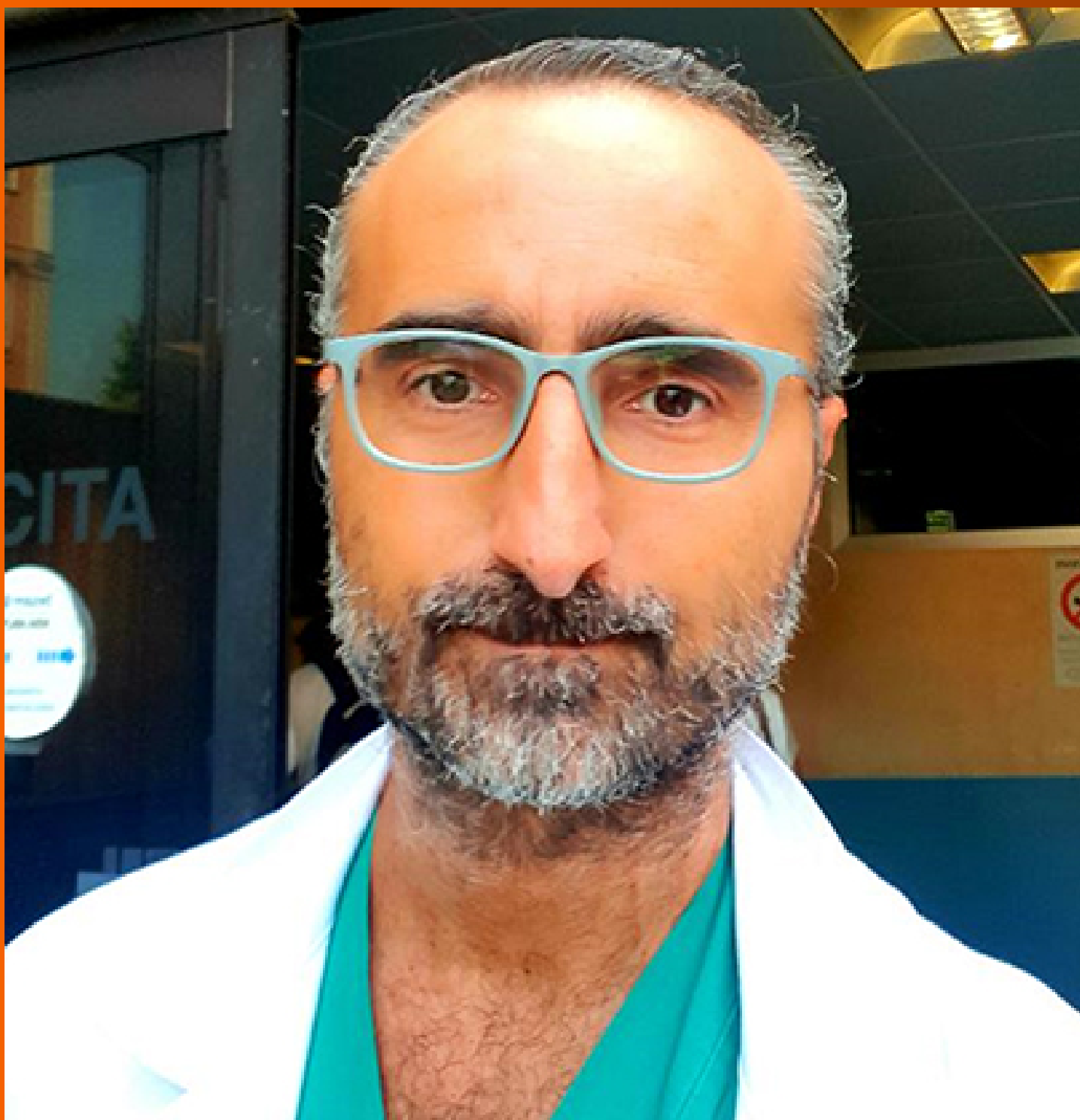


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## A Novel guide extension assisted stenting technique for coronary bifurcation lesions

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### Abstract

A challenging technical scenario frequently encountered in a percutaneous coronary intervention of a coronary bifurcation lesion (CBL) is stent implantation of only the stenosed segment without compromising the other two normal segments in non-true bifurcation lesions. Another is precise stent implantation covering the side branch ostium without leaving excessive stent metal at the other two segments of a bifurcation lesion in complex true bifurcation lesions. The aim of this study was to describe a novel stenting technique for both non-true and true CBLs by using a guide extension catheter (GuideLiner). With the assistance of a guide extension catheter mounted on both the main and the side-branch guidewires and with its intubation down to the bifurcation carina, a stent can be implanted in the side branch segment or distal main segment of the bifurcation lesion appropriately without compromising the other two segments of the coronary bifurcation. Stent implantation is described in three bifurcation lesions in three cases and shown in detail with illustrative figures. The technique facilitates side-branch only stenting in side-branch mono-ostial (medina 0, 0, 1) CBL or only the distal main segment in distal mono-ostial (medina 0, 1, 0) CBL without compromising the other two remaining segments when using the one-stent technique in non-true CBLs without leaving unnecessary excessive stent metal at the bifurcation site and when using a two-stent technique in complex true bifurcation lesions (tri-ostial or medina 1, 1, 1). Consequently, through optimizing stent deployment, the technique may have the potential to reduce the risk of subacute stent thrombosis and future in-stent restenosis. The most appropriate lesions suitable for the technique, and some other practical tips are also described.

**Key Words:** Coronary bifurcation lesion; GuideLiner stenting; Percutaneous coronary intervention; One- or two-stenting technique; Novel descriptive, intelligible and ordered

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**Core Tip:** A novel stenting technique for coronary bifurcation lesions (CBLs) is presented. With the help of a guide extension-assisted technique using a GuideLiner mounted on both guidewires in the branches of the bifurcation lesion and advanced to the carina of the bifurcation, a stent can be implanted at the most possible appropriate site of the side branch in side-branch mono-ostial (medina 0, 0, 1) or in the distal mono-ostial (medina 0, 1, 0) in non-true CBLs. The technique can also be used to stent the side branch in two-stent techniques for complex true CBLs (tri-ostial or medina 1, 1, 1).

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## INTRODUCTION

Percutaneous coronary intervention (PCI) of a coronary bifurcation lesion (CBL) is a challenging procedure for interventionists[1]. The short- and long-term outcomes are closely related to the procedural success and optimization of the bifurcation stenting technique[2,3]. Several one- or two-stent techniques for PCI of CBLs have been described, depending on the type and location of the bifurcation lesions[1,4]. Stenting of the side branch in side-branch mono-ostial[5] (medina 0, 0, 1)[6] bifurcation stenoses is associated with difficulties in stent placement at the proper site with the risk of missing the side branch ostium or of excessive stent protrusion in the main branch. The same applies to stenting only the distal main segment in distal mono-ostial (medina 0, 1, 0) bifurcation stenoses. Consequently, the provisional stenting technique is typically employed in treating a distal mono-ostial stenosis (medina 0, 1, 0) but this requires “unnecessary” stenting of the normal proximal main segment of the bifurcation and the risk of compromising the side branch[1].

The provisional stenting technique is also recommended as the default strategy by most interventionists in tri-ostial (medina 1, 1, 1) or true bifurcation lesions[1]. However, this technique may lead to side-branch occlusion during stenting of the main branch and acute peri-procedural myocardial infarction. Improvements in the protection of the side branch have been reported with the jailed balloon protection of the side branch[7] or modified jailed balloon techniques[8]. The risk of side-branch occlusion is increased in complex tri-ostial (medina 1, 1, 1) bifurcation lesions where a two-stent technique should always be considered. However, the current two-stent techniques for the CBLs, such as crush[9] and culotte[10] stenting, leave multiple layers of stent struts at the bifurcation site causing difficulties in rewiring, balloon re-crossing, and the performance of sequential post-dilatation and final kissing balloon inflation. This may result in stent under expansion, and/or malapposition at the bifurcation site predisposing to acute and sub-acute stent thrombosis. Suboptimal stent implantation is also associated with an increased risk of future in-stent restenosis [1]. To overcome these challenges, the crush technique has evolved to mini-crush and double kissing (DK)-crush techniques[1]. The DK-crush stenting technique facilitates final kissing balloon inflation, but the technique has complex procedural steps and is time consuming. Other two-stent techniques include simultaneous kissing stenting, T-stenting and V-stenting techniques. The T-stenting technique does not leave multiple layers of stent struts, which facilitates final kissing balloon inflation, but has the potential of geographical miss at the side branch. These technical shortcomings highlight the need for a stent implantation technique that avoids unnecessary stenting of the normal segments and not leaving multiple layers of stent struts at the bifurcation site. A guide extension catheter can intubate the coronary arteries down to the carina of the bifurcation site. This may facilitate precise stent implantation at the ostium of the side branch or the distal main segment and thus enhance rewiring,

balloon re-crossing and final kissing balloon inflation in two-stent techniques.

