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Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study

Leif Friberg[1]*, Lina Benson[2], and Gregory Y.H. Lip[3]

[1]Karolinska Institutet and Cardiology Clinic, Danderyd Hospital, SE-182 88 Stockholm, Sweden; [2]Department of Clinical Science and Education, Karolinska Institutet, Södersjukhuset, Stockholm, Sweden; and [3]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK

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Background Patients who have both atrial fibrillation (AF) and renal failure have an increased risk of thrombo-embolism. Renal failure is also a risk factor for bleeding, which makes decisions regarding thromboprophylaxis complicated. Our aim was to determine risks for ischaemic stroke and bleeding in patients with AF and renal failure in relation to anticoagulant strategies.

Methods and results This is retrospective non-randomized study of Swedish health registers comprising 307 351 patients with AF, of whom 13 435 had a previous diagnosis of renal failure. Ischaemic stroke occurred more often in AF patients with renal failure (annual rate, 3.9% vs. no renal failure, 2.9%), but this was related to concomitant comorbidities [adjusted hazard ratio (HR) 1.02, 95% confidence interval (CI) 0.95–1.10].

Adding renal failure to the established stroke risk stratification schemes ($CHADS_2$ and CHA_2DS_2-VASc) did not improve their predictive value. Renal failure was an independent risk factor for intracranial bleeding [adjusted HR: 1.27 (1.09–1.49)]. Most patients with renal failure benefited from warfarin treatment, despite their high bleeding risk. The incidence of the combined endpoint ischaemic or haemorrhagic stroke or death was lower among those who used warfarin than among those who did not use warfarin (adjusted HR: 0.76, CI 0.72–0.80).

Conclusions Patients with both AF and renal failure will probably benefit most from having the same treatment as is recommended for other patients with AF, without setting a higher or lower threshold for treatment. Adding additional points for renal failure to the $CHADS_2$ and CHA_2DS_2-VASc scores did not improve their predictive value.

Keywords Atrial fibrillation • Renal dysfunction • Renal failure • Stroke • Bleeding • Anticoagulation • Net benefit

Introduction

Patients with renal failure are at an increased risk of both ischaemic stroke and of bleeding.[1,2] Atrial fibrillation (AF) is a major cause of ischaemic stroke,[3] which to a large extent can be prevented by treatment with warfarin,[4,5] or one of the novel oral anticoagulants,[6–8] at the cost of an increased risk of bleeding. Finding the optimal treatment for patients who have *both* AF and renal failure may therefore be complicated. These patients are common, because both diseases increase with age, and renal failure promotes the development of AF.[9,10]

Atrial fibrillation patients with renal failure have a higher risk of ischaemic stroke than patients without renal failure.[11,12] It has therefore been proposed that renal failure should be added to the widely used stroke risk stratification schemes for AF, that is, $CHADS_2$ and CHA_2DS_2-VASc,[13–16] effectively lowering the threshold for anticoagulant treatment for these patients. Others have argued that renal failure is a strong risk factor for bleeding complications in conjunction with anticoagulation, and thus, renal failure rather should invoke caution and a raised threshold for initiating anticoagulation especially if the patient is on haemodialysis.[17–21]

To the best of our knowledge, no randomized trials have addressed the risk–benefit ratio of anticoagulant treatment specifically for patients with both AF and renal failure. The aims of the present study were as follows: (i) to determine risks for ischaemic stroke and bleeding in patients with AF and renal failure, in relation to the presence or absence of oral anticoagulant treatment; and (ii) to determine whether the threshold for anticoagulant treatment for these patients ought to be different than for other patients with AF.

* Corresponding author. Tel: +46 701730519, Fax: +46 87534009, Email: leif.friberg@ki.se

Methods

For the study, we used the Swedish health registers, which are based on every individual's unique civic registration number, which makes it possible to follow each individual's contacts with the healthcare system over time. We used the Swedish Patient register to identify all individuals with a diagnosis of AF at any Swedish hospital or hospital affiliated open clinic between 1 July 2005 and 31 December 2010. The diagnostic code used was I48 (with or without subcodes) according to the International Classification of Diseases, 10th revision (ICD-10). Among these we identified patients with renal failure, defined by ICD-10 codes N17-19 or by local Swedish procedure codes for haemodialysis, peritoneal dialysis, or renal transplantation. Information about stage of renal failure and glomerular filtration rates is not available in the Patient register. Thus, identification of patients as having renal failure relied entirely on given clinical diagnoses. Exclusion criteria were death within 14 days of index hospital contact, and valvular AF, defined as mitral stenosis or prior valvular surgery. Patients with other valvular defects common among elderly AF patients were not excluded, but the information was used in the multivariable analyses (Supplementary material online, *Figure S1*).

The Patient register was also used to obtain information about comorbidities and for the detection of events during the follow-up. A list of the diagnostic codes used to define comorbidity and endpoint events is shown in Supplementary material online, *Table S1*. For our two main outcome measures, ischaemic stroke and intracranial haemorrhage, respectively, we only considered diagnoses given as principal or first secondary diagnoses in order to make sure that we only counted new events (and not cases who rightly should have been given the code I69 for sequels of cerebrovascular disease). For the more inclusive secondary endpoints 'thrombo-embolism' and 'any bleeding', we counted all events regardless of coding position.

We calculated individual risks for ischaemic stroke according to the $CHADS_2$[15] and CHA_2DS_2-VASc scores,[16] and individual bleeding risks according to a modified HAS-BLED score[22] as we could not give points for 'labile INR in the patients on warfarin, although it should be noted that Sweden has generally good quality of INR control, as reflected by high average time in therapeutic range (TTR). The constituents of these scores, translated into ICD-10 codes, are shown in Supplementary material online, *Table S2*. To account for alcohol abuse, we used a set of diagnostic codes called 'alcohol index' used by the Swedish Board of Health and Welfare for annual reporting of alcohol-related mortality.

