Clinical Investigation

Comparison of 3 Predictive Clinical Risk Scores

in 603 Patients with Stable Coronary Artery Disease

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No clinical risk score is universally accepted for coronary artery disease. In 603 patients (mean age, 61.2 ± 12.3 yr) with stable coronary artery disease, we investigated the predictive power of clinical risk scores derived from the Framingham, the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), and the Vienna and Ludwigshafen Coronary Artery Disease (VILCAD) studies. Secondary outcomes were the recurrence of an acute thrombotic event (coronary events, strokes, or transient ischemic attacks), or heart failure or death. The primary outcome was the combination of secondary outcomes.

During follow-up (duration, 2.08 ± 0.97 yr), 42 patients had an acute thrombotic event; 22, heart failure or death; and 60, the primary outcome.

The Framingham score predicted acute thrombotic events: hazard ratio (HR)=1.05; 95% confidence interval (CI), 1.01–1.08; P*=0.03; net reclassification index (NRI, calculated to evaluate improvement in prediction gained by adding different risk scores to models constructed with variables excluded from the calculation of that score)=9.7% (95% CI, 9.6–9.8). The LIPID (HR=1.13; 95% CI, 1.04–1.22;* P*=0.005) and VILCAD scores (HR=1.99; 95% CI, 1.48–2.67;* P *<0.001) predicted heart failure or death with NRIs of 5.8% (95% CI, 5.7–5.9) and 18.6% (95% CI, 18.3–18.9), respectively. The primary outcome was predicted by the LIPID (HR=1.1; 95% CI, 1.03–1.17;* P*=0.005) and VILCAD scores (HR=1.39; 95% CI, 1.13–1.70;* P*=0.003). The NRIs (95% CIs) were 3.4% (3.3–3.5) and 19.4% (19.3–19.6), respectively.*

We conclude that the accuracy of these risk scores varies in accordance with the outcome studied. ***(Tex Heart Inst J 2017;44(4):239-44)***

Worldwide, approximately 15 million people died of ischemic heart disease or stroke in 2015,[1] accounting for 26.6% of all deaths that year.[1] Atherosclerosis, a chronic inflammatory condition, can present as stable angina or acute coronary syndrome (ACS).[2] These 2 forms of the same disorder differ in their prognosis.[3] Patients with ACS have a higher incidence of adverse events than do those with stable coronary artery disease (CAD). The incidence of cardiovascular death after ACS is 5% to 8% at 6 months, compared with 0.6% to 1.4% at one year in stable CAD.[4,5] However, stable CAD is more prevalent than ACS, and this population also warrants attention because of the risk of progression to ACS or sudden death.

Currently, clinical risk scales are being used to evaluate patients with ACS and to determine optimal primary prevention.[4-8] However, no scale is widely accepted for patients with chronic CAD.[9]

We investigated the predictive power of 3 previously reported clinical risk scores derived from the Framingham study, the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study, and the Vienna and Ludwigshafen Coronary Artery Disease (VILCAD) score.[10-12] We further investigated how the predictive value of these scores changes in accordance with the selected outcome.

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Patients and Methods

Background. The Biomarkers in Acute Coronary Syndrome and Biomarkers in Acute Myocardial Infarction (BACS and BAMI) studies[13] included 1,898 patients who had been discharged from 4 hospitals in greater Madrid, Spain, from July 2006 through April 2010; these patients were diagnosed with non-ST-segment-elevation ACS (NSTEACS) or ST-segment-elevation myocardial infarction (STEMI), as described previously.[13] The exclusion criteria were: age over 85 years; severe coexisting cardiac disorders, except left ventricular hypertrophy secondary to hypertension; coexisting illness or toxic habits that might limit patients' survival prospects; the impossibility of performing revascularization when indicated; and the impossibility of follow-up evaluation. To avoid variability of findings caused by excessive heterogeneity, the investigators excluded patients who were clinically unstable on the 6th day after the index event.

Current Study. In this substudy of the BACS and BAMI studies, we compared findings obtained during a baseline outpatient reevaluation with follow-up findings in May 2012. The research protocol was approved by the ethics committees of our hospitals, and all patients provided written informed consent. The baseline reevaluations were conducted from January 2007 through February 2011—6 to 12 months after the NSTEACS or STEMI event. Blood was withdrawn, and clinical data were recorded again for comparative analysis of Framingham, LIPID, and VILCAD scores.

