectively protected with an ICD.

FOOTNOTES

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REVIEW

Climatic influences on cardiovascular diseases

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Abstract

Classical risk factors only partially account for variations in cardiovascular disease incidence; therefore, also other so far unknown features, among which meteorological factors, may influence heart diseases (mainly coronary heart diseases, but also heart failure, arrhythmias, aortic dissection and stroke) rates. The most studied phenomenon is ambient temperature. The relation between mortality, as well as cardiovascular diseases incidence, and temperature appears graphically as a ''U'' shape. Exposure to cold, heat and heat waves is associated with an increased risk of acute coronary syndromes. Other climatic variables, such as humidity, atmospheric pressure, sunlight hours, wind strength and direction and rain/snow precipitations have been hypothesized as related to fatal and non-fatal cardiovascular diseases incidence. Main limitation of these studies is the unavailability of data on individual exposure to weather parameters. Effects of weather may vary depending on other factors, such as population disease profile and age structure. Climatic stress may increase direct and indirect risks to human health *via* different, complex pathophysiological pathways and exogenous and endogenous mechanisms. These data have attracted growing interest because of the recent earth's climate change, with consequent increasing ambient temperatures and climatic fluctuations. This review evaluates the evidence base for cardiac health consequences of climate conditions, and it also explores potential further implications.

Key Words: Weather; Climate; Meteorology; Cardiovascular diseases; Myocardial infarction; Angina pectoris

Core Tip: Climatic stress may determine some risks to human health *via* complex pathophysiological pathways. Meteorological factors may influence coronary heart diseases, but also heart failure, arrhythmias, aortic dissection and stroke rates. The most studied phenomenon is temperature. The relation between mortality, as well as cardiovascular diseases incidence, and temperature appears graphically as a ''U'' shape. Other variables, such as humidity, atmospheric pressure, sunlight hours, wind strength and direction and rain/snow precipitations have been studied. These data have attracted growing interest because of the recent earth's climate change. This review evaluates the evidence for cardiac health consequences of climate conditions.

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INTRODUCTION

Despite considerable advances in identifying the conditions that may predispose to atherosclerosis, less information is known about the incident events leading to plaque rupture. Classical risk factors only partially account for variations in cardiovascular disease incidence and mortality. Therefore, also other so far unknown features, among which meteorological factors, may influence cardiovascular diseases rates.

AMBIENT TEMPERATURE AND MORTALITY

Seasonal peaks in respiratory, cardiovascular, and cerebrovascular mortality, with a winter increase in deaths, have been reported in different countries, referred to as ''excess winter mortality''[1-3]. This phenomenon has been strongly linked to changes in temperature[4-8].

The relation between environmental temperature and health has been known for a very long time. Several disorders, such as heat stroke and hypothermia, are directly linked to temperature extremes. Low seasonal temperatures increase the odds of mortality[9,10]. An association between extreme high temperatures and mortality has also been demonstrated[11,12], as confirmed by recent data[13-16]. Actually, a number of ecological time-series studies suggest that the relation between mortality and ambient temperature appears graphically as a ''U'' shape, with mortality rates lower on days in which the average temperatures range between 15° to 25°C, rising progressively as the ambient temperature becomes hotter or colder[17-20]. Most of mortality linked to heat occurs during first days after temperature increase, while the effect of cold has been prolonged for several weeks[21-23]. Spatial and temporal differences have been described in this phenomenon[24-27]. Many heat-related deaths occur in people before they come to medical attention[28]. Investigations carried out in a large number of cities have shown that temperature level corresponding to the minimum mortality varies from place to place and country to country according to the usual climate (heat thresholds were generally higher in communities closer to the equator), probably reflecting adaptations of the population to the usual range of temperature[29]. High respiratory, cardiovascular and influenza mortality in winter leads to lower temperature effects in the following summer[30]. There was a progressive reduction in temperature related deaths over the 20th century, despite an aging population[31-33]. This trend is likely to reflect improvements in social, environmental, behavioural, and health-care factors[34,35]. In the recent COVID-19 pandemic, there was a negative correlation between the cumulative relative risk of death and temperature[36]. Table 1 shows main studies on the relations between weather and general mortality.

In particular, various epidemiological studies have reported greater coronary heart disease (CHD) and acute myocardial infarction (AMI) mortality both in winter[37-40] and in extremely hot summers [25,41,42]. Many authors have postulated that weather-related variables may also explain these seasonal trends, as well as substantial geographic variations in CHD mortality. Cold climate is independently associated to coronary mortality[43-45], but a U-shaped relationship between ambient temperature and cardiovascular mortality has been also described even in milder regions, where either low temperatures or heat waves are exceptional[46-48], with few exceptions[49]. Consensus is lacking, however, on whether this phenomenon reflects variations in incidence or in case fatality rate. Cold effect seems delayed, whereas heat effect is acute, both of which last for several days[34,46,50]. The delay between peak of cold is lower for all-cause mortality and CHD causes than for respiratory ones[51]. Mean temperature had better predictive ability than minimum and maximum one[35,46]. Table 2 shows main studies on the relations between weather and cardiovascular mortality.

Table 1 Main studies on the relations between weather and general mortality

Ref.	Setting and population	Year	Main results
Chung *et al* [11]	Fifteen cities in Northeast Asia	1972-2010	Cold effects had longer time lags (5–11 d) than heat effects, which were immediate (1–3 d). Both cold and heat effects were more significant for cardiorespiratory mortality than for other causes of death
Curriero *et al*[4]	Eleven large eastern United States cities	1973-1994	Current and recent days' temperatures were the weather components most strongly predictive of mortality. Mortality risk generally decreased as temperature increased from the coldest days to a certain threshold temperature, which varied by latitude, above which mortality risk increased as temperature increased. Strong association of the temperature-mortality relation with latitude, with a greater effect of colder temperatures on mortality risk in more-southern cities and of warmer temperatures in more-northern cities
Fernández-Raga *et al* [18]	Castile-Leòn, Spain	1980-1988	Temperatures with lower death risk for patients with cardiovascular diseases (16.8°C) are apparently lower than those for patients with respiratory diseases (18.1°C)
Achebak *et al*[31]	47 major cities in Spain	1980-2015	Reduction in relative risks of cause-specific and cause-sex mortality across the whole range of summer temperatures
Gemmel *et al*[2]	Scotland, United Kingdom	1981-1993	A 1°C decrease in mean temperature was associated with a 1% increase in deaths 1 wk later
Guo *et al*[15]	400 communities from 18 countries/regions	1984-2013	Heat waves had significant cumulative associations with mortality but varied by community. The higher the temperature threshold used to define heat waves, the higher heat wave associations on mortality. The association between heat waves and mortality appeared acutely and lasted for 3 and 4 d. Heat waves had higher associations with mortality in moderate areas than in cold and hot areas
Gasparrini *et al*[22]	305 locations in 9 countries: Australia, Canada, China, Italy, Japan, South Korea, Spain, United Kingdom, and United States	1985-2012	Strong evidence of a reduction in risk over the season. Relative risks for the 99th percentile versus the minimum mortality temperature were in the range of 1.15–2.03 in early summer. In late summer, the excess was substantially reduced or abated, with relative risks in the range of 0.97–1.41
Gasparrini *et al*[27]	384 locations in Australia, Brazil, Canada, China, Italy, Japan, South Korea, Spain, Sweden, Taiwan, Thailand, United Kingdom, and United States	1985-2012	7.71% (95%CI: 7.43–7.91) of mortality was attributable to non-optimum temperature in the selected countries within the study period, with substantial differences between countries, ranging from 3.37% (3.06 to 3.63) in Thailand to 11.00% (9.29 to 12.47) in China. The temperature percentile of minimum mortality varied from roughly the 60th percentile in tropical areas to about the 80–90th percentile in temperate regions
Aylin *et al* [5]	Great Britain	1986-1996	Significant association between mortality and temperature with 1.5 higher odds of dying for every 1°C reduction in winter temperature
The Eurowinter Group[1]	Men and women aged 50–59 and 65–74 in north Finland, south Finland, Baden-Württemburg, the Netherlands, London, and north Italy	1988-1992	Percentage increases in all-cause mortality per 1°C fall in temperature below 18°C were greater in warmer regions than in colder regions. High indices of cold-related mortality were associated with high mean winter temperatures ($P < 0.01$ for all-cause mortality and respiratory mortality; $P > 0.05$ for mortality from ischaemic heart disease and cerebrovascular disease)
Rocklöv *et al* [30]	Stockholm, Sweden	1990-2002	A high rate of respiratory and cardiovascular mortality in winter reduced the heat effect the following summer. The cumulative effect per 1°C increase was 0.95% below and 0.89% above a threshold (21.3°C) after a winter with low cardiovascular and respiratory mortality, but -0.23% below and 0.21% above the threshold after a winter with high cardiovascular and respiratory mortality
Ragettli *et al* [32]	Switzerland	1995-2013	Significant temperature-mortality relationships were found for maximal (1.15; 1.08–1.22); mean (1.16; 1.09–1.23), and minimal (1.23; 1.15–1.32) temperature. Mortality risks were higher at the beginning of the summer. Recent non-significant reduction in the effect of high temperatures on mortality
Chen *et al* [10]	All deaths among residents in Ontario, Canada	1996-2010	In warm seasons, each 5°C increase in daily mean temperature was associated with a 2.5% increase in nonaccidental deaths (95%CI: 1.3%-3.8%) on the day of exposure (lag 0). In cold seasons, each 5°C decrease in daily temperature was associated with a 3.0% (95%CI: 1.8%-4.2%) increase in nonaccidental deaths, which persisted over 7 d. Cold-related effects were stronger for cardiovascular-related deaths (any cardiovascular death: 4.1%, 95%CI: 2.3%-5.9%; CHD: 5.8%, 95%CI: 3.6%-8.1%). Each 5°C change in daily temperature was estimated to induce 7 excess deaths per day in cold seasons and 4 excess deaths in warm seasons
Oudin Åström *et al* [24]	Eastern Esthonia	1997-2013	Immediate increase in mortality associated with temperatures exceeding the 75th percentile of summer maximum temperatures, corresponding to approximately 23°C. This increase lasted for a couple of days
Bell *et al*[21]	Mexico City, Mexico; Sao Paulo, Brazil; Santiago, Chile	1998-2002	Elevated temperatures (in particular same and previous day apparent temperature) are associated with mortality risk
Chan *et al* [12]	Hong Kong, China	1998-2006	An average 18°C increase in daily mean temperature above 28.2°C was associated with a 1.8% increase in mortality. Non-cancer related causes such as cardiovascular and respiratory infection-related deaths were more sensitive to high temperature

