



BMJ Open Outcome disparities in patients with atrial fibrillation based on insurance plan and educational attainment: a nationwide, multicenter and prospective cohort trial

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ABSTRACT

Background Atrial fibrillation (AF) is a complex disease. The management of AF requires continuous patient engagement and integrative healthcare.

Objectives To explore the association between adverse AF-related clinical outcomes and the following two sociodemographic factors: educational attainment and insurance plan.

Design A nationwide, prospective, multicenter, cohort trial.

Setting National registry of 3402 patients with non-valvular AF in Thailand.

Participants All patients enrolled in the registry, except those with missing information on educational attainment or insurance plan. Finally, data from 3026 patients (mean age 67 years, SD 11.3; 59% male sex) were analysed.

Primary outcomes Incidences of all-cause mortality, ischaemic stroke and major bleeding during the 36-month follow-up period. Survival analysis was performed using restricted mean survival time (RMST) and adjusted for multiple covariates. The levels of the educational attainment were as follows: no formal education, elementary (grade 1–6), secondary (grade 7–12) and higher education (tertiary education).

Results The educational attainment of the majority of patients was elementary (N=1739, 57.4%). The predominant health insurance plans were the Civil Servant Medical Benefit Scheme (N=1397, 46.2%) and the Universal Coverage Scheme (N=1333, 44.1%). After 36 months of follow-up, 248 patients died (8.2%), 95 had ischaemic stroke (3.1%) and 136 had major bleeding (4.5%). Patients without formal education died 1.78 months earlier (adjusted RMST difference –1.78; 95% CI, –3.25 to –0.30; p=0.02) and developed ischaemic stroke 1.04 months sooner (adjusted RMST difference –1.04; 95% CI, –2.03 to –0.04; p=0.04) than those attained a level of higher education. There were no significant differences in RMSTs for all three clinical outcomes when considering the type of health insurance plan.

Conclusion Educational attainment was independently associated with all-cause mortality and ischaemic stroke in patients with AF, but adverse clinical outcomes were not related to the types of health insurance in Thailand.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study explored the association between two sociodemographic factors (ie, educational attainment and health insurance plan) and the occurrences of adverse clinical outcomes in patients with atrial fibrillation.
- ⇒ Data were derived from a large prospective and nationwide cohort.
- ⇒ Causal relationships cannot be assumed from the outcomes of a cohort trial.
- ⇒ Some patients were excluded because of missing information, which might have contributed to selection bias.

Trial registration number Thai Clinical Trial Registration; Study ID: TCTR20160113002.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiovascular disease that increases the risks of death and stroke. Over the past two decades, there has been a twofold, global increase in the prevalence of AF, regardless of a country's sociodemographic index.¹ AF is a chronic, complex and multifaceted condition. Treatment of AF requires patients to change their lifestyle and adhere to chronic therapy.² Healthcare providers from multiple specialty have to work together to optimise treatment strategy. Patients themselves need to understand the disease and their responsibilities in their own care.

Education is an important factor for understanding one's own illness.³ Indeed, education has been shown to be a major determinant of cardiovascular and cancer mortality.^{4,5} In the case of a complex and chronic disease such as AF, long-term commitments from patients are necessary to adhere to medications and

lifestyle adjustments. Patients with low educational attainment were shown to be associated with treatment non-compliance,⁶ worsened symptom severity⁷ and poorer prognosis.^{6,8}

The quality and accessibility of healthcare are crucial factors that affects clinical outcomes. Worldwide, achieving universal access to healthcare has been a goal. Accordingly, a health medical plan called universal coverage scheme (UCS) was implemented in Thailand.⁹ UCS is a propoor and unremarkable medical scheme offered to all Thai citizens not eligible for other government based medical plans, namely Civil Servant Medical Benefit Scheme (CSMBS) and compulsory social security scheme (SSS). UCS is currently the most common health insurance plan across Thailand, covering more than 70% of the population.¹⁰ After first being implemented in 2002, UCS is now globally regarded as a highly successful policy.^{9,11} By 2018, uninsured population numbers had been dramatically reduced from approximately 47 million (30% of the total population) to less than 400 000 people (0.06% of the total population).^{9,10} Life expectancy improved from 70.6 years in 2000 to 74.6 years in 2015.⁹ However, the path to achieve universal access to healthcare in Thailand is fraught with challenges. Similar to healthcare reform in many low-income and middle-income countries, UCS faces problems with financial sustainability and quality of services.^{9,11} The benefit package of UCS is less comprehensive than that of CSMBS because of budget limitation.⁹ Previous studies have shown that the clinical outcomes of CSMBS beneficiaries are better than those of UCS beneficiaries.^{12,13} Over the last decade, UCS has responded by strengthening its primary healthcare system and expanding its benefit packages.⁹ However, the impact of these improvements has yet to be investigated. Both education and health coverage are among the major determinants of clinical outcomes. In a middle-income country such as Thailand, services provided by the government in both areas are still developing. In the present cohort trial, we prospectively analysed the AF patients enrolled in the national registry of Thailand. We aimed to explore whether the two sociodemographic factors (ie, educational attainment and insurance plan) were associated in adverse clinical outcomes of all-cause mortality, ischaemic stroke and major bleeding in these patients independent of other comorbidities. We believe that the results of this study can provide new insights into disparities of the education and insurance plan in Thailand as well as in other low and middle-income countries that implemented similar policies.

METHODS

Participant selection

Between 2014 and 2017, patients with AF across Thailand were consecutively enrolled in the cohort of antithrombotic use and optimal international normalised ratio (INR) level in patients with non-valvular atrial fibrillation in Thailand (COOL-AF) registry. Details of the COOL-AF

study have been reported elsewhere.¹⁴ Briefly, patients age>18year with electrocardiography confirmed AF were eligible for the enrolment. The exclusion criteria¹⁴ were as follows: (1) ischaemic stroke within 3 months, (2) haematologic disorders that can increase the risk of bleeding, (3) mechanical prosthetic valve or valve repair, (4) rheumatic valve disease or severe valve disease, (5) AF associated with transient reversible cause, (6) current participation in a clinical trial, (7) life expectancy<3 years, (8) pregnancy, (9) inability to attend follow-up visits and (10) refusal to participate in the study. Written informed consent was obtained from all enrolled patients.¹⁴

This study included all patients enrolled in the registry, except those with missing information on educational attainment or insurance plan. Those who were excluded from the present study remained in the main registry until the end of follow-up (online supplemental appendix figure 1).

