



# INTERVENTIONAL CARDIOLOGY PERSPECTIVES

OFFICIAL JOURNAL OF THE SOCIETY OF CARDIOVASCULAR INTERVENTIONS

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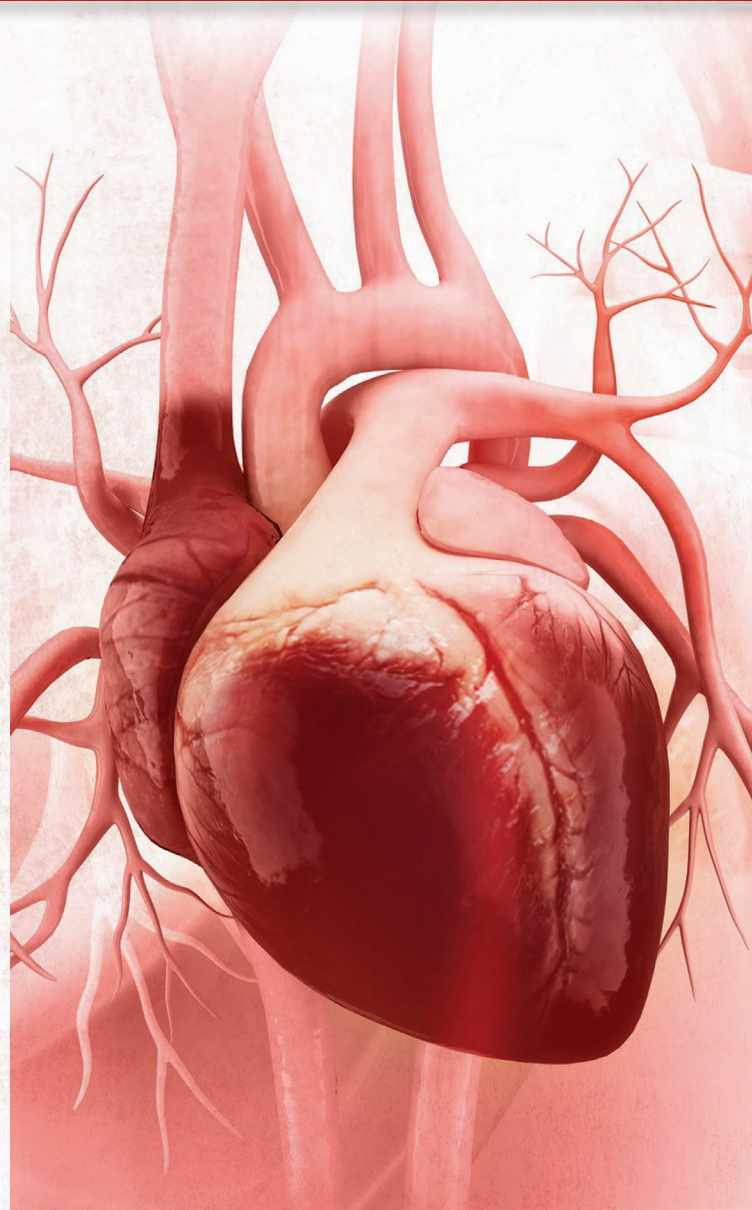
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## EDITORIAL

### Waves of Innovation in a Continuously Evolving Discipline

#### Dear Colleagues,

It is with great enthusiasm that we welcome you to the inaugural issue of *Interventional Cardiology Perspectives*. This journal was not born simply to collect data — it was a place to bring together smart thinking, clinical skills, and new ideas to improve cardiovascular health care.

Interventional cardiology has come a long way. Since the early days of balloon angioplasty, interventional cardiology has grown exponentially. What began with coronary procedures has now evolved to include complex treatments for structural heart disease, peripheral vasculature, congenital defects, and more. The field continues to redefine its own boundaries, not only through procedural innovation but through the progressive transformation of diagnostic paradigms and therapeutic strategies.

Today, transcatheter therapies are transforming how we care for patients with structural heart conditions. Treatments like TAVI, transcatheter mitral and tricuspid repairs, and EVAR are no longer rare or experimental — they are becoming standard approaches for many. The drive toward less invasive, more patient-centered interventions is reshaping the landscape of cardiovascular care.

At the same time, we're entering an era powered by data, technology, and real-world insight. Large datasets, artificial intelligence, and advanced analytics are helping us move beyond traditional clinical trials — offering a clearer view into how patients actually fare in daily practice. Wearable devices and remote monitoring tools are adding a new layer of continuous physiologic feedback, enriching how we manage recovery and long-term outcomes.

At *Interventional Cardiology Perspectives*, our goal is to bring these threads together. We don't just want to publish research — we want to tell the story of modern cardiovascular intervention. We aim to foster thoughtful dialogue, highlight innovation, and present real-world perspectives that resonate with clinicians, researchers, and engineers alike.

#### **Our mission is clear and bold:**

- Share studies that can change the way we care for patients.
- Show cases that teach us how to think better.
- Highlight new tools that push the field forward.
- Encourage new ways of thinking about cardiovascular health care.

From coronary and structural heart disease to imaging, pharmacology, and digital health — we are committed to covering the full spectrum of interventional cardiology. We welcome contributors from all backgrounds — clinicians, scientists, engineers, and data experts — united by a desire to improve patient care through interdisciplinary collaboration.

In a world where science moves faster than practice, *Interventional Cardiology Perspectives* aspires to serve as a bridge — anchoring data within clinical context, aligning technology with therapeutic judgment, and promoting clarity amidst complexity.

This issue is not just the start of a journal — it's the beginning of a community. A global, forward-looking conversation.

To our contributors, thank you for your trust and insight. To our readers, welcome — let's be part of the progress in interventional cardiology together.

Warm regards,

**Harun Kundi, MD, MMSc**

Editor-in-Chief

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## Oncostatin M and Cardiovascular Diseases: A Narrative Review

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### ABSTRACT

Cytokines like oncostatin M (OSM) influence inflammation and immune responses. Interleukin-6 is produced by immune, endothelial, and cardiac cells. OSM plays a role in cardiovascular diseases (CVDs), demonstrating cardioprotective effects by promoting cardiac cell survival and angiogenesis. It may also reduce vascular inflammation and help prevent atherosclerosis, a major risk factor for CVD. However, under certain conditions, OSM contributes to inflammation and tissue damage. It induces inflammatory cytokines, promotes vascular smooth muscle cell migration, and destabilizes atherosclerotic plaques, thereby increasing the likelihood of myocardial infarction or stroke. Elevated OSM levels are linked to worse outcomes in patients with heart failure and pulmonary arterial hypertension. The role of OSM in CVD is complex and context-dependent. Further research is needed to clarify its mechanisms and therapeutic potential. Since CVDs result from a combination of genetic, environmental, and behavioral factors rather than a single cytokine, diagnostic and treatment approaches should adopt a comprehensive clinical perspective.

**Keywords:** Cardiovascular diseases, interleukin-6, oncostatin M, inflammation, atherosclerosis, heart failure, pulmonary arterial hypertension

### INTRODUCTION

Oncostatin M (OSM) is a cytokine involved in inflammation and immune responses. As a member of the interleukin-6 (IL-6) family, it is produced by immune, endothelial, and cardiac cells. OSM is linked to cardiovascular disease (CVD), a group of disorders affecting the heart and blood vessels. Its role in CVD is complex, displaying both protective and harmful effects.<sup>1-5</sup>

OSM activates the IL-6 signaling pathway, which regulates immune responses and tissue homeostasis. Under certain physiological conditions, OSM may be beneficial by reducing pro-inflammatory cytokines and increasing anti-inflammatory mediators, potentially helping to prevent atherosclerosis. It also supports vascular repair by stimulating endothelial cell proliferation and angiogenesis. However, in pathological conditions, OSM can exacerbate inflammation, fibrosis, and tissue damage. In myocardial infarction (MI) and heart failure (HF), OSM accelerates disease progression by enhancing immune cell activation and altering the extracellular matrix. Due to its dual effects, the impact of OSM on CVD depends on several factors, including the duration and severity of inflammation, coexisting health conditions, and the cellular environment.<sup>6</sup>

A temporary increase in OSM levels following injury may support recovery. However, prolonged overexpression of OSM can lead to sustained inflammation and fibrosis, contributing to worse CVD

outcomes. Understanding these mechanisms is crucial for assessing OSM as a potential therapeutic target.<sup>7</sup> This paper aims to provide a comprehensive analysis of both the protective and harmful effects of OSM in CVD, filling the gap left by previous reviews and highlighting its therapeutic potential.

#### Mechanisms of Oncostatin M's Biphasic Effects

OSM exerts both beneficial and adverse effects through different mechanisms, depending on the context.

**Beneficial effects:** OSM supports tissue repair and regeneration by promoting endothelial cell proliferation, angiogenesis, and cardiomyocyte survival. It can also regulate immune cell activity, reducing excessive inflammation by lowering pro-inflammatory cytokine levels. Furthermore, OSM plays a role in extracellular matrix remodeling, aiding tissue recovery after injury.

**Adverse effects:** In pathological conditions, prolonged OSM signaling can drive chronic inflammation, fibrosis, and oxidative stress. It activates immune cells, increasing cytokine production and contributing to tissue damage. In HF and MI, persistent OSM expression leads to maladaptive remodeling, impairing cardiac function. Notably, its involvement in vascular smooth muscle cell migration and extracellular matrix degradation can accelerate the progression and destabilization of atherosclerotic plaques. Understanding the balance between these effects is crucial in

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evaluating whether targeting OSM would be beneficial or detrimental in different types of CVD.<sup>8</sup>

### **Molecular Mechanisms of Oncostatin M**

OSM exerts its effects by interacting with specific signaling pathways and transcription factors. A significant portion of its signaling occurs through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, particularly via STAT3. STAT3 activation influences gene expression related to inflammation, cell survival, and tissue remodeling. While transient activation supports tissue repair, prolonged STAT3 signaling can lead to chronic inflammation and fibrosis. Additionally, OSM activates the mitogen-activated protein kinase and phosphoinositide 3-kinase (PI3K/AKT) pathways, which regulate cellular proliferation, survival, and angiogenesis, contributing to vascular repair.<sup>9</sup>

Disruptions in signaling regulation can contribute to abnormal vascular remodeling and atherosclerosis. The methylation of nuclear factor-kappa B (NF-κB) activates key transcription factors such as NF-κB and hypoxia-inducible factor-1 alpha, leading to increased production of pro-inflammatory cytokines and exacerbating inflammation in CVD. While NF-κB promotes blood vessel growth in low-oxygen conditions, prolonged activation under chronic stress can result in detrimental vascular responses.<sup>10</sup>

### **Coronary Artery Disease**

OSM contributes to atherosclerosis by affecting vascular smooth muscle cells. It interacts with the Yes-associated protein (YAP), linking endplate osteosclerosis to macrophage activity. Patients with CAD who have multiple severe blockages show increased OSM levels, which are associated with coronary artery calcium scores. Additionally, conditions such as obesity and diabetes mellitus (DM) influence OSM production, potentially promoting the formation of calcified plaques.<sup>5-8,10-12</sup>

Shear stress may drive atherosclerotic plaque formation through the YAP-OSM pathway, which could play a role in diabetes-related CVDs. Further research is needed to confirm the clinical significance of YAP in CVD.<sup>13-19</sup>

### **Myocardial Infarction**

OSM levels increase after MI, suggesting a role in post-MI inflammation. It activates immune cells and amplifies inflammation, potentially exacerbating cardiac tissue damage. However, some studies indicate that OSM also supports tissue repair and regeneration. OSM levels peak five days after MI before gradually declining. It may reduce inflammatory monocytes while promoting the presence of resident macrophages that aid in healing. Further research using tissue-specific OSM gene deletion models is needed to confirm these findings.<sup>20-24</sup>

### **Heart Failure**

OSM levels are elevated in HF patients and interact with parathyroid hormone and vitamin D. OSM has both harmful and beneficial effects on the heart. It contributes to inflammation, fibrosis, oxidative stress, and cell apoptosis, all of which worsen HF. However, it also promotes angiogenesis, which may aid in tissue regeneration. Further research is necessary to clarify OSM's role in HF and its potential as a therapeutic target.<sup>25</sup>

### **Ischemic Stroke**

OSM's role in stroke is complex. It can trigger inflammation, leading to increased brain damage, but it may also have neuroprotective effects. OSM supports factors that enhance neuronal survival and promote tissue repair. Its impact likely depends on OSM levels, timing, and biochemical interactions in the brain.

### **Atrial Fibrillation**

OSM may play a role in atrial fibrillation (AF) by influencing inflammation and fibrosis. Chronic inflammation disrupts normal electrical signaling in the heart, increasing the risk of AF. Additionally, OSM promotes fibrosis, which stiffens cardiac tissue and further impairs electrical conduction. However, the exact mechanisms remain unclear and require further investigation.<sup>26</sup>

### **Pulmonary Arterial Hypertension**

OSM may contribute to pulmonary arterial hypertension (PAH) by driving inflammation, fibrosis, and vascular remodeling. It promotes the release of inflammatory mediators and activates immune cells, leading to pulmonary vessel constriction and increased pressure. Fibrosis worsens these effects by making blood vessels more rigid. Further studies are needed to clarify OSM's role in the development and progression of PAH.

### **Recent Studies**

Elevated OSM receptor levels in patients with multiple sclerosis suggest increased OSM signaling.<sup>27</sup> Research on atherosclerosis treatment with OSM should also consider its effects on tissue remodeling, angiogenesis, bleeding, anemia, and NMDA- and glutamate-induced neurotoxicity. Patients with comorbid conditions may require careful monitoring or exclusion to ensure optimal therapy.<sup>28</sup> OSM is implicated in muscular atrophy, bone resorption, fibrosis, and cardiac dysfunction in cancer cachexia.<sup>29</sup> Preoperative plasma OSM levels may help identify infection risks in patients with left ventricular assist devices.<sup>30</sup> Additionally, the dual-sensitive hydrogel approach proposed by Jiang et al.<sup>31</sup> could influence tissue engineering for MI repair and drug delivery.

OSM may influence tissue engineering strategies for MI repair. The OSM receptor gene variant rs1316887 is linked to plaque vulnerability but does not contribute to overall CVD risk.<sup>32</sup> Gajawada et al.<sup>33</sup> found that granuloma formation results from chemoattraction rather than macrophage proliferation. Drug screening targeting the oncostatin/regenerating islet-derived protein 3 (Reg3) axis may have implications for HF.

OSM plays a role in acute intestinal ischemia-reperfusion injury (AIIRI). While OSM receptor deficiency delays lung injury, it increases the risk of renal failure. More OSM receptor-deficient mice succumbed to AIIRI, suggesting that immunomodulation in AIIRI may elevate OSM levels.<sup>34</sup> Insulin resistance (IR) indices, such as QUICKI and HOMA, correlate with OSM and may serve as simpler alternatives to other IR markers.<sup>35</sup> In type 2 DM patients with acute coronary syndrome, measuring Reg3β and OSM levels alongside traditional cardiac markers may aid diagnosis.<sup>36</sup> Stawski and Trojanowska<sup>37</sup> reviewed OSM's role in fibrotic processes, including inflammation, vascular dysfunction, and fibroblast activation. In mice, cholesteryl ester transfer protein reduced

atherosclerosis. Additionally, higher serum OSM levels were associated with improved post-coronary heart disease survival, suggesting a potential cardiovascular benefit.<sup>38</sup>

Setiadi et al.<sup>39</sup> demonstrated that neutrophil-derived OSM directly affects endothelial cell function through paracrine signaling during both normal and pathological inflammation. Han et al.<sup>40</sup> found that in middle cerebral artery occlusion stroke rats, the brain produces OSM and upregulates SDF-1, enhancing the migration of bone marrow-derived mesenchymal stem cells (BMSC). OSM and BMSCs together improve BMSC graft efficacy and neurofunctional recovery. Table 1 summarizes the key findings from recent studies.

## CONCLUSION

OSM regulates inflammation and immune responses, influencing cardiomyocyte viability, angiogenesis, and inflammation in CVD. While it may support cardiac tissue healing and reduce atherosclerosis, it can also intensify inflammation and tissue damage. Elevated OSM levels are linked to worse outcomes in HF and PAH. Its role in CVD is complex and depends on various factors. Further research is needed to clarify its mechanisms and therapeutic potential. Given that CVD results from multiple contributing factors, clinical evaluation and patient-centered care should be prioritized in its management.