Xu *et al*[34]	Barcelona, Spain	1999-2006	The effect of three consecutive hot days was a 30% increase in all-cause mortality (RR = 1.30, 95%CI: 1.24-1.38)
Guo *et al*[23]	Chiang Mai city, Thailand	1999-2008	Both hot and cold temperatures resulted in immediate increase in all mortality types and age groups. Generally, the hot effects on all mortality types and age groups were short-term, while the cold effects lasted longer. The relative risk of mortality associated with cold temperature (19.35°C, 1st centile) relative to 24.7°C (25th centile) was 1.29 (95%CI: 1.16, 1.44) for lags 0–21. The relative risk of mortality associated with high temperature (31.7°C, 99th centile) relative to 28°C (75th centile) was 1.11 (95%CI: 1.00, 1.24) for lags 0–21
Oudin Åström *et al*[24]	Population over 50 years in Rome, Italy, and Stockholm, Sweden	2000-2008	The percent increase in daily mortality during heat waves as compared to normal summer days was 22% (95%CI: 18%-26%) in Rome and 8% (95%CI: 3%-12%) in Stockholm
Zafeiratou *et al*[8]	42 Municipalities within the Greater Athens Area, Greece	2000-2012	Significant effects of daily temperature increase on all-cause, cardiovascular, and respiratory mortality (*e.g.*, for all ages 4.16% (95%CI: 3.73%, 4.60%) per 1 C increase in daily temperature (lags 0–3)
Fu *et al*[14]	India	2001–2013	Mortality from all medical causes, stroke, and respiratory diseases showed excess risks at moderately cold temperature and hot temperature. Moderately cold temperature was estimated to have higher attributable risks [6.3% (95% empirical CI 1.1 to 11.1) for all medical deaths, 27.2% (11.4 to 40.2) for stroke, 9.7% (3.7 to 15.3) for IHD, and 6.5% (3.5 to 9.2) for respiratory diseases] than extremely cold, moderately hot, and extremely hot temperatures
Zeng *et al*[9]	15973 elderly residents of 866 counties and cities, China	2002-2005	Low seasonal temperatures increase the odds of mortality
Argaud *et al*[25]	Lyon, France	2003	Independent contribution to mortality from heatstroke if patients used long-term antihypertensive medication (HR, 2.17; 95%CI: 1.17-4.05), or presented at admission with cardiovascular failure (HR, 2.43; 95%CI: 1.14-5.17)
Zhang *et al*[35]	Wuhan, China	2003-2006	U-shaped relationship between temperature and mortality. Cold effect was delayed, whereas hot effect was acute, both of which lasted for several days. For cold effects over lag 0–21 d, a 1°C decrease in mean temperature below cold thresholds was associated with a 2.39% (95%CI: 1.71, 3.08) increase in non-accidental mortality, 3.65% (95%CI: 2.62, 4.69) increase in cardiovascular mortality, 3.87% (95%CI: 1.57, 6.22) increase in respiratory mortality, 3.13% (95%CI: 1.88, 4.38) increase in stroke mortality, and 21.57% (95%CI: 12.59, 31.26) increase in CHD mortality. For hot effects over lag 0–7 d, a 1 °C increase in mean temperature above the hot thresholds was associated with a 25.18% (95%CI: 18.74, 31.96) increase in non-accidental mortality, 34.10% (95%CI: 25.63, 43.16) increase in cardiovascular mortality, 24.27% (95%CI: 7.55, 43.59) increase in respiratory mortality, 59.1% (95%CI: 41.81, 78.5) increase in stroke mortality, and 17.00% (95%CI: 7.91, 26.87) increase in CHD mortality
Gómez-Acebo *et al*[7]	Cantabria (northern Spain)	2003-2006	Raising maximum or minimum temperatures by 1ºC was associated with a 2% excess in mortality risk throughout the warm period. No effect in mortality on the cold season
Gómez-Acebo *et al*[17]	Cantabria (northern Spain)	2004-2005	The higher OR for cancer mortality was seen on the first day of exposure (OR = 4.91; 95%CI: 1.65–13.07 in the whole population). Cardiovascular (OR = 2.63; 95%CI: 1.88–3.67) and respiratory mortality (OR = 2.72; 95%CI: 1.46–5.08) showed a weaker effect
Analitis *et al*[26]	9 European cities	2004-2010	In the warm season, the percentage increase in all deaths from natural causes per ◦C increase in ambient temperature tended to be greater during high ozone days. For the cold period, no evidence for synergy was found.
McMichael *et al*[19]	Urban populations in Delhi, Monterrey, Mexico City, Chiang Mai, Bangkok, Salvador, Sao Paulo, Santiago, Cape Town, Ljubljana, Bucharest and Sofia.	2007	Most cities showed a U-shaped temperature-mortality relationship, with clear evidence of increasing death rates at colder temperatures and with increasing heat. Heat thresholds were generally higher in cities with warmer climates, while cold thresholds were unrelated to climate
Rabczenko *et al*[20]	Warsaw, Poland	2008-2013	Analysis of dependence between temperature and mortality for whole population as well as for subpopulations with respect to sex and age demonstrated its similar U-shape. Comfort varied between 20 and 24°C, with slight tendency to be higher for woman
Can *et al*[13]	Istanbul, Turkey	2013-2017	Three extreme heat waves in summer months of 2015, 2016, and 2017, which covered 14 days in total, significantly increased the mortality rate and caused 419 excess deaths in 23 d of exposure
Oray *et al*[16]	Izmir province, Turkey	2016	During the study period, the mean number of ED visits and mortality rates were significantly higher than the previous year's same period [320 ± 30/d *vs* 269 ± 27/d, (P < 0.01), and 1.6% *vs* 0.7%, (P < 0.01)]. Although the admission rate was similar between the study period and the other 21 d of June 2016 [320 ± 30/d *vs* 310 ± 32/d, (P = 0.445)] in-hospital mortality rate was significantly higher [1.6% *vs* 0.7%, (P < 0.01)]

CHD: Coronary heart disease; CI: Confidence interval; OR: Odds ratio.

AMBIENT TEMPERATURE AND CARDIOVASCULAR AND NON-CARDIOVASCULAR DISEASES

Weather exposure beyond certain thresholds affects human health negatively[52]. Both cold and heat temperature significantly increased risk of hospitalization for several diseases[53]. However, heat waves have documented a higher impact on mortality than on morbidity (hospital admissions)[41,54,55]. This phenomenon could be explained by the hypothesis that deaths from circulatory disease occur rapidly patients reach a hospital[56]. There are relationships between temperature (in particular its short-term variability) and hospital admissions due to various forms of heart disease[57-61]. Hot and cold temperature are a risk factor for a wide range of cardiovascular, respiratory, and psychiatric illness; yet, in few studies, the increase in temperature reduced the risk of hospital admissions for pulmonary embolism and angina pectoris[62]. Table 3 shows main studies on the relations between weather and hospital admissions.

AMBIENT TEMPERATURE AND ACUTE CORONARY SYNDROMES

Seasonal variations in emergency admission rates and trial recruitment of patients suffering from acute coronary syndromes (ACS) are well described[37], and a number of epidemiological studies have reported a greater winter ACS incidence, with similar seasonal trends in all studied cohorts, including men and women, middle-aged and elderly patients, and patients from northern and southern hemispheres[4].

Over the past few decades, a growing body of epidemiological studies found the effects of ambient temperature on cardiovascular disease, including risk for ACS[63-66]. Inverse relationship between temperature and ACS is well known[67-71], even regardless of season[37,72,73]. In a previous study, we correlated the daily number of AMI cases admitted to a western Sicily hospital and weather conditions on a day-to-day basis over twelve years, showing a significant association between daily number of ACS hospital admission and minimal daily temperature[74]. Effects of low temperature on total ACS cases were more pronounced in years with higher average temperatures and also during summer, suggesting not a pure "cold effect" but an influence of unusual temperature decreases[64,75].

This relation, moreover, could be actually U-shaped, with higher short-term risk of ACS also in extremely hot summer[67,76-79]. Very few studies failed to demonstrate an association between temperature and ACS incidence[80]. A recent meta-analysis, however, confirmed that cold exposure, heat exposure, and exposure to heat waves were associated with an increased risk of ACS[81].

It has been hypothesized that angina's worsening occurs in cold weather, but few studies have investigated variations in hospitalizations due to angina pectoris in relation to climatic variables[3,59]. We showed a significant association between daily number of angina hospital admission and temperature [82]. Table 4 shows main studies on the relations between weather and hospital admissions for ACS.

Main limitation of these studies is the unavailability of data on individual exposure to temperature variability[57]. These seasonal changes, besides, do not seem universal[43,76], as they are absent near the equator or in subpolar regions, with less temperature fluctuations than in temperate regions. For this reason, it seems inadequate to extrapolate results to different environments.

ACS AND OTHER METEOROLOGICAL PHENOMENA BEYOND TEMPERATURE

Ambient humidity

We observed a negative significant relationship between the number of ACS admissions and maximal humidity[74]. This was confirmed as regards angina admissions only in males, in whom we showed also a positive significant relationship between angina and minimal humidity[82]. Previous data for ACS were confounding: although some studies showed an association with low humidity[83,84], and other no association[69], more researches showed high humidity being related to CHD in northern countries[68,76] and in other Mediterranean[48,78], Asian[75], and Oceanian[54] settings. Fernández-Raga *et al*[18] suggested as the optimal relative humidity 24% for patients with respiratory diseases, and 45% for cardiovascular ones.

Atmospheric pressure.

Consequences of atmospheric pressure on cardiovascular diseases have been studied less frequently. Associations between an increase in CHD occurrence and low atmospheric temperatures have been reported from mortality data and hospital admission registries. A morbidity registry (Lille-WHO MONICA Project) detected a linear V-shaped relationship with a minimum at 1016 mbar: a 10-mbar decrease and a 10-mbar increase were associated with significant 12% and 11% increase in event rates, respectively[73]. Ambient pressure had a statistical impact on the incidence of angina or ACS also in Sweden[72], Serbia[83], Slovenia[68], Lithuania[85], and Switzerland[86], but in Mediterranean

Table 2 Main studies on the relations between weather and cardiovascular mortality

Ref.	Population and setting	Year	Main results
Gyllerup *et al* [44]	Men aged 40–64 from 259 municipalities in Sweden	1975-1984	Coronary mortality is more strongly associated with cold climate than with other explanatory factors such as cholesterol, socioeconomic factors, or tobacco
Crawford *et al*[43]	Deaths in Northern Ireland, United Kingdom	1979-1998	Low temperature is associated with highest mortality rates from myocardial infarction
Gerber *et al* [45]	Olmsted County, Minnesota, United States	1979-2002	RR of sudden death, but not of myocardial infarction, was increased in low temperatures (1.20, 95%CI: 1.07-1.35, for temperatures below 0°C *vs* 18°C-30°C). These associations were stronger for unexpected sudden death ($P < 0.05$)
Wichmann *et al*[49]	Gothenburg, Sweden	1985-2010	No evidence of association between temperature and CHD deaths in the entire year, warm or cold periods
Enquselassie *et al*[3]	Australian community-based register of heart disease (the WHO MONICA Project)	1992	Coronary deaths were more likely to occur on days of low temperature (and to a much lesser extent, of high temperature. Patterns of sudden and non-sudden deaths were not associated with weather conditions. Both longer-term seasonal effects and daily temperature effects exist
Dilaveris *et al* [48]	AMI deaths in Athens, Greece	2001	The best predictor was the average temperature of the previous 7 d; the relation between daily myocardial infarction deaths and 7-d average temperature (R2 0.109, $P < 0.001$) was U-shaped
Zhang *et al* [35]	District of Wuhan, China	2003-2010	For cold effects over lag 0–21 d, a 1°C decrease in mean temperature below the cold thresholds was associated with a 3.65% (95%CI: 2.62, 4.69) increase in cardiovascular mortality and 21.57% (95%CI: 12.59, 31.26) increase in CHD mortality. For hot effects over lag 0–7 d, a 1°C increase in mean temperature above the hot thresholds was associated with a 34.10% (95%CI: 25.63, 43.16) increase in cardiovascular mortality and 17.00% (95%CI: 7.91, 26.87) increase in CHD mortality
Wang X *et al* [47]	Beijing and Shanghai, China	2007–2009	The cold effects on cause-specific cardiovascular mortality reached the strongest at lag 0–27, while the hot effects reached the strongest at lag 0–14
Yang J *et al*[6]	Nine Chinese mega-cities	2007–2013	Statistically significant nonlinear associations between temperature and mortality were observed, with a total of 50658 deaths from myocardial infarction attributable to non-optimal temperatures
Yin Q, Wang J[50]	Beijing, China	2010-2012	When extremely high temperatures occur continuously, at varying temperature thresholds and durations, adverse effects on CVD mortality vary significantly. The longer the heat wave lasts, the greater the mortality risk is. When the daily maximum temperature exceeded 35 °C from the fourth day onward, the RR attributed to consecutive days' high temperature exposure saw an increase to about 10% ($P < 0.05$), and at the 5th day, the RR reached 51%

AMI: Acute myocardial infarction; CHD: Coronary heart disease; CVD: Cardiovascular diseases; CI: Confidence Interval; OR: Odds ratio; RR: Relative risk.

population we did not observe any significant relation[82].

