SUPPLEMENTARY DATA

Table S1: Unit cost calculation

Cost Descriptions	Annual cost per patient £
Cost of anticoagulation clinic [a]	241.54
Ischaemic stroke (mean) [b]	11,626
Intracranial bleed (mean) [b]	11,453
Gastrointestinal bleed (mean) [c]	2,629

[a] NICE Clinical Guidelines 36. Arterial Fibrillation 2014 update anticoagulant management clinic costs used to estimate consultation costs [18 30]

[b] Based on a cost-effectiveness analysis of oral anticoagulants[11], and come from a study of patients with atrial fibrillation on a UK stroke registry[19]

[c] Department of Health. NHS Reference Costs 2013-14. London, 2014

Table S2: The association between number of strokes and bleeds per 1,000 patients, per year quarter, and change in relative uptake of DOACs, (n=102,637)

	Calendar quartiles		Patient demographic factors		Disease prevalence		Practice factors	
	IRR (95% CI)	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
Strokes, per 1,000 patients								
per 5% increase	0.999 (0.998, 1.000)	0.007	1.000 (0.999, 1.000)	0.385	1.000 (0.999, 1.001)	0.741	1.000 (0.999, 1.001)	0.876
Bleeds, per 1,000 patients								
per 5% increase	0.999 (0.998, 1.002)	0.140	1.000 (0.999, 1.002)	0.708	1.001 (1.000, 1.003)	0.072	1.001 (1.000, 1.002)	0.202

DOAC: direct oral anticoagulant; IRR: incidence rate ratio; CI: confidence intervals

Multi-level Poisson regression models were used to investigate number of hospital admissions for strokes and bleed associated with a change in the relative uptake of DOACs, with GP practice included as a random-effect to account for clustering. IRR represent the ratio of hospital admissions for a percentage increase in relative uptake of DOACs.

Patient demographic covariates include the percentage of GP registered patients that are male, aged over 65 years, ratio of patients aged 85- to 65-84s year olds, and practice population. Disease prevalence covariates include the percentage of GP registered patients that have been diagnosed with coronary heart disease, chronic kidney disease and diabetes mellitus. Practice factors include measures of experience, preferred GP, trust and communication, collected in the GP-Patient survey, and the total QOF score. Models were restricted to observations with complete information on all variables included in the full model.

Anticoagulants include dabigatran, rivaroxaban, apixaban, and edoxaban (DOACs) and warfarin.

Number of bleeds includes gastrointestinal and cerebral bleeds.

Table S3: Average (mean, SD) cost (£) of one unit (quantity) anticoagulant, per calendar quartile

Calendar, quarter	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
2012q2	1.04 (0.04)	1.94 (0.00)	1.58 (0.00)		0.04 (0.06)
2012q3	1.01 (0.00)	1.94 (0.01)	1.59 (0.01)		0.04 (0.05)
2012q4	1.01 (0.00)	1.94 (0.00)	1.55 (0.13)		0.03 (0.05)
2013q1	1.02 (0.00)	1.94 (0.00)	1.10 (0.19)		0.03 (0.06)
2013q2	1.01 (0.00)	1.94 (0.01)	1.01 (0.01)		0.04 (0.06)
2013q3	1.02 (0.01)	1.94 (0.01)	1.02 (0.00)		0.04 (0.05)
2013q4	1.02 (0.01)	1.94 (0.00)	1.01 (0.00)		0.04 (0.05)
2014q1	1.02 (0.02)	1.94 (0.01)	1.02 (0.00)		0.04 (0.05)
2014q2	1.02 (0.01)	1.94 (0.01)	1.02 (0.01)		0.04 (0.06)
2014q3	1.02 (0.00)	1.94 (0.01)	1.02 (0.01)		0.04 (0.06)
2014q4	1.02 (0.02)	1.94 (0.03)	1.02 (0.00)		0.04 (0.06)
2015q1	1.02 (0.01)	1.94 (0.02)	1.02 (0.01)		0.04 (0.06)
2015q2	1.02 (0.02)	1.94 (0.04)	1.02 (0.01)		0.04 (0.06)
2015q3	1.02 (0.01)	1.94 (0.03)	1.02 (0.01)	1.94 (0.01)	0.04 (0.06)
2015q4	1.02 (0.01)	1.94 (0.03)	1.02 (0.01)	1.94 (0.00)	0.04 (0.06)
2016q1	0.86 (0.05)	1.66 (0.03)	1.02 (0.01)	1.94 (0.00)	0.04 (0.07)
2016q2	0.79 (0.02)	1.67 (0.02)	0.88 (0.01)	1.76 (0.06)	0.04 (0.06)
2016q3	0.79 (0.02)	1.67 (0.02)	0.88 (0.00)	1.72 (0.00)	0.04 (0.07)
2016q4	0.79 (0.01)	1.67 (0.02)	0.88 (0.00)	1.71 (0.00)	0.04 (0.07)
2017q1	0.79 (0.02)	1.67 (0.03)	0.88 (0.00)	1.72 (0.00)	0.04 (0.07)

