“Carol Davila” University of Medicine and Pharmacy

Bucharest

Doctoral School
Medicine

CURRENT MANAGEMENT STRATEGIES IN HIGH PROCEDURAL RISK CORONARY SYNDROMES

ABSTRACT OF THE DOCTORAL THESIS

Doctoral Supervisor:
Prof. Univ. Dr. Bartoș Daniela

Doctoral Student:
Dumitrașcu Silviu Ionuț

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Introduction

Interventional revascularization of patients with ischemic coronary disease represents a fundamental area in cardiology, having a significant impact on patients' quality of life and prognosis. The decision to focus this doctoral paper on high-risk procedures is motivated by the need to better understand the factors contributing to their complexity and to develop effective strategies for this patient category, with the aim of integrating these results with existing knowledge, in order to achieve improved and more effective medical practice. This research topic has the potential to significantly enhance the clinical outcomes of patients and to guide future practices.

The chosen topic is of particular importance due to the high prevalence of ischemic coronary disease and the increasing number of revascularization procedures in both categories of patients included in the studies presented here. The relevance of the topic is supported by the ongoing need to optimize interventional techniques and adapt new technologies to improve patient outcomes in various procedural contexts, especially in high-risk circumstances.

The presence of coronary calcifications increases the interventional risk by hindering the smooth execution of angioplasty steps, while revascularization of left main coronary lesions inherently presents high procedural difficulty due to both the large amount of myocardium at risk and the presence of a critical bifurcation at this location. Thus, it becomes easier to understand why severely calcified LMC lesions represent a distinct category within interventional revascularization, involving a high procedural risk that requires specific treatment strategies.

The presentation as an acute coronary syndrome as STEMI (ST-Elevation Myocardial Infarction) represents a distinct category within the broader scope of high-risk interventional procedures, both due to the absolute number of STEMI cases and the urgent nature of revascularization, and due to the vast diversity of clinical and interventional presentation modes. Despite the decline in STEMI incidence, the absolute number of cases and the mortality rate

remain alarmingly high, highlighting the need for further improvements in the management of this condition.

At the international level, both interventional revascularization of severely calcified lesions and that of STEMI patients are intensely studied topics, with numerous guidelines and recommendations developed to continuously improve practice and enhance clinical outcomes. In the national context, this topic is relevant due to the high incidence of cardiovascular diseases in Romania and the need to align medical practices with international standards.

I. General Section

Chapter 1. Coronary syndromes with high procedural risk

1.1 Definition of High Procedural Risk

There are multiple definitions available that can help in understanding the concept of high procedural risk in the context of interventional revascularization for patients with ischemic coronary disease. The multitude of definitions arises from the possibility of delineating this concept through terms that can vary from the inherent risk of the patient (independent of the type of procedure or cardiac impairment), such as: advanced age, frailty, bleeding risk, presence of comorbidities, etc., to the risk determined by the procedure itself and the degree of cardiovascular impairment. The latter categories contribute to the largest number of definitions of high procedural risk. The diversity in this case stems from the existence of i) cardiac risk factors (myocardial dysfunction, significant valvular disease, etc.), ii) factors related to the nature of coronary disease (severe calcifications, left main coronary lesions, chronic total occlusions (CTO), involvement of a bifurcation, aorto-coronary bypass graft lesions, and iii) clinical factors (presentation as acute coronary syndrome, acute heart failure, cardiopulmonary arrest, electrical storm, etc.).

The presence of coronary calcifications increases the interventional risk by hindering the smooth execution of angioplasty stages, leading to potential procedural complications and/or suboptimal technical results, which may evolve into adverse clinical events. As will be described throughout this manuscript, the use of adjunctive methods for preparing calcified lesions has

become common and essential, but it inherently comes with a significant increase in procedural risk. Similarly, revascularization of left main coronary lesions inherently presents high procedural difficulty, both due to the large amount of myocardium at risk and the presence of a critical bifurcation at this location. Thus, it becomes easier to understand why severely calcified left main lesions represent a distinct category within interventional revascularization, involving a high procedural risk that requires particular strategies. These patients (i.e., with severely calcified left main lesions) remain underrepresented in available studies, necessitating multiple analyses to characterize revascularization strategies and their impact on the subsequent evolution of patients.

The presentation as an acute coronary syndrome as STEMI represents a particular category within the broader scope of high procedural risk, both due to the absolute number of STEMI cases, which makes this condition a continuous challenge, and due to the urgent nature of revascularization and the diversity of clinical presentations. Primary percutaneous coronary intervention (pPCI) is the ideal method for reperfusing STEMI patients, but it arrives with limitations determined by the time window in which it must be performed, the various clinical presentation modes with different degrees of hemodynamic and electrical instability, as well as the nature and distribution of coronary impairment. All these factors lead to high rates of periprocedural difficulties and short- and long-term mortality, contributing to keeping STEMI patients in the category of high procedural risk.

Chapter 2. Coronary calcifications

2.1 Epidemiology and Risk Factors

Coronary arterial calcifications (CAC) represent calcium deposits in the structure of the coronary arterial wall, reflecting the presence of atherosclerosis [1], regardless of its clinical or subclinical manifestation. These calcifications are considered markers of cardiovascular risk, being correlated with an increased incidence of major coronary events, such as myocardial infarction [2].

2.2 Impact of Calcifications on Coronary Angioplasty Procedures

In coronary angioplasties, the presence of severe calcifications is an independent factor of morbidity, particularly in patients with advanced coronary impairment [3]. Calcified lesions are inherently longer, more tortuous, and are associated with a higher likelihood of multi-vessel involvement compared to non-calcified lesions [3]. CAC leads to major procedural difficulties by limiting the effectiveness of balloon angioplasty—such as in the case of lesions that are uncrossable and undilatable—or by causing complications such as dissections or vascular perforations during predilation. Additionally, calcifications affect stages related to stent implantation, including issues such as delivery failure, loss/displacement, polymer and drug substance damage, underexpansion, and the occurrence of adverse events both periprocedurally and in the longer term [4].

