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Net Clinical Benefit of Oral Anticoagulation among Older Adults with Atrial Fibrillation

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Abstract

Background: While guidelines recommend anticoagulation for all atrial fibrillation (AF) patients ≥75 years, evidence for the net clinical benefit (NCB) of anticoagulant in older adults is sparse. We sought to determine the association between age and NCB of anticoagulation in older adults with AF.

Methods and Results: We examined adults ≥75 years with incident AF in the Anticoagulation and Risk Factors in Atrial Fibrillation – Cardiovascular Research Network cohort. Using a Markov state transition model, we estimated the lifetime NCB of warfarin and apixaban relative to no treatment in quality-adjusted life years (QALYs). In the decision model, each month patients face a chance of stroke, hemorrhage, or death from a competing cause; the likelihood of each is a function of individual patients' stroke risk, hemorrhage risk, and life expectancy. We defined minimal clinically relevant lifetime benefit as 0.10 QALYs. In a sensitivity analysis, we examined the effect of competing risks of death on NCB using two models, one including competing risks and the second without competing risks. We included 14946 patients, with a median age of 81 years and median CHA_2DS_2-VASc score of 4. In the main analysis, after age 87, NCB associated with warfarin decreased below 0.10 lifetime QALYs while NCB associated with apixaban did not decrease below 0.10 lifetime QALYs until after age 92. In sensitivity analyses, over a 3-year horizon, removing competing risks of death resulted in higher NCB (at 90 years, median difference using warfarin 0.010 QALYs, 95% CI 0.009–0.013, median difference using apixaban 0.025 QALYs, 95% CI 0.024–0.026).

Conclusions: The NCB of anticoagulation decreases with advancing age. The competing risk of death diminishes the NCB of anticoagulation for older AF patients. Physicians should consider competing mortality risks when recommending anticoagulants to older adults with AF.

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Introduction

Advancing age affects multiple facets of the risk-benefit assessment of anticoagulation for patients with atrial fibrillation. The increased risk of ischemic stroke conferred by atrial fibrillation increases significantly with older age.[1,2] While anticoagulation effectively reduces the risk of ischemic stroke, it increases the risk of hemorrhagic events; importantly, the risk of hemorrhagic events also rises with age.[3,4] Decision-making is complicated further because advancing age increases the likelihood of death from a non-atrial fibrillation related cause (i.e., competing risk of death) thereby limiting the likelihood of actualized benefit or harm from atrial fibrillation and anticoagulation.[5]

Consensus guidelines categorize all patients aged 75 years and older as 'high risk for ischemic stroke' thus warranting anticoagulation after a qualitative assessment of hemorrhage risk.[6] However, evidence for the net benefit of anticoagulant use in older adults with atrial fibrillation is sparse. Older adults, particularly older frail adults, have been under-represented in randomized trials of anticoagulants for thromboprophylaxis in atrial fibrillation. Observational studies suggest older adults may benefit from anticoagulation but these studies are limited by selection; older patients prescribed anticoagulants are generally healthier than those not prescribed anticoagulants.[7,8] Furthermore, few randomized trials or observational studies have examined the effectiveness of anticoagulants accounting for the competing risk of death. A competing risk is an important alternative outcome (e.g., cancer-related death) that alters the probability of the disease-specific outcome (e.g., death from cancer precludes the possibility of ischemic stroke).[9] Clinically this is analogous to a physician questioning if a patient with atrial fibrillation and a six-month prognosis due to pancreatic cancer will benefit from anticoagulation. When treating older adults who often have multiple comorbidities, the competing risk of death is an important consideration and one that is under-addressed in atrial fibrillation outcome studies.[10]

Thus, while clinical guidelines recommend anticoagulation for all adults with atrial fibrillation aged 75 years and older, there is little evidence to guide the use of anticoagulants in these older adults. To examine the net clinical benefit of anticoagulation in older adults, we performed a decision analytic study using a cohort of nearly 15000 adults 75 years and older with incident atrial fibrillation.

Methods

Study Overview

Using the characteristics of 14946 patients aged 75 years and older with incident atrial fibrillation in the Anticoagulation and Risk Factors in Atrial Fibrillation – Cardiovascular Research Network (ATRIA-CVRN) cohort, we estimated the net clinical benefit (NCB) of anticoagulation by age. We used the Atrial Fibrillation Decision Support Tool (AFDST), a well-established 29-state Markov decision analytic model, to estimate the NCB of anticoagulation for each patient in the ATRIA-CVRN cohort in quality-adjusted life years (QALYs).[11,12]

Population used in Decision Analytic Model

We limited the analysis to adults 75 and older since consensus guidelines recommend anticoagulants to all adults 75 and older.[13] The ATRIA-CVRN cohort consists of patients with incident atrial fibrillation in the Kaiser Permanente Northern and Southern California integrated health care delivery systems; we have previously published details of the cohort assembly.[14] In brief, patients were included in the cohort if they had a new diagnosis of atrial fibrillation between January 1, 2006, and June 30, 2009, defined by International Classification of Disease, Ninth Revision (ICD-9) codes, and electrocardiographic data with no prior known diagnosis of atrial fibrillation. Clinical characteristics of patients in the cohort were determined by searching inpatient, outpatient, laboratory, and pharmacy databases for the relevant ICD-9 codes, medications, or lab values in the year before the patient's diagnosis. Since the decision analytic model is not designed to assess the risk of bleeding with concurrent use of anticoagulants and non-aspirin antiplatelet medications (e.g., clopidogrel), we excluded 2028 patients prescribed non-aspirin antiplatelet medications at the time of atrial fibrillation diagnosis.

Main decision analytic model

The AFDST decision analytic model estimates the QALYs that result from treatment strategies including – no antithrombotic therapy, anticoagulation with warfarin, and anticoagulation with any of the currently approved direct oral anticoagulants (DOACs). The net benefit of anticoagulation is calculated as the gain or loss in QALYs for an active treatment compared with no antithrombotic therapy. Since apixaban is the only DOAC to show statistically significant benefit over warfarin in preventing ischemic stroke, we present the results for apixaban.[15–18] Because randomized trials of DOACs excluded patients with chronic kidney disease, the benefits and harms in this population are not known.[15] As a result, we did not test the apixaban strategy in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2 (i.e., chronic kidney disease stage 4 or higher [CKD 4+]).

The decision analytic model tracks each patient's health status as events occur during each monthly cycle. Health status is captured in states defined by significant clinical events (e.g., an ischemic stroke) and the quality of life in those resulting health states, both of which are affected by treatment strategy. During each month, patients face a chance of experiencing the following clinical events: ischemic stroke, extracranial hemorrhage, intracranial hemorrhage, death from another cause. Using published studies, we calculated patient-specific event probabilities based on their individual comorbidities. We calculated patient-specific CHA_2DS_2-VASc and ATRIA stroke scores to estimate the risk of ischemic stroke. We used both scores because while clinical guidelines recommend using the CHA_2DS_2-VASc score, it does not account for the effect of age on stroke beyond 75 years, and it does not perform as well as the ATRIA stroke score.[1,19,20] Since alcohol use information is not available in the ATRIA-CVRN cohort, we used the modified HAS-BLED score (hypertension, abnormal liver or renal function, stroke history, bleeding predisposition, labile internal normalized ratio, elderly, drug use) to estimate the probability of extracranial hemorrhage. Using a multivariable regression model developed in the Swedish population

registry of untreated patients with atrial fibrillation, we estimated patient-specific risk of intracranial hemorrhage.[3]

In the decision analytic model, each abovementioned clinical event results in one of several outcomes. Ischemic stroke and hemorrhage may result in death, mild or severe neurologic sequelae, or symptom resolution. Each health state has an associated quality of life determined using patient-reported preferences.[21] Since outcomes following hemorrhagic events are worse in anticoagulated patients, we used observational studies to model the differential outcome of hemorrhagic events based on treatment status. Patients' risk of death from other non-explicitly modeled causes (i.e., unrelated to AF or anticoagulation therapy) is estimated by accounting for excess mortality risk associated with age, sex, and comorbidities including chronic kidney disease, diabetes, hypertension, and prior stroke. Estimated benefits and harms are then summed over the simulated lifespan (i.e., lifetime horizon). We used 0.1 QALY as a minimal clinically significant gain to consider one strategy better than another.[7,11,22] We summarize base case values for model parameters in Table 1; we describe the decision tree and health states in Appendix Figures 1 and 2.

