# In atrial fibrillation epilepsy risk differs between oral anticoagulants: active comparator, nested case control study

## SUPPLEMENTARY MATERIAL

## Supplementary Text

### Supplementary Results. Sensitivity analyses.

*1 Data source*

Since the preliminary signal generation that motivated this project had been conducted with data provided by the Techniker Krankenkasse (TK) for year 2015 (data not shown), we performed a sensitivity analysis by repeating our main analysis but excluding TK data since 2015. This resulted in a study cohort of 176,750 patients with a diagnosis of atrial fibrillation starting anticoagulant treatment. A total of 1,293 cases with epilepsy or seizures and 13,481 matched controls without these diagnoses were on current treatment with a DOAC or PPC on the (matched) index day. The risk of being diagnosed with epilepsy or seizures was higher in patients treated with a DOAC than in those currently treated with PPC (OR 1.54, 95%CI [1.37; 1.74]; aOR 1.35, 95%CI [1.19; 1.54]), confirming the association of DOAC treatment and epilepsy or seizures across data years and individual insurance provider populations (Table 6D).

*2 Unmeasured confounding*

We computed the E-Value to evaluate the minimum magnitude that unmeasured confounding needs to have in order to account for the observed results.[1] The E-value was developed on the risk ratio scale. As our outcome is rare, we consider the odds ratio (OR) to closely approximate the risk ratio.[2] In our main analysis, we observed an adjusted OR of 1.39 [95% CI 1.24-1.55]. To fully explain away the observed estimate, an unmeasured confounder would have to be associated with both the exposure (DOAC vs. PPC treatment) and the outcome (epilepsy/seizures) with an OR (adjusted for all measured confounders) of 2.13 each.[3] To move the confidence interval such that the observed estimate would no longer be statistically significant, an unmeasured confounder would have to be associated with an adjusted OR of 1.79 with both the exposure and the outcome, respectively.[1,3] Based on this analysis and given the long, comprehensive list of measured confounders including comorbidities and risk factors of epilepsy/seizures (Supplementary Table 1), we believe it is unlikely that the association between DOAC vs. PPC treatment and epilepsy/seizures can be explained by unmeasured confounding.

*3 DOAC dosing*

It has been described in the literature that non-recommended dosing - especially underdosing - may play a considerable role in DOAC treatment.[4,5] We, therefore, performed additional sensitivity analyses to examine the potential impact of DOAC dosing on the risk of epilepsy/seizures.

The “dosing” of DOACs in terms of prescribed doses (i.e. the dosing intended by the prescribing physician) is not available in GePaRD. However, it is possible to obtain detailed information on all dispensations which – under certain assumptions - allow to draw conclusions on intended doses. Thus, we collected among DOAC users the tablet size, i.e. the strength of unit in mg, of the most recent dispensation prior to the index date (date of the event in cases, matched index date in controls). In patients without any treatment restrictions, dispensations of the following tablet sizes would be expected: apixaban 5mg (to be taken twice daily), dabigatran 150mg (to be taken twice daily), edoxaban 60mg and rivaroxaban 20mg. In patients with renal impairment, we would expect the following reduced tablet sizes: dabigatran 110mg (to be taken twice daily), edoxaban 30mg, and rivaroxaban 15mg. Supplementary Table 3 shows the distribution of tablet sizes among DOAC users. To evaluate whether the tablet size was appropriate, we additionally took into consideration whether a history of renal impairment was coded among patients who were dispensed tablet sizes indicating a dose reduction (Supplementary Table 4). Based on this information, DOAC users were stratified into the 2 groups of those with appropriate and those with low tablet size. We reran our main analysis for these 2 subgroups (Supplementary Table 5).

We observed in this stratified analysis that the risk of epilepsy/seizures was even higher in patients who received low tablet sizes of DOACs (adjusted OR 1.56 [95% CI 1.29-1.89]) compared to those receiving tablet sizes indicating appropriate dosing (adjusted OR 1.30 [95% CI 1.16-1.47]). The same applied to the adjusted analysis of individual DOACs, except for edoxaban with very low sample sizes (Supplementary Table 5). We hypothesize that underdosing may be associated with less effective prevention of ischemic events, which may also lead to a higher risk of epilepsy/seizures.

This analysis needs to be interpreted with caution. The tablet size may only approximate intended dosing. Making inferences on the dose based on the dispensed tablet size requires considerable assumptions. For example, patients may be dispensed “inappropriate” tablet sizes in situations where there are shortages of certain tablet sizes. It could also be the case that patients prefer swallowing multiple smaller tablets over one large tablet etc. In addition, patients may have been misclassified based on the presence or absence of codes indicating renal impairment. Here, we had to solely rely on ICD codes for diagnoses and procedure codes for dialysis while no lab results providing insight into the current kidney function were available.

*4 AF ablation procedures*

DOAC users, who were slightly younger than PPC users, might have been more likely to undergo an AF ablation procedure that might lead to covert brain infarctions.[6,7] We evaluated the potential impact that AF ablation procedures might have on our results in a sensitivity analysis. Therefore, we identified the operation and procedure codes ("Operationen- und Prozedurenschlüssel", OPS) that indicate AF ablation procedures.[8] Among cases and controls, we obtained the number of individuals with at least one such code after cohort entry and prior to the diagnosis of epilepsy/seizures (cases) or the matched index date (controls). In addition, we described the proportion of patients by treatment with a DOAC versus PPC at cohort entry.

We identified a total of 401 individuals undergoing AF ablation between cohort entry and the (matched) index date, n= 29 among the 1,828 cases (1.6%) and n= 372 among the 19,084 controls (1.9%, Supplementary Table 6). The proportion of patients was higher among patients using a DOAC versus PPC: 2.1% versus 1.6%.

