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# Angiographically Silent Left Main and Left Anterior Artery Disease Detected by Echocardiography

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## Abstract

***Background:*** *Knowing that stenosis of coronary arteries can be underestimated by coronary angiography.*

***Purpose:*** *We hypothesized that a local high velocity – ≥70 cm/s as measured by Doppler echocardiography – in left main and/or in the proximal portion of left anterior descending (LAD) in patients who had ischemic stress echo test and no/mild stenoses of these arteries by angiography could indicate angiographically silent significant narrowing of the arteries.*

***Methods:*** *Among a cohort of 1001 patients referred for stress echocardiography, we selected as our group persons who had coronary flow velocities at rest ≥70 cm/s in left main/proximal LAD, positive stress echocardiography test with wall abnormalities in LAD territories, and stenoses 0-40% in the corresponding portions of left main/proximal LAD by coronary angiography. The group underwent intravascular ultrasound (IVUS) or fractional flow reserve (FFR) for assessment of the interrogated segment of the coronary artery.*

***Results:*** *We identified 18 patients (15 men, 59±12 years old) who met the inclusion criteria. Eleven patients underwent IVUS, while seven were assigned for FFR. Lesions of left main/proximal LAD segments proved significant in 17 patients (94%, 95% CI 79-99%).*

***Conclusion:*** *A flow velocity in left main/proximal LAD of more than 70 cm/s could be an indication for performing IVUS/FFR in patients with discrepancies between coronary angiography and stress tests.*

**Keywords:** *left main, coronary flow ultrasound, coronary angiography, transthoracic coronary echo*

## Introduction

Diagnosis of coronary artery disease (CAD) is based on the documentation of ischaemia using non-invasive testing before invasive angiography. Coronary angiography represents an invasive imaging modality that permits direct visualization of CAD. The definition of a significant left main stenosis used herein is ≥50% narrowing, and of significant other epicardial stenosis is ≥70% luminal diameter narrowing, by visual assessment, measured in the "worst view" angiographic projection [1]. However, the angiographic assessment of the severity of left main disease and accurate prediction of the significance of other epicardial stenoses has several shortcomings. Therefore, matching of data from functional stress tests to either intravascular ultrasound (IVUS) or fractional flow reserve (FFR) may be necessary [1]. It is advisable to have functional information for stenoses of 50-90%, according ESC guidelines, or 40-70%

narrowing, according AHA/ACC recommendations [1,2]. However, about 15% of stress tests [3] show discrepancies with the angiographic data. In particular, stress echocardiography, which has a high prognostic value independently for angiographic data [4], has about 85% specificity, i.e. "false-positive" tests with stenoses of coronary arteries less than 50%.

Recent studies have described a highly feasible transthoracic ultrasound method of coronary artery flow assessment for left main artery and left anterior descending artery (LAD) [5-7]. The utility of this technique in everyday practice has been demonstrated for "all incoming" patients, with a high prognostic value of aliased coronary flow velocities at rest predicting major adverse cardiac events [8]. Knowing that stenosis of coronary arteries could be underestimated by coronary angiography due to angulation of image acquisition [9], we hypothesized that a local high velocity – ≥70 cm/s – in left main and/or in the proximal portion of LAD in patients who had ischemic stress echo test and no/mild stenoses of these arteries by angiography, could indicate angiographically silent significant narrowing of the arteries.

## Material and Methods

### Study Population

This was a prospective cohort study. All consecutive patients with suspected or known CAD referred for stress echocardiography to a single centre from September 2014 to March 2016 were screened in the study. The inclusion criteria for the study were:

1) coronary flow velocities at rest of ≥70 cm/s in left main/proximal LAD;

2) severe positive stress echocardiography test with wall abnormalities in LAD territories;

3) stenoses less than 40% in the corresponding portions of left main/proximal LAD.

