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Vall d'Hebron Risk Score II for myocardial infarction and cardiac death

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ABSTRACT

Objectives The aim of this study was to create a new Vall d'Hebron Risk Score-II (VH-RS-II) for non-fatal myocardial infarction (MI) and/or cardiac death (CD), excluding patients with coronary revascularisation (CR) during the follow-up.

Methods We analysed 5215 consecutive patients underwent gated single photon emission CT (SPECT); 2960 patients (age 64.2±11, male 58.1%) had no previous MI and/or CR, and 2255 patients (age 63.3±11, male 81.9%) had previous MI and/or CR. During a follow-up of 4.3±2.6 years, the cardiac event (MI and CD) was evaluated. This study was reviewed and approved by the ethics committee of our institution (number form trial register, PR(AG)168.2012). To obtain the predictor model, multivariate Cox regression analysis and multivariate logistic regression analysis were used. RS-VH-II was validated with 679 patients.

Results In patients without previous MI and/or CR, age (HR: 1.01; p<0.001), diabetes (HR: 2.1, p=0.001), metabolic equivalent (METs) (HR: 0.89, p=0.038), ST segment depression (HR: 1.4, p=0.011), ejection fraction (EF) (HR: 0.97, p<0.001) and summed stress score (HR: 1.2, p<0.001) were the independent predictors of CE (C-statistic: 0.8). In patients with previous MI and/or CR, age (HR: 1.06, p<0.001), male (HR: 1.9, p=0.047), smoker (HR: 1.5, p=0.047), METs (HR: 0.8, p<0.001), ST segment depression (HR: 1.4, p=0.002), EF (HR: 0.96; p<0.001) and summed difference score (HR: 1.03, p=0.06) were the independent predictors of CE (C-statistic:0.8).

Conclusion The VH-RS-II obtained from different clinical exercise and gated SPECT variables allow the risk stratification for MI and CD in patients with or without previous MI and/or CR in due form.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Coronary artery disease is the most frequent cause of mortality, and risk stratification for cardiac events remains a challenge.

WHAT THIS STUDY ADDS

⇒ This study is interesting, in particular, because the number of evaluated patients is quite high. Furthermore, the Vall d'Hebron Risk Score method has several particular useful features, primarily, it focuses on patients with different clinical variables, who underwent exercise tests, and myocardial perfusion gated single photon emission CT. It also assesses an individual's cardiac risk for non-fatal myocardial infarction and/or cardiac death.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We must pay attention to the use of multiple clinical and non-clinical variables to improve the risk stratification for the coronary event. Always try to integrate imaging tests to improve the prognostic study.
⇒ We have two different groups of patients for coronary risk stratification: patients with previous myocardial infarction and/or coronary revascularisation, and patients without previous coronary artery disease. This affects the type of predictor variables.

INTRODUCTION

There are multiple articles with different scores[1–12] of cardiovascular risk stratification, and for decades coronary risk stratification has been a challenge.[13–15] The Duke treadmill score (DTS) is most widely used.[5 8] DTS is well recognised as a simple prognostic score in patients with suspected coronary artery disease. Furthermore, it is positioned as a valid clinical tool when clinicians need to make a decision about the catheterisation of patients with suspected CAD.[16] However, over the years, different non-invasive imaging techniques have been positioned as the gold standard for coronary risk stratification. Recently, the Vall d'Hebron Risk Score (VH-RS) was published.[7] This score has several particular useful features. First, it focuses on patients with different clinical variables, and also underwent exercise tests, and myocardial perfusion gated SPECT. Furthermore, it assesses an individual's cardiac risk for a combined end point (non-fatal myocardial infarction (MI), cardiac death (CD) and coronary revascularisation (CR)).

In this new analysis of the VH-RS, patients with CR during the follow-up were excluded. The exclusion is due to the possibility that intervening revascularisation either with percutaneous coronary intervention or coronary artery bypass graft in patients with significant ischaemia may have impacted the outcomes of cardiovascular death or MI. Therefore, the aim of this study was to create a new VH-RS (VH-RS-II) for MI and/or CD according to clinical, exercise and gated