**Table 1.** Key findings from recent studies

Authors/reference no.	Subjects	Main theme
Hermans et al. <sup>27</sup>	MS patients	OSM's role in MS pathology. MS patients exhibited increased OSM receptor expression in lymphocytes, suggesting enhanced OSM signaling. OSM production is elevated in MS brain lesions
Rankouhi et al. <sup>28</sup>	Review	The impact of OSM on tissue remodeling, angiogenesis, bleeding, anemia, and NMDA- and glutamate-induced neurotoxicity should be considered in atherosclerosis treatment. Comorbid patients may require careful monitoring or exclusion for optimal therapy
Jengelley et al. <sup>29</sup>	Patients	OSM contributes to local muscle atrophy, systemic bone loss, tissue fibrosis, and cardiac failure in the absence of IL-6, indicating a role in cancer cachexia
Setiadi et al. <sup>30</sup>	Patients with LVAD	Preoperative plasma OSM levels may help predict infection risk in LVAD patients
Jiang et al. <sup>31</sup>	MI patients	Dual-sensitive hydrogels offer a novel approach in tissue engineering for MI repair and drug delivery
van Keulen et al. <sup>32</sup>	Humans	The OSM receptor gene variant rs1316887 is linked to increased plaque vulnerability but does not contribute to coronary calcification or overall CVD risk. The influence of OSM signaling on plaque morphology occurs through unknown mechanisms. OSM-OSM receptor and leukemia inhibitory factor receptor do not appear to elevate CVD risk
Gajawada et al. <sup>33</sup>	Patients with cardiac sarcoidosis	Granuloma formation is driven by chemoattraction rather than macrophage proliferation. Screening drugs via the oncostatin/Reg3 axis may contribute to heart failure
Young et al. <sup>34</sup>	Mice	OSM plays a role in AIIRI. OSM receptor deficiency delays lung damage but leads to renal failure. AIIRI mortality is higher in OSM receptor-deficient mice, suggesting that AIIRI immunomodulation could enhance OSM activity
Akarsu et al. <sup>35</sup>	Patients with IR	IR indices (QUICKI and HOMA) are associated with OSM and could serve as alternative IR markers for simplicity
Midhuna et al. <sup>36</sup>	Patients with T2DM	Reg3 $\beta$ and OSM levels, alongside cardiac markers, may aid in diagnosing ACS in T2DM patients
Stawski and Trojanowska <sup>37</sup>	Fibrotic diseases	OSM contributes to fibrotic processes, including inflammation, vascular dysfunction, and fibroblast activation. In mice, CETP was found to reduce atherosclerosis
Keulen et al. <sup>38</sup>	CETP mice and humans	Elevated serum OSM levels were linked to improved post-CHD survival, suggesting a potential cardiovascular benefit
Setiadi et al. <sup>39</sup>	Endothelial cells	Neutrophil-derived OSM directly affects endothelial cell function through paracrine signaling during both normal and pathological inflammation

LVAD: Left ventricular assist devices, T2DM: Type 2 diabetes mellitus, IR: Insulin resistance, CETP: Cholesteryl ester transfer protein, CHD: Coronary heart disease, MI: Myocardial infarction, OSM: Oncostatin M, MS: Multiple sclerosis, IL-6: Interleukin-6, ACS: Acute coronary syndrome, Reg3: Regenerating islet-derived protein 3

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# Stent Implantation Results in Long Lesions and Small Coronary Vessels

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## ABSTRACT

**Background:** Data on the outcomes of stent implantation in long lesions ( $\geq 28$  mm) in small ( $\leq 2.5$  mm) coronary vessels is limited.

**Aim:** To investigate the acute outcomes of stenting in long and small coronary lesions.

**Study Design:** Retrospective cohort study.

**Methods:** Patients with stable coronary artery disease or acute coronary syndrome (ACS) who had undergone percutaneous coronary revascularization to native coronary arteries with stents  $\leq 2.5$  mm in size and  $\geq 28$  mm in length were assessed. Post-procedural analyses were performed with using Quantitative Coronary Analysis software system to evaluate stent oversizing. Acute complications, such as edge dissection and distal thrombus embolism were also recorded.

**Results:** A total of 161 consecutive patients (127 male, mean age:  $62.7 \pm 9.0$  years) were included. Most of the lesions were mid or proximal segments of the coronary arteries. Edge dissection was detected in 30 patients. Stent oversizing and reduced post-procedural TIMI flow grade were significantly higher in patients with edge dissection. Stent oversizing emerged as an independent predictor of edge dissection, with oversizing of  $>25\%$  compared to the distal vessel diameter predicted edge dissection with a sensitivity of 83.3% and specificity of 80.2%. In addition to edge dissection, distal embolism was more frequently observed in procedures with stent oversizing. TIMI flow grade 1-2 rates were found to be significantly higher in patients presenting with ACS.

**Conclusion:** Stenting in long lesions with small sized stents is related to a high risk of edge dissection, especially in procedures involving stent oversizing.

**Keywords:** Coronary stenting, edge dissection, stent oversizing

## INTRODUCTION

Coronary stenting has been a treatment of choice for symptomatic coronary artery disease (CAD). With advancements in interventional techniques and devices used in coronary intervention, the corresponding success rates are increasing along with a reduction in the complication rates. Complications occur due to either the existing comorbidities or coronary artery anatomy or the characteristics of the lesions.

Most trials typically include larger vessels ( $\geq 3$  mm) as target vessels and smaller vessels are excluded.<sup>1,2</sup> Early studies involving bare metal stent (BMS) have demonstrated a relation between a smaller final minimal lumen diameter and the occurrence of in-stent restenosis (ISR) during follow-up.<sup>3,4</sup> As under-sizing in coronary lesions may enhance ISR, the selection of appropriate stent size is deemed crucial.

Drug-eluting stents (DES) have better outcomes in contrast to BMS in small vessels due to their ability to significantly suppress neo-intimal proliferation through the drug elution process.<sup>5</sup> However, the benefits

of DES are mostly attenuated in patients with long coronary lesions due to the increased risk of adverse procedural outcomes.<sup>6</sup> Another major complication associated with DES is stent thrombosis (ST). Delayed intimal healing and increased intimal inflammation increase the risk of late ST, especially in high-risk lesions such as long coronary lesions.<sup>7</sup> Late ST is closely related to stent malapposition, and under-expanded stents in coronary lesions result in a higher incidence of ST.<sup>8</sup>

Achieving optimal stent apposition is more challenging in cases where the vessel anatomy is tapered and the lesion is long. In these lesions, there is a distinctive difference between the proximal and distal end of the vessel. The deployment of a stent-targeting distal vessel diameter may lead to the development of late ST as the proximal portion of the stent may be undersized and under-expanded, and the deployment of a stent targeting proximal vessel diameter may result in over-expansion and edge dissection, leading to abrupt vessel closure and ISR.<sup>9</sup>

Data on the evaluation of the effects and outcomes of stent implantation, especially in long ( $\geq 28$  mm) and small ( $\leq 2.5$  mm)

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coronary vessels, are limited. This study aimed to investigate the acute outcomes of stent implantation in small coronary arteries with long target lesions.

## MATERIALS AND METHODS

### Patient Population

This retrospective study was approved by the Marmara University Faculty of Medicine Research Ethics Committee, which waived the requirement for obtaining informed consent for the investigation and presentation of deanonimized medical data. The present investigation adheres with the principles outlined in the Declaration of Helsinki (approval number: 09.2017.532, date: 29.09.2017). A total of 161 consecutive patients aged  $\geq 18$  years, who underwent percutaneous coronary revascularization for native coronary arteries due to stable angina or acute coronary syndrome (ACS), with stents of  $\leq 2.5$  mm in size and  $\geq 28$  mm in length in our cardiology department during 2013-2020 were retrospectively assessed. As the inclusion criteria were long and the diameter of the lesions was small, the lesions in larger vessels such as the left main coronary artery lesions were excluded. Demographic and clinical data of all patients were retrieved from the hospital's electronic medical databank system (MEDIN 3.0, Ankara, Türkiye). Cardiovascular risk factors, such as hyperlipidemia, diabetes mellitus, and smoking were recorded.

Stent implantation was performed in patients admitted with ACS or in symptomatic patients with ischemia symptoms due to CAD. ACS patients were defined as patients who were diagnosed with ST segment-elevated myocardial infarction (MI), non-ST segment elevated MI, or patients with unstable angina pectoris.<sup>10</sup> Patients with stable CAD had documented ischemia based on echocardiography, treadmill test, or cardiac scintigraphy, without any increase in cardiac troponin levels or dynamic ischemic changes in the electrocardiogram.

Previous studies have described stents as long if their length was  $>25$  mm, very long if the length was  $>40$  mm, and small if the cross-sectional area was  $<5.1$  mm<sup>2</sup>, which is approximately  $<2.6$  mm in diameter.<sup>11-13</sup> Therefore, we included patients who were implanted with stents  $\leq 2.5$  mm in diameter and  $\geq 28$  mm in length. All stents used during the procedure were DES.

The following patients were excluded from the study: those implanted with stents of length  $\leq 28$  mm or size  $\geq 2.5$  mm; those with left main coronary disease, severely tortuous coronary vessels, severe vasospasm despite nitroglycerin administration, intervention to non-native coronary artery, and coronary cineangiogram unsuitable for Quantitative Coronary Analysis (QCA); who had failed records in the system; who had cardiogenic shock or mechanical ventilation, allergy to antiplatelet drugs, heparin, contrast agent, or stainless steel.

### Stent Implantation

All patients received the necessary antiplatelet and anticoagulant medication before and during the procedure. After the procedure, the patients received acetylsalicylic acid 100 mg/day as well as either clopidogrel 75 mg/day or ticagrelor 180 mg/day or prasugrel 10 mg/day. The administration of glycoprotein 2b/3a inhibitors was left at the operator's discretion.

Stent implantation procedures was performed according to standard techniques using a commercially available angiographic system (Artis Zee biplane; Siemens Healthcare, Erlangen, Germany). The coronary procedures were performed via trans-femoral (77%) or trans-radial (23%) access, through six or seven French guiding catheters. The location and characteristics of the lesions were recorded based on the American College of Cardiology/American Heart Association classification system.<sup>14</sup> Stents were expanded with nominal or higher pressures, with decisions regarding stent size selection, pre-dilatations, and post-dilatations left to the operator's discretion. The higher pressures applied by the operators in our clinic were defined as the burst pressures (maximum 16 atm), as specified in the user manuals of the branded balloons. The operators could freely decide the stent sizes with different methods, which were either visual estimation or sizing with the pre-dilation balloon or with a coronary analysis system. Intravascular ultrasound (IVUS) or optical coherence tomography (OCT) were not performed routinely during the procedures.

### Angiographic Analysis

All coronary scopic views for each patient before and after the stent implantation were retrospectively evaluated by a single experienced cardiologist using a software system of QCA (Pie Medical Imaging, Maastricht, The Netherlands). The best views demonstrating the reference vessel in the longitudinal axis with a minimal curvature in the scopic view were selected for analysis. The same coronary view angle was maintained for the calculation of parameters before and after stent implantation. In the case of a vasospasm, the vessel was evaluated from the scopic view obtained after nitroglycerin administration. If the vasospasm continued in the subsequent scopic views after nitroglycerin administration, those patients were excluded from the study. During the analysis, calibration was performed using the guiding catheter when filled with contrast agent. The guiding catheter used for calibration was  $\geq 6$  French as advised.<sup>15</sup> After calibration, the scopic view was paused at the diastolic frame, where the coronary artery was most optimally filled with contrast. The measurement of the length was calculated from the non-diseased segments next to the diseased segment of the proximal and distal portions of the coronary lesion. After calibration and tracking of the coronary lesion, the system applied automatic edge detection of coronary vessels and provided the calculated parameters. Reference vessel diameter (RVD), minimal luminal diameter, length of the lesion, and proximal/distal diameters of the stents after implantation and post-dilatation, if performed, were measured in the end-diastolic frame. The best view after stent implantation which showed the stent in a perpendicular line and best filled with contrast agent was chosen. Proximal and distal parts of the stents after implantation were determined as a 3-mm distance from both the edges of the stent.

Since the study included acute and total occlusions. Some patients experienced diminished distal flow. The analysis of these lesions was performed after the first pre-dilation balloon and nitroglycerin administration if applied.

Post-procedural analysis and events such as side-branch occlusion, intramural hematoma, vessel rupture, distal thrombus embolism, edge dissection, in-hospital ST, MI, and death were recorded.

Acute MI was diagnosed according to the latest MI guidelines.<sup>10</sup> Coronary flows was classified based on the results of TIMI analysis.<sup>16</sup> Edge dissection was defined as disruptions of the arterial lumen surface in the stent edges defined as the 5-mm regions immediately adjacent to the stent borders, distally and proximally, which were visible in at least two consecutive cross-sectional angiographic images. Distal thrombus embolism was defined as the presence of a new filling defect or abrupt cutoff in one of the distal coronary artery branches after stenting the target lesions. The oversizing calculation was applied to evaluate the degree of stent oversizing for the target vessel. Oversizing was calculated using the following formula:

$$\text{Nominal stent diameter} - \text{RVD/RVD} \times 100.$$

In case of overlapping stents, the average nominal stent diameter was used for calculation.

The intraobserver coefficient of variation was 2.1%.

### Statistical Analysis

All statistical tests were performed using a commercially available software program (Statistical Package for the Social Sciences version 20.0 for Windows, Chicago, IL, USA). All continuous variables were assessed for normal distribution by the Kolmogorov-Smirnov test and presented as the mean [standard deviation (SD)] values and the categorical variables were expressed as numbers or percentages. A chi-square test was performed to compare categorical variables. Univariable and multivariable logistic regression analyses (with the parameters found to be significant in univariable analysis) were performed to explore the associations with edge dissection. A receiver operating characteristic curve analysis and Youden index [max (sensitivity + specificity – 1)] were performed to detect the optimal cut-off value of stent oversizing in predicting edge dissection. P<0.05 was considered to indicate statistical significance.

## RESULTS

A total of 161 consecutive patients [127 male (78.9%), mean age (SD): 62 (9) years] were included in this retrospective analysis. The characteristics of the patients together with the lesion- and procedure-related characteristics and events are summarized in Table 1. A total of 84 patients had ACS. Most of the lesions were in the mid and proximal segments of the coronary arteries. As a procedural complication, edge dissection was detected in 30 patients. Vasospasm was recorded in nearly half of the patient population, while most of the patients had TIMI flow-grade 3. Side-branch occlusion and MI during the procedure were noted in 15 and 7 patients, respectively.

Table 2 presents the lesion- and procedure-related characteristics and post-procedural events of the patients based on the presence of edge dissection. Stent oversizing and reduced post-procedural TIMI flow grade were significantly higher in patients with edge dissection. ROC analysis and the Youden index were used to detect the optimal cut-off value of stent oversizing for predicting edge dissection. As a result, a stent oversizing of >25% predicted edge dissection with a sensitivity of 83.3% and a specificity of 80.2% (area under curve 85.2) was recorded.

**Table 1.** Patient and lesion- and procedure-related characteristics

Variables	Findings
Age (years)	62±9
Male sex (%)	127 (78.9%)
Smoking (%)	124 (77.0%)
Diabetes mellitus (%)	66 (41.0%)
Family history of coronary artery disease (%)	41 (25.5%)
<b>Admission syndrome</b>	
Stable angina pectoris (elective) (%)	77 (47.8%)
ST segment elevated myocardial infarction (%)	37 (23.0%)
Non-ST segment elevated myocardial infarction (%)	47 (29.2%)
<b>Treated coronary arteries</b>	
Left anterior descending (proximal/mid/distal) (%)	16 (9.9%) / 28 (17.4%) / 5 (3.1%)
Right coronary artery (proximal/mid/distal) (%)	13 (8.1%) / 13 (8.1%) / 8 (5.0%)
Left circumflex artery (proximal/mid/distal) (%)	14 (8.7%) / 22 (13.7%) / 6 (3.7%)
Ramus intermedius artery (%)	6 (3.7%)
Obtuse marginal artery (%)	19 (11.8%)
Diagonal (%)	5 (3.1%)
Posterior descending artery (%)	4 (2.5%)
Posterior lateral artery (%)	2 (1.2%)
<b>Lesion characteristics</b>	
Length (mm)	34.92±12.71
Calcification (%)	94 (58.4%)
<b>Procedural characteristics</b>	
Access (femoral/radial) (%)	124 (77.0%) / 37 (23.0%)
Predilatation (%)	149 (92.5%)
Predilatation balloon size (mm)	2.01±0.25
Predilatation balloon length (mm)	16.97±3.62
Predilatation balloon pressure (ATM)	14.6±1.2
Post-dilatation (%)	77 (47.8%)
Post-dilatation balloon size (mm)	2.63±0.21
Stent overlapping (%)	45 (27.9%)
Stent length (mm)	32.66±6.07
Stent diameter (mm)	2.41±0.11
Stent oversizing (%)	23.18 (19.96)
Stent oversizing >10% (%)	73 (45.3%)
Stent oversizing >25% (%)	51 (31.7%)
<b>Procedural/post procedural events</b>	
Vasospasm (%)	77 (47.8%)
Side branch occlusion (%)	15 (9.3%)
Intramural hematoma (%)	2 (1.2%)
Coronary rupture (%)	1 (0.6%)
Distal embolism (%)	11 (6.8%)
Edge dissection (%)	30 (18.6%)
TIMI flow grade 1-2 vs. 3 (%)	23 (14.3%) / 138 (85.7%)
Acute stent thrombosis (%)	2 (1.2%)
Myocardial infarction associated with PCI (%)	7 (4.3%)
In-hospital cardiovascular death (%)	4 (2.5%)
In-hospital all-cause death (%)	6 (3.7%)

ST: Stent thrombosis, PCI: Percutaneous coronary intervention

Stent oversizing of >25% was observed in 51 patients. Table 3 presents the lesion- and procedure-related characteristics and post-procedural events in accordance with the presence of stent oversizing of >25%. The stent-oversizing group showed significantly higher rates of edge dissection, vasospasm, and distal embolism.