Sunlight

The amount of sunlight hours seems inversely related to winter mortality and ACS risk[72]. Our study in a Mediterranean area did not confirm any relation between sunlight hours and ACS daily admissions [74].

Wind, rain, and snow

ACS incidence during southern wind periods seems significantly greater than during the northern ones [75]. Also, the amount of rain and wind speed seems inversely related to winter mortality and ACS incidence[72,75,85,86]. We, however, failed to observe any significant relationship between wind force and direction, rain, and the number of hospital ACS admissions[74], suggesting these variables are not strong triggers, according to other authors[43]. It is likely that rain intermixed with snow may trigger increased mortality from cardiovascular disease. Snow is somewhat more significant in triggering deaths from heart disease than is air temperature, influencing mortality, mainly in males[87,88]. Snow fall exceeding 2 cm/d was identified as a significant predictor for ACS admission rates[89]. Snow- and rainfall had inconsistent effects in another study[87].

Combination of weather factors

The assessment of air temperature does not allow evaluation of actual discomfort perception caused by the combination of different meteorological parameters. Alternative biometeorological approaches consider Apparent Temperature Index in summer and New United States/Canada Wind Chill Temperature Index in winter, which combine air temperature, relative humidity and wind velocity[90], the presence of anticyclonic and cyclonic air mass[91], as well as specific local climatic conditions, such as the Arctic Oscillation[92].

Table 3 Main studies on the relations between weather and hospital admissions

Ref.	Population and setting	Year	Main results
Ebi *et al*[59]	Three Californian regions, United States	1983-1998	Association between temperature and hospitalizations varied by region, age, and gender
Michelozzi *et al*[41]	Twelve European cities participating in the Assessment and Prevention of Acute Health Effects of Weather Conditions in Europe (PHEWE) project	1990-2001	For an 18°C increase in maximum apparent temperature above a threshold, respiratory admissions increased by 14.5% (95%CI: 1.9–7.3) and 13.1% (95%CI: 0.8–5.5) in Mediterranean and North-Continental cities, respectively. In contrast, the association between temperature and cardiovascular and cerebrovascular admissions tended to be negative and did not reach statistical significance
Vaneckova and Bambrick [52]	Sidney, Australia	1991-2009	On hot days, hospital admissions increased for all major categories. This increase was not shared homogeneously across all diseases. Admissions due to some major categories increased one to three days after a hot day (e.g., respiratory and cardiovascular diseases) and on two and three consecutive days
Goldie *et al* [54]	Darwin, Australia	1993-2011	Nighttime humidity was the most statistically significant predictor ($P < 0.001$), followed by daytime temperature ($P < 0.05$). Hot days appeared to have higher admission rates when they were preceded by high nighttime humidity
Linares and Diaz[28]	Daily emergency admissions between May and September in the Hospital General Universitario Gregorio Maranòn, Madrid, Spain	1995-2000	The temperature above which hospital admissions soar coincides with the temperature limit above which mortality sharply rises, which, in turn, coincides with 95th percentile of the maximum daily temperature series
Chan *et al*[53]	Hong Kong, China	1998-2009	During summer, admissions increased by 4.5% for every increase of 1°C above 29°C; during winter, admissions increased by 1.4% for every decrease of 1°C within the 8.2–26.9 °C range. Admissions for respiratory and infectious diseases increased during extreme heat and cold, but cardiovascular disease admissions increased only during cold temperatures. During winter, for every decrease of 1°C within the 8.2–26.9 °C range, admissions for cardiovascular diseases rose by 2.1%
Yitshak-Sade *et al*[61]	Respiratory, cardiac and stroke admissions of adults ≥ 65 (2015660), New England, United States	2001-2011	The short-term temperature effect was higher in months of higher temperature variability as well. For cardiac admissions, the PM2.5 effect was larger on colder days (0.56% versus −0.30%) and in months of higher temperature variability (0.99% *vs* −0.56%)
van Loenhout *et al*[55]	the Netherlands	2002-2007	Positive relationship between increasing temperatures above 21 °C and the risk for urgent emergency room admissions for respiratory diseases. For admissions for circulatory diseases, there is only a small significant increase of risk within the 85+ age group for moderate heat, but not for extreme heat
Ponjoan *et al* [58]	Catalonia, Spain	2006-2016	The overall incidence of cardiovascular hospitalizations significantly increased during cold spells (RR = 1.120; 95%CI: 1.10–1.30) and the effect was even stronger in the 7 d after the cold spell (RR = 1.29; 95%CI: 1.22–1.36). Conversely, cardiovascular hospitalizations did not increase during heatwaves
Shiue *et al*[60]	Ten percent of daily hospital admissions across Germany	2009-2011	Admissions due to diseases of pericardium, nonrheumatic mitral and aortic valve disorders, cardiomyopathy, atrioventricular block, other conduction disorders, atrial fibrillation and flutter, and other cardiac arrhythmias peaked when physiologically equivalent temperature was between 0 and 10°C
Tian *et al*[57]	184 cities in China	2014-2017	a 1˚C increase in short-term temperature variability (calculated from the SD of daily minimum and maximum temperatures) at 0–1 days was associated with a 0.44% (0.32%–0.55%), 0.31% (0.20%–0.43%), 0.48% (0.01%–0.96%), 0.34% (0.01%–0.67%), and 0.82% (0.59%–1.05%) increase in hospital admissions for cardiovascular disease, ischemic heart disease, heart failure, heart rhythm disturbances, and ischemic stroke, respectively

CHD: Coronary heart disease; CVD: Cardiovascular diseases; CI: Confidence interval; PM: Particulate matter; RR: Relative risk; SD: Standard deviation.

WEATHER AND OTHER CARDIOVASCULAR DISEASE BEYOND CHD

Heart failure

Environmental exposure is an important, but underappreciated, risk factor contributing to development and severity of heart failure. In European warm period (from June to October), there are significant less admissions than that in the cold period (from December to March). Air temperature is the most significant environmental factor related to heart failure hospital admissions, showing an inversed correlation[93,94]. Heart failure admissions peaked when temperature was between 0 and -10°C[68]. Every 1°C decrease in mean temperature and every 1hPa decrease in air pressure were associated, respectively, with an increase in the daily number of emergency admissions for heart failure by 7.83% (95%CI: 2.06-13.25) and 3.56% (95%CI: 1.09-5.96)[71]. Some other features, such as precipitation, are also relevant[94].

Table 4 Main studies on the relations between weather and acute coronary syndromes

Ref.	Population and setting	Year	Main results
Mirić *et al*[78]	Coastal part of middle Dalmatia (Croatia)	1981-1987	Significant association of acute myocardial infarction incidence with increased air temperature four days before, and on the day of the incident ($P < 0.05$)
Danet *et al*[73]	Morbidity registry (Lille-WHO MONICA Project) monitoring 257000 men Aged 25-64 years.	1985-1994	The events rate decreased linearly with increasing atmospheric temperature: a 10°C decrease was associated with a 13% increase in event rates
Wichmann *et al*[49]	AMI hospitalisationsin Gothenburg, Sweden	1985-2010	A linear exposure-response corresponding to a 3% and 7% decrease in AMI hospitalisations was observed for an inter-quartile range increase in the 2-d cumulative average of temperature during the entire year and the warm period, respectively
Abrignani *et al*[74]	Hospital admissions for acute myocardial infarction in Trapani, Italy	1987-1998	Significant association as regards the incidence relative ratio between daily number of myocardial infarction hospital admission and minimal daily temperature
Abrignani *et al*[82]	Hospital admissions for angina pectoris in Trapani, Italy	1987-1998	Significant association between daily number of angina hospital admission and temperature. Significant incidence relative ratios (95%CI) were, in males, 0.988 (0.980–0.996) ($P < 0.004$) for minimal temperature. The corresponding values in females were 0.973 (0.951–0.995) ($P < 0.017$) for maximal temperature and 1.024 (1.001–1.048) ($P < 0.037$) for minimal temperature
Marchant *et al*[37]	633 consecutive patients with myocardial infarction admitted to a coronary care unit in London, United Kingdom	1988-1991	Excess of infarctions on colder days in both winter and summer
Bayentin *et al*[77]	Quebec, Canada	1989-2006	Cold temperatures during winter and hot episodes during summer are associated with an increase of up to 12% in the daily hospital admission rate for CHD. In most regions, exposure to a continuous period of cold or hot temperature was more harmful than just one isolated day of extreme weather
Wolf *et al*[64]	Myocardial infarctions and coronary deaths in the Monitoring Trends and Determinants on Cardiovascular Diseases/Cooperative Health Research in Augsburg (MONICA/KORA) Registry, Germany	1995-2004	A 10°C decrease in 5-d average temperature was associated with a relative risk of 1.10 (95%CI: 1.04-1.15). Effect of temperature on the occurrence of nonfatal events showed a delayed pattern, whereas the association with fatal forms was more immediate
Madrigano *et al*[70]	Patients with a possible discharge diagnosis of AMI in 11 acute care general hospitals serving residents of the Worcester metropolitan area (Worcester Heart Attack Study), United Kingdom	1995, 1997, 1999, 2001, 2003	A decrease in an interquartile range in apparent temperature was associated with an increased risk of acute myocardial infarction on the same day [HR = 1.15 (95%CI: 1.01–1.31)]. Extreme cold during the 2 d prior was associated with an increased risk of acute myocardial infarction [1.36 (1.07–1.74)]. Exposure to heat increased the risk of dying after an AMI
Mohammad *et al*[72]	All myocardial infarctions reported to the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART)	1998-2013	The most pronounced association was observed for air temperature, where a 1-SD increase (7.4°C) was associated with a 2.8% reduction in risk of myocardial infarction (incidence ratio, 0.972; 95%CI: 0.967-0.977; $P < 0.001$). Results were consistent for non–ST-elevation as well as ST-elevation myocardial infarction and across a large range of subgroups and health care regions
Messner *et al*[76]	Subarctic area of Northern Sweden	2001	A 1°C temperature rise was associated with an 1.5% increase in the number of nonfatal acute myocardial infarctions
Chang *et al*[69]	Myocardial infarctions among women aged 15–49 from 17 different countries in Africa, Asia, Europe, Latin America, and the Caribbean	2003	Overall, a 5°C drop in temperature was associated with a 12% increase in admissions for heart attack (incidence rate ratio 0.88 (95%CI: 0.8-0.97)
Misailidou *et al*[65]	Five rural Greek regions (Karditsa, Lamia, Chalkida, Kalamata and Zakinthos)	2003-2004	For an 18°C decrease in temperature there was a 1.6% (95%CI: 0.9%–2.2%) increase in admissions for CHD
Bhaskaran *et al*[63]	84010 hospital admissions for myocardial infarction in the Myocardial Ischaemia National Audit Project (15 conurbations in England and Wales, United Kingdom)	2003-2006	Broadly linear relation between temperature and myocardial infarction, without a threshold: each 1°C reduction in daily mean temperature was associated with a 2.0% (95%CI: 1.1%-2.9%) cumulative increase in risk of myocardial infarction over the current and following 28 d, the strongest effects being estimated at intermediate lags of 2-7 and 8-14 d. Heat had no detrimental effect
Nastos *et al*[80]	Crete, Greece	2004-2007	The impact of weather variability on the ACS incidence is not statistically significant
Ravljen *et al*[68]	ACS treated with coronary emergency catheter interventions in Slovenia	2008-2011	Daily average temperature, atmospheric pressure and relative humidity all have relevant and significant influences on ACS incidences for the entire population. However, the ACS incidence for population over 65 is only affected by daily average temperature

Hori *et al*[71]	Japan	2010	Every 1°C decrease in mean temperature was associated with an increase in the daily number of emergency admissions for ACS by 7.83% (95%CI: 2.06-13.25)
García-Lledó *et al*[66]	Madrid, Spain	2013-2017	The minimum incidence rate of myocardial infarction was observed at the maximum temperature of 18°C. Warmer temperatures were not associated with a higher incidence (RR, 1.03; 95%CI: 0.76-1.41), whereas colder temperatures were significantly associated with an increased risk (IRR, 1.25; 95%CI: 1.02-1.54)
Lin *et al*[67]	Hospitalizations for CHD in New York State, United States	2015	Extremely low universal apparent temperature in winter was associated with increased risk of AMI, especially during lag4-lag6
Sharif Nia *et al*[75]	Hospital admission for AMI in Mazandaran Province, Iran	2015-2016	Daily minimum temperature correlated with ACS events [RR = 0.942 (95%CI: 0.927-0.958), $P < 0.001$]

ACS: Acute coronary syndromes; AMI: Acute myocardial infarction; CHD: Coronary heart disease; CI: Confidence interval; RR: Relative risk; SD: Standard deviation.