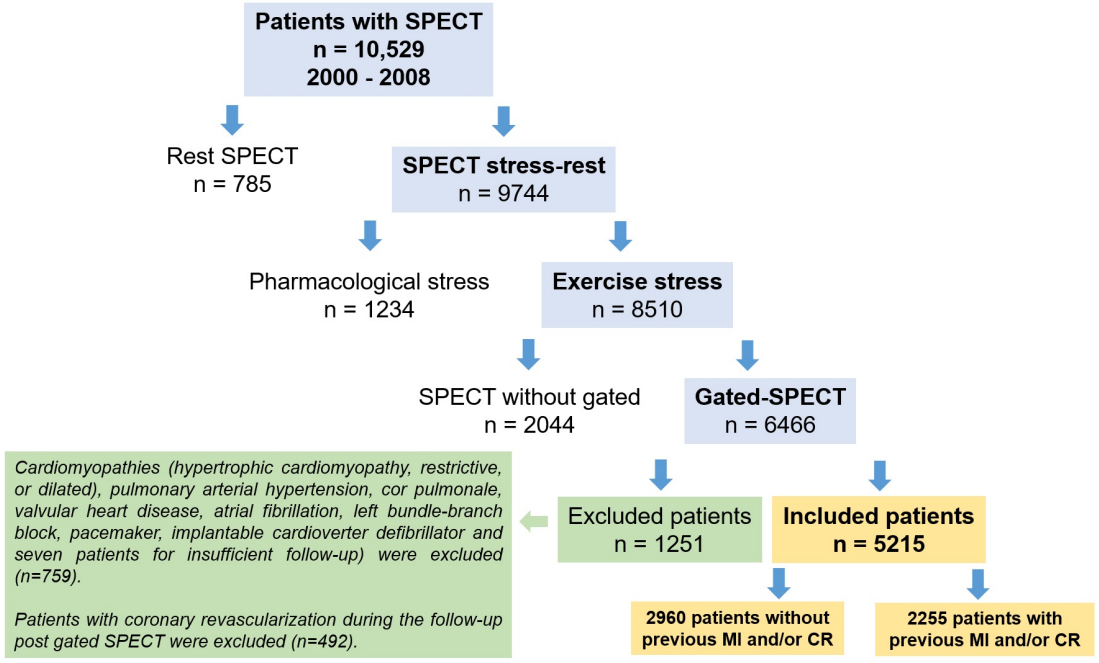

Figure 1 Flow diagram showing the patients included in the study. CR, coronary revascularisation; MI, myocardial infarction; SPECT, single photon emission CT.

single photon emission CT (SPECT) variables, excluding patients revascularised during follow-up.

MATERIALS AND METHODS

Patients

This was a prospective study. The cohort consisted of 5215 consecutive patients who underwent gated SPECT (period 2000–2008) (figure 1). This population is superposed with the previous one.[7] All patients had been referred to our Nuclear Cardiology Unit for risk stratification or evaluation of their disease. This study conformed to the Declaration of Helsinki and was reviewed and approved by the ethics committee of our institution (number form trial register, PR(AG)168.2012). All patients provided written informed consent for stress-rest myocardial perfusion SPECT.

Exercise stress test

All patients underwent standard symptom-limited cycle ergometer (50%) or treadmill testing (50%) using standard protocols with a 12-lead recording and continuous monitoring. Bruce protocol or modified Bruce protocol were used until exhaustion, appearance of symptoms, ST segment depression >2 mm, the appearance of arrhythmias, hypertensive response to physical stress (systolic blood pressure >200 mm Hg or diastolic blood pressure >100 mm Hg) or failure of systemic blood pressure to increase. Angina, peak oxygen consumption estimated in metabolic equivalent (METs) and horizontal and downsloping ST depression ≥1 mm at 0.08 s beyond the J point were analysed.

Myocardial perfusion-gated SPECT

All patients underwent exercise-rest-gated SPECT. As regard the stress-rest studies, a 1-day protocol with ^{99m}Tc-tetrofosmine was performed. The first dose (30–60 s before ending the stress test) was of 8 mCi and the second (at rest) was of 24 mCi, with an interval longer than 45 min in between. The methodology employed for gated SPECT was the same methodology employed in previous publications.[17 18]

Clinical outcomes

The minimum follow-up time was 1 year (maximum 11.4 years), and the mean follow-up was 4.1±2.7 years (median 3.8 years, 25th–75th percentile: 1.6–6.2). All patients were followed up in the hospital, and the follow-up information was obtained by clinical history. There were no missing patients during the follow-up. All patients were followed up for cardiac events (CE). The primary endpoint was the first occurrence of a composite of non-fatal MI (myocardial infarction) and CD.

Statistical analysis

All continuous data were expressed as means (SD) and all non-continuous variables were expressed as percentages. Quantitative variables were compared using the Student's t-test for unpaired samples. Differences between proportions were compared using the χ^2 test. Fisher's exact test was used when <5 patients were expected in any subgroup. The optimal cut-off value for the significant continuous variables related to the CE was determined by analysing the receiver operating characteristic (ROC) curves.

To create the VH-RS-II, we used the same methodology as in VH-RS (**7**). We stratified patients into four risk levels

according to CE/year: very low risk (VLR; <0.7 CE/year), low risk (LR; between 0.7 and 1 CE/year), moderate risk (MR; >1 and <3 CE/year) and high risk (≥3 CE/year) (**7**).

Different Cox regression analyses (FSTEP (LR; forward stepwise, likelihood ratio); the threshold for variable entry into models was p<0.05; and for variable removal, p>0.10) were used to assess the independent predictor variables for CE. There was no evidence of violation of this assumption for any covariate. HR, 95% CIs and statistical significance for each group in the models were determined. Variables were selected for multivariate analysis when they presented significant differences in the univariate analysis or when they were considered of clinical relevance. All statistical tests were two sided. A value of p<0.05 was considered to be indicative of statistical significance. Data were analysed by STATA 18.

RESULTS

Of 5215 patients studied, 2960 (age 64.2±11.2, male 58.1%) had no previous MI or CR, and 2255 (age 63.2±11, male 81.9%) had previous MI (n=1726, 76.5%) or CR (n=1136, 50.4%). The baseline characteristics of the patients with and without previous MI or CR are shown in table 1A and table 1B, respectively. Compared with patients without CE, the patients with CE had significantly higher left ventricular volumes, summed rest score (SRS), summed stress score (SSS), summed difference score (SDS), ↓ ST mm, lower left ventricular ejection fraction (LVEF) and METs, and more male, diabetes, hyperlipidaemia, smoker and medical treatment (beta-blockers, nitrates). During the follow-up, postgated SPECT (adjusted by age, gender, hypertension, hypercholesterolemia, diabetes and smoker), the patients with previous MI or CR had more CE (2.7% vs 5.9%) (Wald: 12 149; HR: 1.8 (95% CI 1.3 to 2.3); p<0.001) than patients without previous MI or CR. In the group of patients with previous MI or CR (n=2255), 1726 (76.5%) had previous MI, 36 (2.1%) of them had a second MI during the follow-up post-gated SPECT; 529 patients did not have previous MI and 3 (0.6%) of them had the first MI during the follow-up post-gated SPECT (McNemar test, p<0.001).

