Journal of the American Heart Association

ORIGINAL RESEARCH

LVS-HARMED Risk Score for Incident Heart Failure in Patients With Atrial Fibrillation Who Present to the Emergency Department: Data from a World-Wide Registry

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BACKGROUND: Heart failure (HF) is a common complication to atrial fibrillation (AF), leading to rehospitalization and death. Early identification of patients with AF at risk for HF might improve outcomes. We aimed to derive a score to predict 1-year risk of new-onset HF after an emergency department (ED) visit with AF.

METHODS AND RESULTS: The RE-LY AF (Randomized Evaluation of Long-Term Anticoagulant Therapy) registry enrolled patients with AF presenting to an ED in 47 countries, and followed them for a year. The end point was HF hospitalization and/or HF death. Among 15 400 ED patients, 9765 had no prior HF (mean age, 64.9±14.9 years). Within 1 year, new-onset HF developed in 6.8% of patients, of whom 21% died of HF. Independent predictors of HF included left ventricular hypertrophy (odds ratio [OR], 1.47; 95% CI, 1.19–1.82), valvular heart disease (OR, 1.55; 95% CI, 1.18–2.04), smoking (OR, 1.42; 95% CI, 1.12–1.78), height (OR, 0.93; 95% CI, 0.90–0.95 per 3 cm), age (OR, 1.11; 95% CI, 1.07–1.15 per 5 years), rheumatic heart disease (OR, 1.77, 95% CI, 1.24–2.51), prior myocardial infarction (OR, 1.85; 95% CI, 1.45–2.36), remaining in AF at ED discharge (OR, 1.86; 95% CI, 1.46–2.36), and diabetes (OR, 1.33; 95% CI, 1.09–1.64). A continuous risk prediction score (LVS-HARMED [left ventricular, valvular heart disease, smoking or other tobacco use, height, age, rheumatic heart disease, myocardial infarction, emergency department discharge rhythm, and diabetes]) had good discrimination (C statistic, 0.735; 95% CI, 0.716–0.755). Validation was conducted internally using bootstrapping (optimism-corrected C statistic, 0.705) and externally (C statistic, 0.699). The 1-year incidence of HF hospitalization and/or HF death across quartile groups of the score was 1.1%, 4.5%, 6.9%, and 14.4%, respectively. LVS-HARMED also predicted incident stroke (C statistic, 0.753; 95% CI, 0.728–0.778).

CONCLUSIONS: The LVS-HARMED score predicts new-onset HF after an ED visit for AF. Preventative strategies should be considered in patients with high LVS-HARMED HF risk.

Key Words: atrial fibrillation ■ epidemiology ■ heart failure ■ prevention ■ risk score ■ risk stratification

The global prevalence of atrial fibrillation (AF) continues to increase.[1] Heart failure (HF) is a common complication of AF[2] and independently increases the risk of death in affected patients.[3] HF is the most common cause of death among people with AF,[4] accounting for more than one third of all deaths in patients with AF worldwide.[4] However; prediction and prevention of HF have received much less attention in

CLINICAL PERSPECTIVE

What Is New?

- New-onset heart failure is a common early complication in patients with atrial fibrillation after an emergency department visit that can be predicted using the LVS-HARMED (left ventricular, valvular heart disease, smoking or other tobacco use, height, age, rheumatic heart disease, myocardial infarction, emergency department discharge rhythm, and diabetes) risk score.

What Are the Clinical Implications?

- Patients with atrial fibrillation who have a high risk of heart failure should be referred for specialist consultation after an emergency department visit for atrial fibrillation.

Nonstandard Abbreviations and Acronyms

AFFORD	Atrial Fibrillation and Flutter Outcomes and Risk Determination
AIC	Akaike information criterion
FHS	Framingham Heart Study
LVS-HARMED	left ventricular, valvular heart disease, smoking or other tobacco use, height, age, rheumatic heart disease, myocardial infarction, emergency department discharge rhythm, and diabetes mellitus
RE-LY	Randomized Evaluation of Long-Term Anticoagulant Therapy

AF research and guidelines than stroke prevention.[5] Furthermore, despite the high risks of HF in patients with AF, no validated HF prevention programs exist for these patients. Prevention trials, targeting modifiable risk factors for HF in patients with AF are therefore needed[5] and would be feasible if patients at high risk for HF could be identified. The emergency department (ED) is a common point of first contact for patients with AF, and AF causes or contributes to a large number of AF hospitalizations every year.[6] Given the success of ED-based interventions to improve oral anticoagulant use, the initiation of HF prevention programs in the ED might also be effective.[7] There is hope that prevention of HF in patients with AF may therefore be successfully conducted via referrals of patients with AF who have a high risk for HF from the ED to specialist care.

Previous studies have investigated risk factors for HF in patients with AF,[8,9] including the development of a 10-year risk score in the FHS (Framingham Heart Study), which included age, left ventricular hypertrophy (LVH), body mass index, diabetes, significant heart murmur, and a history of myocardial infarction.[8] To the best of our knowledge, however, no previous risk prediction scores for HF in patients with AF have been developed for use in the ED, and in populations that include patients from middle- and low-income countries, even though risk factors for AF and related diseases and treatments vary greatly between geographic regions.[10] Accurate prediction of incident HF in patients with AF based on variables obtained in the ED may be useful to select patients for specialist referral, in order to provide medical interventions that reduce HF hospitalizations. The aim of this analysis was to derive a model to predict 1-year risk of new-onset hospitalization or death from HF in the global RE-LY AF (Randomized Evaluation of Long-Term Anticoagulant Therapy) registry.

METHODS

The analytic methods used in this article will be made available to other researchers upon reasonable request to the corresponding author. Institutional review board approval has been obtained.

Study Population and Data Collection

The RE-LY AF registry prospectively enrolled a total of 15 400 patients with AF from 164 sites in 47 countries, representing all inhabited continents. The methods have been previously described in more detail.[4,10] Briefly, patients who presented to an ED with AF or atrial flutter, as identified by the treating physician, either as a primary or a secondary diagnosis, were enrolled. Patients were then assessed after 1 year, either in person or by telephone, and supplemental information was obtained from medical records. The diagnosis of HF was determined according to site discretion. All patients gave written informed consent.

For this analysis, all patients with a history of HF were excluded (n=5350). Participating countries were placed into 4 income groups, based on the 2011 World Bank definitions[11]: low income: Tanzania, Kenya, Mozambique, and Uganda (n=194); low/middle income: India, Sudan, Senegal, Zambia, Cameroon, Nigeria, Egypt, and the Ukraine (n=2337); upper/middle income: Argentina, Brazil, Colombia, Ecuador, Venezuela, Chile, Russia, Latvia, Turkey, Iran, South Africa, Thailand, and China (n=2455); and high income: Japan, South Korea, Singapore, Saudi Arabia, the United Arab Emirates, Poland, Slovakia, Hungary, the Czech Republic,

Bulgaria, Australia, Spain, Italy, the Netherlands, Germany, Austria, the United Kingdom, Sweden, Ireland, Canada, Denmark, and the United States (n=5064). We excluded patients with missing follow-up data for HF hospitalizations and/or HF death (n=285), resulting in a study population of 9765 individuals.

The prediction model was based on 9321 individuals with complete data for all variables evaluated in the final prediction model. The primary end point was a composite of hospitalization for HF and/or HF death, and was retrieved from the case report forms that were completed by the study centers at the end of the follow-up. Qualifying HF hospitalization events had a duration of ≥24 hours. Some patients died as a result of new-onset HF without a reported HF hospitalization.

An external validation of the risk score was conducted in the previously described AFFORD (Atrial Fibrillation and Flutter Outcomes and Risk Determination) study.[12] Briefly, the AFFORD study included 623 patients presenting to the ED with AF; the aim was to derive an ED-based clinical decision aid to identify patients with AF at low risk for adverse events. A convenience sample of patients with signs of symptoms consistent with symptomatic AF who presented between June 9, 2010, and February 28, 2013, to the Vanderbilt University Medical Center ED were recruited; AF diagnoses were confirmed with ECG.

We excluded patients with known prevalent HF or missing information, resulting in a study population of 367 patients, in whom we ascertained 17 cases of incident HF hospitalization and/or death during 365 days of follow-up. The end point was retrieved by medical chart review conducted by 3 trained researchers and clinicians. Each chart was reviewed by multiple abstractors to ensure reliable data capture.

Statistical Analysis

Baseline characteristics were summarized and stratified by country income group, and also separately for individuals with and without subsequent HF hospitalization and/or HF death. These strata were compared using Student t tests for continuous variables and chi-square tests for categorical variables. A logistic mixed effects regression model, with random effects for country, was used to assess the effect of baseline variables on the composite end point of HF hospitalization or death. Variables assessed for inclusion in the model were prespecified, based on the FHS risk score for HF in AF, as well as other variables plausibly related to HF in ED patients, and included age, sex, height, body mass index, systolic blood pressure, a history of smoking or other tobacco use, whether the patient remained in AF at ED discharge (to home or admission to hospital ward), LVH on

ECG or echocardiogram, presence of a pacemaker, history of myocardial infarction, hypertension, rheumatic heart disease, valvular heart disease, diabetes, stroke/transient ischemic attack, or emphysema/chronic obstructive pulmonary disease. Tobacco use was defined as a reported history of smoking or use of any other tobacco product.

The Lasso method with l_1 penalization was used for variable selection. The optimal set of variables was selected by tuning the parameter lambda.[13] The model with the smallest goodness-of-fit statistic was chosen as the best one. Based on these selected variables, a parsimonious risk prediction model was derived in the study population. We then calculated C statistics with 95% CIs for groups of countries based on their income group, as well as by geographic region. Calibration of the score was assessed using the Hosmer-Lemeshow goodness-of-fit test and depicted in a calibration plot.[14] We assessed regional variation in 2 ways: first, by running 2 logistic mixed effects regression models including the final score, one with only a random intercept effect for country and another adding a random slope effect for the final score; we then compared these models with each other using the Akaike information criterion (AIC) and the likelihood ratio test. We also calculated regression coefficients for geographic regions in a logistic mixed effects regression model with a random intercept effect for country, including the final score as well as a variable for geographic region, where North America was set as the reference region. The model was validated internally using bootstrap resampling to measure the optimism in the model.[15] The effect of medication after ED visit was assessed in a mixed effects logistic regression model including all final score components as well as the use of diuretics, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, and digoxin, with clustering on country.

