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REVIEW

Exercise stress echocardiography: Where are we now?

Carlos Alberto Cotrim, Hugo Café, Isabel João, Nuno Cotrim, Jorge Guardado, Pedro Cordeiro, Hortense Cotrim, Luis Baquero

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Abstract

Exercise stress echocardiography (ESE) is a widely used diagnostic test in cardiology departments. ESE is mainly used to study patients with coronary artery disease; however, it has increasingly been used in other clinical scenarios including valve pathology, congenital heart disease, hypertrophic and dilated cardiomyopathies, athlete evaluations, diastolic function evaluation, and pulmonary circulation study. In our laboratories, we use an established methodology in which cardiac function is evaluated while exercising on a treadmill. After completing the exercise regimen, patients remain in a standing position or lie down on the left lateral decubitus, depending on the clinical questions to be answered for further evaluation. This method increases the quality and quantity of information obtained. Here, we present the various methods of exercise stress echocardiography and our experience in many clinical arenas in detail. We also present alternatives to ESE that may be used and their advantages and disadvantages. We review recent advances in ESE and future directions for this established method in the study of cardiac patients and underline the advantage of using a diagnostic tool that is radiation-free.

Key Words: Exercise stress echocardiography; Coronary artery disease; Valve disease; Athletes; Intraventricular gradients; Children

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Core Tip: The fair cost, safety, diagnostic accuracy, ability to evaluate functional capacity, and lack of radiation use associated with exercise stress echocardiography (ESE) render this method a first-line procedure for patients with suspected or confirmed coronary heart disease. The evaluation of Doppler data and the enormous amount of information obtained during and after exercise, including in a standing position if appropriate, in patients with hypertrophic cardiomyopathy, athletes, syndrome X patients and patients with valve and congenital heart disease necessitates the use of ESE.

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INTRODUCTION

Coronary artery disease is highly prevalent and has led to the development of reliable and accessible noninvasive diagnostic techniques. Stress echocardiography is accepted as a valuable method for the detection of myocardial ischemia[1,2] and overcomes the limitations imposed by the widely used treadmill stress test. In our centers, stress echocardiography is preferentially performed using a treadmill exercise protocol. We use pharmacological stress echocardiography only to evaluate aortic stenosis patients with severe compromise of left ventricular function, to determine myocardial viability or when patients cannot exercise adequately.

As a rule of thumb, any patient capable of physical exercise should be tested with an exercise modality, since the integrity of the electrocardiogram (ECG) response is preserved and valuable information regarding functional status is provided. Performing echocardiography at the time of physical stress also allows links to be drawn among symptoms, cardiovascular workload, and wall motion abnormalities. When treadmill exercise is performed, scanning during exercise is hard but possible. Consequently, the first protocols in our and other echo labs[3-5] relied solely on postexercise imaging[6]. In this case, it is imperative to complete postexercise imaging as soon as possible. As an alternative, bicycle exercise echocardiography is conducted with the patient either upright or recumbent and allows imaging during the various levels of exercise, which can be easier and more informative than postexercise imaging with a treadmill. The exercise stress echo in clinical practice is useful in many different conditions aside from coronary disease, from valvular to congenital heart disease and from heart failure to hypertrophic cardiomyopathy (HCM), to optimize risk stratification and timing of intervention.

METHODOLOGY OF EXERCISE STRESS ECHOCARDIOGRAPHY

Exercise tests on a treadmill

Patients are questioned about their symptoms, past cardiovascular medical history, and risk factors for coronary artery disease. After an explanation and preparation for the procedure by a cardiovascular technician, a classic 12-lead ECG is obtained. The Bruce protocol, by routine, is performed. The criteria for test interruption are fatigue, angina with increasing intensity, dizziness, ST-segment depression greater than 3 mm, complex ventricular arrhythmias, systolic blood pressure greater than 240 mmHg or diastolic blood pressure greater than 130 mmHg or a blood pressure drop greater than 20 mmHg during exercise. The test result is considered positive for myocardial ischemia when ST-segment depression occurs, with a horizontal or down-sloping displacement greater than 1 mm measured 0.08 s after the J point. The ECG exercise treadmill test result is considered inconclusive when there are baseline ST-T changes (left bundle branch block, the digitalis effect, or left ventricular hypertrophy) or when the patient does not reach 85% of the theoretical maximum age-adjusted heart rate. The test result is considered negative for myocardial ischemia when the patient's heart rate exceeds 85% of the theoretical maximum age-adjusted heart rate and the previously mentioned changes did not occur.

Exercise stress echocardiography on a treadmill

We started performing exercise stress echocardiography (ESE) with an evaluation of cardiac function during exercise more than 20 years ago. The method was published and is also used by other groups[4, 5].

Patients undergo symptom-limited treadmill exercise tests following the standard Bruce protocol. A modified Bruce protocol can be used for the assessment of non-coronary artery disease, allowing an easier evaluation of Doppler parameters than that offered by the classical Bruce protocol. Standard 12-channel electrocardiographic monitoring is performed. Blood pressure, heart rate, and 12-lead electrocardiography are performed at baseline and at each stage of the exercise protocol. Before starting an exercise test, a baseline echocardiogram is performed in the left lateral decubitus position for an initial assessment, with 2D and M-mode image acquisition in at least four planes, *i.e.*, parasternal long axis, parasternal short axis, apical four-chamber, and apical two-chamber, with Doppler parameters being evaluated and stored based on the patient's condition. Two-dimensional echocardiographic images are obtained from the parasternal (long axis and short axis) and apical (four-chamber and two-chamber) views, in the standing position at rest, during exercise (Figure 1) and at peak exercise, in the immediate postexercise period, and during the recovery period. Peak and immediately postexercise imaging acquisition is obtained using a continuous image-capturing system. After the test, those frames with the best image quality in each view are selected. The acquired digitized images are reviewed and compared in digital side-by-side quad-screen format within the echocardiographic equipment. After the exercise test is stopped, when appropriate, the patient is quickly placed in the left lateral decubitus position, and images are reacquired in the same plane. When relevant, for example, for the detection and evaluation of intraventricular gradients (IVGs) in HCM or in symptomatic athletes, the patient remains standing after finishing the stress test, and echocardiography is carried out in this position. For the evaluation of left ventricular regional wall motion abnormalities, we use the model that divides the left ventricle into 17 segments[7]. Ischemic changes are considered when the segments develop hypokinesia, akinesia or dyskinesia. However, when an akinetic segment becomes dyskinetic, it is not considered to be ischemic. Most groups that use exercise echocardiography in treadmill exercise acquire echocardiographic images only before and after exercise[6].

APPLICATIONS OF ESE

Ischemia detection

Stress echocardiography has demonstrated substantial clinical relevancy in ischemia detection because of its high sensitivity and specificity[8,9] both in patients without antecedents of prior intervention and in those previously submitted to percutaneous coronary intervention[10] or coronary artery bypass graft surgery[11]. Women have a higher rate of false-positive results with exercise electrocardiographic testing. In this group, stress echocardiography has been shown to be an accurate method for ischemia detection[12]. In patients with left ventricular hypertrophy, stress echocardiography has a sensitivity of 84% and a specificity of 75% for the detection of ischemia[13], substantiating its use in clinical practice. Detection of ischemia with exercise electrocardiographic testing is not possible in patients with left bundle bunch block. ESE may also be limited in these patients because of the paradoxical motion of the interventricular septum. In a series of 30 patients with left bundle branch block, Pellika and colleagues showed that ESE had 60% sensitivity for ischemia detection, compared to 88% sensitivity with dobutamine stress echocardiography (DSE)[14]. The prognostic accuracy of myocardial perfusion and stress echocardiography appeared similar. Although these conclusions are based on a small sample study, DSE was preferred to ESE for this subgroup of patients in our center. Detection of ischemia, as well as its magnitude, has obvious prognostic implications. In a study with more than 500 patients, Marwick *et al*[15] demonstrated that the use of stress echocardiography to detect ischemia provides additional prognostic information. The comparative advantage of exercise echocardiography with image acquisition during treadmill exercise was clearly demonstrated by the Peteiro *et al*[16,17], who showed an increased diagnostic accuracy with this methodology compared with evaluation only before and after exercise. Those results confirm our preliminary results from a previous small study. In comparison with other widely available imaging techniques, ESE has some advantages, including greater safety, with only one adverse event in every 7000 exams compared to one adverse event in every 700 dobutamine stress echocardiograms[18]. This issue was addressed by the international practice guidelines[19], reserving drug-induced stress echocardiography for those unable to perform an exercise stress test. Another important advantage of ESE is that the procedure does not involve radiation[20,21].

Evaluation of patients with suspected or confirmed pulmonary hypertension, including patients with mitral stenosis.

The evaluation of pulmonary artery systolic pressure at rest using echocardiography is common and of great clinical importance. A diagnosis of pulmonary arterial hypertension is based on a mean pulmonary artery pressure > 25 mmHg at rest[22]. Although usual assessment is generally carried out at rest, the clinical utility of determining pulmonary artery systolic pressure during exercise has been demonstrated in various clinical situations, such as heart failure, rheumatologic disease, mitral stenosis and mitral regurgitation[23-27].

Figure 1 Echocardiographic data acquisition with the patient in the orthostatic position during exercise on a treadmil. Citation: Cotrim C, João I, Fazendas P, Almeida AR, Lopes L, Stuart B, Cruz I, Caldeira D, Loureiro MJ, Morgado G, Pereira H. Clinical applications of exercise stress echocardiography in the treadmill with upright evaluation during and after exercise. Cardiovasc Ultrasound 2013; 11: 26 [PMID: 23875614 DOI: 10.1186/1476-7120-11-26] Copyright © The Author (s) 2013. Published by BMC part of Springer Nature.

In one study using our methodology[23], we included 56 patients with mitral stenosis and determined the gradient between the right ventricle and right atrium using continuous wave Doppler in left lateral decubitus (LLD) before exercise testing, in the orthostatic position at peak workload before termination of the test, and in LLD in the first 60 s of the recovery period. The mean gradient between the left atrium and left ventricle was also determined at different stages of the test in patients with mitral stenosis. In patients with mitral stenosis, the effect of access to gradient values obtained at peak workload on clinical management was compared to the effect if this parameter had been evaluated only in the immediate recovery period. In this group of patients, basing the decision to treat on pulmonary artery systolic pressure > 60 mmHg at peak workload resulted in 10 patients (18% of those with this pathology) being referred for valvuloplasty or valve replacement. These patients would have continued with medical therapy if the decision had been based on the values obtained during the recovery period.

In the same study's 42 patients with scleroderma, basing the decision for right heart catheterization in patients with systemic sclerosis on the gradient between the right ventricle and right atrium at peak exercise resulted in 13 more patients (30% of those with this pathology) being referred for this procedure than if it had been based on the values obtained only during the recovery period, *i.e.*, as ESE is usually performed in most centers.

In patients with a previous history of thromboembolic pulmonary disease, with mild or moderate pulmonary hypertension or with unclear cause for symptoms, we have used ESE to help in clinical evaluations and decision-making. In one published case[28], right ventricular dilatation occurred that was not seen before exercise and that was detected only during exercise. The right ventricle after exercise was also normal.

It is often difficult to obtain adequate tricuspid regurgitation signals for the measurement of the gradient between the right ventricle and right atrium, potentially leading to its underestimation. Therefore, air-blood-saline contrast during exercise has been utilized to improve the Doppler signal in several clinical situations. We have concluded that the utilization of contrast should probably be limited to patients with a poor tricuspid regurgitation jet signal, to obviate the high number of false positives results that occur. Therefore, contrast should be an aid to obtain a measurable gradient but should not be used routinely in patients submitted to this type of study.

Intraventricular obstruction induced by exercise in athletes with "positive screening" in medical evaluations for participation in sports

The development of IVGs during exercise is a rare finding and occurs usually in association with left ventricular hypertrophy[29,30]. The development of IVGs during exercise has been described in athletes [31]. The clinical meaning of this observation and the most suitable exercise technique (upright exercise *vs* semisupine exercise *vs* lying supine after exercise) to trigger IVGs remain unknown. Supine exercise and lying supine after exercise are less technically demanding but also less physiological than upright exercise.

Importantly, in usual daily life, after exercise, individuals generally do not lay supine, as practiced in postexercise treadmill stress echocardiography in most cardiology departments. Therefore, we have conducted other studies in which we searched for IVGs during ESE, in a standing position after exercise, in athletes who screened positive according to the Guidelines of the European Society of Cardiology[32] and who also had an echocardiogram considered normal at rest. In that investigation[33], 139 athletes (135 were amateur, and four were professional; 30 were female), with a mean age of 22 ± 9.9 years (age

range from 9 to 56 years old), were included. The athletes participated in the following sports: athletics (58), soccer (51), tennis (7), basketball (5), handball (5), swimming (5) and other (8).

As stated, all athletes screened positive: 112 had symptoms (chest pain, dizziness, or syncope) or a positive exercise ECG treadmill test (11 athletes). Of the 27 asymptomatic athletes, four had a history of sudden death in the family, three had slight mitral valve prolapse without mitral regurgitation, 18 had alterations in their ECG, and three had ventricular premature beats on ECG. All the athletes had a normal resting echocardiogram, *i.e.*, no left ventricular hypertrophy or significant valve pathology.

Of all 139 athletes, 52 (37.4%) developed IVGs (group 1), and 87 (62.6%) did not develop IVGs (group 2) (we considered only IVGs greater than 50 mmHg).

Of the 52 athletes in group 1, 23 (63%) developed systolic anterior motion (SAM) of the mitral valve associated with significant IVG during exercise (Figure 2).

In group 1, IVGs were present in all athletes after exercise in the standing position. In seven of these athletes, IVGs were detected only at this timepoint.

Small IVGs are a common phenomenon. Three mechanisms have been proposed by Yotti[34] regarding their significant increase during exercise: (1) Increase in nonobstructive physiological gradients; (2) End-systolic obstruction secondary to ventricular cavity obliteration; and (3) Midsystolic obstruction caused by SAM of the mitral valve with restriction of ejection. However, for SAM to occur, there must be some alteration in the geometry of the ventricular chamber or in the mitral valve apparatus. This was not the case in our athletes, although it has been demonstrated that IVGs can be caused by maneuvers that change loading conditions in structurally normal hearts[35] that participating in sports can bring about such changes. In a study with children[36], IVGs induced by exercise were considered normal; however, the clinical data for the population were not contextually clear[37], and further studies are needed to better clarify the clinical meaning of these gradients.

In our study, the athletes had normal echocardiograms, indicating that a morphological study of their hearts would probably reveal no abnormalities[38,39]. The phenomenon that we detected before, during and after exercise testing, in the standing position – IVG associated with mitral valve SAM at the end of and after exercise – could well have been responsible for the positive screening in the athletes in group 1. Medical examinations of these athletes were carried out mostly because of symptoms arising from intense effort; for most of the athletes, we did not reproduce the symptoms during exercise, but we detected an anomaly in cardiac function[31] that, in our opinion, may explain the symptoms. The abnormality, however, was only detectable before (two athletes), during (41 athletes), and after exercise in the orthostatic position (52 athletes). These phenomena are not among the diagnoses that contraindicate participation in competitive sports according to the recommendations of the 36th Bethesda conference[40] and the European Society of Cardiology[32]. It is possible that the phenomena observed in these athletes could be among the causes of sudden death in cases where anatomopathological examination reveals no abnormalities, and we accordingly advised the athletes to suspend their participation in sports and referred them to a sports medicine center for further assessments. In our opinion, the cases described in which significant abnormalities in cardiac function were found before, during, and more clearly after exercise (Figures 3 and 4) in the standing position suggests that this methodology should be applied to the athletes who have symptoms related to exercise and no structural abnormalities. We emphasize that this phenomenon has almost been excluded as a normal response to exercise in healthy adults[41]. The results of this study underscore the importance that the literature attributes to searching for IVGs as a possible cause of symptoms related to exercise in athletes and in pediatric populations[42,43].

