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TITLE: Oral Anticoagulant and Reduced Risk of Dementia in Patients with Atrial Fibrillation: A Population-Based Cohort Study

SHORT TITLE: Oral Anticoagulant and Risk of Dementia

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Word count: 4997 words with 2 tables and 2 figures

Abstract

Background: It remains unclear whether oral anticoagulation (OAC) can prevent dementia or cognitive impairment (CI) in patients with atrial fibrillation (AF).

Objective: To investigate the risk of dementia/CI among AF patients with and without OAC treatment.

Methods: We conducted a retrospective cohort study using UK primary care data (2000-2017). Participants with newly diagnosed AF without a history of dementia/CI were identified. Inverse probability of treatment weights based on propensity-scores and Cox regression were used to compare the dementia outcomes.

Results: Among 84,521 patients with AF, 35,245 patients were on OAC treatment, 49,276 received no OAC treatment and of these, 29,282 patients were on antiplatelets. Over a mean follow-up of 5.9 years, 5,295 patients developed dementia/CI. OAC treatment was associated with a lower risk of dementia/CI compared to no OAC treatment (hazard ratio (HR) 0.90, 95% confidence interval (CI), 0.85-0.95, $p<0.001$) or antiplatelets (HR=0.84, 95% CI=0.79-0.90, $p<0.001$). No significant difference in dementia risk was observed for direct oral anticoagulants (DOACs) versus warfarin (HR 0.89, 95% CI, 0.70-1.14, $p=0.373$), whereas dual therapy (OAC plus an antiplatelet agent) was associated with a higher risk of dementia/CI compared with no treatment (HR 1.17, 95% CI, 1.05-1.31), $p=0.006$).

Conclusion: OAC use was associated with a lower risk of dementia/CI compared to non-OAC and antiplatelet treatment among AF patients. The evidence for DOAC on cognitive function is insufficient and further studies including randomized clinical trials are warranted.

Keywords: atrial fibrillation, oral anticoagulant, dementia, cognitive impairment, vascular dementia

INTRODUCTION

Atrial fibrillation (AF) is associated with an increased risk of stroke,[1] and dementia is a common consequence of stroke. However, recent evidence suggests that AF is a risk factor for dementia independent of ischemic stroke.[2] Silent cerebral infarct (SCI) is one of the possible mechanisms that has been proposed[3] and it is hypothesized that oral anticoagulant (OAC) could reduce the development of SCI and subsequently reduce the risk of dementia or cognitive impairment (CI) in AF patients.

Existing studies investigating the use of OAC and dementia have conflicting results.[4,5] A previous review demonstrated that OAC use is associated with a reduced risk of dementia in AF patients compared to non-OAC users.[6] However, the results were limited by confounders and heterogeneity of included studies. The previous review found that all previous studies which examined the risk of dementia with OAC use included the very early development of dementia after treatment commencement.[6] As progression to dementia is a gradual process, dementia diagnosed shortly after treatment commencement were unlikely to be related to the treatment effect. Therefore, it remains uncertain whether the observations from previous studies were driven by the effects of OACs or existing baseline differences between the treatment groups. It has also been reported that physicians are less likely to prescribe OACs to patients with dementia compared to those with normal cognitive status.[7] This could lead to confounding by indication.[6] Importantly, the effects of direct oral anticoagulants (DOACs) on dementia remains ill-defined. Therefore, this study aimed to compare the risk of dementia/CI between OAC users and non-users, OAC users compared to antiplatelet users, DOACs compared to warfarin, and dual therapy compared to no treatment in AF patients.

METHODS

Data source

This study used The Health Improvement Network (THIN) database, which comprises primary care electronic health records of the United Kingdom (UK). Anonymized data recorded in THIN include patient demographics, prescribing information, and medical conditions. THIN database has been extensively validated and used to study dementia.[8,9]

The study protocol was approved by the THIN Scientific Review Committee (reference number 18THIN055). Informed consent was waived for this secondary analysis of routinely collected data.

