

Efficacy of Oral Anticoagulants (Warfarin) in End-Stage Renal Disease Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis

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Abstract

Background: Warfarin stays a commonly used anticoagulant in the setting of End-Stage Renal Disease (ESRD) and Atrial Fibrillation (AF). Research has investigated the effectiveness of warfarin in preventing ischemic strokes in ESRD and AF. They found that no randomized clinical trials have tested the function of warfarin, and periodically performed meta-analyses provided irrelevant results. **Aim:** This work aims to determine the efficacy of oral anticoagulants (Warfarin) in End-Stage Renal Disease (ESRD) patients with Atrial Fibrillation (AF). **Materials and Methods:** A systematic search was performed over different medical databases to identify Internal Medicine studies, which studied the outcome of Patients receiving Warfarin versus Patients not receiving Warfarin of ESRD patients. Using the meta-analysis process, either with fixed or random-effects models, we conducted a meta-analysis on, the incidence of ischemic strokes, and incidence of hemorrhagic stroke (as primary outcomes), and incidence of major bleeding and mortality rate (as secondary outcomes). **Results:** Six studies were identified involving 48737 patients, 16255 patients receiving Warfarin, and 32482 patients not receiving Warfarin. The meta-analysis process revealed that all outcome measures (ischemic and hemorrhagic strokes, major bleeding, along with mortality rates), exhibited non-significant differences if Warfarin administered or not ($p > 0.05$ respectively). **Conclusion:** To conclude, Warfarin use appears to have been associated with no change in the incidence of ischemic stroke in patients with atrial fibrillation and end-stage renal disease. However, from the studies reviewed, it does appear to be associated with a significantly higher risk of hemorrhagic stroke, with no significant difference in the risk of major bleeding, and with no change in mortality.

Keywords: Oral anticoagulants; Warfarin; Atrial fibrillation; Dialysis

Introduction

Atrial fibrillation is the commonest cardiac form of arrhythmia and is related to a heightened hazard of ischemic stroke. In comparison with the general population, patients who acquire maintenance dialysis have a 6-fold higher hazard of atrial fibrillation, and a 5- to 10-fold higher hazard of ischemic stroke. This results from uremia-related cardiovascular risk factors for cerebral thrombosis that are highly prevalent in dialysis patients. Nonetheless, there is a paucity of evidence on strategies for stroke prevention between dialysis recipients with atrial fibrillation.^[1]

The prevalence of AF in adults with an ESRD is 11.6%, approximately 11-times higher than the prevalence of AF in the general person population. Between patients with ESRD and AF, the stroke incidence is 5.2/100 person-years and the mortality prevalence is 26.9/100 person-years. Those incidences are higher than stroke prevalence (1.9 per a hundred person-

years) and the prevalence of mortality (13.4 per 100 person-years) in patients with ESRD who do not have AF.^[2]

In general, warfarin use has been observed to be rather low in hemodialysis patients with AF. In a study of old hemodialysis sufferers with AF, only 1 quarter had a Warfarin prescription in a 45-day interval. 26% of American hemodialysis patients with AF were on warfarin therapy. They did not specify the indication for warfarin use (AF or other, e.g., vascular occlusion) or the level of anticoagulation achieved. Of 1671 patients who had preexisting AF and initiated hemodialysis with a big national

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How to Cite this Article: Al Al-Shaikh AF, et al. Efficacy of Oral Anticoagulants (Warfarin) in End-Stage Renal Disease Patients with Atrial Fibrillation: Systematic Review and Meta-analysis. Ann Med Health Sci Res. 2020;10 954-958.

dialysis provider 45% had been reported to have acquired warfarin at dialysis initiation.^[3]

Warfarin stays a commonly used anticoagulant in the setting of ESRD. Research has investigated the effectiveness of warfarin in preventing ischemic strokes in ESRD and AF. They found that no randomized clinical trials have tested the function of warfarin in ESRD and AF, and periodically performed meta-analyses provided irrelevant results. This inconsistency has even prevailed in the recommendations from various societies, where the American coronary heart association/American College of Cardiology guideline recommends anticoagulation in patients with ESRD and AF, the European Cardiovascular Society guideline emphasizes the lack of proof for such a recommendation, and the Kidney disease: improving worldwide Outcomes guideline recommends against the usage of warfarin in such conditions.^[4] This work aims to determine the efficacy of oral anticoagulants (Warfarin) in End-Stage Renal Disease (ESRD) patients with Atrial Fibrillation (AF).

