

1 **Thromboembolic, Bleeding, and Mortality Risks among Patients with Nonvalvular**  
2 **Atrial Fibrillation Treated with Dual Antiplatelet Therapy versus Oral Anticoagulants:**  
3 **A Population-Based Study**  
4 **Running title: Dual Antiplatelet Therapy versus Oral Anticoagulants in Atrial**  
5 **Fibrillation**

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44 **Abstract**

45 **Background:** Dual antiplatelet therapy (DAPT) with aspirin plus clopidogrel is used for  
46 stroke prevention in patients with atrial fibrillation (AF) when patients refuse to use oral  
47 anticoagulants (OAC) in clinical practice. However, there are limited clinical data comparing  
48 these treatments.

49 **Objective:** To compare the clinical outcomes between DAPT and OAC in patients with AF.

50 **Methods:** Cohort study using a population-wide database of the Hong Kong Hospital  
51 Authority. New patients with AF during 2010-2014 and prescribed DAPT or OAC (warfarin  
52 or dabigatran) were followed until July 31, 2016. Outcomes were thromboembolism,  
53 bleeding, and death. Propensity score (PS) matching at 1:2 ratio was used to select DAPT  
54 users with similar characteristics to OAC users, analyzed using Poisson regression.

55 **Results:** Among 51,946 new patients with AF, 8,520 users of OAC and DAPT were  
56 identified. The likelihood of receiving DAPT over OAC increased with older age and  
57 previous intracranial hemorrhage. Among DAPT users, the incidences of thromboembolism,  
58 death, and bleeding per 100 patient-years were 15.8, 17.6, and 5.1 respectively. When  
59 compared to DAPT users, PS-matched analysis indicated a lower incidence of  
60 thromboembolism and/or death among OAC users (incidence rate ratio [IRR]=0.32, 95%  
61 confidence interval [CI]=0.19-0.55 for dabigatran and IRR=0.58, 95%CI=0.36-0.95 for  
62 warfarin), with no significant differences in bleeding events.

63 **Conclusions:** DAPT users were at markedly increased risk of thromboembolism and death  
64 compared to OAC users. These findings indicate the need for improved stroke risk reduction  
65 strategies among patients taking DAPT and the opportunities of using OAC in high risk  
66 groups to prevent more events.

- 67 **Keywords:** non-vitamin K antagonist oral anticoagulants; aspirin; clopidogrel; atrial  
68 fibrillation; stroke; bleeding
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## 70 **Introduction**

71 Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia that increases the  
72 risk of stroke. For many decades, warfarin and other vitamin K antagonists have been the  
73 only class of oral anticoagulation therapy (OAC) available for the prevention of stroke. When  
74 patients refused or are deemed potentially unsuitable for warfarin, dual antiplatelet therapy  
75 (DAPT) with aspirin and clopidogrel may be considered.<sup>1,2</sup> Current understanding of the  
76 effectiveness of DAPT among patients potentially eligible to receive OAC is primarily  
77 derived from a single clinical trial published in 2006.<sup>3</sup> The Atrial fibrillation Clopidogrel  
78 Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) trial suggested that  
79 DAPT was inferior to warfarin for the prevention of stroke, with no difference in bleeding  
80 events.<sup>3</sup> However, the majority of included patients (77%) were prior users of warfarin,<sup>3</sup> who  
81 were likely to tolerate warfarin better. It is also unclear how evidence from a restrictive trial  
82 setting translates to every-day clinical practice.

83 Dabigatran is the first non-vitamin K antagonist oral anticoagulant (NOAC) approved for use  
84 as an alternative to warfarin in patients with nonvalvular atrial fibrillation (NVAf, i.e. AF in  
85 the absence of mitral stenosis or mechanical valves).<sup>4</sup> Although DAPT might also be  
86 considered in patients who refuse dabigatran or any form of OAC,<sup>1,2</sup> existing evidence was  
87 only based on warfarin (ACTIVE-W) and we are not aware of any studies that  
88 simultaneously described the outcomes among users of DAPT, dabigatran, and warfarin in  
89 the same setting.

90 In a population-based healthcare setting, first we assessed a range of effectiveness and safety  
91 outcomes in patients with NVAf treated with DAPT. Second, we examined the factors  
92 associated with prescribing DAPT over OAC. Third, we described the outcomes among

93 DAPT users who were potentially eligible to prescribe OAC, and compared them with the  
94 outcomes among warfarin and dabigatran users.

## 95 **Methods**

### 96 **Data source**

97 This study utilised the electronic medical records of the Clinical Data Analysis and Reporting  
98 System (CDARS) of the Hong Kong Hospital Authority (HA), a statutory body that manages  
99 all public hospitals and their ambulatory clinics in Hong Kong.<sup>5</sup> HA is currently serving a  
100 population of over 7 million through 42 hospitals and institutions, 47 specialist outpatient  
101 clinics, and 73 general outpatient clinics.<sup>5</sup> Computerized patient records, including  
102 demographics, date of registered death, date of hospital admission and discharge, date of  
103 outpatient visits, drug dispensing records, diagnoses, procedures, and laboratory tests are  
104 centralized in CDARS for practice, research, and audit purposes. Patient records are  
105 anonymized to protect patient identity. CDARS had been extensively used for conducting  
106 large population-based studies.<sup>6-12</sup> Data validity has been shown to be high for a variety of  
107 diagnoses, including AF (positive predictive value [PPV]=95%), ischemic stroke (PPV=90%),  
108 intracranial hemorrhage (ICH) (PPV=95%), and gastrointestinal bleeding (GIB)  
109 (PPV=100%).<sup>8-10</sup> Detailed descriptions of CDARS were published previously.<sup>9, 11, 12</sup>

110 The study protocol was approved by the Institutional Review Board of the University of  
111 Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW13-468).  
112 Informed patient consent was not required as the data used in this study were anonymized.