For purposes of comparison, we applied the algorithm for the FHS risk score for HF in AF to the study population. This score predicts 10-year risk of incident HF in patients with AF.[8] We then calculated the C statistics for this score in a logistic mixed effects regression model with random intercept effects for country for the composite end point of HF hospitalization and/or HF death over the 1-year follow-up, in the full RE-LY AF registry, as well as by country income group and by geographic region.

Finally, to explore whether a single score could be used to predict both HF and stroke in patients with AF in an ED setting, the C statistic for the RE-LY AF registry–derived risk prediction score was calculated using incident stroke as the end point. Statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute Inc), except for model selection and calibration, which was performed in the R package

`glmmixedlasso`, and the external validation, which was conducted in Stata version 14.2 (StataCorp). A P value <0.05 was considered to indicate statistical significance.

RESULTS

Baseline characteristics are reported in Table 1. The mean age of the study population was 64.9 years (SD, 14.9 years), 53.8% were men, and 17.6% had LVH on ECG or echocardiogram. At 1 year of follow-up, the end point of HF hospitalization and/or HF death occurred in 664 of 9765 patients (6.8%). The proportion of patients with HF hospitalization and/or HF death during follow-up was 28.0% in low-income countries, 5.3% in low–middle-income countries, 6.9% in upper–middle-income countries, and 6.6% in high-income countries. Univariable analyses of baseline characteristics in patients with and without new-onset HF during follow-up are reported in Table S1. Among patients with new-onset HF, the mean age and proportion of women were higher.

Risk Score Components and Performance

A continuous risk prediction score for new-onset HF within 1 year of presenting to an ED with AF is reported in Table 2. The score includes the following independent predictors: LVH, valvular heart disease, history of smoking or other tobacco use, height, age, history of rheumatic heart disease, history of myocardial infarction, the patient being in AF at ED discharge, and history of diabetes. The acronym LVS-HARMED stands for LVH, valvular heart disease, smoking or other tobacco use, height, age, rheumatic heart disease, myocardial infarction, ED discharge rhythm, and diabetes. The algorithm to calculate the LVS-HARMED score is reported in the footnote to Table 2. Systolic blood pressure, body mass index, hypertension, presence of a pacemaker, sex, history of stroke/transient ischemic attack, and emphysema/chronic obstructive pulmonary disease did not meaningfully contribute to the optimal model and were not included in the final model. The overall discrimination, as measured by the C statistic, was 0.735 (95% CI, 0.716–0.755). Bootstrap resampling of the population with 100 samples was used to estimate the mean optimism to 0.0297, resulting in a mean optimism–corrected C statistic of 0.705. A calibration plot is presented in Figure S1.

The AFFORD study validation population had a mean age of 63.9 years (SD, 14.8), 236 (64.3%) were men, and 143 (39.0%) had LVH on ECG or echocardiogram. The external validation of the LVS-HARMED score in this population resulted in a C statistic of 0.699 (95% CI, 0.583–0.814). A calibration plot for the

AFFORD study can be found in Figure S2 and a calibration table in Table S2; the Hosmer-Lemeshow P value was 0.22.

Risk Score Performance Among Country Income Groups and Regions

The performance of both the LVS-HARMED and FHS risk scores for HF in AF among income groups and geographic regions are reported in Table 3, and receiver operating curves for the LVS-HARMED score in the full registry as well as by income group can be found in Figures S3 through S7. For prediction of 1-year risk of HF, the LVS-HARMED score performed better than the FHS score overall and in each income group. Agreement plots and Bangdiwala statistics for the LVS-HARMED and FHS scores are given in Figure S8. Income group–specific odds ratios (95% CI) for the predictors included in the LVS-HARMED score are reported in Table S3. There was no significant difference in the LVS-HARMED models without or with random slope (AIC for the model without random slope: 4298.9, AIC for the model with random slope: 4297.5; P=0.07). Regression coefficients for geographic regions are given below (Table 2). The association between LVS-HARMED components and new-onset HF was also assessed in a model that also included medication after ED visit (Table S4). The LVS-HARMED coefficients were not substantially altered.

The observed frequencies of HF hospitalizations, HF deaths, and the composite end point of HF hospitalization and/or HF death across quartiles of the score and income groups are given in Table 4 and Figure. In the top quartile of the score, the incidence of HF hospitalization and/or HF death was high in all income groups: 75.0% in low-income countries, 10.5% in lower–middle-income countries, 12.5% in upper–middle-income countries, and 13.9% in high-income countries.

In the full cohort, the composite end point of HF hospitalization and/or death occurred in 14.4% of the upper quartile; there were HF hospitalizations in 12.8%, and 2.7% died from HF. There was evidence of good fit in the full population (calibration slope, 1.07; Hosmer-Lemeshow, P=0.22 [Figure S1]), as well as among income groups (Figures S9 through S12). The bootstrap validated estimate of the calibration slope was 0.934. By comparison, among RE-LY AF registry patients who had follow-up data for HF hospitalizations and/or HF death, but were excluded from the current analysis because of a history of HF (n=5169), 29.6% were either hospitalized for (26.1%) or died (7.5%) of HF within 1 year.

We also assessed the discrimination of the LVS-HARMED score for prediction of 1-year stroke risk. In

Table 1. Baseline Characteristics and Medical History

	Overall	Low-income countries*	Lower–middle-income countries†	Upper–middle-income countries‡	High-income countries§
Patients, N.	N=9765	n=193	n=2246	n=2358	n=4968
Age, mean±SD, y	64.9±14.9	56.3±21.8	58.0±15.8	67.3±13.7	67.3±13.5
Men, %	53.8	51.8	49.7	50.2	57.5
Weight, mean±SD, kg	73.1±19.3	70.7±20.2	63.8±14.9	69.4±14.7	79.1±20.8
Height, mean±SD, cm	167±10.5	165±11.9	162±9.5	166±9.0	169±10.9
BMI, mean±SD, kg/m²	26.2±5.8	26±6.9	24.3±5.2	25.2±4.8	27.5±6.1
Systolic BP, mean±SD, mm Hg	133±25	133±28	128±22	134±25	135±25
Diastolic BP, mean±SD, mm Hg	81±15	81±17	80±13	81±15	81±16
Heart rate, mean±SD, beats per min	103±31	99±32	100±28	101±30	106±33
Prior diagnosis of AF, %	59.1	45.6	39.4	69.5	63.6
Paroxysmal	35.6	27.3	21.8	32.4	41.3
Persistent	23.7	10.2	30.8	24.2	21.8
Permanent	40.7	62.5	47.4	43.4	36.8
Current arrhythmia, %					
AF	92.3	91.2	94.5	94.5	90.2
Atrial flutter	7.7	8.8	5.4	5.5	9.8
Patient in AF/atrial flutter when left ED, %	73.0	78.2	80.1	73.4	69.3
Repeat visits for AF/atrial flutter complications during study period, %	16.8	21.2	5.3	17.2	21.6
Medical history, %					
Myocardial infarction, %	11.2	6.7	14.3	8.1	11.5
Coronary artery disease, %	25.5	9.3	25.0	29.4	24.4
Hypertension, %	59.2	52.8	43.2	64.8	64.1
Stroke/TIA, %	13.2	12.4	8.5	18.1	13.1
Rheumatic heart disease, %	10.7	18.1	30.1	7.8	2.9
Significant valvular heart disease, %	18.3	23.3	42.8	13.4	9.3
Mitral stenosis, % of subjects with valvular heart disease	50.1	46.7	64.3	48.4	22.0
Aortic stenosis, % of subjects with valvular heart disease	10.7	2.2	5.2	10.4	23.1
Mitral regurgitation, % of subjects with valvular heart disease	50.2	73.3	49.5	52.5	47.9
Aortic regurgitation, % of subjects with valvular heart disease	12.7	20.0	10.7	14.2	15.1
Permanent pacemaker, %	3.8	0.5	1.7	3.4	5.0
LVH, %	17.6	40.9	11.9	18.4	18.9
Pericarditis,%	0.5	5.2	0.6	0.4	0.4
Emphysema/COPD,%	8.0	4.7	4.8	9.4	8.9
Diabetes, %	19.5	17.1	19.4	16.4	21.0
Tobacco use, %	16.0	11.4	7.0	19.1	18.8
Alcohol use, standard drinks/wk, (median) mean±SD	(0) 3.3±7.7	(3) 8.5±12.7	(0) 1.2±5.8	(0) 2±8.6	(1) 3.9±7.0
Prior interventions, %					
Prior cardioversions	11.3	14.5	2.3	7.9	16.8
Prior AF catheter, surgical or Maze procedure	2.5	0.5	0.2	1.6	4.0
Prior atrioventricular node ablation	0.5	0.0	0.1	0.6	0.7
Prior left atrial appendage occlusion or amputation	0.1	0.0	0.0	0.1	0.2
Medication use after ED visit, %					
β-Blocker	53.2	47.2	39.7	49.2	61.4

(Continued)

Table 1. Continued

	Overall	Low-income countries*	Lower–middle-income countries†	Upper–middle-income countries‡	High-income countries§
CCB	27.7	22.3	29.9	23.8	28.7
ACEI	27.6	34.7	19.9	24.7	32.2
ARB	15.3	12.4	9.8	18.2	16.6
Digoxin	25.6	42.5	48.6	16.7	18.9
Diuretic	41.0	41.5	66.0	26.1	36.7
Amiodarone	14.8	26.9	21.9	19.2	9.0
Sotalol	3.2	3.1	0.3	1.0	5.5
Flecainide	1.6	1.0	0.2	0.1	3.0

ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; ED, emergency department; LVH, left ventricular hypertrophy; and TIA, transient ischemic attack.

*Includes Tanzania, Kenya, Mozambique, and Uganda.

†Includes India, Sudan, Senegal, Zambia, Cameroon, Nigeria, Egypt, and the Ukraine.

‡Includes Argentina, Brazil, Colombia, Ecuador, Venezuela, Chile, Russia, Latvia, Turkey, Iran, South Africa, Thailand, and China.

§Includes Japan, South Korea, Singapore, Saudi Arabia, the United Arab Emirates, Poland, Slovakia, Hungary, the Czech Republic, Bulgaria, Australia, Spain, Italy, the Netherlands, Germany, Austria, the United Kingdom, Sweden, Ireland, Canada, Denmark, and the United States.

the logistic mixed effects regression model with random intercept effect for country, the C statistic for the stroke end point was 0.755 (95% CI, 0.730–0.780).

