Centre Hospitalier
Universitaire Vaudois

Service d'Angiologie

Clinical Study Protocol

OPPORTUNISTIC SCREENING FOR ABDOMINAL AORTIC ANEURYSM AND POPLITEAL ARTERY ANEURYSM IN AT-RISK POPUATION (DAAP-PR study).

Study Type:	Observational cohort study
Study categorization:	HRO category A
Study Registration	ClinicalTrial.gov
Study Identifier:	DAAP-PR study
Sponsor-Investigator:	Lausanne University Hospital (CHUV) Prof. Lucia Mazzolai, MD, PhD/Dr. Adriano Alatri, MD Division of Angiology Heart and Vessel Department Chemin de Mont-Paisible 18 CH-1011 Lausanne (Switzerland)
Protocol Version and Date:	5.2/ 09.03.2022

CONFIDENTIAL

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2. Study synopsis

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Study title:	OPPORTUNISTIC SCREENING FOR ABDOMINAL AORTIC ANEURYSM AND POPLITEAL ARTERY ANEURYSM IN AT-RISK POPULATION (DAAP-PR study).
Short title:	DAAP-PR study
Protocol Version and Date:	5.2/ 09.03.2022
Trial registration:	Pending
Study category:	Category A
Background and rationale	Abdominal aortic aneurysm (AAA) remains a highly topical issue given the potentially dramatic consequences associated with its rupture. In men, the prevalence of AAA is declining, probably due to improved management of risk factors. However, the most recent studies and international recommendations have reaffirmed that screening for AAA in men is still important and cost-effective. In contrast, data regarding the risk and characteristics of AAA in women are very limited and outdated. For this reason, the recommendations are contrasting and not univocal. About 35% of patients with AAA have a second aneurysm more distally. Popliteal artery aneurysm (PAA) is the most common. Like AAA, PAA is often asymptomatic and its main complication is thrombotic occlusion resulting in acute/chronic ischemia of the affected limb and a high prevalence of permanent sequelae (mainly amputation). Data on epidemiology and risk factors of PAA are very limited in men and absent in women. In addition, the benefit of PAA screening has never been assessed so far. The aim of this study is to describe the prevalence and characteristics of aneurysmal disease in a female population where data are very limited and outdated. In addition, the project represents the first screening programme for popliteal aneurysm. Finally, the results will allow us to better assess need for and modalities of a screening program.
Objectives	To evaluate the prevalence and the characteristics of AAA and PAA in at-risk women.
Study design:	Multicenter, observational, prospective cohort study. It is an opportunistic screening program which will be offered to any at-risk women consulting vascular division and that require a vascular ultrasonography for any reason.
Inclusion/exclusion criteria	*Inclusion criteria* • Women aged ≥65 years who are current smokers • Men aged ≥65 years • Women or Men aged ≥55 years with familial history (first-degree relatives) for AAA or PAA *Exclusion criteria* • Patient with a diagnosis of known and/or previously treated AAA or PAA