In the group of patients without previous myocardial infarction and/or CR 356 (12%) patients had myocardial ischaemia, in 274 of them the ischaemia was mild (SDS between 3 and 4), moderate (SDS between 5 and 7) in 92 and severe (SDS ≥8) in 27 patients.

In the group of patients with previous myocardial infarction and/or CR, 391 (17%) patients had myocardial ischaemia, in 268 of them, the ischaemia was mild (SDS between 3 and 4), moderate (SDS between 5 and 7) in 103 and severe (SDS ≥8) in 20 patients.

Patients with myocardial mild ischaemia in both groups continued with medical treatment and coronary angiography was not performed. Also all patients with moderate and severe ischaemia continued with medical treatment, although half of them were studied with invasive coronary angiography or coronary CT. These patients did not undergo CR following medical decision or patient-medical consensus and coronary anatomy. In the rest of the patients, a study of the coronary anatomy was not carried out due to advanced coronary disease with multiple coronary angiographies, medical decision or by patient medical consensus, advanced age, advanced renal failure and stroke.

Predictors of CEs in patients without previous myocardial infarction and/or coronary revascularisation

In a first multivariate model, clinical variables (age, gender, diabetes mellitus, angina, hyperlipidaemia, smoker, rest blood pressure, beta-blockers, nitrates) were included. Age (Wald: 32,069; HR: 1.1 (95% CI 1.05 to 1.2), p<0.001), diabetes (Wald: 10 980; HR: 2.2 (95% CI 1.4 to 3.4), p=0.001), angina (Wald: 3,749; HR: 1.8 (95% CI 0.9 to 3.1), p=0.053) and nitrates (Wald: 4439; HR: 1.6 (95% CI 1.03 to 2.5), p=0.035) were the independent predictors of CE. In a second multivariate model stress variables (METs, exercise angina and ST segment depression) were considered. METs (Wald: 23 500; HR: 0.8 (95% CI 0.7 to 0.88), p<0.001) and 'mm' of ST segment depression (Wald: 23 738; HR: 1.7 (95% CI 1.4 to 2.1), p<0.001) were the independent predictor of CE. In a third multivariate model gated SPECT variables (left ventricular volumes, EF, SRS, SSS and SDS) were considered. SSS (Wald: 34,631; HR: 1.2 (95% CI 1.1 to 1.3), p<0.001) and the EF (Wald: 10 892; HR: 0.97 (95% CI 0.96 to 0.99), p=0.001) were the independent predictor of CE. In the final model, and for clinical consensus, the significant variables in previous models were included age, gender, diabetes, angina, nitrates, METs, 'mm' of ST segment depression, SSS and EF were included. Age (Wald: 24 573; HR: 1.01 (95% CI 104 to 1.1); p<0.001), diabetes (Wald: 10 104; HR: 2.1 (95% CI 1.3 to 3.4), p=0.001); METs (Wald: 4300; HR: 0.89 (95% CI 0.79 to 0.99), p=0.038); 'mm' of ST segment depression (Wald: 6512; HR: 1.4 (95% CI 1.1 to 1.8), p=0.011), EF (Wald: 16 549; HR: 0.97 (95% CI 0.95 to 0.98), p<0.001) and SSS (Wald: 19 380; HR: 1.2 (95% CI 1.1 to 1.2), p<0.001) were the independent predictors of CE. The final model with the HR of the optimal cut-off value for the significant qualitative variables related to the CE is shown in table 2A, and the final model with ß-coefficients for calculating the probability of CE by means of logistic regression analysis is shown in table 2B. ROC curve analysis was performed to evaluate the ability of this model to predict CE (C-statistic: 0.81 (95% CI 0.75 to 0.85); p<0.001) (figure 2A). When increasing the number of the independent predictors, the prevalence of CE increases too (figure 3A). All patients were stratified in four risk levels: VLR (n=1888), LR (n=611), MR (n=250), HR (n=211). The correlation between the levels of VHRS and number of risk variables, annual CE and relative risk is shown in figure 4A.

Predictors of CEs in patients with previous myocardial infarction and/or coronary revascularisation

In a first multivariate, model clinical variables (age, gender, diabetes mellitus, hyperlipidaemia, smoker, hypertension, nitrates and beta-blockers) were included. Age (Wald: 46 417; HR: 1.07 (95% CI 1.05 to 1.1), p<0.001), male (Wald: 4549; HR: 1.9 (95% CI 1.05 to

Table 1 (A) Characteristics of patients without previous myocardial infarction and/or coronary revascularisation according to cardiac events and (B) characteristics of patients with previous myocardial infarction and/or coronary revascularisation according to cardiac events