Given the overall low proportion of individuals undergoing AF ablation and the small differences between groups, we considered a relevant impact of AF ablation on our results to be unlikely.

**Supplementary Discussion.**

*1 Falsification outcomes*

The study objectives arose from a previous pharmacovigilance study in which several outcomes were investigated, i.e., falsification outcomes were considered. In this previous study,[9] the exposure was defined as rivaroxaban versus PPC treatment. The aim of the previous study was to evaluate techniques to detect adverse event signals. Observed signals were additionally verified. Like in the current study, verification was based on active comparator case-control studies nested in a cohort of new users of rivaroxaban and PPC, with a diagnosis of atrial fibrillation. As expected, rivaroxaban versus PPC treatment was associated with bleeding outcomes: current rivaroxaban compared to PPC users were at increased risk of gastrointestinal bleeding (adjusted OR 1.37 [95%CI 1.27-1.47] and at decreased risk of intracranial bleeding (adjusted OR 0.74 [95%CI 0.66-0.83]). On the other hand, only weak associations between current rivaroxaban versus PPC treatment and acute cystitis (adjusted OR 1.11 [95% CI 1.02-1.21]) or sepsis (adjusted OR 1.10 [95% CI 0.99-1.23]) were found.[9]

**References**


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## Supplementary Tables

**Supplementary Table 1.** Detailed description of confounders: ICD-10-GM, ATC and OPS codes used to define the respective confounder variables.

| Diagnoses | Codes (ICD-10-GM if not further specified) | Measurement period |
|---|---|---|
| **Alcohol and drug abuse** | **F11x** Mental and behavioral disorders due to opioids<br>**F12x** Mental and behavioral disorders due to cannabinoids<br>**F13x** Mental and behavioral disorders due to sedatives and hypnotics<br>**F14x** Mental and behavioral disorders due to cocaine<br>**F15x** Mental and behavioral disorders due to other stimulants including caffeine<br>**F16x** Mental and behavioral disorders due to hallucinogens<br>**F18x** Mental and behavioral disorders due to volatile solvents<br>**F19x** Mental and behavioral disorders due to multiple substance use and other psychoactive substance use<br>**L270** Generalized skin eruption due to drugs and medicaments<br>**L271** Localized skin eruption due to drugs and medicaments<br>**N141** Nephropathy induced by other drugs, medicaments and biological substances<br>**N142** Nephropathy induced by unspecified drug, medicament or biological substance<br>**O355** Maternal care for (suspected) damage to fetus by medicaments or drugs<br>**P044** Fetus and newborn affected by maternal use of medicaments or drugs of addiction<br>**P93** Reactions and intoxications due to medicaments or drugs administered to the fetus or newborn<br>**R784** Finding of other drugs of addictive potential in blood<br>**R785** Finding of psychotropic drugs in blood<br>**R825** Elevated urine levels of drugs, medicaments and biologically active substances<br>**R832** Abnormal findings in cerebrospinal fluid: abnormal levels of drugs, medicaments and biologically active substances<br>**R842** Abnormal findings in specimens from respiratory organs and thorax: abnormal levels of drugs, medicaments and biologically active substances<br>**R852** Abnormal findings in specimens from digestive organs and abdominal cavity: abnormal levels of drugs, medicaments and biologically active substances<br>**R862** Abnormal findings in specimens from male genital organs: abnormal levels of drugs, medicaments and biologically active substances<br>**R872** Abnormal findings in specimens from female genital organs: abnormal levels of drugs, medicaments and biologically active substances<br>**R892** Abnormal findings in specimens from other bodily organs, systems and tissues: abnormal levels of drugs, medicaments and biologically active substances<br>**T509** Poisoning: other and unspecified drugs, medicaments and biologically active substances<br>**T96** Consequences of poisoning with drugs, medicaments and biologically active substances<br>**Z503** Rehabilitation measures for medicament or drug addiction<br>**E244** Alcohol induced cushing's syndrome<br>**O354** Maternal care for (suspected) damage to fetus from alcohol<br>**P043** Newborn affected by maternal use of alcohol<br>**Q860** Fetal alcohol syndrome (dysmorphic)<br>**Z502** Rehabilitation measures for alcoholism | 1 year prior cohort entry |
| | **F10x** Mental and behavioral disorders due to alcohol<br>**K292** Alcoholic gastritis<br>**K852**x Alcohol induced acute pancreatitis<br>**K860** Alcohol-induced chronic pancreatitis<br>**R780** Finding of alcohol in blood<br>**T510** Toxic effect of ethanol<br>**T519** Toxic effect of unspecified alcohol<br>**Z720** Problems related to: use of alcohol, tobacco, medicines or drugs | Half a year prior cohort entry |
| | **E52** Niacin deficiency<br>**G312** Degeneration of nervous system due to alcohol<br>**G621** Alcoholic polyneuropathy<br>**G721** Alcoholic myopathy<br>**I426** Alcoholic cardiomyopathy<br>**K70x** Alcoholic hepatic failure | Any time prior cohort entry |
| **Acute coronary syndrome** | **I21x** Acute myocardial infarction<br>**I22x** Recurrent myocardial infarction<br>**I24x** Other acute ischemic heart diseases | 1 year prior cohort entry |