Arrhythmias

Current paradigm in sudden cardiac death (SCD) requires an abnormal myocardial substrate and an internal or external transient factor (such as a cold spell, an unusually cold weather event) that triggers cardiac arrest. An increased risk of ischaemic SCD was significantly associated with a preceding cold spell[95], and cardiac arrest admissions peaked when temperatures were between 0° and -10°C[60]. These associations were stronger for unexpected SCD than for SCD with prior CHD[45]. However, also higher average daily temperature and larger variation in humidity were associated with increase in appropriate ICD interventions in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy[96].

Aortic dissection

Days with spontaneous type A aortic dissections were significantly colder than those without dissections[97]. There appears to be a significant correlation between mean low monthly pressures and rupture incidence[98].

Stroke

Significant associations between temperature and hospital admission rates for stroke were apparent and generally stronger than in other cardiovascular disease[99-101]. Both increases and decreases in temperature had a marked relationship with stroke deaths, while hospital admissions were only associated with low temperature[102,103]. Overall, a 5°C drop in temperature was significantly associated with a 7% increase in admissions for stroke[69]. Every 1°C increase in mean temperature during the preceding 24 h was associated with a significant 2.1% increase in ischaemic stroke admissions. A fall in atmospheric pressure over the preceding 48 h was associated with increased rate of haemorrhagic stroke admissions. Higher maximum daily temperature gave a significant increase in lacunar stroke admissions than in other ischaemic strokes[100]. In another study, every 1°C decrease in mean temperature was associated with an increase in the daily number of emergency admissions by 35.57% for intracerebral haemorrhage and by 11.71% for cerebral infarction. An increase of emergency admissions due to intracerebral haemorrhage was observed at every 1 hPa decrease in air pressure[71]. A recent metanalysis, finally, confirmed that lower mean ambient temperature is significantly associated with the risk of intracerebral haemorrhage, but not with ischemic stroke and subarachnoid haemorrhage [104].

AGE, SEX, OTHER FACTORS AND CLIMATIC VARIABLES

Effects of weather vary depending on other factors, such as the population disease profile and age structure[19,74]. People with pre-existing medical conditions such as cardiovascular disease or carrying out physically demanding work, and the elderly, particularly those in nursing and care homes, are particularly vulnerable[68,105-108].

Mortality's increase with cold or heat was greater for older age groups[21,63,109]. Diurnal temperature range are related to hospital admissions for all cardiovascular and cerebrovascular disease among elderly, namely in males[59,83,110]. In the elderly, cardiovascular disease curve was U-shaped, showing higher values for cold stress than for heat one[107,109,111,112]. In general, longer duration of heat waves increases the risks of cardiovascular mortality for the elderly[113]. Main predictors of death are: The use of home public-integrated assistance, a higher comorbidity, a higher degree of disability [114], lack of thermal insulation and sleeping right under the roof[113], being confined to bed or unable to care for oneself and pre-existing cardiovascular diseases[115]. Home air-conditioning, visiting cool

environments, dressing lightly, and increasing social contact were instead strongly associated with better outcomes[113,115]. Weak correlation between atmospheric air wind speed and ACS morbidity in older populations was determined[111].

Diurnal temperature range was significantly associated with hospital admissions for all cardiovascular disease, ischemic heart disease and cerebrovascular disease among elderly females[110]. We showed that, in females, a reduction in maximal temperature is associated with more hospital angina admissions[82], whereas the number of angina admissions is positively correlated with an increase in minimal temperature, as observed also by Ebi[59]. Increased outside temperature and sunshine hours were identified as strong positive predictors for ACS occurrence in women[89], as they tend to present with AMI at a later age than men, they will tend to exhibit a more marked seasonal variation[107-109]. A weak correlation between atmospheric air wind speed and MI morbidity in women was determined[111]. Snow fall was identified as a positive predictor for ACS admission rates with a significant effect in men, but not in women[89]. Other studies failed to detect significant difference according to sex[65].

Risk of heat-related death was significantly higher among Black people[112,116] and Australian indigens[105].

Heat-related mortality varied with sociodemographic characteristics such as in people living in low socioeconomic districts[12,106,107,117].

People living in areas with high PM2.5 concentration showed higher vulnerabilities to cold-ACS effects than other groups did[67].

MECHANISMS

Up to date, there are not clear pathophysiological links between weather and cardiovascular diseases. Climatic stress may increase direct and indirect risks to human health *via* different, complex pathophysiological pathways and exogenous and endogenous mechanisms. The pattern of well-known conventional risk factors (such as blood pressure, serum lipids, haematological and coagulation factors, body weight, glucose tolerance), a number of hormones including steroids, environmental factors (such as air pollution) as well as acute infections shows a marked seasonal variation, with a winter clustering of peak values[118,119]. In addition, humans display different seasonal behaviour in diet, activity, housing and smoking habits, psychosocial factors and mood disorders in winter[120]. Other factors, such as overindulgence, or stress on Christmas holidays, might also contribute[121].

Cold

Mechanisms leading to possible influence of cold on ACS or angina onset are most likely multifactorial. Different heart and circulation adjustments occur when humans are acutely exposed to low outdoor temperatures. Increase in circulating levels of catecholamines, secondary to cutaneous thermoreceptor activation[122]. lead to peripheral vasoconstriction and then to increase in blood pressure[123], heart rate, and left ventricular end-diastolic pressure and volume[3,124,125] with, in turn, increased cardiac work and peripheral resistance, greater heart oxygen requirement and reduction of ischemic threshold [3]; they may be clinically relevant when coronary circulation is already compromised[126]. People with normal cardiovascular function, in fact, are unaffected by cold stress, whereas those with IHD may be crippled, although rarely, by exposure to cold, especially if they perform physical work[122]. At the same time, reduced myocardial perfusion may lead to earlier ischemia, angina, and impaired performance. Also having a heart failure deteriorates submaximal and maximal performance in cold conditions[127]. In cold conditions also a greater sodium intake lead to an increase in blood pressure. Cold-induced vasoconstriction results in an early return of reflected pressure waves from the periphery and an increase in central aortic systolic pressure, with increase of central aortic augmentation index [128]. Endothelial dysfunction may be another mechanism. Brachial flow-mediated dilation would vary by temperature (in the Framingham Offspring cohort it was highest in the warmest and lowest in the coldest outdoor temperature quartiles)[129]. Moreover, coronary artery spasm could occur if vasoconstriction extends to the heart vessels. Cold-intolerant patients had a steeper heart rate response in cold conditions and developed ischemia and angina earlier. In cold-tolerant patients, this increase may be offset by a reduction in heart rate if baroreceptor function is normal. Baroreceptor function was impaired in cold-intolerant patients. If baroreceptor function is abnormal, heart rate may not decrease in response to a cold-induced increase in blood pressure. This mechanism may account for some of the variability in tolerance to cold exposure that affects patients with exertional angina[124].

More dramatic events, such as sudden death, may be due to increased frequency of cardiac arrhythmias, or, perhaps through rises in blood pressure, to abrupt rupture of atherosclerotic plaques [3].

Cold, besides, exerts other biological negative effects on inflammatory markers, haemostasis, rheological factors, and lipids (probably related to haemoconcentration), alcohol consumption, and body weight gain[40,124,125,130,131]. A 10°C decrease in temperature led to an increase in platelet counts and fibrinogen and a decrease in C-reactive protein in CHD patients[131]. In cold weather, a

greater tendency to clot in circulatory system has been demonstrated[119,132,133]. This could be related to plasma volume contraction (haemoconcentration) [119,126,134], induced by peripheral vasoconstriction, which can in part also explain the increase in serum lipids. These acute responses to cold conditions could trigger ACS.

Cold conditions may increase also the risk of respiratory infections through suppression of immune responses and direct effects on respiratory tree, and although no association can be claimed between respiratory infections and coronary deaths during cold season[124], a theory links pulmonary inflammation to stroke[99].

Finally, other causes hypothesized to explain the impact of cold are socioeconomic, mainly housing conditions[12,34].

Heat

During summer, ACS patients working outdoors show abnormal hemorheology (high haematocrit and blood viscosity)[135], as dehydration is more likely to occur[29]. Outdoor heat is associated with decreasing blood pressure, and cardiovascular vulnerability may vary primarily by central air conditioning[136]. Higher ambient temperature is associated with decreases in heart rate variability during warm season but not during cold one[137]. Hot weather is associated with an increase in systolic pressure at night in treated elderly hypertensive subjects, likely because of a nocturnal blood pressure escape from effects of a lighter summertime drug regimen[133].

Humidity

When air contains a high percentage of humidity, perspiration and the processes of temperature homeostasis may be hindered, making more difficult the automatic processes of internal temperature control, thus increasing respiratory fatigue and heart rate. However, this mechanism may be important only in more severe ischemic forms.

Rain and wind

A reduction of outdoor excursions when it is raining and windy prevents outdoor cold stress.

Sunshine

Several studies have demonstrated significantly lower levels of vitamin D, synthesized by skin following exposure to ultraviolet radiation, in subjects with CHD, particularly in winter[138]. It has been suggested that vitamin D may be a confounding factor in the association between cholesterol, structurally like it, and CHD risk. This is corroborated by findings of a strong, positive association between latitude and mean blood cholesterol, and a strong negative association between hours of sunshine and CHD mortality[120]. Association between vitamin D levels and CHD, however, has been shown to be independent of total serum cholesterol[138].

Age

With increasing age, winter peak increased. This is likely to reflect a combination of factors: poorer temperature autonomic control, lower physical activity levels, less use of protective clothing, greater time spent at home, more sensitivity to seasonal influenza and blood pressure changes, and poorer household heating and insulation. The predominance of effects of meteorological factors in the elderly could be also explained by the lower impact of genetic AMI determinants.

Sex

Different effects of weather on women may be related to different coronary anatomy in the female sex, as woman have less extensive coronary atherosclerosis, lower coronary size, and lower collateral circulation than males.

Pollution

Interaction between air pollution and weather is often missed in literature[139]. Studies show that ambient temperature and air pollution may interact to affect cardiovascular events *via* autonomic nervous system dysfunction[137]. Much higher PM10 effects on mortality were observed during warmer days[26,140-142], and the hypothesis that such an effect is attributable to enhanced exposure to particles in summer could not be rejected[143].

CONCLUSION

Implications and conclusions

Weather influences on heart diseases remind us that climatic stress can be considered as a new potential risk factor for cardiovascular events and even mortality[3,125]. Such an understanding has several potential implications for developing civil protection policy towards allocation of public healthcare

resources and planning appropriate measures to prevent cardiovascular events[59,116]. Weather-related health effects have sharply attracted growing interest because of the recent observed and predicted earth's climate change, with consequent increasing ambient temperatures and climatic fluctuations, extremes of precipitation (floods and droughts), air pollution, and infectious diseases. Contrary to current predictions, this may mean a paradoxical increase in seasonal cycle of events with greater winter peaks, even as overall global temperatures rise[93]. Thus, increases in heat-related mortality due to global warming are unlikely to be compensated by decreases in cold-related mortality[112]. In a global environment of rapid and extreme climatic events, more populations will be exposed to conditions they are not readily adapted to from a bio-behavioural perspective[60,144]. Adaptation to such changes, that are expected to further increase, would seem to be imperative for medical professionals, health institutions, and general public[41,70].

Public health educational, behavioural and social measures[28,43] have been proposed to reduce adverse cardiovascular consequences of climate variability. We wish here to summarize the most important ones.

