

# Non-Interventional Study (NIS) Report

<b>Document Number:</b>	
<b>BI Study Number:</b>	1160-0308
<b>BI Investigational Product(s):</b>	Pradaxa
<b>Title:</b>	Comparative safety and effectiveness of warfarin, dabigatran, and rivaroxaban among Japanese patients with non-valvular atrial fibrillation (NVAF) and concomitant coronary artery disease (CAD)
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<b>Active substance:</b>	Warfarin, dabigatran, rivaroxaban
<b>Medicinal product:</b>	Coumadin, Pradaxa, Xarelto
<b>Product reference:</b>	1160
<b>Procedure number:</b>	Not applicable
<b>Joint PASS:</b>	No
<b>Research question and objectives:</b>	<p>The study aimed to evaluate the safety and effectiveness comparisons between warfarin, dabigatran, and rivaroxaban in routine clinical practice among Japanese non-valvular atrial fibrillation (NVAF) patients with concomitant coronary artery disease (CAD).</p> <p><b><u>Primary objective:</u></b></p> <p>To compare the risk of major bleeding between dabigatran and warfarin, and between rivaroxaban and warfarin, among Japanese NVAF patients with concomitant CAD.</p> <p><b><u>Secondary objective:</u></b></p>

	<p>To compare the net clinical benefit of dabigatran vs. warfarin, and rivaroxaban vs. warfarin, via the composite outcome and individual components of the composite outcome, among Japanese NVAF patients with concomitant CAD.</p> <p><b><u>Further objective:</u></b></p> <p>It was planned to compare the safety and net clinical benefit of dabigatran vs. rivaroxaban if the required sample size was fulfilled and the baseline characteristics were balanced between the two groups after inverse probability of treatment weighting adjustment, via the fatal or non-fatal major bleeding outcome, the composite outcome, and individual components of the composite outcome, among Japanese NVAF patients with concomitant CAD. In practice, comparison was only conducted for the fatal or non-fatal major bleeding outcome due to sample size limitations.</p>
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## ABSTRACT

<b>Name of company:</b> Boehringer Ingelheim			
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<b>Name of active ingredient:</b> Warfarin, dabigatran, rivaroxaban			
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<b>Title of study:</b>	Comparative safety and effectiveness of warfarin, dabigatran, and rivaroxaban among Japanese patients with non-valvular atrial fibrillation (NVAF) and concomitant coronary artery disease (CAD)		
<b>Keywords:</b>	Atrial fibrillation (AF), non-valvular atrial fibrillation (NVAF), coronary artery disease (CAD), non-vitamin K oral anticoagulant (NOAC), non-interventional, single country		
<b>Rationale and background:</b>	<p>Atrial fibrillation (AF) is a common cardiac arrhythmia and is associated with 15-20% of all strokes. Among AF patients, the prevalence of concomitant coronary artery disease (CAD) is estimated to range from 17% to 46.5%, which can increase the risks of major bleeding, stroke, and mortality. The management of AF is complicated by the presence of concomitant CAD when co-prescription of oral anticoagulation (OAC) with antiplatelet (AP) therapy is needed. Therefore, careful considerations are necessary in choosing antithrombotic therapies to balance the bleeding risk, stroke risk, and other thrombosis risks.</p> <p>The 2020 European Society of Cardiology Guidelines recommended non-vitamin K oral anticoagulant (NOAC) treatments over warfarin for stroke prevention in AF patients. Dabigatran and rivaroxaban were the first two NOACs approved for stroke prevention in AF patients, which were also the two widely used NOACs in Asia. According to Randomized Evaluation of Long-term Anticoagulant Therapy and The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation, both dabigatran and rivaroxaban have shown at least non-inferior efficacy compared to warfarin in the prevention of stroke/systemic embolism (SE), and dabigatran 110 mg</p>		

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	<p>twice daily demonstrated superiority over warfarin in major bleeding and 150 mg twice daily demonstrated superiority over warfarin in stroke prevention among AF patients. Further, analyses of the two pivotal studies indicated consistent superiority in the safety profiles of NOACs vs. warfarin among AF patients with concomitant CAD, in both the overall population and the subgroup population. The safety advantages over warfarin were also shown for dabigatran in the Asian patient population. However, the current literature lacked comparative assessment of clinical outcomes among Asian AF patients with CAD who were managed with warfarin, dabigatran, or rivaroxaban in routine clinical practice. Given the increased risks of major bleeding and recurrent coronary events associated with CAD, it is necessary to evaluate the safety outcomes and net clinical benefits among Asian AF patients with concomitant CAD.</p>		
<b>Research question and objectives:</b>	<p>The study aimed to make safety and effectiveness comparisons between warfarin, dabigatran, and rivaroxaban in routine clinical practice among Japanese non-valvular atrial fibrillation (NVAF) patients with concomitant CAD.</p> <p><b>Primary objective:</b> To compare the risk of major bleeding between dabigatran and warfarin, and between rivaroxaban and warfarin, among Japanese NVAF patients with concomitant CAD.</p> <p><b>Secondary objective:</b> To compare the net clinical benefit of dabigatran vs. warfarin, and rivaroxaban vs. warfarin, via the composite outcome and individual components of the composite outcome, among Japanese NVAF patients with concomitant CAD.</p> <p><b>Further objective:</b></p>		

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	<p>It was planned to compare the safety and net clinical benefit of dabigatran vs. rivaroxaban if the required sample size was fulfilled and the baseline characteristics were balanced between the two groups after inverse probability of treatment weighting (IPTW) adjustment, via the fatal or non-fatal major bleeding outcome, the composite outcome, and individual components of the composite outcome, among Japanese NVAF patients with concomitant CAD. In practice, comparison was only conducted for the fatal or non-fatal major bleeding outcome due to sample size limitations.</p>		