Sensitivity analyses

We performed two sensitivity analyses. First, we examined the effect of the competing risk of death on the relationship between age and NCB. We compared the NCB of anticoagulation in a decision model that accounts for disease-specific mortality (i.e., AF and treatment-related mortality) and competing risk of death (i.e., lifetable-based mortality rates for age and sex as well as excess mortality related to comorbidities) to the NCB of anticoagulation in a decision model that just accounts for disease-specific mortality. The difference between the two estimates of NCB is attributable to the effect of competing risks on the estimation of NCB of anticoagulation. The decision analytic model estimates lifetime benefit by running until the patient's death from a disease-specific cause or competing risks. Removing the competing risk of death would render an estimate of lifetime NCB uninterpretable since we would provide estimates of QALYs accrued over unrealistically long lifespans. Accordingly, for this sensitivity analysis, we estimated NCB over a 3-year window.

Second, we tested the impact of increasing age on risk of ischemic stroke beyond age 75 years. The CHA_2DS_2-VASc score, used in the main model, groups all patients older than 75 years into a single category. However, studies demonstrate that the risk of stroke continues to increase with advancing age beyond 75 years.[1,43] Therefore, in this sensitivity analysis, we increased the base embolic stroke risk by a relative 0.75% for each year beyond age 75.[44]

Statistical methods

We determined net benefit by computing the gain or loss in QALYs afforded by anticoagulant therapy compared with no oral anticoagulation. Because of the small number of patients older than 95 years (n=180), those older than 95 years were examined together. Since the distribution of net benefit was skewed, we compared estimates of median benefit. When determining if the median benefit was different from the pre-specified threshold of 0.10 QALYs or if a sensitivity analysis resulted in statistically similar results as the main

analysis, we used the Sign test. We calculated 95% confidence intervals using 1000 bootstrapped samples. We performed analyses using SAS 9.4 (Cary, NC) and R 3.4.4 (Vienna, Austria). Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the Cardiovascular Research Network managed by the Kaiser Permanente Division of Research at https://cvrn.org/Pages/Collaboration.aspx. This study was approved by the UCSF Human Research Protection Program and the original ATRIA-CVRN cohort study was approved by the institutional review boards of the Kaiser Foundation Research Institute and Kaiser Permanente Southern California. In both cases, no informed consent was required.

Results

Main analysis

We used baseline data from 14946 patients older than 75 years from the ATRIA-CVRN cohort in this analysis (Table 2). Age ranged from 75 to 106 years and 54% were women. At diagnosis of AF, 23% also had chronic heart failure, 88% had hypertension, 3% had a prior ischemic stroke or transient ischemic attack, 27% had diabetes mellitus, and 8% had received dialysis or had an eGFR of < 30 mL/min/1.73m^2. Since age greater than 75 years confers 2 points in the CHA_2DS_2-VASc scoring algorithm, all patients had a CHA_2DS_2-VASc score of 2 or more at diagnosis.

The estimated NCB of anticoagulation with warfarin and apixaban decreased with age (Figure 1). Among patients aged 75 years, using the CHA_2DS_2-VASc score to estimate stroke risk, warfarin resulted in a median lifetime NCB of 0.45 QALYs (interquartile range [IQR] 0.25 to 0.72 QALYs). Among patients aged 87 years, the median lifetime NCB associated with warfarin decreased to 0.10 QALYs (IQR 0.04 to 0.16 QALYs), which was not significantly different from the prespecified threshold for minimal NCB of 0.10 QALYs ($p = 0.28$). Among patients aged 75 years eligible for apixaban therapy (e.g., without CKD 4+), using the CHA_2DS_2-VASc score to estimate stroke risk, apixaban resulted in a median lifetime NCB of 0.74 QALYs (IQR 0.49 to 1.06 QALYs). Among patients aged 92 years, the median lifetime NCB associated with apixaban decreased to 0.10 QALYs (IQR 0.07 to 0.13 QALYs), which was not significantly different from the prespecified threshold for minimal NCB of 0.10 QALYs ($p = 0.75$).

The ATRIA stroke score accounts for increasing stroke risk after 75 years of age. Using the ATRIA score, the estimated NCB of anticoagulation with warfarin and apixaban decreased with age (Figure 2). Among patients aged 75 years, using the ATRIA score, warfarin resulted in a median lifetime NCB of 0.36 QALYs (IQR 0.19 to 0.68 QALYs). Among patients aged 88 years, the median lifetime NCB associated with warfarin decreased to 0.10 QALYs (IQR 0.05 to 0.16 QALYs), which was not significantly different from the prespecified threshold for minimal NCB of 0.10 QALYs ($p = 0.93$). Among patients aged 75 years eligible for apixaban therapy (e.g., without CKD 4+), using the ATRIA score, apixaban resulted in a median lifetime NCB of 0.64 QALYs (IQR 0.46 to 1.03 QALYs). Among patients aged 93 years, the median lifetime NCB associated with apixaban decreased

to 0.09 QALYs (IQR 0.05 to 0.11 QALYs), which was less than the prespecified threshold for minimal NCB of 0.10 QALYs (p = 0.01).

Sensitivity analysis: competing risk of death

Removing the competing risk of death from the estimation of NCB results in a higher estimated NCB; a difference that is more pronounced with apixaban and at older ages (Figure 3). Among patients aged 75 years, over a 3-year window, warfarin resulted in a median NCB of 0.013 QALYs (IQR 0.004 to 0.024) accounting for the competing risk of death and 0.017 QALYs (IQR 0.005 to 0.047) without the competing risk of death (median difference, 0.004 QALYs, 95% confidence interval [CI] 0.002 to 0.004 QALYs). Among patients aged 90 years, over a 3-year window, warfarin resulted in a median NCB of 0.008 QALYs (IQR −0.001 to 0.016 QALYs) accounting for the competing risk of death and 0.018 QALYs (IQR 0.006 to 0.047 QALYs) without the competing risk of death (median difference, 0.010 QALYs, 95% CI 0.009 to 0.013 QALYs).

Among patients aged 75 years, over a 3-year window, apixaban resulted in a median NCB of 0.056 QALYs (IQR 0.044 to 0.061) accounting for the competing risk of death and 0.063 QALYs (IQR 0.049 to 0.065) without the competing risk of death (median difference, 0.007 QALYs, 95% CI 0.006 to 0.008 QALYs). Among patients aged 90 years, over a 3-year window, apixaban resulted in a median NCB of 0.038 QALYs (IQR 0.030 to 0.048) accounting for the competing risk of death and 0.063 QALYs (IQR 0.049 to 0.108 QALYs) without the competing risk of death (median difference, 0.025 QALYs, 95% CI 0.024 to 0.026). As demonstrated in Figure 3, the NCB of anticoagulation remains relatively stable with advancing age when the competing mortality risk, including those associated with advancing age, are removed. Thus, these sensitivity analyses indicate that the competing mortality risk due to advancing age is an important factor in limiting the NCB of anticoagulation in adults over 75 years.