	• AAA/PAA screening or arterial assessment of lower limbs within the last 12 months • Inability to understand and/or sign study consent • Inability to access follow-up controls
Visits and procedures:	*Screening visit:* Any patient requiring a vascular examination will be offered to participate in this screening program by a US of the aorta and popliteal arteries. A detailed medical history will be taken using a targeted questionnaire Depending on the results of the screening three scenarios will be possible. *Follow-up visit:* A US is repeated with variable timing depending on the size of the aneurysm at the time of screening (see also flow chart). For patients with AAA ≥5.0 cm or AAP ≥2.0 cm (or AAP with thrombosis), as proposed by the guidelines, their management will be discussed with vascular surgeons. For these patients, follow-up and data collection stops at this point.
Study duration	78 months
Study schedule	The study was approved by the Ethics Committee of the Canton of Vaud (CER-VD) on 22.03.2022. • Expected duration of recruitment: 42 months • Expected duration of follow-up: 3 years • First patient recruited at Lausanne: 01.06.2020 • First expected international patient recruited: 01.10.2020 • Last patient recruited 31.12.2023 • Last patient, last follow-up-visit: 31.12.2026 Follow-up will be 3 years, exception made for patients with an aneurysm requiring surgical management. For these patients the follow-up will stop at that time.
Investigators:	Prof. Lucia Mazzolai, MD, PhD Dr. Adriano Alatri, MD Division of Angiology Heart and Vessel Department Chemin de Mont-Paisible 18 CH-1011 Lausanne (Switzerland) e-mail: lucia.mazzolai@chuv.ch adriano.alatri@chuv.ch
Statistical analysis:	The annual prevalence of AAA and PAA will be calculated. Patients recruited will be divided into two groups based on the absence or presence of aneurysm. A descriptive analysis of the recruited population will be performed using the following variables: age, sex, BMI (Body Mass Index), cardiovascular risk factors (smoking, hypertension, diabetes, dyslipidemia), chronic renal failure, COPD, history of cardiovascular disease (heart attack, stroke, peripheral arterial disease) and other co-morbidities. The distribution of the different variables among two groups will be analyzed using the chi-square test for categorical variables and the t-test for continuous variables. For the analysis of known or potential risk factors for aneurysm, a univariate and multivariate logistic regression model will be used

3. List of abbreviations

AAA	Abdominal aortic aneurysm
BMI	Body Mass Index
CER-VD	Ethics Committee of the Canton of Vaud
CHUV	Lausanne University Hospital
COPD	Chronic obstructive pulmonary disease
PAA	Popliteal artery aneurysm
TEE	Trans thoracic echocardiography
US	Ultrasonography

4. Background and rationale

4.1. Background

The term aneurysm indicates the focal and permanent dilatation of an artery by >50% compared to the adjacent normal arterial segment. The abdominal aortic aneurysm (AAA) is also defined as a focal and permanent dilation of the aorta >3.0 cm and remains a very topical problem considering the potentially dramatic consequences. The AAA is often asymptomatic until its rupture and represents one of the main causes of sudden death (2000 cases per year in the United Kingdom and 8000 cases per year in the USA) [1, 2]. The prognosis is very variable based on the timing of its management. Mortality at 30 days is 1.4-1.6% in case of elective endovascular repair (EVAR), while it can reach up to 80-90% in case of ruptured AAA, with about half of deaths occurring before the patient reaches the surgical room [1, 2].

Smoking is the main risk factor for AAA with equal effects on growth and risk of rupture [3-5]. More than 90% of patients with AAA have smoked cigarettes at some point in their lifetime. Current smokers are more than seven times more likely to have an aneurysm than nonsmokers, with duration of smoking the most important variable. Each year of smoking increases the relative risk for development of an aneurysm by 4% [3]. In the USA, the decline in consumption of cigarettes is associated with similar decline in in deaths from ruptured AAA [6]. However, in countries where cigarette consumption remains high or is increasing, aneurysm-related mortality continues to increase [7].

Other important risk factors are age (≥65 years), male sex (odds ratio of 5.7) and family history (first-degree relatives of patients with an AAA have an approximately 20% likelihood for development of an AAA) [4, 5]. Hypertension, hypercholesterolemia, obesity, concomitant coronary or cerebrovascular disease, or the presence of other aneurysms are also risk factors but less important. On the other hand, diabetes, black race, and Hispanic ethnicity seem to play a protective role [4, 5].

Abdominal ultrasound is the best screening test currently available. It is a non-invasive test with an excellent sensitivity (94-98%) and specificity (98-100%) when compared to CT scan [8].