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<b>Study design:</b>	<p>This study was a non-interventional cohort study based on existing data. Patients meeting the in/exclusion criteria were selected and defined as 3 patient groups:</p> <p>Group 1: new users of warfarin Group 2: new users of dabigatran Group 3: new users of rivaroxaban</p> <p>Comparative analyses of the study followed a two-step approach. In the first step, the primary and secondary outcomes, as well as baseline characteristics, were compared between Group 1&amp;2 and Group 1&amp;3, respectively.</p> <p>The second step utilized the estimated results from step one, which were hazard ratios (HRs) between Group 1&amp;2 and between Group 1&amp;3 among NVAf patients with concomitant CAD, to carry out a more accurate sample size calculation to compare dabigatran vs. rivaroxaban. Comparisons of step two were made on the same outcomes as in step one.</p>		
<b>Setting:</b>	<p>Study Period: the study period was from 18 Apr 2011 (start of data collection) to 31 Dec 2020 (end of data collection).</p> <p>Patient Selection Period: the time period for which patients were eligible to enter the cohort, which was from 18 Apr 2012 to 31 Dec 2020.</p> <p>Cohort Entry Date: the drug index date, defined as the first date of prescription for warfarin, dabigatran, or rivaroxaban during the patient selection period.</p>		

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	<p>Look-back Period: for entry into the study population, patients were required to have had at least 365 days of enrolment prior to the cohort entry date, i.e., the 365-day period that ended 1 day prior to the cohort entry date. The earliest start date of the look-back period was 18 Apr 2011.</p> <p>Loss of follow-up: the last data point available in the database during the study period.</p> <p>Follow-Up Period: the period starting from the cohort entry date (first prescription of the drug of interest) and ending at the earliest occurrence of the following:</p> <ul style="list-style-type: none"> <li>• Discontinuation of the index OAC, defined as a continuous gap of 45 days or more between the expected refill date and the actual refill date (discontinuation date defined as 45 days after the expected refill date)</li> <li>• Switching to another OAC, if the index OAC was discontinued and another OAC was started within 45 days of the expected refill date of the index OAC</li> <li>• Loss of follow-up</li> <li>• Occurrence of outcomes of interest (for primary outcome: major bleeding; for secondary outcome: the onset of the first occurring individual component event of the composite outcome; for further outcomes: the respective onset of component events)</li> <li>• Death (except for analyses for the composite outcome and all-cause mortality as a component outcome)</li> <li>• End of study period</li> </ul>		
<b>Subjects and study size, including dropouts:</b>	<p>Patients were considered eligible into the study if they fulfilled all the inclusion criteria and none of the exclusion criteria as defined below.</p> <p>Inclusion Criteria</p>		

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<ol style="list-style-type: none"> <li>1. <math>\geq 18</math> years of age</li> <li>2. Had one year of look-back period prior to the index date (defined as the first date of prescription for warfarin, dabigatran, or rivaroxaban during the study period)</li> <li>3. New users of warfarin, dabigatran, and rivaroxaban, defined as patients without historic use of any oral anticoagulants during the look-back period</li> <li>4. Had at least 1 diagnosis of NVAF during the look-back period prior to or on the index date</li> <li>5. Had at least 1 diagnosis of CAD during the look-back period prior to or on the index date</li> </ol> <p>Exclusion Criteria</p> <ol style="list-style-type: none"> <li>1. Diagnosed with end-stage renal disease, or underwent hemodialysis, or experienced pregnancy during the study period</li> <li>2. Initiated warfarin, dabigatran, rivaroxaban due to valvular AF, AF associated with mechanical valve malfunction or mechanical complication of heart valve prosthesis, or rheumatic AF</li> <li>3. Underwent joint replacement procedures or diagnosed with venous thromboembolism during the look-back period prior to or on the index date</li> <li>4. Prescribed with more than 1 OAC on the index date</li> <li>5. Prescribed with more than 2 AP drugs per prescription (triple or quadruple AP use), or prescribed with any AP injection</li> <li>6. Patients with missing or ambiguous age or sex information</li> </ol> <p>A total of 703653 patients were prescribed with OACs (424606, 78949, and 200098 patients prescribed with warfarin, dabigatran, and rivaroxaban, respectively) during the patient selection period (18 Apr 2012 to 31 Dec 2020). After the evaluation of</p>			

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	inclusion/exclusion criteria, 39357 patients were selected for the study (12316, 6712, and 20329 patients in the warfarin, dabigatran, and rivaroxaban groups, respectively).		
<b>Variables and data sources:</b>	<p><b>Exposure</b> Respectively for Group 1, 2, and 3, the initiation of warfarin, dabigatran, or rivaroxaban during the study period (new users of warfarin, dabigatran, or rivaroxaban; dosage and duration were not restricted).</p> <p><b>Outcomes</b> Primary outcome:</p> <ul style="list-style-type: none"> <li>Fatal or non-fatal major bleeding (defined as any blood transfusion and/or any hospitalization with associated bleeding) in all three patient groups</li> </ul> <p>Secondary outcome:</p> <ul style="list-style-type: none"> <li>Composite outcome of stroke, SE, myocardial infarction (MI), all-cause mortality (inpatient), major bleeding, major gastrointestinal (GI) bleeding (hospitalization due to GI bleeding), or intracranial hemorrhage (ICH), in all three patient groups (the first occurrence of any of the component events counted as an event; this outcome indicated the net clinical benefit)</li> </ul> <p>Further outcomes:</p> <ul style="list-style-type: none"> <li>Individual component of the composite outcome, i.e., stroke, SE, MI, all-cause mortality (inpatient), major GI bleeding (hospitalization due to GI bleeding), and ICH, in all three patient groups</li> </ul> <p><b>Covariates</b></p>		

Covariates were recorded with the 10th Revision of the International Classification of Diseases (ICD-10) codes for disease diagnosis and Medical Data Vision Receipt Code for medications.