Sensitivity analysis: risk of ischemic stroke with age

This sensitivity analysis uses the same lifetime horizon as the main model. Under the assumption that the risk of ischemic stroke increases with age beyond 75 years, the lifetime NCB from both warfarin and apixaban anticoagulation is nearly the same as in analyses assuming that ischemic stroke risk is stable beyond 75 years (Figure 4). Under the assumption of rising ischemic stroke risk, warfarin and apixaban resulted in a higher NCB that was statistically significant but not clinically significant (warfarin median increase 0.011, 95% CI 0.011 to 0.012 QALYs; apixaban median increase 0.013, 95% CI 0.012 to 0.013 QALYs).

Discussion

Our study provides evidence that the net clinical benefit (NCB) of anticoagulation decreases with advancing age. We found that warfarin results in minimal lifetime net benefit for the median patient beyond the age of 87 years, while apixaban yields minimal lifetime net benefit after age 92 years. Second, we found that the decline in NCB with advancing age is strongly associated with competing risks of death. Third, we found that the declining benefit

of anticoagulation with advancing age is only modestly affected when accounting for the age-related increase in ischemic stroke risk.

In these analyses, we used quality-adjusted life years (QALYs) as a summary measure of NCB. In prior reports, investigators have measured NCB using stroke equivalents in a non-decision analytic approach.[28,45–47] In this study, we employed a formal decision analytic model that incorporates life expectancy and is inclusive of all relevant outcome events, weighted by published utility weightings. Nevertheless, QALYs are not routinely used in clinical practice. To ground the notion of 0.1 QALYs over a lifetime as "minimal benefit," in Table 3, we list the QALYs gained with selected clinical interventions. For instance, increasing from conventional dose to high dose statin in patients with stable coronary disease results in a lifetime benefit of 0.1 QALYs per person.[49]

While this study finds that the NCB of anticoagulation declines with advancing age, prior observational studies have found the opposite. Prior studies are limited by selection bias (i.e., those treated are more likely to benefit than the untreated)[7] and often do not account for the competing risk of death (i.e., death from non-atrial fibrillation related causes).[51] The decision analytic model used in this study minimizes selection bias by estimating treatment effects for all patients and intrinsically accounts for the competing risk of death. The results demonstrate that the competing risk of death is an important consideration when estimating the NCB of anticoagulation therapy. We find failing to account for competing risks likely overestimates the NCB of anticoagulation, an effect that is more pronounced at older ages and with more effective anticoagulants.

The results of this study have important implications for the clinical care of older adults with atrial fibrillation. If using the CHA_2DS_2-VASc stroke risk score, consensus guidelines recommend anticoagulant use for all adults 75 years and older with atrial fibrillation.[13] This study of adults 75 years and older finds that while most are likely to benefit, the NCB decreases every year beyond 75. Further, the results indicate that competing risks (e.g., life-limiting conditions such as end-stage kidney disease) are a major determinant of reduced NCB at a population level. These results, however, must be translated by clinicians to the care of individual patients. For example, the results indicate that for half of 92-year-olds with atrial fibrillation, apixaban may not confer a net benefit. Clinicians must translate if an individual patient's comorbidity burden will limit the benefits of anticoagulants. This information can then inform a shared decision-making encounter so that the anticoagulation decision advances individual patients' health priorities.

Our study has limitations inherent to the study design and data available. First, the cohort that we examined through the decision analytic model was created from among those insured through Kaiser Permanente Northern California and Southern California. While such a patient sample has broad age, gender, and racial/ethnic diversity and is highly representative of the California adult population, it may not be completely generalizable to all populations in the U.S. or internationally. However, use of a cohort of atrial fibrillation patients that includes outpatients is more generalizable than samples of atrial fibrillation patients selected entirely from hospitals.[3,52] Second, we incorporate multiple estimates of probabilities from varied sources, and there is uncertainty associated with these estimates.

While the decision analytic model does not formally incorporate this variation when measuring benefit, we have performed extensive sensitivity analyses outlined in prior publications.[11] Third, while we endeavored to use high-quality epidemiologic studies to inform the rates, probabilities, and outcomes used decision analytic model, not all risk estimates may be transportable to the ATRIA-CVRN cohort. Fourth, we did not test the model assumption from Friberg et al.[3] that the risk of ICH does not increase beyond age 75. Since an increasing risk of ICH would result in lower NCB, the results of this study represent a conservative estimate of NCB. Finally, this study design could not account for individual patient preferences. We used population averages that physicians and patients must adapt for individual treatment decisions.

In conclusion, we found that the net clinical benefit of anticoagulation decreases with age, and for the typical patient, provides minimal benefit after age 87 years with warfarin and 92 years when using apixaban. Competing risks have an important influence on this declining net clinical benefit. Clinicians should consider competing risks when discussing the potential benefit of anticoagulants with older adults with atrial fibrillation. Future work should focus on incorporating competing risks into estimates of the net clinical benefit of anticoagulation and anticoagulation clinical decision aids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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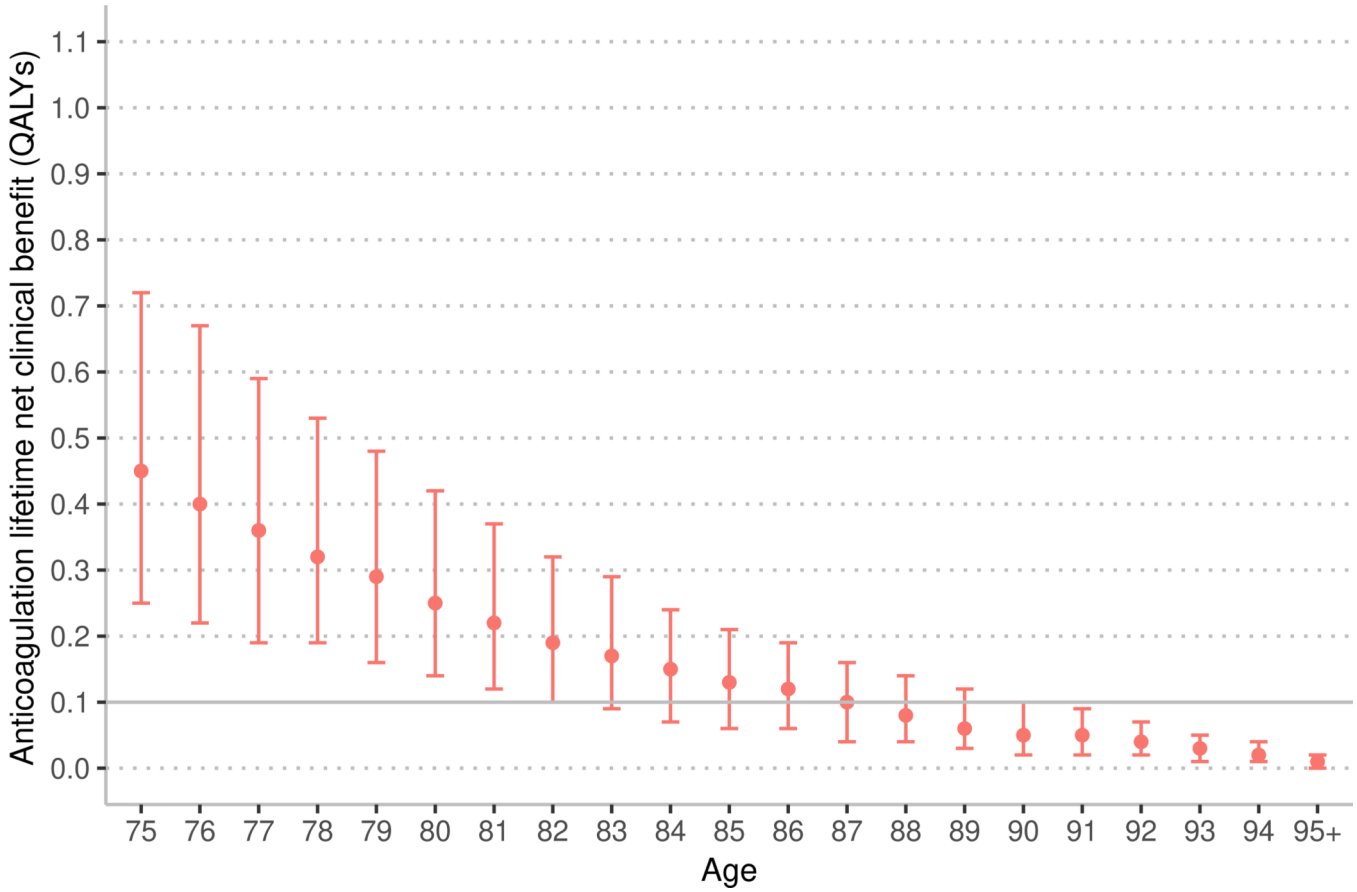
What is known:

- Because aging increases the risk of ischemic stroke, guidelines recommend anticoagulation for all patient 75 years old and older with atrial fibrillation
- However, aging also increases the risk of anticoagulant-associated bleeding complications and the risk of death from other causes (e.g., cancer)
- How these competing risks affect the net clinical of anticoagulation in older adults is not well described

What the study adds:

- Examining a large cohort of patients with atrial fibrillation using a simulation model, we found that the net clinical benefit of anticoagulant use decreases with age beyond 75 years
- The risk of death from other causes (e.g., cancer) have an important influence on the declining net clinical benefit of anticoagulant use



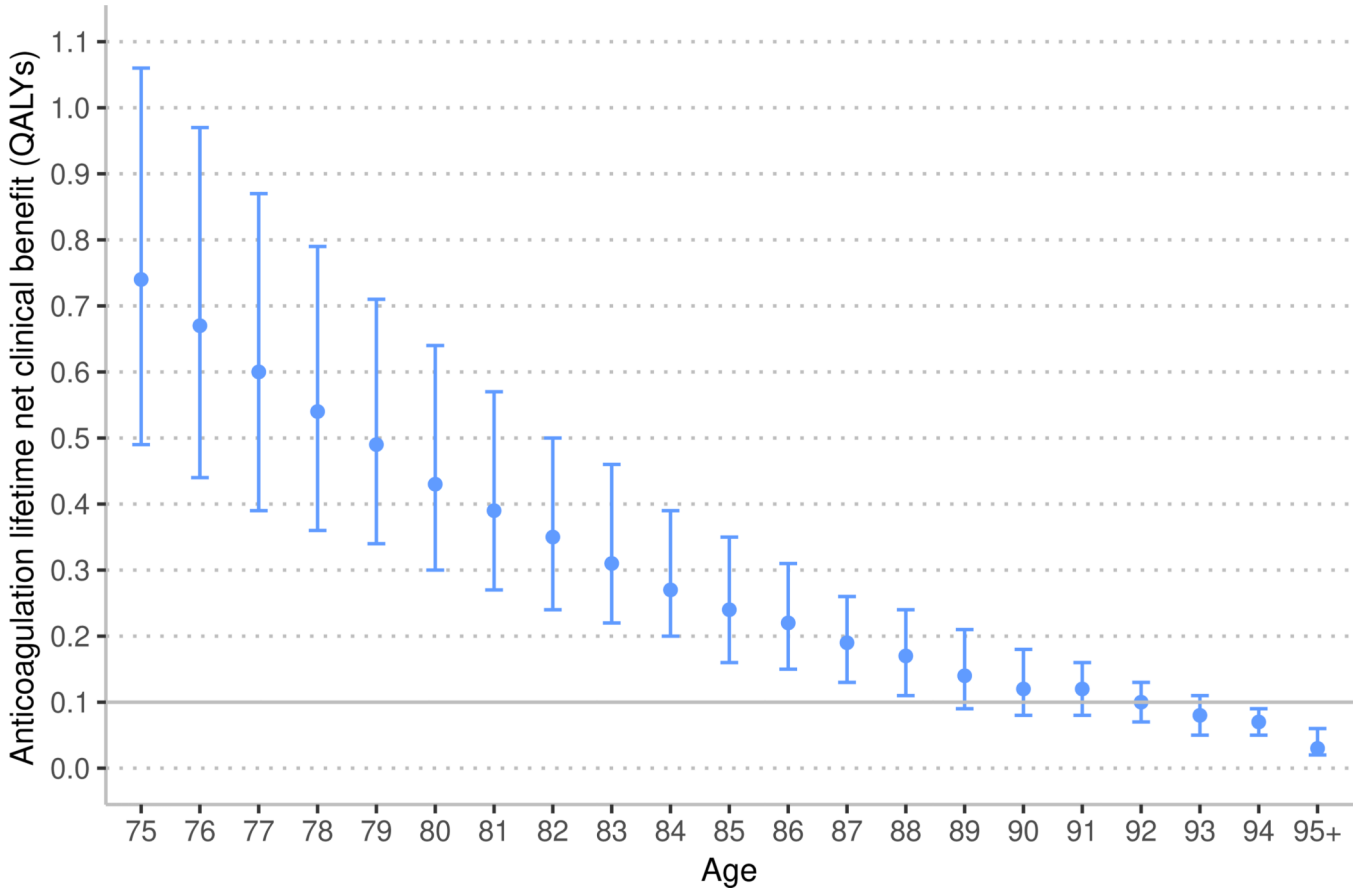
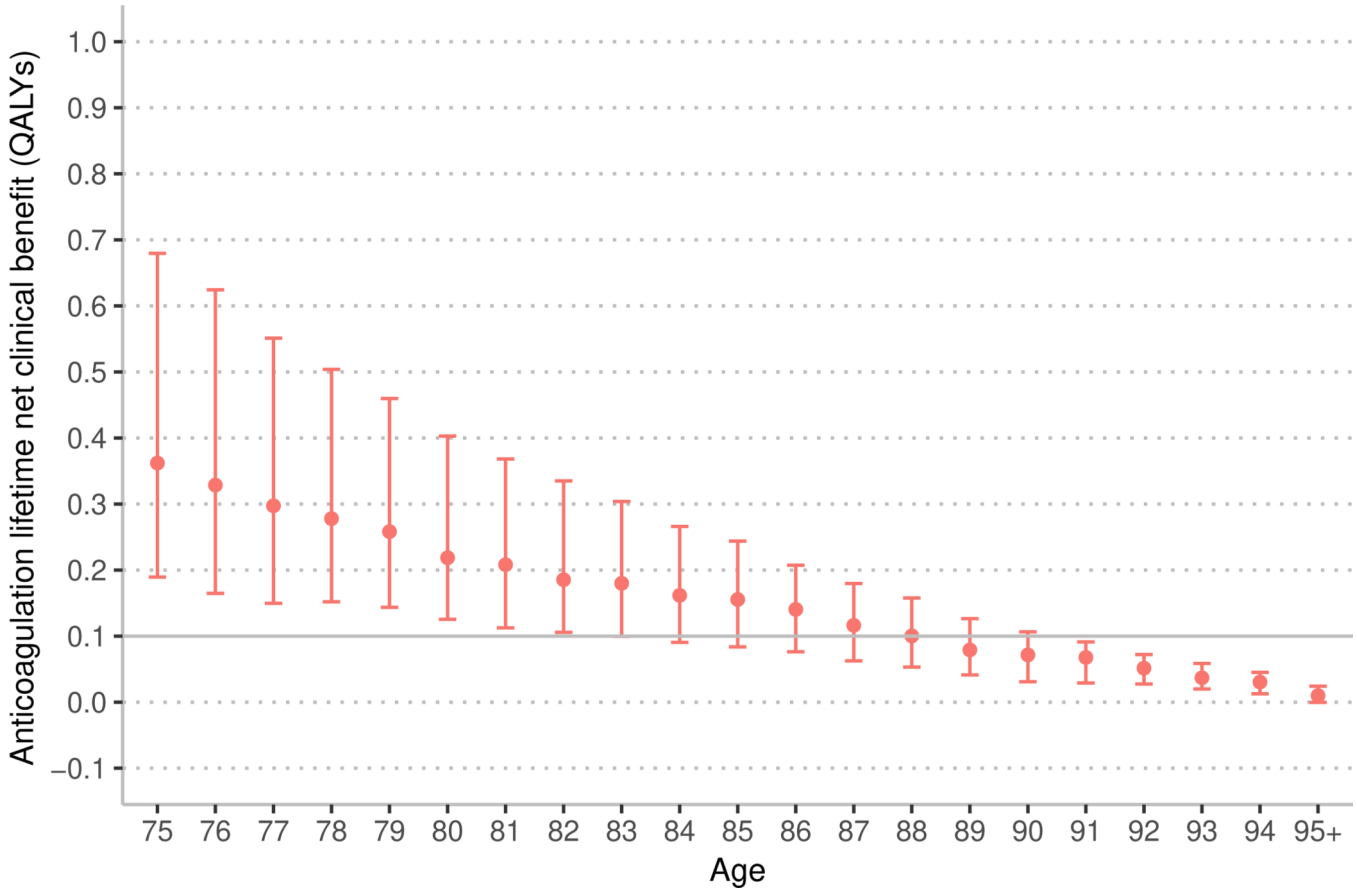


