Restarting Anticoagulant Treatment After Intracranial Haemorrhage in Patients With Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality and Bleeding: A Nationwide Cohort Study

Running title: Nielsen et al.; Anticoagulant treatment after intracranial haemorrhage

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Abstract

Background—Intracranial haemorrhage is the most feared complication of oral anticoagulant treatment. The optimal treatment option for atrial fibrillation patients surviving an intracranial haemorrhage remains unknown. We hypothesised that restarting oral anticoagulant treatment was associated with a lower risk of stroke and mortality compared to not restarting.

Methods and Results—Linkage of three Danish nationwide registries in the period between 1997 and 2013 identified atrial fibrillation patients on oral anticoagulant treatment with incident intracranial haemorrhage. Patients were stratified by treatment regimens (no treatment, oral anticoagulant treatment or antiplatelet therapy) post the intracranial haemorrhage. Event rates were assessed 6 weeks after hospital discharge and compared with Cox proportional hazard models. In 1,752 patients (one year of follow-up) the rate of ischemic stroke/systemic embolism and all-cause mortality (per 100 person-years) for oral anticoagulant treatment treated patients were 13.6, compared to 27.3 for non-treated patients and 25.7 for patients receiving antiplatelet therapy. For recurrent intracranial haemorrhage: 8.0 for oral anticoagulant treated, compared to 8.6 for non-treated, and 5.3 for antiplatelet therapy. The adjusted hazard ratio of ischemic stroke/systemic embolism and all-cause mortality was 0.55 (95%CI 0.39-0.78) in patients on oral anticoagulant treatment compared to no treatment. For ischemic stroke/systemic embolism and for all-cause mortality HRs were 0.59 (95%CI 0.33-1.03) and 0.55 (95%CI 0.37-0.82), respectively.

Conclusions—Oral anticoagulant treatment was associated with a significant reduction in ischemic stroke/all-cause mortality rates, supporting oral anticoagulant treatment reintroduction post-intracranial haemorrhage as feasible. Future trials are encouraged to guide clinical practice in these patients.

Key words: stroke, anticoagulant, hemorrhage, cerebral infarct
Introduction

Patients with atrial fibrillation (AF) are increasingly treated with oral anticoagulation (OAC), which has been shown to reduce the risk of stroke/systemic embolism and all-cause mortality, compared to control \(^1\). Until recently, OAC usually meant Vitamin K Antagonists (VKA, e.g. warfarin), and the most feared complication was major bleeding, particularly intracranial haemorrhage (ICH). More recently, the Non-VKA Oral Anticoagulants (NOACs) have been introduced into clinical practice and are associated with relatively lower – but not zero – risk of ICH, when compared to warfarin \(^2,3\). The acute development of ICH confers a poor prognosis with a high rate of mortality and disability, whether or not a NOAC is used.

Patients with AF who survive an ICH are at an increased risk of subsequent ischaemic stroke \(^4,5\). Thus, a major unanswered question is the efficacy and safety of restarting OAC treatment, relative to not restarting OAC, following a presentation with ICH \(^6-9\). Patients with prevalent ICH were excluded from randomized clinical trials of OAC for stroke prevention, and only small case control or cohort studies are available \(^10-13\). Currently, the optimal treatment option is unknown and requires balancing the competing risk of ischemic stroke and recurrent ICH in AF patients.

Using Danish nationwide registries cohort, we investigated the hypothesis that, amongst AF patients presenting with an ICH, restarting OAC was associated with a lower risk of recurrent stroke and/or mortality, but with a small increase in major bleeding (particularly ICH) compared to not restarting.

Methods

We used the civil registration number assigned to all Danish residents to link three nationwide...
databases 14–16 as follows: (i) discharge diagnoses classified by the International Classification of Diseases (ICD), admission and discharge dates were obtained from the Danish National Patient Registry; (ii) dispensed prescriptions identified by the Anatomical Therapeutic Chemical (ATC) classification code, date of purchase, package size and volume of the medication since 1994 were obtained from the Danish National Prescription Registry; and (iii) information on age, sex, date of birth, emigration and vital status were attained from the Danish Civil Registration System. Retrospective studies do not require ethical approval in Denmark.

