DANNOAC-AF synopsis.

A quality of care assessment comparing safety and efficacy of apixaban, rivaroxaban and dabigatran for oral anticoagulation in patients with atrial fibrillation.

The three anticoagulants apixaban, rivaroxaban and dabigatran (Non-vitamin K antagonist Oral Anticoagulation, NOAC) have been used in Denmark for several years and are being increasingly prescribed.\textsuperscript{1,2} The cost of the three drugs are similar and they are considered to be equal treatment atrial fibrillation. In clinical trials the side effects have been very similar.

No study has compared the three NOACs head-to-head in order to evaluate the safety, efficiency and whether the three NOACs are equally effective in preventing death and hospitalizations without increasing risk of major bleeding. Attempts have been made to compare the drugs based on information from different studies, but these attempts are severely hampered by having different inclusion criteria, definitions of effect/side effects and different event committees to evaluate events in the trials.\textsuperscript{3}

For a variety reasons Danish hospitals commonly select one particular NOAC. This can make the work simpler for the busy clinician, but there can also be economic advantages on a local or a regional large scale. The aim of this study is for a period of three years to replace this selection with a random selection. The hospitals and clinics that participate in this quality monitoring, will be selected to primarily use one specific NOAC one year at the time for three years. This cluster design ensures that all participating hospitals use the three NOACs to same extent. Patients will be informed that the hospital currently uses one NOAC in the moment, and that they are free to choose any other NOAC.
Subsequently, information on hospitalization for bleeding complications, kidney failure, stroke, and heart, and death is obtained using ICD-10 diagnoses in the Danish National Patient Register. Anticoagulation therapy will be validated in the setting of atrial fibrillation and following endpoints will be validated from Danish registries:

- Primary efficacy outcome: stroke, myocardial infarction and/or death - using ICD-10 criteria, the diagnosis of stroke and occurrence of death will be obtained through the Danish National Patient Register and the Central Person Register.

- Primary safety outcome: bleeding requiring hospitalization. ICD-10 codes representing bleeding hospitalizations are identified.

- Other outcomes: discontinuation of therapy, kidney failure and other reasons of admission to hospital.

Compliance will be examined by the Pharmacies Prescription Database. To ensure that Hospitals and medical clinics use the three NOACs equally, the hospitals and medical clinics will be randomly selected to which NOAC to use first, secondly and third.

**Data collection**

There is no collection of data specific to the study other than a central registration of the current allocation of each clinic. All data for the study are collected and analyzed within the research facilities at the Sundhedsdatastyrelsen. A specific project will be registered there. With access to the Central Person Register, The National Patient Register and the National Prescription Register all necessary data are available.
Data analysis

Patients are identified by relevant ICD-10 diagnoses. All patients newly or previously diagnosed with atrial fibrillation who initiates NOAC immediately after hospital contact will be included. Patients are subsequently followed until study end of three years. Patients that are initiated NOAC treatment in general practice will not be included in the present study. Patients are categorized based on the allocation of the clinic and only in secondary analyses will the actual prescription of NOACs be used. The primary comparison will be by a log-rank test and secondary analyses will be Cox proportional hazard models also including age, sex, comorbidity and treatment center.

The study will be conducted as an intention-to-treat analysis and groups compared based on non-inferiority analysis. Data from the State Serum Institute will be used to evaluate cluster (hospital) size, absolute incident rates of the primary combined endpoint and total number of patients initiating NOAC treatment as well as number of patients initiating NOAC treatment per cluster. A patient who is initiation NOAC is defined if the patient redeems a NOAC prescription first time within two weeks after contact to a hospital. We expect that at least 20 hospitals (clusters) will participate in the study. A power of 80 percent will be used for sample size estimation and an absolute incident rate in the primary endpoint less than 0.02 during three years will be considered as non-inferior. All of these information will be used for sample size calculation.

A two-tailed p-value <0.05 is regarded as statistically significant in all statistical analysis.
Ethical considerations

This study is approved by the scientific ethical committee system and the Danish Board of Health. The primary aim of initiate anticoagulation with NOACs is to treat the patient according to guidelines. The aim of the present cohort design is an evaluation the effectiveness of NOACs in real-life practice conditions, and patients are therefore not burdened by the study. Arbitrary choices by the clinics are merely replaced by systematic choices, and patients are being informed that they are free to choose another NOAC. The prices of the drugs are very similar and also taking into account the reimbursement system in Denmark patients will not be burdened differently economically from the study. Since the patients will be treated with NOAC regardless of participation in the trial, the price is similar and the NOACs are used according to summary of product characteristics, the Danish Board of Health has considered that section 3 paragraph §13, no. 2 are fulfilled, which states, that it is not necessary to distribute the NOACs free of charge to the patients.

There is no registration of individual patients as part of the study and all data analysis is handled in a research environment where the identity of the individual patients is protected. Since patients are going to receive NOAC treatment for their medical condition anyhow according to national and international guidelines, and the NOACs are considered to be equivalent in national and international guidelines; participation in the present quality of care assessment of NOAC pose no more than minimal risk. Minimal risk refers to the risks of daily life, and includes the risks associated with routine physical examinations and review of medical records. The ethical committee system has approved that no written informed consent is needed for the present quality assessment study. As a precaution, consent will be obtained from the hospital director as well as the head of department, who will act as a “gatekeeper”. In the literature, a Gatekeeper is defined as “an agent who acts as an advocate on behalf of cluster interests” or “people in either political or
administrative positions who are able to give consent for those within a cluster to be randomized” and whose consent may occur on multiple “levels”. The study protocol will be sent to these gatekeepers for evaluation. Before a given cluster can be included in the present quality assessment approval from the gatekeepers are needed. Furthermore, all patients that are being prescribed NOAC treatment will be informed, that a quality assessment of NOACs is currently being conducted.
Reference List

1. In 2014 6,710 patients were prescribed NOAC with atrial fibrillation as an indication. In the first half of 2015, this number increased with 2% (corresponding to 6,844 patients annually) [Pharmacy Prescription Register and the National Patient Register].


