Protocol for a cohort study to evaluate the effectiveness and cost-effectiveness of general population screening for cardiovascular disease: the Viborg Screening Programme (VISP)

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ABSTRACT

Introduction The prevalence of cardiovascular disease (CVD) is increasing. Furthermore, asymptomatic individuals may not receive timely preventive initiatives to minimise the risk of further CVD events. Paradoxically, 80% of CVD events are preventable by early detection, followed by prophylactic initiatives. Consequently, we introduced the population-based Viborg Screening Programme (VISP) for subclinical and manifest CVD, focusing on commonly occurring, mainly asymptomatic conditions, followed by prophylactic initiatives.

The aim of the VISP was to evaluate the health benefits, harms and cost-effectiveness of the VISP from a healthcare sector perspective. Furthermore, we explored the participants’ perspectives.

Methods and analysis From August 2014 and currently ongoing, approximately 1100 men and women from the Viborg municipality, Denmark, are annually invited to screening for abdominal aortic aneurysm, peripheral arterial disease, carotid plaque, hypertension, diabetes mellitus and cardiac arrhythmia on their 67th birthday. A population from the surrounding municipalities without access to the VISP acts as a control. The VISP invitees and the controls are followed on the individual level by nationwide registries. The primary outcome is all-cause mortality, while costs, hospitalisations and deaths from CVD are the secondary endpoints.

Interim evaluations of effectiveness and cost-effectiveness are planned every 5 years using propensity score matching followed by a Cox proportional hazards regression analysis by the ‘intention-to-treat’ principle. Furthermore, censoring-adjusted incremental costs, life-years and quality-adjusted life-years are estimated. Finally, the participants’ perspectives are explored by semistructured face-to-face interviews, with participant selection representing participants with both negative and positive screening results.

Ethics and dissemination The VISP is not an interventional trial. Therefore, approval from a regional scientific ethical committee is not needed. Data collection from national registries was approved by the Regional Data Protection Agency (record no. 1-16-02-232-15). We ensure patient and public involvement in evaluating the acceptability of VISP by adopting an interviewing approach in the study.

Trial registration number NCT03395509.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Using population-based screening as a tool to identify subclinical and manifest cardiovascular disease (CVD), followed by timely preventive initiatives to minimise the risk of future CVD events.
⇒ Early detection of cardiovascular disease by widely available, portable, inexpensive and safe diagnostic tools with a high prevalence to justify the efforts and costs of screening.
⇒ Elucidating the screening participants’ perspectives of the Viborg Screening Programme setup, including reactions to receiving their screening results, preventive recommendations and potential intersectional transfer.
⇒ The generalisability may be limited to similar age groups in Northern Europe.
⇒ The non-attendees’ perspectives are not explored.

BACKGROUND

Cardiovascular disease (CVD) remains the leading cause of death and accounts for 85 million disability-adjusted life-years annually across the member countries of the European Society for Cardiology alone. Despite remarkable reductions in CVD mortality over recent decades, the absolute number remains at approximately 4 million Europeans each year, of which approximately 1.4 million are diagnosed before the age of 75. The economic consequences amount to approximately €210 billion a year, of which approximately half are direct healthcare costs and the remainder are due to informal care and productivity loss. The epidemiological and economic impacts are expected to increase further due to the general ageing of...
the population combined with the obesity and diabetes epidemic. Moreover, 80% of cardiac events and strokes are considered to be preventable by early detection followed by secondary preventive initiatives that address modifiable cardiovascular risk factors (reduction in mean cholesterol concentration and blood pressure levels, smoking prevalence, etc). Currently, the detection of CVD is based on an individual's responses to symptoms. This indicates a rather advanced state of the diseases before identification, mostly by the patients’ general practitioners (GPs). Consequently, asymptomatic individuals may not receive timely preventive initiatives that minimise the risk of further CVD events, as most individuals with abdominal aortic aneurysm (AAA), peripheral arterial disease (PAD), carotid plaque (CP), hypertension (HT), type 2 diabetes mellitus (T2DM) and cardiac arrhythmia might be asymptomatic.

