The Dutch multicentre study into opportunistically screening Geriatric patients for Atrial Fibrillation using a PPG smartphone App; the Dutch-GERAF Study

Outline of the healthcare innovation project

Background of the project:

The latest European Cardiology Society's guideline (1. Kirchhof et al.) on the management of atrial fibrillation (AF) recommends opportunistic screening for people 65 years and older, and systematic screening might be considered in high risk population. The geriatric population that visits the outpatient service is such a population. Our previous work (2. Zwart et al., 3. Zwart et al.) showed that geriatric patients have a high rate of AF, and furthermore a very high rate of newly detected AF can be found when repeated screening is applied.

Since AF in elderly people often exists without symptoms, paroxysmal AF can easily remain undetected, and therefore untreated (2. Zwart et al.). Because geriatric patients have a very high risk of risk it is very relevant to identify cases of silent AF. To know the rate of paroxysmal AF helps to estimate the magnitude of the problem, and what the yield of repeated screening for AF might be in this population.

However, repeated screening for AF is not the common geriatric practise at this moment. It is very relevant to determine if comparable results are found when repeated screening is applied in multiple geriatric practises, and with a different method of detection. The primary goal of this innovation project is to assess the rate of newly detected AF when using a smartphone-based PPG detection app, and to determine if repeated screening for AF should become standard geriatric practise. This innovation project seeks to address those questions.

Photo-plethysmography (PPG) is a promising technology used in smartphones and smartwatches for heartrate and rhythm assessment. (6) To retrieve PPG measurements a photo-emitter of infrared light is coupled to a photo-receiver. The amount of infrared light absorbed or reflected by blood represents the systolic and diastolic phase. This technology has low costs and does not require additional hardware. Although easy to use and widely available, PPG measurements require good signal quality which may be affected by poorly perfused tissue or tremors. Especially in AF detection proper signal-noise assessment is important because of the irregular depolarization of the ventricles. To overcome these previous issues, we developed an automated PPG based diagnostic algorithm for the smartphone to detect AF. The test characteristics of this technique are robust and described elsewhere. (7)

Principal investigators and steering committee:

Dr. M.E.W. Hemels, cardiologist, Rijnstate hospital Arnhem
Dr. R.W.M.M. Jansen, geriatrician, North West Clinics, Alkmaar
Dr. R. Pisters, cardiologist Rijnstate hospital, Arnhem
Dr. R.K. Riezebos, cardiologist, OLVG, Amsterdam
Dr T. Germans, cardiologist, North West Clinics, Alkmaar

Participating centers:

Dijklander Hospital, Hoorn. Drs. Lennaert A.R. Zwart, geriatrician.

Meander Medical Centre, Amersfoort. Drs. Johan F.H. Wold, geriatrician.
North West Clinics, Alkmaar. Dr. René W.M.M. Jansen, geriatrician.
Rijnstate Hospital, Arnhem. Dr. Diane G. Taekema, geriatrician.
Onze Lieve Vrouwe Gasthuis, Amsterdam. Dr. Robert K. Riezebos, cardiologist.

Aims of the project:

a. To determine the rate of newly detected AF with repeated screening using a PPG based smartphone AF detection algorithm during follow-up visits at a geriatric outpatient center.
b. To determine the rate of (paroxysmal) AF during follow-up visits.
c. To evaluate the predictive value of a single measurement of NTproBNP at the baseline evaluation for the development of new AF.
d. To evaluate the predictive value of the ABC Bleeding Risk Score, compared to the ATRIA Bleeding Risk Score, ORBIT Bleeding Risk Score, and HASBLED score.
e. To evaluate adverse events such as major bleeding, stroke, death and cognitive disorders (Mild Cognitive Impairment or dementia), on the long term, namely: 3 years.

Hypothesis:

a. We expect to find a rate of known AF of approximately 20%, and to find newly detected AF in 4 to 5% of the screened population.
b. We expect to find a rate of paroxysmal AF of 45 to 60%.
c. We expect that the baseline level of NTproBNP or BNP will be predictive of the development of new AF, especially when combined with the findings of the comprehensive geriatric assessment (CGA) and CHA_2DS_2Vasc score.
d. We expect a rate of major bleeding of 3-5% per year.
e. We expect that the ABC bleeding score, using age, GDF-15 and high sensitive Troponin T, will be predictive of major bleeding in the geriatric population.

