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Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Dabigatran (Pradaxa®)			
Name of active ingredient: Dabigatran etexilate mesylate (ATC code: B01AE07)			
Report date: 16 Feb 2024	**Study number:** 1160-0304	**Version/Revision:** 1.0	**Version/Revision date:** NA
Title of study:	Relationship of Advanced Holding Education and ADherence on antithrombotic in younger NVAF patients		
Keywords:	Dabigatran, education, adherence, antithrombotic, non-valvular atrial fibrillation (NVAF)		
Rationale and background:	The overall prevalence of atrial fibrillation (AF) in Taiwanese was 1.4% in men and 0.7% in women in 2008 and was estimated to be 4.01% in 2050. Patients with AF faced a strongly elevated risk of stroke—about 3- to 5-fold higher after adjustment for risk factors. <u>Adherence</u> Lifelong oral anticoagulant (OAC) therapy is the preferred treatment for the prevention of thromboembolic events in the majority of patients with AF. Adherence to medication is essential for valid treatment for OAC therapy. Non-adherent patients (the proportion of days covered for new oral anticoagulants [NOAC] is < 80%) were reported to be 2.08 times more likely to experience ischemic stroke compared to adherent patients in one year. A retrospective study from the USA evaluating the adherence rate of OACs by Morisky 8-Item Medication Adherence Questionnaire (MMAS-8) score concluded that the adherence could be attributed to differences in health knowledge and duration of taking anticoagulant medication. Age is another influencing factor in treatment adherence. Younger patients have significantly worse adherence compared to older ones because of their low awareness of the risks of AF and the benefits of AF treatments regarding the prevention of ischemic events. Patients under 75 years old might have lower risk scores but their poor adherence may increase the incidence of stroke and lifetime economic burden (e.g., work loss and premature death). Providing advanced education material to patients who are under 75 years old to increase their awareness of the importance of early intervention and drug adherence may be a feasible strategy to enhance the adherence rate to OACs among younger patients, to reduce stroke/or recurrent risk, and to contribute to socioeconomic saving. However, such health education has not been		

	implemented in Taiwan currently. Therefore, we initiated a non-interventional study (NIS) in newly diagnosed AF adult patients who were under 75 years old and were prescribed dabigatran. The study aimed to explore whether the advanced educational intervention would improve adherence to dabigatran. <u>Epidemiology</u> The risk of ischemic stroke in AF is heterogeneous, depending on different risk factors with age being the important driver of stroke risk. The optimal assessment should include age and incident comorbidities. In addition, different comorbidities should be identified due to the different relative contributions to stroke. However, preliminary Taiwanese data were limited especially for data from newly diagnosed AF patients. In parallel to treatment adherence, we collected routine clinical practice data on the occurrence of comorbidities in newly diagnosed AF patients prescribed with dabigatran.
Research question and objectives:	The primary objective of this study was to explore whether the advanced educational intervention would improve the adherence to dabigatran, in a 12-month follow-up period for newly diagnosed atrial fibrillation (AF) adult patients under 75 years old. The secondary objectives were to describe comorbidities and CHA_2DS_2-VASc score at baseline and at the end of the study; and to describe stroke, thromboembolic events, and bleeding events in dabigatran patients in a 12-month follow-up period for AF adult patients under 75 years old.
Study design:	This was a multi-center, 1:1 randomized study to evaluate the effects of educational intervention on adherence to dabigatran, for up to 12 months. Adult patients newly diagnosed with AF within 1 month, under 75 years old, and newly prescribed with dabigatran on physician's decision per local labeling were equally randomized to receive standard of care (routine clinical practice) or standard of care (routine clinical practice) with advanced educational intervention. The study did not incorporate any interim analysis. The study duration consisted of a 1-year enrolment period and a 12-month follow-up period consisting of visits at 3, 6, 9, and 12 months. Being an NIS, the time points of follow-up visits were set in accordance with the routine outpatient follow-ups of AF in Taiwan. The educational materials from "Shared decision making of treatment of NOAC in AF patients" (NTA: 180647) and "Atrial Fibrillation Patient Care in Hospitals" (NTA: 190707) were used as the educational materials for the experimental group. The education material was delivered after randomization (baseline); and at 3, 6, and 9 months thereafter. The adherence to dabigatran was measured by MMAS-8 score at 3, 6, 9, and 12 months. The comorbidities, CHA_2DS_2-VASc scores, and HAS-BLED scores were recorded at baseline; and 3, 6, 9, and 12 months. Stroke, thromboembolic events, and bleeding-related events were also captured during 12 months.
Setting:	The study was carried out from 2020 to 2023 at around 23 hospitals, where AF patients were mainly treated in Taiwan. The first patient to be enrolled

