Research Protocol

Finnish AntiCoagulation in Atrial Fibrillation (FinACAF)

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A nationwide register study on the risk of stroke and other cardiovascular events among atrial fibrillation patients with different oral anticoagulation treatments

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BACKGROUND

Atrial fibrillation (AF) is the most common sustained arrhythmia, its prevalence increases with age, and it presents with a wide spectrum of symptoms and severity. Previously, it has been estimated that number of AF patients is about 150 000 in Finland, and this number will be increased at least two-fold until year 2050. AF resulting in an increased risk of stroke and systemic thromboembolism is also by far the most common indication for oral anticoagulation (OAC) treatment (Käypä hoito 2017).

Anticoagulation therapy in AF patients is very effective in decreasing the risk of stroke, but OAC also needs large extent of health care resources, and is costly. It has been estimated that average service provider costs in Finland were approximately 940 euros higher in warfarin users compared with non-users annually (Hallinen 2014). In a very recent national analysis, it was found that the costs of complications associated with anticoagulation treatment even exceeds the costs of the treatment. With an estimation of about 1000 euros annually and more than 100 000 AF patients, the costs of treatment are huge, and taking into account the costs of complications, it is crucial to have current national data of OAC therapy in AF patients. This information is urgently needed for "leading with data" during changing world of medico-economical arrangements.

OAC, while decreasing the risk of embolic events and mortality, also increases the risk of bleeding complications. The benefits of Vitamin K antagonist (VKA), as warfarin, depend strongly on maintaining the International Normalized Ratio (INR) within a relatively narrow range (2.0-3.0). This was also shown in our previous publication of the FinWAF-study, where our major finding regarding the main objectives was that the higher the time in therapeutic range (TTR), the better the outcome. TTR is defined as the duration of time in which the patient's INR values were within a desired range and thus is a better measure of the quality of VKA treatment than just INR values. Especially, the risk of stroke, bleeding events, and mortality were markedly decreased with better TTR. (Lehto et al. 2017). Also, our data demonstrated a direct relationship between the quality of warfarin therapy and the incidence of MI in patients with AF. This was worldwide a novel finding.

However, the follow-up of FinWAF study finished by the end of year 2011, while the first non-vitamin K antagonist anticoagulant (NOAC) for stroke prevention in AF patients received marketing authorization in late 2011. Thus, FinWAF study consisted only AF patients treated with warfarin.

The NOACs currently on market — apixaban, edoxaban, dabigatran and rivaroxaban — have been widely studied in indication of stroke prevention in AF patients, and they have proved to be at least as effective and at least as safe compared to warfarin (Ruff et al. 2015). The NOACs are superseding warfarin as the anticoagulant of AF patients. In the high-income countries, the proportion of anticoagulated patients on a NOAC is more than 50%, while in Finland this proportion is about 40%. The Social Insurance Institution of Finland and the national guidelines – Eteisvärinän Käypä hoito 2017 – considers warfarin treatment balance to be satisfactory if TTR of 80% is reached. This was based on our finding in the FinWAF-study where we found that outcomes continued to improve with increasing TTR values up to a TTR $\geq$ 80%. However, without the data of NOAC treated patients, the optimal OAC treatment was not thoroughly evaluated.

The present study is a register study in focusing on AF. The study provides real-world data on current OAC treatment practices, treatment balance and its consequences in whole Finland. Evidence on TTR through INR monitoring specifically addresses the reimbursement question and the possible unmet medical need for new oral OAC treatment of AF patients. Including also patients who were withhold of any OAC therapy provides a unique information of the spectrum of treatment of all AF patients. The new and so far limitedly investigated point of view in the present study is to include socio-economic data, with information of taxable incomes and education of the patients.

2. RESEARCH QUESTIONS

The aim of this study is to evaluate the incidence and risk of stroke, systemic thromboembolic events, myocardial infarction, major bleeding events, and mortality in relation to different attitudes regarding stroke prevention treatment among AF patients.