## METHODOLOGY

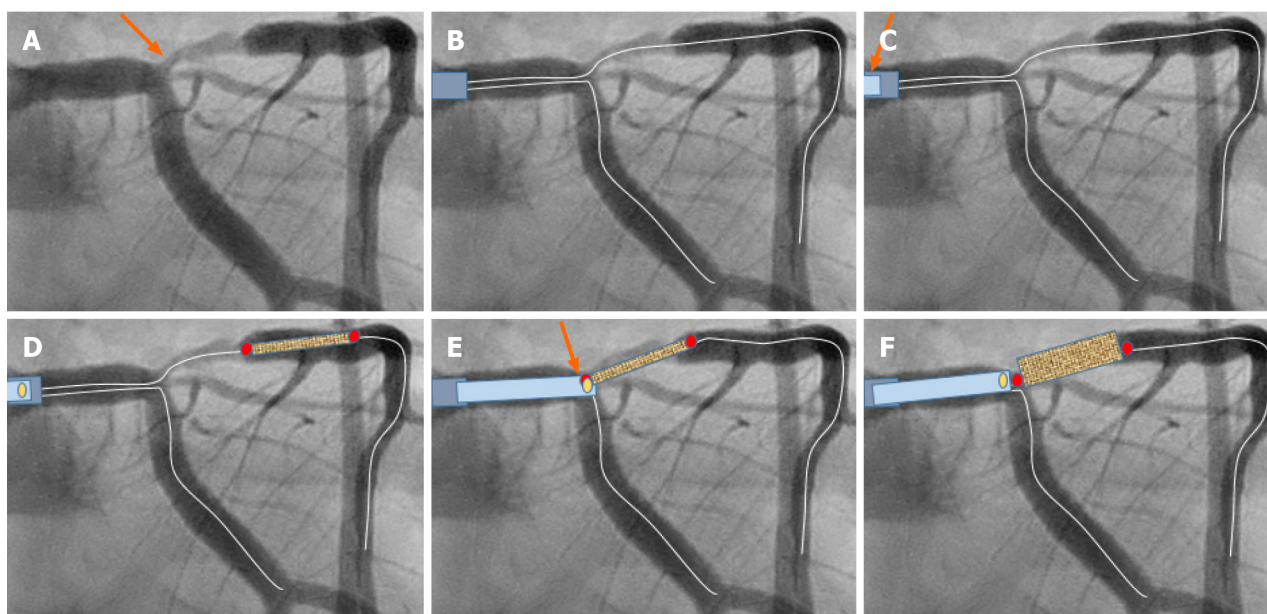
### **Description of the guide extension-assisted stenting technique using a GuideLiner catheter (Vascular Solutions Inc., Minneapolis, MN)**

The GuideLiner is a guide extension catheter that is mounted coaxially on a monorail system extending through the guide catheter. It consists of a coaxial exchange system with a flexible extension of 20 cm and a radio-opaque marker 2 mm proximal to the tip of the catheter. The extension catheter has been used for deep vessel intubation to allow the smooth device delivery of balloons and stent platforms in calcified or tortuous vessel anatomy. Guide extension catheters have also been used to facilitate obtaining good angiographic and optical coherence tomographic (OCT) images by subselective injection of reduced contrast medium, and particularly useful in tortuous vessel or angulated bifurcation anatomy[11]. Further uses include stenting the main branch of a complex bifurcation lesion while retaining guide wires in both side branches of the bifurcation[12] and to facilitate side strut stenting technique for the treatment of right coronary artery ostial in-stent restenosis where there is ostial right coronary artery stent overhang into the aortic root[13].

In this novel technique, the coronary artery is engaged by conventional 6, 7, or 8F guide catheters, through radial (6 and 7F), or femoral (6, 7, and 8F) artery approaches. Two guidewires are placed in the branches of the bifurcation lesion, one in the main branch and one in the side branch (Figure 1A and B). The bifurcation lesion is predilated, preferably with undersized 1.5 or 2 mm balloon, and the ostium of the side branch should be dilated with a cutting or scoring balloon, especially the left anterior descending artery (LAD) ostium or the left circumflex artery (LCx) ostium. The dilated but still stenosed bifurcation lesion helps to prevent to-and-fro movement of the stent during stent implantation especially in LAD. Dilatation of the ostium by a cutting or scoring balloon helps to avoid stent sliding distally during stent implantation. Thereafter, the appropriate (6, 7, or 8F) GuideLiner mounted on both guidewires is introduced and placed near the tip of the guide catheter (Figure 1C). The stent is introduced somewhat distal to the lesion (Figure 1D) and then the GuideLiner introduced to the carina of the bifurcation, and the stent is retracted while the GuideLiner is advanced carefully against the carina until the proximal radio-opaque marker of the stent balloon is overlapping the distal radio-opaque marker of the GuideLiner (Figure 1E). Being mounted on both main and side-branch guidewires, the guide extension catheter will stop at the carina of the bifurcation just adjacent to the ostium of the side branch or ostium of the distal main segment of the main branch. The stent is then implanted slowly to avoid stent displacement (Figure 1F). During stent implantation, the proximal part of the stent balloon pushes the GuideLiner catheter backward. In this way the stent is implanted at the ostial region and distally without compromising the other two segments of the bifurcation (Figures 1-4). The stent balloon catheter is pulled out first followed by the GuideLiner. The stent is then post-dilated, and the stent apposition is checked in the conventional way. In tri-ostial bifurcation lesions (medina 1, 1, 1), and after stenting the side branch by GuideLiner technique described above (Figure 4), the procedure is completed conventionally with stenting of the main branch, proximal optimization technique (POT), rewiring of the side branch, balloon re-crossing of the main branch stent struts, sequential balloon dilatation, and final kissing balloon inflation. The technique is further illustrated and described in three bifurcation cases treated with this guide extension technique in Figures 1-4.

### **Coronary artery bifurcation lesions suitable for the GuideLiner-assisted stenting technique**

This novel guide extension assisted stenting technique is characterized by keeping the guidewire access to both branches of the bifurcation during the whole procedure in side-branch mono-ostial (medina 0, 0, 1), distal mono-ostial (medina 0, 1, 0) CBL, and stenting only the lesion site without compromising the other two segments of the bifurcation. The most appropriate bifurcation sites suitable are the bifurcation lesions situated proximally in the coronary artery trees as left main stem/LAD/LCx, proximal LAD/diagonal, and proximal LCx/marginal bifurcation lesions. The most suitable types of CBLs for this technique are the side-branch mono-ostial (medina 0, 0, 1), the distal mono-ostial (medina 0, 1, 0) and potentially distal bi-ostial (medina 0, 1, 1)



**Figure 1 Schematic description of the guide extension-assisted technique in a coronary bifurcation lesion in the first case.** A: Coronary angiography in a male patient admitted with unstable angina revealed a significant ostial and proximal left anterior descending artery (LAD) stenosis. It was classified as side branch mono-ostial (medina 0, 0, 1), left main stem/left circumflex artery (LCx)/LAD bifurcation stenosis (orange arrow). Evaluation by fractional flow reserve assessment was 0.76, indicating a significant stenosis. The guide extension-assisted percutaneous coronary intervention technique is demonstrated schematically. B: Two guide wires are placed in the left coronary artery (both LAD and LCx); C: After conventional pre-dilatation, the GuideLiner, mounted on both guidewires, is placed proximal to the tip of the mother guide catheter (orange arrow); D: The stent is introduced just distal to the stenosis; E: The GuideLiner is then advanced to the carina of the bifurcation and the stent is pulled back to a level where the proximal radio-opaque marker of the stent balloon overlaps the radio-opaque marker just proximal to the tip of the guide-liner (orange arrow). Because the GuideLiner is mounted on both wires, the carina of the bifurcation will prevent further introduction of the GuideLiner into the LAD or LCx; F: The stent is implanted slowly. Note that the GuideLiner is pushed backwards when the stent balloon is inflated.

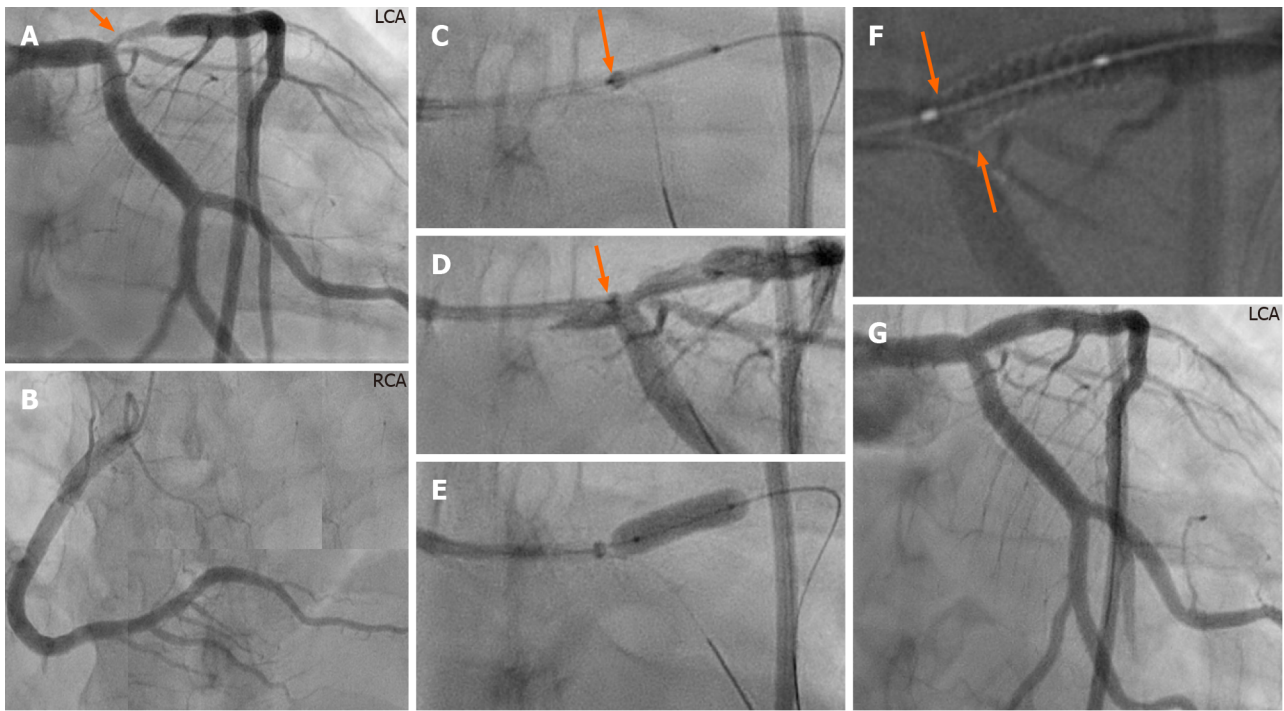
bifurcation lesions when the proximal segment of the main branch is normal. The technique can also be utilized in tri-ostial bifurcation stenosis (medina 1, 1, 1) through stenting the side branch using the guide extension technique (Figure 4) and then conventional stent implantation in the main branch with the advantage of not leaving excessive stent metal at the carina and facilitation of the procedure by proximal optimization, rewiring, sequential balloon dilatation, and final kissing balloon inflation.