Design:

a. Prospective multicentre cohort study
b. We aim to include 1250 geriatric ambulatory patients
c. Inclusion period will last for 6 months, with a consecutive follow up period of 6 months, at 3 years patient files will be accessed for adverse events
d. Scheduled commencement of the study is October 2020
e. Blinding: none
f. Randomization: none

Ethical board:

a. The Commission Human Bound Research region Arnhem-Nijmegen, The Netherlands, has exempted the protocol as a 'niet WMO-plichtig onderzoek'.
b. The record number of this decision is: 2019-5889.

Methods:

a. The PPG measurements will be performed with a specially designed app, this research app will be developed by Happitech. Every participating center will receive a smartphone in order to install the application.

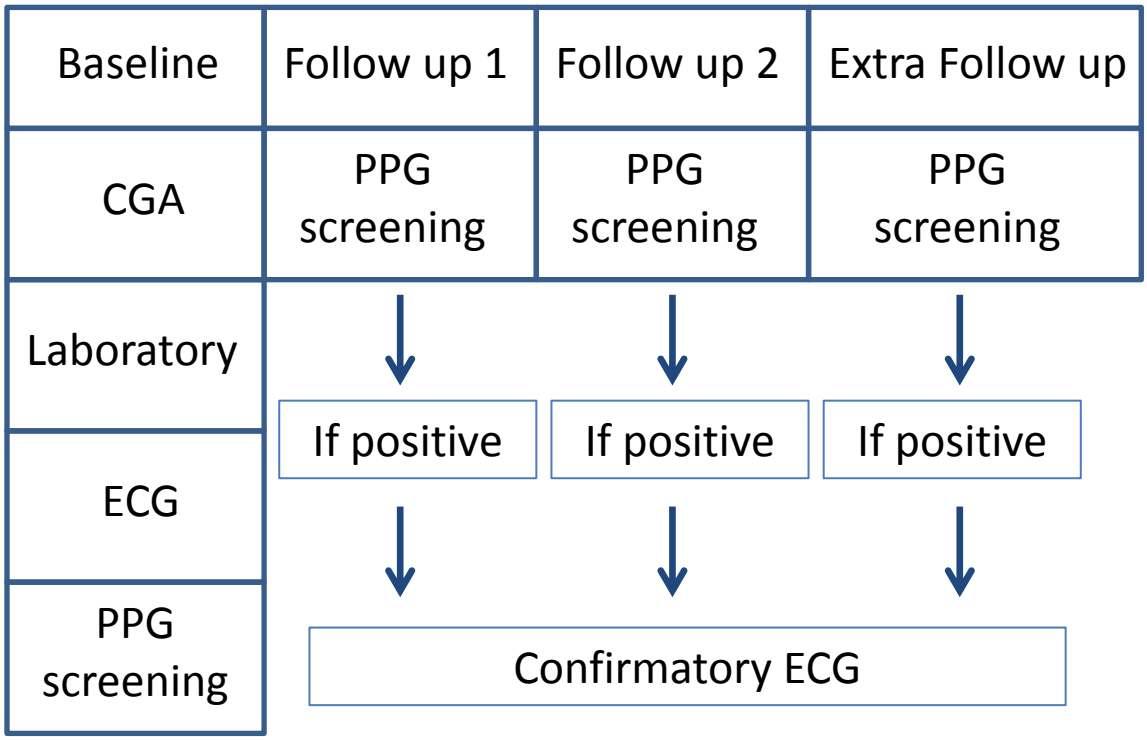
b. All newly referred patients of 65 years and older that visit geriatric outpatient services are eligible (including Fall clinic, Memory clinic, Pre-operative geriatric assessment clinic, or any other geriatric outpatient clinics that are led by a geriatrician).
c. Patients will be sent printed informative material about the project together with their appointment details. This material includes the informed consent form. They are asked to read the material, and fill out the informed consent form at home. At arrival to the outpatient clinic remaining questions will be answered, and the informed consent form collected, scanned, and added to their electronic medical file.
d. Inclusion criteria:
    a. The patient is able and willing to give written informed consent or allows a representative to do so in their name.
    b. The paper copy will remain at the outpatient clinic to serve as a backup.
e. Exclusion criteria:
    a. The patient has a pacemaker or implantable cardioverter defibrillator.
    b. The patient is known with a severe dementia, MoCA ≤ 15 points.
    c. The patient has a severe tremor, from whatever cause, and thus is unable to use the PPG based smartphone AF detection algorithm.
f. Exclusion from analysis:
    a. Less than three measurements with the PPG based smartphone AF detection are performed.
g. Procedure (See also Figure 1, on page 5):
    a. All participating patients will be allocated a study number. The allocation of study numbers will be coordinated by the research nurse, in collaboration with the local investigator and secretary. To ensure patient privacy, it is not allowed to use the hospital's patient number as the study number. Predefined study numbers will be provided to each centre.
    b. The study number will be communicated with the physician by the secretary, and added to the electronic hospital files.
    c. A CGA will be performed at baseline.
    d. A 12 lead ECG will be performed at study entry to assess the baseline heart rhythm.
    e. At every visit to the outpatient service one measurement with the PPG based smartphone AF detection algorithm will be performed.
    f. The application will be made available for patients to install on their own smartphone, or their caretaker's.
    g. Before each measurement the physician/patient/caretaker enters the patient's study number into the PPG app, which allows the investigators to register which measurement belongs to which participant, without accessing their medical files.
    h. Coded, raw data will be analysed by the app, and results automatically sent by email to the principle investigator (Lennaert A.R. Zwart).
    i. The smartphone shows the measurement in real time. In case of artefacts due to movement or otherwise, the PPG based smartphone AF detection algorithm will reveal this and a repeat measurement will be performed.
    j. In case the PPG based smartphone AF detection algorithm detects AF, a 12 lead ECG is performed to confirm and document the diagnosis of AF and appropriate treatment will be initiated by the treating physician.