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| **Heart failure** | **I50x** Heart failure<br>**I110x** Hypertensive heart disease with heart failure<br>**I130x** Hypertensive heart and kidney disease with heart failure | Any time prior cohort entry |
| **Cardiovascular disease** | **I20x** Angina pectoris<br>**I21x** Acute myocardial infarction<br>**I22x** Recurrent myocardial infarction<br>**I23x** Certain current complications following acute myocardial infarction<br>**I24x** Other acute ischemic heart diseases | 1 year prior cohort entry |
| | **I200** Unstable angina pectoris<br>**I25x** Chronic ischemic heart disease<br>**I70x** Atherosclerosis<br>**I71x** Aortic aneurysm and dissection<br>**I72x** Other aneurysm<br>**I73x** Other peripheral vascular diseases | Any time prior cohort entry |
| **Diabetes mellitus** | **E10x** Diabetes mellitus, type 1<br>**E11x** Diabetes mellitus, type 2<br>**E12x** Diabetes mellitus, in conjunction with malnutrition<br>**E13x** Other specified diabetes mellitus<br>**E14x** Unspecified diabetes mellitus<br>**A10** DRUGS USED IN DIABETES | Any time prior cohort entry |
| **Hypertension** | **I10x** Essential (primary) hypertension<br>**I11x** Hypertensive heart disease<br>**I12x** Hypertensive kidney disease<br>**I13x** Hypertensive heart and kidney disease<br>**I15x** Secondary hypertension<br>**C02** Antihypertensives<br>**C03** Diuretics<br>**C09** AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM | Any time prior cohort entry |
| **Hyperlipidemia** | **E78x** Disorders of lipoprotein metabolism and other lipidemias<br>**C10** LIPID MODIFYING AGENTS | Any time prior cohort entry |
| **Obesity** | **E65** Localized adiposity<br>**E66x** Obesity | Any time prior cohort entry |
| **Ischemic stroke** | **I63x** Cerebral infarction<br>**I693** Sequelae of cerebral infarction | Any time prior cohort entry |
| **Transient ischemic attack** | **G45x** Transient cerebral ischemic attacks and related syndromes | 1 year prior cohort entry |
| **Other cerebral lesions** | **S06x** Intracranial injury<br>**S097** Multiple injuries of head<br>**S098** Other specified injuries of head<br>**S099** Unspecified injury of head<br>**G00x** Bacterial meningitis, not elsewhere classified<br>**G01x** Meningitis in bacterial diseases classified elsewhere<br>**G02x** Meningitis in other infectious and parasitic diseases classified elsewhere<br>**G03x** Meningitis due to other and unspecified causes<br>**G04x** Encephalitis, myelitis and encephalomyelitis<br>**G05x** Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere<br>**G06x** Intracranial and intraspinal abscess and granuloma<br>**G07x** Intracranial and intraspinal abscess and granuloma in diseases classified elsewhere | Half a year prior cohort entry |
| | **I61x** Intracerebral hemorrhage | 1 year prior cohort entry |
| | **D330** Benign neoplasm of brain, supratentorial<br>**D331** Benign neoplasm of brain, infratentorial<br>**D332** Benign neoplasm of brain, unspecified<br>**D430** Neoplasm of uncertain or unknown behavior of brain, supratentorial<br>**D431** Neoplasm of uncertain or unknown behavior of brain, infratentorial<br>**D432** Neoplasm of uncertain or unknown behavior of brain, unspecified | Any time prior cohort entry |
| **Dementia** | **F00x** Dementia in Alzheimer's disease<br>**F01x** Vascular dementia<br>**F02x** Dementia in other diseases classified elsewhere<br>**F03** Unspecified dementia<br>**F051** Delirium in dementia<br>**G30** Alzheimer`s disease<br>**G3182** Dementia with Lewy bodies<br>**N06DA53** Donepezil, Memantin and Ginkgo-biloba leave extract<br>**N06DP01** Ginkgo-biloba leave extract<br>**N06DX02** Ginkgo folium | Any time prior cohort entry |
| **Liver disease** | **K704** Alcoholic liver failure<br>**K711** Toxic liver disease with liver necrosis<br>**K72** Hepatic failure, not elsewhere classified<br>**K720** Acute and subacute liver failure | Any time prior cohort entry |