### Side branch stenting

Side branch stenting is challenging for all interventionists. The crucial step is positioning the stent so that it covers the ostium of the side branch without protruding too much into the main branch. Achievement of geographical precision is more difficult when the bifurcation angle is of the “Y-type” and almost impossible when the ostium of the side branch cannot be visualized, which is the case in some bifurcation lesions as shown in Figure 3. One of the disadvantages of the T-stenting technique is that it may miss covering the ostium of the side branch. In contrast, the crush, mini-crush, and culotte stenting techniques[1] leave multiple strut layers in the main branch that may result major difficulty in rewiring the side branch and subsequent sequential and final kissing balloon inflations. The novel guide extension-assisted stenting technique of the side branch reduces the risk of missing the ostium substantially and avoids unnecessary stent protrusion into the main branch.

## RESULTS

Three different types of CBLs in three cases that were successfully treated with PCI using a GuideLiner-assisted stenting technique. Two cases had non-true CBLs and one had a true CBL. The first case had left main stem/LCx/LAD bifurcation stenosis of a side-branch type mono-ostial (medina 0, 0, 1) bifurcation lesion. With a GuideLiner advanced to the carina of the bifurcation, the side branch (LAD) was stented successfully (Figure 2). The stent covered the ostium of the LAD without leaving stent struts in the left main stem or LCx, confirmed by StentBoost imaging (Figure 2F). The

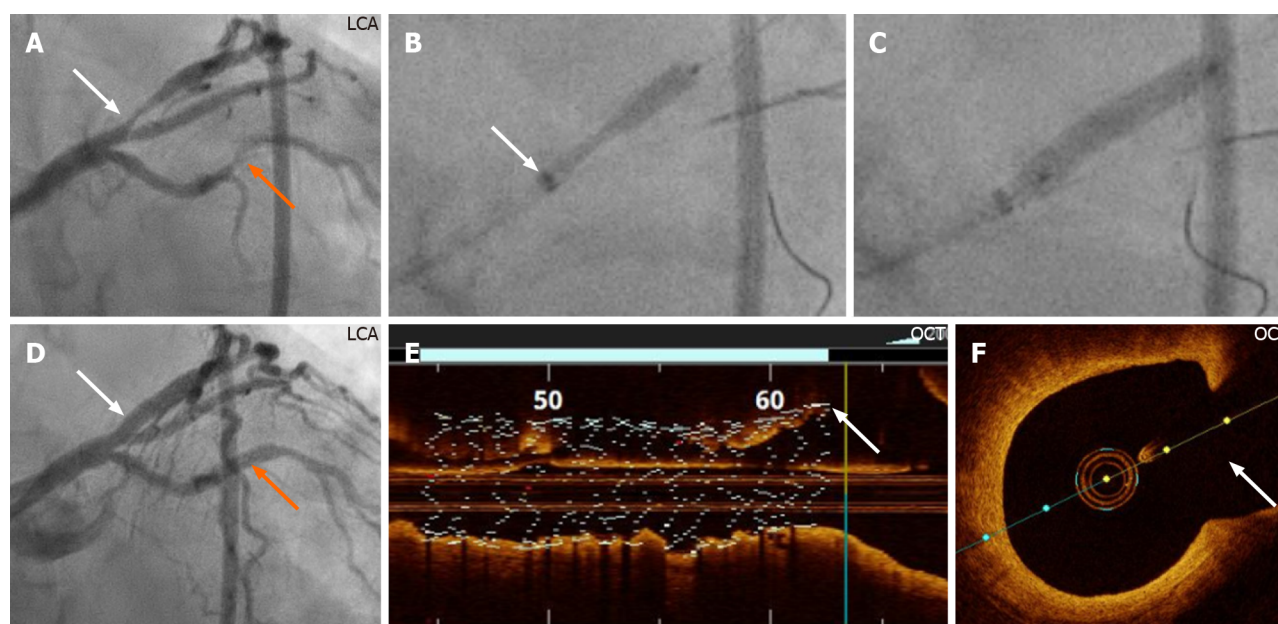


**Figure 2 Annotated description of the guide extension technique in the bifurcation lesion in the first case.** A and B: Left (A) and right (B) coronary angiography of the same patient in figure 1 showing stenosis at the ostium and proximal part of left anterior descending artery (LAD) (A, orange arrow); C and D: After engagement of the left coronary artery with 7F XB 3.5 guide catheter, a 7F GuideLiner, mounted on both guidewires, is advanced carefully against the carina of the bifurcation and the stent is placed at the stenosis site with the proximal radio-opaque marker of the stent balloon overlapping the radio-opaque marker just proximal to the tip of the GuideLiner (D, under contrast injection); E: A 3.5 mm × 15 mm stent was implanted with a pressure of 20 atm; note that the GuideLiner is pushed backwards during stent implantation. The stent is post-dilated in the conventional way; F: The proximal stent edge can be seen accurately placed at the ostium using StentBoost imaging (orange arrows); G: Final result, stent implanted in the LAD without compromising the left main stem or the left circumflex artery ostium. LCA: Left coronary artery; RCA: Right coronary artery.

bifurcation lesion in the second case treated with this novel technique was a LAD/diagonal bifurcation stenosis type distal mono-ostial (medina 0, 1, 0) where the stenosis was restricted to the distal main segment of the bifurcation. It is worth mentioning that visualization of the angle between the diagonal branch and the distal segment of the main branch (LAD) was ambiguous, making it especially suitable for this novel technique. With a GuideLiner intubated down to the carina of the bifurcation, the distal main segment was stented successfully (Figure 3). The stent covered the ostium of the distal main segment without leaving stent struts in proximal main segment or the side branch and this was confirmed by OCT (Figure 3E and F), which also showed a well-apposed stent to the vessel wall. The bifurcation lesion in the third case was a complex LAD/diagonal bifurcation stenosis of type tri-ostial (medina 1, 1, 1) (Figure 4). The side branch was stented by this novel technique after extending the GuideLiner to the carina of bifurcation. The stent covered the side-branch ostium without leaving stent struts at the bifurcation site. The main branch is then stented in the conventional way without leaving multiple layers of stent struts at the bifurcation site. Consequently, the procedure enhanced rewiring, balloon re-crossing and the performance of sequential post-dilatation and final kissing balloon inflations. StentBoost and optical coherence tomography confirmed well-apposed stents at the bifurcation site with no stent struts covering the ostium of the diagonal branch (Figure 4H and I)

## DISCUSSION

The main advantage of the guide extension-assisted stenting technique is precise positioning of the stent at the side branch of a CBL especially in lesions where the side-branch ostium is challenging to visualize or ambiguous. The most appropriate CBLs suitable for this technique are the side-branch mono-ostial (medina 0, 0, 1), distal mono-ostial (medina 0, 1, 0), and potentially distal bi-ostial (medina 0, 1, 1) CBLs. In such lesions, the guide extension-assisted technique avoids stenting of the normal



**Figure 3 Demonstration of the guide extension technique during percutaneous coronary intervention of the bifurcation lesion of the second case.** A: Left coronary artery (LCA) angiography reveals a stenosis in the obtuse marginal branch, (orange arrow) that was stented first after engagement of the left coronary artery with 7F-XB 3.5 guide catheter. There is also a distal mono-ostial (medina 0, 1, 0) left anterior descending artery (LAD)/diagonal bifurcation stenosis (white arrow), which was stented with the guide extension-assisted technique; B: Of note, angiography to visualize the angle between the diagonal branch and the distal segment of the main branch (LAD) was ambiguous, making it especially suitable for this novel technique. The GuideLiner, mounted on both the LAD and diagonal guidewires, was introduced to the carina site of the bifurcation. A Promus Premier 3.0 mm × 16 mm stent (Boston Scientific, Marlborough, MA, United States) positioned at the stenosis with the proximal stent balloon radio-opaque marker positioned on the GuideLiner radio-opaque marker just proximal to the tip of the GuideLiner (white arrow); C: The stent was implanted at a pressure of 22 atm; D: Angiographic final result (white and orange arrows); E and F: The implanted stent, checked by using OCT, is well-apposed to the vessel wall; the proximal stent edge can be seen positioned at the ostium of the distal segment of the main branch (E, white arrow), and no stent struts are seen to cover the diagonal branch ostium (F, white arrow). OCT: Optical coherence tomography.

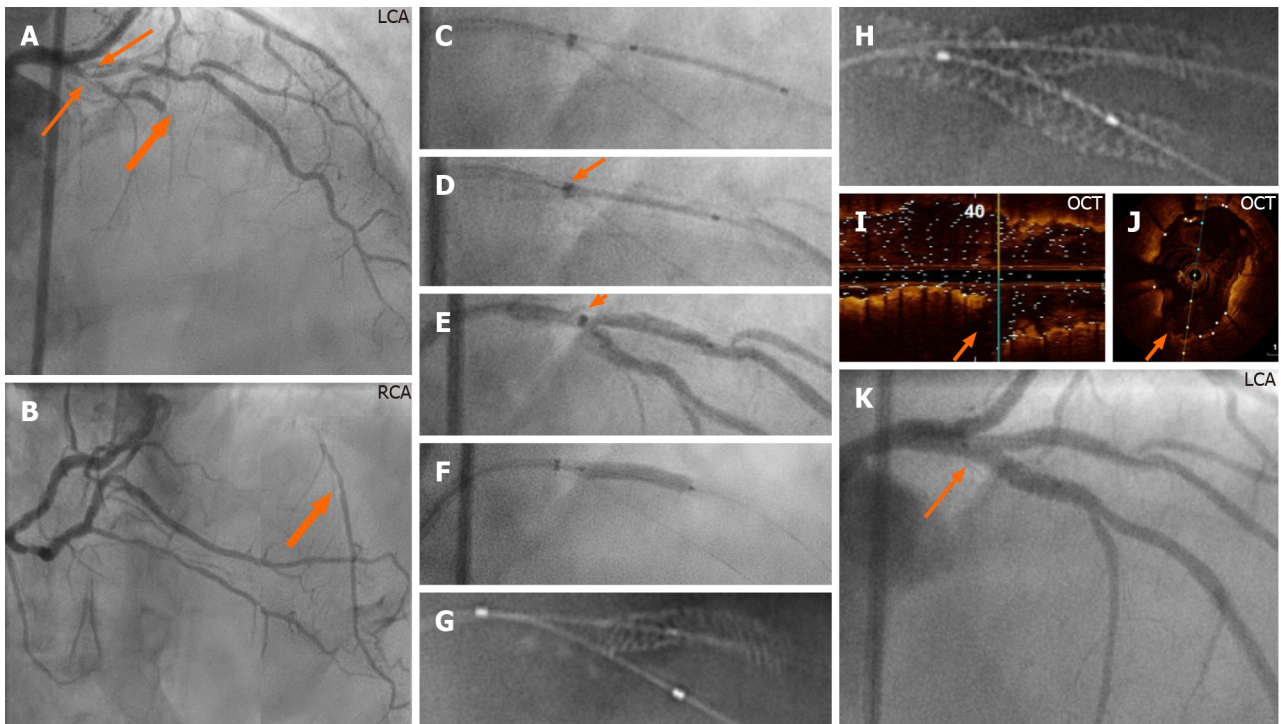
proximal segment of the bifurcation with its subsequent risk of compromising the other branch of the bifurcation, and the subsequent need for re-crossing the stent struts for final kissing balloon inflation. The guide extension assisted technique can also be utilized for stenting the side-branch lesion in complex tri-ostial (medina 1, 1, 1) bifurcation lesions as demonstrated [Figure 4](#).