DISCUSSION

New-onset HF is common in patients following an ED visit for AF, in all countries, regardless of income level. Within 1 year, 1 in 17 patients with AF without prior HF will be hospitalized for HF, and 21% of these patients will die. We derived a 1-year prediction score for new-onset HF in a population of ED patients with AF (LVS-HARMED; www.phri.ca/LVS-HARMED) using 9 variables that can easily be obtained for most patients in an ED. LVS-HARMED identifies one quarter of patients presenting to the ED with AF who have a 1 in 7 risk of death or hospitalization attributable to new-onset HF in the following year. These patients would likely benefit from referral to specialist care upon ED discharge and might benefit from interventions that target known modifiable HF risk factors.[16]

HF is associated with substantial mortality, reduced quality of life, and economic costs.[17] With accurate risk prediction, it may be possible to prevent HF onset in AF, using a variety of interventions. In the ACTIVE-I (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) trial, treatment with the angiotensin receptor blocker irbesartan reduced hospitalizations for HF in patients with AF.[18] In the population as a whole and among HF cases, less than half of the patients were using a renin-aldosterone-angiotensin system blocker at baseline and improved HF prediction and could therefore lead to improved medical therapy in a substantial number of patients. Risk factor management in individuals with a high risk of HF has been shown to be both effective, reducing the risk of new-onset left ventricular dysfunction or HF by almost half, and also cost-efficient in the STOP-HF (St Vincent's Screening to Prevent Heart Failure) trial.[19,20] Several of the predictors identified in the LVS-HARMED score may be suitable targets for intervention. The risk associated with LVH was high, as was the prevalence of LVH, particularly in low-income countries. Effective treatment of known causes of LVH, such as hypertension and valvular heart disease,[21] as well as treatments that improve prognosis after myocardial infarction, may therefore be effective in reducing the risk of HF in

Table 2. Parsimonious Model for 1-Year Risk of HF

	β	OR (95% CI)	P value
Intercept	−0.671		0.4471
LVH	0.387	1.473 (1.190–1.823)	0.0007
Valvular heart disease	0.439	1.552 (1.183–2.035)	0.0021
Smoking/other tobacco use	0.347	1.416 (1.123–1.784)	0.0042
Height, per 3 cm	−0.075	0.928 (0.902–0.954)	<0.0001
Age, per 5 y	0.104	1.110 (1.070–1.151)	<0.0001
Rheumatic heart disease	0.569	1.766 (1.244–2.507)	0.0022
Myocardial infarction	0.613	1.847 (1.446–2.359)	<0.0001
ED discharge rhythm is AF	0.619	1.857 (1.464–2.355)	<0.0001
Diabetes	0.288	1.334 (1.085–1.640)	0.0074

Includes 9321 patients and 628 events. AF indicates atrial fibrillation; ED, emergency department; HF, heart failure; LVH, left ventricular hypertrophy; and OR, odds ratio.

The LVS-HARMED (left ventricular, valvular heart disease, smoking or other tobacco use, height, age, rheumatic heart disease, myocardial infarction, emergency department discharge rhythm, and diabetes) score is calculated as: $\exp(-0.671+xL+xV+xS+xH+xA+xR+xM+xE+xD)/(1+\exp(-0.671+xL+xV+xS+xH+xA+xR+xM+xE+xD))$, where x denotes the individual patient values, and LVS-HARMED the specific β-coefficient.

β-Coefficients (P values) for the different geographic regions are as follows: North America: reference; Western Europe: −0.304 (P=0.55); Eastern Europe: 0.051 (P=0.92); Latin America: −0.749 (P=0.19); the Middle East: −0.3615 (P=0.55); Asia: −0.194 (P=0.71); and Africa: 1.395 (P=0.009).

Table 3. C Statistics for the LVS-HARMED and FHS Score for HF in AF Among Geographic Region and Income Group Levels

	LVS-HARMED		FHS		Patients, No.*	Events, No. (%)
	C statistic	95% CI	C statistic	95% CI		
Overall	0.735	0.716 to 0.755	0.603	0.579 to 0.627	9765	664 (6.80%)
Region						
North America	0.710	0.658 to 0.763	0.650	0.594 to 0.706	1291	90 (7.0%)
Latin America	0.632	0.537 to 0.727	0.582	0.477 to 0.686	689	33 (4.8%)
Western Europe	0.797	0.749 to 0.844	0.718	0.657 to 0.780	1528	78 (5.1%)
Eastern Europe	0.704	0.644 to 0.765	0.654	0.591 to 0.717	1030	73 (7.1%)
Middle East	0.745	0.662 to 0.828	0.677	0.577 to 0.778	604	35 (5.8%)
Africa	0.795	0.732 to 0.857	0.400	0.321 to 0.479	367	79 (21.5%)
Asia	0.703	0.672 to 0.733	0.611	0.575 to 0.647	4256	276 (6.5%)
Income group						
Low-income countries*	0.847	0.782 to 0.913	0.381	0.284 to 0.478	193	54 (28.0)
Lower–middle-income countries†	0.708	0.660 to 0.756	0.537	0.480 to 0.594	2246	119 (5.3)
Upper–middle-income countries‡	0.689	0.648 to 0.730	0.602	0.557 to 0.646	2358	163 (6.9)
High-income countries§	0.733	0.707 to 0.759	0.667	0.637 to 0.698	4968	328 (6.6)

AF indicates atrial fibrillation; FHS, Framingham Heart Study; HF, heart failure; and LVS-HARMED, left ventricular, valvular heart disease, smoking or other tobacco use, height, age, rheumatic heart disease, myocardial infarction, emergency department discharge rhythm, and diabetes.

*Includes Tanzania, Kenya, Mozambique, and Uganda; 193 patients and 54 events.

†Includes India, Sudan, Senegal, Zambia, Cameroon, Nigeria, Egypt, and the Ukraine; 2246 patients and 119 events.

‡Includes Argentina, Brazil, Colombia, Ecuador, Venezuela, Chile, Russia, Latvia, Turkey, Iran, South Africa, Thailand and China; 2358 patients and 163 events.

§Includes Japan, South Korea, Singapore, Saudi Arabia, the United Arab Emirates, Poland, Slovakia, Hungary, the Czech Republic, Bulgaria, Australia, Spain, Italy, the Netherlands, Germany, Austria, the United Kingdom, Sweden, Ireland, Canada, Denmark and the United States; 4968 patients and 328 events.

patients with AF, particularly in low-income countries. A history of myocardial infarction was more prevalent in lower–middle-income countries, where use of β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, which improve prognosis after high-risk myocardial infarctions,[22] was the least prevalent.

Leaving the ED in AF was the strongest single predictor of incident HF hospitalization and/or death. Confounding-by-indication likely explains this association at least to some degree, since sicker patients may be less likely to receive rhythm control therapies in the ED, as are patients with a longer history of AF. However, there is still uncertainty regarding the benefit of rhythm control in this population, and it is possible that persistence of AF at the time of ED discharge could be causally related to incident HF.[23] In the AF-CHF (Atrial Fibrillation and Congestive Heart Failure) and AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trials there was no lack of reduction in adverse cardiac outcomes in the rhythm control arms.[24,25] Patients in these studies had sinus rhythm maintained using antiarrhythmic medications, which had both toxicity and relatively modest efficacy. Catheter ablation for AF has been associated with reduced incidence of HF in a Danish nationwide registry study,[26] and the CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients With Left Ventricular Dysfunction and Atrial Fibrillation) trial reported a reduction in a composite end point of death and HF hospitalization in patients with established HF.[27] Recent results from EAST-AFNET (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial), with reduction in a composite end point of mortality, stroke, and hospitalization for HF or acute coronary syndrome, as well as a nonsignificant association between early rhythm control therapy and reduced risk of HF hospitalization, is in line with these results.[28] As yet, it has not been determined whether the superior rhythm control strategy inherent in ablation could reduce new-onset HF in patients with AF.[29] Further analyses of published studies[30] and future studies, such as the RAFT-AF (Randomized Ablation-based Atrial Fibrillation Rhythm Control Versus Rate Control Trial in Patients With Heart Failure and High Burden Atrial Fibrillation) trial, are needed to determine this.[31]

Predictors for HF in patients with AF have been previously studied in smaller cohorts, notably in the FHS (n=725), which derived a prediction algorithm for the 10-year risk of HF in AF.[8] Several predictors (age, history of myocardial infarction or diabetes, left ventricular hypertrophy, and evidence of significant valvular disease) are included in both the FHS prediction score and LVS-HARMED, and many of the same variables also predict HF in the general population.[32] The RELY AF registry provides complementary data to the

Table 4. Observed Outcomes by Quartiles of Predicted LVS-HARMED Risk Among Income Groups*

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
Full study population					
Total, N	2330	2330	2331	2330	9321
HF death, n (%)	3 (0.13)	32 (1.37)	36 (1.54)	62 (2.66)	133 (1.43)
HF hospitalization, n (%)	24 (1.03)	77 (3.30)	137 (5.88)	299 (12.83)	537 (5.76)
Total HF (hospitalization and/or HF death), n (%)	26 (1.12)	104 (4.46)	162 (6.95)	336 (14.42)	628 (6.74)
Predicted score range	(0.0032, 0.0310)	(0.0310, 0.0515)	(0.0515, 0.0847)	(0.0847, 0.8477)	(0.0032, 0.8477)
Low-income countries†					
Total, N	44	44	44	44	176
HF death, n (%)	0 (0.00)	1 (2.27)	3 (6.82)	1 (2.27)	5 (2.84)
HF hospitalization, n (%)	3 (6.82)	3 (6.82)	14 (31.82)	33 (75.00)	53 (30.11)
Total HF (hospitalization and/or HF death), n (%)	3 (6.82)	3 (6.82)	14 (31.82)	33 (75.00)	53 (30.11)
Predicted score range	(0.0097, 0.0639)	(0.0639, 0.1330)	(0.1330, 0.4623)	(0.4623, 0.8477)	(0.0097, 0.8477)
Lower–middle-income countries‡					
Total, N	532	532	532	532	2128
HF death, n (%)	1 (0.19)	10 (1.88)	16 (3.01)	21 (3.95)	48 (2.26)
HF hospitalization, n (%)	6 (1.13)	8 (1.50)	16 (3.01)	39 (7.33)	69 (3.24)
Total HF (hospitalization and/or HF death), n (%)	7 (1.32)	17 (3.20)	30 (5.64)	56 (10.53)	110 (5.17)
Predicted score range	(0.0055, 0.0266)	(0.0266, 0.0412)	(0.0412, 0.0622)	(0.0622, 0.3905)	(0.0055, 0.3905)
Upper–middle-income countries§					
Total, N	566	567	567	566	2266
HF death, n (%)	4 (0.71)	6 (1.06)	11 (1.94)	21 (3.71)	42 (1.85)
HF hospitalization, n (%)	8 (1.41)	22 (3.88)	33 (5.82)	59 (10.42)	122 (5.38)
Total HF (hospitalization and/or HF death), n (%)	12 (2.12)	28 (4.94)	40 (7.05)	71 (12.54)	151 (6.66)
Predicted score range	(0.0032, 0.0361)	(0.0361, 0.0590)	(0.0590, 0.0921)	(0.0921, 0.3764)	(0.0032, 0.3764)
High-income countries‖					
Total, N	1187	1188	1188	1188	4751
HF death, n (%)	0 (0.00)	8 (0.67)	9 (0.76)	21 (1.77)	38 (0.80)
HF hospitalization, n (%)	8 (0.67)	51 (4.29)	81 (6.82)	153 (12.88)	293 (6.17)
Total HF (hospitalization and/or HF, n (%) death)	8 (0.67)	55 (4.63)	86 (7.24)	165 (13.89)	314 (6.61)
Predicted score range	(0.0039, 0.0313)	(0.0313, 0.0529)	(0.0529, 0.0876)	(0.0876, 0.4300)	(0.0039, 0.4300)

HF indicates heart failure.

