Diagnostic yield of a proactive strategy for early detection of cardiovascular disease versus usual care in adults with type 2 diabetes or chronic obstructive pulmonary disease in primary care in the Netherlands (RED-CVD): a multicentre, pragmatic, cluster-randomised, controlled trial

Amy Groenewegen, Victor W Zwartkruis*, Michiel Rienstra, Nicolaas P A Zuithoff, Monika Hollander, Hendrik Koffijberg, Martijn Oude Wolcherink, Maarten J Cramer, Yvonne T van der Schouw, Arno W Hoes, Frans H Rutten†, Rudolf A de Boer†*

Summary

Background Progressive cardiovascular diseases (eg, heart failure, atrial fibrillation, and coronary artery disease) are often diagnosed late in high-risk individuals with common comorbidities that might mimic or mask symptoms, such as chronic obstructive pulmonary disease (COPD) and type 2 diabetes. We aimed to assess whether a proactive diagnostic strategy consisting of a symptom and risk factor questionnaire and low-cost and accessible tests could increase diagnosis of progressive cardiovascular diseases in patients with COPD or type 2 diabetes in primary care.

Methods In this multicentre, pragmatic, cluster-randomised, controlled trial (RED-CVD), 25 primary care practices in the Netherlands were randomly assigned to usual care or a proactive diagnostic strategy conducted during routine consultations and consisting of a validated symptom questionnaire, followed by physical examination, N-terminal-pro-B-type natriuretic peptide measurement, and electrocardiography. We included adults (≥18 years) with type 2 diabetes, COPD, or both, who participated in a disease management programme. Patients with an established triple diagnosis of heart failure, atrial fibrillation, and coronary artery disease were excluded. In the case of abnormal findings, further work-up or treatment was done at the discretion of the general practitioner. The primary endpoint was the number of newly diagnosed cases of heart failure, atrial fibrillation, and coronary artery disease, adjudicated by an expert clinical outcome committee using international guidelines, at 1-year follow-up, in the intention-to-treat population.

Findings Between Jan 31, 2019, and Oct 7, 2021, we randomly assigned 25 primary care centres: 11 to usual care and 14 to the intervention. We included patients between June 21, 2019, and Jan 31, 2022. Following exclusion of ineligible patients and those who did not give informed consent, 1216 participants were included: 624 (51%) in the intervention group and 592 (49%) in the usual care group. The mean age of participants was 68·4 years (SD 9·4), 482 (40%) participants were female, and 734 (60%) were male. During 1 year of follow-up, 50 (8%) of 624 participants in the intervention group and 18 (3%) of 592 in the control group were newly diagnosed with heart failure, atrial fibrillation, or coronary artery disease (adjusted odds ratio 2·97 [95% CI 1·66–5·33]). This trial is registered with the Netherlands Trial Registry, NTR7360, and was completed on Jan 31, 2023.

Interpretation An easy-to-use, proactive, diagnostic strategy more than doubled the number of new diagnoses of heart failure, atrial fibrillation, and coronary artery disease in patients with type 2 diabetes or COPD in primary care compared with usual care. Although the effect on patient outcomes remains to be studied, our diagnostic strategy might contribute to improved early detection and timely initiation of treatment in individuals with cardiovascular disease.

Funding Dutch Heart Foundation.

Lancet Public Health 2024; 9: e88–99

Published Online December 19, 2023 https://doi.org/10.1016/S2468-2667(23)00269-4

*Joint first author

†Joint last authors

Department of General Practice & Nursing Science, Julius Center for Health Sciences and Primary Care (A Groenewegen MD, M Hollander MD PhD, Prof F H Rutten MD PhD), **Department of Data Science & Biostatistics, Julius Center for Health Sciences and Primary Care** (N P A Zuithoff PhD), **Department of Cardiology** (M J Cramer MD PhD), **Department of Epidemiology and Health Economics, Julius Center for Health Sciences and Primary Care** (Prof Y T van der Schouw PhD), **Medical Faculty and Executive Board** (Prof A W Hoes MD PhD), **University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands; Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands** (V W Zwartkruis MD, Prof M Rienstra MD PhD); **Department of Health Technology & Services Research, University of Twente, Enschede, Netherlands** (Prof H Koffijberg PhD, M Oude Wolcherink); **Department of Cardiology, Erasmus Medical Center, University of Rotterdam, Rotterdam, Netherlands** (Prof R A de Boer MD PhD)

Introduction

Although evidence-based management is available for heart failure, atrial fibrillation, and coronary artery disease,[1–3] these diseases frequently manifest with non-specific symptoms and are often diagnosed late or after an acute event has already occurred.

Previous studies have shown that selective screening improves early detection of heart failure, atrial fibrillation, and coronary artery disease, especially in individuals at high risk, such as patients with type 2 diabetes and chronic obstructive pulmonary disease (COPD).[4–10] Echocardiographic screening of patients in primary care

Correspondence to:
Ms Amy Groenewegen,
Department of General Practice & Nursing Science, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht 3584 CX, Netherlands
a.groenewegen-11@umcutrecht.nl

Research in context

Evidence before this study

Cardiovascular diseases, including heart failure, atrial fibrillation, and coronary artery disease, impose a significant health burden despite advances in disease management. Chronic obstructive pulmonary disease (COPD) and type 2 diabetes are among the most prevalent cardiovascular risk factors, affecting up to 15% of adults in high-income countries. However, cardiovascular diseases often go undetected in individuals with COPD or type 2 diabetes, even though many such patients show symptoms. Early detection of these cardiovascular diseases could potentially alleviate this burden, especially given the availability of evidence-based therapies that can prevent or postpone the onset and development of major cardiovascular and cerebrovascular events.

We searched PubMed with the terms "screening" AND ("COPD" OR "type 2 diabetes") AND ("cardiovascular disease" OR "heart failure" OR "coronary artery disease" OR "atrial fibrillation"). We included clinical trials published from database inception to June 8, 2018, for human studies published in English or Dutch. We identified several published studies on opportunistic screening strategies for cardiovascular diseases in patients with type 2 diabetes and COPD. These primarily focused on asymptomatic individuals and used advanced imaging techniques not available in routine primary care, leading to concerns about cost-effectiveness and applicability. Consequently, international guidelines do not currently advocate for standard cardiovascular screening, even in high-risk populations such as those with COPD or type 2 diabetes.

Two trials on type 2 diabetes patients suggested that N-terminal pro-B-type natriuretic peptide (NT-proBNP) screening could accurately identify individuals who might benefit from accelerated up-titration of renin–angiotensin system antagonists and β blockers to maximum tolerated dosages. Only one of these trials, the STOP-HF study, presented a feasible primary care-integrated screening and treatment strategy. Notably, we did not find any pragmatic trials reporting on integrated diagnostic strategies specifically targeting early symptomatic individuals with COPD or type 2 diabetes in primary care.

Added value of this study

To our knowledge, this study is the first randomised controlled trial assessing an integrated diagnostic strategy tailored for people with type 2 diabetes or COPD in the primary care setting that addresses multiple cardiovascular diseases. By applying a pragmatic design and integrating the strategy into the regular primary care pathways for COPD and type 2 diabetes, we aimed to provide generalisable and policy-relevant evidence.
Our findings show that a streamlined, proactive approach using low-cost and accessible tests (a symptom questionnaire followed by physical examination, electrocardiography, and NT-proBNP measurement) can significantly increase the detection rates of heart failure, atrial fibrillation, and coronary artery disease in individuals with type 2 diabetes or COPD over a 12-month period compared with usual care.

Implications of all the available evidence

The study provides evidence that the integration of an early diagnosis strategy in the existing primary care pathways for COPD and type 2 diabetes can increase detection rates of heart failure, atrial fibrillation, and coronary artery disease. Whether the increased diagnostic yield will translate into improved patient outcomes will be assessed in additional cost-effectiveness analyses and an extension of the study with longer follow-up assessing the development of major cardiovascular events in both study groups.

