Ischaemic stroke, haemorrhage and mortality in elderly patients with chronic kidney disease receiving anticoagulation for atrial fibrillation: a population-based study from UK primary care

Journal:	*BMJ*
Manuscript ID	BMJ.2017.041508
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	17-Sep-2017
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Keywords:	atrial fibrillation, chronic kidney disease, anticoagulation, warfarin

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Word count: 3305
Figures: 2
Tables: 2
Keywords: atrial fibrillation, chronic kidney disease, anticoagulation, warfarin

What is already known on this topic?

- The optimal management of older patients with concomitant non-dialysis chronic kidney disease (ND-CKD) and atrial fibrillation (AF) is hindered by a near-total lack of high-quality clinical guidelines or randomised controlled trial evidence to support clinical decision-making.
- In this patient group, the risk of stroke and haemorrhage increases progressively with declining renal function, which makes the decision over whether to initiate anticoagulation difficult.
- The few observational studies that exist in the literature have provided conflicting results.

What this study adds?

- In our propensity-matched population-based study, we found that anticoagulation was associated with an increased risk of ischaemic stroke and haemorrhage but lower all-cause mortality.
- These paradoxical findings emphasise the urgent need for adequately powered RCTs to provide clarity on correct clinical management.
- Meanwhile, the decision to initiate anticoagulant therapy in CKD patients with new-onset AF should be made on a personalised patient-level basis.

Abstract

Objective: To assess the association between anticoagulation, ischaemic stroke, gastrointestinal and cerebral haemorrhage, and all-cause mortality, in older people with atrial fibrillation (AF) and chronic kidney disease (CKD).

Design: Propensity-matched population-based retrospective cohort analysis from January 2006 through December 2016.

Setting: The Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database population of almost 2.73 million patients from 110 General Practices across England and Wales.

Participants: Patients aged 65 years and over with a new diagnosis of AF and estimated glomerular filtration rate (eGFR) of <50 ml/min/1.73m^2, calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) creatinine equation. Patients with a previous diagnosis of AF or receiving anticoagulation in the preceding 120 days were excluded, along with dialysis-requiring patients and renal transplant recipients.

Intervention: Receipt of an anticoagulant prescription within 60 days of AF diagnosis.

Main Outcome measures: Ischaemic stroke, cerebral or gastrointestinal haemorrhage, and all-cause mortality.

Results: We identified 6,977 patients with CKD and newly diagnosed AF, of whom 2,434 were anticoagulated within 60 days of diagnosis. We matched 2,434 pairs using propensity scores by exposure to anticoagulant and followed for a median of 506 days. The crude rates for ischaemic stroke and haemorrhage were 4.6 and 1.2 following anticoagulation, and 1.5 and 0.4 in non-anticoagulated patients per 100-person years, respectively. The hazard ratios for ischaemic stroke, haemorrhage and all-cause mortality for those anticoagulated were 2.60 (95% confidence interval, 2.00-3.38), 2.42 (1.44-4.05) and 0.82 (0.74-0.91) when compared to those who received no anticoagulation.

Conclusion: Anticoagulating older people with concomitant AF and CKD was associated with an increased risk of ischaemic stroke and haemorrhage but a paradoxical lowered risk of all-cause mortality. Careful consideration should be given before initiating anticoagulation in older people with CKD developing AF. There remains an urgent need for adequately powered randomised trials in this population further to explore these findings and to provide clarity on correct clinical management.

Introduction

Atrial fibrillation (AF) is the most frequently occurring sustained cardiac arrhythmia worldwide.[1 2] The global prevalence of AF in those over 55 years of age is at least 33.5 million and is predicted to more than double over the next 50 years. It is associated with increased morbidity from thromboembolic stroke and cardiac failure, and all-cause mortality.[3-7] The economic burden of AF accounts for 1% of the National Health Service (NHS) budget in the United Kingdom and up to £26 billion in the USA, annually.[8-10]

Chronic kidney disease (CKD) affects around 10-15% of adults globally with concomitant AF occurring in around one third of cases, due to marked co-localisation of shared risk factors of the two conditions, including hypertension, dyslipidaemia, coronary artery disease and diabetes mellitus.[11-13] In this patient population, the risk of stroke and haemorrhage increases progressively as the estimated glomerular filtration (eGFR) declines, which complicates the decision over whether to initiate anticoagulation. To date, research has focused more on end-stage renal disease (ESRD) although such patients account for less than 1% of the AF population.[14] No randomised controlled trial has been performed in the non-dialysis CKD (ND-CKD) population. The few observational studies that have reported on anticoagulation in ND-CKD have yielded conflicting results, are hampered by modest sample size[14-19], highly selected populations[20] and sub-optimal methods for identifying CKD,[18 21 22] thereby limiting the ability to reach definitive conclusions.