The lesion- and procedure-related characteristics and post-procedural events were compared based on their presentation with ACS (Table 4). The frequency of reduced TIMI flow grade was higher in patients presenting with ACS.

**Table 2.** Characteristics and events in accordance with the presence of edge dissection

	Edge dissection (+) (n=30)	Edge dissection (-) (n=131)	p value
TIMI flow grade 1-2/3 (%)	11 (36.7%) / 19 (63.3%)	12 (9.2%) / 119 (90.8%)	<0.001
Stent oversizing (%)	51.43 (21.13)	16.71 (12.82)	<0.001
Stent oversizing >25% (%)	25 (83.3%)	26 (19.8%)	<0.001
Intramural hematoma (%)	0 (0%)	2 (1.5%)	1.0
Vasospasm (%)	15 (50%)	62 (47.3%)	0.79
Coronary rupture (%)	0 (0%)	1 (0.8%)	1.0
Acute stent thrombosis (%)	0 (0%)	2 (1.5%)	1.0
Distal embolism (%)	4 (13.3%)	7 (3%)	0.25
Side branch occlusion (%)	4 (13.3%)	11 (8.4%)	0.48
Myocardial infarction (%)	2 (6.7%)	5 (3.8%)	0.62
In-hospital cardiovascular death (%)	1 (3.3%)	3 (2.3%)	0.57
Stent overlapping (%)	12 (40%)	33 (25.2%)	0.10
Access (femoral/radial) (%)	24 (80%) / 6 (20%)	100 (76.3%) / 31 (23.7%)	0.67
Predilatation (%)	29 (96.7%)	120 (91.6%)	0.47
Predilatation balloon size (mm)	2.1±0.21	2.2±0.22	0.31
Predilatation balloon pressure (ATM)	14.7±1.3	15.6±1.2	0.52
Post-dilatation (%)	15 (50.0%)	62 (47.3%)	0.79
Post-dilatation balloon size (mm)	2.58±1.4	2.61±1.5	0.43
Calcification (%)	18 (60%)	76 (58%)	0.84

**Table 3.** Comparison of characteristics and events according to the extent of stent oversizing

	Stent oversizing (+) (n=51)	Stent oversizing (-) (n=110)	p value
TIMI flow grade 1-2/3 (%)	12 (23.5%) / 39 (76.5%)	11 (10%) / 99 (90%)	0.022
Edge dissection (%)	25 (49%)	5 (4.5%)	<0.001
Vasospasm (%)	32 (62.7%)	45 (40.9%)	0.010
Distal embolism (%)	7 (13.7%)	4 (3.6%)	0.038
Side branch occlusion (%)	6 (11.8%)	9 (8.2%)	0.47
Intramural hematoma (%)	2 (3.9%)	0 (0%)	0.99
Coronary rupture (%)	1 (2%)	0 (0%)	0.32
Acute stent thrombosis (%)	1 (2%)	1 (0.9%)	0.54
Myocardial infarction (%)	4 (7.8%)	3 (2.7%)	0.21
In-hospital cardiovascular death (%)	2 (3.9%)	2 (1.8%)	0.59
Stent overlapping (%)	19 (37.3%)	26 (23.6%)	0.07
Access (femoral/radial) (%)	44 (86.3%) / 7 (13.7%)	80 (72.7%) / 30 (27.3%)	0.06
Predilatation (%)	50 (98%)	99 (90%)	0.11
Predilatation balloon size (mm)	2.0±0.22	2.01±0.21	0.92
Predilatation balloon pressure (ATM)	14.8±1.2	14.4±1.1	0.61
Post-dilatation (%)	27 (52.9%)	50 (45.5%)	0.38
Post-dilatation balloon size (mm)	2.6±1.5	2.5±1.4	0.43
Calcification (%)	34 (66.7%)	60 (54.5%)	0.15

Edge dissection was associated with stent oversizing and the size of the reference vessel, albeit no significant associations were found between edge dissection and lesion length, pressure of pre-dilatation, post-dilatation balloon, and stent inflation pressure. However, only stent oversizing of >25% remained as an independent predictor of edge dissection in the multivariable logistic regression model (odds ratio: 18.82, p<0.001) (Table 5).

## DISCUSSION

The primary objective of this study was to evaluate the impact of stent oversizing during implantation in long lesions in small-sized coronary vessels, with a focus on its association with peri-procedural complications, particularly edge dissection, vasospasm, and distal embolism. This issue has particular clinical relevance, considering that coronary interventions in small and long lesions are associated with lower procedural success rates and higher complication rates.<sup>17</sup> Our findings indicate that oversizing stent during implantation in long, small lesions is associated with an increased risk of peri-procedural complications, particularly edge dissection, vasospasm, and distal embolism. These complications can lead to adverse clinical outcomes, including vessel closure and, possibly, re-intervention. Specifically, oversizing stents by >25% in relation to the distal vessel diameter can significantly increase the risk of edge dissection; this complication can compromise the long-term patency of the vessel.

Our study thus provides valuable insights into the optimal stent-sizing strategies that can mitigate these risks, thereby ultimately enhancing procedural success and reducing the occurrence of complications in this challenging subset of patients.

Due to the potential complications of tapered vessels by their nature, the optimal strategy or appropriate stent deployment in these vessels is critical. Due to the tapered nature of anatomy, there may be a significant difference in size between the distal and the proximal segments of the vessels, especially in long coronary lesions. Stent selection targeting proximal or distal vessel diameters is challenging and may incur procedural complications such as edge dissection and abrupt vessel closure. In most of these procedures, stents are selected based on their distal diameter, and the proximal portion of the stent is post-dilated. However, overexpansion or aggressive post-dilatation may cause a disproportionate increase in the nominal stent diameter, stent strut fracture, or arterial wall dissection.<sup>18</sup> When the stent size is determined according to the proximal or middle-vessel diameter, the risk of distal edge dissection increases because of the significant difference in the distal and middle portion sizes of stents. We demonstrated that distal diameter-referenced stent deployment of <25% oversizing in long lesions had a statistically lower risk of edge dissection when compared to oversizing by >25%. These findings are of clinical significance because they offer a strategy for reducing the risk of complications and improving procedural success rates in a population of patients that is particularly challenging to treat. By

**Table 4.** Comparison of events based on the presentation with acute coronary syndrome or stable angina

	Acute coronary syndromes (n=84)	Stable angina (n=77)	p value
TIMI flow grade 1-2/3 (n, %)	18 (21.4%) / 66 (78.6%)	5 (6.5%) / 72 (93.5%)	<b>0.007</b>
Stent oversizing >25% (n, %)	29 (34.5%)	22 (28.6%)	0.42
Edge dissection (n, %)	11 (13.1%)	19 (24.7%)	0.06
Intramural hematoma (n, %)	1 (1.2%)	1 (1.3%)	1
Vasospasm (n, %)	40 (47.6%)	37 (48.1%)	0.96
Coronary rupture (n, %)	0 (0%)	1 (1.3%)	0.48
Acute stent thrombosis (n, %)	2 (2.4%)	0 (0%)	0.50
Distal embolism (n, %)	8 (9.5%)	3 (3.9%)	0.22
Side branch occlusion (n, %)	10 (11.9%)	5 (6.5%)	0.24
In hospital cardiovascular death (n, %)	2 (2.4%)	2 (2.6%)	1
Stent overlapping (n, %)	22 (26.2%)	23 (29.9%)	0.60

**Table 5.** The results of logistic regression analysis for edge dissection

	Univariable logistic regression			Multivariable logistic regression		
	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
Stent oversizing >25%	20.19	7.05-57.81	<b>&lt;0.001</b>	18.82	3.95-89.62	<b>&lt;0.001</b>
Lesion length	1.02	1-1.05	0.53			
Pre-dilatation balloon pressure	1.1	0.8-1.6	0.39			
Post-dilatation balloon pressure	0.78	0.5-1.1	0.08			
Stent inflation pressure	0.9	0.8-1	0.12			
Size of the reference vessel	0.08	0.02-0.3	<b>0.032</b>	0.1	0.08-1.02	0.54

CI: Confidence interval

carefully selecting the stent sizes based on the distal diameter and by avoiding excessive oversizing, physicians can minimize the risk of edge dissection and enhance the overall outcome of interventions in small-sized coronary vessels.

Our results align with those of previous studies that investigated stent-deployment strategies in tapered arteries. For instance, Shen et al.<sup>19</sup> investigated the best strategy to deploy a coronary stent to the tapered arteries with the best apposition. For this purpose, they compared the selection of proximal, middle, and distal diameters as the RVD so as to deploy a stent and found that the proximal diameter-referenced expansion provided the best apposition together with the highest arterial wall stress, which may have led to edge dissection while the distal diameter-referenced expansion provided the lowest arterial wall stress together with incomplete stent apposition. The authors suggested that middle diameter-referenced expansion resulted in adequate stent apposition with reasonable arterial wall stress. However, their study was not specific to small-sized coronary arteries. For instance, Kitahara et al.<sup>20</sup> evaluated stent-size selection and the outcomes of DES in coronary lesions and speculated that, in small vessels, the selection of larger stents have shown better expansion of the stents while avoiding post-dilatation and without increasing the edge dissection. However, they considered that larger stent-size selections could be inappropriate in chronic total occlusions, severely calcified lesions, and eccentric lesions owing to the increased risk of complication. In their study, the percentage of stent oversizing was defined as >10%. Kobayashi et al.<sup>13</sup> investigated the relation between IVUS-detected edge dissection and DES implantation and demonstrated calcification, stent expansion, and plaque burden as independent predictors for edge dissection. In our study, no significant relation was noted between edge dissection and post-dilatation pressure as well as the presence of calcification. This difference may be attributed to the difference in the diagnostic methods employed to evaluate edge dissection.

A large angiographic study found that the prevalence of edge dissection related to DES was 1.7%.<sup>21</sup> When IVUS was used as an imaging tool for the diagnosis, the prevalence of edge dissection increased to 7.8% with DES, thereby demonstrating a high sensitivity of intravascular imaging in the determination of edge dissection when compared to conventional angiographic evaluation.<sup>22</sup> OCT is even more sensitive relative to IVUS, and higher rates of edge dissection have been detected with OCT in clinical trials.<sup>23</sup> In our study, the prevalence of edge dissection was 18.6%, which was diagnosed visually based on angiography images; this rate was distinctly higher in our study when compared to that in past studies. Moreover, this difference may be associated with the RVD. Most past studies included all coronary vessels treated with percutaneous coronary intervention and were not specific to small and long coronary lesions. In addition, intravascular imaging modalities were not used in the present study, which could have led to the underestimation of edge dissection in some patients. Further studies with intravascular imaging modalities are expected to clarify the exact rate of procedural outcomes in such patients.

In our study, the TIMI flow rate was significantly decreased in patients with ACS after stenting. Although there was no significant difference,

the rate of acute ST, distal embolism, and in-hospital deaths was higher in patients with ACS. These findings are in accordance with the literature as the risk of distal embolism, vasospasm, no-reflow, and reduced TIMI flow rates were higher in patients with ACS.<sup>24</sup> Especially, when pre-dilation or post-dilation was performed in these patients, the risk of no-reflow and reduced TIMI flow increased; therefore, direct stenting was considered a safer approach. However, in the case of vasospasm and reduced coronary flow because of high thrombus burden, evaluating and estimating the distal reference diameter without pre-dilation becomes difficult in patients with ACS. Therefore, intravenous nitrate administration should be considered as an option to evaluate the RVD after gentle pre-dilatation using an under-sized balloon in the lack of contraindication.

Bouki et al.<sup>25</sup> demonstrated that patients with ST-segment elevated MI and small-sized culprit vessels showed a higher incidence of edge dissection when compared with larger vessels. In our study, the rates of edge dissection were similar in patients without or with ACS, suggesting that the improper vessel sizing and over-expanded stent implantation, rather than the presentation with ACS, was the main reason for post-procedural edge dissection. However, large-scale clinical trials including ACS patients with long and small-sized lesions are needed to clarify this aspect.

### Study Limitations

There are several limitations to our study, including the retrospective single-center design of the study. The complications were assessed based on the recorded angiographic views and some complications may have been missed in the absence of proper angiographic view. The best technique for the detection of vessel diameters and the recognition of peri-procedural vascular complications is intravascular imaging modalities. We did not employ IVUS or OCT in our study as that may have caused the underestimation of edge-dissection rates. The characteristics of vessel wall anatomy may affect the outcome of stent implantations. We did not have detailed data about the anatomical characteristics owing to the lack of evaluation with imaging modalities, such as coronary computerized tomography. Finally, we did not evaluate the long-term outcomes of oversizing in small and long coronary lesions, which would provide apparent information about late ST and ISR.

## CONCLUSION

In conclusion, our study findings provide valuable insights into the optimal strategy for stent sizing in long, small coronary lesions, suggesting that limiting oversizing to <25% of the distal diameter can reduce the risk of edge dissection. These findings have important clinical implications, considering that they may facilitate clinicians in selecting the appropriate stent size, thereby improving procedural success rates and reducing the occurrences of peri-procedural complications. Future large-scale trials incorporating advanced imaging techniques, such as IVUS and OCT, are essential to confirm these results and further refine the stent-deployment strategies proposed herein, so as to, ultimately, enhance the outcomes for patients with complex coronary lesions.

**Ethics Committee Approval:** The study was approved by the Marmara University Faculty of Medicine Research Ethics Committee (approval number: 09.2017.532, date: 29.09.2017).

**Informed Consent:** Because it is a retrospective study, informed consent is not required.

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# Long-term Effect of Sacubitril/valsartan Use on Uric Acid Levels in Patients with Heart Failure and Reduced Left Ventricular Ejection Fraction

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## ABSTRACT

**Background:** Heart failure with reduced ejection fraction (HFrEF), characterized by neurohormonal activation and metabolic dysregulation, may lead to elevated serum uric acid (SUA) levels. Although the sacubitril/valsartan (S/V) molecule confers notable cardiovascular benefits and has been observed to influence multiple metabolic parameters, its impact on SUA levels remains incompletely elucidated.

**Aim:** To investigate the long-term impact of the S/V combination on SUA levels in patients with HFrEF.

**Study Design:** Longitudinal retrospective cohort study.

**Methods:** For this single-center, retrospective, cross-sectional analysis, data from patients using S/V for HFrEF were collected from their medical records. In addition to the routine controls, the uric acid levels of patients were measured at the baseline and in the first and second years of their treatment. The parameters obtained at two years included the serum uric acid (SUA) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. The SUA and NT-proBNP levels measured in the first and second years were compared with the baseline value.

**Results:** A total of 148 patients with a functional capacity in New York Heart Association II-IV and those who were using S/V due to HFrEF were included in this study. The mean age of the study patients was 66.6±10.3 years, and 61.5% of them were male. The baseline SUA levels were 6.6±1.6, which reduced to 6.2±1.8 at the end of the first year and to 6±1.6 at the end of the second year ( $p<0.001$ ).

**Conclusion:** The administration of S/V can reduce the SUA concentration in patients with HFrEF.

**Keywords:** Sacubitril/valsartan, heart failure, uric acid, NT-proBNP

## INTRODUCTION

Patients with heart failure (HF) exhibit hyperuricemia with a prevalence rate of 50%,<sup>1,2</sup> probably due to the use of diuretic drugs in the treatment of HF patients. An association has also been observed between poor long-term prognosis and the use of diuretic drugs in these patients.<sup>2,3</sup> In the case of HF patients, the risk of all-cause mortality is increased by 4% with every 1 mg/dL increment in the serum uric acid (SUA) level. Similarly, this increment is associated with a 28% greater risk of hospitalization.<sup>4</sup> Although agents such as allopurinol and febuxostat are available for reducing SUA, researchers are continuing to investigate

novel therapeutic approaches for the treatment of this condition in HF patients.

Sacubitril/valsartan (S/V) has been reported to cause a significant reduction in all-cause mortality, hospitalization, and cardiovascular mortality in HF patients demonstrating HF and reduced ejection fraction (HFrEF).

S/V serves as an angiotensin receptor-neprilysin inhibitor (ARNI)<sup>5</sup> and results in several metabolic changes.<sup>6</sup> The majority of these metabolic changes brought about by this molecule are actually due to the neprilysin inhibitor sacubitril. PARAGON and PARADIGM studies

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involve investigations focusing on the impact of S/V molecules on the concentration of SUA. Nevertheless, the long-term impact of S/V on the SUA levels warrants further investigation. Accordingly, the present research investigated the different long-term effects of S/V on the concentration of SUA in HFrEF patients.

