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Efficacy and safety of warfarin in dialysis patients with atrial fibrillation: a systematic review and meta-analysis

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ABSTRACT

Objective: To systematically review and meta-analyse the risk–benefit ratio of warfarin users compared with non-warfarin users in patients with atrial fibrillation (AF), who are undergoing dialysis.

Methods: We searched PubMed/MEDLINE, EMBASE, SCOPUS, Web of Science, Cochrane Library, grey literature, conference proceedings, trial registrations and also did handsearch. Cohort studies without language restrictions were included. Two investigators independently conducted a full abstraction of data, risk of bias and graded evidence. Effect estimates were pooled using random-effect models.

Main outcome measure: All-cause mortality, total stroke/thromboembolism and bleeding complications.

Results: 14 studies included 37 349 dialysis patients with AF, of whom 12 529 (33.5%) were warfarin users. For all-cause mortality: adjusted HR=0.99 (95% CI 0.89 to 1.10; p=0.825), unadjusted risk ratio (RR) =1.00 (95% CI 0.96 to 1.04; p=0.847). For stroke/thromboembolism: adjusted HR=1.06 (95% CI 0.82 to 1.36; p=0.676), unadjusted incidence rate ratio (IRR) =1.23 (95% CI 0.94 to 1.61; p=0.133). For ischaemic stroke/transient ischaemic attack, adjusted HR=0.91 (95% CI 0.57 to 1.45; p=0.698), unadjusted IRR=1.16 (95% CI 0.84 to 1.62; p=0.370). For haemorrhagic stroke, adjusted HR=1.60 (95% CI 0.91 to 2.81; p=0.100), unadjusted IRR=1.48 (95% CI 0.92 to 2.36; p=0.102). Major bleeding was increased among warfarin users; adjusted HR=1.35 (95% CI 1.11 to 1.64; p=0.003) and unadjusted IRR=1.22 (95% CI 1.07 to 1.40; p=0.003).

Conclusions: Among dialysis patients with AF, warfarin therapy was not associated with mortality and stroke/thromboembolism, but significantly increased the risk of major bleeding. More rigorous studies are essential to demonstrate the effect of warfarin for stroke prophylaxis in dialysis patients with AF.

KEY QUESTIONS

What is already known about this subject?

- Although several studies have described the role of warfarin in dialysis patients with atrial fibrillation, the clinical risk–benefit for stroke prevention has not been fully clarified. Meta-analyses of observational studies have shown that warfarin therapy had no effect for stroke prevention and mortality, but associated with a higher risk of bleeding in these patients. However, they had some major limitations such as quantification of the effect of bias from different types of adjustments across studies, limited interpretation by population heterogeneity, outcomes specification.

What does this study add?

- We comprehensively conducted an updated systematic review and meta-analysis on the risk–benefit of warfarin for stroke prevention, with a specific focus on the current controversy using the totality of the applicable evidences, especially when data from randomised controlled trials are not available to address an urgent issue requiring clinical decision-making. We have shown that warfarin therapy was not associated with mortality and stroke/thromboembolism but have significantly increased the risk of major bleeding.

How might this impact on clinical practice?

- Clinicians should be aware of the risks associated with warfarin use in these patients, and the clinical decision to prescribe warfarin should comprise an individualised approach that takes into account the risk of stroke and the haemorrhagic complications.

INTRODUCTION

End-stage renal disease (ESRD) and atrial fibrillation (AF) are common conditions that often coexist.[1 2] Normally, the prevalence of AF increases with age: 1–4% in the general population and >9% in patients 85 years and over.[3–5] It is substantially higher in the ESRD undergoing haemodialysis population, with a range of 4.5–27%.[6–10] Critically, AF is a potential risk factor for stroke and mortality, particularly in dialysis patients.[1 2 11] The risk of mortality and stroke are at 26.9 and 5.2/100 patient-years versus 13.4 and 1.9/100 patient-years compared with those without AF.[6]

To our knowledge, evidence exists that adjusted-dose warfarin was substantially more

efficacious than placebo and antiplatelet agents for stroke prevention in the general AF population.[12 13] It is well known that dialysis patients have higher risks of bleeding.[14–16] The rate of major bleeding when treated with warfarin raises 10-fold according to the Dialysis Outcomes and Practice Patterns Study.[17] Besides the risk of bleeding, some evidence suggests that warfarin might be associated with an increased risk of calciphylaxis[18 19] and accelerated vascular calcification in dialysis patients.[20–22]

Although several observational studies have described the role of warfarin in dialysis patients with AF, the clinical risk–benefit for stroke prevention has not been fully clarified.[9 23–35] Three meta-analyses of observational studies have shown that warfarin therapy had no effect for stroke prevention and mortality, but associated with a higher risk of bleeding in these patients.[36–38] The major limitations of the studies included: quantification of the effect of bias from different types of adjustments across studies, limited interpretation by population heterogeneity, outcomes specification and lack of recent published literature.

Availability of more robust evidence is crucial to develop guidelines for stroke prevention in these patients. To address this question, we used the totality of the most updated applicable evidences including more participants restricted to dialysis patients and performed comprehensive analyses using all possible and available techniques that lacked in previous meta-analysis studies to specifically focus on current controversy of the risk–benefit of warfarin for stroke prevention, especially when data from randomised controlled trials (RCTs) are not available to address an urgent issue requiring clinical decision-making.

METHODS

Search strategy

We searched the PubMed/MEDLINE, EMBASE, SCOPUS, Web of Science and the Cochrane Library for relevant studies without language restrictions, from inception to 17 January 2016. An extensive search strategy using the terms; *warfarin, oral anticoagulation, vitamin K antagonists, coumarins, coumadin, atrial fibrillation, atrial arrhythmias, end-stage renal disease, dialysis, haemodialysis* and *peritoneal dialysis* as keywords or text words or the MeSH terms. The search strategies used for the databases are available in eTable 1. The studies included were based on the PICOTS Framework (see eTable 2).

The Methods Guide for Effectiveness and Comparative Effectiveness Reviews, 2014 edition was used[39] and in accordance with the MOOSE guidelines for conducting and reporting of meta-analyses of observational studies (see eTable 3).[40]

The reference lists of the studies included, prior systemic reviews and electronic searches from ClinicalTrial.gov, Google Scholar and Jane (Journal/Author Name Estimator) were browsed for identification of additional studies. Relevant abstracts from 2002 to 2015 were searched from major nephrology scientific meetings (European Renal Association–European Dialysis and Transplant Association Congress, American Society of Nephrology; Kidney Week, Renal Week, International Society of Nephrology; World Congress of Nephrology, Annual Dialysis Conference, Annual Conference on Peritoneal Dialysis, International Symposium on Haemodialysis and Annual Symposium on Pediatric Dialysis).