CKD is most prevalent in the elderly. In the US population, almost 40% of those aged over 60 years have CKD compared to 11% in the general population.[23] In those aged 65 years and over, AF affects over 20% with ND-CKD and 27% with ESRD, compared to only 6% in the general population.[24 25] Taken together, older patients with CKD and AF represent an increasing healthcare burden, yet are poorly studied.

In the absence of CKD, anticoagulation confers protection against ischaemic stroke when compared to no antithrombotic or antiplatelet agents alone[26] but the net clinical benefits in CKD are less certain given the greater risk of haemorrhage and other impacts on overall survival.[27] Over a quarter of elderly patients who are anti-coagulated then discontinue warfarin within the first year of prescription due to perceived safety concerns.[28] Older subjects are less likely to be offered anticoagulation in the first place than are their younger counterparts, based on co-morbidities and other individual-level characteristics, such as risk of falls, rather than following the use of established clinical scoring systems.[29]

Only two studies, both originating from Canada, have reported on the outcomes of anticoagulating older people with AF and intercurrent non-end-stage CKD, with conflicting findings.[30 31] The first, a population-based study from Ontario, showed that anticoagulation did not prevent ischaemic stroke, but was associated with an increased rate of haemorrhage while also being associated with improved survival. In contrast, data from the Alberta Kidney Disease Network demonstrated that warfarin therapy was associated with a significantly lower risk for the 1-year composite outcome of all-cause death, ischaemic stroke and transient ischaemic attack (TIA), with excess bleeding only observed in those with an estimated glomerular filtration rate (eGFR) of 60-89 ml/min/1.73m^2. Given the paucity of trial-based data, the conflicting outcome data from the small number of studies, and the lack of specific clinical practice guidelines in this important and frequently occurring clinical setting, the objective of the present study was to further explore the association between ischaemic stroke, haemorrhage and mortality in a large population of older patients with CKD anticoagulated for AF.

Methods

Data source, study design and ethics

We conducted this population-based retrospective cohort study using the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database, one of the longest established primary care sentinel networks, comprising nearly 2.73 million patients across 110 General Practices in the UK.[32] The network reports on 1.7% of all general practices in England, with on-going patient recruitment and is representative of the general UK population.[32 33]

The study was tested against the Health Research Authority (HRA)/Medical Research Council (MRC) “is this research” tool and deemed to be an audit of current practice and therefore specific ethical approval was not required. The protocol was approved by the RCGP. We adhered to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement for reporting observational studies.[34]

Study population

The study spanned an 11-year period from January 1, 2006 to December 31, 2016. Patients aged 65 years and older with a new diagnosis of AF and eGFR of <50 ml/min/1.73m^2, calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) creatinine equation with more than 1 eGFR value, were included.[35] The inclusion criterion was set at this level of renal impairment to align our study with previous major Phase III anticoagulation

trials.[36-39] We excluded patients with a previous diagnosis of AF, those in receipt of an anticoagulation prescription in the 120 days preceding diagnosis, chronic dialysis and renal transplant recipients. AF was defined by Read Codes[40] from the primary care database utilising diagnostic and process of care codes to maximise case identification.[41]

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design or implementation of the study. No patients were asked to advise on interpretation or reporting the results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Exposure and outcome measures

Exposure was defined as receipt of an anticoagulant prescription within 60 days of AF diagnosis, a definition used in a similar contemporary study.[31] Anticoagulants included vitamin K antagonists (VKA), direct oral anticoagulants (DOAC) and heparin-based compounds. Outcomes were ischaemic stroke including transient ischaemic attack, gastrointestinal (GI) or cerebral haemorrhage and all-cause mortality, using previously published Read codes.[42 43] Unclassified strokes were combined with ischaemic strokes, an approach used in other studies,[44] because about 87% of all strokes have ischaemic aetiology.[45] Individuals entered the study on the date of their AF diagnosis and were followed for ischaemic stroke cerebral or gastrointestinal bleeding events, and death, up to December 31, 2016. Exposed patients were censored if there was an interval of greater than 60 days between anticoagulant prescriptions, a timeframe that reflects the typical duration of an anticoagulant prescription issued in UK primary care practice.

Statistical analysis

Data analysis was performed using R (http://www.r-project.org), version 2.15.0 and statistical significance defined as a probability (*P)* less than 0.05 with 2-sided testing. To adjust for potential confounding from imbalances in clinical characteristics between patients receiving and not receiving anticoagulation, propensity score matching was used with the following demographic and relevant clinical variables included in our model. Demographic variables included: age, sex, year of AF diagnosis, index of multiple deprivation (IMD) decile. Clinical variables included smoking status, eGFR, co-morbidities at baseline (myocardial infarction, coronary artery disease, cardiac failure, type 2 diabetes mellitus, hypertension, previous cerebral or gastrointestinal bleed, peripheral artery disease), and drugs at baseline

(antiplatelet agents, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), lipid lowering drugs, beta blockers, aspirin, potassium-sparing diuretics, supraventricular and ventricular antiarrhythmic agents, thiazide diuretics, calcium channel blockers, alpha blockers, loop diuretics, insulin, metformin, cardiac glycosides).