## METHODS

This longitudinal retrospective cohort study examined 148 patients classified as New York Heart Association (NYHA) functional class II-IV who initiated ARNI therapy for HFrEF [left ventricular ejection fraction (LVEF) <40%] during April 2019 to March 2020. ARNI dosing was systematically titrated to the maximum tolerated dose for all participants. The exclusion criteria encompassed severe non-cardiac comorbidities (e.g., end-stage organ dysfunction, dialysis-dependent renal failure, metastatic malignancy, sepsis/septic shock), age <18 years, pregnancy, concomitant serum urate (SUA)-lowering therapy, and irregular clinical follow-up. The study protocol adhered to the Declaration of Helsinki guidelines and received approval from the Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Local Ethics Committee (permission date: 18.07.2022, file number: 431869). All therapeutic interventions were individualized in accordance with contemporary clinical guidelines.

### Definitions

HFrEF was defined as an LVEF <40% accompanied by clinical signs and symptoms of HF, which is consistent with the established diagnostic criteria.<sup>7</sup> Ischemic heart disease (IHD) encompasses a documented history of acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass surgery, or objective evidence of myocardial ischemia via invasive coronary angiography or non-invasive testing (e.g., stress echocardiography and myocardial perfusion imaging).<sup>8</sup> Hypertension (HT) was characterized by either (1) two consecutive seated blood pressure measurements of  $\geq 140/90$  mm Hg recorded during separate clinical encounters or (2) the active use of antihypertensive pharmacotherapy. Diabetes mellitus (DM) was diagnosed on the basis of (1) two independent fasting plasma glucose measurements of  $\geq 126$  mg/dL or (2) the current use of glucose-lowering agents (either oral or injectable). The NYHA functional classification was employed to stratify symptom severity and exercise capacity. Two cardiologists independently evaluated and categorized patients into NYHA classes I-IV through a retrospective chart review, with discrepancies resolved via consensus adjudication. This dual-assessment approach aimed to enhance the classification accuracy and minimize the interobserver variability.

### Transthoracic Echocardiography

Transthoracic echocardiography was conducted using a standardized protocol with the Philips Epiq 7 Ultrasound system (Philips Healthcare, Inc., Andover, MA, USA) equipped with an X5-1 phased-array transthoracic transducer. All examinations adhered to the American Society of Echocardiography guidelines,<sup>9</sup> incorporating M-mode, two-dimensional (2D), and pulsed/continuous-wave Doppler modalities. LVEF was determined using the biplane Simpson's method of discs. Endocardial borders were manually traced in apical four- and two-chamber views during end-diastole and end-systole, taking due care

to ensure orthogonal plane alignment and the inclusion of the entire ventricular cavity from the apex to the mitral annulus. Volumetric calculations were derived from the average of three consecutive cardiac cycles to minimize the beat-to-beat variability.<sup>10</sup> To ensure methodological rigor, two independent cardiac sonographers, blinded to the clinical data, analyzed all the echocardiographic images. Interobserver discrepancies of >5% in LVEF measurements underwent adjudication by a senior cardiologist, with the final values representing the consensus assessment. This protocol minimized the intra- and interoperator variability while maintaining alignment.

### Laboratory Measurements

Venous blood samples were collected in serum separator gel tubes (without anticoagulant). Following centrifugation at  $1,800\times g$  for 15 min, the serum was aliquoted. Biochemical parameters, including the fasting plasma glucose, glycated hemoglobin (HbA1c), NT-proBNP, total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL-C), creatinine, albumin, and SUA, were quantified by standardized enzymatic colorimetric assays. The HbA1c levels were measured via high-performance liquid chromatography, while the N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were determined by electrochemiluminescence immunoassay, in accordance with the corresponding kit manufacturer's protocols.

### Statistical Analysis

All analyses were performed using IBM Statistical Package for the Social Sciences statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The normality of the continuous variables was assessed using the Kolmogorov-Smirnov test. The normally distributed data were presented as the mean  $\pm$  standard deviation, while the nonnormally distributed variables were reported as median with interquartile range (IQR; 25<sup>th</sup>-75<sup>th</sup> percentiles). Categorical variables were expressed as frequencies and percentages. Intergroup comparisons were conducted using Pearson's chi-square test. For the continuous variables, the independent Student's t-test (normal distribution) or Mann-Whitney U test (non-normal distribution) was applied. Longitudinal changes in the SUA levels were evaluated using repeated-measures analysis of variance, while the non-parametric repeated-measures Friedman test was employed for NT-proBNP because of its skewed distribution. A two-tailed  $p < 0.05$  was considered to indicate statistical significance.

## RESULTS

Table 1 summarizes the demographic and clinical characteristics of 148 patients experiencing HFrEF and utilizing ARNI. Of the total study patients, 91 (61.5%) were male. Moreover, the average age of the patients was  $66.6 \pm 10.3$  years. The frequencies of atrial fibrillation, IHD, DM, dyslipidemia, and HT were 37.8%, 67.6%, 58.8%, 81.1%, and 62.2%, respectively. Of the total, 40 (27.0%) patients were using low-dose S/V (24/26 mgx2), while 108 (72.9%) were using high-dose S/V (49/51 mgx2). In addition, 148 (100%) patients were receiving beta-blocker therapy, 106 (71.6%) were on mineralocorticoid receptor antagonists, and 139 (93.9%) were using diuretics. The mean LVEF was found to be  $40.7 \pm 14.3$ . As per the laboratory findings, the creatinine, HbA1c,

glucose, HDL-C, and TC levels were  $1.0\pm 0.3$ ,  $7.0\pm 1.7$ ,  $132.1\pm 54.3$ ,  $46.1\pm 15$ , and  $183.4\pm 46.8$  mg/dL, respectively. The mean SUA and NT-proBNP levels were recorded to be  $6.6\pm 1.9$  mg/dL and 67-32772 pg/mL, respectively.

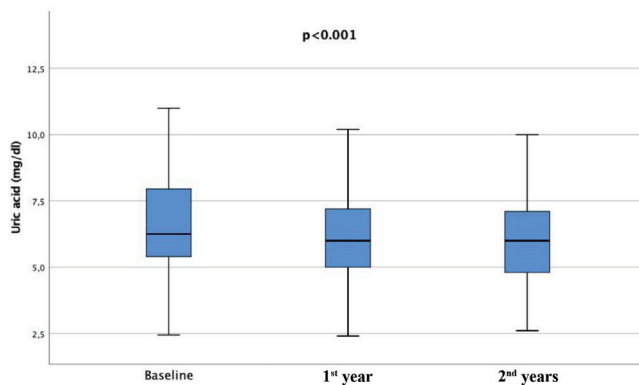
The baseline levels of SUA and NT-proBNP parameters of all patients were compared with the levels recorded in the following years (Figures

1, 2, Table 2). The baseline level of SUA was  $6.6\pm 1.9$  mg/dL and that of NT-proBNP was 1645 (67-32772) pg/mL. However, these levels demonstrated a significant ( $p<0.001$ ) decrement in the following years. Another comparison was drawn between the levels of SUA and NT-proBNP during 1<sup>st</sup> year and the corresponding levels of these parameters in the second year (Figures 1, 2, Table 2). Once again, a

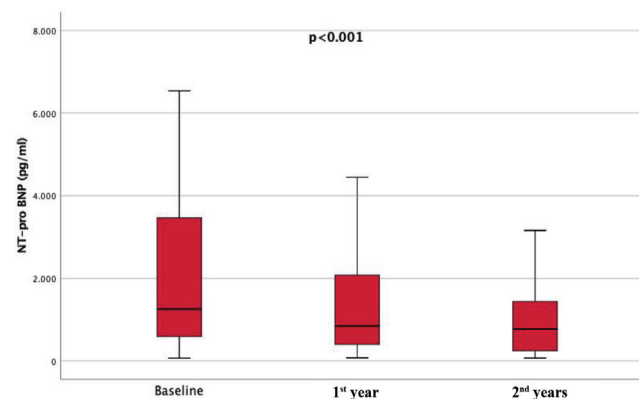
**Table 1.** Demographic and clinical data of the study population

Variables (n=148)	Total (n=148)
Age (years)	66.6±10.3
Male, n (%)	91 (61.5)
Smoke, n (%)	15 (10.1)
Hypertension, n (%)	92 (62.2)
Diabetes mellitus, n (%)	87 (58.8)
Dyslipidemia, n (%)	120 (81.1)
Ischemic heart disease, n (%)	100 (67.6)
Using low dose S/V (24/26 mgx2)	40 (27.0)
Using high dose S/V (49/51 mgx2)	108 (72.9)
Beta-blocker	148 (100)
MRA	106 (71.6)
Diuretic	139 (93.9)
Atrial fibrillation, n (%)	56 (37.8)
Left ventricular ejection fraction (%)	40.7±14.3
Left atrial diameter (mm)	43.9±6.3
Total cholesterol (mg/dL)	183.4±46.8
HDL-C (mg/dL)	46.1±15
Triglyceride (mg/dL)	123 (38-413)
Glucose (mg/dL)	132.1±54.3
HbA1c (%)	7.0±1.7
Creatinine (mg/dL)	1.0±0.3
Serum uric acid (mg/dL)	6.6±1.9
NT-ProBNP (pg/mL)	1645 (67-32772)

HDL-C: High-density lipoprotein cholesterol, HbA1c: Hemoglobin A1c, NT-proBNP: N-terminal pro-B-type natriuretic peptide, MRA: mineralocorticoid receptor antagonists, S/V: Sacubitril/valsartan



**Figure 1.** Changes in the SUA levels at the baseline and the end of the 1<sup>st</sup> and 2<sup>nd</sup> years  
SUA: Serum uric acid



**Figure 2.** Changes in the NT-proBNP levels at the baseline and the end of 1<sup>st</sup> and 2<sup>nd</sup> years  
NT-proBNP: N-terminal pro-B-type natriuretic peptide

**Table 2.** Changes in the 1<sup>st</sup> and 2<sup>nd</sup>-year uric acid level and NT-proBNP level when compared with the baseline values

Variables	Time	Mean	Standard error	Mean difference	p value
Uric acid (mg/dL)	Baseline	6.6	1.6		*a
	1. year	6.2	1.8	0.4	*β
	2. year	6.0	1.6	0.6	aβ
		Median	Min	Max	
NT-proBNP (pg/mL)	Baseline	1645	67	32772	*a
	1. year	987	78	25321	*β
	2. year	854	70	11300	aβ

\*p<0.01 between baseline and 1<sup>st</sup> year; <sup>a</sup>p<0.01 between baseline and 2<sup>nd</sup> year; <sup>β</sup>p<0.01 between 1<sup>st</sup> and 2<sup>nd</sup> year.

NT-proBNP: N-terminal pro-B-type natriuretic peptide, min: Minimum, max: Maximum

significant decrement ( $p < 0.001$ ) was recorded in the levels of the studied parameters during the first and second years.

## DISCUSSION

This research aimed to investigate the long-term effects of S/V on the levels of SUA in HFrEF patients. It was found that patients treated with S/V demonstrated a significant reduction in SUA levels during the first and second years in comparison to the respective baseline levels. Moreover, the NT-proBNP levels showed a significant reduction similar to the SUA levels. These findings highlight the potential metabolic effects of S/V in cardiovascular patients. The mechanisms underlying this effect may involve multiple pathways. Nephilysin inhibition increases natriuretic peptides (such as ANP and BNP), enhancing renal salt and water excretion, which may reduce SUA levels. In addition, angiotensin II inhibition may further promote uric acid excretion by increasing the glomerular filtration rate. These mechanisms, when combined with improvements in cardiac metabolism and hemodynamics, likely contribute to changes in uric acid metabolism, thereby emphasizing the need for further exploration of the broader cardiovascular and metabolic effects.

SUA has proven to be a vital parameter while dealing with patients with acute and chronic HF. SUA has turned into an important predictor of cardiovascular and all-cause mortality in HF patients. For individuals experiencing acute HF, SUA can be used as an adjunctive prognostic biomarker pointing toward adverse outcomes. For patients experiencing moderate-to-severe HF, raised levels of SUA can be considered to act as an independent prognostic marker of impaired prognosis.

In humans, SUA is formed as an end-product of the purine metabolism pathway. Xanthine oxidase (XO) catalyzes the final two steps of this pathway. XO is one of the most important and strong sources of ROS. In addition to XO, UA has been found to trigger the production of ROS in different cells such as renal tubular cells, hepatocytes, vascular smooth muscle cells, and endothelial cells. Increased levels of UA and XO therefore cause ROS-mediated negative outcomes such as mitochondrial damage, inflammatory activation, endothelial dysfunction, and disturbed cardiac contractility, which are usually recorded in the case of HF patients. In the extracellular hydrophilic environment, UA behaves like an antioxidant agent. Conversely, in an intracellular environment, the antioxidant effect is mediated by UA. In the context of the direct impact of UA on cardiomyocytes, the inhibition of myocardial cell activity by hyperuricemia via oxidative stress leading to apoptosis has been reported. Frequently recorded events in HF patients like hypoxia, insulin resistance, augmented catabolism, and cell death, are caused by the upregulation of XO. Researchers have found that XO contributes to the occurrence of HF via cardiac mechano-energetic coupling, myocyte apoptosis, and endothelial dysfunction.<sup>11-13</sup>

Previous studies have reported confusing data relating to the significance of reducing SUA levels in HF patients. An association between allopurinol utilization and a reduced rate of cardiovascular and all-cause mortality was reported by a prospective, double-blinded, multicenter, non-inferiority research that involved 6,190 patients

having CV and gout disease. Of the total, 20% of the patients had HF and their median follow-up duration was 32 months.<sup>14</sup> Although allopurinol has proven to be a drug of choice with no contraindications for reducing the SUA levels in HF patients, no report has indicated whether the SUA-reducing approach is advantageous for left ventricular function, relevant symptoms, or outcomes in HF patients.<sup>15,16</sup> As per the PARADIGM-HF trial, S/V caused an SUA reduction of 0.24 mg/dL during one year ( $p < 0.0001$ ) in comparison to enalapril. Moreover, an association was recorded between the utilization of S/V and improved outcomes, irrespective of the levels of SUA in patients.<sup>17</sup>

In the PARAGON-HF trial, S/V reduced SUA by 0.38 mg/dL (95% confidence interval: 0.31-0.45) when compared with valsartan at 4 months, with greater effect noted in those with elevated SUA vs. normal SUA (-0.51 mg/dL vs. -0.32 mg/dL) ( $p$  value for interaction=0.031). S/V reduced the odds of initiating SUA-related treatments by 32% during follow-up ( $p < 0.001$ ).<sup>18</sup> The meta-analysis by Tamariz et al.<sup>16</sup> revealed a linear association between SUA and all-cause mortality above SUA levels of 7 mg/dL and with several other large prospective studies with longer follow-ups. In the study of Park et al.,<sup>17</sup> the combination of SUA and NT-proBNP levels was more beneficial than either marker alone for short-term outcomes in patients with acute HF. In our study, patients with chronic HF using S/V were evaluated, and, in the long-term follow-up of these patients, the decrease in the NT-proBNP levels was determined in addition to the decrease in the SUA levels.

Although the action mechanism of S/V on the SUA level is not known exactly, various mechanisms have been implicated. S/V increases the excretion of UA by slowing down the decline in renal function. In addition, the co-inhibition of angiotensin-converting enzyme and nephilysin has been demonstrated to have uricosuric effects. Finally, the lower diuretic requirements of patients using S/V (as observed with PARADIGM-HF) may lower the SUA levels.<sup>17,18</sup>

## Study Limitations

Our study has some limitations. First, this study was conducted at a single center. Second, the number of patients was relatively small. Third, the relationship between the change in the SUA levels and the prognosis was not evaluated. Fourth, the effect on patients using SUA-lowering drugs was not evaluated. Another limitation of our study is the absence of a comparative group constituting patients receiving ARB/ACE inhibitors. This comparison would have provided a clearer understanding of the specific effects of S/V on the uric acid levels in contrast to that with the conventional treatments. Future studies should incorporate such a comparison group to further elucidate the benefits and mechanisms of S/V in HF patients.

## CONCLUSION

In conclusion, S/V, which has several metabolic effects, appears to be a cardiovascular drug with pluripotential effects. The use of S/V in patients with HFrEF reduced the SUA levels. Large randomized clinical trials are thus warranted to demonstrate the beneficial clinical and metabolic effects of S/V.

**Ethics Committee Approval:** Permission was obtained from the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Local Ethics Committee for the study (permission date: 18.07.2022, file number: 431869).