(A)			
Variables	**Without CE n=2880**	**With CE n=80**	**P value**
Age (years)	64.1±11.2	70.3±9.5	<0.001
Age>66 (%)	1396 (48.5)	63 (78.8)	<0.001
Male (%)	1669 (58)	51 (63.8)	0.3
Weight (Kg)	74.4±13	72.8±11.8	0.306
Height (cm)	164.3±11.7	162.8±8.6	0.283
Body mass index*	28.2±4	27.5±4	0.687
Obesity (%)†	603 (20.9)	18 (22.5)	0.735
Diabetes (%)	491 (17)	30 (37.5)	<0.001
Hypertension (%)	1699 (59)	51 (63.8)	0.393
Hyperlipidaemia (%)	1396 (48.5)	40 (50)	0.787
Smoker (%)	1144 (39.7)	35 (43.8)	0.468
Angina prior gated SPECT	301 (10.5)	14 (17.5)	0.044
Rest heart rate (bpm)	72.4±14	72.1±15	0.89
Rest systolic blood pressure (mm Hg)	129.7±34	139.4±36.2	0.012
Medical treatment (%)			
Beta-blockers (%)	770 (26.7)	20 (25)	0.729
Nitrates (%)	683 (23.7)	34 (42.5)	<0.001
Calcium channel blockers (%)	504 (17.5)	24 (30)	0.004
Stress test			
METs	6.1±3.1	5.1±1.9	<0.001
METs≤6.08 (%)	1483 (51.5)	62 (77.5)	<0.001
Exercise test angina	379 (13.2)	11 (13.8)	0.878
↓ ST mm	0.3±0.3	0.6±0.4	<0.001
↓ ST mm≥1 (%)	463 (16.1)	29 (36.2)	<0.001
SPECT stress rest			
Summed rest score	5.8±1.7	7.1±2.6	<0.001
Summed rest score>6 (%)	512 (17.8)	39 (48.8)	<0.001
Summed stress score	6.6±2.4	9.1±3.5	<0.001
Summed stress score>6 (%)	1088 (37.8)	60 (75)	<0.001
Summed difference score	0.9±1.5	2.2±2.5	<0.001
Summed difference score≥2 (%)	332 (11.5)	24 (30)	<0.001
Gated			
Left ventricular ejection fraction (%)	61.6±15.4	54.4±15.5	<0.001
Left ventricular ejection fraction≤57% (%)	973 (33.8)	50 (62.5)	<0.001
End-systolic volume (mL)	37.4±34.3	51.5±42	0.02
End-systolic volume>36 mL (%)	1005 (34.9)	48 (60)	<0.001
End-diastolic volume (mL)	85.1±41.9	99.4±48	0.042
End-diastolic volume>77 mL (%)	1387 (48.2)	51 (63.8)	0.006

(B)			
Variable	**Without CE n=2123**	**With CE n=132**	**P value**
Age (years)	62.9±11	68.9±9.4	<0.001
Age>67.8 (%)	796 (37.5)	80 (60.6)	<0.001

Continued

Table 1 Continued

(B)			
Variable	Without CE n=2123	With CE n=132	P value
Male (%)	1728 (81.4)	118 (89.4)	0.021
Weight (Kg)	75.2±13	73.7±14.3	0.199
Height (cm)	164.6±10	165±7.9	0.64
Body mass index*	28.5±17.7	27±4.6	0.363
Obesity (%)†	492 (23.2)	21 (15.9)	0.053
Diabetes (%)	424 (20)	46 (34.8)	<0.001
Hypertension (%)	1156 (54.5)	80 (60.6)	0.168
Hyperlipidaemia (%)	1331 (62.7)	78 (59.1)	0.407
Smoker (%)	1246 (58.7)	87 (65.9)	0.102
Angina prior gated SPECT	265 (12.5)	15 (11.4)	0.705
Rest heart rate (bpm)	66.7±13	74.6±20	0.22
Rest systolic blood pressure (mm Hg)	125.8±28	125.9±29	0.943
Medical treatment (%)			
Beta-blockers (%)	1287 (60.6)	73 (55.3)	0.226
Nitrates (%)	742 (35)	69 (52.3)	<0.001
Calcium channel blockers (%)	384 (18.1)	25 (18.9)	0.805
Stress test			
METs	6.5±2.6	5.2±1.8	<0.001
METs≤5.6 (%)	731 (34.4)	84 (63.6)	<0.001
Angina during stress test	316 (14.9)	20 (15.2)	0.933
↓ ST mm	0.3±0.7	0.55±0.4	0.009
↓ ST mm≥1 (%)	431 (20.3)	38 (28.8)	0.02
SPECT stress-rest			
Summed rest score	8.1±3.1	9.8±3.4	<0.001
Summed rest score>8 (%)	764 (36)	78 (59.1)	<0.001
Summed stress score	9.3±3.4	11.3±3.4	<0.001
Summed stress score>8 (%)	1105 (52)	101 (76.5)	<0.001
Summed difference score	1.25±1.2	1.6±1	0.045
Summed difference score≥2 (%)	296 (13.9)	23 (17.4)	0.265
Gated			
Left ventricular ejection fraction (%)	55.1±14	44.7±14.6	<0.001
Left ventricular ejection fraction≤48 (%)	623 (29.3)	79 (59.8)	<0.001
End-systolic volume (mL)	50.7±40	80.3±40	<0.001
End-systolic volume>46 mL (%)	830 (39.1)	90 (68.2)	<0.001
End-diastolic volume (mL)	101.9±49	133.1±60.8	<0.001
End-diastolic volume>98 mL (%)	895 (42.2)	91 (68.9)	< 0.001

*Quetelet Index: weight (kg)/height (m^2).
†Obesity was defined as a body mass index ≥ 30 kg/m^2.
CE, cardiac events; MET, metabolic equivalent; SPECT, single photon emission CT.