The athletes in whom these findings were detected should also undergo long-term follow-up to accurately assess the clinical significance of the findings.

To the best of our knowledge, our group provided the first report on the importance of the standing position before and after exercise to detect IVGs in symptomatic athletes without left ventricular hypertrophy. Our study of the evaluation of IVGs with continuous wave Doppler also constitutes a new step in the use of stress echo as a diagnostic tool beyond is initial use for coronary heart disease[44] and in the use of a new stressor: the standing position[33,45].

Considering our experience, ESE, with evaluation in an upright position before, during, and after exercise, should possibly be part of a new diagnostic algorithm whenever athletes have a positive screening on a medical evaluation. This is especially true if the athletes have symptoms.

Monitoring beta-blocker use

Because most of the athletes evaluated in the previous study were treated with beta-blockers, we conducted an open-label, prospective, nonrandomized study to provide proof-of-concept that ESE can guide tailored treatment in athletes with positive screenings[46] on medical evaluations for participation in sports and who develop IVG and mitral valve SAM on exertion. Of the 52 athletes who developed IVGs, 35 repeated ESE while taking beta-blockers. Thirty-three had exercise-related symptoms or a positive exercise ECG. Thirty athletes (85%) showed improvement on the follow-up ESE, with a significant reduction in gradients (Figure 5) and SAM.

We concluded that for athletes with positive screening - mostly by symptoms - on medical evaluations for participation in sports and IVG on exertion, treatment with beta-blockers prevented the occurrence of IVGs and SAM or significantly reduced their magnitude. These changes were associated

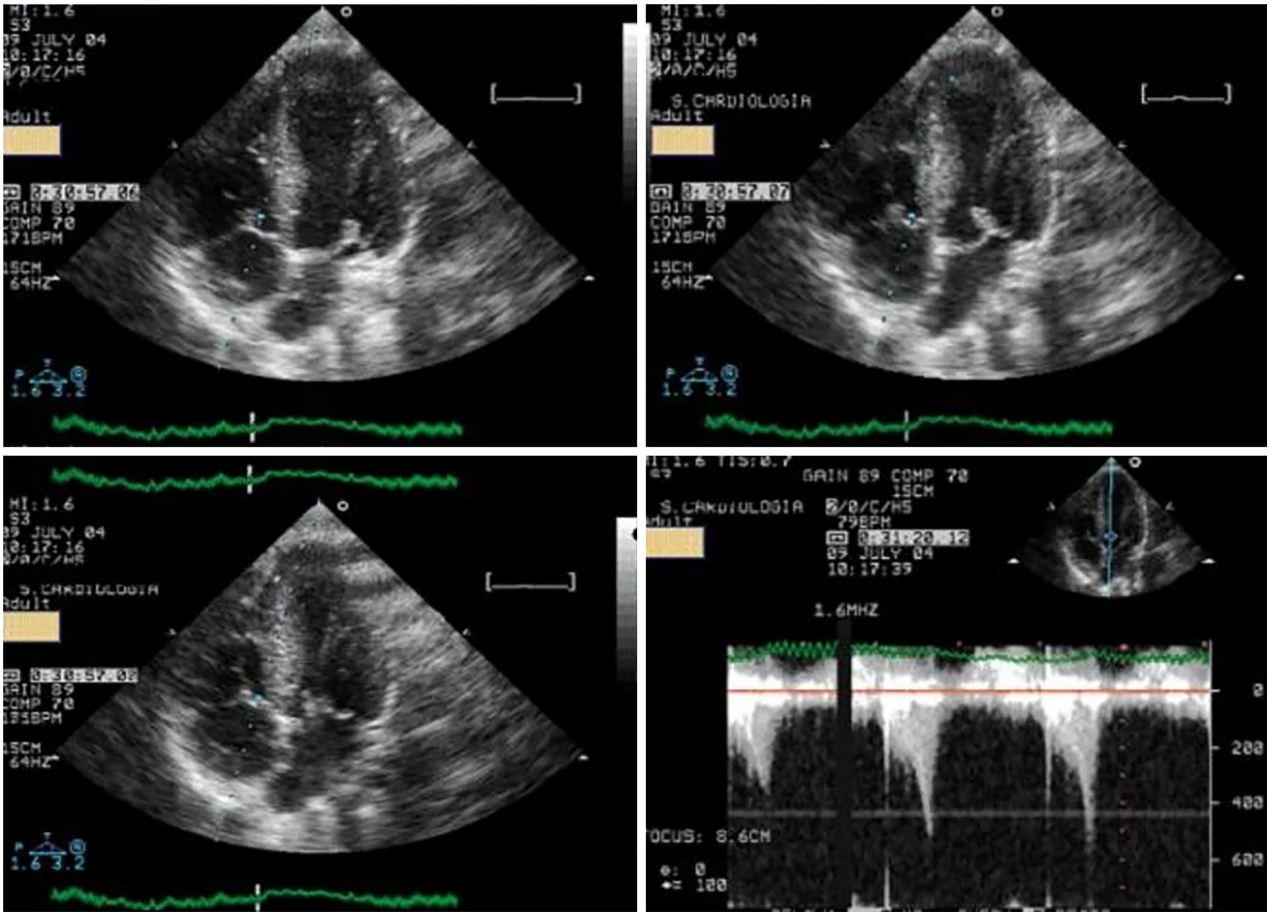

Figure 2 Systolic anterior movement of the mitral valve and significant intraventricular gradient detected at peak exercise. Citation: Cotrim C, João I, Fazendas P, Almeida AR, Lopes L, Stuart B, Cruz I, Caldeira D, Loureiro MJ, Morgado G, Pereira H. Clinical applications of exercise stress echocardiography in the treadmill with upright evaluation during and after exercise. Cardiovasc Ultrasound 2013; 11: 26 [PMID: 23875614 DOI: 10.1186/1476-7120-11-26] Copyright © The Author (s) 2013. Published by BMC part of Springer Nature.

with a significant reduction in heart rate at peak exercise and reflect clinical improvement, which occurred in 85% of the study population.

Exercise echocardiography represents a useful tool to evaluate athletes who screen positive and have a normal rest echocardiogram, allowing identification for beta-blocker therapy. The findings of this study represented a proof-of-concept of tailored beta-blocker therapy, driven by exercise Doppler echocardiography results, in symptomatic athletes and were also observed by other authors[47].

Intraventricular gradients in patients with cardiac X syndrome

The development of IVGs during DSE has been reported and is commonly associated with symptoms during the study[48,49]. The occurrence of IVGs during ESE is rare[29,30]. In a group of 10 patients who developed IVGs during DSE, we performed ESE and found a small IVG in only one patient. A 23-year-old male with angina and a positive treadmill test, a structurally normal heart, and normal coronary angiography underwent an ESE, and during the study, we unexpectedly detected a 102 mmHg IVG[31] and SAM of the mitral valve. A similar case was reported by Lau *et al*[30] and was treated successfully with beta-blockers. After this first case, we conducted a study for IVG detection during ESE in patients with angina, positive stress electrocardiography, normal coronary arteries, and a normal echocardiogram (cardiac X syndrome)[50]. This study included 91 patients, 44 of whom were women. All patients had angina, positive exercise ECG treadmill tests (four patients had only ischemia in a myocardial perfusion study), normal resting echocardiogram - no left ventricular hypertrophy - and no coronary artery disease on coronary angiography.

Of the whole group, 33 patients (36%) developed IVGs, and 58 patients (64%) did not develop IVGs as defined previously by the authors. In the first group, the IVG at peak exercise was 86±34 mmHg (ranging from 30 to 165 mmHg), and 23 patients (70%) developed SAM during exercise, associated with IVGs. No patients developed segmental wall abnormalities. The results of our study, in which 36% of the patients with normal coronary angiograms and positive treadmill exercise tests developed IVGs, suggest that ST-segment depression may be related with the development of IVGs during exercise, which is possibly involved in the genesis of electrocardiographic changes. The possible association between cardiac X syndrome and IVG development during exercise has previously been described[51,

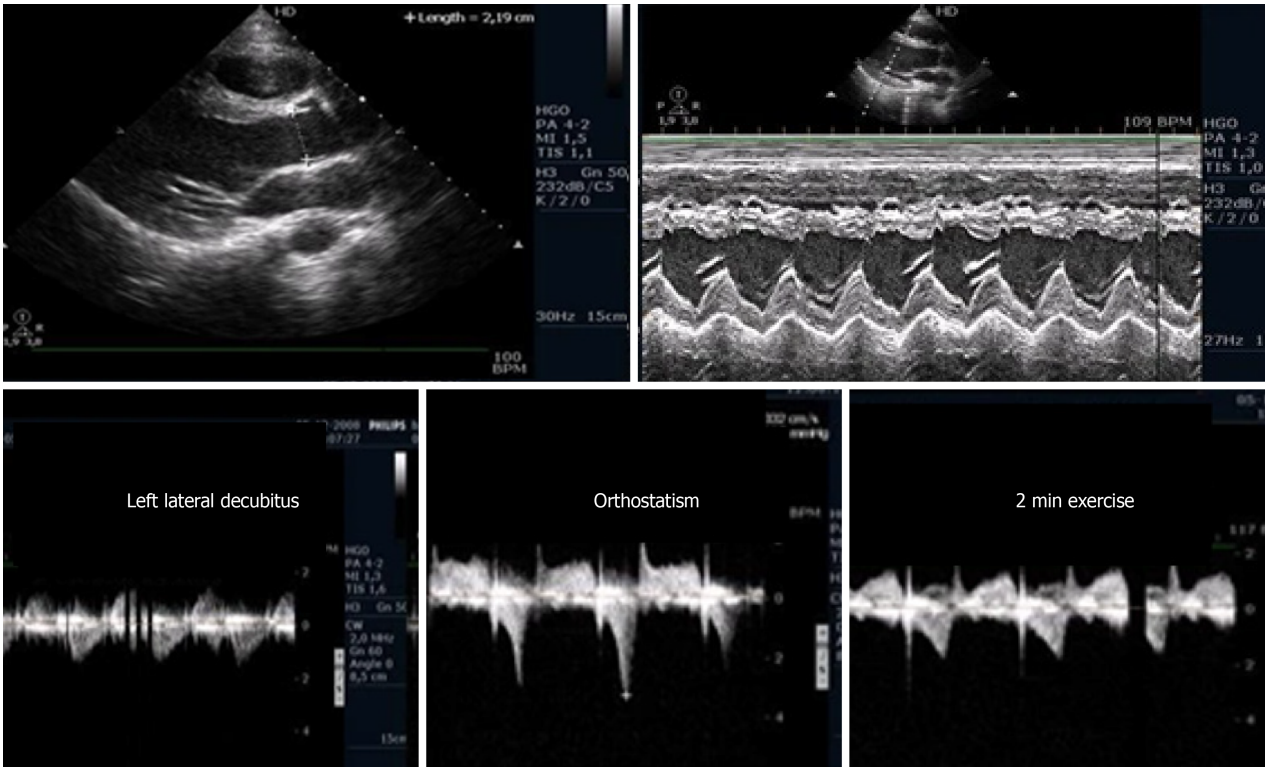

Figure 3 Intraventricular gradient present in the orthostatic position before exercise in an athlete, decreased during the initial phase of exercise testing. Citation: Cotrim C, João I, Fazendas P, Almeida AR, Lopes L, Stuart B, Cruz I, Caldeira D, Loureiro MJ, Morgado G, Pereira H. Clinical applications of exercise stress echocardiography in the treadmill with upright evaluation during and after exercise. Cardiovasc Ultrasound 2013; 11: 26. [PMID: 23875614 DOI: 10.1186/1476-7120-11-26] Copyright © The Author (s) 2013. Published by BMC part of Springer Nature.

52], however, some of the patients from these studies had arterial hypertension and left ventricular hypertrophy, more frequently developed IVGs[29] and were therefore excluded based on the definition of cardiac X syndrome[53].

In our study population, we found a great number of patients who developed SAM of the mitral valve in association with IVGs, in contrast to the findings of other authors. We hypothesize that we can detect SAM in a greater number of patients because we use echo throughout the entire treadmill exercise protocol and in the standing position after exercise[45]. The magnitude of the IVGs that we have detected in our patients is also greater for the same reason.

We conclude that a relevant number of patients with cardiac X syndrome develop significant IVGs during exercise. The authors believe that this phenomenon may constitute a new entity that should be included as a factor in the heterogeneous group of patients with angina, ST-depression during treadmill exercise tests and normal coronary arteriography. Because of these results, we believe that ESE should be part of a new diagnostic algorithm whenever patients with angina are suspected of having cardiac X syndrome.

Evaluation of patients with HCM

In our centers, ESE with image acquisition during treadmill exercise (a representation of regular exercise) is also commonly used for the evaluation of patients with HCM, enabling assessment of the outflow gradient during physiologic exercise and in recovery period in LLD[5]. In patients with obstructive HCM under resting conditions, it has been demonstrated that obstruction may increase after the change in position from supine to standing. The LVOT gradient increases in the orthostatic position and continues to increase at peak exercise, but after exercise, the gradient decreases rapidly when measured in LLD, indicating that the assessment of IVGs during the recovery period in the supine position does not reflect changes during effort. The LVOT gradient measured during the recovery period in the supine position does not reflect patients' daily activities (in their daily lives, patients simply do not assume a supine position after an effort) nor the pathophysiology of this condition[54-58]. We unexpectedly found, in one patient, that after exercise, the IVG continued to increase if the patient remained in the standing position. Based on this observation, a new study was conducted[45] in 17 patients diagnosed with HCM based on echocardiographic findings of a nondilated hypertrophic left ventricle in the absence of diseases known to cause ventricular hypertrophy, including 11 patients with obstructive HCM due to an LVOT gradient greater than 30 mmHg under resting conditions and six patients with nonobstructive HCM. Three patients without resting obstruction developed IVGs during