**Informed Consent:** Because it is a retrospective study, informed consent is not required.

**Authorship Contributions:** Concept: Ö.D., A.Ö.E., Ş.İ.E., S.Ö., Z.Y., Design: Ö.D., A.Ö.E., Ş.İ.E., S.Ö., Z.Y., Data Collection or Processing: Ö.D., A.Ö.E., S.T., Ş.İ.E., K.M., Analysis or Interpretation: A.Ö.E., Ş.İ.E., A.A., Literature Search: Ö.D., S.T., A.A., S.Ö., Writing: Ö.D., K.M., Z.Y.

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# Experience with the New Generation of Lipid-lowering siRNA-based PCSK9 Inhibitor (Inclisiran) in Patients Undergoing LMCA Intervention

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## ABSTRACT

**Background:** Coronary artery diseases are one of the leading risk factors for global death. Reducing the levels of low-density lipoprotein (LDL) cholesterol to the normal value is crucial for its treatment. Although medications such as statins and ezetimibe remain the primary therapeutic options in such cases, more effective treatment choices are warranted for high-risk patients, particularly those with a history of cardiovascular events. The new-generation lipid-lowering siRNA drug PCSK9 inhibitor may offer an advantage in controlling LDL levels in such a patient group, especially when used in combination with other hypolipidemic drugs.

**Aim:** To investigate the effect of PCSK9i in patients with prior left main coronary artery intervention.

**Study Design:** Retrospective cohort study.

**Methods:** This study was conducted in Azerbaijan during 2022-2023 with 279 patients who underwent left main coronary artery (LMCA; angioplasty and bypass) intervention. All patients were initiated on statin-based antilipidemic therapy after the intervention. Over one year, the statin dose was titrated to the maximum levels, and ezetimibe was added to the treatment when needed. At the end of the year, patients who had not yet reached the target LDL levels inclisiran were added to the treatment for those who accepted it. Under inclisiran therapy, the patients were monitored for the next 12 months. After the first dose of inclisiran, the second and third doses were administered at the 3<sup>rd</sup> and 9<sup>th</sup> months, respectively, and LDL levels were measured at the 6<sup>th</sup> and 12<sup>th</sup> months. During the treatment period, LDL levels, liver enzymes, and other potential side effects were monitored.

**Results:** In patients who received inclisiran therapy (15), the average LDL level directly before inclisiran treatment was 134.9 mg/dL, and six months after treatment with inclisiran, this value dropped to 64.6 mg/dL. In other words, 6 months after starting inclisiran therapy, an average reduction of 52% in LDL levels was observed compared with the previous value. In patients who continued inclisiran treatment, the LDL level at the 12<sup>th</sup> month decreased to even lower values (an average of 43.1 mg/dL) compared with the previous measurement. Additionally, only a few patients reported side effects, which were temporary and not clinically significant.

**Conclusion:** Inclisiran significantly reduces LDL levels in patients with LMCA intervention and helps optimize the treatment strategies for achieving target LDL values. However, the high cost and the lack of patient awareness were the key barriers to its widespread use. Reforms in the healthcare system and expanded treatment coverage are expected to improve the effectiveness of Inclisiran and help prevent future cardiovascular diseases.

**Keywords:** Inclisiran, left main coronary artery, LMCA bypass, LMCA stent implantation, LDL, hypercholesterolemia, ischemic heart disease

## INTRODUCTION

According to the World Health Organization, ischemic heart diseases are one of the major causes of death, accounting for nearly 10 million deaths annually.<sup>1</sup> Coronary artery diseases, especially left main coronary

artery (LMCA) stenosis, are significant risk factors for the occurrence of myocardial infarction and cardiovascular complications. Therefore, the management and prevention of ischemic heart disease remain critical in modern medicine. According to the current recommendations, revascularization is recommended for all patients with  $\geq 50\%$  stenosis

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of the LMCA, irrespective of their symptoms or ischemic burden.<sup>2</sup> Reducing morbidity and mortality is closely linked not only to interventions performed but also to a careful follow-up of these patients. We, therefore, aimed not only to focus on revascularization but also to modify risk factors such as hypercholesterolemia as well as emphasize the role of modern treatment methods in achieving the target lipid values.

Aggressive lipid-lowering therapy plays a crucial role in the prevention of atherosclerosis for primary and secondary prevention in patients with high ischemic risk.<sup>3</sup> Statin and ezetimibe therapy, either alone or in combination, are among the primary treatment strategies for lowering the low-density lipoprotein (LDL) levels.<sup>4</sup> The use of new-generation lipid-lowering siRNA-based PCSK9 inhibitors is particularly important for patients intolerant to statins or failing to achieve the target LDL levels.<sup>5</sup>

The present study, which was conducted in Azerbaijan, is a multicenter, retrospective study that aimed to demonstrate the benefit of adding PCSK9 inhibitors to the treatment of patients who had undergone LMCA intervention and were receiving a statin + ezetimibe combination but could not achieve the targeted LDL values. Moreover, the safety of PCSK9 inhibitors in the studied population was evaluated.

## METHODS

This was a multicenter, retrospective study. The subject inclusion criteria were a recent LMCA intervention and no prior antilipidemic therapy. As such, 279 patients were included from across 4 different centers. The patients had received at least 1 year of antilipidemic treatment (with statin or statin + ezetimibe combination) after the intervention. Only patients followed by a cardiologist within 1 year after coronary revascularization were included in the study. The remaining patients were excluded from the study due to the lack of 1-year follow-up data. The target LDL level in the present study was set at <55 mg/dL based on the latest recommendations.<sup>6</sup>

All patients were followed by a cardiologist during the 1 year after the intervention and received statin or statin + ezetimibe combination at the maximum tolerable doses. The maximum dose of statins used in the study was 40 mg for atorvastatin and rosuvastatin. The LDL levels were measured in all patients after 1, 6, and 12 months. In patients who did not achieve the target LDL values by the 6<sup>th</sup> month, the statin + ezetimibe combination was then initiated. A total of 77 patients continued the study with the regular cardiologist follow-up for over 1 year. During the 1-year observation period, among the 77 patients, 63 of those who did not achieve the target LDL levels despite having received the maximum tolerable dose of the statin + ezetimibe combination were recommended to add the PCSK9 inhibitor to their treatment regimen. Because only inclisiran was available in Azerbaijan, it was used as a PCSK9 inhibitor. Only 15 patients accepted inclisiran therapy. The treatment was initiated with inclisiran at a dose of 1.5 mL/300 mg. The LDL levels were rechecked at the end of the 6<sup>th</sup> and 12<sup>th</sup> months after the inclisiran therapy. Patients received the second and third doses of inclisiran at the 3<sup>rd</sup> and 9<sup>th</sup> months, respectively.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and gamma-glutamyl transferase (GGT) levels were assessed before and after inclisiran treatment, and any adverse effects were monitored.

Our study was conducted with the approval of Research Ethic Committee of the National Cardiac Society of Azerbaijan (decision no: 01/2025, date: 05.01.2025).

## Statistical Analysis

Descriptive statistics were employed to summarize the patient characteristics and LDL levels at different time points. Statistical assumptions were examined before conducting the tests. Normality was assessed using the Shapiro-Wilk test and histograms. Continuous variables are presented as the means and standard deviations (SD) for normally distributed data. Categorical variables were reported as frequencies and percentages.

To evaluate the effect of inclisiran treatment on the LDL levels over time, a paired t-test was conducted to compare the LDL levels before treatment with those at 6 months and 1-year post-treatment. The mean differences, SD, standard errors of the mean (SE), 95% confidence interval (CI), t-statistics, and p values were reported.  $P < 0.05$  was considered to indicate statistical significance. All statistical analyses were conducted using Statistical Package for the Social Sciences.

## RESULTS

Out of 77 patients, 35 underwent percutaneous coronary intervention (PCI) and 42 underwent coronary artery bypass grafting (CABG). At the 6<sup>th</sup> month after revascularization, only 2 patients (1 who underwent PCI and 1 who underwent CABG) who received the maximum dose of statin alone showed an LDL value of <55 mg/dL. In the remaining 75 patients, statin + ezetimibe combination therapy was initiated. At the end of the 1-year follow-up, only 12 patients (5 who underwent CABG and 7 who underwent PCI) achieved an LDL value of <55 mg/dL while receiving the statin + ezetimibe combination. The average age of the 77 patients who were followed up was 67 years (age range: 43-85 years, SD  $\pm 9$ ).

At the end of the 1<sup>st</sup> year, 15 out of 63 patients who did not achieve the target LDL values were started on inclisiran therapy. The average age of the 15 patients who received inclisiran therapy was 55 years (SD  $\pm 10.5$ ). Of the 15 patients, 12 had diabetes, while 13 had hypertension. The average LDL value before starting the inclisiran therapy for these 15 patients was 134.9 mg/dL (range: 75-247, SD  $\pm 49$  mg/dL) (Table 1).

After administering 2 doses of inclisiran, the LDL levels were measured at the 6<sup>th</sup> month of follow-up. A significant reduction was then observed in the LDL values at the first follow-up. Specifically, the average LDL cholesterol level decreased to 64.6 mg/dL (range: 22-129, SD  $\pm 32.2$  mg/dL) after the two doses of inclisiran. Among the 15 patients, 7 (46.7%) achieved the target values after the second dose. The mean decrease in LDL at 6 months was 70.27 mg/dL (SD=51.28, SE=13.24), with a 95% CI ranging from 41.87 to 98.67 mg/dL. The t-statistic was 5.307 with

14 degrees of freedom (df), and the p-value was <0.001, indicating a highly significant reduction in the LDL level. After the third dose, only 6 patients attended the LDL control in the 12<sup>th</sup> month. The average LDL value of these 6 patients at the 6<sup>th</sup> month was 63 mg/dL (SD ±24 mg/dL), at the 12<sup>th</sup> month was 43.1 mg/dL (SD ± 24.4 mg/dL), and at 1 year was 82.5 mg/dL (SD=28.85, SE=11.78), with a 95% CI of 52.22-112.78 mg/dL and a t-statistic of 7.005 (df=5, p=0.001). These findings confirm that inclisiran treatment leads to a sustained and significant decrease in LDL levels over time, with the reduction being more pronounced in the first year compared to that at 6 months. These findings suggest that inclisiran treatment causes a substantial and sustained reduction in LDL levels over time (Tables 2, 3).

**Table 1.** Demographic characterization and risk factors

	Sex	Age	Bilirubine mg/dL	Hypertension	Diabetes mellitus
1	M	60	0.4	+	+
2	M	62	0.04	+	+
3	M	51	0.1	-	-
4	F	62	0.5	+	+
5	M	40	0.9	-	+
6	F	47	0.1	+	+
7	M	41	0.05	+	+
8	M	62	0.02	+	+
9	F	74	0.5	+	+
10	F	52	0.6	+	+
11	M	44	0.03	+	-
12	M	69	0.5	+	+
13	M	57	0.8	+	+
14	F	60	0.02	+	-
15	M	42	0.4	+	+

M: Male, F: Female

**Table 2.** Changes in the LDL levels before and after inclisiran treatment

Comparison	Mean difference (mg/dL)	Standard deviation	Standard error	95% confidence interval (lower)	95% confidence interval (upper)	t-value	df	p value
LDL before vs. 6 months after inclisiran	70.27	51.28	13.24	41.87	98.67	5.307	14	<0.001
LDL before vs. 1 year after inclisiran	82.50	28.85	11.78	52.22	112.78	7.005	5	0.001

p<0.05; p<0.01 indicate statistically significant differences.  
LDL: Low-density lipoprotein

**Table 3.** Descriptive statistics for the LDL levels before and after inclisiran treatment

Timepoint	N	Minimum (mg/dL)	Maximum (mg/dL)	Mean (mg/dL)	Standard deviation
Overall LD levels	77	42	331	104	59
Before inclisiran	15	75	247	135	49
6 months after	15	22	129	65	32
1 year after	6	9	75	43	24

LD: Lactate dehydrogenase, LDL: Low-density lipoprotein

In the 3<sup>rd</sup> month of treatment with inclisiran, one patient exhibited a twofold increase in the ALT levels (81 U/L; normal range: 10-40 U/L) and an increase in the AST levels to the upper limit of the normal range (35 U/L; normal range: 9-35 U/L). In addition, one patient experienced a fourfold rise in the GGT levels (246 U/L; normal range: 8-61 U/L) in the 6<sup>th</sup> month of treatment. Changes in the liver enzymes were transient and spontaneously resolved. Subsequent follow-ups revealed that these values had restored; therefore, the inclisiran therapy was continued.

Another patient experienced side effects such as muscle and joint pain. After the use of inclisiran, the bilirubin levels were also checked, and no abnormalities were detected in any of the patients.

Among the 15 patients who received inclisiran therapy, the lowest recorded LDL level was 9 mg/dL. No adverse effects related to the low LDL level were observed in this patient.

More than 50% of the patients who received inclisiran therapy had an LDL level of >120 mg/dL, with an average age of 54 (SD ±10.5). In addition, these patients had risk factors such as diabetes and hypertension.

## DISCUSSION

The present findings demonstrated that the PCSK9 inhibitor, inclisiran, could reduce the LDL cholesterol levels by an average of 52% after two doses in patients who underwent LMCA intervention and received the ezetimibe + statin combination. After the third dose, the patients who continued with the inclisiran therapy exhibited further reductions in their LDL levels, demonstrating its effectiveness in achieving even lower values. No significant side effects were identified during the use of the drug.

Although the risk of restenosis and thrombosis has decreased with the use of intravascular imaging, new-generation stents, and advanced technical methods in stent implantation, failure to achieve the target LDL levels post-procedure remains associated with poor long-term outcomes.

As in all of the ischemic patient groups, statins play a crucial role in LDL control among patients who have undergone LMCA intervention. However, in the majority of patients, the target LDL levels are not achieved. Despite receiving maximal doses of statin + ezetimibe therapy, patients with residual high LDL levels, as well as those with statin intolerance, required additional treatment options. This finding indicated that increasing the use of PCSK9 inhibitors may help reduce future cardiovascular events.

Based on our observations, we suggest that, in complex coronary interventions, particularly in cases of multivessel disease, high thrombotic events, and atherosclerotic vascular diseases with active inflammation, aggressive lipid-lowering therapy and the early addition of PCSK9 inhibitors to the treatment should be considered.

Based on the study results, it can be concluded that, out of the total 279 patients included in the study, only 77 attended regular follow-up visits during one year. This finding shows that educational efforts are important to improve patient adherence to treatment. Our observations suggested that patients' awareness of their condition is not sufficiently high. Several patients have limited information about dyslipidaemia, cardiovascular diseases, and their complications, which leads to irregular medication adherence and inconsistent doctor follow-ups. The results of the SURF CHD II study, which also included patient data from Azerbaijan, highlight the negative factors such as the lack of patient knowledge, irregular drug intake, and patients not attending follow-up appointments for the management of chronic heart diseases.<sup>7</sup>

Under inclisiran treatment, only 2 out of 77 patients who attended the follow-up after 1 year did not reach the target LDL levels. However, a significant reduction in the LDL levels was observed in both of these patients when compared with their baseline levels.

In addition to medical treatment, detailed discussions were held with these patients regarding modifiable risk factors. In a study published during 2019-2021, which included data collected from Azerbaijan, the management of comorbidities and the modification of risk factors in patients with high ischemic risk were emphasized as crucial factors for improving patient outcomes. The study also highlights the gaps in our healthcare system regarding these areas.<sup>8</sup>

Although all patients received statin or statin + ezetimibe combination therapy after the LMCA intervention, the target LDL levels were achieved in only a small number of patients (14 of 77) over the course of 1 year. However, by the end of the 6<sup>th</sup> month, of the 15 patients who received inclisiran, 7 patients had already achieved their target LDL level. One nuance we would like to emphasize is that, no matter how aggressive the lipid-lowering therapy may be, the influence of concomitant risk factors such as familial hyperlipidaemia and diabetes on the LDL levels is undeniable.

During the study, in patients who received statin + ezetimibe combination therapy but did not reach the target LDL level, only 15 out of the 63 patients accepted treatment with inclisiran. An adequate organization of drug provision by the insurance system for regular adherence to lipid-lowering therapy is one of the key factors that can enhance patient compliance. The high cost of inclisiran was observed

as one of the main factors that could prevent reaching the target LDL levels. Resolving these problems, along with improving the quality of treatment in the healthcare system, can significantly contribute toward enhancing patients' health and reducing mortality from cardiovascular diseases. Future clinical trials and reforms in healthcare policy are expected to play a crucial role in this direction. Unfortunately, due to the widespread prevalence of cardiovascular diseases, delays in early diagnosis, and the limited accessibility to healthcare in Azerbaijan, life expectancy here is significantly lower when compared to that in other European countries, only surpassing one country.<sup>9</sup>

Our observations lead us to believe that if siRNA therapy is covered by insurance, there will be a considerable decrease in the number of cardiovascular diseases and their complications, and the outcomes of medical interventions will improve.