Figure 1:

Marker indicates median lifetime net clinical benefit for age, bar indicates interquartile range. QALYs – quality-adjusted life years. Ischemic stroke risk was estimated using the CHA_2DS_2-VASC score.



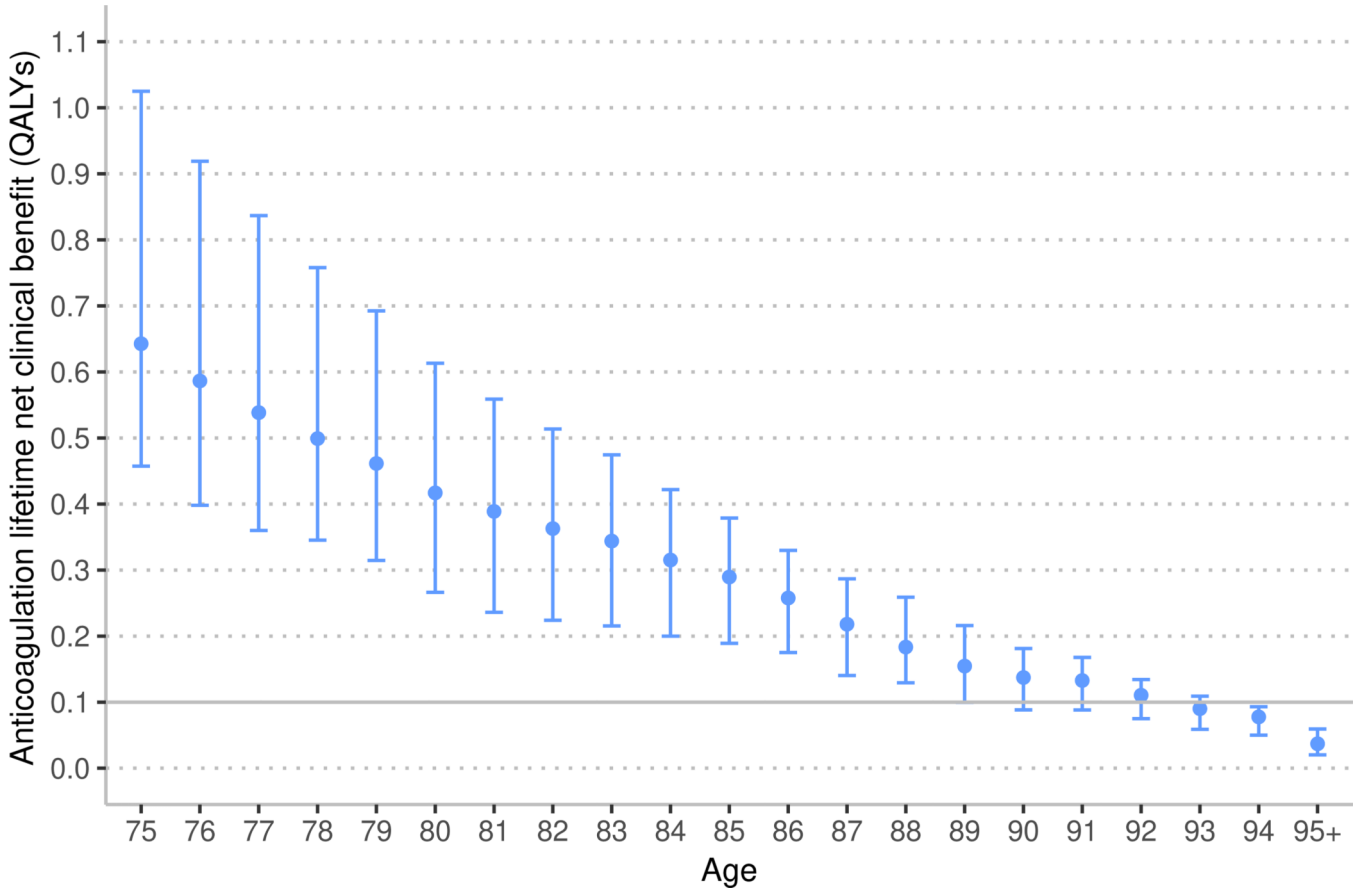
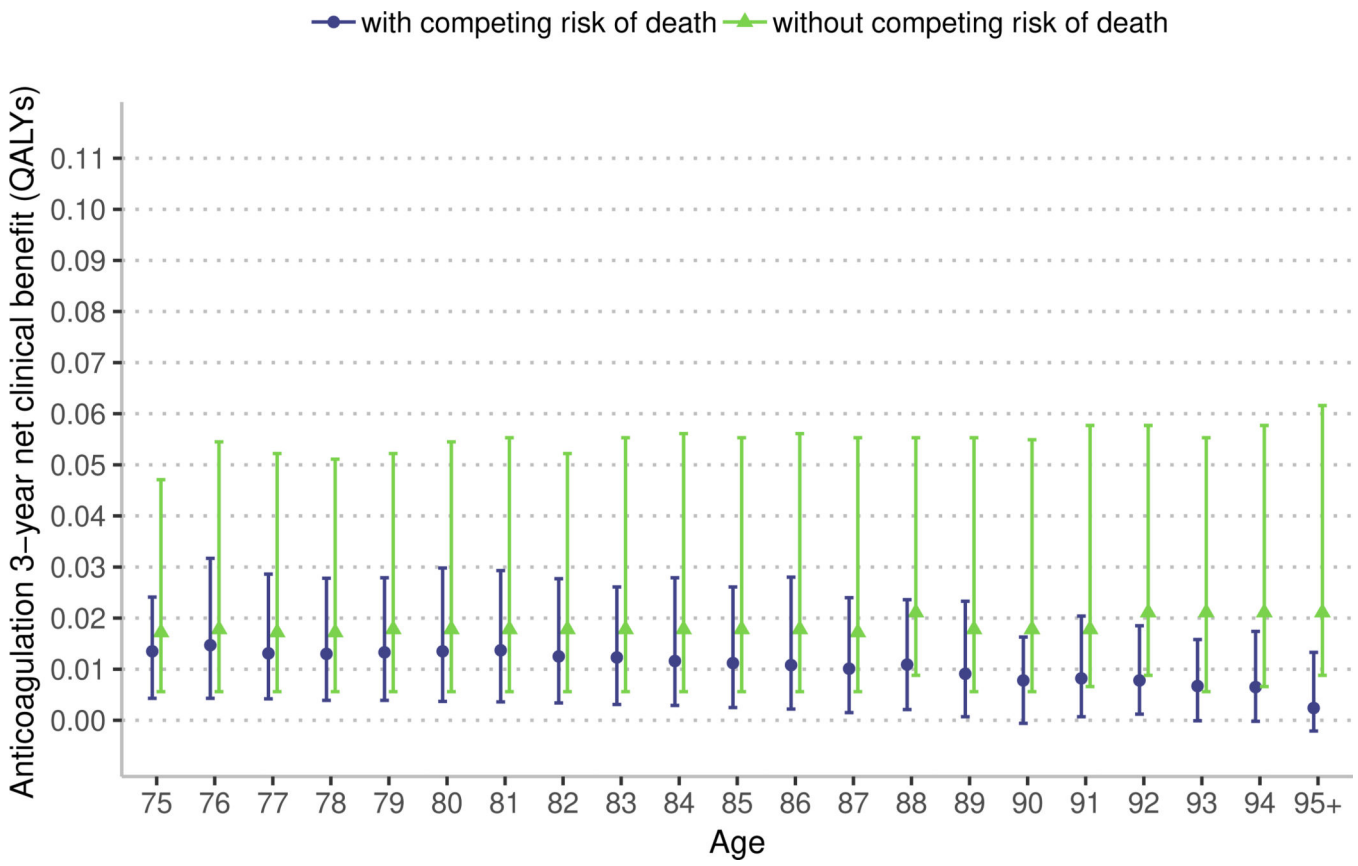


