Meta-Analysis of the Influence of Chronic Kidney Disease on the Risk of Thromboembolism Among Patients With Nonvalvular Atrial Fibrillation

Rui Providência, MD, MSc[a,b,]*, Eloi Marijon, MD, PhD[c], Serge Boveda, MD[a], Sérgio Barra, MD[d], Kumar Narayanan, MD[c,e], Jean-Yves Le Heuzey, MD[c], Bernard J. Gersh, MBChB, DPhil[f], and Lino Gonçalves, MD, PhD[b]

Chronic kidney disease (CKD) and atrial fibrillation (AF) frequently coexist. However, the extent to which CKD increases the risk of thromboembolism in patients with nonvalvular AF and the benefits of anticoagulation in this group remain unclear. We addressed the role of CKD in the prediction of thromboembolic events and the impact of anticoagulation using a meta-analysis method. Data sources included MEDLINE, EMBASE, and Cochrane (from inception to January 2014). Three independent reviewers selected studies. Descriptive and quantitative information was extracted from each selected study and a random-effects meta-analysis was performed. After screening 962 search results, 19 studies were considered eligible. Among patients with AF, the presence of CKD resulted in an increased risk of thromboembolism (hazard ratio [HR] 1.46, 95% confidence interval [CI] 1.20 to 1.76, $p = 0.0001$), particularly in case of end-stage CKD (HR 1.83, 95% CI 1.56 to 2.14, $p <0.00001$). Warfarin decreased the incidence of thromboembolic events in patients with non−end-stage CKD (HR 0.39, 95% CI 0.18 to 0.86, $p <0.00001$). Recent data on novel oral anticoagulants suggested a higher efficacy of these agents compared with warfarin (HR 0.80, 95% CI 0.66 to 0.96, $p = 0.02$) and aspirin (HR 0.32, 95% CI 0.19 to 0.55, $p <0.0001$) in treating non−end-stage CKD. In conclusion, the presence of CKD in patients with AF is associated with an almost 50% increased thromboembolic risk, which can be effectively decreased with appropriate antithrombotic therapy. Further prospective studies are needed to better evaluate the interest of anticoagulation in patients with severe CKD. © 2014 Elsevier Inc. All rights reserved. (Am J Cardiol 2014;114:646−653)

Thromboembolic events are one of the most feared complications of atrial fibrillation (AF).[1] Chronic kidney disease (CKD) is relatively prevalent in patients with AF.[2] The extent to which the presence of CKD may increase the risk of thromboembolism in patients with AF has not yet been fully elucidated. Oral anticoagulation is the mainstay of thromboembolic prevention in patients with AF,[3] but data on efficacy and safety in the CKD and dialysis population have been scarce and contradictory.[4,5] Our aim was to systematically evaluate, through a meta-analysis method, the impact of the presence of CKD in patients with AF as regards risk of thromboembolism and the potential benefit of anticoagulation in that setting.

Methods

We performed a search in MEDLINE (by way of Ovid and PubMed), EMBASE, and Cochrane (from inception to January 3, 2014) databases using the following search string: "atrial fibrillation" AND ("renal failure" OR "chronic renal disease" OR "dialysis") AND ("stroke" OR "thromboembolism"). The reference lists of the accessed full-text reports were further researched for sources of potential information relevant to this analysis. The authors of full-text reports and abstracts were contacted by e-mail to retrieve additional information.

Only longitudinal studies assessing the occurrence of a composite end point of stroke or systemic embolism (and including transient ischemic attack) during follow-up in patients with AF were considered for inclusion. Both registries and randomized trials were considered eligible for analysis. The methods sections of evaluated studies were reviewed to confirm the suitability and composition of the reported end point. Studies assessing only stroke (either ischemic, hemorrhagic, or a composite of both) and providing no data on systemic embolism were not considered representative of the full spectrum of thromboembolism in AF and were excluded from analysis. Similarly, studies only reporting stroke or systemic embolism in association with myocardial infarction, hospitalization, or death not due to stroke or systemic embolism were not included.

