The 2013 ACC/AHA risk score and subclinical cardiac remodeling and dysfunction: Complementary in cardiovascular disease prediction

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The 2013 ACC/AHA Risk Score and Subclinical Cardiac Remodeling and Dysfunction: Complementary in Cardiovascular Disease Prediction

Short title: Cardiac abnormalities and ASCVD risk

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1. INTRODUCTION

Cardiovascular (CV) diseases pose a major burden on public health and healthcare [1,2]. The prevalence of CV diseases remains high as a result of increased life expectancy and risk factors such as hypertension and diabetes mellitus. Of note, in the presence of CV risk factors, the heart gradually remodels [3,4] and its function progressively declines [5,6] years to decades before symptoms present. Recent heart failure guidelines already emphasized the need to adequately detect subclinical phase of cardiac maladaptation and remodeling in order to modify risk factors and timely counter CV pathophysiology [7].

CV risk scores play a central role in tailoring CV preventive strategies. In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) derived sex- and race-specific estimates from 4 population cohorts to calculate the 10-year risk for a first atherosclerotic CV disease (ASCVD) in individuals 40 to 79 years of age [8]. The resulting Pooled Cohort Equations were found to outperform other risk models such as SCORE and the Framingham Risk Score in predicting CV disease [9,10]. Recent CV prevention guidelines now recommend the use of the Pooled Cohort Equations to assess 10-year ASCVD risk and to start a clinician-patient discussion to decide on the type and intensity of CV preventive measures such as initiation of statin therapy [9,11–14].

Risk enhancers such as biochemical and imaging biomarkers might provide incremental information beyond the 2013 ACC/AHA risk score. Therefore, the ACC and the AHA advocate to investigate the incremental value of nontraditional risk enhancers beyond the Pooled Cohort Equations for ASCVD risk prediction [8]. Within this context, detection of subclinical maladaptation and malfunctioning of the heart by echocardiography might augment CV disease prediction of the currently endorsed risk grading. Previously, echocardiographic abnormalities reflecting subclinical yet adverse left ventricular (LV) remodeling [4,15] and systolic [16,17] and diastolic dysfunction [18] were found to independently of traditional risk factors predict CV outcome in the community. Moreover, a combination of echocardiographic remodeling and dysfunction indexes proved

complementary for CV outcome in asymptomatic subjects [16]. So far, the additive value of LV hypertrophy for CV disease prediction has been demonstrated beyond non-endorsed CV risk scores based on traditional risk factors [19,20].

To date, however, no study has yet investigated the potential incremental value of echocardiographic profiles for CV outcome beyond ASCVD risk assessment recommended by cardiology societies. In this population study, we therefore explored for the first time the complementarity between ASCVD risk score and echocardiographic profiling in predicting adverse CV outcome.

2. METHODS

2.1 STUDY POPULATION. The Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO), a large family-based population resource on the genetic epidemiology of cardiovascular phenotypes, received a priori approval from the Ethics Committee of the University of Leuven. We randomly recruited a population sample in northern Belgium [21]. Seven Belgian municipalities provided listings of all inhabitants sorted by address. Households were the sampling unit. We numbered households and generated a random-number list using SAS software (SAS Institute, Cary, NC). Households with a number matching the list were invited; household members older than 18 years were eligible. For this particular sub-study, we invited 1851 individuals for an examination including echocardiography from May 2005 to January 2015. We obtained written informed consent in 1447 participants (participation rate, 78.2%). As the Pooled Cohort Equations apply to individuals between 40-79 years only, we excluded 381 participants either younger than 40 (n=341) or older than 79 years old (n=40). We additionally excluded 82 participants presenting atrial fibrillation (n=7), a cardiac pacemaker (n=5) or suboptimal echocardiographic image quality (n=70). In total, we statistically analyzed 984 subjects (see *Supplemental Figure 1* for study flow chart).

2.2 ECHOCARDIOGRAPHIC PROFILING. Using a Vivid 7 Pro or Vivid E9 (GE Vingmed, Horten, Norway), two experienced observers obtained conventional echocardiographic

images along the parasternal and apical axes [16,22].

One observer (T.K.) performed conventional echocardiographic measurements blinded to the participants' characteristics using EchoPac software version 113 (GE Vingmed, Horten, Norway) as recommended [22] and as detailed in *Supplemental Methods*. LV concentric remodeling was defined as a relative wall thickness (RWT) >0.42 [22]. LV hypertrophy was an LV mass of 50 $g/m^{2.7}$ in men and 47 $g/m^{2.7}$ in women [22,23]. We considered participants with an E/e' ratio (a non-invasive surrogate of LV filling pressure) >8.5 as having LV diastolic dysfunction [18]. Diastolic dysfunction was confirmed using differences in durations between mitral A flow and reverse pulmonary veins flow, tricuspid regurgitation and elevation in left atrial volume index [18]. Two experienced observers (T.K. and N.C.) derived LV longitudinal strain (LS) using myocardial speckle-tracking software (Q-analysis, GE Vingmed) [24]. An absolute global LS below 17.4% in men and 18.5% in women was suggestive of early LV systolic dysfunction. The thresholds used to define the echocardiographic abnormalities were previously shown to predict cardiac events in the community [16,18,23].

2.3 CV RISK PROFILING. We administered a standardized questionnaire to collect information on the subject's medical history, smoking and drinking habits and medication intake. We verified and supplemented self-reported disease by medical records provided by general practitioners and regional hospitals. Brachial blood pressure was the average of 5 auscultatory readings obtained in seated position. Fasting blood samples were drawn for measurement of serum creatinine, total cholesterol, HDL-C and blood glucose. Definitions of hypertension, diabetes mellitus and renal failure are specified in *Supplemental Methods*.

2.4 ASSESSMENT OF 10-YEAR ASCVD RISK. We applied the sex-specific Pooled Cohort Equations for white Caucasians to estimate the 10-year risk for a first ASCVD event as endorsed by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk [8]. These equations enclose age, sex, systolic blood pressure, antihypertensive treatment, total cholesterol, HDL-C, current smoking status, history of diabetes mellitus and interactions between these risk factors [8]. Based on the risk score distribution (*Supplemental Figure 2*),

we categorized participants without a prior CV event as at low (<2.5%, n=292), borderline (2.5-7.5%, n=289) or intermediate-to-high CV risk (≥7.5%, n=300). In the 2018 ACC/AHA lipid guidelines, the 7.5% limit represents the cut-off for eligibility for statin treatment in primary prevention [12]. Participants who had experienced a CV event before the baseline examination (n=103) were assigned to a separate group (very high risk). 47, 31 and 25 subjects respectively experienced 1, 2 or more CV events before the baseline examination. *Supplemental Table 1* lists the cause-specific CV morbidity of these participants at the time of the examination.