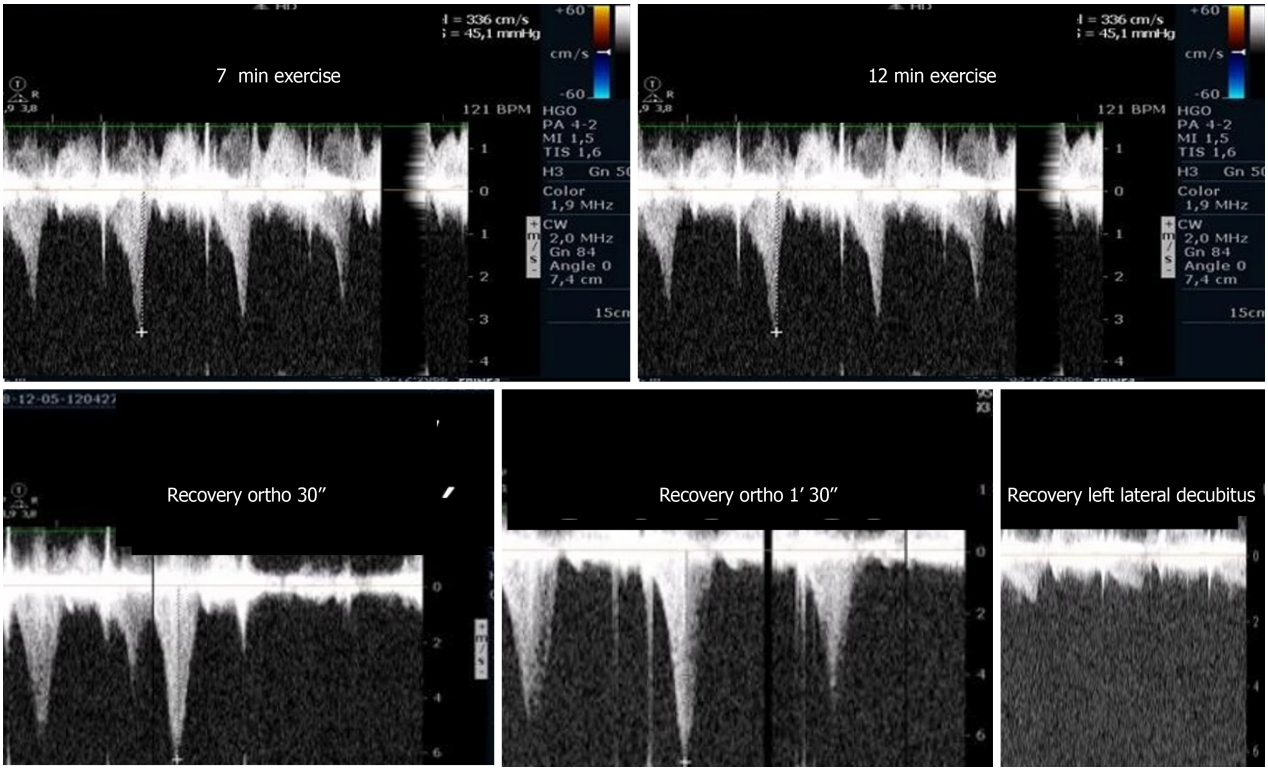

Figure 4 Intraventricular gradient increased during the last portion of the exercise test and after exercise in the orthostatic position. Obstruction suddenly disappeared after placing the athlete in decubitus. Citation: Cotrim C, João I, Fazendas P, Almeida AR, Lopes L, Stuart B, Cruz I, Caldeira D, Loureiro MJ, Morgado G, Pereira H. Clinical applications of exercise stress echocardiography in the treadmill with upright evaluation during and after exercise. Cardiovasc Ultrasound 2013; 11: 26. [PMID: 23875614 DOI: 10.1186/1476-7120-11-26] Copyright © The Author (s) 2013. Published by BMC part of Springer Nature.

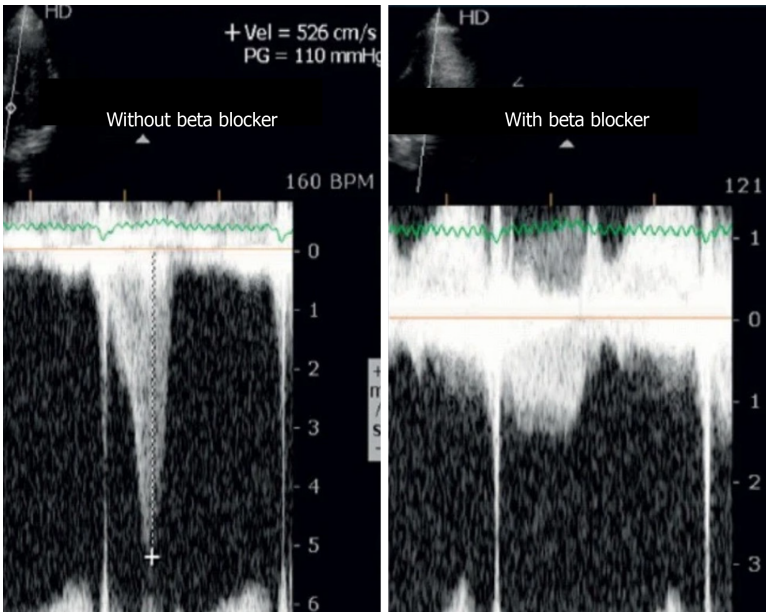

Figure 5 Intraventricular gradient in an athlete assessed before and on beta-blocker therapy. Citation: Cotrim C, João I, Fazendas P, Almeida AR, Lopes L, Stuart B, Cruz I, Caldeira D, Loureiro MJ, Morgado G, Pereira H. Clinical applications of exercise stress echocardiography in the treadmill with upright evaluation during and after exercise. Cardiovasc Ultrasound 2013; 11: 26. [PMID: 23875614 DOI: 10.1186/1476-7120-11-26] Copyright © The Author (s) 2013. Published by BMC part of Springer Nature.

exercise; one patient developed a gradient only during the recovery period in the orthostatic position ; two patients had neither resting nor exercise-induced obstruction. All patients with obstructions exhibited increased IVGs in orthostatic recovery. These findings differ from those reported in other studies in which the participants assume the supine position immediately after exercise[59,60]. The importance of the standing position in this group of patients and in patients with other conditions as an

additional and new stressor with important clinical application has been underscored by our group[61] and by other investigators[62-65]. Reflecting on our experience and referencing the literature, we believe that the standing position is the only way these patients can be correctly evaluated, and the mechanisms of their symptoms understood. The clinical importance of upright evaluation during and particularly after exercise was recently underscored by Dimitrow *et al*[66] and Petkow Dimitrow *et al*[67], and we think that laying patients in a supine position after any type of exercise is meaningless from the clinical point of view because this does not usually happen in real life. We recommend[67] that future guideline of scientific societies should clearly state one uniform methodology to be employed by all groups that study and treat these types of patients, with the aim of having a common language that can be used in the future.

OTHER USES OF EXERCISE STRESS ECHOCARDIOGRAPHY WITH ECHOCARDIOGRAPHIC EVALUATION ALSO DURING EXERCISE IN TREADMILL

Aortic stenosis

Most of the recommendations in the guidelines do not have an extensive evidence base, underscoring the need for more clinical investigations in this area. In valvular heart disease, exercise testing is preferred over pharmacological stress testing because it provides insights regarding exertional symptoms and blood pressure variations[27]. Supine bicycle exercise is recommended because Doppler information can be obtained during the different stages of exercise[19] rather than during post-treadmill imaging when substantial and rapid changes in heart rate and loading conditions occur. We and the Peteiro group[4,68,69] disagree with those recommendations, and we conduct echocardiography during treadmill exercise. Additionally, supine exercise is not as physiologic as is treadmill exercise, the equipment is not nearly as widely available as is a treadmill, and the maximum VO_2 attained is at least 10% lower with a bicycle[70]. We routinely use ESE for the evaluation of patients with asymptomatic aortic stenosis. With the literature as support[24,71-73], we utilize ESE to better understand patients, adding information regarding exercise testing[74] and consider surgery accordingly with recommendations.

About one third[71-74] of asymptomatic patients with severe aortic stenosis submitted to exercise tests are in fact symptomatic, but complications do not usually occur in this group of patients. In selected symptomatic patients with aortic stenosis, we employ ESE to better clarify the mechanism of symptoms. As an example, we have published the case of a symptomatic patient in whom symptoms were due to the development of a significant IVG[75] due to SAM of the mitral valve and were treated with beta-blockers. Patients with severe aortic stenosis in whom there is proof that the symptoms have another cause should be considered, more aptly, symptomatic aortic stenosis patients, with symptoms due to other causes (false symptomatic aortic stenosis).

Mitral regurgitation and aortic regurgitation

The assessment of regurgitant mitral flow, with ESE, is mandatory in valvular heart disease in patients with symptoms and mild-moderate mitral regurgitation at rest and in patients with severe mitral regurgitation who have no symptoms[76]. Mitral regurgitation should also be evaluated when studying patients with HCM or heart failure with preserved ejection fraction or pulmonary edema with unknown etiology. Finally, but importantly, mitral regurgitation should also be evaluated in patients with coronary disease to determine if there is an increase in severity or a new appearance of mitral regurgitation[77]. In all these conditions, the presence of mitral regurgitation may contribute to risk stratification and may provide a potential explanation for clinical data susceptible to specific interventions. In aortic regurgitation, as in mitral regurgitation, the evaluation of the inotropic reserve (increase of 5% in the ejection fraction with exercise) can be used to indicate valve surgery in patients with compromised left ventricular function.

Prosthetic heart valves

A significant percentage of patients with aortic valve disease and mitral valve disease who undergo surgery are given a prosthesis[24]. Most prosthetic valves are inherently stenotic, as the effective orifice area is often too small in relation to the body surface, a phenomenon classified as valve prosthesis-patient mismatch[78]. In clinical practice, it is common for normal and abnormal prostheses to produce similar gradients at rest, and therefore, ESE may be valuable for confirming or excluding the presence of prosthetic valve dysfunction or mismatch. This is particularly true for disagreements between symptoms and the hemodynamic profile evaluated by Doppler echocardiography at rest[79-81]. According to Picano *et al*[27], a disproportionate increase in the transvalvular gradient (greater than 20 mmHg for an aortic prosthesis or greater than 12 mmHg for a mitral prosthesis) generally indicates severe prosthesis dysfunction or mismatch.

We use ESE for patients with valve prostheses whenever there exists a discrepancy[82] between the gradients evaluated *via* echocardiography and the presence of the symptoms (Figure 6). Evidence-based

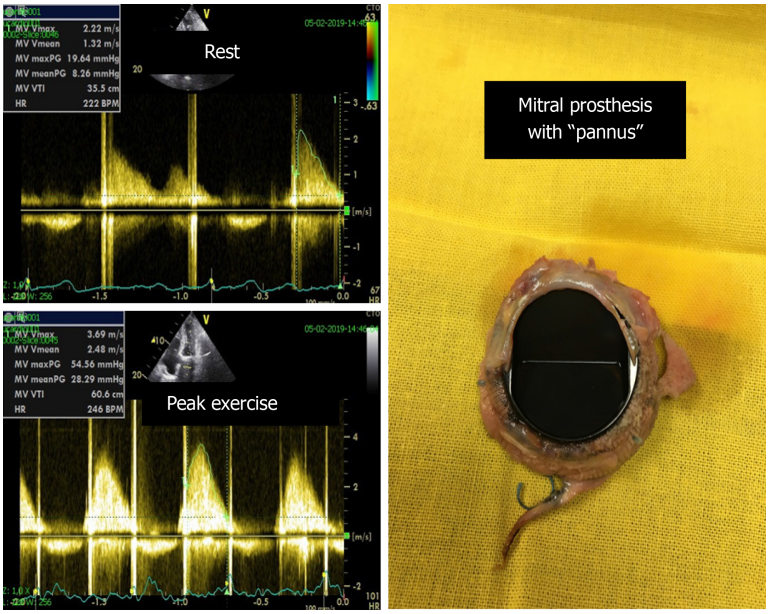

Figure 6 Significant increase in the mean gradient (from 8 mmHg to 28 mmHg) and appearance of severe symptoms with exercise in one patient with a mechanical mitral prosthesis with "pannus".

gradient cut-offs are needed for clinical decision-making. Until such cut-offs are established, we associate exercise Doppler parameters with clinical and exercise test data.

Congenital heart disease and children

ESE is an imaging technique that has been almost exclusively used to evaluate and elucidate cardiac abnormalities in adult patients. Though it may have the potential to offer the same benefit in the pediatric population, it remains an underexplored field, perhaps due to concerns about its safety and applicability in younger children. Given its diagnostic accuracy, ability to assess cardiac reserve and lack of radiation, ESE is increasing in importance as a helpful tool in the clinical assessment of pediatric patients[83].

The usage of ESE in patients with congenital heart disease has been limited despite its potential for broader applications in different clinical scenarios[84]. In patients with congenital heart disease, measuring pulmonary systolic pressure and ventricular function both at rest and during exercise by echocardiography may be essential for determining the etiology of exercise intolerance in these individuals and for better treatment timing.

The presence of any stenotic lesion evaluated by echocardiography can also be studied during exercise, and the data obtained can be used for better clinical decision-making. We performed ESE in one patient with congenital mitral stenosis[3] and evaluated the mean mitral gradient before and at peak exercise and verified the absence of pulmonary hypertension. The exercise Doppler data in conjunction with the exercise data and clinical data led us to keep the patient in close clinical follow-up. The same result was obtained for a young 14-year-old boy, a soccer player, with cor triatriatum sinister who had only a small increase in the mean gradient with exercise (Figure 7).

ESE can also be used to screen for residual narrowing in patients after repair of the coarctation of the aorta by detecting a significant diastolic gradient in the descending aorta during exercise provocation (Figure 8). This evaluation is also feasible with the method that we use to evaluate aortic flow during exercise. A significant increase in the diastolic gradient[85] was used as a guide for patient treatment decisions.

Our group is increasingly using ESE to investigate intraventricular gradients in symptomatic children with normal hearts[33,42,43] or with HCM[86].

We believe that ESE can and should influence clinical decision-making for congenital heart disease patients if pediatric and adult cardiologists with experience in ESE start collaborating.

ESE and diastolic heart failure

We employ ESE in the treadmill evaluation of E/e' as a measure of left ventricular filling pressure. This method has been validated against invasively measured LV filling pressure using simultaneous exercise echocardiography-catheterization[87]. The addition of E/e' during exercise echocardiography improved the sensitivity of the diagnosis of heart failure with preserved heart function compared with that for a resting assessment alone, and the specificity can be improved if the gradient between the right ventricle and right atrium increases above the normal range with exercise. The independent prognostic value of

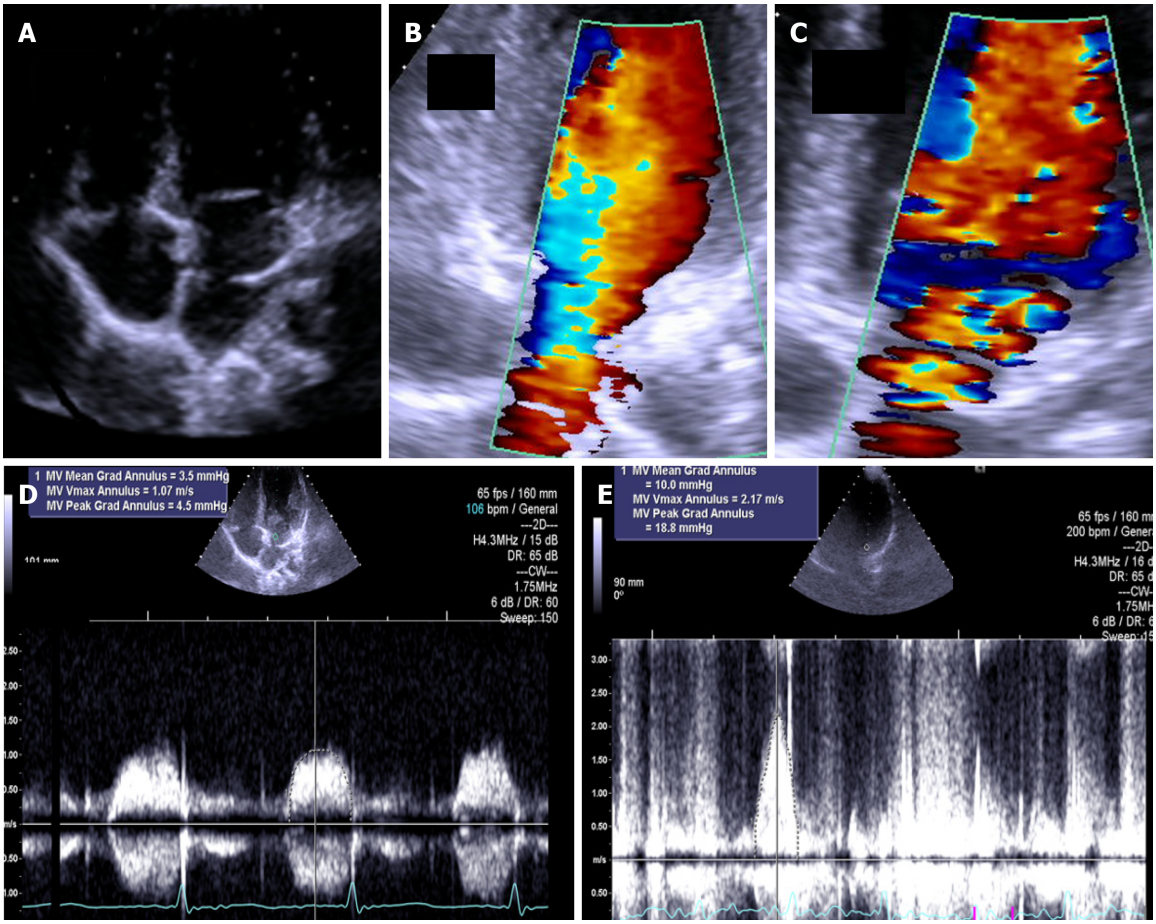

Figure 7 The exercise Doppler data in conjunction with the exercise data and clinical data led us to keep the patient in close clinical follow-up. A: Intraauricular septum in "cor triatriatrium"; B: Color flow before exercise; C: Color flow at peak exercise; D: CW flow before exercise; E: CW flow at peak exercise.