**Study population**

All Danish citizens with an incident nonvalvular AF diagnosis between January 1997 and December 2013 were identified. Patients with a subsequent incident ICH (ICD10: I60-I62; S063C; S064-S066) requiring admission to a hospital were included. Exclusion criteria were valvular AF defined as presence of mitral stenosis or mechanical heart valve (ICD10: I05 and Z952-Z954). Patients with ICH or complications from ICH (ICD10: I690-692) prior to their AF diagnosis were also excluded. We further required patients to be in OAC treatment defined as a claimed VKA or NOAC prescription within 6 months prior to the ICH event. This was done to support the assumption that included patients were indeed in OAC treatment at the time of the incident ICH event. Patients were followed in the National Patient Registry after a ‘quarantine period’ defined as 6 weeks after hospital discharge. This period was chosen to ensure that events could reasonably be attributed to treatment regimens rather than inadequate correction of the initial coagulation deficit, i.e. reversal of the incident ICH (and adjacent) event 9,17–20. Further, the use of a relatively long quarantine period can reduce confounding by indication, as those patients initially deemed at a very high risk of recurrent ICH would probably not be advised to resume anticoagulation within this period (e.g. patients with lobar haemorrhage 21).
Exposure to antithrombotic treatment

We identified all prescriptions of antiplatelet therapy (aspirin/thienopyridines) and OAC treatment (VKA/NOAC) to classify patients by treatment regimens as: ‘No antithrombotic treatment’, ‘Antiplatelet therapy’ or ‘OAC treatment’. The following ATC codes were utilised to account for OAC treatment: B01AA (coumarin derivatives), B01AE07 (dabigatran etexilate); B01AF01-02 (rivaroxaban and apixaban). For antiplatelet therapy the following ATC codes were utilised: B01AC06 (aspirin) and B01AC04, B01AC22 and B01AC24 (Thienopyridines). When discharged from the hospital, all included patients were initially assigned to ‘no antithrombotic treatment’ and if antithrombotic therapy was reinitiated, to either ‘Antiplatelet therapy’ or ‘OAC treatment’ categories, whichever prescription was claimed first [Figure 1]. Treatment exposure was consequently considered as a time-dependent covariate.

Outcome measures

The primary analysis plan used the principal outcomes of ischemic stroke/systemic embolism (SE), all-cause mortality and recurrent ICH. Given the severity of the studied outcomes, we only considered events if the patient was admitted to the hospital \(^{22}\); hence, we did not consider ambulatory diagnosis. Additionally, emergency room coded diagnoses were not included in this study due to poor validity \(^{23}\). The primary study endpoint was a combined endpoint of ischemic stroke/SE (ICD10 diagnosis: I63; I64; I74) and all-cause mortality, given the positive impact of OAC on stroke and mortality \(^{1}\) and recognising that in registry data, some deaths may be due to undiagnosed stroke/SE as neither post-mortems nor cerebral imaging are mandated.

Secondary analyses were carried out for ischemic stroke/SE; for recurrent ICH; for major extra cranial bleeding (ICD10: D62; J942; H113; H356; H431; N02; N95; R04; R31; R58; K250 K260 K270 K280 K290), and for all-cause mortality. If, in the primary analysis, antithrombotic
therapy did show benefit versus being left untreated (commonly seen in practice post-ICH \textsuperscript{5,24}), a secondary analysis calculating net clinical benefit (NCB) of resuming antithrombotic therapy (vs no antithrombotic therapy) was calculated by the methods previously proposed balancing ischaemic stroke reduction versus the increased risk of ICH \textsuperscript{25}. NCB with 95\% confidence intervals (CI) were based on rate differences and standard errors estimated obtained using Poisson regression. We applied a weight of 1 for ischemic stroke/SE and all-cause mortality and a weight of 1.5 for recurrent ICH as proposed by Singer et al \textsuperscript{25}. Accompanying the NCB analysis, we also investigated the event rate for the composite outcome of ischemic stroke/SE/major bleeding (including recurrent ICH). Additionally, we carried out a sensitivity analysis by altering the quarantine period when investigating the outcome of ischemic stroke/SE and all-cause mortality and recurrent ICH. This was done to assess if the choice of quarantine period would differ from the main analysis (using a 6 weeks quarantine period).

**Patient characteristics and concomitant medication**

Comorbidities were ascertained from preceding hospital diagnoses until discharge from the incident ICH event. Filled prescriptions 1 year prior to baseline defined other concomitant medication. The cardiovascular comorbidity and risk of stroke at baseline were assessed by the CHA\textsubscript{2}DS\textsubscript{2}-VASc [congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke, vascular disease, age 65–75 years, and female sex]) score \textsuperscript{26,27}. We calculated the HAS-BLED [hypertension, abnormal renal/liver function, stroke/thromboembolism, bleeding history, labile international normalized ratio (not included), elderly (age >65 years), drug consumption/alcohol excess (aspirin was not included due to status of exposure)] score for each patient to assess the bleeding risk \textsuperscript{28}. **Supplementary Table 1** provides detailed description on outcomes and concomitant medication.
Statistical analyses