Covariates (collected at baseline):

Demographic characteristics

- Age
- Gender (male/female/other)

Stroke characteristics (if available)

- Congestive heart failure, Hypertension, Age  $\geq 75$  years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female) score

Hematologic characteristics (if available)

- Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly ( $> 65$  years), Drugs/alcohol concomitantly score

Comorbidities (had at least 1 diagnosis before or on the index date during the look-back period)

- Heart failure (yes/no)
- Peripheral arterial disorder (yes/no)
- Hypertension (yes/no)
- Diabetes (yes/no)
- Prior stroke/transient ischemic attack/SE (yes/no)
- Cerebrovascular disease (yes/no)
- Myocardial infarction (yes/no)
- Acute Coronary Syndrome (yes/no)
- Unstable angina (yes/no)
- Bleeding history (yes/no)
- Renal dysfunction (yes/no)
- Hepatic dysfunction (yes/no)
- Cancers (yes/no)
- Peptic ulcer disease (yes/no)
- Obesity (yes/no)

Baseline co-medication (had used the drug before or on the index date during the look-back period)

- Antiplatelet drugs (include aspirin, clopidogrel, ticagrelor, prasugrel) (yes/no)

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		<ul style="list-style-type: none"> <li>• The number of AP drugs per prescription (single AP, dual AP, none)</li> <li>• Antiplatelet use duration (single AP use: 6 months to 1 year, single AP use: 1 month to 6 months, single AP use: &lt;1 month, dual AP use: 6 months to 1 year, dual AP use: 1 month to 6 months, dual AP use: &lt;1 month, none; measured from the first AP prescription to baseline)</li> <li>• Nonsteroidal anti-inflammatory drugs (yes/no)</li> <li>• Gastric secretion inhibitors (yes/no)</li> <li>• Statins (yes/no)</li> <li>• Heparins (yes/no)</li> <li>• Proton pump inhibitor (yes/no)</li> <li>• Antihypertensive drugs (yes/no)</li> </ul> <p>Baseline medical procedures (underwent the procedure before or on the index date during the look-back period)</p> <ul style="list-style-type: none"> <li>• Cardioversion procedures (yes/no)</li> <li>• Ablation procedures (yes/no)</li> <li>• Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting (yes/no)</li> </ul> <p>This study was a non-interventional study based on secondary data without involving review or analysis of any individual patient level data. The data were extracted and analysed in an aggregate manner. Therefore, from safety information collecting perspective, no adverse event/adverse drug reaction collection &amp; reporting of individual case safety reports was required.</p> <p>The Medical Data Vision Co. Ltd. (Tokyo, Japan) database is one of the largest databases in Japan, collecting data from over 460 hospitals which account for round 26% of advanced treatment hospitals in Japan. The database contains comprehensive medical record data,</p>	

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	blood test result data, insurance claims data, and pharmacy claims data, covering more than 40 million patients, a significant proportion of whom are $\geq 65$ years old. Each patient is assigned a specific identification number to which all inpatient and outpatient data are linked. The diagnosis is coded according to the ICD-10 codes or local disease codes.		
<b>Results:</b>	<ul style="list-style-type: none"> <li>• A total of 703653 patients were prescribed with OACs (424606, 78949, and 200098 patients prescribed with warfarin, dabigatran, and rivaroxaban, respectively) during the patient selection period (18 Apr 2012 to 31 Dec 2020). After the evaluation of inclusion/exclusion criteria, 39357 patients were selected for the study (12316, 6712, and 20329 patients in the warfarin, dabigatran, and rivaroxaban groups, respectively).</li> <li>• Under the crude population, the mean (SD) age of patients in the warfarin, dabigatran, and rivaroxaban groups was 77.0 (10.2), 71.8 (10.6), and 74.2 (10.6) years, respectively. There were 7868 (63.9%) male and 4448 (36.1%) female patients, 4892 (72.9%) male and 1820 (27.1%) female patients, and 13918 (68.5%) male and 6411 (31.5%) female patients in the warfarin, dabigatran, and rivaroxaban groups, respectively.</li> <li>• With stabilized IPTW (s-IPTW) adjustment or after propensity score (PS) matching, all the demographic and baseline characteristics between the pairwise treatment groups were well balanced, with all absolute standardized differences <math>&lt; 0.1</math>.</li> </ul> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>• Under the crude populations without s-IPTW adjustment during follow-up period, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12316 patients experienced 520 fatal or non-fatal major bleeding events and the incidence rate per</li> </ul> </li> </ul>		

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		<p>1000 person-years was 69 (95% confidence interval [CI]: 63, 75).</p> <ul style="list-style-type: none"> <li>○ In the dabigatran group, 6712 patients experienced 116 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 22 (95% CI: 18, 26).</li> <li>○ In the rivaroxaban group, 20329 patients experienced 547 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 35 (95% CI:32, 38).</li> <li>● Under the s-IPTW adjusted populations during follow-up period, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12231 patients experienced 455 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 52 (95% CI: 47, 57).</li> <li>○ In the dabigatran group, 6682 patients experienced 130 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 26 (95% CI: 22, 31).</li> <li>○ In the rivaroxaban group, 20422 patients experienced 614 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 41 (95% CI: 38, 44).</li> </ul> </li> <li>● Under the PS-matched populations during follow-up period, <ul style="list-style-type: none"> <li>○ In the pair-wise listing 1, 6132 patients in the dabigatran group experienced 113 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 23 (95% CI: 19, 28). Meanwhile 6132 patients in the warfarin group experienced 217 events and the incidence rate per 1000 person-years was 50 (95% CI: 43, 57).</li> <li>○ In the pair-wise listing 2, 11480 patients in the rivaroxaban group experienced 379 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 50 (95% CI: 45, 55). Meanwhile 11480 patients in the warfarin group experienced 459 events and the incidence rate per 1000 person-years was 64 (95% CI: 58, 70).</li> </ul> </li> </ul>	