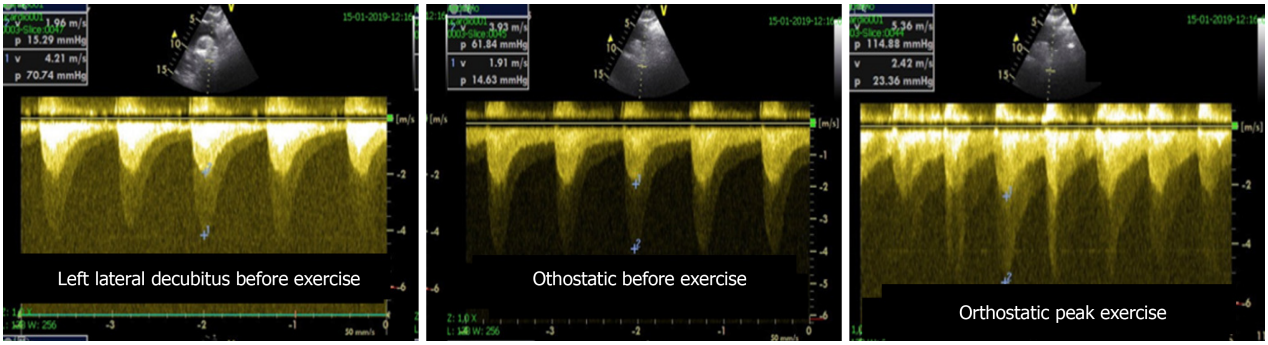

Figure 8 Aortic gradient evaluated in a patient previously treated with a stent. Based on the exercise stress echocardiography results, the patient was treated again.

exercise E/e' has also been documented. We recommend that diastolic stress exercise echocardiography should be considered for patients with unexplained exertional dyspnea and normal diastolic filling pressure on resting echocardiography. The addition of a diastolic assessment to exercise echocardiography improves test sensitivity in patients with dyspnea, and there have been sufficient data that have led us to integrate diastolic exercise testing into our clinical practice.

THE LATEST ADVANCES IN ESE AND THE FUTURE

The exercise stress echo protocol has remained unchanged for more than 40 years[1] and focuses primarily on imaging regional wall motion abnormalities. In recent years, a significant evolution has

occurred, and the technique was further exploited through the inclusion of four variables with recognized clinical, diagnostic, and prognostic importance with ESE, representing the new standard method. The variables are summarized in the ABCD protocol[88]. The four parameters converge conceptually, logistically, and methodologically: (1) Regional wall motion abnormalities[89]; (2) Comets or B-lines measured by lung ultrasound[90]; (3) Left ventricular contractile reserve assessed as the stress/rest ratio of elastance, also called force (systolic arterial pressure by cuff sphygmomanometer/end-systolic volume from 2D)[91]; and (4) Coronary flow velocity reserve in the left anterior descending coronary artery (with color-Doppler-guided pulsed wave Doppler)[92]. This new way to conduct stress echo allows a functional assessment of epicardial coronary artery stenosis (wall motion), lung water (lung comets), myocardial function (left ventricular contractile reserve) and coronary small vessels (coronary flow velocity reserve in the mid or distal left anterior descending artery). In this new "ABCD" protocol, A stands for asynergy (ischemic *vs* nonischemic heart), B stands for B-lines/lung comets (wet *vs* dry lung), C stands for contractile reserve (weak *vs* strong heart), and D stands for Doppler flow evaluation (warm *vs* cold heart because the increase in blood flow increases the local temperature of the myocardium). From the technical and training points of view, B-lines/lung comets are the easiest to evaluate; on the other hand, the acquisition and analysis of left ventricular contractile reserve requires a higher level of competency. Wall motion evaluation is an even more challenging skill to obtain, and coronary flow velocity reserve is the hardest to evaluate. More recently[93], the protocol was amended with E, for EKG-based heart rate reserve (HRR, defined as peak/rest HR < 1.62), which also provides prognostic information, and ABCDE was born. This protocol has been used in the last 5 years in the SE2020 study[94-96], demonstrating utility in defining diagnosis and prognosis criteria with the new data acquired and evaluated with this methodology. This protocol will be now expanded in the new SE2030 study[97], with selected patients by further evaluating flows (mitral regurgitation flow) gradients (intraventricular or valvular gradient), left atrium volume , pulmonary circulation , and right ventricular function . These new steps should be viewed as diagnostic tools that can be used for each patient, according to the clinical condition and question to be answered, to obtain essential information for helping cardiologists design the most appropriate tests for each patient.

ETHICAL AND SAFETY ISSUES RELATED TO CARDIAC IMAGING: THE INSURMOUNTABLE ARGUMENT FOR THE PREFERENTIAL USE OF ESE IN CARDIOVASCULAR PATIENTS

Cardiac imaging methods

When addressing the ethical implications of the diagnostic options for heart disease, the main options include scintigraphy, CT angiography and catheterization, in which the individual is exposed to radiation; magnetic resonance imaging, which may require general anesthesia and intravenous administration of contrast and/or vasodilators; and stress echocardiography, which can be performed using exercise or pharmacological administration.

Regarding pharmacological stress echocardiography, it presents an increased risk of side effects, such as arrhythmias and anaphylactic reactions of greater or lesser severity, related to the administration of dobutamine or dipyridamole and thus requires an ethical review regarding the information to be made available to patients and obtaining informed consent. Regarding stress echocardiography, the European Association of Cardiovascular Imaging and the American Society of Echocardiography emphasize that this is the test of choice for most indications, reinforcing that any patient able to exercise should be tested with an exercise modality because doing so preserves the integrity of the electromechanical response and provides valuable information about functional status. The performance of echocardiography at the time of exercise also allows establishing links between symptoms, cardiovascular workload, wall motion abnormalities and hemodynamic responses, such as pulmonary pressure and transvalvular flows and gradients[98].

In addition to these advantages of exercise echocardiography, it is a radiation-free procedure, significantly reducing the associated ethical implications. Conversely, diagnostic options using radiation present a set of ethical implications that should be considered, namely, patients' right to adequate and complete information, including risks, benefits and alternatives, on the diagnostic procedures available [99].

One of the main risks clearly associated with radiation exposure is the possibility of developing cancer.

According to Brody *et al*[100], there is clear evidence, observed in fundamental cellular processes, that even at in low-dose range of a few tens of mSv, it is scientifically plausible to assume that the risk of cancer will increase in direct proportion to the dose absorbed in organs and tissues. This may explain why cancer rates remain stubbornly high despite the great advances in its prevention and treatment and may, in the United States and soon, surpass heart disease as the main cause of death. One of the explanatory reasons points to the use of radiation in clinical practice, with exposure to medical radiation increasing sixfold between 1980 and 2006, largely due to the use of computed tomography because the

radiation dose from this diagnostic technique is 100 to 1000 times higher than the radiation dose from a conventional radiograph[101].

Informed consent and communication quality

Considering the risks associated with radiation, information and informed consent are some of the ethical aspects to be highlighted. However, the information to be made available to patients involves some challenges, such as defining the exposure dose above which radiation is considered to pose an increased risk of developing radiation exposure-related diseases and determining what type of information should be given; although it is clear that this information should include the type and nature of the procedure, the risks, benefits and possible alternatives, as well as the risks of refusing a certain diagnostic test, it is not easy to define this information because these data vary according to a set of factors, such as patient age and sex[102].

As Picano[103] underscored, these difficulties seem to lead health professionals to develop strategies for risk communication to obtain informed consent to perform diagnostic tests with radiation exposure; such strategies include (1) Not mentioning the risk; (2) Underestimating the risk; and (3) Specifying the risk in detail. Regarding the first strategy, even for interventions with fluoroscopic control, there is no explicit or implicit mention of long-term risks. The risk exists and can be substantial, but it is still not heard by patients or spoken by doctors. Thus, patients' right to information is eclipsed by two forces: efficiency and paternalism. In the second strategy, underestimating risk, obtaining informed consent is part of the "standard" practice of the team, and patients are not exposed to radiation without a consent form being signed. However, information on the actual effects and dose of radiation to be administered is not made available. Finally, the third strategy, full disclosure of risks, addresses the radiation dose to which patients will be exposed as well as the incidence of cancer and/or genetic diseases associated with it, especially if the test is performed for inclusion in a research study.

Regarding the pediatric population, children with congenital or acquired heart disease may be exposed to relatively high cumulative doses of ionizing radiation, resulting from imaging procedures requested, including radiographs, fluoroscopic procedures, such as diagnostic or interventional cardiac catheterizations, electrophysiology tests, CT angiography and nuclear cardiology tests, which in total and because the radiation dose is cumulative, represent an increased risk of cancer throughout life[104].

These children represent a vulnerable population group, considering the continuing need for medical care, and this requires greater ethical and professional responsibility, which underlies the fact that children do not have full decision-making ability nor adequate information about the various available care-related options they consider most suitable for themselves. Thus, health professionals ultimately have the obligation to make decisions that protect the well-being and life of this population and included among these is the decision regarding the diagnostic and therapeutic methods selected, considering the immediate and long-term effects on quality of life[105].

In addition to the previously mentioned ethical implications, such as the right to reliable and complete information and informed consent, which includes the risk of radiation, another ethical aspect is now being recognized, namely, the impact of medical radiation on the planet. This adds a new dimension to the ethical discussion about the best diagnostic approach, namely, the environmental impact, in addition to the medical benefits, costs, and long-term risks of radiation[20,21].

In conclusion, although we are aware of the life-long risks associated with exposure to ionizing radiation and although we recognize the vital role – both diagnostic and therapeutic – of medical imaging procedures, it is only prudent to perform such procedures using the lowest possible radiation doses while also ensuring their diagnostic value[106].

CONCLUSION

Exercise is the most physiologic stressor of all and should thus be preferable in patients who are able to exercise. In coronary artery disease diagnosis, exercise echocardiography is the appropriate first-line test for patients who are asymptomatic or with chest pain or dyspnea as the chief complaint. A major advantage of exercise echocardiography over the other forms of stress is that it may offer helpful and versatile evaluation of valve function and pulmonary hemodynamics and of special subsets of patients, such as patients with heart failure, pulmonary hypertension, valve disease, congenital heart disease, or athletes with symptoms of unknown etiology in search of intraventricular gradients. In all these patients, the physiologic nature of exercise stress and the versatility of the echocardiographic technique allow one to tailor the most appropriate test to the individual patient in the stress echocardiography laboratory. More importantly, the option of ESE is advantageous over techniques with higher cost and radiation burden for effective primary prevention of cancer, which should begin in the cardiac imaging laboratory.

FOOTNOTES

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Observational Study

Barriers and facilitators to participating in cardiac rehabilitation and physical activity: A cross-sectional survey

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Abstract

BACKGROUND

Cardiovascular diseases (CVD) have been shown to be the greatest cause of death worldwide and rates continue to increase. It is recommended that CVD patients attend cardiac rehabilitation (CR) following a cardiac event to reduce mortality, improve recovery and positively influence behaviour around CVD risk factors. Despite the recognised benefits and international recommendations for exercise-based CR, uptake and attendance remain suboptimal. A greater understanding of CR barriers and facilitators is required, not least to inform service development. Through understanding current cardiac patients' attitudes and opinions around CR and physical activity (PA) could inform patient-led improvements. Moreover, through understanding aspects of CR and PA that participants like/dislike could provide healthcare providers and policy makers with information around what elements to target in the future.

AIM

To investigate participants' attitudes and opinions around CR and PA.

METHODS

This study employed a cross-sectional survey design on 567 cardiac patients. Cardiac patients who were referred for standard CR classes at a hospital in the Scottish Highlands, from May 2016 to May 2017 were sampled. As part of a larger survey, the current study analysed the free-text responses to 5 open-ended

questions included within the wider survey. Questions were related to the participants' experience of CR, reasons for non-attendance, ideas to increase attendance and their opinions on PA. Qualitative data were analysed using a 6-step, reflexive thematic analysis.

RESULTS

Two main topic areas were explored: "Cardiac rehabilitation experience" and "physical activity". Self-efficacy was increased as a result of attending CR due to exercising with similar individuals and the safe environment offered. Barriers ranged from age and health to distance and starting times of the classes which increased travel time and costs. Moreover, responses demonstrated a lack of information and communication around the classes. Respondents highlighted that the provision of more classes and classes being held out with working hours, in addition to a greater variety would increase attendance. In terms of PA, respondents viewed this as different to the CR experience. Responses demonstrated increased freedom when conducting PA with regards to the location, time and type of exercise conducted.

CONCLUSION

Changes to the structure of CR may prove important in creating long term behaviour change after completing the rehabilitation programme.

Key Words: Cardiovascular disease; Cardiac rehabilitation; Physical activity; Barriers; Facilitators; Patient experience

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Core Tip: The exercise component of cardiac rehabilitation (CR) is considered key to the success of the programme. However, attendance of CR is sub-optimal. The current study examines cardiac patients' opinions and attitudes around several key elements of CR. Participants provided several ideas going forward to get more patients taking part in CR, which at the moment is a real issue. Experiences around physical activity were also explored, and it was found that patients viewed this as contrasting to CR.

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INTRODUCTION

Cardiovascular diseases (CVDs) are now the greatest cause of death worldwide[1]. In the United Kingdom there are currently 7.4 million people living with a specific heart or circulatory disease, accounting for 27% of all United Kingdom annual deaths[2]. Cardiac rehabilitation (CR) can aid recovery and help manage the long-term impact of CVD[3]. The exercise component of CR (exCR) is considered a priority and key to the success of the programme[4]. In the United Kingdom it is estimated that 100000 patients attend exCR, approximately 50% of eligible participants[2]. Developing new methods to increase attendance at exCR is deemed paramount[5]. Such methods could include telehealth, remote monitoring, or a hybrid approach, to increase accessibility and participation[6].