*Includes patients without missing values for the LVS-HARMED (left ventricular, valvular heart disease, smoking or other tobacco use, height, age, rheumatic heart disease, myocardial infarction, emergency department discharge rhythm, and diabetes) score.

†Includes Tanzania, Kenya, Mozambique, and Uganda.

‡Includes India, Sudan, Senegal, Zambia, Cameroon, Nigeria, Egypt, and the Ukraine.

§Includes Argentina, Brazil, Colombia, Ecuador, Venezuela, Chile, Russia, Latvia, Turkey, Iran, South Africa, Thailand, and China.

‖Includes Japan, South Korea, Singapore, Saudi Arabia, the United Arab Emirates, Poland, Slovakia, Hungary, the Czech Republic, Bulgaria, Australia, Spain, Italy, the Netherlands, Germany, Austria, the United Kingdom, Sweden, Ireland, Canada, Denmark, and the United States.

Framingham analysis by including an ED population and patients from countries representing a range of national income, with variations in the prevalence risk factors for both AF and HF. In contrast to the FHS, the RE-LY AF registry evaluates early, 1-year outcomes in patients following an ED visit with AF, identifying a group of patients who might benefit from early postdischarge referral to specialist care.[19] In this time frame and among ED patients, the LVS-HARMED score had somewhat better discrimination than the FHS score, which is intended to be used to predict 10-year risk. Furthermore, the LVS-HARMED score also had good discrimination for a stroke outcome.[33,34]

Strengths and Limitations

The RE-LY AF registry includes patients from 47 different countries and data from an ED setting. This has permitted us to generate a score that is based
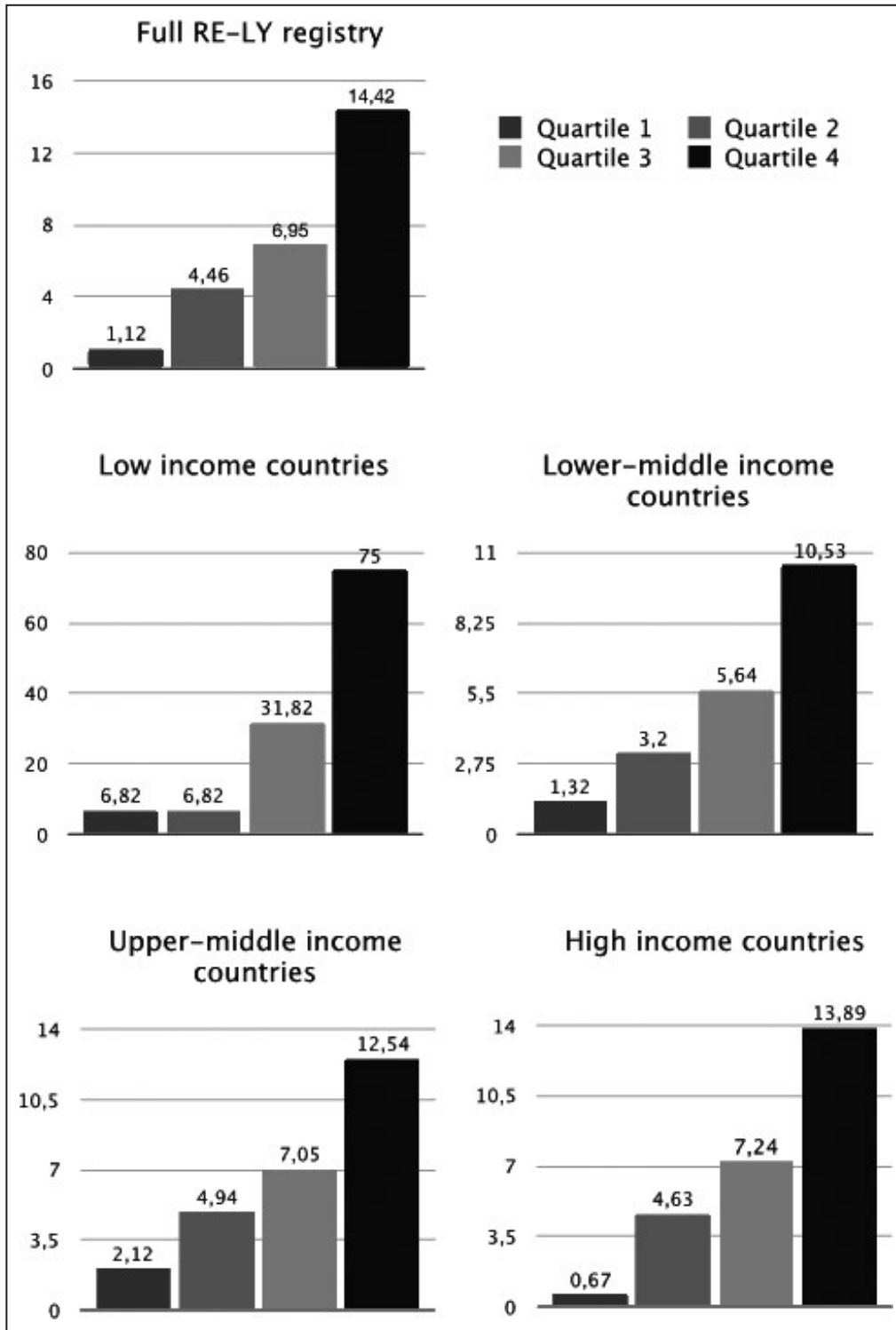
Figure. Observed heart failure (HF) hospitalizations and HF deaths by quartile of LVS-HARMED (left ventricular, valvular heart disease, smoking or other tobacco use, height, age, rheumatic heart disease, myocardial infarction, emergency department discharge rhythm, and diabetes) score.
Observed HF hospitalizations and HF deaths across quartiles of the LVS-HARMED score for 1-year risk of new-onset HF after an emergency consultation for atrial fibrillation among country income groups. RE-LY indicates Randomized Evaluation of Long-Term Anticoagulant Therapy.

on variables that are easy to obtain in the ED and is valid worldwide. Many risk scores are developed in less diverse settings; healthcare access and practices vary widely among the included countries, as do underlying conditions. Despite this, the score had good calibration and discrimination among income groups and geographic regions. Some score components, such as rheumatic heart disease, likely contribute more to the discrimination of the score in some settings, whereas other components likely play a larger role in others. Similarly, factors leading to hospital admission for HF differ among the countries included in the RE-LY registry. No particular testing such as N-terminal pro–brain natriuretic peptide, chest radiograph, or echocardiogram was required to confirm the diagnosis; this would have introduced a bias where high-income countries or in some settings individual patients with sufficient resources to pay for diagnostic testing, would be over-represented as cases. As it is, we would argue that the LVS-HARMED score will in each setting identify the cases that are relevant in that setting. Regrettably, time-to-event data were not captured––the events were recorded as a binary variable at the end of a 1-year follow-up. Individuals from the highest-income countries are over-represented in the RE-LY AF registry, but there appears to have been sufficient numbers from low-income and low/middle-income countries to highlight important differences concerning these populations. However, the smaller number of individuals in these countries precluded dividing the sample into derivation and validation cohorts. Instead, the risk score was validated internally in the full population using bootstrap resampling, as recommended by Steyerberg et al,[14] and showed good discrimination after correction of optimism. External validation of the risk score in the AFFORD cohort yielded similar results. Furthermore, the discrimination of the LVS-HARMED score was acceptable or better in all income groups and geographic regions, demonstrating generalizability of the score to a variety of settings. Rather than creating an integer-based points score, our prediction model weighted predictor variables by their beta-coefficients (rounded to 3 decimals), in order to avoid unnecessary dichotomization of predictors, which may introduce bias and reduce statistical power.[35] Because of the diverse setting of the RE-LY population, the score does not include biomarkers. Future studies are needed to ascertain whether the addition of biomarkers may improve the discrimination of LVS-HARMED in settings where biomarker use is feasible.

CONCLUSIONS

The risk of new-onset HF is high in patients following an ED visit for AF in all countries, regardless of economic status. This risk can be quantified using the LVS-HARMED score. Preventative strategies should be considered in patients with high LVS-HARMED HF risk.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics and Medical History, by hospitalization for heart failure status.