### Study Limitations

One of the main limitations of the study was the lack of randomization and the small number of patients enrolled. Moreover, only a limited number of patients who underwent LMCA intervention attended follow-up. In addition, owing to the lack of basal LDL levels of patients, we could not compare the LDL levels at the end of the 2<sup>nd</sup> year after statin, statin + ezetimibe, and inclisiran therapies. Furthermore, the majority of the patients recommended for inclisiran therapy did not accept it. After 6 months of the initiation of inclisiran, only 6 patients had their LDL levels reassessed at the 12-month follow-up, and the results of the remaining 9 patients' results were not included in the study. Another limitation of the study is that there was no control group for comparison. Risk factors such as smoking and family history were also not fully assessed in the included patients, and concomitant medications (other than anti-lipid treatment) were not included in the study. In the future, the progression of cardiovascular events should be compared between patients who received or did not receive inclisiran therapy.

## CONCLUSION

The results of this multicenter, retrospective study demonstrated that inclisiran significantly reduced the LDL levels in patients undergoing LMCA intervention. In the first follow-up after inclisiran treatment, a 52% reduction was achieved in the LDL levels when compared with that with the statin + ezetimibe combination therapy. After the second and third doses, this value was reduced even further. This finding suggests that inclisiran is a valuable additional treatment for high-risk patients, particularly for those who are intolerant to statins or are unable to reach the target LDL levels. Despite its effectiveness, the high cost and patients' lack of awareness were identified as the major barriers to its widespread use. Addressing these challenges through healthcare system reforms and expanded treatment coverage is expected to increase the effectiveness of inclisiran, thereby helping prevent cardiovascular diseases in the future.

**Ethics Committee Approval:** Our study was conducted with the approval of Research Ethic Committee of the National Cardiac Society of Azerbaijan (decision no: 01/2025, date: 05.01.2025).

**Informed Consent:** Because it is a retrospective study, informed consent is not required.

**Authorship Contributions:** Concept: U.R., E.K., Design: U.R., E.K., Data Collection or Processing: U.R., S.M., L.S., J.T., J.B., Z.S., A.I., K.J., K.M., H.S., V.Z., G.I., Analysis or Interpretation: U.R., K.A., E.K., S.M., Literature Search: U.R., K.A., Z.S., R.G., T.C., Writing: U.R., K.A., E.K., S.M., E.H., R.G., T.C.

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# Effects of Sodium-glucose Co-transporter-2 Inhibitors on Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction

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## ABSTRACT

**Background:** Treatment options for pulmonary hypertension (PH) associated with heart failure (HF) with preserved ejection fraction (HFpEF) remain limited. Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are a novel class of medications for HF, demonstrating efficacy regardless of diabetes status. These agents may lower left ventricular filling pressures, potentially reducing pulmonary pressure and enhancing right ventricular function. This study assessed the impact of SGLT2i on PH-HFpEF.

**Aim:** The aim of this study is to assess the impact of SGLT2i on echocardiographic and biochemical markers in patients with PH associated with HFpEF.

**Study Design:** This is a retrospective cohort study involving nine patients diagnosed with PH-HFpEF, treated at Pamukkale University. The study examines the changes in echocardiographic parameters and biochemical markers, specifically NT-proBNP levels, following long-term treatment with SGLT2i.

**Methods:** A retrospective analysis was conducted on nine patients with PH-HFpEF between April 2018 and October 2020. All exhibited echocardiographic features of HFpEF, had both pre- and postcapillary PH, and were treated with SGLT2i for a median duration of 27 months following standard HF therapy. Seven patients had a history of HF-related hospitalization, and PH was confirmed via right heart catheterization in five cases. Follow-up echocardiography was performed after at least 12 months of SGLT2i treatment.

**Results:** The mean patient age was 67 years, with a predominance of women (66%), and all had diabetes. Following SGLT2i initiation, none required hospitalization for HF. Hemodynamic parameters improved, including reductions in mean right atrial and pulmonary arterial pressures, decreased pulmonary vascular resistance, and enhancements in cardiac index and oxygen saturation. Additionally, tricuspid regurgitation velocity and N-terminal pro-brain natriuretic peptide levels significantly declined, indicating improved cardiac function.

**Conclusion:** Despite the high morbidity and mortality associated with this patient population, the findings suggest that SGLT2i may alleviate ventricular filling pressures, thereby reducing pulmonary pressures and potentially improving right ventricular function. Larger randomized trials are necessary to confirm these results.

**Keywords:** Heart failure with preserved ejection fraction, sodium-glucose co-transporter-2 inhibitors, pulmonary hypertension, echocardiography

## INTRODUCTION

Pulmonary hypertension (PH) is a progressive pulmonary vascular disease characterized by increased pulmonary vascular resistance and elevated pulmonary artery pressure (PAP) due to vascular remodeling. This condition inevitably leads to right heart failure (HF) and, in severe cases, death.<sup>1</sup> While the exact pathogenesis of PH remains unclear, multiple mechanisms contribute to its development.<sup>2</sup> Among these, inflammation plays a key role in pulmonary vascular remodeling. The involvement of inflammation in PH has been recognized for nearly 30 years.<sup>3</sup> Pulmonary vascular cells release inflammatory mediators that attract inflammatory cells, which in turn promote the secretion of cytokines, chemokines, and growth factors. This cascade triggers

vascular cell proliferation and collagen deposition, ultimately leading to pulmonary vascular remodeling.<sup>4,5</sup>

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are a class of medications that enhance glucose excretion through urine and were initially developed for diabetes mellitus (DM) management. However, recent research has identified them as a key treatment for HF, demonstrating benefits in patients both with and without DM, regardless of ejection fraction (EF). Notably, findings from the EMPEROR-Preserved and DELIVER randomized trials have shown that SGLT2i therapy can lower all-cause mortality and reduce hospitalizations in HF patients with mildly reduced or preserved EF.<sup>6,7</sup> N-terminal pro-brain natriuretic peptide (NT-proBNP), a commonly used biomarker in HF studies, is closely associated with ventricular wall tension and pressure

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increases. It serves as the indicator of functional and hemodynamic impairment in PH patients and is widely recognized as a prognostic marker in current guidelines.<sup>8</sup>

The poor prognosis associated with HF with preserved EF (HFpEF) is largely attributed to PH. PH is defined by a mean PAP exceeding 20 mmHg at rest, as measured by cardiac catheterization.<sup>9</sup> In HFpEF patients, the presence of PH is linked to worse clinical outcomes.<sup>10</sup> The reported prevalence of PH in HFpEF ranges from 31% to 88%, depending on disease severity, diagnostic criteria, and the method of assessment, whether echocardiography or cardiac catheterization.<sup>11,12</sup>

In addition to their primary glucosuric, natriuretic, and diuretic effects, SGLT2i have been found to directly inhibit the Na-H exchanger 1 receptor on the cell surface, leading to increased intracellular sodium and calcium levels.<sup>13</sup> Experimental studies have also demonstrated that SGLT2i therapy reduces cardiac fibrosis and oxidative stress.<sup>14</sup> Other benefits include improved endothelial function, decreased secretion of pro-inflammatory chemokines, and lower adipokine levels.<sup>15,16</sup> Beyond these effects, SGLT2i therapy enhances energy metabolism by increasing ketone body production, reduces atherosclerosis, influences the renin-angiotensin system, and elevates glucagon levels.<sup>17</sup> Although these mechanisms contribute to improved clinical outcomes, the exact mode of action of SGLT2i remains incompletely understood.

Subgroup analyses from the EMBRACE HF study have demonstrated that empagliflozin treatment significantly reduces pulmonary artery diastolic pressure.<sup>18</sup> Additionally, the study indicated that pulmonary pressure remained low even one week after discontinuing SGLT2i therapy, suggesting a mechanism of action beyond its diuretic effect. Ongoing research continues to explore new hypotheses regarding the efficacy and potential mechanisms of SGLT2i therapy.

The aim of this study was to evaluate the clinical response to SGLT2i therapy in patients with PH and HFpEF and to assess its effects on cardiac function.

The findings of this study have been previously presented in abstract form.<sup>19</sup>

## METHODS

### Study Design and Setting

This retrospective study was conducted at the Cardiology and Endocrinology Clinics of Pamukkale University between April 2018 and October 2020. Patients who met the inclusion criteria and did not meet the exclusion criteria during this period were enrolled. The study aimed to assess the effects of SGLT2i in patients with PH associated with HFpEF.

### Participants

Participants with DM were eligible for inclusion if they met the following criteria:

- DM was diagnosed based on one of the following: fasting plasma glucose  $\geq 126$  mg/dL, 2-h plasma glucose  $\geq 200$  mg/dL during a 75-g oral glucose tolerance test, random plasma glucose  $\geq 200$  mg/dL accompanied with classic hyperglycemic symptoms, or HbA1c  $\geq 6.5\%$ .<sup>20</sup>

- Diagnosis of HFpEF with echocardiographic evidence of combined pre- and postcapillary PH.

- Initiation of SGLT2i therapy at least 3 months before inclusion and continued use throughout the study.

- Availability of complete medical records and follow-up data for at least 1 year after starting SGLT2i therapy.

Patients were excluded if they:

- Had PH classified as groups 1, 3, 4, or 5.

- Did not have a follow-up period of at least 12 months after initiating SGLT2i therapy.

### Interventions and Measurements

SGLT2i therapy included various agents prescribed as part of standard HF treatment protocols, without preference for a specific drug. The primary interventions consisted of:

- Routine HF therapy, including beta-blockers (BB), renin-angiotensin-aldosterone system inhibitors, and mineralocorticoid receptor antagonists, administered according to the latest guidelines before and during the study. No patient received pulmonary arterial hypertension therapy.

- Echocardiographic and right heart catheterization assessments performed as part of routine clinical care.

### Intervention Details

- **Echocardiography:** Assessments included left ventricular EF, PAP estimates, and diastolic dysfunction parameters (E/ $\dot{e}$  ratio, left atrial volume index). Echocardiographic evaluations were conducted at baseline and 12 months after initiating SGLT2i therapy.

- **Right heart catheterization:** Performed before study enrollment to confirm the diagnosis of PH. This procedure provided measurements of PAP, right atrial (RA) pressure, and cardiac output.

### Data Collection

Patient medical records were reviewed retrospectively to gather data on demographics, medical history, HF management, and outcomes related to hospitalization and echocardiographic changes. The duration of SGLT2i therapy was documented, with an average use of 27 months (range: 15-45 months).

Our study was conducted with the approval of Pamukkale University's Medical Ethics Committee (decision no. 60116787-020/32203, date: 08.05.2018).

### Statistical Analysis

Data analysis was performed using Statistical Package for the Social Sciences version 25.0. Continuous variables were reported as mean  $\pm$  standard deviation or median (minimum-maximum), while categorical variables were expressed as frequencies and percentages. The Shapiro-Wilk test was used to assess data distribution normality. For dependent group comparisons, the paired t-test was applied when parametric assumptions were met, whereas the Wilcoxon matched-pairs signed-rank test was used otherwise. A p value of  $<0.05$  was considered statistically significant for all tests.

## RESULTS

### Demographic and Clinical Characteristics

The study included nine patients with a mean age of 67 years, the majority of whom were female (66%). All patients had a history of DM and multiple risk factors for PH associated with HFpEF. Detailed demographic and clinical characteristics are presented in Table 1.

Following the initiation of SGLT2i therapy, none of the patients required hospitalization due to HF. The majority were classified as World Health Organization functional class III. The mean hemodynamic parameters were as follows: RA pressure,  $10.8 \pm 3.27$  mmHg; pulmonary arterial pressure,  $35.6 \pm 5.59$  mmHg; pulmonary vascular resistance,  $3.6 \pm 1.34$  WU; Fick cardiac index,  $3 \pm 0.87$  l/min/m<sup>2</sup>; and mixed venous oxygen saturation,  $68.2 \pm 9.44\%$ .

Notably, treatment with SGLT2i led to a significant reduction in tricuspid regurgitation velocity (TRV) from  $3.6 \pm 0.7$  m/s to  $3.09 \pm 0.53$  m/s ( $p=0.019$ ). Additionally, NT-proBNP levels showed a significant decline from 2650.44 ng/L to 1288.67 ng/L ( $p=0.028$ ) (Table 2). However, no significant changes were observed in systolic PAP and RA pressure.

These findings highlight significant improvements following SGLT2i therapy, supporting its potential benefits in patients with PH-HFpEF.

## DISCUSSION

Our study demonstrated notable improvements in TRV and NT-proBNP levels following SGLT2i therapy in patients with HFpEF and PH. These results align with previous research supporting the efficacy of SGLT2i in enhancing cardiac function and hemodynamics. For example, a retrospective study reported improved right ventricular (RV) systolic function and reduced pulmonary arterial stiffness after 6 months of SGLT2i therapy in patients with HF with reduced EF (HFrEF).<sup>21</sup>

Additionally, another study observed significant enhancements in RV systolic functions within three months of adding SGLT2i to optimal medical therapy in HFrEF patients.<sup>22</sup> Experimental models further support these findings, showing that dapagliflozin can improve echocardiographic parameters and reduce cardiomyocyte apoptosis, which may aid in pulmonary artery remodeling and alleviate RV dysfunction.<sup>23</sup> The same study suggested that these benefits could be attributed to reduced apoptosis in RV cardiomyocytes. Previous research has emphasized the role of apoptosis in RV remodeling, indicating that increased apoptosis contributes to the progression of right HF.<sup>24</sup> These findings suggest that the antiapoptotic properties of SGLT2i therapy may play a role in improving clinical outcomes in this patient population.

An experimental PH model study found that combining dapagliflozin with sildenafil may be beneficial for pulmonary vascular remodeling. The study showed that dapagliflozin lowered RV systolic pressure, reduced RV hypertrophy and pulmonary vascular remodeling, and suppressed inflammatory mechanisms.<sup>25</sup> Consistent with these findings, our study also observed a significant reduction in the TRV values following SGLT2i treatment.

Additionally, a subgroup analysis of the multicenter, randomized, double-blind EMBRACE-HF study demonstrated that empagliflozin significantly lowered pulmonary artery diastolic pressure in patients with HFpEF or HFrEF who had CardioMEMS PAP sensors, compared to placebo.<sup>18</sup> While that study did not find a significant change in NT-proBNP levels, our study observed a notable reduction in NT-proBNP following SGLT2i therapy.

**Table 1.** Demographic and clinical characteristics of patients

Patient	Sex	Age	HT	DM	CKD	COPD	CAD	AF	OSAS	Treatment (month)	Med	Pre TRV	Pre sPAP	Pre SAA	Pre NT-proBNP	Pre VKI	Pre TRV	Post sPAP	Post RAA	Post NT-proBNP	Post VCI	mSAP	PVR	fCI	mVO2	mPAP
1	F	66	+	+	-	+	-	-	-	27	Empa	3.3	48	25	129	18	3.2	47	25	110	15	7	3	NR	75	35
2	F	67	+	+	-	-	+	+	-	27	Empa	3.6	60	30	4284	21	3.4	65	27	2399	NR	12	3	2.4	73	33
3	M	67	+	+	-	-	-	-	-	29	Empa	3.3	47	22	103	15	3.2	45	NR	32	18	8	3	4	75	28
4	F	71	+	+	-	-	+	+	-	38	Empa	3.5	52	20	572	22	2.9	39	17	742	14	15	6	2.6	65	40
5	M	66	-	+	-	-	+	-	-	45	Empa	2.63	31	NR	1964	NR	2.1	NR	NR	1026	NR	NR	NR	NR	NR	NR
6	M	70	+	+	+	+	-	+	-	38	Empa	3.7	61	20	3724	NR	2.9	39	NR	3701	18	NR	NR	NR	NR	NR
7	F	67	+	+	+	-	+	+	-	16	Dapa	3	46	NR	3372	19	3	45	32	2048	22	NR	NR	NR	NR	NR
8	F	62	-	+	+	+	-	-	-	15	Dapa	4.7	90	NR	8092	NR	3	42	14	268	13	NR	NR	NR	NR	NR
9	F	67	+	+	+	-	-	-	+	16	Dapa	4.7	100	25	1614	22	4.1	77	NR	1272	22	12	3	NR	53	42

F: Female, M: Male, HT: Hypertension, DM: Diabetes mellitus, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, AF: Atrial fibrillation, OSAS: Obstructive sleep apnea syndrome, Pre: Pre-treatment with sodium-glucose co-transporter 2 inhibitor (SGLT2i), Post: Post-treatment with sodium-glucose co-transporter 2 inhibitor (SGLT2i), TRV: Tricuspid regurgitation velocity, sPAP: Systolic pulmonary artery pressure, RAA: Right atrium area, NT-proBNP: N-terminal Pro B-type natriuretic peptide, VCI: Inferior vena cava, mSAP: Mean right atrium pressure, PVR: Pulmonary vascular resistance, fCI: Fick cardiac index, mVO2: Mixed venous oxygen saturation, mPAP: Mean pulmonary artery pressure, Dapa: Dapagliflozin, Empa: Empagliflozin

**Table 2.** Echocardiographic changes before and after SGLT2i treatment

		Before treatment	After treatment	p	Delta
TRV (n=9)	Mean±SD	3.6±0.7	3.09±0.53	0.019*	0.51±0.53
	Med (min-max)	3.5 (2.63-4.7)	3 (2.1-4.1)		0.53 (0-1.7)
NT-proBNP (n=9)	Mean±SD	2650.44±2565.75	1288.67±1225.11	0.028*	13.13±17.48
	Med (min-max)	1964 (103-8092)	1026 (32-3701)		342 (170-7824)
sPAP (n=8)	Mean±SD	63±20.71	49.88±13.73	0.071	1361.78±2521.48
	Med (min-max)	56 (46-100)	45 (39-77)		7.5 (5-48)
RA (n=3)	Mean±SD	25±5	23±5.29	0.157	2±1.73
	Med (min-max)	25 (20-30)	25 (17-27)		3 (0-3)

\*p<0.05 indicates statistical significance. Delta, difference before and after treatment. Post-treatment, after treatment with the SGLT2i. Pre-treatment, before treatment with the SGLT2i.