Literature Review

Our review came following the (PRISMA) statement guidelines.^[5]

Study eligibility

The included studies should be in English, a journal published article, and a human study describing ESRD patients with AF patients. The excluded studies were non-English, or animal studies or describing ESRD patients, without AF, or not on dialysis program.

Study identification

Basic searching was done over the PubMed, Cochrane library, and Google scholar using the following keywords: Oral Anticoagulants, Warfarin, Atrial Fibrillation, and Dialysis.

Data extraction and synthesis

RCTs, clinical trials, and comparative studies, which studied

the outcome of Patients receiving Warfarin versus Patients not receiving Warfarin of ESRD patients with AF patients, will be reviewed. Outcome measures included the incidence of ischemic strokes, and the incidence of hemorrhagic stroke (as primary outcomes), and the incidence of major bleeding and mortality rate (as secondary outcomes).

Study selection

We found 244 records, 195 excluded based on title and abstract review; 49 articles are searched for eligibility by full-text review; 13 articles cannot be accessed; 10 studies were reviews and case reports; 11 were not describing our outcomes; the desired anticoagulant not administered in 9 studies leaving 6 studies that met all inclusion criteria.

Statistical methodology

The pooling of data, odds ratios (ORs), with 95% confidence intervals (CI) were done, using MedCalc ver. 18.11.3 (MedCalc, Belgium). According to heterogeneity across trials using the I²-statistics; a fixed-effects model or random-effects model were used in the meta-analysis process.

Results

The included studies published between 2011 and 2020. Regarding the type of included studies, all 6 studies were retrospective [Table 1]. Regarding patients' characteristics, the total number of patients in all the included studies was 48737 patients, 16255 patients receiving Warfarin and 32482 patients not receiving Warfarin, while their average follow-up time was (2.8 years), and mean age of all patients was (69.6 years) [Table 1].^[6-11]

A meta-analysis study was done on 6 studies that described and compared the 2 different groups of patients: with an overall number of patients (N=48737) [Table 2].^[6-11]

Table 1: Patients and study characteristics.

N	Author	Type of study	Total	Number of patients		Age (average years)	Follow-up time (average years)
				Patients receiving Warfarin	Patients not receiving Warfarin		
1	Winkelmayer et al. ^[6]	Retrospective	2313	249	2064	69	1.76
2	Shen et al. ^[7]	Retrospective	12284	1838	10446	61	-
3	Kai et al. ^[8]	Retrospective	4286	989	3297	68	2.1
4	Lee et al. ^[9]	Retrospective	2356	589	1767	70	2
5	Tan et al. ^[10]	Retrospective	5765	1651	4114	74	5
6	Makani et al. ^[11]	Retrospective	21733	10939	10794	75.5	3.4

Table 2: Summary of outcome measures in all studies.

N	Author	Primary outcomes				Secondary outcomes			
		Ischemic stroke		Hemorrhagic stroke		Major bleeding		Mortality	
		Warfarin	Control	Warfarin	Control	Warfarin	Control	Warfarin	Control
1	Winkelmayer et al. ^[6]	29	135	11	46	48	215	181	750
2	Shen et al. ^[7]	62	501	29	188	153	888	831	4596
3	Kai et al. ^[8]	67	304	2	45	126	368	495	1813
4	Lee et al. ^[9]	48	51	6	35	-	-	340	1050
5	Tan et al. ^[10]	93	644	-	-	407	1559	476	3349
6	Makani et al. ^[11]	1640	1720	98	78	1295	1512	613	133

Each outcome was measured by:

- **Odds Ratio (OR) for:**
 - a) Incidence of ischemic strokes.
 - b) Incidence of hemorrhagic strokes.
 - c) Incidence of major bleeding.
 - d) Mortality rate.