Data collection

Baseline data including demographics, educational attainment level, insurance plan, medical history and administered medications taken were obtained from medical records and patient interviews at the enrolment. For educational attainment, data were self-report. Patient or their families completed the educational attainment questionnaire in the hospital registration form. The insurance plan information was centrally linked to the government database and available in the patients' medical record. All patients were prospectively followed for the endpoints of death from any causes, ischaemic stroke or major bleeding. Data on adverse outcomes were collected from medical records and telephonic interviews every 6 months until the end of the 36-month follow-up period. All adverse outcome events were validated by an adjudication committee. Ischaemic stroke and major bleeding were defined according to the standard criteria.^{15,16}

Data classifications

The levels of educational attainment were defined as follows: no formal education, elementary education (grades 1–6), secondary education (grades 7–12) and higher education (ie, tertiary education or education beyond secondary education). The categories of the insurance plans were as follows: (1) SSS, a contributory and compulsory scheme for non-government employees; (2) CSBMS, a fringe benefit provided for government employees; (3) UCS, a non-contributory insurance scheme provided for all citizens of Thailand who were not covered by (1) or (2); and (4) non-government-based scheme (NGS), which included private insurance, opt-out of the plan and out-of-pocket payments.

According to standard guidelines,² stroke and bleeding risks were assessed using congestive heart failure, hypertension, age≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex (female) (CHA₂DS₂-VASc) and hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition,

labile INR, elderly (>65 years), drugs/alcohol concomitantly (1 point each) (HASBLED) scores, respectively. In general, patients without clinical stroke risk factors do not typically require anticoagulation therapy, while patients with stroke risk factors (ie, $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$) are likely to benefit from anticoagulant.² The HASBLED is a bleeding risk score. A higher HASBLED score is related to a higher risk of bleeding.²

The types of anticoagulants were grouped as follows: none, vitamin K antagonist (VKA) and direct oral anticoagulant (DOAC).

Statistical analysis

All analyses were performed using SAS software, V.9.4_M6 of the SAS OnDemand for Academics (SAS Institute). Categorical variables are expressed as numbers and percentages, and continuous variables are expressed

as means and SDs. Chi-square and one-way analyses of variance were used to compare differences in baseline characteristics.

Event probabilities were assessed by restricted mean survival time (RMST) analyses using LIFETEST and RMSTREG procedures in the SAS/STAT software V.15.1. We initially chose to use a Cox proportional hazard model for the analyses. However, the proportionality hazard assumption of all three primary outcomes was violated (ie, $p < 0.05$ based on the weighted Schoenfeld residual (online supplemental appendix table 1)). RMST analysis was selected as an alternative method. The RMST is equivalent to the area under the entire survival curve up to a fixed time point. It is widely advocated as an alternative to the Cox proportional hazard model, especially when proportionality is violated.^{17 18}

Table 1 Baseline characteristics by insurance plans (N=3026)

	All (N=3026)	UHC (N=1333)	SSS (N=142)	NGS (N=154)	CSMBS (N=1397)	P value
Age, mean (SD), years	67.3 (11.3)	66.7 (11.2)	56.6 (10.5)	65.4 (11.9)	69.2 (10.6)	<0.001
Male, No. (%)	1779 (58.8%)	732 (54.9%)	100 (70.4%)	91 (59.1%)	856 (61.3%)	<0.001
$\text{CHA}_2\text{DS}_2\text{-VASc}$, mean (SD)	3.0 (1.7)	3.0 (1.6)	2.1 (1.7)	2.8 (1.7)	3.2 (1.7)	<0.001
HASBLED, mean (SD)	1.5 (1.0)	1.5 (1.0)	1.2 (1.1)	1.3 (1.0)	1.6 (1.0)	<0.001
CAD, No. (%)	478 (15.8%)	198 (14.9%)	19 (13.4%)	21 (13.6%)	240 (17.2%)	0.255
CHF, No. (%)	829 (27.4%)	419 (31.4%)	33 (23.2%)	33 (21.4%)	344 (24.6%)	<0.001
Hypertension, No. (%)	2061 (68.1%)	865 (64.9%)	81 (57.0%)	109 (70.8%)	1006 (72.0%)	<0.001
Dyslipidaemia, No. (%)	1703 (56.3%)	616 (46.2%)	77 (54.2%)	102 (66.2%)	908 (65.0%)	<0.001
Diabetes, No. (%)	730 (24.1%)	278 (20.9%)	36 (25.4%)	47 (30.5%)	369 (26.4%)	0.002
Stroke/TIA, No. (%)	530 (17.5%)	237 (17.8%)	25 (17.6%)	20 (13.0%)	248 (17.8%)	0.512
Vascular disease, No. (%)	510 (16.9%)	209 (15.7%)	20 (14.1%)	24 (15.6%)	257 (18.4%)	0.200
Current smoker, No. (%)	98 (3.2%)	60 (4.5%)	8 (5.6%)	4 (2.6%)	26 (1.9%)	<0.001
Alcohol use, No. (%)	129 (4.3%)	53 (4.0%)	9 (6.3%)	10 (6.5%)	57 (4.1%)	0.289
History of bleeding, No. (%)	304 (10.0%)	127 (9.5%)	19 (13.4%)	6 (3.9%)	152 (10.9%)	0.022
Abnormal renal function, No. (%)	90 (3.0%)	39 (2.9%)	6 (4.2%)	2 (1.3%)	43 (3.1%)	0.507
Abnormal liver function, No. (%)	67 (2.2%)	29 (2.2%)	6 (4.2%)	3 (1.9%)	29 (2.1%)	0.418
Antiplatelets, No. (%)	802 (26.5%)	343 (25.7%)	39 (27.5%)	42 (27.3%)	378 (27.1%)	0.863
Anticoagulants						<0.001
VKA, No. (%)	2075 (68.6%)	995 (74.6%)	93 (65.5%)	107 (69.5%)	880 (63.0%)	
DOAC, No. (%)	182 (6.0%)	5 (0.4%)	1 (0.7%)	10 (6.5%)	166 (11.9%)	
None, No. (%)	769 (25.4%)	333 (25.0%)	48 (33.8%)	37 (24.0%)	351 (25.1%)	
Educational attainment						<0.001
No formal education, No. (%)	213 (7.0%)	152 (11.4%)	2 (1.4%)	11 (7.1%)	48 (3.4%)	
Elementary, No. (%)	1526 (50.4%)	921 (69.1%)	54 (38.0%)	59 (38.3%)	492 (35.2%)	
Secondary, No. (%)	639 (21.1%)	206 (15.5%)	40 (28.2%)	42 (27.3%)	351 (25.1%)	
Higher education, No. (%)	648 (21.4%)	54 (4.1%)	46 (32.4%)	42 (27.3%)	506 (36.2%)	

CAD, coronary artery disease; $\text{CHA}_2\text{DS}_2\text{-VASc}$, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischaemic attack (TIA), vascular disease, age 65–74 years, sex category; CHF, congestive heart failure; CSMBS, civil servant medical benefit scheme; DOAC, direct oral anticoagulant; HASBLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly; NGS, non-government-based scheme; SSS, social-security scheme; UCS, universal coverage scheme; VKA, vitamin K antagonist.