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| | **K721** Chronic liver failure<br>**K729** Liver failure, not elsewhere classified | |
| **Hepatitis** | **B15x** Acute hepatitis A<br>**B16x** Acute hepatitis B<br>**B17x** Other acute viral hepatitis<br>**B19x** Unspecified viral hepatitis | Half a year prior cohort entry |
| | **B18x** Chronic viral hepatitis | Any time prior cohort entry |
| **Mild chronic kidney disease** | **N181** Chronic kidney disease stage 1<br>**N1881** Chronic kidney disease stage 1<br>**N182** Chronic kidney disease stage 2<br>**N1882** Chronic kidney disease 2<br>**N18** Chronic kidney disease<br>**N188x** Other chronic kidney disease<br>**N1880** Unilateral chronic kidney disease<br>**N1889** Chronic non-terminal kidney disease, stage unspecified<br>**N189** Chronic kidney failure, unspecified<br>**N19** Unspecified kidney failure | Any time prior cohort entry |
| **Moderate/ severe chronic kidney disease** | **N180** Terminal kidney failure<br>**N183** Chronic kidney disease, stage 3<br>**N184** Chronic kidney disease, stage 4<br>**N185** Chronic kidney disease, stage 5<br>**N1883** Chronic kidney failure, stage III<br>**N1884** Chronic kidney failure, stage IV<br>**8-853*** Hemofiltration<br>**8-854*** Hemodialysis<br>**8-855*** Hemodiafiltration<br>**8-856*** Hemoperfusion<br>**8-857*** Peritoneal dialysis | Any time prior cohort entry |
| **Other chronic kidney failure** | **N189** Chronic kidney failure, unspecified | Any time prior cohort entry |
| **Hyperglycemia** | **R73** Elevated blood glucose level | Half a year prior cohort entry |
| **Hypoglycemia** | **E15** Hypoglycemic coma, nondiabetic<br>**E160** Drug-induced hypoglycemia without coma<br>**E161** Other hypoglycemia<br>**E162** Hypoglycemia, unspecified | Half a year prior cohort entry |
| **Electrolyte abnormalities** | **E834** Disorders of magnesium metabolism<br>**E871** Hypo-osmolality and hyponatremia<br>**E876** Hypokalemia | Half a year prior cohort entry |
| **Rare disorders** | **I677** Cerebral arteritis, not elsewhere classified<br>**M30x** Panarteritis nodosa and related conditions<br>**P90** Convulsions of newborn<br>**R560** Febrile convulsions<br>**E752** Other sphingolipidosis<br>**E76x** Disorders of glycosaminoglycan metabolism<br>**E802** Other porphyria<br>**F842** Rett's syndrome<br>**Q850** Neurofibromatosis (nonmalignant)<br>**Q851** Tuberous (brain) sclerosis<br>**Q90x** Down syndrome<br>**Q91x** Edwards syndrome and Patau syndrome<br>**Q932** Ring chromosome and dicentric chromosome<br>**Q933** Deletion of short arm of chromosome 4<br>**Q935** Other deletions of part of a chromosome<br>**Q992** Fragile X chromosome | Any time prior cohort entry |
| | **R392** Extrarenal uremia | Half a year prior cohort entry |
| **Medications** | **Codes (ATC)** | **Measurement period** |
| **Antipsychotics and antidepressants** | **N07BA02** Bupropion<br>**A08AA62** Bupropion and naltrexone<br>**N05A** ANTIPSYCHOTICS<br>**N06A** ANTIDEPRESSANTS | Half a year prior index date |
| **Benzodiazepine derivatives** | **N05BA** Benzodiazepine derivatives<br>**N05CD** Benzodiazepine derivatives<br>**N03AE** Benzodiazepine derivatives | Half a year prior index date |
| **Antiepileptic drugs** | **N03AA** Barbiturates and derivatives<br>**N03AB02** Phenytoin<br>**N03AB52** Phenytoin, combinations<br>**N03AF01** Carbamazepine<br>**N03AF02** Oxcarbazepine | Half a year prior index date |
| **Antibiotics** | **J01** ANTIBACTERIALS FOR SYSTEMIC USE<br>**A02BD** Combinations for eradication of Helicobacter pylori<br>**P01AB01** Metronidazole<br>**P01AB51** Metronidazole, combinations<br>**A01AB17** Metronidazole<br>**G01AF01** Metronidazole<br>**J04AB02** Rifampicin<br>**J04AB04** Rifabutin | Half a year prior index date |

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| | **J04AC01** Isoniazid<br>**J04AC51** Isoniazid, combinations<br>**J04AK01** Pyrazinamide<br>**J04AM** Combinations of drugs for treatment of tuberculosis | |
| **Virustatics** | **S01AD03** Aciclovir<br>**S01AD09** Ganciclovir<br>**J05AB01** Aciclovir<br>**J05AB06** Ganciclovir<br>**J05AB11** Valaciclovir<br>**J05AB12** Cidofovir<br>**J05AD01** Foscarnet | Half a year prior index date |
| **Other antiinfectives** | **A01AB04** Amphotericin B<br>**A07AA07** Amphotericin B<br>**G01AA03** Amphotericin B<br>**J02AA01** Amphotericin B<br>**J05AC04** Amantadin<br>**N04BB01** Amantadin | Half a year prior index date |
| **Cardiovasular system** | **C01A** CARDIAC GLYCOSIDES<br>**C01B** ANTIARRHYTHMICS, CLASS I AND III<br>**C01D** VASODILATORS USED IN CARDIAC DISEASES<br>**C07** Beta blocking agents<br>**C08** CALCIUM CHANNEL BLOCKERS | Any time prior cohort entry |
| **Immuno-suppressants** | **L04A** IMMUNOSUPPRESSANTS<br>**S01XA18** Ciclosporin | Half a year prior index date |
| **CYP-/P-glycoprotein inhibitors** | **C09DX02** Valsartan and aliskiren<br>**C09XA02** Aliskiren<br>**C09XA52** Aliskiren and hydrochlorothiazide<br>**C09XA53** Aliskiren and amlodipine<br>**C09XA54** Aliskiren, amlodipine and hydrochlorothiazide<br>**C01BD01** Amiodarone<br>**J05AE05** Amprenavir<br>**R05GB07** Erythromycin, combinations<br>**J01FA15** Telithromycin<br>**J01FA01** Erythromycin<br>**J01FA09** Clarithromycin<br>**J01RA10** Ciprofloxacin and metronidazole<br>**A02BA01** Cimetidine<br>**A02BA51** Cimetidine, combinations<br>**R06AX11** Astemizole<br>**C10AA05** Atorvastatin<br>**C10BA05** Atorvastatin and ezetimibe<br>**C10BA08** Atorvastatin and omega-3 fatty acids<br>**C10BX03** Atorvastatin and amlodipine<br>**C10BX11** Atorvastatin, amlodipine and perindopril<br>**C10BX15** Atorvastatin and perindopril<br>**C08EA02** Bepridil<br>**C07AG02** Carvedilol<br>**C07BG02** Carvedilol und Thiazide<br>**C07FX06** Carvedilol and ivabradine<br>**C01BA01** Quinidine<br>**C01BA51** Quinidine, combinations excl. psycholeptics<br>**C01BA71** Quinidine, combinations with psycholeptics<br>**C08DA81** Verapamil in combination with quinidine<br>**J01MA02** Ciprofloxacin<br>**J01MA06** Norfloxacin<br>**J01BA01** Chloramphenicol<br>**J01BA51** Chloramphenicol, combinations<br>**N05AA01** Chlorpromazine<br>**A02BD04** Pantoprazole, amoxicillin and clarithromycin<br>**A02BD05** Omeprazole, amoxicillin and clarithromycin<br>**A02BD06** Esomeprazole, amoxicillin and clarithromycin<br>**A02BD07** Lansoprazole, amoxicillin and clarithromycin<br>**A02BD09** Lansoprazole, clarithromycin and tinidazole<br>**A02BD12** Rabeprazole, amoxicillin, clarithromycin<br>**A02BD14** Vonoprazan, amoxicillin, clarithromycin<br>**C05AE03** Diltiazem<br>**C08DB01** Diltiazem<br>**B01AC07** Dipyridamole<br>**B01AC36** Dipyridamole and acetylsalicylic acid<br>**C01DX22** Dipyridamole<br>**C01DX72** Dipyridamole, combinations<br>**N07BB01** Disulfiram<br>**P03AA04** Disulfiram<br>**P03AA54** Disulfiram, combinations<br>**D04AX01** Doxepin<br>**N06AA12** Doxepin<br>**C01BD07** Dronedarone | Half a year prior index date |

