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Integrated cardiovascular risk management programme versus usual care in high CV risk patients: an observational study in general practice

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Abstract

Background
Cardiovascular diseases (CVD) are the leading cause of death and cardiovascular (CV) risk factors are often insufficiently controlled in high risk patients. Recently, integrated multidisciplinary cardiovascular risk management (CVRM) programmes were introduced in primary care.

Aim
The present study investigates the effects of a CVRM programme on systolic blood pressure (SBP) and LDL-cholesterol.

Design and setting
A prospective observational study, in high CV risk patients aged 40-80 years in general practice, comparing integrated CVRM care with usual care.

Methods
Intervention and usual care patients were matched at baseline on age, gender and presence of CVD. During one year of follow-up patients received integrated or usual CVRM care in general practice. Primary outcomes were SBP and LDL-cholesterol. Secondary outcomes included calculated 10-year CV risk, BMI, lifestyle (smoking, physical activity, dietary habits), medication use, patient satisfaction, health care consumption, morbidity, comorbidity and mortality. We used mixed-model analyses to assess the outcomes.

Results
We included 372 and 317 patients in the intervention and usual care group, respectively. Mean age at baseline was 65.1 and 66.2 years respectively and 42% were women in both groups. After one year, we observed no difference in SBP (137.2 mmHg vs 139.0 mmHg in the intervention and usual care group, respectively) and LDL-cholesterol (2.6 mmol/L in both groups), nor in any of the secondary outcomes.

Conclusion
Integrated CVRM care in general practice did not lead to a lower SBP or LDL-cholesterol in patients at high CV risk. Further research is needed to improve CVRM.

Trial registration: The ZWOlle Transmural Integrated Care for CArdiovaScular Risk Management Study; ClinicalTrials.gov; Identifier: NCT03428061; date of registration: 09-02-2018.

Keywords
Cardiovascular Diseases; Prevention; General practice; Delivery of Health Care, Integrated
How this fits in

In some European countries, integrated and multidisciplinary CVRM programmes were introduced in primary care in recent years. Studies on the effectiveness of CVRM programmes are scarce and the available evidence is inconsistent. In the present study one year of integrated primary care for CVRM following usual care did not lead to better outcomes for SBP (137.2 mmHg vs. 139.0 mmHg) and LDL-cholesterol (2.6 mmol/L in both groups), or any of the secondary outcomes of the study, as compared to usual care. This study adds relevant insight into effectiveness of integrated CVRM in a real world environment and guides clinicians to look for improvements in the quality of CVRM programmes.

Introduction

Cardiovascular diseases (CVD) remain the leading cause of mortality worldwide.1,2 The ESC recommends preventive, multidisciplinary programmes for cardiovascular risk management (CVRM), also in primary care.3 However, survey studies have shown that CVRM in primary care is suboptimally implemented, as control rates of cardiovascular risk factors are disappointing.4-6

In some European countries, integrated and multidisciplinary CVRM programmes were introduced in primary care in recent years. Core elements of these programmes include systematic selection, invitation, cardiovascular risk assessment, shared decision in treatment and follow-up of eligible patients, stimulation of self-management, registration of patient data in clinical information systems and yearly feedback to general practitioners (GPs) on delivered CVRM care.7 So far, studies on the effectiveness of CVRM programmes are scarce and the available evidence is inconsistent.8-10

Some studies showed a trend towards improved lifestyle, but did not show an effect on cardiovascular risk factors and cardiovascular outcomes.11-13 However, the studies were heterogeneous in design, target population and interventions tested and adequate comparison with usual care was often lacking.

The present ZWOT-CASE study (ZWOlle inTegrated care for CArdiovaScular risk managEment study) reports the effects of the implementation of an integrated CVRM care programme on systolic blood pressure (SBP) and LDL-cholesterol in general practice as compared to usual care.

Methods

Design

A prospective observational study comparing integrated care for CVRM with usual care during 1 year of follow-up. The details of the study design have been described elsewhere.14
Setting

The study was performed in the Zwolle region in the Netherlands, including 56 general practices, affiliated to a care group ‘Medrie’. All practices delivered usual care prior to the implementation of integrated care for CVRM. From January 2016, 37 general practices implemented integrated CVRM care and 19 general practices continued usual care. All practices were invited to participate in the study; 17 intervention and 9 usual care practices participated.

Patients

In total, we aimed to include 370 patients in each group consisting of respectively i) 185 patients with CVD and ii) 185 patients with a high (>10%) ten year risk of CVD morbidity and mortality based on the Dutch Guideline for CVRM and a modifiable risk factor (SBP > 140 mmHg, LDL-cholesterol > 2.5 mmol/L, smoking or BMI > 30 kg/m2). We ensured that 50% was aged below 65 years and 50% over 65 years. In- and exclusion criteria are shown in box 1.