Given the increasing prevalence of cardiovascular diseases and cardiovascular risk factors such as obesity, hypertension, and type 2 diabetes, combined with the ongoing shift of healthcare services from hospitals to community care for cost containment, we expect this streamlined diagnostic approach to become increasingly relevant.

revealed previously unrecognised heart failure in 21% of patients with COPD and 28% with type 2 diabetes.[5,9] Coronary CT angiography identified moderate-to-severe coronary artery disease in 41% of patients with type 2 diabetes and in 26% of long-term smokers with or without COPD.[7,8] In a cluster-randomised, controlled trial in primary care including nearly 15 000 community-dwelling individuals aged 65 years or older, pulse palpation and subsequent electrocardiography (ECG) yielded 60% more cases of atrial fibrillation compared with usual care (1·6% *vs* 1·0% in 1 year).[6]

Symptoms are highly common in those with unrecognised cardiovascular disease[5,11,12] but frequently remain unnoticed because symptoms are often not reported by patients or are attributed to pre-existing conditions, such as COPD. Similarly, although diabetes itself might not directly cause symptoms such as shortness of breath or chest pain, concomitant obesity and its associated symptoms might obscure the early signs of cardiovascular conditions, particularly when patients are reluctant to report these symptoms because of perceived self-blame.[13]

General Practitioners (GPs) usually only refer patients for additional investigations if patients report symptoms and have a sufficiently high probability of disease according to the initial assessment. However, tools and strategies developed to improve the accuracy and efficiency of screening for cardiovascular diseases generally target asymptomatic individuals at high risk and apply expensive screening methods with limited availability—eg, echocardiography and CT scans. Moreover, screening strategies tend to focus on individual

cardiovascular diseases, disregarding the considerable overlap in risk factors, signs, and symptoms.[14] Therefore, an urgent need exists for a proactive screening strategy targeting the entire cardiovascular disease continuum in groups at high risk (eg, those with COPD or type 2 diabetes) in primary care.

We aimed to assess the diagnostic yield of a proactive strategy consisting of a symptom and risk factor questionnaire and low-cost and accessible tests (physical examination, ECG, and N-terminal pro-B-type natriuretic peptide [NT-proBNP] measurement) to detect heart failure, atrial fibrillation, and coronary artery disease compared with usual care in community-dwelling individuals with COPD or type 2 diabetes in primary care.

Methods

Study design and participants

In this multicentre, cluster-randomised, controlled trial (RED-CVD), adults (≥18 years) with COPD, type 2 diabetes, or both, were screened for heart failure, atrial fibrillation, and coronary artery disease, or received care as usual, at 25 primary care centres in the Netherlands (appendix p 2). We initiated contact with GP collaborations via telephone or email, distributing an invitation letter through their networks. Interested GPs were provided with further details about the trial, while comprehensive information about the intervention was exclusively disclosed to practices in the intervention group after randomisation, ensuring the prevention of contamination within the control group.

Together with trained practice nurses, GPs provide care for patients with type 2 diabetes and COPD in disease management programmes in the Netherlands, functioning as gatekeepers and managing care of most patients with COPD and type 2 diabetes.[15,16] Patients were eligible for enrolment if they participated in a disease management programme for COPD or type 2 diabetes. Eligible patients received an invitation letter from their GP, informing them about an upcoming study focused on cardiovascular diseases and health-related quality of life at their practice. These invitation letters were the same for all practices, irrespective of group allocation. Patients who showed interest were subsequently contacted by a member of our research team for additional information and further engagement in the study.

The main exclusion criterion was an established triple diagnosis of heart failure, atrial fibrillation, and coronary artery disease. Other key exclusion criteria included severe cognitive impairment or the inability to give informed consent. Detailed inclusion and exclusion criteria are provided in the appendix (p 2). Sex data were collected from the primary care electronic health records, where sex is self-reported. Data on ethnicity were not collected.

The authors at the initiating centres designed and oversaw the conduct of the trial and undertook site monitoring and data analysis, which included rigorous data monitoring by two researchers (AG and VWZ) who reviewed the electronic health records of all participants, including laboratory values, hospital discharge letters, and specialist consultation notes. The trial protocol was approved by the medical ethics review committee at the University Medical Center Utrecht (NL65798.041.18), was registered with the Netherlands Trial Registry, NTR7360, and has been reported in a previous publication.[17]

Given that the risk associated with participating in this trial was assessed to be negligible, the requirement for both a data safety monitoring board and the routine collection and reporting of adverse events was waived. All participants provided written informed consent.

Randomisation and masking

General practices were randomly assigned as clusters (ie, including all eligible individuals within the practice) to either the intervention group or the control group using off-site computerised block randomisation on the basis of practice size. To prevent contamination in the control group, participating practices received detailed information about the intervention only after their practice was randomly assigned to the intervention group. Participants in the control group were masked to the intervention and were asked only for informed consent for filling out health-related quality of life (HRQoL) questionnaires and extraction of data from their electronic health records. Members of the clinical outcome adjudication committee were masked to group allocation.

See Online for appendix

The randomisation sequence for the practices was generated using the Research Online software. Enrolment of practices and assignment to trial groups were conducted by an investigator (AG), who also played a role in various other aspects of the study.

Procedures

The QNE strategy is a step-wise approach to detect heart failure, atrial fibrillation, and coronary artery disease, consisting of three steps: first, a self-administered questionnaire on risk factors and symptoms, to be filled out at home before the next scheduled routine visit of a type 2 diabetes or COPD management programme. Points can be scored for risk factors (age, sex, BMI, and smoking habits) and symptoms (palpitations, chest pain, dyspnoea, reduced exercise tolerance, claudication, and health-related stress). The questionnaire and score model are provided in the appendix (p 3). Second, a physical examination aimed at signs of heart failure or atrial fibrillation by the practice nurse, NT-proBNP measurement, and 12-lead ECG to be done in participants who scored above a certain threshold on the questionnaire. To minimise the occurrence of false negatives in the questionnaire responses, the threshold was established at 24 points. This threshold aligned with a sensitivity of 91% and a specificity of 41% in the

	Intervention (n=624)	Usual care (n=592)	p value
Age, years	67·9 (9·8)	68·8 (8·9)	0·10
Sex			
Female	253 (41%)	229 (39%)	0·51
Male	371 (59%)	363 (61%)	..
Comorbidities at baseline			
Hypertension	426 (68%)	438 (74%)	0·028
Hypercholesterolaemia	489 (78%)	442 (75%)	0·13
Type 2 diabetes	541 (87%)	511 (86%)	0·85
COPD	122 (20%)	123 (21%)	0·59
COPD and diabetes	40 (6%)	42 (7%)	0·63
Peripheral artery disease	34 (5%)	32 (5%)	0·97
Stroke	24 (4%)	28 (5%)	0·45
Transient ischaemic attack	34 (5%)	29 (5%)	0·63
Abdominal aortic aneurysm	16 (3%)	19 (3%)	0·42
Valvular disease			
Aortic valve stenosis	11 (2%)	9 (2%)	0·74
Aortic valve regurgitation	3 (1%)	1 (<1%)	0·34
Mitral valve stenosis	1 (<1%)	0	0·33
Mitral valve regurgitation	9 (1%)	4 (1%)	0·19
Other	4 (1%)	2 (0%)	0·44
Smoking			
Current	83 (13%)	78 (13%)*	0·94
Previous	357 (57%)	323 (56%)*	0·35
Never	183 (29%)	176 (30%)*	0·88
Target diagnoses at baseline			
Heart failure	13 (2%)	17 (3%)	0·38
Atrial fibrillation or atrial flutter	59 (10%)	68 (12%)	0·25
Coronary artery disease (angina pectoris, previous myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention)	105 (17%)	101 (17%)	0·91
Previous myocardial infarction	59 (9%)	44 (7%)	0·21
Any target diagnosis (atrial fibrillation, any coronary artery disease, heart failure) at baseline	154 (25%)	159 (27%)	0·39
Medication use at baseline			
Anticoagulants	65 (10%)	78 (13%)	0·13
Antiplatelets	166 (27%)	154 (26%)	0·81
Nitrates	31 (5%)	18 (3%)	0·088
Loop diuretics	23 (4%)	23 (4%)	0·86
Other diuretics	181 (29%)	201 (34%)	0·063
β blockers	185 (30%)	181 (31%)	0·73
ACE-inhibitors or angiotensin-receptor blockers	310 (50%)	330 (56%)	0·034
Calcium channel blockers	162 (26%)	143 (24%)	0·47
Oral glucose lowering drugs	412 (66%)	366 (62%)	0·13
Insulin	86 (14%)	87 (15%)	0·65
Lipid lowering drugs or statins	435 (70%)	389 (66%)	0·14
Thyroid hormones	41 (7%)	39 (7%)	0·99

COPD=chronic obstructive pulmonary disease. ACE=angiotensin-converting enzyme. *Information on smoking status was missing in 15 (2%) patients in the usual care group; percentages were calculated with 577 as the denominator.