Patients were followed until occurrence of the following censoring events: a claimed prescription indicating dual treatment regimen (both OAC and antiplatelet treatment), occurrence of a study endpoint, emigration, end-of-study, or death whichever came first [Figure 1]. For outcome analyses events were ascertained from 6 weeks after hospital discharge. Exposure to antithrombotic treatment was regarded as two time-dependent covariates (one for OAC treatment and one for antiplatelet therapy) with one irreversible binary transition (from 0 to 1). We calculated crude events rates at 1 and 5 years by dividing the number of events occurring during follow-up with the person-years of follow-up for each treatment group. To compare event rates associated under antithrombotic treatment regimens vs no antithrombotic treatment, crude and adjusted hazard ratios (HR) were estimated by means of the Cox proportional hazards model. The adjusted analyses included information on age (restricted cubic spline); gender (binary); year of inclusion (categories of five years); time since last claimed OAC prescription before the incident ICH event (restricted cubic spline); and categories of the CHA2DS2-VASc score (0; 1; ≥2 points) and HAS-BLED score (0-2; ≥3 points). We additionally used information on ischemic stroke/SE and/or recurrent ICH events during the quarantine period (binary). The reasoning behind this adjustment was that such events could affect the choice of antithrombotic treatment before the observation time commenced. Additionally, a sensitivity analysis was conducted by excluding patients who experienced an event within the quarantine period.

To depict the overall five year prognosis, we obtained the Kaplan-Meier estimates. The patients were stratified according to purchase of OAC (respectively, antiplatelet drugs) during the quarantine period (6 weeks landmark) and patients with dual treatment exposure were excluded (prescription claim of both an OAC and antiplatelet drug). To assess the impact of
allowing more time for claiming a prescription used for treatment regimen allocation, we made a
sensitivity analysis by setting the landmark to 180 days.

We used a two-sided p-value threshold of \( p<0.05 \) for statistical significance. Statistical
analyses were performed by using SAS 9.3 (SAS Institute) and Stata version 13 (StataCorp LP).

Results

A total of 6,138 patients with non-valvular AF who suffered an incident ICH were identified in
the period from January 1\textsuperscript{st} 1997 to December 31\textsuperscript{st} 2013. Within the quarantine period of 6 weeks
1,652 patients died, while 32 patients were excluded due to insufficient follow-up time (i.e.
encountered study-end within the quarantine period). The study population was comprised of
1,752 patients who fulfilled the inclusion criteria by having claimed an OAC prescription within
six months of the incident ICH event and were still alive after the 6 weeks quarantine period; see
\textbf{Figure 1} for flowchart and \textbf{Table 1} for study population characteristics. The proportion of
patients included in the analysis with prior OAC treating receiving VKA was 65\%, and the
combination of VKA and antiplatelet therapy in 33\%. With NOACs, the proportion was 2\%
while \(<1\%\) received combination therapy with a NOAC and antiplatelet therapy. The mean
\( \text{CHA}_2\text{DS}_2\text{-VASc} \) score was 3.9 and the mean HAS-BLED score was 3.2, indicating a study
population at high risk of both thromboembolic events as well as high risk of bleeding.

Of the patients who resumed OAC treatment (\( n=621 \)), 77\% claimed an OAC prescription
within first 3 months after hospital discharge, with an overall median days of 34 to first claimed
prescription. For those who received antiplatelet therapy (\( n=759 \)), 65\% claimed a prescription
within first 3 months, with an overall median time of 24 days. During the first year of follow-up,
218 patients either shifted treatment or initiated dual antithrombotic treatment and were
accordingly censored.

**Stroke/SE and all-cause mortality**

A total of 39 patients suffered an ischemic stroke/SE during the quarantine period of 6 weeks; of those, 5 patients had already claimed an OAC prescription, while 11 patients received antiplatelet therapy. The overall event rates (expressed as per 100 person-years) using 1 year of follow-up of the combined endpoint of ischemic stroke/SE and all-cause mortality in OAC treated vs no antithrombotic treatment were 13.6 vs 27.3 (adjusted HR: 0.55, 95%CI 0.39-0.78), and 25.7 for antiplatelet therapy (adjusted HR: 0.87, 95%CI 0.67-1.14) [Table 2 and Figure 2]. The event rates for ischemic stroke/SE in OAC treated vs no antithrombotic treatment were 5.3 vs 10.4 at one year of follow-up (adjusted HR: 0.59, 95%CI 0.33-1.03), whilst for antiplatelet therapy, 10.3 (adjusted HR: 0.98, 95%CI 0.65-1.49). For all-cause mortality, the event rates were 9.7 for OAC treated vs 19.1 for no antithrombotic treatment (adjusted HR: 0.55, 95%CI 0.37-0.82), and 19.5 for antiplatelet therapy (adjusted HR: 0.90, 95%CI 0.67-1.21). The crude and adjusted analyses contrasting treatment regimens were comparable. Supplementary Table 2 provides event rates based and adjusted hazard ratios based on 5 years of follow-up, showing consistency.

