Atrial fibrillation (AF) is estimated to affect 2.5 million people in the United States, and results in a fivefold increase in the risk of ischemic stroke. The associated costs exceed $7 billion annually. Antithrombotic agents have proven benefits in preventing stroke in AF patients. Until recently, vitamin K antagonists such as warfarin were the only form of oral thromboprophylactic anticoagulation treatment. Although clinically effective and inexpensive, warfarin increases the risk of hemorrhage, interacts with many drugs, and, because of the considerable variability in patient response, requires careful monitoring.

Newer oral anticoagulants, which include the direct thrombin inhibitor dabigatran etexilate (hereafter referred to as dabigatran) and the direct factor Xa inhibitors rivaroxaban and apixaban, have recently been developed. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study evaluated two doses (110 and 150 mg twice daily) of dabigatran as an alternative to warfarin in 18,113 patients with at least one risk factor for stroke. The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) compared rivaroxaban with warfarin in 14,264 patients at elevated risk of stroke. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial compared apixaban with warfarin in 18,201 patients with at least one risk factor for stroke.

After a median follow-up period of ~2 years, the primary outcome of stroke or systemic embolism showed a potential improvement in the intention-to-treat population with all three alternatives, demonstrating superiority of the licensed 150 mg dose of dabigatran (1.11 vs. 1.71% per year; P < 0.001) and apixaban (1.27 vs. 1.60% per year; P = 0.01) and non-inferiority of rivaroxaban (2.1 vs. 2.4% per year; P = 0.12), as compared with warfarin. The rates of major bleeding were not significantly different between dabigatran 150 mg and warfarin or between rivaroxaban and warfarin, but apixaban was associated with a lower risk of major bleeding (2.13 vs. 3.09% per year; P < 0.001).

All three newer anticoagulants have been approved by the US Food and Drug Administration. Although their efficacies in relation to warfarin have been demonstrated, their comparative effectiveness remains unknown. With no prospect of a head-to-head...
In the base-case analysis, apixaban, dabigatran, and rivaroxaban extended life by 2.05, 1.51, and 1.10 months, respectively, as compared with warfarin (Table 1). The corresponding incremental net health benefits were 0.130 (95% central range (CR) −0.030 to 0.264), 0.106 (95% CR −0.048 to 0.248), and 0.095 (95% CR −0.052 to 0.242) QALYs, respectively. In pairwise comparisons using warfarin as the comparator, apixaban, dabigatran, and rivaroxaban were associated with a positive incremental net health benefit in 90, 84, and 82% of simulations, respectively. Using rivaroxaban as a comparator, apixaban and dabigatran were associated with an incremental net health benefit in 65% of simulations, and finally apixaban was associated with an incremental net health benefit against dabigatran in 65% of simulations.

Lifetime incidences of stroke or systemic embolism were 33.6% lower with apixaban, 17.0% lower with dabigatran, and 6.7% lower with rivaroxaban, as compared to warfarin. Lifetime incidences of major hemorrhagic events were 21.3% lower with apixaban, but 7.0 and 1.3% higher with rivaroxaban and dabigatran, respectively. Incidences of myocardial infarction were 10.7% lower with rivaroxaban and 6.5% lower with apixaban but 22.3% higher with dabigatran.

The relative effects of each treatment on the two constructs of the QALY—health-related quality of life and life-years gained—are illustrated in Supplementary Figure S1 online.

### Sensitivity analyses

The results of univariate parameter sensitivity analysis are presented in the form of tornado plots (Figure 1).

In the probabilistic sensitivity analysis of structural uncertainty, the base-case ordering of QALYs (apixaban, dabigatran, rivaroxaban, warfarin, in descending order) was replicated in 65.1% of simulations. The alternative ordering (dabigatran, apixaban, rivaroxaban, warfarin) occurred in 17.2% of simulations, and the ordering (apixaban, rivaroxaban, dabigatran, warfarin) occurred in 13.4% of simulations. No other ordering occurred in more than 1% of simulations. Overall, apixaban accrued the highest number of QALYs in 79.9% of simulations, dabigatran in 18.0%, and rivaroxaban in 2.1%, with warfarin never accruing the highest number. Using a Markov model instead of a discrete event simulation led to changes in both event rates and the numbers of QALYs in 79.9% of simulations, dabigatran in 18.0%, and rivaroxaban in 2.1%, with warfarin never accruing the highest number.