Patients who received anticoagulation were matched in a 1:1 ratio with those who were not anticoagulated and differences in clinical characteristics assessed using standardised differences, with values <0.1 considered well-balanced. We calculated the incidence of ischaemic stroke, haemorrhage and all-cause mortality per 100 person-years of follow up. Kaplan-Meier survival curves were generated for the outcomes of interest grouped by anticoagulation status. Cox proportion regression were reported as adjusted hazard ratios (HRs) with accompanying 95% confidence intervals (CIs). Because all baseline characteristics were balanced in the propensity matched model, our Cox regression models only included receipt of anticoagulation as an independent variable.

Sensitivity analyses

We undertook a series of sensitivity analyses to confirm our findings. An intention-to-treat analysis was performed, where we did not censor patients after initiation of anticoagulation, irrespective of the time interval between anticoagulant prescriptions. We repeated the analysis censoring patients at a 160-day interval between anticoagulation prescriptions (rather than 60 days used in the primary analysis), to detect additional events after discontinuation of anticoagulation.

Results

Baseline characteristics of all patients

A total of 6,977 patients met the inclusion criteria (Figure 1). Of these, 2,424 received an anticoagulant within 60 days of AF diagnosis. The anticoagulants used were VKA (1739, 71.7%), rivaroxaban (307, 12.7%), apixaban (261, 10.8%), dabigatran (69, 2.8%) unfractionated or low molecular weight heparin (44, 1.8%) and edoxaban (4, 0.17%). The mean number of days from AF diagnosis to first prescription of an anticoagulant was 17.8 (range 0-59, IQR 2-29).

Patients prescribed anticoagulants tended to be younger (mean 81.7 years vs. 83.2 years), female (54.7%) and not current smokers (8.6% vs. 12.1%) compared to those not anticoagulated (Table 1). The groups were well-matched in terms of socioeconomic profile

by the index of deprivation decile. Anticoagulated patients were less likely to have prior cerebral (0.7% vs 1.6%) or gastrointestinal haemorrhage (2.8% vs 5.1%). The mean $CHADS_2$-VASc score of 4.2 (SD ± 1.2) did not differ between the groups and the mean eGFR was also similar in anticoagulated and non-anticoagulated patients (38.6 vs. 37.4). Coronary artery disease was more frequent in the anticoagulated group (14.0% vs 10.2%), as was the prescription of ACE-I (46.8% vs 34.9%), ARBs (11.4% vs 7.4%), alpha-blockers (11.4% vs 7.4%), beta-blockers (62.8% vs 47.2%), thiazide diuretics (23.9% vs 13.1%), calcium channel blockers (39.4% vs 26.7%), lipid lowering agents (58.7% vs 46.6%), metformin (11.1% vs 7.2%) and aspirin (16.3% vs 11.6%).

Propensity matched model

In the propensity score matched cohort of 2,424 pairs, there were no major differences between the two groups (Table 1). The median follow-up time was 506 days (IQR, 175-1131 days) for the 8,484 patients included in the analysis. There were a total of 309 ischaemic strokes (6.4%), 79 GI or cerebral haemorrhage events (1.6%) and 1410 all-cause fatalities (29.1%). The crude rates for ischaemic stroke and haemorrhage were 4.6 and 1.2 following anticoagulation, and 1.5 and 0.4 in non-anticoagulated individuals per 100 person-years, respectively. Kaplan-Meier survival curves by receipt of anticoagulation for ischaemic stroke, haemorrhage and all-cause mortality are shown in Figure 2. In the Cox proportion regression models, the hazard ratios for ischaemic stroke, haemorrhage and all-cause mortality for anticoagulated patients were 2.60 (95% confidence interval, 2.00-3.38), 2.42 (1.44-4.05) and 0.82 (0.74-0.91) compared to those who received no anticoagulation.

These findings were consistent in the sensitivity analyses. In the intention-to-treat analysis, anticoagulation was associated with a higher hazard ratio for stroke (HR: 2.62 (2.04 – 3.46)) and haemorrhage (HR: 2.46 (1.47 – 4.09)) but lower all-cause mortality (HR: 0.84 (0.75 – 0.93)). Increased stroke persisted when using a 160-day interval between prescriptions as a censoring event (HR: 2.59 (1.99-3.37) as did haemorrhage (HR: 2.41 (1.44-34.04). Reduced all-cause mortality was seen when using the 160-day (HR: 0.83 (0.76-0.92) interval between prescriptions as a censoring event. The proportional hazards assumption was checked using the methodology of Grambsch and Therneau and the models were found to be not faulted.[46]

Discussion

In this propensity-matched population-based study of older people with CKD and new-onset AF, we found that anticoagulation was associated with an increased risk of ischaemic stroke and haemorrhage but lower all-cause mortality. The crude rates of ischaemic stroke and

haemorrhage were 4.6 and 1.2 following anticoagulation, and 1.5 and 0.4 in non-anticoagulated patients per 100 person-years, respectively. The hazard ratios for developing ischaemic stroke, haemorrhage and all-cause mortality in the anticoagulated group were 2.60 (95% CI, 2.00-3.38), 2.42 (1.44-4.05) and 0.82 (0.74-0.91) compared to non-anticoagulated counterparts. These findings proved consistent after performing several sensitivity analyses.

