JACC: CASE REPORTS VOL. 4, NO. 6, 2022

CASE REPORT

ADVANCED

CLINICAL CASE SERIES

First-in-Human Computational Preprocedural Planning of Left Main Interventions Using a New Everolimus-Eluting Stent

Yiannis S. Chatzizisis, MD, PhD,[a] Janaki Makadia, MBBS,[a] Shijia Zhao, PhD,[a] Anastasios Panagopoulos, MD,[a] Mohammadali Sharzehee, PhD,[a] Behram Khan, MD,[a] Saurabhi Samant, MBBS,[a] Muhammad Fayaz, MBBS,[a] Jitendra Pandya, MBBS,[b] Haysam Akkad, MD,[b] Gregory Pavlides, MD, PhD,[b] Edward O'Leary, MD, MBA,[b] Wei Wu, PhD[a]

ABSTRACT

Left main coronary artery stenting requires rigorous planning and optimal execution. This case series presents a new approach to left main stenting guided by preprocedural patient-specific computational simulations. Three patients with significant left main artery disease underwent simulation-guided intervention using a novel stent scaffold purpose-built for large coronary arteries. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2022;4:325-335) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

"By failing to prepare, you are preparing to fail."
—Benjamin Franklin[1]

INTRODUCTION

Angiographically significant (>50%) left main (LM) coronary artery disease (CAD) is present in 4% to 6% of all angiograms.[2] Percutaneous coronary intervention (PCI) is a viable alternative for anatomically complex LM coronary artery disease not amenable to surgical revascularization. The size of LM (average lumen diameter of 5 mm) and the fibrocalcific nature and anatomical location (ostium or bifurcation) of LM disease make PCI of an unprotected LM challenging.[2] Synergy Megatron everolimus-eluting stent (Boston Scientific) is a new purposely designed stent with improved strength and expansion capabilities that is suitable for large proximal coronary artery interventions, including LM.[3] The stent received Food and Drug Administration approval on January 22, 2021.

Preprocedural planning of LM interventions appears to be essential for angiographic, procedural,

LEARNING OBJECTIVES

- To present a novel methodology of patient-specific computational stent simulations.
- To understand the role of computational stent simulations in preprocedural planning of complex LM coronary artery percutaneous interventions.

From the [a]Cardiovascular Biology and Biomechanics Laboratory, Cardiovascular Division, University of Nebraska Medical Center, Omaha, Nebraska, USA; and the [b]Cardiovascular Division, University of Nebraska Medical Center, Omaha, Nebraska, USA.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 24, 2021; revised manuscript received January 13, 2022, accepted February 3, 2022.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2022.02.001

JACC: CASE REPORTS, VOL. 4, NO. 6, 2022
MARCH 16, 2022:325–335

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CFD = computational fluid dynamics

HD IVUS = high-definition intravascular ultrasound

LAD = left anterior descending

LCx = left circumflex

LM = left main

PCI = percutaneous coronary intervention

3D = 3-dimensional

and clinical (short- and long-term) success. Patient-specific computational simulations have the potential to help interventional cardiologists preprocedurally plan complex interventions, including LM. Here we report for the first time in humans the feasibility and safety of computationally preplanned LM PCI using the Synergy Megatron stent.

HISTORY OF PRESENTATION AND PAST MEDICAL HISTORY

The clinical and imaging characteristics of the patients described in this report are summarized in Table 1. The 3 patients are as follows:

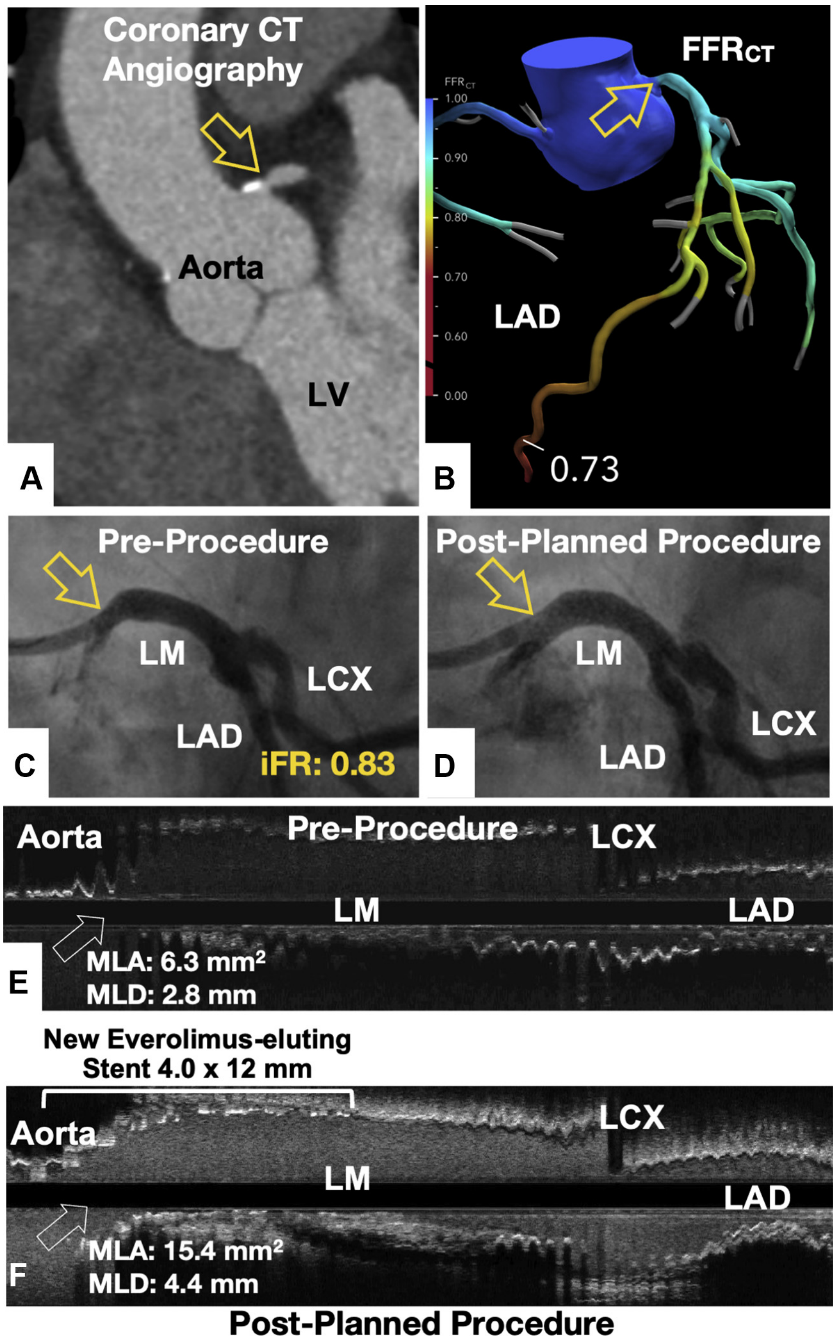
- Patient 1: A 61-year-old woman with a history of intermediate CAD in the mid left anterior descending (LAD) coronary artery presented with new severe exertional angina.
- Patient 2: A 60-year-old woman with type 2 diabetes mellitus, ischemic cardiomyopathy, and CAD status post primary PCI in the right coronary artery a few months ago, as well as in the LAD and first diagonal branch 10 years ago, presented with worsening exertional shortness of breath.
- Patient 3: A 69-year-old woman presented with worsening exertional angina refractory to optimal medical therapy.