3.5), p=0.033), diabetes (Wald: 5216; HR: 1.5 (95% CI 1.1 to 2.1), p=0.022), smoker (Wald: 5699; HR: 1.6 (95% CI 1.1 to 2.4), p=0.017) and nitrates (Wald: 5620; HR: 1.5 (95% CI 1.1 to 2.2), p=0.018) were the independent predictors of CE. In a second multivariate model, stress variables (METs, exercise angina and ST segment depression) were considered. METs (Wald: 23 500; HR: 0.7 (95% CI 0.67 to 0.8), p<0.001) and 'mm' of ST segment depression (Wald: 13 351; HR: 1.4 (95% CI 1.2 to 1.7), p<0.001) were the independent predictors of CE. When gated SPECT variables were considered (left ventricular volumes, EF, SRS, SSS and SDS) the EF (Wald: 70,618; HR: 0.95 (95% CI 0.94 to 0.96), p<0.001), and SDS (Wald: 3844; HR: 1.08 (95% CI 1 to 1.2), p=0.05) were

Table 2 (A) Multivariate Cox regression analysis results in patients without and with previous myocardial infarction and/or coronary revascularisation and (B) multivariate logistic regression analysis model for calculated probability of hard events in patients without and with previous myocardial infarction or coronary revascularisation

Without previous myocardial infarction and/or coronary revascularisation					
Variables	**Wald**	**HR**	**95% CI**		**P value**
Age>66 years*	20 854	3.6	2.1	6.3	<0.001
Diabetes	7475	1.9	1.2	3.1	0.006
METs≤6.08*	7893	2.2	1.2	3.5	0.005
↓ ST≥1 mm*	5813	1,8	1.13	2.9	0.016
LVEF≤57*	28 902	3.7	2.5	6.7	<0.001
SSS>6*	14 770	2.9	1.9	5.6	<0.001
With previous myocardial infarction and/or coronary revascularisation					
Age>67.8 years*	20 588	2.3	1.6	3.4	<0.001
Male	6456	2.2	1.1	3.9	0.011
Smoker	2115	1.3	0.9	1.9	0.146
METs≤5.6*	31 001	2.9	1.9	4.1	<0.001
↓ ST≥1 mm*	2186	1.3	0.9	1.9	0.139
LVEF≤48*	43 822	3.3	2.3	4.6	<0.001
SDS>2*	1202	1.3	0.8	1.9	0.273

(B)			
Without previous myocardial infarction or coronary revascularisation†			
Model	**ß-coefficient**	**SE**	**Wald**
Age	0.060261	0.015	16 584
Diabetes	1.029161	0.249	17 131
METs	0.032996	0.051	0.441
↓ ST mm	0.436628	0.132	10 859
LVEF	0.016993	0.008	4919
SSS	0.197207	0.035	31 985
Constant	8.470211	1.298	42 853
With previous myocardial infarction or coronary revascularisation‡			
Age	0.047983	0.010	21 053
Male	0.699643	0.323	4684
Smoker	0.435163	0.211	4241
METs	0.175602	0.044	16 110
↓ ST mm	0.357188	0.107	11 050
LVEF	0.046193	0.006	52 663
SDS	0.046383	0.050	0.845
Constant	3.700713	0.919	16 212

Diabetes, 0 = no and 1 = yes; male, 0 = women and 1 = men; smoker, 0 = no and 1 = yes.
*The cut-off value of these quantitative variables (age, LVEF, SSS, SDS, METs, and mm ST depression) was calculated by means of ROC analysis.
†Cox-Snell r^2: 0.037; Nagelkerke r^2: 0.168; Hosmer and Lemeshow Test: χ^2: 2,705; p = 0.168.
‡Cox-Snell r^2: 0.059; Nagelkerke r^2: 0.165; Hosmer and Lemeshow Test: χ^2: 2,150; p = 0.976.
LVEF, left ventricular ejection fraction; ROC, receiver operating characteristic; SDS, summed difference score; SSS, summed stress score.

the independent predictors of CE. In the final model, and for clinical consensus, the significant variables in previous models were included age, male, diabetes, smoker, nitrates, METs, 'mm' of ST segment depression, EF and SDS. Age (Wald: 28 825; HR: 1.06 (95% CI 1.03 to 1.08), p<0.001); male (Wald: 3935; HR: 1.9 (95% CI 1.01 to 3.4), p=0.047); smoker (Wald: 3947; HR: 1.5 (95% CI 1.1 to 2.2), p=0.047); METs (Wald: 22 687; HR: 0.8 (95% CI 0.72 to 0.87), p<0.001); 'mm' of ST segment depression (Wald: 9825; HR: 1.4 (95% CI 1.1 to 1.7),

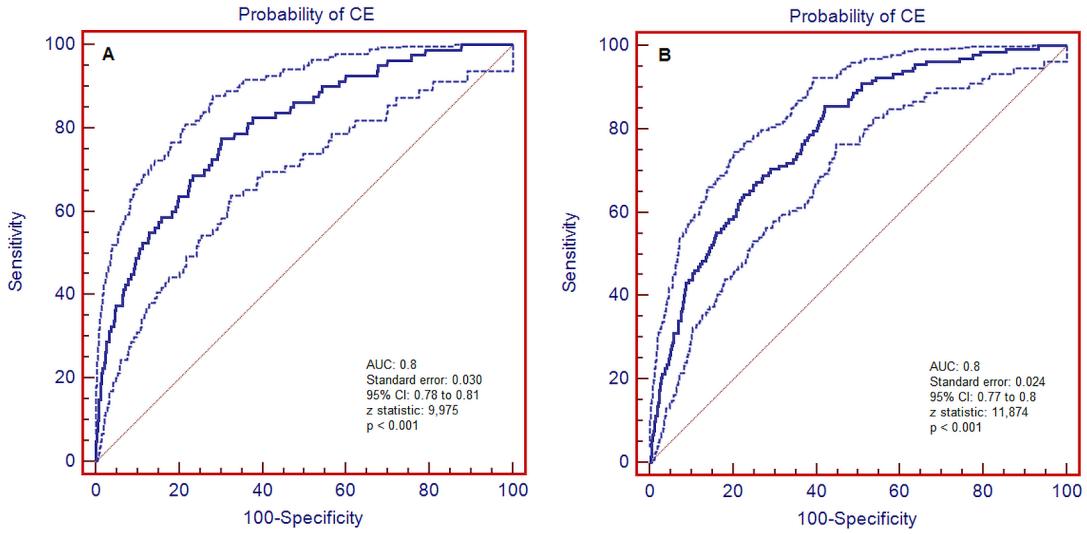

Figure 2 ROC curve analysis to evaluate the ability of the final model to predict cardiac events (CE) in patients without (A) and with (B) previous myocardial infarction and/or coronary revascularisation show an acceptable predictive value (AUC, area under curve: 0.8). ROC, receiver operating characteristic.