Selection of patients

A population-based cohort study from January 1, 2000 and September 26, 2017 was conducted. Patients were included if they were aged ≥ 18 years and had a first ever AF diagnosis (Supplemental Table S1). Patients diagnosed with valvular heart disease and transient causes of AF (hyperthyroidism, pericarditis or myocarditis) were excluded, as were patients with less than 12-month of medical history prior to the first AF diagnosis. Patients were also excluded if they died during their first AF episode, received OAC within one-year prior to the first AF diagnosis, prescribed more than one OAC simultaneously at any time during the study period, had a record of dementia/CI or prescribed anti-dementia drugs, had a history of brain tumor, brain infection, head injury, epilepsy, schizophrenia, intellectual disability, autism, multiple sclerosis, or Parkinson's disease prior to, or on, the index date. Patients who had been diagnosed with dementia/CI less than one-year after the index date were also excluded as they were most likely prevalent cases due to a prodromal phase prior to dementia onset.[10,11] Further, people who had less than one-year of follow-up were excluded (Figure 1).

Exposure and outcome definitions

130   To handle immortal time bias, we used the landmark method which establishes a point

131   in time after AF diagnosis. We considered that point as the index date. The index date was

132   defined as day 60 after the first AF diagnosis. OAC prescriptions are issued by the primary

133   care physician except when the OAC is started in hospital. This 60-day period is used to

134   account for the transfer of OAC prescribing from hospital to primary care.[12] The exposure of

135   interest was the initiation of OACs within 60-days after AF diagnosis. The non-exposure was

136   defined as patients who did not receive OACs within the 60-day window. OACs included

137   warfarin and DOACs (dabigatran, rivaroxaban, apixaban or edoxaban). Subgroup

138   comparisons were made: i) warfarin versus non-OAC, ii) DOACs versus non-OAC, iii) OAC

139   versus antiplatelet, iv) DOACs versus warfarin, and v) dual therapy (OAC plus one

140   antiplatelet) versus no treatment. Patients were categorized as antiplatelet users if they filled a

141   single prescription for aspirin, clopidogrel, prasugrel, or ticagrelor during the initial 60-day

142   period. For DOACs versus warfarin, and DOACs versus non-OAC, only patients diagnosed

143   with AF from 2011 onwards were included, as DOACs were first approved for stroke

144   prevention in AF from August 2011 in the UK. Dual therapy users were defined as patients

145   who concurrently received OAC and antiplatelet during the 60-day period.

146   The outcome was the composite of new-onset dementia/CI, defined as the recording

147   of any Read codes for dementia/CI or the prescription of antidementia drugs (Supplemental

148   Table S2).[13-15]

149   **Baseline covariates**

150   Factors associated with developing dementia were included as covariates

151   (Supplemental Table S3).[16] All baseline covariates and risk-stratification of

152   thrombosis/bleeding were evaluated within one year before or on index date.

153   **Statistical analysis**

154   Baseline characteristics were presented descriptively. Crude incidence rates were

155   expressed as rates per 1000 person-years. Person-time at risk was calculated from one-year

156   after the treatment ascertainment period, because dementia/CI in the first year would unlikely

157   be related to treatment effects and were excluded from the analyses.[11] Propensity score (PS)

158   with inverse probability of treatment weighting (IPTW) was used to estimate population

159   average treatment effects (Supplemental Method 1).[17] Absolute standardized differences were

160   estimated to assess covariate balance before and after IPTW. A threshold of 0.1 was

161   considered negligible.[18] Cox proportional hazards regression was used to compare dementia

162   outcomes. Outcomes are reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

163   The primary analysis was undertaken analogously to the intention to treat approach based on

164   complete case analysis. The analysis was conducted according to the initial treatment,

165   regardless of subsequent changes to their exposure status.[4,19,20] We followed patients from

166   their index date until the development of dementia/CI, death, transfer out of the general

167   practice, or end of the study period, whichever came first.

168   **Subgroup and sensitivity analyses**

169   Pre-specified subgroup analyses were conducted with regard to the key patient

170   characteristics. Moreover, we investigated the association between OAC use and dementia

171   subtypes.