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[a]Département de Rythmologie, Clinique Pasteur, Toulouse, France; [b]Faculty of Medicine, University of Coimbra, Coimbra, Portugal; [c]Paris Descartes University and European Georges Pompidou Hospital, Paris, France; [d]Papworth Hospital NHS Foundation Trust, Cambridge, United Kingdom; [e]Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California; and [f]Mayo Clinic, Rochester, Minnesota. Manuscript received April 9, 2014; revised manuscript received and accepted May 27, 2014.

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*Corresponding author: Tel: (+33) 5 62 21 16 45; fax: (+33) 5 62 21 16 41.

E-mail address: rui_providencia@yahoo.com (R. Providência).

Search on MEDLINE (via OVID and PubMED), EMBASE and COCHRANE (from inception to 3rd January 2014) using the following search string:
"atrial fibrillation" AND ("renal failure" OR "chronic kidney disease" OR "dialysis") AND ("stroke" OR "thromboembolism")

962 results were found of which the abstract was revised for inclusion and exclusion criteria.

Subject out of the scope of the review
• 783
Duplicated entries
• 106

73 results possibly addressing the purpose of the review of which the full manuscript was revised or abstract (if conference abstract) for inclusion and exclusion criteria.

Reviews, Comments and Editorials
• 31
Not assessing the pre-specified endpoint
• 29
Abstracts later published as full-text
• 3

Sub-studies providing further data
• 6
Manual searches using alternate expressions
• 3

19 selected entries (full-text articles) addressing the systematic review purpose.
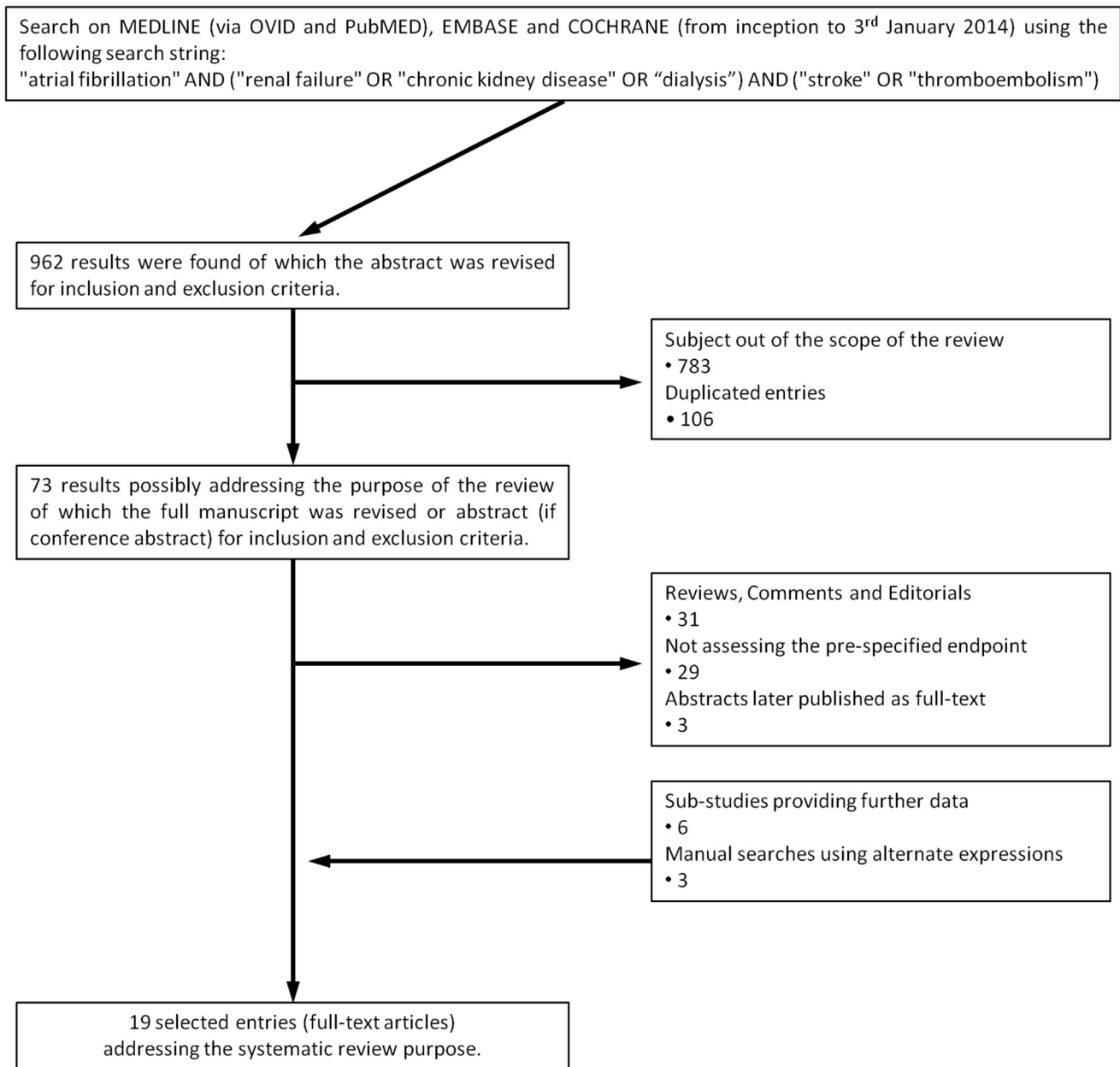
Figure 1. Flowchart diagram illustrating study selection.