p=0.002); EF (Wald: 56 578; HR: 0.96 (95% CI 0.95 to 0.97); p<0.001) and SDS (Wald: 0.322; HR: 1.03 (95% CI 0.9 to 1.2), p=0.06) were the independent predictors of CE. The final model with the HR of the optimal cut-off value for the significant qualitative variables related to the CE is shown in table 2A, and the final model with ß coefficients for calculated the probability of CE by means of logistic regression analysis is shown in table 2B. ROC curve analysis was performed to evaluate the ability of this model to predict CE (C-statistic: 0.81 (95% CI 0.75 to 0.82)) (figure 2B). When increasing the number of independent predictors, the prevalence of CE increases too (figure 3B). All patients were stratified in four risk levels: VLR (n=299), LR (n=1145), MR (n=616) and HR (n=195). The correlation between the levels of VH-RS and number of risk variables, annual CE and relative risk is shown in figure 4A.

Validation group

To validate the VH-RS-II in patients with and without previous MI and/or CR, the following formula was used: $\text{probability}_{\text{risk at 4 years}} = 1 / 1 + \exp^{-(\text{prognostic index})}$.

For patients without previous MI and/or CR, the prognostic index was −8.470211 + (age at clinical evaluation x 0.060261) + (diabetes x 1.029161) − (METs x 0.032996) + (ST depression x 0.436628) − (EF x 0.016993) + (SSS x 0.197207).

For patients with previous MI and/or CR, the prognostic index was −3.700713 + (age at clinical evaluation x 0.047983) + (male x 0.699643) + (smoker x 0.435163)

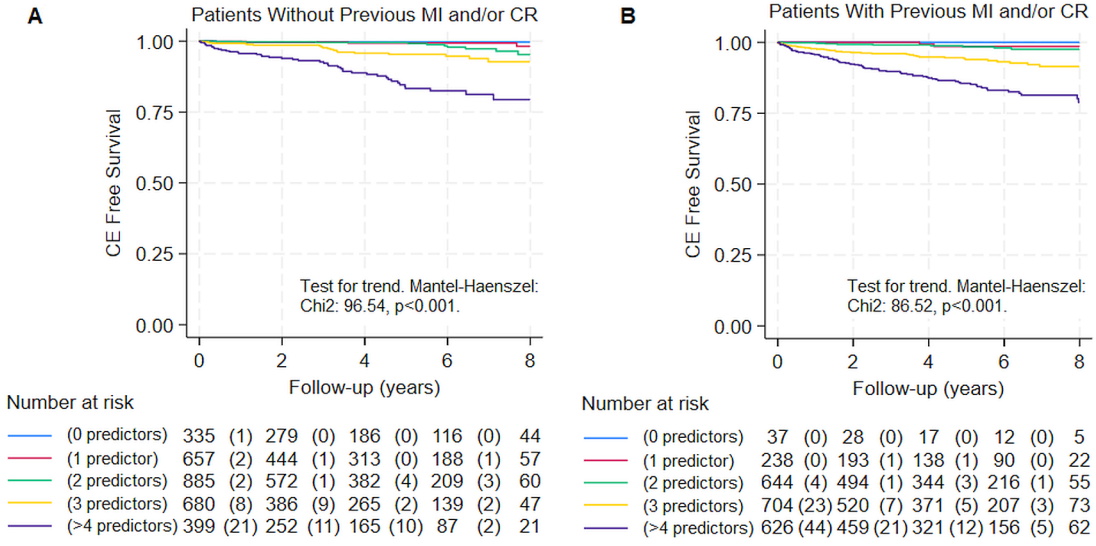

Figure 3 Kaplan-Meier curve for number of predictive variables. (A) Patients without previous myocardial infarction (MI) and/or coronary revascularisation (CR) (for a one-unit increase in number of variables the rate ratio to CE increases 2.5 (95% CI: 2 to 2.9, p<0.001); and (B) patients with previous MI and/or CR (for a one-unit increase in number of variables the rate ratio to CE increases 2.1 (95% CI: 1.8 to 2.5, p<0.001). CE, cardiac events.

A

(i) Levels of VH-RS in patients without previous myocardial infarction or coronary revascularization

Very Low Risk: R < 2; Low Risk: R ≥ 2 < 4; Moderate Risk: R ≥ 4 < 7; High Risk: R ≥ 7.

Levels of VH-RS		Number of Risk Variables 0	1	2	3	≥4	Total	CE/year	RR, Mean (95% CI)
Very Low Risk	N	335	640	700	200	13	1888	0.22	0.8 (0.79-0.83)
	%	100,0%	97,4%	79,0%	29,3%	3,2%	63,8%		
Low Risk	N	0	13	166	335	97	611	0.99	2.58 (2.54-2.6)
	%	0,0%	2,0%	18,7%	49,1%	24,2%	20,6%		
Moderate Risk	N	0	4	13	108	125	250	1.8	4.8 (4.7-4.9)
	%	0,0%	0,6%	1,5%	15,8%	31,2%	8,4%		
High Risk	N	0	0	7	39	165	211	4.0	13.2 (12.2-14.2)
	%	0,0%	0,0%	0,8%	5,7%	41,2%	7,1%		
Total	N	335	657	886	682	400	2960		

Risk Variables:

Age > 66 years
Diabetes
METS ≤ 6.08
↓ ST ≥ 1 mm
EF ≤ 57%
SSS > 6

(ii) Levels of VH-RS in patients with previous myocardial infarction or coronary revascularization

Very Low Risk, R ≤ 1; Low Risk > 1 < 5; Moderate Risk, ≥ 5 < 13; High Risk, ≥ 13.