Baseline characteristics and medical history	Overall	No HF during follow up	With HF during follow-up	P-value
Number of Patients - with follow-up data	N=9765	N=9101	N=664	
Age(yrs), mean±SD	64.9±14.9	64.7±14.7	68.2±16.5	<0.001
Sex (male), , %	53.8	54.3	46.5	<0.001
Weight (kg), mean±SD	73.1±19.3	73.4±19.2	69.2±19.5	<0.001
Height (cm), mean±SD	166.6±10.5	166.8±10.5	163.8±11.3	<0.001
BMI (kg/m2), mean±SD	26.2±5.8	26.2±5.8	25.6±5.9	0.006
Systolic Blood Pressure(mmHg), mean±SD	133.0±24.5	133.1±24.3	132.0±26.4	0.329
Diastolic Blood Pressure(mmHg), mean±SD	80.5±15.0	80.6±15.0	79.0±15.8	0.009
Heart Rate (bpm), mean±SD	103.4±31.0	103.6±31.0	101.5±30.8	0.090
Prior diagnosis of Atrial Fibrillation, %	59.1	58.8	64.3	0.007
- Paroxysmal, %*	35.6	36.4	25.3	<.001
- Persistent, %*	23.7	24.2	17.3	0.001
- Permanent, %*	40.7	39.4	57.4	<.001
Current arrhythmia				
- Atrial Fibrillation, %	92.3	92.2	93.1	0.416
- Atrial Flutter, %	7.7	7.8	6.9	0.421
Patient in atrial fibrillation/atrial flutter when left ED, %	73.0	72.2	83.7	<0.001
Repeat visits for atrial fibrillation/atrial flutter complications during study period	16.8	15.3	36.9	<0.001
History of				
- Myocardial infarction, %	11.2	10.8	17.3	<0.001
- Coronary artery disease, %	25.5	24.6	37.2	<0.001
- Hypertension, %	59.2	58.8	65.8	<0.001
- Stroke/transient ischemic attack, %	13.2	13.0	15.7	0.053
- Rheumatic heart disease, %	10.7	10.3	15.5	<0.001
- Significant Valvular heart disease, %	18.3	17.8	25.2	<0.001
- Emphysema/chronic obstructive pulmonary disease, %	8.0	7.7	11.9	<0.001
- Diabetes mellitus, %	19.5	19.0	26.1	<0.001
- Permanent pacemaker, %	3.8	3.7	5.1	0.060
- Left ventricular hypertrophy, %	17.6	17.0	26.7	<0.001
Tobacco use, %	16.0	15.8	19.3	0.018
Alcohol use - # standard drinks/week, (median) mean±SD deviation	(0)3.3±7.66	(0)3.4±7.74	(0)3.1±6.09	0.644
Prior interventions				
Beta blocker, %	53.2	53.0	55.9	0.150
Calcium channel blocker, %	27.7	27.6	29.4	0.314
Angiotensin converting enzyme-inhibitor, %	27.6	27.0	36.7	<.0001

Angiotensin receptor blocker, %	15.3	15.5	13.0	0.078
Digoxin, %	25.6	24.9	36.1	<.0001
Diuretic, %	41.0	39.7	58.1	<.0001
Amiodarone, %	14.8	14.3	21.5	<.0001
Sotalol, %	3.2	3.3	1.1	0.001
Flecainide, %	1.6	1.7	0	0.001
Prior cardioversions, %	11.3	11.3	11.0	0.793
Prior atrial fibrillation catheter, surgical or Maze procedures, %	2.5	2.6	1.1	0.014
Prior AV-node ablation, %	0.5	0.5	0.9	0.129
Prior left atrial appendage occlusion or amputation, %	0.1	0.1	0	0.370
Medication use after emergency department visit				
Beta blocker, %	53.2	53.0	55.9	0.150
Calcium channel blocker, %	27.7	27.6	29.4	0.314
Angiotensin converting enzyme-inhibitor, %	27.6	27.0	36.7	<.0001
Angiotensin receptor blocker, %	15.3	15.5	13.0	0.078
Digoxin, %	25.6	24.9	36.1	<.0001
Diuretic, %	41.0	39.7	58.1	<.0001
Amiodarone, %	14.8	14.3	21.5	<.0001
Sotalol, %	3.2	3.3	1.1	0.001
Flecainide, %	1.6	1.7	0	0.001

SD= Standard deviation
[*] Based on the total number of patients with prior atrial fibrillation.

Table S2. Calibration table for the LVS-HARMED score in AFFORD.

Predicted probability	N	Observed, n (%)	Expected, n (%)
0-0.019	129	1 (0.8)	5.1 (3.9)
0.02-0.04	207	13 (6.2)	9.1 (4.4)
0.04-0.06	20	1 (5.0)	1.3 (6.7)
0.06-0.08	6	1 (16.7)	0.5 (8.9)
Total	367	17 (4.6)	17.0 (4.6)

Hosmer Lemeshow p = 0.22

Table S3. Odds ratios for LVS-HARMED score components across country income groups.

	Low income countries*		Lower-middle income countries[†]		Upper-middle income countries [‡]		High income countries[§]	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Left ventricular hypertrophy	0.797 (0.135-4.708)	0.7112	1.058 (0.472-2.371)	0.8646	1.407 (0.865-2.289)	0.1517	1.609 (1.214-2.134)	0.0021
Valvular heart disease	2.308 (0.309-17.23)	0.2773	1.118 (0.504-2.478)	0.7171	0.741 (0.338-1.627)	0.4195	1.948 (1.356-2.797)	0.0010
Smoking/other tobacco use	2.210 (0.261-18.70)	0.3225	2.444 (1.039-5.751)	0.0441	1.172 (0.713-1.928)	0.4999	1.474 (1.074-2.023)	0.0186
Height, per cm	0.994 (0.952-1.037)	0.7727	0.961 (0.940-0.981)	0.0002	0.979 (0.959-1.000)	0.0468	0.983 (0.972-0.995)	0.0068
Age, per year	1.008 (0.978-1.038)	0.6088	1.010 (0.995-1.026)	0.1807	1.024 (1.009-1.040)	0.0019	1.036 (1.024-1.048)	<.0001
Rheumatic heart disease	1.129 (0.092-13.91)	0.8877	2.006 (0.762-5.285)	0.1061	2.385 (1.029-5.529)	0.0440	1.383 (0.698-2.742)	0.3329
Myocardial infarction	2.764 (0.000-36x10^4)	0.5274	2.191 (0.616-7.794)	0.1171	1.769 (0.974-3.210)	0.0591	1.727 (1.250-2.384)	0.0020
ED discharge rhythm is AF	0.486 (0.039-6.048)	0.3436	2.582 (1.089-6.121)	0.0369	1.682 (1.035-2.734)	0.0381	1.809 (1.291-2.534)	0.0015
Diabetes mellitus	0.539 (0.017-17.00)	0.5214	1.092 (0.512-2.329)	0.7632	1.579 (1.006-2.477)	0.0474	1.369 (1.036-1.808)	0.0290

* Includes Tanzania, Kenya, Mozambique, and Uganda; 193 subjects and 54 events.

†Includes India, Sudan, Senegal, Zambia, Cameroon, Nigeria, Egypt, and the Ukraine; 2246 subjects and 119 events.

‡ Includes Argentina, Brazil, Colombia, Ecuador, Venezuela, Chile, Russia, Latvia, Turkey, Iran, South Africa, Thailand and China; 2358 subjects and 163 events.

§ Includes Japan, South Korea, Singapore, Saudi Arabia, the United Arab Emirates, Poland, Slovakia, Hungary, the Czech Republic, Bulgaria, Australia, Spain, Italy, the Netherlands, Germany, Austria, the United Kingdom, Sweden, Ireland, Canada, Denmark and the United States of America; 4968 subjects and 328 events.

Table S4. Odds ratios for LVS-HARMED coefficients in a model that also includes medication use after emergency department discharge.

	β	Odds Ratio (95% CI)	P-value
Intercept	-1.117		0.2134
Left ventricular hypertrophy	0.377	1.458 (1.175- 1.809)	0.0010
Valvular heart disease	0.270	1.309 (0.994- 1.725)	0.0552
Smoking/other tobacco use	0.324	1.383 (1.096- 1.746)	0.0075
Height, per 3 cms	-0.070	0.932 (0.907- 0.959)	<.0001
Age, per 5 years	0.099	1.104 (1.064- 1.146)	<.0001
Rheumatic heart disease	0.480	1.616 (1.135- 2.300)	0.0091
Myocardial infarction	0.587	1.799 (1.403- 2.307)	<.0001
ED discharge rhythm is AF	0.501	1.650 (1.296- 2.101)	0.0001
Diabetes mellitus	0.242	1.273 (1.032- 1.572)	0.0256
Diuretic after ED	0.640	1.896 (1.555- 2.313)	<.0001
Calcium channel blocker (any) after ED	-0.031	0.970 (0.797- 1.180)	0.7551
Beta blocker after ED	0.094	1.099 (0.913- 1.323)	0.3110
Angiotensin Receptor blocker (ARB) after ED	-0.318	0.728 (0.556- 0.954)	0.0223
ACE-inhibitor after ED	0.042	1.043 (0.848- 1.282)	0.6842
Digoxin after ED	0.267	1.307 (1.066- 1.602)	0.0113

Figure S1. Calibration plot for the LVS-HARMED score in the RE-LY registry.

P= 0.217 (Hosmer–Lemeshow test)
Intercept= 0
Slope= 1.07 (0.99 , 1.15)