TABLE 1 Clinical, Angiographic, IVUS, and Procedural Characteristics

	Patient #1	Patient #2	Patient #3
Clinical			
Age, y	61	60	69
Sex	Female	Female	Female
Diabetes	No	Yes	No
Hyperlipidemia	Yes	Yes	Yes
Hypertension	Yes	Yes	Yes
Chronic kidney disease	No	No	Yes
Chronic obstructive pulmonary disease	No	No	Yes
Canadian Cardiovascular Society class	3	N/A	3
Clinical presentation	Exertional angina	Exertional shortness of breath	Exertional angina
Cardiomyopathy	No	Ischemic cardiomyopathy	No
Previous percutaneous coronary intervention	Mid-LAD	RCA and LAD/D1	No
Left ventricular ejection fraction, %	60	34	45
SYNTAX score	Low	Intermediate to high	Low
Angiographic			
Location of left main disease	Ostial	Distal	Ostial
IVUS			
Nature of stenosis	Fibrotic	Fibrocalcific	Fibrotic
Eccentricity	Eccentric	Concentric	Eccentric
Prestent minimum lumen area, mm^2	6.3	4.9	4.9
Prestent mean lumen diameter, mm	2.8	2.1	2.3
Poststent minimum lumen area, mm^2	15.4	16.4	11.8
Poststent mean lumen diameter, mm	4.4	4.6	4.0
Procedural			
Predilation	3.5 × 12 mm Emerge balloon (Boston Scientific) inflated at 7 atm	3.5 × 12 mm Emerge balloon (Boston Scientific) inflated at 8 atm	3.5 × 12 mm Emerge balloon (Boston Scientific) inflated at 7 atm
Stenting	4.0 × 12 mm Synergy Megatron inflated at 12 atm with 0.7 mm protrusion into the aorta	3.5 × 16 mm Synergy Megatron (Boston Scientific) inflated at 12 atm with 1.0 mm protrusion into the aorta	4.0 × 8 mm Synergy Megatron (Boston Scientific) inflated at 11 atm with 0.6 mm protrusion into the aorta
Postdilation	4.0 × 8 mm NC Emerge balloon (Boston Scientific) inflated at 19 atm (effective 4.2 mm)	Not performed	4.5 × 8 mm NC Euphora balloon (Medtronic) inflated at 9 atm (effective 4.3 mm)
Proximal optimization technique	Not performed	4.5 × 12 mm NC Emerge balloon (Boston Scientific) inflated at 18 atm (effective 4.7 mm)	Not performed

D1 = first diagonal branch; IVUS = intravascular ultrasound; LAD = left anterior descending (coronary artery); N/A = not applicable; NC = noncompliant; RCA = right coronary artery.