### 113 **Study design and selection of patients**

114 This was a retrospective cohort study. We selected new patients who received their first AF  
115 diagnosis (International Classification of Disease, Ninth Revision, Clinical Modification

116 [ICD-9-CM]=427.3) between January 1, 2010 and December 31, 2014 from CDARS.  
117 Possible cases of transient AF, including those who had cardiac surgery, myocarditis,  
118 pericarditis, or pulmonary embolism within 3 months before their first AF occurrence were  
119 excluded. Patients who were diagnosed with mitral stenosis, hyperthyroidism, or underwent  
120 valve replacement at or prior to their first AF occurrence were excluded (ICD-9-CM;  
121 Supplemental Table 1), as were patients with missing date of birth or sex information,  
122 aged <18 years, or died at first AF occurrence.

123 Patients were classified into respective treatment group based on their first prescription of  
124 DAPT (aspirin in combination with clopidogrel), warfarin, or dabigatran following AF  
125 diagnosis. Index date was defined as the date of the first prescription following AF. To select  
126 new users only, patients who were exposed to either therapy within 180 days prior to index  
127 date were excluded. Compared to OACs, DAPT is more commonly indicated for ischemic  
128 heart disease such as myocardial infarction instead of AF.<sup>1</sup> To minimize this potential  
129 systematic differences between OACs and DAPT groups, we excluded patients with ischemic  
130 heart disease (ICD-9-CM=410-414) to include only those who were likely to receive  
131 treatment because of AF. Sensitivity analyses were conducted by repeating the main analyses  
132 without exclusion of patients with ischemic heart disease. Patients who died within 7 days of  
133 index date were excluded as any deaths occurred on the first few days after treatment  
134 commencement is likely related to the condition that led to the initiation of treatment (e.g. AF  
135 and ischemic stroke) rather than the treatment itself. Post-hoc analyses were conducted with  
136 inclusion of patients who died within 7 days of index date.

### 137 **Outcomes**

138 The primary effectiveness outcome was a composite of ischemic stroke, systemic embolism,  
139 and death from any cause. The secondary safety outcome was bleeding events, including ICH

140 and GIB. Net benefit was assessed by a composite of all effectiveness and safety endpoints.<sup>13</sup>  
141 Outcome events were identified from diagnosis records using physician-assigned ICD-9-CM  
142 codes (Supplemental Table 1). Stratified analyses were conducted for each individual  
143 component in the composite outcomes. Deaths were further stratified into vascular and non-  
144 vascular deaths (Supplemental Table 1). In this stratified analysis patients with unknown  
145 cause of death were censored and not classified as having an outcome.

#### 146 **Follow-up**

147 The follow-up for each patient commenced from the index date until occurrence of outcome,  
148 end of study period (July 31, 2016), discontinuation of treatment, switching to other therapy  
149 (between apixaban, dabigatran, rivaroxaban, warfarin, and DAPT), or death, whichever came  
150 first. Discontinuation of DAPT was determined by either stopping aspirin or clopidogrel.  
151 Treatment was assumed to be continuous unless a bleeding event was recorded (GIB or  
152 ICH).<sup>3, 14</sup> In Hong Kong, aspirin can also be obtained over-the-counter whereas dabigatran,  
153 warfarin, and clopidogrel are available only by prescription.<sup>15</sup> For the drugs that require a  
154 prescription (dabigatran, warfarin, and clopidogrel), we additionally assessed the time gap  
155 between consecutive prescription refills in CDARS after index date, where treatments were  
156 assumed to be continuous when any apparent treatment break was within 5 days.

#### 157 **Statistical analysis**

158 Propensity score (PS) was calculated for each patient to estimate their likelihood to receive  
159 DAPT over warfarin and dabigatran.<sup>16</sup> It was estimated using logistic regression based on age,  
160 sex, index year, number of hospitalizations within one year prior to index date, medical  
161 history (recorded any time on or before index date, Supplemental Table 1) of congestive heart  
162 failure, hypertension, diabetes mellitus, ischemic stroke/transient ischemic attack  
163 (TIA)/systemic embolism, vascular disease, renal disease, ICH, GIB, other bleeding (a



164 composite of epistaxis, hematuria, hemarthrosis, hemopericardium, hemoptysis, and  
165 hemorrhage from kidney, throat, and vagina);<sup>10</sup> Charlson Comorbidities Index (CCI); recent  
166 use ( $\leq 90$  days on or prior to index date) of angiotensin-converting enzyme (ACE)  
167 inhibitors/angiotensin receptor blockers (ARBs), beta-blocker, amiodarone, dronedarone,  
168 nonsteroidal anti-inflammatory drugs (NSAIDs), histamine type-2-receptor antagonists  
169 (H2RAs), proton pump inhibitors (PPIs), statins, and selective serotonin reuptake inhibitors.  
170 The resulting odds ratios of the PS were reported to examine the factors associated with  
171 prescribing DAPT over OAC.