	was from 21-Sep-2020, and the last patient's last visit was on 26-Jun-2023. A total of 897 patients were screened and signed the ICF, and 873 patients were eligible to be enrolled in the analysis.
Subjects and study size, including dropouts:	Inclusion criteria Patients were included if ALL the following criteria were met: (1) Provide written informed consent prior to participation (2) Female or male patients aged ≥ 20 years and < 75 years, newly diagnosed with non-valvular atrial fibrillation (NVAF) within 1 month and newly prescribed with dabigatran on physician's decision before study enrolment. Exclusion criteria Patients were not included if ANY ONE of the following criteria was met: (1) Contraindication to the use of dabigatran (i.e., active pathological bleeding, history of a serious hypersensitivity reaction to dabigatran [e.g., anaphylactic reaction or anaphylactic shock], severely impaired renal function [Ccr < 30 mL/min], hemorrhagic manifestations, bleeding diathesis, mechanical prosthetic heart valve, congenital or acquired coagulation disorders, organic lesions with bleeding tendency, or concomitantly use systemic ketoconazole, cyclosporine, and itraconazole) (2) Participated in other interventional trials currently or in the past 30 days
Variables and data sources:	Baseline characteristics ▪ Demographics (date of birth, gender, race, etc.) ▪ AF-related medical histories ▪ CHA_2DS_2-VASc score ▪ HAS-BLED score (modified HAS-BLED for newly initiated patients) ▪ Kidney function (creatinine clearance [CrCl] and estimated glomerular filtration rate [eGFR]) ▪ Comorbidities ▪ Concomitant therapies related to bleeding and AF ▪ Dosing of dabigatran Primary outcome The proportion of patients with high adherence to dabigatran treatment which was defined as achieving the MMAS-8 score of 8 points at 12 months in patients with and without advanced educational intervention Secondary outcomes

	(1) The proportion of patients with high adherence to dabigatran treatment which was defined as achieving the MMAS-8 score of 8 points at 3, 6, and 9 months in patients with and without advanced educational intervention (2) The proportion of patients with medium (MMAS-8 score: 6 – 7 points) and low (MMAS-8 score < 6 points) adherence to dabigatran treatment at 3, 6, 9, and 12 months in patients with and without advanced educational intervention (3) The mean MMAS-8 score at 3, 6, 9, and 12 months in patients with and without advanced educational intervention (4) The discontinuation rate of dabigatran and reasons for discontinuation (switch or stop treating dabigatran) in patients with and without advanced educational intervention <u>Further outcomes</u> <u>Among pooled patient set (dabigatran patients with and without advanced educational intervention) following outcomes are presented</u> (1) To describe the CHA_2DS_2-VASc score at baseline and at the end of study visit (2) To describe newly identified risk factors (including hypertension, diabetes, congestive heart failure, vascular disease [myocardial infarction, peripheral artery disease, and complex aortic plaque], ischemic heart disease, left ventricular dysfunction, stroke, transient ischemic attack, thromboembolism, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 µmol/L, or eGFR < 60 mL/min/1.73 m^2), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia) at baseline and at the end of the study (3) Stroke and thromboembolic events during the 12-month follow-up (4) Bleeding-related events during the 12-month follow-up (5) HAS-BLED score at baseline and the end of study (6) Other ADRs
Results:	**Demographics** The baseline demographics were distributed comparably among the Standard care only group (control group, n = 441) and the Standard care with advanced educational intervention (experimental group, n = 432), with no statistical difference among the two groups. The study population was mostly Taiwanese 871 (99.8%) subjects, consisting of more male (n = 525, 60.1%) subjects compared with female (n = 348, 39.9%), and had a mean age of 65.0 ± 7.60 years. For the educational level, 38 (4.4%) subjects were not educated, 224 subjects (25.8%)