### Clinical outcomes and net health benefit

Table 1: Lifetime estimates of event rates, net health benefits, and incremental differences vs. comparator, derived from probabilistic sensitivity analysis

| Referent                  | Mean estimate (95% central range) | Mean difference (95% central range) | Comparator          |
|---------------------------|-----------------------------------|-------------------------------------|---------------------|
| **Quality-adjusted life-years** |                                   |                                     |                     |
| Warfarin                  | 5.636 (5.546, 5.733)               | −0.095 (−0.242, 0.052)              | Rivaroxaban         |
| Rivaroxaban               | 5.731 (5.631, 5.834)               | −0.011 (−0.164, 0.144)              | Dabigatran          |
| Dabigatran                | 5.742 (5.652, 5.854)               | −0.024 (−0.174, 0.130)              | Apixaban            |
| Apixaban                  | 5.766 (5.652, 5.881)               | 0.130 (−0.029, 0.265)               | Warfarin            |
| **Life-years**            |                                   |                                     |                     |
| Warfarin                  | 9.638 (9.498, 9.737)               | −0.092 (−0.286, 0.120)              | Rivaroxaban         |
| Rivaroxaban               | 9.729 (9.579, 9.865)               | −0.034 (−0.241, 0.172)              | Dabigatran          |
| Dabigatran                | 9.763 (9.604, 0.893)               | −0.045 (−0.254, 0.147)              | Apixaban            |
| Apixaban                  | 9.808 (9.655, 9.946)               | 0.171 (−0.031, 0.362)               | Warfarin            |
| **Stroke or systemic embolism** |                                   |                                     |                     |
| Warfarin                  | 0.303 (0.264, 0.339)               | 0.020 (−0.033, 0.074)               | Rivaroxaban         |
| Rivaroxaban               | 0.283 (0.238, 0.319)               | 0.031 (−0.029, 0.083)               | Dabigatran          |
| Dabigatran                | 0.251 (0.213, 0.301)               | 0.050 (−0.001, 0.099)               | Apixaban            |
| Apixaban                  | 0.201 (0.169, 0.254)               | −0.102 (−0.154, −0.050)             | Warfarin            |
| **Transient ischemic attack** |                                   |                                     |                     |
| Warfarin                  | 0.123 (0.091, 0.158)               | 0.031 (−0.019, 0.084)               | Rivaroxaban         |
| Rivaroxaban               | 0.092 (0.070, 0.123)               | −0.006 (−0.057, 0.046)              | Dabigatran          |
| Dabigatran                | 0.097 (0.069, 0.128)               | 0.020 (−0.034, 0.069)               | Apixaban            |
| Apixaban                  | 0.077 (0.055, 0.104)               | −0.046 (−0.093, 0.008)              | Warfarin            |
| **Intracranial hemorrhage** |                                   |                                     |                     |
| Warfarin                  | 0.073 (0.064, 0.081)               | 0.014 (−0.002, 0.026)               | Rivaroxaban         |
| Rivaroxaban               | 0.059 (0.052, 0.066)               | 0.018 (0.000, 0.025)                | Dabigatran          |
| Dabigatran                | 0.040 (0.035, 0.047)               | −0.002 (−0.015, 0.014)              | Apixaban            |
| Apixaban                  | 0.042 (0.033, 0.047)               | −0.031 (−0.046, −0.013)             | Warfarin            |
| **Major bleed (including intracranial hemorrhage)** | | | |
| Warfarin                  | 0.307 (0.262, 0.347)               | −0.021 (−0.076, 0.036)              | Rivaroxaban         |
| Rivaroxaban               | 0.328 (0.283, 0.374)               | 0.017 (−0.037, 0.069)               | Dabigatran          |
| Dabigatran                | 0.311 (0.274, 0.363)               | 0.069 (0.014, 0.115)                | Apixaban            |
| Apixaban                  | 0.242 (0.205, 0.278)               | −0.065 (−0.116, −0.010)             | Warfarin            |
| **Nonfatal myocardial infarction** | | | |
| Warfarin                  | 0.067 (0.047, 0.086)               | 0.007 (−0.013, 0.029)               | Rivaroxaban         |
| Rivaroxaban               | 0.059 (0.043, 0.080)               | −0.022 (−0.043, −0.002)             | Dabigatran          |
| Dabigatran                | 0.081 (0.063, 0.099)               | 0.019 (−0.002, 0.033)               | Apixaban            |
| Apixaban                  | 0.062 (0.044, 0.086)               | −0.004 (−0.022, 0.019)              | Warfarin            |

Table 1: Lifetime estimates of event rates, net health benefits, and incremental differences vs. comparator, derived from probabilistic sensitivity analysis

Of the 270 articles published in Volume 94, Number 1, one article was selected for detailed analysis. The article assessed the tradeoffs in thrombotic and bleeding risks for all four anticoagulants and incorporated a preference-based, patient-centered outcome—the quality-adjusted life-year (QALY)—to combine health-related quality of life with survival. Our analysis acknowledges differences in trial designs and populations, as well as their potential impacts on estimated comparative effectiveness, by adopting a probabilistic approach for a range of plausible scenario analyses.

