Preventive Medicine 138 (2020) 106143

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Proactive screening for symptoms: A simple method to improve early detection of unrecognized cardiovascular disease in primary care. Results from the Lifelines Cohort Study

Victor W. Zwartkruis[a], Amy Groenewegen[b], Frans H. Rutten[b], Monika Hollander[b], Arno W. Hoes[b], M. Yldau van der Ende[a], Pim van der Harst[a,c], Maarten Jan Cramer[c], Yvonne T. van der Schouw[b], Hendrik Koffijberg[d], Michiel Rienstra[a], Rudolf A. de Boer[a,*]

[a] University Medical Center Groningen, University of Groningen, Department of Cardiology, Groningen, the Netherlands
[b] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[c] University Medical Center Utrecht, Utrecht University, Department of Cardiology, Utrecht, the Netherlands
[d] University of Twente, Department of Health Technology & Services Research, Enschede, the Netherlands

ARTICLE INFO

Keywords:
Early diagnosis
Signs and symptoms
Cardiovascular diseases
Atrial fibrillation
Heart failure
Coronary artery disease
Cohort studies
Diagnostic screening programs
Primary health care

ABSTRACT

Cardiovascular disease (CVD) often goes unrecognized, despite symptoms frequently being present. Proactive screening for symptoms might improve early recognition and prevent disease progression or acute cardiovascular events. We studied the diagnostic value of symptoms for the detection of unrecognized atrial fibrillation (AF), heart failure (HF), and coronary artery disease (CAD) and developed a corresponding screening questionnaire. We included 100,311 participants (mean age 52 ± 9 years, 58% women) from the population-based Lifelines Cohort Study. For each outcome (unrecognized AF/HF/CAD), we built a multivariable model containing demographics and symptoms. These models were combined into one 'three-disease' diagnostic model and questionnaire for all three outcomes. Results were validated in Lifelines participants with chronic obstructive pulmonary disease (COPD) and diabetes mellitus (DM). Unrecognized CVD was identified in 1325 participants (1.3%): AF in 131 (0.1%), HF in 599 (0.6%), and CAD in 687 (0.7%). Added to age, sex, and body mass index, palpitations were independent predictors for unrecognized AF; palpitations, chest pain, dyspnea, exercise intolerance, health-related stress, and self-expected health worsening for unrecognized HF; smoking, chest pain, exercise intolerance, and claudication for unrecognized CAD. Area under the curve for the combined diagnostic model was 0.752 (95% CI 0.737–0.766) in the total population and 0.757 (95% CI 0.734–0.781) in participants with COPD and DM. At the chosen threshold, the questionnaire had low specificity, but high sensitivity. In conclusion, a short questionnaire about demographics and symptoms can improve early detection of CVD and help pre-select people who should or should not undergo further screening for CVD.

1. Introduction

Despite the plethora of diagnostic methods available today, cardiovascular disease (CVD) is often diagnosed late. By then, serious and irreversible damage has often already occurred due to prolonged disease progression or acute cardiovascular (CV) events such as myocardial infarction (MI), decompensated heart failure (HF), or stroke. Therefore, improving early recognition and subsequent treatment of CVD is essential.

Proactive screening can uncover unrecognized CVD in a substantial number of people using a variety of screening methods. In a cluster-randomized trial in 14,802 primary care patients ≥65 years, 60% more cases of atrial fibrillation (AF) were detected through opportunistic screening with pulse taking and subsequent electrocardiography (ECG)

Abbreviations: AF, atrial fibrillation; AUC, area under the curve; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; ECG, electrocardiography; GP, general practitioner; HR-QoL, health-related quality of life; LASSO, least absolute shrinkage and selection operator; MI, myocardial infarction; NPV, negative predictive value; PCI, percutaneous coronary intervention; PPV, positive predictive value; RED-CVD, Reviving Early Diagnosis of CardioVascular Disease; T2DM, type 2 diabetes mellitus

* Corresponding author at: University Medical Center Groningen, Department of Cardiology, AB31, PO Box 30.001, 9700 RB Groningen, the Netherlands.
E-mail address: r.a.de.boer@umcg.nl (R.A. de Boer).

https://doi.org/10.1016/j.ypmed.2020.106143
Received 28 January 2020; Received in revised form 20 April 2020; Accepted 24 May 2020
Available online 27 May 2020

compared to usual care (1.6% vs. 1.0%) (Fitzmaurice et al., 2007). Screening may yield even better results in patients with chronic obstructive pulmonary disease (COPD) and type 2 diabetes mellitus (T2DM): in two studies in primary care patients with COPD (≥65 years) and T2DM (≥60 years), extensive screening including medical history, physical examination, ECG, and echocardiography revealed unrecognized HF in 20% and 28% of participants, respectively (Rutten et al., 2005; Boonman-De Winter et al., 2015). In two other studies, coronary CT angiography revealed moderate to severe coronary artery disease (CAD) in 41% of adult diabetes patients and 26% of long-term smokers with and without COPD (Muhlestein et al., 2014; Rasmussen et al., 2013).