**Figure 3** depicts the Kaplan-Meier estimates of 5 year survival in patients who resumed OAC treatment, respectively received antiplatelet therapy, and those who did not. A landmark at 6 weeks (quarantine period) was used to allocate patients treatment regimens: 1,089 were assigned to the no antithrombotic treatment group; 303 to OAC treatment; and 360 to the antiplatelet therapy group.

**Recurrent ICH and major bleeding**

Of a total of 298 recurrent ICH events, 177 events (60%) occurred during the quarantine period,
i.e. before the observation time commenced; of these 27 patients had claimed an OAC prescription, while 35 patients received antiplatelet therapy. For recurrent ICH using one year of follow-up, the rates were 8.6 for OAC treated vs 8.0 for no antithrombotic treatment (adjusted HR: 0.91, 95%CI 0.56-1.49), and 5.3 for antiplatelet therapy (adjusted HR: 0.60, 95%CI 0.37-1.03). The event rates of major extra cranial bleedings in OAC treated vs no antithrombotic treatment were 1.5 vs 1.5 (adjusted HR: 0.92, 95%CI 0.30-2.76), and 2.6 for antiplatelet therapy (adjusted HR: 1.57, 95%CI 0.62-3.92) [Table 2 and Figure 2]. The crude and adjusted analyses contrasting treatment regimens for bleeding outcomes were broadly comparable.

Secondary analysis

The one-year event rate for the combined endpoint of ischemic stroke/SE/major bleeding (including ICH) was 27.4 for no antithrombotic treatment, 17.1 for OAC treatment, and 23.2 for patients who receiving antiplatelet therapy. As OAC did demonstrate a significant reduction in stroke/SE and all-cause mortality, we calculated the one year NCB of OAC or antiplatelet therapy use versus no antithrombotic treatment. The NCB was calculated as a weighted sum of rate differences for the combined endpoint of ischemic stroke/SE and all-cause mortality and recurrent ICH. The NCB for OAC vs versus no antithrombotic treatment was 14.6 (95%CI 6.4-22.8), while the NCB was non-significant for antiplatelet therapy vs versus no antithrombotic treatment, 6.5 (95%CI -2.1-15.2).

Sensitivity analysis

A sensitivity analysis of the Kaplan-Meier estimates stratified according to treatment regimens using a landmark at 180 days (relative to hospital discharge) for treatment allocation is shown in Supplementary Figure S1. A total of 1541 patients contributed to this analysis, and the survival curves were alike to those presented in Figure 3 supporting OAC treatment.
Altering the quarantine period ranging from 2 weeks to 10 weeks did essentially not affect the primary outcome of ischemic stroke/SE and all-cause mortality, see Figure 4. The total number of patients contributing to these analyses was 1.838; 1.793; 1.752; 1.732; 1.712 using 2; 4; 6; 8; and 10 weeks quarantine period, respectively. Contrary, the outcome of recurrent ICH was somewhat affected by the choice of quarantine period. The HR contrasting OAC treatment vs no treatment was ranging from 0.41 (95%CI 0.27-0.63) for 2 weeks quarantine period, to HR 1.42 (95%CI 0.83-2.43) when applying a 10 weeks quarantine period. The obtained results on HR contrasting treatment regimens were generally not affected by excluding those patients who experienced an event (ischemic stroke/SE and/or recurrent ICH) during the quarantine period. However, the outcome of recurrent ICH for patients on OAC treatment displayed an adjusted HR of 1.30 (95%CI 0.75-2.27).

Discussion
In this analysis we found that AF patients who suffer an ICH are very high risk of ischaemic stroke and mortality, if they are not on antithrombotic therapy. Patients who were not on OAC treatment had the worse adverse outcomes, which were similar to rates seen with antiplatelet therapy. Importantly, OAC treatment was associated with a significant reduction in subsequent ischaemic stroke and all-cause mortality.