### RESULTS

The results of simulations at 2 years matched the results of each trial. No value deviated by more than 3.2% (data not shown), a level of variability that was expected given the stochastic nature of the simulation. At 2 years, apixaban accrued 0.15 more quality-adjusted life-weeks than dabigatran, 0.26 more than rivaroxaban, and 0.78 more than warfarin.

The relative effects of each treatment on the two constructs of the QALY—health-related quality of life and life-years gained—are illustrated in Supplementary Figure S1 online.
Figure 2

the differences in net health benefits changed, with groups ing remained consistent across patient subgroups, although for all newer agents as compared with warfarin. This order - and the risks of intracranial hemorrhage, which were lower Differences were driven principally by differential stroke rates son, apixaban appears to be the most effective oral antico - allocation and that results in an adjusted, indirect compari - research that preserves the randomization of treatment Based on an accepted method of comparative effectiveness CLInICAL phARm ACOLOgY & ThERApEUTICS DISCUSSION

Vascular death rates-dabigatran (H/L)
Vascular death rates-dabigatran (L/H)
Vascular death rates-apixaban (H/L)
Vascular death rates-apixaban (L/H)
Medication utility losses (none)
Linear reduction in treatment benefit
Bleed rates-warfarin (L/H)
Bleed rates-rivaroxaban (L/H)

Figure 1 Tornado plots of univariate sensitivity analysis. Each figure presents the 10 parameters that led to the greatest change in overall QALYs. L/H refers to lower and higher limits of parameter estimates. QALY, quality-adjusted life-year.

Subgroup analyses
Among the subgroups analyzed, the ordering of anticoagu - lants according to mean QALYs and probability of being most effective was consistent with the base-case analysis (Table 2, Figure 2). Apixaban had the highest probability of being the most effective in patients with impaired renal function, and the lowest in older populations (≥75 years), but these probabilities were over a very narrow range (50.1–61.6%).

DISCUSSION
Based on an accepted method of comparative effectiveness research that preserves the randomization of treatment allocation and that results in an adjusted, indirect compari - on, apixaban appears to be the most effective oral antico - agulant, followed by dabigatran, rivaroxaban, then warfarin. Differences were driven principally by differential stroke rates and the risks of intracranial hemorrhage, which were lower for all newer agents as compared with warfarin. This ordering remained consistent across patient subgroups, although the differences in net health benefits changed, with groups having lower risks of stroke associated with smaller differ - ential QALYs.

There is no subgroup in which the probability of apixaban being the most effective is below 50% and none in which the probability of warfarin being the most effective is above 5%.

The sensitivity analyses indicate that the parameters to which the outcome was most sensitive were stroke rates and vascular death rates.

We are aware of two other adjusted\textsuperscript{11,12} and one unadjusted\textsuperscript{13} indirect treatment comparisons. Lip et al.\textsuperscript{12} concluded that there were no discernable differences among treatments, whereas the analysis by Mantha et al.,\textsuperscript{11} although both based on the same clinical trial data, indicated that apixaban was equally effective as dabigatran 150 mg, more effective than rivaroxaban, and associated with less major bleeding than both. The crude estimates of net clinical benefit calculated by Banerjee et al.\textsuperscript{13} for a Danish population are subject to bias because the odds ratios derived from the trials were not adjusted. None of the analyses modeled patients representative of the US AF population; used a preference-based, patient-centered outcome measure; used an
Table 2 Net benefit results for subgroups, based on probabilistic sensitivity analysis