Table: **Baseline characteristics**

validation cohort.[54] Third, interpretation of the results of step 1 and 2 by the GP (appendix pp 2–3). Decisions regarding pharmacotherapy, further diagnostics, and referral to secondary care were left to the GP's discretion. Information on the derivation and validation of the model used as a basis for the questionnaire was published previously.[12] Full details of the intervention are provided in the published protocol.[17]

Usual care within the disease management programmes can vary between patients and practices, but generally involves one to four visits per year, during which a practice nurse or GP discusses symptoms of hyperglycaemia and hypoglycaemia (in the case of diabetes) or pulmonary symptoms (in the case of COPD), diet and exercise, and therapy adherence. In patients with diabetes, blood pressure and fasting glucose are also measured.

Data on medication use were manually retrieved by the practice nurse (and cross-checked by a researcher) at baseline and after 1 year of follow-up from participants' electronic medical records using an electronic case report form. HRQoL was assessed by the EQ-5D-5L questionnaire, measured at baseline and after 1 year of follow-up. The EQ-5D-5L comprises five dimensions (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression), which are divided into five degrees of severity by a Likert scale, ranging from "no problems" to "extreme problems". Additionally, the patient's self-rated health is recorded on a visual analogue scale (VAS) ranging from 0 to 100, with higher scores indicating better HRQoL.

Outcomes

The primary outcome was a composite of newly diagnosed heart failure, atrial fibrillation, or coronary artery disease after 1 year of follow-up. All outcomes were adjudicated by the members of a clinical outcome committee, according to prespecified criteria based on the European Society of Cardiology guidelines (appendix p 4).[1–3] The clinical outcome committee consisted of three authors (FHR, MR, and RAD). Heart failure diagnosis required presence of signs or symptoms of heart failure alongside objective confirmation of cardiac dysfunction (eg, echocardiography or MRI). We used the HFA-PEFF score to diagnose heart failure with preserved ejection fraction.[8,38] The HFA-PEFF scoring method is a consensus-based algorithm based on echocardiographic indices and natriuretic peptide measurement. Atrial fibrillation was identified through ECG rhythm analysis, Holter ECG, or loop recording. Coronary artery disease diagnosis necessitated a positive stress test or any imaging modality showing anatomical evidence of (obstructive) coronary pathology.

Secondary outcomes were changes in medication prescription, HRQoL, and cost-effectiveness. Results of the cost-effectiveness analyses will be published separately.

Statistical analysis

Considering the prevalence in previous screening studies of unrecognised heart failure (21–28%)[5,9] and coronary

artery disease (65%)[7] in individuals with COPD or type 2 diabetes and the prevalence of unrecognised atrial fibrillation (1%)[6] in the population aged 65 years or older, we anticipated to find these cardiovascular diseases in 10% of the participants in the intervention group, compared with 5% with usual care. To detect this 5% difference, accounting for clustering with an estimated intracluster correlation coefficient (ICC) of 0·01[6,18,19] and an anticipated loss to follow-up of 10%, we conservatively needed to include 650 participants per group to be able to include at least 1170 participants in the analysis.

We compared the number of new diagnoses of participants included in the intervention group with those in the control group. As cluster randomisation was done and informed consent was obtained from participants after practices were randomly assigned, differences in baseline characteristics might be present. We therefore pre-specified to report both unadjusted outcomes and outcomes adjusted for age, sex, hypertension, hypercholesterolaemia, smoking status, and cardiovascular comorbidities. To identify potential post-randomisation selection bias, we formally tested for imbalances of patient-level data at baseline. Although this increases transparency, reporting p values at baseline remains a contentious issue even in cluster-randomised trials because doing so increases the risk of chance findings due to multiple testing. The findings in the table should be interpreted with that in mind.[20–22]

For the composite outcome of newly diagnosed cardiovascular disease, we applied linear mixed models with a random intercept to account for clustering within practices and adjusted for the aforementioned covariates as fixed effects. Additionally, we calculated incidence rates per 1000 person-years for each group. Participants contributed person-time from baseline until date of first diagnosis, death, loss to follow-up, or the end of the study.

Because patients with non-obstructive coronary artery disease are a heterogeneous group and the clinical relevance of non-obstructive coronary artery disease is not always evident, we calculated odds ratios (ORs) including cases of only obstructive coronary artery disease separately in a post-hoc analysis. We assessed differences between the groups in medication use at follow-up with generalised mixed linear models for each class of medication separately, using robust estimators and a Poisson distribution with log link. Again, clusters were added as a random effect and we adjusted for medication use if appropriate (ie, in case of significant differences in use of that class of medication at baseline). Additionally, we used the exact version of McNemar's test for paired proportions to assess differences in medication use between baseline and follow-up within each group separately. All analyses were done on an intention-to-treat basis, as prespecified in the study protocol. All analyses were done using SPSS (version 27), SAS (Studio 3.8), and R (4.3.0). Data verification was done by an independent monitor on a sampling basis.