2.5 ASSESSMENT OF OUTCOME. To study the incidence of CV events in relation to baseline ACC/AHA risk score and subclinical echocardiographic abnormalities, we collected outcome data on average 7.5±3.6 years after the baseline examination. We ascertained the vital status of the participants until January 17, 2017. During follow-up, 73 participants died. We applied the International Classification of Disease codes for the immediate and underlying cause of death [16]. We assessed the incidence of non-fatal events via a follow-up visit or a telephone interview, repeating the standardized questionnaire used at baseline. All self-reported diseases were ascertained and supplemented by medical records provided by general practitioners and regional hospitals [16]. Fatal and non-fatal CV events comprised coronary events, heart failure, atrial fibrillation, life-threatening arrhythmias, pulmonary hypertension, stroke, transient ischemic attack, aortic aneurysm, arterial embolism and arterial revascularization. Only the first event was considered in outcome analyses. *Supplemental Table 2* lists the cause-specific incidence of CV mortality and morbidity during follow-up.

2.6 STATISTICAL ANALYSIS. We used SAS version 9.4 (SAS Institute, Cary, NC, USA) for database management and statistical analysis. Means and proportions were compared by a large sample z-test and χ^2 test, respectively. Level of significance was set at a 2-sided $P<0.05$. We evaluated the distributions of all variables and normalized them by logarithmic transformation if needed. We used the Kaplan-Meier method for estimation of the CV event

free survival according to the ASCVD risk profile and the presence of LV abnormalities (LV remodeling, abnormal LS and/or diastolic dysfunction). Excluding subjects with previous CV events, we also calculated Cox regression hazard ratios for CV events per ASCVD/LV profile subgroup, expressing the hazard ratio versus the average risk of the 881 subjects at primary CV risk. Finally, we assessed the improvement in CV event prediction when adding the echocardiographic features to the ACC/AHA risk score by evaluating the improvements in C-statistic, integrated discrimination (IDI) and continuous net reclassification (NRI) indexes [25].

3. RESULTS

3.1 CHARACTERISTICS OF PARTICIPANTS.

The mean age of the 984 participants (52.3% women, 51.5% hypertensive) was 57.0 (SD, 10.1) years. *Table 1* lists the clinical and echocardiographic characteristics per CV risk group. As expected, participants at intermediate-to-high ASCVD risk were significantly older and had a higher prevalence of hypertension, diabetes mellitus and renal failure than the <7.5% risk groups (P<0.001; *Table 1*). Left atrial volume, RWT, LV mass, and E/e' ratio were significantly higher whereas E/A ratio and e' peak were significantly lower in participants at intermediate-to-high risk than in those with a low or borderline 2013 ACC/AHA risk score (P<0.001; *Table 1*).

Of note, the prevalence of hypertension, diabetes mellitus and renal failure did not differ between the group with intermediate-to-high 2013 ACC/AHA risk score and the patients with previous CV events (P≥0.050; *Table 1*). In contrast, left atrial volume and LV mass indexes and E/e' ratio were significantly higher in the CV patients than in the participants at intermediate-to-high ASCVD risk (P≤0.0073; *Table 1*).

3.2 LV REMODELING AND DYSFUNCTION AND THE 2013 ACC/AHA RISK SCORE.

The prevalence of LV remodeling, an abnormal LS and diastolic dysfunction was respectively 32.9%, 23.5% and 11.4% in the 881 participants without previous CV events and 66.0%, 39.9% and 47.6% in the 103 CV patients (*Figure 1A*). The prevalence of LV remodeling and dysfunction increased progressively from low to intermediate/high 10-year ASCVD risk

(*Figure 1B-C*). Indeed, participants at intermediate-to-high ASCVD risk and those with a previous CV event had significantly higher odds to present LV concentric remodeling (OR, 4.84 and 4.30), LV hypertrophy (OR, 5.93 and 12.3), abnormal LS (OR, 2.04 and 3.05) and LV diastolic dysfunction (OR, 25.3 and 65.3) than participants at low risk (*P*<0.001 for all; *Supplemental Figure 3*). In support, the probability for maladaptive LV phenotypes rose progressively with the 10-year ASCVD risk increasing on a continuous scale (*Supplemental Figure 4*).

3.3 PREDICTION OF INCIDENT CV EVENTS BY 10-YEAR ASCVD RISK AND ECHOCARDIOGRAPHIC PROFILES.

The median follow-up time was 7.8 years (5^{th} to 95^{th} percentile, 2.3-12.3). During 7334 person-years of follow-up, 116 participants experienced at least one fatal or nonfatal CV endpoint (15.8 events per 1000 person-years). *Supplemental Figure 5* presents the CV event rates per 1000 person-years by ASCVD risk quintiles and LV profiles. With increasing 10-year ASCVD risk, the CV event rate increased stronger in participants with at least one LV abnormality at baseline (*Supplemental Figure 5*).

Figure 2 shows the CV event-free survival by combinations of 10-year ASCVD risk (<7.5% vs ≥7.5%) and the presence or absence of ≥1 LV abnormality. In subjects with a 10-year ASCVD risk above 7.5%, the incidence of CV events increased significantly if at least one LV abnormality was present at baseline (*Figure 2A*). In contrast, the presence of an LV abnormality at baseline did not discriminate the incidence of CV events in subjects with a 10-year ASCVD risk below 7.5% (*Figure 2A*). In support, compared to the average population risk of subjects free from CV events at baseline, only those who had a 10-year ASCVD risk ≥7.5% and ≥1 LV abnormality at baseline presented a higher risk for a first CV event during follow-up (HR: 3.00; 95% CI, 2.13-4.23, *P*<0.001) (*Figure 2B*). *Supplemental Figure 6* provides Cox HRs for CV events associated with 10-year ASCVD risk (<7.5% vs ≥7.5%) and each cardiac maladaptive profile (normal LV versus concentric remodeling, hypertrophy, abnormal LS and diastolic dysfunction).

For prediction of adverse CV events, C-statistic increased with 0.029 (95% CI: 0.004 to 0.053; *P*=0.024), relative IDI was 14.6% (*P*=0.0085) and continuous NRI valued 0.54 (95%CI: 0.33 to 0.76; *P*<0.001) when adding the presence of at least 1 LV abnormality to a ASCVD risk score-based model (*Table 2*). Adding the presence of ≥1 LV abnormality to a ASCVD risk score-based model yielded significant improvement in C-statistics (0.029; *P*=0.024), integrated discrimination (14.6%; *P*=0.0085) and net reclassification (0.54; *P*<0.001) indexes for adverse CV events. When adding the LV features separately to a ASCVD risk score-based model, particularly including of LV diastolic dysfunction improved the prognostic accuracy for CV events, given the significant increase in C-statistic (0.026), the relative IDI (23.9%) and the NRI (0.46) (*P*≤0.016 for all) (*Table 2*).

4. DISCUSSION

In this community-based study, we explored the complementarity between the 2013 ACC/AHA risk grading and echocardiographic profiling in predicting CV outcome. We observed that: i) in subjects at intermediate-to-high ASCVD risk (≥7.5%), the incidence of adverse CV events increased significantly if at least one LV abnormality was present at baseline; and that ii) addition of echocardiographic features to the 2013 ACC/AHA risk score improved the prognostic accuracy for predicting future CV outcome.