Observed Proportion Having the Outcome

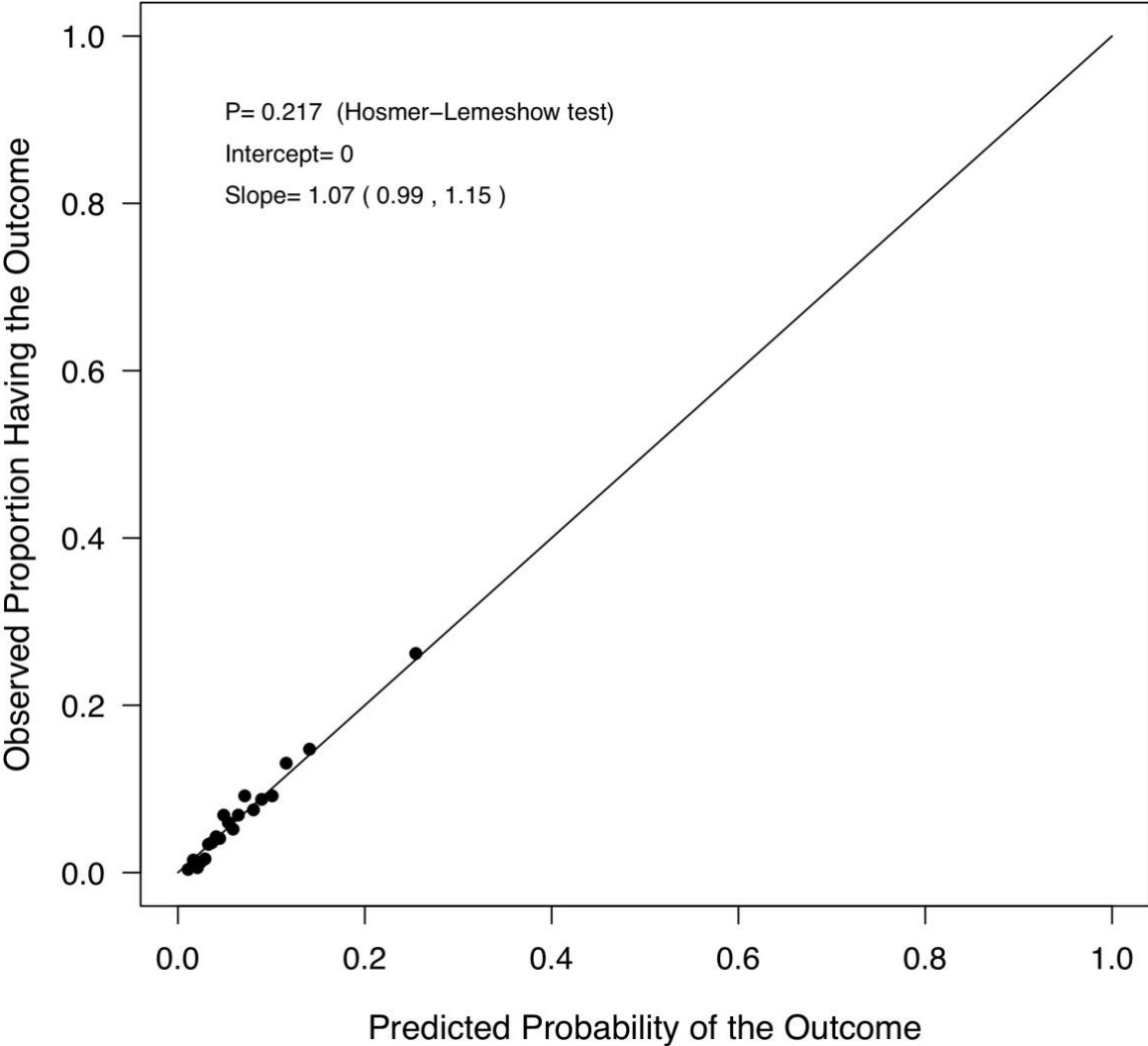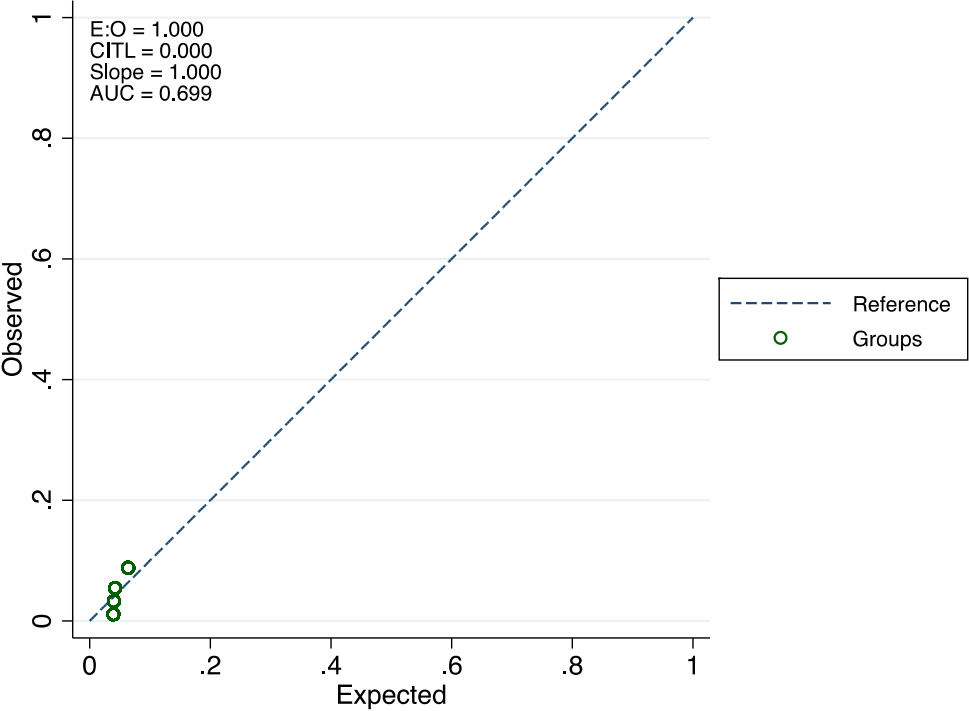Predicted Probability of the Outcome

Figure S2. Calibration plot for the LVS-HARMED score in the Atrial Fibrillation and Flutter Outcomes & Risk Determination (AFFORD) study study.

E:O = Expected vs observed ratio
CITL = Calibration in the large
AUC= Area under the curve

Figure S3. Receiver operator characteristic (ROC) curve for the LVS-HARMED score in the full RE-LY registry.
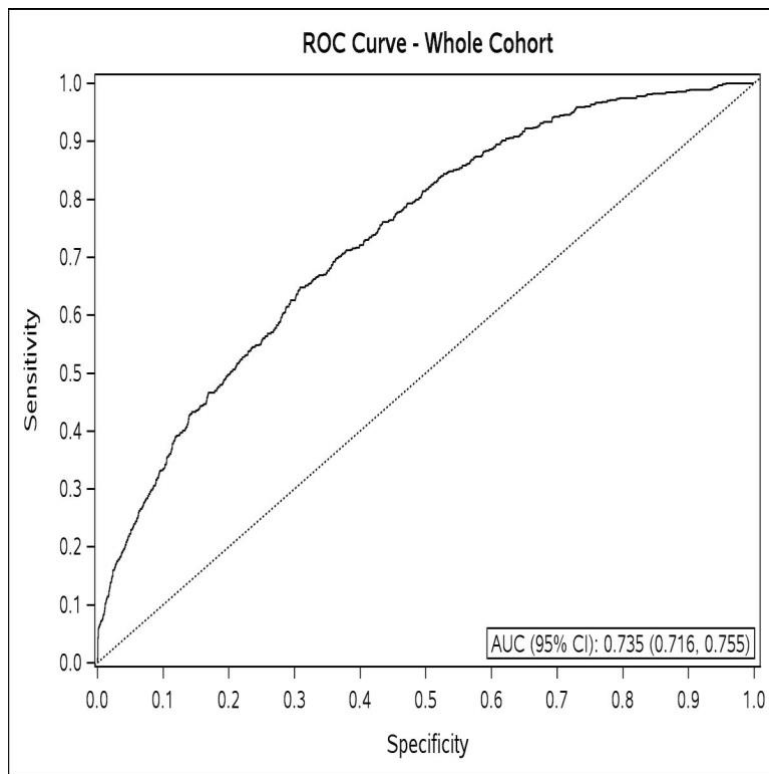
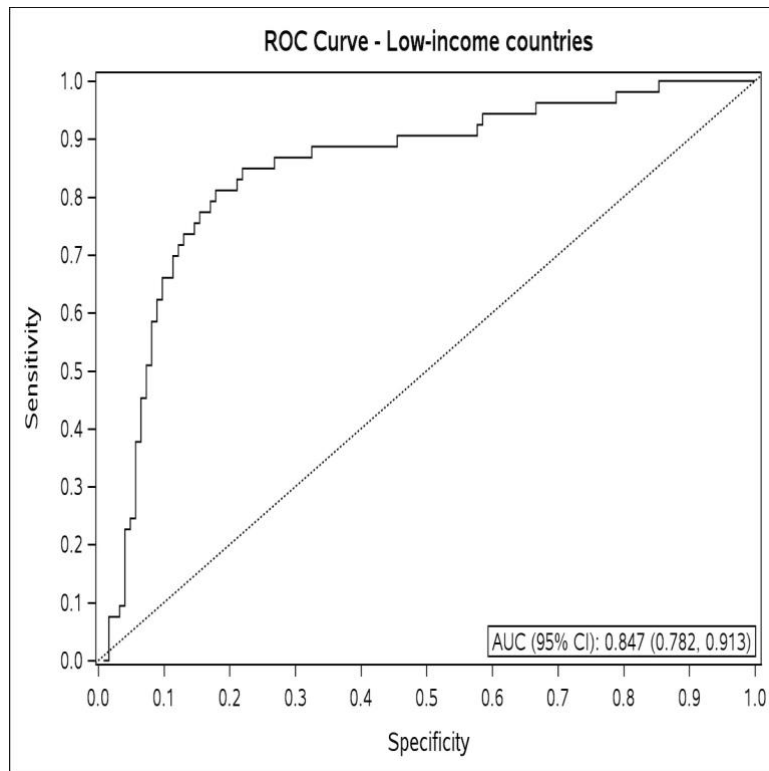**Figure S4. Receiver operator characteristic (ROC) curve for the LVS-HARMED score in low income countries.**

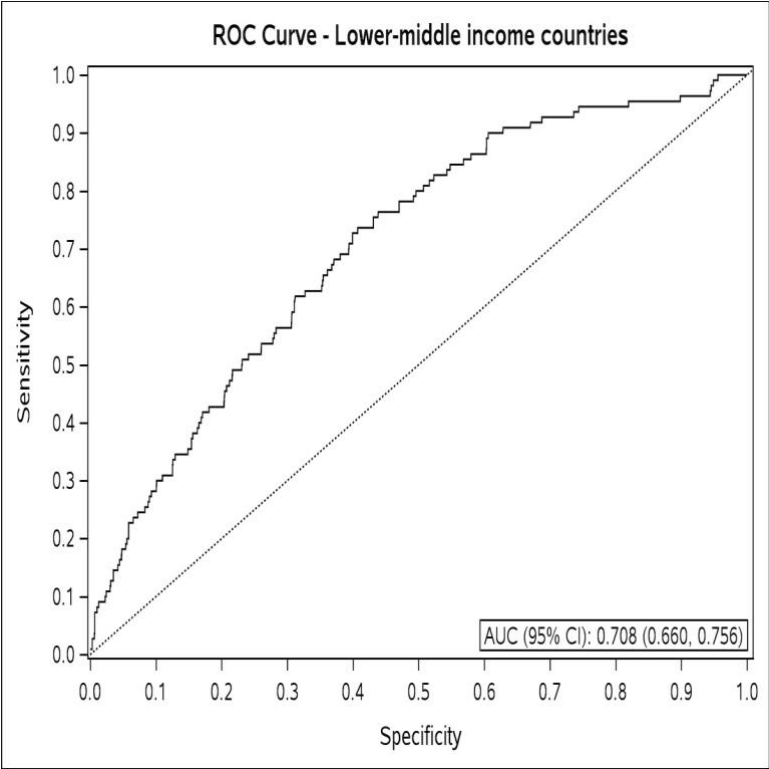ROC Curve - Low-income countries

AUC (95% CI): 0.847 (0.782, 0.913)

Figure S5. Receiver operator characteristic (ROC) curve for the LVS-HARMED score in lower-middle income countries.