Figure 2:

Marker indicates median lifetime net clinical benefit for age, bar indicates interquartile range. QALYs – quality-adjusted life years. Ischemic stroke risk was estimated using the ATRIA score.



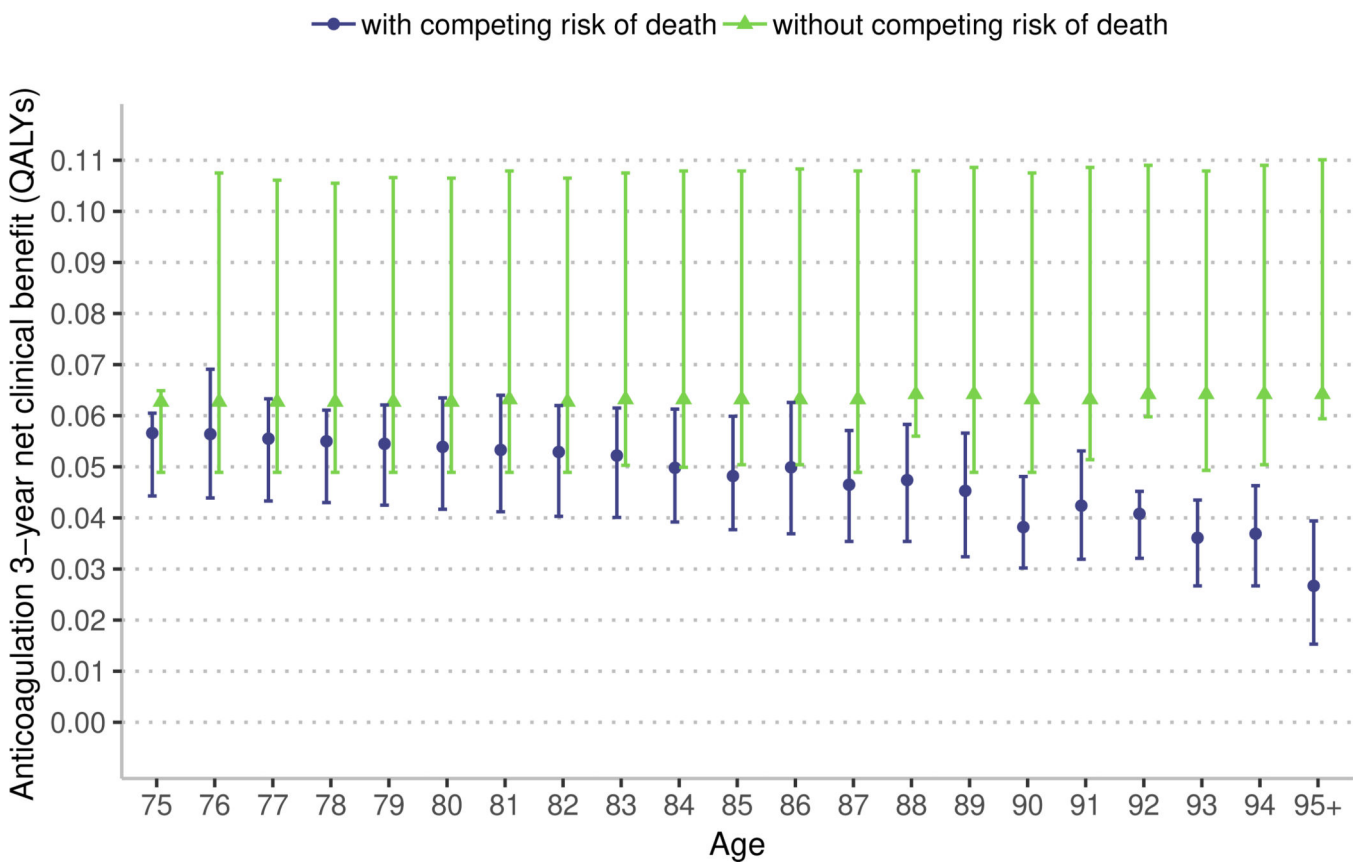
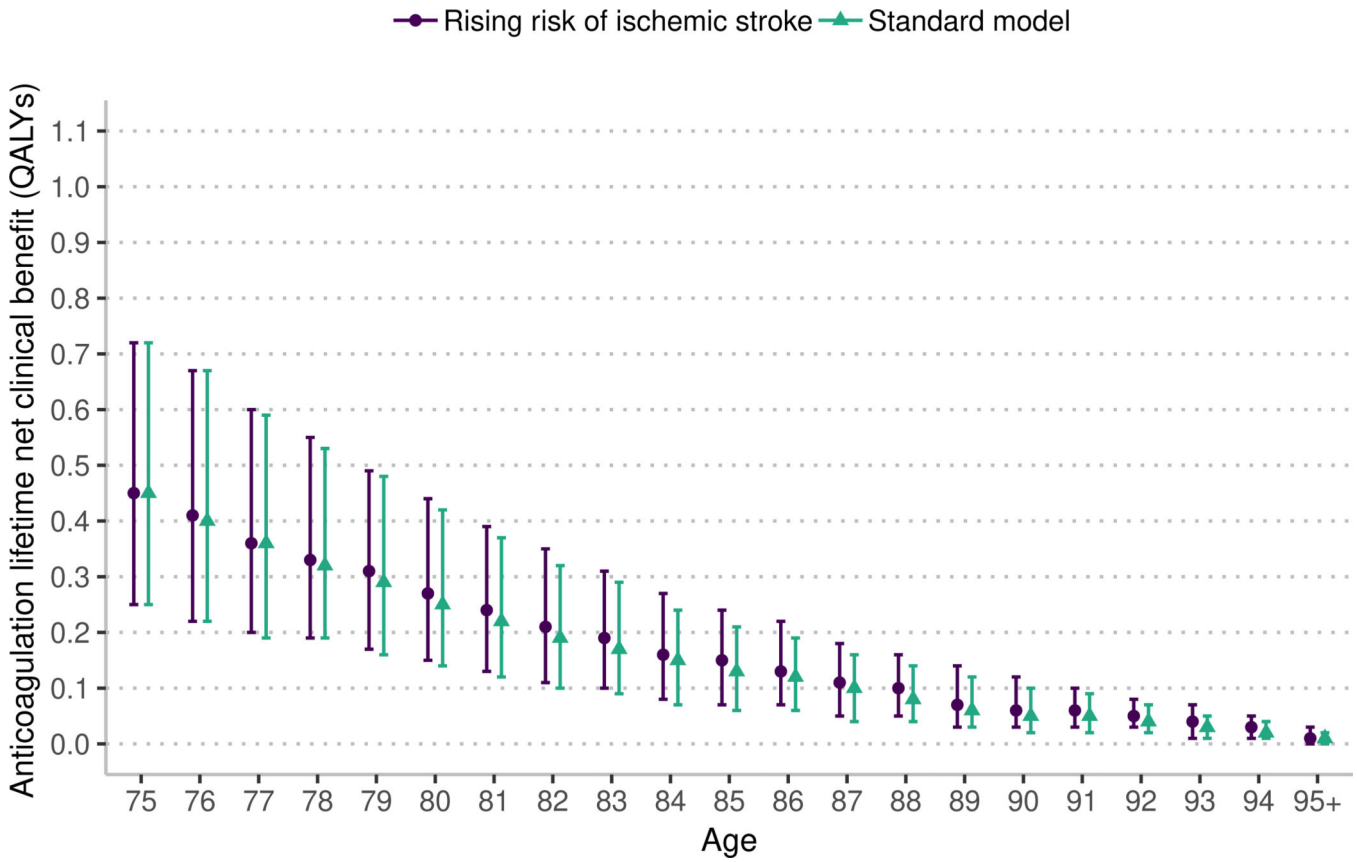