The index date was defined by the first occurrence of a diagnosis of AF after 1 July 2005. We applied a 'blanking period' of 14 days after index for events during the follow-up, with the consequence that time at risk for survival analyses actually started counting on Day +14 after index. This was done because transfers between hospitals and clinics are common, and early re-appearances of a diagnosis are often related to a preceding hospital period, for example, a new code for an event that had been registered at another clinic a few days earlier.

Information about medication was obtained from the National Prescribed Drugs register that automatically stores details about every prescription that is handled in every pharmacy throughout the country and therefore is almost 100% complete. Medication at baseline was defined as drugs that had been collected at a pharmacy within 5 months before, and up to 1 month after the index date. The only registered oral anticoagulant in Sweden during the study period was warfarin, with phenprocoumon as an alternative on special license for a very small number of patients intolerant to warfarin.

Information about the quality of warfarin treatment for individual patients, expressed as International normalized ratio (INR) and time in therapeutic range (TTR),[23] was obtained from Auricula, which is one of the most commonly used warfarin dispensing tools in Sweden. This information was only available for a minority of the patients (8%) and was therefore not used in the multivariable analyses.

Statistical methods

Baseline characteristics were presented descriptively, and tested with Student's *t*-test and the χ^2 test. Incidences were calculated as events per 100 years at risk (expressed as percentages in the text) and presented with Poisson rate confidence intervals. Survival was graphically presented with the Kaplan–Meier method, and analysed using univariable and multivariable Cox regressions. In the multivariable models, we included comorbidities and medication with known association with stroke, bleeding, or mortality presented in *Table 1*. In the tables where warfarin vs. no warfarin was investigated, adjustment was made using the propensity score covariate derived from a logistic regression with warfarin as an outcome. Censoring was done at the specified event, death, or end of the follow-up (31 December 2010), whichever occurred first. Subgroup analyses were performed by modelling interaction effects between warfarin and renal failure as well as warfarin and the HAS-BLED score. Modelling interactions directly in the Cox model render similar interpretation as if separate Cox regressions had been performed on subgroups but with the additional advantage of testing for differences between subgroups.

The scaled Schoenfeld residuals from the models with ischaemic stroke, intracranial haemorrhage, and death as endpoints were investigated for violations to the proportional hazards assumption. The assumption was not fulfilled for the covariate 'previous thromboembolic event' for the endpoint ischaemic stroke and was therefore stratified for in models with endpoints including ischaemic stroke. Year of inclusion was included as a strata variable in all models. When investigating the 'dfbetas', no extreme outliers were detected. The linear relationship between age and stroke was investigated for the Martingale residuals and found to be acceptable and age was therefore included as a continuous covariate in all models.

Renal failure was included in the calculation of the $CHADS_2$ and CHA_2DS_2-VASc by adding 1 or 2 extra points for renal failure to the score. To compare the original scores with the scores including renal disease, the *c*-indices (and 95% CI) were calculated for the primary endpoint to assess concordance between model predictions and observed outcomes.[24] We also calculated the categorical net reclassification improvement (NRI) at 1 and 5 years using the Kaplan–Meier estimator. We set the risk cut-offs to 0.05 ('low risk'), 0.1 ('intermediate risk'), and 0.2 ('high risk'). The confidence intervals for NRI were estimated with the percentile bootstrap method using 1000 iterations.[25]

P-values <0.05 were considered as significant. Preparation of data for further analyses was done in SAS v.9.2 (SAS Institute, Cary, NC, USA). Analyses were performed in R version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS v 20.0.0 (IBM SPSS, IBM Corporation, Armonk, NY, USA).

The study was approved by the ethical committee of Karolinska Institute (EPN 2010/852-31/3 and EPN 2012/456-32).

Results

From the Swedish Patient register, we identified 307 351 unique individuals who received a diagnosis of AF between 1 July 2005 and 31

Table 1 Baseline characteristics of patients with and without renal failure

	Renal failure (n = 13 435)	No renal failure (n = 270 534)
Age (mean ± SD)[a]	78.4 ± 10.3	74.8 ± 12.5
Sex[a]		
Men	8633	147 201
Women	4802	123 333
Duration AF, years ± SD[a,b]	2.1 ± 3.1	1.9 ± 3.0
$CHADS_2$ score ± SD	2.8 ± 1.4	1.9 ± 1.4
CHA_2DS_2-VASc score ± SD	4.5 ± 1.7	3.3 ± 1.9
HAS-BLED score ± SD	3.7 ± 1.1	2.1 ± 1.2
Arterial thrombo-embolism (%)		
Ischaemic stroke	16.8	13.8
Unspecified stroke	3.3	2.4
TIA	7.1	6.1
Peripheral embolism	2.6	1.3
All arterial embolism[a]	24.6	20.0
Venous thrombo-embolism (%)		
Pulmonary embolism	4.3	2.6
Deep venous thrombosis	3.7	2.1
All venous thrombo-embolism[a]	7.2	4.3
Bleeding (%)		
Subdural	0.5	0.3
All intracranial[a]	1.7	1.3
Gastrointestinal	12.9	5.2
Other bleeding	21.4	8.9
Any bleeding	30.5	14.1
Anaemia[a]	30.2	9.0
Platelet or coagulation defect[a]	3.6	1.5
Ischaemic heart disease (%)		
Myocardial infarction	35.0	17.1
IHD without infarction	15.8	12.7
PCI procedure	8.1	5.3
CABG procedure	14.0	8.8
Peripheral arterial disease	17.2	5.9
Vascular disease (as in CHA_2DS_2-VASc)[a]	43.9	21.2
Heart failure[a]	59.1	27.9
Pericarditis[a]	1.3	0.6
Valvular disease (other than exclusion criteria)[a]	10.5	6.4
Endocarditis within 90 days	0.4	0.1
Pacemaker or ICD[a]	10.1	7.2
Hypertension[a]	64.7	44.2
Duration hypertension, years[b]	4.2 ± 3.3	2.9 ± 3.2
Diabetes[a] (%)	34.0	15.6
Duration diabetes, years[b]	5.2 ± 3.3	3.8 ± 3.3
Liver disease[a] (%)	3.1	1.1
Thyroid disease[a] (%)	8.2	6.6
Thyrotoxicosis within 90 days (%)	0.4	0.6
Chronic obstructive pulmonary disease[a] (%)	12.2	6.9
Alcohol index[a] (%)	3.2	2.6
Dementia[a] (%)	4.7	3.9
Cancer within 3 years[a] (%)	20.2	13.5
Medication at baseline (%)		
Warfarin[a]	28.0	39.9
Acetylsalicylic acid[a]	54.2	48.4
Clopidogrel[a]	7.1	4.9
NSAID[a]	10.4	13.6
Beta-blocker[a]	70.6	66.6
Class I antiarrhythmic drug[a]	0.5	2.0
Class III antiarrhythmic drug[a]	4.5	7.2
Digoxin[a]	18.1	22.6
Diuretic[a]	76.9	48.6
Calcium blocker[a]	31.8	22.8
ACE-inhibitor/ARB[a]	53.8	44.5
Statin[a]	34.8	27.8
Antidiabetic medication	25.1	12.7