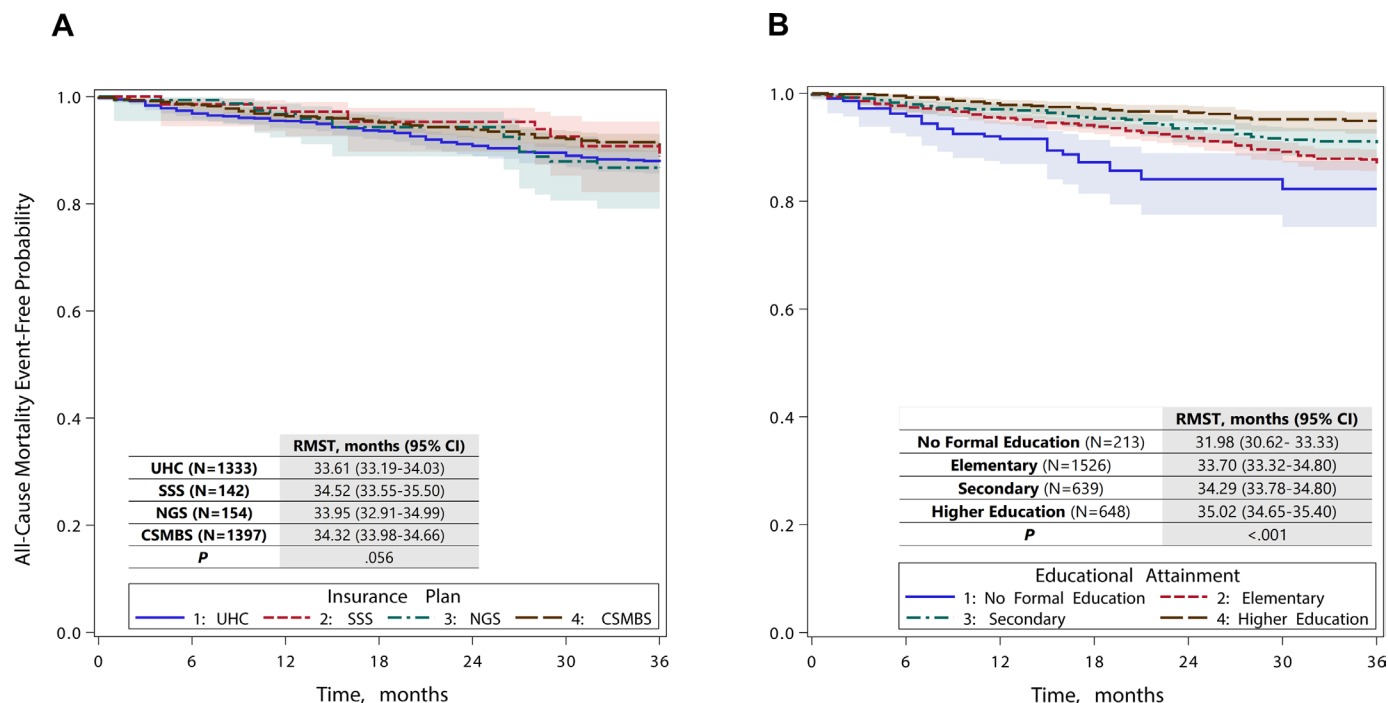


Figure 1 Kaplan-Meier curve for all-cause mortality with 95% confidence limits. (A) Kaplan-Meier curve for all-cause mortality by insurance plans. (B) Kaplan-Meier curve for all-cause mortality by educational attainment. CSMBS, civil servant medical benefit scheme; NGS, non-government-based scheme; SSS, social-security scheme; UCS, universal coverage scheme.

Here, we computed RMST to the time horizon of 36 months using Kaplan-Meier method for survival probability estimation. We then adjusted RMST with multiple covariates using pseudovalue linear regression model.¹⁹ The model consisted of age, sex, educational attainment, insurance plan, types of anticoagulant, CHA₂DS₂VASc and HASBLED scores. We also calculated adjusted RMST to ischaemic stroke and major bleeding among patients who were still alive at the end of the follow-up, to account for the competing risk of death.²⁰ The results were presented as the differences of RMSTs and 95% CI for each covariate.

The RMST difference estimated months gain or loss of event-free time over a period of 36 months. P values were reported for all between-group comparisons. A p value<0.05 was considered significant.

RESULTS

Participants

The COOL-AF registry comprises of 3402 patients. Of these, 376 patients had incomplete data and were excluded from the study (online supplemental appendix figure 1 and table 2). Finally, data from 3026 patients were included in the analyses. None of the patients were lost to follow-up. The participant population (table 1) was approximately 67 years old and primarily male (N=1779, 58.8%). The most common comorbidity was hypertension (N=2061, 68.1%), followed by congestive heart failure (N=829, 27.4%) and diabetes (n=730, 24.1%). The mean CHA₂DS₂VASc and HASBLED scores were 3.0 (SD 1.7) and 1.5 (SD 1.0), respectively.

Insurance plan

The participant population was predominantly insured by either CSMBS (N=1397, 46.2%) or UCS (N=1333, 44.1%). Patients insured by CSMBS were at greater risk of stroke and bleeding as assessed by CHA₂DS₂VASc (CSMBS, 3.2; UCS, 3.0; NGS, 2.8; SSS, 2.1; p<0.001) and HASBLED (CSMBS, 1.6; UCS, 1.5; NGS, 1.3; SSS, 1.2; p<0.001) scores.

Educational attainment

More than one-third of the patients attained at least a secondary education level (N=1287, 42.5%). Among these patients, the male sex was predominant (N=948, 73.7%). Age, CHA₂DS₂VASc and HASBLED scores (online supplemental appendix table 3) were higher in those patients with no formal education (mean age, 74 years; CHA₂DS₂VASc, 3.9; HASBLED, 1.7) compared with those who attained an elementary (mean age, 69 years; CHA₂DS₂VASc, 3.3; HASBLED, 1.6), secondary (mean age, 64 years; CHA₂DS₂VASc, 2.7; HASBLED, 1.5) or higher level of education (mean age, 63 years; CHA₂DS₂VASc, 2.6; HASBLED, 1.4; p<0.001 for all comparisons).