### Transthoracic Echocardiography of Coronary Arteries

A persistent flow velocity of ≥70 cm/s was defined as the threshold for a significant abnormality, based on our previous experience and recent scientific data [10]. Scanning of the coronary arteries was performed before stress tests. Patients were examined with the ultrasound diagnostic systems Vivid 7 Dimension (GE Healthcare, USA, manufactured in Liestal, Switzerland) connected to a standard M4S transthoracic transducer and Vivid E9 (GE Healthcare, USA, manufactured in Horten, Norway) connected to a standard M5S transthoracic transducer. We used the manufacturer preset 'Coronary'. The transducers were multifrequency phased-array sector scan probes with second harmonic technology. The scanning was performed following the detailed description in the study by Vegsundvåg J et al. [9] and in our previous publications [7,8]. The initial color Doppler scanning was at a Nyquist limit of 0.20 m/s. If necessary, the Nyquist limit was subsequently adjusted up to 0.65 m/s to provide optimal imaging of the aliased zone. The Nyquist limit was therefore 0.20-0.65 m/s (Figure 1). Pulsed wave Doppler registered blood flow velocity using a sample volume (2-3.0 mm) placed on the color signal. The maximal diastolic velocity was used for analysis (Figure 2). Before stress test we also measured ejection fraction using the biplane method of disks.

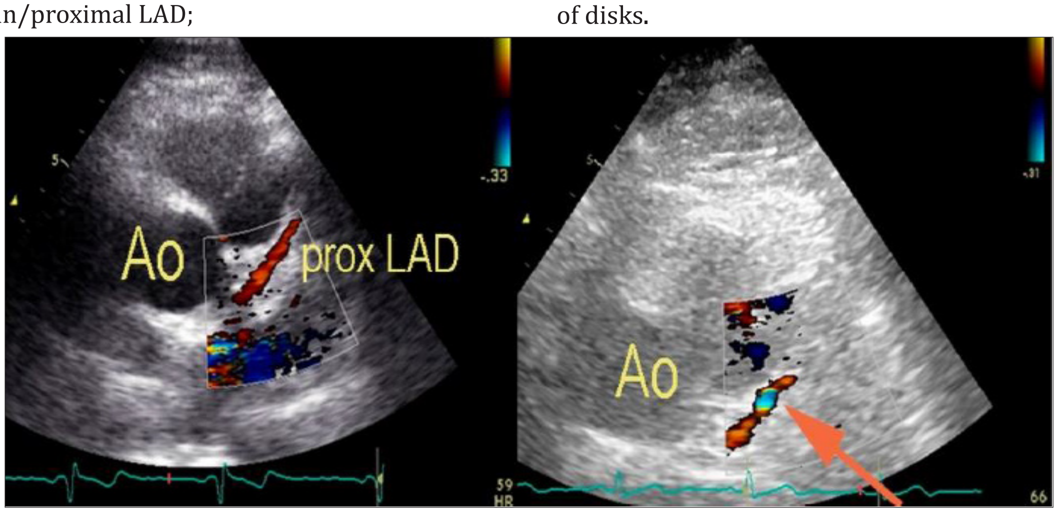


**Fig1.** *Color Doppler visualization of normal (A) and turbulent flow (B) in proximal segment of left anterior descending artery (LAD).*