P-values for all differences between the groups were <0.0001 except for subdural haematomas ($P = 0.015$) and for thyrotoxicosis ($P = 0.011$).
[a]Factors used in the full-multivariable model have been marked with a superscript 'a'.
[b]Duration refers to the number of years since the first occurrence of a diagnosis in the Swedish Patient register.

December 2010. We excluded 13 039 patients with mitral stenosis or prior valvular surgery and 10 343 patients who died in conjunction with the index hospitalization (Supplementary material online, *Figure S1*). After exclusions, 283 969 patients remained in the study. Of those, 13 435 patients (4.7%) had a history of renal failure. 'Chronic renal failure' (N18) was the most common diagnosis affecting 8904 patients. Only 833 patients (6.2%) of the patients with renal failure had been on dialysis and only 314 (2.3%) had undergone renal transplantation.

Patients with renal failure were older, and had more comorbidities than patients without renal failure (*Table 1*). As expected, patients with renal disease had higher risk scores both for ischaemic strokes and for bleeding than AF patients without renal failure.

During a median follow-up of 2.1 years, 19 493 ischaemic stroke events occurred. There were also 3582 intracranial haemorrhages, as well as 27 857 other bleeding events and 85 488 deaths. The annual mortality rate was very high among patients with renal failure (36%), and far higher than both rates of ischaemic stroke (3.9%) and of intracranial bleeding (0.8%) (*Figure 1* and *Table 2*).

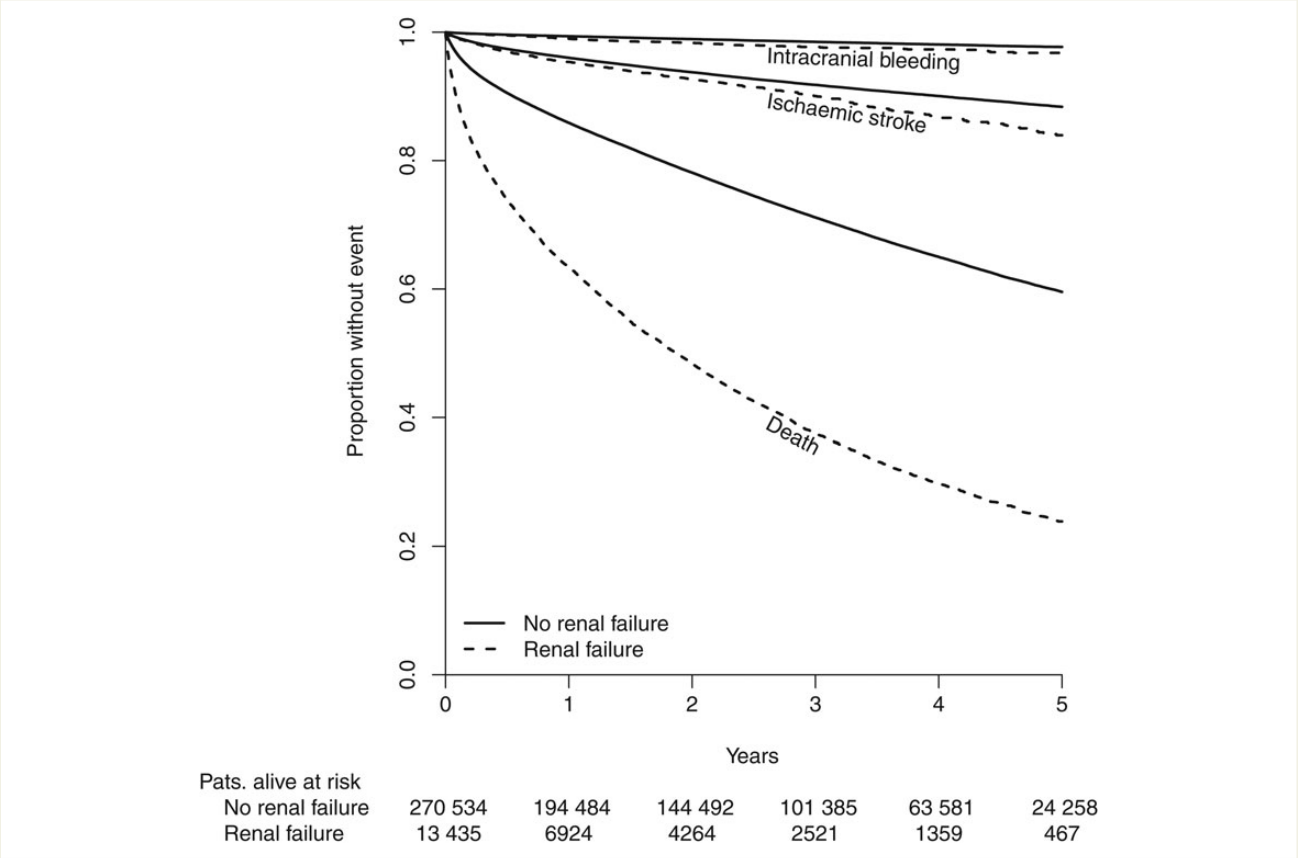

Figure 1 Kaplan–Meier plot showing ischaemic stroke, intracranial bleedings and death from any cause in atrial fibrillation patients in relation to renal failure.