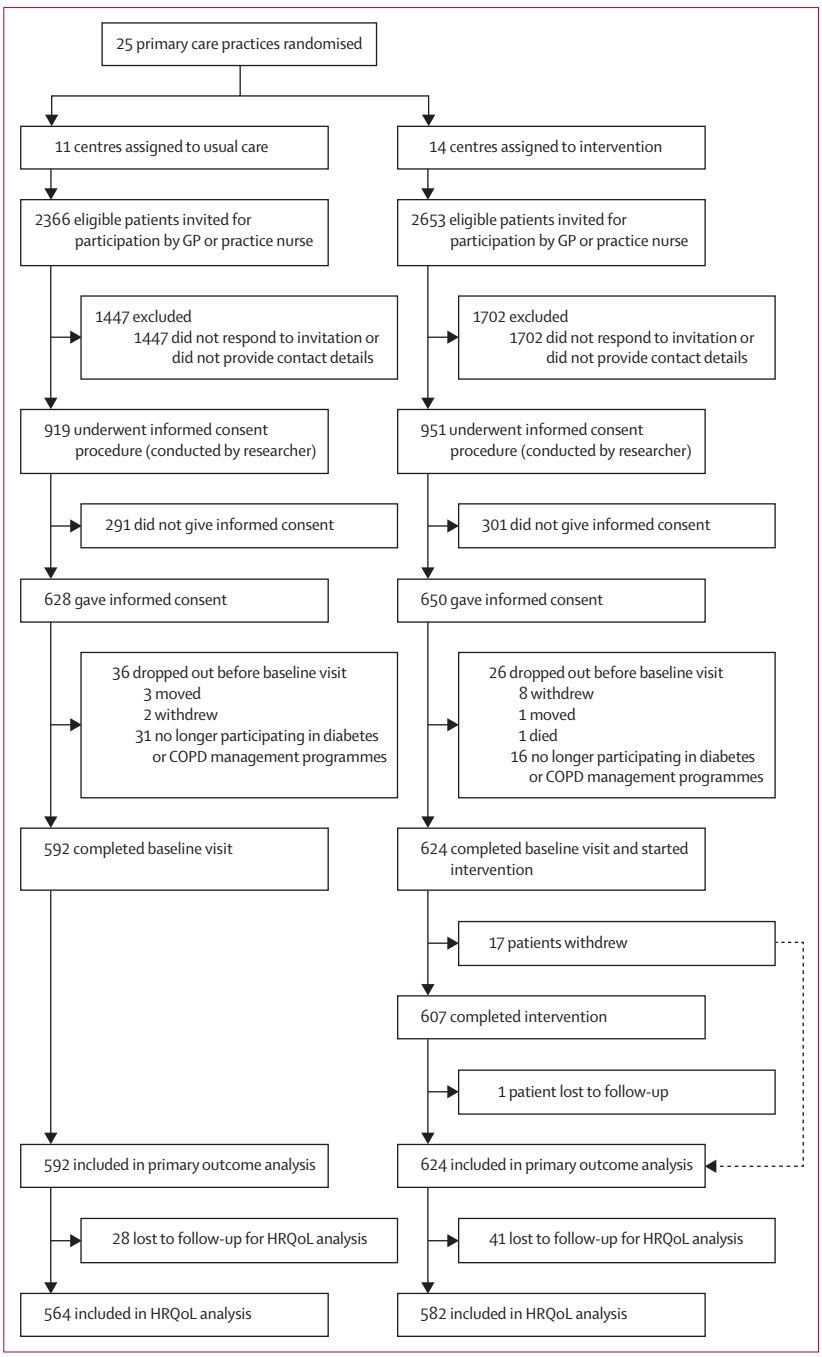

Figure 1: **Trial profile**
GP=general practitioner. HRQoL=health-related quality of life.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

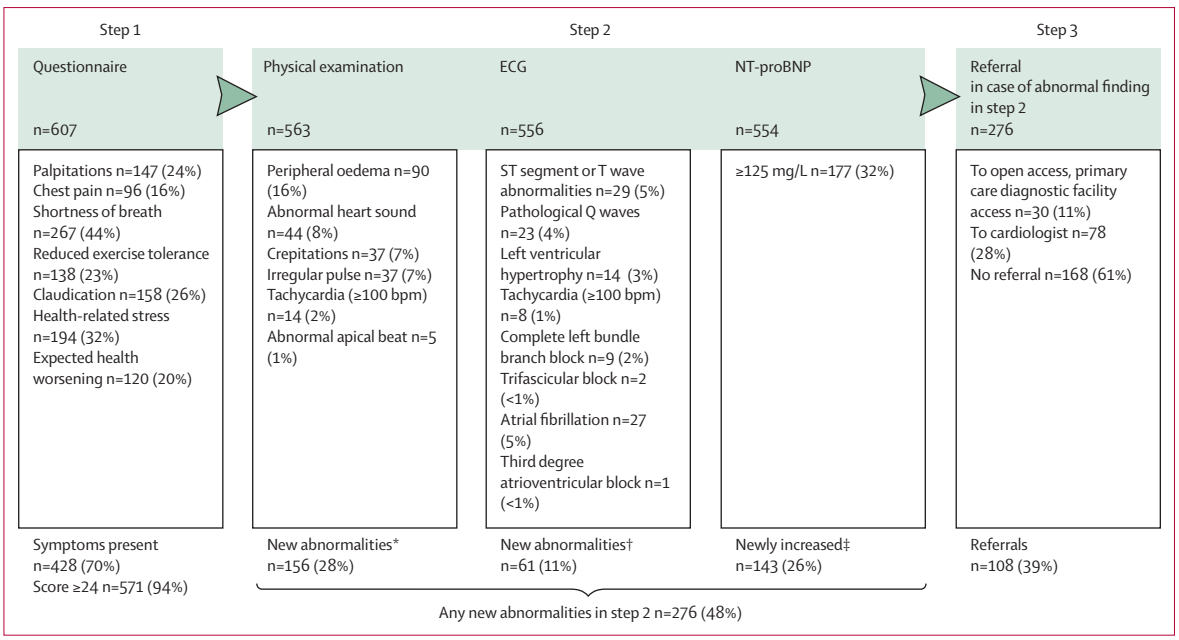

Figure 2: **Components of the QNE strategy**
ECG=electrocardiography. NT-proBNP=N-terminal pro-B-type natriuretic peptide. QNE=questionnaire, N-terminal-pro-B-type natriuretic peptide, electrocardiography, and physical examination. *Excluding irregular pulse in case of known atrial fibrillation and excluding peripheral oedema, crepitations, and abnormal apical beat in case of heart failure. †Excluding abnormal ST segment, Q waves, left bundle branch block, and trifascicular block in the case of known coronary artery disease; excluding atrial fibrillation in the case of known atrial fibrillation; and excluding left ventricular hypertrophy in the case of known heart failure. ‡Excluding increased NT-proBNP in the case of heart failure and in the case of a concurrent episode of atrial fibrillation on ECG.

Results

Between Jan 31 2019, and Oct 7, 2021, we randomly assigned 25 primary care practices: 11 (44%) to usual care and 14 (56%) to the intervention (figure 1). Between June 21, 2019, and Jan 31, 2022, 5019 individuals were invited to participate in the trial by their GPs: 2366 (47·1%) in the usual care group and 2653 (52·9%) in the intervention group (figure 1). 650 patients in the intervention group and 628 in the usual care group provided informed consent; however, 26 (4%) participants in the intervention group and 36 (6%) participants in the usual care group left the study before the baseline visit, either because they withdrew consent, moved, or died, or because they quit participation in a primary care disease management programme. This dropout was mostly because the study was halted in all practices for 6 months (from March 18, 2020) because of the COVID-19 pandemic. 1216 individuals were included for analysis, meeting the required sample size: 624 participated in the intervention group (participation rate 24% [624/2637]) and 592 in the usual care group (participation rate 25% [592/2366]; figure 1). Median cluster size was 39 participants (IQR 20–51) in the intervention group and 38 (24–70) in the usual care group. The estimate of the observed ICC based on the collected data was 0·008.

Mean age was 68·4 years (SD 9·4), 482 (40%) participants were female, and 734 (60%) were male. Of all included participants, 1052 (87%) had type 2 diabetes, and 245 (20%) had COPD (82 [7%] had both; table). Percentages of previously diagnosed cardiovascular diseases were similar across groups (table). Patients who responded to the invitation by their GP but decided not to participate after receiving further information by the researchers (n=592) were more often female (246 [50%] of 496 individuals with known sex) and were of similar age (69·7 years [SD 10·2]) compared with those who did participate.

During follow-up, 27 (2·2%) participants died, five of whom died because of COVID-19. Deaths were distributed equally across groups (15 [2·4%] in the intervention group and 12 [2·0%] in the usual care group; appendix p 6). 82 (13%) participants in the intervention group and 90 (15%) participants in the control group were admitted to hospital at least once (appendix p 6).

Of 624 participants included in the intervention group, 607 (97%) completed the symptom and risk factor questionnaire (step 1). In 571 (94%) of these, the questionnaire score was 24 points or higher and additional testing was indicated. 428 (71%) of 607 participants had at least one symptom of cardiovascular disease (figure 2; appendix p 5). Shortness of breath during exercise was the most common symptom (267 [44%]; 174 [36%] of 488 in patients without COPD), followed by claudication (158 [26%] overall; 45 [38%] in participants with COPD).