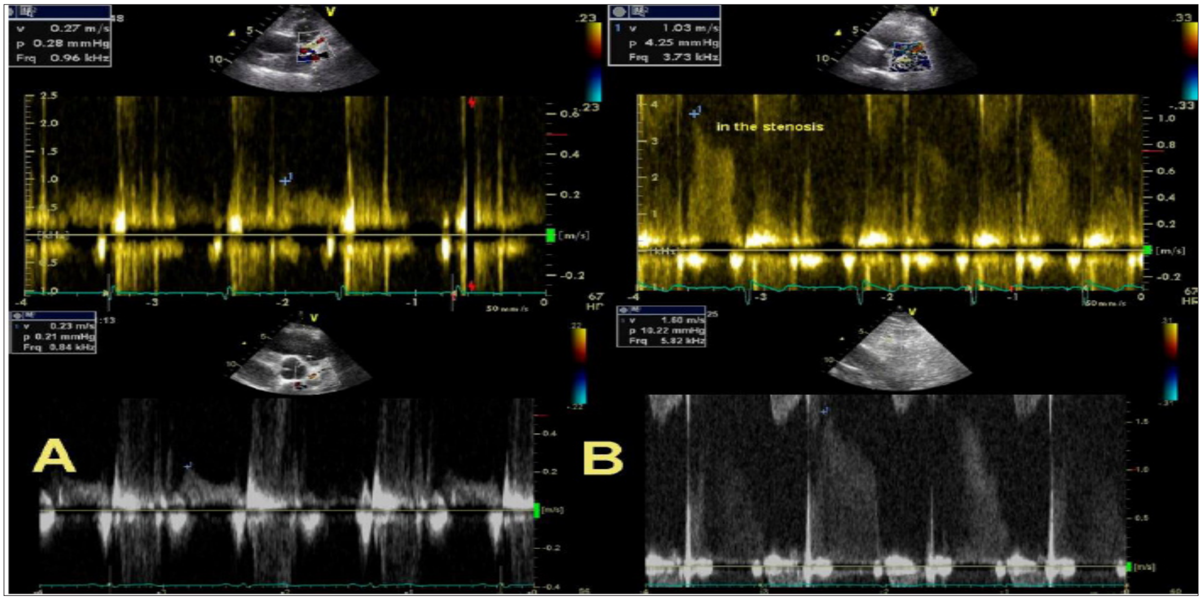


**Fig2.** *Normal velocity (row A) in comparison with high velocity (row B) of coronary flow in proximal segment of left anterior descending artery (LAD).*

## Stress Echocardiography

All patients underwent a symptoms-limited, semi-supine bicycle test with the conventional visual assessment of wall motion abnormalities using e-Bike EL&BP (General Electric, USA). Graded testing was employed, starting with an initial workload of 50 Watts and lasting for two minutes. The workload was increased gradually by 25 Watts at two-minute intervals until standard endpoints were reached [11]. ECG and arterial pressure were monitored during the test. All studies were continuously recorded on hard drive and DVD for off-line analysis. Echocardiographic imaging was performed from parasternal long axis view, short axis view, and four- and two-chamber view, using conventional two-dimensional echocardiography. Echocardiographic images were acquired at rest and consistently at all stages of test activity. Post-stress images, analogous to those at rest, were obtained as soon as possible after stopping exercise, and not later than 60 seconds. The images at rest, during stress, and after stopping were compared side by side in a cineloop display. Wall-motion score index was calculated in each patient at baseline and peak stress, according to the recommendation of the ASE/EAE from one (normal) to four (dyskinetic) in a 17-segment model of the left ventricle [12].

## Coronary Angiography

Patients underwent coronary angiography within 24± 20 days after stress echocardiography, using standard techniques to determine obstructive CAD. Multiple projections were recorded for each vessel. The proximal section of LAD was defined as from the left main coronary artery to the first major septal branch. Cine-fluoroscopic images were analyzed at an independent angiographic core laboratory. The results of the two invasive cardiologists were averaged.

All patients who met inclusion criteria were examined using IVUS or FFR at the discretion of an angiographer in both methods. IVUS was performed mostly in cases with high coronary flow velocities in left main and/or the ostial part of LAD, while FFR was performed in the cases with lesions of the middle part of the proximal LAD.

## IVUS

The patients underwent IVUS using a 20 to 45 MHz transducer. The resolution was 80 microns axially and 160 to 200 microns laterally. The pullback speed was 0.5-1.0 mm/s. IVUS analyses were performed using validated and automated edge-detection software (Medis QCA CMS 6.0/XA 7.2 and Medis QCU 1.0 [Medis Medical Imaging Systems Inc., Leiden, the Netherlands], Boston scientific Ilab Ultrasound Imaging System Inc. (Natick, Massachusetts, USA), and VIAS-Volcano Image Analysis Software (Volcano Inc., Rancho Cordova, California). Images were analyzed by an experienced independent angiographer. For left main coronary artery stenoses, a minimum lumen diameter of <2.8 mm or a minimum lumen area of <6 $mm^2$ was considered as a significant lesion [13]. Ostial lesions were considered significant with a plaque burden ≥70% and minimal lumen area ≤4 $mm^2$.

## FFR

FFR was performed as described previously [14]. A pressure monitoring guide wire (Ilumien, St. Jude Medical, Inc., Massachusetts, USA) was advanced distal to the coronary artery stenosis. Hyperaemia was obtained after administration of intravenous adenosine (continuous infusion of 140 µg/kg/min). Fractional flow reserve was defined as the ratio of the simultaneously recorded mean arterial pressure distal to the stenosis and the mean aortic pressure at the tip of the guiding catheter during stable, steady-state hyperaemia. FFR ≤0.80 was considered abnormal.

### Statistics

Continuous variables were described by means and standard deviations, with categorical data being expressed in percentages. The confidence interval was calculated using Fisher's exact test. The Statistica, statistical package version 10.0 (Stat Soft Inc., Tulsa, Oklahoma, USA) was used.