For the general population, there is overwhelming evidence from large-scale randomised controlled trials supporting the use of oral anticoagulation in the context of AF for stroke thrombo-prophylaxis, and this has been universally adopted in clinical practice guidelines.[47 48] However, this may not apply in the management of AF patients with CKD. Anticoagulation for AF in patients requiring chronic dialysis treatments has been previously studied and continues to be a contentious issue, lacking convincing RCT outcomes. Large studies have described a 2-fold increase in risk of stroke following anticoagulation [49 50] and a heightened risk of intracranial haemorrhage and major systemic bleeding.[51 52] However, subsequent meta-analyses have found no association between anticoagulation and ischaemic stroke whilst there remains a continued risk of major bleeding events.[53 54]

The role of anticoagulation in non-dialysis CKD patients is even less certain. There is a dearth of data in respect of the efficacy and safety in individuals with ND-CKD and AF treated with anticoagulant therapies (Table 2). In a study from Danish national registries considering patients with ND-CKD, warfarin was not associated with a statistically significant decrease in risk of stroke and systemic thromboembolism, but both warfarin and aspirin increased bleeding risk.[21] However, a limitation of the study was the absence of data pertaining to the degree of renal impairment, with broad categorisation of patients into those with no renal impairment, ND-CKD, or requiring renal replacement therapy. Carrero *et al* followed survivors of acute myocardial infarction with AF who were prescribed warfarin prior to hospital discharge.[20] In this cohort, patients with all stages of CKD including dialysis-requiring, who were anticoagulated had reduced ischaemic stroke, lower all-cause mortality and no significant increased risk of major bleeding but this highly selected population limits the generalisability of their observations. Our study corroborated the results of a large prospective study of AF patients that reported anticoagulated CKD patients had reduced all-cause mortality and increased bleeding, but contrary to our findings there was a reduction in the incidence of ischaemic strokes.[19] A 15-year register-based cohort study from Denmark reported that warfarin was associated with a higher rate of bleeding with the exception of those with CKD stage I, but afforded protection against stroke in non-end-stage CKD.[22] Results from a Canadian healthcare database indicated that anticoagulating elderly ND-CKD

patients with an eGFR of 45 ml/min/1.73m^2 or less did not confer protection against ischaemic strokes, induced major haemorrhage but was associated with significantly less mortality. Interestingly, a time-varying analysis of their cohort raised the possibility that anticoagulation may in fact increase the risk of ischaemic stroke. Most recently, in a cohort of elderly patients, Jun *et al* found that warfarin use was associated with a significantly lower risk for the 1-year composite outcome of all-cause death, ischaemic stroke and TIA across all eGFR strata. Unexpectedly, warfarin use was associated with 5-29% less bleeding, and excess haemorrhage noted only in patients with an eGFR of 60-89 ml/min/1.73m^2. This may reflect residual confounding in the study or incomplete outcome data.

We describe for the first time an association between a paradoxical increase in ischaemic stroke and the receipt of an anticoagulant prescription in ND-CKD patients with new-onset AF, previously only reported in end-stage kidney disease complicated by AF. This unexpected finding is at odds with a systematic review of observational studies of CKD patients with concomitant AF, which concluded that there was an overall reduction in ischaemic stroke and thromboembolic events after anti-coagulation.[54] There are several possible explanations for our findings. We focused on older people who are at the highest risk of suffering complications related to anticoagulation, resulting in the frequent discontinuation of both warfarin and DOACs, due to the safety concerns of prescribers.[28 55] However, our sensitivity analyses enabled us to detect events occurring up to 160 days after discontinuation of anticoagulant therapy. Some transient ischaemic attacks (TIAs) and ischaemic stroke events may have been subclinical and therefore not coded in the data, but we feel that this is unlikely given that our event rates for all outcomes were comparable to similar studies in the literature.[30] VKA, used in over 70% of the anticoagulated patients in our study, accelerate vascular calcification (VC) through carboxylation of matrix GLA protein, MGP, a potent tissue-bound inhibitor of calcification in the arterial wall.[56] This is especially relevant in elderly patients, who have the highest burden of VC. Furthermore, VC is markedly accelerated in CKD and contributes to a higher rate of cardiovascular events and mortality.[12 57] It is plausible (but not known) that increased VC in elderly anticoagulated patients may have led to a greater incidence of ischaemic strokes or lacunar infarcts in watershed vascular territories. Also of concern is the finding that CKD patients are at greater risk of developing warfarin-related nephropathy,[58] potentially further compromising kidney function thereby compounding the risk of ischaemic and haemorrhagic stroke.[59]