An important part of the study is assessment of cost effectiveness of different OAC therapies. Also, when the socio-economic status of patients is included, we can study relations of socio-economic status with treatments the patients are given, the quality of OAC as well as with the major outcomes.

INR target is defined as 2.0-3.0 according to current care treatment guidelines (ESC 2016, Eteisvärinän Käypähoito 2017). The risks mentioned above are separately evaluated with different management levels of warfarin therapy as well as with different NOACs and in patients without OAC treatment. The study population is also characterized according to co-morbidity, interactive medications and antiarrhythmic drugs in use. Additional study questions are related to initiation, discontinuation and duration of OAC treatment. The interactions with anemia and kidney dysfunction, as well as thrombocytopenia in association with different treatment schemes and outcomes will also be studied.

Because all the available contacts with the health care institutions and organizations are evaluated this database allows a unique possibility to investigate cost effectiveness in relation to different OAC treatments.

3. OBJECTIVES

Primary Objectives

1. To investigate risk of stroke, systemic thromboembolism, bleeding events and myocardial infarction among AF patients in relation to different OAC treatments including warfarin treatment with the data of different TTR levels **compared also with patients without any OAC treatment**.

2. To investigate risk of all-cause and cardiovascular death in relation to different OAC treatments including warfarin treatment with the data of different TTR levels **compared also with patients without any OAC treatment**.

Secondary Objectives

3. To investigate use of health care services in relation to different OAC treatments.

4. To investigate cost effectiveness in relation to different OAC treatments.

5. To investigate relations of socio-economic status with treatments the patients are given, the quality of OAC as well as with the major outcomes.

6. To investigate relations of presence of dementia and psychiatric illness with treatments the patients are given, the quality of OAC, as well as with the major outcomes.

7. To investigate use of private health care system, cost and imbursement of it, and cost of reimbursed transportation services.

8. To investigate risk of dementia in relation to different OAC treatments as well as with different socio-economic positions

9. To investigate risk of stroke, systemic thromboembolism, myocardial infarction, and major bleeding events among AF patients after initiation of OAC treatment.

10. To investigate risk of stroke, systemic thromboembolism, and major bleeding events in relation to time from AF diagnosis to time of initiation of OAC treatment.

11. To investigate risk of stroke, systemic thromboembolism, myocardial infarction, and major bleeding events among AF patients who have stopped using OAC for any reason.

Exploratory Objectives

12. To investigate incidence of anemia and renal impairment among AF patients in relation to different OAC treatments including warfarin treatment with different TTR levels.

13. To investigate risk of stroke, systemic thromboembolism, myocardial infarction, and bleeding events among AF patients in relation to discontinuation of OAC treatment due to surgical operations and interventions.

14. To investigate how long it takes to achieve INR target in treatment initiators.

15. To investigate the quality of warfarin treatment (TTR level).

16. To characterize the use of antiarrhythmic medication in AF patients

17. To characterize the use of medications with known interactions with OAC, and the association of the use of these medications with the main outcomes.

18. To characterize the use of other cardiovascular medications in AF patients (ACE-inhibitors, ARBs, beta blocking agents, antiarrhythmics, cardiac glycosides, diuretics etc.), and the association of the use of these medications with the main outcomes.

19. To characterize the use of other medications with a meaningful role in AF patients (diabetes and lipid lowering medication, drugs for gastrointestinal acid related disorders etc.), and the association of the use of these medications with the main outcomes.

20. To investigate how long it takes to achieve elective cardioversion performed (procedure code TFP20) in OAC treatment initiators.

21. To investigate risk of stroke, systemic thromboembolism, and bleeding events associated with different procedures (cardioversion, AF-ablation etc.).

22. To investigate the use of blood products in the study cohort.

23. To investigate risk of stroke, systemic thromboembolism, and bleeding events particularly in the subgroup of patients with diagnosis of cancer.

24. To investigate recurrent stroke and bleeding risk. This will be done particularly in patients with co-morbidity of vascular disease (coronary heart disease, peripheral arterial disease, carotid/intracranial atherosclerotic disease).