| Subgroup                                | Warfarin (QALY) | Rivaroxaban (QALY) | Dabigatran (QALY) | Apixaban (QALY) |
|------------------------------------------|----------------|--------------------|-------------------|----------------|
| Base case                                | 5.637 (0.024)  | 5.735 (0.159)      | 5.745 (0.266)     | 5.767 (0.551)  |
| Age ≥75 years                             | 3.848 (0.047)  | 3.940 (0.177)      | 3.948 (0.270)     | 3.972 (0.506)  |
| CHADS2 score ≥3                          | 5.482 (0.014)  | 5.590 (0.149)      | 5.617 (0.234)     | 5.649 (0.603)  |
| RE-LY population                         | 5.658 (0.027)  | 5.746 (0.176)      | 5.769 (0.296)     | 5.784 (0.501)  |
| ROCKET-AF population                     | 5.582 (0.022)  | 5.666 (0.151)      | 5.678 (0.232)     | 5.710 (0.595)  |
| ARISTOTLE population                     | 5.651 (0.038)  | 5.747 (0.181)      | 5.761 (0.266)     | 5.786 (0.515)  |
| Previous stroke or transient ischemic attack | 5.460 (0.006) | 5.545 (0.152)      | 5.562 (0.305)     | 5.582 (0.537)  |
| Creatinine clearance 30–50 ml/min        | 5.561 (0.010)  | 5.664 (0.140)      | 5.677 (0.234)     | 5.701 (0.616)  |
| Vitamin K antagonist naive               | 5.641 (0.028)  | 5.729 (0.171)      | 5.742 (0.260)     | 5.766 (0.541)  |

ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial; CHADS2, congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke/transient ischemic attack; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; QALY, quality-adjusted life-year.

appropriate time horizon of analysis; or considered alternative scenarios of analysis.

By contrast, our analysis adopts a lifetime horizon, uses QALYs to synthesize the differential impacts of benefits and harms on health, and considers both structural and parameter uncertainty. QALYs may reveal differences among treatments that might be less apparent when considering individual clinical events. Adjusted, indirect treatment comparisons are accepted by health-care decision-makers across several jurisdictions as the method of choice in situations in which data from head-to-head trials are unavailable. This Bayesian approach results in a meaningful outcome for prescribers, that is, the probability of a treatment being the best option. Judgments based on confidence intervals and hypothesis tests, based on the frequentist notion of assuming the null hypothesis until sufficient evidence indicates otherwise, can be criticized as inappropriate in this context because decisions regarding treatment alternatives cannot be deferred given that such evidence is unlikely to become available. Moreover, a lack of statistical significance does not necessarily imply equivalence in outcome.

There are potential caveats to our comparative effectiveness research methodology, however. First, there were many important differences across trials in terms of their design (e.g., RE-LY being open-label; use of sham international normalized ratio testing only in ROCKET-AF), patient populations (e.g., higher risk of stroke, greater experience of previous stroke or transient ischemic attack, and less time in international normalized ratio range in ROCKET-AF), and reporting (e.g., differences in definitions of some clinical events). These are discussed extensively elsewhere and, collectively, potentially undermine the assumption necessary for indirect comparison methodology—that any such differences do not affect the comparative effectiveness of the treatments being assessed. Although there is no method available for testing the validity of this assumption, there is no prospect of a head-to-head comparison among newer anticoagulants, and prescribers will in any case make qualitative judgments or naive, unadjusted comparisons of competing treatment options. Our analysis is a more valid approach than simply comparing individual trials or trial arms in an unadjusted way.

Second, the modeled extrapolation to a lifetime horizon of analysis is necessary to reflect differential impacts of treatments on health and survival that extend beyond the protocol-defined trial follow-up period. The analysis used a discrete event simulation method, given that there are no obvious discrete disease states into which patients can be classified. However, this required an assumption that risk equations derived from 2-year data apply beyond that time. Relaxing this assumption by analysis at 2 years resulted in the same rank ordering of net health benefits, as did the use of an alternative, the Markov model structure.

Despite these limitations, there was a high level of consistency in the ranking of treatment effectiveness across all the different simulations performed. Had the results been dependent on any specific modeling assumption, then this would be apparent in the sensitivity analysis. We can reasonably conclude that any biases in our analysis, if present, are inherent in the data and therefore impossible to correct under any modeling framework.
It is important to note that the analysis did not consider additional factors that impinge on treatment choice. These include cost-effectiveness, patient convenience, preference (or aversion) to individual treatments, relative forgiveness of treatments to missed doses, lack of antidotes to over-anticoagulation with the newer oral anticoagulants, merits or otherwise of patients being monitored regularly when prescribed warfarin, and longer term and rarer adverse events that might become apparent only with more extensive experience of use in routine practice. Furthermore, the newer agents also interact with other drugs, and there are specific safety considerations in certain vulnerable populations (e.g., the very elderly and those with severe renal impairment). There may also be subgroup(s) of patients that were not explored in the present analysis—such as those with genetic polymorphisms of CYP2C9 or VKORC1—in which the balance of harms and benefits differs significantly from the mean.