ICH is the most feared complication of OAC treatment, being associated with a high mortality and morbidity, and survivors often have greater disability. Patients with ICH were not included in randomised trials, and it is an open problem to decide the best time window to reintroduce OAC treatment following a presentation with ICH. Our analysis does not define the best time window to reintroduce OAC but makes the observation in this non-randomised
observational cohort that OAC use was associated with significantly lower risks of ischaemic stroke and all-cause mortality.

The risk of recurrent ICH was also high in our patients, and was equally high amongst non-OAC treated or OAC-treated, while slightly lower in patients who received antiplatelet therapy. Factors contributing to recurrent ICH have been reported in different studies and include increasing age, concomitant use of aspirin or NSAIDs, uncontrolled hypertension, etc. As previously shown in clinical trial and nationwide registries, the HAS-BLED score is the only bleeding risk score that is predictive of major bleeding risk, and reflects the risk factors commonly associated with this complication.

Common practice is to consider no antithrombotic treatment or antiplatelet therapy (commonly aspirin) as a ‘safer’ alternative to OAC following a presentation with ICH, and the AHA/ASA guideline provides a Class IIb recommendation of antiplatelet therapy after all types of ICH (and “OAC might be considered after non-lobar ICH”) 52. Our data do not support such an approach with a higher ischaemic stroke and substantially higher mortality, with a non-significant reduction in recurrent ICH amongst antiplatelet therapy users. Even in randomised trials of stroke prevention in AF, the risk of ICH (and major bleeding) is no different between OAC and aspirin treated patients, especially in the elderly 33,34. Also, our secondary analyses show that the NCB for OAC treatment was positive, vs no antithrombotic therapy – whilst the NCB for aspirin vs no antithrombotic therapy was non-significant.

The present study has clinical implications, in that it supports OAC re-introduction as soon as clinically feasible. However, given the non-randomized design and data limitations caution on over-interpretation the results are warranted: we were not able to distinguish between the severities of risk factors, which may reflect physician’s choices of OAC resumption.
Potentially correctable risk factors for ICH should be addressed including assessment of the HASBLED score, correction of uncontrolled high blood pressure, concomitant use of aspirin or NSAIDs, etc. ICH can sometimes be related to trauma or a vascular anomaly, and for the latter, liaison with a neurosurgical service is important.

**Limitations**

We did not have data on INR values hence no estimate of OAC intensity, and we also recognise the importance of the quality of anticoagulation control, as reflected by time in therapeutic range. VKAs are associated with a relatively higher rate of ICH compared to NOACs, but the latter were only used in a minority of patients in our study. We also did not have any cerebral imaging data, to distinguish the subtypes of ICH, but our principal hypothesis pertained to the simple question of whether or not restarting OAC after ICH was associated with a beneficial effect on stroke and mortality, in patients with AF. Indeed, the presence of microbleeds is an important risk for ICH, and many stroke physicians would be cautious about restarting OAC in a patient with widespread cerebral microbleeds.

There is a potential risk of misclassification of recurrent ICH events due to routine procedures after hospital discharge: patients are likely to be re-admitted to a hospital for a follow-up computerized tomography scan examining re-bleedings. This re-admission could inherit the coding from the incident ICH with no evidence of any recurrent bleeding. This conjecture was supported by the sensitivity analyses of altering the quarantine period, and also by excluding those patients who experienced an event during the quarantine period. On the other hand, with the lack of information on cause of death, the number of ischemic events or recurrent ICH could be underestimated if they carried a terminal outcome. Our analysis on treatment
initiation was performed using an assumption of adherence to treatment (unless changed from OAC to antiplatelet therapy or vice versa), recognising the limitations of a ‘real world’ cohort design, where patients could change from treatment (and doses) to no treatment over time. We also only included patients with an index hospitalisation for AF, and documented ICH – thus, confounding by indication and selection bias could be evident, and our results may not be generalizable to the ‘general’ non-hospitalised AF population. Nonetheless, most patients with an ICH would require hospitalisation, and AF-related hospitalisations are common (and increasing); thus, our analysis would reflect the likely burden of AF patients in healthcare systems. Although this was a nationwide study, the ethnic background of the Danish population is presumably Caucasian, and thus the obtained results might not generalise to all ethnic groups.

In conclusion, AF patients who suffer an ICH are at very high risk of ischaemic stroke and death, and our data indicates positive clinical benefit from anticoagulant treatment. OAC treatment resulted in a significant reduction in subsequent ischaemic stroke and all-cause mortality. As such, this study supports OAC reintroduction post-ICH, but due to risk of bias by unmeasured confounding, future randomized controlled trials investigating resumption of OAC treatment post-ICH are encouraged to provide further evidence to guide clinical practice.