High risk identification: Prevention programs must be based around rapid identification of high-risk conditions and people, such as frails with cardiovascular disease, or the elderly[53,107]. Protective measures, in fact, should be directed towards susceptible groups, rather than the population as a whole, with the creation of an up-to-date database and care of vulnerable high-risk individuals[21,24,110,114].

Specific interventions: In the community, at home, and in institutions that care for elderly or vulnerable people, such as hospitals, a comfortable temperature should be granted[63,65]. Educational measures should be suggested to high-risk people. During the passing atmospheric front, as well as in extreme ambient temperature periods, *i.e.*, coronary patients should stay at home, and avoid both physical and psychological stress[78].

Provision of targeted advice: Many weather-related diseases may be preventable by and appropriate response to emergencies. Operative health weather watch/warning systems link public health actions to meteorological forecasts of dangerous weather. We need development of a short-term forecast system of daily demand using weather variables.

Remodulation of health services offer: During severe climatic conditions, it should be granted a greater deployment of ambulance services and an adequate reinforcement of health personnel in order to meet the unexpected increase in demands, and to avoid potential mismatch between the occurrence of acute cardiovascular events and medical service capacities[108].

Future perspectives: In the long term, improvements in infrastructures, residential architecture, working environment and urban planning must be adapted[113].

In conclusion, the problem of climate change is serious, urgent and getting worse[144]. Fairly obvious connections between climate change and cardiovascular health have been outlined in this article. Medical professionals, and societies of medical professionals, easily capable of understanding the physical and statistical methods used by climatologists, are in a good position to give politicians and leaders in industry and agriculture their necessary support[144].

Further large, exhaustive, population-based cohort research with consistent methodology over long periods in geographical areas with homogeneous meteorological variables should be carried out to further clarify climatic influences on CHD occurrence, to identify underlying pathophysiological mechanisms, to show vulnerable populations and individuals and to develop cost-effective strategies to promote resilience against provocations of climate change[86,113].

FOOTNOTES

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Abstract

Functional mitral regurgitation is a common finding among heart failure patients with ischemic and non-ischemic dilated cardiomyopathies. The presence of moderate or severe mitral regurgitation is associated with higher morbidity and mortality. Heart failure patients meeting electrocardiogram and left ventricle function criteria are good candidates for cardiac resynchronization therapy, which may reduce the degree of functional mitral regurgitation in the short and long term, specifically targeting myocardial dyssynchrony and inducing left ventricle reverse remodeling. In this article, we analyze data from the literature about predictors of mitral regurgitation improvement after cardiac resynchronization therapy implantation.

Key Words: Functional mitral regurgitation; Cardiac resynchronization therapy; Predictors; Mitral regurgitation improvement; Dyssynchrony

Core Tip: Functional mitral regurgitation is a common finding among heart failure patients and, if moderate or severe, is associated with higher morbidity and mortality. Cardiac resynchronization therapy, as a therapy for a subset of heart failure patients, may determine a reduction of the degree of functional mitral regurgitation specifically targeting myocardial dyssynchrony and inducing left ventricle reverse remodeling. Here, we analyze predictors of mitral regurgitation improvement after cardiac resynchronization therapy implantation.

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INTRODUCTION

Functional mitral regurgitation (FMR) is a common finding of left ventricular (LV) dysfunction and remodeling, occurring both in ischemic and non-ischemic heart disease[1]. The prevalence of FMR varies from 20% to 50% of heart failure (HF) patients[2,3], with 40% of patients presenting with moderate or severe mitral regurgitation (MR)[4]. Data from the literature suggest that any degree of FMR is associated with increased morbidity and reduced survival in patients with LV dysfunction[3-5]. In this setting, there is no conclusive evidence for a survival benefit after mitral valve intervention. The limited data regarding FMR result in a low level of evidence for treatment recommendations and highlight the importance of decision-making by the patient's heart team. According to the latest guidelines, surgery is indicated in patients with severe secondary mitral regurgitation undergoing coronary artery bypass graft and LV ejection fraction > 30%[6,7]. When revascularization is not indicated, optimal medical therapy in line with the HF guidelines should be the first step. Furthermore, patients with HF and FMR eligible for cardiac resynchronization therapy (CRT) could benefit from resynchronization in terms of reduction of the degree of FMR[8,9]. Unlike medical therapy, CRT specifically targets myocardial dyssynchrony, which is an important factor of FMR onset. However, in a subset of CRT patients, significant MR persists and may even worsen.

The purpose of this paper is to provide a comprehensive review on predictors of improvement in FMR after CRT.

ACUTE AND LONG-TERM EFFECTS OF CRT ON FMR IN THE PRESENCE OF DYSSYNCHRONY

FMR results from multiple factors: ventricular remodeling, decreased contractility, impairment of mitral annular function, imbalance between tethering and closing forces, and mechanical dyssynchrony. LV mechanical dyssynchrony could be a potential contributing factor to FMR through several mechanisms. First, LV dilatation due to dyssynchrony leads to displacement of papillary muscles with consequent lack of leaflet coaptation. Second, uncoordinated regional mechanical activation due to dyssynchrony results in distorted mitral valve apparatus geometry[10]. Lastly, LV dyssynchrony generates a positive pressure gradient between the LV and the left atrium, leading to a diastolic FMR during incomplete mitral valve closure[11].

CRT effects may be distinguished as acute or chronic. Acute, short-term FMR reduction occurs suddenly after CRT implantation, while chronic, long-term FMR reduction occurs weeks to months after CRT implantation. Immediately after CRT device implantation, global LV contraction efficiency improves and closing forces increase consequently. Breithardt *et al*[12] first showed that an increase in LV dP/dt after CRT is directly correlated to MR reduction. Indeed an increase in LV dP/dt leads to an increase in transmitral pressure gradients that facilitate mitral valve leaflet coaptation. Furthermore, CRT acutely determines resynchronization of the papillary muscles leading to a shortening of MR duration and later onset of MR. Indeed, Kanzaki *et al*[13] showed that the inter-papillary muscleactivation time delay is the main determining factor related to MR in HF patients with left bundle branch block and that this delay is immediately improved by CRT.

Data from the literature suggest that short-term reduction in FMR after CRT implantation predicts a favorable clinical response, whereas FMR persistence is associated with reduced survival[14]. In addition to the early effect of CRT on FMR, long-term beneficial effects on FMR have been described. They are mainly represented by the increase of the closing forces and the global LV remodeling. Specifically, LV dimensions, shape and function are main determinants of FMR, and CRT attenuates LV remodeling, which therefore improves FMR. These results could be achieved after 3–6 mo of CRT on top of optimized medical treatment and are even more evident during longer follow-up[15].

Large randomized trials have confirmed short and long-term reduction of FMR following CRT implantation, although the magnitude of this reduction is modest (20%–35% using different quantification methods)[16,17]. In 20%–25% of CRT patients, significant MR persists and may even worsen in 10%-15%. Specifically, this concerns patients with grade ≥ 2 FMR who have a significantly worse outcome than other CRT patients. This subset of patients is often found to be CRT non-responders, and the reasons why these patients do not benefit from CRT are still unclear.

PREDICTORS OF IMPROVEMENT OF FMR AFTER CRT IMPLANTATION

Data from the literature show that reductions in MR occur mainly in patients with response to CRT. However, FMR reduction was also demonstrated in CRT non-responders. Porciani *et al*[18] reported that FMR may improve even in CRT non-responders because of the reversal of LV dyssynchrony. Reversal of LV mechanical dyssynchrony, especially at the papillary muscle level, has been suggested as one of the mechanisms implicated in CRT-induced FMR improvement[19]. Reviewing the literature, several predictors of MR improvement in CRT patients were found and can be distinguished by patient, clinical, imaging and electric-targeting LV lead-related predictors.

PATIENT-RELATED PREDICTORS

Karaca *et al*[20] analyzed142 patients who received biventricular pacemaker devices and found that ΔQRS (baseline - paced) after CRT [hazard ratio (HR): 1.242, 95% confidence interval (CI): 1.019-1.465, P = 0.028] was associated with LV reverse remodeling and reduced FMR at 6 mo. There were also lower rates of death or hospitalization at midterm follow-up. The cut-off ΔQRS value to predict FMR response after CRT was 20 mo, with a sensitivity of 72% and a specificity of 85%. Multivariate analysis found that ΔQRS was an independent predictor of FMR response at 6 mo. The same authors observed that non-ischemic HF etiology [odds ratio (OR): 3.13, 95%CI: 1.169-8.380, P = 0.021] and the baseline presence of left bundle branch block morphology (OR: 2.49, 95%CI: 1.086-5.714, P = 0.032) were independent predictors of "reverse mitral remodeling" and predictors of MR amelioration[21]. The abovementioned preoperative features are those that the majority of previous CRT studies found as "classical" predictors of CRT response.

Sadeghian *et al*[22], in a small study of 69 patients, found that independent predictors of early MR improvement (48 h after CRT implantation) were older age and longer baseline QRS duration. Among the MR improvement group, the mean age was 60 ± 7 years (*vs* 55 ± 12 years in the no MR improvement group), and baseline QRS width was 172 ± 31 ms (*vs* 147 ± 28 ms).

Profibrotic biomarkers were also evaluated as potential predictors of FMR reduction. It was found that at the time of CRT device implantation, elevated concentrations of gal-3, a protein (lectin family) upregulated in HF that is involved in fibrogenesis, are associated with a lack of MR amelioration (OR: 0.14, 95%CI: 0.03-0.58, P = 0.007)[23]. These result are consistent with molecular changes in HF settings where fibroblast proliferation and collagen production have a pivotal role on LV remodeling and consequently in mitral annulus dilatation/dysfunction.

IMAGING-RELATED PREDICTORS

Sitges *et al*[24] found that baseline mitral valve tenting area, as a remodeling parameter of the mitral valve, was a powerful independent predictor of MR reduction with CRT(OR: 8.05, 95%CI: 1.15-56.60, P = 0.03). A cut-off value > 3.8 cm^2yielded sensitivity of 53% and specificity of 89% to predict the absence of a significant reduction in MR with CRT. Similar results have been reported for predicting the success of restrictive annuloplasty in patients with functional MR who undergo surgery. Indeed, Magne *et al*[25] reported that a tenting area > 2.5 $cm^2$was associated with failed mitral valve repair in these patients. Results described by Sitges *et al*[24] were confirmed subsequently by Karaca *et al*[21]. In that study, baseline tenting area was identified as an independent predictor of FMR response at 6 mo (HR: 2.011, 95%CI: 1.268-2.754, P = 0.012). Values of tenting area differed significantly in FMR responders compared with non-responders (4.68 ± 1.02 cm^2 *vs* 3.22 ± 0.88 cm^2, P = 0.002). These data suggest that the more advanced the LV remodeling and the more distorted the LV geometry, the lower the probability of effective treatment for functional MR.

Subsequently, studies were performed with tissue Doppler imaging (TDI) and speckle tracking echocardiography to elucidate the role of myocardial dyssynchrony in the genesis of FMR in HF patients. Sadeghian *et al*[22] showed that septolateral delay by TDI was a significant predictor of MR improvement. In a previous small study with moderate/severe MR patients, Karvounis *et al*[26] showed that inferior papillary muscle time delay (R^2 = 0.945, P = 0.04) together with an increase in posterior papillary muscle longitudinal negative strain (R^2 = 0.727, P = 0.01) (both evaluated with TDI) were significant predictors of reduction in MR volume post-CRT implantation.

Naqvi *et al*[27] found that septolateral delay of > 60 ms was a univariate but not a multivariate predictor of MR reduction and demonstrated that the combined presence of delayed longitudinal strain in the mid inferior LV segment along with preserved systolic strain in the basal and mid posterior segments predicted reduction in MR severity post-CRT. The sensitivity and specificity of this composite variable to predict follow-up MR was 88% and 93%, respectively. These aforementioned findings added important information about acute MR reduction post-CRT. Indeed, patients who developed significant MR reduction had discoordination at the mid ventricle level. Therefore, the mid anterolateral segments were the earliest, and the mid inferoposterior segments were the most delayed as well as viable

segments. This suggested delayed posterior papillary muscle compared to anterior papillary muscle contraction resulted in malcoaptation of mitral leaflets and MR. Therefore, CRT in the MR improvement group probably reduced MR by correcting the mid inferoposterior wall delay and by improving function in these viable segments as assessed by strain and strain rate.