In step 2 of the QNE strategy (physical examination, NT-proBNP, and ECG), 276 (48%) of 571 participants had at least one abnormality not explained by previously

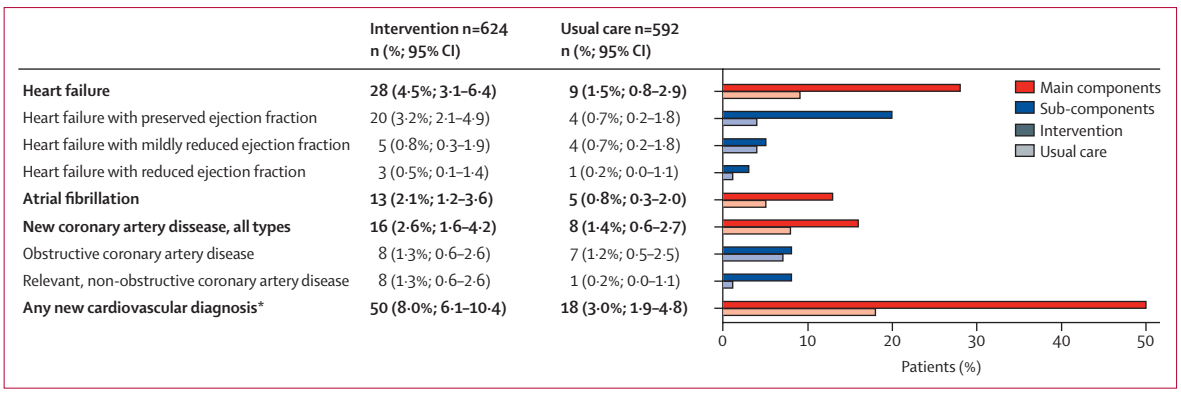

Figure 3: **Numbers of new cardiovascular diagnoses per group at 1 year of follow-up**
*The total number of patients with a new diagnosis is lower than the combination of the individual components because some patients received a double diagnosis. In the intervention group, 50 patients received 57 diagnoses and in the control group, 18 patients received 22 diagnoses.

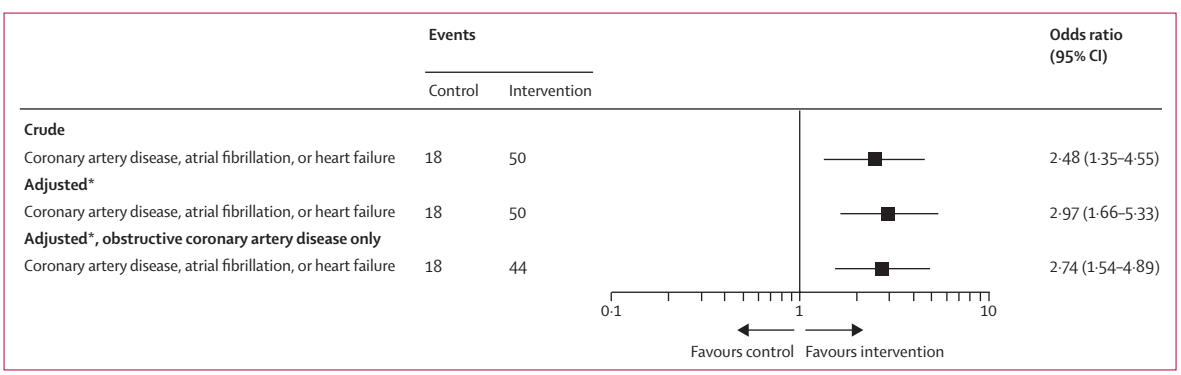

Figure 4: **Forest plot of odds ratios for new diagnoses between the comparative groups**
*Adjusted for age, sex, hypertension, hypercholesterolaemia, smoking status, and cardiovascular disease (coronary artery disease, atrial fibrillation, or heart failure) at baseline.

diagnosed heart failure, atrial fibrillation, or coronary artery disease (figure 2). Of these, 78 (28%) were referred directly to a cardiologist. In another 30 (11%), the GP ordered additional tests (eg, an exercise test or echocardiography) in a primary care diagnostic facility. The main reasons given by GPs for not referring participants with abnormal findings in step 2 were normal (50 [30%] of 168 participants who were not referred) or mildly increased (35 [21%]) NT-proBNP levels, or that the patient was already being monitored by a cardiologist (20 [12%]).

During 1 year of follow-up, 50 (8·0% [95% CI 6·1–10·4]) of 624 participants in the intervention group and 18 (3·0% [1·8–4·8]) of 592 participants in the control group received at least one new diagnosis of heart failure, atrial fibrillation, or coronary artery disease (figure 3). Heart failure was the most common new diagnosis (28 [5%] in the intervention group *vs* nine [2%] in the control group), followed by coronary artery disease (16 [3%] *vs* eight [1%]) and atrial fibrillation (13 [2%] *vs* five [1%]). The difference in the number of new heart failure diagnoses between the groups was more pronounced for cases with a preserved ejection fraction (20 [3%] *vs* four [1%]) than for those with a mildly reduced ejection fraction (five [1%] *vs* four [1%]) and those with a reduced ejection fraction (three [1%] *vs* one [<1%]; figure 3; appendix p 5). The adjusted OR was 2·97 (95% CI 1·66–5·33) for any new cardiovascular disease diagnosis after adjustment for age, sex, hypertension, hypercholesterolaemia, previously diagnosed cardiovascular disease, and smoking (figure 4; appendix p 5). In participants without previously diagnosed heart failure, atrial fibrillation, or coronary artery disease, the adjusted OR was 3·56 (1·47–8·72). After exclusion of individuals with non-obstructive coronary artery disease, the adjusted OR was 2·74 (1·54–4·89; figure 4; appendix p 5). Incidence rates for newly diagnosed cardiovascular disease were 85·1 per 1000 person-years in the intervention group and 31·2 per 1000 person-years in the usual care group (incidence rate ratio 2·73 [95% CI 1·59–4·68]).

158 (25% [95% CI 22·1–28·9]) of 624 participants in the intervention group and 93 (16% [13·0–19·6]) of 592 in the control group consulted a cardiologist at least once. The percentage of new referrals was also higher in the intervention group than in the control group (103 [17%; 13·8–19·6] *vs* 44 [7%; 5·6–9·8]). Compared with the usual care group, more participants in the intervention group had ECG (193 [30·9%] *vs* 127 [21·5%]; p<0·0002) and

echocardiography (139 [22·3%] *vs* 55 [9·3%]; p<0·0001). We found no differences for other diagnostic tests, including Holter ECG, exercise stress tests, coronary angiography, or other cardiac imaging (appendix p 9).

Compared with treating doctors, the adjudication committee more often diagnosed heart failure (37 *vs* 21) and coronary artery disease (24 *vs* 22). Differences were most pronounced for heart failure with preserved ejection fraction (24 *vs* 12; appendix p 9).

We found no overall differences in medication prescriptions between groups at follow-up (appendix pp 7–8). Among participants with a new diagnosis, we found increases in the use of β blockers, renin–angiotensin system inhibitors, anticoagulants, statins, and antiplatelet therapy in both groups, but found no significant differences in medication use between groups at follow-up (appendix pp 7–8). Numbers of non-pharmacological interventions (percutaneous coronary intervention, coronary artery bypass grafts, catheter ablation, cardioversion, and valve surgery) were also similar across both groups.

In the intervention group, the overall HRQoL, measured on a VAS scale ranging from 0 to 100, declined from 76·0 points to 74·9 points (mean change 1·1 [95% CI –0·05 to 2·34). In the control group, HRQoL declined from 77·6 to 74·5 (average change 3·1 [1·92 to 4·24]).

Discussion

In this multicentre, cluster-randomised, controlled trial, we showed that our proactive diagnostic strategy consisting of a questionnaire and low-cost and accessible tests more than doubled the detection rate of heart failure, atrial fibrillation, and coronary artery disease over 1 year of follow-up compared with usual care in primary care patients with COPD or type 2 diabetes. We found no differences in medication use between groups. Participants with a new, screen-detected diagnosis in the intervention group were receiving similar pharmacological therapies to those with a new diagnosis in the usual care group. The mean overall change in HRQoL at follow-up versus baseline was also similar in both groups.