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| | **B01AC86** Esomeprazole and acetylsalicylic acid<br>**M01AE52** Naproxen and esomeprazole<br>**J02AC01** Fluconazole<br>**J01RA07** Azithromycin, fluconazole and secnidazole<br>**N05AB02** Fluphenazine<br>**N05AD01** Haloperidol<br>**A01AC03** Hydrocortisone<br>**A07EA02** Hydrocortisone<br>**C05AA01** Hydrocortisone<br>**C05AA51** Hydrocortisone, combinations<br>**H02AB09** Hydrocortisone<br>**R01AD60** Hydrocortisone, combinations<br>**L04AD02** Tacrolimus<br>**L04AD01** Ciclosporin<br>**S01XA18** Ciclosporin<br>**J02AC02** Itraconazole<br>**J02AB02** Ketoconazole<br>**A07DA03** Loperamide<br>**A07DA05** Loperamide oxide<br>**A07DA53** Loperamide, combinations<br>**C10AA02** Lovastatin<br>**C10BA01** Lovastatin and Nicotinic acid<br>**P01BC02** Mefloquine<br>**P01BF02** Artesunate and mefloquine<br>**A02BD01** Omeprazole, amoxicillin and metronidazole<br>**A02BD11** Pantoprazole, Amoxicillin, Clarithromycin und Metronidazole<br>**C08CA04** Nicardipine<br>**C07FB03** Atenolol and nifedipine<br>**C07FB22** Metoprolol and nifedipine<br>**C07FB26** Acebutolol and nifedipine<br>**C08CA05** Nifedipine<br>**C08CA55** Nifedipine, combinations<br>**C08GA01** Nifedipine and diuretics<br>**J01MA01** Ofloxacin<br>**J01RA09** Ofloxacin and ornidazole<br>**S01AA17** Erythromycin<br>**G03DA04** Progesterone<br>**G03DD01** Progesterone<br>**G03FA04** Progesterone and estrogen<br>**C01BC03** Propafenone<br>**C07AA05** Propranolol<br>**C07BA05** Propranolol and thiazides<br>**C07CA05** Propranolol and other diuretics<br>**C07DA25** Propranolol, hydrochlorothiazide and triamterene<br>**C07EA05** Propranolol and vasodilators<br>**C07FX01** Propranolol and other combinations<br>**J05AE02** Indinavir<br>**J05AE01** Saquinavir<br>**J05AE03** Ritonavir<br>**J05AE04** Nelfinavir<br>**J05AE09** Tipranavir<br>**A10BH52** Gemigliptin and rosuvastatin<br>**C10AA07** Rosuvastatin<br>**C10BA06** Rosuvastatin and ezetimibe<br>**C10BA07** Rosuvastatin and omega-3 fatty acids<br>**C10BX05** Rosuvastatin and acetylsalicylic acid<br>**C10BX07** Rosuvastatin, amlodipine and lisinopril<br>**C10BX09** Rosuvastatin and amlodipine<br>**C10BX10** Rosuvastatin and valsartan<br>**C10BX13** Rosuvastatin, perindopril and indapamide<br>**C10BX14** Rosuvastatin, amlodipine and perindopril<br>**C10BX16** Rosuvastatin and fimasartan<br>**J01FA06** Roxithromycin<br>**C10BX06** Atorvastatin, acetylsalicylic acid and ramipril<br>**C10BX08** Atorvastatin and acetylsalicylic acid<br>**C10BX12** Atorvastatin, acetylsalicylic acid and perindopril<br>**A10BH51** Sitagliptin and simvastatin<br>**C10AA01** Simvastatin<br>**C10BA02** Simvastatin and ezetimibe<br>**C10BA04** Simvastatin and fenofibrate<br>**C10BX01** Simvastatin and acetylsalicylic acid<br>**C10BX04** Simvastatin, acetylsalicylic acid and ramipril<br>**N06AX06** Nefazodone<br>**N06AB08** Fluvoxamine<br>**C07AB13** Talinolol<br>**L02BA01** Tamoxifen | |