Selection of studies

After deduplication, two investigators (SN and CR) independently reviewed titles and abstracts. Full articles were retrieved if a decision could not be made based on the abstracts. Disagreement regarding the inclusion of a study was resolved by discussion; if a consensus could not be reached, a third party (RA) served as the final arbiter.

Inclusion criteria

For inclusion in the study, the following criteria had to be met (see eTable 2): (1) prospective/retrospective cohort studies regarding AF in dialysis patients; (2) two or more groups of which one group was warfarin users; (3) containing data of mortality, stroke/thromboembolism and bleeding. Exclusion criteria were case–control studies, case series/case report, kidney transplantation patients and <90 days of follow-up. In studies with overlapping samples, data with the longest follow-up period, the most detailed information and/or the most relevant to our outcomes were included.

Data extraction

An extraction form was constructed. Elements abstracted included general trial and patient characteristics, stroke/bleeding risk score, risk of bias assessment and predefined outcomes. SN and CR independently extracted data using a standardised form and RA verified the accuracy. Any disagreement was resolved by RA Missing data or unclear information was sought by contacting the corresponding authors. When this was not possible and they were considered to introduce serious bias, a sensitivity analysis was conducted.

Risk of bias assessment

SN and CR independently assessed the risk of bias using the Newcastle–Ottawa Scale (NOS)[41] including selection of the exposed/unexposed cohort, comparability of the study group and the outcome assessment. Studies with a total score ≥8 were defined as the highest quality. Disagreements were resolved by RA if a consensus could not be reached.

Strength of evidence grading

The Grading of Recommended Assessment, Development and Evaluation (GRADE) system, was used to grade the strength of evidence (SOE) based on five key domains; study limitations, consistency, directness,

precision and reporting bias.[42] The ratings were classified to insufficient-quality, low-quality, moderate-quality or high-quality evidence. SN and CR independently assessed SOE domains for each outcome and resolved the differences by RA.

Outcome measures

The primary outcomes included all-cause mortality, stroke/thromboembolism, ischaemic stroke, haemorrhagic stroke and major bleeding.

Major bleeding was defined according to the International Society on Thrombosis and Haemostasis.[43] For reasons of clinical relevance, however, a definition by the investigators of each study and gastrointestinal events that required hospitalisation or related with death were considered as major bleeding (see eTable 4).

The secondary outcomes extracted were death from stroke, cardiovascular death, fatal bleeding and gastrointestinal bleeding. If the quality of warfarin control in terms of the international normalised ratio (INR) or percentage of time in the therapeutic range (TTR) were provided, we explored evidence for dose–response effects.

Statistical analysis

All statistical analyses were performed using STATA statistical software V.14.0 (StataCorp LP). For primary analysis, we restricted to trials published in full-text articles. Generally, incomplete reporting in abstracts limits the ability to describe the quality of trials and is therefore maybe of questionable value.[44]

To address biases from different types of adjustments across studies, statistical analyses for adjusted and unadjusted risks of outcomes were performed.[45] With survival data, log HR and its variance were calculated.[46 47] Incidence rate ratios (IRRs) were used when available.[48] For primary analysis, the results from multivariable models or propensity score analysis were applied. The overall HRs and IRRs were pooled by random-effect models.[49] For studies that reported results separately, the fixed-effects model was used to estimate risk before including the data in the overall analysis.

Homogeneity was assessed using the Cochran Q test, with $p<0.10$.[50] The degree of inconsistency was estimated by I^2 and the tau-squared (t^2) statistics. The I^2 value indicated low (<25%), moderate (25–75%) and high (>75%) heterogeneity,[50] while, the t^2 value indicated low (≤0.04), moderate (>0.04–<0.36) and high (≥0.36) heterogeneity.[51]

Publication bias was examined by a contour-enhanced funnel plot of each study's effect size against the precision (1/SE).[52] The Funnel plot was assessed by Begg's and Egger's test at $p<0.10$.[53 54] Furthermore, the trim and fill method was used to calibrate for publication bias.[55]

Preplanned subgroup analyses were conducted to investigate whether associations varied across the studies and the patients' key characteristics. Sensitivity analyses were performed restricted to the highest-quality study, adjustment for key determinants of stroke/bleeding risk scores, post hoc meta-analysis adding unpublished studies, the 'leave one out' approach and the analytical methods (multivariate analysis vs propensity score matching analysis). Robustness of findings was determined by consistency of pooled adjusted and unadjusted models using different parameters, that is, HR, RR, IRR. A random-effect univariate meta-regression was then performed to explore heterogeneity.

RESULTS

Search strategy and study characteristics

The literature search details are described in figure 1, Bonde *et al*,[26] 2014 was included instead of the Denmark cohort study by Olesen *et al*,[56] 2012 because it provided more detailed and update information. Thus, 14 full-text studies were identified through database search.[9 23–35] Studies of each analysis, measurement and definition of clinical endpoint are provided (see eTables 5 and 6). A total of 37 349 patients were involved, 12 529 (33.5%) were warfarin users and have mainly undergone haemodialysis (8 studies). The databases are described (see eTable 7), and the characteristics of the studies are summarised in table 1.

The participants' characteristics and medications used at baseline are shown. Thromboembolic and bleeding risk among comparators were similar (see eTables 8 and 9). Comparators were varied across studies including placebo, aspirin, clopidogrel, aspirin–clopidogrel, dabigatran or rivaroxaban. Notably, most of the studies did not provide INR/TTR (see eTable 10). The NOS results have shown high quality in most studies, ranging from 7 to 9 point (see eTable 11).

Outcomes

A meta-analysis can be pooled for seven outcomes: all-cause mortality, cardiovascular death, stroke/thromboembolism, ischaemic stroke, haemorrhagic stroke, major bleeding and gastrointestinal bleeding. A dose–response between INR/TTR and outcomes cannot be estimated due to limited data on warfarin monitoring. The summary of the outcomes and SOE are shown in table 2 and eTable 12.

Mortality outcomes

In the adjusted HR analysis (7 studies,[23–26 31 33 34] n=8477) and unadjusted analysis (8 studies,[24 25 28 31–35] n=15 797), there were no difference in the all-cause mortality between warfarin users or non-warfarin users. The adjusted HR and unadjusted RR were 0.99 (95% CI 0.89 to 1.10; p=0.825; figure 2A) and 1.00 (95% CI 0.96 to 1.04; p=0.847; figure 2B), respectively.

