DANNOAC-AF synopsis.

A quality of care assessment comparing safety and efficacy of edoxaban, 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.[1,2] In addition another well documented NOAC, edoxaban, has recently been approved in Denmark. The cost of the four drugs issimilar and their preventive effect is considered equal. In clinical trials the side effects have been very similar.

No study has compared the four NOACs head-to-head in order to evaluate the safety, efficiency and whether the four 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.[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 two 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 6 months at the time for two years. This cluster design ensures that all participating hospitals use the four 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, tromboemboli 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.
- Secondary 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.
- Finally, the primary endpoint will be analyzed according to gender and age.

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

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

The cross-over design yields that each cluster acts as its own control and hence all time-constant clusters effects are removed by the analysis.

Cluster Size for Atrial Fibrillation Substudy

Number of cluster: 37

Minimum cluster: 6

Biggest cluster: 175

Total expected number of patients per period in 2786

Total expected number of patients in the study: 11144

Pilot Study Results

As input to the power calculations, we analyzed the Danish registry data from 2013 (Input for atrial fibrillation study). We enrolled patients at the time they redeemed a prescription for one of the available NOACs and assessed the combined endpoint two years later for atrial fibrillation study. However, registry data provides non-randomized observational data. We therefore used a G-formal approach to mimic results from a randomized study and standardize the risks. The basis for the standardized risk per NOAC is a cause-specific Cox regression analysis adjusted for the following covariates:

- Atrial fibrillation substudy: heart failure + hypertension + age (continuous variable) + Diabetes + prior stroke vascular disease + sex.

Within the limitations of the risk factors available in the registers, the g- formula approach allows to estimate the difference in outcome risks as if the patients were randomized individually to one of the NOACs.[4]

Power Calculation

The calculations are based on the intention-to-treat principle, the assumption of no period effect, and a moderate cluster effect on the outcome. The expected sample size per period is based on register data from 2014. In order to account for non-compliance, we assume that a patient will break randomization with a probability of 3%. Clusters will be excluded from the analysis if non-compliance is greater than 20% .

Analysis Method

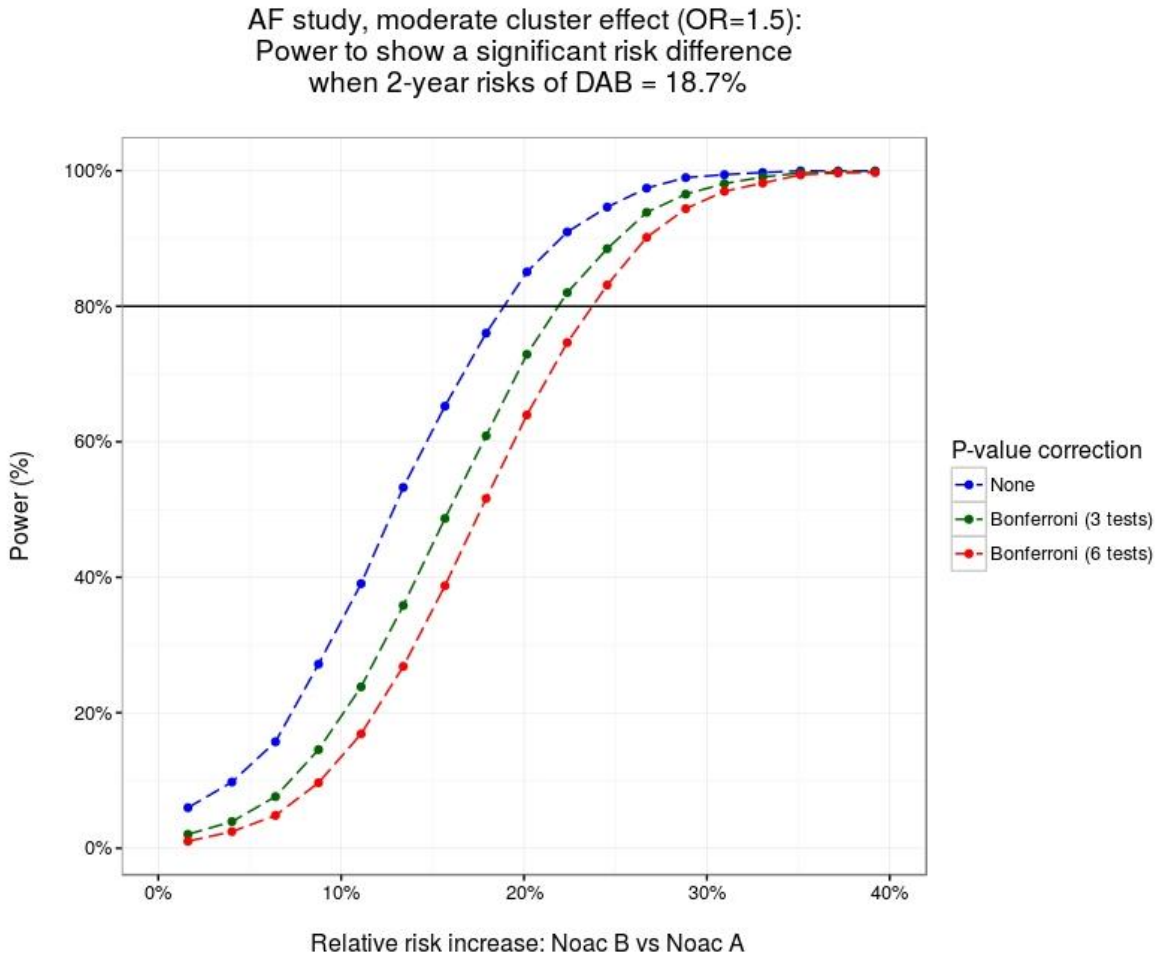
Null hypothesis: The risk of combined endpoint is the same for NOAC A and NOAC B. Data from two NOACs compared to a fixed-effect meta-analyzes (Mantel-Haenszel method) across the clusters.