2.3 Calcified Left Main Coronary Lesions

Patients with severe calcifications of left main coronary stenoses are frequently excluded or underrepresented in studies, creating difficulties in extrapolating reasonable estimates for this patient subgroup. Thus, to date, the available data are not entirely clear regarding the outcomes of patients with severely calcified left main lesions after revascularization through PCI compared to non-calcified left main lesions. Left main lesions represent the subgroup of coronary lesions with the largest amounts of myocardium at risk, leading to an inherently higher risk for any revascularization procedure involving the left main coronary artery. This risk is clinically manifested by a significant increase in cardiovascular morbidity and mortality compared to other locations of coronary arterial disease [5].

2.4 Dedicated Devices for Modifying Calcified Plaque

Specific tools used for calcified coronary lesions are divided into three categories: i) balloon-based techniques, ii) ablative techniques, iii) intravascular lithotripsy.

2.5 Dedicated Devices for Coronary Calcified Lesions in Left Main Lesions

While dedicated devices have demonstrated their utility for classic coronary locations, for left main coronary lesions the available literature data is much less robust, being largely limited to retrospective studies or post-hoc analyses from various registries. It remains challenging to

anticipate the procedural and, especially, post-procedural course for patients requiring dedicated devices to facilitate revascularization of left main lesions.

Chapter 3: ST-Elevation Myocardial Infarction

Ischemic heart disease is the most frequent cause of cardiovascular death, accounting for 38% of cardiovascular deaths among women and 44% among men [6]. STEMI is one of the most severe forms of coronary syndrome and remains a major public health issue despite significant advances in prevention and treatment. The incidence of STEMI has varied over the past decades, reflecting changes in the prevalence of cardiovascular risk factors, improvements in primary and secondary prevention, and advances in medical management. In developed countries, the incidence of STEMI is gradually declining [7]. This trend can be attributed to public health campaigns and preventive treatments, such as the widespread use of pharmacological therapies that have a significant impact on cardiovascular risk, along with increasingly active lifestyle modification interventions. Nevertheless, STEMI remains a leading cause of morbidity and mortality, with death rates reaching up to 10-12% [8,9].

3.1 Interventional Treatment Strategy for STEMI

Primary percutaneous coronary intervention (pPCI) has become the ideal reperfusion strategy for patients diagnosed with STEMI, involving the emergency performance of coronary angiography and PCI. Compared to thrombolysis, this strategy immediately showed its advantages—restoring coronary flow and almost completely eliminating cerebral hemorrhages [10-12]. This was followed by long-term confirmation of the benefits of pPCI, which rapidly led to increased survival and significant improvement in the outcomes for STEMI patients [13]. From the early stages, pPCI—compared to thrombolysis—demonstrated substantial reductions in relative risk for mortality (28%), myocardial reinfarction (63%), and stroke (50%) [14].

3.2 Importance of Time Intervals in Primary PCI

As described earlier, STEMI represents a major medical emergency that requires rapid intervention to restore blood flow in the affected coronary artery. Thus, time is a critical factor in the treatment of STEMI, and every minute counts to minimize myocardial damage and

improve short- and long-term clinical outcomes. The concept of "time is muscle" reflects the importance of promptness in interventional revascularization. The importance of time intervals in the interventional revascularization of STEMI patients cannot be overstated. Rapid restoration of blood flow through primary PCI is essential for reducing mortality, limiting infarct size, and preventing major complications [15, 16].

3.3 The National STEMI Program in Romania – Its Role in Optimizing Time Intervals

The National STEMI Program in Romania began in 2010 and was established to optimize the treatment of STEMI patients. Although the national network has brought notable improvements, there are still challenges that need to be addressed, and it remains unknown whether the benefits of the national STEMI program have plateaued, with potential modifiable gaps existing between guideline recommendations and the current efficiency of the healthcare system.

3.4 Time Intervals with Prognostic Implications in STEMI

- Total ischemic time
- Patient delay
- Medical system delay
- Door-to-balloon time

II. Personal Contributions

Chapter 4. Study I: Outcomes after Percutaneous Coronary Intervention in Patients with Extremely Calcified Left Main Lesions

4.1 Introduction

As with PCI for calcified lesions anywhere in the coronary tree, preparing left main lesions using rotational atherectomy (CdD) is known to be feasible, but the outcomes for these patients remain largely unknown, especially compared to classic PCI (i.e., for lesions without significant calcification) in the left main coronary artery. The reluctance in common practice to use dedicated devices for calcium modification in left main lesions could be explained by the increased procedural risk associated with this location, the added complexity due to the presence of a critical bifurcation, insufficient operator expertise, higher costs, and the lack of dedicated studies proving long-term benefits. Thus, this study aimed to retrospectively investigate the in-hospital and 1-year clinical outcomes of patients with highly calcified left main lesions after PCI facilitated by calcium dedicated devices.

4.2 Methods

Design and Patients

We retrospectively included all consecutive patients who underwent PCI in the left main coronary artery at a single center in Belgium over a 12-month period (January 2021 - December 2021). Outcomes were evaluated during the initial hospitalization and at 12 months post-procedure using clinical evaluation data, phone interviews (if clinical follow-up was not conducted), or national death registries. The study included a total of 70 patients. All left main procedures were performed by a single experienced operator. There were no exclusion criteria.

Data Collection

Patients were stratified based on the need for additional plaque modification using CdD for left main lesions, dividing the study population into a group of highly calcified left main lesions (CdD group) and a second group used as a control (classic PCI of the left main coronary

artery – rLM group). It should be noted that the dividing factor—the need for CdD—was independent of the degree of angiographic severity of calcification (aspect discussed in Design).

Statistical Analysis

Categorical variables are presented as absolute and relative frequencies. Continuous variables are presented as mean ± standard deviation if normally distributed, or as median and interquartile range (IQR) if the distribution is abnormal. Normality tests were performed using histograms and the Shapiro-Wilk test. Inter-group comparisons for categorical variables were made using the chi-square test (or Fisher's exact test where necessary). For continuous variables, Student's t-test or Mann-Whitney-Wilcoxon test were used. All reported p-values are two-tailed, and values <0.05 were considered significant.