172   A set of sensitivity analyses were performed: (i) the "on-treatment" approach was

173   done to reduce exposure misclassification[4] (details are provided in the Supplemental Method

174   2)—in brief, patients who received OAC prescriptions covering 80% of the time at risk,

175   grouped as OAC users, and including patients who never received an OAC prescription as

176   non-OAC users; (ii) reanalyzing using extended exposure ascertainment periods (90, 120, and

177   180 days); (iii) PS trimming was conducted by excluding the 1st percentile of the PS

178   distribution in OAC-treated and the 99th percentile of the PS in non-OAC treated[21]; (iv) the

179 Fine and Gray sub-distribution hazard model[22] was performed to account for the competing

180 risk of death; (v) the missing data on alcohol consumption, smoking status, Townsend

181 deprivation and body mass index were imputed by the multiple imputation method[23]

182 (Supplemental Method 3); (vi) reanalyzing by including patients who developed dementia/CI

183 within one-year after the treatment ascertainment and those with less than one year of follow-

184 up; (vii) because vascular dementia (VaD) can be a relatively sudden disease, we repeated the

185 analysis by not excluding vascular dementia within the first year; and (viii) the E-value was

186 calculated to assess the robustness of the results to unmeasured confounding.[24]

187 All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

188 Two-tailed P-value of < 0.05 was considered statistically significant.

189

190 **RESULTS**

191 **Patient characteristics**

192 A total of 84,521 AF patients were included, 41.7% of whom were prescribed OACs

193 (Figure 1). At baseline, before IPTW, the proportion of individuals with prior history of

194 stroke/TIA/SE in OAC users was approximately two-fold those not prescribed OACs (9.3%

195 versus 4.2%). Non-OAC users were more likely to be prescribed antiplatelet drugs (59.4%

196 versus 27.8%). The baseline characteristics of OAC group and non-OAC group, and other

197 subgroup comparisons are shown in Supplemental Table S3-S8.

198 Over the 412,570 person-years at risk, 5,295 patients (6.3%) developed dementia/CI,

199 resulting in a crude incidence rate of 12.8 per 1,000 person-years (95% CI, 12.5-13.2). Over a

200 mean follow-up time of 5.9 years, the dementia/CI incidence rate in the OAC group and non-

201 OAC group was 12.1 and 13.3 per 1000 person-years, respectively (Table 1).

202 **Association between OAC use and risk of dementia/CI**

203 *OAC use versus non-OAC use*

204   After IPTW, OAC use was associated with a 10% lower risk of dementia/CI

205   compared to non-OAC use (HR 0.90, 95% CI, 0.85-0.95, $p<0.001$). For sub-analyses,

206   warfarin use was significantly associated with lower dementia/CI risk (HR 0.90, 95% CI,

207   0.85-0.95, $p <0.001$) than non-OAC use. For the DOAC and non-OAC comparison, there was

208   no statistically significant difference between groups with respect to the occurrence of

209   dementia/CI (HR 0.94, 95% CI, 0.74-0.19, $p=0.588$). Kaplan-Meier curves for the incidence

210   of dementia/CI are shown in Supplemental Figure S1.

211   *OAC use versus antiplatelet use*

212   During a mean follow-up time of 5.8 years (SD; 3.7), OAC use was significantly

213   associated with a 16% lower risk of dementia/CI compared to antiplatelet use (HR 0.84, 95%

214   CI, 0.79-0.90, $p<0.001$).

215   *DOAC use versus warfarin use*

216   For the direct comparison of DOACs and warfarin, there was no significant difference

217   in risk of developing dementia/CI (HR 0.89, 95% CI, 0.70-1.14, $p=0.373$).

218   *Dual therapy versus no treatment*

219   Dual therapy use was associated with increased risk of dementia/CI compared with no

220   treatment (HR 1.17, 95% CI, 1.05-1.31, $p=0.006$).

221   **Subgroup analysis**

222   OAC use compared to no treatment was significantly associated with lower risks of

223   VaD (HR 0.89, 95% CI, 0.80-0.99, $p=0.049$) and unspecified dementia (HR 0.74, 95% CI,

224   0.66-0.83, $p<0.001$), but not Alzheimer's disease (AD) (Table 2). An association of a lower

225   risk of dementia/CI with OAC use were consistently observed across all subgroups (Figure

226   2).