Intervention

Implementation of the integrated CVRM programme was coordinated by the care group ‘Medrie’ in accordance with the regional hospital and the regionally largest health care insurance company, based on the Dutch CVRM guideline and the practical manual for CVRM provided by the Dutch Society of General Practitioners. GPs screened their practice population for eligible patients and invited them for an intake consultation for the integrated CVRM programme, mostly done by PNs under supervision of the GP. During this consultation the researchers identified patients for the study. To prevent a Hawthorne effect, GPs and patients were not informed about the identification. Patients received the integrated CVRM programme as previously described. In short, prior to the intake, a blood sample was taken to measure lipids, renal function (MDRD), and glucose. The intake included assessment of cardiovascular complaints, lifestyle (smoking habits, diet, alcohol, physical activity), prescribed medication, measurement of blood pressure and BMI, estimation of the 10-year CV risk according to the Dutch CVRM guideline in patients without CVD, and defining individual treatment goals in shared decision. Patients were monitored at least once a year for control of cardiovascular risk factors. If necessary, other disciplines were involved, including dieticians, physiotherapists and medical specialists. All disciplines had access to the patient data in the multidisciplinary information system, facilitating care coordination across organizations and ensuring a consistent policy in individual patients. After one year the study patients were revealed to the GP and received a letter from their GP to inform them about the study. After agreement to participate, written informed consent was obtained during the endpoint visit.
Usual care
Practices in the usual care group continued usual care. Patients were consecutively matched with intervention patients at baseline, on the basis of age (5 years categories), gender and presence of CVD. Similar to the intervention group, the patients and their GPs were not informed about the identification. After one year, the matched patient was invited for a CVRM consultation if the corresponding intervention patient agreed to participate. Written informed consent was obtained and endpoints were measured during this consultation.

Outcomes
The primary outcomes were SBP and LDL-cholesterol. Secondary outcomes included diastolic blood pressure, achievement of treatment goals (blood pressure < 140/90 mmHg, LDL-cholesterol ≤ 2.5 and ≤ 1.8 mmol/L for all patients and those with CVD, respectively), smoking status, BMI, 10-year cardiovascular morbidity or mortality risk (according to SMART and the Dutch guideline for patients with and without CVD, respectively)\textsuperscript{15,18}, healthy food habits (according to Dutch guideline for CVRM\textsuperscript{15} and guideline Healthy Food of the Dutch Health Council\textsuperscript{19}), alcohol consumption, physical activity (squash questionnaire)\textsuperscript{20}, medication use (antihypertensive drugs, lipid lowering drugs and anticoagulants), primary treating practitioner in CVRM (GP or medical specialist), total number of consultations in general practice, patient satisfaction regarding the provided care (Patient Reported Experience Measure (PREM)), quality of life (EQ-5D and SF-12), anxiety and depression (Hospital Anxiety and Depression Scale (HADS)), newly developed (co)morbidity and mortality.

Data collection
Prior to the endpoint visit, patients filled out a paper questionnaire (including the squash questionnaire, EQ-5D, SF-12, PREM, HADS and food habits) and a blood sample was taken for measurement of lipids, renal function, glucose and hs-CRP for CVD patients (to calculate SMART risk). During the endpoint visit practice nurses (PNs) assessed office blood pressure\textsuperscript{16}, BMI, smoking status, alcohol consumption and primary treating practitioner. After the endpoint visit we manually scrutinized electronic medical records to assess baseline data, medication use, health care consumption, (co)morbidity and mortality, and whether a patient received previous CVRM care, defined as at least yearly visiting the general practice for a CVRM consultation, including measurement of lipids, renal function and blood pressure.

We pseudonymised all data relating to patients. The Isala hospital Review Board reviewed the study and exempted it from full assessment under the Medical Research Involving Human Subjects Act (reference number 16.06104).
Sample size
The sample size was based on a 5 mmHg (SD 15.9) absolute reduction in SBP and a 0.3 mmol/L (SD 1.0) reduction in LDL-cholesterol in the intervention group as compared to usual care after 1 year of follow-up, with an alpha of 0.05, a power of 80% and an intra-cluster correlation coefficient of 0.05 for the general practice cluster level. This led to a need of 370 patients in both groups. Accounting for a response rate of 70% in the intervention group, we planned to invite 587 intervention patients. Anticipating a 50% response rate in the usual care group, each intervention patient was matched to 2 usual care patients, resulting in $587 \times 2 = 1174$ patients in the usual care group.

Statistical analyses
We used generalized linear mixed-model analyses. For continuous, count and dichotomous outcomes we assumed a linear, poisson and logistic distribution, respectively. For skewely distributed continuous outcomes we conducted analyses with a logarithmic transformed variable if appropriate and calculated the reversed logarithm of the B values and confidence intervals resulting into a ratio (interpreted as a multiplication factor).