Previous observational studies reported associations between the 2013 ACC/AHA risk score and other subclinical CV organ damage such as silent brain infarctions [26] and the presence [27] and progression of coronary artery calcification [28]. Other community-based studies observed that the risk for LV hypertrophy increased with greater overall CV risk [29,30]. To our knowledge, our population study is the first to report associations between an ASCVD risk score and subclinical cardiac abnormalities. Indeed, we observed that the likelihood for subclinical heart remodeling and both systolic and diastolic dysfunction rose significantly with increasing 10-year ASCVD risk.

The 2013 ACC/AHA risk score endorsed by American cardiology societies seemed to be able to identify individuals at high risk for subclinical cardiac maladaptation and

malfunctioning, particularly for early LV diastolic dysfunction. Myocardial ischemia as induced by an atherosclerotic disease such as coronary artery disease (CAD) slows ventricular relaxation, impairs ventricular distensibility and, in consequence, can trigger diastolic dysfunction [31]. In support of our findings, in 2042 participants of the Olmsted County study, subclinical LV diastolic dysfunction was detected in 57.7% of the participants with a history of CAD and only in 24.7% of the participants free from CAD [32]. Of note, metabolites of fatty acid oxidation and inflammation were upregulated in CAD patients with advance stage of diastolic dysfunction [33], highlighting metabolic pathways that might modulate the interrelationship between CAD and LV diastolic dysfunction.

CV risk stratification might be optimized by risk enhancers that provide incremental information to the 2013 ACC/AHA risk score [12,13]. Within this context, population studies previously reported an incremental value of markers of subclinical CV organ damage such as coronary artery calcification [27] and an aggregate biomarker score [35] beyond the Pooled Cohort Equations to predict CV events. Along these lines, echocardiographic profiles indicative of subclinical LV abnormalities seem promising for CV risk stratification given their independent predictive value for CV events in the community [15,16,18]. To our knowledge, our longitudinal population study was the first to assess the incremental value of echocardiographic profiles for CV disease prediction beyond an ASCVD risk score that has been clinically endorsed by professional cardiology societies. So far, previous studies only demonstrated the additive value of LV hypertrophy for CV disease prediction to population-based CV risk scores [19,20]. For instance, in 3980 CARDIA participants LV mass predicted future CV events independently of the Framingham Risk Score and significantly improved discrimination and reclassification of future CV disease [20].

In our outcome analyses, we demonstrated an incremental prognostic value of echocardiographic profiling beyond the 2013 ACC/AHA risk score only in subjects with an intermediate-to-high ASCVD risk. Indeed, in subjects with a 10-year ASCVD risk above 7.5% at baseline, the risk for a CV event increased significantly if at least one LV abnormality was present. Compared to the average population risk for a CV event, the risk of having a CV

event during follow-up were three-fold higher in subjects with a 10-year ASCVD risk ≥7.5% and ≥1 LV abnormality at baseline. Particularly the addition of LV diastolic dysfunction to a ASCVD risk score-based model improved the prognostic accuracy in predicting future CV events. In contrast, echocardiographic profiling did not improve the CV risk prediction beyond the 2013 ACC/AHA risk score in individuals with a 10-year ASCVD risk below 7.5%.

In contrast to laboratory testing and a 12-lead electrocardiogram, current guidelines do not support the use of cardiac imaging modalities such as echocardiography for basic screening in primary prevention [13,23]. Among other risk enhancers [12], echocardiographic profiling might nevertheless supplement the approach currently used for prediction and prevention of CV disease. Based on our findings, individuals with a 10-year ASCVD risk exceeding the 7.5% threshold might benefit from an echocardiographic screening examination. Such targeted imaging approach would enhance the cost-benefit ratio and applicability of echocardiography in risk stratification and management of CV disease.

In the future, echocardiographic findings might thus steer the discussion between clinicians and patients at substantial ASCVD risk and help decide on the type and intensity of preventive measures. Evidently, further studies should first confirm the complementarity between preselection by traditional ASCVD risk grading and echocardiographic screening for CV disease prediction. Moreover, large-scale outcome studies should evaluate the usefulness of echocardiographic profiling for guiding downstream testing and therapies in CV prevention and should, in extent, assess the applicability and cost-effectiveness of such echocardiographic screening.

STUDY LIMITATIONS. Our study has to be interpreted within the context of its limitations and strengths. First, echocardiographic measurements are prone to measurement errors due to signal noise, acoustic artefacts and angle dependency. However, two experienced observer recorded all echocardiographic images using a standardized imaging protocol. All echocardiographic recordings were centrally post-processed by two experienced observers with good reproducibility. Second, although the 2013 ACC/AHA risk score was not specified

for heart failure (in contrast to other population-based risk scores [19,36]), it is the only ASCVD risk score endorsed by American cardiology societies for risk assessment in primary prevention. Third, the participation of exclusively Caucasian Europeans in our study limits the extrapolation of our findings to other ethnicities.

CONCLUSIONS. Echocardiographic profiling enhanced CV risk stratification in individuals at intermediate-to-high ASCVD risk. Future studies should investigate the clinical utility and cost-effectiveness of the complementary use of traditional ASCVD risk scores and targeted echocardiographic screening for CV disease prediction and management.

PERSPECTIVES. In primary prevention, non-invasive imaging tools such as echocardiography might prove useful to better stratify the risk for future CV disease in subjects with an elevated ASCVD risk as assessed by traditional risk scoring. Our findings justify further studies to investigate the effects of targeted echocardiographic screening on CV disease prevention in individuals at moderate-to-high ASCVD risk. We advocate studies evaluating the clinical utility and cost-effectiveness of combined use of endorsed ASCVD risk scores and targeted echocardiographic screening for the prediction and prevention of CV disease.

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Legend to figure

Figure 1. Prevalence of Subclinical Left Ventricular Abnormalities by History of Cardiovascular Disease (panel A) and 10-year ASCVD Risk (panels B and C). [a]*P*<0.05 versus <2.5% 10-year ASCVD risk; [b]*P*<0.05 versus <7.5% 10-year ASCVD risk; [c]*P*<0.05 versus all 10-year ASCVD risk groups. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; LS, longitudinal strain.

Figure 2. Risk for Cardiovascular (CV) Events by 10-Year ASCVD Risk and Left Ventricular (LV) Profile. (A) Kaplan-Meier survival estimates for CV events by 10-year ASCVD risk and left ventricular (LV) profiles. Low and high CV risk was defined as a low-to-borderline (<7.5%) and intermediate-to-high (≥7.5%) 10-year ASCVD risk, respectively. (B) Cox regression hazard ratios (95% CI) by 10-year ASCVD risk and LV profiles express the relative risk for CV events compared to the average risk of the 881 subjects at primary risk (excluding those with CV events prior to the baseline examination).

Table 1. Clinical and Echocardiographic Characteristics of 984 FLEMENGHO Participants.