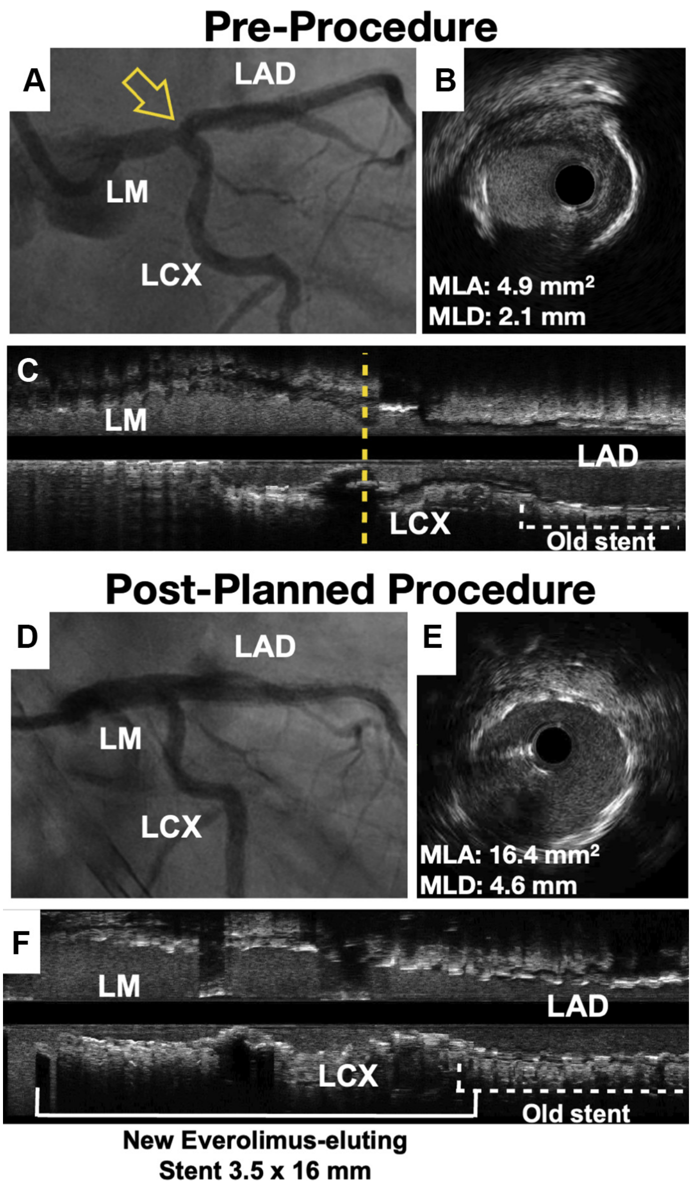
FIGURE 1 Preprocedural and Postprocedural Imaging of Patient 1



(A) Coronary computed tomography (CT) angiography showing a severe fibrocalcific ostial left main (LM) coronary artery stenosis **(yellow arrow). (B)** Fractional flow reserve computed tomography (FFR_{CT}) analysis showing the pressure drop distal to the LM ostium **(yellow arrow;** fractional flow reserve 0.73 in the distal left anterior descending artery [LAD]). **(C)** Preprocedural angiogram showing the ostial LM stenosis **(yellow arrow). (D)** Final angiogram after computationally planned LM stenting **(yellow arrow)**. **(E)** Preprocedural long view of high-definition intravascular ultrasound showing the ostial LM stenosis with calculated minimum lumen area (MLA) and mean lumen diameter (MLD) **(white arrow). (F)** Postprocedural high-definition intravascular ultrasound long view showing the deployed new everolimus-eluting stent (Boston Scientific) at the left main ostium **(white arrow)**. LV = left ventricle; LCx = left circumflex artery; iFR = instantaneous wave-free ratio.

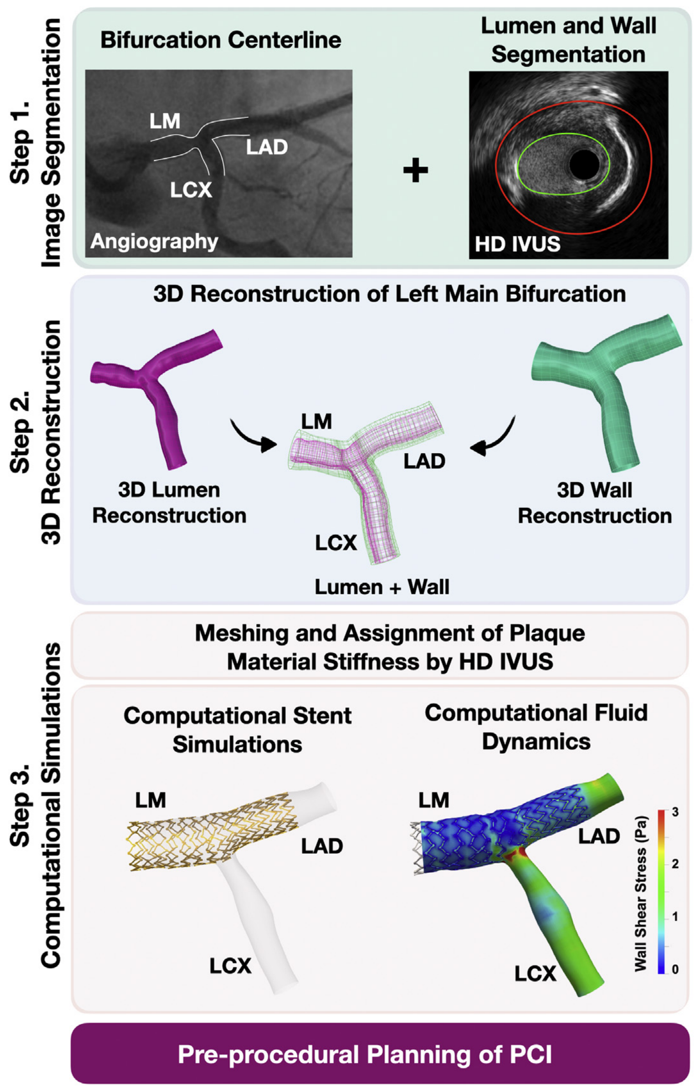
JACC: CASE REPORTS, VOL. 4, NO. 6, 2022
MARCH 16, 2022:325-335

FIGURE 2 **Preprocedural and Postprocedural Imaging of Patient 2**



(A to C) Preprocedural angiogram and high-definition intravascular ultrasound showing severe fibrocalcific stenosis at the distal left main (LM) coronary artery **(yellow arrow in A and dashed line in C)** with **(B)** a minimum lumen area (MLA) of 4.9 mm^2. **(D to F)** Final angiogram and high-definition intravascular ultrasound following computational stent planning. A new everolimus-eluting stent (Boston Scientific) 3.5 x 16 mm was deployed from the proximal left anterior descending artery (LAD) to the LM coronary artery ostium covering the ostium of the left circumflex artery (LCx) according to the provisional technique. Note the differential expansion of the stent from 3.4 mm into LAD artery to 4.8 mm into the proximal LM artery with adequate scaffolding of the LCx ostium as predicted by the computational planning. MLD = mean lumen diameter.

