

### Project description (5 pages)

*The project description should include: background, hypotheses, materials and methods, research plan, perspectives and should clearly state the applicant's part in the research.*

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Project title: **1. Introduction**

Cardiovascular disease (CVD) is a leading cause of death, morbidity and disability (1;2). In Denmark the prevalence of CVD is 7.5% (420.000 of 5.500.000 Danes) with an incidence of 0.9% each year. The incidence and prevalence of CVD are expected to increase due to the aging population. The numbers of deaths caused by CVD have decreased by 46% from 1995 to 2012, due to a healthier population, better prevention and treatment, as well as unknown factors. Danes only having a primary school education have a significantly higher risk of developing CVD than those with a higher education (3).

Effective prevention of progression of CVD requires systematic screening for subclinical and manifest vascular disease, effective secondary prevention (4-7) and compliance to the prescribed treatment (8-12). Randomized trials have shown that general health checks and screening programs for CVD such as hypertension, diabetes, obesity and hypercholesterolemia have not reduced morbidity or mortality due to CVD, in the population group between 30-60 years. Not even with the involvement of information about changes in health behavior (13;14). Most of the trials are old, from the 1960s and 1970s. Thresholds for treating cardiovascular risk factors and diabetes are lower today. This has led to increased prescription of preventive drugs with demonstrated efficacy, for example statins and antihypertensive drugs (14).

Screening for subclinical and manifest vascular diseases such as abdominal aortic aneurysm (AAA) and peripheral atherosclerosis (PAD) has a documented reduction in mortality for men age 65-74 years (15;16), and is cost-effective (17;18).

Qualitative studies have demonstrated that screening results confirmed the participants' feeling of being all right (19) but when CVD risk or manifest vascular disease was found at screening, it was difficult to adhere to lifestyle changes, if persons' quality of life was adversely affected (20). People were not well informed or prepared for the screening program and the risk of being diagnosed with vascular disease (21;22), and some participants overestimate the benefit from screening programs (23).

To understand the efficacy of a screening program it is of great importance to know the extent of non-compliance to prescribed pharmacological therapy and health advice when tested positive by screening.

**The overall objective of this research project is to identify predictors of non-adherence to pharmacological therapy in order to target and individualize patient information and follow-up programs.**

The research project consists of three studies. The first study is based on qualitative methods. The second study is an observational cohort study. The third is a randomized controlled trial.

The project will be based on two unique screenings cohorts:

1. Viborg Municipality is the first municipality in Denmark which has decided to invite all of the municipality's 67-year-old citizens to CVD screening beginning August 2014 (24). The screening initiative is collaboration between Regional Hospital Viborg - represented by the departments of vascular surgery, cardiology and pulmonary medicine - and Viborg Municipality. The project screens for COPD, DM, abdominal aortic aneurysm, hypertension, peripheral arterial disease, carotid plaque and atrial fibrillation. The aim is to achieve a higher state of health and quality of life through improved secondary prevention among the municipality's older citizens and reduce the need for health services (25).
2. The Central Denmark Region is a world leader in cardiovascular screening studies. Using the Viborg Vascular Screening Program (VIVA) (26), which now has 5 years follow-up data, including vital status and outcome, we can



examine associations between baseline characteristics and the participants' adherence and persistence to prescribed pharmacological therapy and health advice. Data are available.

## 2. What do the participants expect when they participate in a screening program? (Study 1)

### 2.1. Background

Little is known about participants' thoughts before they accept the invitation for screening examinations (21-23;27). Why do they participate? What do they expect? Have they considered the consequences of a negative outcome? Do they intend to follow the health recommendations provided from the health professional? What are their past experiences for screening programs and health changes? To find answers to these questions a qualitative study is chosen.

### 2.2. Aim

The aim of this study is to examine screening participants' attitudes, thoughts and expectations and past experiences

### 2.3. Method

Participants from Viborg Municipality Screening Project will be invited to participate in individual semi-structured interviews (28). By interviewing them, we can obtain information about their views on participation and their expectations of the screening program as well as access to the language and the discourses they use to describe their thoughts (28). To reach saturation (28) ten men will be interviewed based on a semi-structured interview guide, inspired from the literature on expectations to a screening program and by Kvale's seven stages of interview surveys (28). The men will be contacted and informed about the project by telephone. The interviews will take place in the participant's own home, one to three days before the screening. The interview will be conducted by PhD student Ina Qvist. The interview guide will be prepared and developed by interviewing firstly two test persons from our health staff and then two participants from the screening program, the guide will be reviewed subsequently. The interviews also include a standard set of structured questions regarding socio-demographic status. The interviews will be transcribed and presented for the analysis phase by Ina Qvist and an assistant by using the NVIVO software program. From a thematic analysis (29), the themes will be uncovered and supported by relevant literature. Analysis and discussion stages will be implemented in close co-operation with the supervisor.