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		<ul style="list-style-type: none"> <li>○ In the pair-wise listing 3, 6710 patients in the dabigatran group experienced 116 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 22 (95% CI: 18, 26). Meanwhile 6710 patients in the rivaroxaban group experienced 168 events and the incidence rate per 1000 person-years was 32 (95% CI: 28, 38).</li> <li>● Under the crude populations without s-IPTW adjustment during the follow-up period of 3 years, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12316 patients experienced 505 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 78 (95% CI: 72, 86).</li> <li>○ In the dabigatran group, 6712 patients experienced 107 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 24 (95% CI: 20, 29).</li> <li>○ In the rivaroxaban group, 20329 patients experienced 514 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 38 (95% CI:35, 41).</li> </ul> </li> <li>● Under the s-IPTW adjusted populations during the follow-up period of 3 years, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12231 patients experienced 439 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 61 (95% CI: 55, 67).</li> <li>○ In the dabigatran group, 6682 patients experienced 121 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 29 (95% CI: 24, 34).</li> <li>○ In the rivaroxaban group, 20422 patients experienced 585 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 45 (95% CI: 42, 49).</li> </ul> </li> </ul>	

- Under the PS-matched populations during the follow-up period of 3 years,
  - In the pair-wise listing 1, 6132 patients in the dabigatran group experienced 105 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 26 (95% CI: 21, 32). Meanwhile 6132 patients in the warfarin group experienced 211 events and the incidence rate per 1000 person-years was 59 (95% CI: 51, 67).
  - In the pair-wise listing 2, 11480 patients in the rivaroxaban group experienced 361 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 54 (95% CI: 49, 60). Meanwhile 11480 patients in the warfarin group experienced 444 events and the incidence rate per 1000 person-years was 73 (95% CI: 66, 80).
  - In the pair-wise listing 3, 6710 patients in the dabigatran group experienced 107 fatal or non-fatal major bleeding events and the incidence rate per 1000 person-years was 24 (95% CI: 20, 29). Meanwhile 6710 patients in the rivaroxaban group experienced 158 events and the incidence rate per 1000 person-years was 35 (95% CI: 30, 41).
- Compared with warfarin, both NOACs (dabigatran and rivaroxaban) were associated with a significantly lower risk of fatal or non-fatal major bleeding events with s-IPTW adjustment or after PS matching (dabigatran vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.5 [0.402, 0.622] and PS-matched HR [95% CI] was 0.481 [0.383, 0.605]; rivaroxaban vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.784 [0.686, 0.896] and PS-matched HR [95% CI] was 0.795 [0.694, 0.91]).
- Compared with rivaroxaban, dabigatran was associated with a significant lower risk of fatal or non-fatal major bleeding events with s-IPTW adjustment or after PS matching (s-IPTW adjusted HR [95% CI] was 0.637 [0.514, 0.791] and PS-matched HR [95% CI] was 0.684 [0.541, 0.865]).
- The results of the risk of fatal or non-fatal major bleeding events during the follow-up period of 3 years were consistent with those during follow-up period (dabigatran vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.481 [0.384, 0.604] and PS-matched HR [95% CI] was 0.461 [0.364, 0.583]; rivaroxaban vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.765 [0.668, 0.877] and PS-matched HR [95% CI] was 0.777 [0.676, 0.892]; dabigatran vs. rivaroxaban: s-IPTW adjusted HR [95% CI] was 0.629 [0.503, 0.788] and PS-matched HR [95% CI] was 0.677 [0.53, 0.865]).

### Secondary outcome

- Under the crude populations without s-IPTW adjustment during follow-up period,
  - In the warfarin group, 12316 patients experienced 2149 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 338 (95% CI: 324, 353).
  - In the dabigatran group, 6712 patients experienced 872 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 189 (95% CI: 176, 202).
  - In the rivaroxaban group, 20329 patients experienced 2839 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 205 (95% CI: 198, 213).
- Under the s-IPTW adjusted populations during follow-up period,
  - In the warfarin group, 12231 patients experienced 2055 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 275 (95% CI: 264, 288).
  - In the dabigatran group, 6682 patients experienced 922 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 213 (95% CI: 200, 228).
  - In the rivaroxaban group, 20422 patients experienced 2963 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 228 (95% CI: 220, 237).
- Under the PS-matched populations during follow-up period,
  - In the pair-wise listing 1, 6132 patients in the dabigatran group experienced 816 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 196 (95% CI: 183, 210). Meanwhile 6132 patients in the warfarin group experienced 1007 events