Since evidence-based therapies exist for AF, HF, and CAD, proactive screening of high-risk patients may prevent acute CV events or progression to more severe CVD. For example, in people with CV risk factors, natriuretic peptide-based screening and subsequent intensified treatment reduces the incidence of left ventricular dysfunction and the number of hospitalizations for major adverse cardiac events (Ledwidge et al., 2013). Several ongoing trials will reveal if screening for AF and CAD can also improve patient outcomes (Friberg et al., 2013; Engdahl et al., 2017; Vonder et al., 2018).

Despite its potential, CVD screening is generally not included in the guidelines for primary care disease management programs for COPD and T2DM. Therefore, the Reviving Early Diagnosis of CardioVascular Disease (RED-CVD) consortium aims to develop a novel early diagnosis strategy to improve early detection and subsequent treatment of AF, HF, and CAD in primary care patients enrolled in these disease management programs.

Since diagnostic resources in primary care are generally limited compared to hospitals, some screening methods used in previous studies (e.g. echocardiography, coronary CT) are not feasible in primary care. Thus, simple and easily implementable screening methods are needed. Screening for symptoms indicative of CVD could be an efficient and effective first step to identify patients who could benefit from further screening, since symptoms are common in unrecognized CVD. For instance, dyspnea is present in 85% of patients with unrecognized HF and more than half of those with unrecognized MI (Boonman-De Winter et al., 2015; Afzal Ammar et al., 2006). Despite the fact that unrecognized CVD is very common in this group, primary care patients with COPD and T2DM are rarely proactively asked about specific symptoms of CVD during regular (quarterly, half-yearly, or yearly) checkups, because (local) guidelines do not specifically recommend this. Furthermore, symptoms of unrecognized CVD are often falsely interpreted as related to advanced age or previously diagnosed disease. Therefore, increased awareness and attention to symptoms might contribute to timely detection of CVD.

Since symptoms overlap between different CVDs and because AF, HF, and CAD all predispose to one another (Börschel and Schnabel, 2019; Qureshi et al., 2018), an integrative approach that looks at *multiple* CVDs is essential. Thus, we aimed to study the diagnostic value of symptoms and develop a concise questionnaire for the detection of unrecognized AF, HF, and CAD in the general adult population as well as patients with COPD and/or T2DM.

2. Methods

2.1. Study population and procedures

The study was performed with data from the Lifelines Cohort Study (www.lifelines.nl), which has been extensively described elsewhere (Scholtens et al., 2015). In short, Lifelines is a multidisciplinary, prospective population-based cohort study examining the health and health-related behaviours of 167,729 participants living in the North of The Netherlands in a unique three generation design. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics (Scholtens et al., 2015). Participants were recruited from 2006 to 2013, initially by participating GPs, who invited all patients aged 25–50 from their own practices. Participants were then encouraged to invite family members to participate in Lifelines as well. People who were not invited could also participate by registering themselves through the Lifelines website. The Lifelines study was approved by Medical Ethical Committee of the University Medical Center Groningen and performed in agreement with the Declaration of Helsinki, and all participants provided written informed consent (Scholtens et al., 2015).

Participants were asked to complete extensive questionnaires about a wide range of health-related topics at home. Next, they were invited for a physical visit, which included anthropometry and blood pressure measurements, electrocardiography, pulmonary function testing, and collection of blood, urine, and genetics samples. Additionally, current medication use was recorded. With a planned follow-up of at least 30 years, the Lifelines study is currently still ongoing. Participants are sent follow-up questionnaires approximately every 1.5 years and are invited for physical follow-up visits approximately every 5 years (Scholtens et al., 2015).

Since we aimed to perform a diagnostic, cross-sectional study, we primarily used data from the Lifelines baseline questionnaire and baseline visit. All baseline questionnaire items on symptoms and health-related quality of life (HR-QoL) with < 10% missing values (n = 72) were included in the analyses. This included items from the general Lifelines health questionnaire about self-reported diagnoses and symptoms (Scholtens et al., 2015), the RAND-36-item Health Survey (RAND-36) about HR-QoL (Hays and Morales, 2001), the somatization subscale of the Symptom Checklist 90 (SCL-90) about somatic complaints during the past week (Derogatis et al., 1973), and the Long-term Difficulties Inventory (LDI) about stress during the past year (Rosmalen et al., 2012). All Lifelines participants aged 40 years or older were included in the present analyses.

2.2. Definitions

Three outcomes were defined: unrecognized atrial fibrillation (AF), unrecognized heart failure (HF), and unrecognized coronary artery disease (CAD).

The diagnosis of unrecognized AF was based on the presence of AF on the baseline ECG in the absence of previously diagnosed AF. Previously diagnosed AF was considered present if participants had (i) a self-reported physician-diagnosis of arrhythmia and (ii) registered use of anticoagulants. Additionally, participants with (i) AF on the baseline ECG and (ii) registered anticoagulant use were also considered to have previously diagnosed AF. AF was diagnosed using a 12-lead ECG with an automated interpretation algorithm (Welch Allyn DT100) (Welch Allyn, 2016).

Since echocardiography and natriuretic peptide measurements were not performed in Lifelines, baseline unrecognized HF was considered present if (i) participants did not self-report HF at baseline, but (ii) did report newly recognized HF in the first follow-up questionnaire, which was completed by participants after a median follow-up duration of only 13 months.