| | | |
|---|---|---|
| | **C09BB10** Trandolapril and verapamil<br>**C08DA01** Verapamil<br>**C08DA51** Verapamil, combinations<br>**C08DA81** Verapamil, combinations with quinidine<br>**C08GA23** Verapamil and hydrochlorothiazide<br>**C08GA53** Verapamil, hydrochlorothiazide and triamterene<br>**J02AC03** Voriconazole | |
| **CYP inducer** | **N06AP01** St. John's wort<br>**N06AP51** St. John's wort, combinations<br>**J04AB02** Rifampicin<br>**J04AB04** Rifabutin<br>**J04AM02** Rifampicin and isoniazid<br>**J04AM05** Rifampicin, pyrazinamide and isoniazid<br>**J04AM06** Rifampicin, pyrazinamide, ethambutol and isoniazid<br>**J04AM07** Rifampicin, ethambutol and isoniazid | Half a year prior index date |
| **Other drugs** | **N06DA53** Donepezil, memantine and Ginkgo folium<br>**N06DP01** Ginkgo folium<br>**N06DX02** Ginkgo folium<br>**N02AB02** Pethidine<br>**N02AB52** Pethidine, combinations excl. psycholeptics<br>**N02AB72** Pethidine, combinations with psycholeptics<br>**N02AG03** Pethidine and antispasmodics<br>**N02AJ13** Tramadol and paracetamol<br>**N02AJ14** Tramadol and dexketoprofen<br>**N02AJ15** Tramadol and other non-opioid analgesics<br>**N02AX02** Tramadol<br>**R03DA04** Theophylline<br>**R03DA54** Theophylline, combinations excl. psycholeptics<br>**R03DA74** Theophylline, combinations with psycholeptics<br>**R03DB04** Theophylline and adrenergics<br>**C01EB28** Theophylline<br>**C01EX66** Theophylline, combinations | Half a year prior index date |

**Supplementary Table 2.** Baseline characteristics of patients with venous thromboembolism (VTE) starting oral anticoagulation.

| **Characteristics** | **PPC N=60,488** | **DOAC N=89,030** | **Apixaban N=17,807** | **Dabigatran N=1,885** | **Edoxaban N=3,759** | **Rivaroxaban N=65,579** |
|---|---|---|---|---|---|---|
| Male sex | 28,155 (46.5%) | 40,410 (45.4%) | 8,103 (45.5%) | 852 (45.2%) | 1,699 (45.2%) | 29,756 (45.4%) |
| Age[a] | 66 (52, 76) | 64 (50, 75) | 66 (52, 77) | 67 (53, 77) | 65 (53, 77) | 63 (50, 75) |
| $CHA_2DS_2VASc$[a,b] | 4.00 (3.00, 6.00) | 4.00 (2.00, 6.00) | 4.00 (3.00, 6.00) | 4.00 (3.00, 6.00) | 4.00 (3.00, 6.00) | 4.00 (2.00, 5.00) |
| 0 | 1,833 (3.0%) | 4,105 (4.6%) | 773 (4.3%) | 57 (3.0%) | 123 (3.3%) | 3,152 (4.8%) |
| 1 | 3,745 (6.2%) | 7,896 (8.9%) | 1,491 (8.4%) | 127 (6.7%) | 263 (7.0%) | 6,015 (9.2%) |
| 2 | 7,204 (11.9%) | 11,932 (13.4%) | 2,185 (12.3%) | 215 (11.4%) | 453 (12.1%) | 9,079 (13.8%) |
| 3 | 11,325 (18.7%) | 17,184 (19.3%) | 3,135 (17.6%) | 326 (17.3%) | 732 (19.5%) | 12,991 (19.8%) |
| 4 | 9,719 (16.1%) | 13,368 (15.0%) | 2,606 (14.6%) | 269 (14.3%) | 543 (14.4%) | 9,950 (15.2%) |
| 5 | 8,775 (14.5%) | 11,577 (13.0%) | 2,329 (13.1%) | 264 (14.0%) | 526 (14.0%) | 8,458 (12.9%) |
| 6 | 7,760 (12.8%) | 9,822 (11.0%) | 2,081 (11.7%) | 252 (13.4%) | 481 (12.8%) | 7,008 (10.7%) |
| 7 | 5,682 (9.4%) | 7,238 (8.1%) | 1,707 (9.6%) | 201 (10.7%) | 332 (8.8%) | 4,998 (7.6%) |
| 8 | 3,337 (5.5%) | 4,471 (5.0%) | 1,097 (6.2%) | 123 (6.5%) | 245 (6.5%) | 3,006 (4.6%) |
| 9 | 1,108 (1.8%) | 1,437 (1.6%) | 403 (2.3%) | 51 (2.7%) | 61 (1.6%) | 922 (1.4%) |
| HAS-BLED[a,c] | 2.00 (1.00, 3.00) | 2.00 (1.00, 3.00) | 2.00 (1.00, 4.00) | 2.00 (1.00, 4.00) | 2.00 (1.00, 3.00) | 2.00 (1.00, 3.00) |
| **Selected medical history any time before initiation of anticoagulant therapy** | | | | | | |
| Intracerebral bleeding (I61x) | 126 (0.2%) | 257 (0.3%) | 70 (0.4%) | 20 (1.1%) | 11 (0.3%) | 156 (0.2%) |
| Ischemic stroke | 3,045 (5.0%) | 4,436 (5.0%) | 1,151 (6.5%) | 168 (8.9%) | 181 (4.8%) | 2,936 (4.5%) |
| Transient ischemic attack | 1,114 (1.8%) | 1,431 (1.6%) | 325 (1.8%) | 56 (3.0%) | 64 (1.7%) | 986 (1.5%) |
| Deep vein thrombosis | 26,714 (44.2%) | 28,505 (32.0%) | 5,453 (30.6%) | 654 (34.7%) | 1,350 (35.9%) | 21,048 (32.1%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Pulmonary embolism | 20,526 (33.9%) | 27,613 (31.0%) | 6,305 (35.4%) | 618 (32.8%) | 944 (25.1%) | 19,746 (30.1%) |
| CAD including myocardial infarction | 16,795 (27.8%) | 21,580 (24.2%) | 4,731 (26.6%) | 577 (30.6%) | 907 (24.1%) | 15,365 (23.4%) |
| Hypertension | 40,578 (67.1%) | 56,505 (63.5%) | 11,906 (66.9%) | 1,303 (69.1%) | 2,497 (66.4%) | 40,799 (62.2%) |
| Heart failure | 13,560 (22.4%) | 18,011 (20.2%) | 4,384 (24.6%) | 488 (25.9%) | 824 (21.9%) | 12,315 (18.8%) |
| Peripheral arterial disease | 13,599 (22.5%) | 18,608 (20.9%) | 4,352 (24.4%) | 450 (23.9%) | 851 (22.6%) | 12,955 (19.8%) |
| Diabetes | 14,435 (23.9%) | 19,693 (22.1%) | 4,378 (24.6%) | 482 (25.6%) | 896 (23.8%) | 13,937 (21.3%) |
| COPD | 11,768 (19.5%) | 16,085 (18.1%) | 3,563 (20.0%) | 417 (22.1%) | 695 (18.5%) | 11,410 (17.4%) |
| Liver disease | 16,074 (26.6%) | 23,230 (26.1%) | 5,030 (28.2%) | 517 (27.4%) | 1,064 (28.3%) | 16,619 (25.3%) |
| Renal disease | 11,642 (19.2%) | 14,424 (16.2%) | 3,787 (21.3%) | 345 (18.3%) | 707 (18.8%) | 9,585 (14.6%) |
| Chronic kidney disease [CKD≥3] | 10,241 (16.9%) | 12,090 (13.6%) | 3,210 (18.0%) | 278 (14.7%) | 585 (15.6%) | 8,017 (12.2%) |
| Alcohol abuse | 1,835 (3.0%) | 2,504 (2.8%) | 505 (2.8%) | 60 (3.2%) | 99 (2.6%) | 1,840 (2.8%) |
| Smoking | 4,644 (7.7%) | 6,847 (7.7%) | 1,411 (7.9%) | 117 (6.2%) | 297 (7.9%) | 5,022 (7.7%) |
| **Selected medication any time before initiation of anticoagulant therapy** | | | | | | |
| Antiarrhythmic drugs | 607 (1.0%) | 521 (0.6%) | 105 (0.6%) | 35 (1.9%) | 24 (0.6%) | 357 (0.5%) |
| Antihypertensive drugs | 31,401 (51.9%) | 43,216 (48.5%) | 9,326 (52.4%) | 1,031 (54.7%) | 1,926 (51.2%) | 30,933 (47.2%) |
| Antiplatelet drugs | 9,449 (15.6%) | 12,454 (14.0%) | 2,961 (16.6%) | 376 (19.9%) | 550 (14.6%) | 8,567 (13.1%) |
| NSAID | 50,290 (83.1%) | 76,028 (85.4%) | 15,451 (86.8%) | 1,614 (85.6%) | 3,257 (86.6%) | 55,706 (84.9%) |
| Proton pump inhibitor | 25,834 (42.7%) | 38,080 (42.8%) | 7,981 (44.8%) | 908 (48.2%) | 1,565 (41.6%) | 27,626 (42.1%) |
| Corticosteroids | 10,945 (18.1%) | 16,000 (18.0%) | 3,325 (18.7%) | 359 (19.0%) | 699 (18.6%) | 11,617 (17.7%) |

