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Prognostic value of dual imaging stress echocardiography following coronary bypass surgery

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ABSTRACT

Aims: To assess the prognostic value of dual imaging stress echocardiography after coronary artery bypass grafting (CABG). Dual imaging stress echocardiography, combining the evaluation of regional wall motion and Doppler echocardiographic derived coronary flow velocity reserve (CFVR) of the left anterior descending artery (LAD), is the state-of-the-art methodology during vasodilatory stress.

Methods and results: In a prospective, multicenter, observational study, 349 patients (270 men; 69 ± 9 years; 262 symptomatic) with history of CABG underwent high-dose dipyridamole (0.84 mg/kg over 6 min) stress echocardiography with CFVR evaluation of LAD by Doppler. The composite endpoint of death and myocardial infarction was considered in the survival analysis. Positivity rate with either criteria was 13% in the 262 symptomatic patients with appropriate and 6% in the 87 asymptomatic patients with maybe/rarely appropriate indications on the basis of 2014 American College of Cardiology Foundation guidelines. During a median follow-up of 22 months (1st quartile 8, 3rd quartile 44), there were 56 (16%) events: 21 deaths, and 35 nonfatal myocardial infarctions. At Cox analysis, ischemia at stress echo (HR 4.80, 95% CI 2.69–8.55; $p < 0.0001$), and CFVR of LAD ≤2 (HR 2.28, 95% CI 1.32–3.95; $p = 0.003$) were multivariable prognostic predictors. Considering the group with no ischemia, patients with CFVR ≤2 showed 2.5 fold higher yearly hard events as compared to those with CFVR >2 (7.5 vs 2.9%; $p = 0.002$).

Conclusions: Dual imaging stress echocardiography provides useful prognostic information following CABG. Inducible ischemia and abnormal CFVR are strong and independent prognostic indicators in patients with appropriate and rarely/maybe appropriate indications.

1. Background

Stress echocardiography has a class I indication in symptomatic patients after coronary artery bypass grafting (CABG), but not in the post-procedure period [1]. The indication is more questionable in asymptomatic patients, in whom noninvasive stress testing may be appropriate ≥5 years after CABG and is considered rarely appropriate <5 years after CABG [2]. The technique has been proved to be effective in risk stratification after surgical revascularization in several studies showing that the evidence of ischemia adds significant prognostic information to that provided by clinical data and resting echo [2–6]. Appropriate and inappropriate stress echocardiography after CABG account for 5 to 10% of all indications in large volume laboratories [7–9]. However, the assessment of the value of the technique is made difficult by the lack of reliable data with state-of-the-art protocols. In particular, after CABG the assessment of ischemia due to a stenosis in the graft is complicated by several confounding features, including the potential for microvascular abnormalities due to ischemic fibrosis and scarring, pre-existing or bypass-surgery myocardial infarction, chronic low-flow ischemia or reversible damage due to inflammatory state with increased oxidative stress [10]. In the last decade, stress echocardiography evolved to include coronary flow velocity reserve (CFVR) of the left anterior descending artery (LAD) as an add-on to standard regional wall motion analysis as the new standard providing information on abnormalities of coronary microcirculation which are unable to induce myocardial ischemia. Vasodilator dual imaging stress echocardiography has entered the clinical practice and it has been proved to provide additive prognostic information in several clinical conditions [11–14]. Therefore, the aim of this study was to assess the additive prognostic value of Doppler-derived CFVR of LAD in patients with history of CABG.