Ischaemic stroke and thrombo-embolism

Ischaemic stroke occurred more frequent in patients with (than without) renal failure (3.9 vs. 2.9% annually, *Table 2*). For the endpoint of 'thrombo-embolism', the unadjusted rates were 8.2% with, and 5.2% without, renal failure. After adjustment for cofactors, no excess risk related to renal failure remained for the main endpoint of ischaemic stroke (HR: 1.02, CI: 0.95–1.10), but for the less stringent endpoint 'thrombo-embolism', which also includes transient ischaemic attacks (TIA) TIAs and 'unspecified strokes' (which may include intracranial bleeding), there was a modest association with renal failure (HR: 1.12, CI: 1.07–1.18) (*Table 2*).

The association between renal failure and ischaemic stroke remained the same when patients were analysed according to a specific diagnostic code given at the index contact, that is, acute renal failure [HR: 1.05 (0.93–1.19)], chronic renal failure [HR: 1.00 (0.92–1.09)], unspecified renal failure [HR: 1.02 (0.89–1.18)], dialysis [HR: 0.90 (0.63–1.27)], and renal transplantation [HR: 1.41 (0.89–2.24)].

We tested if adding 1 or 2 points for renal failure to the $CHADS_2$ and CHA_2DS_2-VASc scores would improve the predictive power of the schemes, but found no additive predictive value. The *c*-index was 0.72 both for the original $CHADS_2$ scheme as well as for a 'new' R-$CHADS_2$ or R_2-$CHADS_2$ scheme, where 1 and 2 points, respectively, were added for renal failure ('R'). For the CHA_2DS_2-VASc score, the c-index remained 0.71 irrespective of whether 0, 1, or 2 points was added for renal failure (*Table 3*). The net reclassification improvement (NRI) was minimally improved by the addition of 1 point for renal failure. Adding 2 points for renal failure made the schemes perform worse than the original schemes at 1 year; but at 5 years, the results were essentially the same as when 1 point was added (*Table 3*).

Intracranial and other bleeding

Intracranial bleeding was more common in AF patients with renal failure (annualized rates, 0.8% vs. no renal failure, 0.5%) (*Table 2*). In absolute numbers, there were only 173 intracranial bleeding events among patients with renal failure, but the statistical difference was nevertheless statistically highly significant ($P < 0.001$). Our secondary (and more inclusive) endpoint of 'any bleeding' occurred more often in AF patients with renal failure (9.8% vs. no renal failure, 4.1%) (*Table 2*). Multivariable adjustment for cofactors showed that renal failure was an independent risk factor for intracranial bleeding [HR: 1.27 (CI: 1.09–1.49)] in AF patients, and even more so for the endpoint of 'any bleeding' [HR: 1.56 (CI: 1.48–1.63)] (*Table 2*).

The association between renal failure and intracranial bleeding and the specific diagnostic codes were as follows: for acute renal failure [HR: 1.26 (0.96–1.64)]; chronic renal failure [HR: 1.32 (1.10–1.59)]; unspecified renal failure [HR: 1.31 (0.97–1.77)]; dialysis [HR: 1.62 (0.89–2.93)]; and renal transplantation [HR: 2.87 (1.54–5.37)].

Table 2 Event rates and hazard ratios for atrial fibrillation patients with renal failure with atrial fibrillation patients without renal failure as a reference

Endpoint	Events per 100 years at risk (95% CI)		Univariable HR (95% CI)	Multivariable adjustment for					
	Renal failure (n = 13 435)	No renal failure (n = 270 534)		Age and sex HR (95% CI)	CHA_2DS_2-VASc		HAS-BLED		Full model[b] HR (95% CI)
					By score sum HR (95% CI)	By cofactors[a] HR (95% CI)	By score sum HR (95% CI)	By cofactors[a] HR (95% CI)	
Ischaemia									
Stroke	3.9 (3.7–4.2)	2.9 (2.8–2.9)	1.25 (1.16–1.34)	1.13 (1.05–1.21)	0.89 (0.83–0.95)	1.05 (0.97–1.12)			1.02 (0.95–1.10)
Thrombo-embolism	8.2 (7.8–8.6)	5.2 (5.2–5.3)	1.42 (1.35–1.49)	1.27 (1.21–1.33)	0.99 (0.94–1.04)	1.15 (1.09–1.21)			1.12 (1.07–1.18)
Bleeding									
Intracranial	0.8 (0.7–0.9)	0.5 (0.5–0.5)	1.50 (1.28–1.74)	1.31 (1.13–1.53)			0.86 (0.73–1.01)	1.16 (0.99–1.35)	1.27 (1.09–1.49)
Any bleeding	9.8 (9.3–10.2)	4.1 (4.0–4.1)	2.24 (2.14–2.35)	2.01 (1.91–2.10)			1.41 (1.34–1.48)	1.75 (1.67–1.84)	1.56 (1.48–1.63)
Death									
	36.0 (35.2–36.8)	11.5 (11.4–11.6)	2.90 (2.83–2.97)	2.37 (2.31–2.43)	2.09 (2.04–2.14)	1.93 (1.88–1.98)	1.64 (1.60–1.68)	2.32 (2.27–2.38)	1.68 (1.64–1.72)
Combined endpoints									
Ischaemic stroke or intracranial bleeding	4.7 (4.4–5.0)	3.3 (3.3–3.4)	1.28 (1.20–1.36)	1.15 (1.08–1.22)	0.93 (0.87–0.99)	1.07 (1.00–1.14)	0.61 (0.57–0.65)	1.04 (0.97–1.11)	1.05 (0.98–1.12)
Ischaemic stroke, intracranial bleeding or death	39.1 (38.2–39.9)	13.7 (13.6–13.7)	2.62 (2.56–2.68)	2.17 (2.12–2.22)	1.90 (1.85–1.94)	1.81 (1.77–1.85)	1.44 (1.41–1.48)	2.10 (2.05–2.15)	1.60 (1.56–1.64)