k. If AF is detected at home, patients will be invited for the 12 lead ECG in the outpatient clinic.
l. Only patients who are known with AF and have an ECG or Holter registration showing AF in their medical record will be classified as patients with 'known AF'.
m. Patients will be classified as 'newly detected AF' if AF is detected by the PPG device and consecutively confirmed on a 12 lead ECG. These ECGs will be periodically collected by the research nurse, in order to be reviewed to confirm the diagnosis for research purposes, by an independent cardiologist (Martin Hemels or Ron Pisters).
n. All positive measurements with the PPG based smartphone AF detection algorithm, will be assessed by an independent cardiologist (Martin Hemels or Ron Pisters).
o. Patients known with AF will also be screened with the device in the same fashion, making it possible to estimate the proportion of paroxysmal AF, but a confirmatory ECG will not be necessary as AF is already documented in those patients.
p. In patients with newly detected AF, the algorithm will still be used in follow up visits, in order to determine the rate of paroxysmal AF.
q. At study entry the baseline characteristics will be collected, including:
    i. Medical history and medication use (as part of the CGA).
    ii. MoCA.
    iii. Functional measures such as pattern of gait and muscle weakness (as part of the CGA) and basic measurements such as weight and blood pressure (as part of the CGA)
    iv. Standard blood samples including kidney function, blood count, electrolytes and INR if applicable. Blood will be taken during the routine blood sampling, to assess the HS Troponine T, NTproBNP and GDF-15 at an external location (Dijklander Hospital). A separate protocol can be found on page 6 of this protocol.
r. Information about the study will be available in print at every participating centre. This information folder is added as an attachment.
s. Of all patients at least 3 measurements with the PPG based smartphone AF detection algorithm will be collected, including the measurement at study entry, during a 6 months follow-up period. After 3 years adverse events will be accessed.
t. A designated research nurse will have access to the code list (patient identifier and study code) at each participating centre collect participating centres, collect data on the baseline characteristics, and the measurements with the PPG based smartphone AF detection algorithm.

h. Frailty will be calculated as a Frailty Index, based on the accumulation of deficits model. It will incorporate a combination factors: functional, cognitive, physical and social. As proposed in literature (4. Searle et al., 5. Rockwood et al.), a number between 30 and 40 factors will be used to calculate the index. A detailed list of the variables and their definition is added as an attachment.
i. A detailed plan for the statistical analysis can be found on page 7 of this protocol.
j. Statistical analysis will be performed by Lennaert A.R. Zwart, geriatrician at the Dijklander Hospital, and PhD student at the Free University in Amsterdam, under supervision of the principal investigators.

k. First draft of the manuscript will be written by Lennaert A.R. Zwart, geriatrician at the Dijklander Hospital, and PhD student at the Free University in Amsterdam, in collaboration with the principal investigators.
l. Privacy: To protect patient privacy patients will be assigned a unique study code. The key to the code will be stored at a secure location at each hospital with limited access. Only coded data will be used for any data processing. The Board of Directors of the participating hospitals will be asked for approval the protocol. In addition, they will also be asked to appoint the research nurse for 0 fte (without salary) in their hospital.
m. After 3 years, all patient files will be checked for the occurrence of: incident major bleeding, stroke, death or cognitive disorders (mild cognitive impairment or dementia + subtypes).

