International Journal of Cardiology 262 (2018) 38–42

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Implant success and safety of left atrial appendage occlusion in end stage renal disease patients: Peri-procedural outcomes from an Italian dialysis population☆

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ARTICLE INFO

Article history:
Received 3 November 2017
Received in revised form 9 March 2018
Accepted 16 March 2018

Keywords:
Oral anticoagulant therapy
Left atrial appendage occlusion
Atrial fibrillation
Dialysis
Thromboembolism
Bleeding

ABSTRACT

Aims: To estimate the safety and the efficacy of the off label left atrial appendage (LAA) occlusion in chronic dialysis patients with atrial fibrillation (AF). In this preliminary paper, we report the design of the study and the data on peri-procedural complications.
Methods: This is a prospective cohort study. Primary endpoints are i) incidence of peri-procedural complications, ii) cumulative incidence of two-year thromboembolic events iii) cumulative incidence of two-year bleedings iiii) mortality at two years. Adverse events and death within 30 days of the procedure were recorded.
Results: Fifty patients who underwent LAA occlusion between May 2014 and September 2017 were recruited. Both the mean age of the sample study and the dialysis duration were high [71.8 (9.6) years and 59.4 (78.2) months, respectively]. Most patients (84%) were hypertensive and 62% suffered a previous major bleeding. About half of them presented cardiovascular diseases. CHA_2DS_2VASCs and HASBLED scores were 4.0 (1.5) and 4.4 (0.9), respectively. Most patients (88%) showed atrial dilatation and 44% left ventricular hypertrophy; 32% had left ventricular ejection fraction <50%. Fifty five percent of patients had permanent AF and 32% paroxysmal AF. All devices were implanted successfully. No deaths or major adverse events were reported during a 30-day follow-up. Three episodes of peri-procedural access site bleeding were reported, requiring no transfusion.
Conclusions: Our preliminary data suggest the feasibility and safety of LAA occlusion in patients undergoing dialysis. Only the follow-up of these patients over time can provide evidence that LAA occlusion is effective in preventing of thromboembolic events in this very high-risk population.

1. Introduction

Cardiology guidelines recommend oral anticoagulant therapy (OAT) with vitamin K antagonists (VKAs) or direct inhibitors of thrombin or activated factor X (DOACs) in patients with non-valvular atrial fibrillation (AF) and a thromboembolic score (CHA_2DS_2VASc score) >2 [1]. In some categories of patients, however, high haemorrhagic risk may render OAT prescription problematic. Left Atrial Appendage (LAA)

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcard.2018.03.083
0167-5273/

occlusion has been proven non-inferior to warfarin in preventing thromboembolic events in this clinical setting [2,3]. The randomized, controlled trials (RCTs) supporting the procedure, however, were performed in a population without a contraindication to OAT. Thus, current cardiology guidelines offer only a weak indication (IIb, B) for LAA occlusion as an alternative to OAT for those subjects with high risk of bleeding who, in real life, would mostly benefit from the procedure [1].

Patients with end stage renal disease (ESRD) undergoing dialysis therapy have high prevalence and incidence of AF [4,5], along with high haemorrhagic risk [6]. VKAs increase bleeding fourfold in haemodialysis patients with AF [7] and it has been shown that chronic kidney disease (CKD) is associated with more limited time in treatment range in patients on VKAs [8]. Besides, the use of VKAs in patients with renal failure is controversial, due to an increase in tissue calcification and enhanced atherosclerosis [9]. DOACs, which show a higher safety profile compared to VKAs in patients with mild to moderate CKD and AF [10], are unfortunately not recommended by cardiology guidelines in subjects with estimated glomerular filtration rate (eGFR) <30 ml/min; accordingly, in the RCTs that compared warfarin and DOACs, severe CKD was an exclusion criterion [1].

There is no evidence in the literature on the safety and efficacy of LAA occlusion in patients with ESRD. The purpose of our study was to follow prospectively a group of dialysis patients with AF who underwent off-label LAA occlusion to estimate the safety and the efficacy of the procedure in protecting against thromboembolic events. In this preliminary paper, we report the design of our study and the data on peri-and post-procedural complications of the procedure.

2. Methods/Design

This is an Italian, multi-institutional, prospective, non-blind, cohort study. Participation in the study does not involve the execution of any additional or different procedures from common clinical practice. All implanting physicians were highly skilled in the procedure, in order to minimize patient risk. The choice of the type of device used was left to implanting physicians, as was the choice of antithrombotic regimen following the procedure. Adverse events reported in this study include peri-procedural events and events occurring during a 30-day follow-up, since the aim of this phase of the study was to obtain data on peri-procedural success and complications. Follow-up is ongoing and will continue through 2 years after the device implant. The present study began in May 2014 and will conclude 2 years after the final allocation of patient enrolment. The study protocol adhered to the Helsinki Declaration for Ethical Treatment of Human Subjects, with local ethics committee approval. All subjects provided an informed consent.

2.1. Inclusion criteria

1. ESRD requiring replacement renal therapy (haemodialysis or peritoneal dialysis).
2. Documented AF (paroxysmal, persistent or permanent).
3. CHA_2DS_2VASc score ≥ 1 in men and ≥ 2 in women.
4. HAS-BLED score ≥ 3 or contra-indications for long-term anticoagulant treatment (e. g. previous life-threatening bleeding without a reversible cause).
5. Age >18 years.
6. Informed consent to participate in the study.

Moreover, in each patient an individual risk/benefit evaluation for OAT vs. LAA occlusion was performed jointly by the cardiologist and the nephrologist.