$P < 0.0001$ for all differences in event rates.

[a]In analyses 'by cofactors' adjustments have been made by inclusion of the individual constituent factors in respective scheme, rather than by the score sum.

[b]Factors used in the multivariable model were renal failure, age (continuous), sex, year of inclusion, duration since first AF diagnosis, previous thrombo-embolism, venous thrombo-embolism, intracranial bleeding, anaemia, coagulopathy or platelet defect, vascular disease, heart failure, pericarditis, other valvular disease (not qualifying as exclusion criteria), pacemaker or ICD, hypertension, diabetes, liver disease, thyroid disease, chronic obstructive pulmonary disease, recent cancer, alcohol index, dementia, baseline use of warfarin, ASA, clopidogrel, NSAID, beta-blocker, class 1 antiarrhythmic agents, class III antiarrhythmic agents, digoxin, diuretics, calcium channel blocker, ACE/ARB, statin.

Table 3 The effects of adding points for renal failure on the ability of risk scores to predict ischaemic stroke

	Points for renal failure	C-index (95% CI)	NRI % (95% CI)[a]	
			At 1 year	At 5 years
$CHADS_2$	0	0.72 (0.72–0.73)	–	–
R-$CHADS_2$	1	0.72 (0.72–0.72)	0.4 (0.1–0.8)	0.4 (0.0–0.7)
R_2-$CHADS_2$	2	0.72 (0.71–0.72)	−5.3 (−16.1–0.6)	0.6 (0.1–1.1)
CHA_2DS_2-VASc	0	0.71 (0.71–0.72)	–	–
R-CHA_2DS_2-VASc	1	0.71 (0.71–0.72)	0.5 (0.0–0.8)	0.4 (0.0–0.8)
R_2-CHA_2DS_2-VASc	2	0.71 (0.70–0.71)	−4.6 (−5.5–3.0)	0.7 (0.2–1.3)

[a]Compared with $CHADS_2$ and $CHA2DS_2$-VASc, respectively.

Combined endpoints

The incidence of the combined endpoint 'stroke', including both ischaemic stroke and intracranial bleeding, was 28% higher in patients with renal failure (4.7% vs. no renal failure, 3.3% annually) (*Table 2*). After multivariable adjustment for comorbidities, this difference was no longer statistically significant (HR: 1.05, CI: 0.98–1.12). When 'death from any cause' was added to the combined endpoint, the incidence rate was 2.62-fold higher among renal failure patients; this difference remained highly significant after adjustment for co-morbidities (HR: 1.60, CI: 1.56–1.64) (*Table 2*). Indeed, death was significantly increased in AF patients with renal failure (adjusted HR: 1.68, CI: 1.64–1.72).

Benefit of anticoagulant treatment in renal failure

Among renal failure patients, $n = 3766$ used warfarin at baseline. Irrespective of renal function, AF patients who used warfarin at baseline had a lower risk of ischaemic stroke, thrombo-embolism, and death than patients without warfarin (*Figure 2*). The hazard ratio for ischaemic stroke with warfarin compared with no warfarin was 0.69 in renal failure patients and 0.70 in patients without renal failure [*P*-value for interaction (P_{int}) = 0.865].

Warfarin use was associated with an increased risk of bleeding, which was similar in patients with and those without renal failure. The risk of any bleeding was increased by 10% with warfarin in patients with renal failure and by 15% in non-renal failure patients ($P_{int} = 0.368$). For the endpoint of intracranial bleeding, warfarin tended to increase bleeding risk more in renal failure patients (HR: 1.56) than in patients without renal failure (HR: 1.29) although the interaction was not statistically significant ($P_{int} = 0.238$).

While still having some benefit from warfarin treatment, AF patients with renal failure appeared to have less net benefit of warfarin treatment than non-renal failure patients when it came to the composite endpoints. For the composite endpoint of 'ischaemic stroke or intracranial bleeding', the HR for renal failure patients was 0.81 (CI: 0.70–0.93) in favour of warfarin compared with 0.76 (CI: 0.74–0.79) for patients without renal failure ($P_{int} = 0.447$). For the composite endpoint of 'ischaemic stroke, intracranial bleeding or death', a clear benefit of warfarin treatment was seen for both groups, but more so for non-renal failure patients [renal failure HR: 0.74 vs. no renal failure HR: 0.63, *P*-value for the interaction ($P_{int} < 0.001$; *Figure 2*)].

Even patients at high-bleeding risk (HAS-BLED score ≥3) appeared to benefit from warfarin. Based on $n = 888$ ischaemic stroke or intracranial bleeding events among 10 670, renal failure patients with an HAS-BLED score ≥3, the hazard ratio in favour of warfarin treatment was HR 0.82, CI 0.70–0.98. For the composite endpoint of 'ischaemic stroke, intracranial bleeding or death', the benefit of warfarin in these patients with high-bleeding risk was statistically significant (HR: 0.74, CI: 0.70–0.79).