4.3 Results

Baseline Characteristics of the Population

During the analyzed period, a total of 870 PCI procedures were performed at the studied center, of which 70 involved left main angioplasty and were included in this study. 22 patients (31.4%) required the use of CdD and were included in the CdD Group (72.7% men, mean age 68.64 ± 7.63 years), with the remaining 48 patients in the rLM Group (70.8% men, mean age 65.58 ± 11.29 years). Multivessel coronary disease was a common finding in both groups, with trifurcation disease observed in 14 (63.6%) of the CdD Group and 26 (54.1%) of the rLM Group, p = 0.20. The mean SYNTAX score for the entire population was 28.45 ± 8.89, with no significant differences between the two groups (29.18 ± 9.92 in CdD Group vs 28.11 ± 8.47 in rLM Group, p = 0.84). The total number of patients with a SYNTAX score >32 was 22 (31.4%), numerically higher in the CdD Group (36.3%) compared to the LM Group (29.1%), p = 0.17.

Procedural Details

Procedural details and angiographic characteristics, with comparisons between groups, are detailed in Table 4.2. A minority of procedures were performed ad-hoc, significantly fewer in the CdD Group (13.6% vs 33.4%, p = 0.03). Overall, the preferred access site was radial in 61 patients (87.1% of the total population), with no significant differences between groups.

Left main stenosis ≥70% was observed in 36 patients (51.1%) of the total population, numerically more in the CdD Group (59.1% vs 47.9%, p = 0.38). The left main ostium was

involved in 2 cases (9.1%) in the CdD Group and 4 cases (8.3%) in the rLM Group, p = 0.91. Angiographically, no calcifications were identified in 2 patients from the CdD Group, while severe and moderate calcifications were identified in 4 (8.3%) and 16 (33.3%) patients in the rLM Group, respectively. In total, new-generation drug-eluting stents were implanted in 69 patients (98.6%), while drug-eluting balloons were used in one case (1.4%) (for treating in-stent restenosis).

Stenting of the left main without involving the bifurcation was performed in one case (1.4%). Bifurcation techniques with two stents were used in 17 cases (24.3%) of the total (comparisons between groups and detailed techniques used are presented in Table 4.3).

In the CdD Group, techniques for calcium modification are shown in Figure 4.1, and technical details are displayed in Table 4.4. Rotational atherectomy was used in 9 cases (12.9% of the total population), of which 5 were considered to have insufficient lesion preparation after rotational atherectomy, and additional preparation with another calcium modification device was used. Intravascular lithotripsy (IVL) was used in 3 cases for additional lesion preparation after rotational atherectomy and in another 3 cases for additional preparation after cutting balloon or scoring balloon. In 6 cases (8.5% of the total population), IVL was used as the sole calcium modification device and was found to be sufficient for lesion preparation before stent implantation. One patient required rotational atherectomy followed by cutting balloon, scoring balloon, then IVL, and OPN balloon to achieve satisfactory lesion preparation. The cutting balloon was used alone in 3 cases (4.2%) and adequately prepared the lesion without the aid of other calcium modification devices (Figure 4.1).

Complete revascularization during the index procedure was achieved in 53 patients (75.7%), with no significant differences between groups (77.3% in CdD Group vs 75% in rLM Group, p = 0.83). Multi-territorial PCI was performed during the index procedure for 41 patients (58.6%), with at least one other complex lesion (B2/C lesion according to ACC/AHA classification) treated in 23 patients (32.8%), with no significant differences between groups (Table 4.5).

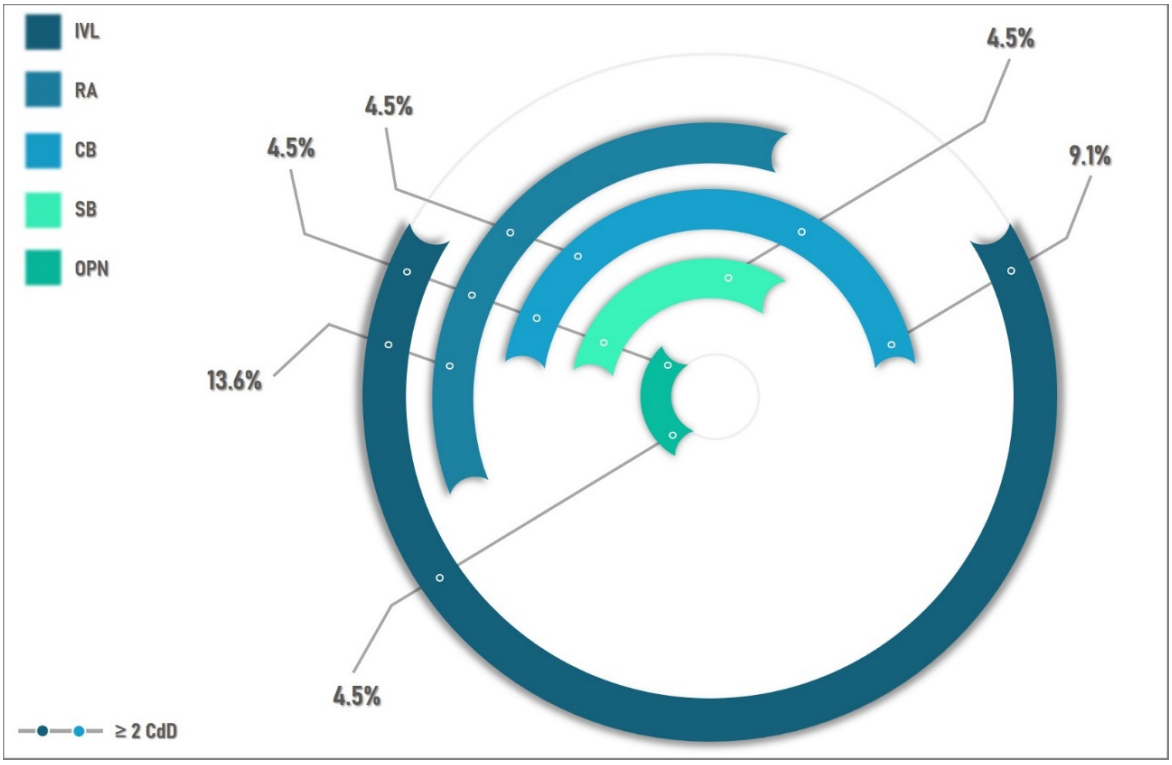

Figure 4.1. CdD Group – Visual depiction of the usage of dedicated devices and their synergistic combination. IVL was the most used technique (63.6% in total; 27.2% of cases as the single CdD), followed by RA (40.9% in total; 18.1% of cases as the single CdD) and cutting balloon (31.8% in total; 13.6% of cases as the single CdD). Scoring and OPN balloons were each used in 2.8% of cases, only associated with other CdD. In 40.9% of cases, a synergistic combination of at least two CdD was necessary – the greatest utility was observed with RA followed by IVL (13.6%).