For cardiovascular death, the adjusted HR (4 studies,[24 26 31 33] n=7028) and unadjusted RR (5 studies,[24 28 31–33] n=14 116) were 0.94 (95% CI 0.84

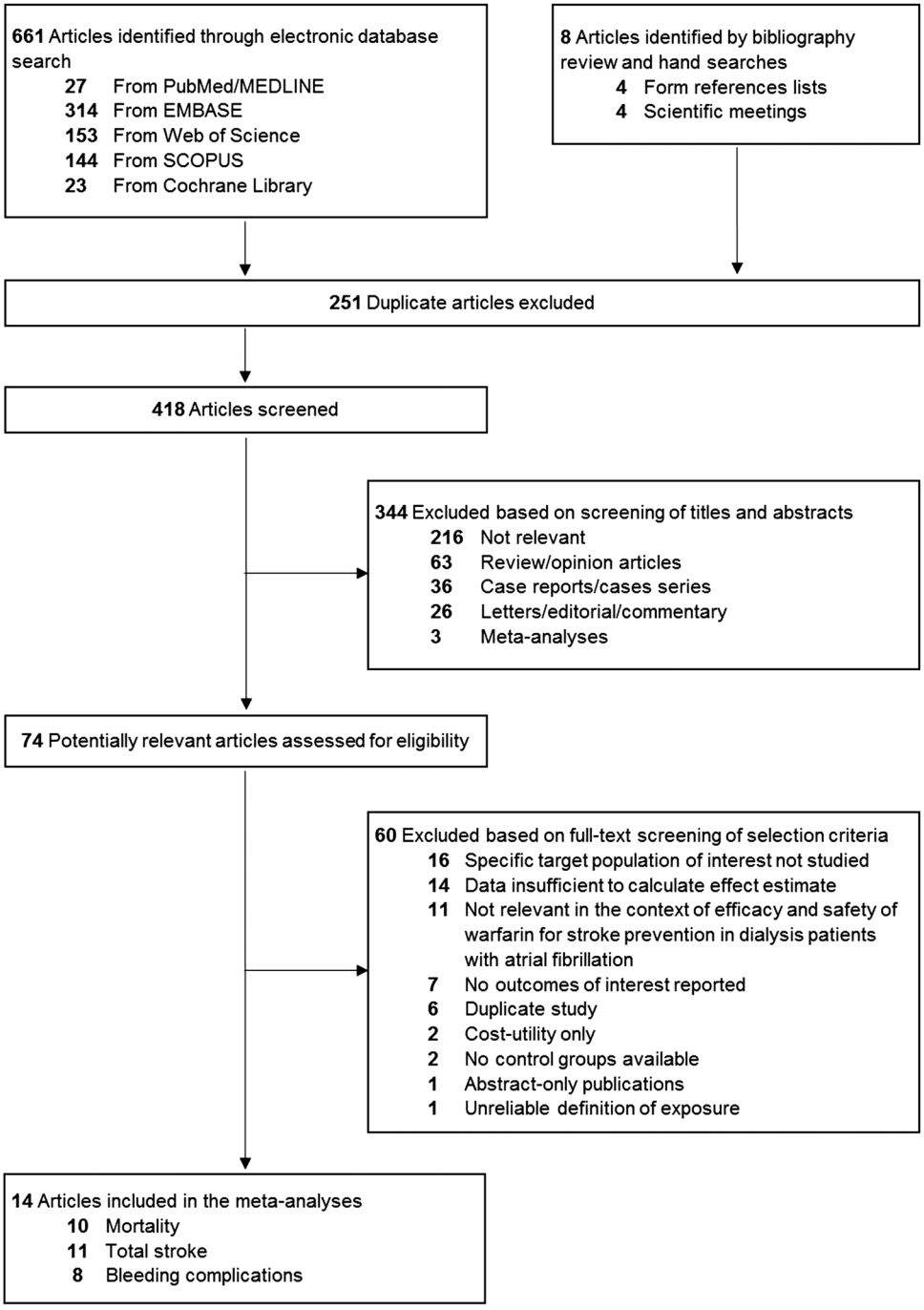

Figure 1 Flowchart of the literature review process.

to 1.06; p=0.347; see eFigure 1A) and 0.92 (95% CI 0.74 to 1.14; p=0.467; see eFigure 1B), respectively.

Stroke/thromboembolism outcomes

The adjusted HR (11 studies,[9 24 25 27–31 33–35] n=26 539) and unadjusted IRR (7 studies,[24 25 27–29 31 33] n=31 723) have shown no significant association of stroke/thromboembolism between warfarin users and non-warfarin users: HR=1.06 (95% CI 0.82 to 1.36; p=0.676; figure 3A), IRR=1.23 (95% CI 0.94 to 1.61; p=0.133; figure 3B).

For ischaemic stroke/TIA, adjusted HR (7 studies,[24 25 27 28 30 33 34] n=8584) and unadjusted IRR (7 studies,[24 25 27–29 31 33] n=31 723) between warfarin users and non-warfarin users were 0.91 (95% CI 0.57 to 1.45; p=0.698; see eFigure 2A) and 1.16 (95% CI 0.84 to 1.62; p=0.370; see eFigure 2B), respectively.

Similarly, no association of haemorrhagic stroke among warfarin users and non-warfarin users was found. The adjusted HR (5 studies,[24 25 29 33 34] n=21 262) and unadjusted IRR (5 studies,[24 25 29 31 33] n=30 037) were 1.60 (95% CI 0.91 to 2.81; p=0.100; see

Table 1 Characteristics of studies included in the meta-analysis

First author, Year	Study design	Country enrolment	Sample size	Age in years, Mean (SD)	Female, No (%)	Race; White/ Caucasian, No (%)	Dialysis modality	Data collection	Follow-up time
Abbott,[23] 2003	Retrospective	USA	123	NR	NR	NR	HD, PD	1996–2000	Mean 2.92±1.1 years
Chan,[24] 2009*	Retrospective	USA	1671 (1492 for PS-matched 1:1)	72.4 (10.3)	890 (59.7)	1206 (80.8)	HD	2003–2007	Mean 1.6 years, 2740 patient-years
Wizemann,[9] 2010	Prospective	International Collaboration	3245	≤65 (30.9%) 66–75 (35.0%) >75 (34.1%)	NR	NR	HD	DOPPS I; 1996–2001, DOPPS II; 2002–2004	4348 patient-years
Winkelmayer,[25] 2011*	Retrospective	USA	1185 for PS matched 1:4	69.4 (11.9)	1329 (57.5)	1498 (64.8)	HD, PD	1994–2006	2287patient-years
Bonde,[26] 2014	Retrospective	Denmark	1680	NR	NR	NR	HD, PD	1997–2010	NR
Shah,[27] 2014	Retrospective	Canada	1626	75.2 (8.3)	634 (39.0)	NR	HD, PD	1998–2007	NR
Wakasugi,[28] 2014	Prospective	Japan	60	68.1 (8.9)	21 (35.0)	0	HD	2008–2011	110 patient-years
Chan,[29] 2015	Prospective	USA. Columbia, and the Territory of Puerto Rico	14 607	70.2 (10.8)	5910 (40.5)	10 902 (74.6)	HD	2010–2014	7260 patient-years
Chan,[30] 2015	Retrospective	Hong Kong, China	271	70.4 (11.1)	109 (40.2)	0 (0.0)	PD	1997–2011	1.5 years
Genovesi,[31] 2015	Prospective	Italy	290	<65 (20.7%) 65–74 (25.9%) ≥75 (53.4%)	116 (40.0)	NR	HD	2010–2012	2 years
Mitsuma,[32] 2015	Retrospective	Japan	82	70.7 (9.6)	23 (28.0)	0 (0.0)	HD	2011–2015	Mean 3.0 years (423 patient; AF and non-AF)
Shen,[33] 2015	Retrospective	USA	12 284 (3658 for PS-matched 1:1)	61.7 (13.4)	6284 (51.2)	6082 (49.5)	HD	2007–2011	16 617 patient-years
Wang,[34] 2015	Retrospective	New Zealand	141	61.2 (11.3)	54 (38.3)	53 (37.6)	HD, PD	2000–2014	Mean 3.4±2.5 years
Yodogawa,[35] 2015	Retrospective	Japan	84	70 (10.4)	25 (29.8)	0 (0.0)	HD	2003–2012	Mean 3.9 years