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has served as an investigator for Janssen Scientific Affairs, LLC and Boehringer Ingelheim. Associate Professor Larsen and Professor Rasmussen have been on the speaker bureaus for Bayer, BMS/Pfizer, Roche Diagnostics, Boehringer Ingelheim and Takeda Pharma. Other authors – none declared.

References:


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Table 1. Baseline characteristics of the cohort.

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<thead>
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<th>Total population</th>
<th>Intracerebral bleeding</th>
<th>Subdural bleeding</th>
<th>Subarachnoid bleeding</th>
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<td>812</td>
<td>755</td>
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<td>Age, median (IQR)</td>
<td>78 (71-83)</td>
<td>78 (71-83)</td>
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<td>Male gender No. (%)</td>
<td>1,081 (62)</td>
<td>471 (58)</td>
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<td>1,145 (65)</td>
<td>507 (62)</td>
<td>508 (67)</td>
<td>130 (70)</td>
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<td>NOAC</td>
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<td>571 (33)</td>
<td>290 (36)</td>
<td>232 (31)</td>
<td>49 (27)</td>
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<td>8 (&lt;1)</td>
<td>4 (&lt;1)</td>
<td>3 (&lt;1)</td>
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<td>Comorbidity no. (%)</td>
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<td>198 (24)</td>
<td>220 (29)</td>
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<td>494 (61)</td>
<td>490 (65)</td>
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<td>Beta-blockers</td>
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<td>123 (7)</td>
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<td>754 (93)</td>
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<td>164 (89)</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>363 (21)</td>
<td>155 (19)</td>
<td>170 (23)</td>
<td>38 (21)</td>
</tr>
<tr>
<td>≥3</td>
<td>1,389 (79)</td>
<td>657 (81)</td>
<td>585 (77)</td>
<td>147 (79)</td>
</tr>
</tbody>
</table>

Table 2. Event rates of various outcomes according to stratification on treatment regimen using 1 year of follow-up.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No antithrombotic treatment</th>
<th>OAC treatment</th>
<th>Antiplatelet therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischemic stroke/SE/ and all-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>179</td>
<td>43</td>
<td>83</td>
</tr>
<tr>
<td>Person-time (100 years)</td>
<td>655</td>
<td>316</td>
<td>335</td>
</tr>
<tr>
<td>Event rate (95% CI)</td>
<td>27.3 (23.6 - 31.6)</td>
<td>13.6 (10.1 - 18.3)</td>
<td>25.7 (20.7 - 31.9)</td>
</tr>
<tr>
<td><strong>Ischemic stroke/SE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>69</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>Person-time (100 years)</td>
<td>666</td>
<td>322</td>
<td>329</td>
</tr>
<tr>
<td>Event rate (95% CI)</td>
<td>10.4 (8.2 - 13.1)</td>
<td>5.3 (3.3 - 8.5)</td>
<td>10.3 (7.4 - 14.4)</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>130</td>
<td>32</td>
<td>69</td>
</tr>
<tr>
<td>Person-time (100 years)</td>
<td>682</td>
<td>330</td>
<td>353</td>
</tr>
<tr>
<td>Event rate (95% CI)</td>
<td>19.1 (16.0 - 22.6)</td>
<td>9.7 (6.9 - 13.7)</td>
<td>19.5 (15.4 - 24.7)</td>
</tr>
<tr>
<td><strong>Recurrent ICH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>57</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>Person-time (100 years)</td>
<td>662</td>
<td>313</td>
<td>339</td>
</tr>
<tr>
<td>Event rate (95% CI)</td>
<td>8.6 (6.6 - 11.2)</td>
<td>8.0 (5.4 - 11.8)</td>
<td>5.3 (3.3 - 8.4)</td>
</tr>
<tr>
<td><strong>Major extracranial bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>10</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Person-time (100 years)</td>
<td>677</td>
<td>329</td>
<td>349</td>
</tr>
<tr>
<td>Event rate (95% CI)</td>
<td>1.5 (0.8 - 2.7)</td>
<td>1.5 (0.6 - 3.7)</td>
<td>2.6 (1.3 - 5.0)</td>
</tr>
</tbody>
</table>
Figure Legends:

**Figure 1.** Flowchart of the study design and population.

**Figure 2.** Forest plot of adjusted hazard ratios on treatment regimen of various outcomes using one-year follow-up (adjusted for sex, age, year of inclusion, time since last claimed OAC prescription, and occurrences of ischemic stroke/SE and recurrent ICH events during the quarantine period).