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2. Methods

The study population consisted of 349 patients [270 men; mean (±SD) age 69 ± 9 years] with history of CABG who were evaluated at four Italian Cardiology Institutions (Lucca, Benevento, Mestre, Pisa) from August 2003 to November 2015 for enrollment in a study focused on assessing the prognostic value of CFVR in the setting of known or suspected coronary artery disease. The study design is observational, not randomized, prospective and patients were entered the databank at the time of initial assessment. All patients underwent stress echocardiography with wall motion and CFVR assessment of LAD by transthoracic Doppler ultrasound. Exclusion criteria were significant valvular or congenital heart disease, prognostically relevant non-cardiac diseases (cancer, end-stage renal disease, or severe obstructive pulmonary disease), and inadequate acoustic window precluding satisfactory imaging of left ventricle (for 2D echo) or of LAD flow Doppler (for CFVR assessment). Follow-up information was available for all patients. Reasons for testing were the presence of symptoms suggestive of ischemic origin in 262 (75%) and screening for asymptomatic progression of the disease in 87 (25%) patients (Table 1).

According to individual needs and physician's choices, 156 (45%) patients were evaluated after anti-anginal drugs had been discontinued, and 193 (55%) patients were evaluated during anti-anginal treatment (Table 1). Phylline-containing drugs or beverages were discontinued at least 24 h before testing. All patients gave their written informed consent when they underwent stress echocardiography. When patients signed the written informed consent they also authorized physicians to use their clinical data. Stress echo data were collected and analysed by stress echocardiographers not involved in patient care. Diabetes mellitus [15], arterial hypertension [16], and hypercholesterolemia [17] were defined according to standard criteria.

2.1. Stress echocardiography

Transthoracic stress echocardiographic studies were performed with commercially available ultrasound machine (Sonos 7500 or iE 33, Philips Ultrasound, Andover, Mass; Vivid System 7, GE/Vingmed, Milwaukee, Wis; Sequoia C256 Acuson Siemens Mountain View, Calif) equipped with multifrequency phased-array sector scan probe (S3–S8 or V3–V7) and with second harmonic technology. Two-dimensional echocardiography and 12-lead electrocardiographic monitoring were performed in combination with high-dose dipyridamole (up to 0.84 mg over 6 min) [18]. Echocardiographic images were semi-quantitatively assessed using a 17 segments, 4-point scale model of the left ventricle [19]. A wall motion score index (WMSI) was calculated by dividing the sum of individual segment scores by the number of interpretable segments. Ischemia was defined as stress-induced new and/or worsening of preexisting wall motion abnormality. A test was considered positive for ischemia only on the basis of wall motion analysis. Rest wall motion abnormality was akinetic or dyskinetic myocardium with no thickening during stress. Left ventricular ejection fraction was assessed in the standard 4-chamber view using the area-length method [19]. CFVR was assessed during the standard stress echo examination by an intermittent imaging of both wall motion and LAD flow [18]. Coronary flow in the mid-distal portion of LAD was searched in the low parasternal long-axis section under the guidance of colour Doppler flow mapping [18]. Contrast was not used for the assessment of CFVR in any of the study patients. All studies were digitally stored to simplify off-line reviewing and measurements. Coronary flow parameters were analysed off-line using the built-in calculation package of the ultrasound unit. Flow velocities were measured ≥2 times for each study, namely at baseline and at peak stress (before aminophylline injection). At each time point, 3 optimal profiles of peak diastolic Doppler flow velocities were measured, and the results were averaged. CFVR was defined as the ratio between hyperemic peak and basal peak diastolic coronary flow velocities. A CFVR value ≤2.0 was considered abnormal [11]. All investigators of contributing centers passed quality control criteria for regional wall motion and Doppler interpretation prior to entering the study as previously described [20]. The feasibility of CFVR assessment on LAD is 94% [21]. The previously assessed intra- and inter-observer variability for measurements of Doppler recordings and regional wall motion analysis assessment were <10% [21].

Table 1
Clinical and echocardiographic characteristics for patients with CFVR of left anterior descending artery >2 and <2.