Research has explored factors that prevent and promote patient attendance. Previous systematic reviews have shown that women, older patients, the unemployed and those with comorbidities and depression are less likely to take up the opportunity to conduct exCR[7,8]. In contrast patients who are more affluent, have higher levels of education and who do not smoke are more likely to attend[7,8]. There is also evidence that geographical location may influence uptake but not drop out[8]. Castellanos *et al*[9] found that rural participants or those who live further from CR classes attended fewer sessions in comparison to those in urban areas. This was due to transport, distance and cost related factors. It appears that those with most to gain are the least likely to attend the sessions. Medical staff referral is also a key factor in CR participation and therefore barriers can exist based on general practitioners' (GP) or cardiologists' preconceptions of CR[10].

Reasons that prevent patients regularly attending exCR interventions are not fully understood, however, a large percentage that start do not finish[9,11,12]. The National Audit of Cardiac Rehabilitation[13] found that 77% of patients complete the full CR programme in the United States. However, Ritchey *et al*[14] found only 26.9% of patients above 65 years old in America completed the full

programme. The low rates of uptake and completion are a concern given the known benefits of CR. There is a need to better understand patients' experiences of CR and the influences on attendance and completion.

This study reports on the experiences of CR patients living in the Scottish Highlands. The aim of the present study was to explore participants' experience of CR and their attitudes, opinions, and perceptions of physical activity (PA) by answering the following research questions.

What are the barriers and facilitators to PA and CR attendance and programme completion?

What are the patients' views around deliverable service modifications with a view to improving attendance and completion?

MATERIALS AND METHODS

Design

The data employed in this study was from a larger cross-sectional survey[15]. Cardiac patients who were referred for standard CR classes at a hospital in the North of Scotland from May 2016 to May 2017 were sampled. Participants were excluded from taking part in the study if they had been previously referred, did not live in the catchment area, were < 18 years old, had a non-cardiac or unclear diagnosis or if CR, PA or completing the questionnaire was considered inappropriate for the specific patient. The full methods for this study are reported in Foster *et al*[15].

Procedures

Ethical approval was obtained from the Bromley Research Ethics Committee (study reference number 17/LO/1389, project number 231385). Identified participants were sent a "study pack" consisting of a cover letter, participant information sheet, consent form and questionnaire. A reminder was sent to the participants 2-3 wk later for those that had not responded. The current study analysed the free-text responses to 5 open-ended questions included within the wider survey. Participants were invited to respond to the following open-ended questions on their experience of CR and PA: (1) Did you find the CR classes useful? Please tell us why? (2) We would like to improve attendance at the CR classes- is there anything you think we could do to help you, or others attend? (3) If you did not attend any CR classes could you please tell us your reasons for not attending? (4) How important do you think being physically active is to your health and recovery? And (5) If there is anything else you would like to tell us then please use the space below to do so (*e.g.*, what do you think the local govern-ment/community or NHS could do to help improve the amount of activity you do or make it easier for you to be active?).

Analysis

A thematic analysis following the 6-step method of Braun and Clarke[16] was used to analyse the data. The themes are provided below in the results section, along with quotations from the respondents. The respondents' gender, age and attendance of classes is also provided.

RESULTS

Overall characteristics of patients

A total of 567 participants were invited to take part in the study, 293 (52%) returned a response. 76.7% of respondents were male, and the average age of the participants was 68.4 ± 10.4 years (range 33-90)[15]. In total 279 participants responded to at least one open-ended question of these 70 (25.1%) responded to 1 question, 88 (31.5%) responded to 2 questions, 104 (37.3%) responded to 3 questions and 17 (6.1%) responded to all 4 questions). Participants had a range of heart conditions (NSTEMI, STEMI, stable/unstable angina, heart failure, valve stenosis/regurg, arrhythmia, aortic aneurysm/dissection, type 2 myocardial infarction and valve/angina coronary artery disease) and had on average 2.59 comorbidities. In terms of smoking status, 139 participants were ex-smokers, 112 had never smoked, 24 currently smoked, 4 did not answer. PA levels were wide-ranging, 132 participants conducted "high" levels, 81 conducted "moderate" levels, 58 conducted "low" levels of PA and 8 did not respond. The table below breaks down the responses to the different questions (Table 1).

Responses were explored under two broad topic areas: "Cardiac rehabilitation experience" and "Physical activity". The two topic areas were made up of several sub-themes and codes, and a hierarchy tree diagram was created to display these (Figure 1)[17].

Main topic: CR experience

A wide range of themes were explored within the main topic of "cardiac rehabilitation experience". These were grouped in-to three sub-themes: "Barriers and reasons for non-attendance", "benefits" and "solutions and ideas to increase attendance". Table 2 displays the topic along with the sub-themes, elements, and exemplar quotes. For a detailed explanation of each element see the codebook (Appendix

Table 1 Response rate to questions

Question	Response rate
1	162 (55.2%)
2	130 (44.3%)
3	98 (33.4%)
4	236 (80.5%)

1).

Barriers and reasons for non-attendance

This sub-theme was related to barriers to attending CR classes. These included the type of activity conducted at the classes and physical limitations of respondents due to health conditions. Moreover, the location of the classes was highlighted as an issue especially for those in rural areas where this increases travel time considerably. With regards to timing, the duration and the time the classes were held at, meant those who work during the day could not attend. Whilst some responses reflect the desire to take responsibility for their own rehabilitation, for some it appears that the group exercise environment is not appealing. With respondents citing barriers such as not feeling comfortable in the group environment and in some cases feeling embarrassed. Finally, many respondents noted that poor communication in terms of a lack of advertising or information being available to patients around where or when the classes were to take place was a barrier. Within barriers around communication, respondents also highlighted on several occasions that the follow-up time was lengthy and deemed unacceptable.

Striving for independence

Several respondents highlighted that they chose not to attend CR and felt that they wanted to take responsibility for their own rehabilitation. Reasons included already being active enough, personal preference, feelings that they should take responsibility for their own wellbeing and living in a remote area.

Health benefits

On the whole responses were positive in relation to the outcomes of exCR. Respondents cited both physical and mental health benefits. Physical health benefits included improved fitness and weight loss. Mental health benefits included being able to learn coping strategies and relaxing. Additionally, with reference to the sub-theme of "peer support" respondents noted that being monitored and being able to ask staff questions improved psychological aspects of health. Respondents also noted that following the education element of CR they now knew significantly more about their condition and the best ways to manage it. There were some respondents however that noted they felt no benefits from attending the exCR classes to their health.

Peer support

Respondents highlighted that the social element of CR was important to them. A frequently cited area was in relation to exercising and meeting people with a similar condition. The ability to interact and communicate with like-minded/bodied people came across as one of the most important aspects of attending the group-based CR programme.

Healthcare provider support

Within the element of “benefits” there were several links with reference to the environment and atmosphere created by staff and other attendees. Moreover, being able to gain knowledge and understanding around PA and their condition was important, in addition to feeling free to ask questions helped regain confidence and understanding around their condition. However, it should be noted though that not all respondents felt this way, with some reporting in some instances that they felt out of place. Respondents indicated that staff play a significant role in the exCR experience and in some instances are crucial in promoting uptake, attendance, and completion of these programmes. Generally, most participant responses highlighted that they deemed the support offered from the staff as essential, encouraging, and supportive. Specific types of staff mentioned were physiotherapists, nurses, cardiologists, and gym instructors.

Being in safe hands

Responses consistently referred to increased levels of confidence within a range of contexts but primarily the increased belief that the respondents could exercise without fear. This code was related to

Table 2 Topic: Cardiac rehabilitation experience

Sub-theme	Element	Description	Example quotes
Barriers and reasons for non-attendance	Barriers to attending regular cardiac rehabilitation	Barriers to attending class. Includes aspects such as the type of activity, distance and timing of the classes as well as lack of information on when the classes are or failure to be referred.	Participant 74: "*Inconvenience, chest pains, shortness of breath when doing physical work*." (Male, 60-79, no classes). Participant 318: "*I found the traveling, 1 hour each way too much*." (Male, 80+, some classes). Participant 135: "*No classes out with working hours*." (Male, 60-79, 9 classes). Participant 259: "*It was difficult to get information as to where and when these classes were*." (Male, 60-79, some classes). Participant 354: "*6 months wait to be contacted regarding rehab is not good enough. We don't all live in large towns or cities*." (Male, 40-59, no classes). P243: "*It is difficult in rural areas to travel to venue far away*." (Male, 60-79, all classes)
	Striving for independence	Wanting to take responsibility for own health, feeling the need to figure it out independently.	Participant 360: "*Living in a relatively remote place I feel it is particularly incumbent on me to take responsibility for my own rehabilitation - and I feel that this should be an underlying principle. This would mean that resources could then be focussed on those who, for whatever reasons, cannot do this themselves*." (Male, 60-79, no classes). Participant 542: "*I had already started my own rehabilitation exercises at local gym.*" (Male, 60-79, some classes).
Benefits	Peer support	Being amongst other people who have shared experiences. This is not always perceived as a good thing.	Participant 575: "*Good to be able to talk to people with similar problems as me. Made me realise I was getting better and helped me regain some confidence.*" (Female, 60-79, some classes). Participant 282: "*Mixed with others and talked about how others coped*." (Male, 40-59, all classes). Participant 441: "*Just felt embarrassed and out of place*." (Male, 40-59, some classes). Participant 48: "*Assumed it would involve group activity. I'm not very good with group activity*." (Male, 60-79, no classes).
	Healthcare provider support	Being supported by knowledgeable staff.	Participant 33: "*They were carried out locally with excellent physiotherapist who carefully provided and monitored exercise which suited each individual member of small group. Relaxed atmosphere, advice and encouragement. Benefit felt*." (Female, 60-79, all classes) Participant 52: "*The pace and programme were tailored to my needs. The physios were superb - always supportive and encouraging. Meeting with and talking to, others in a similar situation was reassuring. It was great to see my heart-rate recovery time improving as the weeks went by. The post-exercise discussions and presentations were very helpful*." (Male, 60-79, all classes).
	Being in safe hands	Being cradled gently in safe hands. Being supported and encouraged to take the steps necessary to return to physical activity. This leads to increasing confidence and motivation.	Participant 430: "*To be able to exercise in an Hospital where I can feel safe. If anything happens to me I know that I have the full benefits to immediate health care that isn't available in the local communities*." (Male, 40-59, all classes). Participant 473: "*I could exercise under supervision which took away anxiety about how much to do, how much to push myself. I could ask questions, no questions too small or silly, provided reassurance and enabled me to do exercise at home without having to worry*." (Female, 40-59, some classes). Participant 327: "*After my cardiac event I felt some apprehension to participating in physical activity, but after attending a session, I felt more confident.*" (Male, 60-79, all classes). Participant: 367: "I felt motivated and encouraged to carry on with exercises at home." (Female, 60-79, all classes).
	Health benefits	Benefits and outcomes gained through attending classes. Includes both physical and mental benefits as well as increased knowledge of their condition.	Participant 146: "*They restored my fitness following surgery. They were convenient and well run*." (Male, 60-79, all classes). Participant 449: "*Controlled and supervised exercise giving much benefit to wellbeing and fitness*." (Male, 60-79, all classes). Participant 599: "*They helped me to understand that exercise helps not hinders recovery*." (Male, 60-79, all classes).

		Participant 149: "*Understanding of illness explained well and why the exercises and diet helped recovery taking into account my Parkinson's disease.*" (Male, 60-79, all classes). P49: "*Did not feel any significant difference to my condition - but I'm sure they are beneficial.*" (Male, 60-79, all classes). P50: "*I only attended one session, because I was getting reasonable exercise at home and thought there would be others who would benefit more than me .*" (Male, 60-79, some classes).
Solutions and ideas to increase attendance	Time and duration	Participant 599: "*The classes I attended were on the afternoon, which was not a problem for me, but could be for those still in employment. It may help to hold some classes in the evening.*" (Male, 60-79, all classes). Participant 5: "*Would have liked a class every day or every other day instead of once a week.*" (Male, 40-59, all classes). Participant 466: "*Would have liked longer than 8 weeks cardiac rehab.*" (Female, 60-79, all classes). P67: "*Make it sooner after the OP/procedure.*" (Male, 60-79, all classes).
	Class Structure	Participant 116: "*Not really, I would like to have been worked harder; however, as the classes have to satisfy different age groups and conditions, it would be difficult.*" (Male, 60-79, some classes). Participant 325: "*Give more interest, doing the same exercises every week is boring - virtually no equipment is used.*" (Male, 60-79, some classes). P6: "*As far as I know I attended all my classes, there was talk of more advanced classes, but I haven't heard any more news. I would like to attend more classes if there are any.*" (Male, 40-59, all classes). P101: "*I do find any gym based exercise very boring, perhaps any walking activities could be explored? A booklet on country walks suitable for people with heart problems, local community green gyms etc. Any outdoor activity organised in the Summer months to bring local communities together.*" (Male, 60-79). P44: "*Have more experts to give talks on cardiac problems and how to avoid another event. This may include food, exercise, medical advice etc.*" (Male, 60-79, all classes).
	Location	P141: "*Make them more reliable in my part of the world (Highlands - Caithness).*" (Male, 60-79, some classes). P133: "*Include them at the local gym so that people could attend whenever the wanted to. (Cost may be prohibitive though).*" (Male, 60-79, all classes). P227: "*Make the classes available in all medical centres.*" (Female, 60-79, some classes) P430: "*Help with travel arrangements and travel expenses out with Inverness for people not on benefits. Possible age-related groups and group buddies.*" (Male, 40-59, all classes). P41: "*Information on local support groups that are available. Discounted fees on joining local sports centres.*" (Male, 60-79, some classes).

safety and reassurance, in that feeling safe to exercise increased feelings of confidence and motivation. Respondents believed that the environment the classes were conducted in allowed them to work harder than they typically would. The role staff play in monitoring, encouraging, and supporting was deemed vital in creating feelings of safety. By monitoring the type of exercise and intensity, respondents noted that they could 'push themselves harder' with the confidence that if an adverse event occurred, the correct procedures were in place. Moreover, many respondents expressed increased confidence in their ability to do everyday tasks again, regaining their independence and thus increasing their motivation to keep exercising.