Four large randomized clinical trials, performed in the 1990, that included 127,891 men aged between 65 and 75 years of age, have demonstrated that ultrasound screening is effective in reducing aneurysm-related mortality. [9-12]. Overall, there was a 50% reduction of mortality. This benefit begins within 3 years of testing and persists up to 15 years [8]. In addition, a 50% reduction in the risk of rupture as well as 56% reduction in the need for emergency surgery was showed [8].

In these four studies, the prevalence of AAA was between 4.0% and 7.6%. This prevalence has certainly decreased in the last 20 years because of an increased awareness of AAA disease and an improvement in the management of different cardiovascular risk factors, and can currently be estimated between 1.4 and 2.2% [13-16]. However, recent studies showed that AAA screening remains cost-effective even with prevalence rates as low as 1% [17-19]. For these reasons, American and European guidelines continue recommending AAA screening for men aged >65 [1, 2, 20, 21].

Contrary to what observed in men, the data available for AAA in women are much more limited. There is only one population screening study, also carried out in the 1990s, which evaluated 9,342

women aged between 65 and 79 years, showing that prevalence was lower (1.3%), while average age was higher [22]. In addition, the study did not find a significant reduction in the risk of rupture after 5 and 10 years of follow-up respectively [22]. A recent meta-analysis confirmed that in ever smoker women, and in those over 70 years of age, AAA prevalence is over 1% [23]. For these reasons, the current recommendations of different scientific societies are contrasting and not univocal [1, 2, 20, 21].

Population screening is time-consuming and, could require, qualified personnel specifically dedicated to a single project. An alternative could be an opportunistic screening, defined as the use of ultrasound to detect AAA (while abdominal imaging is not specifically planned) in situations where both the ultrasound machines and expertise are easily accessible [24]. Two recent studies showed the feasibility of this approach (>95%) [25, 26]. Aboyans et coll evaluated 1382 consecutive patients requiring trans thoracic echocardiography (TEE) for any reason. Abdominal aorta imaging was feasible in 96.7% of patients with a median delay of 1.7 minutes and a prevalence of AAA of 3.7% in men and 1.3% in women [25]. In a second study, Matsumura et coll evaluated 1495 Japanese women aged ≥50 years needing a TTE for any reason. Abdominal aorta was visualized in 95.1% of patients, the test required <5 additional minutes and the prevalence of AAA was 1.9% [26]

Finally, about 35% of patients with AAA have a second aneurysm more distally. Popliteal artery aneurysm (PAA) is the most common. Like AAA, PAA is often asymptomatic and its main complication is thrombotic occlusion resulting in acute/chronic ischemia of the affected limb and a high prevalence of permanent sequelae (mainly amputation). Data on epidemiology and risk factors of PAA are very limited and the benefit of PAA screening has never been assessed so far.

4.2. Rationale

The AAA remains a highly topical issue given the potentially dramatic consequences associated with its breakdown. The most recent studies and recommendations have reaffirmed that screening men for AAA is still important and cost-effective. However, data regarding the risk and characteristics of AAA in women are very limited and outdated, and the recommendations are not unambiguous. On the other hand, data on PAA is very are very limited in men and absent in women. Finally, the benefit of PAA screening has never been assessed so far.

The aim of this study is to describe the prevalence and characteristics of AAA and PAA in a female population as well as of PAA in male population. The project represents the first screening programme for popliteal aneurysm. Finally, the results will allow us to better assess need for and modalities of a screening program.

5. Study objectives

5.1. General objective

To evaluate by an opportunistic screening the prevalence and characteristics of aneurismal disease in at-risk women.

5.2. Primary objectives:

- To evaluate the prevalence of AAA and PAA
- To evaluate the characteristics of AAA and PAA

5.3. Secondary objectives:

- To evaluate the feasibility of screening
- To evaluate the time-consuming of screening

6. Study design and course of study

6.1. Study design:

Multicenter, observational, prospective cohort study. It is an opportunistic screening program which will be offered to any at-risk women consulting vascular division requiring a vascular ultrasonography (US) for any reason.