With 4 NOACs there are six possible comparisons: (A vs. B, A vs. C, A vs D, B vs C, B vs D, C vs D) and the attached pictures of power calculations show Bonferroni corrected results (6 tests). We also shows the Bonferroni corrected power of three experiments, as this is equivalent to analyzing the three NOACS against a NOAC (A vs B vs A C vs A D).

Results Atrial Fibrillation Substudy

Period per NOAC 6 months, dabigatran as a reference, and an expected 18.7% risk of the combined endpoint within 2 years. Figure 1 shows the power depending on the difference between the outcome of risk between two NOACs with moderate cluster effect. Figure 1 shows that the DANNOAC atrial fibrillation substudy have an 80% power to show a difference in the relative risk of 18% without the Bonferroni correction, or 22% with the Bonferroni correction for 6 tests.

Figur 1.



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.[5] 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 study responsible person, in the literature 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".[6] The study protocol will be sent to these study responsible persons for evaluation. Before a given cluster can be included in the present quality assessment approval from the study responsible persons are needed. Furthermore, all patients that are being prescribed NOAC treatment will be informed, that a quality assessment of NOACs is currently being conducted.

To ensure that all patients are given correct information, a pocket card with study information as well as information about price and adverse effect of the NOACs are given to all physicians and nurses at participating clusters (folder attached). In addition, a patient information folder will be available at all participating clusters in layman's term (folder attached). All clusters will be educated in the use of the 4 NOACs, including stricter reporting of adverse effects for rivaroxaban and edoxaban. Finally, the primary sector will be informed in "Praksisnyt" as agreed by PLO.

The study is sponsored solely by The Danish Heart Foundation.

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]. In 2014 2,850 patients were prescribed NOAC with deep vein thrombosis or pulmonary embolism as an indication. This number increased by 9% in the first half of 2015 (corresponding to 3,300 patients annually).*

2. *Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation 2012;126:2381-2391.*

3. *Cohen AT, Hamilton M, Mitchell SA, Phatak H, Liu X, Bird A, Tushabe D, Batson S. Comparison of the Novel Oral Anticoagulants Apixaban, Dabigatran, Edoxaban, and Rivaroxaban in the Initial and Long-Term Treatment and Prevention of Venous Thromboembolism: Systematic Review and Network Meta-Analysis. PLoS One 2015;10:e0144856.*

4. *Hernan MA, Robins JM. Estimating causal effects from epidemiological data. J Epidemiol Community Health. 2006; 60: 578-586.*

5. *Weijer C, Miller PB. When are research risks reasonable in relation to anticipated benefits? Nat Med 2004;10:570-573.*

6. *Weijer C, Grimshaw JM, Taljaard M, Binik A, Boruch R, Brehaut JC, Donner A, Eccles MP, Gallo A, McRae AD, Saginur R, Zwarenstein M. Ethical issues posed by cluster randomized trials in health research. Trials 2011;12:100.*