In the absence of cause-specific death data, we can only speculate on the possible explanation for reduced all-cause mortality in the anticoagulated patients. This may be attributable to a lower rate of fatal strokes and protection afforded against subsequent

myocardial events, a finding demonstrated with both warfarin[60] and rivaroxaban.[61] Notwithstanding the well-matched nature of our groups, we cannot exclude the possibility of residual confounding by receipt of anticoagulation. Our finding of increased haemorrhage in anticoagulated patients corroborates a number of existing studies.[19 21 24 30] Haemostatic dysfunction occurs early in CKD, with uraemic toxins augmenting bleeding risk by altering platelet function both in terms of recruitment and activity, and this is accentuated by anticoagulation.[12 25 62 63]

To the best of our knowledge, this is the largest study to consider the efficacy and safety of anticoagulating elderly patients with AF and CKD in terms of ischaemic stroke, risk of bleeding and all-cause mortality. We used an established sentinel network of 110 UK primary care practices spanning 2.73 million patients, known to be representative of the general UK population. [32 33] The CKD-EPI creatinine equation was chosen as a surrogate marker of kidney function, now widely acknowledged as the most accurate currently available in routine clinical practice.[64] A further strength was the relatively long follow-up period, almost twice as long as a comparable study in this clinical scenario.[30]

Our work is not without limitations. The study population was derived from real-world evidence with the inherent limitations of diagnostic coding and case ascertainment.[65] Misclassification bias may have occurred as we were unable to review electrocardiograms and neuroimaging. We cannot exclude the possibility that some clinical coding was incomplete resulting in events being undetected. Reassuringly, our stroke and mortality rates are similar to a comparable study in this setting.[30] Haemorrhage rates were lower in our work but we used restrictive code-based definitions for gastrointestinal and cerebral bleeding, rather than non-specific indicators such as the need for a blood transfusion, used in other studies.[30] Despite well-matched groups after propensity-score matching, residual confounding cannot be excluded and it is possible that those anticoagulated had an inherent increased baseline risk of stroke. Furthermore, an assumption was that patients were adequately anticoagulated within the therapeutic range of internationalised normal ratio (INR) when receiving warfarin, though this may be harder to achieve consistently in severe CKD.[66]. Our work is based on dispensed anticoagulation prescriptions but there were no data on patient adherence. Lastly, despite our large cohort, the proportion of patients receiving DOACs was small and so a comparison with VKAs could not be undertaken.

Conclusions

Anticoagulation with vitamin K antagonists and, more recently, DOACs has been clearly shown to be beneficial in mitigating the risk of thromboembolism in patients with AF in the

general population. Application of this approach to older people with CKD who develop AF may not be appropriate because there is an intrinsic higher bleeding risk, and an increase, rather than reduction, in ischaemic stroke. Lower all-cause mortality described in our study in those receiving anticoagulation may reflect an undefined protective effect of anticoagulation. The paradoxical findings in our study, together with conflicting outcome data from the very few studies specifically focussing on ND-CKD, highlight the really urgent need for adequately powered RCTs to address this question. Meanwhile, the decision to initiate anticoagulant therapy in ND-CKD patients with new-onset AF should be made on a personalised patient-level basis, weighing up the known risks and potential benefits, and where possible taking into account patients' wishes.

Acknowledgements

Patients and practices who are members of the RCGP RSC and allow their data to be shared. EMIS, In Practice Systems and TPP SystmOne who help facilitate data extraction. Apollo medical systems for expertise in secure data processing. The core surveillance function of RCGP RSC is funded by Public Health England. Jeremy van Vlymen for his assistance in using the software package R.

Funding

None

Transparency agreement

Transparency: The senior author (AJC) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Contributors

All authors contributed to the design, analysis, interpretation of data, drafting the article, or revising it critically for important intellectual content and approved the final version to be published. Professor Camm is the senior and corresponding author and guarantor.

Competing interests

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: AJC has received institutional grants and personal fees related to advice to Boehringer Ingelheim, Bayer, Daiichi Sankyo and Pfizer/BMS, outside the submitted work; SdL reports grants from Darzi Fellow attached to the Department , grants from NIHR Research for Patient Benefit, grants from Eli Lilly Real World Evidence Centre, grants from Astra-Zeneca, outside the submitted work; SK, AM, AC, MH, PG, SJ and DG have nothing to declare.