First author, Year	Warfarin use defined as	Warfarin use, No. (%)	Comparison group	Stroke risk stratification	Bleeding risk stratification	Outcomes reported	Total NOS Score
Abbott,[23] 2003	Baseline use; day 60 of dialysis	NR	Non-warfarin users (non-specify)	NR	NR	All-cause mortality	7
Chan,[24] 2009*	Baseline use; any use in the first 90 days	746 (44.6)	Non-warfarin users (placebo/clopidogrel/ aspirin/clopidogrel +aspirin)	$CHADS_2$ score	NR	All-cause mortality, cardiovascular death, stroke/ TE, bleeding events	8

Continued

Table 1 Continued

First author, Year	Warfarin use defined as	Warfarin use, No. (%)	Comparison group	Stroke risk stratification	Bleeding risk stratification	Outcomes reported	Total NOS Score
Wizemann,[9] 2010	NR	509 (15.7)	Non-warfarin users (non-specify)	NR	NR	Stroke/TE	7
Winkelmayer,[25] 2011*	Baseline use; prescription within 30 days from index date	249 (10.8)	Non-warfarin users (non-specify)	NR	NR	All-cause mortality, stroke/TE, bleeding events	7
Bonde,[26] 2014	Baseline use	NR	Non-warfarin users (no antithrombotic)	CHA_2DS_2-VASc score	Modified HAS-BLED score†	All-cause mortality, cardiovascular death	8
Shah,[27] 2014	Baseline use; prescription within 30 days from index date	756 (46.5)	Non-warfarin users (non-specify)	$CHADS_2$ score	Modified HAS-BLED score‡	stroke/TE, bleeding events	8
Wakasugi,[28] 2014	Baseline use	28 (46.7)	Non-warfarin users (non-specify)	$CHADS_2$ score	NR	All-cause mortality, stroke/TE, bleeding events	7
Chan,[29] 2015	Baseline use	8064 (55.2)	Non-warfarin users (aspirin/dabigatran/rivaroxaban)	$CHADS_2$ score	Outpatient Bleeding Risk Index	stroke/TE, bleeding events	9
Chan,[30] 2015	Baseline use	67 (24.7)	Non-warfarin users (placebo/aspirin)	CHA_2DS_2-VASc score	HAS-BLED score	Stroke/thromboembolism	7
Genovesi,[31] 2015	Baseline use; prescription at recruitment or starting within 2 weeks following recruitment	156 (53.8)	Non-warfarin users (non-specify)	CHA_2DS_2-VASc score	Modified HAS-BLED score†	All-cause mortality, cardiovascular death, stroke/TE, bleeding events	8
Mitsuma,[32] 2015	Baseline use	27 (32.9)	Non-warfarin users (non-specify)	NR	NR	All-cause mortality, cardiovascular death	7
Shen,[33] 2015	Baseline use; prescription within 30 days from index date	1838 (15.0)	Non-warfarin users (non-specify)	$CHADS_2$ score	Modified HAS-BLED score†	All-cause mortality, cardiovascular death, stroke/TE, bleeding events	9
Wang,[34] 2015	Baseline use	59 (41.8)	Non-warfarin users (placebo/clopidogrel/aspirin)	$CHADS_2$/CHA_2DS_2-VASc score	HAS-BLED score	All-cause mortality, stroke/TE, bleeding events	7
Yodogawa,[35] 2015	Baseline use	30 (35.7)	Non-warfarin users (non-specify)	$CHADS_2$ score	NR	All-cause mortality, stroke/TE	7

*Data based on propensity score-matched.
†Modified HAS-BLED score for estimating the risk for bleeding (not included the score related to labile INR).
‡Modified HAS-BLED score for estimating the risk for bleeding (not included the score related to labile INR and alcohol intake).
AF, atrial fibrillation; HD, haemodialysis; INR, international normalised ratio; NOS, the Newcastle-Ottawa Scale; NR; not reported; PD, peritoneal dialysis; PS, propensity score; TE, thromboembolism.

Table 2 Summary of findings and strength of evidence from trials assessing warfarin therapy for atrial fibrillation patients undergoing dialysis

Outcomes	Studies, (n)	Participants, (n)	Effect estimate (95% CI)	p Value	Heterogeneity				Strength of evidence
					Q Statistic	p Value	I^2 Index (%)	τ^2	
Efficacy outcomes									
All-cause mortality	7[23–26 31 33 34]	8477	Adjusted HR 0.99 (0.89 to 1.10)	0.825	9.22	0.162	34.9	0.007	Low (no benefit)
	8[24 25 28 31–35]	15 797	Unadjusted RR 1.00 (0.96 to 1.04)	0.847	5.67	0.579	0.0	<0.001	
Cardiovascular death	4[24 26 30 31]	7028	Adjusted HR 0.94 (0.84 to 1.06)	0.347	1.46	0.691	0.0	<0.001	Low (no benefit)
	5[24 28 31–33]	14 116	Unadjusted RR 0.92 (0.74 to 1.14)	0.467	10.20	0.037	60.8	0.024	
Stroke/thromboembolism	11[9 24 25 27–31 33–35]	26 539	Adjusted HR 1.06 (0.82 to 1.36)	0.676	25.50	0.004	60.8	0.085	Low (no benefit)
	7[24 25 27–29 31 33]	31 723	Unadjusted IRR 1.23 (0.94 to 1.61)	0.133	26.67	<0.001	77.5	0.085	
Ischemic stroke/TIA (fatal or nonfatal)	7[24 25 27 28 30 33 34]	8584	Adjusted HR 0.91 (0.57 to 1.45)	0.698	23.55	0.001	74.5	0.260	Low (no benefit)
	7[24 25 27–29 31 33]	31 723	Unadjusted IRR 1.16 (0.84 to 1.62)	0.370	29.33	<0.001	79.5	0.136	
Safety outcomes									
Haemorrhagic stroke (fatal or nonfatal)	5[24 25 29 33 34]	21 262	Adjusted HR 1.60 (0.91 to 2.81)	0.100	11.26	0.024	64.5	0.231	Insufficient
	5[24 25 29 31 33]	30 037	Unadjusted IRR 1.48 (0.92 to 2.36)	0.102	12.85	0.012	68.9	0.165	
Major bleeding	7[24 25 27 29 31 33 34]	23 178	Adjusted HR 1.35 (1.11 to 1.64)	0.003	14.75	0.022	59.3	0.031	Low (harm)
	7[24 25 27–29 31 33]	31 723	Unadjusted IRR 1.22 (1.07 to 1.40)	0.003	12.39	0.054	51.6	0.013	
Gastrointestinal bleeding	2[25 33]	4843	Adjusted HR 1.10 (0.82 to 1.46)	0.527	1.47	0.225	32.0	0.014	Insufficient
	3[25 29 33]	28 076	Unadjusted IRR 1.10 (0.93 to 1.31)	0.273	5.78	0.056	65.4	0.014	