172 Each DAPT user was intended to be matched with up to two dabigatran users and two  
173 warfarin users by PS using the greedy matching algorithm, which has been demonstrated to  
174 perform well in both actual and simulation studies.<sup>17</sup> Patients were eligible for inclusion in  
175 every cohort where that treatment was being assessed. Standardized differences were  
176 calculated to assess the similarity of baseline characteristics between treatment groups, with  
177 difference  $< 0.1$  considered negligible.<sup>16</sup> Sensitivity analyses were conducted with exclusion  
178 of patients with PS in extreme values (lower and upper 1% of the distribution in the exposed  
179 and unexposed group respectively) to reduce any residual patient differences arising from  
180 unmeasured confounding factors.<sup>16</sup>

181 The risks of outcome events were compared using Poisson regression stratified on matched  
182 groups. The scale parameters were held fixed and the offset variable was the natural  
183 logarithm of the days of follow-up measured from the index date through the date of the  
184 outcome/the first censoring event. Result estimates were expressed in terms of incidence rate  
185 ratio (IRR) with 95% confidence interval (CI). Post-hoc analyses were conducted using Cox  
186 regression model. A two-sided p-value  $< 0.05$  was considered as statistically significant. SAS  
187 (version 9.3; SAS Institute, Inc, Cary, NC) and R (version: 3.1.1) were used for statistical  
188 analyses.

## 189 **Results**

### 190 **Baseline characteristics**

191 There were 51,946 new patients with AF identified in CDARS between January 1, 2010 and  
192 December 31, 2014. Following patient exclusion, a total of 8,520 new users of dabigatran,  
193 warfarin, and DAPT remained (Figure 1). The most common dosage of dabigatran was 110  
194 mg bid (n=1,955; 75%), followed by 150 mg bid (n=345; 13%), and 75 mg bid (n=222; 9%).

### 195 **Factors associated with prescribing DAPT over OAC**

196 Male gender, vascular disease, baseline use of statins, H2RAs, and PPIs were associated with  
197 an increased likelihood to prescribe DAPT over both warfarin and dabigatran. Older age was  
198 associated with a higher likelihood to prescribe DAPT over warfarin only; whereas higher  
199 CCI, congestive heart failure, ICH, and renal disease, and baseline use of amiodarone was  
200 associated with a higher likelihood of prescribing DAPT over dabigatran only (Supplemental  
201 Table 2).

202 In contrast, those with prior ischemic stroke/TIA/systemic embolism or baseline NSAIDs use  
203 were associated with a lower likelihood to receive DAPT over both warfarin and dabigatran.  
204 Patients with baseline use of ACE inhibitors and/or ARBs were less likely to receive DAPT  
205 over dabigatran only.

### 206 **Propensity-score matching**

207 669 DAPT users were successfully matched to 1,241 warfarin users; and 560 DAPT users  
208 were successfully matched to 964 dabigatran users. All observed baseline characteristics had  
209 standardized differences <0.1 after matching (Supplemental Tables 3 and 4, Supplemental  
210 Figures 1 and 2). In the sensitivity analyses without exclusion of patients with ischemic heart

211 disease, 1,837 DAPT users were matched to 2,511 warfarin users; and 1,049 DAPT users  
212 were matched to 1,480 dabigatran users.

### 213 **Effectiveness outcomes**

214 The crude incidence of ischemic stroke/systemic embolism and death per 100 patient-years  
215 were 15.8 and 17.6 respectively among DAPT users; 5.4 and 3.1 respectively among warfarin  
216 users; and 4.6 and 2.5 respectively among dabigatran users (Supplemental Table 5).

217 Within the PS-matched cohort, both warfarin and dabigatran use was associated with a lower  
218 risk of ischemic stroke/systemic embolism and/or death when compared to DAPT use  
219 (IRR=0.58, 95%CI=0.36-0.95 and IRR=0.32, 95%CI=0.19-0.55, respectively). Results of  
220 stratified analyses indicated that warfarin and dabigatran use was associated with fewer  
221 deaths from all causes and vascular deaths when compared to DAPT (Table 1, Figure 2).

222 An association with lower risk of non-vascular death was observed in dabigatran users  
223 compared with DAPT (IRR=0.16, 95%CI=0.05-0.54). Although numerically fewer non-  
224 vascular deaths were seen with warfarin users than DAPT users, the confidence intervals  
225 were wide and include 1.0 (IRR=0.48, 95%CI=0.21-1.19). No significant association  
226 between the ischemic stroke/systemic embolism and DAPT users versus dabigatran/warfarin  
227 users were found (Table 1). The results were similar in the analyses that did not exclude  
228 patients with ischemic heart disease (Table 2, Figure 2).

### 229 **Safety outcomes**

230 The crude incidence of overall bleeding per 100 patient-years among users of DAPT,  
231 warfarin, and dabigatran were 5.1, 3.4, and 3.3 respectively (Supplemental Table 5). Among  
232 the PS-matched cohorts, overall bleeding events were numerically more common in patients  
233 receiving dabigatran than DAPT, but no significant association in overall bleeding risk for all

234 head-to-head comparisons were found (Table 1, Figure 2). In the analyses that did not  
235 exclude patients with ischemic heart disease, dabigatran was associated with a lower risk of  
236 ICH (IRR=0.14, 95%CI=0.03-0.59) but a higher risk of GIB when compared to DAPT  
237 (IRR=4.54, 95%CI=1.48-16.1). The resulting overall bleeding risk was not significantly  
238 different between dabigatran and DAPT groups (Table 2, Figure 2).