	Before matching			After matching		
	Anticoagulated n = 2424	Non-anticoagulated n = 4553	Standardised difference	Anticoagulated n = 2424	Non-anticoagulated n = 2424	Standardised difference
Age (mean +- SD)	81.7 (7.2)	83.2 (7.1)	0.24	81.7 (7.2)	81.9 (7.4)	
Males (%)	1098 (45.3)	2747 (60.3)	0.11	1098 (45.3)	1072 (44.2)	0.01
Females	1326 (54.7)	186 (39.7)	0.11	1326 (54.7)	1352 (55.8)	0.01
IMD decile						
1	134 (5.5)	264 (5.8)	0.02	134 (5.5)	142 (5.9)	
2	162 (6.7)	330 (7.2)	0.02	162 (6.7)	176 (7.3)	0.02
3	186 (7.7)	324 (7.1)	0.02	186 (7.7)	177 (7.3)	0.01
4	180 (7.4)	421 (9.2)	0.07	180 (7.4)	201 (8.3)	0.03
5	234 (9.7)	459 (10.1)	0.01	234 (9.7)	243 (10.0)	0.00
6	214 (8.8)	477 (10.5)	0.06	214 (8.8)	221 (9.1)	0.00
7	282 (11.6)	556 (12.2)	0.02	282 (11.6)	288 (11.9)	0.00
8	330 (13.6)	604 (13.3)	0.01	330 (13.6)	327 (13.5)	0.00
9	355 (14.6)	602 (13.2)	0.04	355 (14.6)	337 (13.9)	0.00
10	343 (14.2)	502 (11)	0.09	343 (14.2)	308 (12.7)	0.04
Missing	4 (0.2)	14 (0.3)	0.04	4 (0.2)	4 (0.2)	0.00
Smoking						
Active	209 (8.6)	551 (12.1)	0.15	209 (8.6)	226 (9.3)	0.04
Ex	1557 (64.2)	2700 (59.3)	0.10	1557 (64.2)	1555 (64.2)	0.02
Non-smoker	630 (26.0)	1179 (25.9)	0.00	630 (26.0)	619 (25.5)	0.01
Missing	28 (1.2)	123 (2.7)	0.14	28 (1.2)	24 (1.0)	0.01
Type 2 Diabetes	629 (25.9)	1075 (23.6)	0.05	629 (25.9)	598 (24.7)	0.02
Coronary artery disease	340 (14.0)	465 (10.2)	0.11	340 (14.0)	325 (13.4)	0.01
History of myocardial infarction	410 (16.9)	823 (18.1)	0.03	410 (16.9)	432 (17.8)	0.03
Hypertension	1950 (80.4)	3522 (77.4)	0.08	1950 (80.4)	1938 (80.0)	0.00
Peripheral artery disease	224 (9.2)	463 (10.2)	0.03	224 (9.2)	243 (10.0)	0.03
Heart failure	533 (22.0)	1107 (24.3)	0.06	533 (22.0)	552 (22.8)	0.02
Previous ischaemic stroke/TIA	525 (21.7)	1034 (22.7)	0.03	525 (21.7)	532 (21.9)	0.02
Previous GI haemorrhage	67 (2.8)	232 (5.1)	0.14	67 (2.8)	61 (2.5)	0.00
Previous cerebral haemorrhage	18 (0.7)	73 (1.6)	0.11	18 (0.7)	15 (0.6)	0.00
eGFR +-SD	38.6 (9.2)	37.4 (9.0)	0.04	38.6 (9.2)	38.4 (9.4)	0.04
Medications						
ACE-I	1134 (46.8)	1588 (34.9)	0.24	1134 (46.8)	1060 (43.7)	0.05
ARB	276 (11.4)	338 (7.4)	0.12	276 (11.4)	246 (10.1)	0.04
α-Blocker	276 (11.4)	338 (7.4)	0.12	276 (11.4)	246 (10.1)	0.04
B-Blocker	1522 (62.8)	2150 (47.2)	0.32	1522 (62.8)	1453 (59.9)	0.06
Thiazide diuretic	580 (23.9)	595 (13.1)	0.25	580 (23.9)	476 (19.6)	0.09
Loop diuretic	1035 (42.7)	1809 (39.7)	0.06	1035 (42.7)	1011 (41.7)	0.00
CCB	955 (39.4)	1217 (26.7)	0.26	955 (39.4)	867 (35.8)	0.08
Potassium sparing diuretics	210 (8.7)	284 (6.2)	0.09	210 (8.7)	197 (8.1)	0.02
Lipid Lowering agent	1423 (58.7)	2121 (46.6)	0.25	1423 (58.7)	1360 (56.1)	0.03
Anti-platelet therapy	1427 (58.9)	2885 (63.4)	0.09	1427 (58.9)	1488 (61.4)	0.06
Supraventricular antiarrhythmics	102 (4.2)	249 (5.5)	0.06	102 (4.2)	96 (4.0)	0.02
Cardiac glycosides	376 (15.5)	845 (18.6)	0.08	376 (15.5)	380 (15.7)	0.02
Ventricular antiarrhythmics	98 (4.0)	226 (5.0)	0.05	98 (4.0)	92 (3.8)	0.02
Metformin	269 (11.1)	327 (7.2)	0.12	269 (11.1)	226 (9.3)	0.05
Insulin	156 (6.4)	215 (4.7)	0.07	156 (6.4)	146 (6.0)	0.01
Aspirin	396 (16.3)	527 (11.6)	0.13	396 (16.3)	336 (13.9)	0.05

Table 1. Demographic and clinical characteristics of the study cohort before and after propensity score matching.