CB – cutting balloon; CdD – Calcium-dedicated device; IVL – intravascular lithotripsy; RA – rotational atherectomy; SB – scoring balloon; OPN – Super high-pressure balloon.

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Detailed Procedural Aspects

Chronic Total Occlusion (CTO) PCI was performed during the index procedure in 4 cases (5.7% of the total population). The mean total length of non-LM stents during the index procedure was 44.56 mm ± 21.9 in the CdD Group and 51.10 mm ± 33.79 in the rLM Group, with a p-value of 0.85.

Intravascular imaging was used in 5 cases in the CdD Group (22.7%) and in 9 cases (18.8%) in the rLM Group, with a p-value of 0.69. Details regarding the procedural phase in which intravascular imaging was used or the morphological characteristics of the lesions were not recorded. No additional steps were needed for optimizing the stent after intravascular imaging.

During the index procedure, a total of 2 complications occurred, both in the rLM Group. These included longitudinal compression of the LM stent in one patient (treated by repeated POT) and one coronary perforation during PCI of a non-TC vessel (successfully treated by covered stent implantation). Procedural success was achieved in all patients.

In-Hospital Events

Clinical success was achieved in all 70 cases (100%). During the index hospitalization, the incidence of in-hospital morbidity was 2.9% (2 cases): one case of minor gastrointestinal bleeding in the CdD Group and one case of contrast-induced nephropathy in the rLM Group, both managed with conservative treatment. In-hospital events are detailed in Table 4.6.

Clinical Follow-Up Events

Clinical data and patient status at 12 months were available for 68 patients (97.1%). Twelve-month survival data were available for all 70 patients (100%). Clinical events during follow-up are described in Table 4.7.

The primary endpoint of Major Adverse Cardiac and Cerebrovascular Events (MACCE) occurred in 4.2% (3 patients) of the total population, with all events occurring in the rLM Group (6.2%) (Table 4.8). The rate of one-year survival without events was 98.5% for the entire study population, with one death occurring at 10 months in a patient from the rLM Group. The patient died shortly after being hospitalized for decompensated chronic heart failure presenting as cardiogenic shock.

Elective coronary angiography during follow-up was performed if symptoms arose, if there was myocardial ischemia on non-invasive tests, or based on the physician's assessment of the estimated risk during the index procedure (according to local protocols for high-risk procedures).

Therefore, repeat coronary angiography was available for 43 patients in the entire study population (61.4%), with 15 patients from the CdD Group (68.1%) and 28 patients from the rLM Group (58.3%), p=0.18. The median time until repeat angiography was 44.4 weeks, with

no significant differences between groups. Relevant findings from the repeat angiography are presented in Table 4.7. Restenosis of the secondary branch was found in 2 patients from the rLM Group (4.1%). Significant de novo lesions unrelated to the index procedure were found in 2 patients (one from each group, 4.5% and 2%, respectively, p=0.87). No statistically significant differences between groups were identified regarding patient outcomes (Table 4.7). Kaplan-Meier curves and log-rank tests for comparison were ultimately considered redundant due to the unexpectedly low event rate during follow-up.

Table 4.8. Individual Description of MACCE

CdD: Calcium Modification Devices; LVEF: Left Ventricular Ejection Fraction; LM: Left Main Coronary Artery; MACCE: Major Adverse Cardiac and Cerebrovascular Events; PCI: Percutaneous Coronary Intervention; rSS: Residual SYNTAX Score; SB: Side-Branch; STEMI: ST-Elevation Myocardial Infarction; SS: SYNTAX Score; TAP: T-and-Protrusion

	MACCE	Time to MACCE	Age	SS	rSS	CdD	LVEF	Initial presentation	Procedure	Non-LM PCI
Patient 1	Cardiac death	10	74	33	0	No	30%	Silent ischemia	Provisional stenting	Conventional
Patient 2	SB restenosis	12	55	29	0	No	55%	STEMI	2-stent strategy (TAP)	Conventional
Patient 3	SB restenosis	12	58	18	0	No	55%	Non-STE ACS	Provisional stenting	Provisional

4.2 Discussions

The analysis presented reveals several key points:

1. Patients with extremely calcified lesions of the left main coronary artery (LMCA) seem to have a favorable prognosis after percutaneous coronary intervention (PCI) facilitated by dedicated devices. This suggests that the use of CdD is effective in improving outcomes for patients with severe calcifications.
2. Aggressive lesion preparation strategies, which include the use of CdD, appear to be safe, as they did not result in a significant increase in immediate complications compared to standard lesion preparation. This indicates that using CdD does not compromise procedural safety and can be a viable option for severe calcifications.
3. The overall incidence of adverse clinical events in the total population of LM patients was unexpectedly low at 1-year compared to existing data. This suggests that, in the context of using CdD, patients with extremely calcified LMCA lesions may have a favorable long-term outcome.

4.5 Conclusions

Patients with extremely calcified lesions of the left main coronary artery treated with PCI and aggressive lesion preparation using CdD, show a favorable prognosis. The use of CdD, including combinations of dedicated devices, was not associated with a higher frequency of significant peri-procedural adverse events compared to conventional PCI. Clinical outcomes at 1-year were similar between groups and demonstrated a low incidence of adverse events. These findings could influence clinical decision-making regarding the use of CdD in PCI for extremely calcified LMCA lesions, highlighting the potential benefits of aggressive lesion preparation in improving long-term outcomes.

Chapter 5. Study 2: Critical Appraisal of Medical System Performance for STEMI Management – a Comprehensive Analysis of Time Efficiency

5.1 Introduction

There is currently a broader objective underway to evaluate and characterize the current state of the national STEMI program to identify potential elements that could benefit from specific refinements. This study aims to assess the capability of the regional STEMI network to achieve the guideline-recommended time intervals for primary PCI (pPCI) and to measure the occurrence and extent of such time delays. With its secondary objectives, this study intends to provide a general characterization of the contemporary STEMI population, aspects related to the pPCI procedure, and a brief overview of in-hospital outcomes. The following analysis reflects exclusively the management and outcomes of a single center and cannot fully generalize the results to the entire STEMI network.