Characteristic	10-year ASCVD risk			Previous CV event (n=103)
	<2.5% (n=292)	2.5-7.5% (n=289)	≥7.5% (n=300)	
Anthropometrics				
Age, years	47.6 (4.9)	54.4 (6.3)*	64.7 (7.6)*,†	68.6 (7.4)*,†,‡
Female sex, No. (%)	228 (78.1)	131 (45.3)*	108 (36.0)*,†	38 (36.9)*
Body mass index, kg/m²	25.6 (4.2)	27.1 (4.1)*	27.6 (3.9)*	26.8 (3.5)*
Systolic BP, mmHg	122.7 (12.8)	129.9 (13.5)*	141.5 (16.6)*,†	143.3 (19.3)*,†
Diastolic BP, mmHg	80.5 (8.7)	83.2 (8.6)*	84.1 (9.8)*	79.1 (9.2)†,‡
Heart rate, bpm	60.9 (9.6)	61.1 (8.7)	60.8 (9.9)	56.5 (8.9)*,†,‡
Biochemical data				
Serum creatinine, μmol/L	74.9 (14.6)	79.1 (13.3)*	83.4 (15.5)*,†	90.0 (27.0)*,†,‡
eGFR, ml/min per 1.73 m²	84.6 (15.8)	85.0 (16.8)*	80.2 (17.9)*,†	74.6 (19.2)*,†,‡
Total cholesterol, mg/dL	198.7 (35.5)	206.6 (33.5)*	208.0 (37.3)*	182.2 (32.9)*,†,‡
HDL, mg/dL	63.0 (15.6)	55.3 (13.1)*	53.3 (14.3)*	52.3 (13.7)*,†
Blood glucose, mmol/L	4.69 (0.40)	4.84 (0.70)*	5.00 (0.84)*,b	5.11 (1.29)*,†
Questionnaire and clinical data				
Current smoking, No. (%)	30 (10.3)	64 (22.2)*	71 (23.7)*	13 (12.6)†,‡
Drinking alcohol, No. (%)	104 (35.6)	124 (42.9)*	124 (41.3)	35 (34.0)
Hypertensive, No. (%)	69 (23.6)	130 (45.0)*	222 (74.0)*,†	86 (83.5)*,†
Treated for hypertension, No. (%)	27 (9.3)	68 (25.5)*	128 (42.7)*,†	72 (69.9)*,†,‡
On lipid-lowering drugs, No. (%)	26 (8.9)	43 (14.9)*	66 (22.0)*,†	49 (47.6)*,†,‡
History of diabetes, No. (%)	5 (1.7)	5 (1.7)	31 (10.3)*,†	12 (11.7)*,†
Renal failure, No. (%)	10 (3.4)	9 (3.1)	25 (8.3)*,†	22 (21.4)*,†
Echocardiographic data				
LA volume index, ml/m²	29.4 (6.9)	30.9 (8.3)*	33.7 (10.0)*,†	38.6 (12.8)*,†,‡
LV relative wall thickness	0.35 (0.048)	0.38 (0.055)*	0.40 (0.062)*,†	0.40 (0.063)*,†
LV mass/body height$^{2.7}$, g/m$^{2.7}$	37.1 (8.3)	41.9 (8.8)*	46.5 (10.6)*,†	52.2 (14.9)*,†,‡
LV ejection fraction, %	62.0 (5.8)	61.2 (5.8)	60.6 (5.7)*	59.1 (7.4)*,†
LV global LS, %	19.8 (1.9)	19.2 (2.1)*	19.0 (2.4)*	18.4 (2.9)*,†
E/A ratio	1.39 (0.38)	1.14 (0.30)*	0.94 (0.25)*,†	0.95 (0.35)*,†
e' peak, cm/s	12.1 (2.3)	10.2 (2.2)*	8.36 (2.06)*,†	7.40 (2.20)*,†,‡
E/e' ratio	6.59 (1.47)	7.10 (1.72)*	8.22 (2.40)*,†	9.39 (4.15)*,†,‡

Values are mean (SD), number of participants (%) or median (10-90 percentile interval). *P<0.05 versus <2.5% ASCVD risk; †P<0.05 versus 2.5-7.5% ASCVD risk; ‡P<0.05 versus >7.5% ASCVD risk. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LA, left atrium; LS, longitudinal strain; LV, left ventricular.

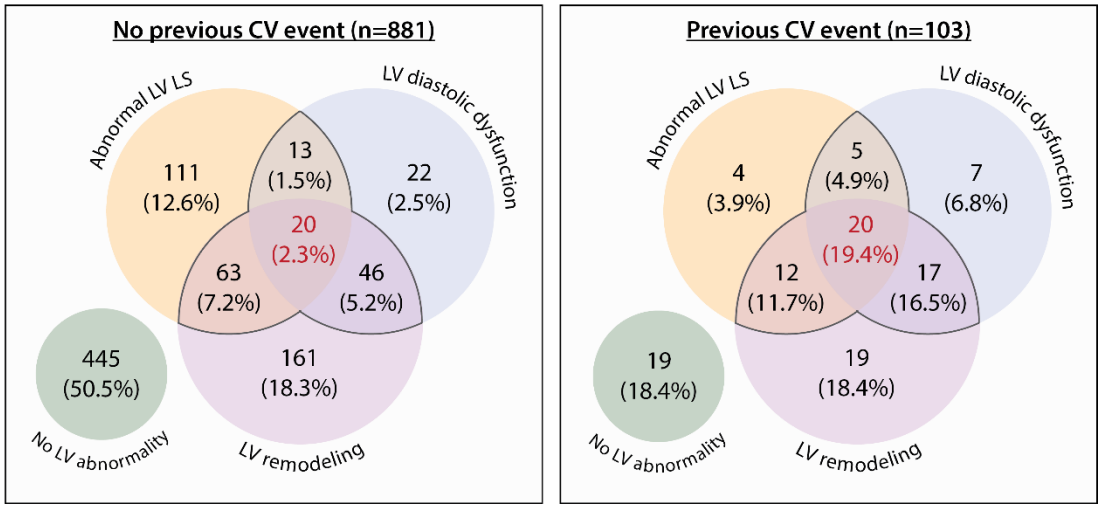
Table 2. Improvements in C-Statistic and Reclassification Indexes in Prediction of Future Cardiovascular Events by Abnormal Echocardiographic Features beyond 10-Year ASCVD Risk

	C-statistic		Integrated Discrimination Improvement		Net Reclassification Improvement	
Model	ΔAUC (95% CI)	*P* value	Absolute IDI (%)	*P* value	NRI (95% CI)	*P* value
Low-to-borderline vs intermediate-to-high 10-year ASCVD risk						
+ LV concentric remodeling	0.010 (-0.014 to 0.034)	0.40	0.0003 (0.42%)	0.81	0.25 (0.030 to 0.46)	0.026
+ LV hypertrophy	0.024 (-0.001 to 0.049)	0.059	0.0038 (5.87%)	0.25	0.37 (0.15 to 0.60)	0.0011
+ Abnormal LV LS	0.027 (0.001 to 0.053)	0.040	0.0065 (9.99%)	0.16	0.31 (0.087 to 0.53)	0.0066
+ LV diastolic dysfunction	0.026 (0.007 to 0.046)	0.0087	0.016 (23.9%)	0.016	0.46 (0.25 to 0.67)	<0.001
+ ≥ 1 LV abnormality	0.029 (0.004 to 0.053)	0.024	0.0096 (14.6%)	0.0085	0.54 (0.33 to 0.76)	<0.001