The bifurcation PCI principle of “keep it open” for the side branch and the provisional side-branch stenting, is currently regarded as the default procedure in the majority of bifurcation lesions, in part attributable to the fact that the two-stent techniques (crush and culotte) are more complex and may leave stent struts under expanded or malapposed, with increased risk of acute or subacute stent thrombosis and future in-stent-restenosis. However, in complex bifurcation lesions, the risk of compromising the side branch is substantial with a provisional approach. The incidence of side-branch occlusion was 13.4% for true bifurcation and 4.0% for non-true bifurcation lesions in a bifurcation stenting registry enrolling 2227 cases of bifurcation PCIs treated by the one-stent approach[14]. For this reason, a two-stent technique is frequently necessary for complex true bifurcation lesions. The DK-crush technique has been shown to be superior to the provisional side-branch stenting as well as to culotte techniques in terms of efficacy and safety[1,3]. Nonetheless, it must be recognized that the DK-crush technique is technically demanding and time consuming.

A simplified two-stent technique, which does not leave excess layers of stent struts at the bifurcation site, is thus highly desirable. The guide extension-assisted stenting technique for the side branch does not leave unnecessary stent metal in the main branch as may occur with crush and culotte techniques and consequently avoids the subsequent risks of subacute stent thrombosis and difficulties in performing rewiring, balloon re-crossing the stent strut toward the side branch, sequential balloon dilatation, and final kissing balloon inflation.

### Limitations

The main limitation of the technique is that in Y-shaped side branch angulation, it is impossible to implant a stent covering the whole side-branch ostium circumferentially; in such cases the stent either protrudes somewhat into the main branch at the lower



**Figure 4 Demonstration of the guide extension technique in a complex true bifurcation lesion in the third case.** A and B: Left (A) and right (B) coronary angiography. The left anterior descending artery (LAD) system reveals a proximal tri-ostial (medina 1, 1, 1) LAD/diagonal bifurcation stenosis where the LAD is subtotally occluded (thick orange arrows); B: The distal part of the LAD is filled by collateral circulation from the right coronary artery (thick orange arrow); C: The left coronary artery engaged with 7F-XB 3.5 guide catheter. After placing two guidewires, one in the LAD and another in the diagonal artery, and then conventional predilatation of both the main and the side branches, the GuideLiner, mounted on both guidewires, is positioned at the bifurcation carina. A Promus Premier (Boston Scientific, Marlborough, MA, United States) 2.5 mm × 16 mm stent is placed in the diagonal artery; D and E: The stent is retracted so that the proximal stent balloon radio-opaque marker overlaps the radio-opaque marker just proximal to the tip of the GuideLiner (D: Without contrast; E: With contrast; orange arrows); F: The stent was implanted at a pressure of 22 atm; the stent balloon pushes the guide extension catheter backwards; G: StentBoost imaging (Philips Medical Systems, Eindhoven, the Netherlands) shows that the proximal stent edge is positioned at the side-branch ostium. After stent implantation in the main branch with a Promus Premier (Boston Scientific, Marlborough, MA, United States) 3.0 mm × 24 mm stent post-dilated with a 3.5 mm high pressure balloon, rewiring of the side branch, sequential balloon dilatation, proximal optimization technique, and final kissing balloon inflation; H: StentBoost imaging reveals a precisely stented bifurcation lesion without unnecessary layers of struts; I and J: Optical coherence tomography confirmed a well-apposed stent and no struts covering the ostium of the diagonal artery (orange arrows); K: Final result (orange arrow). LCA: Left coronary artery; RCA: Right coronary artery.

edge of the side-branch ostium or misses somewhat the upper edge of the side-branch ostium. Care must also be taken to ensure that the proximal stent balloon marker is not proximal to the guide extension radio-opaque marker during stent implantation to avoid inadvertent “trapping” of the guide extension.

In addition, the use of guide extensions is associated with complications such as proximal dissection due to deep intubation, air embolism due to insufficient de-airing, and ischemia, which may limit the length of time that the equipment can be kept in place.

Finally, other guide extension catheters are currently available, including Guidezilla (Boston Scientific), Telescope (Medtronic), and Gudion (IMDS). The technique should be applicable to these platforms even though they were not tested in this reported experience.

## CONCLUSION

A novel guide extension-assisted stenting technique for selected CBLs is described. This technique facilitates stenting only the diseased side branch or distal main segment in non-true bifurcation lesions without compromising the other branches. It may also facilitate precise stenting implantation in the side branch when using two-stent techniques in complex true bifurcation stenoses without leaving excess stent struts at the bifurcation site, which facilitates easier rewiring, balloon re-crossing, and performing final kissing balloon inflation. The technique may potentially reduce the risks of acute and subacute stent thrombosis as well as future in-stent restenosis and is worthy of further investigation.

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## Is branched-chain amino acid nutritional supplementation beneficial or detrimental in heart failure?

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### Abstract

Sarcopenia or cachexia is often complicated in heart failure. Nutritional support, particularly branched-chain amino acid (BCAA) supplementation, is a candidate treatment for improving sarcopenia or cachexia in elderly patients. However, the efficacy of BCAA supplementation in patients with heart failure has not been established, and the issue is comparatively more complex. Indeed, there are conflicting reports on the efficacy of BCAA supplementation. The evidence for including BCAA supplementation in treating patients with heart failure was reviewed, and the complexity of the issue was discussed.

**Key Words:** Branched-chain amino acid; Heart failure; Sarcopenia; Cachexia; Nutrition; Branched-chain a-ketoacids

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**Core Tip:** The pros and cons of branched-chain amino acid (BCAA) supplementation can vary depending on the patient and their specific conditions. Particularly, BCAA supplementation for patients with cardiac dysfunction, who could easily be presumed to have metabolic dysfunction, should be carefully considered.

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## INTRODUCTION

Sarcopenia or cachexia is often complicated in heart failure, which aggravates the clinical course of the disease. Sarcopenia and cachexia were reported to be present in approximately 20% of patients with heart failure; however, there were differences in their percentages among different studies[1]. Also, both of them sometimes coexist in approximately 10% of patients with heart failure[2]. Low physical performance and reduced cardiopulmonary capacity influence sarcopenia and cachexia[3]. These comorbidities are independent predictors of the clinical course of patients with heart failure[4]. Therefore, the therapeutic strategy for sarcopenia or cachexia is a critical issue in managing heart failure. However, there is no standard management strategy at this time.

Nutritional support might be one candidate treatment for the improvement of sarcopenia or cachexia. Amino acid supplementation was effective for sarcopenia in elderly patients. Rondanelli *et al*[5] demonstrated nutritional supplementation with whey protein, essential amino acids, and vitamin D for twelve weeks, significantly increasing fat-free mass and muscle strength. Among several amino acid supplementation types, branched-chain amino acids (BCAAs) were beneficial in forming skeletal muscles because they account for a large part of the essential amino acids that form these skeletal muscles[6]. Ottestad *et al*[7] reported that BCAA levels decreased by 10% in sarcopenic adults, whereas nonessential amino acid levels did not change, suggesting the importance of BCAAs in skeletal muscle maintenance.

## BENEFICIAL EFFECT OF BCAA IN PATIENTS WITH HEART FAILURE

Several reports about BCAA's effect on cardiopulmonary performance in other populations exist (Table 1). Chang *et al*[8] demonstrated that BCAA and arginine supplementation improved performance in intermittent sprints by reducing perceived exertion. Other reports on experimental and clinical conditions, according to the effect of improvement in exercise capacity by BCAA supplementation, were also presented [9-11]. Additionally, BCAA supplementation also reduced the muscle damage associated with endurance exercise[12]. Therefore, BCAA supplementation might have favorable effects on improving and maintaining exercise capacity, which might help patients with heart failure and reduced exercise capacity. Furthermore, several reports about the efficacy of BCAA supplementation for the improvement of sarcopenia also exist. Ko *et al*[13] demonstrated that BCAA administration for five weeks improved several parameters, including bioelectrical-impedance-analysis-derived skeletal mass index by approximately 10% and grip strength by about 10%. BCAA supplementation before and after exercise has shown beneficial effects in decreasing exercise-induced muscle damage and promoting muscle-protein synthesis[14]. Leucine supplementation also enhances myofibrillar protein synthesis, leading to increased muscle strength[15,16]. These effects could be partly explained by the shift to anabolic signaling of the skeletal muscle through the mammalian target of rapamycin complex 1 pathway[17]. Indeed, the anabolic pathway decreased because of alterations in the insulin-like growth factor 1/growth hormone axis and increased catabolism, induced by proinflammatory cytokines, in the presence of heart failure with sarcopenia[18]. There were several reports of the impact of BCAA on the treatment of sarcopenia.