We included 838 of the original 1,898 patients. The remaining patients were excluded because of disorders or toxic habits limiting survival prospects (29%), loss of contact or the impossibility of follow-up evaluation (21.3%), age over 85 years (17.3%), the impossibility of performing cardiac revascularization (14.5%), clinical instability beyond the 6th day after the index event (9.1%), the coexistence of a severe cardiac condition (6.8%), and refusal to participate in the study (2%). Of the 838 included patients, 7 died before the second visit, and 608 had available clinical data and adequate blood samples at that time. These 608 underwent the baseline reevaluations (January 2007–February 2011) and follow-up evaluations in May 2012.

Study Design. During the baseline visit, blood was drawn for storage, and complete clinical variables were recorded for all patients. Twelve-hour-fasting venous blood samples were collected in EDTA. Patients were seen every year at their hospital. At the end of the follow-up period (mean, 2.08 ± 0.97 yr; range, 15–40 mo), the medical records were reviewed, and each patient's status was confirmed through telephone contact.

In addition to investigating the predictive power of risk scores in a population with stable CAD, we sought to establish which score best predicted the development of different outcomes.

The primary outcome was a combination of acute thrombotic events (NSTEACS, STEMI, stroke, and transient ischemic attack [TIA]) plus all-cause death and heart failure. Secondary outcomes were the recurrence of an acute thrombotic event, or heart failure or death. We defined NSTEACS and STEMI as recommended in clinical practice guidelines. A past myocardial infarction (MI) was diagnosed in the electrocardiographic presence of new pathologic Q waves, along with a new myocardial scar identified with use of echocardiography or nuclear magnetic resonance. Stroke was defined as the rapid onset of a neurologic deficit, attributable to a focal vascular cause lasting longer than 24 hours or supported by new ischemic cerebral lesions on images. A TIA was defined as a stroke with signs and symptoms resolving within 24 hours and without acute ischemic cerebral lesions on images. Two or more investigators of the study adjudicated the events, and they were assisted by a neurologist for cerebrovascular events.

Laboratory Determinations. Venous blood samples were placed in a centrifuge at 2,500 g for 10 min. Plasma was stored at –80 °C in the biobank of IIS-Fundación Jiménez Díaz. The investigators who performed the laboratory studies were unaware of clinical data. High-sensitivity C-reactive protein was measured by means of latex-enhanced immunoturbidimetry with use of an ADVIA® 2400 Clinical Chemistry System (Siemens Healthcare GmbH; Erlangen, Germany). Lipid, glucose, and creatinine measurements were obtained in standard fashion by using the ADVIA system.

Definitions of Predictive Risk Scores

The Framingham score (the relationship between risk factors and the occurrence of coronary heart disease events for persons with a history of previous events) evaluates risk as the cumulative number of points, as follows: in men, from 0 points (age, 35–39 yr) to as many as 10 points (age, 70–74 yr); a combination of total cholesterol and high-density-lipoprotein cholesterol (HDL-C) (from 0 points for total cholesterol ≤160 and HDL-C ≥80 mg/dL to 16 points for total cholesterol ≥300 and HDL-C ≤25 mg/dL); and diabetes mellitus (DM) (0 points when absent and 4 points when present). In women, scores were added for systolic blood pressure (0 points if <110 mmHg and up to 13 points for ≥245 mmHg) and smoking (0 points for nonsmokers and 4 points for smokers).[10] The scores for DM (8 vs 0 points for diabetic vs nondiabetic patients) and age (from 0 for 35–39 yr to 7 points for 70–74 yr) changed slightly, and the lipid score was identical to that used in men. Total scores ranged from 0 to 30 points in men and from 0 to 48 points in women.

In the LIPID score (prediction of coronary heart disease death or nonfatal MI), risk is estimated from accumulated points in accordance with these variables: age 60–64 years, 1 point; age 65–69 years, 2 points;

and ≥70 years, 3 points; male sex, 2 points; total cholesterol ≥212.7 mg/dL, 1 point; HDL-C ≤38.7 mg/dL, 2 points; current smoker, 3 points; DM, 3 points; hypertension, 1 point; previous stroke, 3 points; single MI, 1 point; multiple MIs, 6 points; and revascularization during the last acute ischemic event, –4. The remaining categories scored 0 in all cases. The score ranged from –4 to 24 points.[11]

We used the simplified VILCAD score (developed for prediction of survival) because we did not determine cholinesterase levels in our population; this simplified score has had a strong predictive value.[12] In this scale, risk is estimated as the cumulative number of points in accordance with these variables: age ≥75 years, 2 points; moderate left ventricular systolic dysfunction, 1 point, and severe, 2 points; hemoglobin A_{1c} ≥6.5% in patients with known DM, 1 point; creatinine ≥1.3 mg/dL, 1 point; and heart rate ≥75 beats/min, 1 point. The remaining categories scored 0 in all cases. This score ranges theoretically from 0 to 7 points.