HR, hazard ratio; IRR, incidence rate ratio; RR, risk ratio; and TIA, transient ischemic attack.

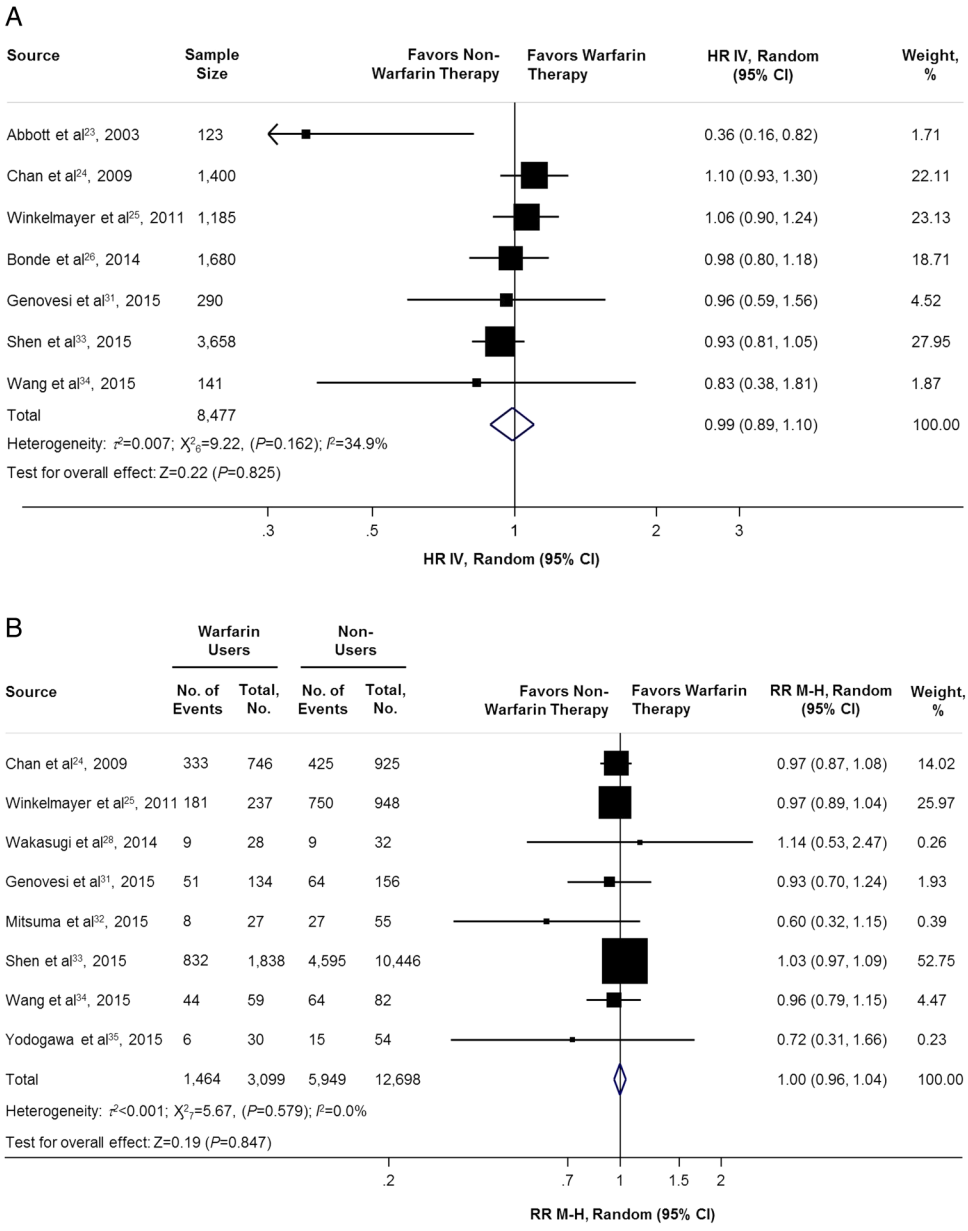

Figure 2 Adjusted and unadjusted of all-cause mortality comparing warfarin users versus non-warfarin users. HR IV, hazard ratio inverse variance method; RR M-H, risk ratio Mantel-Haenszel method.

eFigure 3A) and 1.48 (95% CI 0.92 to 2.36; p=0.102; see eFigure 3B), respectively.

Bleeding outcomes

Not surprisingly, warfarin therapy was associated with an increased risk of major bleeding for adjusted (7 studies,[24 25 27 29 31 33 34] n=23 178) and unadjusted (7 studies,[24 25 27–29 31 33] n=31 723) analyses. The adjusted HR and unadjusted IRR were 1.35 (95% CI 1.11 to 1.64; p=0.003; figure 4A) and 1.22 (95% CI 1.07 to 1.40; p=0.003; figure 4B), respectively.

However, there was no association in gastrointestinal bleeding among warfarin users and non-warfarin users. The adjusted HR (2 studies,[25 33] n=4843) and unadjusted IRR (3 studies,[25 29 33] n=28 076) were 1.10 (95% CI 0.82 to 1.46; p=0.527; see eFigure 4A) and 1.10 (95% CI 0.93 to 1.31; p=0.273; see eFigure 4B), respectively.