Concerning the primary outcome measures, we found 6 studies reported the incidence of ischemic strokes with a total number of patients (N=48737). I2 (inconsistency) was 96% with highly significant Q test for heterogeneity ($p < 0.0001$), so random-effects model was carried out; with overall OR=0.94 (95% CI 0.588 to 1.527).

Using the random-effects model, the meta-analysis process revealed a non-significant difference in the incidence of ischemic strokes in Patients receiving Warfarin compared to Patients not receiving Warfarin ($p=0.825$) [Figure 1]. We found 5 studies reported the incidence of hemorrhagic strokes with a total number of patients (N=42972).

I2 (inconsistency) was 75% with highly significant Q test for heterogeneity ($p=0.0025$), so random-effects model was carried out; with overall OR=0.88 (95% CI 0.522 to 1.493). Using the random-effects model, the meta-analysis process revealed a non-significant difference in the incidence of hemorrhagic strokes in Patients receiving Warfarin compared to Patients not receiving Warfarin ($p=0.642$) [Figure 2].

Concerning the secondary outcome measures, we found 5 studies reported the incidence of major bleeding with a total

number of patients (N=46381). I2 (inconsistency) was 95% with highly significant Q test for heterogeneity ($p < 0.0001$), so random-effects model was carried out; with overall OR=0.97 (95% CI 0.712 to 1.340). Using the random-effects model, the meta-analysis process revealed a non-significant difference in the incidence of major bleeding in Patients receiving Warfarin compared to Patients not receiving Warfarin ($p=0.886$) [Figure 3].

We found 6 studies reported mortality rates with a total number of patients (N=48737). I2 (inconsistency) was 99.6% with highly significant Q test for heterogeneity ($p < 0.0001$), so random-effects model was carried out; with overall OR=1.08 (95% CI 0.361 to 3.256). Using the random-effects model, the meta-analysis process revealed a non-significant difference in mortality rate in Patients receiving Warfarin compared to Patients not receiving Warfarin ($p=0.886$) [Figure 4].

Discussion

This work aims to determine the efficacy of oral anticoagulants (Warfarin) in End-Stage Renal Disease (ESRD) patients with Atrial Fibrillation (AF). The included studies published between 2011 and 2020. Regarding the type of included studies, all 6 studies were retrospective. Regarding patients' characteristics, the total number of patients in all the included studies was 48737 patients, 16255 patients receiving Warfarin, and 32482 patients not receiving Warfarin, while their average follow-up time was (2.8 years), and mean age of all patients was (69.6 years). A meta-analysis study was done on 6 studies that described and compared the 2 different groups of patients: with an overall number of patients (N=48737). Concerning the primary outcome measures, we found 6 studies reported the