In terms of new diagnoses, the most notable increase was in new cases of heart failure, particularly heart failure with preserved ejection fraction. Smaller increases were seen for atrial fibrillation and non-obstructive coronary artery disease. This distribution of diagnoses aligns with our strategy, which prioritises signs of fluid overload and increased intracardiac pressure, rather than coronary artery disease. The physical examination focuses on signs of fluid retention, and an increased NT-proBNP is an established biomarker of left ventricular wall stress. ECGs have only limited sensitivity (52%) in predicting coronary artery stenosis in patients with new-onset chest pain, often becoming abnormal only after permanent ischaemic damage has occurred.[55] The predominance of heart failure with preserved ejection fraction over heart failure with reduced ejection fraction in our study is in line with echocardiographic screening studies in patients with type 2 diabetes aged 60 years or older;[5] heart failure with preserved ejection fraction is unrecognised more easily and for a longer period of time than heart failure with reduced ejection fraction.[23]

In the past almost 40 years, most research has focused on improving care through improvement of treatment of established cardiovascular disease. This study is among the first to create an evidence base for a structured approach to improve early diagnosis to improve health outcomes in cardiovascular diseases for which evidence-based treatments are available. Previous studies[24,25] have suggested that components of the QNE strategy might be useful for identification of patients at increased risk of cardiovascular disease, and that early detection of these individuals leads to patient benefits downstream through initiation or up-titration of evidence-based medication. Most notably, the PONTIAC[24] and STOP-HF[25] trials have shown the effective use of natriuretic peptides for identification and treatment of individuals at high risk of developing heart failure in primary care. In patients with type 2 diabetes without a history of cardiovascular disease in the PONTIAC trial, up-titration of renin–angiotensin aldosterone system inhibitors and β blockers in those with NT-proBNP concentrations of 125 ng/L or higher resulted in a 65% reduced risk of cardiovascular hospitalisation or death.[24] In the STOP-HF trial, up-titration of renin–angiotensin system inhibitors and β blockers reduced the occurrence of asymptomatic left ventricular dysfunction and overt heart failure by 39%.[25] Furthermore, during 4·2 years of follow-up, major cardiovascular events occurred less frequently in the intervention group (OR 0·69 [95% CI 0·49–0·98]; p=0·04).[25] Interestingly, the changes in cardiovascular drug prescription in those with increased natriuretic peptides, considered by the authors of the STOP-HF trial to be the main driving force behind the prognostic benefits of NT-proBNP screening, were similar to the trends observed in our study. In the STROKESTOP study,[26] systematic screening for atrial fibrillation with 14-day intermittent ECG recording led to a small (4%) yet significant (p=0·045) reduction in the risk of the primary endpoint of ischaemic or haemorrhagic stroke, systemic embolism, hospitalisation for bleeding, or all-cause mortality. Among individuals who were screened (ie, excluding non-participants in the intervention group), there was a 24% lower risk of ischaemic stroke compared with controls. In the LOOP study,[27] screening for atrial fibrillation using an implantable loop recorder was associated with a significant reduction in the risk of stroke or systemic embolism in individuals with increased NT-proBNP, but not in those with normal NT-proBNP, indicating that NT-proBNP might help to identify patients with atrial fibrillation who are at the highest risk of stroke.[27] In the ongoing STROKESTOP II

trial,[28] a single index ECG revealed new atrial fibrillation in only one (0·04%) of 2549 participants with normal NT-proBNP, compared with 28 (0·7%) participants with increased NT-proBNP, with a further 136 (3·6%) of those with increased NT-proBNP being diagnosed with new atrial fibrillation after an additional 14-day intermittent ECG screening. Taken together, these trials indicate that NT-proBNP and ECG screening might be used in conjunction to identify individuals at risk of heart failure and atrial fibrillation and to initiate timely treatment to prevent progression of disease or acute cardiovascular events. For coronary artery disease, little is known about the effects of screening on patient outcomes.[29] Results from the population-based Lifelines study[30] show that a single resting ECG can identify a substantial number of individuals with possible unrecognised myocardial infarction who are at increased risk of death. However, whether screening for coronary artery disease using resting ECGs can lead to improved patient outcomes is unknown.[29]

On the basis of the results of the STOP-HF and PONTIAC trials, the American Diabetes Association now recommends annual NT-proBNP measurement in patients with diabetes.[31] The RED-CVD study is the first comparative trial to substantiate the efficacy of such an approach in terms of diagnostic yield, rather than identification of individuals at risk. However, unlike the STOP-HF and PONTIAC trials, our study protocol did not include mandatory steps to be taken if NT-proBNP concentrations exceeded a particular threshold. Instead, the decision to refer was at the discretion of the GP, which likely led to fewer referrals and additional testing compared with non-pragmatic trials with a stricter protocol. Even if symptoms were present, GPs often did not refer participants with mildly increased NT-proBNP (typically 125–300 ng/L). The use of a higher-than-recommended threshold of NT-proBNP by GPs has been observed previously.[32] This finding implies that the implementation of a structured diagnostic intervention within the somewhat unstructured primary care environment could yield greater improvements in terms of patient outcomes if combined with collaborative care and a strict treatment protocol. However, the trial commenced before the publication of pivotal trials showing the benefits of SGLT2 inhibitor use in patients with heart failure with preserved ejection fraction, and data on SGLT2 inhibitor use were not collected.[33,34] As such, further studies are needed to investigate whether the improved diagnostic yield of the QNE strategy leads to improved patient outcomes in the long term, especially with effective treatment for heart failure with preserved ejection fraction now available.

The RED-CVD study used a pragmatic design, extending the generalisability of results to most patients with type 2 diabetes and COPD managed in primary care. Other strengths include a low rate of loss to follow-up and comprehensive review and adjudication of heart failure, atrial fibrillation, and coronary artery disease diagnoses by an expert panel following international guidelines.

However, some limitations should be noted. First, selection bias remains an inherent risk associated with a cluster-randomised design, in which individual patients receive detailed information only after randomisation at practice level. To mitigate this bias, we adjusted analyses for the pre-defined covariates age, sex, smoking, and comorbidities, which had a minimal impact on effect estimates. However, selection bias might still be present, particularly because the participation rate was suboptimal (25%). Second, the study population (mean age 68 years) was older than the population in which the questionnaire was derived (52 years),[12] resulting in reduced discriminatory power; a large proportion of participants scored high points for age and most participants (94%) continued to the second step after completing the questionnaire. This finding suggests that the QNE strategy could be executed without the questionnaire, making it even less time consuming. However, patients often have substantially more symptoms than they report spontaneously in the doctor's office.[35] Both our study and previous research indicate that use of questionnaires, regardless of the care setting, can assist patients to identify symptoms that might otherwise be overlooked.[35–37] For example, despite informing their cardiologists that there were no new developments, many participants in this study reported several unresolved symptoms when completing the questionnaire. Recognition of symptoms might also increase therapy adherence and willingness to make lifestyle changes.

Given the pragmatic design, the decision to refer participants was left to the discretion of GPs, with further investigations determined by cardiologists' judgment. This design probably led to an underestimation of new cases of cardiovascular disease detected through the intervention. Only 39% of patients with an abnormal physical examination, ECG, or NT-proBNP concentration unexplained by pre-existing clinical conditions underwent additional investigations. The COVID-19 pandemic might have hindered willingness to refer patients, especially during periods of reduced hospital capacity. Additionally, the cardiologists' work-up was not always comprehensive. At times, clinicians omitted tests such as tissue Doppler imaging, global strain imaging, and coronary angiography in patients for whom the adjudication panel believed these tests were necessary. Functional coronary imaging for coronary spasms or microvascular dysfunction was never done. Consequently, both study groups probably had underdiagnosis of coronary artery disease and heart failure with preserved ejection fraction. However, the pragmatic design allowed for realistic results, aligning with everyday clinical practice.

Patients who were currently or previously monitored by a cardiologist were not excluded from the trial.

Inclusion of such patients might increase the risk of overdiagnosis and redundant diagnostic testing, and some of these patients might already have been receiving optimal treatment, rendering the identification of an additional cardiovascular disease of minimal therapeutic consequence; however, the risk of repetitive diagnostic testing is small because of the distinct diagnostic approaches for heart failure, atrial fibrillation, and coronary artery disease. Even if patients have undergone a comprehensive assessment at one stage, their condition can change, necessitating continuous monitoring. Additionally, post-diagnosis follow-up by cardiologists might become less rigorous with the prevailing trend of shifting specific hospital care components to GPs, particularly because of increasing health-care costs and the increasing workload of hospital specialists. Our strategy might minimise gaps in follow-up and management given the ongoing and progressive nature of cardiovascular diseases. Excluding individuals with evidence of cardiovascular disease at baseline might therefore have been counterintuitive, given that these individuals have the most prominent known causal factor and are at increased likelihood of developing another cardiovascular disease. Notably, the decision to refer after positive screening was at the discretion of GPs and was not mandatory in the trial protocol, which probably further minimised the risk of unnecessary testing.