IMD – index of multiple deprivation, TIA – transient ischaemic attack, GI – gastrointestinal, ACE-I – angiotensin converting enzyme inhibitor, ARB – angiotensin II receptor blocker, CCB – calcium channel blocker

Report	Study design	Population selection	Sample size	Outcome of anticoagulation vs. no anticoagulation	Median follow up duration in years	Event rate per 100 person-years (95% CI) in study population	Hazard ratio or relative risk for anticoagulation (95% CI)	Summary of findings
Olesen JB et al, 2012	Retrospective	All patients with AF at hospital discharge. NDD-CKD defined by ICD codes.	n = 3587, 609 anticoagulated	Stroke – no effect Bleeding – increased		6.44 (6.02–6.89) 8.77 (8.26–9.30)	0.84 (0.69–1.01) 1.36 (1.17–1.59)	Anticoagulating NDD-CKD patients increased bleeding without reducing strokes.
Keskar V et al, 2017	Retrospective	Patients aged ≥66 years with an eGFR of < 45 developing AF. ESRD patients excluded.	n = 6554, 1417 anticoagulated, 1417 propensity-matched non-anticoagulated	Stroke – no effect Bleeding – increased All-cause mortality – reduced	[a]0.73 [a]0.73	[a]4.13 (3.33-5.07) [a]6.13 (5.15-7.24) [a]12.3 (10.9-13.8)	1.10 (0.78-1.56) 1.42 (1.04-1.93) 0.74 (0.62-0.88)	In elderly patients, anticoagulation was associated with increased bleeding, reduced mortality and no effect on stroke.
Jun M et al, 2017	Retrospective	Patients aged ≥66 years with available eGFR data. ESRD patients excluded.	n = 21530, 7446 anticoagulated, 7446 propensity-matched non-anticoagulated	Composite outcome at 1-year for all-cause death, ischaemic stroke and TIA: eGFR ≥ 90 – Reduced eGFR 60-89 – Reduced eGFR 45-59 – Reduced eGFR 30-44 – Reduced eGFR < 30 – Reduced	NA	NA	0.59 (0.35-1.01) 0.61 [0.54-0.70) 0.55 [0.47-0.65) 0.54 [0.44-0.67) 0.64 [0.47-0.87)	In elderly patients, anticoagulation reduced the composite outcome at 1-year for death, ischaemic stroke and TIA.
Current study	Retrospective	Patients aged ≥65 years with an eGFR of < 50 developing AF. ESRD patients excluded.	n = 6977, 2434, anticoagulated, 2434 propensity-matched non-anticoagulated	Stroke – increased Bleeding – increased All-cause mortality – reduced	1.39 overall	[a]4.6 [a]1.2 NA	2.60 (2.00-3.38) 2.42 (1.44-4.05) 0.82 (0.74-0.91)	In elderly patients, anticoagulation was associated with increased stroke and bleeding but reduced mortality.

Notes:
1. 95% confidence intervals (CI) in brackets where provided
2. [a] refers to anticoagulated group rather than the whole study population

Table 2. Summary findings of studies investigating the outcomes of anticoagulation vs. no anticoagulation in the non-dialysis CKD population with AF

Figure 1. The study population

RCGP-RSC – Royal College of General Practitioners Research and Surveillance Centre, RRT – renal replacement therapy

Figure 2 Kaplan-Meier survival curve by anticoagulation status

(a) ischaemic stroke

(b) haemorrhage

(c) all-cause mortality

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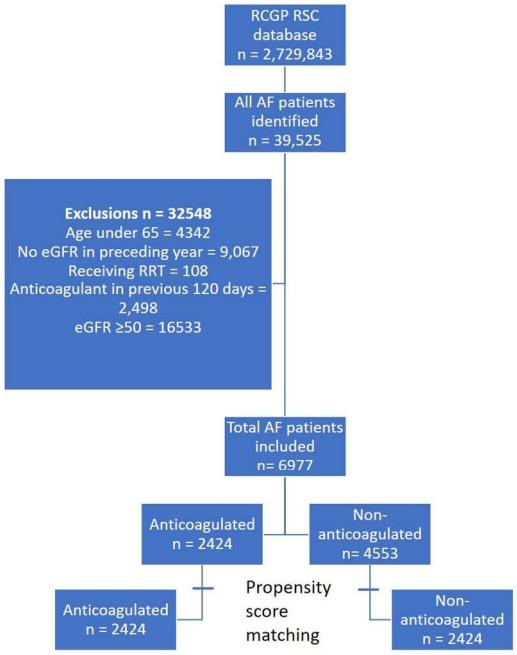

Figure 1. The study population
RCGP-RSC – Royal College of General Practitioners Research and Surveillance Centre, RRT – renal replacement therapy

446x295mm (96 x 96 DPI)