2.2. Outcomes

2.2.1. Primary outcomes

1. Incidence of peri-procedural complications.
2. Cumulative incidence of two-year thromboembolic events (first event).
3. Cumulative incidence of two-year bleeding events (first event).
4. Mortality at two years.

2.2.2. Secondary outcomes

1. Cumulative incidence of two-year bleeding events (all events occurring within two years)
2. Cumulative incidence of two-year thromboembolic events (all events occurring in two years)
3. Cumulative incidence of two-year cardiovascular events (acute coronary syndrome, myocardial infarction, cardiac failure, major arrhythmias).

All times will be calculated from the date of the procedure.

2.3. Sample size calculation

This study aimed at estimating fairly and accurately primary and secondary outcomes. Consecutive enrolment of eligible patients was requested to minimize selection bias. Sample size was determined in order to achieve the highest level of precision for primary outcomes within a clinically relevant timeframe. Assuming an incidence of peri-procedural complications less or equal to 7% [2] about 80 patients should be evaluated in order to reduce the margin of error (E, maximum value of the difference between upper limit of the 95% confidence interval and point estimate and the difference between point estimate and lower limit of the 95% confidence interval. E formula is: max[of (upper 95%CI - point estimate); (point estimate - lower 95%CI)]) for a 95% exact confidence interval below 10% with a probability >99.5%. Assuming no >10% of patients lost to follow-up in the first 2 years, and a cumulative distribution function (CIF) of the events with a constant incidence rate of 3.7 thromboembolic and 11.8 haemorrhagic events per 100 patient years [7], 5 thromboembolic events [2.5th – 97.5th percentile: 0.5–9.5 events] and 15 haemorrhagic events [2.5th – 97.5th percentile: 8.5–22 events] are expected to be collected in the first 2 years of follow-up. Therefore the E indices for the CIF curves at 2 years of follow-up will be respectively below 8% and 11% with a probability >97.5%. Assuming the same proportion of patients lost to follow-up in the first 2 years and a survival curve with a constant incidence rate of 23.8 events per 100 patients years [7], 27 deaths [2.5th – 97.5th percentile: 18.5–35 events] are expected to be collected in the first 2 years. Therefore the E index for the survival curve at 2 years of follow-up will be below 12% with a probability >97.5%.

2.4. Data collection and definitions

For all patients, data were collected regarding the cause of ESRD, dialysis duration, comorbidities, echocardiographic parameters and classification of AF type at the time of procedure.

All data were centrally managed through a single database (SG, GC and LP).

The following comorbidities were reported: arterial hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or whenever a patient received anti-hypertensive medications); diabetes mellitus; dyslipidemia (LDL cholesterol ≥130 mg/dl or whenever a patient received lipid lowering-agents); peripheral arterial disease; ischemic heart disease (previous hospitalization due to acute coronary syndrome and/or surgical or percutaneous coronary revascularization procedures); heart failure [presence of left ventricular dysfunction (left ventricular ejection fraction, LVEF <50% at ultrasound examination) and/or previous hospitalization due to acute or chronic heart failure], chronic obstructive pulmonary disease (COPD); systemic thromboembolism (imaging-proven); major bleeding [a fall in haemoglobin level of 2 g/dl or more or documented transfusion of at least 2 units of packed red blood cells, or an involvement of a critical anatomical site (intracranial, spinal, ocular, pericardial, articular, intramuscular with compartment syndrome, retroperitoneal) [11]].

The following echocardiography parameters were collected: presence of left ventricular hypertrophy, LVH (defined as a left indexed ventricular mass, LVMI > 115 g/m^2 in men and >95 g/m^2 in women), left ventricular dysfunction (left ventricular ejection fraction, LVEF < 50%), atrial dilation (anterior-posterior left atrial diameter > 40 mm and/or left atrial volume > 34 ml/m^2).

Different types of AF were defined in agreement with the European Society of Cardiology [1].

Paroxysmal AF was defined as a self-terminating episode, usually within 48 h but potentially persisting up to 7 days.

Persistent AF was defined as an AF episode that either lasted >7 days or required termination by cardioversion, either pharmacological or electrical.

Permanent AF was defined as AF lasting >7 days, combined with a joint decision by the patient and clinician to cease further attempts to restore and/or maintain sinus rhythm.

In all patients, the thromboembolic (CHA_2DS_2VASc) and haemorrhagic (HASBLED) scores were determined, to quantify patient-specific risk of thromboembolic and bleeding events [12].

Adverse events were recorded in terms of stroke, systemic thromboembolism, bleeding, pericardial effusion, displacement of the device, cardiac tamponade and death within 30 days of the procedure.

2.5. Statistical analyses

Statistical analysis will be performed on the enrolled patients satisfying all eligibility criteria. Exact methods will be used to estimate the 95%CI of the incidence of peri-procedural complications. The Kaplan–Meier method will be used for estimating the 95% confidence interval (CI) of survival times at 2 years, CIF curves and the median survival times. Adverse events will be tabulated using absolute and percentage frequencies. The Cox proportional hazards model will be used in an exploratory manner to identify risk factors. Baseline covariate distributions will be summarized using descriptive statistics (mean and standard deviation for continuous variables, and absolute and percentage frequencies for categorical variables).

An unplanned interim analysis was performed after 50 out of 80 (62.5%) consecutive eligible patients were enrolled to communicate robust although preliminary peri-procedural safety outcomes (i.e. within 30 days of the procedure).