Figure 3:

Marker indicates median 3-year net clinical benefit for age, bar indicates interquartile range. QALYs – quality-adjusted life years. The model with competing risk of death accounts for disease-specific mortality and competing risk of death from non-AF related causes. The model without competing risks just accounts for disease-specific mortality. In the main model we use a lifetime estimate of net clinical benefit. In this sensitivity analysis, we estimate net clinical benefit over 3-years because removing the competing risk of death would result in a model with an unrealistically long lifespan and generate an uninterpretable estimate of lifetime net clinical benefit.



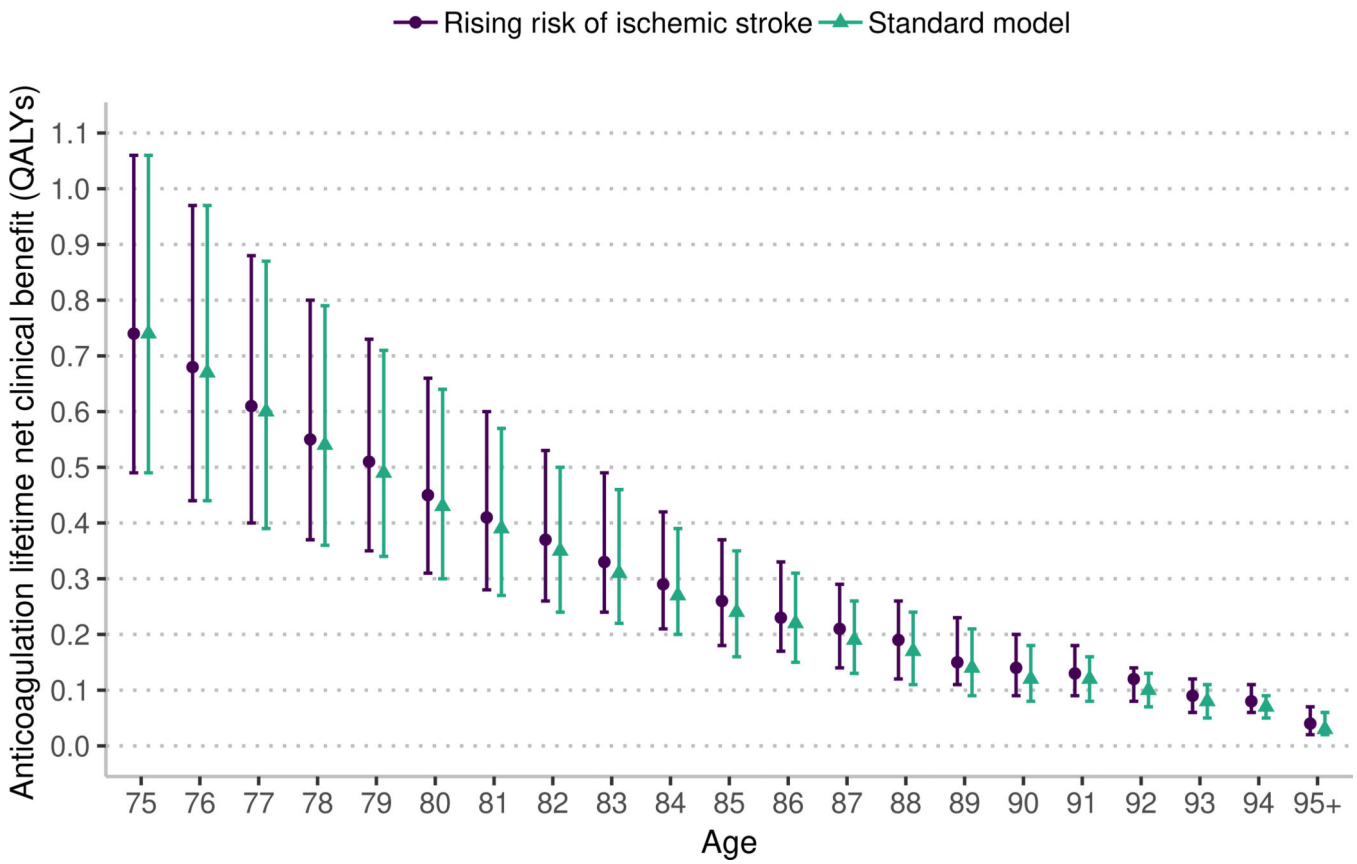


Figure 4:

Marker indicates median lifetime net clinical benefit for age, bar indicates interquartile range. QALYs – quality-adjusted life years. The rising risk of ischemic stroke increases the base stroke risk by 0.75% annually based on the risk model by Hijazi et at.[43,44]

Table 1.