Two innovative screening trials are currently testing the value of population screening for CVD among men. The Viborg Vascular (VIVA) Screening Trial combined screening for AAA by ultrasound scanning and PAD and HT screening using the Ankle-Brachial Blood Pressure Index and demonstrated the tests to be cost-effective together with a relative reduction in overall mortality of 7% after 5 years of follow-up. In The Danish Cardiovascular Screening Trial (DANCAVAS), the screening tests further included low-dose non-contrast CT to detect and quantify the coronary artery calcification score, aortic/iliac aneurysms and atrial fibrillation and blood sample measurements of cholesterol and haemoglobin A1c (HbA1c) to detect T2DM and hypercholesterolaemia. The preventive potential in the baseline findings was even more promising than that in the VIVA trial, with 42% of screening participants receiving test results that warranted additional CVD prevention. Longer-term consequences are unknown, as is the value of screening for CVD in women.

CT might be a bottleneck to population-scale initiatives and exposes participants to radiation, although at minimal risk. Another non-invasive imaging modality for the assessment of cardiovascular risk is an ultrasound scan for CP, with a high level of accuracy for detecting plaques (sensitivity 78.5%; specificity 93.6%). CP is reported to have a 46.7% prevalence in an asymptomatic American population of both sexes (mean age 62.2 years) without pre-existing CVD. Among Danish women aged 60–77 years, CP was found in 40%. Asymptomatic CP among adults is associated with an increased risk of future major adverse cardiovascular events (MACEs) compared with a population without CP with HRs of 1.96 (95% CI 0.91 to 4.25, p=0.015) for primary MACEs and 3.13 (95% CI 1.80 to 5.51, p=0.001) for secondary MACEs.

The Viborg Screening Programme (VISP) investigates whether population-based CVD screening for AAA, PAD, CP, HT, T2DM and ECG-verified cardiac arrhythmia and/or ischaemia is acceptable for the target population and whether it is effective and cost-effective as a future strategy for healthcare to moderate the burden of CVD. It represents an ambitious investment of one Danish municipality, which decided to offer all citizens a CVD screening session by the time they turned 67 years old beginning from 1 August 2014. The programme was inspired by the abovementioned VIVA and DANCAVAS trials but is the first example in the international context where women are also invited to participate. The legitimacy of using tax-based funds for CVD screening lies in the value to citizens, the health and quality-of-life effects and the cost-effectiveness of using the budget on this particular form of prevention as opposed to other methods. The premise, therefore, is that the programme will be evaluated every 5 years, and if early and longer-term results appear beneficial, the goal will be to sustain the programme and to extend it to other municipalities in Denmark. We hypothesise that population-based CVD screening compared with usual practice is both effective and cost-effective with regard to reducing CVD-related morbidity and mortality and increasing quality of life.

**Objectives**

To evaluate the value of population-based screening for CVD, as opposed to usual practice, from participants’ perspectives and by assessments of effectiveness and cost-effectiveness from a healthcare perspective every 5 years after screening to inform short-term and longer-term consequences on CVD-related morbidity and mortality.

**METHODS**

**Design**

This is a prospective, population-based, longitudinal inter-sectional screening study of all 67-year-old citizens in the municipality of Viborg. Control populations from neighbouring municipalities where screening is not offered will be drawn in the analytical phase. The control population was identified, completely register-based without contact with individuals, from neighbouring municipalities where the population is comparable to the population invited to VISP concerning demographic and socioeconomic factors.

**Time**

The programme was initiated on 1 August 2014, and prospective inclusion is planned until a decision of permanent sustainment and/or expansion of the programme to other municipalities is made. Interim evaluations are planned every 5 years.

**Setting**

The Municipality of Viborg, Denmark, is the geographical setting of the study. A total of 96,921 people inhabit an area of 142,105 km² and are representative of the Danish population regarding age and sex distribution, educational status, comorbidity and mortality. The initial screening and follow-up in the primary and secondary
healthcare sectors is free of charge for the participants, as the Danish healthcare system is tax financed.

**Organisation**
The steering committee consists of the head of the Health Centre of Viborg Municipality (MB), screening nurses, experts in vascular diseases (AH, MD and JSL), experts in cardiology (MD and JR), especially cardiac arrhythmia and HT, a GP (N-JM) and a health economist (RS). All practical issues concerning the screening, follow-up and data sampling are handled by the steering committee. In addition, the steering committee will participate as an author in the reporting of the primary endpoints. The screening sessions are performed by the two screening nurses who will be supported by the clinical experts on request.