Subgroup analysis

When the data was pooled as unadjusted IRRs, study design and location were the significant sources of heterogeneity of stroke/thromboembolism, and haemorrhagic stroke. Additionally, sample size was also a source of heterogeneity of haemorrhagic stroke. However, subgroup analyses of all-cause mortality, cardiovascular death, and ischaemic stroke/TIA were similar to the primary results. Several preplanned subgroup analyses could not be performed because of limited statistical power, that is, $CHADS_2$/CHA_2DS_2VASc score, and

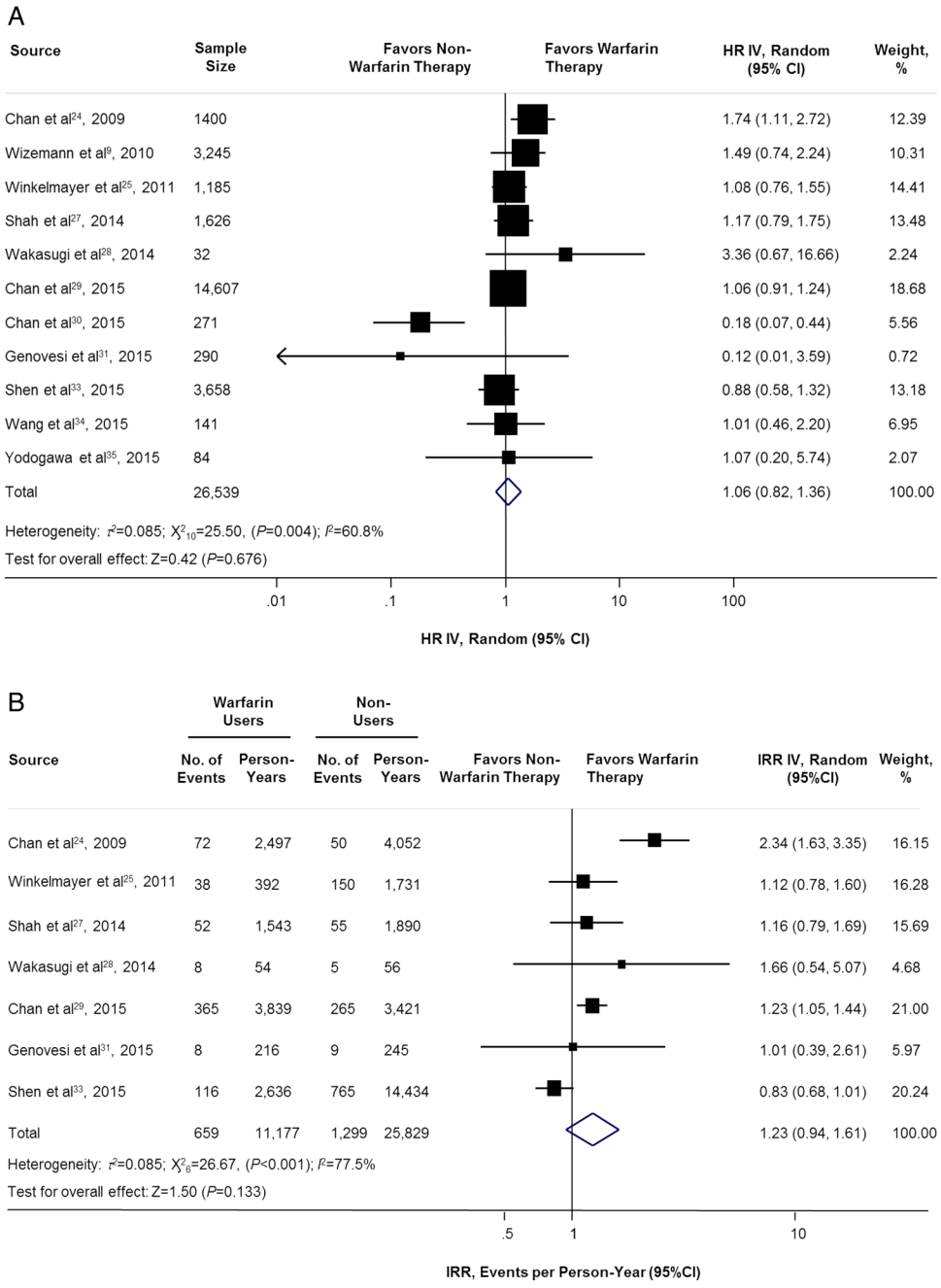

Figure 3 Adjusted and unadjusted of stroke/thromboembolism comparing warfarin users versus non-warfarin users. HR IV, hazard ratio inverse variance method; IRR IV, incidence rate ratio inverse variance method.

bleeding risk score such as the HAS-BLED score. Furthermore, clinically and statistically meaningful conditions that increase the risks of major bleeding were defined; warfarin used in haemodialysis patients; sample size; and the location of the study. Details are presented in eTable 13.

Sensitivity analysis

After restricting the analyses to the highest-quality study, stroke/bleeding risk score and adding an unpublished study, it illustrated that there was no effect on the main findings. Results are summarised (eTables 14–16). The 'leave one out' analyses were performed (eTable 17). All-cause mortality, ischaemic stroke/TIA, major bleeding and gastrointestinal bleeding appeared to be robust. However, after the removal of Shen *et al*,[33] warfarin reduced cardiovascular death (RR=0.79 (95% CI 0.68 to 0.91; p=0.001)) and increased stroke/thromboembolism (IRR 1.36 (95% CI 1.05 to 1.75; p=0.019)). Interestingly, after the removal of Chan *et al*[29] 2015 and Shen *et al*,[33] warfarin increased the risk of haemorrhagic stroke: HR=1.99 (95% CI 1.03 to 3.84; p=0.040), and IRR=1.63 (95% CI 1.25 to 2.11; p<0.001), respectively.

Finally, a multivariate analysis or propensity score matching approach did not affect the main findings, except for adjusted HR for major bleeding. The pooled