We used crude mixed model analyses with a random intercept to correct for clustering within practices and additionally corrected for a priori defined potential confounding baseline covariates (use of antihypertensive and lipid lowering drugs and anticoagulants, comorbidity (chronic obstructive pulmonary disease (COPD), heart failure, atrial fibrillation, renal failure) and practice characteristics (number of PNs, GPs, and patients)).

We examined potential effect modification of differences in practice characteristics (practice organization (solo/duo/group), availability of CVRM protocol and existence of other disease management programmes (COPD, DM) and CVRM usual care given prior to the intervention (yes or no), by adding them as interaction terms to the crude model. If an interaction term was statistically significant ($p < 0.05$), we conducted stratified analyses.

Statistical analyses were conducted in R studio (version 3.5.1, Copyright (C) 2018 The R Foundation for Statistical Computing).

Results
In total, 689 patients were included; 372 intervention and 317 usual care patients (figure 1). In the intervention and control group, 439 (54%) and 384 (54%) of the invited patients did not participate, respectively (50% and 45% were women, mean age was 63.5 years and 39% had CVD in both groups). Mean age in included patients was 65.1 vs. 66.2 years, respectively and in both groups 42% were women (table 1). At baseline, we observed no differences in cardiovascular risk factors, CVD,
comorbidities and medication use across the groups. Prior to the study, the proportion receiving CVRM care was higher in the intervention than in the usual care group (67% vs 51%, p < 0.001). In the intervention and usual care group we were able to collect data on SBP in 96% and 94% of the patients and data on LDL-cholesterol in 93% and 98% of the patients, respectively. We did not observe differences in both mean SBP and LDL-cholesterol between the intervention and usual care group at the endpoint (137.2 mmHg vs. 139.0 mmHg, respectively and 2.6 mmol/L in both groups) (table 2 and 3). None of the interaction terms for the primary outcomes were statistically significant (data not shown). Therefore, stratified analyses were not performed. Treatment goals for blood pressure and LDL-cholesterol were achieved in slightly more than half of the patients in both groups (table 2); 60% vs. 59% reached a blood pressure target of <140/90 mmHg and 51% vs. 54% achieved target of LDL-cholesterol <2.5 mmol/L. In CVD patients, 27% vs. 36% reached a LDL-cholesterol < 1.8 mmol/L. Smoking rates were 9% vs 10%, respectively. BMI, CV risk, physical activity, alcohol consumption and food habits did not differ between both groups. Approximately one-third of participants in both groups achieved healthy food habits regarding vegetables and fats and 50-60% reported a healthy dietary pattern concerning intake of fruit, red meat, fatty fish and snacks. We observed no difference between the groups in medication use, number of consultations during follow-up (median 6), satisfaction with the delivered care (median 3.7 on a scale of 1 to 5) and recommendation scores to their GP (median 8 on a scale of 0 to 10). We observed similar results for quality of life and anxiety and depression scores.

Discussion

Summary

In this observational study one year of integrated primary care for CVRM following usual care did not lead to better outcomes for SBP and LDL-cholesterol or any of the secondary outcomes of the study, as compared to usual care.

Strengths and limitations

Strengths of the ZWOT-CASE study are its prospective design, the real-world setting, the matched groups from the same environment and the reliably measurable outcomes and reasoned statistical methods. However, the lack of random allocation to the two study arms may have led to confounding bias. Ample measures have been taken (notably matching of patients, multivariable analyses) to prevent and correct for confounding and baseline characteristics were comparable between both groups. Also, we found that given care before implementation of integrated CVRM care did not affect the effect of the intervention. Although residual confounding is possible, we
believe that the observational design of our study is of large value, as randomisation of regionally implemented complex interventions is hardly possible.

All the general practices in this study were from the region of Zwolle and affiliated to the care group ‘Medrie’. Therefore, usual care may have changed in the direction of the intervention and consequently the effect of the intervention may have been underestimated. However, this setting reflects real practice as integrated CVRM care is always implemented regionally in the Netherlands.

Another limitation is the lower statistical power than calculated a priori due to the 14% lower participation rate in the usual care group. However, a post-hoc power analysis showed that we still would have been able to find a difference of 3.65 mmHg in SBP, which we consider as still clinically relevant.

In both groups, the response rates were lower than expected. We assume that reasons for (non) participation are similar in both groups but cannot rule out that this has led to some bias.

Finally, we had some missing outcome data in both groups. Since missing data were not extensively present in the primary outcomes and we did not observe important differences in missing endpoints between both groups, we expected that imputation would not change our results.