Unrecognized CAD was considered present if participants (i) did not report prior MI, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) at baseline, but (iia) did report new MI, PCI, or CABG in the first follow-up questionnaire or (iib) had evidence of prior MI on their baseline ECG. The identification of unrecognized MI on Lifelines ECGs was performed manually and has previously been reported in detail (van der Ende et al., 2017a). Comorbidities were defined with previously described definitions for Lifelines (van der Ende et al., 2017b).

2.3. Statistical analyses

Participant characteristics of those with unrecognized CVD and no CVD were compared using independent *t*-tests for continuous data or Pearson Chi-square tests for binary data. Questionnaire items with multiple response levels were recoded into binary variables, in order to facilitate comparison between items from different questionnaires and since we aimed to develop a simple questionnaire with only yes/no questions.

We performed univariable logistic regression with questionnaire items as predictors. Items with a univariable p-value < 0.15 were included as predictors in a multivariable logistic regression analysis, as were age, sex, BMI, and current smoking. The univariable and initial multivariable analyses were performed for each outcome (unrecognized AF, HF, and CAD) separately, to ensure that predictors of a less prevalent outcome could also be identified and included in the final, combined model for all three types of CVD. Participants with previously diagnosed AF (n = 841) were excluded from analyses with unrecognized AF as the outcome. Similarly, for analyses with unrecognized HF or CAD as the outcome, participants with previously diagnosed HF (n = 991) or CAD (n = 2693) were excluded, respectively. Since Monte Carlo simulation analyses have shown that the minimum number of events per variable in multivariable regression analyses is ten (Peduzzi et al., 1995), predictors were excluded based on univariable significance and clinical utility if the number of events per variable exceeded ten. If multiple items relating to the same symptom remained significant in the multivariable model, they were combined into one item to produce a more concise model. Model shrinkage was performed using manual backwards selection, excluding predictors with p-values > 0.10 step-by-step. Model building was repeated using the least absolute shrinkage and selection operator (LASSO) method for initial shrinkage, which yielded similar results. p-Values for logistic regression were based on the Wald test. Unless noted otherwise, a p-value < 0.05 was considered statistically significant.

2.4. Development of the diagnostic model and questionnaire

Since we aimed to develop a single questionnaire for the simultaneous detection of unrecognized AF, HF, and/or CAD, we combined the predictors and their respective scores from the three separate models into a 'three-disease' diagnostic model. For each separate model, scores for the individual predictors were calculated by multiplying the original regression coefficient (beta) by 10 and rounding it to the nearest integer (Mehta et al., 2016). If a predictor was included in more than one model, a composite score was determined by calculating a weighted average based on the original regression coefficients of the predictor and the prevalence of the respective outcomes. Next, we evaluated the performance of the combined diagnostic model for the detection of unrecognized AF, HF, and/or CAD. Diagnostic performance was assessed in the general study population and subsequently validated in adult Lifelines participants with COPD and/or diabetes mellitus (DM).

Using all items and their respective scores from the combined diagnostic model, we constructed a corresponding patient questionnaire. Awaiting future external validation, a preliminary threshold for the diagnostic model and questionnaire was determined based on the sensitivity and specificity at different cut-off values. Since our questionnaire was not intended as a standalone screening tool, but rather as a tool to pre-select patients who should or should not undergo further screening, high sensitivity (± 90%) was preferred over high specificity in order to minimize the number of false negatives.

3. Results

We included 100,311 Lifelines participants aged 40 years or older. Mean age was 52 ± 9 years and 58% were women. Previously diagnosed CVD at baseline was present in 3856 individuals (3.8%): 841 (0.8%) had AF, 991 (1.0%) HF, and 2693 (2.7%) CAD. Unrecognized CVD was identified in 1325 participants (1.3%): 131 had (0.1%) unrecognized AF, 599 (0.6%) unrecognized HF, and 687 (0.7%) unrecognized CAD. Among the 1325 participants with unrecognized CVD, there were 92 (7%) participants with two types of unrecognized CVD (17 with AF & HF, 3 with AF & CAD, and 72 with HF & CAD). No participants had three types of unrecognized CVD. Of all patients with unrecognized CVD, 179 (14%) already had another previously diagnosed CVD at baseline.

Table 1
Baseline characteristics of participants with unrecognized cardiovascular disease and without cardiovascular disease.

Characteristics	Unrecognized CVD (n = 1325)	No CVD (n = 95,309)	p-Value
Age (years)	59 ± 11	51 ± 9	< 0.001
BMI (kg/m^2)	28 ± 4	27 ± 4	0.010
Female sex	548 (41%)	56,111 (59%)	< 0.001
Current smoking	253 (19%)	17,428 (18%)	0.501
SBP (mmHg)	134 ± 18	128 ± 16	< 0.001
DBP (mmHg)	78 ± 10	75 ± 10	< 0.001
Heart rate (beats per minute)	71 ± 13	71 ± 11	< 0.001
Diabetes mellitus	144 (11%)	3766 (4%)	< 0.001
COPD	266 (20%)	13,073 (14%)	< 0.001
Hypertension	804 (61%)	30,385 (32%)	< 0.001
Hypercholesterolemia	434 (33%)	17,996 (19%)	< 0.001
Prior stroke	35 (3%)	857 (1%)	< 0.001

Abbreviations: BMI = body mass index, COPD = chronic obstructive pulmonary disease, CVD = cardiovascular disease, DBP = diastolic blood pressure, SBP = systolic blood pressure.
Data presented as mean ± standard deviation or count (%).