### 239 **Net benefit**

240 Dabigatran use was associated with a more favorable outcome of net benefit compared to  
241 DAPT users (IRR=0.47, 95%CI=0.29-0.79). The risk estimate also pointed towards a trend  
242 for a beneficial outcome among warfarin users over DAPT users (IRR=0.70, 95%CI=0.45-  
243 1.11) (Table 1, Figure 2). Sensitivity and post-hoc analyses all yielded similar results (Table  
244 2 and Supplemental Tables 6-8).

### 245 **Discussion**

246 This study showed that among patients with NVAf, the likelihood of prescribing DAPT over  
247 OAC increased with bleeding risk factors including older age and previous ICH. However,  
248 DAPT use was associated with a moderate risk of bleeding but a remarkably high risk of  
249 thromboembolism. Among the DAPT patients who were potentially eligible for OAC (i.e.  
250 had similar baseline characteristics with OAC group), we found a higher risk of ischemic  
251 stroke/systemic embolism and/or death than seen in those prescribed OAC, with no  
252 significant differences in bleeding risk. The results were robust to all sensitivity analyses that  
253 reduced any residual patient differences arising from unmeasured confounding factors.

### 254 **Risk-benefit of using DAPT**

255 Among DAPT users, the risk of ischemic stroke/systemic embolism and overall bleeding was  
256 15.8 vs. 5.1 per 100 patient-years, suggesting that the risk of thromboembolism, which can be

257 effectively reduced by OAC, was about 3 times higher than that of bleeding. The  
258 thromboembolism-bleeding ratio remained high among DAPT users who were estimated to  
259 have had similar baseline characteristics to those who received warfarin (15.8 vs. 5.2) or  
260 dabigatran (16.9 vs. 3.5). This underscores the potential for improved thromboembolism risk  
261 reduction strategies among any patients receiving DAPT. Our results showed that patients  
262 prescribed DAPT generally had more risk factors for bleeding, such as prior ICH or older age,  
263 than those prescribed OAC. This suggests that patients at high risk of bleeding were likely  
264 channeled to DAPT; however, it turned out DAPT users had a moderate risk of bleeding but a  
265 remarkably high risk of thromboembolism. Although this strategy might have reduced the  
266 risk of bleeding, it probably did not translate into a net benefit in clinical practice. On the  
267 whole, our findings indicate the need for a refinement of current strategy on weighing the  
268 risks and benefits of using DAPT and OAC, and suggest that greater use of OACs among  
269 high risk groups may be warranted.

### 270 **Comparison with other studies**

271 Current understanding of the effectiveness of OAC vs DAPT is only based on the ACTIVE-  
272 W trial.<sup>3</sup> This trial reported a lower rate of vascular events with warfarin against DAPT, but  
273 the authors highlight the limitation that most subjects (77%) had been on warfarin at study  
274 entry.<sup>3</sup> Patients who had been on warfarin were more likely to tolerate it better than other  
275 alternatives, and therefore the study results were largely driven by a group of patients who  
276 were already benefiting from warfarin use. Consistently, in patients who were randomised to  
277 receive OAC, those who had already been on OAC at study entry had less major bleeding  
278 events compared to those who had not been on OAC previously. Conversely, in patients who  
279 were randomised to receive DAPT, those who had already been on OAC at study entry had  
280 more major bleeding events compared to those who had not been (p-value for  
281 interaction=0.028).<sup>3</sup> The trial also excluded high-risk patients likely to be encountered in

282 clinical practice, such as those with a history of peptic ulcer disease and ICH.<sup>3</sup> Addressing the  
283 limitations of ACTIVE-W, our study was based on the usage of antithrombotic therapy in AF  
284 patients outside restrictive trial settings. We used a new user design to minimise survival bias,  
285 where patients who were previously on either treatment were excluded.

286 Comparing our results with ACTIVE-W, both studies support that warfarin is more effective  
287 in preventing stroke and/or death than DAPT. In ACTIVE-W, results were consistent with a  
288 smaller reduction in vascular death, but the difference did not reach statistical significance  
289 (risk ratio=0.88, 95%CI=0.68-1.14).<sup>3</sup> Although there was a reduction in vascular events in  
290 ACTIVE-W (risk ratio=0.69, 95%CI=0.57-0.85), most vascular events such as strokes  
291 occurring in ACTIVE-W were non-fatal,<sup>3</sup> and thus a reduction of which did not lead to a  
292 reduction in vascular death. Regarding bleeding risk, our results are consistent with ACTIVE-  
293 W, where the major bleeding risk is comparable between warfarin and DAPT groups,  
294 suggesting that bleeding risk should not be the only factor for choosing between DAPT and  
295 warfarin.<sup>1</sup>

### 296 **Clinical implications**

297 Current guidelines on the use of DAPT in AF are inconsistent. The 2012 European Society of  
298 Cardiology (ESC) guideline recommends the use of DAPT in patients who refuse or cannot  
299 tolerate any OAC<sup>1</sup> and discourage its use for this indication in the latest guideline in 2016.<sup>18</sup>  
300 However, both the most recent 2014 American Heart Association/American College of  
301 Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guideline in the United States and the  
302 2014 National Institute for Health and Care Excellence (NICE) guideline in the United  
303 Kingdom does not make a specific recommendation regarding the use of DAPT.<sup>4, 19</sup> Despite  
304 this, a considerable volume of antiplatelet medication (alone or in combination) is prescribed  
305 as a “softer” option over OAC, even after the introduction of NOACs – particularly in Asia.<sup>10</sup>

306 Our findings contradict this perception, based on current limited evidence, dabigatran or  
307 warfarin should be considered for stroke prevention instead of DAPT, with DAPT is an  
308 inferior treatment strategy that is not perhaps safer than OAC.