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		<p>and the incidence rate per 1000 person-years was 272 (95% CI: 255, 289).</p> <ul style="list-style-type: none"> <li>○ In the pair-wise listing 2, 11480 patients in the rivaroxaban group experienced 1782 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 275 (95% CI: 262, 288). Meanwhile 11480 patients in the warfarin group experienced 1994 events and the incidence rate per 1000 person-years was 329 (95% CI: 315, 344).</li> <li>○ In the pair-wise listing 3, 6710 patients in the dabigatran group experienced 872 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 189 (95% CI: 177, 202). Meanwhile 6710 patients in the rivaroxaban group experienced 830 events and the incidence rate per 1000 person-years was 181 (95% CI: 168, 193).</li> <li>● Under the crude populations without s-IPTW adjustment during the follow-up period of 3 years, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12316 patients experienced 2072 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 372 (95% CI: 356, 389).</li> <li>○ In the dabigatran group, 6712 patients experienced 836 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 213 (95% CI: 198, 228).</li> <li>○ In the rivaroxaban group, 20329 patients experienced 2742 stroke, SE, MI, all-cause mortality (inpatient), major</li> </ul> </li> </ul>	

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		<p>bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 227 (95% CI: 219, 236).</p> <ul style="list-style-type: none"> <li>• Under the s-IPTW adjusted populations during the follow-up period of 3 years, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12231 patients experienced 1961 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 310 (95% CI: 296, 324).</li> <li>○ In the dabigatran group, 6682 patients experienced 889 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 238 (95% CI: 223, 255).</li> <li>○ In the rivaroxaban group, 20422 patients experienced 2874 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 252 (95% CI: 243, 261).</li> </ul> </li> <li>• Under the PS-matched populations during the follow-up period of 3 years, <ul style="list-style-type: none"> <li>○ In the pair-wise listing 1, 6132 patients in the dabigatran group experienced 785 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 222 (95% CI: 206, 238). Meanwhile 6132 patients in the warfarin group experienced 964 events and the incidence rate per 1000 person-years was 307 (95% CI: 288, 327).</li> <li>○ In the pair-wise listing 2, 11480 patients in the rivaroxaban group experienced 1731 stroke, SE, MI, all-cause mortality</li> </ul> </li> </ul>	

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		<p>(inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 299 (95% CI: 285, 313). Meanwhile 11480 patients in the warfarin group experienced 1921 events and the incidence rate per 1000 person-years was 363 (95% CI: 347, 380).</p> <ul style="list-style-type: none"> <li>○ In the pair-wise listing 3, 6710 patients in the dabigatran group experienced 836 stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, and the incidence rate per 1000 person-years was 213 (95% CI: 199, 228). Meanwhile 6710 patients in the rivaroxaban group experienced 801 events and the incidence rate per 1000 person-years was 200 (95% CI: 186, 214).</li> <li>● Compared with warfarin, both NOACs (dabigatran and rivaroxaban) were associated with a significantly lower risk of the composite outcome of stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events with s-IPTW adjustment or after PS matching (dabigatran vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.78 [0.714, 0.851] and PS-matched HR [95% CI] was 0.747 [0.682, 0.818]; rivaroxaban vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.827 [0.777, 0.88] and PS-matched HR [95% CI] was 0.853 [0.801, 0.909]).</li> <li>● The results of the risk of the composite outcome of stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events during the follow-up period of 3 years were consistent with those during follow-up period (dabigatran vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.785 [0.718, 0.858] and PS-matched HR [95% CI] was 0.75 [0.683, 0.823]; rivaroxaban vs. warfarin: s-IPTW</li> </ul>	

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		<p>adjusted HR [95% CI] was 0.833 [0.782, 0.888] and PS-matched HR [95% CI] was 0.857 [0.803, 0.914]).</p> <p><b>Further outcomes</b></p> <p><u>Systemic embolism (SE)</u></p> <ul style="list-style-type: none"> <li>• Under the crude populations without s-IPTW adjustment during follow-up period, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12316 patients experienced 291 SE events and the incidence rate per 1000 person-years was 38 (95% CI: 34, 43).</li> <li>○ In the dabigatran group, 6712 patients experienced 69 SE events and the incidence rate per 1000 person-years was 13 (95% CI: 10, 16).</li> <li>○ In the rivaroxaban group, 20329 patients experienced 211 SE events and the incidence rate per 1000 person-years was 13 (95% CI: 12, 15).</li> </ul> </li> <li>• Under the s-IPTW adjusted populations during follow-up period, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12231 patients experienced 287 SE events and the incidence rate per 1000 person-years was 33 (95% CI: 29, 37).</li> <li>○ In the dabigatran group, 6682 patients experienced 67 SE events and the incidence rate per 1000 person-years was 13 (95% CI: 10, 17).</li> <li>○ In the rivaroxaban group, 20422 patients experienced 213 SE events and the incidence rate per 1000 person-years was 14 (95% CI: 12, 16).</li> </ul> </li> <li>• Under the PS-matched populations during follow-up period, <ul style="list-style-type: none"> <li>○ In the pair-wise listing 1, 6132 patients in the dabigatran group experienced 64 SE events and the incidence rate per 1000 person-years was 13 (95% CI: 10, 17). Meanwhile 6132 patients in the warfarin group experienced 158 events and</li> </ul> </li> </ul>	

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		<p>the incidence rate per 1000 person-years was 36 (95% CI: 31, 42).</p> <ul style="list-style-type: none"> <li>○ In the pair-wise listing 2, 11480 patients in the rivaroxaban group experienced 113 SE events and the incidence rate per 1000 person-years was 15 (95% CI: 12, 18). Meanwhile 11480 patients in the warfarin group experienced 270 events and the incidence rate per 1000 person-years was 37 (95% CI: 33, 42).</li> <li>○ In the pair-wise listing 3, 6710 patients in the dabigatran group experienced 69 SE events and the incidence rate per 1000 person-years was 13 (95% CI: 10, 16). Meanwhile 6710 patients in the rivaroxaban group experienced 69 events and the incidence rate per 1000 person-years was 13 (95% CI: 10, 17).</li> </ul> <ul style="list-style-type: none"> <li>● Compared with warfarin, both NOACs (dabigatran and rivaroxaban) were associated with a significantly lower risk of SE events with s-IPTW adjustment or after PS matching (dabigatran vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.411 [0.31, 0.545] and PS-matched HR [95% CI] was 0.375 [0.28, 0.501]; rivaroxaban vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.43 [0.356, 0.52] and PS-matched HR [95% CI] was 0.401 [0.322, 0.499]).</li> </ul> <p><u>All-cause mortality (inpatient)</u></p> <ul style="list-style-type: none"> <li>● Under the crude populations without s-IPTW adjustment during follow-up period, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12316 patients experienced 412 all-cause mortality (inpatient) events and the incidence rate per 1000 person-years was 53 (95% CI: 48, 58).</li> <li>○ In the dabigatran group, 6712 patients experienced 100 all-cause mortality (inpatient) events and the incidence rate per 1000 person-years was 19 (95% CI: 15, 23).</li> </ul> </li> </ul>	