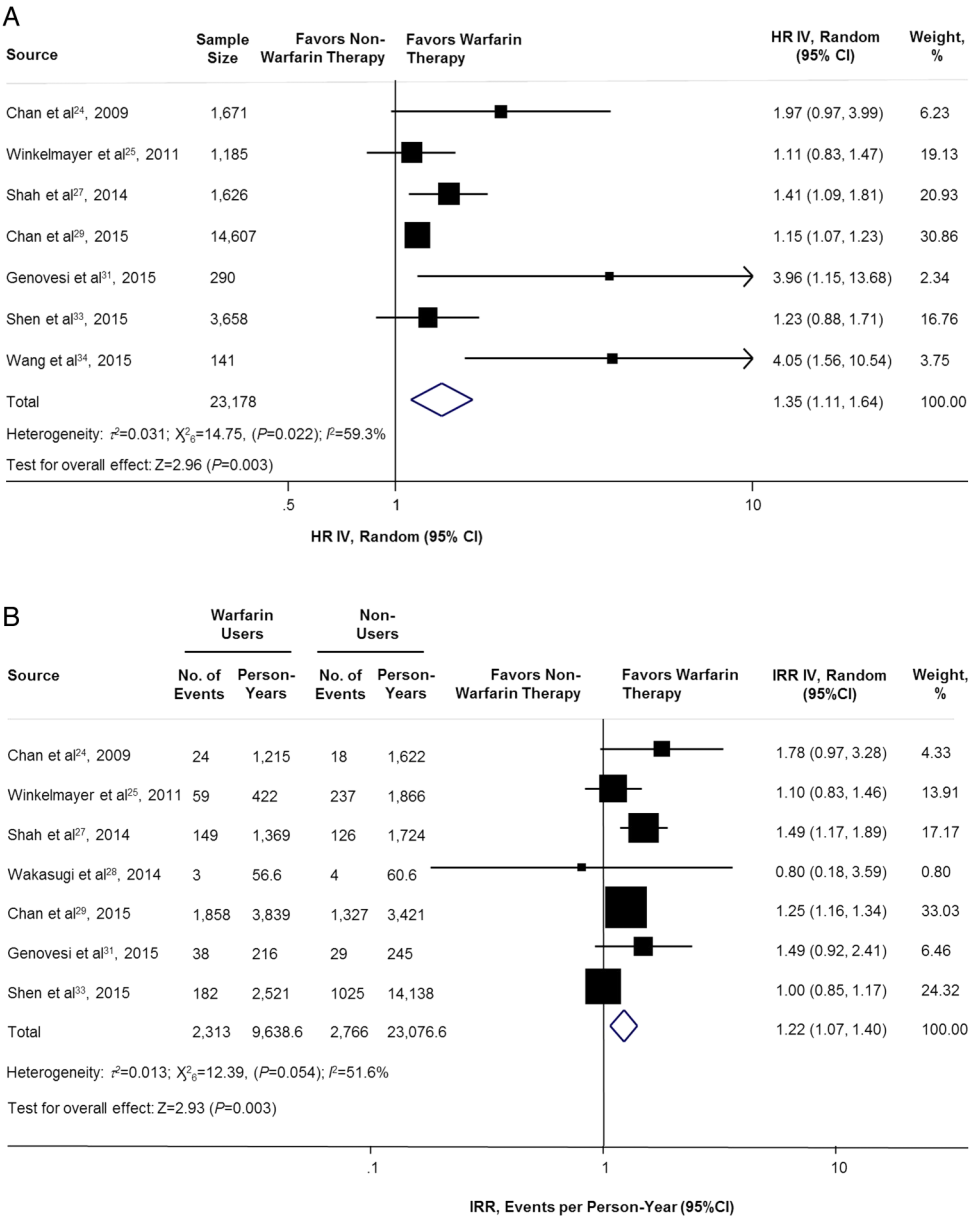

Figure 4 Adjusted and unadjusted of major bleeding comparing warfarin users versus non-warfarin users. HR IV, hazard ratio inverse variance method; IRR IV, incidence rate ratio inverse variance method.

estimated of major bleeding was no longer associated with warfarin therapy when using propensity score matching results (HR=1.16 (95% CI 0.93 to 1.44; p=0.181; eTable 18).

Meta-regression

Warfarin use was not associated with adjusted and unadjusted risk for all-cause mortality, cardiovascular death and ischaemic stroke. However, a history of hypertension was associated with an increased risk of stroke/thromboembolism; adjusted HR=1.09 per percentage of the difference (95% CI 1.00 to 1.18; p=0.048; see eFigure 5A). A history of hypertension and prior stroke/TIA were found to increase the risk of haemorrhagic stroke; adjusted HR=1.35 per percentage of the difference (95% CI 1.00 to 1.82; p=0.050; see eFigure 5B) and unadjusted IRR=1.20 per percentage of the difference (95% CI 1.01 to 1.42; p=0.042; see eFigure 5C), respectively. Moreover, a history of diabetes mellitus and prior stroke/TIA were a risk for unadjusted of major bleeding (IRR=1.05 (95% CI 1.00 to 1.11) per percentage of the difference; p=0.049; see eFigure 5D, IRR=1.06 (95% CI 1.01 to 1.12) per percentage of the difference; p=0.025; see eFigure 5E, respectively). eTable 19 shows the estimated effects.

Publication bias

There was no evidence of publication bias by Begg's or Egger's test, with the exception of unadjusted RR for all-cause mortality (p=0.030 for Egger's) and adjusted HR for major bleeding (p=0.035 and p=0.018 for Begg's and

Egger's, respectively). After calibration for publication bias by the trim and fill method, the results did not substantively alter the pooled effect estimate from the primary analysis (eTable 20). The contour-enhanced funnel plots are illustrated in eFigure 6.

DISCUSSION

This systematic review and meta-analysis had challenged the value of warfarin for stroke prevention in dialysis patients with AF. The main findings indicated that warfarin therapy does not mitigate the risk of death and total stroke, but is associated with a significant increased risk of major bleeding by 35%. According to the GRADE system, the SOE for the association was low or insufficient.

Evidence has shown that diminished kidney function is related to stroke associated with AF and may be characterised as an independent risk factor for stroke.[57 58] Nevertheless, the rigorous mechanism of the complex interrelationship among dialysis patients, AF and stroke are not well established. Despite the traditional risk factors, weak evidence suggests that warfarin might increase the risk of ischaemic stroke by accelerated vascular calcification in dialysis patients.[20–22] In this study, however, no association between warfarin and ischaemic stroke was shown.

On the other hand, there are several mechanisms regarding warfarin and the risk of bleeding in dialysis patients.[2 59] Moreover, the routine practice of dialysis requires systemic anticoagulation with heparin to prevent clotting that may increase the risk of further bleeding. More importantly, the risk of bleeding can be aggravated by the combination of antiplatelet therapy and comorbid illness. Notably, no apparent impact on all-cause mortality was found from the increased risk of major bleeding in this study. This may be due to indifference of haemorrhagic stroke and GI bleeding, which are the prognostic factors for mortality between warfarin users and non-warfarin users. Giving that the patients in our study were prescribed anticoagulants due to high thromboembolism risk and low bleeding risk, the lack of difference in mortality may demonstrate the efficacy of warfarin. The sensitivity analysis supported the fact that difference of major bleeding disappeared with the propensity matched results.

Generally, the benefit of warfarin for stroke prevention in AF needs to be outweighed against bleeding risks. As recommended by international guidelines, the $CHADS_2/CHA_2DS_2VASc$ score are frequently used for risk stratification of stroke and help to guide towards oral anticoagulation therapy.[60–62] They have been fully clarified and validated in the general AF population, but are still limited in dialysis patients, as well as bleeding risk.

Within the general AF population receiving warfarin, the incidence rate of stroke/thromboembolism was estimated to be 1.66% per year with an acceptable risk of major bleeding ranging from 1.40% to 3.40%.[63] A recent Chinese cohort,[64] reported an annual rate of major bleeding of 9.7% in non-warfarin users. The authors speculate that anticoagulation therapy may be suitable for patients with ESRD with AF who had $CHADS_2 \geq 4$ or $CHA_2DS_2VASc \geq 6$, based on data stating that the annual risk of ischaemic stroke was 9.9% and 10.0%, respectively. More evidence is needed to confirm these specific cut-off points.