**Figure 3.** Five years Kaplan-Meier survival curve for restarting OAC treatment, receiving antiplatelet therapy, and for not receiving antithrombotic treatment using a landmark at 6 weeks (relative to discharge from hospital) for treatment regimens stratification.

**Figure 4.** Sensitivity analysis investigating the outcomes of ischemic stroke/SE and all-cause mortality and recurrent ICH, stratified according to treatment regimen and to applied quarantine period.
AF patients with incident ICH discharged from hospital
n = 6,138

6 weeks quarantine period

Study population
n = 1,752

Start of follow-up

No antithrombotic treatment

Resumed OAC treatment within quarantine period
(n = 303)

Received antiplatelet therapy within quarantine period
(n = 360)

Patients excluded due to:
- No OAC treatment within last 6 months, n = 2,702

Patients excluded due to:
- Death within quarantine period (6 weeks), n = 1,652
- Censored, n = 32

Antiplatelet therapy

OAC treatment

Censoring events:
- End-of-study
- Occurrence of study endpoint
- Emigration
- Initiation of dual treatment

Figure 1
Figure 2

Treatment vs No antithrombotic treatment

Outcome / Treatment

Ischemic stroke/SE and all-cause mortality

- OAC treatment
  - Hazard ratio (95% CI): 0.50 (0.37; 0.70)
  - 0.55 (0.39; 0.78)

- Antiplatelet therapy
  - Hazard ratio (95% CI): 0.90 (0.69; 1.17)
  - 0.87 (0.67; 1.14)

Ischemic stroke/SE

- OAC treatment
  - Hazard ratio (95% CI): 0.55 (0.33; 0.95)
  - 0.59 (0.33; 1.03)

- Antiplatelet therapy
  - Hazard ratio (95% CI): 1.02 (0.67; 1.55)
  - 0.90 (0.65; 1.49)

All-cause mortality

- OAC treatment
  - Hazard ratio (95% CI): 0.49 (0.33; 0.72)
  - 0.55 (0.37; 0.82)

- Antiplatelet therapy
  - Hazard ratio (95% CI): 0.94 (0.70; 1.26)
  - 0.90 (0.67; 1.21)

Recurrent ICH

- OAC treatment
  - Hazard ratio (95% CI): 0.93 (0.57; 1.51)
  - 0.91 (0.56; 1.49)

- Antiplatelet therapy
  - Hazard ratio (95% CI): 0.60 (0.37; 1.02)
  - 0.60 (0.37; 1.03)

Major extracranial bleeding

- OAC treatment
  - Hazard ratio (95% CI): 0.93 (0.30; 2.79)
  - 0.92 (0.30; 2.76)

- Antiplatelet therapy
  - Hazard ratio (95% CI): 1.55 (0.62; 3.83)
  - 1.57 (0.62; 3.92)
Figure 3
**Figure 4**

**Ischemic stroke/SE and all-cause mortality**

**Recurrent ICH**
Restarting Anticoagulant Treatment After Intracranial Haemorrhage in Patients With Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality and Bleeding: A Nationwide Cohort Study

Peter Brønnum Nielsen, Torben Bjerregaard Larsen, Flemming Skjøth, Anders Gorst-Rasmussen, Lars Hvilsted Rasmussen and Gregory Y.H. Lip

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## SUPPLEMENTAL MATERIAL

### Supplementary Table 1: Definitions of outcomes and medication

<table>
<thead>
<tr>
<th>Condition</th>
<th>International Classification of Diseases 10th revision (ICD-10) code</th>
<th>Anatomical Therapeutic Chemical (ATC) code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>I11.0; I13.0; I13.2; I42.0; I50</td>
<td>CO3C</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>I50.1; I50.9</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>See specified definition*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>E10.0; E10.1; E10.9; E11.0; E11.1; E11.9</td>
<td>A10</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>I63; I64</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>I74</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic disease</td>
<td>G45</td>
<td></td>
</tr>
<tr>
<td>Aortic plaque</td>
<td>I70.0</td>
<td></td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>I70.2-I70.9; I71; I73.9; I74</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>I21-I23</td>
<td></td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61</td>
<td></td>
</tr>
</tbody>
</table>
Abnormal hepatic function  B15.0; B16.0; B16.2; B19.0;
K70.4; K72; K76.6; I85

Prior Bleeding  I60-I62; D62; J94.2; H11.3; H35.6;
H43.1; N02; N95; R04; R31; R58;
K25.0; K26.0; K27.0; K28.0;
K29.0; S06.3C; S06.4; S06.5;
S06.6