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		<ul style="list-style-type: none"> <li>○ In the rivaroxaban group, 20329 patients experienced 433 all-cause mortality (inpatient) events and the incidence rate per 1000 person-years was 27 (95% CI: 24, 29).</li> <li>● Under the s-IPTW adjusted populations during follow-up period, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12231 patients experienced 366 all-cause mortality (inpatient) events and the incidence rate per 1000 person-years was 40 (95% CI: 36, 45).</li> <li>○ In the dabigatran group, 6682 patients experienced 120 all-cause mortality (inpatient) events and the incidence rate per 1000 person-years was 24 (95% CI: 20, 28).</li> <li>○ In the rivaroxaban group, 20422 patients experienced 464 all-cause mortality (inpatient) events and the incidence rate per 1000 person-years was 30 (95% CI: 28, 33).</li> </ul> </li> <li>● Under the PS-matched populations during follow-up period, <ul style="list-style-type: none"> <li>○ In the pair-wise listing 1, 6132 patients in the dabigatran group experienced 97 all-cause mortality (inpatient) events and the incidence rate per 1000 person-years was 20 (95% CI: 16, 24). Meanwhile 6132 patients in the warfarin group experienced 161 events and the incidence rate per 1000 person-years was 36 (95% CI: 31, 42).</li> <li>○ In the pair-wise listing 2, 11480 patients in the rivaroxaban group experienced 296 all-cause mortality (inpatient) events and the incidence rate per 1000 person-years was 38 (95% CI: 34, 43). Meanwhile 11480 patients in the warfarin group experienced 389 events and the incidence rate per 1000 person-years was 52 (95% CI: 47, 58).</li> <li>○ In the pair-wise listing 3, 6710 patients in the dabigatran group experienced 100 all-cause mortality (inpatient) events and the incidence rate per 1000 person-years was 19 (95% CI: 15, 23). Meanwhile 6710 patients in the rivaroxaban group experienced</li> </ul> </li> </ul>	

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		<p>121 events and the incidence rate per 1000 person-years was 23 (95% CI: 19, 27).</p> <ul style="list-style-type: none"> <li>Compared with warfarin, both NOACs (dabigatran and rivaroxaban) were associated with a significantly lower risk of all-cause mortality (inpatient) events with s-IPTW adjustment or after PS matching (dabigatran vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.577 [0.455, 0.733] and PS-matched HR [95% CI] was 0.555 [0.431, 0.713]; rivaroxaban vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.733 [0.633, 0.85] and PS-matched HR [95% CI] was 0.724 [0.622, 0.843]).</li> </ul> <p><u>Major GI bleeding (hospitalization due to GI bleeding)</u></p> <ul style="list-style-type: none"> <li>Under the crude populations without s-IPTW adjustment during follow-up period, <ul style="list-style-type: none"> <li>In the warfarin group, 12316 patients experienced 474 major GI bleeding (hospitalization due to GI bleeding) events and the incidence rate per 1000 person-years was 63 (95% CI: 58, 69).</li> <li>In the dabigatran group, 6712 patients experienced 164 major GI bleeding (hospitalization due to GI bleeding) events and the incidence rate per 1000 person-years was 31 (95% CI: 27, 36).</li> <li>In the rivaroxaban group, 20329 patients experienced 498 major GI bleeding (hospitalization due to GI bleeding) events and the incidence rate per 1000 person-years was 32 (95% CI: 29, 34).</li> </ul> </li> <li>Under the s-IPTW adjusted populations during follow-up period, <ul style="list-style-type: none"> <li>In the warfarin group, 12231 patients experienced 425 major GI bleeding (hospitalization due to GI bleeding) events and the incidence rate per 1000 person-years was 49 (95% CI: 44, 54).</li> <li>In the dabigatran group, 6682 patients experienced 166 major GI bleeding (hospitalization due to GI bleeding) events and the incidence rate per 1000 person-years was 34 (95% CI: 29, 39).</li> </ul> </li> </ul>	