FIGURE 3 Patient-Specific Computational Stent Simulation Workflow



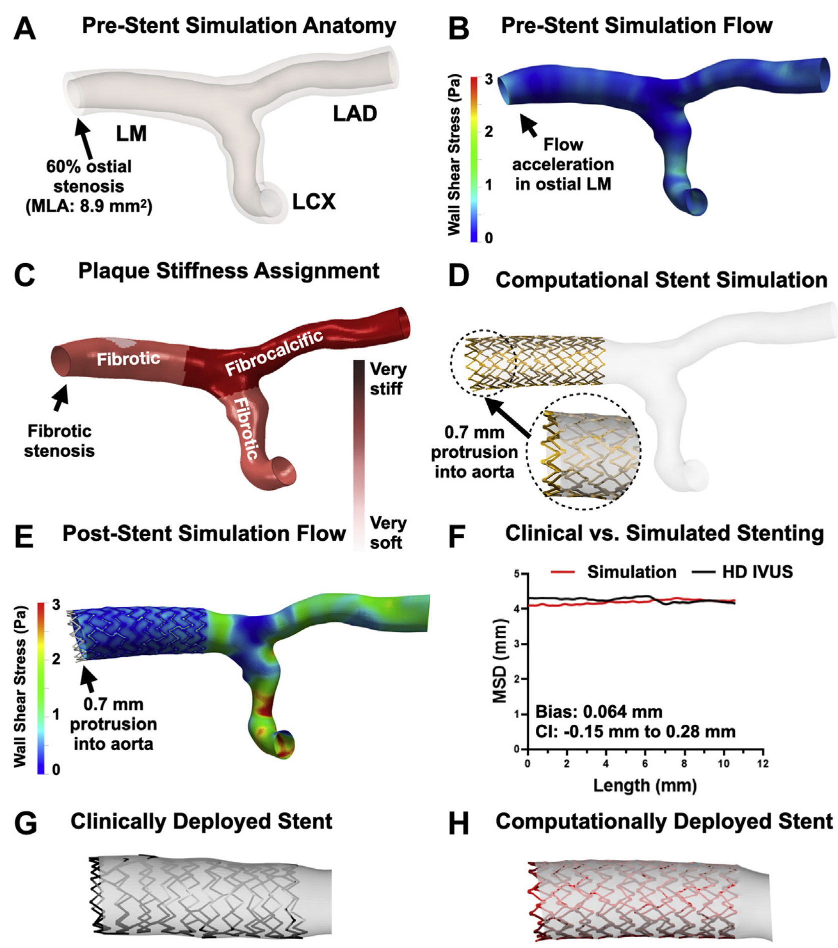
Representative example using data from patient 2. HD IVUS = high-definition intravascular ultrasound; PCI = percutaneous coronary intervention; 3D = 3-dimensional; other abbreviations as in Figure 1.

INVESTIGATIONS

PATIENT #1. Initial screening with coronary computed tomography angiography followed by fractional flow reserve computed tomography analysis demonstrated anatomically and hemodynamically significant ostial LM disease (Figures 1A and 1B). Invasive angiography (Figure 1C), high-definition intravascular ultrasound (HD IVUS) (Figure 1E), and invasive functional studies (instantaneous wave-free ratio: 0.83) confirmed the significance of ostial LM disease. The mid LAD disease was angiographically unchanged. Following the heart team's discussion that considered the low SYNTAX score and the patient's preference, a decision for LM PCI was made.

PATIENT #2. Coronary angiography and HD IVUS during the primary PCI to RCA revealed significant disease in the distal LM (Figures 2A to 2C), obtuse marginal branch, and distal LAD. Cardiac magnetic resonance imaging showed moderate to severe ischemic cardiomyopathy with viable myocardium in the left coronary territory and transmural scar in the

FIGURE 4 Computational Preprocedural Planning of Patient #1



(A) Baseline anatomy, **(B)** computational flow dynamics, and **(C)** plaque stiffness by high-definition intravascular ultrasound (HD IVUS), showing the fibrocalcific ostial left main (LM) coronary artery stenosis producing flow acceleration. **(D)** Computational stent deployment from mid LM artery to the aortic ostium with 0.7 mm protrusion into the aorta. The actual stent protrusion into the aorta after percutaneous coronary intervention was 1.0 mm. **(E)** Wall shear stress after computational LM stenting. **(F to H)** 3-dimensional reconstruction of the clinically deployed stent from HD IVUS and comparison with the computationally deployed stent. Note the high quantitative and qualitative agreement between the clinically and computationally deployed stent. MSD = mean stent diameter; other abbreviations as in Figure 1.