**Population inclusion and exclusion criteria**
The screening population is identified from the Danish Civil Registration System17 by residence in Viborg municipality and invited to participate in the VISP on their 67th birthday (ongoing from 1 August 2014) without any exclusion criteria (the case group). Approximately 1100 citizens are invited per year. Likewise, a control population is identified from the surrounding municipalities in the Central Denmark Region without access to the VISP.

**Screening programme**
VISP focuses on the following commonly occurring and mainly asymptomatic conditions: atherosclerotic disease (PAD and CP), AAA, HT, ECG-detectable cardiac disease and T2DM. Further details of the screening procedures, diagnostic criteria, confirmation of screening results and measures are available in table 1.

A digital invitation to the VISP is sent by ‘E-boks’ (a part of the Danish national consecutive digital infrastructure) and by physical mail to those without ‘E-boks’. The invitation includes a prebooked time for screening and details allowing the invitees to reschedule or decline the invitation by phone or mail. Furthermore, the invitation includes a plain language statement, a questionnaire

<table>
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<th>Table 1</th>
<th>Screening examination, diagnostic criteria and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>The screening examinations</td>
<td>Diagnostic criteria</td>
</tr>
<tr>
<td>Infrarenal aortic ectasia and abdominal aortic aneurysm (AAA)</td>
<td>Two-dimensional B-mode ultrasonography. Aortic ectasia is defined as an anterior-posterior, right-angled aortic diameter ≥25 mm in peak systole and AAA as a diameter≥30 mm. The inner-to-inner measurement approach is used.</td>
</tr>
<tr>
<td>Peripheral arterial disease (PAD)</td>
<td>PAD is defined as an Ankle-Brachial Pressure Index of &lt;0.9 or ≥1.4.</td>
</tr>
<tr>
<td>Carotid plaque (CP)</td>
<td>Two-dimensional B-mode ultrasonography imaging in cross-sectional and longitudinal view of the carotid arteries is performed in the supine position. CP is defined as a focal structure encroaching into the arterial lumen of ≥0.5 mm or ≥50% of the surrounding vessel.</td>
</tr>
<tr>
<td>Hypertension (HT)</td>
<td>Arm blood pressure (BP) is measured synchronously in both arms. In total, three measurements are obtained in the arm with the highest systolic pressure. A BP ≥160/100 mm Hg is used as the cut-off for potential HT. Participants with a normal BP for ≥3 months or known white coat HT are not registered as having unknown HT. In case of potential HT, the albumin level in a urine sample is tested.</td>
</tr>
<tr>
<td>Arrhythmia and ischaemia</td>
<td>A single 12-lead ECG</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>Unknown T2DM is diagnosed if the HbA1c level ≥48 mmol/mol.</td>
</tr>
</tbody>
</table>

*Women and men with AAA, PAD and/or CP are recommended to receive antplatelet and cholesterol-lowering therapy provided that such therapy is not contraindicated. GP, general practitioner; HbA1c, haemoglobin-A1c; T2DM, type 2 diabetes mellitus.
regarding the self-reported use of pharmacological drugs, comorbidities, lifestyle parameters, height, weight, smoking and drinking habits, walking-related pain (the Walking Impairment Questionnaire), sense of loneliness and quality of life (the EQ-5D-5L (European Quality of life five-dimension five-level instrument)). Those who do not attend or decline the invitation are reinvited once.

Two nurses trained in CVD screening, including vascular ultrasonography and the initiation of secondary medical cardiovascular prevention, performed the screening examinations. The accuracy of the screening tests used is addressed and summarised in online supplemental table 1.

**Prophylactic actions after screening**

In the case of screen-detected AAA, CP and/or PAD, a 30 min follow-up appointment is allocated for retesting for PAD and counselling recommendations concerning lifestyle factors and secondary medical prevention (aspirin 75 mg and atorvastatin 20 mg). If aspirin and atorvastatin have not already been initiated and no clinical contraindication is suspected, a prescription is given without measurement of lipid status. If potential contraindications exist, then the participant is recommended to discuss initiation with their GP. More specifically:

**CP or PAD**

If CP or PAD is found, secondary medical prevention is recommended. Participants with PAD are offered participation in a peer-driven exercise programme within the framework of Viborg municipality, partially initiated by the participants themselves.