Adverse outcomes

During the 36 months follow-up, 248 patients died (8.2%), 95 had ischaemic stroke (3.1%) and 136 had major bleeding (4.5%). There were no significant differences in the rates of adverse events between those with missing information who were initially excluded and those patients whose data were included in the final analysis (online supplemental appendix table 2). Figure 1A,B shows the Kaplan-Meier survival curves of all-cause

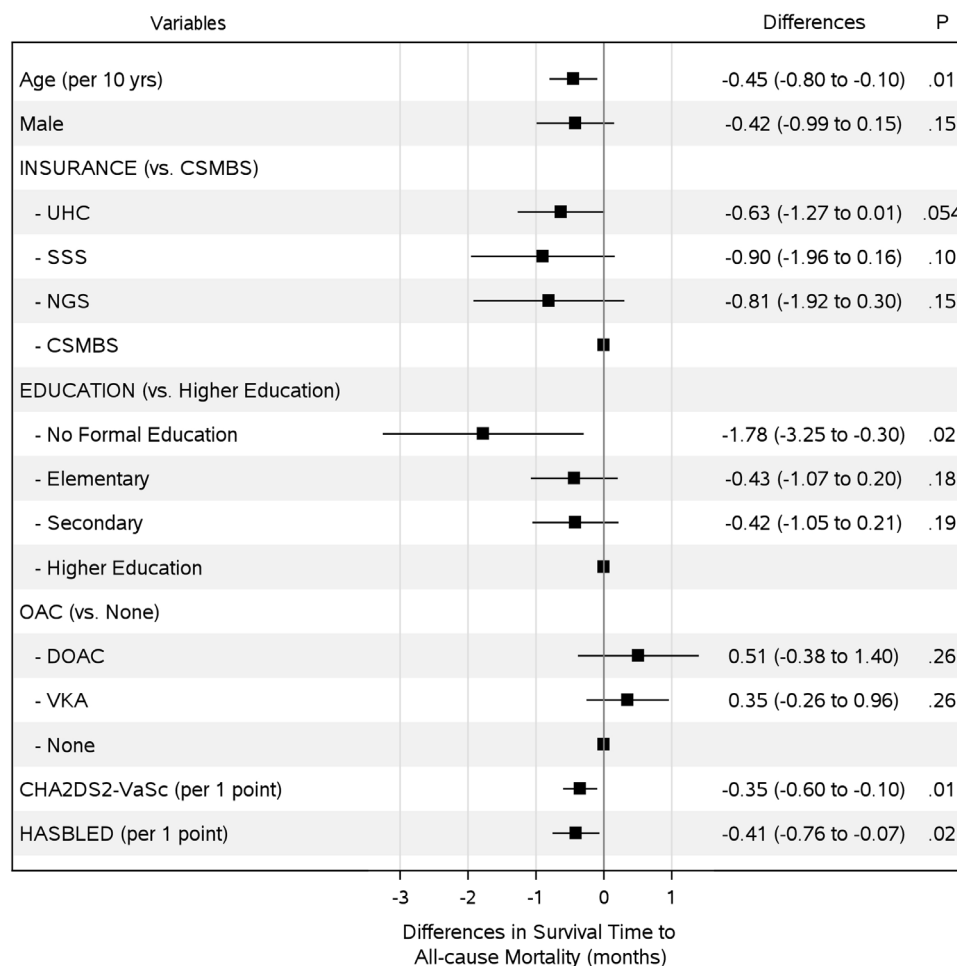


Figure 2 Differences in adjusted restricted median survival time to all-cause mortality over a period of 36 months. The model was adjusted for of age, sex, educational attainment, insurance plan, types of anticoagulant, CHA₂DS₂VAS_c, and HASBLED scores. CAD, coronary artery disease; CHA₂DS₂VAS_c, congestive heart failure, hypertension, age≥75 years, diabetes mellitus, stroke or transient ischaemic attack (TIA), vascular disease, age 65–74 years, sex category; CHF, congestive heart failure; CSMBS, civil servant medical benefit scheme; DOAC, direct oral anticoagulant; HASBLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly; NGS, non-government-based scheme; SSS, social-security scheme; UCS, universal coverage scheme; VKA, vitamin K antagonist.

mortality by insurance plan and educational attainment, respectively. Patients with higher levels of educational attainment survived longer than those with lower levels (RMST for higher education vs secondary vs elementary vs no formal education, 35.02 vs 34.29 vs 33.70 vs 31.98 months; $p<0.001$). They also experienced longer event-free time to ischaemic stroke (RMST for higher education vs secondary vs elementary vs no formal education, 35.58 vs 35.46 vs 35.11 vs 34.15 months; $p=0.004$) and major bleeding (RMST for higher education vs secondary vs elementary vs no formal education, 35.31 vs 34.72 vs 37.82 vs 34.18 months; $p=0.03$) than those with lower educational attainment (online supplemental appendix table 4). The RMSTs of all three adverse outcomes did not differ among patients with different insurance plans (online supplemental appendix table 5).

In the multivariate analyses, educational attainment was associated with all-cause mortality and ischaemic stroke, independently of comorbidities (figures 2 and 3). After adjusting for death as a competing risk of ischaemic

stroke, educational attainment remained independently associated with ischaemic stroke (online supplemental appendix table 6). Over the 36-month follow-up, patients with AF and no formal education lost 1.78 months before they died (RMST difference -1.78 ; 95% CI, -3.25 to -0.30 ; $p=0.02$) and 1.04 months before they developed ischaemic stroke (RMST difference -1.04 ; 95% CI, -2.03 to -0.04 ; $p=0.04$) compared with those attained a level of higher education.

Older age and higher CHA₂DS₂VAS_c score also shortened the survival time to all-cause mortality. Survival time was lost by 0.45 months for every 10year increase in age (RMST difference, -0.45 ; 95% CI, -0.8 to -0.1 ; $p=0.01$), and 0.35 months for every single point increase in CHA₂DS₂VAS_c score (RMST difference, -0.35 ; 95% CI, -0.6 to -0.1 ; $p=0.01$). Time to major bleeding (figure 4) was lost in patients with older age (RMST difference per 10 years, -0.35 ; 95% CI, -0.59 to -0.11 ; $p=0.003$), those of male sex (RMST difference, -0.68 ; 95% CI, -1.11 to -0.25 ; $p=0.002$) and with the use of VKA (RMST difference,