Comparison with existing literature

Our results are in line with previous studies, showing disappointing findings.9 One Dutch study on the effect of disease management programmes (DMPs) for CVRM in general practice, showed a trend towards improved lifestyle (physical activity, smoking) after 2 years.13 However, this study included a heterogeneous population (some DMPs targeted only CVD patients, some included high risk patients without CVD as well) and comparison with usual care and assessment of clinical outcomes (SBP, lipids) was lacking.

A cluster randomized controlled trial (RCT) compared a tailored implementation of CVRM in general practice to usual care and found a significant improvement in physical activity, but not in other outcomes (SBP, LDL-cholesterol, smoking status, BMI, and diet) after 6 months.12 However, this intervention is not easily comparable to ours as it focused on motivational interviewing, online education for PNs and e-health options for patients.

The follow-up time of the current study was shorter than the follow-up in a Dutch cluster RCT (1 vs 5.4 years). In that study, a CVRM programme in primary care significantly reduced SBP with 2.39 mmHg in older adults (70 – 78 years) without CVD. However, this reduction was largely obtained in the first year of follow-up.21 This suggests that we would have been able to observe an effect after
one year. However, it is known that it takes time to implement a new programme and to improve health care as practices have to adapt to new standards of quality and reorganize their practice. Therefore, we can’t rule out that a longer follow-up time would have resulted in better outcomes. Comparison with other studies is difficult, given the heterogeneity in study design, interventions tested, outcomes measured and target populations. Overall, most studies point towards no robust effect on cardiovascular risk factors or outcomes.

Several reasons could explain the lack of effectiveness. First, the intervention itself could be ineffective due to insufficient intensity, lack of personalized health promotion or multidisciplinary collaboration. Possibly, PNs are insufficiently prepared, as their workload increases and patients become more complex.

Besides, intensifying medication according to the guidelines if needed may have failed. Although GPs received yearly feedback on the state of cardiovascular risk factors of their CVRM population in the intervention group, not achieving treatment goals had no consequences. A reward system might enhance risk factor control and a continuous feedback system could improve CVRM in daily practice. Further, patient-related factors, such as inadequate risk and lifestyle perception, nonadherence to lifestyle advice and medication could have played a role. More insight in the patient perspective of CVRM care could lead to better communication about CV risk, more patient empowerment and possibly, better adherence to the advised therapy. Moreover, the efforts of primary care need support from government and society regarding lifestyle improvement.

A second reason could be that usual care was already of high quality, diminishing the contrast between the intervention and usual care. As more than half of the patients in both groups received usual CVRM care previous to our study, the largest reduction in SBP and LDL-cholesterol may already have been gained, leaving little room for further improvement. Still, there is room for improvement, as less than 60% reached blood pressure and LDL-targets.

Implications for research and practice

Despite the lack of effect, we should not depreciate the potential of CVRM programmes to reduce CV risk, but look for potentials to improve their quality. To help reshaping CVRM in primary care, a process evaluation is needed to provide a deeper understanding of the lack of effectiveness of the intervention in the present study. For GPs participating in a programme for CVRM we would recommend to critically evaluate the process of care in their daily practice and to organize direct and adequate feedback regarding adherence to CVRM guidelines, if possible supported by information and communication technology.
Furthermore, the effect of CVRM programmes in countries with lower quality of CVRM in usual primary care should be evaluated, as they may be more effective there. Also, out-of-the-box strategies to organise CVRM care should be considered, e.g. other settings than general practice or a more multidisciplinary approach. Finally, modernisation of prevention programmes, for example by a more continuous telemetric risk factor control, may be promising.

Author contributions
SM, [AH]1, [AH]2 and MH designed the study. SM and SD acquired the data. SM performed the statistical analyses. SM, [AH]1, [AH]2 and MH had regular meetings to interpret the data. SM and MH drafted the manuscript. All authors critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Acknowledgements
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Conflict of interests
The authors declare that there is no conflict of interest.

List of abbreviations
BMI, body mass index
CVD, cardiovascular disease(s)
CV risk, cardiovascular risk
CVRM, cardiovascular risk management
DM, diabetes mellitus
eGFR, estimated glomerular filtration rate
ESC, European Society of Cardiology
GP, general practitioner
HDL, high-density lipoprotein
LDL, low-density lipoprotein
MDRD, Modification of Diet in Renal Disease study
PN, practice nurse
SBP, systolic blood pressure
TC, total cholesterol
TIA, transient ischaemic attack

References


20. de Hollander EL, Zwart L, de Vries SI, Wendel-Vos W. The SQUASH was a more valid tool than the OBiN for categorizing adults according to the dutch physical activity and the combined guideline. *J Clin Epidemiol*. 2012;65(1):73-81.