Markov Model Inputs, Including, Rates, Outcomes, and Quality of Life

Parameter	Value
Ischemic stroke	
Annual rate of ischemic stroke (off-anticoagulation) by CHA_2DS_2-VASc Score[23]	
0	0
1	1.3
2	2.2
3	3.2
4	4
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2
Annual rate of ischemic stroke (off-anticoagulation) by ATRIA Score[1]	
0	0.08
1	0.43
2	0.99
3	0.73
4	0.64
5	0.99
6	1.91
7	2.50
8	3.86
9	4.33
10	6.35
11	6.18
12	10.95
13	7.52
14	16.36
15	0
Efficacy of warfarin[24]	0.68
Relative risk of ischemic stroke with apixaban (relative to warfarin)[25]	0.71
Extracranial hemorrhage	
Annual rate of warfarin-associated extracranial bleeding by HAS-BLED score[26]	
0	0
1	0.7
2	1.9
3	2.4

Parameter	Value
4	3.4
5	5.7
6	15.5
Hazard in the untreated (relative to warfarin) [26]	0.42
Hazard of apixaban (relative to warfarin)[25]	0.51
Intracranial hemorrhage	
Annual rate of ICH, based on multivariate hazard ratios (untreated) [3,27]	
Referent risk	0.0004
Age < 65	1.00
Age 65–74	1.97
Age > 75	2.43
Female	0.70
Prior ischemic stroke	1.21
History of ICH	8.92
History of severe bleed	3.10
History of myocardial infarction	0.82
History of ischemic heart disease	0.81
History of poorly controlled HTN *	1.32
Hazard of warfarin (relative to no treatment)[4,28]	4.1
Hazard of apixaban (relative to warfarin)[25]	0.54
Subdural hematoma	
Annual rate of subdural hematoma (untreated)[24,28,29]	0.00027
Hazard of anticoagulation (warfarin and apixaban relative to no treatment) [24,29,30]	5.5
Death from other causes (annual rates)	
Life expectancy[31]	Age, sex-specific
Excess annual mortality rates from selected comorbidities	
CKD 3a[32]	0.20
CKD3b[32]	0.80
CKD 4[32]	2.20
CKD 5[32]	4.90
Diabetes[33]	0.19
CHF, male[34]	0.21
CHF, female[34]	0.17
Hypertension[35]	0.001
Stroke, male[36]	0.05
Stroke, female[36]	0.03
Probability of outcomes	
Ischemic stroke outcome probability[24,37,38]	
Death	0.16
Permanent severe disability	0.30

Parameter	Value			
Permanent mild disability			0.14	
Good recovery			0.40	
Hemorrhage outcome probability off-anticoagulant[39–42]	Lobar ICH	Deep ICH	Subdural Hematoma	Extracranial
Death	0.19	0.21	0.27	0.02
Permanent severe disability	0.43	0.44	0.07	
Permanent mild disability	0.20	0.19	0.40	
Good recovery	0.19	0.17	0.26	0.98
Hemorrhage outcome probability on-anticoagulant[39–42]	Lobar ICH	Deep ICH	Subdural Hematoma	Extracranial
Death	0.38	0.41	0.27	0.05
Permanent severe disability	0.43	0.42	0.09	
Permanent mild disability	0.11	0.10	0.50	
Good recovery	0.08	0.07	0.14	0.95
Health states				
Long-term health state relative utility[21]				
Well			1.00	
Well while receiving apixaban			1.00	
Well while receiving warfarin			0.99	
Mild long-term disability			0.76	
Severe long-term disability			0.11	
Death			0.00	
Short-term health state relative utility				
ICH[†]			0.79	
Ischemic stroke[†]			0.79	
Extracranial bleed[‡]			0.84	

CHA_2DS_2-VASc score - congestive heart failure/hypertension/age/diabetes/stroke/vascular disease;

HAS-BLED score – hypertension/abnormal liver or renal function/stroke history/bleeding predisposition/labile INR/elderly/drug or alcohol usage

ICH – intracerebral hemorrhage

HTN – hypertension

SDH – subdural hematoma

CKD – chronic kidney disease

[*] poorly controlled hypertension given by a recorded systolic BP > 160 mmHg in 12 months before AF diagnosis

[†] Assumes quality of life is 0 for the duration of hospitalization. Length of stay for specific cerebrovascular disorders except for transient ischemic attack (diagnosis-related group, 14) is 6.4 days.

[‡] Duration of short-term utility loss for major extracranial bleed is 12 months.

Table 2:

Baseline Characteristics of the ATRIA-CVRN Cohort Used in the Decision Model

	ATRIA-CVRN Cohort (n = 14946)
DEMOGRAPHICS	
Age, median (range)	81 (75, 106)
Women	8024 (54%)
Race	
White	12500 (84%)
Black	753 (5%)
Native American	23 (0.2%)
Asian	799 (5%)
Other	436 (3%)
Unknown	435 (3%)
Hispanic ethnicity	1495 (10%)
COMORBIDITIES	
Chronic heart failure	3472 (23%)
Hypertension	13137 (88%)
Poorly controlled hypertension	3424 (23%)
Prior ischemic stroke	689 (5%)
Prior transient ischemic attack	497 (3%)
Vascular disease	
Peripheral arterial disease	780 (5%)
Other systemic arterial thromboembolism	112 (1%)
Diabetes mellitus	4100 (27%)
Chronic kidney disease	
eGFR < 30 ml/min/1.73 m^2	940 (6%)
Dialysis	196 (1%)
Chronic liver disease	214 (1%)
Bleeding history	
Intracranial hemorrhage	100 (1%)
Hospitalized gastrointestinal bleed	537 (4%)
Other hospitalized bleeding	80 (1%)
Prescribed aspirin or NSAID	3208 (21%)
Coronary heart disease	1412 (9%)
Prior acute myocardial infarction	649 (4%)
CHA_2DS_2-VASc SCORE	
0	0 (0%)
1	0 (0%)
2	688 (5%)
3	3476 (23%)
4	5900 (39%)

	ATRIA-CVRN Cohort (n = 14946)
5	3081 (21%)
6	1288 (9%)
7	400 (3%)
8	96 (1%)
9	18 (0%)
HAS-BLED SCORE (modified)	
0	0 (0%)
1	6266 (42%)
2	6037 (40%)
3	2177 (15%)
4	438 (3%)
5	27 (0%)
6	2 (0%)

Table 3.

Gain in Quality-adjusted Life Years for Selected Medical Interventions

Selected Interventions	Lifetime QALY gain
Lung cancer screening (age 55–75 years with 30 pack-year history)[48]	0.02
High vs. conventional dose statin for stable coronary artery disease[49]	0.10
Aspirin for primary prevention with new diagnosis of diabetes[50]	0.19
High vs. conventional dose statin following acute coronary syndrome[49]	0.35

All studies cited use a lifetime window. QALYs – quality-adjusted life years.