### 309 **Strengths and limitations**

310 To our knowledge, this is the first study that examined the effect of DAPT among patients  
311 with NVAf in real-life practice. Our study was based on the large electronic patient records  
312 in CDARS, which covers 80% of all hospital admissions in Hong Kong.<sup>20</sup> The validity of  
313 coding in CDARS has been shown to be high, where the PPVs of the outcome events in this  
314 study are ranged from 90-100%.<sup>8-10</sup> We applied a new user design to eliminate the residual  
315 effect of previous exposure on the study outcomes. Our study cohort was well-matched by PS  
316 with respect to important comorbidities and concurrent medications, and all measurable  
317 patient characteristics were comparable between groups after matching.

318 This study has limitations. The number of bleeding cases was relatively small, which limits  
319 the power to detect a statistical association and affects the precision of the result estimates.  
320 Nonetheless, our results suggest that the high incidence of thromboembolism and mortality  
321 with DAPT users seems more concerning than any difference in bleeding risk when  
322 compared to OAC users.

323 We have identified some very strong protective associations between dabigatran and warfarin  
324 when compared with DAPT. What matters is whether and to what extent these associations  
325 are causal. For example, dabigatran would not be expected to reduce the risk of non-vascular  
326 events, and so the observation that dabigatran was associated with a lower risk of non-  
327 vascular death compared to DAPT and warfarin warrants further investigations. This could be  
328 explained by (i) an effect of dabigatran that indirectly reduces the likelihood of non-vascular  
329 deaths, (ii) misclassification of cause of death, with some of those classified as non-vascular



330 actually being vascular or (iii) confounding whereby people receiving DAPT are generally  
331 sicker and at risk of adverse outcome, independent of AF treatment choice. At baseline,  
332 patients prescribed DAPT generally possessed more comorbidities than those prescribed  
333 dabigatran and warfarin. In addition, a higher proportion of DAPT users died within the first  
334 7 days of treatment than in the other treatment groups, again suggesting a sicker population  
335 was given DAPT. Although patients were well-matched on many comorbidities using  
336 propensity score matching, an overestimation of any association with lower risk of adverse  
337 outcomes with dabigatran and warfarin vs DAPT is possible if the observed comorbidities  
338 were unable to account for the underlying differences between patients. To reduce residual  
339 confounding, we excluded patients who previously exposed to the treatment of interest or had  
340 ischemic heart disease to assemble comparable study groups. We also conducted sensitivity  
341 analyses, and the results were found to be robust.

## 342 **Conclusions**

343 This study showed that DAPT users were at markedly increased risk of thromboembolism  
344 and death compared to OAC users. Much of these increased risks were likely to be  
345 attributable to patient characteristics. These findings indicate the need for improved risk  
346 reduction strategies among patients who refuse or are deemed unsuitable for OAC, and  
347 suggest wider use of OACs among higher risk groups may be beneficial because the higher  
348 absolute risk provides opportunities to prevent more events.