### 2.4 Study plan

Appendix 1

## 3. Predictors for non-adherence to medical recommendations following a positive test result (Study 2)

### 3.1. Background

Non-adherence to medication prescribed to patients with CVD is a major cause of morbidity, hospitalization, mortality, and health care costs (9-11;30). Most CVD are preventable, which is why primary prevention is important in reducing CVD events. If patients already have established CVD, secondary prevention is essential to reduce recurrent events, improve survival and quality of life (5;6;31). Pharmacological treatment is the best proven intervention for cardiovascular diseases but suboptimal adherence and persistence reduces effectiveness (32).

Many indicators are associated with non-adherence to cardiovascular therapy among these are: Asymptomatic disease, side effects, patient's lack of belief in beneficial gain from the treatment, patient's knowledge of the illness, poor staff-patient relationship, cognitive impairment, inadequate follow-up, psychological problems, opposition to accepting treatment or medication, complexity of treatment and cost of medication (33). However, there is not information about the significance of self-perception of health in relation to compliance. It will be of great significance if baseline characteristics of self-perception of health can predict participants who will be adherent or non-adherent to health counselling by screening (34). Can we identify specific characteristics among the participants who need more support to be adherent and persistence to medical guidance?

The VIVA cohort study obtained information about self-perception of health at baseline.

### 3.2. Aim



To examine the association between self-perception of health and adherence or persistence to prescribed pharmacological therapy and health advice following a positive CVD screening result.

### 3.3. Hypothesis

We hypothesize that there is an association between one's perception of health status and adherence or persistence to prescribed pharmacological therapy and health advice; specifically men with a high perception of health status are more adherent than the men with a low perception of health status.

### 3.4. Method

A follow-up study. The source population consist of a cohort of men aged 65-74 from the Viborg Vascular screening trial (VIVA)(26), a randomized controlled trial (RCT) for Abdominal Aortic Aneurysm (AAA), Peripheral Arterial Disease (PAD) and hypertension. Enrolment was from October 2008 to October 2010.

The study population consists of 1963 men (10.5%) with a screening blood pressure > 160/100 mm Hg and no earlier hypertension diagnosis. They were recommended to have their blood pressure checked by their own general practitioner (GP) and started on antihypertensive drug treatment where indicated. 561 men (3%) had AAA and 2038 men (10.9%) had PAD. They were informed by the project nurse about discovery concerns, risk modification and implementation of preventive measures. They were given a prescription for statin and aspirin for a 3 months treatment period and were informed about subsequent prescription renewal by the GP. Men with AAA were followed for project control once a year for 5 years and men with PAD were checked by a VIVA project nurse one year after screening.

#### 3.4.1. Exposure and outcome measure

##### **Exposure:**

Perception of health status was assessed by six items of the validated questionnaire Medical Outcome Study Short Form-12 (SF-12) (35) on following components: mobility, self-care, usual activities, pain and discomfort, anxiety and depression and a linear scale of 0 to 100, where 100 is the best imaginable health. The measurement of perception of health status will be categorised into quartiles.

##### **Outcome:**

Adherence to a medication regimen is generally defined as the extent to which patients take medications as prescribed by their health care providers (33). Medication persistence refers to the act of continuing the treatment for the prescribed duration. It may be defined as "the duration of time from initiation to discontinuation of therapy" (36). In the present study, we will use these terms accordingly, so:

**Table 1**

<p><b>Persistence</b> (primary outcome in randomised trial and prediction study) Time to end of use = time to more than 100 days between prescription, and in sensitivity analysis = time to more than 200 days between prescription</p>
<p><b>Adherence (secondary outcome)</b> Proportion of users among survivors at year 1 (+/-50 days)</p>
<p><b>Adherence (tertiary outcome)</b> Proportions of users among survivors at year 2, 3, 4, 5 (+/- 50 days)</p>

Information on reimbursed prescriptions will be retrieved from the Danish National Database of Reimbursed Prescriptions (DNDRP) (37). ACT codes for relevant drugs are listed in Appendix 2.