**Aortic ectasia or aneurysm**

If an infrarenal aortic diameter ≥30 mm is verified, the participants are referred to a vascular surgery outpatient clinic to obtain more information concerning the disease and are included in a surveillance programme. Those with ectasia at the 5-year rescreening are not followed further.

**Cardiac arrhythmia**

A cardiac expert nurse assesses all ECGs, and ECGs with changes are further assessed by a cardiologist, who assesses whether a cardiacological workup is needed.

**Hypertension**

If a blood pressure ≥160/100 mm Hg is detected, a urine sample is tested for the albumin level, and 3-day home monitoring is initiated. If one of these tests verifies HT, the participant is referred for a cardiological workup, including the initiation or optimisation of medical treatment.

**Type 2 diabetes mellitus**

Participants with unknown T2DM and an HbA1c level ≥48 mmol/mol are recommended for follow-up with their GP, including a remeasurement of HbA1c levels to verify T2DM in accordance with current guidelines.

**Data collection and management**

Screening results are registered on preformatted case report forms. All results, except the ECG results, are given verbally and in writing to the participants on the examination day. Participants receive the ECG results in their E-boks within 14 days. In addition, the participants’ GPs receive the screening results electronically after approval from the participants, including information on any prophylactic therapy initiated or any need for further follow-up by a vascular surgeon, cardiologist or GP. The data from the case report forms and the completed questionnaires were entered into a secured web-based database (Research Electronic Data Capture). To ensure the validity of the entered data, several steps have been implemented. Each invitee’s unique social security number is entered twice to validate the VISP participant’s identity. For continuous variables such as aorta size, range checks were added. Only the scientific committee members have access to the complete VISP database.

Outcome variables: (online supplemental table 2: Coding of outcomes in supplemental material):

- **The primary endpoint is overall mortality.**
- **Secondary endpoints:**
  - MACEs defined as non-fatal and fatal myocardial infarction or stroke, unstable angina and cardiac revascularisation.
  - Major adverse limb events were defined as major lower limb amputation and/or lower limb revascularisation due to acute or chronic critical limb ischaemia. Additional secondary outcomes are hospitalisations and deaths from CVD-specific mortalities:
  - Angina pectoris (use of long-acting nitroglycerin (C01DA) or cardiac revascularisation without previous AMI).
  - Harms: Intracranial and abdominal bleeding leading to hospitalisation, lower limb revascularisation due to intermittent claudication screenings detecting the impact of CVD on quality of life and side effects of statin use.

**Data sources**

Information on vital status (all cause and specific cardiovascular mortality) is obtained from the Danish Civil Registration system and The Cause of Death Registry, respectively.

Inpatient and outpatient admissions according to the 10th version of International Classification of Diseases system and data on surgical and interventional procedures (using the NOMESCO classification of surgical procedures) are collected from The Danish National Patient Registry, combined with data concerning major vascular procedures that are retrieved from the Danish national vascular Register.

In Denmark, secondary medical prevention is available only by prescription. Drugs that are bought over the counter or dispensed during a hospital stay are not included in the used register, including low-dose aspirin, and are therefore not included in the later analysis.
Data on prescriptions regarding antidiabetic, antithrombotic, antihypertensive and lipid-modifying agents were obtained from the Medical Registry of the Danish Medical Agency according to the Anatomical Therapeutically Chemical (ATC) classification system.\textsuperscript{27,28}

To describe the initiation rate and medical adherence (aspirin 75 mg × 1 per day and/or atorvastatin 20 mg × 1 per day), all filled prescriptions are identified as a minimum of 80% of an annual consumption from one-year before screening and 3 and 6 months after participation in the VISP.

Daily intake, including dosage and quantity, is predefined by the WHO standards based on the average dose per day (ref.). This proxy parameter allows for comparison independent of pack size and difference between doses.

Data on socioeconomic status (employment, marital status, gross income in quartiles and educational level) are collected from relevant registries at Statistics Denmark.\textsuperscript{15,29,30} Data related to the use of primary care services are obtained from the National Health Insurance Service Registry.\textsuperscript{31}

**Costing**

The microcosts of the screening programme will be based on time recording and market prices for valuation. Categories include:

1. Salaries including vacations and pensions for the various staff members and taking non-productive time by a load factor into account.
2. Invitation administration
4. Equipment costs.