5.2 Methods

Design and Patient Selection.

The present analysis considers only patients admitted to the "Prof. Dr. C.C. Iliescu" Emergency Institute for Cardiovascular Diseases, referred to as the "PCI center" throughout this document. We prospectively included 500 consecutive patients admitted with a working diagnosis of STEMI over a period of 14 months (April 2022 to May 2023).

Statistical Analysis.

Categorical variables are presented as absolute and relative frequencies. Continuous variables are presented as mean ± standard deviation for normally distributed values, or as median and interquartile range (IQR) for non-normally distributed values. Histograms and the Shapiro-Wilk test were used to assess normality. Comparison between groups for categorical variables was performed using the chi-square test (or Fisher's exact test if necessary). For continuous variables, the Student's t-test or Kolmogorov-Smirnov test were used. All reported p-values are bilateral, and significance was set at <0.05.

5.3 Results

Baseline Characteristics.

The final analysis includes a total of 500 patients. Initial characteristics and admission data for the study population are presented in Table 5.1. The majority of patients were male (74.6%), with an overall average age of 61.7 ± 12.08 years. There was also a clear predominance of active or former smokers (63.4%). Hypertension was the most common comorbidity (75.2%), followed by type 2 diabetes mellitus (23.4%).

Procedural Details.

Single-vessel involvement was the most common diagnosis, occurring in 52.2% of cases, followed by two-vessel involvement in 26.6% of cases. Significant LMCA involvement was identified in 5.8% of cases, most frequently associated with three-vessel disease. The right coronary artery was the culprit vessel in 41.7% of cases, followed by the left anterior descending artery (38.8%) – see Figures 5.2 and 5.3.

Successful PCI was achieved in 96.6% of attempted PCI cases. Angioplasty with at least one stent was performed in 428 patients (85.6% of the total population) with a total of 540 stents implanted (Table 5.2). The average stent length was 23 mm, and the average diameter was 3 mm. Drug-eluting balloons (DEB) were used in 3 cases (0.5%) in secondary culprit vessels: one diagonal artery and two marginal branches of the circumflex artery. The average diameter of DEBs was 2.5 mm. Plain old balloon angioplasty (POBA) was used in 33 lesions (5.7%). Complete revascularization during the index procedure was achieved in 53.8% of patients. The rate of peri-procedural events was 7.4%, with details presented in Table 5.9. Pharmacological and mechanical vascular support was needed in 5.4% and 2.6% of cases, respectively.

Key Time Intervals – General Analysis.

An analysis of the main components of total ischemic time is detailed in Table 5.14. In general, the main time intervals are: Patient delay 209 minutes, EMS delay 66 minutes, and PCI center delay 70 minutes, totaling an ischemic time of approximately 389 minutes (6.4 hours). Analysis by category of total ischemic time reveals that 41.5% of patients are revascularized between 2 and 6 hours from the onset of symptoms, while a large number of patients are revascularized between 6 and 12 hours.

As expected, for the subgroup of patients with pre-hospital thrombolysis, total ischemic time was significantly longer compared to patients with primary PCI (i.e., an additional 154

minutes, p=0.01), with the difference coming from time intervals before arrival at the PCI center (Table 5.15).

Comparison of Bucharest vs. Outside Bucharest

Regarding patients coming from outside Bucharest, regardless of the mode of transport, all EMS times are significantly longer, resulting in a total ischemic time of 454 minutes (7.5 hours) compared to 303 minutes (5.05 hours) for patients coming from Bucharest, creating a difference of 151 minutes (2.5 hours), $p< 0.0001$ – see Tables 5.11 and 5.12. Given that the majority of patients arrived via transfer from another hospital (295 patients), a sub-analysis was conducted on the difference between arrivals from within Bucharest compared to those from outside (Table 5.13). Although there are numerically larger time intervals for the secondary route from outside Bucharest, the difference in total ischemic time was 62 minutes without reaching statistical significance ($p= 0.46$). Categorical analysis for these subgroups reveals that patients coming from Bucharest are largely revascularized within the first 6 hours from the onset of symptoms, while 66.2% of external patients are revascularized after 6 hours, with 17.6% having a total ischemic time exceeding 12 hours (Table 5.11).

Arrival by ambulance directly from the symptom onset scene shows the best time intervals (Tables 5.4, 5.5, and Figure 5.5). The median time from the First Contact with the ambulance to arrival at the PCI center was 60 minutes, while the time from diagnosis (First ECG) to Guidewire Crossing was 112 minutes, contributing to a PCM to Revascularization time of 134 minutes and a total ischemic time of 260 minutes (4.3 hours). In comparison, a provisional stop at another hospital adds an additional 113 minutes (1.8 hours) to diagnosis and 83 minutes (1.3 hours) from diagnosis to revascularization, totaling an additional ischemic time of 3.1 hours (Figure 5.6 and Table 5.4). Categorical analysis reveals that 62.6% of patients are revascularized before the 6-hour ischemic mark if arriving directly by ambulance, compared to less than one-third if there is a provisional stop at another hospital (Table 5.5).

Table 5.7. Achievement of target time intervals.
Data computed for primary PCI patients.
ECG – electrocardiogram; FMC – first medial contact.

Interval	Target	Percentage achieved
FMC to ECG	≤10 minutes	63 (40.3%)
Diagnostic to wire crossing (overall)	≤120 minutes	159 (35.5%)
Diagnosis to wire crossing (for self-presenters)	≤60 minutes ≤120 minutes	14 (29.1%) 29 (60.4%)
Diagnosis to wire crossing (for ambulance arrival)	≤120 minutes	73 (46.7%)
Diagnosis to wire crossing (for transfers)	≤120 minutes	56 (18.9%)
Door-to-balloon	≤90 minutes	300 (67.1%)