Levels of VH-RS		Number of Risk Variables 0	1	2	3	≥4	Total	CE/year	RR, Mean (95% CI)
Very Low Risk	N	30	122	114	30	3	299	0.08	0.3 (0.28 to 0.31)
	%	81,1%	51,3%	17,6%	4,3%	0,5%	13,3%		
Low Risk	N	7	116	494	407	121	1145	0.7	1.27 (1.24 to 1.3)
	%	18,9%	48,7%	76,5%	57,8%	19,2%	50,8%		
Moderate Risk	N	0	0	37	246	333	616	1.9	3.7 (3.6 to 3.8)
	%	0,0%	0,0%	5,7%	34,9%	52,9%	27,3%		
High Risk	N	0	0	1	21	173	195	7.6	8.8 (8.5 to 9.1)
	%	0,0%	0,0%	0,2%	3,0%	27,5%	8,6%		
Total	N	37	238	646	704	630	2255		

Risk Variables:

Age > 67.8 years
Male
Smoker
METs ≤ 5.6
↓ ST ≥ 1 mm
EF ≤ 48%
SDS > 2

B

(i) Validation VH-RS for patients without previous myocardial infarction or coronary revascularization

Very Low Risk, R < 2; Low Risk, R ≥ 2 < 4; Moderate Risk, R ≥ 4 < 7; High Risk, R ≥ 7.

Levels of VH-RS		Number of Risk Variables 0	1	2	3	≥4	Total	CE/year	RR, Mean (95% CI)
Very Low Risk	N	69	117	111	30	1	328	0.02	0.2 (0.22 to 0.27)
	%	100,0%	98,3%	92,5%	63,8%	5,9%	88,2%		
Low Risk	N	0	2	7	12	3	24	0.8	1.26 (1.2 to 1.4)
	%	0,0%	1,7%	5,8%	25,5%	17,6%	6,5%		
Moderate and High Risk	N	0	0	2	5	13	20	1.8	9.9 (4.8 to 15)
	%	0,0%	0,0%	1.7%	10.6%	76%	5.4%		
Total	N	69	119	120	47	17	372		

(ii) Validation VH-RS for patients with previous myocardial infarction or coronary revascularization

Very Low Risk, R ≤ 1; Low Risk > 1 < 5; Moderate Risk, ≥ 5 < 13; High Risk, ≥ 13.

Levels of VH-RS		Number of Risk Variables 0	1	2	3	≥4	Total	CE/year	RR, Mean (95% CI)
Very Low Risk	N	5	18	13	7	1	44	0	0.3 (0.28 to 0.35)
	%	83,3%	60,0%	24,5%	5,8%	1,0%	14,3%		
Low Risk	N	1	12	38	70	24	145	0.8	1.4 (1.27 to 1.44)
	%	16,7%	40,0%	71,7%	57,9%	24,7%	47,2%		
Moderate and High Risk	N	0	0	2	44	72	118	1.3	3.2 (2.7 to 3.7)
	%	0,0%	0,0%	3,8%	32,2%	43,3%	27,0%		
Total	N	6	30	53	121	97	307		

CE, cardiac events; CI, confidence interval; RR, relative risk; VH-RS, Vall d'Hebron Risk Score.

Figure 4 Relationship between the levels of Vall d'Hebron Risk Score-II (VH-RS-II), number of risk variables and CE/year. (A) During the follow-up (mean 3.8±2.3 years) of (i) patients without previous MI and/or CR (n=2960), the annual CE (n=80, 2.7%) was 0.72 %/year. In (ii) patients with previous MI and/or CR (n=2255), the annual CE (n=132, 5.9) was 1.4 %/year. (B) Validation group (n=679). During the follow-up (mean 5.4±0.4 years) of (i) patients without previous MI and/or CR (n=372), the annual CE (n=6, 1.6%) was 0.03 %/year. During the follow-up (mean 2.6±1 years) of (ii) patients with previous MI and/or CR (n=307), the annual CE (n=7, 2.3%) was 1 %/year. CE, cardiac events; CR, coronary revascularisation; MI, myocardial infarction; SSS, summed stress score.

– (METs x 0.175602) + (mm ST depression x 0.357188) – (EF x 0.046193) + (SDS x 0.046383).

RS-VH-II was validated with 679 patients; 372 patients (age 67.2±13, male 55.1%, follow-up 5.5±1.1 years) had no previous MI and/or CR and 307 patients (age 63.5±11, male 85.3%, follow-up 3±0.5 years) had previous MI. All patients without previous MI and/or CR, and without risk variables had VLR (figure 4B). Only 14.3% of patients with previous MI and/or CR before gated SPECT had VLR (figure 4B).

DISCUSSION

This new VH-RS-II has a good accuracy for risk stratification according to MI and/or CD. This VH-RS-II has the same study methodology as the VH-RS published previously (**7**). The score is based on a large cohort of participants (n=5215, follow-up mean 4.3 years) from a tertiary hospital, with suspected coronary disease who were referred for exercise testing with a mean follow-up of 4 years, and without CR during the follow-up. For patients without previous MI and/or CR, this score included six variables (age, diabetes, METs ≤6.08, ↓ST ≥1 mm, LVEF ≤57 and SSS >6), and for patients with previous MI and/or CR, the score included seven variables (age, males, smoker, METs ≤5.6, ↓ST ≥1 mm, LVEF ≤48 and SDS >2) to quantify an adult's risk of CE.