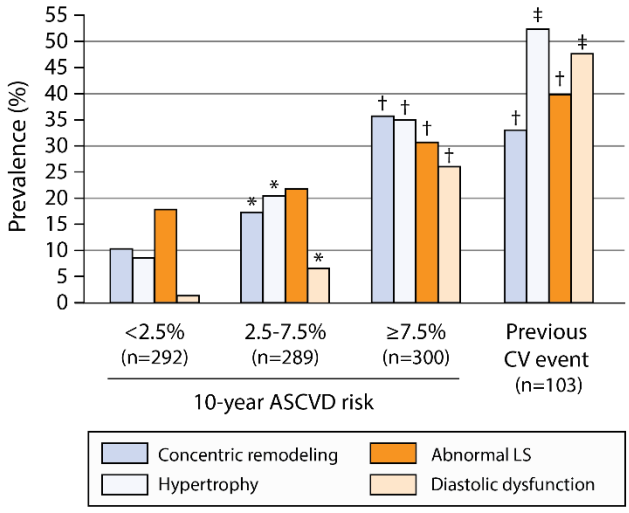
Analysis included the 881 subjects free from CV events at the baseline examination. ASCVD, atherosclerotic cardiovascular disease; AUC, area under the receiver operating characteristic curve; LS, longitudinal strain; LV, left ventricular.

Figure 1. Prevalence of Subclinical Left Ventricular Abnormalities by History of Cardiovascular Disease (panel A) and 10-Year ASCVD Risk (Panels B and C). **P*<0.05 versus <2.5% 10-year ASCVD risk; †*P*<0.05 versus <7.5% 10-year ASCVD risk groups. ‡*P*<0.05 versus all 10-year ASCVD risk groups. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LS, longitudinal strain; LV, left ventricular.

A) LV remodeling and dysfunction by history of cardiovascular disease



B) LV remodeling and dysfunction by 10-year ASCVD risk



C) No. of LV abnormalities by 10-year ASCVD risk

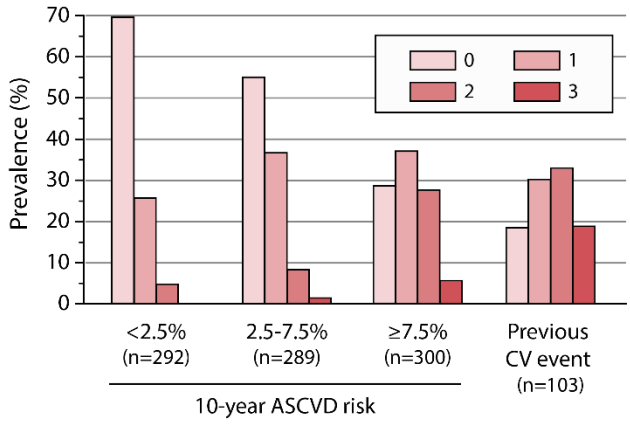
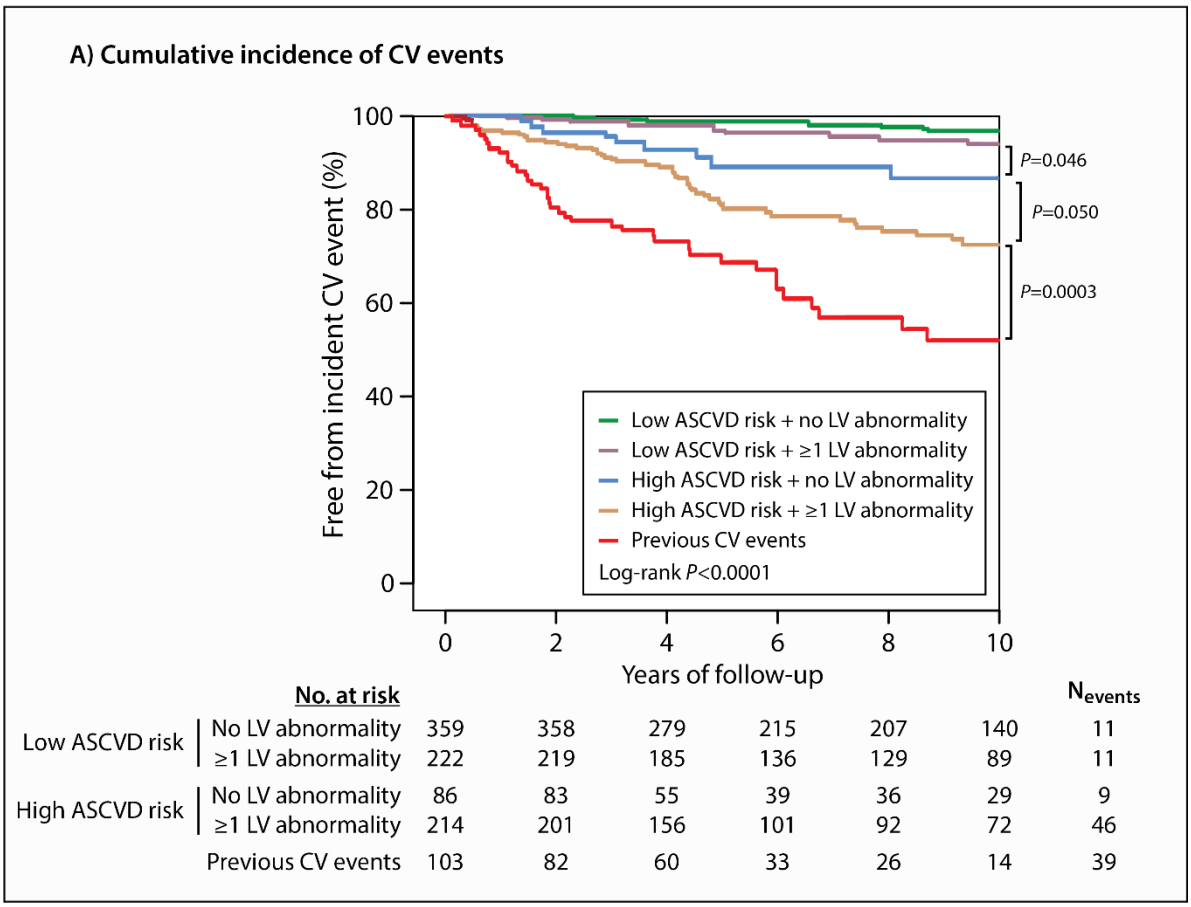
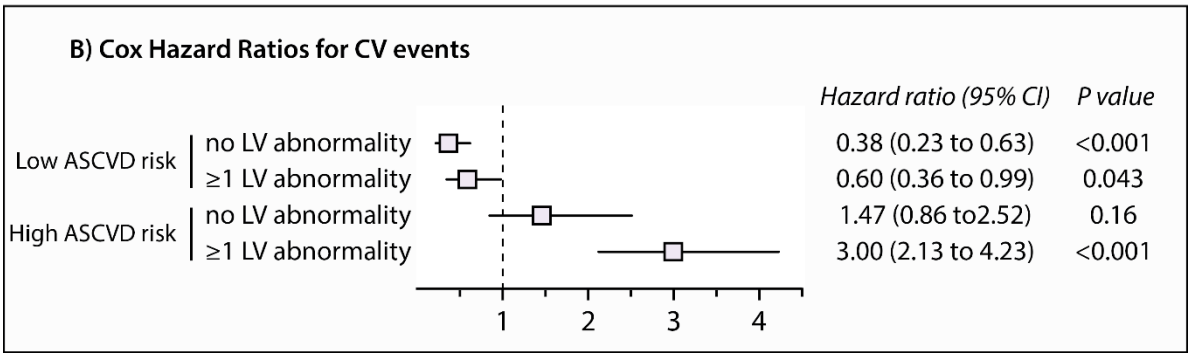