Values are numbers (percentages) unless stated otherwise

[a] Median (IQR)

[b] $CHA_2DS_2VASc$ score: congestive heart failure (1 Point); hypertension (1 Point); aged ≥ 75 years (2 Points); diabetes mellitus (1 Point); stroke/transient ischaemic attack (2 Points); vascular disease (1 Point), aged 65–74 years (1 Point), female sex (1 Point).

[c] HAS-BLED sum score: hypertension (1 Point), abnormal renal or liver function (each 1 Point), previous stroke (1 Point), bleeding history or predisposition (anemia) (1 Point), Elderly (> 65 years) (1 Point), Drugs (other antiplatelet agents or NSAIDs) or alcohol (each 1 Point), Labile INR not included.

**Abbreviations:** *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *DOAC* direct oral anticoagulant, *IQR* interquartile range, *NSAID* nonsteroidal anti-inflammatory drug, *PPC* Phenprocoumon. *SD* standard deviation, *VTE* venous thromboembolism.

**Supplementary Table 3.** Distribution of tablet sizes of DOACs among cases and controls.

| DOAC | Cases | | | Controls | | |
|---|---|---|---|---|---|---|
| | Total N | Tablet size (mg) | N (%) | Total N | Tablet size (mg) | N (%) |
| Apixaban | 433 | 2.5 | 162 (37.4) | 3,034 | 2.5 | 948 (31.2) |
| | | 5 | 271 (62.6) | | 5 | 2,086 (68.8) |
| Dabigatran | 188 | 75 | 2 (1.1) | 1,603 | 75 | 20 (1.2) |
| | | 110 | 104 (55.3) | | 110 | 872 (54.4) |
| | | 150 | 82 (43.6) | | 150 | 711 (44.4) |
| Edoxaban | 27 | 30 | 11 (40.7) | 381 | 30 | 103 (27.0) |
| | | 60 | 16 (59.3) | | 60 | 278 (73.0) |
| Rivaroxaban | 617 | 2.5 | 0 | 6,362 | 2.5 | 1 (0.0) |
| | | 10.0 | 13 (2.1) | | 10.0 | 78 (1.2) |
| | | 15.0 | 231 (37.4) | | 15.0 | 1,873 (29.4) |
| | | 20.0 | 373 (60.5) | | 20.0 | 4,410 (69.3) |