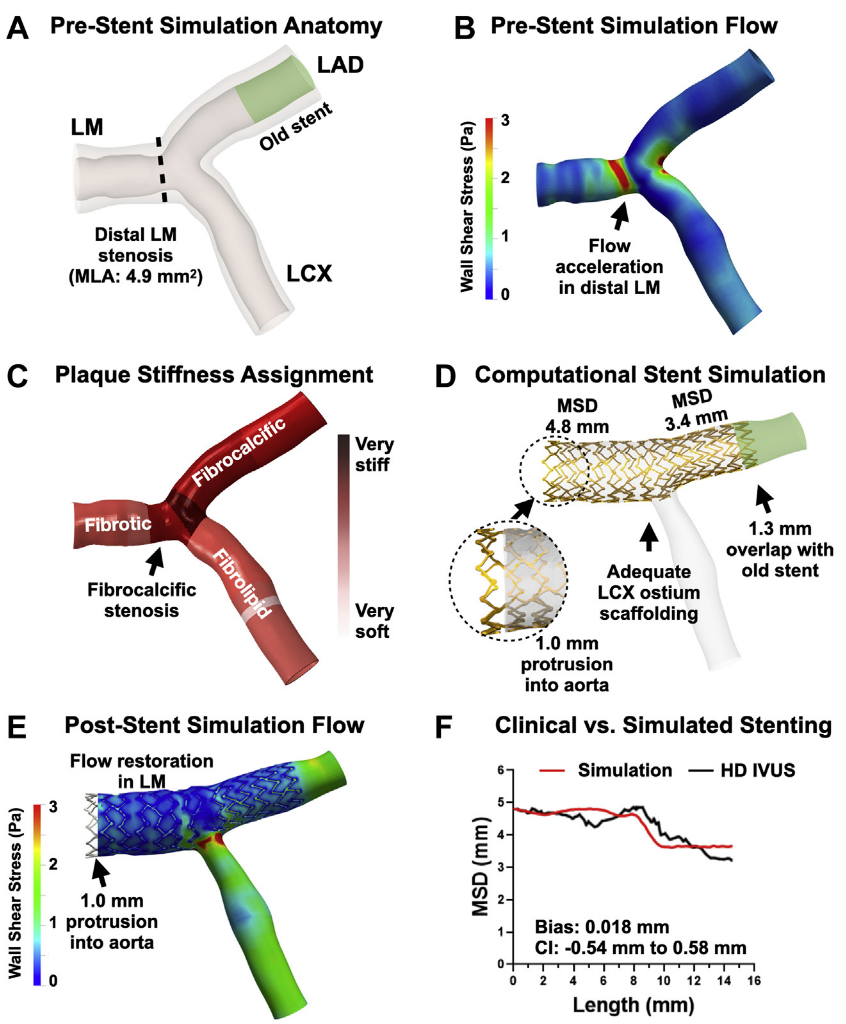
right coronary territory. The patient declined the heart team's recommendation for surgical revascularization given her multivessel CAD, cardiomyopathy, and diabetes. The decision was made to proceed with multivessel PCI to the LM bifurcation.

PATIENT #3. Invasive angiography and HD IVUS revealed significant ostial LM disease (Supplemental Figures 1A to 1C). Echocardiography showed mild to moderate cardiomyopathy. Following the heart team's discussion that considered the low SYNTAX score and the patient's preference, a decision for LM PCI was made.

MANAGEMENT

PREPROCEDURAL PLANNING WITH PATIENT-SPECIFIC COMPUTATIONAL STENT SIMULATIONS. The computational stent simulation steps are summarized in Figure 3. Detailed description of the methods used for stent simulations and computational fluid dynamics (CFD) is provided in Supplemental Table 1.[4] Initially, we 3D reconstructed patient-specific LM anatomies on the basis of angiography and HD IVUS (Figures 4A, 4B, 5A, 5B, 6A, and 6B).[3-6] The 3D reconstructed LM anatomies were meshed and