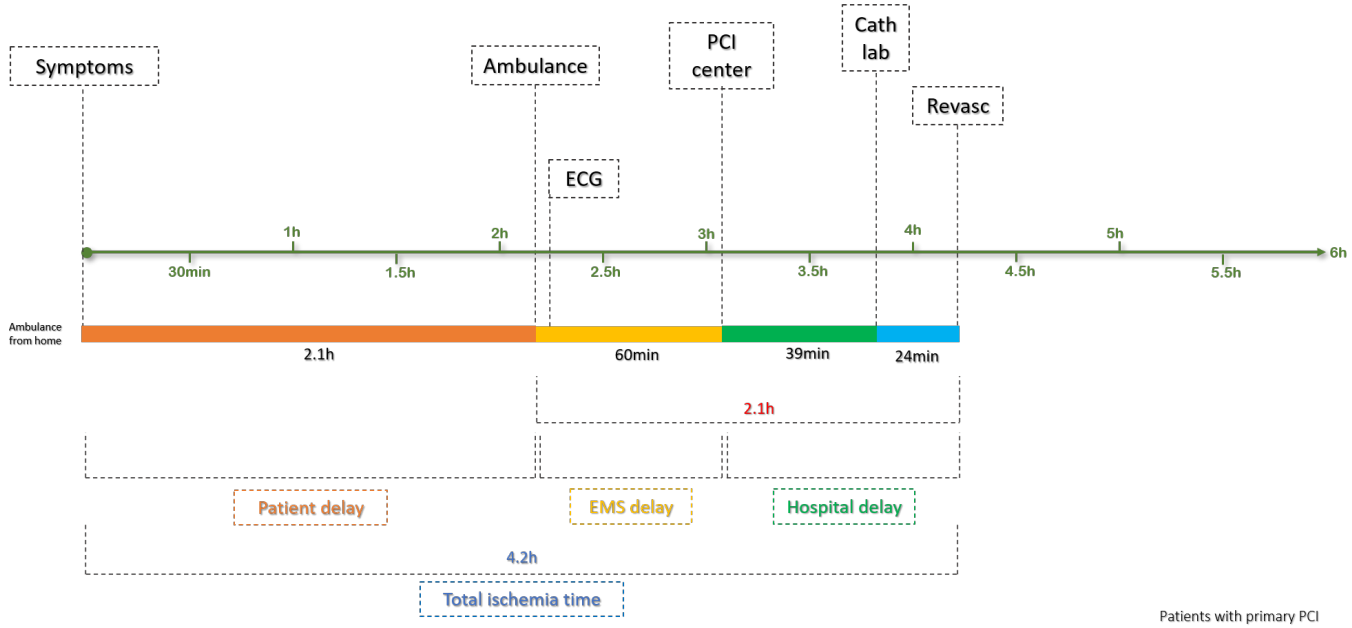

Figure 5. Visual representation of time intervals for patients arriving to the PCI center via primary route. (6-hour time scale)

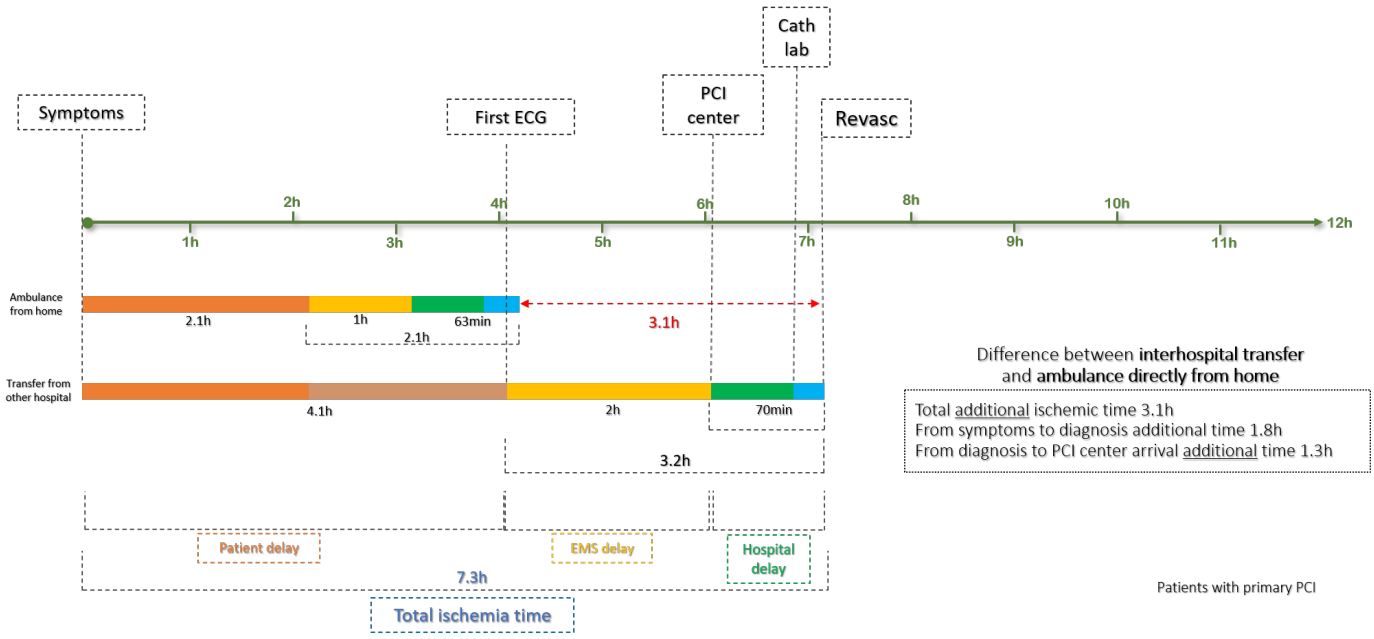

Figure 6. Visual representation of time intervals for patients arriving to the PCI center via secondary route and comparison with primary route. (12-hour time scale)

5.5 Discussion

Several key elements can be extracted from this analysis:

1. Most patients arrived at the PCI center through secondary routes (transfers from other hospitals) in 59% of cases, with the majority coming from outside Bucharest (75%).
2. The overall median ischemic time was 389 minutes (6.4 hours), with the longest delays observed in patients arriving via secondary routes from outside Bucharest (472 minutes, 7.8 hours). Conversely, the most favorable ischemic intervals were seen in patients arriving via primary routes (total ischemic time of 260 minutes, 4.3 hours).
3. For patients arriving via secondary routes, there was a median delay of 1.8 hours in diagnosing STEMI and an additional 1.3 hours from diagnosis to arrival at the PCI center, resulting in more than 3 hours of additional ischemic time compared to those using primary routes.
4. The goal of revascularization within 120 minutes of STEMI diagnosis was achieved in 35.5% of cases overall. The highest achievement was among those arriving directly by ambulance from home (46.7%), while only 18.9% of transfers met this goal.
5. Pre-hospital Thrombolysis: Thrombolysis was performed in 6.4% of cases, though potential benefits of pre-hospital pharmacological reperfusion could have been anticipated in 64.5% of cases based on estimated times to PCI.