All 56 GP practices in region of Zwolle invited to participate

26 GP practices included

17 intervention practices. Total population n = 114,996
9 usual care practices. Total population n = 46,507

CVRM population 40-80 years, n = 12,384
CVRM population 40-80 years, n = 4,894

Intake visit september – december 2016, n = 3,411

Patients matched on age, sex and risk category, n = 1,174

Initially invited to participate, n = 587. Extra invited to participate, n = 226.*
Totally invited, n = 813

Included, n = 372

Excluded during endpoint visit:
- CVR < 10%, n = 1
- Stayed abroad > 3 months, n = 1

Included, n = 317

CVD, n = 172
High CVR, n = 200
CVD, n = 162
High CVR, n = 155

Excluded:
- Agreed by telephone but did not attend endpoint visit, n = 53
- CVR <10%, n = 2
- No treatable risk factor, n = 1
- Diabetes mellitus, n = 1

Figure 1. ZWOT-CASE study flow diagram


* As the response rate in the intervention group was lower than the expected 70%, we did not reach the required sample size after we invited 587 intervention patients. Therefore we had to invite 226 extra patients in the intervention group (totally invited n = 813) and matched them retrospectively to the usual care group.
**Box 1. In- and exclusion criteria**

**Inclusion criteria for patients with CVD:**

- Patients with a history of atherosclerotic CVD, including angina pectoris, myocardial infarction, chronic ischemic heart disease, coronary sclerosis, transient ischaemic attack (TIA), cerebral infarction, intermittent claudication or aneurysm of the abdominal aorta and
- The patient is primarily managed by the general practitioner (GP) and
- Aged 40 to 80 years

Inclusion criteria for high CV risk patients:

- No previous CVD and
- Use of antihypertensive or lipid lowering drugs or
- A 10-year CV risk > 10%, based on the Dutch guideline for CVRM and i) either 1 strongly CV risk enhancing factor or 2 mildly CV risk enhancing factors (based on family history of CVD, physical activity, BMI and renal function) or ii) > 1 CV risk factor (current smoking, SBP>140 mmHg, LDL>2.5 mmol/L, TC/HDL-ratio > 8, chronic renal impairment (age < 65 years: eGFR < 60 ml/min/1,73 m²; age ≥ 65 years: eGFR < 45 ml/min/1,73 m², and/or (micro)albuminuria) or
- A 10-year CV risk of >20% and > 1 CV risk factor, as mentioned above and
- At least one modifiable risk factor and
- The patient is primarily managed by the GP and
- Aged 40 to 80 years

Exclusion criteria for all patients:

- Diabetes mellitus (DM), as these patients receive CVRM in a DM programme
- Limited life expectancy
- Cognitive impairment
- No Dutch language proficiency
- Staying abroad > 3 months
- Patient receives CVRM in the hospital or outpatient clinic from a medical specialist
### Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intervention group (n = 372)</th>
<th>Usual care group (n = 317)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (SD)</td>
<td>65.1 (8.3)</td>
<td>66.2 (7.5)</td>
</tr>
<tr>
<td>Age &lt; 65</td>
<td>175 (47)</td>
<td>132 (42)</td>
</tr>
<tr>
<td>Female</td>
<td>158 (42)</td>
<td>132 (42)</td>
</tr>
<tr>
<td>Western</td>
<td>358 (99)</td>
<td>299 (99)</td>
</tr>
</tbody>
</table>

**Cardiovascular risk factors**
- Hypertension \(^a\) 280 (77) 234 (75)
- Hypercholesterolemia \(^a\) 91 (25) 91 (29)
- Current smoking \(^b\) 43 (12) 32 (11)
- Chronic kidney disease \(^c\) 40 (11) 51 (16)
- Micro-albuminuria \(^c\) 15 (4) 10 (3)
- Rheumatoid arthritis \(^a\) 4 (1) 10 (3)

**Cardiovascular diseases \(^a, d\)**
- Myocardial infarction 41 (11) 48 (15)
- Coronary sclerosis 46 (13) 44 (14)
- Angina pectoris 44 (12) 39 (12)
- Transient ischaemic attack 33 (9) 31 (10)
- Cerebral infarction 35 (10) 17 (5)
- Aneurysm aortae 8 (2) 11 (4)
- Intermittent claudication 12 (3) 13 (4)
- Atherosclerosis 4 (1) 4 (1)

**Comorbidities (including other CVD) \(^a\)**
- COPD 9 (2) 14 (4)
- Atrial fibrillation 23 (6) 16 (5)
- Heart failure 1 (0) 3 (1)

**Medication use \(^b\)**
- Antihypertensive agents 299 (83) 251 (81)
- Statins/lipid lowering agents 190 (52) 167 (54)
- Anticoagulants 169 (47) 154 (50)

**Measurements \(^c\)**
- Mean SBP in mmHg (SD) 136.7 (15.2)
- Mean DBP in mmHg (SD) 80.3 (9.5)
- Mean LDL-cholesterol in mmol/L (SD) 2.8 (0.9)
- Mean BMI (SD) 27.7 (4.0)

SD, standard deviation. CVD, cardiovascular diseases. COPD, chronic obstructive pulmonary disease. SBP, systolic blood pressure. DBP, diastolic blood pressure. LDL, low-density lipoprotein. BMI, body mass index.