	CFR > 2 (n = 218)	CFR ≤ 2 (n = 131)	p value
Age (years)	69 ± 8	70 ± 10	0.43
Males	166 (76%)	104 (79%)	0.48
Symptoms after CABG	158 (72%)	104 (79%)	0.15
Clinical history			
Family history of CAD	61 (28%)	45 (34%)	0.21
Diabetes mellitus	59 (27%)	53 (40%)	0.009
Arterial hypertension	167 (77%)	97 (74%)	0.59
Hypercholesterolemia	158 (72%)	95 (72%)	0.99
Smoking habit	67 (31%)	45 (34%)	0.48
Left bundle branch block	13 (6%)	11 (8%)	0.38
Prior myocardial infarction	126 (58%)	77 (59%)	0.86
Anti-ischemic therapy at the time of test			
β-Blockers	99 (45%)	67 (51%)	0.30
Calcium antagonists	39 (18%)	26 (20%)	0.65
Nitrates	24 (11%)	28 (21%)	0.008
At least one medication	117 (54%)	76 (58%)	0.43
Resting echocardiogram			
WMA at rest	123 (56%)	87 (66%)	0.06
WMSI at rest	1.26 ± 0.34	1.37 ± 0.38	0.006
Left ventricular ejection fraction %	54 ± 8	51 ± 10	0.001
Stress echocardiography			
Ischemic result	26 (12%)	38 (29%)	<0.0001
WMSI at peak stress	1.26 ± 0.32	1.44 ± 0.41	<0.0001
Resting velocity of LAD (cm/s)	30 ± 9	35 ± 16	<0.0001
CFVR of LAD	2.60 ± 0.60	1.72 ± 0.24	<0.0001

Data presented are mean value ± SD or number (%) of patients.
CABG = coronary artery bypass grafting; CAD = coronary artery disease; WMA = wall motion abnormality; WMSI = wall motion score index; LAD = left anterior descending artery; CFVR = coronary flow velocity reserve.

2.2. Follow-up data

Follow-up data were obtained from review of the patient's hospital record, personal communication with the patient's physician and review of the patient's chart, a telephone interview with the patient or a patient's close relative conducted by trained personnel, a staff physician visiting the patients at regular intervals in the out-patient clinic. Clinical events were defined as death and non-fatal acute myocardial infarction. In order to avoid misclassification of the cause of death [22,23], overall mortality was considered. Coronary revascularization (surgery or angioplasty) was also registered; however, it was not identified as clinical event. Follow-up data were analysed for the prediction of hard events (death, myocardial infarction). When more than one of these events occurred, the patient was censored at the time of the most severe event.

2.3. Statistical analysis

Continuous variables are expressed as mean ± SD. Differences between groups were compared using Student's t and chi-square test, as appropriate. Hard event rates were estimated with Kaplan-Meier curves and compared by the log-rank test. Patients undergoing coronary revascularization were censored at the time of the procedure. The association of selected variables with outcome was assessed with the Cox's proportional hazard model using univariate and stepwise multivariate procedures. A significance of 0.05 was required for a variable to be included into the multivariate model, whilst 0.1 was the cut-off value for exclusion. Hazard ratios (HR) with the corresponding 95% confidence interval (CI) were estimated. Statistical significance was set at $p < 0.05$. Statistical Package for the Social Sciences (IBM, SPSS Statistics, version 21) was used for analysis.

3. Results

3.1. Stress echocardiographic findings

No complication occurred during the test.

Mean CFVR of LAD was 2.27 ± 0.65. At individual patient analysis, 131 (38%) individuals had CFVR ≤2 and 218 (62%) had CFVR >2. Stress echo was positive for ischemia in 64 (18%) subjects: 38 of 131 with CFVR ≤2 and 26 of 218 with CFVR >2 (29 vs 12%; $p < 0.0001$) (Table 1). Thirty-eight patients (11%) had both ischemia and CFVR ≤ 2, whilst 192 (55%) patients had no ischemia and CFVR >2. Positivity rate with either criteria was 13% in the 262 symptomatic patients and 6% in the 87 asymptomatic patients.