Solutions and ideas to increase attendance

Participants were asked to describe methods to increase attendance of exCR. There were a range of ideas suggested, three main elements were seen within respondents' responses, and these were related to time, structure, and location around CR. Within the element of time, frequent responses were seen around what time classes were held, a want for more classes across the week and an increase to the duration of the overall programme. In terms of structure, respondents highlighted a want for varying intensities, more variety of exercises which can be advanced and more elements to the classes such as education or teaching. Location frequently came up within responses and these were related to

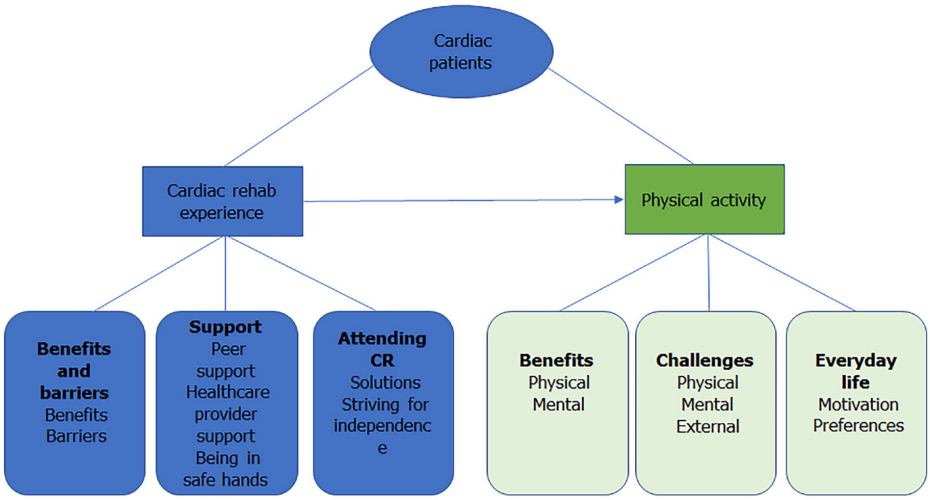

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Figure 1 Hierarchy of the topics, themes, and sub-themes from the qualitative analysis.

reliability of classes and a desire to have the programme conducted at local gyms and more medical centres in the future.

With the primary goal of CR to create long-term health behaviour change particularly with respect to PA the following section outlines participant responses related to PA. The two modes can be considered different due to patients having to take responsibility for planning and conducting their own PA and the locations in which it is conducted unlike exCR. The two main themes are also interconnected in that following completion of the exCR programme it is anticipated that participants will continue with regular PA.

Main topic: Physical activity

Within the main topic of "physical activity" there were similar and contrasting themes to those for "cardiac rehabilitation experience". The theme of "physical activity" was comprised of three sub-themes: "Benefits of being active", "challenges to being active" and "reasons for staying physically active". Table 3 shows this theme along with the sub-themes, elements, and exemplar quotes. For a detailed explanation of each element see the code book in Appendix 1.

Benefits of being active

Perceptions of PA appeared to be different to that of the exercise component of CR. Respondents recognized that they could conduct PA in a range of locations besides indoor environments, they could select when they wanted to conduct PA, there is more variety when conducting PA, and they can conduct PA whilst achieving other goals (*e.g.*, housework). Yet the range of benefits to participating in PA both in terms of psychological and physical benefits were similar to those reported for exCR.

Physical and mental benefits from PA

Respondents identified many benefits to their health from being physically active, including "maintaining weight, improving breathing, managing other diseases and ability to do things you enjoy." They also cited improvements in their mental health because of being more physically active, including "Improved confidence, wellbeing, stimulated mind, increased optimism and bringing joy and energy to their lives."

Barriers to physical activity

As within the main topic of "cardiac rehabilitation experience", barriers to PA were frequently discussed and these were grouped as physical, mental, and external barriers.

Physical

This included health – from other conditions as well as their heart. Respondents also referred to their age as a barrier.

Mental

Mental barriers included a lack of confidence and anxiety about being safe whilst exercising. Respondents also discussed that mental health issues such as anxiety and depression, which may also be linked to their cardiac issue, prevented them from taking part in regular PA.

Table 3 Topic: Physical activity

Sub-theme	Element	Description	Example quotes
Benefits	Physical	Physical benefits from being active.	Participant 33: "*Physical activity can help other/many other illnesses/diseases e.g., diabetes. It can also help you to feel better.*" (Female, 60-79, all classes). Participant 423: "*Keeping my weight at a good level is important and regular walking helps this. Walking helps me keep fit and helps with a good breathing pattern.*" (Male, 40-59, all classes). Participant 101: "*Being physically active not only improves recovery but stimulates the mind, especially when walking outdoors.*" (Male, 72, some classes). Participant 49: "*I am not PA as above - but I always endeavour to be active daily by other means i.e., gardening, walking, household etc., relevant to my age/weather conditions etc.*" (Male, 79, all classes).
	Mental	Mental benefits from being active.	Participant 358: "*Physical activity has given me a positive outlook for the future.*" (Male, 60-79, all classes). Participant 90: "*Improved confidence and mental wellbeing.*" (Male, 60-70, all classes).
Challenges	Physical challenges	Physical health barriers to being active.	Participant 28: "*At present I am troubled with retention of fluid which is affecting my breathing. If something could be done about this, I feel I would be able to get back to my golf and fishing.*" (Male, 80+, 8 classes). Participant 531: "*Because of my age and state of health I would find it very difficult to exercise.*" (Male, 80+, no classes).
	Mental challenges	Mental barriers to being active.	Participant 87: "*I don't go out by myself in case I suffer a bad turn. It's not just a physical barrier with some patients it's a mental barrier that stops them from exercise.*" (Male, 60-79, no classes). Participant 103: "*I have suffered from severe depression my whole life and lately it's been getting worse with everything that's going on so it's a bad place I'm in just now*" (Male, 40-59, no classes). Participant 450: "*To be honest I feel very anxious about strenuous or prolonged exercise: close to paranoia!*" (Male, 60-79, no classes).
	External challenges	External barriers to being active.	Participant 61: "*Normally in good weather my husband and myself are out walking about 3 d a week but with all the snow and ice we have had we have hardly been out of doors.*" (Female, 60-79, no classes). Participant 278: "*I really enjoy lifting weights and as my local gym does not have much I use a private gym. It has all health questions and if you have a health problem (heart attack etc.) you need a doctor's letter which is £30. This could put people off.*" (Female, < 39, 8 classes).
Reasons for staying physically active	Motivation	Motivation for being physically active.	Participant 160: "*Would like to keep active for my grandchildren and my great grandchildren and also for my remaining son and family.*" (Female, 60-79, 8 classes). Participant 115: "*Being physically fit, for your age, helps to be mentally fit and become able to participate in family and community events.*" (Male, 60-79, 8 classes).
	Preferences	Preferences of types of activity.	Participant 318: "*Most of my activity is concerned with work around the home e.g., cutting trees for wood burner, splitting logs for wood burner, digging garden, looking after chicken, mowing grass etc.*" (Male, 80+, some classes). Participant 258: "*I've been involved with physical activity in my work environment all my working life. Most of my hobbies focus around exercise skiing, biking, golf, swimming and walking. Don't like to be unfit.*" (Female, 40-59, no classes).

External

External barriers included factors such as where they lived, distance from leisure facilities, the cost of leisure facilities, the need for medical notes to gain access to gyms which cost money and the weather.

Reasons for staying physically active

This sub-theme includes two elements: "Motivation" and "preferences" and discusses instances where respondents suggested why PA is important for their lives and what activities they like to do.

Motivation

This sub-theme related to motives and reasons for being active or becoming more active. When noting elements around their condition and PA, many responses were related to aspirations, plans and goals for their future after overcoming the event and attending CR. Respondents highlighted a want to be able to conduct more regular forms of PA and regain their independence, they had prior to having their cardiac issue. Other responses were in relation to behaviour change and living a more active lifestyle with the aim of prolonging life and living better mentally and physically. Finally, respondents also noted improving their lifestyle so that they can continue to see their family and friends.

Preferences

Respondents described types of activities that they now preferred to participate in. In some instances, as outlined within the 'solutions and ideas to increase attendance' sub-theme, some of these types of PA could be considered within future rehabilitation programmes. Specifically, most participants noted that they prefer to participate in PA outdoors.

DISCUSSION

This study, conducted in cardiac patients in the North of Scotland, demonstrates a range of opinions and attitudes around CR. The two main topics from the data were termed "cardiac rehabilitation experience" and "physical activity". Each topic was made up of several sub-themes and codes. Whilst the two main topics are different, they are connected in that once attending CR programmes, individuals should progress to conducting levels of PA that meet the national guidelines.

Respondents outlined benefits to taking part in exCR, including improved fitness, mood, and mindset. Respondents also noted that following the education element of CR they knew significantly more about managing their condition which may be important in creating long-term behaviour change. Conversely, respondents frequently cited distance and travel as reasons for non-attendance. Other barriers were related to age, health/injury status, accessibility, and timings (classes during working hours). These barriers were similar to those found in previous CR research[18,19]. External barriers included communication around the referral process, specifically a lack of advertising or information availability. Respondents noted not being informed and unacceptable lengths of follow up. Foster *et al* [15] found "perceived need" to be the single most important factor in patient non-attendance to CR where perceived need consisted of patient and healthcare factors. Healthcare factors include lengthy referral process, a lack of contact, information, or knowledge[20]. The current findings are consistent with the quantitative phase of the larger study[15]. In terms of barriers to PA, there was little mention of time, location, or distance. However, the feeling of safety was removed when conducting PA and worry around adverse events was an issue. This, however, is a common misconception and more needs to be done to reassure patients after a cardiac event that PA is safe[21].

Consistent with previous research into CR[15,22], responses demonstrated that being monitored and shown the correct exercise form alongside enhanced understanding of managing their condition could result in increased self-efficacy for conducting PA. The social cognitive theory[23] describes how learning drives human behaviour. Self-efficacy is one of the most powerful predictors of behaviour in health environments[24]. Patient education has also been shown to increase self-efficacy[25]. Such evidence is supported by Frohmader *et al*[26] who found that following interviews, patients' confidence increased to develop lifestyle changes as a result of viewing their own success and positive reinforcement by mentors. The use of telehealth, specifically videoconferencing, may be one method for increasing accessibility to such interviews and overcoming patient barriers to attendance[27]. Thus, focusing on methods to increase patient confidence could increase adherence to CR programmes.

Responses were positive and demonstrate the role that staff play in facilitating attendance to CR through creating safe, enjoyable environments. Participants highlighted that exercising alongside others with similar conditions made them more likely to attend CR and enhanced their levels of enjoyment and support. Moreover, group dynamics such as looking out of place or embarrassment which are often cited as barriers to exercise[28] are potentially removed when exercising with people with a similar health condition. These responses show CR to be more than just an "exercise regime", individuals create friendships and socialise, creating mental and physical benefits. Contrastingly, in some cases group exercise was considered a barrier to attendance and this demonstrates the complexities of trying to increase CR attendance.

The second research question analysed patient feedback to increasing attendance of CR. Numerous studies have developed methods to increase attendance in CR programmes[29,30]. However, few have considered patient generated ideas and whether they will be relevant to patients in rural areas. Karmali *et al*[29] considered the use of structured telephone calls, visits from staff following leaving hospital, the creation of peer support groups, early appointments, motivational letters, and a gender-tailored cardiac programme. The review found that many of these methods were successful in increasing attendance, however many displayed high levels of bias which makes it challenging to generalise. A clear barrier identified within the current research to attending CR classes was related to the organisation or accessibility of the sessions. A lack of classes and no classes out with work hours were frequently cited. One clear method to overcoming these is to provide more classes, especially for rural patients where travel time and distance are typically large. Particularly in the Scottish Highlands, it is likely financial and staffing constraints will mean this is challenging to implement, but possibilities may exist with regards to increase provision through local companies such as Highlife Highland or Argyll Active.

In relation to increasing the number of CR classes, new methods away from centre-based CR have been developed[31]. Further, due to the COVID-19 pandemic changes to where CR is conducted have occurred[32]. Even before the pandemic, many CR services began to implement home-based exCR[33]. Previous research has investigated online home-based exercise and post-exercise telemonitoring.

Anderson *et al* (2017)[33] and Batalik *et al*[27] found such modes to be at least equally as effective as centre-based rehabilitation, increasing access and participation. Such methods of delivery may facilitate attendance for individuals who dislike exercising in groups, in that they attend the group classes without being viewed. However, in rural areas connectivity (Wi-Fi and 4G/5G) may be substandard and considered a barrier to such forms of CR[34].

Other methods to overcome the barriers that were identified within the current study include peer support groups, third sector partnerships and patient travel funds supporting results seen within other similar studies[30]. Currently, if a patient lives more than 30-miles from the clinic or have a co-morbidity they are entitled to travel reimbursement[35], which it appears respondents were unaware of, highlighting the need again for better communication. The distance to the classes may not be solely responsible for non-attendance and perhaps the lack of awareness around funding or alternative methods of travel are a greater issue. The healthcare team and referral staff should make sure on discharge that patients have information about these funds and even provide details of low-cost travel such as dial-a-bus services running in their area.

Many of the ideas to overcome the barriers are related to communication, providing better information and perhaps this comes down to creating more streamlined services or educating staff about their roles, responsibilities, and the importance of CR. Previous research has shown that patients pick up on doctors' perceptions and how their beliefs and values can shape behaviour[10]. Thus, if a GP or doctor does not deem CR to be necessary then it is unlikely that the patient will consider attending. Quirk *et al*[36] note that poor maintenance of PA post CR is common, and that regular attendance of CR does not guarantee regular PA following completion of the CR programme. The patients' responses highlight that greater emphasis should be placed upon strategies to increase self-efficacy and self-regulation.

Physical activity

The responses demonstrated respondents that attended CR now have a good understanding of why they should conduct regular PA, highlighting that the education element of the programme is effective. Respondents recognise exCR and PA as two separate entities, much as exercise and PA are different in definition in the literature[37]. Differences centred on the structured nature of CR. Respondents identified that PA can be conducted at any time and place, whereas exCR classes take place at a set location and time. This gives patients less freedom, restricting the time they can spend doing other activities.

As exCR is typically conducted indoors this presents another way in which the two forms of activity differ. When referring to types of PA, many responses were related to activities conducted outdoors and in natural areas. This perhaps warrants discussion with regards to the locations of where exCR is conducted. Previous research has shown decreased levels of motivation when conducting exercise indoors[38]. Whilst clearly weather is a barrier to implementation, patient responses show that exCR outdoors may increase attendance. Respondents noted that they would like to see more walking and cycling clubs included to increase participation. Specific responses were termed "reasons for staying physically active" and how respondents prefer to conduct PA such as housework or cleaning whereby they can achieve both health and day-to-day goals. Many respondents considered the future, expressing they conducted PA to maintain their health, feel better and external reasons such as to see their grandchildren grow up. There is a myriad of reasons individuals will select to adopt new behaviours. Finding ways to make the exercise element of CR more like PA is a concept that requires attention.

Future research

The current study provides ideas and directions for future research and policies. Further qualitative research in the form of interviews and focus groups should be conducted to gain more in depth understanding of factors associated with non-attendance. It should not only be patients who are sampled however, collecting more data from the referral staff may provide a greater understanding with regards to CR. An evaluation report of referral processes may allow understanding into why so many do not receive adequate communication about CR classes. Following on from this, investigating new methods of referral such as those outlined in the discussion to understand if they improve attendance is warranted. Finally, future research may look to use longitudinal or follow-up study designs to understand how the behaviours of those individuals who both attended CR and those who chose not to attend differed.

Limitations

Whilst the study displays a range of responses with regards to respondents' attitudes and perceptions of both CR and PA, there was a large amount of data brevity or responses due to the format of the questionnaire. This resulted in an inability to probe and ask follow-up questions. Moreover, not all participants replying to the questionnaire was deemed a limitation.

CONCLUSION

The current study provides several suggestions for increasing attendance of CR. Self-efficacy is a large aspect of what CR offers patients and this is built up through effective communication, socialising with similar people and the safe environment that exCR provides. However, before individuals can achieve such benefits, successful methods to get them to attend exCR need to be better investigated. Barriers to exCR range from age and health to the distance and starting times of the classes, resulting in increased travel time and costs. To overcome these barriers respondents outlined a range of ideas such as the provision of more classes held out with working hours, a greater variety of classes and classes conducted in different locations. Finally, financial incentives to help conduct PA from travel reimbursements to reductions at fitness centres were also highlighted. As a result of the findings of the current study, future studies should continue to attempt to develop, test and evaluate methods to increase the uptake and attendance of CR based on the current low statistics of eligible patients' attendance.