Statistical Analysis

Quantitative data did not follow a normal distribution per the Kolmogorov-Smirnov test and are expressed as median and interquartile range. Qualitative variables are expressed as percentages.

A Cox proportional-hazards model with backward stepwise selection was used, wherein the cumulative points of each score were studied like a variable and were adjusted for the characteristics shown in Table I, except for those used in the calculation of that score. A *P* value <0.05 was considered statistically significant. Variables with a *P* value <0.05 were entered into the model, and those with *P* values >0.1 were removed. The hazard ratios (HR) for every score represented the increase in risk for every increment of one unit in that score. The net reclassification index (NRI) was calculated to evaluate the improvement in prediction gained by adding different risk scales to models constructed with the variables not included in the calculation of that score.[14]

Analyses were performed with SPSS 19.0 (IBM Corporation; Endicott, NY) and R 3.0.1 (http://www.r.project.org).

TABLE I. Baseline Characteristics of the 603 Patients

Variable	Value
Age (yr)	60 (52–72)
Male	453 (75.1)
Body mass index (kg/m^2)	28.2 (25.7–30.8)
Smoker	42 (7)
Diabetes mellitus	69 (11.4)
Hypertension	379 (62.9)
Dyslipidemia	343 (56.9)
HDL cholesterol (mg/dL)	42 (37–50)
LDL cholesterol (mg/dL)	81 (66–97)
Triglycerides (mg/dL)	108 (80–150)
High-sensitivity C-reactive protein (mg/L)	1.95 (0.84–3.89)
Cerebrovascular events	16 (2.7)
Peripheral artery disease	22 (3.6)
Atrial fibrillation	30 (5)
LV ejection fraction <0.40	70 (11.6)
Complete revascularization at last ACS	404 (67)
GFR (mL/min/1.73 m^2)	77.6 (63.6–89.9)
Medications	
Aspirin	553 (91.7)
Clopidogrel	406 (67.3)
Acenocumarol	35 (5.8)
Statins	534 (88.6)
Angiotensin-converting enzyme inhibitors	336 (55.7)
Angiotensin receptor blockers	90 (14.9)
β-blockers	456 (75.6)

ACS = acute coronary syndrome; GFR = glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration criteria; HDL = high-density-lipoprotein; LDL = low-density-lipoprotein; LV = left ventricular

Data are expressed as median and interquartile range or as number and percentage.

Results

The duration of follow-up was 2.08 ± 0.97 years. Five patients were lost to follow-up, leaving 603 patients in the analysis (Table I).

Forty-two patients (7%) met the secondary outcome of having an acute thrombotic event. There were 3 cases of STEMI, 17 of NSTEMI, 12 of unstable angina, 7 of stroke, and 9 of TIA. Four patients had 2 events, and 1 patient had 3 events. Upon multivariate analysis, the Framingham score was the only statistically significant predictor of this outcome (Table II). The NRI yielded an improvement in individual risk classification of 9.71% (95% CI, 9.59–9.83) for the Framingham score (Table II), 0.18% (95% CI, 0.17–0.19) for the VILCAD, and –1.01% (95% CI, –1.08 to –0.94) for the LIPID scores.