There is no doubt about the efficacy of the newer oral anticoagulants and the favorable risk–benefit profile as compared to warfarin in the pivotal trials; however, there are important differences among the agents, and our analysis currently points to the likely superiority of apixaban over others. We recommend, however, that analyses of population databases of real-life user populations be performed to test hypotheses derived from our model. Certainly our results, and those from any observational studies, would not be expected to supplant evidence from randomized controlled trials but should be kept under review as the evidence matures.

**METHODS**

Comparative effectiveness was assessed using an indirect analysis that extrapolated benefits and harms to a lifetime horizon, consistent with AF being a lifelong condition requiring indefinite treatment. The analysis is based on a discrete event simulation model we described previously, and which allows for explicit incorporation of both structural and parameter uncertainty. The model simulates clinical events and outcomes experienced by individual patients. The risks of their occurrence are determined from patients’ characteristics that are updated according to time and event history. Comparative effectiveness was determined from incremental net health benefits, measured as the differences between treatments in QALYs, and from modeled clinical event rates.

**Model population.** In the base-case analysis, patients’ baseline characteristics, which were assumed to be uncorrelated, were representative of the stroke risk profile of the US AF population. Patients had a mean age of 73.0 years, with 38.8, 36.8, 18.0, and 6.4% having CHADS\textsubscript{2} (congestive heart failure, hypertension, age \textgreater 75, diabetes mellitus, prior stroke/transient ischemic attack) scores of 1, 2, 3, and \textgreater 4, respectively.30

| Baseline characteristics | RE-LY | ROCKET-AF | ARISTOTLE |
|-------------------------|-------|-----------|-----------|
| Number of patients      | 18,113| 14,264    | 18,201    |
| Hypertension (ref. 7–9) | 78.9% | 90.5%     | 87.4%     |
| Diabetes (refs. 7–9)    | 23.3% | 39.9%     | 25.0%     |
| Heart failure (refs. 7–9)| 32.0% | 62.5%     | 35.4%     |
| Prior stroke (ref. 7)   | 12.5% | 34.4%\textsuperscript{b} | 11.9%\textsuperscript{b} |
| Prior transient ischemic attack (ref. 7) | 9.2% | 25.3%\textsuperscript{b} | 8.7%\textsuperscript{b} |
| Prior myocardial infarction (refs. 7–9) | 16.6% | 17.3% | 14.2% |
| Prior intracranial hemorrhage (ref. 7) | 3.9% | 10.7%\textsuperscript{b} | 3.7%\textsuperscript{b} |

ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial; CHADS\textsubscript{2}, congestive heart failure, hypertension, age \textgreater 75, diabetes mellitus, prior stroke/transient ischemic attack; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism in Atrial Fibrillation.

**Interventions.** The analysis considered a dose of 5 mg twice daily of apixaban and the licensed doses of dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, and dose-adjusted warfarin.

**Clinical parameters.** Annualized clinical event rates were extracted from the RE-LY, ROCKET-AF, and ARISTOTLE trials\textsuperscript{7–9} and identified from a systematic review of the literature.\textsuperscript{16} Based on the method of Bucher et al.,\textsuperscript{10} indirect comparisons were adjusted according to the results of their direct comparisons with warfarin. This adjustment accounts for differing baseline risks between trials by assuming a constant relative treatment effect; for example, for two trials comparing A and B, and B and C, with relative risks for a given event of RR\textsubscript{AB} and RR\textsubscript{BC}, respectively, the indirect, relative effect of C vs. A is estimated as:

\[
\ln(\text{RR}_{AC}) = \ln(\text{RR}_{AB}) + \ln(\text{RR}_{BC})
\]

Event rates for dabigatran, apixaban, and rivaroxaban were calculated by multiplying relative treatment effects by warfarin event data, calculated from a meta-analysis of the warfarin arms of the three trials (Table 4). Hypertension and diabetes incidence rates were taken from US general population data,\textsuperscript{31,32} as were age-specific nonvascular mortality data,\textsuperscript{33} all with the assumption that these accurately reflect the AF population. Whenever necessary data were not available (e.g., a particular parameter was not reported for a given trial), values were imputed based on data from the other trials and US population data (Tables 4 and 5). All assumptions were assessed through sensitivity analysis (see sections on sensitivity analysis, below).