DOAC: direct oral anticoagulant; SD: standard deviation; q: quarter

Table S4: The association between total cost per 1,000 patients, per year quarter, and change in relative uptake of DOACs, (n=102,637)

	Calendar quartiles		Patient demographic factors		Disease prevalence		Practice factors	
	Coef (95% CI)	**p-value**	**Coef (95% CI)**	**p-value**	**Coef (95% CI)**	**p-value**	**Coef (95% CI)**	**p-value**
per 5% increase	-0.002 (-0.003, -0.001)	0.001	0.002 (0.001, 0.002)	<0.001	0.002 (0.002, 0.003)	<0.001	0.002 (0.001, 0.003)	<0.001

DOAC: direct oral anticoagulant; Coef: coefficient; CI: confidence intervals

Generalised linear models (GLM) were used to estimate the total costs associated with a change in relative uptake of DOACs, whereby the logarithm of the conditional expectation of cost was estimated, and the relationship of the mean to variance in the outcome data was assessed and modelled. CCG was included as a random-effect to account for clustering. Robust standard errors were used to allow for potential misspecification of the link and family function.

Covariates were added sequentially. Patient demographic covariates include the percentage of GP registered patients that are male, aged over 65 years, ratio of patients aged 85- to 65-84s year olds, and practice population. Disease prevalence covariates include the percentage of GP registered patients that have been diagnosed with coronary heart disease, chronic kidney disease and diabetes mellitus. Practice factors include measures of experience, preferred GP, trust and communication, collected in the GP-Patient survey, and the total QOF score. All measures were standardised (using sample mean values and SDs), and non-linear associations for all continuous measures were investigated, and likelihood ratio tests determined whether they were included in the final model. Models were restricted to observations with complete information on all variables included in the full model.

Anticoagulants include dabigatran, rivaroxaban, apixaban, and edoxaban (DOACs) and warfarin.

Total cost includes cost of anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban, and warfarin), management costs of warfarin, and costs associated with a hospital admission for ischeamic stroke, and intracranial and gastrointestinal bleed

Box S1: GP Patient Survey questions

‘Overall, how would you describe your experience of your GP surgery?’ (five categories dichotomised as ‘very good’ and ‘fairly good’, vs. ‘neither’, ‘fairly poor’, and ‘poor’)

‘How often do you see or speak to the GP you prefer?’ (five categories dichotomised as ‘always’, ‘almost always’ and ‘a lot’ vs. ‘some’, ‘never’, and ‘not tried’)

‘Did you have confidence and trust in the GP you saw or spoke to?’ (four categories dichotomised as ‘yes definitely’ and ‘to some extent’ vs. ‘no’, and ‘don’t know’).

Box S2: Detailed statistical analysis

Variation in, and practice-level factors associated with, relative uptake of DOACs. January to March 2017

To investigate practice-level factors associated with levels of DOAC dispensing in January to March 2017, a mixed-effect logistic regression model with a binomial distribution was fitted to calculate odds ratios (OR) and 95% confidence intervals (CIs). Observed number of patients dispensed a DOAC (numerator) and number of patients dispensed an anticoagulant (DOAC or warfarin) (denominator) were used to allow within unit variation comparisons[21]. A random-intercept term for CCG was included to allow for differences in dispensing as a within-CCG. Thus, the OR represent the changes in odds of dispensing when covariates differ within the same CCG. The random-effect for CCG in a model was used to explore the unmeasured variation in dispensing of DOACs between CCGs.

Univariable analysis was used to investigate the association of DOAC use with each covariate, before including them all simultaneously in the full model. All measures were standardised using respective sample mean values and standard deviations (SD).

DOAC uptake, adverse events, and economic outcomes. 2012 to 2017

Multi-level Poisson regression models[22] were used to investigate the number of hospital admissions for ischaemic stroke and bleeds associated with a five-percent change in anticoagulants dispensed being a DOAC, with GP included as a random-effect to account for clustering. Thus, the rate ratios represent the changes in admission rates when the other variables change within the same GP.

Generalised linear models (GLM) with a Gaussian family and log link[23 24] were used to estimate the total costs associated with a five-percent change in anticoagulants dispensed being a DOAC. CCG was included as a random-effect, and robust standard errors were used to allow for potential mis-specification of the link and family function[25 26].

Marginal effects were calculated and represent a change in the outcome for an increase in the exposure, keeping all other covariates at their observed levels, and averaged over all patients. Thus, the marginal effect can be interpreted as the hypothetical change in the outcome if all practices only differed in the percent of anticoagulants dispensed being a DOAC, and not any other covariate. Models were adjusted for demographic, clinical and practice factors, and non-linear associations for all continuous measures were investigated. Likelihood ratio tests determined whether they were included in the final model. Models were restricted to observations with complete information on all variables included in the full

model. NHS Digital did not have information available before 1st April 2013 so the final models are restricted to after this date.