Heart, Lung and Circulation (2016) **25,** 243–249
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2015.08.012

ORIGINAL ARTICLE

Relationships between Anticoagulation, Risk Scores and Adverse Outcomes in Dialysis Patients with Atrial Fibrillation

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Received 7 June 2015; received in revised form 17 August 2015; accepted 20 August 2015; online published-ahead-of-print 25 September 2015

Background Atrial fibrillation (AF) is the commonest cardiac arrhythmia including in end-stage renal failure patients, but controversy remains whether these patients benefit from anticoagulation. We reviewed the characteristics, management and outcomes of end-stage renal failure patients on dialysis with AF.

Methods All patients started on dialysis at Middlemore Hospital between January 2000 and December 2008 who had AF were studied. Data regarding demographics, co-morbidities, renal disease, AF and embolic, bleeding and/or mortality events were recorded.

Results There were 141 out of 774(18.2%) dialysis patients with AF followed-up for 4.4+/-2.5 years, and 41.8%(59) were on warfarin. Incidence of all embolic events, ischaemic stroke, all bleeding and intracranial bleed were 4.1, 3.1, 9.6 and 0.82/100 person years respectively. Warfarin anticoagulation was associated with increased risk of intracranial bleed (hazards ratio=11.1, P=0.038), but not total embolic, bleeding events or mortality during follow-up (P=0.317-0.980). All three scores (CHADS2, CHA2DS2-VASc and HAS-BLED) could detect all embolic events (c=0.808-0.838), but not bleeding events (c=0.459-0.498).

Conclusions Anticoagulation with warfarin didn't significantly reduce embolism or mortality in dialysis patients with AF, but increased the risk of intracranial bleeds. Convention risk scores predict embolic but not bleeding events in these patients.

Keywords Atrial fibrillation • Dialysis • Chronic kidney failure • Warfarin • Stroke

Introduction

Atrial fibrillation (AF) is the commonest form of cardiac arrhythmia estimated at 1-2% in the general population in developed countries [1]. The prevalence is even higher in those with end-stage renal failure (ESRF) on dialysis at over 10-27% [2–5]. Anticoagulation is recommended for the prevention of ischaemic stroke in high-risk patients with AF [1,6,7]. The role of anticoagulation remains controversial for patients with ESRF and AF due to heterogeneous results from observational studies that suggest minimal if not harmful effects on both embolic and bleeding events and absence of randomised trials [5,8–14]. We reviewed the characteristics, management and outcomes of ESRF patients with AF on dialysis at our centre, with a focus on anticoagulation and risk scores.

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Material and Methods

All patients with end-stage renal disease who started dialysis during January 2000 to December 2008 were obtained from the Department of Renal Medicine database at Middlemore Hospital, Auckland, New Zealand. Those who had pre-existing AF or developed AF confirmed on electrocardiogram while on dialysis were retrospectively studied, with the start date of each patient being the first day they had AF and were on dialysis. The end date was the date of death, renal transplantation or June 30, 2014 whichever was the earliest. Baseline demographics, co-morbidities and characteristics of the end-stage renal disease recorded in the database were all recollected to ensure accuracy using standard definitions.

Atrial fibrillation was defined as paroxysmal or permanent as per international guidelines [1]. Demographic, renal, co-morbidities and treatment data were recorded. Anticoagulation regimens with or without aspirin and/or warfarin were recorded – no patients were on novel oral anticoagulants. We pre-specified the main comparative analyses to be between those anticoagulated with warfarin to those without, regardless of whether they were on aspirin. The embolic risk scores CHADS2 [15] and CHA2DS2-VASc [16] as well as bleeding risk score HAS-BLED [17] were calculated for all patients.

In terms of outcomes, embolic events encompasses ischaemic stroke (focal neurological deficit lasting >24 hours with radiological evidence on computed tomography or magnetic resonance imaging of the brain) and other arterial embolism. Bleeding events include intracranial bleed, gastrointestinal bleed, dialysis site bleed (fistula or catheter-related) and other (non-intracranial, gastrointestinal or dialysis site) bleed. Intracranial bleed required radiological confirmation, while gastrointestinal, dialysis site and other bleeds required having a blood transfusion to be counted.