FIGURE 5 Computational Preprocedural Planning of Patient #2

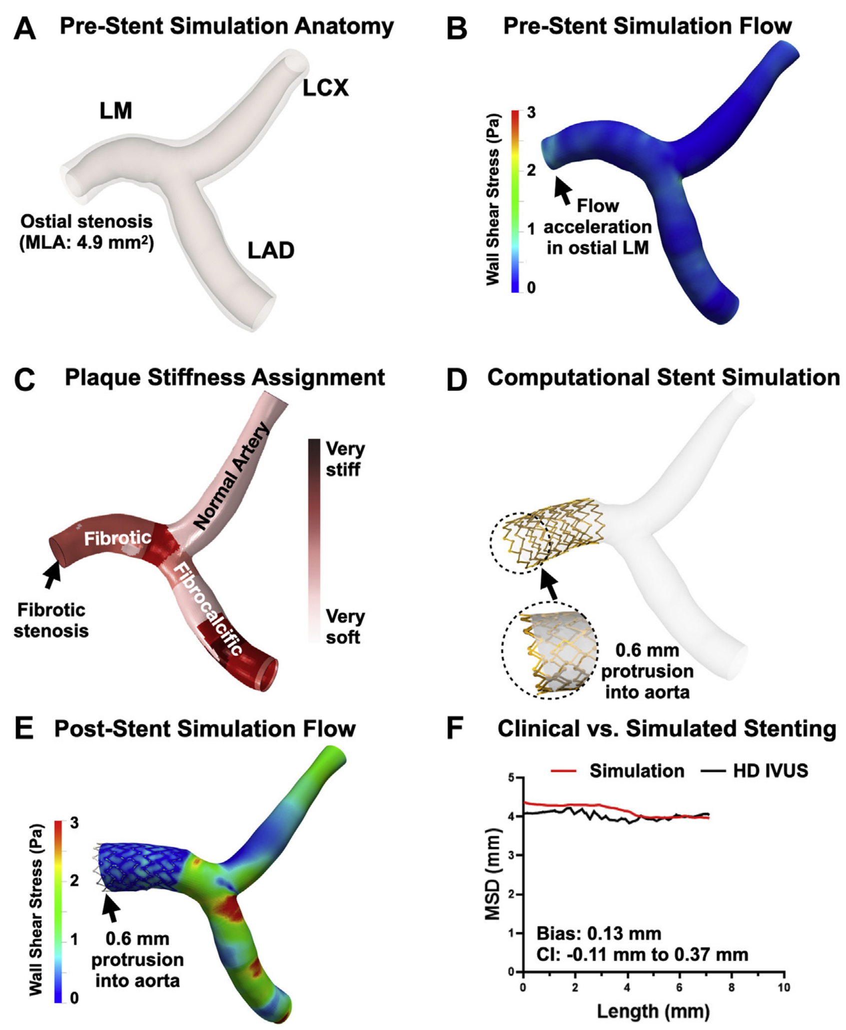


(A) Baseline anatomy, **(B)** computational flow dynamics, and **(C)** plaque stiffness by high-definition intravascular ultrasound (HD IVUS), showing the fibrocalcific distal left main (LM) coronary artery stenosis with associated flow acceleration. **(D)** Provisional technique with crossover stenting from the proximal left anterior descending artery (LAD) to the LM ostium with 1.0 mm protrusion into the aorta. Computational simulation showed adequate stent scaffolding at the ostium of left circumflex artery (LCx) with minimum lumen area (MLA) and mean lumen diameter (MLD) of 5.2 mm^2 and 2.6 mm, respectively. After the actual percutaneous coronary intervention, the minimum lumen area and mean lumen diameter achieved at the same location were 4.6 mm^2 and 2.4 mm, respectively. Note the **(E)** flow restoration in the computationally stented LM bifurcation and **(F)** high agreement in mean stent diameter (MSD) between the clinically and computationally deployed stent.

assigned realistic plaque stiffness properties considering the longitudinal and circumferential plaque heterogeneity derived from HD IVUS (Figures 4C, 5C, and 6C).[3,4] After performing computational stent simulations and CFD analyses (Figures 4D, 4E, 5D, 5E, 6D, and 6E, Videos 1 to 3), we selected the optimal stent positioning, sizing (length, diameter, inflation pressures), and strategy for each individual patient (Figure 7). In these computational simulations, we used the new everolimus-eluting stent design provided by the manufacturer (Boston Scientific). The patient-specific stent simulations and CFD studies showed that the flow environment became more homogeneous within the stented regions, whereas downstream to the stented regions, the wall shear stress in both the LAD and left circumflex (LCx) arteries increased to physiologic levels (1-2 Pa), thus