**Measure of persistence 1-5 years:** Time to end of use = time to more than 100 days between prescription (Table 1). The other baseline variables obtained from the VIVA screening cohort (Appendix 3) will be considered as potential confounders in the statistical analysis.

##### **Measure of adherence 1 year:**

Reimbursed prescriptions for any hypertensive drug between day 0-365 after baseline and any cholesterol lowering drug and aspirin drug between day 80-365 after baseline. (Proportion of users year 1 (day 365 +/- 50 days). The proportion will



be calculated in 2 manners: a) the proportion of users among those alive and b) the proportion of user among those alive and without a hospital diagnosis of cardiovascular disease.

**Measure of adherence 2-5 years:** A reimbursed prescription for any hypertensive drug, any cholesterol lowering drug and aspirin drug between day 365-730 after baseline, day 730-1099, day 1099-1440, and day 1440-1825, corresponding to being on treatment year 2, 3, 4 and 5 (Table 1). The proportion will be calculated in 2 manners: a) the proportion of users among those alive and b) the proportion of user among those alive and without a hospital diagnosis of cardiovascular disease.

### 3.4.2. Statistical analysis

Data will be entered into EpiData and analyzed in STATA. Adherence with treatment over time will be analysed using Kaplan Meier survival analysis. Hazard ratios will be computed using Cox proportional hazards regression analysis using quartiles of "perception of health status" as the exposure and without and with control for confounders. Observation will end in case "end of adherence or persistence", emigration or death. Sensitivity analyses will include a) censoring for any hospital diagnosis of cardiovascular disease during follow-up and b) different definitions of adherence.

### 3.4.3. Methodological considerations

**Selection bias:** In general participants in screening studies are healthier than non-participants. Although this in general will call for some caution when interpreting the findings, it is probably less likely that the association between self perception of health and drug adherence is dramatically different among participants and non-participants.

**Information bias:** The baseline data are in general considered of high quality and valid, because data were prospectively sampled by trained study nurses in a systematic way.

**Confounding:** There is information on a range of potential confounders including education, smoking and blood pressure. We have no information about alcohol consumption and leisure time exercise activities.

**Reverse causation:** We cannot know if a good health perception stems from being adherent to drugs at baseline. This will be examined in an explorative statistical analysis, by stratification for adherence to medical treatment before inclusion in VIVA.

**Random error:** The study cohort is relatively large. This will reduce risk of random error.

### 3.4.4. Studyplan

The data of the participants are available. Extract from the Danish National Database of Reimbursed will be done by the PhD student, with support and guidance of supervising health economist Rikke Sjøgaard. Study plan, Appendix 1.

## 4. Telephone contact to improve the participants' adherence to behavioural response (Study 3)

### 4.1. Background

Few studies found that a follow-up telephone call can improve compliance to health counselling (38;39), but no study has evaluated the efficacy of a follow-up telephone call by the project-nurse for a screening population with manifest CVD.

### 4.2. Aim

Can a simple intervention such as a phone call, enhance participants' adherence and persistence to prescribed pharmacological therapy and health advice and what are the characteristics of those who will benefit from a phone call?

### 4.3. Hypothesis

A follow-up telephone call 3 month after participation in a screening program for CVD can improve the participants' adherence to medicine and health counselling.

### 4.3. Method

Randomised controlled trial (RCT). The study population, the same as described in study 2, was randomized 50/50 to a 3 months follow-up telephone call or no telephone call. The telephone call was non-blinded. The participants were informed in advance, in accordance to being randomized or not, that they were called 3 months after the visit. Project nurses phoned the participants who were randomized to the telephone call about 3 months after screening. If there was no contact on the first call, the second or third call was done. If there was no contact after the third call, the participant will be treated as intention to treat in the statistical analysis.

#### 4.3.1. Outcome measure



**Primary outcome:** Time to end of use = time to more than 100 days between prescription (Table 1).

Participants' characteristics at baseline: Same as study 2.

**Secondary outcome:** Redeemed prescriptions for any hypertensive drug, any cholesterol lowering drug and aspirin drug between baseline and telephone call and from telephone call to day 365 +/- 50 days after baseline (Table 1).