Nichols *et al*[19] performed a systematic review of the effect of amino acid supplementation in heart failure. They demonstrated that essential amino acid supplementation could improve important outcome measures related to sarcopenia. For instance, amino acid supplementation increased the six-minute walk test distance by approximately 20%. In contrast, few reports demonstrated BCAA efficacy in the improvement of heart failure[20,21]. Oral intake of AAs is presumed to improve exercise capacities through its beneficial effect on the skeletal muscle in patients with heart failure. Furthermore, BCAA treatment decreased the heart rate, preserved cardiac function, and prolonged survival in heart failure with reduced ejection fraction model rats[20]. Uchino *et al*[21] reported that in-hospital heart failure patients with hypoalbuminemia showed increased serum albumin, decreased cardiothoracic ratio (CTR), and increased cholinesterase after BCAA supplementation. Another beneficial effect of BCAA is that it activates rapamycin's mammalian target (mTOR), promoting albumin synthesis[22]. The increase in serum albumin might favorably affect the clinical course of heart failure. The improvement in CTR could be due to decongestion efficiently induced by BCAA administration.

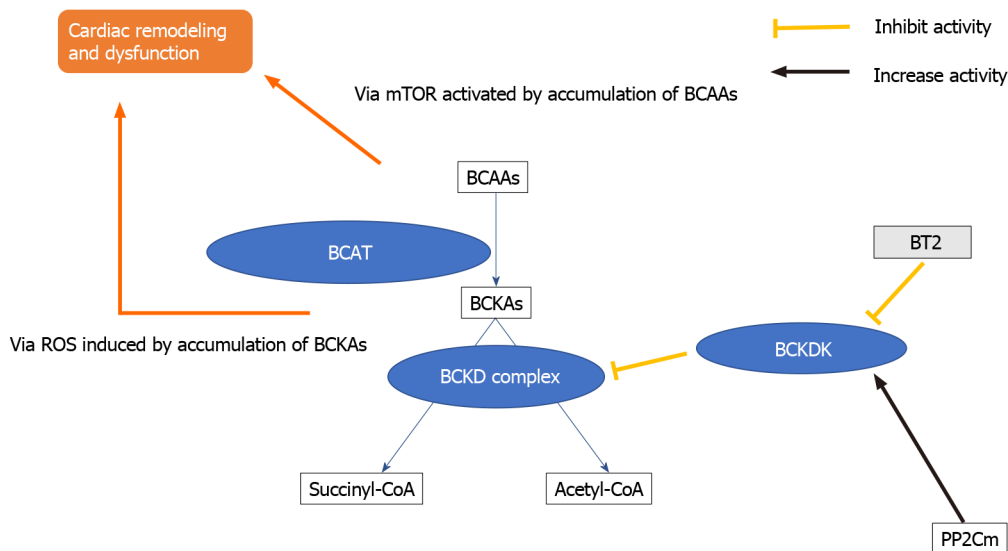
**Table 1 Outcomes of branched-chain amino acid administration in clinical trials**

Ref.	Study design	Sample size	Subjects	Dose	Length	Outcome
Chang <i>et al</i> [8]	Double-blind, randomized	22	Well-trained handball players	0.17 g/kg BCAA and 0.04 g/kg arginine together	1 d	Improve the performance in intermittent sprint
Watson <i>et al</i> [11]	Double-blind, randomized	8	Healthy male	12 g/L BCAA	Every 15 mins during exercise	Exercise capacity change observed between subjects in response to BCAA ingestion
Coombes and McNaughton [12]	Prospective, assigned to one of two groups	16	Males	12 g/d BCAA	14 d	Supplementary BCAA decreased serum concentrations of the intramuscular enzymes
Ko <i>et al</i> [13]	Quasi-experimental single-arm intervention	33	Middle-aged and elderly	Leucine 0.54 g, isoleucine 0.43 g, valine 0.36 g, glutamine 0.65 g, arginine 0.61 g and other amino acids 1.01 g	Twice daily for 5 wk	Short-term positive effects on sarcopenic parameters
Komar <i>et al</i> [15]	Systematic review and meta-analysis	999	-	Each reference	Each reference	Beneficial effects on body weight, body mass index, and lean body mass in older persons
Murphy <i>et al</i> [16]	Randomized, single-blind, parallel-group, placebo-controlled crossover study	20	Men, 65-85 yr of age, BMI (in kg/m <sup>2</sup> ) from 20 to 35, nonsmokers, and generally healthy	Higher protein intake group (1.2 g/kg/d) or lower protein intake group (0.8 g/kg/d)	9 d	Enhances the anabolic effect of resistance exercise
Glynn <i>et al</i> [17]	Prospective	14	Young participants (6 men, 8 women)	10 g essential amino acids	180 min post ingestion	Induce a maximal skeletal muscle protein anabolic response
Nichols <i>et al</i> [19]	Systematic review and meta-analysis	167	-	Each reference	Each reference	Increase lean body mass and 6-minute walk test distance in patients with heart failure
Uchino <i>et al</i> [21]	Randomized, controlled trial	18	In-hospital heart failure patients with serum albumin < 3.5 g/dL	One pack of BCAA granules containing 1144 mg of l-valine, 1904 mg of l-leucine, and 952 mg of l-isoleucine	28 d, 3 time a day	Increased serum albumin and decreased ctr in-hospital hf patients with hypoalbuminemia

BCAA: Branched-chain amino acid.

## DETRIMENTAL EFFECT OF BCAA IN PATIENTS WITH HEART FAILURE

A clinical trial on the efficacy of BCAA supplementation in cardiac rehabilitation was conducted[23]. However, the issue might be more complex. Conversely, there are reports of BCAA's pathological role in heart failure. In clinical studies, several reports about the link between the high level of circulating BCAA and the risk of cardiovascular diseases, including heart failure, are present[24-27]. For instance, in the study of type 2 diabetes patients free of cardiovascular and renal diseases, patients with incident heart failure had 5.6% higher serum BCAAs than those without heart failure (HF). Serum BCAAs had a positive linear association with incident HF, adjusting for age, sex, and duration of diabetes. They demonstrated that high levels of BCAA corresponded to the increased event risk of atherosclerotic diseases and heart failure. Recent studies reported that BCAA catabolism is impaired in a failing heart, downregulating catabolic enzyme expression[28,29]. This catabolic derangement increases the levels of BCAAs and branched-chain  $\alpha$ -ketoacids (BCKAs), which reportedly have a direct effect on cardiac remodeling and dysfunction through mTOR activation and reactive oxygen production (Figure 1)[30]. In basic experiments, incubation with BCKAs led to decreased cell survival and increased apoptosis in primary cardiomyocytes[31]. Moreover, increased BCAA concentration in the heart was shown to suppress glucose metabolism, enhancing ischemia-reperfusion injury by enhancing the GCN2/ATF6/PPAR- $\alpha$  pathway[32]. BCKA dehydrogenase (BCKD) activity, a critical step in BCAA catabolism, is regulated by the phosphorylation of regulatory subunit E1 $\alpha$ . BCKD kinase (BCKDK) phosphorylates E1 $\alpha$  to inhibit BCKA dehydrogenase activity, increasing BCKDK expression in defective hearts[33]. From these findings, the additional increase of BCAA through BCAA supplementation might exacerbate BCAA



**Figure 1 Branched-chain amino acid and its catabolic pathway in patients with heart failure.** Branched-chain amino acid (BCAA) are degraded into their final products of acetyl-CoA and succinyl-CoA, however the decrease of branched-chain keto acid (BCKA) dehydrogenase leads to the increase of BCKA. The increases of BCAAs and BCKAs potentially exacerbate heart failure. mTOR: Mammalian target of rapamycin; BCAA: Branched-chain amino acid; BCKA: Branched-chain keto acid; BCAT: Branched chain aminotransferase; ROS: Reactive oxygen species; BCKD: Branched-chain keto acid dehydrogenase; BCKDK: Branched-chain keto acid dehydrogenase kinase; BT2: 3,6-dichlorobenzo[b]thiophene-2-carboxylic acid; PP2Cm: Protein phosphatase 2C in mitochondria.

metabolites' burden in a failed heart, worsening the clinical course further in heart failure.

By contrast, some hopeful hints about the BCAA metabolic pathway in heart failure therapy might exist. In BCKDK regulation, 3,6-dichlorobenzo[b]thiophene-2-carboxylic acid (BT2), a small-molecule BCKDK inhibitor, blocks BCKD phosphorylation, leading to increased BCAA catabolism[34]. Moreover, BT2 might alleviate oxidative stress by reducing BCKA or mTOR complex 1 activity by lowering BCAA concentrations, thereby improving cardiac function[35]. A study of BT2 administration to mice suggested that BT2 treatment improved cardiac function and led to remodeling without apparent toxicity[34].

The transcriptional factor Kruppel-like factor 15 (KLF15) also has a critical role in cardiac BCAA catabolic regulation[28]. KLF15-deficient hearts displayed reduced BCAT2 expression, another critical step in BCAA catabolism, whereas intramyocardial BCKA levels were elevated in KLF15-null hearts. KLF15 is reportedly a direct transcriptional activator of BCAT2[36]. KLF15 expression is lower in human cardiomyopathy. Therefore, the loss of KLF15 is a critical molecular mechanism underlying stress-induced BCAA catabolic defects in the diseased heart[37,38]. The modification of the KLF15 pathway could help the diseased heart in the BCAA metabolic pathway; however, its overexpression evoked arrhythmia due to its regulatory role in the potassium channel[39].

Additionally, the mitochondrial matrix-targeted 2C-type ser/thr protein phosphatase 2C family member (PP2Cm) is the endogenous phosphatase of the BCKD and functions as a key regulator of BCAA catabolism and homeostasis. The PP2Cm expression in the heart is dynamically regulated in the failing heart[40]. A study on PP2Cm-deficient mice revealed that PP2Cm deficiency led to heart failure signs, including weight gain, reduced left ventricular ejection fraction (LVEF), and chamber dilation[30]. The study findings suggested the impact of BCAA metabolism on the pathogenesis of heart failure. Furthermore, BT2 overturned the dysfunction induced in PP2Cm-knockout mice, significantly preserved LVEF, and reduced chamber dilation. The efficacy of BT2 treatment for the reinforcement of the BCAA metabolic pathway might be more than expected for the dysfunctional heart[41]. These basic findings would present some hints for treating heart failure, which is associated with the BCAA pathway.

## CONCLUSION

Studies have shown that BCAAs are beneficial in heart failure. Conversely, BCAAs

could act as exacerbators of heart failure. Nevertheless, improving BCAA metabolism might lead to an effective treatment strategy for the disease. In conclusion, the pros and cons of BCAA supplementation could vary depending on the patient and their specific conditions. Particularly, BCAA supplementation for patients with cardiac dysfunction, who could easily be presumed to have metabolic dysfunction, should be carefully considered.