Compared to participants without CVD, participants with unrecognized CVD were older, had slightly higher BMI, and had higher systolic and diastolic blood pressure (Table 1). Furthermore, participants with unrecognized CVD were less often female and showed a higher prevalence of comorbidities such as COPD, DM, hypertension, hypercholesterolemia, and stroke (Table 1). Of the 72 questionnaire items included in the analyses, 12 were significant univariable predictors for unrecognized AF. For unrecognized HF and CAD, 70 and 48 questionnaire items were significant univariable predictors, respectively (Supplementary Tables 1A–C).

Age, sex, and BMI were independent predictors in all three multivariable models, while current smoking only remained significant in the CAD model (Table 2). Of the included questionnaire items, only palpitations independently predicted unrecognized AF. The multivariable AF model had a c-statistic of 0.899 (95% confidence interval (CI) 0.871–0.927). Palpitations, chest pain, dyspnea, exercise intolerance, health-related stress in the past year, and the expectation that one's own health will worsen were independent predictors of unrecognized HF, with a c-statistic of 0.818 (95% CI 0.800–0.836). Chest pain, exercise intolerance, and claudication independently predicted unrecognized CAD, with a c-statistic of 0.710 (95% CI 0.690–0.730) (Table 2).

Table 3 displays how the predictors and scores from the three separate multivariable models were combined into one diagnostic model. From this combined model, we subsequently derived a corresponding 11-item questionnaire. The combined diagnostic model had an area under the curve (AUC) of 0.752 (95% CI 0.737–0.766) for the detection of the composite endpoint of unrecognized AF, HF, and/or CAD. A decile-based calibration plot indicated good calibration. For the detection of the individual endpoints, the combined model performed almost similarly to the separate models, with an AUC of 0.870 (95% CI 0.839–0.900) for unrecognized AF, 0.814 (95% CI 0.795–0.832) for HF, and 0.680 (95% CI 0.659–0.701) for CAD.

The combined diagnostic model performed similarly in participants with DM and/or COPD, with an AUC of 0.753 (95% CI 0.729–0.776). AUC improved slightly to 0.757 (95% CI 0.734–0.781) if those with

Table 2
Multivariable logistic regression models for unrecognized atrial fibrillation, heart failure, and coronary artery disease.

Characteristics	Unrecognized AF (n = 131)	Unrecognized HF (n = 599)	Unrecognized CAD (n = 687)
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Age per year	1.122 (1.103-1.142)	1.081 (1.072-1.089)	1.064 (1.056-1.073)
Male sex	7.789 (4.725-12.839)	2.267 (1.906-2.696)	2.008 (1.712-2.356)
BMI ≥ 30 kg/m^2	1.837 (1.202-2.806)	1.238 (1.018-1.507)	1.320 (1.091-1.596)
Current smoking	-	-	1.646 (1.367-1.981)
Palpitations	5.326 (3.637-7.801)	2.849 (2.377-3.414)	-
Chest pain	-	1.477 (1.229-1.775)	1.386 (1.171-1.642)
Dyspnea	-	1.506 (1.252-1.811)	-
Exercise intolerance	-	1.488 (1.224-1.811)	1.316 (1.101-1.573)
Claudication	-	-	1.223 (1.021-1.466)
Health-related stress	-	1.535 (1.273-1.851)	-
Expected health worsening	-	1.289 (1.066-1.559)	-
C-statistic (95% CI)	**0.899 (0.871-0.927)**	**0.818 (0.800-0.836)**	**0.710 (0.690-0.730)**

Abbreviations: AF = atrial fibrillation, BMI = body mass index, CAD = coronary artery disease, CI = confidence interval, HF = heart failure.

COPD were not given points for dyspnea (as nearly all patients with COPD have dyspnea). Here, the calibration plot indicated a slight overestimation of risk for the lower deciles, but reasonable calibration for the other deciles.

Given the target sensitivity of 90%, the threshold for further diagnostic work-up was set at 20 points for the general population ≥40 years (sensitivity 90%, specificity 36%) and 24 points for those with DM and/or COPD (sensitivity 91%, specificity 41%). A (translated) example of the resulting patient questionnaire is included in the Supplementary data.

4. Discussion

We demonstrated that a diagnostic model with symptoms and basic demographics has substantial discriminative value for diagnosing unrecognized CVD. Based on these diagnostic models, we developed a concise questionnaire (see Supplementary data), which may serve as an easy first step in a screening strategy for early detection of unrecognized AF, HF, and CAD.

Many patients with CVD first present in primary care, where diagnostic possibilities are generally limited compared to hospital settings. Therefore, simple diagnostic tools to select those who need more extensive investigations to confirm or exclude CVD are essential. Since symptoms are common in unrecognized CVD (Boonman-De Winter et al., 2015; Afzal Ammar et al., 2006), a simple questionnaire about symptoms indicative of CVD could improve the detection of unrecognized CVD in primary care. The added value of such a questionnaire may be especially large in patients with COPD and T2DM, since they have a high prevalence of unrecognized CVD (Rutten et al., 2005; Boonman-De Winter et al., 2015; Muhlestein et al., 2014; Rasmussen et al., 2013), but are rarely proactively and systematically asked about symptoms indicative of CVD.