To be included in the systematic review, the studies needed to have a design allowing extraction of information concerning at least 1 of the 2 main aims of this study: (1) assessment of the incidence of stroke and systemic embolism in patients with AF according to the presence of CKD (including dialysis treatment) and (2) estimating the impact of anticoagulation in patients with CKD and AF. The population, intervention, comparison, and outcome approach was used for this aim.[6] The population of interest included patients with nonvalvular AF with CKD or treated with dialysis. The term end-stage CKD was used for patients with disease requiring renal replacement therapy, either dialysis or transplantation. Non−end-stage CKD was used for the remaining patients with renal disease. The intervention was anticoagulation. Comparisons were performed among the following groups: adjusted-dose warfarin (target international normalized ratio of 2 to 3) versus no treatment, aspirin or low dosage non−adjusted-dose warfarin (target international normalized ratio <1.5); warfarin versus novel oral anticoagulants; and novel oral anticoagulants versus aspirin. The outcome has been defined previously.

Two independent reviewers (RP and SCB) screened all abstracts and titles to identify potentially eligible studies. The full text of these potentially eligible studies was then evaluated to determine the eligibility of the study for the review and meta-analysis. Disagreements regarding eligibility were resolved by consensus with the help of a third reviewer (SB).

Data extraction and presentation for the preparation of this report followed the recommendations of the Preferred

Table 1
Selected studies for the systematic review: baseline information and main findings