ARTICLE HIGHLIGHTS

Research background

Cardiovascular disease remains the largest cause of death globally and rates continue to rise. The exercise component of cardiac rehabilitation (CR) is regarded as an important element of such interventions. Recent statistics have demonstrated that attendance of CR programmes is low, despite continued calls for methods to increase attendance.

Research motivation

Such a study is warranted as low rates of uptake and completion of rehabilitation programmes are a concern. The barriers and facilitators towards CR are still somewhat unknown. Patients should continue to conduct regular exercise and physical activity after completing the rehabilitation programme. Thus, understanding patient perspectives on this area is also necessary. Exploring such topics should allow researchers and health care staff to target specific elements of service delivery to improve attendance in the future.

Research objectives

The aims of the present research study were to identify the barriers and facilitators to CR and physical activity. The study also aimed to explore cardiac patient views around service modification and ideas to increase attendance at such programmes.

Research methods

The data analysed in this study was from a larger cross-sectional survey. Cardiac patients from the North of Scotland, who were referred for standard CR classes at a hospital were sampled. The current study qualitatively analysed the free-text responses to 5 open-ended questions included within a wider survey. A 6-step thematic analysis was used to analyse the data.

Research results

Patient responses were explored under two main topic areas: "Cardiac rehabilitation experience" and "physical activity". Patients described barriers to CR including time of day, location, a lack of communication and group dynamics. Patient generated ideas to increase the uptake of such programmes included more available classes, a greater variety of intensities and types of exercise and a change to the location of classes. Patients highlighted various benefits to both mental and physical health as a result of conducting the classes and physical activity.

Research conclusions

It appears based on the findings of the current study that CR increases patients' self-efficacy through a number of mechanisms. Key barriers to attending CR in this cohort included age and physical health, distance to the classes and the cost of attendance. With regards to these barriers, participants highlighted a range of methods to overcome these including provision of more classes held out with working hours, classes conducted in different locations and the need for a greater variety of exercise classes.

Research perspectives

The study provides several ideas which future research can implement or examine. Future studies should attempt to develop, test, and evaluate methods to increase the uptake and attendance of CR based on the current low statistics of eligible patients' attendance.

FOOTNOTES

Author contributions: Foster E, Gorely T and Leslie S designed the research study; Foster E and Leslie S performed the research; Fraser M, Gorely T and Walters R analysed the data; Fraser M, Gorely T, Walters R and Leslie S wrote the manuscript; All authors have read and approved the final manuscript.

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SYSTEMATIC REVIEWS

Untangling the difficult interplay between ischemic and hemorrhagic risk: The role of risk scores

Simone Persampieri, Diego Castini, Alessandro Lupi, Marco Guazzi

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Abstract

BACKGROUND

Bleedings are an independent risk factor for subsequent mortality in patients with acute coronary syndromes (ACS) and in those undergoing percutaneous coronary intervention. This represents a hazard equivalent to or greater than that for recurrent ACS. Dual antiplatelet therapy (DAPT) represents the cornerstone in the secondary prevention of thrombotic events, but the benefit of such therapy is counteracted by the increased hemorrhagic complications. Therefore, an early and individualized patient risk stratification can help to identify high-risk patients who could benefit the most from intensive medical therapies while minimizing unnecessary treatment complications in low-risk patients.

AIM

To review existing literature and gain better understanding of the role of ischemic and hemorrhagic risk scores in patients with ischemic heart disease (IHD).

METHODS

We used a combination of terms potentially used in literature describing the most common ischemic and hemorrhagic risk scores to search in PubMed as well as references of full-length articles.

RESULTS

In this review we briefly describe the most important ischemic and bleeding scores that can be adopted in patients with IHD, focusing on GRACE, CHA2DS2-Vasc, PARIS CTE, DAPT, CRUSADE, ACUITY, HAS-BLED, PARIS MB and

PRECISE-DAPT score. In the second part of this review, we try to define a possible approach to the IHD patient, using the most suitable scores to stratify patient risk and decide the most appropriate patient treatment.

CONCLUSION

It becomes evident that risk scores by themselves can't be the solution to balance the ischemic/bleeding risk of an IHD patient. Instead, some risk factors that are commonly associated with an elevated risk profile and that are already included in risk scores should be the focus of the clinician while he/she is taking care of a patient affected by IHD.

Key Words: Acute coronary syndrome; Ischemic heart disease; Risk score; Bleeding; Mortality; Percutaneous coronary intervention

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Core Tip: We present a review of the most relevant scores developed or adjusted for the risk stratification of patients affected by ischemic heart disease. For each score, the strengths, weaknesses, statistical pertinence and applicability are evaluated.

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INTRODUCTION

Hemorrhagic complications have emerged as an independent risk factor for subsequent mortality in patients with acute coronary syndromes (ACS) and in those undergoing percutaneous coronary intervention (PCI), representing a hazard equivalent to or greater than that for recurrent ACS[1-4]. As known, dual antiplatelet therapy (DAPT) represents the cornerstone in the secondary prevention of thrombotic events in ACS[2]. However, the benefit of such therapy is counteracted by the increased hemorrhagic complications: major bleeding also considerably prolongs the hospital stay and increases resource consumption. Minimizing bleeding complications, most of which are attributable to the use of potent antiplatelet and antithrombin medications, is therefore an important objective in the management of patients with ischemic heart disease (IHD). It must be noted that, similarly to ischemic risk, risk of bleeding is not homogeneous, and various predictive models have been developed to stratify both bleeding and ischemic risk in patients affected by IHD[5]. Clinical guidelines recommend that optimal management of patients with IHD should include early, individualized patient risk stratification by the treating physician[6,7]. In addition to informing patients about their prognosis, accurate risk assessment can help to identify high-risk patients who could benefit the most from intensive medical therapies while minimizing unnecessary treatment complications in low-risk patients. The development of simple-to-use risk scores could standardize quality of care and patient outcomes. Risk stratification could also be employed to compare outcomes across different clinical studies.

MATERIALS AND METHODS

We screened the titles and abstracts of studies against predefined terms using PubMed, EMBASE and Cochrane databases. Key words used have been "GRACE score", "CHA2DS2-Vasc score", "PARIS CTE score", "DAPT score", "CRUSADE score", "ACUITY score", "HAS-BLED score", "PARIS MB score", "PRECISE-DAPT score", "derivation" and "validation" in order to identify relevant articles published. The title and available abstracts of all returned articles were reviewed to identify relevant articles for a full-length review. Reference lists from the articles were reviewed to identify additional relevant articles. All studies that contained material applicable to the topic were considered. Data was analyzed using descriptive statistics.

RESULTS

Ischemic risk

GRACE score: The GRACE risk prediction model was developed from an earlier cohort of GRACE (Global Registry of Acute Coronary Events) patients (a total of 11389 patients enrolled in 14 countries from April 1, 1999, to March 31, 2001)[8]. It evaluates the probability of death within 6 mo of hospital discharge in patients with ACS. The components of the GRACE score are systolic blood pressure, age, Killip class, heart rate, cardiac arrest, serum creatinine, ST-segment deviation and cardiac biomarker increase. All variables refer to data at patient presentation. GRACE score was subsequently validated in a cohort of 3972 GRACE patients and 12142 GUSTO-IIb trial patients. It has been demonstrated an important predictor of in-hospital mortality across the whole spectrum of the ACS population[9]. However, the substantial geographic variation of patient cohorts used to develop the GRACE do not confirm its applicability in all the ACS patient populations and additional assessment has been performed to validate the score. Currently, GRACE score is suggested by ESC Guidelines to stratify patients according to their estimated risk of future ischemic events in order to overcome the so called "risk-treatment paradox"[10,11]. Indeed, it is well recognized that the delivery of guideline-directed care is inversely related to the estimated risk of the patient with NSTEMI and a GRACE risk score-based risk assessment has been found to be superior to the subjective physician assessment for the occurrence of death or ACS[12,13].

Moreover, benefit with an early invasive strategy is strongly associated with the patient's risk profile. In a pre-specified subgroup analysis, patients with a GRACE risk score > 140 benefited from an early invasive strategy while those with a GRACE risk score < 140 did not (TIMACS trial: HR = N0.65, 95%CI: 0.48-0.89 *vs* HR = 1.12, 95%CI: 0.81-1.56, *P* for interaction = 0.01; VERDICT trial: HR = 0.81, 95%CI: 0.67-1.00 *vs* HR = 1.21, 95%CI: 0.92-1.60; *P* for interaction = 0.02)[14,15].

C-statistics in the derivation study: 0.81 for predicting death and 0.73 for death or myocardial infarction.

CHA2DS2-VASc score: The CHA2DS2-VASc score is a well validated risk model for predicting thromboembolic events and guiding anticoagulant therapy in patients affected by atrial fibrillation (AF). It has been developed as a refinement of the older CHADS2 score by incorporating female sex and vascular disease and by assigning two points for age ≥ 75 years[16,17]. Although being developed for thromboembolic risk prediction in AF patients, both these scores contain common cardiovascular risk factors that are associated with thromboembolic events regardless of the presence of AF and are well known predictors of both coronary atherosclerosis and major cardiac adverse events (MACE) in patients with known coronary artery disease and ACS[18,19].

C-statistics in the derivation study: 0.61.

PARIS CTE score: The PARIS CTE score has been derived from The Patterns of Nonadherence to Antiplatelet Regimens in Stented Patients (PARIS) registry, an observational study of patients undergoing percutaneous coronary intervention (PCI) and stenting. From that registry, PARIS risk scores for major bleeding (MB) and for coronary thrombotic events (CTE) were created. The PARIS CTE risk score predicts the stent thrombosis and myocardial infarction risk for up to 2 years after PCI. It considers diabetes, ACS, smoker, creatinine clearance, prior PCI and prior CABG[20]. The score showed very good results both in the derivation and validation cohort. Once external validation studies had been performed, they showed limited to poor discrimination thus far. As the simplicity of the CTE score might be favorable for clinical use, its value compared to other ischemic scores is yet to be established.

C-statistics in the derivation study: 0.70.

DAPT score: The dual-antiplatelet therapy (DAPT) score is recommended by Guidelines as a tool to stratify ischemic and bleeding risk. However, the score can be used to distinguish patients suitable for standard term DAPT and long term DAPT, so it is our opinion that it can be considered mostly an ischemic risk score. The prediction rule assigns 1 point each for myocardial infarction at presentation, prior myocardial infarction or PCI, diabetes, stent diameter less than 3 mm, smoking, and paclitaxel-eluting stent; 2 points each for history of congestive heart failure/Low ejection fraction and vein graft intervention; −1 point for age 65 to younger than 75 years; and −2 points for age 75 years or older[21]. The DAPT score has been validated in several studies outside its derivation cohort; however, these studies have yielded conflicting results in which some have confirmed its predictive value and some have not[22]. Of note, most of the analyses were from registries and a substantial number of patients were treated with bare-metal stents or first-generation DES. Moreover, the present score considers among its items the use of paclitaxel-eluting stents, that are no more considered a standard in most catheterization laboratories. It is well known that using newer-generation DES mitigates the ischemic risk of patients treated with PCI. It becomes evident looking at C-statistics: in the derivation/validation study, the C-statistic for ischemic and bleeding outcomes were 0.64/0.70 and 0.68/0.64, respectively; among the validation studies, the C-statistics for composite outcomes ranged from 0.53 to 0.71 for ischemic outcomes and 0.49 to 0.71 for bleeding outcomes[23].

Bleeding risk

CRUSADE score: CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) score has been developed by investigators of the CRUSADE registry as a stratification tool for in-hospital major bleeding among NSTEMI patients[24]. Variables included are female sex, diabetes mellitus, peripheral artery disease, heart rate, systolic blood pressure, congestive heart failure, hematocrit, and creatinine clearance. Considering only the variables present at admission, the CRUSADE bleeding score is an easily applicable and useful tool in predicting patient risk that showed adequate calibration and excellent discriminatory powers in the whole population as well as in the different treatment subgroups, except in patients treated with ≥ 2 antithrombotics who did not undergo cardiac catheterization[24,25].

C-statistics in the derivation study: from 0.56 to 0.81 in different subgroups.

ACUITY: Mehran *et al*[26], using data from the ACUITY and the HORIZONS-AMI trials (17421 patients), developed a bleeding risk score. Six independent baseline predictors for major bleeding were identified: female sex, age, creatinine, white blood cell count, anemia and ST-segment-elevation. The risk score differentiated patients with a 30-d rate of non-CABG-related major bleeding ranging from 1% to over 40%. As a difference with the other bleeding risk scores, this one includes white blood cell count as a risk factor for major bleeding. It has been compared with CRUSADE score in subsequent observational study and shows an acceptable discriminative capacity[27].

C-statistics in the derivation study: 0.74.

HAS-BLED score: The HAS-BLED score, initially developed to assess the bleeding risk in patients with AF receiving chronic anticoagulant therapy[28], has shown to predict cardiovascular events and long-term outcomes in these patients. The observation by Pisters *et al*[28] that HAS-BLED predictive efficacy was particularly high in patients receiving antiplatelet therapy led to its evaluation in predicting bleeding events and major acute cardiovascular events (MACE) in patients receiving DAPT after PCI and stenting with or without AF[29]. Moreover, the HAS-BLED score predictive performance was tested in patients with ACS receiving DAPT or triple antithrombotic therapy, showing moderate accuracy[28].

C-statistics in the derivation study: 0.72 overall; 0.91 with antiplatelet only therapy.

PARIS MB score: The PARIS risk score for major bleeding was developed from the same previously mentioned PARIS registry, in which also patients on oral anticoagulation were included. This six-item risk score (age, BMI, smokers, anemia, creatinine clearance and triple therapy) showed reasonable discrimination for major bleeding up to 2 years post-PCI across different validation cohorts[20].

C-statistics in the derivation study: 0.72.

PRECISE-DAPT score: The PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) score is a simple bedside risk assessment tool, recommended from the ESC Guidelines, which can be easily implemented in everyday clinical practice, and that might be particularly useful for its applicability at the time of treatment initiation[6,7,30]. It has been developed for prediction of bleeding risk during DAPT after PCI using pooled data of 8 randomized clinical trials. It comprises 5 variables: age, creatinine clearance, hemoglobin, white blood cell count and previous spontaneous bleeding. In patients with high bleeding risk (PRECISE-DAPT score ≥ 25), the bleeding risk of 12-mo or longer DAPT could outweigh the benefit of ischemic prevention. Patients not at high bleeding risk (score < 25) might receive a standard (*i.e.* 12 mo) or prolonged (*i.e.* > 12 mo) treatment without being exposed to significant bleeding liability.

C-statistics in the derivation study: 0.71.

DISCUSSION

Risk scores or risk factors?

We now move forward looking at the multivariate analysis from which every score has been developed, focusing on repeated items among scores belonging to ischemic or bleeding category and on the real weight of these items in the score (*i.e.* the OR or HR values). We want to specify that we do not apply this analysis to the GRACE score that is composed by items of the acute phase of ACS that are not common to other scores and that has a very strong predictive value for mortality by itself. We think that the GRACE score should be applied in every ACS patient, in order to define the patient prognosis, regardless of ischemic and bleeding risk which should be analyzed separately.

