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SHORT COMMUNICATIONS

NONinvasive Monitoring for Early Detection of Atrial Fibrillation: rationale and Design of the NOMED-AF study

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INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia worldwide, affecting 1% to 2% of the general population, with an increasing prevalence and incidence in the elderly [1–3]. ‘Silent AF’ is diagnosed in individuals who are asymptomatic and is usually discovered based on
The frequency of silent AF in the general population is less certain, ranging from 1% to 10%, and is deemed the cause of 4.4% of all episodes of ischemic stroke [1, 6]. While long-term ECG monitoring allows for early detection of AF in larger groups of individuals compared with short-term electrocardiogram (ECG) recordings, there are currently no registered or approved noninvasive systems for heart rhythm monitoring for long-term use.

The aims of the NOMED-AF study are to determine the prevalence of AF in the Polish population using long-term ECG monitoring in individuals aged ≥ 65 years, and to ascertain the independent risk factors for the clinically symptomatic and asymptomatic forms of AF.

METHODS
The NOMED-AF study is a cross-sectional, observational study aimed to assess the prevalence of AF and its correlation with cardiovascular disease risk factors in the Polish population based on a representative sample of adults aged ≥ 65 years. The main aim of the survey is to assess the prevalence of AF and the associated comorbidities.

The assessment of AF prevalence uses an ECG monitoring system developed and validated during the first and second phases of the project as well as a detailed questionnaire, follow-up data sheet, blood pressure (BP) measurements, and blood/urine sample collection.

An outline of the study protocol is shown in Figure 1 and Table 1A. The study was approved by the Local Bioethical Committee (26/2015) and is registered on clinicaltrials.gov (NCT03243474; https://clinicaltrials.gov/ct2/show/NCT03243474). Enrolment began on March 15, 2017, and the study was registered on August 9, 2017. Further details see Supplement on-line (see journal website).

Study population
A total of 3000 individuals (both men and women) are planned to be enrolled in this part of the study. The inclusion criterion is unselected individuals aged ≥ 65 years; the exclusion criterion is age < 65 years.

Study questionnaires
The first visit questionnaire includes the questions introduced in Table 1B. The standardised Geriatric Depression Scale includes 15 questions. The second visit questionnaire includes 10 questions focused on AF symptoms, fasting status, and any adverse events during use of the
ECG monitoring system. The third visit questionnaire includes 20 questions similar to the second visit but further includes questions regarding outpatient visits, hospitalisations, and changes in medications. On the third visit, the Mini-Mental State Examination is completed as well. Finally, the fourth phone visit questionnaire includes 30 questions and has a similar scope of data as the third visit but is expanded for survival status.

The following laboratory tests are planned to be performed from blood: sodium, potassium, chloride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (direct method and calculated), triglycerides, creatinine, estimated glomerular filtration rate (calculated according to the Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration), glucose, thyrotropin hormone, total bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, haemoglobin A1c, high-sensitivity C-reactive protein, and N-terminal prohormone of B-type natriuretic peptide. Creatinine, albumin, and urine albumin-to-creatinine ratio are planned to be tested from collected urine samples.

*Follow-up chart*

The follow-up chart comprises two parts, the first concerned with AF and the second with adverse events within the follow-up period. The first part contains fields to be filled out with data on symptomatology (European Heart Rhythm Association scale), approach to treatment (no treatment or rhythm/rate control), and methods used (drugs/ablation). The second part contains fields to be filled out with data on every potential adverse event, including unplanned hospitalisation, unscheduled outpatient visit, emergency service callout, or death. This part includes the date of an event, its type, and a detailed description.

*Endpoints*

The primary endpoint is the prevalence of AF, especially the silent type, in Polish individuals aged ≥ 65 years. The secondary endpoint is to determine the independent risk factors for the occurrence of AF, especially the silent type. Additional endpoints include the prevalence of heart failure, stroke, hypertension, and vascular diseases.

*Monitoring system*

The noninvasive, long-term ECG monitoring system used in the study was developed by Comarch Healthcare based on GSM technology. This system comprises a mobile long-term ECG vest with dry silver ECG electrodes, exchangeable recorders fixed to the vest, a docking
station acting as a charger, a GSM transmitter, and the patient monitoring platform (PMP) for data analysis and storage. All study participants will be equipped with two recorders to maintain continuous ECG acquisition during charging and data transmission every 24 h to the monitoring platform. Participant training in use of the ECG monitoring device will be performed at the first visit by the study nurse. Further details see supplement on-line.

Statistical analysis
As the study will analyse equivalent age strata, the sample will not reflect the structure of the elderly population (age ≥ 65 years). After the end of the study, it is planned to calculate weighted adjustments for epidemiologic analyses. Statistical analyses of the data will be performed using SAS software for Windows (version 9.4) and R (The R Foundation). Basic statistical analyses involving estimation of the indicators defined in the study objectives will be conducted using the SURVEYFREQ and SURVEYMEANS procedures of the SAS package, considering the complex sample and design.