Absolute numbers (%) are presented unless stated otherwise.

\(^a\) Based on International Classification of Primary Care (ICPC)-coded diagnoses.

\(^b\) Based on medical records.

\(c\) Based on ICPC-coded diagnoses and/or laboratory measurements. Micro-albuminuria: albumin-creatinine ratio > 3 mg/mmol. Chronic kidney disease: ≥ 3 months impaired renal function (eGFR < 60 ml/min/1.73m\(^2\)) and/or micro-albuminuria.
Cardiovascular diseases as inclusion criteria for integrated CVRM care and for the study.

Baseline measurements of the control group at t=0 are not presented, as there was no routine intake consultation.
### Table 2. Primary and secondary outcomes, descriptives

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Intervention group (n = 372)</th>
<th>Usual care group (n = 317)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean systolic blood pressure in mmHg (SD)</td>
<td>358 a 137.2 (16.2)</td>
<td>298 b 139.0 (16.8)</td>
</tr>
<tr>
<td>Mean LDL-cholesterol in mmol/L (SD)</td>
<td>347 c 2.6 (0.8)</td>
<td>310 e 2.6 (1.0)</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean diastolic blood pressure in mmHg (SD)</td>
<td>358 80.3 (10.2)</td>
<td>298 80.6 (10.1)</td>
</tr>
<tr>
<td>Blood pressure ≤ 140/90 mmHg (%)</td>
<td>358 214 (60)</td>
<td>298 175 (59)</td>
</tr>
<tr>
<td>LDL-cholesterol ≤ 2.5 mmol/L (%)</td>
<td>347 178 (51)</td>
<td>310 168 (54)</td>
</tr>
<tr>
<td>LDL-cholesterol ≤ 1.8 mmol/L (%)</td>
<td>166 45 (27)</td>
<td>163 58 (36)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>363 31 (9)</td>
<td>311 30 (10)</td>
</tr>
<tr>
<td>Mean BMI (SD)</td>
<td>349 27.3 (5.2)</td>
<td>300 27.7 (4.8)</td>
</tr>
<tr>
<td>10-year CVD morbidity or mortality risk in %</td>
<td>317 22.0 (11.7 - 36.4)</td>
<td>267 24.0 (13.7 - 38.0)</td>
</tr>
<tr>
<td>All patients, median (IQR)</td>
<td>Patients with CVD, median (IQR)</td>
<td></td>
</tr>
<tr>
<td>Patients with CVD, median (IQR)</td>
<td>159 26.2 (17.9 - 38.5)</td>
<td>144 27.8 (18.7 - 39.5)</td>
</tr>
<tr>
<td>Patients without CVD, median (IQR)</td>
<td>158 15.5 (5.4 - 31.9)</td>
<td>123 18.7 (8.4 - 34.3)</td>
</tr>
<tr>
<td>Healthy food habits (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetables &gt; 150 - 200 grams/ day</td>
<td>360 142 (39)</td>
<td>294 99 (34)</td>
</tr>
<tr>
<td>Fruits &gt; 200 grams/ day</td>
<td>354 214 (60)</td>
<td>294 187 (64)</td>
</tr>
<tr>
<td>Red meat ≤ 300 grams/ week</td>
<td>356 207 (58)</td>
<td>286 155 (54)</td>
</tr>
<tr>
<td>Fatty fish &gt; 1/ week</td>
<td>358 244 (68)</td>
<td>296 187 (63)</td>
</tr>
<tr>
<td>Unhealthy fat products ≤ 3/ week &amp; healthy fat products &gt; 3/ week</td>
<td>352 121 (34)</td>
<td>289 75 (26)</td>
</tr>
<tr>
<td>Sweet &amp; salty snacks ≤ 3/ week</td>
<td>357 196 (55)</td>
<td>295 157 (53)</td>
</tr>
<tr>
<td>Table salt ≤ 3/ week</td>
<td>360 335 (93)</td>
<td>294 265 (90)</td>
</tr>
<tr>
<td>Alcohol consumption, units/week, median (IQR)</td>
<td>311 3 (0 - 7)</td>
<td>292 2 (0 - 7)</td>
</tr>
<tr>
<td>Physically active (%)</td>
<td>303 230 (76)</td>
<td>250 178 (71)</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive drugs (%)</td>
<td>174 137 (79)</td>
<td>160 121 (76)</td>
</tr>
<tr>
<td>Lipid lowering drugs (%)</td>
<td>174 139 (80)</td>
<td>160 127 (79)</td>
</tr>
<tr>
<td>Anticoagulants (%)</td>
<td>174 160 (92)</td>
<td>160 146 (91)</td>
</tr>
<tr>
<td>Patients without CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive drugs (%)</td>
<td>187 167 (89)</td>
<td>149 126 (85)</td>
</tr>
<tr>
<td>Lipid lowering drugs (%)</td>
<td>188 52 (28)</td>
<td>149 46 (31)</td>
</tr>
<tr>
<td>GP as primary treating practitioner (%) h</td>
<td>368 366 (99)</td>
<td>314 307 (98)</td>
</tr>
<tr>
<td>Consultations in general practice, median (IQR)</td>
<td>361 6 (3 - 10)</td>
<td>311 6 (3 - 10)</td>
</tr>
<tr>
<td>Patient satisfaction (PREM) (1-5) j, mean (SD)</td>
<td>359 3.6 (0.7)</td>
<td>283 3.5 (0.8)</td>
</tr>
<tr>
<td>Recommendation score (0-10) j, mean (SD)</td>
<td>352 8.3 (1.3)</td>
<td>275 8.2 (1.3)</td>
</tr>
<tr>
<td>EQ-5D-5L index score (-0.45-1) j, mean (SD)</td>
<td>353 0.9 (0.1)</td>
<td>290 0.8 (0.1)</td>
</tr>
<tr>
<td>SF-12 Mental component (7.9-72.0) j, mean (SD)</td>
<td>353 53.9 (7.5)</td>
<td>290 52.3 (9.3)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td></td>
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<tr>
<td>--------------------------------------------</td>
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<tr>
<td>SF-12 Physical component (5.2-64.7) j</td>
<td>353</td>
<td></td>
</tr>
<tr>
<td>HADS Anxiety (0-7) j, mean (SD)</td>
<td>342</td>
<td></td>
</tr>
<tr>
<td>HADS Depression (0-7) j, mean (SD)</td>
<td>347</td>
<td></td>
</tr>
<tr>
<td>Newly developed CVD (%) k</td>
<td>364</td>
<td></td>
</tr>
<tr>
<td>Newly developed comorbidity (%) l</td>
<td>363</td>
<td></td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>372</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- SD, standard deviation; LDL, low-density lipoprotein; BMI, body mass index; CV, cardiovascular; IQR, interquartile range; CVD, cardiovascular disease; GP, general practitioner; PREM, Patient Reported Experience Measure; EQ-5D, five-level EuroQoL-5 Dimensions; SF-12, Short Form–12 Health Survey; HADS, Hospital Anxiety and Depression Scale.
- a Reasons for missing data: died before endpoint (n = 5), not measured (n = 7), data not available due to change of GP (n = 2)
- b Reasons for missing data: died before endpoint (n = 3), not measured (n = 16)
- c Reasons for missing data: died before endpoint (n = 5), not measured (n = 16), data not available due to change of GP (n = 4)