Twenty-two patients (3.6%) met the secondary outcome of heart failure or death: 14 died, and 12 had heart failure (4 patients had 2 events). Seven deaths were related to cardiovascular causes, and 2 to cancer; 2 were of unknown origin; bowel ischemia, pancreatitis, and gastrointestinal bleeding accounted for 1 death each. Upon multivariate analysis, the VILCAD and LIPID scores, but not the Framingham score, were significant predictors of this endpoint. The NRI showed an improvement in individual risk classification of 18.6% (95% CI, 18.31–18.9) for the VILCAD score, –1.54

TABLE II. Results of Multivariate Modeling

Variable	Acute Thrombotic Events		Heart Failure or Death		Acute Thrombotic Events, Heart Failure, or Death	
	HR (95% CI)	***P* Value**	**HR** (95% CI)	***P* Value**	**HR** (95% CI)	***P* Value**
Framingham Score	1.046 (1.012–1.082)[a]	0.029	1.052 (0.996–1.112)	0.12	1.039 (1.002–1.077)	0.072
Hypertension	2.296 (1.056–4.994)	0.023	7.922 (1.058–59.294)	0.005	2.298 (1.109–4.761)	0.015
Body mass index	1.067 (1.009–1.128)	0.03	—	—	1.063 (1.012–1.116)	0.018
Acenocumarol use	—	—	3.931 (1.840–8.398)	0.001	—	—
GFR	—	—	0.957 (0.939–0.975)	<0.001	0.975 (0.962–0.987)	<0.001
Atrial fibrillation	—	—	—	—	2.412 (1.291–4.507)	0.011
LIPID Score	1.060 (0.983–1.144)	0.137	1.126 (1.041–1.217)[b]	0.005	1.096 (1.031–1.165)[c]	0.005
GFR	0.981 (0.967–0.996)	0.014	0.958 (0.940–0.976)	<0.001	0.971 (0.959–0.983)	<0.001
Body mass index	1.088 (1.031–1.149)	0.004	—	—	1.072 (1.021–1.126)	0.007
Atrial fibrillation	—	—	4.501 (2.071–9.785)	0.001	2.587 (1.385–4.833)	0.007
VILCAD Score	0.984 (0.720–1.344)	0.919	1.988 (1.480–2.670)[d]	<0.001	1.387 (1.132–1.700)[e]	0.003
Hypertension	2.254 (0.966–5.261)	0.044	9.546 (1.261–72.26)	0.002	2.911 (1.349–6.282)	0.003
GFR	0.979 (0.959–1.000)	0.046	—	—	—	—
Body mass index	1.088 (1.023–1.157)	0.013	—	—	1.063 (1.006–1.122)	0.038
Acenocumarol use	—	—	5.141 (1.965–13.451)	0.004	—	—
LDL cholesterol	—	—	0.983 (0.965–1.000)	0.047	—	—

CI = confidence interval; GFR = glomerular filtration rate; HR = hazard ratio; LDL = low-density-lipoprotein; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease; VILCAD = Vienna and Ludwigshafen Coronary Artery Disease

Net reclassification index (95% CI):
[a] 9.7% (9.6–9.8)
[b] 5.8% (5.7–5.9)
[c] 3.4% (3.3–3.5)
[d] 18.6% (18.3–18.9)
[e] 19.4% (19.3–19.6)

A Cox proportional hazards model with backward, stepwise selection was used; the cumulative points of each score were studied like a variable adjusting for the characteristics shown in Table I, except for those used in the calculation of that score. Variables with a *P* value <0.05 were entered into the model, and those with *P* >0.1 were removed.

P <0.05 was considered statistically significant.

(95% CI, –1.6 to –1.48) for the Framingham score, and 5.76% (95% CI, 5.68–5.85) for the LIPID score.

Sixty patients (10%) met the primary outcome. Eight patients had 2 events, and 3 patients had 3 events. Upon multivariate analysis, the VILCAD score (*P*=0.003) and the LIPID score (*P*=0.005), but not the Framingham score (*P*=0.072), independently predicted this outcome. The NRI showed an improvement in individual risk classification of 19.42% (95% CI, 19.27–19.57) for the VILCAD score, 5.99% (95% CI, 5.91–6.07) for the Framingham score, and 3.36% (95% CI, 3.26–3.45) for the LIPID score.

Discussion

Because of the high prevalence of CAD, preventing recurrent events in patients with established cardiovascular disease is a major public health objective.