Our scores (VH-RS and VH-RS-II) include, in addition to clinical and exercise test variables, the gated SPECT variables, because they had incremental prognostic value over clinical and exercise test variables in predicting CE both in patients without or with previous MI and/or CR. Furthermore, the higher sensitivity and specificity of stress myocardial perfusion over that of the exercise test may reduce the unnecessary invasive coronary angiography.[16 19 20] For patients without previous MI and/or CR, the gated SPECT variables were LVEF and SSS. As for patients with previous MI and/or CR, the gated SPECT variables were LVEF and SDS. The patients with previous MI and/or CR had more perfusion alterations than patients without MI and/or CR. Therefore, the SDS was the predictor variable in contrast with patients without previous MI and/or CR. This finding is in agreement with previous VH-RS study, which include patients with CR during the follow-up postgated SPECT.

In this new analysis of VH-RS-II, there are some differences from VH-RS: the VH-RS study includes patients with CR during the follow-up post-gSPECT, and the CE was non-fatal MI+CD+CR. The new VH-RS-II study did not include patients with CR during the follow-up post-gSPECT, and the CE was: non-fatal MI and CD.

Moreover, in VH-RS, the predictor variables for patients with suspected CAD were 9: age >67 years, male, hyperlipidaemia, nitrates, LVEF≤57%, SSS>6, METs≤6.2, exercise angina, and ST segment depression. While in the VH-RS-II the predictor variables for patients without previous MI and/or CR were less (six variables): age>66, diabetes, METs≤6.08, ST segment depression, LVEF≤57%, SSS>6. The gender, hyperlipidaemia and nitrates variables in VH-RS were replaced by diabetes in VH-RS-II.

On the other hand, in VH-RS, the predictor variables for patients with established CAD were eight: age >67 years, smoker, nitrates, LVEF ≤53%, SDS ≥2, METs ≤6.4, exercise angina and ST segment depression, whereas, in VH-RS-II, the predictor variables for patients with previous MI and/or CR were seven: age >67 years, male, smoker, METs ≤5.6, ST segment depression, LVEF ≤48, S DS≥2. The nitrates and exercise angina variables are not significant in the multivariate analysis and gender appears as a predictor variable.

Despite these differences, both scores are powerful for stratifying cardiac risk (VH-RS: AUC 0.8, VH-RS-II: AUC 0.8). When we stratify the risk, differences between these different end points (VH-RS, VH-RS-II) are important since the strong events are the non-fatal MI and CD. The CR is a therapeutic procedure that may have impacted the outcomes of cardiovascular death or non-fatal MI.

Recently in a new series of 673 patients with previous MI and/or CR with LVEF ≤40% (ischaemic cardiomyopathy) who underwent gated SPECT, VH-RS for risk stratification was used.[21] These patients were stratified into five-risk levels: VLR, LR, MR, HR and very HR (> 6%/year) for MACEs (MI, CD, CR and heart failure hospitalisation). In addition, the cardiac resynchronisation therapy and the implantable cardioverter defibrillator were investigated. There were no patients with ischaemic cardiomyopathy in VLR and LR. Most patients with MACEs were in very HR level, and the haemoglobin and estimated glomerular filtration rate values do not properly improve the risk stratification obtained by the VH-RS. VH-RS was effective in evaluating risk of patients with stable ischaemic cardiomyopathy (AUC: 0.82, p<0.001).[21]

In VH-RS-II, the risk of each patient was analysed and then grouped into four risk levels: VLR (≤0.4%/year); LR (0.5 to <1%/year); MR (≥1 to <3%/year) and HR (≥3%/year) with a mean 4-year follow-up. The majority of patients without previous MI and/or CR had VLR (63.8%). Patients, with or without previous MI and/or CR, without predictor variables, corresponded to VLR level; and the majority of patients with MR to HR risk level had two or more prognostic variables (figure 4). In patients with previous MI and/or CR, the prevalence of patients with VLR was low (13.3%); and the percentage of patients with MR to HR levels was higher (35.9%) than in group of patients without previous MI and/or CR (15.5%) (figure 4). This is because these patients had already had these events before gated SPECT.

As we can see, in the coronary risk stratification of patients with or without previous coronary artery disease, it is necessary to include different clinical variables associated with a non-invasive imaging test. This study shows the risk stratification from a nuclear cardiology Unit, although the same variables could be obtained by other imaging modalities.

It is indeed true that coronary CT with analysis of atheromatous plaque has a very important prognostic and

diagnostic value, especially in non-revascularised patients. However, having plate/atherosclerotic burden information does not mean that it is better than information on myocardial ischemia. Both complement each other. On the other hand, in our study, we do not have coronary CT in all patients, hence, opting out of analysing it. Furthermore, It should be noted that the VH-RS includes in the model different clinical variables that as a whole have a good prognostic capacity (C-statistic: 0.8), and this could improve or complement the information of the coronary CT.

In the future, we will study whether the effect of left ventricular synchrony, remodelling, coronary CT and the study of myocardial flow influence the risk stratification obtained by the VH-RS and VH-RS-II.

Limitations

First, this analysis was conducted in a single tertiary teaching hospital. Therefore, indiscriminate extrapolation of the findings should be used with caution; although this study presents a high number of enrolled patients who have been followed up for a long period of time. On the other hand, in the group of patients for external validation, the number of CEs is low. Despite this, all CEs were correctly detected and classified.

CONCLUSIONS

The VH-RS-II obtained from different clinical exercise and gated SPECT variables allow the risk stratification for MI and CD in patients with or without previous MI and/or CR in due form.

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