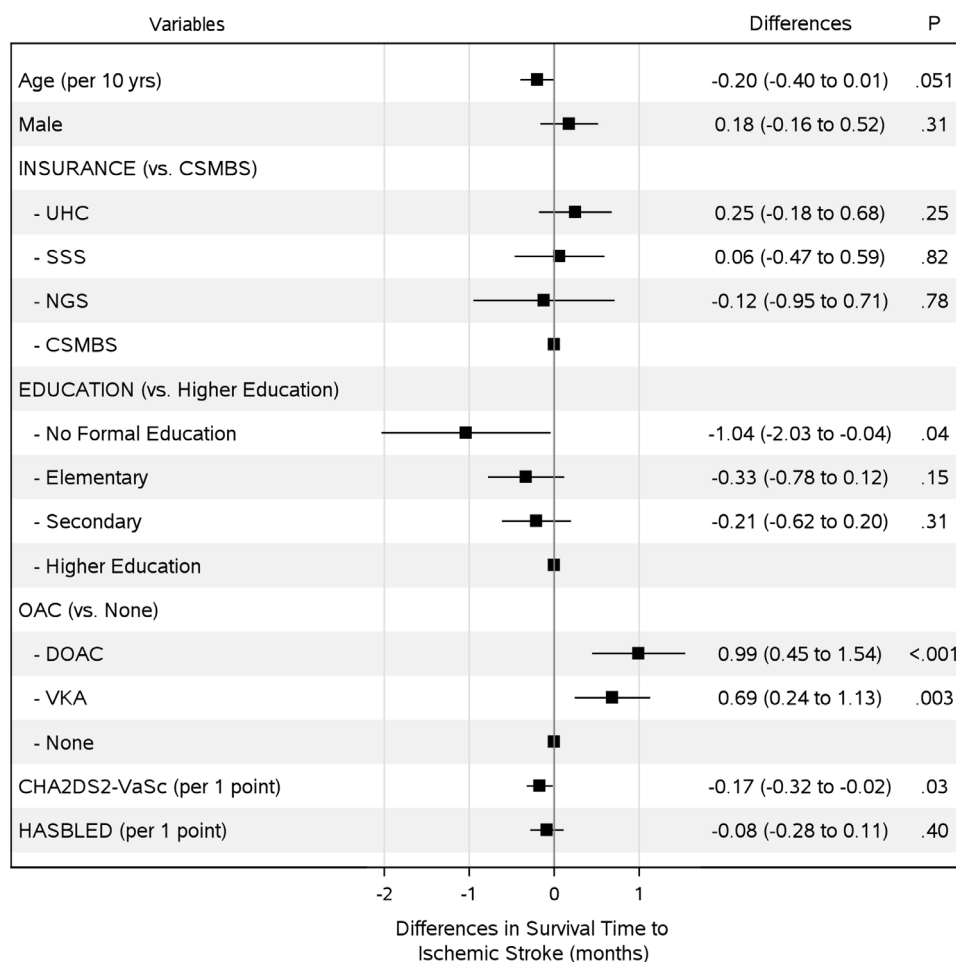


Figure 3 Differences in adjusted restricted median survival time to ischaemic stroke over a period of 36 months. The model was adjusted for age, sex, educational attainment, insurance plan, types of anticoagulant, CHA₂DS₂VAS_c and HASBLED scores. CAD, coronary artery disease; CHA₂DS₂VAS_c, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischaemic attack (TIA), vascular disease, age 65–74 years, sex category; CHF, congestive heart failure; CSMBS, civil servant medical benefit scheme; DOAC, direct oral anticoagulant; HASBLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly; NGS, non-government-based scheme; SSS, social-security scheme; UCS, universal coverage scheme; VKA, vitamin K antagonist.

–0.65; 95% CI, –1.04 to –0.26; $p=0.001$). For all three major outcomes, the type of insurance plan was not associated with a gain or loss in survival times (figures 2–4), even after adjusting for the competing risk of death (online supplemental appendices tables 6 and 7).

DISCUSSION

In the COOL-AF registry of patients with AF across Thailand, educational attainment was associated with all-cause mortality and ischaemic stroke, independently of age, sex, stroke and bleeding risks, anticoagulant use, and types of insurance. Over the 36-month follow-up period, those with no formal education died approximately 1.8 months sooner and suffered stroke 1 month sooner than those attained the level of higher education. UCS, the propoor medical scheme, was not linked to elevated risks of all-cause mortality, ischaemic stroke or major bleeding.

The significant impact of education on cardiovascular outcome has been demonstrated globally.^{8 21–23} Among

Asian population, data from the Asia Pacific Cohort Studies Collaboration²³ reported that Asians attained the lowest level of education had a 54% higher risk of stroke and 78% higher risk of cardiovascular mortality than those with a tertiary education. Among patients with AF, a large-scale study in Norway reported an educational gradient in mortality between patients who attained higher education level and those who attained a high school education or less.⁸ Findings from a patient survey showed that higher levels of educational attainment were associated with a better understanding of anticoagulant therapy and lower incidence of bleeding.²⁴ In this prospective cohort study, we explored the association between educational attainment and three adverse outcomes, namely all-cause mortality, ischaemic stroke and major bleeding. We reported educational disparities in all-cause mortality and ischaemic stroke but not major bleeding. Disparities were detected between the educational attainment level of no formal education and higher education, independently