The diagnostic value of symptoms for the detection of CVD has been questioned, mainly because symptoms are often non-specific (Brunetti et al., 2012; Ponikowski et al., 2016; Rovai et al., 2015). However, a systematic review about the detection of HF in primary care concluded that several symptoms do have substantial diagnostic value, with some (e.g. dyspnea) having high sensitivity and others (e.g. orthopnea) high specificity (Mant et al., 2009). In T2DM patients ≥60 years in primary care, a diagnostic model with just medical history and symptoms had good discriminative ability for unrecognized HF (Boonman-De Winter et al., 2015). In the population-based Rotterdam study, items from the Rose Angina Questionnaire correlated strongly with calcium scores on coronary CT (Oei et al., 2004). Finally, patient-reported symptoms are fairly accurate in estimating frequency and duration of AF episodes in 85% of people with documented AF (Garimella et al., 2015).

In our study, performance of the separate multivariable models for unrecognized AF, HF, and CAD ranged from moderate to excellent. The AF model had a very high c-statistic (0.899), which may in part be driven by age, which is a major risk factor for AF (Börschel and Schnabel, 2019). Consistent with previous findings (Boonman-De Winter et al., 2015), our HF model had a high c-statistic (0.818). Contrary to previous diagnostic models for unrecognized HF (Rutten et al., 2005; Boonman-De Winter et al., 2015), orthopnea, paroxysmal

Table 3
Scores from the separate and combined models for the detection of unrecognized atrial fibrillation, heart failure, and coronary artery disease.

Variable	Scores from individual models (beta * 10)			Weighted average	Combined score
	AF (n = 131)	HF (n = 599)	CAD (n = 687)		
Age per year > 40 years	1.2	0.8	0.6	0.7	**1**
Male sex	20.5	8.2	7.0	8.7	**9**
BMI ≥30 kg/m^2	6.1	2.1	2.8	2.8	**3**
Current smoking			5.0	5.0	**5**
Palpitations	16.7	10.5		11.6	**12**
Chest pain		3.9	3.3	3.6	**4**
Dyspnea		4.1		4.1	**4**
Exercise intolerance		4.0	2.7	3.3	**3**
Claudication		4.3		4.3	**4**
Health-related stress		2.5		2.5	**3**
Expected health worsening			2.0	2.0	**2**

Abbreviations: AF = atrial fibrillation, BMI = body mass index, CAD = coronary artery disease, HF = heart failure.

nocturnal dyspnea, ankle edema, and claudication did not remain significant in our multivariable model, although they were significant univariable predictors of unrecognized HF. The CAD model had a moderate c-statistic of 0.710. Unfortunately, only absence or presence of chest pain was recorded in Lifelines. Possibly, model performance would have been better if more specific chest pain questions had been included, as in a previous study on the prediction of CAD in patients with stable chest pain, which reported a c-statistic of 0.77 for a model with only age, sex, and (aspecific, atypical or typical) chest pain (Genders et al., 2012).

Previous studies have underlined the importance of an integrative approach of CVD. For instance, one study demonstrated that NT-proBNP not only independently predicts HF, but also CAD and stroke (Natriuretic Peptides Studies Collaboration et al., 2016). Similarly, our results show that one symptom can be an independent predictor of multiple CVDs. Additionally, a substantial proportion of participants with unrecognized CVD had at least one other type of previously diagnosed or unrecognized CVD. Nevertheless, to the best of our knowledge, no diagnostic models for the detection of *multiple* CVDs have been published, which makes our model unique. Our combined diagnostic model had relatively good diagnostic performance for the detection of a composite endpoint of unrecognized AF, HF and/or CAD. Furthermore, compared to the three separate models for AF, HF, and CAD, the combined diagnostic model had nearly equal discriminative value for the individual endpoints. Thus, our study confirms the importance and feasibility of an integrative approach of CVD.

Among Lifelines participants aged ≥40 years, we identified 1325 people (1.3%) with unrecognized CVD (0.1% AF, 0.6% HF, and 0.7% CAD). Thus, the prevalence of unrecognized CVD in our study was rather low. In previous population-based studies, unrecognized AF was present in 0.5% to 1.6% (Schnabel et al., 2012; Frewen et al., 2013; Claes et al., 2012). Data from the population-based Olmsted County study suggested a high prevalence of unrecognized HF: of participants without previously diagnosed HF, 4.9% and 1.1% had left ventricular ejection fraction ≤50% and ≤40%, respectively, while another 6.8% had moderate to severe diastolic dysfunction (Redfield et al., 2003). ECG-detected unrecognized MI was reported in 4.0% to 8.2% of participants in other population-based studies (Friberg et al., 2013; Dehghan et al., 2014; Øhrn et al., 2018). The low prevalence rates of AF, HF, and CAD in our study may in part be explained by the fact that our population was younger compared to previous population-based studies. Additionally, the prevalence rates in our study are probably underestimations of the true prevalence. Cases of paroxysmal AF were likely missed in Lifelines, since only a single ECG was made at baseline. In addition, cases of HF and CAD may have been missed because natriuretic peptide measurement, echocardiography, and coronary imaging were not performed. Finally, use of self-reported data may have caused an underestimation of the prevalence of unrecognized CVD, notably HF. While self-report has relatively high sensitivity for CAD, self-report has only moderate sensitivity for HF when compared to physician-reported diagnosis (Okura et al., 2004; Englert et al., 2010). Nonetheless, self-report does have excellent specificity for CVD (Okura et al., 2004; Englert et al., 2010). Therefore, false positives are unlikely.