227   **Sensitivity analyses**

9

228   According to the set of sensitivity analyses, our results revealed almost identical to the

229   primary analysis (Supplemental Table S9-S13). However, we detected a significant

230   association between the use of DOACs versus non-OAC use and a lower risk of dementia/CI

231   when using different exposure ascertainment periods (Supplemental Table S14). Moreover,

232   when repeating the analysis including patients who developed dementia/CI or died during the

233   first year of treatment commencement, the results showed that OAC use was associated with

234   lower risk of dementia/CI compared to non-OAC use (Supplemental Table S15). The E-value

235   for the point estimate and upper confidence bound for dementia/CI were 1.46 and 1.29,

236   respectively (Supplemental Table S16).

237

238   **DISCUSSION**

239   This study demonstrated AF patients treated with OAC had a 10% lower risk of

240   dementia/CI compared to patients not receiving OAC. Risk of VaD and unspecified dementia

241   was also lower for OAC use compared to non-OAC use.

242   Our findings are in-line with previous studies using the Swedish[4] and Korean

243   database.[25] However, the effect estimate from the Swedish registry is much stronger

244   compared to our study result (HR 0.71 versus HR 0.90).[4] This could be explained by possible

245   channeling bias leading to detection of dementia within one year of AF diagnosis in the

246   Swedish study. Dementia cases occurring early during follow-up are most likely prevalent

247   cases due to a long prodromal phase prior to dementia diagnosis being recorded in data.[10,11]

248   This could ultimately lead to an overestimation of the protective effects of OAC in reducing

249   dementia risk. Our study addressed this limitation, by excluding likely prevalent dementia/CI

250   cases in the first year of follow up. Further, our study results support the hypothesis of SCI

251   contributing to cognitive dysfunction in AF. A population-based study indicated that SCI

252   visualized on MRI doubled the risk of dementia compared to those without evident SCI.[26]

253 Therefore, SCI could be a possible mechanism linking AF to cognitive decline. Indeed,

254 anticoagulation could prevent the development of SCI. In our present study, the benefit from

255 OAC was favorable in all subgroup populations. Our finding reaffirmed the previous study[27]

256 that the use of OAC was associated with a lower risk of dementia among low-risk AF patients

257 (CHA_2DS_2-VASc<2). Moreover, we expanded the existing evidence that the use of OAC is

258 likely to lower the risk of dementia among high-risk AF patients (CHA_2DS_2-VASc$\geq$2).

259 However, further studies are warranted to confirm our findings.

260 Our study found a significant association with OAC use and lower risk of VaD and

261 unspecified dementia compared to non-OAC use. AF may cause cerebral infarction including

262 SCI via embolic mechanisms of thrombus formation within heart chambers, which could

263 translate to increased risk of VaD.[28] Hence, it is biologically plausible that OAC could

264 prevent VaD by reducing cerebral infarction burden. By contrast, there was no statistically

265 significant association between OAC use and risk of AD.

266 Significant differences were observed for dementia/CI risk in OAC users compared

267 with antiplatelet users. Our results contradict previous findings, which found no difference in

268 cognitive function between warfarin and aspirin users.[5] The trial's follow-up period was

269 shorter than the mean follow-up time of our study, which could have hampered efforts to

270 detect significant differences. Furthermore, we found a trend towards DOAC treatment being

271 associated with reduced dementia/CI development compared to non-OAC use, but failed to

272 reach statistical significance. This might be due to the smaller sample sizes in DOAC group.

273 Nonetheless, our results by extending the ascertainment periods, DOAC users had a lower

274 risk of dementia/CI compared to non-OAC users. This demonstrated that there is an

275 uncertainty associated with DOAC users versus non-OAC users and the potential

276 misclassification bias cannot be eliminated. Therefore, the results of this comparison should

277 be interpreted with caution and further studies are needed to confirm the role of DOAC on the

278 risk of dementia/CI.

279   It has been hypothesized that DOACs could have superior neuroprotective effects

280 than warfarin in preventing dementia due to lower variability in anticoagulation control and

281 lower risks for intracranial bleeding.[1] However, our study did not demonstrate a significant

282 protective effect against dementia/CI development for DOAC treatment compared with

283 warfarin. However, a previous observational study[29] showed a significantly lower incidence

284 rate of dementia in DOAC compared to warfarin users, which is contrary to our findings.