Unlike these studies, Goland *et al*[28] evaluated radial instead of longitudinal strain and used a two-dimensional method of strain assessment instead of TDI. It was found on multivariable logistic analysis that time to peak two-dimensional radial strain between inferior and anterior LV segments of > 110 ms (OR: 8.4, 95%CI: 8.4–54.0, P = 0.02) and two-dimensional radial strain in the posterior segment of > 18% were significant predictors of early post-CRT MR improvement (OR: 7.6, 95%CI: 1.2–72.4, P = 0.006). These results confirmed the role of viability and dyssynchrony of the areas adjacent to posterior papillary muscle. Obviously, the presence of non-severe MR predicted MR reduction after CRT as suggested by MR jet area/Left area ratio (OR: 8.1, 95%CI: 1.2–52.4, P = 0.02).

Onishi *et al*[29], in a large series, showed that anteroseptal to posterior wall radial strain dyssynchrony > 200 ms (OR: 2.65, 95%CI:1.11–6.30, P = 0.0277) and end systolic dimension index < 29 mm/m^2 (OR: 2.53, 95%CI: 1.03–6.20, P = 0.0420) predicted MR improvement at 6 mo after CRT implantation. Therefore, the present study combined the presence of radial dyssynchrony and lack of excessive LV dilatation (simply measured by end-systolic diameter index) with strong amelioration of significant MR. Furthermore, it added another important element: the lack of echocardiographic scar at the papillary muscle insertion site (wall motion score index ≤ 2.5) that resulted as a significant predictor of MR improvement (OR: 2.59, 95%CI: 1.06–6.30, P = 0.0360).

An interesting study was recently conducted by Galand *et al*[30]. It included 54 HF patient candidates for CRT who underwent dual-source computed tomography (CT) scan imaging in order to guide the CRT implantation procedure. Cardiac dual-source computed tomography is an ideal non-invasive imaging modality with very fast features, so patients receive less radiation. It also creates sharper images. This study evaluated the impact of LV wall thickness using dual-source CT in response to CRT and MR improvement. In multivariable analysis, an area ≥ 25% of LV wall thickness < 6 mm including at least one papillary muscle insertion was the only predictor of no MR improvement at 6 mo (OR: 16.82, 95%CI: 1.72–164.2, P = 0.015). The study confirmed the crucial role of papillary muscle insertion site and suggested that normal wall thickness could promote a mitral valve apparatus remodeling after CRT.

ELECTRIC-TARGETING LV LEAD-RELATED PREDICTORS

Among invasive electric predictors of the response to CRT, a commonly studied measure of electric delay is the QLV interval, which is the time from the onset of the QRS complex on the surface electrocardiogram to the local LV activation at the site of the LV lead[31]. Previous studies demonstrated the predictive value of QLV interval as a measure of LV electric delay for acute hemodynamic changes and clinical outcome with CRT[32]. Recently, Upadhyay *et al*[33] provided an interesting link between a simple electric measurement, such as QLV, and improvement in MR. They demonstrated that greater changes in MR were achieved by targeting the LV lead in regions of longer QLV at implant (multivariate β coefficient = 0.0040, P = 0.0072).

Chatterjee *et al*[34] analyzed data from patients enrolled in the SMART-AV study[29] and provided strong evidence of the association between baseline QLV and reduction in MR after CRT. After multivariable adjustment, increasing QLV was an independent predictor of MR reduction at 6 mo as reflected by an increased odds of MR response (OR: 1.13, 95%CI: 1.03–1.25/10 ms increase QLV, P = 0.02).

STUDY LIMITATIONS

This was not a systematic review. Heterogeneity among included studies was widespread. Studies included showed variations in study design, cohort characteristics and response definitions. Another source of heterogeneity is that CRT implantation techniques and indications have evolved over the last 20 years. These limitations are particularly important to consider in future research studies.

CONCLUSION

Over the past two decades, numerous invasive and non-invasive predictors of the response to CRT have been proposed, and it was shown that reductions in MR occurred mainly in patients with response to CRT (Table 1). However, not all CRT responders are "MR responders," and FMR reduction was also demonstrated in CRT non-responders, hence the importance of identifying MR improvement predictors after CRT implantation. Among "MR predictors" proposed, the possibility to recognize viability and dyssynchrony by imaging, especially near papillary muscles, is very useful. Also the measurement of

Table 1 Variables that predict mitral regurgitation improvement or lack of improvement

Predictor category	Predictors of MR improvement	Ref.	HR	*P* value
Clinical parameters	ΔQRS (at least 20 ms) after CRT	[20]	1.242	0.028
	Non ischemic HF etiology	[20]	3.13	0.021
	Baseline presence of LBBB morphology	[20]	2.49	0.032
	QRS narrowing after CRT	[21]	NA	0.001
	Older age	[23]	NA	0.001
	Baseline longer QRS duration	[23]	NA	0.001
Echo imaging	Septal-lateral delay by TDI	[23]	NA	0.001
	Baseline tenting area < 3.8 cm^2	[24]	NA	0.02
	Baseline tenting area	[21]	NA	0.01
	Septal-lateral delay by TDI	[22]	NA	0.001
	Baseline inferior papillary muscle time delay	[26]	NA	0.04
	Increase in posterior papillary muscle longitudinal negative strain	[26]	NA	0.01
	Combined presence of delayed longitudinal strain in the mid inferior LV segment and preserved systolic strain in the basal and mid posterior segments	[27]	NA	0.001
	Time to- peak 2-DRS between inferior and anterior LV segments of > 110 ms	[28]	8.4	0.02
	Preserved radial strain in posterior segments assessed by 2-DRS	[28]	7.6	0.006
	MR jet area/left atrium area ratio < 40%	[28]	8.9	0.02
	Anteroseptal to posterior wall radial strain dyssynchrony > 200 ms	[29]	NA	0.028
	Lack of severe left ventricular dilatation (end-systolic dimension index < 29 mm/m^2)	[29]	NA	0.042
	Lack of echocardiographic scar at papillary muscle insertion sites	[29]	NA	0.036
Electric-Targeting LV Lead	Degree of delay at the LV lead site	[34]	1.13	0.02
	Predictors of lack of MR improvement			
CT imaging	≥ 25% of LVWT < 6 mm inclusive of at least one papillary muscle insertion using CT	[30]	1.04	0.032
Biomarkers	Higher levels of galectin 3	[23]	0.16	0.01

CRT: Cardiac resyncronization therapy; TDI: Tissue Doppler imaging; 2DRS: 2D radial strain; MR: Mitral regurgitation; LVWT: Left ventricular wall thickness; CT: Computed tomography; LV: Left ventricular; NA: Not available.

LV electric ventricular delay, such as QLV, is simple, does not require echocardiography or surface electrocardiographic measurements and has the potential to be measured automatically by devices that would further simplify lead optimization.

The concept that more advanced LV remodeling remains valid. Therefore, the lower the probability of successful CRT treatment for FMR and other treatment strategies to reduce MR should be evaluated. Long-term results in a larger cohort together with new imaging techniques, such as three-dimensional imaging, are needed to keep track of the developments and the changes in this exciting field.

FOOTNOTES

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Retrospective Study

Risk profiles and outcomes of patients receiving antibacterial cardiovascular implantable electronic device envelopes: A retrospective analysis

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Abstract

BACKGROUND

Cardiovascular implantable electronic devices (CIEDs) are implanted in an increasing number of patients each year, which has led to an increase in the risk of CIED infection. Antibacterial CIED envelopes locally deliver antibiotics to the implant site over a short-term period and have been shown to reduce the risk of implant site infection. These envelopes are derived from either biologic or non-biologic materials. There is a paucity of data examining patient risk profiles and outcomes from using these envelope materials in the clinical setting and comparing these results to patients receiving no envelope with their CIED implantation.

AIM

To evaluate risk profiles and outcomes of patients who underwent CIED procedures with an antibacterial envelope or no envelope.

METHODS

After obtaining Internal Review Board approval, the records of consecutive patients who underwent a CIED implantation procedure by a single physician between March 2017 and December 2019 were retrospectively collected from our hospital. A total of 248 patients within this period were identified and reviewed through 12 mo of follow up. The CIED procedures used either no envelope (n = 57), a biologic envelope (CanGaroo®, Aziyo Biologics) that was pre-hydrated by the physician with vancomycin and gentamicin (n = 89), or a non-biologic envelope (Tyrx™, Medtronic) that was coated with a resorbable polymer containing the drug substances rifampin and minocycline by the manufacturer (n

= 102). Patient selection for receiving either no envelope or an envelope (and which envelope to use) was determined by the treating physician. Statistical analyses were performed between the 3 groups (CanGaroo, Tyrx, and no envelope), and also between the No Envelope and Any Envelope groups by an independent, experienced biostatistician.

RESULTS

On average, patients who received any envelope (biologic or non-biologic) were younger (70.7 ± 14.0 *vs* 74.9 ± 10.6, $P = 0.017$), had a greater number of infection risk factors (81.2% *vs* 49.1%, $P < 0.001$), received more high-powered devices (37.2% *vs* 5.8%, $P = 0.004$), and were undergoing more reoperative procedures (47.1% *vs* 0.0%, $P < 0.001$) than patients who received no envelope. Between the two envelopes, biologic envelopes tended to be used more often in higher risk patients (84.3% *vs* 78.4%) and reoperative procedures (62.9% *vs* 33.3%) than non-biologic envelopes. The rate of CIED implant site pocket infection was low (any envelope 0.5% *vs* no envelope 0.0%) and was statistically equivalent between the two envelope groups. Other reported adverse events (lead dislodgement, lead or pocket revision, device migration or erosion, twiddler's syndrome, and erythema/fever) were low and statistically equivalent between groups (biologic 2.2%, non-biologic 3.9%, no envelope 1.8%).

CONCLUSION

CIED infection rates for biologic and non-biologic antibacterial envelopes are similar. Antibacterial envelopes may benefit patients who are higher risk for infection, however additional studies are warranted to confirm this.

Key Words: Cardiovascular implantable electronic device envelope; Defibrillator; Extracellular matrix; Implantable cardioverter-defibrillator; Infection; Pacemaker

Core Tip: This retrospective study was performed to determine risk profiles and clinical outcomes of patients who underwent cardiovascular implantable electronic device (CIED) procedures with a biologic or non-biologic antibacterial envelope, or no envelope. A total of 248 patient records were reviewed containing 89 biologic, 102 non-biologic, and 57 no envelope patients. Pre-procedurally, patients who received any envelope (biologic or non-biologic) were at higher infection risk than patients who received no envelope. Biologic envelopes tended to be used more often in higher risk patients than non-biologic envelopes. The rate of CIED pocket infection was low and equivalent between the two envelopes.

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INTRODUCTION

Expanding indications for cardiovascular implantable electronic devices (CIEDs) have increased the number of these devices that are implanted[1], but considering the common comorbidities seen in this patient population, complications such as infection are also increasing[2-4]. Reported infection rates of de novo CIED implantation range between 0.7%-4.6%, and can be as high as 7% for re-operations[5]. Thus, a better understanding of patient risk factors and available prophylactic techniques could potentially lower the risk of infection in this population[5-8]. CIED envelopes are intended to securely hold pacemakers or defibrillators when implanted in the body, and antibacterial CIED envelopes additionally provide short-term local antibiotic delivery which can reduce the risk of infection at the device implant site[9]. Available antibacterial CIED envelopes are either fabricated from biologic material (extracellular matrix hydrated with antibiotics by physician choice) or from non-biologic material (synthetic mesh coated with antibiotics by the manufacturer). The biologic envelope (CanGaroo®, Aziyo Biologics, Inc., Roswell, GA, United States) is made of decellularized extracellular matrix derived from porcine intestinal submucosa (SIS-ECM) which is rehydrated in solution for 1–2 min prior to use, whereas the non-biologic envelope (TYRX™, Medtronic PLC, Mounds View, MN, United States) is made from an absorbable synthetic substrate mesh coated with a bioresorbable

polymer containing the drug substances rifampin and minocycline. Both envelopes have been reported to release antibiotics over a period of seven days in separate studies[10-13].