Patients with CFVR ≤2 were more frequently diabetics, had higher resting velocity of LAD, higher WMSI, and lower left ventricular ejection fraction on the resting echocardiogram than patients with CFVR >2 (Table 1). In the subset of 280 patients with no inducible ischemia, history of diabetes was present in 35 out of 93 with CVFR ≤2 and in 50 out of 192 with CVFR > 2 (38 vs 26%; $p = 0.04$). Hypertension was equally prevalent in the 2 groups: 67/93 and 150/192 (72 vs 78%; $p = 0.26$). Ejection fraction was lower in patients with reduced CVFR (52 ± 10 vs 55 ± 8; $p = 0.01$).

3.2. Outcomes

During a median follow-up of 22 months (1st quartile 8, 3rd quartile 44), 56 (16%) events were registered: 21 deaths, and 35 nonfatal myocardial infarctions.

According to the physician's judgement, 45 (13%) patients underwent myocardial revascularization (10 surgery, and 35 percutaneous intervention) after a median of 149 days (1st quartile 30, 3rd quartile 271) from the index stress echo. There were 21 revascularizations in patients with ischemia and 24 in those without ischemia at stress echo (33 vs 8%; $p < 0.0001$). In addition, there were 31 revascularizations in patients with CFVR ≤2 and 14 in those with CFVR >2 (24 vs 6%; $p < 0.0001$). Of the 10 asymptomatic patients with positive test, 7 (2 with inducible myocardial ischemia and 5 with no ischemia) were revascularized at 341 ± 361 days from testing.

3.3. Outcome prediction

Patients evaluated for symptoms suggestive of myocardial ischemia had a non-significant higher annual hard event-rate than those asymptomatic (7.5 vs 4.5%; $p = 0.16$).

Univariate predictors of hard events are reported in Table 2. At multivariate analysis, ischemia at stress echo ($p < 0.0001$), and CFVR of LAD ≤2 ($p < 0.0001$) were the only independent prognostic indicators.

The 3-year hard event rate was 59% in patients with both ischemia and abnormal CFVR, 42% in patients with ischemia only, 21% in patients with abnormal CFVR only, and 7% in patients with no ischemia and normal CFVR (Fig. 1). In pairwise comparisons, all groups significantly differed from each other except in the ischemic population between subjects with CFVR ≤ 2 and those with CFVR > 2 (Fig. 1). In Fig. 2 is shown the yearly hard event-rate in patients with both ischemia and abnormal CFVR, ischemia only, abnormal CFVR only, and no ischemia and normal CFVR. Of note, a negative stress result with a normal CFVR was associated to 2.5 fold lower risk of death or myocardial infarction than a negative stress result with an abnormal CFVR (2.9 vs 7.5%; $p = 0.002$) (Fig. 2). In addition, dual imaging stress echo result provided useful prognostic information both in the 262 symptomatic patients with appropriate and in the 87 asymptomatic patients with maybe/rarely appropriate indication for testing (Fig. 3).

4. Discussion

In CABG patients who underwent vasodilator dual imaging stress echocardiography with the assessment of both wall motion and CFVR, it is possible to identify different strata of risk, being the highest for the symptomatic subset and inducible wall motion abnormalities and the lowest for the asymptomatic subset, no wall motion abnormalities and normal CFVR. The use of routine stress echocardiography after surgical revascularization remains controversial and the time lag (5 years) indicated by appropriateness criteria may be quite arbitrary. Stress echocardiography, however, remains a very performing clinical tool able to provide critical information with a high accuracy and an excellent ability to identify a wide spectrum of risk, putting together different parameters showing the severity of disease. In our data set, inducible ischemia and abnormal CFVR were strong and independent prognostic indicators. Of interest, a negative stress result with a normal CFVR was associated to 2.5 fold lower annual risk of death or myocardial infarction than a negative stress result with an abnormal CFVR.