DISCUSSION
Current guidelines recommend that AF screening should be provided for all individuals who have symptoms and for those who are asymptomatic and have a high risk for thromboembolism. AF screening may be performed using simple methods, e.g. pulse palpation or in those with cardiac implanted electronic devices, using high atrial rate analysis during interrogation. Nevertheless, the AF diagnosis should always be confirmed by standard ECG recording [7, 8].

A short-lasting, asymptomatic episode of AF may result in a 2.8-fold higher risk of ischemic stroke and a 2.5-fold higher risk of fatality [9]. Among elderly individuals, episodes of arrhythmia are often mildly symptomatic or completely asymptomatic, which may significantly hinder the possibility of diagnosing the arrhythmia [10]. Fernandez et al. [11] showed that 24-h monitoring of individuals with acute-phase ischemic stroke enables AF detection in as many as 10% of hospitalised patients. Grond et al. [3] determined that monitoring of individuals with a recent (within 72 h) ischaemic stroke is in direct correlation with a higher AF detection rate and thus results in earlier introduction of optimal treatment and prevention. Early results of the PROFIL-AF study indicate that the simple action of taking the pulse and interviewing individuals regarding symptoms suggesting arrhythmia enables AF detection, with an additional 3.4% of individuals aged > 65 years who had never
before been diagnosed with AF. Studies reporting the incidence of silent AF have been summarised in Supplemental Table 1 (see journal website).

Such high detection rates were based on a single test of an individual and may therefore assume that long-term monitoring would facilitate AF detection in larger groups. Episodes of clinically silent AF are strictly correlated with a higher frequency of so-called silent stroke [12], as detected based on nuclear magnetic resonance imaging, with a prevalence of 8% to 28%. The main causes of silent stroke are AF (28%) and hypertension [13]. The silent stroke doubles the risk of dementia, especially among elderly individuals [14].

Thus, asymptomatic AF is an important and underestimated clinical issue. A correct and early diagnosis of arrhythmia would enable introduction of the correct treatment and thus would help to prevent thromboembolic complications by the use of oral anticoagulants [15]. Improvements in the field of monitoring and detecting arrhythmia through the implementation of simple, easy-to-use, noninvasive devices capable of registering electric activity of the heart, performing preliminary rhythm analysis, and enabling long-term monitoring and remote data transmission may facilitate this.

In conclusion, the NOMED-AF study will determine the true proportion of individuals with asymptomatic AF, and help to ascertain the independent factors predisposing to this arrhythmia. The study will indicate the population of older individuals requiring AF screening.

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**Conflict of interest:** none declared

**Table 1A. Schedule of assessments**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>At patients'</td>
<td>At patients'</td>
<td>After 10 days</td>
<td>After 30 days</td>
<td>After 1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 4 days</td>
<td>± 4 days</td>
<td>± 7 days</td>
</tr>
<tr>
<td></td>
<td>Phone call</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>homes</strong></td>
<td><strong>homes</strong></td>
<td><strong>homes</strong></td>
<td></td>
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</tr>
<tr>
<td>-----------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>✓</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Monitoring NOMED</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ECG system installation</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ECG monitoring (PMP)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telemonitoring Centre</td>
<td></td>
<td>Continuously</td>
<td>continuously</td>
<td>continuously</td>
</tr>
<tr>
<td>Monitoring system return</td>
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<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Medical and social questionnaire completing</td>
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<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Present status monitoring questionnaire</td>
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<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Adverse event monitoring questionnaire</td>
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<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Geriatric depression scale</td>
<td></td>
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</tr>
<tr>
<td>Blood pressure measurements</td>
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<tr>
<td>Heart rate</td>
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<tr>
<td>Anthropometric measurements</td>
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</tr>
<tr>
<td>Blood and urine samples</td>
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<td></td>
</tr>
</tbody>
</table>

ECG — electrocardiogram; PMP — patient monitoring platform (Comarch Healthcare)

**Table 1B.** The questionnaire for the first visit

<table>
<thead>
<tr>
<th><strong>Issues raised in the questionnaire</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data (e.g. education, marital status, employment)</td>
</tr>
<tr>
<td>Clinical symptoms and diseases</td>
</tr>
<tr>
<td>Medications taken</td>
</tr>
<tr>
<td>Past medical history</td>
</tr>
<tr>
<td>Awareness of cardiovascular risk factors</td>
</tr>
<tr>
<td>Family medical history in first degree relatives</td>
</tr>
<tr>
<td>Detailed information of atrial fibrillation/flutter episodes (symptoms, duration, treatment, hospitalisations)</td>
</tr>
</tbody>
</table>
Habits (smoking, drinking)
Physical activity
Knowledge about health, disease and prevention

References


Figure 1. Study work-flow

3000 subjects aged 65 years

long-term ECG monitoring vest

subjects with atrial fibrillation or atrial flutter

symptomatic

asymptomatic

subjects without atrial fibrillation or atrial flutter