With its current thresholds, our model had high sensitivity, but low specificity. We did not report positive and negative predictive value (PPV and NPV), since these are heavily influenced by prevalence of the outcome (Altman and Bland, 1994). As expected with the low prevalence of CVD in our study, PPV value was very low, while NPV was very high. While low specificity and PPV may seem at odds with effective screening, our model was not intended as a standalone screening tool. Rather, it was intended as a simple tool to pre-select patients who should or should not undergo further screening. During subsequent diagnostic steps, established tests with higher specificity and PPV may be used to accurately diagnose unrecognized CVD. In fact, given its ability to accurately rule out CVD, adding our model as a first step to established screening strategies may reduce the number of people who have to undergo diagnostic examinations such as ECG, natriuretic peptide measurement, or coronary CT.

4.1. Strengths and limitations

The major strength of our study lies in the fact that we developed a diagnostic model for the simultaneous detection of *multiple* types of CVD. This integrative outlook makes our early diagnosis strategy more efficient compared to screening strategies for separate CVD. The fact that we developed a concise questionnaire which may be easily filled out by patients also contributes to the practical utility in the busy practice of primary care or other settings. Furthermore, our model was derived from a large contemporary cohort and validated in a subset of patients with COPD and DM. Therefore, our results are widely applicable to the general population and patients with COPD or DM.

Limitations include the fact that we did not (yet) externally validate our model and the use of self-reported diagnoses. Underestimation of the prevalence of unrecognized CVD may theoretically have diluted our results due to the presence of participants with unrecognized CVD in the reference group. Since natriuretic peptide measurements, echocardiography, and coronary imaging were not performed in Lifelines, we used data from the first follow-up questionnaire (median follow-up duration 13 months) for the definition of unrecognized HF and CAD. This approach was based on the assumption that CVD must already have been present to some extent at baseline in people reporting new-onset CVD just 13 months later. Finally, the Lifelines population is predominantly Caucasian, which limits the generalizability of our results.

5. Conclusions

We demonstrated that a single diagnostic model containing symptoms and basic demographics has substantial discriminative value for uncovering unrecognized AF, HF, and CAD. Our results underline that patients at increased CV risk should be proactively and systematically asked about symptoms indicative of CVD. Furthermore, our study confirms that symptoms may overlap between different CVDs, highlighting the importance of comprehensive screening that focuses on multiple CVDs. Based on our diagnostic model, we developed a concise, easily implementable questionnaire to pre-select patients who should or should not undergo further screening for AF, HF, *and* CAD. Before being implemented into practice, the RED-CVD questionnaire should be externally validated and its added value to existing screening methods and patient outcomes assessed.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2020.106143.

Disclosures

For the current manuscript, the authors declare no potential conflicts of interest. Outside of the submitted work, the authors disclose the following financial support: FHR reports unrestricted institutional grants from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb-Pfizer, and Daiichi Sankyo. RAdB reports grants from the Dutch Heart Foundation [CVON DOSIS, grant 2014-40; CVON SHE-PREDICTS-HF, grant 2017-21; and CVON PREDICT2, grant 2018-30] and the European Research Council [SECRETE-HF, ERC-COG 818715]. The UMCG, which employs RAdB, has received research grants and/or fees from AstraZeneca, Abbott, Bristol-Myers Squibb, Novartis, Novo Nordisk, and Roche. RAdB reports speaker fees from Abbott, AstraZeneca, Novartis, and Roche.

Funding

This work was supported by the Dutch Heart Foundation [CVON RED-CVD, grant 2017-11]. The sponsor played no role in the study

design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the article for publication.

CRediT authorship contribution statement

Victor W. Zwartkruis: Methodology, Formal analysis, Writing - original draft. **Amy Groenewegen**: Methodology, Formal analysis, Writing - review & editing. **Frans H. Rutten**: Conceptualization, Methodology, Supervision, Writing - review & editing. **Monika Hollander**: Conceptualization, Writing - review & editing. **Arno W. Hoes**: Conceptualization, Methodology, Supervision, Writing - review & editing. **M. Yldau van der Ende**: Resources, Writing - review & editing. **Pim van der Harst**: Resources, Writing - review & editing. **Maarten Jan Cramer**: Conceptualization, Writing - review & editing. **Yvonne T. van der Schouw**: Conceptualization, Writing - review & editing. **Hendrik Koffijberg**: Conceptualization, Writing - review & editing. **Michiel Rienstra**: Conceptualization, Methodology, Supervision, Writing - review & editing. **Rudolf A. de Boer**: Conceptualization, Methodology, Supervision, Writing - review & editing.

Acknowledgements

We thank all participants of the Lifelines study, as well as all other people involved in the Lifelines study, for making this study possible.

References

Afzal Ammar, K., Makwana, R., Redfield, M.M., Kors, J.A., Burnett, J.C., Rodeheffer, R.J., 2006. Unrecognized myocardial infarction: the association with cardiopulmonary symptoms and mortality is mediated via echocardiographic abnormalities of global dysfunction instead of regional dysfunction: the Olmsted County Heart Function Study. Am. Heart J. 151, 799–805. https://doi.org/10.1016/j.ahj.2005.09.028.