25. To investigate ECG-database collected from the laboratory databases:

    AF pattern:

    - Only atrial fibrillation/flutter present in the ECGs
    - Both AF and sinus rhythm present

    From the last ECG with sinus rhythm

    - P-wave analysis (PA, PD, PPA V1, P-axis), PR-interval, (RAE, LAE, BAE),

    From the last ECG

    - QRS duration, QTc, left ventricular hypertrophy, bundle branch blocks, late QRS transition, (R<S in V4), QRS axis, T-wave axis, T-wave amplitude (in V2-V6, I, aVL, aVF)

    Prevalence of ECG findings in AF population and their correlations with endpoints are studied.

4. STUDY DESIGN

Overview of Study Design

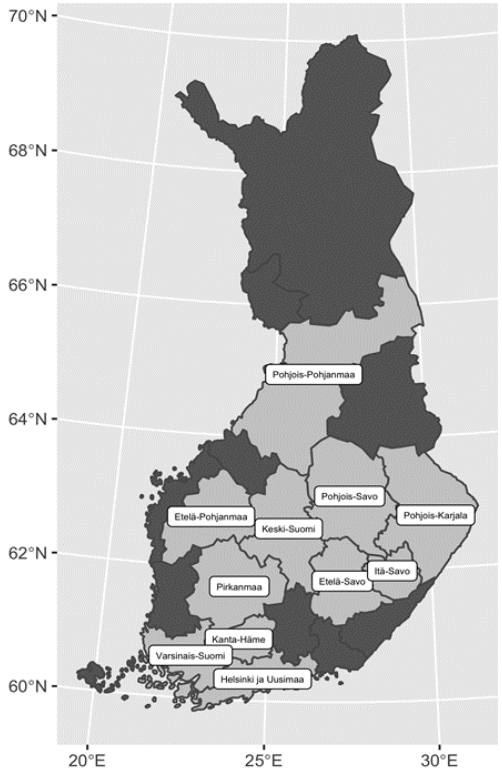
The study with cohort design is conducted as a nationwide retrospective register-based linkage study using data obtained from the Finnish health care registers. The study population consists of all AF patients during 1.1.2004 – 31.12.2018, with a special emphasis on patients of selected hospital district areas where laboratory data is also available. Index date is defined as the date of first time of diagnosis of AF during 1.1.2004 – 31.12.2018; ICD-10-code I48 in any of the used registries.

Follow-up of the patients starts on the index date, and ends on 31.12.2018, at time of death or at time of emigration whichever occurs first. Treatment and co-morbidity history are gathered from the period 1.1.2004 – 31.12.2018.

Study Population

The study population consists of all AF patients in Finland during 1.1.2004 – 31.12.2018. The included geographically defined hospital districts with the laboratory data (1.1.2010 – 31.12.2018) are Northern Ostrobotnia, Northern Savonia, Central Finland, Tampere University Hospital district, Southwest, and Helsinki and Uusimaa (Figure 1). The catchment population of these hospital districts is about 4.2 million; 77 % of the total Finnish population 5.5 million.

Figure 1. The included hospital districts with laboratory data.



Inclusion Criteria
Patients fulfilling the following criteria are included in the study:

- patient has an International Classification of Diseases (ICD-10 version 10) diagnosis code I48 for AF during 1.1.2004-31.12.2018 in any of the used registries