Author, Ref	Study Design, Acronym	Sample Size (pts)	Intervention or Baseline Anti-thrombotics	Dialysis pts (%) HD/PD	CKD pts (%) eGFR Cutoff (ml/min)	Length of FUP (yrs)	Association of CKD With Stroke and/or SE			Anticoagulation in pts With CKD	
							Variable Outcome	HR 95% CI	Endpoint	Intervention Outcome	HR 95% CI
Roldan[10,11]	Prospective Single-center Observational	978	Acenocoumarol 100%	NA	eGFR 30−59, 28% eGFR <30, 3%	Median 2.4	eGFR NS	1.06 0.69−1.63	Stroke or SE	—	—
Banerjee[12]	Retrospective Regional (4 hospitals) Observational	5,912	VKA 52.5% Antiplatelet 30.8% None 26.0%	Baseline or FUP 2.2%	eGFR 30−59, 20.2% eGFR <30, 5.8%	Mean 2.5	Renal impairment NS eGFR NS	1.06 0.75−1.49 1.09 0.84−1.41	Stroke or SE Stroke or SE	—	—
Olesen[5]	Retrospective Nationwide Observational	132,372	W 28.3% A 18.9% W + A 8.4%	Baseline RRT 0.7% FUP RRT 1.0% (78%HD/15% PD)	NA	Maximum 12	CKD (non-endstage) ↑ RRT ↑	1.49 1.38−1.59 1.83 1.57−2.14	Stroke or SE Stroke or SE	W NS ↓ trend W ↓	0.84 0.69−1.01 0.44 0.26−0.76
Friberg[13,14]	Retrospective Nationwide Observational	170,291	W baseline 40% W baseline/FUP 47%	NA	Renal disease ≈6.0%	Mean 1.5	Renal failure ↑	1.16 1.05−1.28	Ischemic stroke/ US/TIA/SE	—	—
Eikelboom[15] Connolly[16]	RCT AVERROES	5,599	Apixa vs A (1:1) 5mg* bid vs 81 −324 mg od	Exclusion criteria	eGFR 30−60, 30.3% eGFR ≤30, 0.4%	Mean 1.1	Stage III CKD ↑	1.6 NA (p <0.01)	Stroke or SE	Apixa vs A ↓	0.32 0.18−0.55
Cha[17]	Retrospective Single-center Observational	695	W 26.0% A 61.4% None 12.5%	NA	eGFR <60, 20.8%	Median 5.5	eGFR <60 ↑	3.63 1.57−8.42	Ischemic stroke/ TIA/SE	W ↓	0.39 0.16−0.99
Patel[18] Piccini[19]	RCT ROCKET-AF	14,264	Riva vs W (1:1) 20 mg* od	Exclusion criteria	eGFR <50, 20.7%	Median 1.9	eGFR ↑	1.12 1.07−1.16	Stroke or SE	Riva vs W NS	0.88 0.65−1.19
Hart[20]	RCT SPAF-III	1,936	Low risk A 46.1% High risk 1:1 W vs low W + A† 53.9%	NA	eGFR 30−59, 41.6% eGFR ≤30, 1.5%	Low risk Mean 2 High risk Mean 1.1	Stage III CKD (pts treated with A) ↑	2.0 1.2−3.3	Ischemic stroke or SE	W vs A + low W ↓	0.24 0.10−0.38
Granger[21] Hohnloser[22]	RCT ARISTOTLE	18,201	Apixa vs W (1:1)	Exclusion criteria	eGFR ≤50, 16.6% eGFR ≤30, 1.5%	Median 1.8	—	—	Stroke or SE	Apixa vs W NS	0.79 0.55−1.14
Lai[23]	Retrospective Single-center Observational	399	W 58.1% A 41.4%	23% HD	eGFR <60, 100% eGFR <15, 33.1%	Mean W 2.6 No W 1.9	—	—	Ischemic stroke or SE	W ↓	0.28 0.16−0.50

Author	Design	Study	N	Treatment	CKD definition	eGFR category	FUP		HR (95% CI)	Outcome	Comparison	HR (95% CI)
Go[2] Singer[24]	Prospective Multicentric Observational	ATRIA	10,908	W None	NA eGFR <15 0.9% ♂ 0.7% ♀	eGFR 45–59, 18.5% eGFR <45, 9.9%	Pt-yrs 33,165	Proteinuria ↑ eGFR <45 ↑	1.54 1.29–1.85 1.39 1.13–1.71	Ischemic stroke or SE	—	—
Connolly[25] Hijazi[26]	RCT	RE-LY	17,951	High Dabi/Low Dabi vs W 150 mg bid 110 mg bid (1:1:1)	Exclusion criteria eGFR <50	eGFR <50, 18.8%	Median 2.0	—	—	Stroke or SE	High Dabi vs W ↓ Low Dabi vs W NS	0.56 0.37–0.85 0.85 0.59–1.24

A = aspirin; AF = atrial fibrillation; Apixa = apixaban; ARISTOTLE = Apixaban for reduction in stroke and other ThromboemboLic events in atrial fibrillation; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; AVERROES = Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; CI = confidence interval; CKD = chronic kidney disease; Dabi = dabigatran; eGFR = estimated glomerular filtration rate; FUP = follow-up; yrs = years; HR = hazard ratio; NA = not available; pts = patients; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; Riva = rivaroxaban; 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; RRT = renal replacement therapy; SE = systemic embolism; SPAF-III = Stroke Prevention in Atrial Fibrillation III; TIA = transient ischemic attack; US = unspecified stroke; W = warfarin.

* Apixa (from 5 mg bid to 2.5 mg bid) and Riva (from 20 mg od to 15 mg od) presented dose adjustment for patients with a certain degree of CKD.
† Target INR in all RCT was 2.0 to 3.0, except in the A + low dose W arm of the SPAF-III trial, where a mean INR of 1.3 was achieved as a result of the daily 1 to 3 mg warfarin alongside with A 325 mg od.