349



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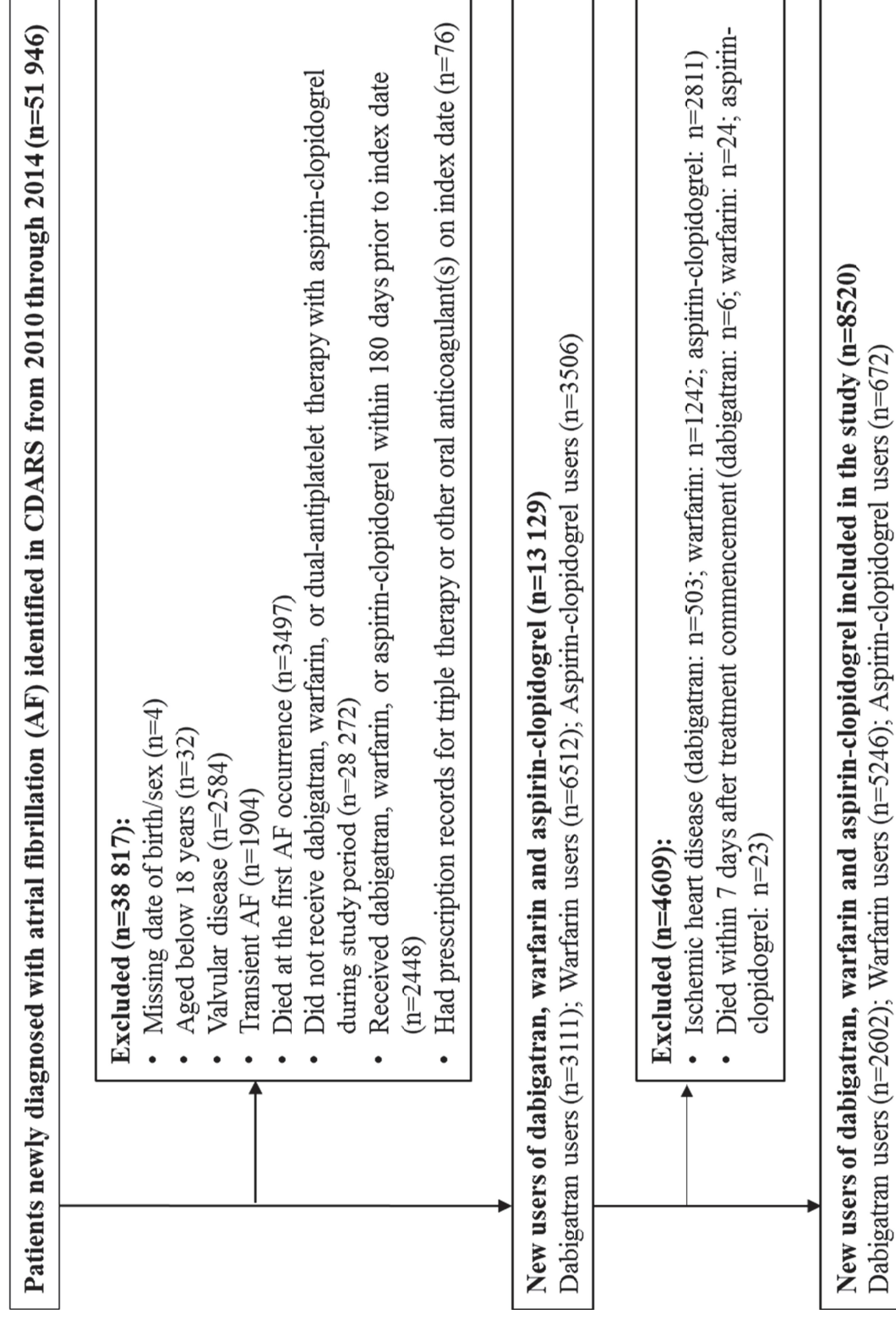
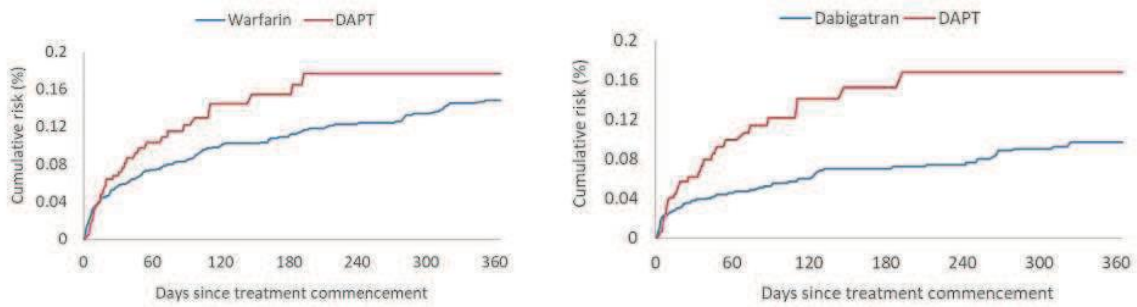
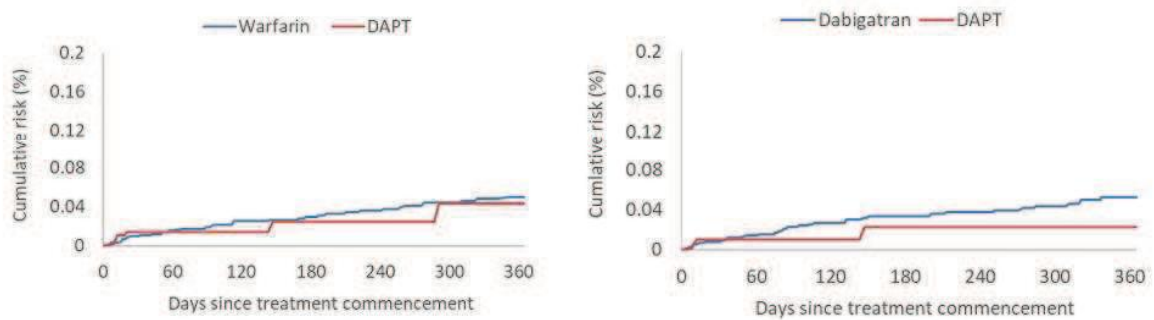
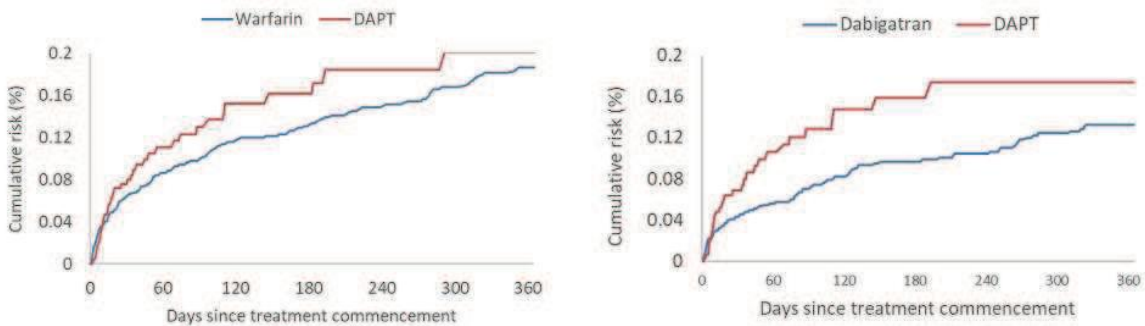


Figure 1. Selection of patients

**Effectiveness (composite of ischemic stroke, systematic embolism, and death)****Safety (composite of intracranial hemorrhage and gastrointestinal bleeding)****Net benefit (composite of effectiveness and safety outcomes)**