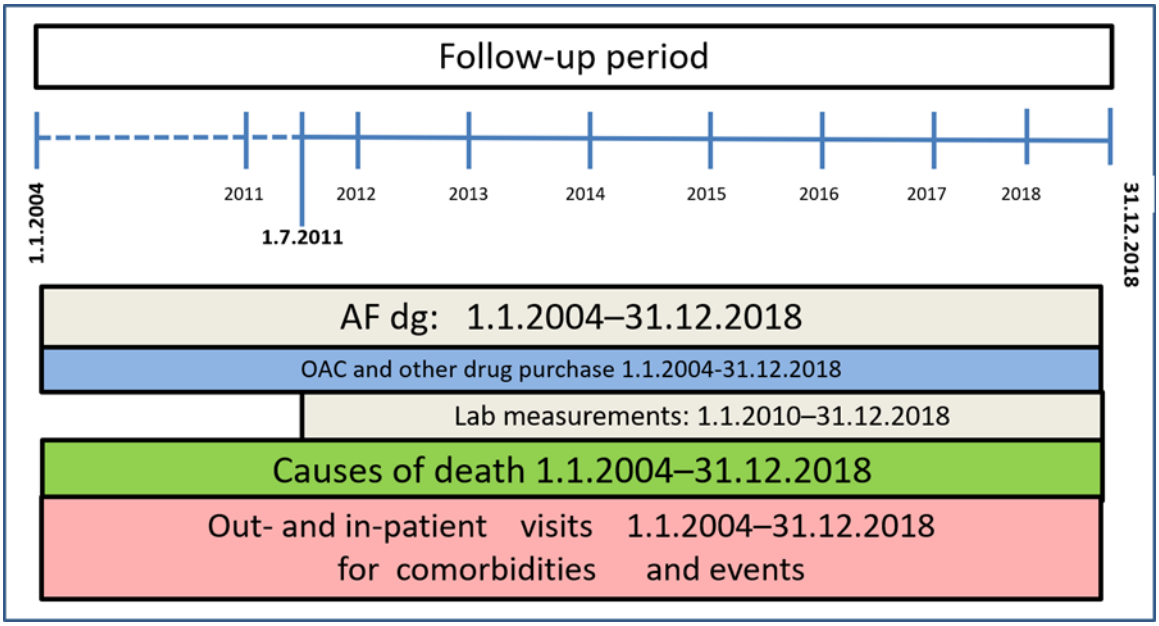
Exclusion Criteria

- Patients with permanent residence in Finland less than 12 months prior to index date.
- Patients with age below 18 years at index date.

Data Source/Data Collection Process

The studied outcomes (endpoint variables of interest) and co-mordities with ICD-10-codes, collected laboratory variables, medications of interest with their ATC-codes as well as ECG parameters collected from MUSE (ECG in the HUH only) for each individual from all ECGs are given in the Appendix.

Figure 2. The study timelines



The registers used in the study

Register	Register Holder	Information obtained
National Prescription Register	Kela – The Social Insurance Institution of Finland	Drug purchases (ATC codes)
National Reimbursement Register	Kela	Reimbursement decisions for chronic diseases
Finnish Care Register, HILMO	National Institute for Health and Welfare	Diagnoses (ICD10 codes) and interventions with codes
Finnish Care Register, AvoHILMO	National Institute for Health and Welfare	Diagnoses (ICD-10 and ICPC-2) and interventions with codes
National Causes of Death Register	Statistics Finland	Deaths and causes of deaths.
National Cancer Registry	Finnish Cancer Registry	Registry of all cancer cases in Finland.
Laboratory databases	HUSLAB, Helsinki; TYKSLAB, Turku; FIMLAB, Tampere and FIMLAB, Central Finland; ISLAB, Kuopio; and NORDLAB, Oulu	INR and other relevant laboratory measurements
Population Register	Population Register Center	Places of domicile
Social HILMO	National Institute for Health and Welfare	Other institutionalizations than hospitalization
Tax Register	Tax Administration	Taxes
The Register of Completed Education and Degrees	Statistics Finland	Education of the patients

5. STUDY SCHEDULE

Milestone	Due date
Study protocol approved by the steering committee	Q3 / 2017
Ethics committee approval	Q4 / 2017
Data permit approvals and Receipt of data from register holders	Q4 / 2018
Data collection completed	Q3 / 2019
Preliminary analyses and report of the data	Q1 / 2020
Manuscripts of the abstracts of the main results	Q3/ 2020
Manuscripts of the main results	Q4 / 2020 – Q1 / 2021