Figure S6. Receiver operator characteristic (ROC) curve for the LVS-HARMED score in upper-middle income countries.
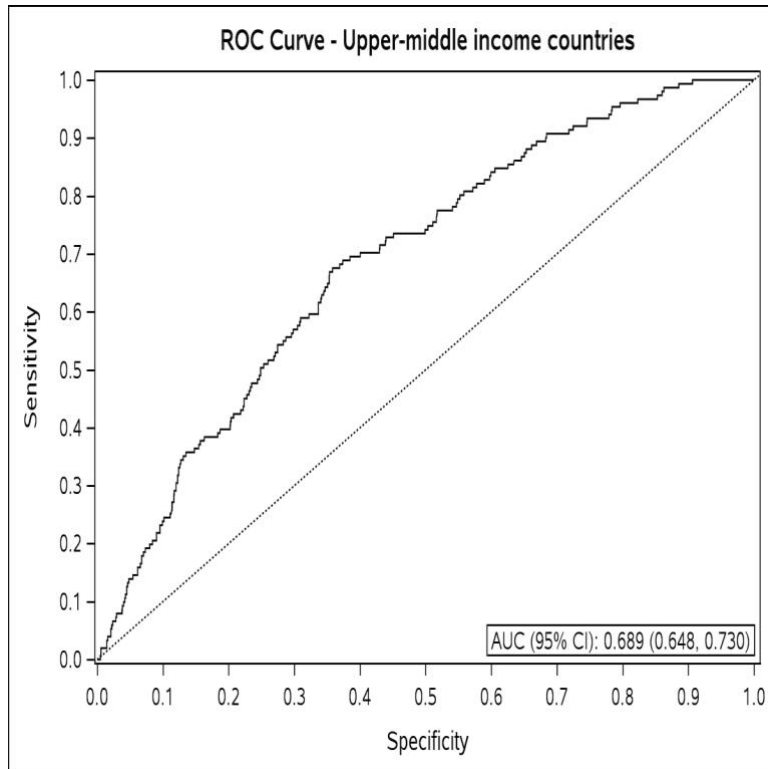
Figure S7. Receiver operator characteristic (ROC) curve for the LVS-HARMED score in high income countries.
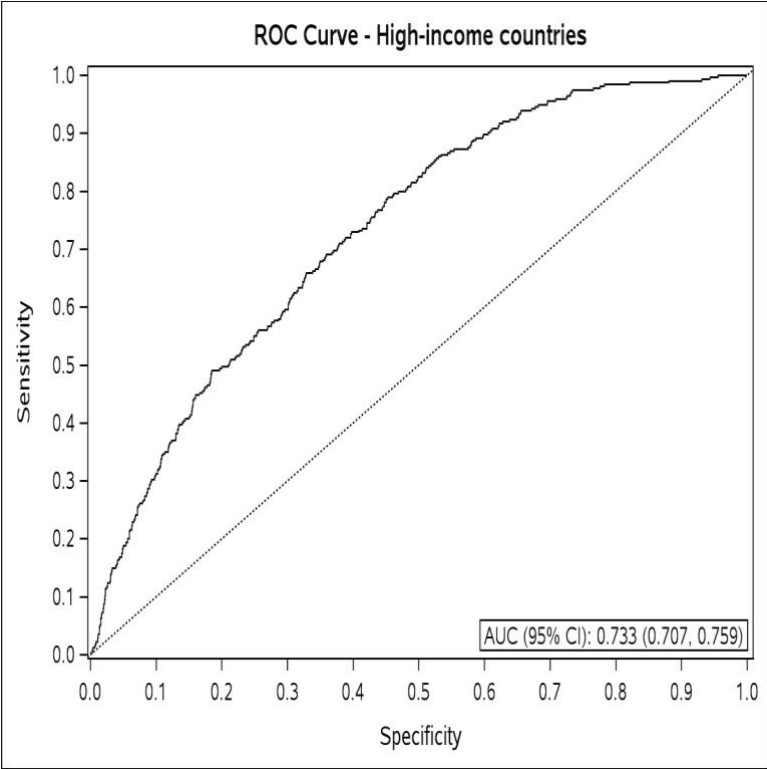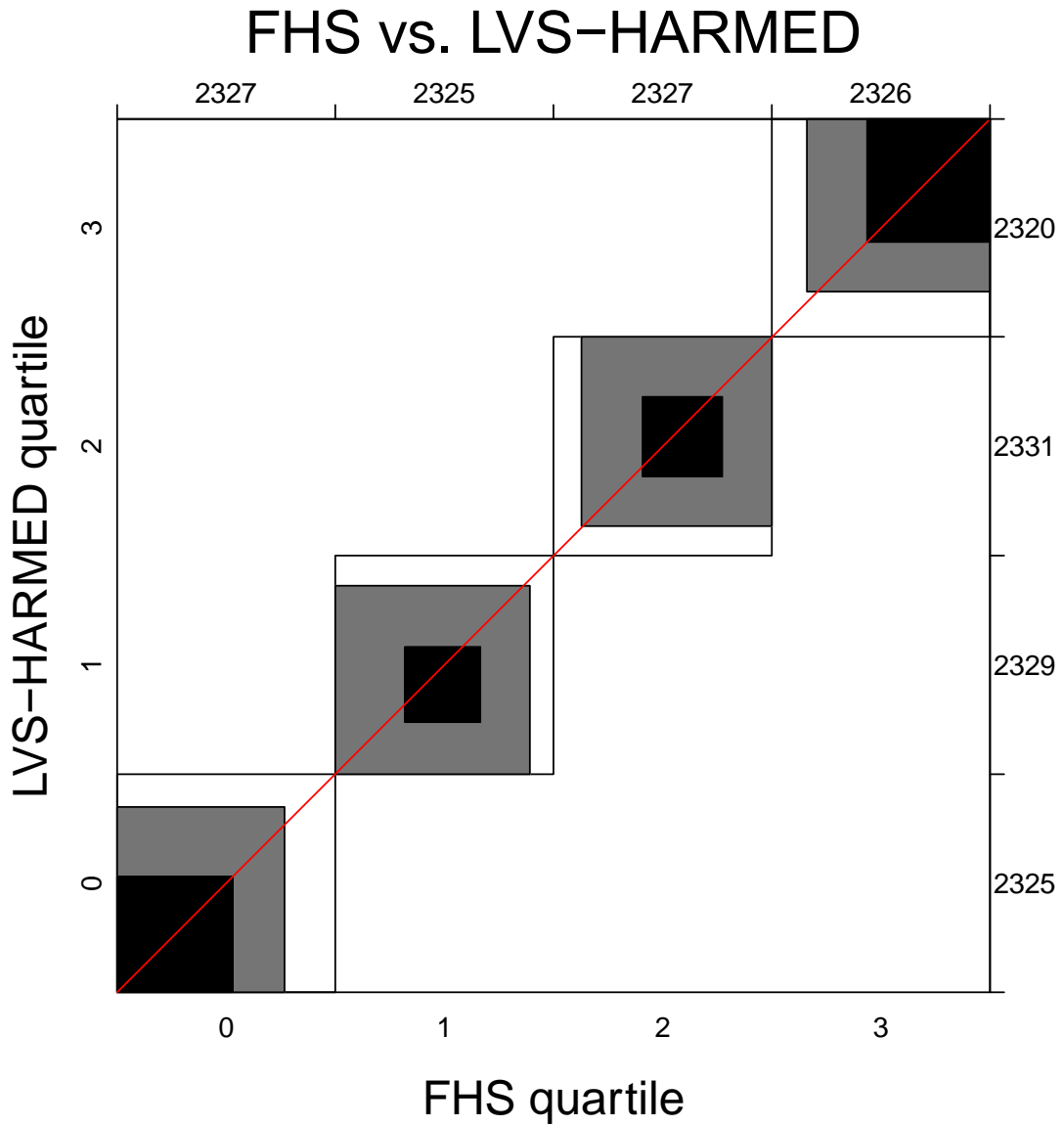
Figure S8. Agreement plot for the LVS-HARMED and FHS scores.

Bangdiwala statistics for the agreement between LVS-HARMED and FHS scores= 0.654

Black squares denote observed agreement, grey squares denote partial agreement and white squares denote the total within each quartile.

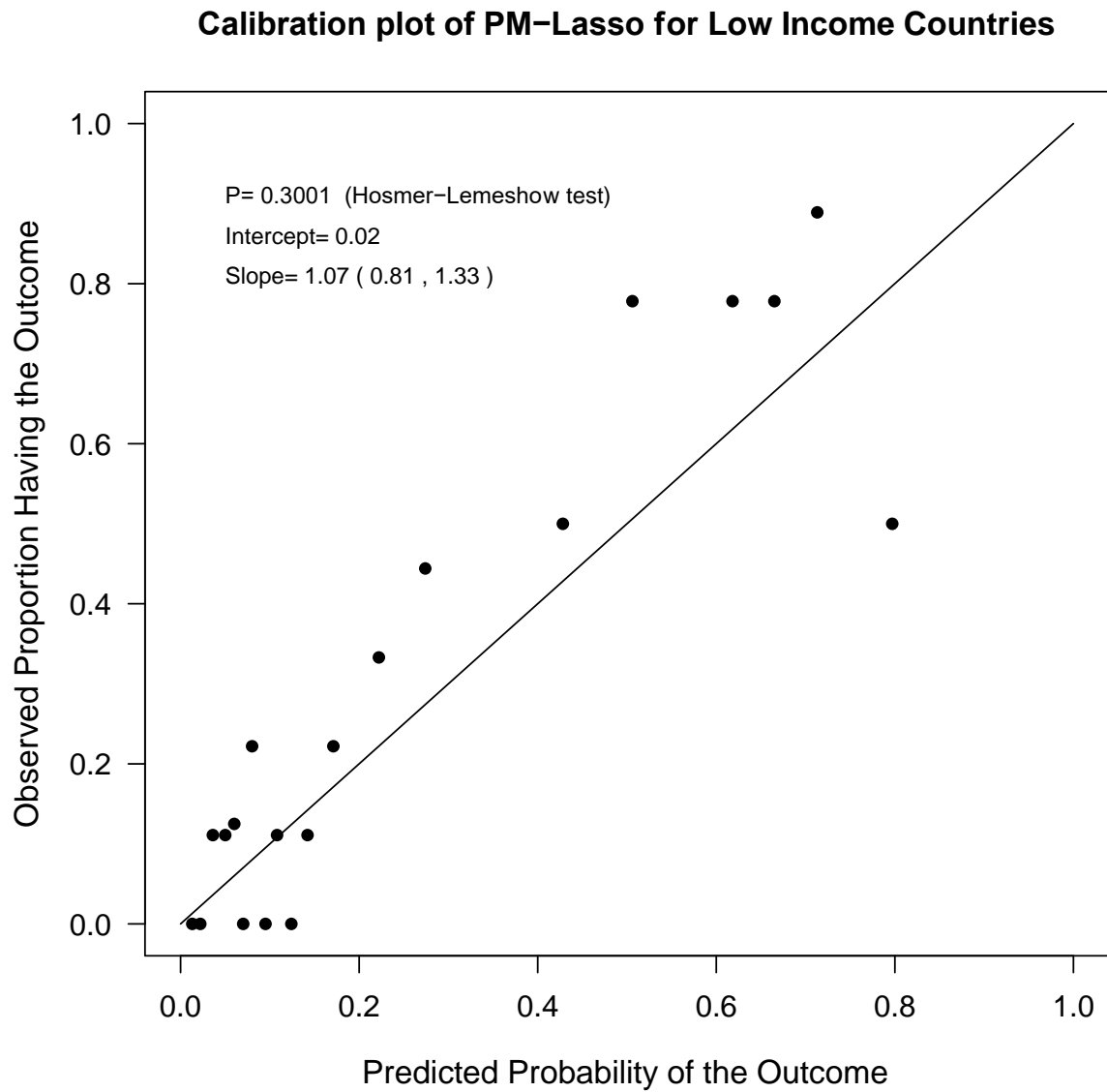**Figure S9. Calibration plot for the LVS-HARMED score in low income countries.**