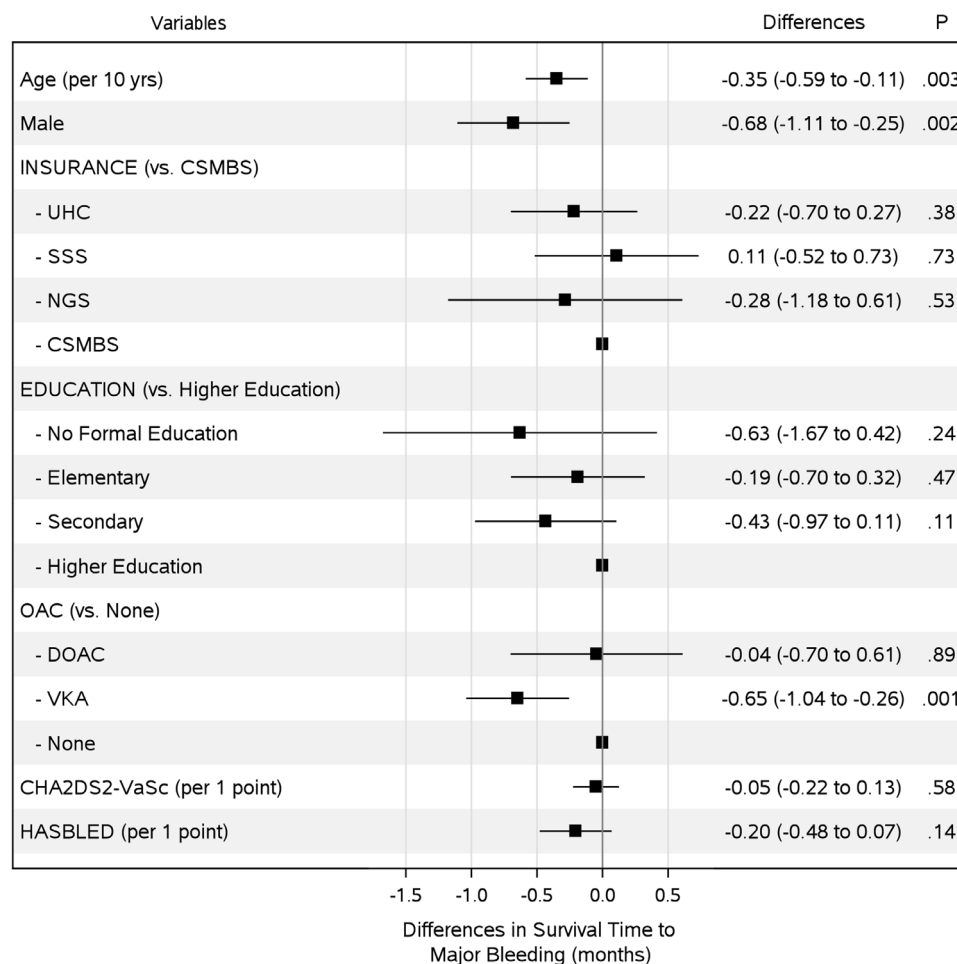


Figure 4 Differences in adjusted restricted median survival time to major bleeding over a period of 36 months. The model was adjusted for of age, sex, educational attainment, insurance plan, types of anticoagulant, CHA₂DS₂VAS_c and HASBLED scores. CAD, coronary artery disease; CHA₂DS₂VAS_c, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischaemic attack (TIA), vascular disease, age 65–74 years, sex category; CHF, congestive heart failure; CSMBS, civil servant medical benefit scheme; DOAC, direct oral anticoagulant; HASBLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly; NGS, non-government-based scheme; SSS, social-security scheme; UCS, universal coverage scheme; VKA, vitamin K antagonist.

of age, sex, bleeding and stroke risk, type of insurance plan, and anticoagulant use. Patients with no formal education are more likely to be having a reduced health literacy, which subsequently lead to poorer outcomes especially for chronic disease such as AF.^{4 24}

Low-education and low-income statuses often coincide. Low income could lead to a lack or poor choice of health insurance. In Thailand, these consequences have been ameliorated with the implementation of UCS. The UCS provides healthcare coverage to the unemployed, who primarily are in the low-income group. According to the 2004 national health insurance data, half of UCS beneficiaries were from the two poorest quintiles while half of CSMBS insurers were in the richest quintile.²⁵ Unlike other insurance plans for the poor, UCS provides extensive and comprehensive benefit packages.¹⁰ High-cost services, such as percutaneous cardiac intervention, heart transplantation or catheter ablation, are currently covered by UCS.^{9 10} A remaining discrepancy between the UCS and CSMBS packages is the drug plan. UCS restricts

access to medications outside the National List of Essential Medicines, notably DOAC. In contrast, CSMBS covers the use of DOACs for some conditions.⁹ In this cohort of patients with AF, discrepancies in the coverages provided by different types of insurance plans did not result in outcome disparities. UCS beneficiaries had RMSTs for all-cause mortality, ischaemic stroke and major bleeding similar to beneficiaries of other plans.

However, outcome disparities between UCS and CSMBS have been previously reported.^{12 13} In a retrospective analysis from 2010 National Insurance Database, 5-year mortality after AF admission was higher in UCS beneficiaries than in CSMBS beneficiaries.¹³ In contrast to previous studies, patients in our cohort were prospectively enrolled and subjected to structured followed up. The enrolment process took place after the third strategic plan of the UCS began in 2012.¹⁰ With the implementation of the plan, the benefits were expanded to seasonal influenza vaccination, screening of complications from diabetes and hypertension, and long-term care for dependent elderly.

The differences in trial designs and timing of enrolment periods could explain the discrepancies between our results and those of previous trials focusing on outcome disparities between UCS and CSMBS beneficiaries.

In this study, we reported the effect size of educational disparities using months loss. The reported value may appear small, but they indicate a time loss over a fixed period of 36 months. For those patients with no formal education, losing 1.8 months of survival time equates to losing 5% of their lifetime during follow-up. In the health production function analyses conducted in 35 members countries of Organisation for Economic Co-operation and Development countries,⁴ a 10% increase in education of the population was associated with a gain of 3.2 months in life expectancy and a 100% increase in education of the population was associated with a gain of 23.8 months.

Our results provide some insights to the national health insurance policy in Thailand. We have shown that in a moderate-to-high income country such as Thailand, the disparity in insurance coverage could be reduced or even removed by a well maintained, propoor health insurance, such as the UCS. Our findings also emphasise the utmost importance of national education level. Education can keep people healthier.⁴ For a chronic condition such as AF, adherence to the therapy requires some understanding towards the disease, which entails education.²⁴ In our cohort, the educational attainment level of higher education was associated with better clinical outcomes, but this level is only attained in a minority of Thai population. According to the government reports,²⁶ less than 25% of the working age population have attained higher education, and more than 20% of students left schools after completion of the compulsory, lower secondary level. Clearly, there is ample of room for improvement to make education more inclusive and accessible.

Our trial is prospective and nationwide in nature. The enrolment and follow-up were well structured and validated. To accurately analyse the outcomes that occurred at non-constant rates, we chose to use an RMST approach rather than the log-rank test or Cox proportional hazard model for the survival analysis. The truncation time for the analysis was the prespecified follow-up time, which was optimal for the performance of the test.¹⁸

Approximately 10% of patients were excluded from the present analysis because of missing educational attainment data. However, the event rates of the excluded patients were not different from those remained in the present trial. Another potential bias is that patients enrolled in the registry were more likely to have a high socioeconomic status. However, 44% of patients in this cohort were insured by the UCS indicating that these participants were more likely to have low socioeconomic statuses.

Differences were observed in the numbers of baseline comorbidities. Even after adjustment were made in the multivariate analyses, some confounders may have remained. Owing to the non-randomised nature of the

trial, only assumptions about associations and not causal relationships can be made. Causal links between educational attainment, types of insurance plans and adverse clinical outcomes cannot be guaranteed by our analyses.