Although our initial protocol aimed to collect laboratory values at baseline for renal, thyroid, and liver functions, we identified a potential bias because these tests are more routinely done for patients with diabetes than for those with COPD. This potential missing-not-at-random scenario led us to pivot to using episodes registered by the GP in the electronic health records for assessment of comorbidities instead of laboratory values, which might be at increased risk of misclassification and under-reporting. To mitigate this risk, we used rigorous data monitoring, involving two researchers who reviewed the electronic health records of all participants, including laboratory values, hospital discharge letters, and specialist consultation notes. Data on ethnicity were also not collected.

Lastly, the expert panel applying the HFA-PEFF score[38] diagnosed heart failure with preserved ejection fraction more frequently than did treating cardiologists in both study groups. The lack of consensus on echocardiographic abnormalities indicating left ventricular diastolic dysfunction and, until recently, the absence of proven therapies for heart failure with preserved ejection fraction might contribute to under-recognition of this condition by cardiologists and GPs in daily practice. Because the true value of increased diagnostic yield is dependent on clinician diagnosis, as opposed to panel diagnosis, recognition of heart failure with preserved ejection fraction by clinicians is key for effective treatment that improves health. Fortunately, the past 5–10 years have already seen an increase in awareness and recognition of heart failure with preserved ejection fraction among cardiologists[39] and the emergence of beneficial treatments for heart failure with preserved ejection fraction[33,34] is likely to accelerate this trend, highlighting the potential of our QNE strategy.

The increasing global burden of cardiovascular disease is exacerbated by delayed diagnoses, which adversely affect patient outcomes and increase health-care costs, primarily via unnecessary hospitalisations.[40–43] 80% of cases of heart failure are identified in hospital settings, even though 40% of patients have symptoms warranting earlier intervention.[44] Individuals with newly identified atrial fibrillation often have minimal symptoms, potentially postponing diagnosis yet not mitigating stroke risk compared with patients with more overt symptoms.[45–47] Similarly, many patients presenting with acute myocardial infarction experience prodromal symptoms in the period before diagnosis.[48] Advances in drug and device therapies continue to enhance the prognosis of patients with heart failure, atrial fibrillation, and coronary artery disease, with prompt initiation optimising the benefits.[1–3]

In light of public health considerations, an affordable screening tool to detect conditions such as atrial fibrillation, heart failure, or coronary artery disease aligns well with the principal criteria for a screening programme: addressing a public health priority and facilitating intervention in an early symptomatic phase through available, evidence-based therapies. In our trial, we found an increase in the use of evidence-based medications among newly diagnosed patients in both groups, suggesting that cases detected through screening were not treated any less aggressively than those detected conventionally. However, we found no marked difference in treatments between the groups at follow-up, leaving open the question of whether identifying new diagnoses leads directly to improvements in patient outcomes. Further studies are warranted to ascertain the effect on patient results. A cost-effectiveness analysis on the RED-CVD trial is underway and the study is extended by 3 years to allow assessment of the development of major cardiovascular events in both study groups.

Primary care serves as the cornerstone of a robust and equitable health-care system, facilitating early detection and prevention of diseases, while promoting holistic wellbeing through sustained patient–doctor relationships. By addressing cardiovascular health issues at their nascent stages, GPs not only safeguard individual health but also mitigate the strain on public health resources. Because COPD and type 2 diabetes are among the most prevalent risk factors for cardiovascular disease, targeting these groups will ensure that our strategy reaches many individuals at risk.[49,50] In many European countries, structured disease management programmes exist for both of these conditions[51–53] and

the QNE strategy can easily be integrated into this existing infrastructure.

Our strategy uses affordable components and can be performed by trained practice nurses and be integrated into routine care, minimising the burden on healthcare resources and time. This approach thus offers a promising addition to standard care, especially in countries where GPs act as gatekeepers, which is common in many European countries. Although the questionnaire was validated specifically in patients with COPD and type 2 diabetes, other groups at high risk might also benefit, despite minor variations in symptoms among different populations. Core components of the intervention such as NT-proBNP measurement and ECG are likely to remain effective across diverse patient profiles. The tool might have increased efficiency in older populations or in those in economically disadvantaged regions, given their increased cardiovascular risk and prevalence of cardiovascular disease.

Contributors

FHR, RAdB, MR, HK, MJC, YTvdS, and AWH contributed to conceptualisation of this study, design of the methodology, and funding acquisition. AG and VWZ collected the data. Data curation and formal analysis was performed by AG and VWZ, under the supervision of FHR, NPAZ, and RAdB. All authors had access to the data and vouch for the accuracy and completeness of the data. AG and VWZ directly accessed and verified the underlying data reported in the manuscript. All authors contributed to data interpretation. AG was responsible for data visualisation and wrote the original draft of this manuscript. All authors critically reviewed and edited the manuscript and agreed with the decision to submit for publication.

Declaration of interests

RAdB has received research grants from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals, Novo Nordisk, and Roche; has had speaker engagements with Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Novartis, and Roche; has received honoraria from Abbott, AstraZeneca, Bristol Myers Squibb, Cardior Pharmaceuticals, NovoNordisk, and Roche; and has received travel support from Abbott, Cardior Pharmaceuticals, and NovoNordisk. FHR received a single fee from Novartis for speaker engagements in 2022. MR received consultancy fees from Bayer, Microport, and InCarda Therapeutics to the Department of Cardiology, UMC Groningen. All other authors declare no competing interests.

Data sharing

All of the individual participant data collected during the trial, after de-identification, as well as the study protocol, statistical analysis plan, informed consent form, and analytical code, can be made available following publication of this Article. Researchers with an interest can express to receive the data with a preliminary project proposal, which will be evaluated for originality and checked with other proposals to avoid duplicate research. If requirements are met, the researchers are requested to provide a methodologically sound proposal. Proposals and enquiries should be directed to f.h.rutten@umcutrecht.nl; to gain access, data requestors will need to sign a data access agreement.

Acknowledgments

This work was supported by a grant from the Dutch Heart Foundation and is conducted in collaboration with and supported by the Dutch CardioVascular Alliance (2017B011, RED-CVD). RAdB is further supported by the Dutch Heart Foundation (2017B021, 2018B030, and 2020B005), by the leDucq Foundation (Cure-PlaN), and by the European Research Council (ERC CoG 818715). MR is further supported by ZonMW and the Dutch Heart Foundation (848090001), the Netherlands Cardiovascular Research Initiative (2014–9), and Top Sector Life Sciences & Health (2018B017).

References

1 Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; **42:** 373–498.

2 Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020; **41:** 407–77.

3 McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; **42:** 3599–726.

4 Boonman-de Winter LJM, Rutten FH, Cramer MJ, et al. Efficiently screening heart failure in patients with type 2 diabetes. *Eur J Heart Fail* 2015; **17:** 187–95.

5 Boonman-De Winter LJM, Rutten FH, Cramer MJM, et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia* 2012; **55:** 2154–62.

6 Fitzmaurice DA, Hobbs FDR, Jowett S, et al. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. *BMJ* 2007; **335:** 383.

7 Muhlestein JB, Lappé DL, Lima JAC, et al. 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. *JAMA* 2014; **312:** 2234–43.

8 Rasmussen T, Køber L, Pedersen JH, et al. Relationship between chronic obstructive pulmonary disease and subclinical coronary artery disease in long-term smokers. *Eur Heart J Cardiovasc Imaging* 2013; **14:** 1159–66.

9 Rutten FH, Moons KGM, Cramer M-JM, et al. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. *BMJ* 2005; **331:** 1379.