4.1. Comparison with previous studies

There is no a large dataset showing the ability of CFVR in risk stratifying patients after CABG. Several studies have used Doppler-derived CFVR for the assessment of graft patency, showing its clinical utility and demonstrating that the improvement after revascularization was related to a better outcome [24,25]. In a previous study [5] from our group we have shown that stress echocardiography represents an effective tool for the risk stratification of patients with previous CABG independently of the presence of symptoms suggestive of ischemic origin. In particular, the evidence of inducible ischemia added significant prognostic information to that provided by clinical data and resting echo [5]. However, in that previous report no data on CFVR was obtained. CFVR has been proved to provide an additive prognostic information in patients with known or suspected coronary artery disease, identifying the subset at risk of death in the follow-up [13]. It was also shown that in patients with normal coronary arteries and no inducible ischemia, the microvascular impairment was related to highest level of risk when compared to patients with no microvascular disease [26]. Also in this setting, microvascular impairment was related to a worse outcome in the face of normal rest and peak left ventricular function. It is interesting to note that similar results were obtained in a subgroup of patients with diabetes and no symptoms for coronary artery disease [27], again confirming that symptoms may not be a perfect marker of disease.

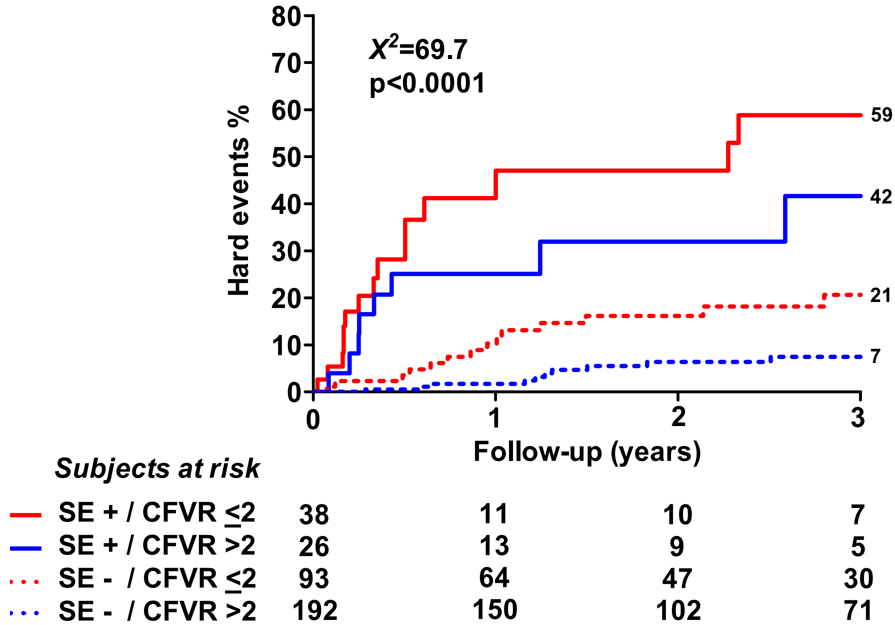
4.2. Clinical implications

The present study was undertaken to shed light on the clinical management of patients who had undergone surgical coronary revascularization. Management remains quite controversial and stress testing indication does not always modulate treatment. These patients are

Table 2
Univariable and multivariable predictors of hard events (death, acute myocardial infarction).

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.02 (0.99–1.05)	0.29		
Male sex	1.38 (0.69–2.73)	0.36		
Family history of CAD	0.74 (0.41–1.34)	0.31		
Diabetes mellitus	1.85 (1.09–3.15)	0.02		
Arterial hypertension	1.19 (0.63–2.26)	0.58		
Hypercholesterolemia	1.53 (0.78–2.97)	0.21		
Smoking habit	1.33 (0.78–2.26)	0.30		
Left bundle branch block	1.86 (0.84–4.12)	0.12		
Symptoms after CABG	1.63 (0.82–3.23)	0.16		
Prior myocardial infarction	1.10 (0.65–1.88)	0.72		
Ongoing anti-ischemic therapy	1.06 (0.62–1.82)	0.82		
WMA at rest	2.12 (1.17–3.76)	0.01		
WMSI at rest	2.39 (1.24–4.64)	0.01		
Ischemia at stress echo	6.55 (3.80–11.30)	<0.0001	4.80 (2.69–8.55)	<0.0001
Peak WMSI	4.96 (2.71–9.07)	<0.0001		
Resting velocity of LAD	1.04 (1.03–1.06)	<0.0001		
CFVR of LAD <2	2.91 (1.70–4.98)	<0.0001	2.28 (1.32–3.95)	0.003

Abbreviations as in Table 1.