Figure 2. Risk for Cardiovascular (CV) Events by 10-Year ASCVD Risk and Left Ventricular (LV) Profile. (A) Kaplan-Meier event-free survival by 10-year ASCVD risk and LV profiles. Low and high ASCVD risk was defined as a low-to-bordeline (<7.5%) and intermediate-to-high (≥7.5%) 10-year ASCVD risk, respectively. (B) Cox regression hazard ratios (95% CI) by 10-year ASCVD risk and LV profiles express the relative risk for CV events compared to the average risk of the 881 subjects at primary risk (excluding those with CV events prior to the baseline examination).



	No. at risk							N_{events}
Low ASCVD risk	No LV abnormality	359	358	279	215	207	140	11
	≥1 LV abnormality	222	219	185	136	129	89	11
High ASCVD risk	No LV abnormality	86	83	55	39	36	29	9
	≥1 LV abnormality	214	201	156	101	92	72	46
	Previous CV events	103	82	60	33	26	14	39



SUPPLEMENTAL MATERIAL

The 2013 ACC/AHA Risk Score and Subclinical Cardiac Remodeling and Dysfunction: Complementary in Cardiovascular Disease Prediction

EXPANDED METHODS

Echocardiographic measurements. Measurements were averaged over three heart cycles for statistical analysis. LV internal diameter and interventricular septal and posterior wall thickness were measured from 2D-guided M-mode tracing at end-diastole. Relative wall thickness (RWT) was calculated as 0.5 x (interventricular septum + posterior wall) / LV internal diameter at end-diastole. End-diastolic LV dimensions were used to calculate LV mass using an anatomically validated formula. The E/e' ratio, a non-invasive surrogate of LV filling pressure, was the transmitral early diastolic peak blood velocity (E) divided by the peak early diastolic velocity of the mitral annulus (e') averaged from septal, lateral, inferior and posterior acquisition sites. Using myocardial speckle-tracking for assessment of LV longitudinal strain, the LV endocardial border was traced manually at the end-systolic frame of the 4-chamber apical view. The software automatically tracked myocardial speckle motion while dividing the region of interest in LV basal, mid and apical segments. We adjusted the region of interest after visual evaluation of the tracking. Images were rejected if tracking was inadequate in ≥2 segments. We used absolute values of 4-chamber peak systolic midwall LS (i.e. global LS) in statistical analyses.

CV risk profiling. Hypertension was defined as a blood pressure exceeding 140 mmHg systolic and/or 90 mmHg diastolic and/or the use of antihypertensive drugs. Diabetes mellitus was determined by self-report, a fasting serum glucose level above 126 mg/dL and/or the use of antidiabetic agents. Renal failure was defined by self-report or an estimated glomerular filtration rate below 60 mL/min/1.73 m².

SUPPLEMENTAL TABLES

Supplemental Table 1. Cardiovascular Diseases Prior to the Baseline Examination in 103 Participants

History of cardiovascular disease	Number
Cerebrovascular disease	
Stroke	13
Transient ischemic attack	7
Ischemic heart disease	
Angina pectoris	12
Myocardial infarction	21
Chronic ischemic heart disease	27
Pulmonary heart disease	3
Atrial fibrillation/pacemaker	17
Heart failure	8
Diseases of arteries and arterioles	
Aortic aneurysm	6
Peripheral arterial disease	26
Arterial embolism and thrombosis or pulmonary embolism or infarctions	14
Total number of reported CV diseases at baseline	154

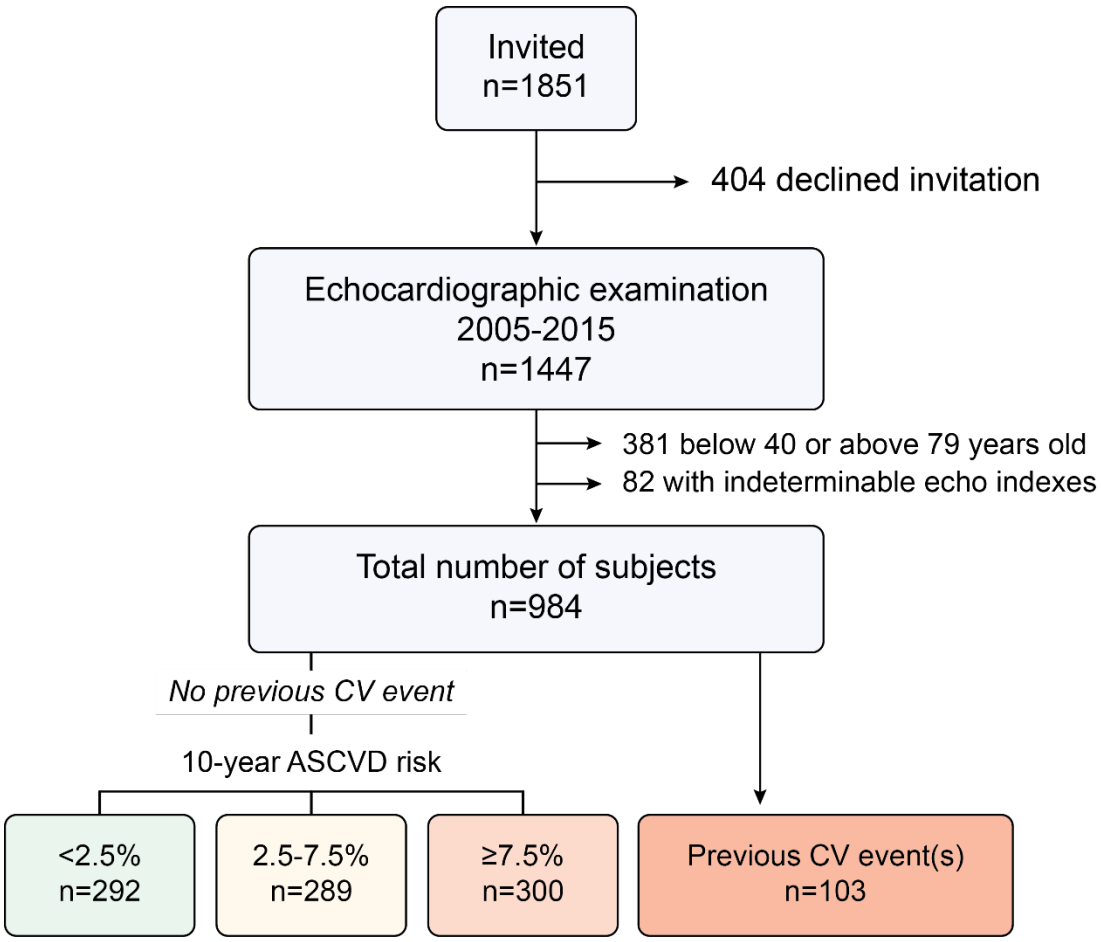
Supplemental Table 2. Fatal and Nonfatal Cardiovascular Events in 984 Participants during Follow-Up