Reporting Items for Systematic Reviews and Meta-Analyses group.[7] The following data were extracted for characterizing each patient sample in the selected studies, whenever available: criteria for defining CKD, number of patients with CKD (and when available, number in each estimated glomerular filtration rate [eGFR] category of the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative classification[8]) or on dialysis in each study, and type and frequency of antithrombotic treatment (warfarin or other vitamin K antagonists, novel oral anticoagulants, aspirin, or other antiplatelet agents).

Data were pooled using random effects, according to the Mantel-Haenszel model, through Review Manager (RevMan), version 5.1 (The Nordic Cochrane Center, The Cochrane Collaboration, 2011, Copenhagen, Denmark). The measurement of treatment effect and AF, CKD, or dialysis exposure was performed using dichotomous adjusted hazard ratios (HR) and 95% confidence intervals (CI). Pairwise comparisons were performed for the primary end point in the settings defined in the third paragraph of the Methods section. Comparison of the treatment effect of adjusted-dose warfarin versus the novel oral anticoagulants was performed through the use of risk ratios (number of events or the incidence in each treatment group) from randomized controlled trials. Additional sensitivity analyses were performed, whenever data were available, regarding end-stage CKD on dialysis treatment. Statistical heterogeneity on each outcome of interest was assessed and quantified using the Cochran Q test and the I^2 statistic, respectively. The I^2 statistic describes the percentage of total variation across studies due to heterogeneity rather than chance. Values of <25%, 25% to 50%, and >50% are by convention classified low, moderate, and high degrees of heterogeneity, respectively. The presence of publication bias was evaluated through the use of funnel plots if the appropriate requisites concerning the minimum number of included studies in a forest plot were met (at least 10 studies).[9]

Results

Overall, 962 entries were retrieved for title and abstract analysis. Of these, 783 were excluded as they did not meet inclusion criteria for the meta-analysis and 106 were duplicate entries. The remaining 73 studies were carefully evaluated, and after full-text review, only 19 studies (all full-text reports) were finally considered eligible.[2,5,10–26] The stepwise selection process is illustrated in Figure 1. There was complete agreement between investigators on the inclusion of all the selected trials. Information on risk stratification, study design, number of participants, and the main findings in each study are provided in Table 1. Following the predefined inclusion and exclusion criteria, ≤5 studies were included in each of the traced forest plots. Accordingly, no funnel plots were drawn.

Of the selected studies, 10 provided information concerning the impact of CKD on the incidence of stroke or systemic embolism in patients with AF.[2,5,10,12,13,15,17,18,20,21] Different equations were used for estimating the eGFR and classifying patients as having CKD: Cockcroft-Gault formula was used in 5 studies[15,18,20,21,25] and the Modification of Diet in Renal Disease was used in 5.[2,10,12,23,25] Also, in 2 investigations[21,25] the chronic kidney disease epidemiology

Stroke or systemic embolism in patients with atrial fibrillation
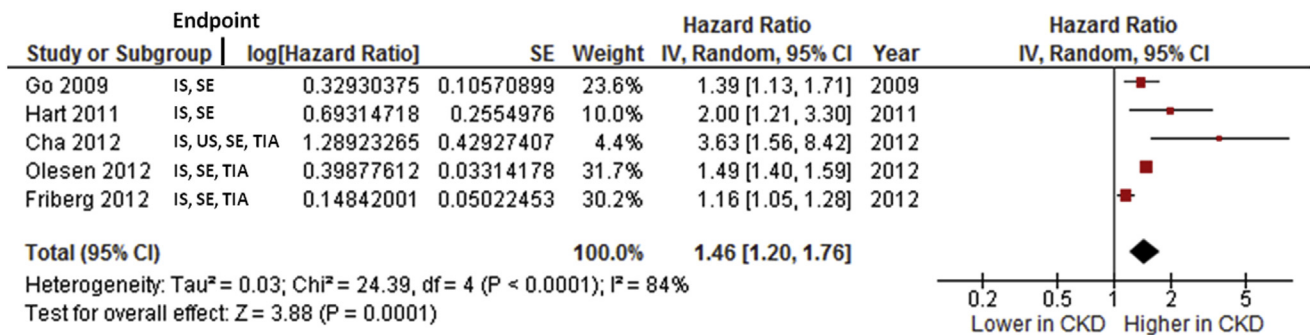

Figure 2. Forest plots illustrating the association of stroke or systemic embolism with the presence of kidney disease in patients with AF. IV = inverse variance; IS = ischemic stroke; SE = systemic embolism; TIA = transient ischemic attack; US = stroke of uncertain origin.