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## Cardiogenic shock in the setting of acute myocardial infarction: Another area of sex disparity?

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### Abstract

Cardiogenic shock in the setting of acute myocardial infarction (AMI) carries significant morbidity and mortality, despite advances in pharmacological, mechanical and reperfusion therapies. Studies suggest that there is evidence of sex disparities in the risk profile, management, and outcomes of cardiogenic shock complicating AMI. Compared with men, women tend to have more comorbidities, greater variability in symptom presentation and are less likely to receive timely revascularization and mechanical circulatory support. These factors might explain why women tend to have worse outcomes. In this review, we highlight sex-based differences in the prevalence, management, and outcomes of cardiogenic shock due to AMI, and discuss potential ways to mitigate them.

**Key Words:** Cardiogenic shock; Myocardial infarction; Sex; Morbidity

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**Core Tip:** Sex disparities exist among different cardiovascular diseases and therapies. Cardiogenic shock is a leading cause of death among patients with acute myocardial infarction. Although some studies suggest that cardiogenic shock is more prevalent among women, women are less likely to receive guideline-recommended management including revascularization, which might explain why are more likely to experience worse outcomes.

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## INTRODUCTION

Acute myocardial infarction (AMI) is the one of the leading causes of death in the United States and worldwide[1]. In recent years, there has been a decline in the incidence and case fatality of AMI, which is partly attributed to the advancements in management including timely reperfusion and medical therapies[2,3]. Despite these improvements, sex disparity still has an impact on AMI management and outcomes[3].

Cardiogenic shock is the most common cause of death in patients with AMI, resulting from left ventricular pump failure or as a consequence of post-MI mechanical complications such as papillary muscle rupture, ventricular septal rupture, free wall rupture or right ventricular failure[4,5]. Cardiogenic shock affects 5%-10% of AMI cases and is associated with high mortality (up to 30%-40%), despite advances in pharmacological, mechanical and reperfusion endeavors[6,7]. Similar to AMI without cardiogenic shock, sex differences exist in management and outcomes among those with cardiogenic shock[8]. In this review, we discuss the sex disparities in the risk profile, management, and outcomes of cardiogenic shock in the setting of AMI, and present few solutions to the existing challenges.

## SEX DISPARITY IN AMI

Women with AMI tend to have a higher cardiovascular risk profile on presentation, as they are likely older and have a higher prevalence of traditional cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, and obesity, compared with men[9,10]. Women also have greater variability in symptom presentation, since they often present with fatigue, dyspnea, dizziness, nausea, and upper back pain, while men usually complain of chest pain and diaphoresis[11]. This difference in presentation partly explains why the diagnosis of AMI is sometimes delayed or missed among women[12]. Women are also less likely to receive guideline-directed medical therapies or undergo timely pharmacological and mechanical reperfusion, as well as other invasive procedures[10,13]. Consequently, women are at a higher risk of AMI-related complications including cardiogenic shock and have a higher unadjusted mortality[10]. Indeed, some studies have indicated that female sex does not confer an additional risk of mortality after accounting for the differences in revascularization [14].

## SEX DIFFERENCES IN THE PREVALENCE AND PRESENTATION

Some studies have suggested that cardiogenic shock in the setting of AMI occurs more frequently among women[9,15,16]. For example, data from the French Registry of acute ST-elevation or non-ST-elevation myocardial infarction (FAST-MI), that included > 10000 patients between 1995 and 2010, showed that the rate of cardiogenic shock was significantly higher among women compared with men (8.2% *vs* 4.8%;  $P < 0.001$ )[9]. Female sex was independently associated with an increased risk of developing cardiogenic shock after adjusting for age, type of AMI, and other baseline characteristics [odds ratio (OR) 1.20, 95% confidence interval (CI): 1.00-1.45][9]. Data from a prospective registry in Germany, The Maximal Individual Therapy of Acute Myocardial Infarction PLUS registry, that included 36643 patients with ST elevation myocardial infarction also showed that women are more likely to develop cardiogenic shock (12.9% *vs* 9.3%;  $P < 0.001$ ), even after adjusting for other confounding variables (OR 1.19, 95% CI: 1.09-1.30)[15]. Another study that examined 9750 patients with cardiogenic shock in the setting of AMI between 1992 and 2008 from the Ontario Myocardial Infarction Database revealed that the rate of cardiogenic shock was also higher among women (3.7% *vs* 2.7%;  $P < 0.001$ )[16].

Similar to AMI without cardiogenic shock, women with cardiogenic shock tend to have a higher cardiovascular risk profile than men. Women usually have a higher comorbidity burden including hypertension, diabetes, hyperlipidemia, and metabolic syndrome[9,16]. Women are less likely to have a history of prior MI, percutaneous coronary intervention (PCI) or coronary artery bypass graft[15]. These findings have

also been observed even among younger patients. An analysis of the National Inpatient Sample (NIS) (the largest inpatient administrative database in the United States) of AMI complicated by cardiogenic shock admissions aged 18-55 years, between 2000 to 2017, found that younger women also tend to have higher burden of comorbidities[17]. **Table 1** summarizes the studies comparing the prevalence and risk profile between women and men.

## SEX DISPARITY IN MANAGEMENT

Timely reperfusion remains the cornerstone in the management of AMI complicated by cardiogenic shock[18]. Studies examining AMI complicated by cardiogenic shock reveal that significant sex-based differences still exist. In an analysis of the NIS database, including > 134000 older ( $\geq 75$  years) patients who were hospitalized between 2000 and 2014, women were less likely to undergo coronary angiography (55.4% *vs* 49.2%;  $P < 0.001$ ), PCI (36.3% *vs* 34.4%;  $P < 0.001$ ), and receive mechanical circulatory support devices (34.3% *vs* 27.2%;  $P < 0.001$ ) compared with men[8]. Similar results were reflected in another NIS analysis of younger adults (18-55 years), which showed that women less frequently received coronary angiography (78.3% *vs* 81.4%), early coronary angiography (defined as angiography performed on the day of admission) (49.2% *vs* 54.1%), PCI (59.2% *vs* 64.0%), and mechanical circulatory support devices (50.3% *vs* 59.2%; all  $P < 0.001$ ) compared with younger men[17]. The Canadian-based Ontario Myocardial Infarction Database also showed that women were less likely to be revascularized (12.6% *vs* 17.6%;  $P < 0.001$ ) and less likely to be transferred when they presented to non-revascularization sites (11.3% *vs* 14.2%;  $P < 0.001$ )[16].

Notably, some sex disparities were observed in randomized trials of interventions for patients with cardiogenic shock in the setting of AMI. An exploratory analysis of the Should we emergently revascularize occluded coronaries for cardiogenic shock? (SHOCK) trial of 1190 patients showed that although the rates of thrombolytic treatment, PCI and surgical revascularization were not different between both sexes, intra-aortic balloon pump (IABP) use was less frequent among women (48% *vs* 55%;  $P = 0.05$ ), despite exhibiting lower cardiac index[19]. In another trial, Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) that included 600 patients undergoing early revascularization with or without IABP, although there was no evidence of interaction for IABP treatment based on sex, women were less likely to have undergone resuscitation before randomization[20]. Lastly, a secondary analysis of the CULPRIT SHOCK trial (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) showed that although the use of mechanical circulatory support was not different between women and men, women were less likely to receive therapeutic hypothermia[21]. **Table 2** depicts the differences in in-hospital procedures between women and men.

## SEX DISPARITY IN OUTCOMES

Many studies have indicated that women have higher unadjusted mortality rates compared with men, primarily explained by older age, higher co-morbidity burden and lower likelihood of receiving reperfusion therapy and mechanical circulatory support devices. Data from the NIS database for older patients ( $\geq 75$  years) revealed that despite a steady decrease in in-hospital mortality during the study period between 2000 and 2014, adjusted trends showed consistently higher in-hospital mortality among women compared with men[8]. Female sex remained an independent predictor of higher in-hospital mortality (adjusted OR 1.05; 95%CI: 1.02-1.08;  $P < 0.001$ ) [8]. Similarly, NIS data for younger patients (18-55 years) also showed that women experienced higher hospital mortality, and that female sex was an independent predictor of in-hospital mortality (adjusted OR 1.11, 95%CI: 1.07-1.16;  $P < 0.001$ )[17] (**Figure 1**). The timely use of reperfusion strategies could potentially improve survival among women. For example, data from the French FAST-MI registry showed that although 1-year mortality was significantly decreased for both men and women due to primary PCI, primary PCI was an independent predictor of 1-year survival among women (hazard ratio [HR] 0.55, 95%CI: 0.37-0.81), but not men (HR 0.85, 95%CI: 0.61-1.19)[9]. Although these studies showed that women were less likely to receive reperfusion therapy and mechanical circulatory support devices, data about the angiographic findings and other clinical variables were not available in these studies.