Endpoint	Number of events
Cerebrovascular disease	
Stroke	
Fatal	3
Nonfatal	14
Transient ischemic attack	
Nonfatal	7
Ischemic heart disease	
Angina pectoris	
Nonfatal	11
Myocardial infarction	
Fatal	1
Nonfatal	10
Acute coronary syndrome	
Nonfatal	4
Coronary revascularization	
Nonfatal	30
Pulmonary heart disease	
Nonfatal	5
Atrial fibrillation	
Nonfatal	21
Pacemaker implantation	
Nonfatal	13
Heart failure	
Fatal	6
Nonfatal	12
Diseases of arteries and arterioles	
Aortic aneurysm	
Fatal	1
Nonfatal	5
Peripheral arterial diseases/ revascularization	
Nonfatal	29
Arterial embolism and thrombosis or pulmonary embolism or infarctions	
Nonfatal	5
Total number of all events	177

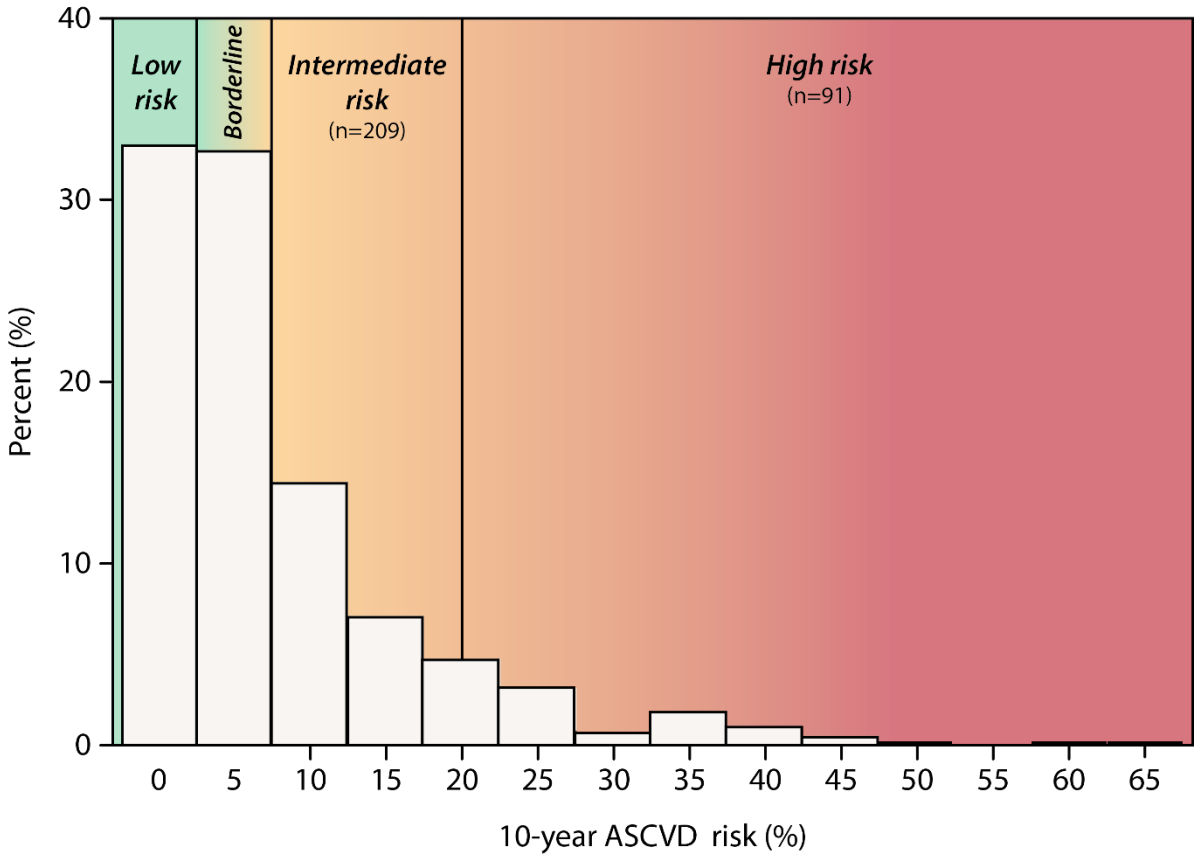
SUPPLEMENTAL FIGURES

- **Supplemental Figure 1:** Flow Chart of the FLEMENGHO Study.
- **Supplemental Figure 2:** Histogram of 10-Year ASCVD Risk Score and Guideline-Based Risk Classification.
- **Supplemental Figure 3.** Association between the Presence of Left Ventricular Abnormalities and 10-Year ASCVD Risk. Squares and horizontal lines represent the odds ratios (OR) and 95% confidence interval for each risk group.
- **Supplemental Figure 4.** Predicted Probabilities for Left Ventricular Abnormalities with 10-year ASCVD risk. Shaded areas represent the 95% confidence interval of the regression line.
- **Supplemental Figure 5:** Event Rate by 10-Year ASCVD Risk Quintiles and LV Profiles. Regression line represents the cubic spline fit. ASCVD risk scores >15% were pooled.
- **Supplemental Figure 6:** Risk for Cardiovascular (CV) Events by 10-Year ASCVD Risk and Left Ventricular (LV) Profiles. Cox regression hazard ratios (95% CI) are presented by combinations of 10-year ASCVD risk and LV abnormalities (concentric remodeling, hypertrophy, abnormal longitudinal strain and diastolic dysfunction) and reflect the risk for CV events to the average risk of the 881 subjects without CV events prior to the baseline examination. Low and high CV risk was defined as a low-to-borderline (<7.5%) and intermediate-high (≥7.5%) 10-year ASCVD risk, respectively.