Figure 1. Study protocol



Laboratory Protocol

For the Dutch GERAF health care innovation project

As part of the Comprehensive Geriatric Assessment blood samples are taken. The number of measurements may differ between the participating centres, for example in which vitamins are analysed.

For the Dutch GERAF health care innovation project the standard laboratory testing should include measurement of:
Hemoglobine in mmol/L
eGFR in mL/min
TSH in mU/L
FT4 in pmol/L
Glucose in mmol/L
HbA1C in mmol/mol
INR

For study purposes one extra Lithium Heparine tube should be drawn, during the standard blood sampling.
This extra Heparine tube should be frozen at -20 degrees Celcius and stored after sampling at the participating centre.

The following extra analyses will be performed, for research purposes only:
GDF-15 in pg/mL
NT-proBNP in pg/mL
High sensitive Troponin T in ng/L

All samples will be transported to the Dijklander Hospital and will be analysed there by the Diagnostic Centre West Friesland (DCWF).
After analysis, Lennaert A.R. Zwart will collect the outcomes and add them to the anonymised dataset.
Costs for the analysis and storage will be covered by Roche Diagnostics.

Statistical analysis plan

1. Automated generation of variables, based on collected data:

1. CHA_2DS_2VASc score
2. HAS-BLED score
3. ORBIT Bleeding Risk Score
4. ABC Bleeding Score
5. ATRIA Bleeding Risk Score
6. Class of impaired renal function
7. BMI
8. Underweight
9. Anemia
10. Abnormal score on MoCA
11. Frailty Index, based on accumulation of deficits model

2.1 Univariate analysis:

Comparison of groups at baseline

1. Patients with sinus rhythm at baseline
2. Patients with known AF at baseline

2.2 Univariate analysis:

Comparison of sensitivity and specificity of the bleeding risk assessment scores

1. Comparing Area Under the ROC curve
2. Comparing sensitivity, specificity and predictive values at the per score predefined cut-off values

3.1 Univariate analysis

Comparison of groups including follow up data

1. Patients with sinus rhythm during entire study
2. Patients with newly detected AF

Correction for age if necessary

3.2 Multivariate analysis

Correction/multivariate analysis of significant differences found in the univariate analysis 3.1

4. Multivariate analysis / Regression analysis

1. Factors predicting newly detected AF
2. NT-proBNP and/or GDF-15 predicting newly detected AF
3. Factors predicting death, or major bleeding, or composite outcome (death + major bleeding)

References

1. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. EP Europace, Volume 18, Issue 11, November 2016, 1609-1678.

2. Zwart LAR, Germans T, Simsek S, Ruiter JH, Jansen RWMM. Atrial fibrillation, anticoagulation and major bleeding in geriatric patients at risk of falling. OBM Geriatrics 2019, Volume 3, Issue 3, doi:10.21926/obm.geriatr.1903071

3. Zwart LAR, Jansen RWMM, Germans T, Simsek S, Ruiter JH, Hemels MEW. Opportunistic screening for atrial fibrillation with a single lead device in geriatric patients. Journal of Geriatric Cardiology (2020) 17: 149-154.

4. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatrics 2008, 8:24.

5. Rockwood K and Mitnitski A. Frailty in relation to the accumulation of deficits. Journal of Gerontology 2007, Vol. 62A, No. 7, 722-727.

6. Moraes JL, Rocha MX, Vasconcelos GG, Vasconcelos Filho JE, de Albuquerque VHC, Alexandria AR. Advances in Photopletysmography Signal Analysis for Biomedical Applications. Sensors (Basel, Switzerland). 2018;18(6).

7. Riezebos K et al. Article in press in HRS Cardiovascular Digital Health Journal.