Overhead costs will be evaluated by the standard overhead rate of 18%. Derived consequences for the routine-based healthcare system are drawn from administrative registries and valued by the included tariffs: Diagnosis-related grouping casemix tariffs for hospital services and tariffs of the collective agreements for primary care. Costs will be reported in a common price year and adjusted for inflation.

**Statistical analyses**

**Baseline descriptive statistics**

A baseline, report will assess population characteristics including demographic, socioeconomic and risk factors for CVD, attendance at screening, screening test results and the initiation of prophylactic therapy, all stratified by sex.

Continuous variables are presented as the mean±SD, and categorical data are given as numbers (percentages). Non-normally distributed continuous variables are presented as medians and 25th–75th percentiles. Normality will be assessed visually using quantile–quantile plots. Comparisons between groups will be performed using the non-paired Student’s t-test or Wilcoxon signed-rank test depending on normality.

**Effectiveness**

Propensity score matching will be used to balance individuals invited to VISP (living in Viborg municipality) and the control group (individuals who are not invited for screening, living in neighbouring municipalities). Simple nearest neighbour matching will be used. Propensities will be based on a wide range of individual characteristics available in national registries (demographics, socioeconomic, historical use of healthcare service, recent use of prescription medication, etc). The quality of matching will be assessed from the distributions of the propensity scores, common support and balancing of individual covariates. Interim evaluations of effectiveness are planned every 5 years based on inclusion from the screening population (eg, August 2019 ‘sample size’ = 5250 participants).

The benefit and harm endpoints (see the ‘Outcome variables’ section) are compared for the two groups using a Cox proportional hazards regression analysis by the ‘intention-to-treat’ principle, including adjustment according to the propensity scores. The comparison of overall mortality between the groups is illustrated by the Kaplan-Meier method.

**Cost-effectiveness**

The propensity score matching of the effectiveness evaluation will be reused to assess cost-effectiveness, and evaluations will follow the same timing in terms of years of follow-up, with a healthcare system perspective.

Intention-to-treat-based, censoring-adjusted incremental costs, life-years and quality-adjusted life-years using Danish preference weights of the normal population will be estimated using Lin’s average estimator method. The incremental net benefit will be estimated using Willan’s estimator.

**The participants’ perspectives**

Semistructured face-to-face interviews were conducted. The interviews focus on the participants’ experiences of the following: being invited and motives for attending; the VISP setup; receiving their screening results; intersectional transfers based on their screening results; and preventive recommendations (eg, smoking cessation and the initiation of secondary medical prevention). Participants are selected by a purposeful sampling strategy including sex as well as those with negative and different positive screening results.\textsuperscript{32} An interview guide was developed with references to the literature. Additionally, reflective notes on the interview context are documented.\textsuperscript{33} To facilitate and structure the analysis process, NVivo software is used.\textsuperscript{34} The following analysis entails the inductive content analysis as recommended by Elo and Kyngäs.\textsuperscript{35} Reporting will follow the COREQ (COnsolidated criteria for REporting Qualitative research) checklist.\textsuperscript{36}

**Patient and public involvement**

Patients or the public were not involved in the design of VISP or in the data collection. We involved patients
and the public in our evaluation of the acceptability of VISP by adopting an interviewing approach. Exploring the participants’ perspectives provide an in-depth understanding of their experiences of VISP. Such knowledge is essential to evaluating whether it is necessary to rethink VISP to advance the acceptability of the programme while encouraging adherence to preventive recommendations. Furthermore, participants will participate in the analysis and dissemination of the interview findings.

Lay summaries of main VISP findings will continuously be made available at the websites of Healthcare Centre Viborg and the regional hospital and will also be published on social media.

ETHICS AND DISSEMINATION

Ethics

To survey the consequences of introducing VISP, a matched control group was established, without contact with the participants or controls, followed by an epidemiological approach based on registry data. The VISP participants are encouraged to have relatives attend the screening and potential follow-up consultations. In addition to the written information attached to the invitation, the VISP participants receive verbal information about the screening examinations, as well as the consequences in case of positive findings, when they arrive at the screening site. The participants are given time to decide whether to participate or not. For preparation before the follow-up consultation, it is recommended that participants write down any questions they may have; they also receive a folder explaining topics for the follow-up consultations, including the scheduled time.