Alcohol intake  E22.4; E52.9A; F10; G31.2;
G62.1; G72.1; I42.6; K29.2; K70;
K86.0; L27.8A; O35.4M; T51;
Z71.4; Z72.1

Atrial fibrillation  I48

Major bleeding  D62 J942 H113 H356 H431 N02
N95 R04 R31 R58

Intracranial bleeding  I60 I61 I62

Traumatic intracranial bleeding  S063C S064 S065 S066

Retinal bleeding  H356

Sequelae of cerebrovascular disease  I690; I691; I692

Medication

Dabigatran  B01AE07

Rivaroxaban  B01AE07
* We identified subjects with hypertension from combination treatment with at least two of the following classes of antihypertensive Drugs:

I. Alpha adrenergic blockers (C02A, C02B, C02C)

II. Non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52)

III. Vasodilators (C02DB, C02DD, C02DG, C04, C05)

IV. Beta blockers (C07)

V. Calcium channel blockers (C07F, C08, C09BB, C09DB)
VI. Renin-angiotensin system inhibitors (C09).
**Supplementary Table 2:** Event rates and adjusted hazard ratios of various outcomes according to stratification on treatment regimen using 5 years of follow-up.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No OAC therapy</th>
<th>OAC therapy</th>
<th>Antiplatelet therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischemic stroke/SE and all-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>326</td>
<td>106</td>
<td>240</td>
</tr>
<tr>
<td>Person-time (100 years)</td>
<td>1392</td>
<td>996</td>
<td>1204</td>
</tr>
<tr>
<td>Event rate (95% CI)</td>
<td>23.4 (21.0 - 26.1)</td>
<td>10.6 (8.8 - 12.9)</td>
<td>19.9 (17.6 - 22.6)</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)</td>
<td>Reference</td>
<td>0.54 (0.43 – 0.67)</td>
<td>0.85 (0.81 – 1.00)</td>
</tr>
<tr>
<td><strong>Ischemic stroke/SE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>108</td>
<td>35</td>
<td>76</td>
</tr>
<tr>
<td>Person-time (100 years)</td>
<td>1413</td>
<td>1014</td>
<td>1217</td>
</tr>
<tr>
<td>Event rate (95% CI)</td>
<td>7.6 (6.3 - 9.2)</td>
<td>3.5 (2.5 - 4.8)</td>
<td>6.2 (5.0 - 7.8)</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)</td>
<td>Reference</td>
<td>0.55 (0.37 – 0.81)</td>
<td>0.87 (0.65 – 1.17)</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>266</td>
<td>91</td>
<td>227</td>
</tr>
<tr>
<td>Person-time (100 years)</td>
<td>1470</td>
<td>1072</td>
<td>1420</td>
</tr>
<tr>
<td>Event rate (95% CI)</td>
<td>18.1 (16.0 - 20.4)</td>
<td>8.5 (6.9 - 10.4)</td>
<td>16.0 (14.0 - 18.2)</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)</td>
<td>Reference</td>
<td>0.56 (0.44 – 0.71)</td>
<td>0.87 (0.72 – 1.04)</td>
</tr>
<tr>
<td><strong>Recurrent ICH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>72</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>Person-time (100 years)</td>
<td>1408</td>
<td>1012</td>
<td>1315</td>
</tr>
<tr>
<td>Event rate (95% CI)</td>
<td>5.1 (4.1 - 6.4)</td>
<td>3.6 (2.6 - 4.9)</td>
<td>2.6 (1.8 - 3.6)</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)</td>
<td>Reference</td>
<td>0.79 (0.52 – 1.19)</td>
<td>0.56 (0.37 – 0.84)</td>
</tr>
<tr>
<td><strong>Major extra cranial bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>20</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>Person-time (100 years)</td>
<td>1449</td>
<td>1052</td>
<td>1382</td>
</tr>
<tr>
<td>Event rate (95% CI)</td>
<td>1.4 (0.9 - 2.1)</td>
<td>1.3 (0.8 - 2.2)</td>
<td>1.9 (1.3 - 2.8)</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)</td>
<td>Reference</td>
<td>0.90 (0.44 – 1.81)</td>
<td>1.31 (0.73 – 1.76)</td>
</tr>
</tbody>
</table>
Supplementary Figure S1: Five years Kaplan-Meier survival curve for restarting OAC treatment, receiving antiplatelet therapy, and for not receiving antithrombotic treatment using a landmark at 180 days (relative to discharge from hospital) for treatment regimens stratification. A total of 505 patients were allocated to ‘no antithrombotic treatment; 509 to OAC treatment; 527 patients to the antiplatelet therapy group.