6.2. Study duration and study schedule

The study was approved by the Ethics Committee of the Canton of Vaud (CER-VD) on 17.02.2020.

- Expected duration of recruitment: 42 months
- Expected duration of follow-up: 3 years
- First patient recruited at Lausanne: 01.06.2020
- First expected international patient recruited: 01.10.2020
- Last patient recruited 31.12.2023
- Last patient, last follow-up-visit: 31.12.2026

Follow-up will be 3 years, exception made for patients with an aneurysm requiring surgical management. For these patients the follow-up will stop at that time.

7. Study population

The study population will be based on patients who have given their consent and who meet the inclusion criteria and no exclusion criteria.

7.1. Inclusion Criteria

- Women aged ≥65 years who are current smokers
- Men aged ≥65 years
- Women or men aged ≥55 years with familial history (first-degree relatives) for AAA or PAA

7.2. Exclusion Criteria

- Patient with a diagnosis of known and/or previously treated AAA or PAA
- AAA/PAA screening or arterial assessment of lower limbs within the last 12 months

- Inability to understand and/or sign study consent
- Inability to access follow-up controls

8. Visits

8.1. Recruitment and screening visit (V1)

Will be carried out by the vascular physicians. Any patient requiring a vascular examination will be offered to participate in this screening program by a US of the aorta and popliteal arteries. Only experienced physicians (at least 3 years of experience or at least 100 abdominal aortic and lower limb US performed) will be able to perform the screening examination.
A detailed medical history will be taken using a targeted questionnaire
Depending on the results of the screening three scenarios will be possible:

- Scenario 1. Patients with an abdominal aortic diameter of <2.6 cm and a popliteal artery diameter of <1.2 cm are excluded from follow-up.
- Scenario 2. Patients with AAA with diameter ≥5.0 cm, or with saccular abdominal aneurysm, or with AAP with diameter ≥2.0 cm or thrombosed AAP. As proposed by the guidelines, management of these patients will be discussed with vascular surgeons [1, 2]. For these patients, follow-up and data collection stops at this point.
- Scenario 3. All other patients will receive follow-up visits.

N.B. For patients who are found to have an aneurysm, the timing of follow-up visits in the study is consistent with the usual management of aneurysms at CHUV (Lausanne University Hospital).

8.2. First follow-up visit (V2)

This is the first follow-up visit after discovery of the aneurysm. A US is repeated with variable timing depending on the size of the aneurysm at the time of screening (see also flow chart):

8.2.1. Abdominal aorta

- Diameter 2.6-2.9 cm: US repeat after 5 years
- Diameter 3.0-3.9 cm: US repeat after 12 months
- Diameter 4.0-4.9 cm: US repeat after 6 months

8.2.2. Popliteal artery

- Diameter 1.2-1.9 cm: US repeat after 6 months

For patients with AAA ≥5.0 cm, or growth ≥1 cm/year or AAP ≥2.0 cm or with thrombosis, as proposed by the guidelines, their management will be discussed with vascular surgeons [1, 2]. For these patients, follow-up and data collection stops at this point.

8.3. Additional monitoring visits (V3-Vx)

In all patients with an aneurysm, but without surgical indication, an angiology evaluation will be performed every 6-12 months depending on the size of the aneurysm.

8.4. Schedule of the study according to the visits

Type of intervention	V1	V2	V3-Vx
Recruitment - presentation of protocol and information sheet	X		
Signing the consent form	X		
Medical history by targeted questionnaire	X		
US aorta and popliteal arteries	X	X	X

9. Research methods

9.1. Medical history of patient

As previously mentioned, the medical history will be collected using a targeted questionnaire. The anamnestic questionnaire will assess the cardiovascular risk factors (smoking, high blood pressure, diabetes, dyslipidemia) as well as the personal and family history for cardiovascular diseases (arterial aneurysm, infarction, stroke, peripheral arteriopathy of the lower limbs, venous thromboembolism).