**Table 1 Sex differences in the prevalence and risk profile**

Ref.	Country	Prevalence of cardiogenic shock (%)		Mean age, yr		Hypertension (%)		Diabetes (%)		Prior myocardial infarction (%)		Prior percutaneous coronary intervention (%)		Smoking (%)	
		Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Isorni <i>et al</i> [9]	France	4.8	8.2	68.9	80.2	57	80	31	44	21	18.5	21	13	25	7
Koeth <i>et al</i> [15]	Germany	9.3	12.9	68	76.3	37	45.3	25.2	39.1	25.6	19.9	13.2	6.7	36	17.9
Abdel-Qadir <i>et al</i> [16]	Canada	2.7	3.7	71.1	75.5	NA	NA	24.4	26.9	NA	NA	NA	NA	NA	NA
Vallabhajosyula <i>et al</i> [8]	United States	NA	NA	82	83.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Vallabhajosyula <i>et al</i> [17]	United States	NA	NA	48.8	48.3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Wong <i>et al</i> [19]	United States, Canada	NA	NA	66.8	71.4	45.6	62.1	28.3	40.8	44.7	32	7.6	5.1	57.5	40.7
Fengler <i>et al</i> [20]	Germany	NA	NA	68	74	66	76	29	40	25	16	31	15	39	25
Gimenez <i>et al</i> [21]	Switzerland, Germany, Poland, Austria, France, Italy	NA	NA	67	75	58.3	66.7	30.3	39.4	18.5	11.3	20.2	14.4	29	18.1

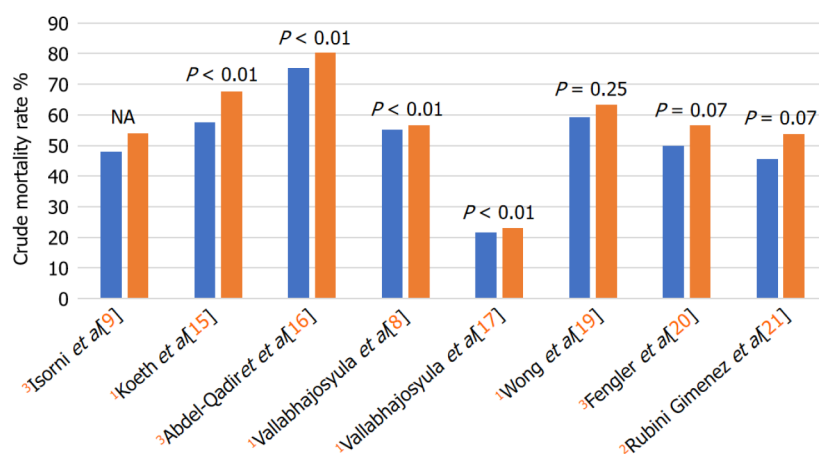
NA: Not available.

**Table 2 Sex differences in in-hospital procedures**

Studies	Percutaneous coronary intervention (%)		Coronary artery bypass graft (%)		Mechanical circulatory support (%)	
	Men	Women	Men	Women	Men	Women
Isorni <i>et al</i> [9]	76.5	68.5	NA	NA	NA	NA
Koeth <i>et al</i> [15]	18	11	NA	NA	NA	NA
Abdel-Qadir <i>et al</i> [16]	14	10.6	4.3	2.3	NA	NA
Vallabhajosyula <i>et al</i> [8]	36.3	34.4	12	8.1	34.3	27.2
Vallabhajosyula <i>et al</i> [17]	64	59.2	20.1	18.3	59.2	50.3
Wong <i>et al</i> [19]	31.1	35.4	17.3	12.1	55.2	48.1
Fengler <i>et al</i> [20]	96.6	94.1	0.7	1.6	52	48
Gimenez <i>et al</i> [21]	100	100	-	-	28.6	27.2

NA: Not available.

Secondary analyses of randomized trials of cardiogenic shock in the setting of AMI have also suggested that there was no difference in treatment effect based on sex[19-21]. As such, these findings support the notion that women should be treated similar to men (*i.e.* timely reperfusion, and consideration of mechanical circulatory support devices if indicated). Noteworthy, despite the higher prevalence of cardiogenic shock among women in many studies, women have consistently been underrepresented in these interventional trials. While women in the SHOCK and IABP-SHOCK-II trials comprised 32% and 31% of the participants, respectively, women constituted only 24% of the study population in the CULPRIT SHOCK trial that was conducted about 2 decades later.



**Figure 1 Studies showing crude mortality rates among women vs men.** <sup>1</sup>In-hospital mortality; <sup>2</sup>30-d mortality; <sup>3</sup>1-year mortality. NA: Not available.

## CHALLENGES AND POTENTIAL SOLUTIONS

Sex-based differences exist in the clinical presentation of AMI and might subsequently result in treatment delays. Women often present late and with non-classical symptoms of AMI and thus are often misdiagnosed resulting in delays in care, and potentially preventable adverse outcomes. This highlights the importance of using objective measures of risk stratification among patients with suspected AMI. Minimizing provider bias together with focusing on educating women at risk about the symptoms of AMI warrant priority.

With regards to clinical trials pertinent to cardiogenic shock in the setting of AMI, women continue to be underrepresented despite a higher incidence of cardiogenic shock among women in many studies. Clinical trials form the foundation for guidelines that shape our clinical practice, and the underrepresentation of women can result in some important information deficits with regards to management and outcomes. Well-designed clinical research studies with adequate women representation will ensure unbiased and reliable findings to guide clinical decision. An adequate representative sample is necessary for sex-based comparative analysis of the interventional strategy/therapy, as well as the outcomes. In this regard, there is a need to examine the role of sex-based differences in socioeconomic, logistic and enrollment barriers that might impede a proportionate representation of women[22].

## CLINICAL IMPLICATIONS AND CLINICAL PRACTICE

Women, despite having higher comorbidity and varied symptom manifestation, derive similar benefit with guideline-directed management as men. This important message needs to be translated into action and reflected in our clinical practice, where unfortunately women are seen more often to be misdiagnosed and undertreated than men, resulting in worse outcomes. In the real world, there is a need to identify and address individual-based and system-based factors that trigger unconscious biases and impede the provision of high-quality and equitable healthcare irrespective of the sex differences. Since women with AMI have a higher cardiovascular risk profile and sometimes delayed presentations than men, clinicians are encouraged to keep a lower threshold for initiating work-up for diagnosis, and institute prompt delivery of care and employ aggressive treatment strategies when indicated.

In the meantime, there is a need to increase awareness among women to identify symptoms, and to seek immediate care. It is essential to emphasize both primary and secondary preventative strategies that are appropriate for women from numerous backgrounds, and could be applicable in various clinical settings. The foremost step towards personalized medicine involves paying attention to sex-specific details and recognizing sex-disparity in the clinical settings, which will help improve awareness, diagnosis, treatment and eventually outcomes in women.

## CONCLUSION

Cardiogenic shock is the leading cause of death among AMI patients. Sex disparity in the management and outcomes of patients with cardiogenic shock in the setting of AMI exist. Although some studies indicate that cardiogenic shock occurs more frequently among women, women do not receive adequate management as evidenced by the lower rates compared of revascularization and mechanical circulatory support devices. Given these differences, women continue to experience worse outcomes. Future studies are needed to understand the reasons behind these differences and efforts are needed to minimize these disparities.

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## Novel economic treatment for coronary wire perforation: A case report

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### Abstract

#### BACKGROUND

Coronary artery perforation is a rare but potentially life-threatening complication of percutaneous coronary intervention (PCI), however if recognized and managed promptly, its adverse consequences can be minimized. Risk factors include the use of advanced PCI technique (such as atherectomy and chronic total occlusion interventions) and treatment of severely calcified lesions. Large vessel perforation is usually treated with implantation of a covered stent, whereas distal and collateral vessel perforations are usually treated with embolization of coils, fat, thrombin, or collagen. We describe a novel and cost-effective method of embolisation using a cut remnant of a used angioplasty balloon that was successful in sealing a distal wire perforation. we advocate this method as a simple method of managing distal vessel perforation.

#### CASE SUMMARY

A 73-year-old male with previous coronary Bypass graft operation and recurrent angina on minimal exertion had undergone rotablation and PCI to his dominant left circumflex. At the end of the procedure there was evidence of wire perforation at the distal branch and despite prolonged balloon tamponade there continued to

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be extravasation and the decision was made to seal this perforation. A cut piece of an angioplasty balloon was used and delivered on the original angioplasty wire to before the perforation area and released which resulted in sealing of the perforation with no unwanted clinical consequences.

## CONCLUSION

The use of a balloon remnant for embolization in coronary perforation presents a simple, efficient and cost-effective method for managing coronary perforations and may be an alternative for achieving hemostasis and preventing poor outcome. Prevention remains the most important part with meticulous attention to the distal wire position, particularly with hydrophilic wires.

**Key Words:** Percutaneous coronary intervention; Coronary perforation; Coronary guide wire; Collagen; Coronary angioplasty balloon; Coil; Case report

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**Core Tip:** The use of a remnant balloon for sealing a coronary perforation can be a cost-effective method of treating this complication using a readily available material. In cases where the sealing of the perforation is indicated, a careful and controlled approach for delivering the balloon remnant will ensure the safe and effective delivery and the sealing of the perforation which in turn will help stabilize and safe the patient by controlling any further bleeding.

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## INTRODUCTION

The use of a balloon remnant for embolization in coronary perforation presents a simple, efficient and cost-effective method for managing coronary perforations and may be an alternative for achieving hemostasis and preventing poor outcome. Prevention remains the most important part with meticulous attention to the distal wire position, particularly with hydrophilic wires.

## CASE PRESENTATION

### Chief complaints

A 73-year-old male presented with recurrent angina on minimal exertion with poor functional capacity despite optimal medical treatment.

### History of present illness

He suffered with recurrent angina for 3 mo before the procedure.

### History of past illness

He has a history of previous coronary artery bypass grafting 16 years earlier, bronchiectasis, chronic kidney disease, Barrett's esophagus and hypertension.

### Personal and family history

No family history of ischemic heart disease.

### Physical examination

Within normal limits.

**Laboratory examinations**

Blood tests were normal.

**Imaging examinations**

Echocardiogram showed normal left ventricular function. He underwent coronary angiography which showed patent left internal mammary artery graft to left anterior descending artery (LAD), patent saphenous vein graft to right coronary artery (RCA), occluded LAD and RCA, severe long and calcific lesion in proximal to mid co-dominant left circumflex artery (LCX) with no visualized patent graft.

**FINAL DIAGNOSIS**

The final diagnosis of the presented case is distal wire coronary artery perforation sealed with an embolized cut angioplasty balloon.

**TREATMENT**

The procedure was performed from the right radial artery with planned rotablation. The proximal LCX was wired with a Gladius wire to the distal left posterior descending artery (LPDA) (Figure 1A). A Turnpike microcatheter was advanced over the Gladius wire and the wire exchanged for an extra-support rotablation wire. Rotablation was then performed with 1.25 mm then 1.75 mm burrs then a Sion black introduced with subsequent predilatation with 3.5 mm non-compliant balloon (Figure 1B). Following on a synergy drug eluting stent (DES) 4.0 mm × 24 mm was deployed and post dilated with 4.5 mm non-compliant balloon with excellent results (Figure 1C).

There was evidence of contrast staining and extravasation distally in the LPDA territory which appeared as a wire perforation. There was no evidence of hemodynamic compromise. In addition, there was dissection in the obtuse marginal (OM) branch.