Although both envelopes have similar indications and antibiotic elution abilities, the material each envelope is created from may affect the biologic response upon implantation into the patient. Synthetic (non-biologic) absorbable and non-absorbable materials have been reported to initiate a strong foreign body reaction, resulting in chronic inflammation leading to hypovascular fibrotic tissue surrounding the implanted material[14-18], which a previously-marketed non-absorbable synthetic envelope leveraged to stabilize the electronic device upon implantation[19]. Conversely, ECM (the material that the biologic envelope is made from) has been shown to promote constructive remodeling and healthy tissue restoration[20-23]. Both biologic and non-biologic envelopes have been reported to support clinical infection prevention strategies[12,24-26].

This is an analysis of a retrospective, real-world study which assessed the risk profiles and clinical outcomes of patients who underwent a CIED procedure and received an antibacterial envelope (biologic or non-biologic), or no envelope (CARE Plus, NCT04351269). To our best knowledge, this study contains the first reporting of biologic and non-biologic antibacterial envelopes reported together in the clinical setting.

MATERIALS AND METHODS

Records of consecutive patients undergoing CIED procedures from a single center performed by a single physician between March 2017 and December 2019 were retrospectively reviewed for up to 12 mo of follow-up. The study protocol was reviewed and approved by an independent internal review board (IRB) [WIRB-Copernicus Group® (WCG)] prior to the chart review. A waiver of informed consent and HIPAA was obtained due to the retrospective nature of the study.

The study aimed to determine risk profiles and clinical outcomes of patients who were undergoing a CIED procedure and received either no envelope, a biologic envelope (CanGaroo®) hydrated by the implanting physician for 1 – 2 minutes with a vancomycin and gentamicin solution before implantation, or a non-biologic envelope (TYRX™) coated by the manufacturer with a bioresorbable polymer containing the drug substances rifampin and minocycline. The implanting physician made all decisions regarding device type, which envelope and envelope size was used, and biologic envelope hydration solution (if one was used). Aside from the pre-hydration of the biologic envelope, the implanting technique of both the biologic and non-biologic envelope was similar. The no envelope group's CIED implantation procedure was identical to the envelope CIED implantation procedure, just without the use of an envelope. The pre- and post-operative protocol was the same for all 3 groups.

Information was extracted in detail from medical records, including medical history, infection risk factors, surgical details, and adverse events from the initial procedural visit out to 12 mo post-op. Infection risk factors were defined by previous literature[4,27,28] which identified elements that were significantly associated with increased risk for CIED infection, including renal insufficiency, diabetes, obesity, peripheral vascular disease, chronic obstructive pulmonary disease, congestive heart failure, malignancy, coronary artery disease, hypertension, chronic steroid use, oral systemic anticoagulants, malnutrition, smoking, the presence of two or more leads, pocket re-entry within 2 wk of the initial implant, prior device infection, and reoperative procedure. The number of risk factors was counted for each patient to examine the relative levels of infection risk between patient groups. Infection risk was categorized for each patient as lower risk (0–1 infection risk factors) or higher risk (2 or more risk factors), based on the quantity of established clinical risk factors present in each patient from above. An independent, biomedical statistician performed analyses between the 3 groups (CanGaroo, Tyrx, and no envelope), and also between the no envelope and any envelope groups by using means with standard deviations for continuous variables and counts with percentages for categorical variables. Continuous variables were checked for normality. Fisher's exact tests were used when ≥ 1 expected cell counts were < 5, and Pearson chi-square tests were used for categorical variable comparisons when cell counts were ≥ 5. Statistical significance was set to a $P < 0.05$. SPSS version 26 (IBM, Armonk, NY, United States) was used for statistical analyses.

RESULTS

Among 248 enrolled patients who underwent CIED procedures, 191 (77%) received an envelope. These included 89 (46.6%) biologic and 102 (53.4%) non-biologic envelopes (Table 1).

Surgical procedure details

Patients who received high-powered devices, including implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT) devices, were more likely to receive an envelope (P = 0.001) (Table 1). Patients undergoing reoperative procedures (generator changes, upgrades, other

Table 1 Comparison across cohorts

	Total	Biologic envelope	Non-biologic envelope	No envelope	[1]*P* value	Any envelope	[2]*P* value
	(*N* = 248)	(*n* = 89)	(*n* = 102)	(*n* = 57)		(*n* = 191)	
Age (yr, mean ± SD)	71.6 ± 13.3	73.6 ± 13.3	68.2 ± 14.0	74.9 ± 10.6	**0.002**	70.7 ± 14.0	**0.017**
BMI, mean ± SD	29.9 ± 7.1	28.0 ± 6.2	31.0 ± 7.9	31.0 ± 6.3	**0.008**	29.6 ± 7.3	0.206
BMI category					**0.016**		0.080
Underweight (< 18.5)	5 (2.0%)	2 (2.2%)	2 (2.0%)	1 (1.8%)		4 (2.1%)	
Normal (18.5 - < 25.0)	54 (21.8%)	30 (33.7%)	19 (18.6%)	5 (8.8%)		49 (25.7%)	
Overweight (25.0 - < 30.0)	73 (29.4%)	20 (22.5%)	31 (30.4%)	22 (38.6%)		51 (26.7%)	
Obese (30.0 - < 40.0)	97 (39.1%)	34 (38.2%)	38 (37.3%)	25 (43.9%)		72 (37.7%)	
Morbidly obese (40.0 ±)	19 (7.7%)	3 (3.4%)	12 (11.8%)	4 (7.0%)		15 (7.9%)	
Medical history							
Heart failure	106 (42.7%)	41 (46.1%)	49 (48.0%)	16 (28.1%)	**0.037**	90 (47.1%)	**0.011**
Systemic antico-agulant use	99 (39.9%)	43 (48.3%)	40 (39.2%)	16 (28.1%)	0.050	83 (43.5%)	**0.037**
CIED device type					**0.004**		**0.001**
Pacemaker	152 (61.3%)	52 (58.4%)	52 (51.0%)	48 (84.2%)		104 (54.5%)	
CRT-P	12 (4.8%)	8 (9.0%)	4 (3.9%)	0 (0.0%)		12 (6.3%)	
ICD	54 (21.8%)	17 (9.1%)	30 (29.4%)	7 (12.3%)		47 (24.6%)	
S-ICD	2 (0.8%)	0 (0.0%)	52 (51.0%)	1 (1.8%)		1 (0.5%)	
CRT-D	24 (9.7%)	10 (11.2%)	13 (12.7%)	1 (1.8%)		23 (12.0%)	
N/A	4 (1.6%)	2 (2.2%)	2 (2.0%)	0 (0.0%)		0 (0.0%)	
CIED category					**0.006**		**0.004**
Low-powered	164 (66.1%)	60 (67.4%)	56 (54.9%)	48 (84.2%)		116 (60.7%)	
High-powered	80 (32.3%)	27 (30.3%)	44 (43.1%)	9 (5.8%)		71 (37.2%)	
N/A	4 (1.6%)	2 (2.2%)	2 (2.0%)	0 (0.0%)		4 (2.1%)	
Procedure type					**< 0.001**		**< 0.001**
De novo	158 (63.7%)	33 (20.9% de novo)	68 (43.0% de novo)	57 (36.1% de novo)		101 (63.9% de novo)	
Re-operative	90 (36.3%)	56 (62.2% re-op)	34 (37.8% re-op)	0 (0.0% re-op)		90 (100% re-op)	
Infection risk factors					**< 0.001**		**< 0.001**
0-1	65 (26.2%)	14 (15.7%)	22 (21.6%)	29 (50.9%)		36 (18.8%)	
≥ 2	183 (73.8%)	75 (84.3%)	80 (78.4%)	28 (49.1%)		155 (81.2%)	
Hematoma (total)	6 (2.4%)	5 (5.6%)	1 (1.0%)	0 (0.0%)	**0.046**	6 (3.0%)	0.176
Requiring intervention	6 (2.4%)	5 (5.6%)	1 (1.0%)	0 (0.0%)		6 (3.0%)	
Infection							
Pocket infection	1 (0.4%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0.408	1 (0.5%)	0.584
Minor infection	1 (0.4%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0.408	1 (0.5%)	0.584

[1]*P* value across 3 cohorts: Biologic, non-biologic, and no envelope.

[2]*P* value across 2 cohorts: Any envelope and no envelope.

Values are reported as: *n* (%) unless specified otherwise. BMI: Basal metabolic index; CIED: Cardiovascular implantable electronic device; CRT-D: Cardiac resynchronization therapy/defibrillator; CRT-P: Cardiac resynchronization therapy/pacemaker; ICD: Implantable cardioverter defibrillator; N/A: Not applicable; S-ICD: Subcutaneous implantable cardioverter defibrillator; SD: Standard deviation.

reoperative procedures such as lead or pocket revisions) received an envelope significantly more often than no envelope (100.0% *vs* 0.0%, $P < 0.001$) and tended to be more likely to receive a biologic than a non-biologic envelope ($n = 56$, 62.9% *vs* $n = 34$, 33.3%). Those with de novo implants tended to be more likely to receive a non-biologic envelope ($n = 68$, 66.6%) than a biologic envelope ($n = 33$, 37.1%).

Clinical characteristics and infection risk factors

Patients who received any envelope were younger on average (70.7 ± 14.0 *vs* 74.9 ± 10.6 years, $P = 0.017$) and had higher rates of comorbid risk factors such as heart failure (47.1% *vs* 28.1%, $P = 0.011$) and systemic anticoagulation (43.5% *vs* 28.1%, $P = 0.037$) than those who did not receive an envelope (Table 1). Patients with biologic envelopes tended to be somewhat older (mean 73.6 ± 13.3 *vs* 68.2 ± 14.0 years) and less overweight (22.5% *vs* 30.4%) than those with non-biologic envelopes. Differences in systemic anticoagulation among the 3 groups were statistically significant (biologic 48.3%, non-biologic 39.2%, no envelope 28.1%, $P = 0.050$). Patients who received any envelope had a significantly higher number of infection risk factors (≥ 2) than those with no envelope (81.2% *vs* 49.1%, $P < 0.001$), and biologic envelopes tended to be used more frequently for these higher risk patients (84.3% *vs* 78.4%).

Infection outcomes

Pocket infection rates were low (envelope 0.5%, no envelope 0.0%), with no significant difference between biologic and non-biologic envelopes (Table 1). Among the patients who received an envelope, one (0.5%) developed a major CIED infection (pocket infection), and one (0.5%) developed a minor CIED infection (superficial surgical site infection). However, the incidence of major or minor infection did not significantly differ between the 3 cohorts.

Other adverse events

Pocket hematoma (requiring surgical intervention) developed in 6 patients (2.4%): 5 patients (5.6%) with biologic envelopes, 1 patient (1.0%) with a non-biologic envelope, and 0 patients without an envelope (0.0%) ($P = 0.046$) (Table 1). However, there was no significant difference in hematoma between any envelope (3.0%) and no envelope (0.0%). There were no reported hematoma that led to infections in this study. Other adverse events included 3 Lead dislodgements (1 in the biologic group, 2 in the non-biologic group), 1 Lead revision (non-biologic group), 1 hemothorax (non-biologic group), and 1 site drainage (biologic group) in the envelope cohorts and erythema/fever in 1 patient in the no envelope cohort. Rates of adverse events other than pocket hematoma did not significantly differ among the 3 cohorts.