NT-proBNP: N-terminal B-type natriuretic peptide (pg/mL), TRV: Tricuspid regurgitation velocity (m/sn), RA: Right atrium (mm), sPAP: Systolic pulmonary artery pressure (mmHg), SD: Standard deviation, Mean: Average, Med: Median, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, min-max: Minimum-maximum

The benefits of SGLT2 inhibitors go beyond simple intravascular decongestion. Research by Pabel et al.<sup>26</sup> has shown that empagliflozin can reduce myocardial filament passive stiffness and improve diastolic function. These effects are believed to result from decreased oxidative stress and inflammation, increased nitric oxide availability, and reduced myocardial fibrosis and hypertrophy.<sup>27-29</sup> These molecular mechanisms may explain the pathophysiological improvements observed in our study participants, highlighting a broader impact on cardiac function in HFpEF with PH.

In HFpEF, while multiple factors contribute to disease pathogenesis, diastolic dysfunction remains a key underlying cause.<sup>30</sup> Elevated left ventricular filling pressures lead to passive pulmonary venous congestion and postcapillary PH.<sup>31</sup> This progression triggers pulmonary vasoconstriction and hypertension, ultimately placing increased strain on the right ventricle. Pulmonary arteriolar resistance plays a central role in these pathological processes, raising the question of whether pharmacological treatment can slow or reverse this deterioration. Our findings suggest that SGLT2i therapy may influence these mechanisms, potentially preventing the progression of PH and RV overload—both of which contribute to worsening clinical outcomes in these patients. To date, therapies such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and BB have been explored, but with limited effectiveness. In particular, BB have not been demonstrated improvements in mortality or hospitalization rates among patients with HFpEF.<sup>32</sup>

Treatment with SGLT2i has shown significant benefits in patients with HFpEF, both through its molecular effects on key pathophysiological processes and in clinical trials such as EMPEROR-PRESERVED and DELIVER.<sup>33</sup> These studies have provided strong evidence supporting the role of SGLT2i therapy in managing this complex condition. Consistent with these findings, our study further highlights the efficacy of SGLT2i, demonstrating significant reductions in TRV and NT-proBNP levels—markers of reduced cardiac stress and improved heart function in patients with HFpEF and PH. These results not only reinforce previous research but also contribute to a deeper understanding of the potential

mechanisms through which SGLT2i may slow the progression of PH and RV overload, both of which are key factors in worsening clinical outcomes for this patient group.

### Study Limitations

Despite the promising results, our study has several limitations. As a pilot study assessing the potential effects of SGLT2i in a specific patient population, it included only nine patients, which restricts its generalizability and statistical power. All eligible patients who met the inclusion criteria and did not meet the exclusion criteria were included; therefore, a power analysis was not conducted. Additionally, the retrospective design limits the ability to establish direct causality. Since the study was conducted at a single center, the findings may not be broadly applicable to other clinical settings. These limitations highlight the need for future research, particularly prospective, multicenter studies with larger sample sizes, to confirm and expand upon our results. Such studies would provide a more comprehensive evaluation of the efficacy and safety of SGLT2i and further clarify their mechanisms of action.

Furthermore, the absence of a control group and the relatively short follow-up period restricted the ability to compare different treatment groups and assess long-term outcomes. Due to the small sample size, comparisons between different SGLT2i, such as empagliflozin and dapagliflozin, were not conducted. Additionally, no significant renal side effects or decline in estimated glomerular filtration rate were observed, which aligns with existing literature indicating that such effects are uncommon. However, the short follow-up period and limited sample size may have prevented the detection of rarer or delayed adverse effects.

### CONCLUSION

This study demonstrated the efficacy of SGLT2i therapy in patients with HFpEF and PH, as evidenced by significant improvements in TRV and NT-proBNP levels. However, the study's retrospective design, single-center setting, and small sample size represent key limitations. The

study specifically included diabetic patients with echocardiographic evidence of combined pre- and postcapillary PH who had received SGLT2i therapy for at least one year, with follow-up echocardiographic assessments conducted after one year of treatment.

These findings may provide valuable insights for future large-scale studies focused on HFpEF patients with PH. Further prospective research with larger sample sizes could help validate and expand upon these results, potentially revealing more significant clinical outcomes. Additionally, this study highlights the need for further investigation into the impact of SGLT2i therapy on the necessity and outcomes of invasive right heart catheterization, which is traditionally used for PH management. Experimental models of PH could also be developed to explore the early effects of SGLT2i treatment in a controlled setting.

**Ethics Committee Approval:** Our study was conducted with the approval of Pamukkale University's Medical Ethics Committee (decision no. 60116787-020/32203, date: 08.05.2018).

**Informed Consent:** Because it is a retrospective study, informed consent is not required.

**Authorship Contributions:** Concept: I.T., Y.T.Y., G.F.Y., Design: I.T., Y.T.Y., G.F.Y., Data Collection or Processing: Y.T.Y., G.F.Y., Analysis or Interpretation: Y.T.Y., Literature Search: I.T., Writing: I.T.

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**CASE REPORT**

# Simultaneous Percutaneous Closure of a Patent Foramen Ovale and Left Atrial Appendage

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## ABSTRACT

Percutaneous closure of the left atrial appendage (LAA) is an alternative treatment for stroke prevention in patients with atrial fibrillation who cannot tolerate oral anticoagulation. The conventional method involves transeptal puncture to access and seal the LAA. However, recent studies have investigated the possibility of performing LAA closure through a patent foramen ovale (PFO) tunnel. This case aims to illustrate the simultaneous closure of both the LAA and PFO using the PFO tunnel as the access route.

**Keywords:** Interventional cardiology, left atrial appendage, patent foramen ovale, percutaneous closure

## INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia, with its prevalence increasing with age. Stroke is a frequent complication of non-valvular AF (NVAF). Percutaneous left atrial appendage (LAA) closure is a key treatment for stroke prevention in patients with NVAF, particularly those who cannot tolerate oral anticoagulation.<sup>1</sup> Both the LAA in patients with AF and a patent foramen ovale (PFO) or atrial septal defect (ASD) are major sources of cardioembolic stroke. Combining LAA closure with PFO/ASD closure may offer an optimal approach to stroke prevention. This report describes a case of simultaneous percutaneous closure of a PFO and LAA.

## CASE REPORT

A 76-year-old woman with permanent AF, hypertension, diabetes mellitus, and dyslipidemia was referred for transesophageal echocardiography (TOE) and LAA closure. One month earlier, she had been hospitalized for massive gastrointestinal bleeding while on warfarin, requiring a blood transfusion of approximately 14 units. Her CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores were both 5. She was switched to apixaban at discharge but subsequently experienced an ischemic stroke while on medication.

Electrocardiography showed AF with a mean heart rate of 90 bpm. Chest radiography was remarkable, and there was no significant family history. Blood tests revealed mildly elevated glucose and cholesterol levels, along with an increased D-dimer level. Physical examination

showed mild swelling in the left leg, and Doppler ultrasonography confirmed deep vein thrombosis in the same leg. Preprocedural TOE identified a small shunt in the interatrial septum, consistent with a PFO (Figure 1A, Video 1). A bubble study demonstrated a significant right-to-left shunt, and the LAA was visualized with no thrombus (Figure 1B, Video 2). Given her medical history and comorbidities, simultaneous PFO and LAA closure was selected to eliminate the need for oral anticoagulation.

Intravenous proton pump inhibitor therapy was initiated, and oral anticoagulation was replaced with subcutaneous low-molecular-weight heparin. The procedure was performed under general anesthesia using right femoral vein access, with fluoroscopic and 2D/3D TOE guidance. A 25-mm Amplatzer Amulet LAA occluder and a 25-mm Amplatzer PFO occluder were selected. Transeptal access was achieved using an SL 1 sheath and Inoue wire, followed by the insertion of a 12 Fr delivery sheath.

The LAA occlusion device was carefully advanced, and its position was confirmed using fluoroscopy and TOE (Figure 1C, Video 3). Deployment was adjusted to ensure optimal placement, with contrast imaging used to verify device position and assess for leakage (Figure 1D, Video 4). The PFO occluder was implanted using the standard technique (Figure 1E, Video 5). Device positioning was evaluated in the left anterior oblique view (Figure 1F). A follow-up TOE performed 45 days later showed no device-related complications, with both the PFO or LAA occluders in stable positions (Figures 1G and 1H).

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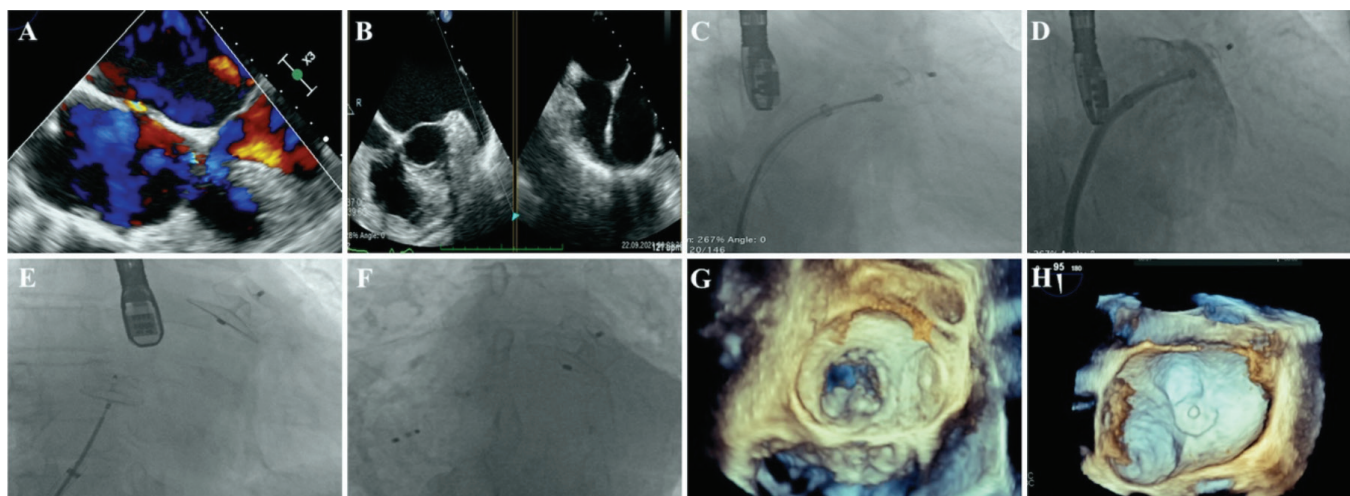
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**Figure 1.** A) Transesophageal echocardiography with color Doppler showing a small shunt in the interatrial septum, consistent with a patent foramen ovale. B) Transesophageal echocardiography confirming the absence of thrombus in the left atrial appendage. C) Optimal positioning of the device was verified. D) Contrast imaging confirmed the absence of leakage. E) Implantation of the patent foramen ovale occlusion device. F) Confirmation of device positions. G, H) Follow-up transesophageal echocardiogram performed 45 days later showed no device-related anomalies in the patent foramen ovale and left atrial appendage positions

## DISCUSSION

The PFO was positioned anterosuperiorly, while the LAA was located anterolaterally. Transeptal access via the PFO can be challenging due to the cranioanterior orientation of the LAA. Proper alignment may require external rotation and the assistance of two operators.<sup>2</sup> Studies have reported high success rates for device implantation, with major complication rates similar to those of standard techniques.<sup>3</sup> Long-term outcomes of transeptal access through a PFO or ASD have demonstrated comparable efficacy in stroke prevention and similar safety profiles. Simultaneous PFO/ASD closure did not prolong fluoroscopy time but required a higher contrast volume. Additionally, this approach was associated with a lower incidence of stroke and transient ischemic attacks compared to other methods.

## CONCLUSION

Transeptal access via a PFO or ASD allows entry into the left atrium while reducing the risk of complications associated with transeptal puncture, such as perforation of the left atrial free wall or aortic root. Compared to transeptal puncture, utilizing a PFO or ASD for left atrial access is a viable and safe alternative when using Amplatzer systems for LAA closure. Additionally, performing simultaneous PFO or ASD closure may offer further protection against systemic embolization without increasing procedural risk.

**Informed Consent:** Written consent was obtained from the patient and their relatives for the inclusion of case details and personal information.

**Authorship Contributions:** Surgical and Medical Practices: Z.E.G., R.Z., Concept: R.Z., Design: R.Z., Data Collection or Processing: Z.E.G., Analysis or Interpretation: R.Z., Literature Search: Z.E.G., Writing: Z.E.G.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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**Video 1.** Transesophageal echocardiogram visualization of the patent foramen ovale shunt



<https://www.youtube.com/watch?v=VzPj-M19XWs>

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**Video 2.** Confirmation of the absence of thrombus in the left atrial appendage



<https://www.youtube.com/watch?v=3xs9vAAhu2A>

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**Video 3.** Implantation of the Amulet device



<https://www.youtube.com/watch?v=bR83v1cwSEI>

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**Video 4.** Verification of no contrast leakage upon injection



<https://www.youtube.com/shorts/7i3RvkTGoPg>

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**Video 5.** Implantation of the patent foramen ovale occlusion device



<https://www.youtube.com/watch?v=eaV8HPrM6tc>

**CASE REPORT**

# A Life-threatening Focal Refractory Vasospasm: Is Stenting the Last or First Option?

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**ABSTRACT**

Coronary vasospasm typically occurs in the epicardial coronary arteries and presents with a range of clinical manifestations. Its management is primarily conservative, involving medical therapy with nitrates and calcium channel blockers. Percutaneous coronary intervention (PCI) is rarely required and is generally not considered the first-line treatment. However, for cases of focal vasospasm, percutaneous coronary stenting may serve as a definitive therapeutic option. This report presents a case of focal refractory vasospasm successfully treated with PCI.

**Keywords:** Coronary vasospasm, interventional cardiology, refractory variant angina, ventricular tachycardia

**INTRODUCTION**

Coronary vasospasm is a condition that can affect both focal and diffuse segments of the epicardial or microvascular coronary arteries. It is frequently associated with variant angina, which is characterized by angina episodes at rest, preserved exercise capacity, and transient ST-segment changes on electrocardiography (ECG).<sup>1</sup> A significant proportion of myocardial infarctions associated with nonobstructive coronary arteries is attributed to coronary vasospasm.<sup>2</sup> This condition may present as a focal event involving a single vessel or as a diffuse phenomenon affecting multiple vessels.<sup>3</sup> The clinical spectrum varies, and prolonged angina can lead to severe complications such as myocardial infarction, atrioventricular (AV) block, ventricular arrhythmias, cardiac arrest, and even death.<sup>4</sup>

The primary management approach includes lifestyle modifications, nitrates, and calcium channel blockers. However, in cases of vasospastic angina that are refractory to medical therapy, percutaneous coronary intervention (PCI) with stent implantation may be considered, particularly in patients with focal vasospasm.<sup>5</sup> This case report describes a patient with refractory vasospastic angina caused by a focal coronary lesion.

**CASE REPORT**

A 47-year-old male smoker with a history of hypertension and diabetes presented with acute coronary syndrome due to anginal symptoms

persisting for several hours. ECG showed ST-segment changes in the anterior leads (Figure 1). Coronary angiography revealed critical stenosis in the proximal left anterior descending (LAD) artery (Figure 2A). However, this stenosis resolved after intracoronary nitrate administration, confirming the presence of vasospasm (Figure 2B). The patient was initiated on nitrate therapy, a calcium channel blocker, a statin, and aspirin, along with lifestyle modifications.

Seven days later, he presented to another emergency department with recurrent chest pain. During hospitalization, ventricular tachycardia (VT) occurred, requiring cardiopulmonary resuscitation for 3 min. He was subsequently transferred to our facility via ambulance, and an implantable cardioverter-defibrillator was planned. Coronary imaging findings remained consistent with those of the previous angiography.