	received elementary school education, 177 (20.4%) subjects received junior high school education, 268 (30.9%) subjects received senior high school education, and 160 (18.5%) subjects received college or higher education, while 6 were missing. Most subjects were non-alcoholic (n = 812, 93.1%), and the average height and weight of the eligible population were 163.6 ± 8.83 cm and 70.8 ± 14.84 kg. **Primary outcome** The primary outcome was to describe the proportion of patients with high adherence to dabigatran treatment which was defined as achieving an MMAS-8 score of 8 points at 12 months for each group. Subjects without MMAS-8 value recorded at 12 months were excluded from the analysis of the primary endpoint. All tests were done under a statistical level of 0.05. For the MMAS-8 scores, 380 (73.5%) of the total eligible subjects at 12 months were classified as having high adherence to dabigatran treatment. Of the population, the number of participants with high adherence at the end of the study at 12 months was 199 (73.4%) in the control group and 181 (73.6%) in the experimental group who completed the study. The two groups had no statistical difference regarding adherence to the treatment with or without advanced educational intervention (P = .97). **Secondary outcome** The secondary outcome of the Mean MMAS scores at 3, 6, 9, and 12 months were compared between patients with and without advanced educational intervention using Chi-square, Fisher's exact, or other appropriate tests for categorical data and using t-test or Wilcoxon rank-sum test for continuous data. Similarly, subjects without MMAS-8 value recorded at a specific visit were excluded from the analysis of corresponding secondary endpoints. Other secondary outcomes in patients with and without advanced educational intervention separately and further outcomes only within the pooled patient set (e.g., comorbidities, stroke/ thromboembolic/ bleeding events, risk factors, ADR, etc.) were all analyzed in a descriptive manner. (1) For the MMAS-8 scores, 453 subjects (62.3%) at 3 months, 417 (69.2%) at 6 months, and 388 (71.1%) at 9 months of the total eligible subjects were classified as high adherence to dabigatran treatment. Of the population, the proportion of participants with high adherence at 3, 6, and 9 months were 224 (61.7%), 199 (66.3%), and 204 (71.8%) in the control group; and were 229 (62.9%), 218

	(71.9%), and 184 (70.2%) in the experimental group. The two groups had no statistical difference regarding the adherence to the treatment with or without advanced educational intervention at 3 months (*P* = .74), 6 months (*P* = .14), and 9 months (*P* = .68). (2) For the medium adherence to dabigatran treatment, the number of participants with medium adherence at 3, 6, 9, and 12 months was 83 (22.9%), 66 (22.0%), 52 (18.3%), and 50 (18.5%) in the control group; and were 77 (21.2%), 57 (18.8%), 53 (20.2%), and 51 (20.7%) in the experimental group. The two groups had no statistical difference regarding the adherence to the treatment with or without advanced educational intervention at 3 months (P = .58), 6 months (P = .33), 9 months (P = .57), and 12 months (P = .51). For the low adherence to dabigatran treatment, the proportion of participants with low adherence at 3, 6, 9, and 12 months was 56 (15.4%), 35 (11.7%), 28 (9.9%), and 22 (8.1%) in the control group; and were 58 (15.9%), 28 (9.2%), 25 (9.5%), and 14 (5.7%) in the experimental group. The two groups had no statistical difference regarding the adherence to the treatment with or without advanced educational intervention at 3 months (P = .85), 6 months (P = .33), 9 months (P = .90), and 12 months (P = .28). (3) For the mean MMAS-8 score at 3, 6, 9, and 12 months in patients with and without advanced educational intervention, the average MMAS-8 scores for the control group at 3, 6, 9, and 12 months were 7.0 ± 1.65 (n = 363) at 3 months, 7.2 ± 1.41 (n = 300) at 6 months, 7.4 ± 1.25 (n = 284) at 9 months, and 7.4 ± 1.21 (n = 271) at 12 months; and for the experimental group were 7.0 ± 1.72 (n = 364) at 3 months, 7.3 ± 1.38 (n = 303) at 6 months, 7.3 ± 1.27 (n = 262) at 9 months, and 7.5 ± 1.07 (n = 246) at 12 months. The two groups had no statistical difference regarding the adherence to the treatment with or without advanced educational intervention at 3 months (P = .67), 6 months (P = .13), 9 months (P = .72), and 12 months (P = .80). (4) For the discontinuation rate of dabigatran and reasons. Of all the 873 subjects, 438 (50.3%) complied with the dabigatran treatment while 348 (40%) discontinued, the rest were either marked as not done for 85 (9.8%) subjects or missing for 2 subjects. For the control group of 441 subjects, 225 (51.1%) complied with the dabigatran treatment while 167 (38%) discontinued, and 60 (35.9%) subjects switched to other treatment; the rest were either marked as not done for 48 (10.9%) subjects or missing for 1 subject. For the experimental group of 432 subjects, 213 (49.4%) complied with the Dabigatran treatment while 181 (42%) discontinued 70 (38.7%) subjects switched to other treatment, the rest were either marked as not done for 37 (8.6%) subjects or