6. ETHICAL ASPECTS

This study will comply with the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct as well as Clinicaltrials.gov and will be registered into the ENCePP e-register (http://www.encepp.eu) and Clinicaltrials.gov/ct2/hom. The ethical permission is permitted by ethical committee of the Medical Faculty of Helsinki University, Helsinki Finland (nr. 15/2017) and the study permission from the Helsinki University Hospital (HUS/46/2018). The data permits are also be requested from the Social Insurance Institute (SII) (138/522/2018), the National Institute for Health and Welfare (THL) (THL/2101/5.05.00/2018), Population Register Centre (VRK/1291/2019-3), Statistics Finland (TK-53-1713-18 / u1281) and Tax Register (VH/874/07.01.03/2019). The THL will perform pseudonymization of the data.

This is a register-based study and patients will not be contacted in any phase of the study. Thus, no patient consents will be needed according to Finnish legislation.

All patient data handled by the researchers will anonymous, ensuring full data protection of the patients.

7. STUDY GROUP AND ASSIGNMENT

The academic researchers, study lead, PI Mika Lehto and Juhani Airaksinen, Pirjo Mustonen as well as Jukka Putaala, Jari Haukka and Miika Linna have operated with the study from the planning phase, and are the steering group of the study. Jari Haukka is the leading epidemiologist and statistician of the study. Miika Linna, adjunct professor from Aalto University will be responsible of cost-effectiveness studies of the FinACAF.

Because of the vast amount of data, there will be several different aspects to be explored in the FinACAF study. Presently it is planned to have several separate Academic Theses prepared from the FinACAF data.

During the FinACAF -study we will have several collaborators. The steering committee is consisted of national experts on the field of atrial fibrillation and OAC from Helsinki University Hospital and University of Helsinki, Turku University Hospital and University of Turku, Central Finland Central Hospital and University of Eastern Finland as well as Aalto University. The steering committee has large amount of contacts with national and international experts and researchers, and there will be collaboration with all reasonable connections to get the best benefit of this vast database.

8. ESTIMATION OF COSTS

Estimation of costs for the national authorities and data holders for study approvals and data permissions is estimated to be 40 000 €.

Thereafter the main cost will be to cover support for academic researchers; Mika Lehto, Juhani Airaksinen, Pirjo Mustonen, Jukka Putaala, Miika Linna, Olli Halminen, Jari Haukka and Juha Hartikainen as well as Jussi Niiranen, Paula Tiili, Saga Itäinen-Strömberg, Anita Ylimäki, Aapo

Aro, Tuukka Helin, Tero Penttilä, Alex Luojus, Janne Kinnunen, Santeri Jolkkonen, Kati Kaartinen, Lotta Joutsi-Korhonen, Jaakko Inkovaara, Ksenia Kalatsova, Mikko Niemi, Jaana Kuoppala, Jarno Satopää, Miikka Korja, Mika Niemelä, Heini Jyrkilä, Elis Kouki, Leena Martola and Elin Karlsson. Because of the very large amount of data, there will be also new, presently unnamed academic researchers during the FinACAF-project. It is estimated that at least 84 months of full-time research work per year during the years 2019 - 2023 would be essential.

Other costs for material (e.g. laptops) and immaterial (e.g. software, costs for printing and open access publication) as well congress excursions are estimated to be 30 000 €.

9. SIGNIFICANCE OF THE RESULTS

The most important discoveries will be to find out Finnish atrial fibrillation patients characteristics, how are they treated and what are their risks for different endpoints, especially mortality. A very central substudies will be cost-effectiveness with different treatments and investigations of socio-economical profile associations with clinical endpoints. Most probably our findings will have guidance for national regimens and guidelines when atrial fibrillation patients are treated. Also, knowledge of cost-effectiveness as well as patients' socio-economical profiles will markedly help "leading with data" when the increasing number of AF patients are treated.

10. REFERENCES

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