	X^2	*p value*
SE + / CFVR ≤2 *vs* SE + / CFVR >2	1.4	0.23
SE + / CFVR ≤2 *vs* SE - / CFVR ≤2	19.3	<0.0001
SE + / CFVR ≤2 *vs* SE - / CFVR >2	68.7	<0.0001
SE + / CFVR >2 *vs* SE - / CFVR ≤2	6.1	0.01
SE + / CFVR >2 *vs* SE - / CFVR >2	31.9	<0.0001
SE - / CFVR ≤2 *vs* SE - / CFVR >2	9.2	0.002

Fig. 1. Long-term hard event-rate for the study population separated on the basis of presence (+) or absence (−) of ischemia at stress echocardiography (SE) and coronary flow velocity reserve (CFVR) of left anterior descending artery ≤2 or >2. Number of patients per year is shown.

difficult for their anatomy and stress testing interpretation may be difficult. However, there are some scenarios that can be envisioned on the basis of the present results: 1. Symptomatic patients with stress echo positivity for wall motion criteria show the highest rate of events over time and merit an aggressive treatment; 2. Patients with sole microvascular impairment show a rate of events which is double to that of patients with no microvascular impairment. This subset of patients, although unsuitable for revascularization should be treated with optimal medical therapy. In the face of the scarcity of data on CFVR in CABG patients, the assessment of microvascular dysfunction should be included in the clinical armamentarium due to its high value in modulating stress echo response. It is also interesting to note that symptoms were related to a worse outcome but this difference did not reach statistical significance.

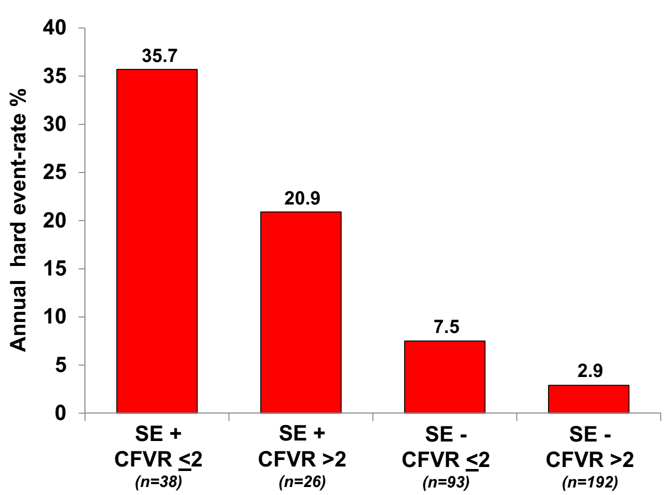


Fig. 2. Annual hard event-rate for the study population separated on the basis of presence (+) or absence (−) of ischemia at stress echocardiography (SE) and coronary flow velocity reserve (CFVR) of left anterior descending artery ≤2 or >2.

Due to the wide spectrum of disease progression occurring in patients with prior CABG [10], an optimal approach to noninvasive stress testing after CABG should probably include dual imaging, focused not only on the detection of large arteries (native vessels or grafts) stenosis inducing regional wall motion abnormalities but also on assessment of CFVR (or perfusion abnormalities). Post-CABG patients may develop new obstructive disease in native vessels not bypassed in the first operation and new stenoses in existing bypass grafts, which are mirrored by new wall motion abnormalities during noninvasive stress testing. There is also another pathway, unable to induce myocardial ischemia, and linked to microcirculation abnormalities, due to anatomic (scar and ischemic fibrosis due to infarction and chronic low flow ischemia) or functional, partially reversible damage of the coronary microcirculation possibly due to a systemic inflammatory response, which promotes coronary microvascular disease, and may be due to contact of blood with the bypass circuit, myocardial ischemia during bypass, aortic cross-clamping and reperfusion injury [28]. The microcirculatory target is mirrored in CFVR reduction in the absence of new wall motion abnormalities [29]. Both wall motion abnormalities and CFVR parameters offer complementary information, target different mechanisms and - not surprisingly - show clearly additive prognostic power [30]. On the basis of these results we are not advocating the use of stress echocardiography in post-op patients outside the conventional recommendations because this may raise the number of unnecessary testing and downstream costs.

