Detecting Abdominal Aortic Aneurysms in First Degree Relatives (Adult Offsprings) to AAA Patients (DAAAD) - Statistical Analysis Plan (SAP)

SAP Signatures

I give my approval for the attached SAP, dated 2020-10-02

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Introduction

AAA is an asymptomatic widening of the infrarenal aortic diameter to ≥3cm. Male sex, increasing age, and heredity are important non-modifiable risk factors for development of the disease. This multifactorial disease has life-threatening consequences; if rupture occurs, mortality is 100 % if left untreated. The risk for rupture is closely related to the size of the AAA, and identification of patients with smaller AAA is therefore crucial. Fewer women than men in the population have AAA (1:5) but women diagnosed with AAA suffer a higher aneurysm growth rate, higher rupture risk, higher complication rate when treated, and have a more challenging aneurysm anatomy. Women are not included in any national screening program.
In 2016 the Swedish National Board of Health and Welfare (NBHW) published guidelines recommending population based screening of 65-year old men, based on a reported 40% reduction in aneurysm-related death in screened men. We have recently reported on the 4% annual decline in aneurysm mortality in invited men. The incremental cost-efficiency ratio was 8000 Euro/QALY. (Circulation, Wanhainen, 2016).
Family History – and Gender Aspects.
We have, as others, reported on the high hereditary risk for AAA, but no systematic screening targeting FDR of AAA patients is presently performed although recommended in international guidelines. We have tested a nurse-based active detection route in three Swedish Vascular Departments to invites siblings to be screened, and succeed with in a participation rate of 80%, and prevalence rate of 10% in them.
In a local FDR screening program performed in 2012 in our institution, less than 10% of siblings had been screened before our invitation. It is highly probable that the adult offspring of AAA patients have an even lower awareness due to younger age at the probands onset of disease, and lower participation in the care of diseased relatives for younger next-of-kin.
Genetic Associations. In a twin study from our group: 172,890 twins registered at the time of the study, gave a study base of 265 twins (81% men; mean age 72 years; range, 48-94) with AAA. In the structural equation models, genetic effects accounted for 70% (95% CI 0.33-0.83), nonshared environmental effects for 30% (95% CI 0.17-0.46). Concordances and correlations were higher in MZ compared with DZ twins, indicating genetic effects.

Study Objectives and Endpoints

Aim: Primary aim. To investigate the prevalence of AAA in adult offsprings to AAA patients compared to controls, stratified by sex
Hypothesis The prevalence of AAA in adult offsprings to AAA patients is 4-fold higher than in persons in the population.

Secondary aim. To investigate the awareness of the hereditability for AAA in adult offspring to AAA patients compared to controls, including anxiety levels.

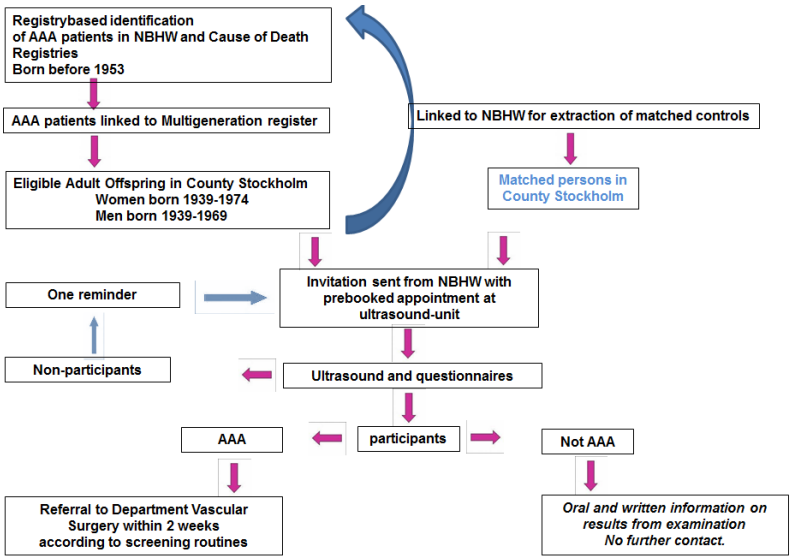
Hypothesis The adult offspring to AAA patients have a low awareness of AAA risk, but higher than persons in the population.