The study protocol was approved by an ethics committee. All patients gave informed consent before stress tests, coronary angiography, IVUS or FFR.

## Results

### Patients

We prospectively 1001 out-patients (631 men, 56±9 years old) with known (55%) or suspected coronary artery disease (45%) who were referred for exercise echocardiography for diagnostic purposes or for stratification of risk. The full range of inclusion criteria were identified in 18 persons (15 men, 59±12 years old). Eight patients (47%) had typical angina; four patients (24%) had limited functional capacity due to dyspnea; four persons (24%) had a history of myocardial infarction. Five patients (29%) had previously undergone percutaneous coronary intervention in different segments of coronary arteries (three in right coronary, one in left circumflex, and one in LAD). Two patients had angina, and two patients had a history of myocardial infarction. There were two patients with diabetes mellitus, 12 with arterial hypertension, and 12 persons were former or current smokers. All of them were recommended statins, acetylsalicylic acid, angiotensin converting enzyme inhibitors, or angiotensin II receptor blockers by their cardiologists. Sixteen patients took beta-blockers.

### Transthoracic Coronary Artery Scanning

There were four cases with local high velocity in left main, eight cases in the ostial or near ostial parts of LAD, and six cases in the middle portion of proximal LAD. The maximal velocity in the alteration segments was 92±18 cm/s.

### Resting and Stress Echocardiography

Average ejection fraction at rest was 65±7%, and the index of end-diastolic volume was 52±8 ml/m$^2$. All patients completed a satisfactory bicycle test. There were no adverse events during or after exercise. The exercise capacity was 68±26 Wt, and maximal heart rate during exercise was 106±16 beats/min. The test was severe positive for wall motion criteria. Index of wall motion abnormality at rest was 1.14±0.21, and at the peak of exercise was 2.03±0.33, delta of change for the indices was 0.89±0.33.

### Conclusions of the First Coronary Angiography

Stenoses of left main or proximal LAD of more than 40% (0-40%) were not found in the study group. An example of coronary angiography with the Doppler data of a patient can be seen in Figure 3.

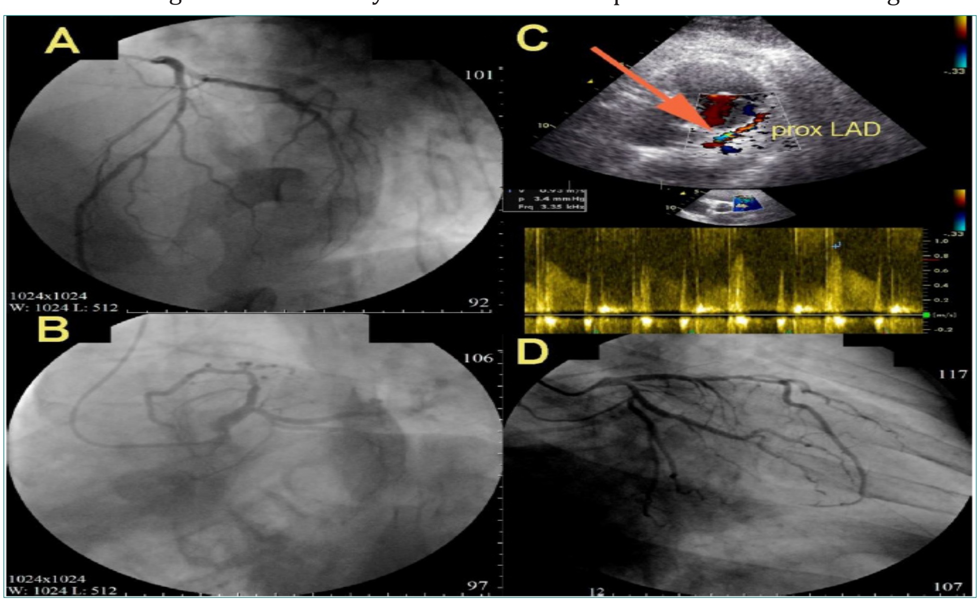


**Fig3.** *A man, 61 years old, with typical everyday angina of third functional class. Coronary angiography without significant stenoses. A, B, D – different projections of left coronary artery; C – Color and pulsed-wave Doppler of proximal left anterior descending artery.*

## IVUS

Intravascular ultrasound was chosen for eleven patients. Stenoses were identified as significant by IVUS criteria in ten of the eleven patients. Furthermore, during repeat angiography of three patients before IVUS, projections with significant stenoses of left main/proximal LAD lesions were found. An example of coronary angiography with the Doppler and IVUS data of a patient can be seen in Figure 4.