Even patients with extreme bleeding risk (defined as a HAS-BLED score ≥6) appeared to benefit from warfarin treatment, although there were only 103 renal failure patients with this high-bleeding risk that were treated with warfarin which makes confidence intervals wide. These patients tended to have a lower risk of ischaemic stroke or intracranial bleeding (HR: 0.74, CI: 0.39–1.40) than those not given warfarin, and for the composite including death, the apparent benefit of warfarin treatment was statistically significant (HR: 0.56, CI: 0.42–0.76) (*Table 4*).

For a minority of the warfarin-treated patients ($n = 542$), information about dosages and TTRs was available from the dose-dispensing register, Auricula, showing that a mean daily dose of 3.6 mg warfarin produced a TTR of 66.7%, with 21.0% of the time below, and 12.3% of the time above the therapeutic range. Patients with renal failure and TTR >70% suffered fewer strokes and bleedings than patients with lower TTR, but the differences were not statistically significant, due to the lack of statistical power (*Table 5*) . For AF patients without renal failure where information was available in Auricula ($n = 21\,116$), the mean daily dose of warfarin was 4.2 mg and TTR was 74.6% with 14.7% of the time below, and 10.7% of the time above the therapeutic range. The difference between the groups was statistically significant regarding both doses used and TTRs achieved ($P < 0.001$).

Discussion

The discussion about whether renal failure is an *independent* risk factor for ischaemic stroke or not, is essentially a question of whether AF patients with renal failure should be treated differently than other AF patients in terms of the threshold for initiating anticoagulation. It is well established that AF patients with renal failure have a

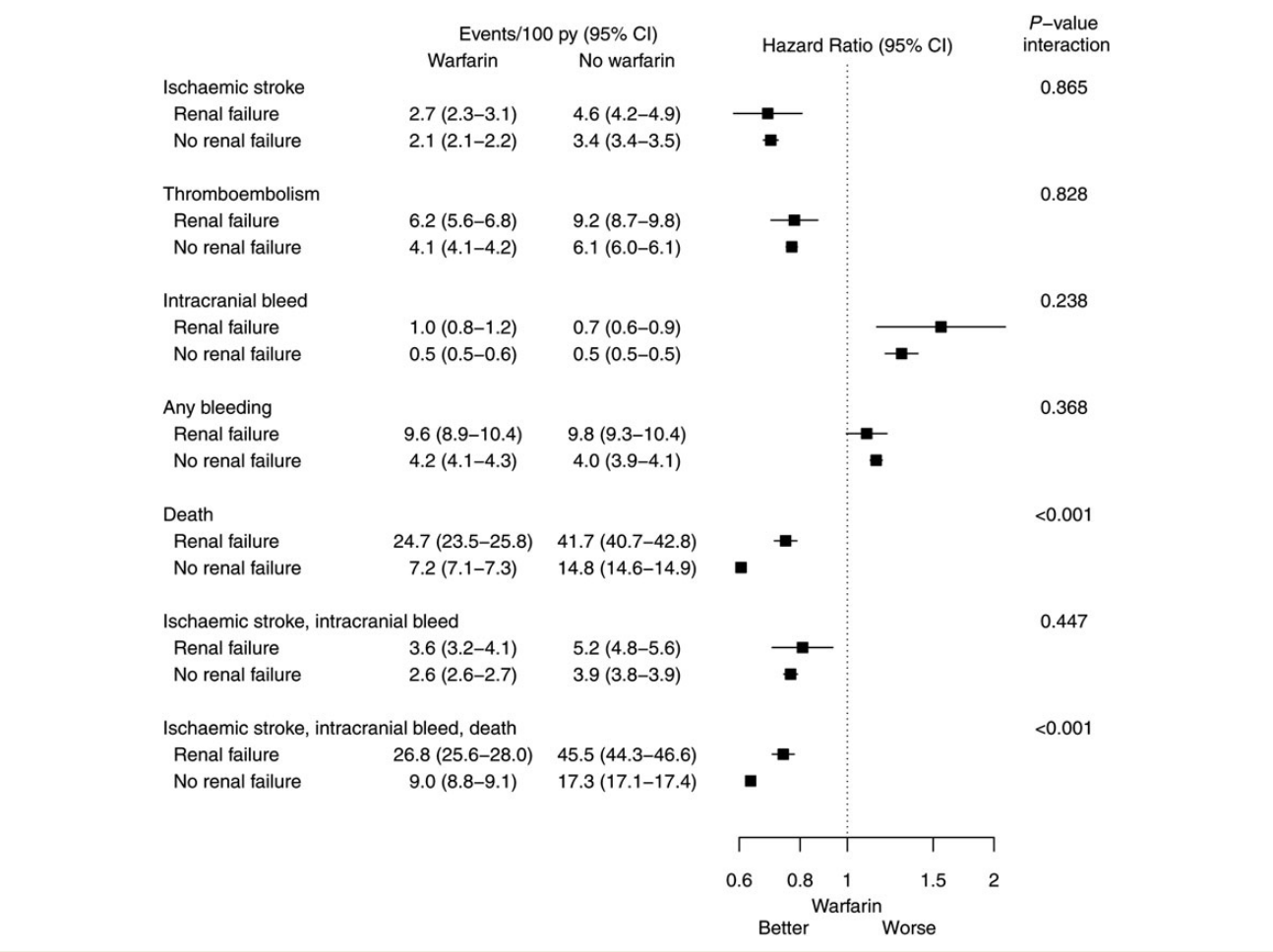

Figure 2 Forest plot with the association between warfarin treatment and outcome in patients with and without renal failure. Multivariable adjustments to the hazard ratio and corresponding 95% CI been made for the same cofactors as in the full model in *Table 2*.