A prolonged inflation of 2.0 mm balloon distally just before the site of perforation failed to stop the extravasation. Echocardiogram showed no evidence of tamponade.

At this stage, coil delivery was planned however and instead of delivering a coil, the operator thought that any compatible particle that can be delivered and block the distal artery should be helpful. The distal tip of the already used 2.0 mm balloon was cut (Figure 1D) and mounted on to the wire in the LPDA and then pushed with another intact balloon to the distal LPDA (Figure 1E) just before the perforation area then the wire and the pushing balloon were removed. There was no evidence of any further increase in the contrast staining. The OM branch was treated with 2 DES with excellent final angiographic results.

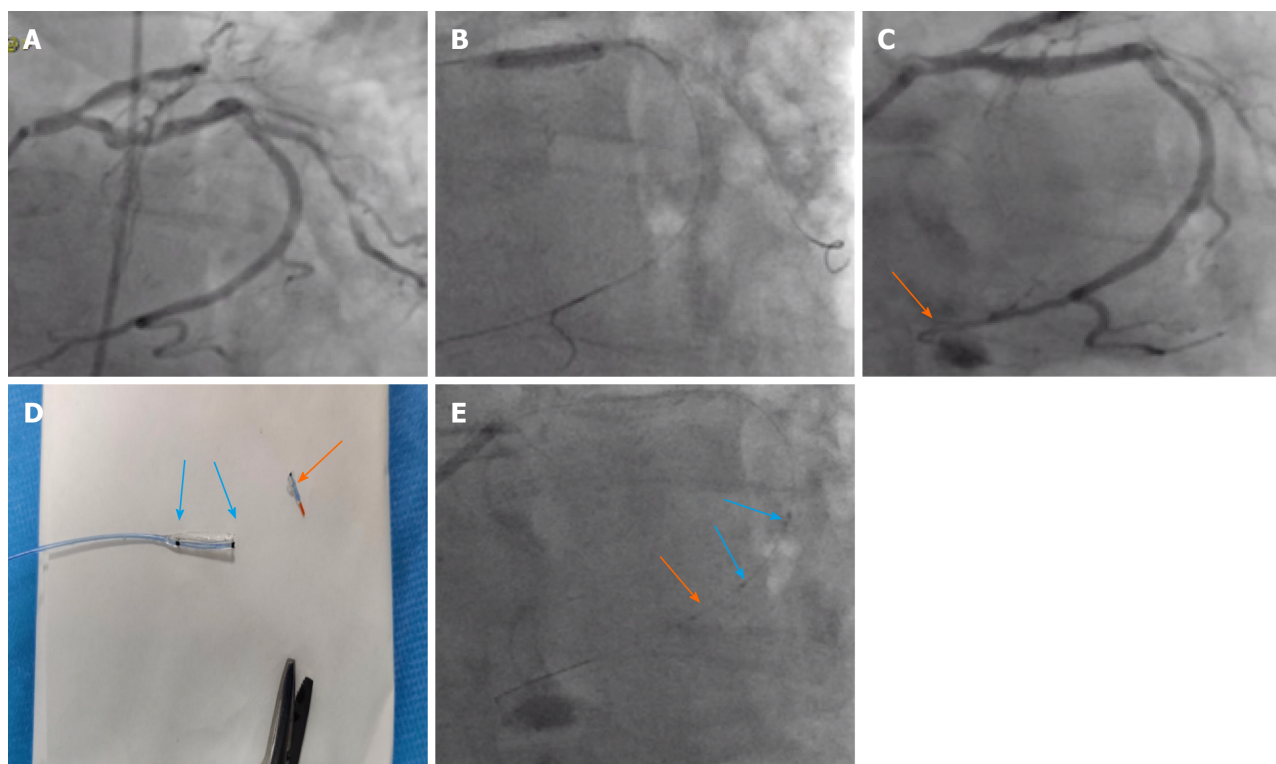
**OUTCOME AND FOLLOW-UP**

The patient had an uneventful postoperative clinical course and he was allowed home in a stable condition. He was doing well and asymptomatic on follow up 3 mo later.

**DISCUSSION**

Coronary perforations (large, distal, and collateral vessels) remain relatively rare<sup>[1,2]</sup>, but have potentially increased with the higher use of adjunctive devices in calcified lesions<sup>[3-6]</sup>. Immediate recognition and rapid action will help prevent potential catastrophic outcome<sup>[3,7]</sup>. The balloon part, as was used in this case, is readily available and would substitute expensive equipment, and requires no specific expertise.

Rapid and clear management algorithms should be adopted. The first step is balloon tamponade with a 1/1 ratio for 5-10 min proximal or at the site of perforation. Repeated 5-10 min balloon inflation can be done till either successful sealing of the perforation or evidence of significant ischemia. Intravenous fluids and vasopressor may be needed and beneficial on occasions. Echocardiogram is important to rule out



**Figure 1 The proximal left circumflex artery.** A: Calcific proximal dominant left circumflex artery (LCX) lesion; B: Distal wire position when predilatation; C: Distal wire perforation in the LCX (orange arrow); D: Tip of the balloon cut for embolization; E: The cut balloon tip with the marker for X-Ray visibility (orange arrow) pushed by another intact balloon with two markers (blue arrows).

cardiac tamponade where pericardiocentesis should be performed immediately. X-Ray Fluoroscopy can show pericardial collection as the dye escapes into the pericardium. In our experience, pericardiocentesis can be performed under fluoroscopy using the pericardial dye collection as a guide without the use of echocardiography.

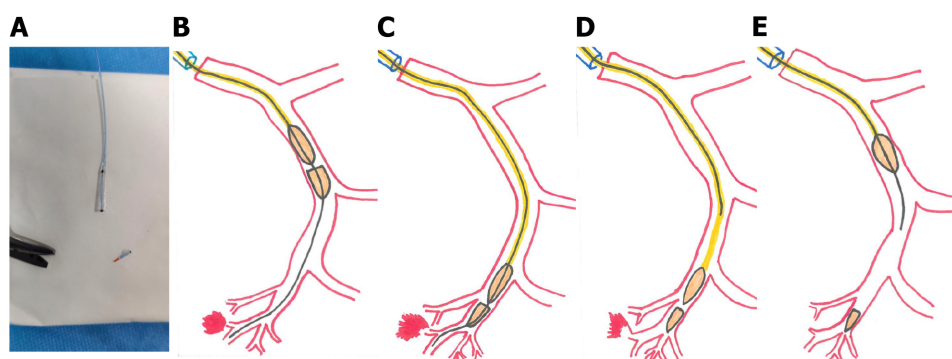
Furthermore, follow up echo is crucial especially in wire induced perforation as delayed pericardial effusion can occur hours later.

A crucial aspect of this complication is anticoagulation reversal which seems to be put forward as a first step approach. Perforation is a mechanical problem and reversal of anticoagulation will not solve it. It is not recommended to reverse anticoagulation as a first approach and should only be considered once the perforation is sealed and equipment removed from the coronary arteries. This is important to avoid any intracoronary thrombosis. The reversal is usually accomplished by protamine sulphate and occasionally with platelets transfusion[6].

More specific treatment lines may be needed if the previous measures were unsuccessful. In large vessel perforation, covered stents or occasionally even surgery may be needed[8]. Due to their bulkiness, deployment of covered stent may be difficult or may fail in tortuous and small vessels. In addition, these covered stents can also be used in the management of distal perforation by deployment across the side branch ostium. In distal vessel perforation, embolization or deployment of a covered stent across the ostium of the perforated branch to occlude it from the origin can be used[9].

Distal embolization can be done by different materials such as subcutaneous fat, thrombin and coils[5]. In addition, less commonly methods have been used such as injection of fibrin or synthetic glue through the lumen of microcatheter or an over-the-wire balloon[10]. Embolization of collagen, which is available commercially in femoral occlusion angioseal devices, can be used to occlude distal perforation[11]. Injection of polyvinyl alcohol particles through the lumen of inflated over the wire balloon has also been used to seal distal vessel perforation. Furthermore, injection of autologous blood clot or autologous subcutaneous fat particles through the micro catheter can occlude distal perforation.

The mechanism by which embolic material stop the bleeding is by the formation of artificial clot which trigger more clotting and occlude the vessel. After that, this embolic material will cause a foreign body granuloma which differs in its nature according to the embolized material.



**Figure 2 Schematic steps for sealing distal wire perforation using balloon remnant.** A: Distal half of already used balloon is cut by scissors; B and C: The remnant piece is mounted on to the wire in the perforated vessel and pushed with another intact balloon to the distal vessel before the perforation; D and E: Withdrawal of the wire and the intact pushing balloon with the remnant part left distally as the embolization materials.

In our case, we used part of a PCI balloon that is readily available in all PCI cases. This offers a rapid, simple and cost-effective way for managing coronary perforations.

There are several important points and cautions to be highlighted and considered.

Most wire perforations are self-contained and require no significant treatment. If the decision is made to treat, then this balloon remnant method can be considered.

It can be argued that fat embolization is cheaper and not a foreign material, but it is not as easy or straight forward to use as any other method and particularly this newly described balloon remnant method.

The delivery of the balloon remnant can be perceived as uncontrolled and if there is resistance and inability to deliver it, then it cannot be retrieved. Furthermore, it could also be perceived that this remnant can be advanced too distal and may exit through the perforation and cause more bleeding. This in fact is not the case. (Figure 2) The balloon remnant would be delivered after another normal balloon has passed and has been used and inflated to temporarily block the artery and stop the extravasation. This would indicate that the remnant balloon will pass too. In addition, the anatomy and the site of perforation would be clear to any experienced operator which in turn ensures that the release of the remnant is well before the perforation site itself and will have no chance of exiting through the perforation and making matters worse.

Since this case, we have used this method in a second wire perforation case that needed embolization with sealing of the perforation and excellent outcome. The patient in this case was seen in the outpatient clinic 3 mo later and he was angina free and doing well.

## CONCLUSION

The use of a balloon remnant for embolization in coronary perforation presents a simple, efficient and cost-effective method for managing coronary perforations and may be an alternative for achieving hemostasis and preventing poor outcome. Prevention remains the most important part with meticulous attention to the distal wire position, particularly with hydrophilic wires.

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