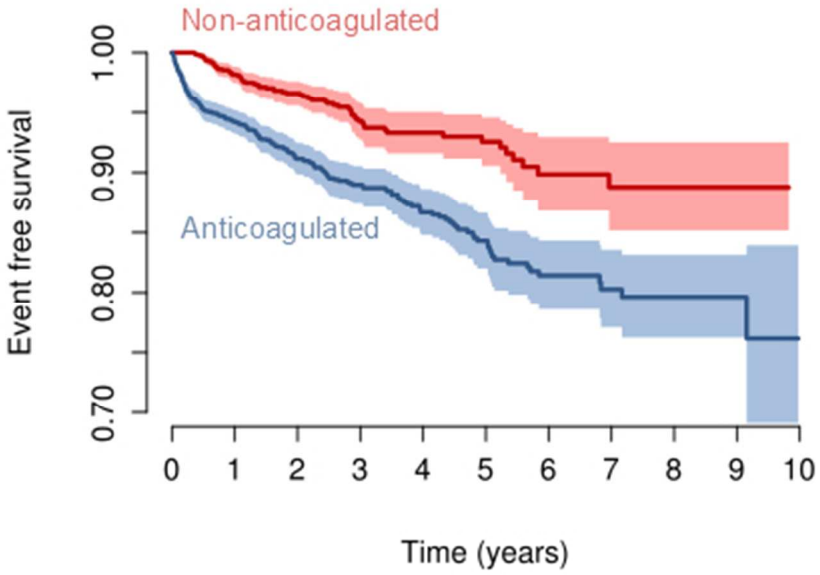

Figure 2 Kaplan-Meier survival curve by anticoagulation status
(a) ischaemic stroke

158x127mm (72 x 72 DPI)

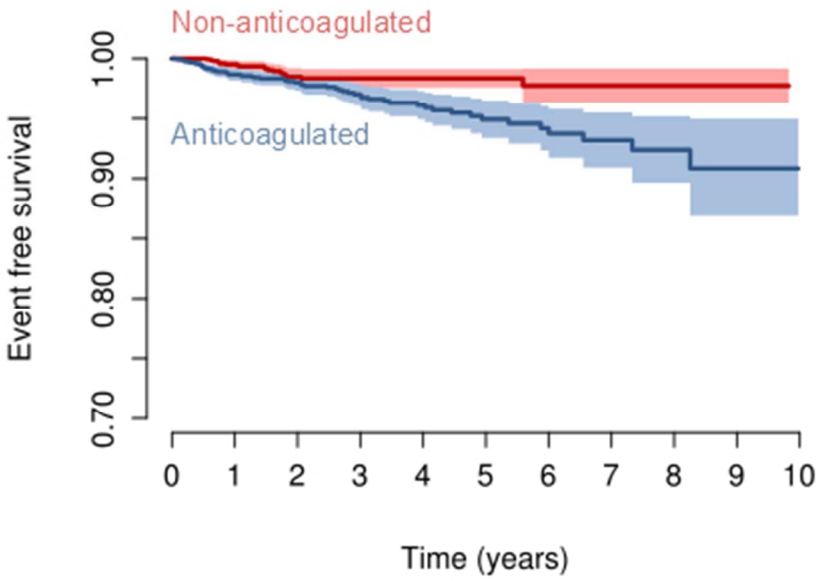

Figure 2 Kaplan-Meier survival curve by anticoagulation status
(b) haemorrhage

158x127mm (72 x 72 DPI)

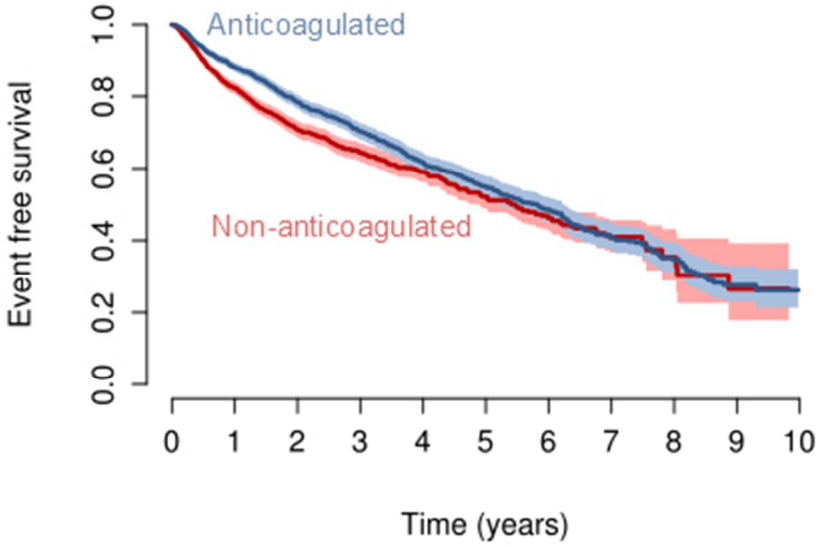

Figure 2 Kaplan-Meier survival curve by anticoagulation status
(c) all-cause mortality

158x127mm (72 x 72 DPI)