Table 4 Combined endpoints among 13 435 patients with renal failure in relation warfarin use and bleeding risk

	Ischaemic stroke or intracranial bleed			Ischaemic stroke, intracranial bleed, or death		
	Events per 100 years at risk (95% CI)		Multivariable	Events per 100 years at risk (95% CI)		Multivariable
HAS-BLED	Warfarin (n = 3766)	No warfarin (n = 9669)	HR (95% CI)	Warfarin (n = 3766)	No warfarin (n = 9669)	HR (95% CI)
1–2	2.1 (1.4–2.9)	2.8 (2.0–3.7)	0.81 (0.51–1.27)	24.1 (21.8–26.7)	34.4 (31.6–37.3)	0.86 (0.75–0.98)
3–5	4.0 (3.5–4.6)	5.3 (4.9–5.7)	0.83 (0.70–0.99)	27.5 (26.1–28.9)	46.1 (44.9–47.4)	0.75 (0.70–0.80)
6–8	6.8 (3.4–12.1)	10.2 (7.8–13–1)	0.74 (0.39–1.40)	30.2 (22.3–39.9)	65.1 (58.8–72.0)	0.56 (0.42–0.76)
All	3.6 (3.2–4.1)	5.2 (4.8–5.6)	0.82[a] (0.70–0.97)	26.8 (25.6–28.0)	45.5 (44.4–46.6)	0.76[a] (0.72–0.80)

Multivariable adjustments have been made for the same cofactors as in the full model in Table 2. *P*-value interaction between warfarin and HAS-BLED: 0.940 (ischaemic stroke or intracranial bleed) and 0.558 (ischaemic stroke, intracranial bleed, or death).
[a]Stratified for HAS-BLED.

higher stroke risk than other AF patients. The unanswered question is as follows: 'If renal failure is an independent stroke risk factor, should it be incorporated into stroke risk stratification scores, such as $CHADS_2$ and CHA_2DS_2-VASc?' If so, it will essentially lower the threshold for anticoagulation for these patients.

In a recent analysis, Piccini *et al.*[14] advocated the addition of 2 more points for renal disease to the classical $CHADS_2$ scheme, making it into the so-called R_2CHADS_2 score. This scheme was derived from patients in the ROCKET-AF trial[7] in which all the subjects were treated on anticoagulants, in a selected clinical trial cohort at

Table 5 Events per 100 years at risk in relation to time in therapeutic range among warfarin-treated atrial fibrillation patients with and without renal failure

	Events per 100 years at risk					
	Renal failure			No renal failure		
	TTR <60% (*n* = 167)	TTR 60–69% (*n* = 109)	TTR ≥70% (*n* = 266)	TTR <60% (*n* = 3506)	TTR 60–69% (*n* = 3079)	TTR ≥70% (*n* = 14 528)
Stroke	3.3 (1.8–5.7)	3.8 (1.8–7.0)	2.2 (1.2–3.6)	2.8 (2.5–3.2)	2.5 (2.2–2.9)	1.7 (1.6–1.8)
Thrombo- embolism	8.4 (5.7–12.1)	7.5 (4.5–11.7)	4.7 (3.1–6.7)	5.0 (4.6–5.5)	4.3 (4.0–4.8)	3.4 (3.2–3.6)
Intracranial bleed	1.0 (0.3–2.6)	0.7 (0.1–2.6)	0.4 (0.1–1.3)	0.5 (0.4–0.7)	0.4 (0.3–0.6)	0.2 (0.2–0.3)
Any bleeding	11.5 (8.2–15.6)	9.2 (5.8–13.8)	5.9 (4.1–8.2)	4.9 (4.5–5.4)	4.1 (3.7–4.5)	2.7 (2.6–2.9)
Death	9.3 (6.5–12.8)	9.0 (5.8–13.3)	5.9 (4.2–8.0)	4.5 (4.1–5.0)	3.1 (2.8–3.5)	1.6 (1.5–1.7)
Ischaemic stroke or intracranial bleeding	3.9 (2.2–6.4)	4.2 (2.1–7.5)	2.5 (1.4–4.0)	3.3 (3.0–3.7)	2.9 (2.5–3.3)	1.9 (1.8–2.1)
Ischaemic stroke, intracranial bleeding, or death	11.8 (8.7–15.8)	12.6 (8.6–17.6)	8.0 (6.0–10.5)	7.2 (6.6–7.8)	5.5 (5.1–6.1)	3.3 (3.2–3.6)

Note that TTR values only were available for 21 655 patients

'high-stroke risk' (mean $CHADS_2$ score 3.5 and only 10% of trial population had a $CHADS_2$ score = 2; where 55% already had experienced a thrombo-embolic event, none had renal failure (since creatinine clearance <30 mL/min was an exclusion criteria) and haemorrhagic stroke was included in the primary endpoint. Piccini *et al.*[14] found that renal dysfunction, defined as estimated glomerular filtration rate 30–59 mL/min, was strongly associated with that mixed endpoint, and that the new R_2CHADS scheme reclassified 3 out of 11 patients with the $CHADS_2$ score of 1 to higher scores and thus made them eligible for warfarin treatment. Application to patients in the ATRIA cohort[26] found that it reclassified 21% of the patients in $CHADS_2$ class 0–1 to higher risk scores and that it was better at identifying patients with a low risk of ischaemic stroke (0.4 and 1.3% annual risk for score 0 and 1, respectively).

Identification of true low-risk patients who will not benefit from anticoagulation is important, as advocated in the recent 2012 focused update of the ESC guidelines.[27] The practical consequence of adding renal failure to the $CHADS_2$ score will weigh the balance in favour of anticoagulant treatment and result in more aggressive anticoagulant treatment of AF patients with renal failure than of other AF patients. Thus, an analysis of the net benefit of warfarin treatment for these patients would have been appropriate.