Going back to the analysis in Table 1 and Table 2, we summarized the OR or HR derived from the multivariate analysis of the derivation cohorts and the ischemic and bleeding risk scores, respectively.

At first, looking at ischemic risk scores, it becomes evident that in the CHA2DS2-Vasc score, only the female sex was really statistically significant in the logistic regression analysis, while the other items were not. This is because, in the derivation and validation study, rather than considering the single item, patients have been grouped in 3 groups according to the score, that were low risk (0 point), intermediate risk (1 point) and high risk (≥ 2 points), and the authors demonstrated a better discrimination capacity

Table 1 Ischemic risk scores items and OR/HR

Item	OR/HR (CI)
CHA2DS2-Vasc (OR)	
Congestive HF	0.72 (0.27-1.88) NS
Hypertension	1.01 (0.38-2.66) NS
Age ≥ 65	NR
Age ≥ 75	1.46 (0.63-3.35) NS
Diabetes mellitus	1.79 (0.73-4.40) NS
Stroke	2.22 (0.78-6.35) NS
Vascular disease	2.27 (0.94-5.46) NS
Female sex	2.53 (1.08-5.92)
DAPT (OR)	
Age, per 10 yr increase	1.54 (1.34-1.78) (on bleedings)
Current smoking	1.4 (1.11-1.76)
Diabetes mellitus	1.38 (1.1-1.72)
Acute coronary syndrome	1.65 (1.31-2.07)
PCI or prior ACS	1.79 (1.43-2.23)
Stent diameter < 3 mm	1.61 (1.3-1.99)
Paclitaxel stent	1.57 (1.26-1.97)
Congestive HF	1.88 (1.35-2.62)
Saphenous vein graft stenting	1.75 (1.13-2.73)
PARIS-CTE (HR)	
Current smoking	1.69 (1.14–2.52)
CrCl < 60 mL/min	2.12 (1.46–3.05)
Diabetes mellitus	
Non-insulin dependent	1.69 (1.14–2.52)
Insulin dependent	3.42 (2.32–5.04)
Acute coronary syndrome	
Troponin negative	1.47 (1.03–2.08)
Troponin positive	2.09 (1.24–3.53)
Previous revascularization	
Previous PCI	1.91 (1.38–2.66)
Previous CABG	1.80 (1.24–2.61)

CI: Confidence interval; CrCl: Creatinine clearance; HF: Heart failure; HR: Hazard ratio; NR: Not reported; NS: Not significant; OR: Odds ratio.

of the CHA2DS2-Vasc score compared to the CHADS2 score. Therefore, they still included variables not independently associated to the outcomes but that fit the prognostic model[17]. Moving on, the other 2 scores, we found a precise statistical derivation with every single item being statistically significant.

As evident, two variables are common to all scores, these are diabetes mellitus and vascular disease (considered also as previous ACS or PCI). Some others like heart failure, age and smoking, are common to 2 out of 3 scores. Diabetes mellitus and vascular disease are also the items with the higher OR or HR in every score and that means that they have more influence on the ischemic outcome.

Diabetes is a major independent risk factor for IHD[31], particularly for myocardial infarction. The pattern of coronary artery disease in diabetic patients is often complex, with multiple lesions and widespread involvement, making it difficult to achieve complete revascularization and adversely affecting long-term prognosis[31]. Several studies have also found a greater risk of death after ACS in patients with diabetes than in those without diabetes[32,33] in every subtype of coronary syndromes

Table 2 Bleeding risk scores items and HR/OR

Item	HR/OR (CI)
PARIS-MB (HR)	
Current smoking	1.94 (1.18–3.20)
CrCl < 60 mL/min	1.81 (1.16–2.82)
Age, per year increase	1.02 (1.00–1.04)
BMI	
< 25 kg/m^2	1.68 (1.09–2.60)
≥ 35 kg/m^2	1.79 (1.04—3.08)
Anemia	2.72 (1.83–4.04)
Triple therapy on discharge	1.93 (1.08–3.43)
CRUSADE (HR)	
Heart rate per 10 bpm increase	1.08 (1.07–1.10)
Systolic blood pressure	
≤ 110 mmHg	1.26 (1.16–1.36)
≥ 180 mmHg	1.24 (1.14–1.35)
Hematocrit < 36%	2.28 (2.11–2.46)
CrCl, per 10 mL/min decrease	1.12 (1.10–1.13)
Sign of HF	1.23 (1.15–1.31)
Vascular disease	1.19 (1.12–1.27)
Diabetes	1.16 (1.10–1.23)
Female sex	1.31 (1.23–1.39)
ACUITY (OR)	
Age, per 5 yr increase	1.17 (1.13–1.21)
Acute coronary syndrome	
NSTEMI	1.26 (1.04–1.54)
STEMI	1.92 (1.52–2.44)
White blood cell count, giga/L	1.10 (1.07–1.12)
Serum creatinine, per 0.1 mg/dL increase	1.09 (1.07–1.12)
Anemia	1.98 (1.65–2.37)
Bivalirudin monotherapy	0.56 (0.47–0.67)
Female sex	2.32 (1.98–2.72)
HAS-BLED (OR)	
Age > 65 yr	2.66 (1.33-5.32) NS
Systolic blood pressure >160 mmHg	0.60 (0.21-1.72) NS
Creatinine > 2.26 mg/dL or > 200 μmol/L or cirrhosis or bilirubin > 2 x normal with AST/ALT/AP > 3 x normal	2.86 (1.33-6.18)
Prior major bleeding or anemia	7.51 (3.00-18.78)
Medication predisposing to bleeding	0.81 (0.43-1.51) NS
Stroke	0.94 (0.32-2.86) NS
Labile INR	NR
Alcohol use, ≥ 8 drinks/wk	0.00 (0.00) NS
PRECISE-DAPT (OR)	
Hemoglobin, per 1 g increase	0.67 (0.53-0.64)

White-blood-cell count, per 103 cells per μL increase	1.06 (0.99-1.13)
Age, per 10 yr increase	1.34 (1.11-1.48)
CrCl, per 10 mL/min increase	0.9 (0.82-0.99)
Previous bleeding	4.14 (1.22-14.02)

CI: Confidence interval; CrCl: Creatinine clearance; HF: Heart failure; HR: Hazard ratio; NR: Not reported; NS: Not significant; OR: Odds ratio.

(unstable angina, STEMI and NSTEMI)[34,35].

The incidence of peripheral arterial disease (PAD) increased by 23.5% in the first 10 years of this century and 3%–12% of the earth's population is affected[36]. PAD patients share most of their atherosclerotic risk profiles with patients diagnosed with coronary artery disease. In the Global Atherothrombosis Assessment (AGATHA) study, approximately 50% of patients with PAD had IHD, and 20% of IHD patients was affected also by PAD[37]. Advanced stent technology and more potent antiplatelet agents and anticoagulant therapy have resulted in an improvement in outcomes among the overall population of patients undergoing coronary interventions. However, PAD patients demonstrated a lower benefit increase. Of note, their risk of major adverse cardiovascular events outcomes following PCI has remained unchanged across the early bare-metal stent (BMS) and drug-eluting stent (DES) eras: the only benefit has been demonstrated for a reduction in the rate of repeated PCI. Singh *et al*[38] found that patients with PAD that underwent PCI in the BMS era had an 84% relative-risk increase of an in-hospital mortality and a 48% relative-risk increase of death over a period of 3-years compared to patients without PAD. And this was evident also after adjustment for concomitant risk factors. In the Tirofiban and Reopro Give Similar Efficacy Outcome Trial (TARGET), PAD was independently associated with a 2- to 3-fold increase in mortality 12 mo after PCI. Similar to findings in the BMS era, in the DES era the study by Ramzy *et al*[39] suggests that PAD continues to be independently associated with approximately a two-fold increased risk of 12 mo mortality. Assessment of Dual AntiPlatelet Therapy with Drug Eluting Stents (ADAPT-DES) study was conducted with the aim to determine the relationship between platelet reactivity, PAD and subsequent adverse outcomes. In the study population, there was a 10.2% prevalence of PAD among the 8582 patients, all of whom received DESs. Data analysis showed PAD to be an independent predictor of MACE (adjusted HR = 1.34, P = 0.003)[40].

At last, we want to focus on Chronic Kidney Disease (CKD) which is only considered in the PARIS CTE score. As known, CKD is a well-known ischemic risk factor and bleeding risk factor at the same time[41]. Some studies have demonstrated that including CKD in known risk scores, increases the predictive value of the score. A modified CHA2DS2-Vasc score including CKD with a different definition showed a better discriminative capacity than the original score in mortality prediction in an ACS patient population[42].

However, the double association with ischemic and bleeding events in IHD patients is not simple to manage for the clinician and, according to this consideration, we move forward with the analysis of the bleeding risk scores, to put some lights on this risk factor.

Variables of some of the most adopted bleeding scores are summarized in Table 2. Prior bleeding/anemia and CKD are the only variables common to all scores. In particular, baseline anemia was assessed as one of the most important independent predictors of bleeding in PARIS MB and PRECISE-DAPT. As evident, HAS-BLED included some variables that were not statistically significant in the derivation cohort, like age, blood pressure, medication predisposing to bleeding and previous stroke: however, these variables were still included due to their known association with bleeding events derived from previous literature[28]. On the other hand, all scores do not consider some important variables known to be associated with increased bleeding risk because these are not common in patients with IHD or those undergoing PCI (like thrombocytopenia) or because they were rarely recorded in the derivation data. The mentioned differences in risk prediction scores are directly linked to heterogeneity in the populations studied, the variables assessed and the bleeding definitions used in the development cohorts.

Information about the subsequent bleeding risk in patients that undergo PCI with a history of prior bleeding event is scarce. Nonetheless, a prior spontaneous bleed at any time was assessed as an important predictor of bleeding in the PRECISE-DAPT score and, by itself, rises the patient bleeding risk in the highest quartile[30].

Anemia defined by World Health Organization criteria (hemoglobin < 13 g/dL in men and < 12 g/dL in women) is not uncommon in patients undergoing PCI and is directly related with the risk of future bleeding[43]. A meta-analysis of 44 studies including more than 230000 patients undergoing PCI, anemia (defined by World Health Organization criteria in the majority of studies) prevalence was 16% and was associated with a doubled risk of subsequent bleeding [as defined in individual studies; adjusted risk ratio, 2.31 (95%CI: 1.44–3.71)][44]. Furthermore, bleeding risk increased with increasing severity of anemia. In PARIS MB, anemia at baseline (defined as hemoglobin < 12 g/dL in men and < 11 g/dL in women) was assessed as an important predictor of 2-year BARC 3 or BARC 5 bleeding [9.5%

with *vs* 2.7% without anemia; adjusted HR = 2.72 (95%CI: 1.83–4.04); $P < 0.0001$][20]. In PRECISE-DAPT a reduction in the risk of TIMI major/minor bleeding at 1 year was independently associated with every 1 g/dL increase in hemoglobin between 10 and 12 g/dL [adjusted HR = 0.67 (95%CI: 0.53–0.84); $P = 0.001$][31].

Estimated glomerular filtration rate (eGFR) < 30 mL/min, which configures a severe or end-stage CKD, is considered a major ARC-HBR criterion, while eGFR between 30–59 mL/min (moderate CKD) is considered a minor ARC-HBR criterion. Unfortunately, patients with severe CKD have generally been excluded from randomized trials and only approximately 30% of patients undergoing PCI have an eGFR < 60 mL/min[45]. However, it has been demonstrated that the bleeding risk increases incrementally with worsening CKD and even mild CKD is an independent risk factor for bleeding after PCI [46-49]. In the PRECISE-DAPT score, eGFR < 30 mL/min by itself increases patients bleeding risk to the highest quartile, whereas milder CKD is associated with a slight to moderate risk. It must be noticed that in the DAPT score, CKD is not considered as a variable because the associated increased bleeding risk was balanced by an almost identical increased ischemic risk[22].

CONCLUSION

According to our analysis, it becomes clear that a single score can't be the real solution to balance the ischemic/bleeding risk of a patient. Instead, some risk factors that are commonly associated with an elevated risk profile and that are already included in risk scores should be the focus of the clinician while he/she is taking care of a patient affected by IHD. In particular, we found that diabetes mellitus and vascular disease clearly increase the risk of ischemic events, while previous bleeding, anemia and CKD bring a high risk of further bleeding events. Some scores include too many variables that can mislead the clinician choice: since a perfect score could not exist we suggest clinicians apply the most user friendly and at the same time, evaluate the cited variables separately. As suggested by Guidelines, PRECISE-DAPT could be the most suitable bleeding risk score since it is more influenced by CKD, anemia and history of bleeding, while PARIS CTE should be the ischemic risk score of choice, including diabetes mellitus and vascular disease. However, the final result of a clinical reasoning should not be the right score result but the most fitted patient therapy.

ARTICLE HIGHLIGHTS

Research background

Bleedingsare an independent risk factor for subsequent mortality in patients with acute coronary syndromes (ACS) and in those undergoing percutaneous coronary intervention, representing a hazard equivalent to or greater than that for recurrent ACS. Dual antiplatelet therapy (DAPT) represents the cornerstone in the secondary prevention of thrombotic events, but the benefit of such therapy is counteracted by the increased hemorrhagic complications.

Research motivation

An early and individualized patient risk stratification can help to identify high-risk patients who could benefit the most from intensive medical therapies while minimizing unnecessary treatment complications in low-risk patients.

Research objectives

In order to review existing literature and gain better understanding of the role of ischemic and hemorrhagic risk scores in patients with ischemic heart disease (IHD).

Research methods

The authors used a combination of terms potentially used in the literature describing the most common ischemic and hemorrhagic risk scores to search in PubMed, as well as references of full-length articles. The authors briefly describe the most important ischemic and bleeding scores that can be adopted in patients with IHD, focusing on GRACE, CHA2DS2-Vasc, PARIS CTE, DAPT, CRUSADE, ACUITY (Mehran *et al*), HAS-BLED, PARIS MB and PRECISE-DAPT score.

Research results

A single score can't be the real solution to balance the ischemic/bleeding risk of a patient. Instead, some risk factors that are commonly associated with an elevated risk profile and that are already included in risk scores should be the focus of the clinician while he/she is taking care of a patient affected by IHD. In particular, we found that diabetes mellitus and vascular disease clearly increase the risk of ischemic events, while previous bleeding, anemia and CKD bring a high risk of further bleeding events. Some

scores include too many variables that can mislead the clinician's choice: since a perfect score could not exist we suggest the clinician apply the most user friendly and at the same time evaluate the cited variables separately. As suggested by Guidelines, PRECISE-DAPT could be the most suitable bleeding risk score, since it is more influenced by CKD, anemia and history of bleeding, while PARIS CTE should be the ischemic risk score of choice with diabetes mellitus and vascular disease.

Research conclusions

Risk scores by themselves can't be the single solution to balance the ischemic/bleeding risk of an IHD patient. Instead, some risk factors that are commonly associated with an elevated risk profile and that are already included in risk scores should be the focus of the clinician while he/she is taking care of a patient affected by IHD.

Research perspectives

Future research should try to elaborate an omni-comprehensive score to be adopted in IHD and at the same time be easy to use and reliable.

FOOTNOTES

Author contributions: Persampieri S and Castini D participated in the development of the proposal to research the topic, performed literature search and review, and wrote the draft of the manuscript, reviewed, edited and approved the manuscript; Lupi A and Guazzi M participated in the supervision of the research on the topic, reviewed, wrote and revised the manuscript as senior authors.

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