**Supplementary Table 4.** Evaluation of DOAC tablet sizes taking into consideration renal impairment. Highlighted in green are those cases and controls treated with the recommended dose for the indication atrial fibrillation as indicated by the tablet size. Written in **bold** font are tablet sizes indicating the recommended doses. If applicable, tablet sizes written in *italic* font are indicating the recommended dose reductions in patients with renal impairment.

| DOAC | Cases | | | | Controls | | | |
|---|---|---|---|---|---|---|---|---|
| | Total N | Tablet size (mg) | Renal impairment | N (%) | Total N | Tablet size (mg) | Renal impairment | N (%) |
| Apixaban | 433 | 2.5 | | 162 (37.4) | 3,034 | 2.5 | | 948 (31.2) |
| | | **5** | | 271 (62.6) | | **5** | | 2,086 (68.8) |
| Dabigatran | 188 | 75 | | 2 (1.1) | 1,603 | 75 | | 20 (1.2) |
| | | *110* | no | 76 (40.4) | | *110* | no | 672 (41.9) |
| | | | yes | 28 (14.9) | | | yes | 200 (12.5) |
| | | **150** | | 82 (43.6) | | **150** | | 711 (44.4) |
| Edoxaban | 27 | *30* | no | 2 (7.4) | 381 | *30* | no | 48 (12.6) |
| | | | yes | 9 (33.3) | | | yes | 55 (14.4) |
| | | **60** | | 16 (59.3) | | **60** | | 278 (73.0) |
| Rivaroxaban | 617 | 2.5 | | 0 | 6,362 | 2.5 | | 1 (0.0) |
| | | 10 | | 13 (2.1) | | 10 | | 78 (1.2) |
| | | *15* | no | 128 (20.7) | | *15* | no | 1,139 (17.9) |
| | | | yes | 103 (16.7) | | | yes | 734 (11.5) |
| | | **20** | | 373 (60.5) | | **20** | | 4,410 (69.3) |

**Supplementary Table 5.** Estimated risk of epilepsy/seizures: main analysis in the subgroups of patients with recommended DOAC dosing and with low DOAC dosing as indicated by the tablet size.

| | **Cases N= 1,828** | **Controls N= 19,084** | **Crude odds ratio (95% CI)** | **Adjusted odds ratio (95% CI)** |
|---|---|---|---|---|
| **PPC** | 563 | 7,704 | Reference | Reference |
| ***Recommended DOAC dosing as indicated by the tablet size*** | | | | |
| **Any DOAC** | 882 | 8,474 | 1.43 (1.28 - 1.60) | 1.30 (1.16 - 1.47) |
| **Apixaban** | 271 | 2,086 | 1.79 (1.53 - 2.09) | 1.59 (1.35 - 1.87) |
| **Dabigatran** | 110 | 911 | 1.65 (1.33 - 2.05) | 1.34 (1.06 - 1.68) |
| **Edoxaban** | 25 | 333 | 1.05 (0.69 - 1.60) | 1.07 (0.69 - 1.65) |
| **Rivaroxaban** | 476 | 5,144 | 1.27 (1.12 - 1.45) | 1.19 (1.04 - 1.36) |
| ***Low DOAC dosing as indicated by the tablet size*** | | | | |
| **Any DOAC** | 383 | 2,906 | 1.81 (1.54 - 2.14) | 1.56 (1.29 - 1.89) |
| **Apixaban** | 162 | 948 | 2.42 (1.92 - 3.05) | 1.73 (1.33 - 2.25) |
| **Dabigatran** | 78 | 692 | 1.44 (1.08 - 1.91) | 1.38 (1.00 - 1.90) |
| **Edoxaban** | 2 | 48 | 0.93 (0.21 - 4.20) | 0.61 (0.12 - 3.06) |
| **Rivaroxaban** | 141 | 1,218 | 1.64 (1.31 - 2.06) | 1.55 (1.19 - 2.02) |

**Supplementary Table 6.** AF ablation procedures after cohort entry and prior to the diagnosis of epilepsy/seizures (cases) or the matched index date (controls).

| | Cases (N = 1,828) | | Controls (N = 19,084) | |
|---|---|---|---|---|
| | **N** | **%** | **N** | **%** |
| AF ablation procedure | 29 | 1.6 | 372 | 1.9 |

**Supplementary Table 7.** Patients with a history of epilepsy at study entry were excluded. The history of epilepsy was based on the outpatient or hospital diagnoses anytime before cohort entry containing the following ICD-10-GM codes.

| **ICD-10-GM codes** | |
|---|---|
| G40 | Epilepsy |
| G400 | Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset |
| G4000 | Pseudo-Lennox syndrome |
| G4001 | CSWS [Continuous spikes and waves during slow-wave sleep] |
| G4002 | Benign psychomotor epilepsy [terror fits] |
| G4008 | Other localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset |
| G4009 | Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, unspecified |
| G401 | Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures |
| G402 | Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures |
| G403 | Generalized idiopathic epilepsy and epileptic syndromes |
| G404 | Other generalized epilepsy and epileptic syndromes |
| G405 | Special epileptic syndromes |
| G406 | Grand mal seizures, unspecified (with or without petit mal) |
| G407 | Petit mal seizures, unspecified, without grand mal seizures |
| G408 | Other epilepsy |
| G409 | Epilepsy, unspecified |
| G41 | Status epilepticus |
| G410 | Grand mal status |
| G411 | Petit mal status |
| G412 | Status epilepticus with complex partial seizures |
| G418 | Other status epilepticus |
| G419 | Status epilepticus, unspecified |
| R568 | Other and unspecified convulsions |

## Supplementary Figures

**Supplementary Figure 1.** Distribution of baseline $CHA_2DS_2$-VASc scores in cases and controls on current treatment with a DOAC or PPC.