5.6 Conclusions

The current perspective on the STEMI program suggests that further improvements are needed to meet the recommended time targets set by guidelines. Patients with STEMI often reach the PCI center via secondary routes, leading to significantly increases in ischemic times. Ambulance alert systems and primary routes to the PCI center remain the most effective pre-hospital approaches, although they are still imperfect. Pharmacological reperfusion therapy could temporarily address some gaps in the current system performance, but is significantly underutilized.

Chapter 6. Conclusions and Personal Contributions

Study I: Outcomes after Percutaneous Coronary Intervention in Patients with Extremely Calcified Left Main Lesions

The objectives of this study were achieved as expected. The study aimed to investigate the clinical outcomes during hospitalization and at 1 year for patients with severely calcified left main coronary artery lesions when PCI is facilitated by dedicated devices for calcified plaque modification. The collected data allowed for a detailed assessment of procedural and clinical success, major adverse events, and in-hospital and post-hospital morbidity and mortality. Patients with severely calcified left main lesions treated with PCI demonstrated a favorable prognosis if angioplasty was facilitated through more aggressive lesion preparation using dedicated devices. A lower threshold for using dedicated devices and their combination did not trigger significant peri-procedural adverse events compared to conventional PCI.

The use of dedicated devices in severely calcified left main lesions showed high procedural and clinical success, with a low rate of procedural complications and in-hospital morbidity, ensuring more complete revascularization and better long-term outcomes. However, the use of advanced calcium modification technologies involves significant costs, which can be an economic disadvantage for healthcare systems and patients. Additionally, these procedures involve a high level of technical complexity and require advanced expertise, which may limit their accessibility and applicability in all medical centers.

Although the overall rate of adverse events was reduced, they were not completely eliminated, indicating the existence of a threshold that might not be easily exceed with available revascularization technologies. Furthermore, the relatively small number of patients and low use of IVUS in the study represent limitations that may affect the interpretation and generalization of the results.

To improve outcomes and address unresolved issues, research should continue with larger patient cohorts to validate results and ensure better generalization of conclusions.

Study II: Critical Appraisal of Medical System Performance for STEMI Management – a Comprehensive Analysis of Time Efficiency

In this study, the initially established research objectives were largely achieved. The detailed analysis of critical time intervals between the onset of STEMI symptoms and revascularization via pPCI is a key step in optimizing these intervals to reduce mortality and short- and long-term complications. The collected and analyzed data allowed for the identification of major factors contributing to delays in revascularization. The study successfully highlighted the importance of an efficient rapid intervention network and the appropriate use of medical resources to achieve optimal clinical outcomes.

Implementing standardized protocols based on the study results can lead to uniform clinical practices and overall improvements in patient care quality. However, the implementation of new strategies and optimization of intervention networks may require significant investments in equipment and medical staff training. Ensuring optimal distribution of medical resources can be challenging due to varying needs, necessitating efficient and ongoing coordination.

Although the study identifies numerous solutions for optimizing intervention times, unresolved issues still require attention. These include:

1. Variations in medical infrastructure and resource availability between regions may affect the uniform implementation of proposed solutions.
2. The demonstrated difficulty in improving patient education and awareness regarding the recognition of STEMI symptoms and the importance of seeking prompt medical help.
3. Ensuring that all medical centers have access to advanced technologies and that personnel are well-trained in their use.

To address unresolved issues and continue improving STEMI management, future research should focus on:

- Studying the effects of public education programs on response times to STEMI symptoms and clinical outcomes.

- Investigating new diagnostic and treatment technologies that could further reduce time intervals and complications associated with STEMI.
- Comparing different rapid intervention network models from various countries to identify the most effective practices that can be implemented nationally.

Selective References

1. DH. B. Coronary arterial calcification: a review. Am J Med Sci. 1961;242:41-9.
2. Williams MC, Moss AJ, Dweck M, Adamson PD, Alam S, Hunter A, et al. Coronary Artery Plaque Characteristics Associated With Adverse Outcomes in the SCOT-HEART Study. J Am Coll Cardiol. 2019;73(3):291-301. doi: 10.1016/j.jacc.2018.10.066. PubMed PMID: 30678759; PubMed Central PMCID: PMC6342893.
3. Genereux P, Madhavan MV, Mintz GS, Maehara A, Palmerini T, Lasalle L, et al. Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes. Pooled analysis from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) TRIALS. J Am Coll Cardiol. 2014;63(18):1845-54. Epub 20140219. doi: 10.1016/j.jacc.2014.01.034. PubMed PMID: 24561145.
4. Mosseri M, Satler LF, Pichard AD, Waksman R. Impact of vessel calcification on outcomes after coronary stenting. Cardiovasc Revasc Med. 2005;6(4):147-53. doi: 10.1016/j.carrev.2005.08.008. PubMed PMID: 16326375.
5. Lee PH, Ahn JM, Chang M, Baek S, Yoon SH, Kang SJ, et al. Left Main Coronary Artery Disease: Secular Trends in Patient Characteristics, Treatments, and Outcomes. J Am Coll Cardiol. 2016;68(11):1233-46. doi: 10.1016/j.jacc.2016.05.089. PubMed PMID: 27609687.
6. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, et al. European Society of Cardiology: cardiovascular disease statistics 2021. Eur Heart J. 2022;43(8):716-99. doi: 10.1093/eurheartj/ehab892. PubMed PMID: 35016208.
7. Ahuja KR, Saad AM, Nazir S, Ariss RW, Shekhar S, Isogai T, et al. Trends in Clinical Characteristics and Outcomes in ST-Elevation Myocardial Infarction Hospitalizations in the United States, 2002-2016. Curr Probl Cardiol. 2022;47(12):101005. Epub 20211007. doi: 10.1016/j.cpcardiol.2021.101005. PubMed PMID: 34627825.

8. Pascual I, Hernandez-Vaquero D, Almendarez M, Lorca R, Escalera A, Diaz R, et al. Observed and Expected Survival in Men and Women After Suffering a STEMI. J Clin Med. 2020;9(4). Epub 20200419. doi: 10.3390/jcm9041174. PubMed PMID: 32325887; PubMed Central PMCID: PMC7230566.