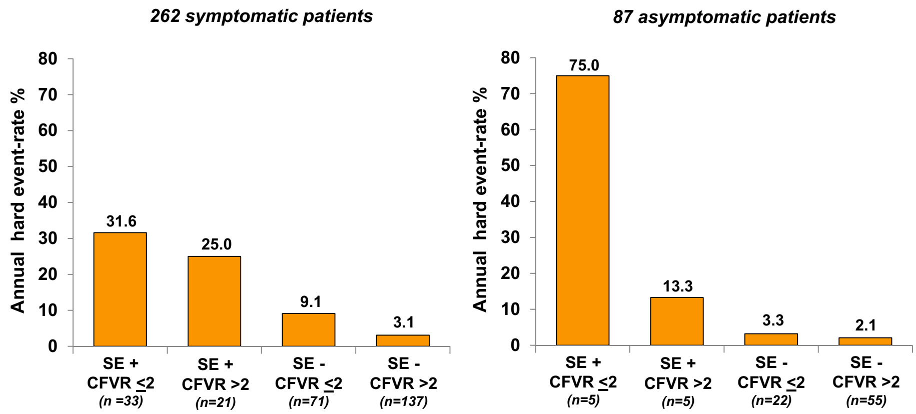


Fig. 3. Annual mortality for the 262 symptomatic patients and the 87 asymptomatic patients separated on the basis of presence (+) or absence (−) of ischemia at stress echocardiography (SE) and coronary flow velocity reserve (CFVR) of left anterior descending artery ≤2 or >2.

Nonetheless, the work-up of these patients is difficult and dual imaging stress echocardiography is potentially an ideal tool because of its ability to dissect macro from micro-vascular disease.

4.3. Study limitations

Several limitations have to be acknowledged to the present results: 1. The retrospective nature of the analysis; 2. Stress results were available to the referring physician but it is conceivable that in most cases CFVR was not included as a parameter of stress positivity, reducing, at least in part, the power of discrimination of stress testing; 3. There was no central reading and interpretation of both wall motion and CFVR was left to the peripheral laboratories; however, all centers enrolled in the analysis had a long lasting experience in stress echocardiography reducing a potential high inter-centre variability; 4. The ultimate decision for re-revascularization was left to surgeons and stress echocardiography is one of many different parameters that are evaluated in decision-making; 5. Most of these patients underwent dual-imaging stress echocardiography as a first-line exam due to the high false positive results of exercise ECG. It is, then, not possible to extrapolate how exercise ECG compares with dual imaging stress echocardiography. 6. There is a high prevalence of men in the group under investigation. However, this is not a selection bias, but reflects the reality of large stress echo laboratories.

5. Conclusions

The assessment of patients who had undergone surgical revascularization is clinically challenging. Appropriateness criteria indicate that asymptomatic patients should not be tested before 5 years from intervention; even after this period of time stress echo result should be put into context (normal left ventricular function, suboptimal medical therapy) before a re-revascularization. The present study was aimed at assessing how wall motion and CVFR contribute in risk stratification of CABG patients. The results indicate that in such a complex subset of patients, the refinement of risk stratification with several parameters may be critical. The dichotomy response positive/negative for myocardial ischemia may not be enough in this setting. Both macrovascular and microvascular dysfunction contribute to risk profiling and as stand alone parameters may not be sufficient to identify patients at highest risk. The results of this retrospective analysis will be tested prospectively in the ongoing large scale, multicenter, effectiveness Stress echo 2020 study [31].

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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