CONCLUSIONS

In a large nationwide prospective cohort of patients with AF in Thailand, educational attainment was independently associated with all-cause mortality and ischaemic stroke. Over a period of 36 months, RMSTs to all-cause mortality and ischaemic stroke of those patients who attained higher education levels were extended by 1.8 and 1 months, respectively, compared with those who attained no formal education. UCS beneficiaries had the same incidences of all-cause mortality, ischaemic stroke and major bleeding as beneficiaries of other insurance plans.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The study was approved by Siriraj Institutional Review Board (COA no. Si 317/2014) and Central Research Ethics Committee (COA-CREC 003/2014). Participants gave informed consent to participate in the study before taking part.

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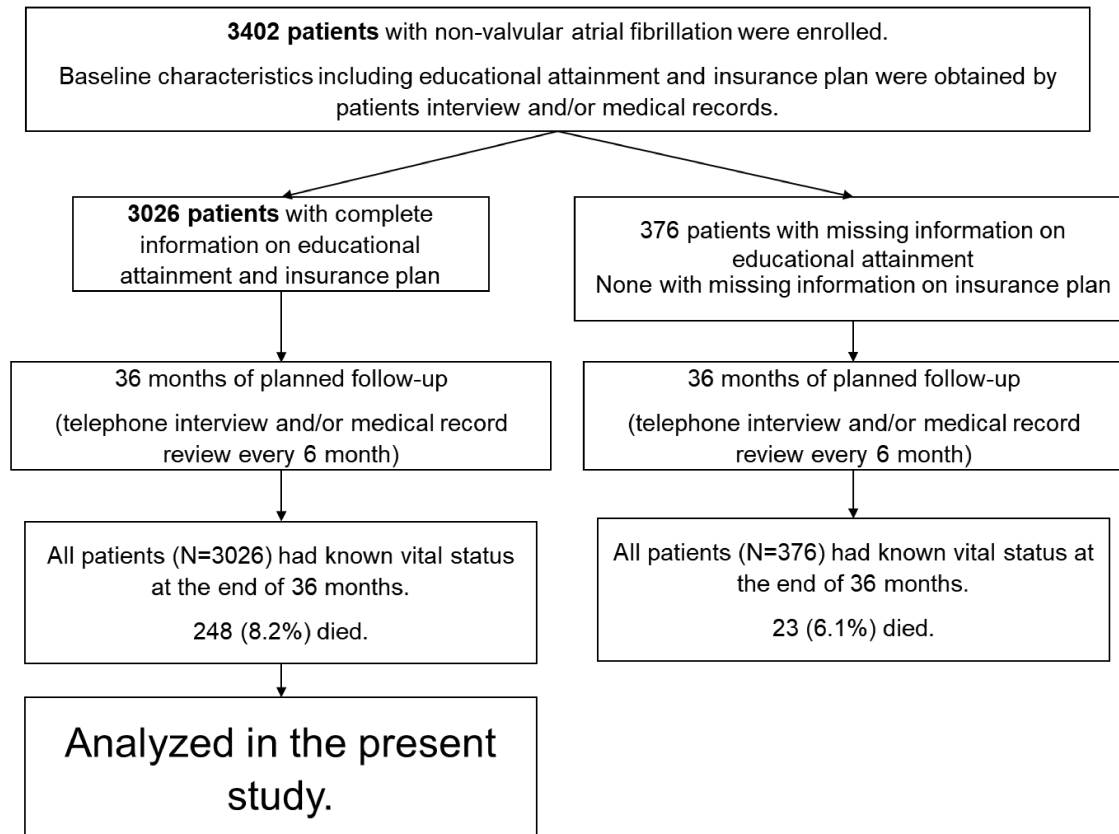
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Appendix Figure 1. Study profile

Appendix Table 1. Tests for proportional hazard assumption of time to events of interest based on weighted Schoenfeld residuals

Variables	<i>P</i> value for Events of Interest		
	All-cause Mortality	Ischemic Stroke	Major Bleeding
Educational Attainment			
- No formal education	0.013	<0.001	0.001
- Elementary	0.035	0.005	0.007
- Secondary	0.193	0.110	0.147
- Higher education (reference)	.	.	.
- Global Test	0.052	0.003	0.005
Insurance Plan			
- UHC	0.011	0.004	0.003
- SSS	0.296	0.442	0.326
- NGS	0.381	0.434	0.394
- CSMBS (reference)	.	.	.
- Global Test	0.029	0.015	0.012

*A significant *P* value indicates that proportional hazard assumption is violated.

Abbreviations: CSMBS, civil servant medical benefit scheme; NGS, non-government-based scheme; SSS, social-security scheme; UCS, universal coverage scheme.

Appendix Table 2. Characters and events rate of patients with missing information (N=376) compared to those who remained in the study (N=3026).

	Patients with missing information (N=376)	All patients remained in the study (N=3026)	P
Age, mean (SD), y	68.0 (11.2)	67.3 (11.3)	0.235
Male, No. (%)	201 (53.5%)	1779 (58.8%)	0.048
CHA ₂ DS ₂ -VAS _c , mean (SD)	3.1 (1.6)	3.0 (1.7)	0.162
HASBLED, mean (SD)	1.5 (1.0)	1.5 (1.0)	0.337
Event rate, No. (%)			
- Death	23 (6.1%)	248 (8.2%)	0.160
- Ischemic stroke	8 (2.1%)	95 (3.1%)	0.280
- Major bleeding	16 (4.3%)	136 (4.5%)	0.832

Abbreviations: CHA₂DS₂-VAS_c, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category; HASBLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly.

Appendix Table 3. Baseline Characteristics by Educational Attainment
(N=3026)

Characters	No Formal Education (N=213)	Elementary (N=1526)	Secondary (N=639)	Higher Education (N=648)	P
Age, mean (SD), y	74.4(10.0)	69.3 (10.2)	64.3 (12.1)	63.3 (11.1)	<.001
Male, No. (%)	61 (28.6%)	770 (50.5%)	476 (74.5%)	472 (72.8%)	<.001
CHA ₂ DS ₂ -VASc, mean (SD)	3.9(1.5)	3.3(1.6)	2.7(1.7)	2.6(1.7)	<.001
HASBLED, mean (SD)	1.7 (0.9)	1.6 (1.0)	1.5 (1.0)	1.4(1.0)	<.001
CAD, No. (%)	23 (10.8%)	248 (16.3%)	99 (15.5%)	108 (16.7%)	0.199
CHF, No. (%)	63 (29.6%)	451 (29.6%)	177 (27.7%)	138 (21.3%)	.001
Hypertension, No. (%)	157 (73.7%)	1061 (69.5%)	435 (68.1%)	408 (63.0%)	.006
Dyslipidemia, No. (%)	92 (43.2%)	831 (54.5%)	387 (60.6%)	393 (60.6%)	<.001
Diabetes, No. (%)	39 (18.3%)	363 (23.8%)	162 (25.4%)	166 (25.6%)	0.148
Stroke/TIA, No. (%)	42 (19.7%)	261 (17.1%)	104 (16.3%)	123 (19.0%)	0.468
Vascular Disease, No. (%)	26 (12.2%)	263 (17.2%)	105 (16.4%)	116 (17.9%)	0.258
Current Smoker, No. (%)	3 (1.4%)	52 (3.4%)	32 (5.0%)	11 (1.7%)	.003