Altman, D.G., Bland, J.M., 1994. Statistics notes: diagnostic tests 2: predictive values. BMJ. 309, 102. https://doi.org/10.1136/bmj.309.6947.102.

Boonman-De Winter, L.J.M., Rutten, F.H., Cramer, M.J., et al., 2015. Efficiently screening heart failure in patients with type 2 diabetes. Eur. J. Heart Fail. 17, 187–195. https://doi.org/10.1002/ejhf.216.

Börschel, C.S., Schnabel, R.B., 2019. The imminent epidemic of atrial fibrillation and its concomitant diseases – myocardial infarction and heart failure - a cause for concern. Int. J. Cardiol. 287, 162–173. https://doi.org/10.1016/j.ijcard.2018.11.123.

Brunetti, N.D., De Gennaro, L., Pellegrino, P.L., Dellegrottaglie, G., Antonelli, G., Di Biase, M., 2012. Atrial fibrillation with symptoms other than palpitations: incremental diagnostic sensitivity with at-home tele-cardiology assessment for emergency medical service. Eur. J. Prev. Cardiol. 19, 306–313. https://doi.org/10.1177/1741826711406060.

Claes, N., van Laethem, C., Goethals, M., et al., 2012. Prevalence of atrial fibrillation in adults participating in a large-scale voluntary screening programme in Belgium. Acta Cardiol. 67, 273–278. https://doi.org/10.2143/AC.67.3.2160714.

Dehghan, A., Leening, M.J.G., Solouki, A.M., et al., 2014. Comparison of prognosis in unrecognized versus recognized myocardial infarction in men versus women > 55 years of age (from the Rotterdam Study). Am. J. Cardiol. 113, 1–6. https://doi.org/10.1016/j.amjcard.2013.09.005.

Derogatis, L.R., Lipman, R.S., Covi, L., 1973. SCL-90: an outpatient psychiatric rating scale—preliminary report. Psychopharmacol. Bull. 9, 13–28.

Engdahl, J., Svennberg, E., Friberg, L., Al-Khalili, F., Frykman, V., Kemp Gudmundsdottir, K., Fredriksson, T., Rosenqvist, M., 2017. Stepwise mass screening for atrial fibrillation using N-terminal pro b-type natriuretic peptide: the STROKESTOP II study design. Europace. 19, 297–302. https://doi.org/10.1093/europace/euw319.

Englert, H., Müller-Nordhorn, J., Seewald, S., et al., 2010. Is patient self-report an adequate tool for monitoring cardiovascular conditions in patients with hypercholesterolemia? J. Public Health (Oxf). 32, 387–394. https://doi.org/10.1093/pubmed/fdq013.

Fitzmaurice, D.A., Hobbs, F.D.R., Jowett, S., et al., 2007. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. Br. Med. J. 335, 383–386. https://doi.org/10.1136/bmj.39280.660567.55.

Frewen, J., Finucane, C., Cronin, H., et al., 2013. Factors that influence awareness and treatment of atrial fibrillation in older adults. QJM. 106, 415–424. https://doi.org/10.1093/qjmed/hct060.

Friberg, L., Engdahl, J., Frykman, V., Svennberg, E., Levin, L.-Å., Rosenqvist, M., 2013. Population screening of 75- and 76-year-old men and women for silent atrial fibrillation (STROKESTOP). Europace. 15, 135–140. https://doi.org/10.1093/europace/eus217.

Garimella, R.S., Chung, E.H., Mounsey, J.P., Schwartz, J.D., Pursell, I., Gehi, A.K., 2015. Accuracy of patient perception of their prevailing rhythm: a comparative analysis of monitor data and questionnaire responses in patients with atrial fibrillation. Heart Rhythm. 12, 658–665. https://doi.org/10.1016/j.hrthm.2015.01.012.

T.S.S. Genders, E.W. Steyerberg, M.G.M. Hunink, et al., Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts., BMJ. 344 (2012) e 3485. doi:https://doi.org/10.1136/bmj.e3485.

R.D. Hays, L.S. Morales, The RAND-36 measure of health-related quality of life., Ann. Med. 33 (2001) 350–7.

Ledwidge, M., Gallagher, J., Conlon, C., et al., 2013. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. J. Am. Med. Assoc. 310, 66–74. https://doi.org/10.1001/jama.2013.7588.

J. Mant, J. Doust, A. Roalfe, et al., Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care., Health Technol. Assess. (Rockv). 13 (2009) 1–207. doi:https://doi.org/10.3310/hta13320.

Mehta, H.B., Mehta, V., Girman, C.J., Adhikari, D., Johnson, M.L., 2016. Regression coefficient–based scoring system should be used to assign weights to the risk index. J. Clin. Epidemiol. 79, 22–28. https://doi.org/10.1016/j.jclinepi.2016.03.031.

Muhlestein, J.B., Lappé, D.L., Lima, J.A.C., et al., 2014. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. J. Am. Med. Assoc. 312, 2234–2243. https://doi.org/10.1001/jama.2014.15825.