Notably, beside the risks of bleeding, dialysis patients appear to present with atherothrombotic stroke rather than embolic stroke due to their high risk of developing atherosclerotic disease. Therefore, this situation could elucidate the reduced benefit of warfarin for stroke prevention in AF.

The prescribed warfarin in practice among dialysis patients with AF was highly variable in this review, ranging from 10.8% to 55.2%. This is not unexpected as there is a lack of a reliable protocol for anticoagulation decision-making in this special population. Regarding several international guidelines,[65–67] there is no further recommendation of warfarin use in dialysis patients with AF because of the indefinite risk–benefit. However, the 2014 guidelines from the American Heart Association, the American College of Cardiology Foundation and the Heart Rhythm Society[60] recommended warfarin use with a target INR of 2.0–3.0 for primary stroke prevention in high-risk patients ($CHADS_2/CHA_2DS_2VASc \geq 2$ points).

Our findings are consistent with the meta-analysis by Li *et al*,[36] Dahal *et al*,[37] and Liu *et al*[38] that warfarin therapy cannot prevent strokes in dialysis patients with AF, but associated with a higher risk of bleeding. Another meta-analysis conducted by Providência *et al*,[68] 2014 to evaluate efficacy and safety of warfarin in chronic kidney disease with nonvalvular AF demonstrated in a subgroup analysis of dialysis patients that warfarin exhibited a protective effect and did not increase risk of bleeding. However, only 1 study with dialysis patients by Olsen *et al*[56] was included, leading to inconclusive results. Indeed, it should be noted that there are key differences among the previous and the current study. First, this study explicitly identified the population that was limited to patients with AF, who are undergoing dialysis, while Li *et al*[36] and Liu *et al*[38] included studies in patients who underwent dialysis and kidney transplant, who had wide variation in their kidney function. Second, Li *et al*,[36] did not quantify the association between warfarin and mortality outcomes. All of the reviews did not discuss specific stroke risks (ischaemic/haemorrhagic stroke) due to limited data. Third, we performed more comprehensive analyses than the other studies to estimate the effects of adjusted and unadjusted models.

Strengths and limitations

The strength of this meta-analysis consisted of more expansive and up to date evidences, which reflect real-world practices, than previous studies. The analyses have

been driven by comprehensively reviewed and rigorous statistical approaches. Robustly, the main findings were consistent between pooled adjusted and unadjusted models. Furthermore, we also evaluated the SOE to further support guideline development.

There are several potential limitations inherent in our evidence that should be mentioned. First, the multifactors for stroke/bleeding risks, dialysis modality and imbalances in comorbidities are the major sources of bias. Using study level data rather than individual patient data (IPD) may limit analysis in certain groups of patients. Access to IPD would help to clarify these questions and provided more reliable evidence to balance risk–benefit of warfarin therapy for stroke prevention in dialysis patients.

Second, this study is observational in nature and mostly relies on medical claim data, which could be prone to information bias and might affect the association between warfarin therapy and the outcomes. The associations revealed could not be causative owing to residual confounding. Misclassification can be noticed due to a lack of a standardised protocol for AF diagnosis and detecting the outcomes. As warfarin prescription was taken at baseline or from a prescription claim database; adherence over time could not be ascertained. Although sophisticated analyses were performed, confounding by indication may not be totally excluded. In addition, it is expected that outcomes maybe underestimated because of reporting bias. To address all these bias, we conducted several sensitivity analyses and applied the GRADE system to define the certainty of the evidence.

Third, the difference due to studies and patients' characteristics appeared to be substantial sources for explaining such heterogeneity. We, therefore, performed random-effect models. However, unmeasured variables still cannot be ruled out.

Fourth, genetic factors, INR/TTR values, various types of comparator agents such as novel oral anticoagulants, and a subset of race/ethnicity cannot be indicated. In addition, comedication such as heparin used to prevent clotting during dialysis cannot be identified. Theoretically, heparin may have interaction with warfarin resulting in the decrease of warfarin effect or increase risk of bleeding. Thus, an interpretation needs to be performed with caution.

Last, publication bias was detected in the major bleeding outcome, which may be explained by the variation in the definition of bleeding. After calibration with trim-and-fill analysis, the direction of findings was unchanged. Moreover, either contour-enhanced plot or Begg's and Egger's test may be underpowered to detect the publication bias due to the small number of studies being analysed.

Implications and future research

Despite some inconsistence and limitations, our findings may have implications for clinical decision-making: (1) the routine use of warfarin for stroke prevention in dialysis patients may not be recommended due to a lack of benefit, particularly in patients with a history of previous life-threatening haemorrhage, high risk of bleeding or frail patients due to concerns related to dementia and due to risk of falls. However, for prior embolic stroke, known atrial thrombus or valvular/rheumatic heart disease, warfarin therapy may be reasonable for secondary stroke prevention with shared decision-making between patients and clinicians. If initiated, more frequent INR monitoring is required; (2) an alternative treatment or novel non-pharmacological approach, such as the left atrial occlude devices may be considered for lowering the risk of stroke in dialysis patients but this also requires further, well-controlled studies.

Critically, given the knowledge gaps in regard to the role of warfarin for stroke prevention in patients with AF undergoing dialysis observed in this review, there is an urgent need for future research focusing on: (1) The elucidation of the complex interrelationship between the pathophysiology and outcomes of stroke in these patients that might favour the expansion of effective strategies. (2) The risk scoring scheme of stroke/bleeding risk, to define and quantify those at risk. (3) Well-designed RCTs are needed to explore the risk–benefit of warfarin therapy in this special population; however, the possibility of such study may be limited by very small treatment effects size leading to very large number of sample sizes. From our data such a study may be powered for non-inferiority of warfarin versus non-anticoagulant treatment. Our suggestion is to develop the collaboration research networks for AF registries in patients undergoing dialysis using IPD to identify the risk–benefit of anticoagulant therapy, and obtain rich data to help guide an appropriate treatment approach. (4) Further studies should be comparison of warfarin versus pharmacological and non-pharmacological treatments such as dual antiplatelet therapy and other novel treatments.

CONCLUSIONS

This study has shown that warfarin therapy in patients with AF, who are undergoing dialysis, was not associated with mortality and stroke/thromboembolism, but significantly increased the risk of major bleeding. Until more data are obtained, clinicians should be aware of the risks associated with warfarin use in these patients, and the clinical decision to prescribe warfarin should comprise an individualised approach that takes into account the risk of stroke and the haemorrhagic complications. Indisputably, more rigorous studies are needed to settle the optimal preventive strategies and therapeutic modalities in these vulnerable populations.

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