Due to persistent anginal attacks and troponin levels exceeding 10 times the normal limit, repeat coronary angiography was performed. The findings confirmed focal vasospasm with critical stenosis in the proximal LAD (Figure 3A). Given that the vasospasm was refractory to medical therapy, induced ECG changes in the anterior leads, and was associated with VT, a drug-eluting stent was implanted (Figure 3B). The patient remained asymptomatic throughout a 6-month follow-up period.

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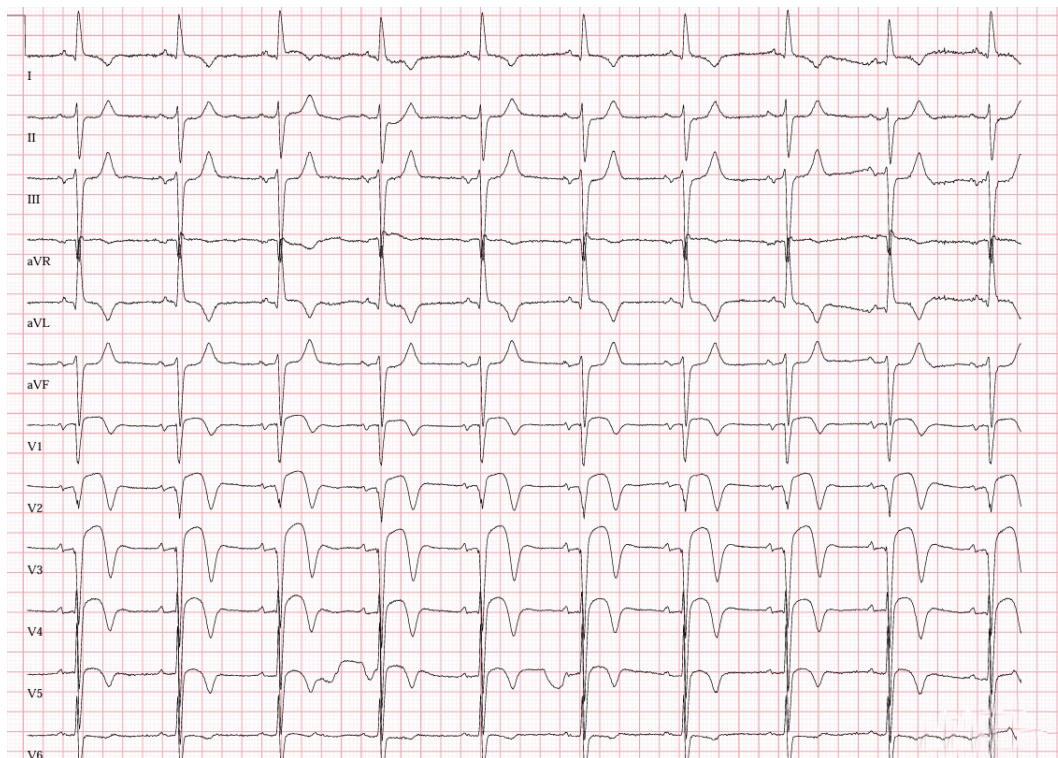
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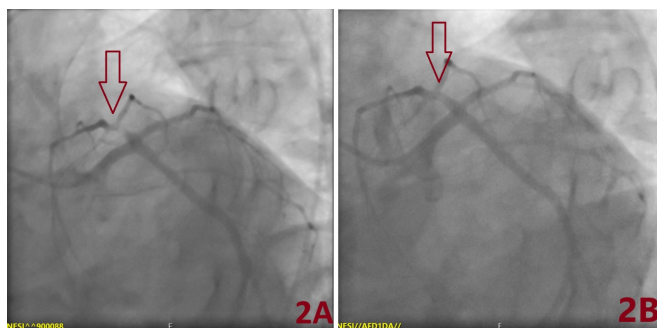
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**Figure 1.** Electrocardiography during angina



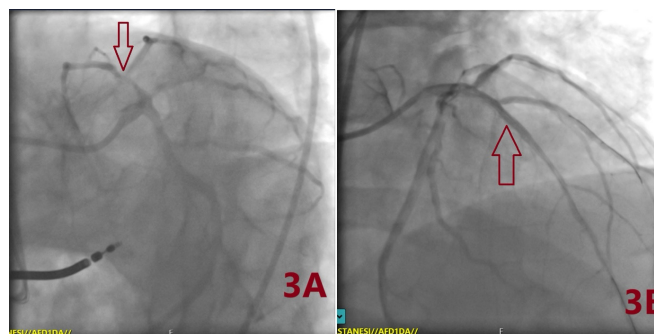
**Figure 2.** A) Critical stenosis in the LAD artery. B) After nitrate control image  
LAD: Left anterior descending

## DISCUSSION

Coronary artery vasospasm is a diagnosis of exclusion in cases of acute coronary syndrome. When indicated, provocative tests should be conducted to confirm the diagnosis, as early identification is crucial for preventing life-threatening complications such as arrhythmias and heart failure.<sup>6</sup>

## CONCLUSION

In this case, focal, refractory, and life-threatening vasospasm was successfully managed with PCI. While lifestyle modifications and pharmacological therapy remain the first-line treatments, stenting should be considered in refractory cases. In particular, for focal vasospasms affecting coronary arteries that supply large myocardial territories-such as the proximal LAD-stenting may be an appropriate



**Figure 3.** A) Focal vasospasm in the proximal LAD. B) Image after stent implantation  
LAD: Left anterior descending

intervention, especially in patients with associated life-threatening ventricular arrhythmias.

**Informed Consent:** Written informed consent was obtained from the patient.

**Authorship Contributions:** Concept: E.Y., U.V., F.K., Design: E.Y., U.V., C.Ö., Data Collection or Processing: C.Ö., E.Y., O.D., U.V., Analysis or Interpretation: U.V., F.K., Literature Search: E.Y., U.V., F.K., C.Ö., Writing: E.Y., U.V.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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## Endurance Cycling and Coronary Collateral Development: A Case Report of a Natural Bypass

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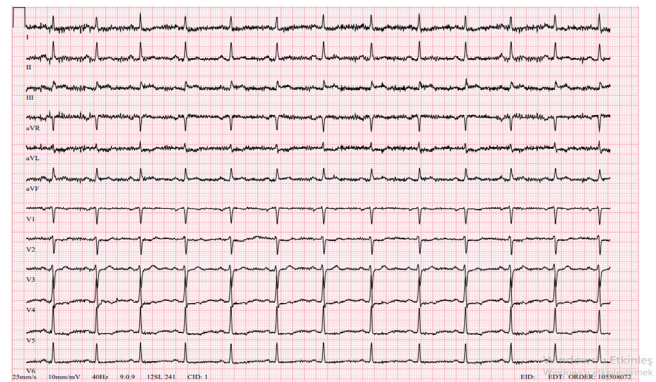
**Keywords:** Chronic total occlusion, coronary collateral, cycling

Chronic total occlusions (CTOs) are defined as complete blockages of the coronary arteries persisting for at least 3 months.<sup>1</sup> Typically, patients with CTO experience stable angina pectoris unless additional coronary lesions progress, leading to unstable angina. During acute myocardial infarction or elective percutaneous coronary intervention (PCI), the presence of a CTO in one coronary artery that receives blood supply from another via coronary collaterals presents an interventional challenge.<sup>2,3</sup> Coronary collaterals are natural connections between arteries that facilitate blood flow to the myocardial region supplied by an occluded vessel, partially or fully preserving its integrity. The diameters of these collaterals range from 40 to 200  $\mu\text{m}$ , with most being smaller than the spatial resolution of coronary angiography, limiting their visualization. This report presents a case in which a well-developed coronary collateral, functioning as a natural bypass graft, originates near the right coronary artery (RCA) ostium at the level of the right sinus of Valsalva and extends retrogradely to the left anterior descending (LAD) ostium. Angiographic images will illustrate the case of a patient who underwent coronary angiography due to acute myocardial infarction.

A 67-year-old man with a history of hypertension presented to the emergency department with epigastric pain. He had no prior history of angina pectoris or angina-equivalent symptoms and reported long-term participation in cycling. Electrocardiography revealed ST elevation in the inferior leads, prompting his transfer to the coronary angiography laboratory (Figure 1). Imaging of the left coronary system did not reveal the LAD ostium. Given the possibility of separate origins for the LAD and circumflex (Cx) arteries, a non-selective search was conducted at the level of the left sinus of Valsalva, but no additional ostium was identified. Consequently, the LAD was presumed to be occluded at its ostium. Additionally, Rentrop 1 collateral flow to the RCA was observed in left system imaging.

Visualization of the right coronary system revealed a proximal total occlusion of the RCA, along with a collateral vessel originating from the RCA ostium and supplying the left system, providing Rentrop 3 flow to the LAD ostium. This collateral had an approximate diameter of 2.6-mm. A thin collateral was also noted extending from the RCA ostium to the LAD ostium. Using a JR4 diagnostic catheter, selective imaging was performed, showing that this collateral supplied retrograde grade 2 flow to the RCA (Figure 2). During selective imaging, the patient's hemodynamic status deteriorated, leading to ventricular fibrillation. Immediate defibrillation was performed, successfully restoring normal sinus rhythm. The patient regained consciousness, and hemodynamic parameters returned to normal.

Selective insertion of the JR4 guiding catheter into the RCA was performed rapidly. A floppy guidewire successfully crossed the total occlusion and was advanced to the distal RCA. After predilatation using a 2.0 $\times$ 15-mm percutaneous transluminal coronary angioplasty balloon, a 2.75 $\times$ 24-mm drug-eluting stent was implanted proximally



**Figure 1.** ST elevation in the inferior leads on ECG  
ECG: Electrocardiography

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in the RCA with optimal ATM. In-stent optimization was then carried out using a 3.0×20-mm non-compliant balloon, followed by proximal optimization at high ATM. Postprocedure imaging confirmed TIMI-3 distal flow in the RCA, and retrograde flow to the distal LAD was observed after PCI to the RCA. The procedure was successfully completed (Figure 3). The final angiographic image demonstrated a complex circulatory connection between the right and left coronary systems, characterized by a well-developed collateral network and thin collateral vessels. This intricate vascular structure exhibited unique anatomical and physiological properties, functioning as alternative pathways. The patient was scheduled for monitoring in the coronary intensive care unit.

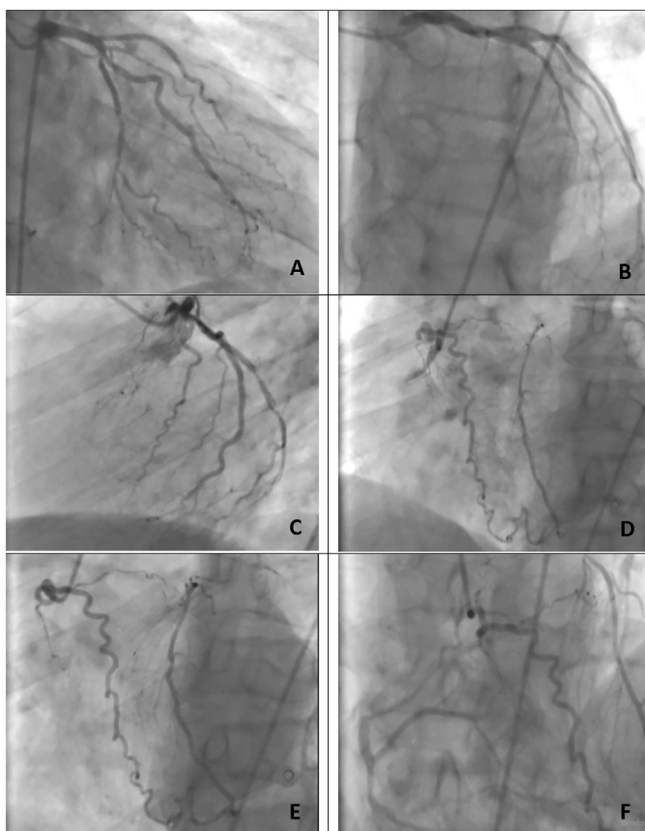
Follow-up transthoracic echocardiography revealed an ejection fraction of 55%, with hypokinesia in the inferior wall of the left ventricle. However, no contraction abnormalities were observed in the myocardial regions corresponding to the LAD territory. The patient remained under observation postprocedure, and medical therapy was adjusted accordingly. Given the presence of a 50-60% intermediate stenosis in the mid-Cx region observed on angiography, myocardial perfusion scintigraphy was planned, and the patient was subsequently discharged.

Coronary collateral circulation plays a crucial role in preventing ischemia and offers several benefits, including reducing infarct size, improving left ventricular function postinfarction, and enhancing long-term survival. Adequate coronary collateral circulation is present in approximately one-third of patients with hemodynamically significant coronary lesions. Identifying the factors that promote the development of this circulation could contribute to better cardiovascular outcomes.

During exercise, both cardiac output and coronary blood flow increase, creating a pressure gradient across a stenotic lesion. This pressure difference directs blood toward anastomotic channels that may serve as precursors for collateral formation. However, multiple studies have not established a clear association between exercise and the development of coronary collaterals in patients with coronary artery disease.

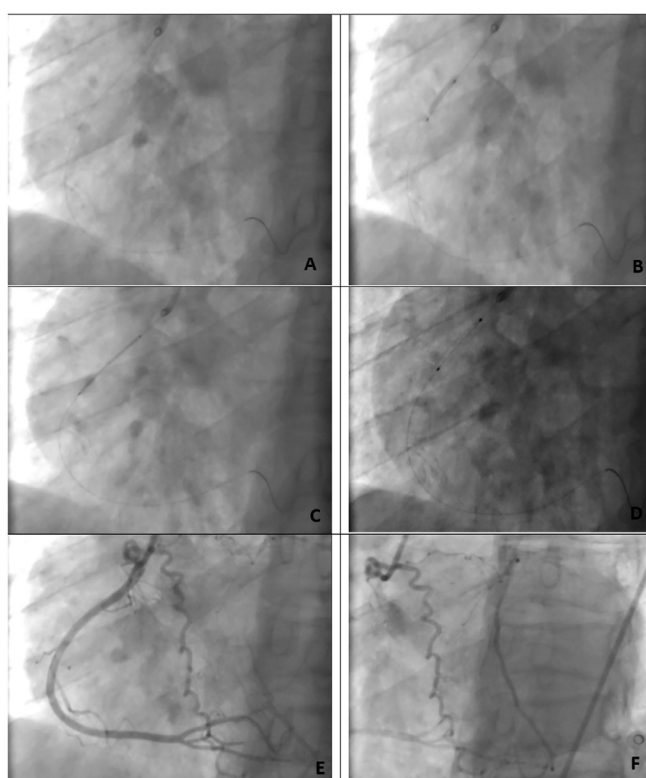
A previous study examining the impact of coronary collaterals on the clinical characteristics of coronary artery disease included 119 patients, comparing 61 patients with angiographically visible collaterals to 58 patients without collaterals. The study found no significant relationship between collateral presence and a physically active lifestyle.<sup>4</sup>

In another study, 20 male patients with acute myocardial infarction were divided into exercise and control groups. No difference was



**Figure 2.** A, B, C) Left-system imaging demonstrates total occlusion of the LAD. D) Right-system coronary imaging reveals proximal total occlusion of the RCA. E) Selective imaging shows Rentrop 3 collateral filling of the LAD. F) The same collateral vessel provides grade 2 retrograde filling of the RCA

LAD: Left anterior descending, RCA: Right coronary artery



**Figure 3.** A) Crossing the RCA lesion with floppy guidewire. B) Predilatation of the lesion using a PTCA balloon. C) Proximal stent implantation in the RCA. D) Proximal optimization with an NC balloon following stent placement. E) Postprocedure control image showing TIMI-3 distal RCA flow. F) Final image displaying the RCA, LAD, and collateral vessel

PTCA: Percutaneous transluminal coronary angioplasty, NC: Non-compliant, LAD: Left anterior descending, RCA: Right coronary artery

observed in the development of new collaterals between patients who participated in an exercise program and those who did not.<sup>5</sup>

In our patient, the completely occluded LAD continues to supply blood through a collateral vessel that functions similarly to a natural bypass, sustaining a vital ventricular region. This well-developed collateral circulation positively impacts the patient's prognosis by helping prevent complications such as aneurysm formation or heart failure in the left ventricle.

This case highlights that a well-developed collateral in a patient who has dedicated a significant portion of his life to cycling and remains physically active can prevent the onset of anginal symptoms or heart failure.

From this perspective, the case contributes to the literature and may provide insights for future large-scale studies on the potential positive impact of exercise and lifestyle on cardiovascular outcomes.

**Informed Consent:** Informed consent was obtained from the patient for the article.

**Authorship Contributions:** Concept: E.Ç., M.A.Ç., Ç.K., Design: E.Ç., M.A.Ç., Ç.K., Data Collection or Processing: E.Ç., M.A.Ç., Ç.K., Analysis or Interpretation: E.Ç., M.A.Ç., Ç.K., Literature Search: E.Ç., M.A.Ç., Ç.K., Writing: E.Ç.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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