285 Compared to our study, the previous study had a shorter follow-up time in DOAC (0.5 years

286 versus 2.2 years) and warfarin (0.8 years versus 3.8 years) groups and differences in baseline

287 characteristics of DOAC and warfarin users. DOAC users were younger and healthier than

288 warfarin users which could confound associations between treatment and outcomes.

289 However, our study results are in-line with a previous study[4] which demonstrated non-

290 statistically significant results with regards to dementia risk in DOAC versus warfarin.

291 Recently, among AF population in the United States, DOAC users had a lower risk of

292 dementia compared to warfarin users.[30] Nevertheless, data from a Danish population

293 demonstrated no significant different in dementia development between DOAC and warfarin

294 users, apart from those 80 years and older.[31] Therefore, considering our study results in the

295 context of currently available evidence, we highlight the need for future studies with longer

296 follow-up time and large sample sizes to understand DOAC treatment effects on dementia

297 compared to warfarin. At present, there are two ongoing RCTs that focus on the impact of

298 DOACs and warfarin on neurocognitive decline (ClinicalTrials.gov Identifier: NCT01994265

299 and NCT03061006).

300   Our study has several strengths. First, we conducted a population-based cohort which

301 represents the UK population with longer follow-up periods. Second, we excluded patients

302 who were diagnosed with dementia within the first year of treatment commencement, as they

303 were most likely prevalent cases. Third, our study filled the remaining knowledge gaps of

304 previous studies by investigating the association of OAC with dementia subtypes. Our study

305 also has some unique results such as no effect on Alzheimer's risk, which supports

306 mechanistic rationale of SCI. This is a critical issue that warrants further validating studies in

307 different populations. Fourth, we applied the landmark method which could help reduce

308 immortal time bias. This method performs well when the treatment effect is small which

309 applied to our study. However, the results could vary according to the landmark time and

310 choosing an appropriate landmark time should be based on the natural time of clinical

311 significance.[32] We conducted sensitivity analyses using different landmark times and the

312 results were consistent. Finally, we captured outpatient incidence cases using an extensively

313 studied and supported national database in the UK.

314   Our study has limitations. First, even though the process of PS IPTW accomplished

315 balanced patient characteristics between comparison groups, the possibility of residual

316 confounding cannot be excluded. We conducted a sensitivity analysis and calculated the E-

317 value (=1.46), which indicated that the observed HR of 0.90 for the incident of dementia/CI

318 could be explained away by an unmeasured confounder that was associated with both OAC

319 use and risk of dementia/CI by a HR of 1.46-fold each, above and beyond the measured

320 confounders, but weaker confounding could not do so.[24] Second, a previous systematic

321 review demonstrated a high percentage of time in therapeutic range (TTR) was associated

322 with a significantly decreased risk of dementia.[6] However, we were unable to accurately

323 measure anticoagulation control in our study, thus urge future studies to confirm the effects

324 of TTR and risk of dementia/CI. Third, we lacked information about diagnostic brain imaging

325 and autopsy to confirm the accuracy of dementia diagnosis. However, a validation study of

326 dementia recording reported a specificity of a general practice recorded dementia diagnosis of

327 83 % and no false negatives in a sample without recorded dementia.[33] Finally, our study is

328 lack of information regarding to medication adherence and information about over-the-

329 counter medications such as NSAIDs or aspirin. However, this may influence only the small

330 number of patients.

331 **CONCLUSIONS**

332   The use of OAC was associated with a lower risk of new onset dementia/CI. Indeed,

333 these results support the hypothesis that silent brain infarcts represent the mechanistic link

334 between AF and dementia. However, the evidence of DOAC treatment is currently

335 insufficient to make a conclusion whether it provides a neuroprotective effect on cognition in

336 patients with AF. A RCT may be required, or longer term follow-up of DOAC treated

337 patients to understand whether there are any differences in dementia risk between DOACs

338 and warfarin in AF.

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Figure Legends

Figure1. Identification of cohort study

Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulant; OAC, oral anticoagulant

Figure2. Hazard ratios for dementia or cognitive impairment subgrouped by baseline characteristics

Abbreviations: TIA, transient ischemic attack; SE, systemic embolism; OAC, oral anticoagulant

Rhythm or rate control drugs included amiodarone, disopyramide, dronedarone, flecainide, propafenone, digoxin, beta-blockers, and calcium channel blockers (verapamil and diltiazem). Procedural treatment included catheter ablation, cardioversion, and cardiac pacemaker.