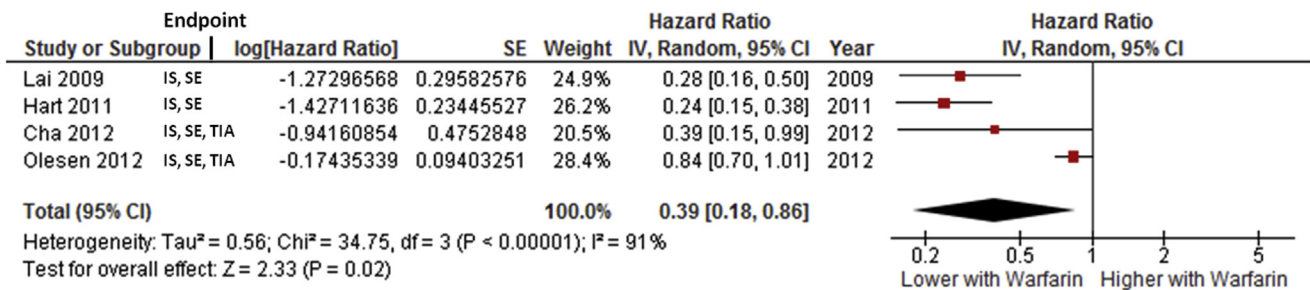## Stroke or systemic embolism in patients with atrial fibrillation and CKD

Figure 3. Forest plot illustrating the effect of anticoagulation on the incidence of stroke or systemic embolism in patients with AF and CKD. IV = inverse variance; IS = ischemic stroke; SE = systemic embolism; TIA = transient ischemic attack.

Stroke or systemic embolism in patients with atrial fibrillation and CKD
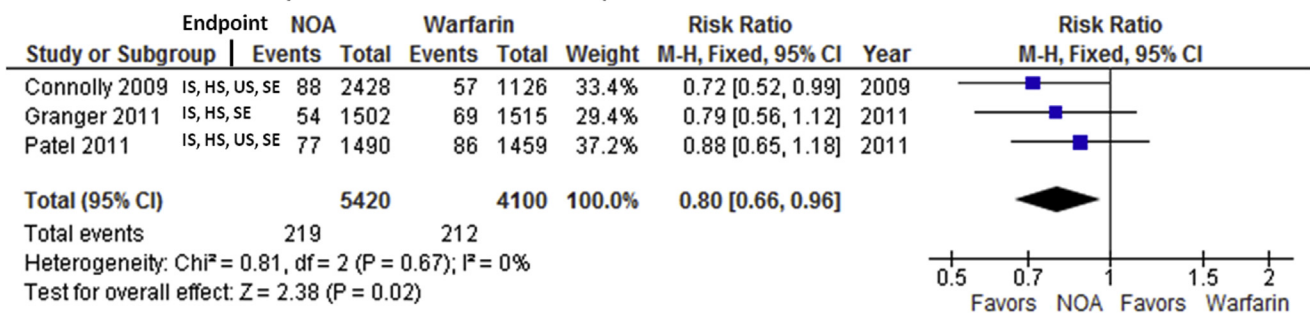

Figure 4. Forest plot illustrating the comparison of warfarin versus the novel oral anticoagulants in the prevention of stroke or systemic embolism in patients with CKD. HS = hemorrhagic stroke; IS = ischemic stroke; M-H = Mantel-Haenszel; NOA = novel oral anticoagulants; SE = systemic embolism; US = stroke of uncertain origin.

collaboration and cystatin C clearance were also used for assessing the safety and efficacy of apixaban and dabigatran at different levels of eGFR. The remaining selected studies for the systematic review did not use any of these, because the diagnosis of CKD was retrieved from codification.[5,13,14] A cutoff of 50 to 60 ml/min was used in most studies for defining the presence of CKD.