Calibration plot of PM−Lasso for Low Income Countries

P= 0.3001 (Hosmer−Lemeshow test)

Intercept= 0.02

Slope= 1.07 (0.81 , 1.33)

Observed Proportion Having the Outcome

Predicted Probability of the Outcome

Figure S10. Calibration plot for the LVS-HARMED score in lower-middle income countries

Calibration plot of PM−Lasso for Lower−middle Income Countries

P= 0.8477 (Hosmer−Lemeshow test)

Intercept= 0

Slope= 1.11 (0.9 , 1.32)

Figure S11. Calibration plot for the LVS-HARMED score in upper-middle income countries.

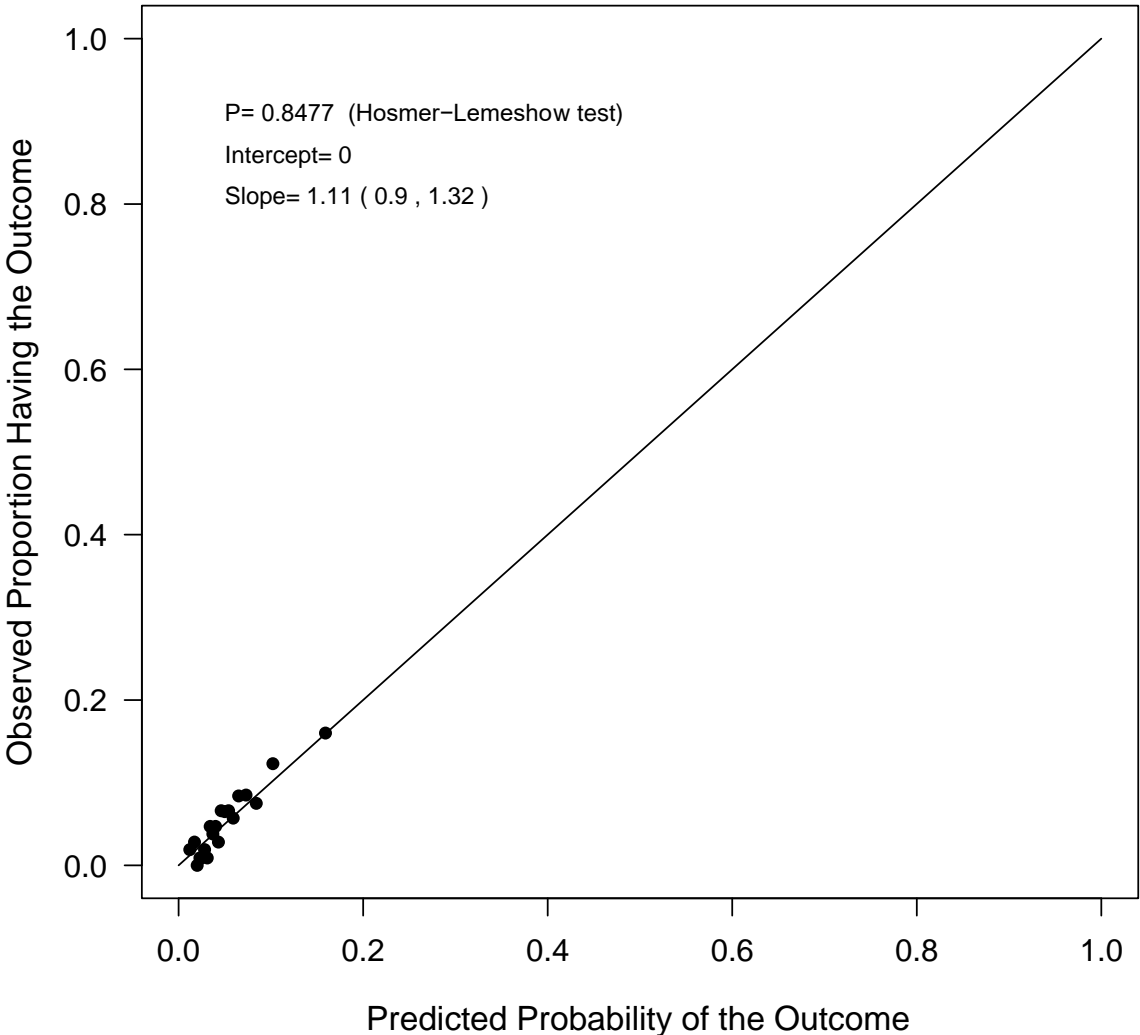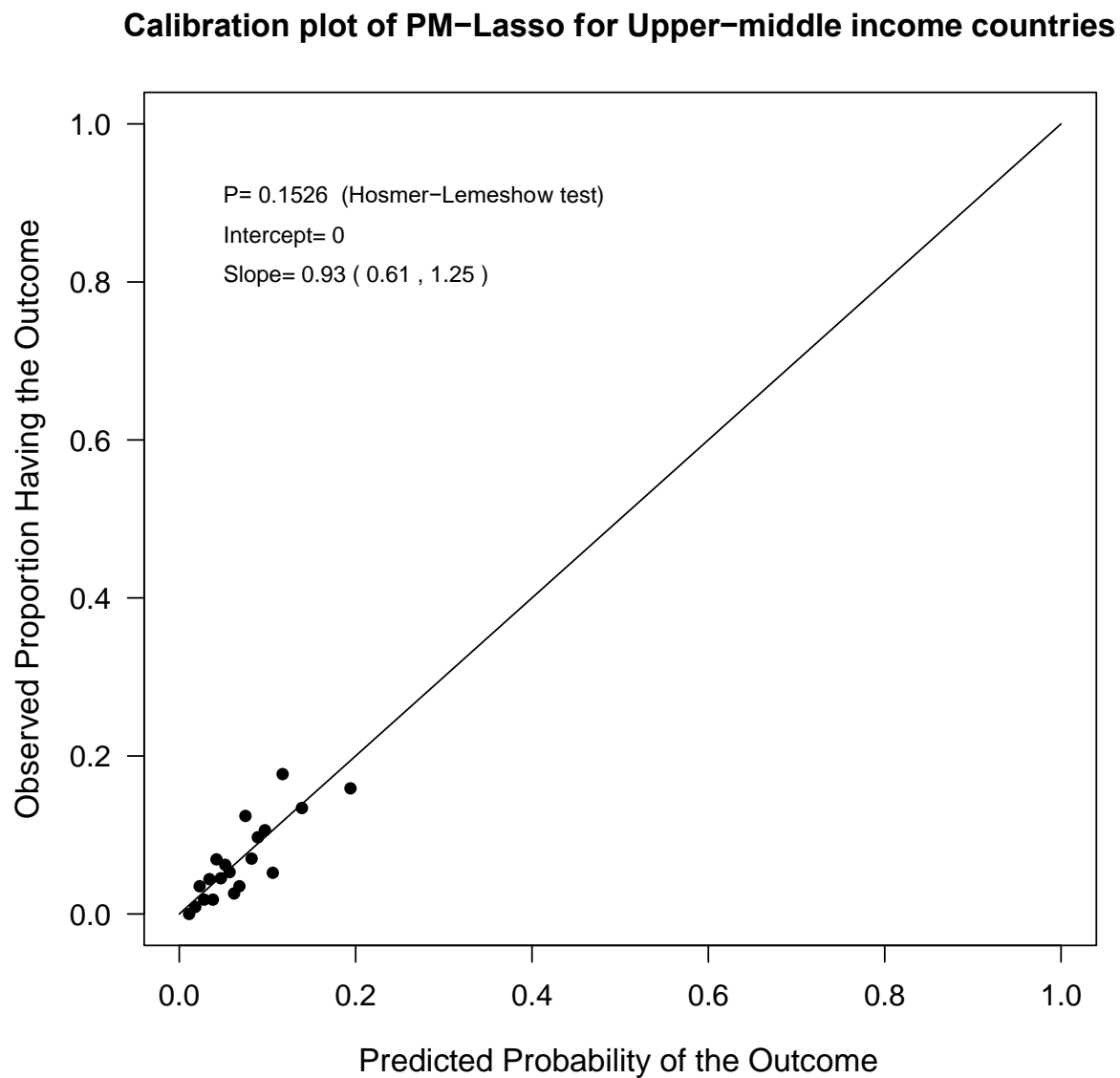Calibration plot of PM−Lasso for Upper−middle income countries

Figure S12. Calibration plot for the LVS-HARMED score in high income countries.

Calibration plot of PM−Lasso for High Income Countries

P= 0.2275 (Hosmer−Lemeshow test)
Intercept= −0.01
Slope= 1.09 (0.95 , 1.23)

Observed Proportion Having the Outcome

Predicted Probability of the Outcome