- d Reasons for missing data: died before endpoint (n = 3), not measured (n = 3), data not available due to change of GP (n = 1)
- e For patients with CVD, n = 175 in intervention group and n = 164 in usual care group.
- f For patient with known CVD the SMART-function was used to calculate the risk; for patients without CVD the risk was based on the risk chart in the Dutch guideline (based on the SCORE risk function).
- g > 5 days a week moderate intense physical activity > 30 minutes/day.
- h Primary treating practitioner could be the GP or a medical specialist.
- i Including all visits and telephone calls with the general practice for all reasons.
- j Minimum and maximum possible values.
- k Including cardiovascular diseases as inclusion criteria for integrated CVRM care and for the study.
- l Including diabetes mellitus, chronic obstructive pulmonary disease, heart failure, atrial fibrillation and chronic renal impairment.
Table 3. Effect of integrated CVRM care on the primary and secondary outcomes compared to usual care, using generalized mixed model analyses.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Crude model</th>
<th>Adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>656 -1.75</td>
<td>647 -1.78</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>657 0.05</td>
<td>653 0.01</td>
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<tr>
<td><strong>Secondary outcomes, continuous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>656 0.04</td>
<td>647 -0.37</td>
</tr>
<tr>
<td>BMI</td>
<td>649 -0.27</td>
<td>641 0.09</td>
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<tr>
<td>EQ-5D-5L index score</td>
<td>643 0.01</td>
<td>633 0.01</td>
</tr>
<tr>
<td>SF-12 Mental component</td>
<td>643 1.61</td>
<td>633 1.39</td>
</tr>
<tr>
<td>SF-12 Physical component</td>
<td>643 1.45</td>
<td>633 1.01</td>
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<tr>
<td>Patient satisfaction (PREM)</td>
<td>642 0.13</td>
<td>631 0.14</td>
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<tr>
<td>Recommendation score</td>
<td>627 0.13</td>
<td>616 0.11</td>
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<tr>
<td>HADS Anxiety</td>
<td>628 -0.39</td>
<td>618 -0.35</td>
</tr>
<tr>
<td>HADS Depression</td>
<td>630 -0.61</td>
<td>620 -0.45</td>
</tr>
<tr>
<td><strong>Secondary outcomes, log transformed</strong></td>
<td></td>
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<tr>
<td>10-year CV risk</td>
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<tr>
<td>All patients</td>
<td>584 0.87</td>
<td>583 0.90</td>
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<tr>
<td>Patients with CVD</td>
<td>303 0.98</td>
<td>303 1.04</td>
</tr>
<tr>
<td>Patients without CVD</td>
<td>281 0.81</td>
<td>280 0.80</td>
</tr>
<tr>
<td><strong>Secondary outcomes, dichotomous</strong></td>
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<tr>
<td>Blood pressure ≤ 140/90 mmHg</td>
<td>656 0.96</td>
<td>647 0.97</td>
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<tr>
<td>LDL-cholesterol ≤ 2.5 mmol/L</td>
<td>657 0.89</td>
<td>653 1.13</td>
</tr>
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<td>LDL-cholesterol ≤ 1.8 mmol/L</td>
<td>329 0.64</td>
<td>326 0.70</td>
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<tr>
<td>Smoking</td>
<td>674 0.87</td>
<td>671 1.00</td>
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<tr>
<td>Healthy food habits e</td>
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<tr>
<td>Vegetables</td>
<td>654 1.28</td>
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<td>Fruits</td>
<td>648 0.88</td>
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<td>Red meat</td>
<td>642 1.17</td>
<td>632 1.21</td>
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<td>Fatty fish</td>
<td>654 1.30</td>
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<td>Fatty products</td>
<td>641 1.49</td>
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<td>Snacks</td>
<td>652 1.07</td>
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<td>Table salt</td>
<td>654 1.47</td>
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<td>Physical activity</td>
<td>553 1.29</td>
<td>543 1.31</td>
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<tr>
<td><strong>Medication use</strong></td>
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<tr>
<td>Patients with CVD</td>
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<td></td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>334 1.19</td>
<td>334 5.09</td>
</tr>
<tr>
<td>Lipid lowering drugs</td>
<td>334 1.03</td>
<td>334 0.97</td>
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<tr>
<td>Anticoagulants</td>
<td>334 1.10</td>
<td>334 1.52</td>
</tr>
<tr>
<td>Patients without CVD</td>
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<td></td>
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<tr>
<td>Antihypertensive drugs</td>
<td>336 1.52</td>
<td>336 1.23</td>
</tr>
<tr>
<td>Lipid lowering drugs</td>
<td>337 0.86</td>
<td>337 0.71</td>
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<tr>
<td>-----------------------------------</td>
<td>----</td>
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<tr>
<td>GP as primary treating practitioner</td>
<td>682</td>
<td>3.93</td>
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<tr>
<td>Newly developed CVD</td>
<td>675</td>
<td>0.85</td>
</tr>
<tr>
<td>Newly developed comorbidity</td>
<td>674</td>
<td>0.91</td>
</tr>
<tr>
<td>Mortality</td>
<td>689</td>
<td>1.48</td>
</tr>
</tbody>
</table>