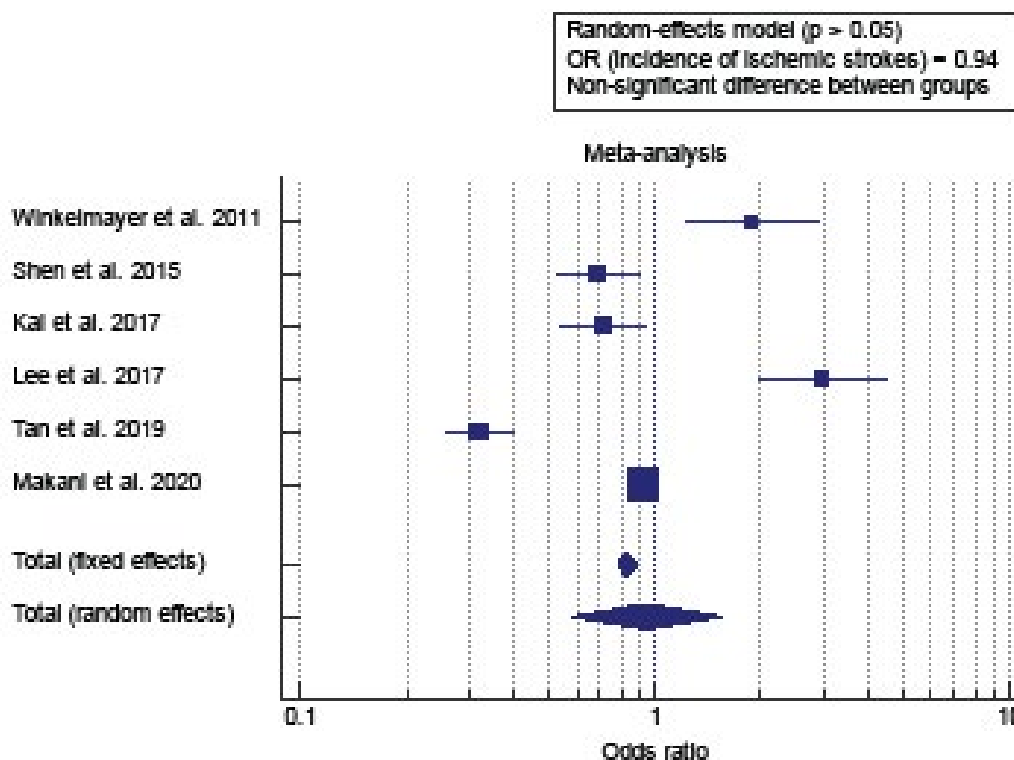


Figure 1: Forest plot for (Ischemic stroke incidence).

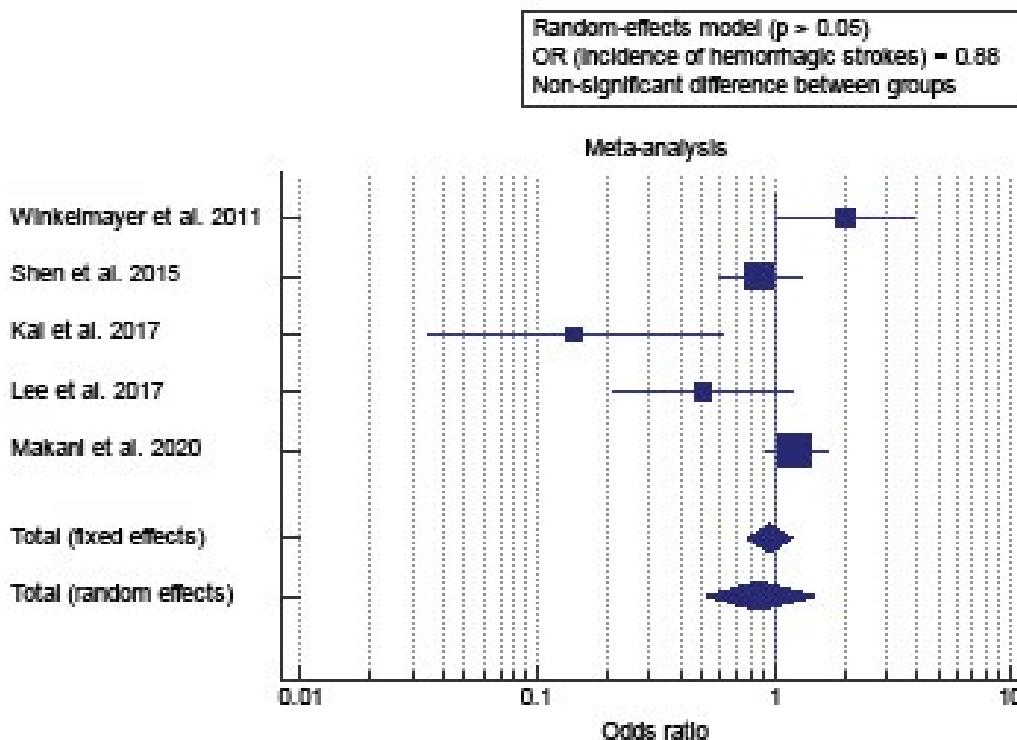


Figure 2: Forest plot demonstrating (Haemorrhagic stroke incidence).