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		<ul style="list-style-type: none"> <li>○ In the rivaroxaban group, 20422 patients experienced 549 major GI bleeding (hospitalization due to GI bleeding) events and the incidence rate per 1000 person-years was 37 (95% CI: 34, 40).</li> <li>● Under the PS-matched populations during follow-up period, <ul style="list-style-type: none"> <li>○ In the pair-wise listing 1, 6132 patients in the dabigatran group experienced 152 major GI bleeding (hospitalization due to GI bleeding) events and the incidence rate per 1000 person-years was 32 (95% CI: 27, 37). Meanwhile 6132 patients in the warfarin group experienced 204 events and the incidence rate per 1000 person-years was 47 (95% CI: 41, 54).</li> <li>○ In the pair-wise listing 2, 11480 patients in the rivaroxaban group experienced 341 major GI bleeding (hospitalization due to GI bleeding) events and the incidence rate per 1000 person-years was 45 (95% CI: 41, 50). Meanwhile 11480 patients in the warfarin group experienced 431 events and the incidence rate per 1000 person-years was 60 (95% CI: 55, 66).</li> <li>○ In the pair-wise listing 3, 6710 patients in the dabigatran group experienced 164 major GI bleeding (hospitalization due to GI bleeding) events and the incidence rate per 1000 person-years was 31 (95% CI: 27, 36). Meanwhile 6710 patients in the rivaroxaban group experienced 153 events and the incidence rate per 1000 person-years was 30 (95% CI: 25, 35).</li> </ul> </li> <li>● Compared with warfarin, both NOACs (dabigatran and rivaroxaban) were associated with a significantly lower risk of major GI bleeding (hospitalization due to GI bleeding) events with s-IPTW adjustment or after PS matching (dabigatran vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.69 [0.566, 0.842] and PS-matched HR [95% CI] was 0.705 [0.571, 0.871]; rivaroxaban vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.751 [0.653, 0.863] and PS-matched HR [95% CI] was 0.765 [0.664, 0.881]).</li> </ul>	

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		<p><u>Intracranial hemorrhage (ICH)</u></p> <ul style="list-style-type: none"> <li>• Under the crude populations without s-IPTW adjustment during follow-up period, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12316 patients experienced 61 ICH events and the incidence rate per 1000 person-years was 8 (95% CI: 6, 10).</li> <li>○ In the dabigatran group, 6712 patients experienced 12 ICH events the incidence rate per 1000 person-years was 2 (95% CI: 1, 4).</li> <li>○ In the rivaroxaban group, 20329 patients experienced 63 ICH events and the incidence rate per 1000 person-years was 4 (95% CI: 3, 5).</li> </ul> </li> <li>• Under the s-IPTW adjusted populations during follow-up period, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12231 patients experienced 63 ICH events and the incidence rate per 1000 person-years was 7 (95% CI: 5, 9).</li> <li>○ In the dabigatran group, 6682 patients experienced 10 ICH events and the incidence rate per 1000 person-years was 2 (95% CI: 1, 4).</li> <li>○ In the rivaroxaban group, 20422 patients experienced 65 ICH events and the incidence rate per 1000 person-years was 4 (95% CI: 3, 5).</li> </ul> </li> <li>• Under the PS-matched populations during follow-up period, <ul style="list-style-type: none"> <li>○ In the pair-wise listing 1, 6132 patients in the dabigatran group experienced 11 ICH events and the incidence rate per 1000 person-years was 2 (95% CI: 1, 4). Meanwhile 6132 patients in the warfarin group experienced 32 events and the incidence rate per 1000 person-years was 7 (95% CI: 5, 10).</li> <li>○ In the pair-wise listing 2, 11480 patients in the rivaroxaban group experienced 34 ICH events and the incidence rate per 1000 person-years was 4 (95% CI: 3, 6). Meanwhile</li> </ul> </li> </ul>	

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		<p>11480 patients in the warfarin group experienced 55 events and the incidence rate per 1000 person-years was 7 (95% CI: 6, 10).</p> <ul style="list-style-type: none"> <li>○ In the pair-wise listing 3, 6710 patients in the dabigatran group experienced 12 ICH events and the incidence rate per 1000 person-years was 2 (95% CI: 1, 4). Meanwhile 6710 patients in the rivaroxaban group experienced 20 events and the incidence rate per 1000 person-years was 4 (95% CI: 2, 6).</li> <li>● Compared with warfarin, both NOACs (dabigatran and rivaroxaban) were associated with a significantly lower risk of ICH events with s-IPTW adjustment or after PS matching (dabigatran vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.298 [0.156, 0.57] and PS-matched HR [95% CI] was 0.32 [0.161, 0.635]; rivaroxaban vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.615 [0.419, 0.902] and PS-matched HR [95% CI] was 0.606 [0.396, 0.927]).</li> </ul> <p><u>Stroke</u></p> <ul style="list-style-type: none"> <li>● Under the crude populations without s-IPTW adjustment during follow-up period, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12316 patients experienced 470 stroke events and the incidence rate per 1000 person-years was 63 (95% CI: 57, 68).</li> <li>○ In the dabigatran group, 6712 patients experienced 246 stroke events and the incidence rate per 1000 person-years was 48 (95% CI: 42, 54).</li> <li>○ In the rivaroxaban group, 20329 patients experienced 618 stroke events and the incidence rate per 1000 person-years was 40 (95% CI: 36, 43).</li> </ul> </li> <li>● Under the s-IPTW adjusted populations during follow-up period,</li> </ul>	

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		<ul style="list-style-type: none"> <li>○ In the warfarin group, 12231 patients experienced 475 stroke events and the incidence rate per 1000 person-years was 55 (95% CI: 50, 60).</li> <li>○ In the dabigatran group, 6682 patients experienced 234 stroke events and the incidence rate per 1000 person-years was 48 (95% CI: 42, 55).</li> <li>○ In the rivaroxaban group, 20422 patients experienced 650 stroke events and the incidence rate per 1000 person-years was 44 (95% CI: 41, 47).</li> <li>● Under the PS-matched populations during follow-up period, <ul style="list-style-type: none"> <li>○ In the pair-wise listing 1, 6132 patients in the dabigatran group experienced 231 stroke events and the incidence rate per 1000 person-years was 50 (95% CI: 43, 56). Meanwhile 6132 patients in the warfarin group experienced 232 events and the incidence rate per 1000 person-years was 54 (95% CI: 47, 61).</li> <li>○ In the pair-wise listing 2, 11480 patients in the rivaroxaban group experienced 373 stroke events and the incidence rate per 1000 person-years was 50 (95% CI: 45, 55). Meanwhile 11480 patients in the warfarin group experienced 443 events and the incidence rate per 1000 person-years was 62 (95% CI: 56, 68).</li> <li>○ In the pair-wise listing 3, 6710 patients in the dabigatran group experienced 246 stroke events and the incidence rate per 1000 person-years was 48 (95% CI: 42, 54). Meanwhile 6710 patients in the rivaroxaban group experienced 171 events and the incidence rate per 1000 person-years was 33 (95% CI: 28, 39).</li> </ul> </li> <li>● Compared with warfarin, rivaroxaban was associated with a significantly lower risk of stroke events, and dabigatran had HR below 1 but without statistical significance, with s-IPTW adjustment or after PS matching (dabigatran vs. warfarin: s-IPTW</li> </ul>	