**Secondary outcomes, count**

<p>| | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Alcohol consumption</td>
<td>601</td>
<td>0.88</td>
<td>0.65, 1.19</td>
<td>0.39</td>
<td>594</td>
<td>0.81</td>
<td>0.60, 1.09</td>
</tr>
<tr>
<td>Consultations in general practice</td>
<td>672</td>
<td>1.05</td>
<td>0.89, 1.25</td>
<td>0.54</td>
<td>670</td>
<td>1.04</td>
<td>0.89, 1.21</td>
</tr>
</tbody>
</table>

CI, confidence interval; LDL, low-density lipoprotein; BMI, body mass index; EQ-5D, five-level EuroQoL-5 Dimensions; SF-12, Short Form–12 Health Survey; PREM, Patient Reported Experience Measure; HADS, Hospital Anxiety and Depression Scale; CV, cardiovascular; CVD, cardiovascular disease; GP, general practitioner.

- a Corrected for clustering within practices.
- b Corrected for clustering within practices and predefined confounders.
- c Difference between intervention and usual care group.
- d Ratio, should be interpreted as a multiplication factor. For example, a ratio of 1.05 should be interpreted as a 5% higher outcome score in the intervention group compared with the usual care group.
- e Healthy food habits: Vegetables > 150 - 200 grams/day; Fruits > 200 grams/day; Red meat < 300 grams/wk; Fatty fish > 1/wk; Unhealthy fatty products < 3/wk & healthy fatty products > 3/wk; Sweet & salty snacks < 3/wk; Table salt < 3/wk.