DISCUSSION

This retrospective study examined clinical profiles and outcomes of patients receiving CIEDs implanted with antibacterial biological envelopes hydrated with gentamicin and vancomycin (biologic envelopes), CIEDs implanted with synthetic (non-biologic) antibacterial envelopes, and CIEDs with no envelope. Non-biologic antibacterial envelopes have been previously shown in a large, randomized study to reduce infection risk in patients who are at increased risk for CIED infection[12]. To the best of our knowledge, this is the first reporting of clinical outcomes from using either biologic or non-biologic antibacterial envelopes, or no envelope within the same dataset.

Patient selection for envelope use

Patient selection by the implanting physician is reflected in the study findings. Envelopes were selected significantly more often for younger patients, patients undergoing device replacement procedures, high-powered device implantations, those on systemic anticoagulation, patients with heart failure, and patients with 2 or more risk factors for CIED infection. Treatment preferences can be observed by envelope usage for at-risk patients who may benefit most from the local delivery of antibiotics to their CIED implant site. Interestingly, there was no statistical difference in observed infection rates between the envelope and no envelope groups, even though the envelope group contained significantly more patients with ≥ 2 infection risk factors. Our results and those of other studies[9,12,24,26], support that the utilization of antibacterial envelopes (biologic or non-biologic) may reduce the potential risk burden of patients with multiple concurrent infection risk factors who are undergoing CIED procedures. However, further studies are needed to determine if there are specific patient types that could benefit the most from receiving an antibacterial envelope.

Complications

There were no significant differences in individual adverse event rates between groups, except that more patients with biologic envelopes were reported to have hematoma requiring intervention compared to the other two groups. However, this observation may have been due to the greater use of systemic anticoagulation and reoperative procedures in the biologic envelope group, which have both

been shown to be risk factors for hematoma formation in previous studies[29,30]. In fact, a recent analysis of hematoma from the 6800 patients included in the WRAP-IT trial reported a hematoma occurrence of 2.2%, which was significantly associated with an increased risk of infection for the no envelope (control) group and a significantly lower risk of major infection in the non-biologic envelope group (2.5% *vs* 13.1%, $P = 0.03$)[31]. No hematoma in our dataset led to subsequent infection, which further supports a potential benefit from using antibacterial envelopes (biologic or non-biologic) to reduce the risk of hematoma manifesting to CIED implant site infection.

Infections at the CIED implantation site have serious morbidity, mortality, and economic consequences[1,32]. The use of antibacterial envelopes may reduce the risk of infection and could potentially reduce these serious complications and healthcare costs[33]. In our dataset, antibacterial envelopes were used significantly more often to treat patients with multiple comorbid risk factors, and biologic envelopes tended to be used more often in higher risk patients than non-biologic envelopes. We observed a 0.4% overall rate of pocket infection, which is lower than previously-reported studies of 0.7% to 4.6% for de novo implantations and up to 7% for reoperative procedures[5-8]. No significant difference was found in major CIED (pocket) infection rates between the 3 groups. A previous study reported that infection rate can differ depending upon various patient- and procedure-related circumstances (such as device type, procedure type, antibacterial envelope use, or perioperative antibiotics)[7], thus along with the major infection rates reported for high risk patients in the WRAP-IT (0.7%)[12] and PADIT (0.7%)[34] studies, the low pocket infection rate observed in our preliminary results (0.4%) supports that high infection risk factors can be countered with infection prophylaxis techniques such as the use of antibacterial envelopes.

Antibacterial CIED envelope types

There are currently two commercially available CIED envelopes in the United States. The biologic envelope (CanGaroo®) is manufactured from two sheets of 4-ply SIS-ECM material which can be hydrated by the implanting physician with an antibiotic solution prior to implantation, and the non-biologic envelope (TYRX™) is fabricated from an absorbable synthetic substrate mesh coated with a bioresorbable polyarylate polymer containing the drug substances rifampin and minocycline. In separate studies, the release of antibiotics occurs similarly from both envelopes over a period of seven days[10-13]. Both envelopes are intended to stabilize the CIED post-implantation, yet the host response to these different materials may vary. All biomaterials (biologic and non-biologic) interact with the body upon implantation, and certain characteristics of these materials can influence the host response to the implant[35,36].

Extensive studies have shown that implanted biologic materials (such as non-crosslinked decellularized SIS-ECM) stimulate the production of site appropriate, functional tissue (termed "constructive remodeling"[37])[20-23,36]. The ability to elicit a remodeling response post-implantation is due to the natural degradation of the implanted ECM by proteases which release intrinsic bioactive peptides and growth factors such as FGF-2 and VEGF *in situ*[22,38-40]. When implanted, for example into a CIED pocket, these bioavailable signaling molecules can influence the healing milieu surrounding the implant site by directing cellular activities such as differentiation, chemotaxis, adhesion, and angiogenesis[22,41-43]. Non-biologic materials do not contain these bioactive components.

Limitations

Limitations to this study include non-randomization of patients to the treatment groups, a limited period of follow up, and all implantations performed by a single physician at one institution. The choice of patients receiving an envelope (and which envelope was used) creates selection bias observed in the differing patient factors between groups. However, the intent of this report was to evaluate and define physician practice patterns instead of assessing superiority between the three therapies. Longer-term (> 1 year) follow up may have captured late adverse events, which cannot be ruled out in this study.

CONCLUSION

In this real-world study, patients at higher risk for CIED infection received antibacterial envelopes and lower infection risk patients did not receive envelopes, yet the CIED pocket infection rate did not differ between groups. There was also no significant difference in observed pocket infection rates for patients receiving biologic *vs* non-biologic antibacterial envelopes. These findings support that use of an antibacterial envelope may benefit patients who are at higher risk for infection, however further work will continue to refine patient selection and clinical decision-making for optimal utilization of antibacterial envelopes during CIED implantation.

ARTICLE HIGHLIGHTS

Research background

An increase in cardiac implantable electronic device (CIED) implantation has led to an increase in observed complication rates, including infection. Antibacterial CIED envelopes have been shown to reduce the risk of infection complications, even in high-risk patient groups. There are currently two different CIED envelopes in clinical use which differ in the material from which they are made.

Research motivation

There is a paucity of data describing real-world physician practice patterns when using antibacterial CIED envelopes. Understanding clinical rationale and outcomes from the use of this prophylactic therapy could improve future patient outcomes.

Research objectives

Patient risk profiles and outcomes were compared from patients undergoing CIED procedures receiving either no envelope, or one of two antibacterial envelopes.

Research methods

In this retrospective analysis, the records of consecutive CIED procedure patients were reviewed at one center through a follow-up time of 12 mo.

Research results

Patients who were selected to receive an antibacterial CIED envelope were at significantly higher risk for infection than patients who did not receive an envelope (81.2% *vs* 49.1%, $P < 0.001$). Among the infection risks, envelope patients were undergoing more reoperative procedures (47.1% *vs* 0.0%, $P < 0.001$) and received more high-powered devices (37.2% *vs* 5.8%, $P = 0.004$) than patients who received no envelope. There was a propensity for the physician choosing a biologic envelope in patients who were higher risk than non-biologic patients (84.3% *vs* 78.4%), and those that were undergoing reoperative procedures (62.9% *vs* 33.3%). The rate of pocket infection was low (any envelope 0.5% *vs* no envelope 0.0%), with no significant difference between the two envelope groups.

Research conclusions

There is an apparent benefit for using antibacterial envelopes in patients who are at higher risk of implant site infection. When using antibacterial envelopes, there was no significant difference in infection rate for biologic and non-biologic envelopes.

Research perspectives

Future studies should further explore patient and procedural factors that play a role in antibacterial envelope usage for specific patient types to further improve patient outcomes.

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FOOTNOTES

Author contributions: Woodard D led the conception, design, data collection and analysis, and drafting of the manuscript; Nilsson K and Kim G contributed their expertise to the analysis/interpretation of data and editing of the manuscript; and all authors accept accountability for the accuracy of this work, and drafted, revised, and approved the final version of the manuscript to be published within this journal.

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the WIRB-Copernicus Group®.

Informed consent statement: A waiver of informed consent and HIPAA due to the retrospective nature of this study was obtained. This study was conducted in accordance with the ethical principles in the Declaration of Helsinki and conducted according to United States and international standards of Good Clinical Practice in accordance with applicable Federal regulations, International Council for Harmonization guidelines, and institutional research

policies and procedures.

Conflict-of-interest statement: Woodard D is a consultant for Aziyo Biologics, Inc. The other authors have no relevant financial relationships to disclose.

Data sharing statement: The dataset supporting the conclusions of this article is available upon reasonable request to the corresponding author.

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LETTER TO THE EDITOR

Electrocardiographic alterations in patients with chronic obstructive pulmonary disease

Mehmet Eyuboglu

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Abstract

Patients with chronic obstructive pulmonary disease (COPD) have an increased risk for cardiovascular events, and electrocardiography has an important role in detecting cardiac side effects of COPD-related hypoxia.

Key Words: Electrocardiography; Chronic obstructive pulmonary disease; QT interval; QT dispersion; Frontal plane QRS-T angle; Fragmented QRS

Core Tip: QT parameters and frontal plane QRS-T angle may provide useful information regarding subclinical left ventricular dysfunction in patients with chronic obstructive pulmonary disease. In addition to standard electrocardiography parameters, these parameters may also be useful in demonstrating cardiac side effects of chronic obstructive pulmonary disease.

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TO THE EDITOR

I have read with great interest the article by Gupta *et al*[1] in which the authors reported the important electrocardiography (ECG) changes in patients with chronic obstructive pulmonary disease (COPD). Patients with COPD are at increased risk for cardiovascular events and ECG may provide useful information in monitoring these

patients. In their article, Gupta *et al*[1] mentioned various important ECG alterations in patients with COPD. However, I would like to point out some other important ECG parameters which may be significantly associated with myocardial damage and should not be neglected in patients with COPD.

COPD causes alterations in the cardiac conduction system and is associated with increased risk for cardiac arrhythmias and cardiovascular events[2,3]. Importantly, repolarization parameters QT interval and QT dispersion are the most important ECG parameters in predicting future arrhythmic events, and these parameters seem to be significantly altered in patients with COPD[3,4]. Alterations in these repolarization parameters seem to be associated with COPD-related hypoxia and significantly predict arrhythmic events in patients with COPD. Hence, QT parameters may be useful in the monitoring of patients with COPD for adverse cardiovascular events.

Additionally, frontal plane QRS-T angle (fQRST angle) which could be easily measured from standard 12-lead ECG as the absolute difference between QRS axis and T wave axis, maybe a useful ECG parameter in the monitoring of patients with COPD. fQRST angle describes the angular difference between depolarization and repolarization directions and increased fQRST angle is significantly associated with adverse cardiovascular events[5,6]. Importantly, fQRST angle seems to be associated with subclinical myocardial damage even in the absence of overt cardiovascular disease[7-9]. Moreover, COPD seems to cause an increase in fQRST angle, and fQRST angle seems to be associated with the severity of COPD[10]. Therefore, as a sign of ventricular repolarization heterogeneity, fQRST angle may be a useful ECG parameter in the clinical evaluation of patients with COPD.

Another important ECG parameter that should be considered in patients with COPD may be QRS fragmentation. In addition to its predictive value for myocardial scar tissue, presence of a narrow fragmented QRS complex (fQRS) on ECG is significantly associated with subclinical myocardial fibrosis even in the absence of manifest cardiovascular disease[11-14]. Importantly, fQRS also seems to be a sign of hypoxia-related subclinical left ventricular dysfunction in patients with the pulmonary disease[15]. Although its clinical importance in patients with COPD has not been demonstrated yet, QRS fragmentation patterns may be useful in detecting subclinical left ventricular dysfunction in patients with COPD.

In conclusion, various ECG changes may be seen in patients with COPD, and these ECG alterations seem to be associated with adverse cardiovascular events in these patients. However, besides the other ECG parameters, QT interval, QT dispersion and fQRST angle should be considered to demonstrate COPD's cardiac side effects. Also, evaluation of QRS fragmentation patterns may provide useful information in detecting subclinical myocardial dysfunction in patients with COPD.

FOOTNOTES

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