According to data on Figure 2, in patients with AF the presence of CKD was associated with a higher rate of thromboembolic events (HR 1.46, 95% CI 1.20 to 1.76, p = 0.0001). All included studies were in favor of the association of CKD with an increase in thromboembolism in

patients with AF. However, their high heterogeneity is shown by the I^2 statistic of $\geq$80%. Information concerning the risk of stroke or systemic embolism in patients with AF who were also on dialysis was provided by only 1 study: in the national Danish registry thromboembolism was found to be increased in this specific population (HR 1.83, 95% CI 1.56 to 2.14, p <0.00001).[5]

Baseline data, design, and the main findings of trials providing information regarding warfarin in this setting[5,15,17,18,20,21,23,25] are listed in Table 1. Information concerning time in therapeutic range is only known for the 3 included randomized controlled trials of the novel oral

anticoagulants controlled with warfarin (64% in Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY],[25] 55% in 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],[18] and 62% in Apixaban for Reduction In STroke and Other ThromboemboLic Events in atrial fibrillation [ARISTOTLE][21] trials). As regards the presence of heparin treatment in patients on dialysis, this information was absent or lacked details concerning the protocol used in the included studies.

The use of warfarin was associated with a major decrease in thromboembolic events (HR 0.39, 95% CI 0.18 to 0.86, p <0.00001) in patients with CKD. The effect was present in all studies but one (which revealed a strong trend for benefit of warfarin; Figure 3). Despite the overall favorable trend, a high heterogeneity, I^2 statistic of 91%, was observed driven by the differences in treatment effect. Only 1 study assessing the role of warfarin in the prevention of thromboembolism in patients on dialysis met the inclusion criteria for this meta-analysis. There, warfarin displayed a protective effect (HR 0.44, 95% CI 0.26 to 0.74, p = 0.002). Also, the use of warfarin did not lead to an increased risk of bleeding (HR 1.27, 95% CI 0.91 to 1.77, p = 0.15).[5]

In Table 1, data concerning renal function subanalysis of 4 randomized controlled trials involving the use of the novel oral anticoagulants in patients with AF are listed. In the Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial, aspirin was the treatment of the control arm, and in the others, the RE-LY, ROCKET-AF, and ARISTOTLE trials, warfarin was used. Data concerning the effectiveness of the novel oral anticoagulants versus warfarin and also versus aspirin in patients with CKD (moderate or preterminal CKD) and AF are shown in Figure 4. A very low level of heterogeneity was found among the 3 selected trials ($I^2 = 0$%) showing an overall benefit of the novel oral anticoagulants compared with warfarin (HR 0.80, 95% CI 0.66 to 0.96, p = 0.02). Apixaban was more effective than aspirin in preventing stroke or systemic embolism in the non−end-stage CKD population (HR 0.32, 95% CI 0.19 to 0.55, p <0.0001). In these novel oral anticoagulants trials, only a small minority of patients had eGFR <30 ml/min[15,21] and no patients on dialysis were included.

Discussion

The observed findings in this meta-analysis suggest an increased risk of thromboembolism when CKD is present in patients with AF, with an incremental relation between the severity of renal dysfunction and the risk of thromboembolism. Anticoagulation seems to be effective in decreasing thromboembolic events in non−end-stage CKD, with a particular benefit of novel oral anticoagulants in the moderate CKD population (eGFR 30 to 60 ml/min) with AF. Regarding end-stage CKD, data result from a single large national registry and seem in favor of benefit from warfarin. However, data on the novel oral anticoagulants in patients with end-stage or severe CKD with eGFR <25 to 30 ml/min are currently lacking.

Preliminary evidence has suggested that adding CKD to the currently available risk stratification schemes for thromboembolism in patients with AF may be worth further evaluation. In a subanalysis of the AVERROES trial, when adjusting for the CHADS$_2$ score in multivariate analysis, stage III CKD remained an independent predictor of stroke or systemic embolism (HR 1.6, p <0.01).[15]

Piccini et al have tested the impact of adding CKD to the CHADS$_2$ score and developed the R$_2$CHADS$_2$ score (CHADS$_2$ plus 2 points if creatinine clearance <60 ml/min). This was derived from the ROCKET-AF cohort and validated in the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study population. They found that, when using the R$_2$CHADS$_2$ score, almost 20% of patients were successfully reclassified into a more appropriate risk category (i.e., it improved the net reclassification index by 17.4% relative to CHADS$_2$; 95% CI 12.1% to 22.5%), even if C statistics displayed similar values (CHADS$_2$ = 0.673 vs R$_2$CHADS$_2$ = 0.672).[19]