Mean+/-standard deviation and percentage (frequency) were used to present continuous and categorical variables, and univariate analyses for these were performed with the Mann-Whitney U test and Fisher's exact test respectively. Variables with P<0.10 in univariate analyses were incorporated into multivariate models using logistic regression to calculate odds ratios (OR) or Cox proportional hazards regression used to calculate hazards ratios (HR) for cross-sectional and longitudinal outcomes respectively, with 95% confidence intervals (95%CI). Receiver-operative characteristics analysis was used to calculate the c-statistic (area under the curve) for the risk scores at detecting adverse outcomes. Statistical analyses were conducted with SPSS (Version 17.0, SPSS Inc., Chicago, IL, USA) and Prism (Version 5, GraphPad Software, San Diego, CA, USA), and P<0.05 deemed statistically significant. Ethical approval was obtained from our institution's research office prior to the commencement of the study.

Results

During January 2000 to December 2008, 774 end-stage renal disease patients were commenced on long-term dialysis at Middlemore Hospital, 141 (18.2%) of which had pre-existing or developed AF. Baseline characteristics are listed in Table 1. Mean age was 61.2+/-11.3 years and 38.3% (54) were female. Diabetes was the commonest pathology for end-stage renal failure at 44.7% (63). The majority of patients were on haemodialysis at 68.8% (97). Warfarin was used for anticoagulation in 41.8% (59), and compared to those not on warfarin was associated with lower prevalence of paroxysmal AF (45.8% vs 63.4%, P=0.041) and higher prevalence of hypertension (98.3% vs 89.0%, P=0.045).

Table 2 shows the characteristics and management of atrial fibrillation in our cohort. There were 75 (53.2%) with pre-existing AF and 66 (46.8%) who developed AF after starting dialysis. Paroxysmal AF was present in 56.0% (79) and less commonly in those who were on warfarin (45.8% vs 63.4%, P=0.041). Only 2.4% (4) of the cohort had clopidogrel for three to six months while on dialysis. Mean CHADS2, CHA2DS2-VASc and HAS-BLED scores were 2.4+/-1.2, 3.8+/-1.6 and 3.3+/-1.0 respectively. CHADS2 (2.6 vs 2.2, P=0.159) and CHA2DS2-VASc (3.9 vs 3.7, P=0.676) were not significantly higher in patients on warfarin. Beta-blocker was the most commonly used rate-control medication at 59.6% (84).

Rates of adverse outcomes during the mean follow-up period of 3.4+/-2.5 years are listed in Table 3. Incidence of ischaemic stroke and intracranial bleed were 10.6% (3.1/100 person years) and 2.8% (0.82/100 per years) respectively, and all embolic events and bleeding events were 13.8% (4.1/100 person years) and 32.6% (9.6/100 person years) respectively. The majority of patients died during the follow-up period at 76.6% (108). Patients on warfarin had a significantly higher incidence of intracranial bleed (6.8% vs 0.0%, P=0.029).

In multivariate analyses, permanent, rather than paroxysmal, AF was the only independent predictor of warfarin use (OR 2.07, 95%CI 1.02-4.21, P=0.044). Table 4 displays results of the multivariate analyses of outcomes. Warfarin anticoagulation was independently associated with intracranial bleed (HR 11.1, P=0.038) and other bleed (HR 3.26, P=0.028), but was not associated with change in all embolic events (HR 1.01, P=0.980), ischaemic stroke (HR 0.667, P=0.482), all bleeding events (HR 1.44, P=0.317) or mortality during follow-up (HR 0.825, P=0.631). History of cerebrovascular disease predicted all embolic events (HR 9.92, P<0.001), ischaemic stroke (HR 12.6, P<0.001) and mortality during follow-up (HR 1.95, P=0.007).

Results of the receiver-operative characteristics analyses are shown in Table 5. All three scores (CHADS2, CHA2DS2-VASc and HAS-BLED) were able to detect all embolic events (c=0.808-0.838), ischaemic stroke (c=0.825-0.880) and other arterial embolism (c=0.673-0.833). None of the scores could detect all bleeding events and individual bleeding outcomes, except that the HAS-BLED score detected dialysis site bleed (c=0.718). The CHA2DS2-VASc and HAS-BLED scores were also able to detect mortality during follow-up (c=0.638 and 0.627 respectively).