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		<p>adjusted HR [95% CI] was 0.873 [0.736, 1.034] and PS-matched HR [95% CI] was 0.936 [0.78, 1.123]; rivaroxaban vs. warfarin: s-IPTW adjusted HR [95% CI] was 0.796 [0.697, 0.91] and PS-matched HR [95% CI] was 0.812 [0.709, 0.931]).</p> <p><u>Myocardial infarction (MI)</u></p> <ul style="list-style-type: none"> <li>• Under the crude populations without s-IPTW adjustment during follow-up period, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12316 patients experienced 667 MI events and the incidence rate per 1000 person-years was 92 (95% CI: 85, 100).</li> <li>○ In the dabigatran group, 6712 patients experienced 339 MI events and the incidence rate per 1000 person-years was 67 (95% CI: 60, 75).</li> <li>○ In the rivaroxaban group, 20329 patients experienced 1184 MI events and the incidence rate per 1000 person-years was 79 (95% CI: 75, 84).</li> </ul> </li> <li>• Under the s-IPTW adjusted populations during follow-up period, <ul style="list-style-type: none"> <li>○ In the warfarin group, 12231 patients experienced 673 MI events the incidence rate per 1000 person-years was 80 (95% CI: 74, 86).</li> <li>○ In the dabigatran group, 6682 patients experienced 385 MI events and the incidence rate per 1000 person-years was 82 (95% CI: 74, 90).</li> <li>○ In the rivaroxaban group, 20422 patients experienced 1179 MI events and the incidence rate per 1000 person-years was 84 (95% CI: 79, 89).</li> </ul> </li> <li>• Under the PS-matched populations during follow-up period, <ul style="list-style-type: none"> <li>○ In the pair-wise listing 1, 6132 patients in the dabigatran group experienced 318 MI events and the incidence rate per 1000 person-years was 70 (95% CI: 62, 78). Meanwhile 6132 patients in the warfarin group experienced 323 events and</li> </ul> </li> </ul>	

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<b>Name of finished medicinal product:</b> Coumadin, Pradaxa, Xarelto			
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	<p>the incidence rate per 1000 person-years was 78 (95% CI: 70, 87).</p> <ul style="list-style-type: none"> <li>○ In the pair-wise listing 2, 11480 patients in the rivaroxaban group experienced 706 MI events and the incidence rate per 1000 person-years was 100 (95% CI: 93, 107). Meanwhile 11480 patients in the warfarin group experienced 629 events and the incidence rate per 1000 person-years was 91 (95% CI: 84, 99).</li> <li>○ In the pair-wise listing 3, 6710 patients in the dabigatran group experienced 339 MI events and the incidence rate per 1000 person-years was 67 (95% CI: 60, 75). Meanwhile 6710 patients in the rivaroxaban group experienced 326 events and the incidence rate per 1000 person-years was 66 (95% CI: 59, 74).</li> <li>● Compared with warfarin, both NOACs (dabigatran and rivaroxaban) did not show statistically significant difference in the risk of MI events with s-IPTW adjustment or after PS matching (dabigatran vs. warfarin: s-IPTW adjusted HR [95% CI] was 1.007 [0.87, 1.166] and PS-matched HR [95% CI] was 0.919 [0.788, 1.071]; rivaroxaban vs. warfarin: s-IPTW adjusted HR [95% CI] was 1.013 [0.912, 1.124] and PS-matched HR [95% CI] was 1.085 [0.974, 1.209]).</li> </ul>		
<b>Discussion:</b>	<p>Among Japanese NVAf patients aged 18 years and older with concomitant CAD, the risks of fatal or non-fatal major bleeding events were significantly lower for both NOACs (dabigatran and rivaroxaban) vs. warfarin. Likewise, the significantly lower risks of the composite outcome of stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH events, were observed for both NOACs vs. warfarin. The risks of individual outcomes of SE, all-cause mortality (inpatient), major GI bleeding (hospitalization due to GI bleeding), and ICH events were also significantly lower for both NOACs vs.</p>		

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	<p>warfarin. However, only rivaroxaban was associated with a significantly lower risk of stroke events vs. warfarin, while statistical significance of the risks of MI events was not achieved for both NOACs vs. warfarin. Furthermore, the risks of fatal or non-fatal major bleeding events for dabigatran were significantly lower compared with rivaroxaban.</p> <p>In conclusion, in adult Japanese NVAf patients with concomitant CAD, the risks were significantly lower for both NOACs (dabigatran and rivaroxaban) vs. warfarin with regards to major bleeding and the composite outcome of stroke, SE, MI, all-cause mortality (inpatient), major bleeding, major GI bleeding (hospitalization due to GI bleeding), or ICH, and were significantly lower for dabigatran vs. rivaroxaban with regards to major bleeding.</p>		
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