To better reflect the use of oral anticoagulants in routine care, the analysis also included the trial-derived probabilities of (and reasons for) discontinuation of treatment. Patients who discontinued dabigatran, rivaroxaban, or apixaban because of a bleed or who discontinued warfarin for any reason were assumed to have switched to aspirin, whereas other discontinuing patients were assumed to have switched to warfarin. This assumption was tested by sensitivity analysis. Relative risks of events for aspirin came from a published meta-analysis of trials comparing warfarin and aspirin,\textsuperscript{34} and the AVERROES (Apixaban Versus Acetylsalicylic acid to Prevent Strokes) trial comparing apixaban with aspirin in patients deemed unsuitable for vitamin K antagonist therapy.\textsuperscript{35}

QALYS were discounted at 3% per annum to reflect time preference, but no discounting was applied to discrete clinical events.

**Utility estimates.** The age-adjusted baseline health utility for a person with AF, together with the utility decrements associated with cardiovascular sequelae (excluding stroke) and hemorrhagic events, was taken from the EQ-5D scores in a US Medical Expenditure Panel Survey of several thousand patients.\textsuperscript{37,38} The permanent utility decrement associated with stroke was derived from the European Stroke Prevention Study, based on the proportions of disabling to nondisabling strokes (43% of nonfatal strokes were nondisabling across RE-LY, ROCKET-AF, and ARISTOTLE trials; however, there are important differences among the agents, and our analysis currently points to the likely superiority of apixaban over others. We recommend, however, that analyses of population databases of real-life user populations be performed to test hypotheses derived from our model. Certainly our results, and those from any observational studies, would not be expected to supplant evidence from randomized controlled trials but should be kept under review as the evidence matures.

**Table 3 Patients’ baseline characteristics**

| Baseline characteristics | RE-LY | ROCKET-AF | ARISTOTLE |
|-------------------------|-------|-----------|-----------|
| Number of patients      | 18,113| 14,264    | 18,201    |
| Hypertension (ref. 7–9) | 78.9% | 90.5%     | 87.4%     |
| Diabetes (refs. 7–9)    | 23.3% | 39.9%     | 25.0%     |
| Heart failure (refs. 7–9)| 32.0% | 62.5%     | 35.4%     |
| Prior stroke (ref. 7)   | 12.5% | 34.4%\textsuperscript{b} | 11.9%\textsuperscript{b} |
| Prior transient ischemic attack (ref. 7) | 9.2% | 25.3%\textsuperscript{b} | 8.7%\textsuperscript{b} |
| Prior myocardial infarction (refs. 7–9) | 16.6% | 17.3% | 14.2% |
| Prior intracranial hemorrhage (ref. 7) | 3.9% | 10.7%\textsuperscript{b} | 3.7%\textsuperscript{b} |

ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial; CHADS\textsubscript{2}, congestive heart failure, hypertension, age \textgreater 75, diabetes mellitus, prior stroke/transient ischemic attack; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism in Atrial Fibrillation.

\textsuperscript{a}Percentage in initial population. \textsuperscript{b}These values were imputed from the data available in the RE-LY study and the distributions of CHADS\textsubscript{2}, scores at the start of the trial, which were known for all three studies, under the assumption that the ratio of strokes to transient ischemic attacks and intracranial hemorrhages would be consistent between trials. Probability of prior stroke or transient ischemic attack in ROCKET-AF was 55% and in ARISTOTLE was 19%.
### Table 4 Clinical event rates