**Figure 2. Cumulative risks of the outcomes (DAPT: dual antiplatelet therapy with aspirin plus clopidogrel)**

**Table 1. Effectiveness and safety outcomes after propensity score matching**

	Warfarin vs DAPT			Dabigatran vs DAPT		
	Warfarin (N=1,241)	DAPT (N=669)	IRR <sup>a</sup> (95% CI)	Dabigatran (N=964)	DAPT (N=560)	IRR <sup>a</sup> (95% CI)
<b>Composite of ischemic stroke, systemic embolism, and death</b>						
Ischemic stroke and/or systemic embolism	171 (11.9)	44 (33.2)	0.58 (0.36-0.95)*	97 (8.5)	35 (31.1)	0.32 (0.19-0.55)*
Death	97 (6.7)	21(15.8)	0.75 (0.37-1.59)	63 (5.5)	19 (16.9)	0.59 (0.28-1.30)
Vascular death	85 (5.5)	24 (17.7)	0.43 (0.23-0.81)*	41 (3.4)	17 (14.7)	0.18 (0.09-0.39)*
Non-vascular death	22 (1.4)	10 (7.4)	0.26 (0.08-0.91)*	10 (0.8)	7 (6.1)	0.09 (0.02-0.34)*
	49 (3.1)	11 (8.1)	0.48 (0.21-1.19)	21 (1.7)	8 (6.9)	0.16 (0.05-0.54)*
<b>Composite of intracranial hemorrhage and gastrointestinal bleeding</b>						
Intracranial hemorrhage	75 (4.8)	7 (5.2)	1.09 (0.39-3.64)	44 (3.6)	4 (3.5)	2.71 (0.77-13.5)
Gastrointestinal bleeding	33 (2.1)	4 (2.9)	0.88 (0.22-5.04)	8 (0.7)	2 (1.7)	1.96 (0.18-41.6)
	42 (2.7)	3 (2.2)	1.38 (0.30-9.97)	36 (3.0)	2 (1.7)	3.15 (0.67-30.4)
<b>Net benefit</b>						
Composite of ischemic stroke, systemic embolism, death, intracranial hemorrhage, and gastrointestinal bleeding	232 (16.1)	48 (36.2)	0.70 (0.45-1.11)	132 (11.6)	37 (32.9)	0.47 (0.29-0.79)*

Values are expressed as number of cases (incidence per 100 patient-years). Abbreviations: DAPT, dual antiplatelet therapy; IRR, incidence rate ratio; CI, confidence interval. \*p<0.05.

<sup>a</sup>The incidence rate ratios were obtained by Poisson regression stratified by propensity score matching id.

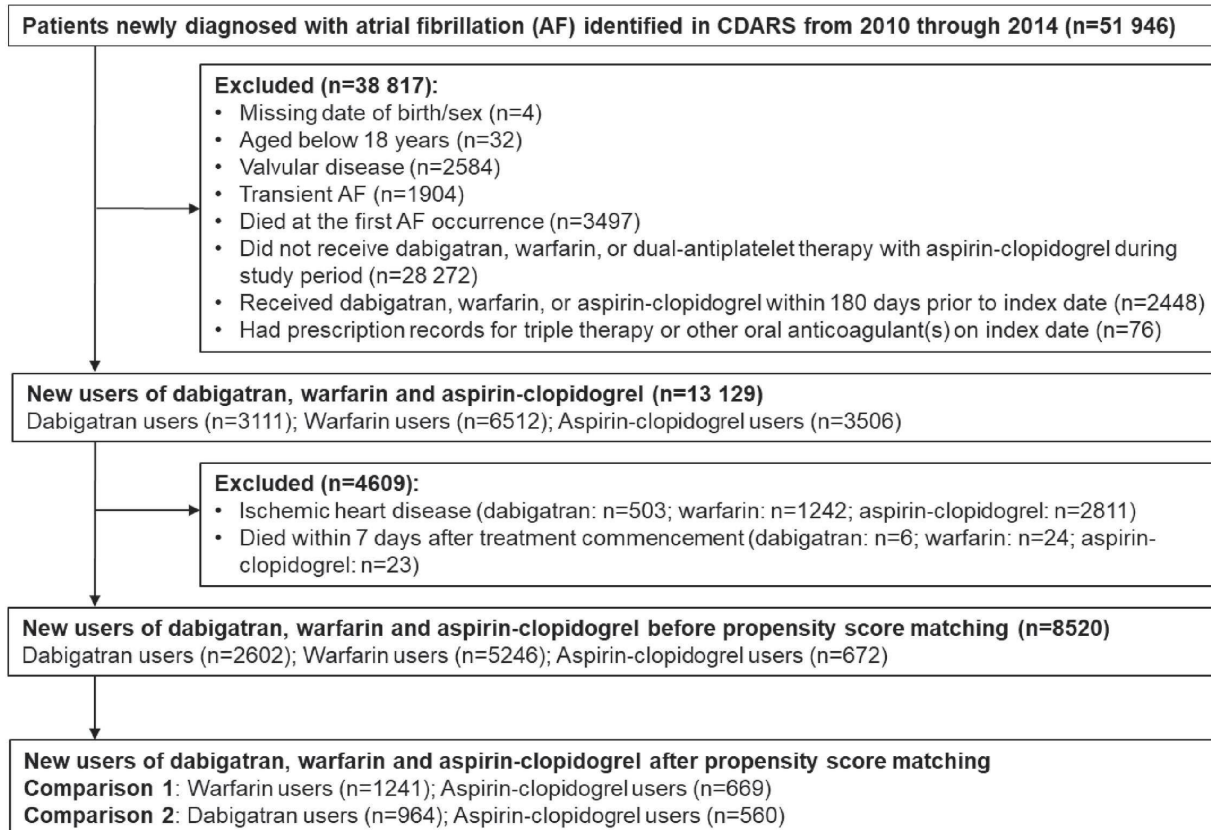
**Table 2. Sensitivity analyses without exclusion of patients with ischemic heart disease**