Potential screening-related psychological and physical consequences have mainly been investigated concerning solitary diseases, with a focus on AAA and DM. However, in the VIVA screening programme (males aged 65–74 years examined for AAA, PAD and HT), no differences concerning anxiety and depression were found when compared with a sex-matched and age-matched non-screened population. Furthermore, an increase in quality of life was seen between screening and 1 year of follow-up among the invitees enrolled in follow-up. This trend was significantly true overall and for the subgroup who tested positive for PAD but not for the subgroup who tested positive for AAA.

In the VISP, participants with screen-detected AAA, PAD and CP are recommended to initiate prophylactic medical therapy (aspirin 75 mg and atorvastatin 20 mg), and possible side effects are assessed. The main side effect of aspirin is major gastrointestinal and extracranial bleeds, which occur in 0.10% of users vs 0.07% of non-users per year. However, the risk of CVD is decreasing from 0.57% for non-users to 0.51% for users per year. Statins have been reported to increase the risk of diabetes by 9% (from 1.12% to 1.22% per year), but the CVD preventive effect outweighs this in all age groups. When focusing on individuals ≥70 years of age, a relative risk reduction of 26% was seen (HR 0.74; 95% CI 0.61 to 0.91; p=0.0048) concerning a combined CVD endpoint.

Dissemination

Our dissemination plans include presentations at international scientific meetings and publications in high-impact, open-access, peer-reviewed journals. In addition, the evaluation of VISP outcomes will be presented to decision-makers in the healthcare sector for rationale for planning future population-based combined CVD screening programmes. Furthermore, estimating the cost-effectiveness of population-based screening programmes is highly relevant before implementation on a national scale.

Curation

Since 1 August 2014, the VISP has been a part of the Viborg municipality initiatives to improve public health. The steering committee of the VISP comprises representatives from Viborg municipality, clinicians representing cardiology, vascular surgery and GPs in Viborg municipality, and health economists and researchers who are experts in statistical and epidemiological modelling and the analysis of qualitative empirical data. Audits of the project’s conduct are performed twice per year and presented to members of the Steering Committee. In addition, the screening nurses and the Steering Committee members who are responsible for the VISP on a daily basis have meetings every other month.

Project status

Approximately 1000 persons have participated each year since 1 August 2014. In fall 2022, the analysis concerning the screening results (response rate, CVD prevalence and microcosts per invitee) will be performed. The interviews will also be initiated in 2022 with an expected period of 1 year including data analysis. In 2023, the 5-year effectiveness study will be conducted, followed by the 10-year follow-up in 2028, when the estimates for conducting a cost-effectiveness analysis will be available.

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nurses, Høgh A, BMJ Open 2023; et al

The study was followed by JSL, MD, RS and AH. MD organised a 30-day introduction programme for the screening nurses, who then were offered ongoing training by AH and MD. Vascular and cardiology advice was offered by AH, DS, JR and MD. MD, AH, DS, JR, MB and N-JM participated in the data collection and securing the feasibility of the study and the daily operations of the VISP. JSL, RS, MD and AH were drafting the article and JR, DS, MB and N-JM contributed with fruitful criticism during the preparation of the manuscript, and all have approved the final manuscript. In addition, all authors are members of the VISP Steering Committee.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES


24 Committee NM-S. NOMESCO classification of surgical procedures S (NCSP), 2009.


Supplementary Table 1. Accuracy of the diagnostic tests used in the screening programme, Adapted from Dahl (42)

<table>
<thead>
<tr>
<th>Diagnostic tool</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Notes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>US for AAA</td>
<td>97.5 (94.2-99.2)</td>
<td>98.9 (97.9-99.5)</td>
<td></td>
<td>(37)</td>
</tr>
<tr>
<td>US for CP</td>
<td>78.5 (69.9-86.1)</td>
<td>93.6 (89.1-98.1)</td>
<td>Absence or presence of plaque</td>
<td>(11)</td>
</tr>
<tr>
<td>ABI</td>
<td>79</td>
<td>96</td>
<td>Pooled value for ABI ≤0.90</td>
<td>(43)</td>
</tr>
<tr>
<td>Office blood pressure</td>
<td>74.6 (60.7-94.8)</td>
<td>74.6 (47.9-90.4)</td>
<td>Blood pressure ≥ 140/90 mm Hg</td>
<td>(44)</td>
</tr>
<tr>
<td>Home blood pressure</td>
<td>85.7 (78.0-91.0)</td>
<td>62.4 (48.0-75.0)</td>
<td>Blood pressure ≥ 135/85 mm Hg</td>
<td>(44)</td>
</tr>
<tr>
<td>HbA1c levels</td>
<td>78-81</td>
<td>79-84</td>
<td>HbA1c level of 6.1 mmol/mol</td>
<td>(45)</td>
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<tr>
<td>ECG for atrial fibrillation</td>
<td>97.1 (89.8-99.6)</td>
<td>100 (99.7-100)</td>
<td></td>
<td>(46)</td>
</tr>
</tbody>
</table>