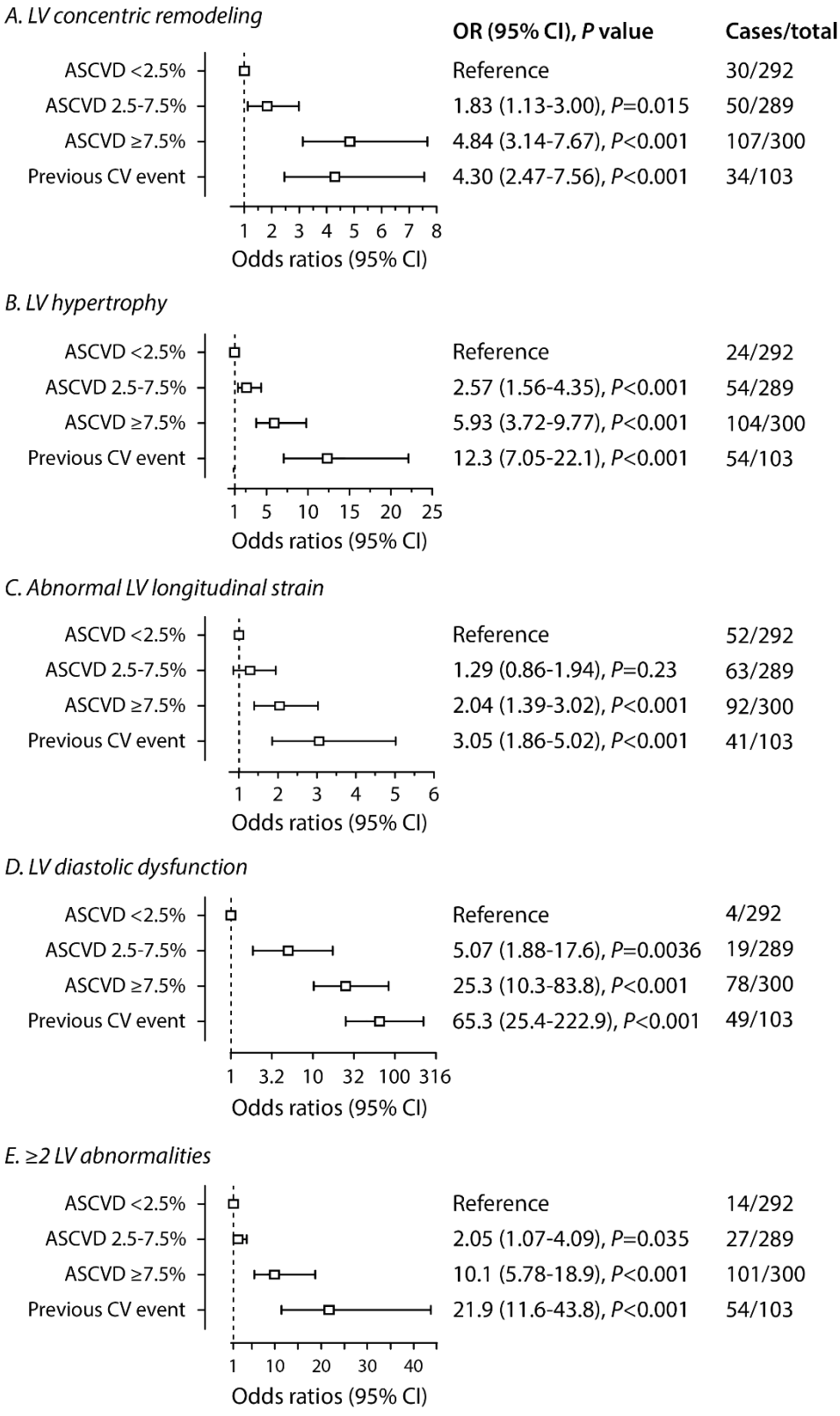
Supplemental Figure 1. Flow Chart of the FLEMENGHO Study



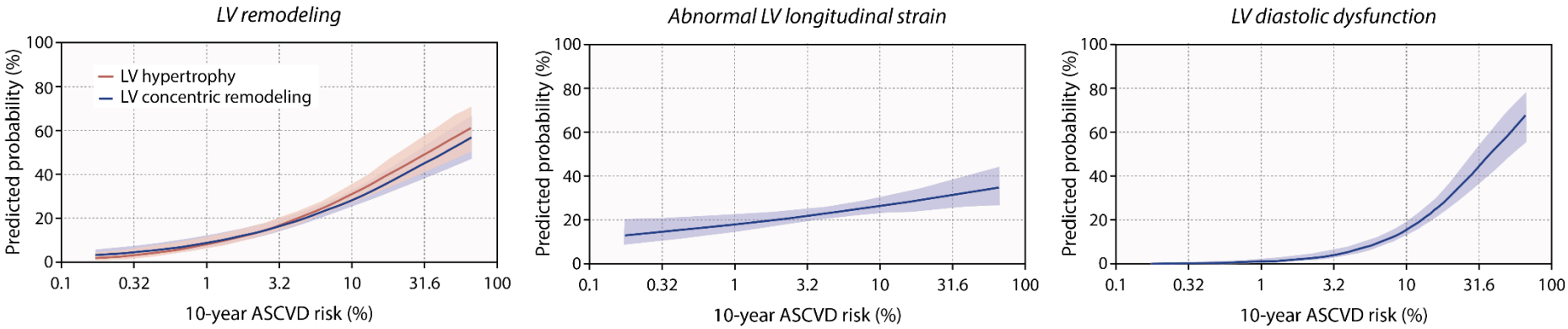
Supplemental Figure 2. Histogram of 10-Year ASCVD Risk Score and Guideline-Based Risk Classification



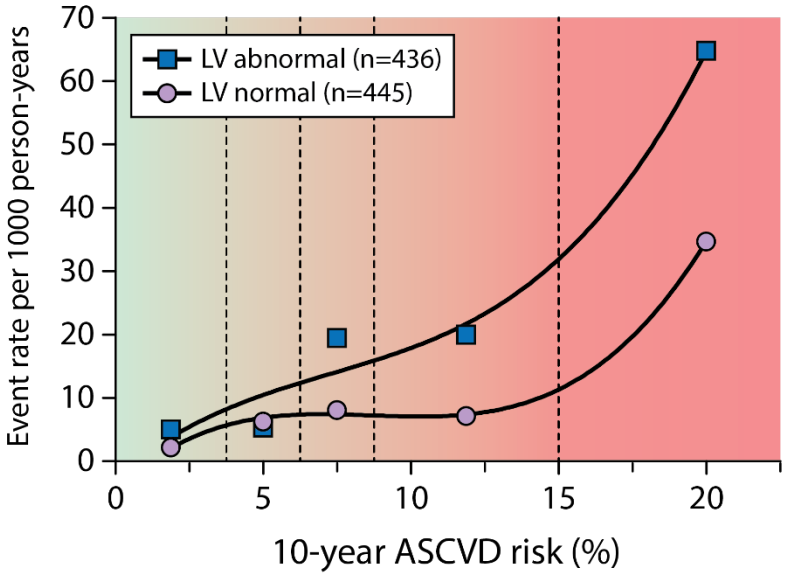
Supplemental Figure 3. Association between the Presence of Left Ventricular Abnormalities and 10-Year ASCVD Risk. Squares and horizontal lines represent the odds ratios (OR) and 95% confidence interval for each risk group.



Supplemental Figure 4. Predicted Probabilities for Left Ventricular Abnormalities with 10-year ASCVD risk. Shaded areas represent the 95% confidence interval of the regression line.



Supplemental Figure 5. Event Rate by 10-Year ASCVD Risk Quintiles and LV Profiles. Regression line represents the cubic spline fit. ACC/AHA scores >15% were pooled.



Supplemental Figure 6. Risk for Cardiovascular (CV) Events by 10-Year ASCVD Risk and Left Ventricular (LV) Profiles. Cox regression hazard ratios (95% CI) are presented by combinations of 10-year ASCVD risk and LV abnormalities (concentric remodeling, hypertrophy, abnormal longitudinal strain and diastolic dysfunction) and reflect the risk for CV events relative to the average risk of the 881 subjects without CV events prior to the baseline examination. Low and high CV risk was defined as a low-to-borderline (<7.5%) and intermediate-to-high (≥7.5%) 10-year ASCVD risk, respectively.