	missing for 1 subject. The two groups show no statistical difference (P = .33) for the discontinuation rate of dabigatran, and the reason for discontinuation (P = .60). The reason for discontinuation were switched to other treatment, consisting of 130 (37.4%) subjects, with other reason consisting of 218 (62.6%) subjects. The more common reason for subjects to switch to other treatments was the occurrence of adverse events, with 12 (20.0%) subjects in the control group and 13 (18.6%) subjects in the experimental group, which showed no statistical difference (P = .80). **Further outcome** For the further outcome analysis including the change of CHA2DS2-VASc score from baseline, the identification of newly identified risk factors, the stroke and thromboembolic events and bleeding-related events during the study, and the HAS-BLED score were comparable among the two groups. **Safety Analysis** For the safety analysis, seventeen (3.9%) patients in the control group experienced 17 adverse events and 18 (4.2%) patients in the experimental group experienced 19 adverse events. Of those in the control group, 11 (2.5%), 1 (0.1%), 2 (0.5%), 0 (0.0%), and 3 (0.7%) had AEs graded as severity in mild, moderate, severe, life-threatening/disabling, and death related to AE, while in the experimental group the distribution was 13 (3.0%), 0 (0.0%), 0 (0.0%), 0 (0.0%), and 5 (1.2%), respectively, with no statistical difference (P = .42). Regarding to the severe adverse event (SAE), 4 (0.9%) patients experienced 4 SAEs in the control group, and 5 (1.2%) patients experienced 6 SAEs in the experimental group, having no statistical difference (P > .99). Of all the AEs, 15 (3.4%) in the control group and 13 (3.0%) in the experimental group were suspected to have a relationship to Dabigatran, also with no statistical difference (P = .40). After the occurrence of AEs, no actions were needed to be taken in 3 (0.7%) patients in the control group, and 1 (0.2%) patient in the experimental group (P = .34); the study drug was permanently discontinued due to the AEs in 11 (2.5%) patients for the control group, and 15 (3.5%) in the experimental group (P = .26). Though 13 patients (N = 2.9) and 10 (2.3%) patients suffering from AEs recovered in the control and experimental groups, 1 (0.2%) and 3

	(0.7%) had persisting AEs in each group, and 3 (0.7%) and 5 (1.2%) patients died in each group with no statistical difference (P = .40). Overall, advanced educational intervention did not yield statistical significance in dabigatran adherence across criteria.
Discussion:	This study explored the impact of advanced education on antithrombotic adherence in younger non-valvular atrial fibrillation (NVAF) patients under 75 years old. The primary objective assessed whether advanced educational intervention improves dabigatran adherence over a 12-month follow-up, defining high adherence as an MMAS-8 score of 8 points. Despite education's importance, barriers to effective medication use persisted, including poor communication, insufficient drug understanding, skepticism, and economic constraints. The study's generalizability may be compromised by the unique circumstances of the COVID-19 pandemic, and a notably dropout rate, distinct from other period studies, introduces potential bias that could limit the broader applicability of the findings. While education alone might not guarantee adherence, adopting a patient-centered approach and leveraging technology, like mobile apps, enhances adherence. The study tailored its focus to younger NVAF patients, suggesting older patients might exhibit better adherence due to health concerns. Emerging technologies, such as mobile apps, demonstrated success in improving medication management for elderly AF patients, emphasizing the potential of a multifaceted approach to enhance medication adherence in this population. In conclusion, the study provided comprehensive insights into the adherence patterns of patients receiving dabigatran treatment with and without advanced educational intervention. Despite the diligent examination of multiple outcomes over various time intervals, the results consistently indicated that the inclusion of advanced educational measures did not lead to significant differences in adherence outcomes compared to routine clinical practice alone. The absence of statistically significant variations in adherence metrics, discontinuation rates, and reasons for discontinuation may be restricted by the COVID-19 pandemic, which suggested that the impact of advanced educational interventions might be limited in this context. Further research might be warranted to explore alternative strategies or tailor interventions based on specific patient characteristics to enhance treatment adherence.
Marketing Authorisation Holder(s):	Boehringer Ingelheim International GmbH
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