Reference list

Supplementary Table 2: Coding of outcomes (hospital admission, surgical procedures, cause of death, and prescription of medication)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Codes included</th>
<th>Time</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>I70 ex I701, I73 ex I739B, I74 ex I742, L979B, DL979E</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Aortic aneurysm and dissection</td>
<td>I71</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>I21 – I23</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ischaemic heart diseases</td>
<td>I20</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ischaemic stroke or TIA</td>
<td>I63 – I67</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Intracerebral haemorrhage</td>
<td>I60-61</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hypertension</td>
<td>I10 – I15</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>I40 – I47</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Acute and chronic kidney disease</td>
<td>N17 – N19</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>E10 – E11</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Atrial fibrillation and atrial flutter</td>
<td>I48</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Other arrhythmia, ischaemia, and 3rd degree AV blocks</td>
<td>I44, I45, I49</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cancer</td>
<td>C</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical procedures</th>
<th>Codes included</th>
<th>Time</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical procedures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute peripheral arterial disease repair</td>
<td>1*</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Elective abdominal aortic aneurysm repair</td>
<td>3*</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Acute abdominal aortic aneurysm repair</td>
<td>4-5*</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Claudication-related peripheral arterial disease repair</td>
<td>16*</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chronic ischaemia-related peripheral arterial disease repair</td>
<td>17-19*</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Coronary artery bypass graft</td>
<td>KFNA-E</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Percutaneous coronary intervention</td>
<td>KFG02, KFG05, KFPB</td>
<td>X</td>
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<tr>
<td>Cardiac pacemaker procedures</td>
<td>BFCA01-BFCA04, BFCA09</td>
<td>X</td>
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<tr>
<td>Major amputations</td>
<td>KNHQ00, KNGQ19, KNGQ09, KNFQ19, KNFQ09, KNEQ19</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

* The National Vascular Registry (25, 26) includes a variable defining the indication for procedures; we used it for identification of key procedures (variable value 1-19).
### Prescription of Medication:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Codes included</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiabetic agent</td>
<td>A10</td>
<td>X X</td>
</tr>
<tr>
<td>Non-vitamin K antagonist</td>
<td>B01A, B01AF01, B01AF02, B01AF03, B01AE07, B01AX</td>
<td>X X</td>
</tr>
<tr>
<td>Vitamin K antagonist</td>
<td>B01AA03 and B01AA04</td>
<td>X X</td>
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<tr>
<td>Antiplatelet agent</td>
<td>B01AC</td>
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<tr>
<td>Lipid-lowering agent</td>
<td>C10</td>
<td>X X</td>
</tr>
<tr>
<td>Antihypertensive agent</td>
<td>C02, C03 and C07-C09</td>
<td>X X</td>
</tr>
<tr>
<td>Long-acting nitroglycerin</td>
<td>C01DA</td>
<td>X X</td>
</tr>
<tr>
<td>Anti-arrhythmic medication</td>
<td>C01B</td>
<td>X X</td>
</tr>
<tr>
<td>Antihypertensive agent</td>
<td>C02, C03 and C07-C09</td>
<td>X X</td>
</tr>
</tbody>
</table>

### Cause of death:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Codes included</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause of death</td>
<td>ICD-10</td>
<td>Baseline</td>
</tr>
<tr>
<td>Cancer</td>
<td>C</td>
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<tr>
<td>Cardiovascular disease</td>
<td>I</td>
<td>X</td>
</tr>
<tr>
<td>Other</td>
<td>All codes except C and I</td>
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</tr>
<tr>
<td>Unknown cause</td>
<td>R98 and R99</td>
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</tr>
</tbody>
</table>