**Tertiary outcome:** A reimbursed prescription for any hypertensive drug, any cholesterol lowering drug and aspirin drug between day 365-730 after baseline, day 730-1099, day 1099-1440, and day 1440-1825, corresponding to being on treatment year 2, 3, 4 and 5 (Table 1).

#### 4.3.2. Statistical analysis

Baseline descriptive statistics to characterise the study population include frequency distributions for categorical variables and mean  $\pm$  SD for continuous variables. Analysis will be done according to the intention to treat principle. The Pearson's chi-square will be used when comparing differences between groups. Adherence with treatment over time will be analysed using Kaplan Meier survival analysis and Cox regression analyses.

#### 4.3.3. Study power calculation

A sample size calculation was based on a 5 percentage increase in adherence to prescribed pharmacological therapy being a relevant difference. From the literature levels around 65% adherence has been observed without intervention (38).

Using a significance level of 0.05 and a power of 0.80 the required N to demonstrate a 5 percentage points increase from a baseline of 65% is 2600 participants, randomly allocated 1:1.

#### 4.3.4. Methodological considerations

**Selection bias:** The participants had an equal chance of being allocated to the two treatment arms and underwent standardised follow-up using health care registries, which reduced the risk of loss to follow-up.

**Information bias:** The risks appear low since data were collected prospectively and in a standardised way. Any misclassification of adherence is likely to be non-differential between the intervention and the control group.

**Confounding:** Minimal risk due to randomisation.

**Random error:** Risk of random error is considered low due to the large study size.

#### 4.3.5. Study plan

Data are available. Study 3 will be executed in parallel with study 2 by the PhD student. Appendix 1.

### 5. Ethical deliberations and Application of data

The VIVA trial is registered in ClinicalTrials.gov NCT00662480. VIVA: Biomedical Research Ethics Committee of the Regions Midt see. J.no. M-20080028 and register the establishment approved by the Region Midt legal office referred J.no. 1-16-02-1-08. The participants signed informed consent. The Danish Data Protection Agency will be asked for permission to sample and compile data.

### 6. Feasibility

The supervisor has data from VIVA study and funding for data sampling.

The supervisor and project nurse are scientifically responsible for the collaboration between Viborg Regional Hospital and Viborg Municipality.

The supervisors have extensive experience in qualitative and quantitative RCTs and registry studies.

A statistician will be attached to the study group as needed

### 7. Perspectives

We expect to gain important scientific information in relation to participants' expectation concerning screening, adherence to medical guidance and characteristics of non adherence participants, which can be used to individualize information and follow-up to positive test results of cardiovascular diseases. Increasing the participants' adherence to medical guidance can reduce CVD events and cost of hospitalization and health care.



## Appendix 1

### Study plan for PhD student

	1. semester	2. semester	3. semester	4. semester	5. semester	6. semester
Study 1	Developing the interview guide.	10 interview conducted and transcription.	Decision of analysis method and verification of data	Dissemination		Thesis
Study 2	Acquiring of register data	Acquiring of register data	Analysis	Analysis	Dissemination	Thesis
Study 3	Acquiring of register data	Acquiring of register data	Analysis	Analysis	Dissemination	Thesis

## Appendix 2

### AC T codes for relevant drugs

Hypertension	ATC kode
ACE-hæmmere og angiotensin II-antagonister	C09
Calciumantagonister	C08
Diuretika	C03
Hydralazin	C02DB
α-blokerende midler	C02CA
β-blokkere	C07A
<b>Cholesterol lowering drug</b>	C10
<b>Aspirin</b>	B01AC06
<b>Clopidogrel (can not tolerate aspirin)</b>	B01AC04
<b>Vitamin k antagonist</b>	B01AA
<b>Dabigatranetexilat</b>	B01AF07
<b>Rivaroxaban</b>	B01AF01
<b>Apixaban</b>	B01AF02



### Appendix 3

#### Baseline measurements from the VIVA screening cohort:

	AAA (aortic diameter of $\geq 30$ mm)	PAD (ABI <0.9mm or > 1.4mm)	Co- mobi- ditet (CVD)	Smoking	Lipids	State of health (EurQol score)	Claudi- cation	Age	Alcohol	Family history	Diabe- tes	Known Hyper- tension
BT >160/100	x	x	x	x		x	x	x		x	x	x
AAA	x	x	x	x	x	x	x	x	x	x	x	x
PAD	x	x	x	x	x	x	x	x		x	x	x

Education and marital status of the participants will be sought from Statistics Denmark.

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