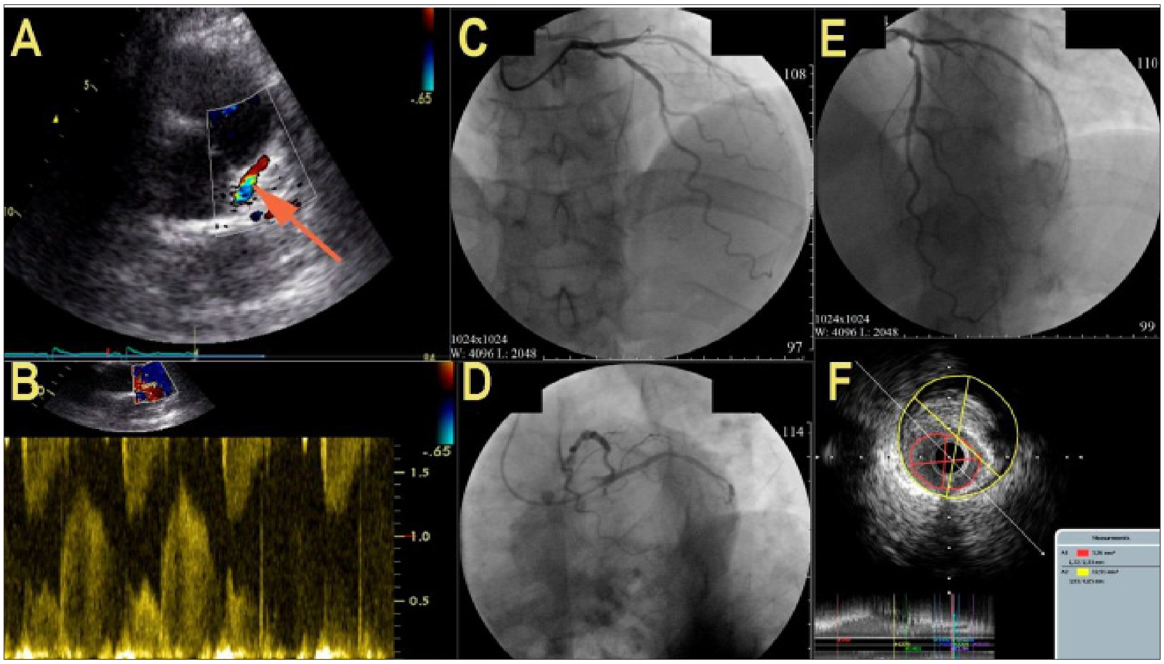


**Fig4.** *A man, 47 years old, with typical angina and diabetes mellitus. A, B - Color and pulsed-wave Doppler of proximal left anterior descending artery; C, D, E - different projections of left coronary artery; F – IVUS data.*

## FFR

All seven patients referred for FFR had significant stenoses according to the aforementioned criteria. The average FFR value was 0.75±0.05. An example of coronary angiography with Doppler data for the middle portion of proximal LAD can be seen in Figure 5.