The third aim is to evaluate the cost efficiency of the program, compared to sibling screening and screening in 65-year old men.
Hypothesis The selective registry-based screening in adult offsprings to AAA patients is as cost-efficient in detection of persons at risk as the program for 65-year old men.

Fourth Aim. To evaluate the registrybased detetion model- an evaluation of the feasibility.
Hypothesis The selective registry-based screening can be effective and work in a national setting.

Study Methods

Study Design. Population based case-control point-prevalence study.



Estimated Sample Size "Power analysis"

Aim: Primary aim. To investigate the prevalence of AAA in adult offspring to AAA patients compared to controls.**Hypothesis** The prevalence of AAA in adult offspring to AAA patients is higher than in persons in the population.
Power analysis. We estimate the participation rate to be lower than in the population-based screening (80%) due to lower age in invited adult offspring ; approximately 65%. Therefore an additional 200 women and 180 men will be invited, in order to obtain the examined persons below.
MEN: POWER: Alfa 0.05; power 0.80; estimated prevalence 7 % in offspring, 1.0% in controls; minimum of 166 persons in each group is requested. (men). 65% participation. Invitation: 100 persons more: **350 invited men in offspring and 350 in control group**
WOMEN: POWER: Alfa 0.05; power 0.80; estimated prevalence 5 % in offspring, 0.5% in controls; minimum of 206 persons in each group is requested. 65% participation. Invitation: 100 persons more: **400 women in offspring and 400 in control group**.

Table 1. Study assessments.

Visit	Baseline
Time window	At US
Informed consent	X

Demographic data	X
Medical history and clinical examination	X
Concomitant medication	X
US Aortic diameter	X
Questionnaires	X
Cases referred to vascular center	

[a]Age, sex, civil status, education level. [b] Current medical conditions and medical history, blood pressure, ankle-brachial index, pulse, height and weight. [c] Creatinine (mmol/L). [d] HADS and EQ-5D and self reported knowledge of AAA risks.

General Analysis Considerations

Final analyses will be performed when lowest possible number of participants have been examined.
Contiunous checks on participation is performed according to power calculation.
Invitations are however sent two weeks before examination.
All data will be deidentified and transferred to an SPSS file for statistical analysis.
The Adult offspring or control, women and men will be presented separately. Missing cases, non-participants will be presented. Index persons, their parents with AAA will be presented with sex and age at AAA diagnosis.
Multiple imputations or random effects models will not be used.
Per protocol analysis will be performed, based on the four groups; sex (2) and heredity (yes/no).

Summary of Study Data

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean and standard deviation. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by groups and stratified by sex. All summary tables will be structured with a column for each group (Adult offspring or control, women and men). Primary endpoint; prevalence will be presented for each strata and group. They will be presented also for age groups.
Demographic variables, concurrent illnesses and baseline variables are outlined as usual. Their apprehention of their risk for disease will be presented for the four groups also including their data on the index person.
Derived variables to be included in the analyses are the subscales of the HADS instrument, HADS-Anxiety (HADS-A) and HADS-Depression (HADS-D) as well as the subscales of the EQ-5D.

Efficacy Analyses

$\chi 2$ test will be used to analyse categorical variables and independent *t* test to analyse continuous data. For comparisons of independent groups, Student's t test will be used for normally distributed data, and Mann-Whitney for non-parametric data or small samples. Categorical data will be analysed by Fischer's test where possible. Continuous variables are presented as means (SD), categorical variables are presented as counts and proportions as appropriate.

Reporting Conventions

P-values ≥ 0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median,or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

Quality Assurance of Statistical Programming

All statistical analyses will be performed in SPSS version 26, and in Stata (Version IC.16.1 Stata Corp, College Station, TX) when performed in collaboration with the reviewing statistician (Sverker Svensjö, Uppsala). The reviewing statistician will have an overview of the entire analyses and will explicitly check the code producing tables 1, 2 and 3 as well as any other pieces of code as desired.

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