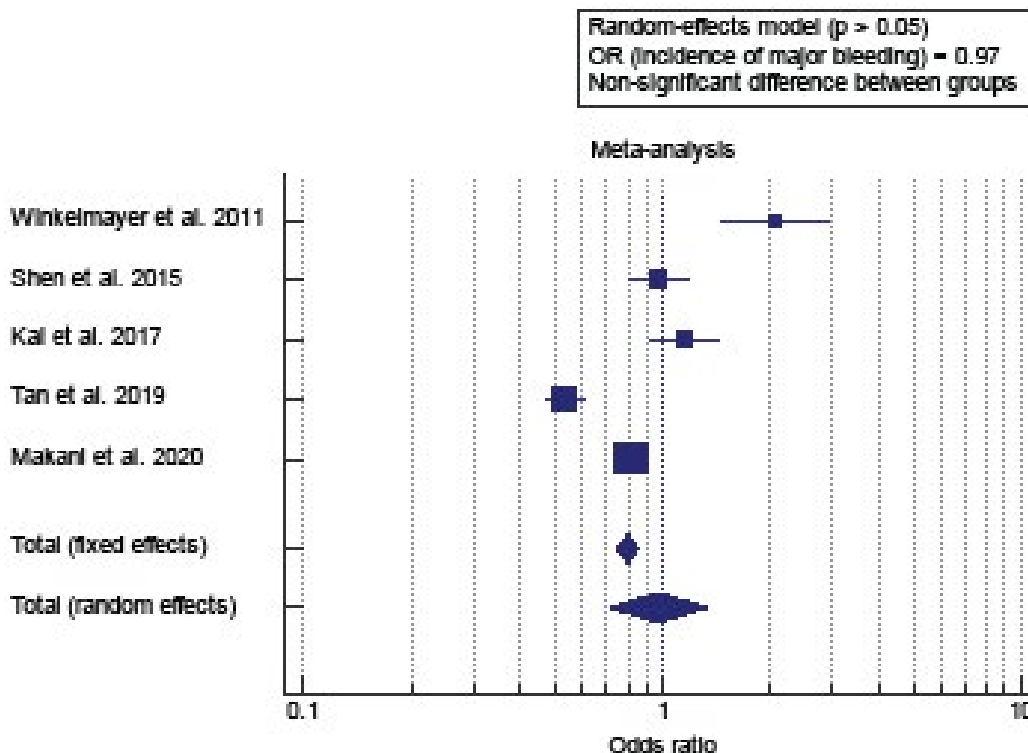


Figure 3: Forest plot for (Major bleeding incidence).

incidence of ischemic strokes with a total number of patients (N=48737).

The meta-analysis process revealed a non-significant difference in the incidence of ischemic strokes in patients receiving Warfarin compared to patients not receiving Warfarin ($p=0.825$). We found 5 studies reported the incidence of hemorrhagic strokes

with a total number of patients (N=42972). The meta-analysis process revealed a non-significant difference in the incidence of hemorrhagic strokes in Patients receiving Warfarin compared to Patients not receiving Warfarin ($p=0.642$), which came in agreement with Harel et al. [1] Randhawa et al. [4] Belley-Cote and Eikelboom [12] and Sarratt, Nesbit, and Moye. [13]