| Parameter | Warfarin | Dabigatran | Rivaroxaban | Apixaban | Aspirin |
|-----------|----------|------------|-------------|----------|---------|
| Stroke (CHADS<sub>2</sub> score ≤1)<sup>a</sup> | 0.092 | 0.054 | 0.075<sup>b</sup> | 0.068 | 0.149 |
| Stroke (CHADS<sub>2</sub> score 2)<sup>a</sup> | 0.141 | 0.082 | 0.126 | 0.121 | 0.227 |
| Stroke (CHADS<sub>2</sub> score 3)<sup>a</sup> | 0.196 | 0.116<sup>b</sup> | 0.134 | 0.113<sup>b</sup> | 0.316 |
| Stroke (CHADS<sub>2</sub> score 4)<sup>a</sup> | 0.312 | 0.215<sup>b</sup> | 0.244 | 0.210<sup>b</sup> | 0.503 |
| Stroke (CHADS<sub>2</sub> score 5)<sup>a</sup> | 0.290 | 0.240<sup>b</sup> | 0.279 | 0.233<sup>b</sup> | 0.468 |
| Stroke (CHADS<sub>2</sub> score 6)<sup>a</sup> | 0.364 | 0.310<sup>b</sup> | 0.351 | 0.302<sup>b</sup> | 0.587 |
| Systemic embolism<sup>a</sup> | 0.014 | 0.011 | 0.003 | 0.012 | 0.022 |
| Pulmonary embolism<sup>a</sup> | 0.008 | 0.011 | 0.009<sup>c</sup> | 0.006<sup>c</sup> | 0.013 |
| Transient ischemic attack<sup>a</sup> | 0.084 | 0.072 | 0.066<sup>c</sup> | 0.062<sup>c</sup> | 0.135 |
| Myocardial infarction<sup>a</sup> | 0.076 | 0.101 | 0.062 | 0.067 | 0.076 |
| Congestive heart failure<sup>a</sup> | 0.062 | 0.048 | 0.049<sup>c</sup> | 0.045<sup>c</sup> | 0.062 |
| Vascular death (excluding stroke and systemic and pulmonary embolism)<sup>a</sup> | 0.228 | 0.208 | 0.216 | 0.212 | 0.228 |
| Probability of death from stroke or systemic embolism | 2.546 | 2.546 | 2.546 | 2.546 | 2.546 |
| Probability of death from pulmonary embolism | 1.591 | 1.591 | 1.591 | 1.591 | 1.591 |
| Major bleed (CHADS<sub>2</sub> score ≤1)<sup>a</sup> | 0.261 | 0.198 | 0.225<sup>b</sup> | 0.159 | 0.115 |
| Major bleed (CHADS<sub>2</sub> score 2)<sup>a</sup> | 0.318 | 0.292 | 0.338<sup>b</sup> | 0.243 | 0.140 |
| Major bleed (CHADS<sub>2</sub> score ≥3)<sup>a</sup> | 0.443 | 0.467 | 0.480<sup>b</sup> | 0.306 | 0.194 |
| Probability that major bleed is intracranial hemorrhage | 2.336 | 1.023 | 1.495 | 1.407 | 2.336 |
| Minor bleed<sup>a</sup> | 1.656 | 1.502 | 1.714 | 1.178 | 0.726 |
| Diabetes<sup>a</sup> | 0.141 | 0.141 | 0.141 | 0.141 | 0.141 |
| Hypertension<sup>a</sup> | 0.323 | 0.323 | 0.323 | 0.323 | 0.323 |
| Probability of discontinuation (year 1)<sup>a</sup> | 1.447 | 2.205 | 1.448 | 1.423 | N/A |
| Probability of discontinuation (year 2 onward)<sup>a</sup> | 0.676 | 0.670 | 0.722 | 0.498 | N/A |

CHADS<sub>2</sub>, congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke/transient ischemic attack; N/A, not applicable; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy.

<sup>a</sup>Presented as rates per 1,000 person-years. <sup>b</sup>Where stratified event rates were not available, unknown stratified risks were imputed based on the assumption that the relative risks of events for patients with different CHADS<sub>2</sub> scores would be independent of treatment. <sup>c</sup>Imputed, based on the relative risks of different events from the RE-LY study, on the assumption that the relative risks of different thromboembolic events would be independent of treatment.

### Table 5 Health state utilities assigned to treatments and clinical events, and the corresponding duration of acute events