Our findings confirm that renal failure, defined by diagnostic or procedural codes, is an independent risk factor for bleeding in AF patients and thus support inclusion of renal failure as a risk factor in the HAS-BLED score for bleeding risk assessment.[28] We found that renal failure confers a larger relative increase in bleeding risk, than in ischaemic stroke risk in AF patients. This relationship was also found by Olesen *et al.*[12] in a nationwide cohort study of AF patients in the Danish health registers, where non-end-stage chronic kidney disease (i.e. renal failure without dialysis or transplantation) conferred a 49% increase in the risk of systemic thromboembolism, and a 124% increase in risk of bleeding.

Importantly, although the bleeding risk is high, most renal failure patients with AF still appear to benefit from warfarin treatment. In our study, ischaemic stroke was approximately five times more common than intracranial bleeding in all subgroups. Renal failure patients who used warfarin had more favourable net outcome than those who did not use warfarin, with a lower risk of the combined endpoint 'ischaemic stroke or intracranial bleeding' (HR: 0.85, CI: 0.74–0.98), and also a lower risk of the other combined endpoint of 'ischaemic stroke, intracranial bleeding, or death' (HR: 0.76, CI: 0.72–0.80).

It should be noted that information about comorbidity in registers is mostly binary. In real life, however, risks are a continuum. Assessment of the net clinical benefit of anticoagulant treatment for patients with AF and renal failure, and especially patients on dialysis, who are at high risk of both AF-related stroke and disastrous bleeding therefore calls for careful *individualized* assessment of specific weights of risk factors, for example, severity of renal failure, hypertension, diabetes, bleeding predisposition, etc.

Lastly, we found that patients with AF in combination with renal failure were not prescribed warfarin as often as other AF patients, although their risk for ischaemic stroke is higher. Only 28% of AF patients with and renal failure received warfarin compared with 40% without renal failure, indicating underutilization of warfarin according to current guidelines. In 'real-world' clinical practice, the threshold for initiating warfarin treatment, therefore, appears to be *higher* for renal failure patients with AF than for other AF patients, although the addition to existing scores would make the treatment threshold *lower*. This is probably out of concern for bleeding risks, although we find it very unlikely that 72% of these patients have such extreme bleeding risks that they would not benefit from anticoagulation. The threshold for warfarin treatment in renal failure patients with AF should not be lower than for other AF patients, but neither should it be higher as it seems to be in current clinical practice.

Limitations

Our definition of renal failure by means of diagnostic codes for renal failure, dialysis or transplantation is imprecise and may also include some patients with renal dysfunction, rather than outright renal failure. Also, our information about comorbidity was limited to

information that was available in registries. Such information is seldom complete. Information about life style factors such as smoking, obesity, and physical activity is not available through the registers we used. We also lack information about education, economic conditions, and unemployment—and such factors may affect morbidity and mortality. Patients with many diseases may not get codes for everything. Also, most of the information in the registries is binary, and while this may not be a problem for diagnoses such as stroke or myocardial infarction which are discrete event(s), but may be a problem for chronic diagnoses such as hypertension where mild and severe forms are coded in the same way. Thus, it is almost certain that there is residual confounding that we do not know anything about, and, therefore, cannot fully adjust for.

In the case of medications, it is likely that there are circumstances that affect decisions about treatment that the codes do not reveal. For example, if patients with a poor prognosis are not given warfarin and if this is not fully reflected by diagnostic codes, they will be categorized for analyses as non-warfarin patients and the protective effect of warfarin will be exaggerated. On the other hand, if patients stop taking warfarin because of serious illness, but enter the analyses in the warfarin group, this will make warfarin appear be less beneficial than it is.

We are therefore only able to make the observation that overall AF patients with renal failure who used warfarin at baseline fared better, but we do not know if it was warfarin that made the difference.

Validity of national registers

A diagnosis of AF or atrial flutter in the Swedish Patient register has a positive predictive value of 97%.[29] The register is subjected to annual quality control to ascertain completeness of information, and >99% of the registrations are technically correct.[30] For some important diagnoses such as myocardial infarction and heart failure, external validation of the diagnostic accuracy is good.[31,32] For many other diagnoses, we know little about the validity of the register, and there may be under-reporting of some comorbidity, especially hypertension, while over-reporting is much rarer. Patients may therefore have more risk factors than we are aware of, and consequently been given lower risk scores than would have been the case with full knowledge about comorbidity.

Confounding by indication

The patients were not randomized to warfarin or 'no warfarin' and hence no conclusions regarding cause and effect of that treatment can be drawn. A placebo-controlled study would be unacceptable for ethical reasons. Large-scale observational studies are substitutes and have to be interpreted with caution, since there may be selection bias as to which patients get treatment and which does not.

Applicability of results

We had no information about how anticoagulant treatment was managed with regard to INR values and TTR for the majority of the patients. Warfarin treatment in Sweden is generally very well managed compared with the situation in most other countries with average TTRs ~75%.[33,34] However, among AF patients where TTR data were available, the mean TTR was clearly lower than among other AF patients but still better than in some of the recent clinical trials that compared warfarin to the new oral anticoagulants.[6–8] Previous studies have shown that over-anticoagulation, i.e. when INR values repeatedly exceed 6, is associated with further deterioration of renal function.[35] In the Swedish AF cohort, over-anticoagulation was generally rare, both among patients with and without renal failure. Thus, the results in the present study may not be applicable in countries with less well-managed anticoagulant treatment where the risk of ischaemic stroke as well as of bleeding and accelerated renal failure may be much higher.

Conclusion

Patients with both AF and renal failure will probably benefit most from having the same treatment as is recommended for other patients with AF, without setting a higher or lower threshold for treatment. Adding points for renal failure to the $CHADS_2$ and CHA_2DS_2-VASc scores does not improve their predictive value. There appear to be wide spread under-treatment of this patient group despite the fact that they would probably benefit the most by being treated as other AF patients, but with carefully individualized considerations of net benefit, optimal management of other risk factors for ischaemic stroke and bleeding, as well as rigorous control of INR values.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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