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450   **Table1**. Number of events, follow-up time, incidence rates, and HRs for dementia or cognitive impairment for a primary analysis

Exposure group	Group	No. of event	Person-years at risk[†], year	Mean follow-up time(SD)	IR, per 1000 person-years (95% CI)	HR (95% CI),p-value
OAC vs non-OAC	OAC user (n=35245)	1936	159640	5.5 (3.6)	12.13 (11.60-12.68)	0.90
(Ref=Non-OAC)	Non-OAC user (n=49276)	3359	252930	6.1 (3.8)	13.28 (12.84-13.74)	(0.85-0.95),p<0.001
Warfarin vs Non-OAC	Warfarin user (n=30587)	1862	153843	6.0 (3.6)	12.10 (11.57-12.67)	0.90
(Ref=Non-OAC)	Non-OAC user (n=49276)	3359	252930	6.1 (3.8)	13.28 (12.84-13.74)	(0.85-0.95),p<0.001
DOAC vs Non-OAC	DOAC user (n= 4657)	74	5790	2.2 (0.9)	12.78 (10.18-16.05)	0.94
(Ref=Non-OAC) (from 2011)	Non-OAC user (n=15990)	536	44166	3.8 (1.6)	12.14 (11.15-13.21)	(0.74-1.19),p=0.588
OAC vs Antiplatelet	OAC-user (n=25435)	1345	115094	6.0 (3.6)	11.69 (11.08-12.33)	0.84
(Ref=Antiplatelet)	Antiplatelet user (n=29282)	2275	147581	5.5 (3.7)	15.42 (14.79-16.06)	(0.79-0.90),p<0.001
DOAC vs warfarin	DOAC user (n= 4657)	74	5790	2.2 (0.9)	12.78 (10.18-16.05)	0.89
(Ref=Warfarin) (from 2011)	Warfarin user (n=12880)	460	35685	3.8 (1.5)	12.89 (11.76-14.12)	(0.70-1.14),p=0.373

Exposure group	Group	No. of event	Person-years at risk[†], year	Mean follow-up time(SD)	IR, per 1000 person-years (95% CI)	HR (95% CI),p-value
Dual therapy vs no treatment	Dual therapy user (n=6794)	432	31029	5.6 (3.4)	13.92 (12.67-15.30)	1.17
(Ref=no treatment)	No treatment (n=19994)	1084	105348	6.3 (4.1)	10.29 (9.69-10.92)	(1.05-1.31),p=0.006

451 **Abbreviations:** OAC, oral anticoagulant; DOAC, direct oral anticoagulant; SD, standard deviation; IR, incidence rate; CI, confidence interval; HR, hazard ratio; Ref,

452 reference category

453 [†]Time at risk started one year after treatment ascertainment period

454 **Table2.** Subgroup analysis based on types of dementia, comparing OAC use vs non-OAC use

Type of dementia	Group	No. of event	Person-year at risk†, year	Mean follow-up time (SD)	IR, per 1000 Person-y	HR (95% CI),p-value
Alzheimer's disease	OAC	315	163512	5.6 (3.6)	1.93 (1.73-2.15)	0.99 (0.86-1.14),p=0.868
(Ref=Non-OAC)	Non-OAC	520	259834	6.3 (3.8)	2.00 (1.84-2.18)	
Vascular dementia	OAC	482	163173	5.6 (3.6)	2.95 (2.7-3.23)	0.89 (0.80-0.99),p=0.049
(Ref=Non-OAC)	Non-OAC	803	259375	6.3 (3.8)	3.1 (2.89-3.32)	
Unspecified dementia	OAC	400	163379	5.6 (3.6)	2.45 (2.22-2.70)	0.74 (0.66-0.83),p<0.001
(Ref=Non-OAC)	Non-OAC	873	259174	6.3 (3.8)	3.37 (3.15-3.60)	

455 **Abbreviations:** SD, standard deviation; IR, incidence rate; HR, hazard ratio; CI, confidence interval; OAC, oral anticoagulant; Ref, reference category

456 †Time at risk started at one year after treatment ascertainment period