JACC: CASE REPORTS, VOL. 4, NO. 6, 2022
MARCH 16, 2022:325–335

FIGURE 6 Computational Preprocedural Planning of Patient #3

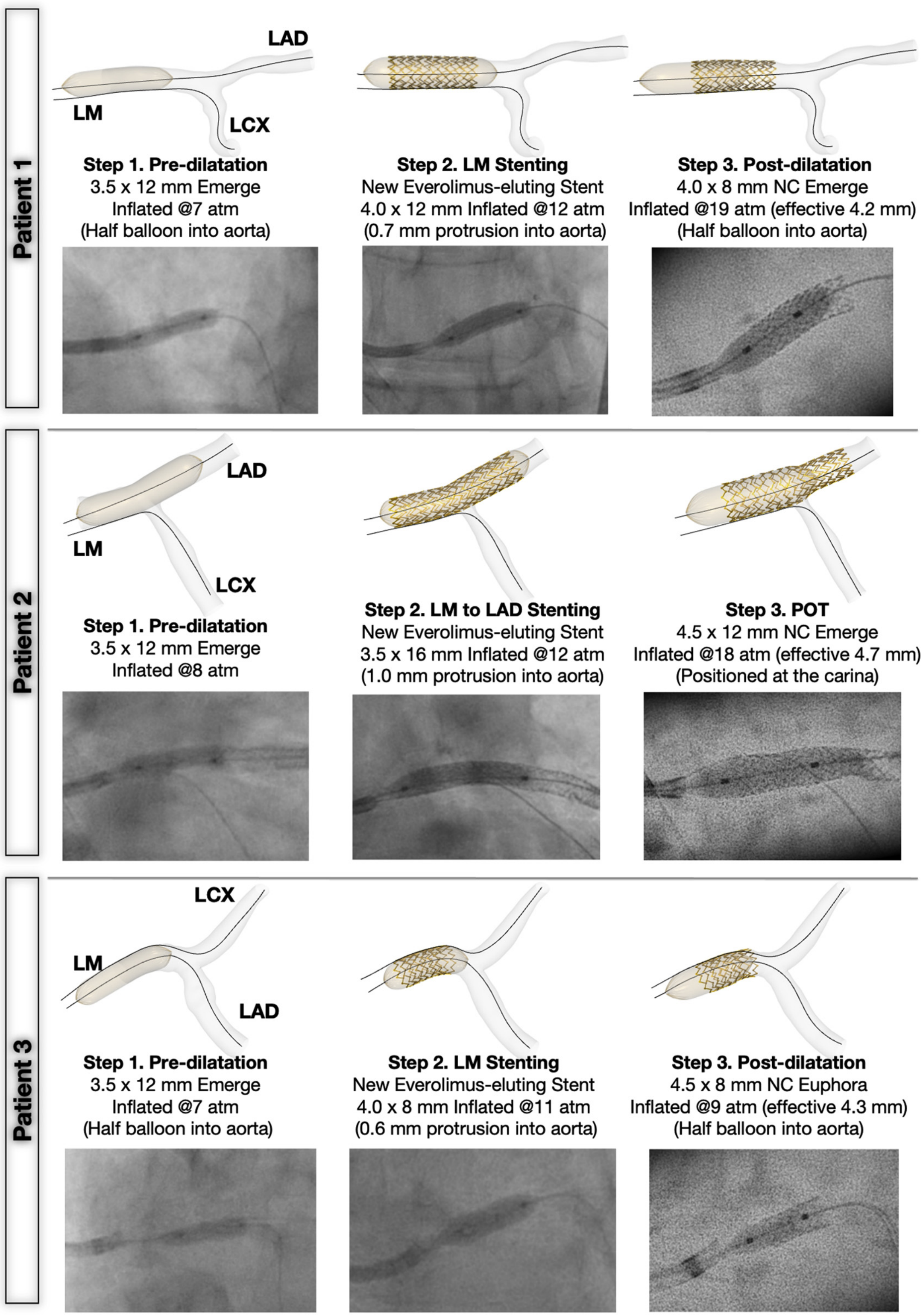


(A) Baseline anatomy, **(B)** computational flow dynamics, and **(C)** plaque stiffness by high-definition intravascular ultrasound (HD IVUS), showing the fibrotic ostial left main (LM) coronary artery stenosis with associated flow acceleration. **(D)** Computational stent deployment at the ostium of the LM artery with 0.6 mm protrusion into the aorta. Note the **(E)** high agreement in mean stent diameter between the **(F)** clinically and computationally deployed stent. Abbreviations as in Figure 1.

potentially attenuating the propensity to atherosclerosis and stent restenosis (Figures 4E, 5E, and 6E). Interestingly, in patient #2, stenting of the LM caused a focal increase of wall shear stress at the ostium of the LCx that normalized in the immediate downstream region (Figure 5E).

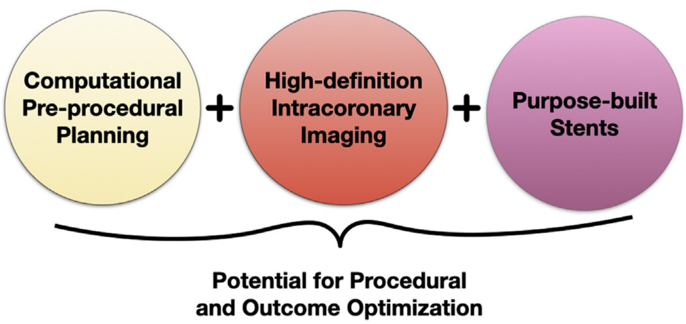
INTERVENTIONAL PROCEDURES AND COMPARISON WITH PREPROCEDURAL COMPUTATIONAL PLANNING. Informed consent was obtained from all 3 patients. Using the preprocedural computational simulations as reference, we proceeded to the PCIs with Impella support (Abiomed). In each patient, we faithfully replicated all the computational procedural steps, using the same materials and inflation pressures and in the same sequence according to the computational simulations (Table 1, Figure 7). All 3 procedures were completed seamlessly and successfully without periprocedural or postprocedural complications. Notably, patients #1 and #2 received the first 2 Megatron implants in the United States. Postprocedural angiography and HD IVUS revealed optimally expanded and apposed stents with optimal coverage of the LM ostium

FIGURE 7 **Computationally Planned Left Main Interventions**



Note the similarities between the computationally planned procedures and the actual percutaneous coronary interventions.
NC = noncompliant; POT = proximal optimization technique; other abbreviations as in Figure 1.

FIGURE 8 Conceptual Framework for the Optimization of Percutaneous Interventional Procedures and Outcomes



Advanced preprocedural planning and improved stent scaffolds have the potential to optimize anatomically complex percutaneous coronary interventions (eg, left main, bifurcations).

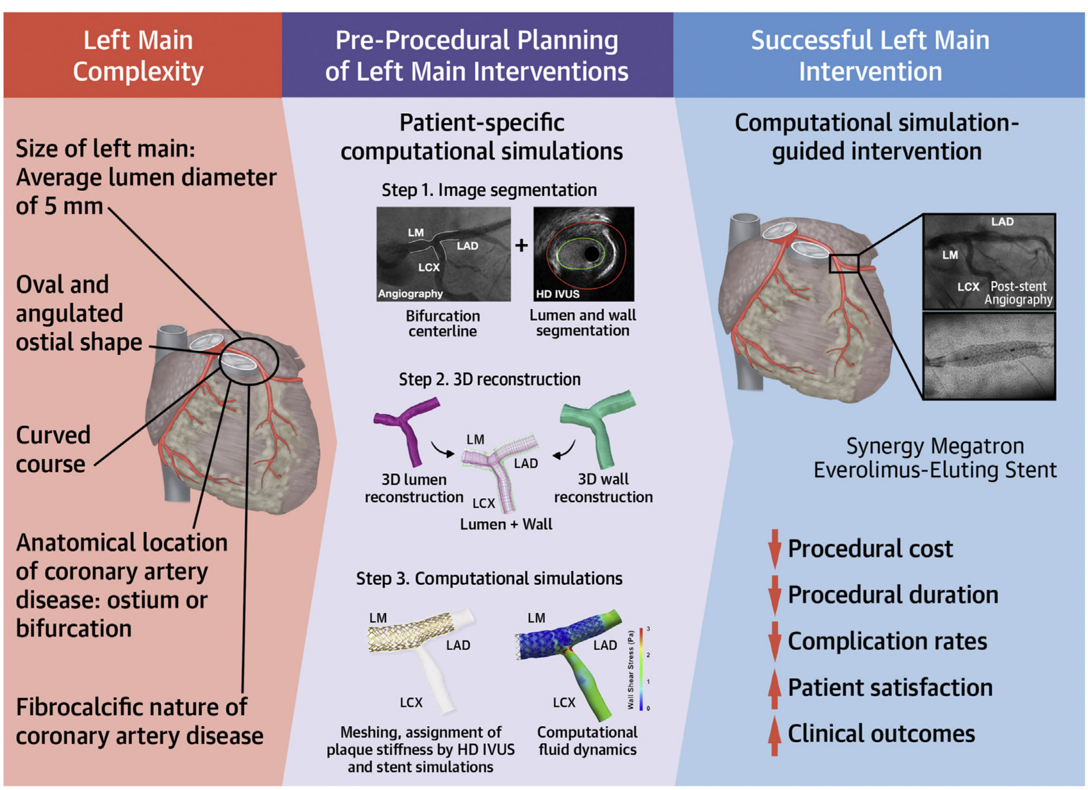
in patients 1 to 3 and adequate scaffolding of the LCx ostium in patient 2 (**Figures 1D, 1F, 2D to 2F, and** Supplemental Figures 1D to 1F). The mean stent diameter and shape of the clinically vs computationally deployed stents exhibited remarkable agreement (**Figures 4F to 4H, 5F, and 6F**).