Prognoses associated with CAD have been studied in numerous clinical trials of anti-anginal therapy, preventive therapy, and revascularization. However, these studies might be biased because of the selection criteria used to include patients. Estimates for annual mortality rates range from 1.2% to 2.4%,[15-20] with an annual incidence of cardiac death of 0.6% to 1.4%, and of nonfatal MI from 0.6% in the Second Randomized Intervention Treatment of Angina (RITA-2) to 2.7% in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trials.[15-18] These estimates are consistent with observational registry data.[21]

These data summarize the population average. However, within the population with stable CAD, prognosis can vary considerably, depending on each patient's characteristics. Furthermore, when acute thrombotic events develop, many patients die before receiving medical attention.[22]

The 2013 guidelines of the European Society of Cardiology for the management of stable CAD recommend evaluating prognosis as an important part of the treatment of these patients. One can thus identify patients with more severe forms of disease—those at high risk whose outcomes might improve after more intensive treatment and monitoring. It is equally important to identify patients whose prognosis is good, to avoid applying resources to their treatment unnecessarily.[9]

Clinical risk scores are unanimously accepted for ACS and primary prevention, but not for CAD. In the

current study, we investigated the predictive power of the Framingham, LIPID, and VILCAD scores for different outcomes in 603 patients with stable CAD. We studied thrombotic events separately from death and heart failure because there are different underlying pathophysiologic mechanisms: a given score could predict only one outcome, given the different variables.

In the Framingham study, 1,176 patients (61% men) were included, with a median follow-up duration of 2 years. The median age was 60 years, most patients were nonsmokers (67%), and only 15.3% had DM. In the LIPID study, 8,557 patients were included; most were men (83%) and nonsmokers (90%), and 9% had DM. The VILCAD included 547 patients with a median follow-up duration of 11.8 years. The baseline characteristics of these patients are unknown. Our study population is similar to the earlier populations: median age, 60 years; men, 75%; nonsmokers, 93%; and DM prevalence, 15%.

Only the Framingham score independently predicted the incidence of acute thrombotic events, classifying 9.71% of the patients more accurately than when they were classified with the NRI. However, the LIPID and VILCAD scores independently predicted the risk of heart failure or death, VILCAD having the best NRI. Results were similar for the combined primary outcome, and the VILCAD score again yielded the best NRI.

The differences in the prognostic power of these clinical risk scores could be related to the variables used by each for calculation. The Framingham variables essentially incorporate the major risk factors for atherosclerosis.[10] However, the LIPID and VILCAD scores include variables related to heart failure. The LIPID score includes the occurrence of one or more previous MIs, and VILCAD accounts for moderate or severe left ventricular dysfunction. In addition to this, VILCAD uses plasma creatinine levels in the risk calculation. Although it would have been even better to use the estimated glomerular filtration rate, plasma creatinine levels give a rough estimation of renal function. This is important, because patients with CAD can be affected by other conditions that might compromise survival. In fact, half the deaths in our population were from noncardiovascular causes. Moreover, approximately 20% of patients with CAD have an estimated glomerular filtration rate below 60 mL/min/1.73 m^2.[23]

Also important is the difficulty in using each risk score. In our study, although both LIPID and VILCAD independently predicted the primary combined outcome, VILCAD was easier to use, because its simplified version (which we used) comprises only 5 items that are easy to extract from a standard clinical record. On the other hand, the LIPID score requires the evaluation of 10 variables that include age, sex, the classical risk factors for CAD, and information from cardiovascular history; this makes it more time-consuming to use than VILCAD. However, the lack of variables estimating left ventricular and renal function is probably responsible at least in part for the lower NRI obtained with this scale. Using hemoglobin A_{1c} instead of DM could have contributed to the higher performance of the VILCAD score, because this criterion has been related to the prognosis of diabetic patients.[24] In addition, the VILCAD score was developed in a European population, whereas the LIPID and the Framingham risk scales used data obtained from patients from Australia and Massachusetts, respectively.[10-12,25] Thus, it is possible that the profiles and lifestyles of the patients used to develop the VILCAD scale were more similar to those of our Spanish population than were those of the other 2 risk scores.

Finally, data in the Framingham study were collected before 1987; in LIPID, from 1990 through 1992; and in VILCAD, from 1999 through 2000.[10-12] Because secondary-prevention strategies for CAD have evolved over the years,[26] it is highly probable that the patients used to design the VILCAD score received treatment that more closely resembles current practice than was the case during the Framingham and LIPID studies.

In conclusion, we found that the effectiveness of the 3 clinical risk scores to predict prognoses in patients with stable CAD varies in accordance with the outcome studied. The VILCAD seems to have been the most effective in our series of Spanish patients with stable CAD. Future efforts to develop clinical risk scores for CAD should take into account the type of outcome predicted when selecting the variables to be included in the score.

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