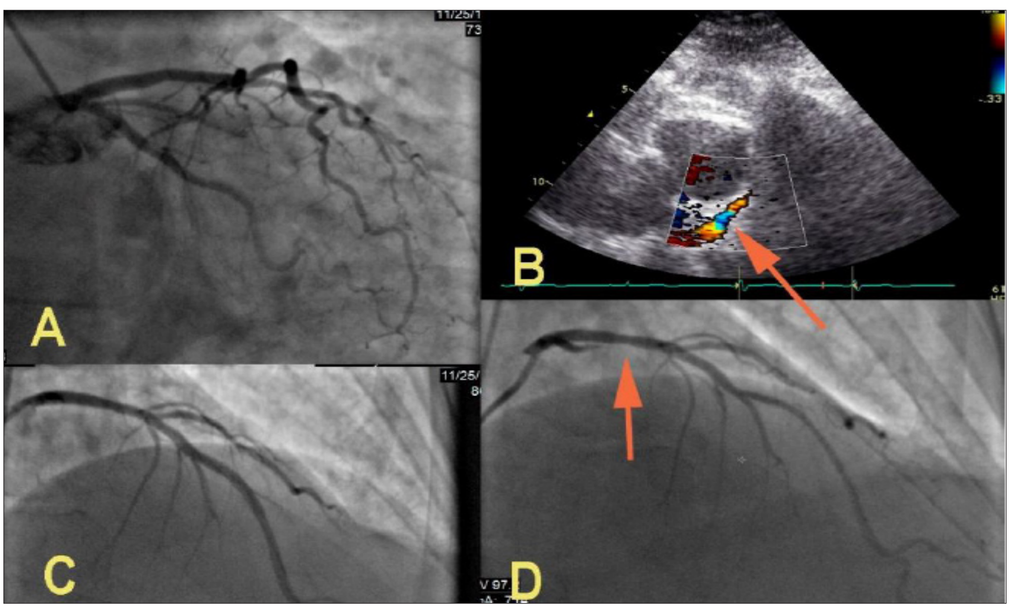


**Fig5.** *A man, 45 years old, with no specific symptoms and two cases of sudden death without previous symptoms due to CAD in close relatives. B - Color pulsed-wave Doppler of proximal left anterior descending artery, A, C, D - different projections of left coronary artery.*

In summary, seventeen patients of the study group (94%, 95% CI 79-99%) were found to have lesions of left main/proximal LAD segments that proved significant.

## Discussion

The integration of anatomical and functional data from coronary arteries is a cornerstone of diagnosis and strategy for patients with CAD. On the physiological side, safe and simple stress echocardiography tests give valuable diagnostic and prognostic information independently of other data [4]. Coronary angiography, meanwhile, is the most often used invasive anatomic method for CAD diagnosis for strategy decision-making. There is a discrepancy of about 15% between these two most widely used methods [3]. On the one hand, this can partly be explained by the subjectivity of stress echocardiography [15], the non-coronary nature of some wall motion abnormalities [16], microvascular dysfunction [17], artifacts etc. On the other hand, a number of studies have reported the shortcomings of coronary angiography [9, 18, 19]. A lack of sufficient projections or different lesion shapes can easily cause discrepancies, as can overlapping of images of the two vessels near the branch point or an overestimation of the lumen diameter by angiography in severely diseased arteries because of a lack of a true normal frame of reference distal to the affected segment [9]. A discrepancy between two these important methods can influence the patient's prognosis. The poor prognosis of patients with severe positive stress echo test and negative coronary angiography data has been shown previously [4]. To clarify the significance of coronary stenosis, the clinical guidelines recommend the additional use of FFR/IVUS. However, the indication to use these methods for assessment of left main is not clear: "other assessments such as IVUS or FFR may be needed." FFR is recommended for assessment of stenoses 40-70% [1] or 50-90% [2].

Noninvasive transthoracic Doppler visualization of coronary arteries with measurement of their velocity parameters has previously been shown to potentially help in diagnosing significant coronary artery stenoses in comparison with coronary angiography [20-22]. This study demonstrated the potential of this method to reveal angiographically silent stenoses of the most important segments of coronary arteries. Indeed, 94% of the study patients had a severe lesion of left main/proximal portion of LAD as demonstrated by IVUS/FFR, despite angiographically non-significant stenoses. This group of patients had silent stenoses of 0-40% in angiograms, and would not have been examined with clarifying methods had it not been for their pathological Doppler coronary artery flow data. These data agreed with a previous pilot investigation [23]. The authors found that, in angiographically borderline left main disease, resting Doppler left main flow velocity from transthoracic echocardiography increases in the presence of an increased plaque burden as revealed by IVUS. However, they define a velocity cut-off of 112 cm/sec as a significant borderline [23]. In our study, we use the predisposed lesser value of coronary flow velocity at rest, as it was recently shown in a prospective large group study that patients whose velocity in left main/proximal LAD was more than ≥70 cm/s had serious prognosis during the following 10 months [8].

## Limitations

This is a pilot small single-center investigation. Larger investigations are needed to confirm the results.

Despite maximum efforts to achieve parallel alignment of the Doppler beam with coronary blood flow, the angles between them could still influence the velocity values.

## Conclusion

In summary, transthoracic coronary artery flow velocity assessment is a useful additive tool for diagnosis of significant left main/proximal LAD stenoses. A flow velocity in left main/proximal LAD of more than 70 cm/s could be an indication for performing IVUS/FFR in patients with discrepancies between coronary angiography and stress tests.

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