DISCUSSION

In this case series, we demonstrate the feasibility and safety of advanced patient-specific computational preprocedural planning of high-risk LM PCI (**Central Illustration**). There were several novelties in our work:

1. For the first time, a well-validated patient-specific computational stent simulations platform[4] was used for preprocedural planning of coronary interventions. This platform could help interventional cardiologists familiarize themselves with

CENTRAL ILLUSTRATION Patient-Specific Computational Planning of Left Main Coronary Artery Stenting



Chatzizisis YS, et al. J Am Coll Cardiol Case Rep. 2022;4(6):325-335.

3D = 3-dimensional; HD = high definition; IVUS = intravascular ultrasound; LAD = left anterior descending; LCX = left circumflex; LM = left main.

anatomically complex cases (eg, LM, bifurcations) and optimize the equipment selection (eg, stents, balloons) and procedural steps (eg, lesion preparation, 1-stent vs 2-stent technique, postdilatation technique) in a safe, radiation- and contrast-free environment.

2. We used a new everolimus-eluting stent, purpose-built for large proximal coronary artery interventions.[3] Current drug-eluting stents are used indistinctively in all coronary segments. However, large proximal coronary artery usually develop more calcified plaques that require stents with improved radial and axial strength (as in patients #1 and #3). Moreover, LM interventions require stents with improved overexpansion and differential expansion capabilities to address the size mismatch between LM and LAD or LCx (as in patient #2).

3. We introduced 2 technical novelties with important clinical implications: 3D reconstruction of coronary artery bifurcation from the fusion of angiography with HD IVUS (**Figures 4A, 5A, and 6A**) and 3D stent reconstruction from HD IVUS (**Figure 4G**).[5,6]

This case series provides a paradigm on how the use of 21st century computational technologies could transform the operations in the cardiac catheterization laboratory of the future. Patient-specific computational preprocedural guidance of coronary interventions could reduce procedural costs and duration and improve procedural efficiency, complication rates, patient satisfaction, and short- and long-term clinical outcomes. Prospective clinical trials are warranted to validate this perspective. As technology evolves, application of faster computing systems (eg, supercomputer clusters, quantum computing) and integration of artificial intelligence algorithms (eg, machine or deep learning, statistical emulation) have the potential to allow real-time application of computational preprocedural planning in the cardiac catheterization laboratory.

FOLLOW-UP

All 3 patients were discharged home on the first postprocedural day and were symptom-free in the 12-month clinical follow-up. Notably, a 6-month angiographic follow-up of patient 1 showed no changes in the ostial LM stent and mid LAD disease.

CONCLUSIONS

Advanced computational preprocedural planning of LM interventions, combined with stent scaffolds purpose built for large coronary arteries (**Figure 8**), appears to be a feasible and safe approach that could optimize LM PCI and clinical outcomes (**Central Illustration**).

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was funded by the National Institutes of Health grant (R01 HL144690) and by the Dr Vincent Miscia Cardiovascular Research Fund, University of Nebraska Medical Center. Dr Chatzizisis has received speaker honoraria, advisory board fees, and research grant support from Boston Scientific; has received advisory board fees and research grant support from Medtronic; has a holding U.S. patent No. 11,026,749; has an international patent pending (PCT/US2020/057304) for the invention titled "Computational simulation platform for the planning of interventional procedures"; and is a cofounder of ComKardia. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Yiannis S. Chatzizisis, Cardiovascular Biology and Biomechanics Laboratory, Cardiovascular Division, University of Nebraska Medical Center, 982265 Nebraska Medical Center, Omaha, Nebraska 68198, USA. E-mail: ychatzizisis@icloud.com.

REFERENCES

1. Franklin B. By failing to prepare, you are preparing to fail. Goodreads Quotes. Accessed February 18, 2022. https://www.goodreads.com/quotes/15061-by-failing-to-prepare-you-are-preparing-to-fail

2. Burzotta F, Lassen JF, Banning AP, et al. Percutaneous coronary intervention in left main coronary artery disease: the 13th consensus document from the European Bifurcation Club. *EuroIntervention*. 2018;14:112-120.

3. Samant S, Wu W, Zhao S, et al. Computational and experimental mechanical performance of a new everolimus-eluting stent purpose-built for left main interventions. *Sci Rep*. 2021;11:8728.

4. Zhao S, Wu W, Samant S, et al. Patient-specific computational simulation of coronary artery bifurcation stenting. *Sci Rep*. 2021;11:16486.

5. Wu W, Samant S, de Zwart G, et al. 3D reconstruction of coronary artery bifurcations from coronary angiography and optical coherence tomography: feasibility, validation, and reproducibility. *Sci Rep*. 2020;10:18049.

6. Wu W, Khan B, Sharzehee M, et al. Three dimensional reconstruction of coronary artery stents from optical coherence tomography: experimental validation and clinical feasibility. *Sci Rep*. 2021;11:12252.

KEY WORDS computational simulations, coronary artery disease, imaging, left main, percutaneous coronary interventions, stents

APPENDIX For supplemental videos, a figure, and a table, please see the online version of this paper.