A score comprising 8 variables (age, previous stroke, female gender, diabetes mellitus, heart failure, hypertension, proteinuria, and eGFR <45 ml/min or end-stage renal disease) has been recently derived using data from the ATRIA cohort. Its external validation has shown promising results with higher C statistics (0.70; 95% CI 0.67 to 0.72) than the CHADS$_2$ (0.66; 95% CI 0.64 to 0.69) or CHA$_2$DS$_2$-VASc (0.68; 95% CI 0.66 to 0.70) score for the discrimination of all thromboembolic events.[24] The discriminative performance of this score was even better if only severe thromboembolic events were considered (C statistic = 0.75; 95% CI 0.73 to 0.78), remaining better than CHADS$_2$ (C statistic = 0.71; 95% CI 0.68 to 0.73) and CHA$_2$DS$_2$-VASc (C statistic = 0.72; 95% CI 0.69 to 0.74) scores. When assessing the net reclassification improvement obtained by the use of the new score, it was verified that 24% to 25% of patients were correctly reclassified into an adequate risk category, compared with CHADS$_2$ and CHA$_2$DS$_2$-VASc scores, respectively (the percentage increased to 33% if only severe events were measured).

In contrast, different findings were observed by Roldan et al in a smaller population of patients with nonvalvular AF stable on oral anticoagulation for >6 months, where adding eGFR (1 point to eGFR 30 to 59 ml/min and 2 points to <30 ml/min) to the CHADS$_2$ and CHA$_2$DS$_2$-VASc scores resulted in no significant improvement in C statistics or integrated discrimination improvement.[10] In addition, Banerjee et al found that renal impairment and/or eGFR (codified as 3 different categories: <30, 30 to 59, and ≥60 ml/min) did not increase the risk of ischemic stroke or systemic thromboembolism after adjustment for the CHADS$_2$ risk factors. Thus, if added to CHADS$_2$ or CHA$_2$DS$_2$-VASc risk scores, eGFR did not independently add to the predictive value of any of these.[12]

The increased risk of thromboembolism when CKD is present may be explained by the coexistent platelet dysfunction, a prothrombotic and inflammatory state, and more severe vascular disease, frequently found in these patients.[2] It has also been proposed that the presence of CKD may be a marker of target organ lesion.[27] Furthermore, an association of low eGFR with an increased prevalence of markers of left atrial stasis (dense spontaneous echocardiographic contrast and low flow velocities in the left atrial appendage) in patients with AF

on transesophageal echocardiogram may also account for this thromboembolic trend.[28]

Oral anticoagulants were advantageous in the prevention of stroke or systemic embolism in patients with non—end-stage CKD. Among patients on dialysis, the only study assessing the efficacy of warfarin in the prevention of thromboembolism demonstrated a benefit of this drug.[5] Besides scarcity of data, the increased risk of hemorrhagic stroke in this population when treated with warfarin[29] may deter the practicing physician from starting anticoagulation.

The observed advantage of the novel oral anticoagulants in the eGFR 30 to 60 ml/min strata mimics the results observed in meta-analysis of the recent trials involving these agents,[30] suggesting that their advantage concerning efficacy is maintained despite the presence of moderate CKD. Also, according to data from the subanalysis of the AVERROES trial in the stage III CKD population, apixaban displays a higher efficacy compared with aspirin, with a similar bleeding risk.[15] However, only a minority of patients with eGFR 25 to 30 ml/min and none with lower eGFR values have been included in these trials, which does not allow any firm conclusions concerning the use of these agents in those specific types of patients.

There are several limitations to this investigation, which are in part inherent to the meta-analysis method: some of the selected studies were small and the majority was retrospective. Different methods for stroke definition have been used (e.g., with variable usage of imaging), and some uncertainties also remain concerning the chosen AF classification in some studies or even the reliability of its identification. Furthermore, a high heterogeneity of the assessed populations was illustrated by the relatively elevated I^2 score in most forest plots.

Disclosures

The authors have no conflicts of interest to disclose.

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