Natriuretic Peptides Studies Collaboration, P. Willeit, S. Kaptoge, et al., Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant-data meta-analysis., Lancet Diabetes Endocrinol. 4 (2016) 840–9. doi:https://doi.org/10.1016/S2213-8587(16)30196-6.

Oei, H.H.S., Vliegenthart, R., Deckers, J.W., Hofman, A., Oudkerk, M., Witteman, J.C.M., 2004. The association of Rose questionnaire angina pectoris and coronary calcification in a general population: the Rotterdam Coronary Calcification Study. Ann. Epidemiol. 14, 431–436. https://doi.org/10.1016/j.annepidem.2003.09.009.

Øhrn, A.M., Schirmer, H., von Hanno, T., et al., 2018. Small and large vessel disease in persons with unrecognized compared to recognized myocardial infarction: the Tromsø Study 2007–2008. Int. J. Cardiol. 253, 14–19. https://doi.org/10.1016/j.ijcard.2017.10.009.

Okura, Y., Urban, L.H., Mahoney, D.W., Jacobsen, S.J., Rodeheffer, R.J., 2004. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. J. Clin. Epidemiol. 57, 1096–1103. https://doi.org/10.1016/j.jclinepi.2004.04.005.

P. Peduzzi, J. Concato, A.R. Feinstein, T.R. Holford, Importance of events per independent variable in proportional hazards regression analysis II. Accuracy and precision of regression estimates, J. Clin. Epidemiol. 48 (1995) 1503–1510. doi:https://doi.org/10.1016/0895-4356(95)00048-8.

Ponikowski, P., Voors, A.A., Anker, S.D., et al., 2016. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur. Heart J. 37, 2129–2200. https://doi.org/10.1093/eurheartj/ehw128.

Qureshi, W.T., Zhang, Z.M., Chang, P.P., et al., 2018. Silent myocardial infarction and long-term risk of heart failure: the ARIC Study. J. Am. Coll. Cardiol. 71, 1–8. https://doi.org/10.1016/j.jacc.2017.10.071.

Rasmussen, T., Køber, L., Pedersen, J.H., et al., 2013. Relationship between chronic obstructive pulmonary disease and subclinical coronary artery disease in long-term smokers. Eur. Heart J. Cardiovasc. Imaging 14, 1159–1166. https://doi.org/10.1093/ehjci/jet057.

Redfield, M.M., Jacobsen, S.J., Burnett Jr., J.C., Mahoney, D.W., Bailey, K.R., Rodeheffer, R.J., 2003. Burden of systolic and diastolic ventricular dysfunction in the community. J. Am. Med. Assoc. 289, 194. https://doi.org/10.1001/jama.289.2.194.

Rosmalen, J.G.M., Bos, E.H., De Jonge, P., 2012. Validation of the long-term difficulties inventory (LDI) and the list of threatening experiences (LTE) as measures of stress in epidemiological population-based cohort studies. Psychol. Med. 42, 2599–2608. https://doi.org/10.1017/S0033291712000608.

Rovai, D., Neglia, D., Lorenzoni, V., Caselli, C., Knuuti, J., Underwood, S.R., 2015. Limitations of chest pain categorization models to predict coronary artery disease. Am. J. Cardiol. 116, 504–507. https://doi.org/10.1016/j.amjcard.2015.05.008.

Rutten, F.H., Moons, K.G.M., Cramer, M.J.M., et al., 2005. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. Br. Med. J. 331, 1379–1385. https://doi.org/10.1136/bmj.38664.661181.55.

Schnabel, R.B., Wilde, S., Wild, P.S., Munzel, T., Blankenberg, S., 2012. Vorhofflimmern: Prävalenz und Risikofaktorenprofil in der Allgemeinbevölkerung. Dtsch. Arztebl. Int. 109, 293–299. https://doi.org/10.3238/arztebl.2012.0293.

S. Scholtens, N. Smidt, M.A. Swertz, et al., Cohort Profile: LifeLines, a three-generation cohort study and biobank., Int. J. Epidemiol. 44 (2015) 1172–80. doi:https://doi.org/10.1093/ije/dyu229.

van der Ende, M.Y., Hartman, M.H.T., Schurer, R.A.J., et al., 2017a. Prevalence of electrocardiographic unrecognized myocardial infarction and its association with mortality. Int. J. Cardiol. 243, 34–39. https://doi.org/10.1016/j.ijcard.2017.05.063.

van der Ende, M.Y., Hartman, M.H.T., Hagemeijer, Y., et al., 2017b. The LifeLines Cohort Study: prevalence and treatment of cardiovascular disease and risk factors. Int. J. Cardiol. 228, 495–500. https://doi.org/10.1016/j.ijcard.2016.11.061.

Vonder, M., van der Aalst, C.M., Vliegenthart, R., van Ooijen, P.M.A., Kuijpers, D., Gratama, J.W., de Koning, H.J., Oudkerk, M., 2018. Coronary artery calcium imaging in the ROBINSCA trial: rationale, design, and technical background. Acad. Radiol. 25, 118–128. https://doi.org/10.1016/j.acra.2017.07.010.

Welch Allyn. MEANS ECG Physicians' Manual for Welch Allyn CP Series Electrocardiographs. https://www.welchallyn.com/content/dam/welchallyn/documents/sap-documents/LIT/80011/80011564LITPDF.pdf. Revised July 2016. Accessed September 2019.