9.2. Abdominal aorta and popliteal artery diameters measured by US

For each artery (infra-renal abdominal aorta and popliteal arteries), the anteroposterior diameter is measured by US in the largest segment, in accordance with the "outer to outer" method (from the anterior external wall to the posterior external wall) [27]. An aneurysm is defined as a dilatation >50% compared to the diameter of the normal segment next to it. Alternatively, for the infrarenal abdominal aorta, if the diameter is ≥3.0 cm.

10. Statistical analysis

10.1. Statistical methods

The annual prevalence of AAA and PAA will be calculated. Patients recruited will be divided into two groups based on the absence (AA-no) or presence of aneurysm (AA-yes). The latter will be divided into 3 subgroups: AAA alone, AAP alone, AAA and concomitant AAP. A descriptive analysis of the recruited population will be performed using the following variables: age, sex, BMI (Body Mass Index), cardiovascular risk factors (smoking, hypertension, diabetes, dyslipidemia), chronic renal failure, COPD, history of cardiovascular disease (heart attack, stroke, peripheral arterial disease) and other co-morbidities. The distribution of the different variables among AA-no and AA-yes will be analyzed using the chi-square test for categorical variables and the t-test for continuous variables.

For the analysis of known or potential risk factors for aneurysm, a univariate and multivariate logistic regression model will be used

An interim analysis is planned after the first 6 months.

10.2. Limitations of the study

10.2.1. Selection bias

In order to avoid selection bias, all subjects will come from the same population and will be recruited prospectively and consecutively. A list of all subjects excluded (not recruited) from the study will be drawn up with the reasons for exclusion.

10.2.2. Information Bias

A weekly check for missing medical data will be carried out by the research nurse. If necessary, the subject will be contacted by telephone and/or summoned. Regarding the follow-up of the subjects, in order to guarantee the good quality of the study, a loss at follow-up ≤10% will be considered acceptable.

10.2.3. Ad interim analysis

In order to evaluate the proper functioning of the study, an interim analysis is planned 6 months after recruitment of the first subject. We will also carry out a prospective monitoring of the inclusions in order to guarantee the rate of inclusion and to take the necessary measures in case of problems.

11. Data collection and analysis

Data collection will be carried out by the investigators and the research nurse. At CHUV the medical database will be managed by the research nurse (Ms. Salvi) and the principal investigator (Dr. Alatri). Analyses will be carried out by the investigators.

The investigators will use electronic case report forms (eCRF), one for each enrolled study participant, to be filled in with all relevant data pertaining to the participant during the study.

For data and query management, monitoring, reporting and coding an internet-based secure electronic data capture system RedCap, which is hosted by the Centre de Recherche Clinique (CRC) at CHUV, Lausanne will be used for this study. REDCap was developed by an informatics core at Vanderbilt University in 2004, with ongoing support from US National Center for Research Resources (NCRR) and US National Institute of Health (NIH), grants NIH/NCATS UL1 TR000445. REDCap was specifically developed around HIPAA security guidelines and is GCP-compliant and fulfills the Swiss regulatory requirements regarding the collection of patient data in clinical trials or non-interventional studies and patient registries and the Swiss/EU data protections laws

The data will be made available to the investigator and to the CER-VD. The coded data may be used for scientific publication without revealing the identity of the subjects. If consent is revoked, the data collected shall remain stored in coded form but may no longer be used.

The data will be stored on the secure server of the CHUV, then archived according to the procedure in force at the CHUV and kept for 10 years. Paper data will also be kept in the CHUV archives for 10 years before destruction.

12. Risk assessment/ Ethical considerations

Subjects will have the option of participating in the study or refusing to participate. They may also withdraw from the study at any time. Subjects participating in the study will be monitored as a standard part of the study. No additional therapeutic procedures will be performed for the purposes of this study.

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14. FLOW CHART