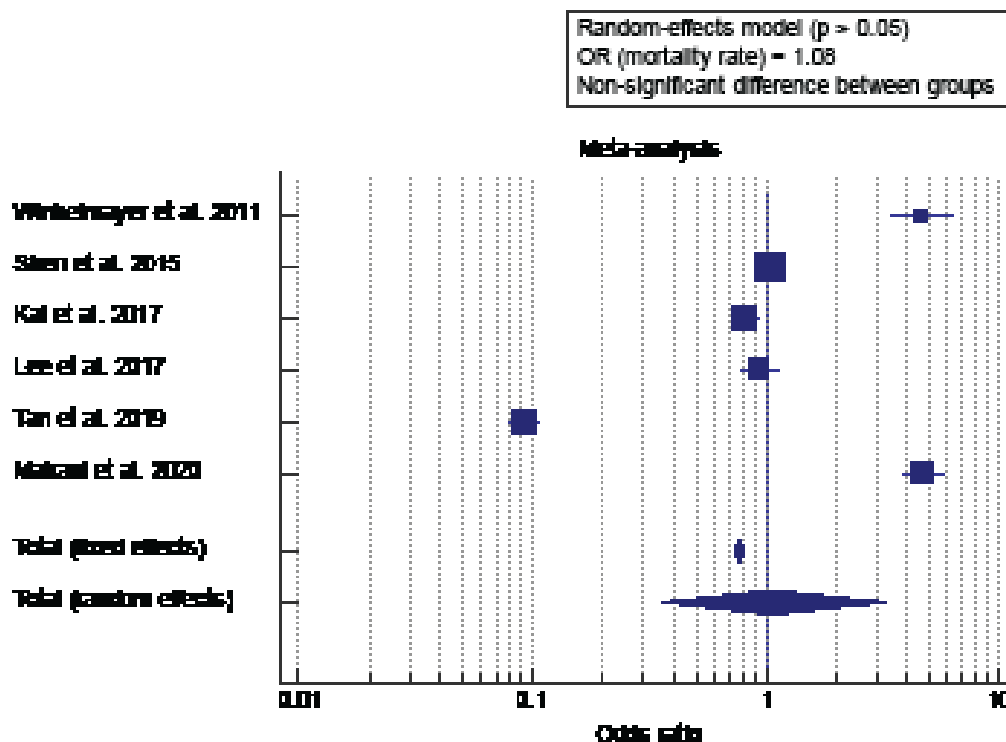


Figure 4: Forest plot for (Mortality rate).

Harel et al. reported that all research (n=20,398 members) mentioned at the outcome of ischemic stroke or systemic thromboembolism. Warfarin was not associated with ischemic stroke or thromboembolism (HR, 0.77). In four research comprised of 15,726 members, hemorrhagic stroke/intracranial hemorrhage was not associated with warfarin (HR, 1.93). In the three studies (n=14,693) that mentioned the outcome of gastrointestinal bleeding, warfarin was not associated with a higher risk of gastrointestinal bleeding.^[1]

Randhawa et al. reported that (22%) of patients were taking warfarin, with a mean (SD) follow-up period of 2.6 (1.4) years. Warfarin use was related to no great alternate for the hazard of ischemic stroke (HR, 0.96), with a significantly higher hazard of hemorrhagic stroke (HR, 1.49), with no significant difference in the hazard of major bleeding (HR, 1.20).^[4] Belley-Cote and Eikelboom reported that, the outcomes of an up to date meta-analysis of 15 observational research reporting the outcomes of 47 480 patients with atrial fibrillation (AF) and end-level renal disorder (ESRD) according to whether or not or not they have been treated with warfarin. Patients treated with warfarin (10 445 [22.0%]), compared with those not treated with warfarin, had similar rates of ischemic stroke (7.7% vs. 7.1%; risk ratio [HR], 0.96), major bleeding (16.1% vs. 15%; HR, 1.20).^[12]

Sarratt, Nesbit, and Moye reported that a total of 160 patients (warfarin group, n=120; apixaban group, n=40). There have been 7 major bleeding events in the warfarin group in comparison with 0 in the apixaban group (p=0.34). There had been similar rates of clinically relevant non major bleeding activities (12.5% vs. 5.8%, p=0.17) and minor bleeding (2.5% vs. 2.5%, p=0.74) events in patients receiving apixaban and warfarin.^[13]