Alcohol Use, No. (%)	1 (0.5%)	57 (3.7%)	44 (6.9%)	27 (4.2%)	<.001
History of Bleeding, No. (%)	20 (9.4%)	156 (10.2%)	64 (10.0%)	64 (9.9%)	0.981
Abnormal Renal Function, No. (%)	5 (2.3%)	44 (2.9%)	23 (3.6%)	18 (2.8%)	0.733
Abnormal Liver Function, No. (%)	4 (1.9%)	35 (2.3%)	19 (3.0%)	9 (1.4%)	0.273
Antiplatelets, No. (%)	42 (19.7%)	420 (27.5%)	163 (25.5%)	177 (27.3%)	0.094
Anticoagulants					<.001
- VKA, No. (%)	179 (84.0%)	1081 (70.8%)	427 (66.8%)	388 (59.9%)	
- DOAC, No. (%)	3 (1.4%)	48 (3.1%)	50 (7.8%)	81 (12.5%)	
- None, No. (%)	31 (14.6%)	397 (26.0%)	162 (25.4%)	179 (27.6%)	

Abbreviations: CAD, coronary artery disease; CHA₂DS₂-VAS_c, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category; CHF, congestive heart failure; DOAC, direct oral anticoagulant; HASBLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly; VKA, vitamin K antagonist.

Appendix Table 4. Incidence and Restricted Mean Survival Time of Clinical Outcomes by Educational Attainment

		No Formal Education (N=213)	Elementary (N=1526)	Secondary (N=639)	Higher Education (N=648)	P
All-cause Mortality (N=248)	Incidence, No. (%)	30 (14.1%)	146 (9.6%)	45 (7.0%)	27 (4.2%)	<.001
	RMST, months (95% CI)	31.98 (30.62-33.33)	33.70 (33.32-34.80)	34.29 (33.78-34.80)	35.02 (34.65-35.40)	<.001
Ischemic Stroke (N=95)	Incidence, No. (%)	14 (6.6%)	55 (3.6%)	14 (2.2%)	12 (1.9%)	.002
	RMST, months (95% CI)	34.15 (33.21-35.10)	35.11 (34.87-35.36)	35.46 (35.16-35.75)	35.58 (35.32-35.84)	.004
Major Bleeding (N=136)	Incidence, No. (%)	13 (6.1%)	70 (4.6%)	35 (5.5%)	18 (2.8%)	0.066
	RMST, months (95% CI)	34.18 (33.22-35.14)	34.82 (34.54-35.11)	34.72 (34.27-35.17)	35.31 (34.98-35.64)	.03

Abbreviations: RMST, restricted mean survival time.

Appendix Table 5. Incidence and Restricted Mean Survival Time of Clinical Outcomes by Insurance Plan

		UHC (N=1333)	SSS (N=142)	CSMBS (N=1397)	NGS (N=154)	P
All-cause Mortality (N=248)	Incidence, No. (%)	122 (9.2%)	10 (7.0%)	100 (7.2%)	16 (10.4%)	0.183
	RMST, months (95% CI)	33.61 (33.19- 34.03)	34.52 (33.55- 35.50)	34.32 (33.98- 34.66)	33.95 (32.91- 34.99)	.06
Ischemic Stroke (N=95)	Incidence, No. (%)	36 (2.7%)	3 (2.1%)	51 (3.7%)	5 (3.2%)	0.468
	RMST, months (95% CI)	35.27 (35.03- 35.51)	35.64 (35.21- 36.07)	35.17 (34.92- 35.41)	35.14 (34.38- 35.90)	.31
Major Bleeding (N=136)	Incidence, No. (%)	65 (4.9%)	3 (2.1%)	60 (4.3%)	8 (5.2%)	0.451
	RMST, months (95% CI)	34.75 (34.43- 35.07)	35.61 (35.07- 36.15)	34.91 (34.62- 35.19)	34.86 (34.02- 35.69)	.06

Abbreviations: CSMBS, civil servant medical benefit scheme; NGS, non-government-based scheme; RMST, restricted mean survival time; SSS, social-security scheme; UCS, universal coverage scheme.

Appendix Table 6. Adjusted* restricted median survival time (RMST) to ischemic stroke among alive patients by educational attainment and insurance plan.

	RMST (months)	95% CI	P
Insurance Plan (vs. CSMBS)			
- UHC	0.18	-0.16 to 0.52	0.290
- SSS	0.02	-0.48 to 0.51	0.946
- NGS	-0.12	-0.85 to 0.60	0.737
Educational Attainment (vs. higher education)			
- No formal education	-0.57	-1.26 to 0.11	0.103
- Elementary	-0.45	-0.79 to -0.10	0.011
- Secondary	-0.26	-0.57 to 0.05	0.105

*The model was adjusted for of age, sex, educational attainment, insurance plan, types of anticoagulant, CHA₂DS₂VAS_c, and HASBLED scores.

Abbreviations: CHA₂DS₂-VAS_c, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category; CSMBS, civil servant medical benefit scheme; HASBLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly; NGS, non-government-based scheme; RMST, restricted median survival time; SSS, social-security scheme; UCS, universal coverage scheme.

Appendix Table 7. Adjusted* restricted median survival time (RMST) to major bleeding among alive patients by educational attainment and insurance plan.

	RMST (months)	95% CI	P
Insurance Plan (vs. CSMBS)			
- UHC	-0.09	-0.47 to 0.29	0.651
- SSS	0.04	-0.59 to 0.65	0.912
- NGS	-0.06	-0.76 to 0.62	0.851
Educational Attainment (vs. higher education)			
- No formal education	-0.46	-1.35 to 0.43	0.315
- Elementary	-0.08	-0.54 to 0.37	0.720
- Secondary	-0.14	-0.60 to 0.33	0.567

*The model was adjusted for of age, sex, educational attainment, insurance plan, types of anticoagulant, CHA₂DS₂VAS_c, and HASBLED scores.

Abbreviations: CHA₂DS₂-VAS_c, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category; CSMBS, civil servant medical benefit scheme; HASBLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly; NGS, non-government-based scheme; RMST, restricted median survival time; SSS, social-security scheme; UCS, universal coverage scheme.