10 van Mourik Y, Bertens LCM, Cramer MJM, et al. Unrecognized heart failure and chronic obstructive pulmonary disease (COPD) in frail elderly detected through a near-home targeted screening strategy. *J Am Board Fam Med* 2014; **27:** 811–21.

11 Ammar KA, Makwana R, Redfield MM, Kors JA, Burnett JC Jr, Rodeheffer RJ. 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* 2006; **151:** 799–805.

12 Zwartkruis VW, Groenewegen A, Rutten FH, et al. Proactive screening for symptoms: a simple method to improve early detection of unrecognized cardiovascular disease in primary care. Results from the Lifelines Cohort Study. *Prev Med* 2020; **138:** 106143.

13 Browne JL, Ventura A, Mosely K, Speight J. 'I call it the blame and shame disease': a qualitative study about perceptions of social stigma surrounding type 2 diabetes. *BMJ Open* 2013; **3:** e003384.

14 Börschel CS, Schnabel RB. The imminent epidemic of atrial fibrillation and its concomitant diseases - Myocardial infarction and heart failure—a cause for concern. *Int J Cardiol* 2019; **287:** 162–73.

15 Campmans-Kuijpers MJE, Baan CA, Lemmens LC, Rutten GEHM. Diabetes quality management in Dutch care groups and outpatient clinics: a cross-sectional study. *BMC Res Notes* 2014; **7:** 497.

16 Willink RP, Vos RC, Looijmans-van den Akker I, Hart HE. Type 2 diabetes and COPD: treatment in the right healthcare setting? An observational study. *BMC Fam Pract* 2021; **22:** 78.

17 Groenewegen A, Zwartkruis VW, Rienstra M, et al. Improving early diagnosis of cardiovascular disease in patients with type 2 diabetes and COPD: protocol of the RED-CVD cluster randomised diagnostic trial. *BMJ Open* 2021; **11:** e046330.

18 Smeeth L, Ng ES-W. Intraclass correlation coefficients for cluster randomized trials in primary care: data from the MRC Trial of the Assessment and Management of Older People in the Community. *Control Clin Trials* 2002; **23:** 409–21.

19 Uittenbogaart SB, Verbiest-van Gurp N, Erkens PMG, et al. Detecting and Diagnosing Atrial Fibrillation (D2AF): study protocol for a cluster randomised controlled trial. *Trials* 2015; **16:** 478.

20 Bolzern JE, Mitchell A, Torgerson DJ. Baseline testing in cluster randomised controlled trials: should this be done? *BMC Med Res Methodol* 2019; **19:** 106.

21 Donner A, Klar N. Pitfalls of and controversies in cluster randomization trials. *Am J Public Health* 2004; **94:** 416–22.

22 Puffer S, Torgerson D, Watson J. Evidence for risk of bias in cluster randomised trials: review of recent trials published in three general medical journals. *BMJ* 2003; **327:** 785–89.

23 Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart failure with preserved ejection fraction: JACC scientific statement. *J Am Coll Cardiol* 2023; **81:** 1810–34.

24 Huelsmann M, Neuhold S, Resl M, et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. *J Am Coll Cardiol* 2013; **62:** 1365–72.

25 Ledwidge M, Gallagher J, Conlon C, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA* 2013; **310:** 66–74.

26 Svennberg E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. *Lancet* 2021; **398:** 1498–506.

27 Xing LY, Diederichsen SZ, Højberg S, et al. Effects of atrial fibrillation screening according to N-terminal pro-B-type natriuretic peptide: a secondary analysis of the randomized LOOP study. *Circulation* 2023; **147:** 1788–97.

28 Kemp Gudmundsdottir K, Fredriksson T, Svennberg E, et al. Stepwise mass screening for atrial fibrillation using N-terminal B-type natriuretic peptide: the STROKESTOP II study. *Europace* 2020; **22:** 24–32.

29 Jonas DE, Reddy S, Middleton JC, et al. Screening for cardiovascular disease risk with resting or exercise electrocardiography: evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2018; **319:** 2315–28.

30 van der Ende MY, Hartman MHT, Hagemeijer Y, et al. The LifeLines Cohort Study: prevalence and treatment of cardiovascular disease and risk factors. *Int J Cardiol* 2017; **228:** 495–500.

31 Pop-Busui R, Januzzi JL, Bruemmer D, et al. Heart failure: an underappreciated complication of diabetes. A consensus report of the American Diabetes Association. *Diabetes Care* 2022; **45:** 1670–90.

32 Valk M, Hoes AW, Mosterd A, Broekhuizen B, Zuithoff N, Rutten FH. Time trends in the use and appropriateness of natriuretic peptide testing in primary care: an observational study. *BJGP Open* 2020; **4:** 1–6.

33 Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; **385:** 1451–61.

34 Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022; **387:** 1089–98.

35 Elnegaard S, Andersen RS, Pedersen AF, et al. Self-reported symptoms and healthcare seeking in the general population—exploring "the symptom iceberg". *BMC Public Health* 2015; **15:** 1–11.

36 Burmester B, Leathem J, Merrick P. Assessing subjective memory complaints: a comparison of spontaneous reports and structured questionnaire methods. *Int Psychogeriatr* 2015; **27:** 61–77.

37 Wallander MA, Dimenäs E, Svärdsudd K, Wiklund I. Evaluation of three methods of symptom reporting in a clinical trial of felodipine. *Eur J Clin Pharmacol* 1991; **41:** 187–96.

38 Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2019; **40:** 3297–317.

39 Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail* 2020; **22:** 1342–56.

40 Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014; **63:** 1123–33.

41 Bottle A, Kim D, Aylin P, Cowie MR, Majeed A, Hayhoe B. Routes to diagnosis of heart failure: observational study using linked data in England. *Heart* 2018; **104:** 600–05.

42 Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013; **6:** 606–19.

43 Kwok CS, Satchithananda D, Mallen CD. Missed opportunities in coronary artery disease: reflection on practice to improve patient outcomes. *Coron Artery Dis* 2022; **33:** 233–38.

44 National Health Service. The NHS long term plan. Jan 7, 2019. https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf (accessed March 1, 2023).

45 Huisman MV, Ma CS, Diener HC, et al. Antithrombotic therapy use in patients with atrial fibrillation before the era of non-vitamin K antagonist oral anticoagulants: the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) Phase I cohort. *Europace* 2016; **18:** 1308–18.

46 Engdahl J, Holmen A, Rosenqvist M, Stromberg U. A prospective 5-year follow-up after population-based systematic screening for atrial fibrillation. *Europace* 2018; **20:** f306–11.

47 Gibbs H, Freedman B, Rosenqvist M, et al. Clinical outcomes in asymptomatic and symptomatic atrial fibrillation presentations in GARFIELD-AF: implications for AF screening. *Am J Med* 2021; **134:** 893–901.e11.

48 Hwang SY, Zerwic JJ, Jeong MH. Impact of prodromal symptoms on prehospital delay in patients with first-time acute myocardial infarction in Korea. *J Cardiovasc Nurs* 2011; **26:** 194–201.

49 Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. *Lancet Respir Med* 2022; **10:** 447–58.

50 Sun H, Saeedi P, Karuranga S, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract* 2022; **183:** 109119.

51 Kostial C, Manuwald U, Schulze J, Kugler J, Rothe U. Disease-management-programs in the field of diabetes mellitus with identification of the best practice in Europe: a scoping review. *Horm Metab Res* 2020; **52:** 149–57.

52 Poot CC, Meijer E, Kruis AL, Smidt N, Chavannes NH, Honkoop PJ. Integrated disease management interventions for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2021; **9:** CD009437.

53 Wangler J, Jansky M. Attitudes to and experience of disease management programs in primary care-an exploratory survey of general practitioners in Germany. *Wien Med Wochenschr* 2021; **171:** 310–20.

55 Mahmoodzadeh S, Moazenzadeh M, Rashidinejad H, Sheikhvatan M. Diagnostic performance of electrocardiography in the assessment of significant coronary artery disease and its anatomical size in comparison with coronary angiography. *J Res Med Sci* 2011; **16:** 750–55.