| Parameter | Value | Probabilistic sensitivity analysis distribution |
|-----------|-------|-----------------------------------------------|
| Atrial fibrillation (age 67) (ref. 37) | 0.774 | 1−γ (43.06, 0.005) |
| Stroke/systemic embolism (permanent disutility) (ref. 39) | 0.235 | Normal (0.235, 0.003) |
| Stroke/systemic embolism (temporary disutility) (refs. 37,38) | 0.139 | Normal (0.139, 0.01) |
| Stroke/systemic embolism (temporary disutility, years) (ref. 38) | 0.083 | Uniform (0, 0.183) |
| Myocardial infarction (permanent disutility) (ref. 37) | 0.041 | Normal (0.041, 0.002) |
| Myocardial infarction (temporary disutility) (refs. 37,38) | 0.125 | Normal (0.125, 0.01) |
| Myocardial infarction (temporary duration, years) (ref. 38) | 0.083 | Uniform (0, 0.183) |
| Intracranial hemorrhage (permanent disutility) (ref. 37) | 0.052 | Normal (0.052, 0.001) |
| Pulmonary embolism (temporary disutility) (refs. 37,38) | 0.139 | Normal (0.139, 0.01) |
| Pulmonary embolism (temporary duration, years) (ref. 38) | 0.083 | Uniform (0, 0.183) |
| Transient ischemic attack (temporary disutility) (refs. 37,38) | 0.103 | Normal (0.103, 0.01) |
| Transient ischemic attack (temporary duration, years) (ref. 38) | 0.014 | Uniform (0, 0.027) |
| Major bleed (temporary disutility) (refs. 37,38) | 0.139 | Normal (0.139, 0.01) |
| Major bleed (temporary duration, years) (ref. 38) | 0.083 | Uniform (0, 0.183) |
| Minor bleed (temporary disutility) (ref. 38) | 0.060 | Normal (0.06, 0.01) |
| Minor bleed (temporary duration, years) (ref. 38) | 0.014 | Uniform (0, 0.027) |
| Warfarin disutility (ref. 39) | 0.013 | γ (1.3, 0.01) |
| Dabigatran/rivaroxaban/apixaban disutility | 0.002 | γ (0.2, 0.01) |
| Aspirin disutility (ref. 39) | 0.002 | γ (0.2, 0.01) |
ROCKET-AF, and ARISTOTLE). The analysis incorporated utility losses inherent to warfarin (e.g., as a result of monitoring) and aspirin (assumed to be the same for dabigatran, rivaroxaban, and apixaban). Multiple utility decrements were assumed to be additive; utility values are given in Table 5.

To assess the sensitivity of the model to the choice of utility parameters, a sensitivity analysis was conducted, replacing base-case utility values with those from an alternative cost-effectiveness study in AF. Parameter sensitivity analysis. Univariate sensitivity analyses of each parameter in the model were conducted to assess the effect of varying assumptions on the stability of the results. Ninety-five percent confidence intervals were used as the upper and lower limits for parameters or, where these were not available, plausible percentage ranges.

A probabilistic parameter sensitivity analysis was also conducted as a Monte Carlo simulation of 2,000 sets of parameters sampled from appropriate distributions. This provided estimates of the 95% CIs (2.5th to 97.5th percentile) for clinical event rates and net health benefits, and the probability of each treatment option resulting in the highest net health benefit.

Structural sensitivity analysis. The model necessitated a large number of assumptions, either for simplification purposes or because the desired data were not available in the necessary format. The robustness of the results in relation to different assumptions was assessed quantitatively.

Univariate analyses considered the different options presented in Supplementary Table S1 online. A probabilistic analysis was performed by sampling 10,000 times, at random, from the subspace of possible structural assumptions, with each assumption having equal likelihood to be selected. As described previously, the outputs are presented as the probabilities with which each treatment option results in the highest net health benefit.

To assess whether the choice of a discrete event simulation framework had a significant impact on the results, a secondary analysis was performed, replacing our simulation model with a published Markov model.

Scenario analyses. Subgroup analyses were performed to calculate the net health benefits (and associated 95% CIs) in the prespecified populations. Analyses for patients aged 75 or older, patients with a CHADS2 score of 3 or more, patients with the baseline characteristics of those in each of the three studies, and patients who had previously had a stroke or transient ischemic attack were performed by altering the baseline patient characteristics in the model. Separate, indirect comparisons were made for patients with impaired renal function (30–50 ml/min creatinine clearance) and patients who were naive to vitamin K antagonist treatment.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

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AUTHOR CONTRIBUTIONS

D.A.H., J.P., and M.P. wrote the manuscript. D.A.H. and J.P. designed the research. J.P. performed the research. D.A.H., J.P., and M.P. analyzed the data.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Dabigatran, rivaroxaban, and apixaban are effective alternatives to warfarin in the prevention of thromboembolic stroke in AF patients. However, there is no evidence on their direct comparative effectiveness.

WHAT QUESTION DID THIS STUDY ADDRESS?

The study addresses the question of which oral anticoagulant is most effective in terms of modeled QALYs. An indirect treatment comparison was made in patients who are representative of the US AF population.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

Among the alternatives, apixaban was ranked highest both in terms of absolute number of QALYs accrued over a lifetime and the probability of achieving the greatest QALY gains.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

This evidence can help inform treatment selection, particularly because there is no prospect of a definitive trial to compare the treatments directly.

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