Our result came in disagreement with Pilote.^[14] Pilote conducted a study on 1,626 dialysis patients and 204,210 non-dialysis patients. Amongst dialysis patients, 46% had been prescribed warfarin. Between dialysis patients, warfarin users had more congestive coronary heart failure and diabetes however much less prior bleeding event as compared to controls. Warfarin use was not associated with a decrease hazard for stroke (HR: 1.14) but became associated with a 44% higher risk for bleeding (HR: 1.44) after adjusting for potential confounders.^[14]

Concerning the secondary outcome measures, we found 5 studies reported the incidence of major bleeding with a total number of patients (N=46381). The meta-analysis process revealed a non-significant difference in mortality rate in Patients receiving Warfarin compared to Patients not receiving Warfarin (p=0.886), which came in agreement with Belley-Cote and Eikelboom,^[12] Randhawa et al.^[4] Wang et al.^[15] Winkelmayr et al.^[6] and Harel et al.^[1] Belley-Cote and Eikelboom reported that they believe that the net harm should discourage the warfarin use. Different sobering findings revealed that patients with ESRD have a high rates of major bleeding (about 15%), which, even in the absence of warfarin therapy, had been double those of ischemic stroke, and mortality rates of 40% to 50%.^[12]

Randhawa et al. 2020 reported that, among 29623 patients, 6090 patients (20.6%) who received Warfarin. The mortality rate was 43.4% for warfarin users and 52.5% for warfarin non-users, with an overall HR of 0.95. This recommends that overall mortality does not appear to be associated with anticoagulation for those patients.^[4]

Wang et al. reported that there have been 141 out of 774 (18.2%) dialysis patients with AF followed-up for 4.4 ± 2.5 years, and

41.8% (59) have been on warfarin. Incidence of all embolic events, ischemic stroke, and all bleeding and an intracranial bleed have been 4.1, 3.1, 9.6, and 0.82/100 person-years, respectively. Warfarin anticoagulation was associated with an increased hazard of intracranial bleed (hazard ratio=11.1, $p=0.038$), however not total embolic, bleeding events, or mortality during follow-up ($p=0.317-0.980$).^[15]

Harel et al. reported that, overall, 1490 citations met the search criteria. After excluding 279 duplicate citations, 1211 citations were evaluated, of which 32 were reviewed in detail. They subsequently excluded 17 research due to the fact they consisted of systematic or narrative reviews ($n=5$), did not contain information on our outcomes of interest ($n=4$), contained missing information that could not be obtained from the authors ($n=6$), or constituted case collection ($n=2$). All-cause mortality (reported in 7 studies; $n=16,172$) was not associated with receipt of warfarin (HR, 0.89; I²=79%).^[1] Our result came in disagreement with Shen et al.^[7]

Shen et al. reported that, in their study of a large cohort of patients on hemodialysis therapy with newly diagnosed AF, they observed that only 15% of patients initiated warfarin use within 30 days of the index AF event; only 11% of patients without an initially filled warfarin prescription initiated treatment among 30 days and 1, 12 months. Even though null in ITT analyses, in all as-treated analyses, warfarin use versus non-use showed a statistically significant trend toward decreased hazard of death. It is far possible that the reduced threat for all-cause mortality for warfarin users within the as-treated analyses is because of the drug lowering the hazard of other fatal thromboembolic events.^[7]

Conclusion

To conclude, Warfarin use appears to have been associated with no change in the incidence of ischemic stroke in patients with atrial fibrillation and end-stage renal disease. However, from the studies reviewed, it does appear to be associated with a significantly higher risk of hemorrhagic stroke, with no significant difference in the risk of major bleeding, and with no change in mortality.

Competing Interests

The authors declare that they have no competing interests. All the listed authors contributed significantly to the conception and design of study, acquisition, analysis, and interpretation of data and drafting of the manuscript, to justify authorship.

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