	Warfarin vs DAPT			Dabigatran vs DAPT		
	Warfarin (N=2,511)	DAPT (N=1,837)	IRR <sup>a</sup> (95% CI)	Dabigatran (N=1,480)	DAPT (N=1,049)	IRR <sup>a</sup> (95% CI)
<b>Composite of ischemic stroke, systemic embolism, and death</b>	341 (11.8)	129 (29.6)	0.64 (0.48-0.86)*	156 (8.6)	72 (29.7)	0.40 (0.27-0.61)*
Ischemic stroke and/or systemic embolism	165 (5.7)	52 (11.9)	1.14 (0.71-1.86)	99 (5.4)	34 (14.0)	0.89 (0.49-1.68)
Death	202 (6.6)	79 (17.7)	0.53 (0.37-0.76)*	65 (3.4)	40 (16.2)	0.21 (0.12-0.36)*
Vascular death	55 (1.8)	35 (7.9)	0.29 (0.16-0.56)*	13 (0.7)	16 (6.5)	0.10 (0.03-0.27)*
Non-vascular death	103 (3.4)	29 (6.5)	0.58 (0.34-1.03)	39 (2.0)	16 (6.5)	0.42 (0.18-0.98)*
<b>Composite of intracranial hemorrhage and gastrointestinal bleeding</b>	151 (4.9)	40 (9.0)	0.86 (0.53-1.41)	69 (3.6)	14 (5.7)	1.48 (0.65-3.58)
Intracranial hemorrhage	48 (1.6)	12 (2.7)	0.88 (0.34-2.37)	11 (0.6)	7 (2.8)	0.14 (0.03-0.59)*
Gastrointestinal bleeding	104 (3.4)	28 (6.3)	0.91 (0.52-1.67)	58 (3.0)	7 (2.8)	4.54 (1.48-16.1)*
<b>Net benefit</b>						
Composite of ischemic stroke, systemic embolism, death, intracranial hemorrhage, and gastrointestinal bleeding	470 (16.3)	160 (36.7)	0.72 (0.56-0.94)*	215 (11.8)	81 (33.5)	0.59 (0.41-0.86)*

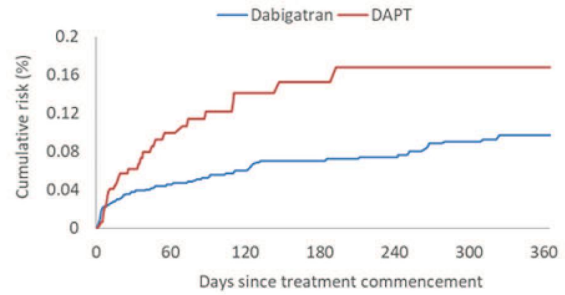
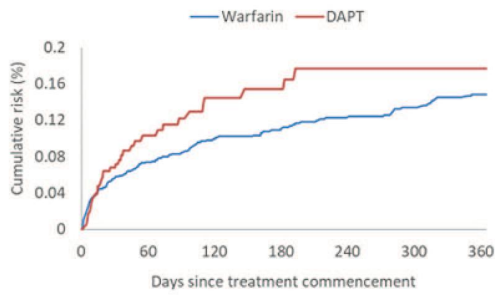
Values are expressed as number of cases (incidence per 100 patient-years). Abbreviations: DAPT, dual antiplatelet therapy; IRR, incidence rate ratio; CI, confidence interval. \*p<0.05.

<sup>a</sup>The incidence rate ratios were obtained by Poisson regression stratified by propensity score matching id.

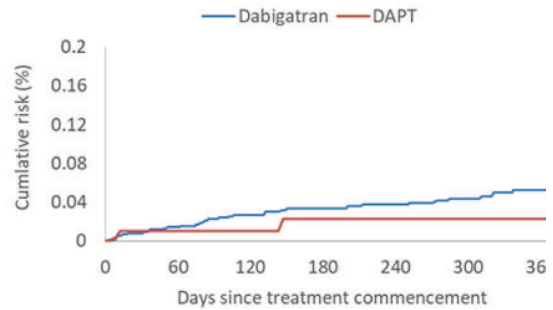
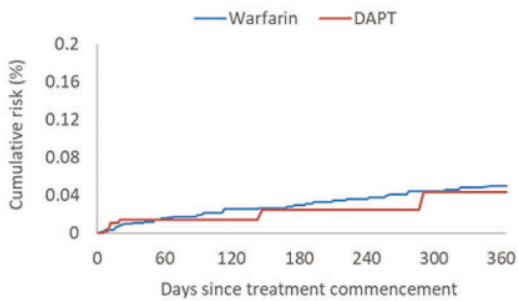




**Effectiveness (composite of ischemic stroke, systematic embolism, and death)**



**Safety (composite of intracranial hemorrhage and gastrointestinal bleeding)**



**Net benefit (composite of effectiveness and safety outcomes)**