9. Pedersen F, Butrymovich V, Kelbaek H, Wachtell K, Helqvist S, Kastrup J, et al. Short- and long-term cause of death in patients treated with primary PCI for STEMI. J Am Coll Cardiol. 2014;64(20):2101-8. Epub 20141110. doi: 10.1016/j.jacc.2014.08.037. PubMed PMID: 25457398.

10. Gibbons RJ, Holmes DR, Reeder GS, Bailey KR, Hopfenspirger MR, Gersh BJ. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. The Mayo Coronary Care Unit and Catheterization Laboratory Groups. N Engl J Med. 1993;328(10):685-91. doi: 10.1056/NEJM199303113281003. PubMed PMID: 8433727.

11. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med. 1993;328(10):673-9. doi: 10.1056/NEJM199303113281001. PubMed PMID: 8433725.

12. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med. 1993;328(10):680-4. doi: 10.1056/NEJM199303113281002. PubMed PMID: 8433726.

13. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. J Am Coll Cardiol. 2016;67(10):1235-50. Epub 20151021. doi: 10.1016/j.jacc.2015.10.005. PubMed PMID: 26498666.

14. SJ. B. In: Topol E, ed. Textbook of Interventional Cardiology. 5th ed. Philadelphia: WB Saunders. 2008:285–302.

15. Nallamothu B, Fox KA, Kennelly BM, Van de Werf F, Gore JM, Steg PG, et al. Relationship of treatment delays and mortality in patients undergoing fibrinolysis and primary

percutaneous coronary intervention. The Global Registry of Acute Coronary Events. Heart. 2007;93(12):1552-5. Epub 20070625. doi: 10.1136/hrt.2006.112847. PubMed PMID: 17591643; PubMed Central PMCID: PMC2095752.

16. Park J, Choi KH, Lee JM, Kim HK, Hwang D, Rhee TM, et al. Prognostic Implications of Door-to-Balloon Time and Onset-to-Door Time on Mortality in Patients With ST -Segment-Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention. J Am Heart Assoc. 2019;8(9):e012188. doi: 10.1161/JAHA.119.012188. PubMed PMID: 31041869; PubMed Central PMCID: PMC6512115.

Published articles

Dumitrașcu Silviu, Bartos Daniela, Ungureanu Claudiu. Outcomes after Percutaneous Coronary Intervention in Patients with Extremely Calcified Left Main Lesions. Medicina (Kaunas). 2023 Apr 23;59(5):825. doi: 10.3390/medicina59050825. PMID: 37241057; PMCID: PMC 10222037. Indexare Web of Science (ISI), FI 2.948. Contribuții personale, Capitolul 4 (35-65), Studiul I.

Medicina | Free Full-Text | Outcomes after Percutaneous Coronary Intervention in Patients with Extremely Calcified Left Main Lesions (mdpi.com)

Silviu Dumitrașcu, Alexandru Cîrjan, Daniela Bartoș, Ovidiu Chioncel, Mihai Ștefan, Dan Deleanu. Critical Appraisal of Medical System Performance for STEMI Management – a Comprehensive Analysis of Time Efficiency. Journal of Cardiovascular Emergencies 2024;10(1):27-37 DOI: 10.2478/jce-2024-0008. Indexare Web of Science (Emerging Sources Citation), FI 0.6. Contribuții personale, Capitolul 5 (66-103), Studiul II.

Critical Appraisal of Medical System Performance for STEMI Management – a Comprehensive Analysis of Time Efficiency » JCE - Journal of Cardiovascular Emergencies

Silviu Dumitrașcu, Iulian Călin, Daniela Bartoș, Marin Postu. Confronting Yesterday's Challenges with Today's Solutions: A Case of Intravascular Lithotripsy for Stent Underexpansion in a High-Risk Patient. Journal of Cardiovascular Emergencies. Acceptat spre publicare. Indexare Web of Science (Emerging Sources Citation), FI 0.6. Contribuții personale, Capitolul 5 (66-103), Studiul II.

Ungureanu C, Gasparini GL, Aminian A, Blaimont M, **Dumitrascu S**, Lepièce C, Colletti G. RailTracking: A Novel Technique to Overcome Difficult Anatomy During Transradial Approach. J Invasive Cardiol. 2022 Nov;34(11):E757-E762. Epub 2022 Sep 16. PMID: 36121925.

The RailTracking Technique During Transradial Approach (hmpgloballearningnetwork.com)

Claudiu Ungureanu, **Silviu Dumitrascu**, Giuseppe Colletti, Marc Blaimont, Manuel Mignon, Philippe van de Borne. Evaluation of Peripheral Vascular Function After Distal Radial Artery Access for Invasive Percutaneous Coronary Procedures. Romanian Journal of Cardiology | Vol. 33, No. 1, 2023. https://doi.org/10.2478/rjc-2022-0028

rjc-2022-0028 (sciendo.com)

Ungureanu C, Natalis A, Cocoi M, **Dumitrascu S**, Noterdaeme T, Gach O, Jossart A, Soetens R, Colletti G. The impact of the bifurcation angle for the Nano-Crush two-stent coronary bifurcation technique on long-term outcomes in a real-world clinical population. Cardiovasc Revasc Med. 2024 Jul;64:54-59. doi: 10.1016/j.carrev.2024.02.017. Epub 2024 Mar 12. PMID: 38494371.

The impact of the bifurcation angle for the Nano-Crush two-stent coronary bifurcation technique on long-term outcomes in a real-world clinical population - ScienceDirect

Scientific presentations

Silviu Dumitrașcu. Rotational Atherectomy – Why? When? How? – ROTAPRO REGIONAL WORKSHOP. *Learning by problem solving in Rotational Atherectomy.* November, 2021, La Louviere, Belgium

Silviu Dumitrașcu. Timing of coronary revascularization in a TAVI patient. – EuroPCR May 2023, Paris, France

Silviu Dumitrașcu. A peculiar coronary angiogram in the setting of inferior-posterior STEMI. – EuroPCR May 2023, Paris, France

Silviu Dumitrașcu. A coronary twist of fate. EuroPCR May 2023, Paris, France

Silviu Dumitrașcu. A side branch that is hard to kill. CHIP Romania, March 2024, Bucharest, Romania.