Beyond Hypertension and Cardio-Renal Syndrome: The Need to Acknowledge and Incorporate Renal Disease in Cardiac Electrophysiology Trials

Luke J. Laffin^a Marion A. Hofmann-Bowman^b

^aDepartment of Medicine, Section of Cardiology, University of Chicago Medicine, Chicago, IL, USA;

^bDepartment of Medicine, Section of Cardiology, University of Michigan, Ann Arbor, MI, USA

Increasingly, but still insufficiently, cardiologists recognize the increased risk of death associated with comorbid conditions such as chronic kidney disease (CKD) and diabetes mellitus. While maintaining appropriate blood glucose levels and arresting the progression of renal disease are important treatment goals in these patients, a majority of patients are intensely affected by and die of cardiovascular (CV) disease.

In this issue of the *American Journal of Nephrology*, Airy and colleagues analyze health care records of over 62,000 patients with at least stage 3 CKD that were non-dialysis dependent. With a median follow-up of 4 years, the authors find that the presence of atrial fibrillation (in 6,639 patients, 10.6% of the cohort) was associated with a 23% higher risk of all-cause mortality and a 45% higher risk of CV mortality [1].

The above findings are important in that they confirm the findings of prior studies demonstrating the excess mortality that atrial fibrillation portends in CKD patients. Importantly, the study provides incremental novel findings by linking the Electronic Health Record-based CKD

registry at the Cleveland Clinic with the Ohio Department of Health mortality data. This provides specific information as to the cause of death grouped into (i) CV death, (ii) malignancy related death, and (iii) non-CV and non-malignancy-related death. Multivariable analysis showed atrial fibrillation to be associated with a significantly increased risk of mortality (adjusted HR 1.23, 95% CI 1.18–1.29) with 49% of all deaths due to CV diseases. Among CV causes of death, atrial fibrillation had an increased risk of death from heart failure (HR 1.58, 95% CI 1.25–1.98) compared to cerebrovascular disease (HR 1.31, 95% CI 1.06–1.61) and ischemic heart disease (HR 1.21, 95% CI 1.09–1.34). It is important to point out that the excess risk for CV mortality in CKD patients with atrial fibrillation was seen across the spectrum of CV diseases, and not just death from stroke/cerebrovascular disease.

A second interesting finding of this large single-center cohort study is that CKD stage 4 is an independent risk factor for atrial fibrillation and as such can be added to the list of validated risk factors for atrial fibrillation,

namely, age, diabetes, hypertension, male sex, African American race, coronary artery disease, congestive heart failure, and valvular heart disease.

However, this and other studies raise the following questions: Why do we observe this excess of CV mortality among patients with atrial fibrillation and CKD? Is atrial fibrillation a marker for more advanced CV disease? Are the metabolic and electrolyte abnormalities seen in CKD more pronounced or detrimental in those with atrial fibrillation? And finally, perhaps more provocatively, could the treatment paradigms commonly used to treat atrial fibrillation, that is, rate or rhythm control together with anticoagulation, be ineffective, or even detrimental, to those patients with CKD?

The answers to the first 2 questions are likely yes. Mechanistically, it is conceivable that cardiac fibrosis, left ventricular hypertrophy, ischemia, autonomic imbalance, and rapid fluid and electrolyte shifts commonly associated with kidney disease predispose patients to cardiac arrhythmia and myocardial dysfunction. However, for the third question, the answer is unknown. This is unknown, not only because the majority of clinical trials of atrial fibrillation management include a limited share of patients with renal disease but also because we often-times have no idea of the proportion of patients with CKD enrolled in these trials.

A prime example is the highly touted CASTLE-AF trial published earlier this year [2]. CASTLE-AF suggests that catheter ablation for symptomatic atrial fibrillation in patients with heart failure is superior to medical therapy with regard to the primary endpoint, which was the composite of all-cause mortality and unplanned hospitalization for worsening heart failure. Among this cohort with substantial proportions of hypertension, obesity, and diabetes, there is no mention of renal function in the manuscript or in the supplement. The only note in the trial's entry criteria is that patients on dialysis should not be enrolled. Perhaps future publications from this cohort will better delineate if any patients with CKD were enrolled, and if their outcomes differed from those seen in the population without renal disease. However, until then, we should not assume that CKD patients, at least the group with more advanced CKD, will behave similarly to those in the trial. Until we have more data on outcomes, catheter ablation for atrial fibrillation in CKD and ESRD patients should be reserved for very selected and individualized situations [3].

Unfortunately, early hallmark trials of atrial fibrillation management strategies similarly lack acknowledgement and comment on the proportion of participants

with CKD (Table 1). The 2 most prominent trials of rate versus rhythm control in atrial fibrillation are AFFIRM and RACE. Although AFFIRM made clear its exclusion of dialysis patients, neither trial reported baseline renal function nor did either report results stratified by degree of renal disease. The only significant prospective cohort analysis of CKD and atrial fibrillation, comparing a rate versus rhythm control strategy, was performed using the GUSTO-III data, a post-myocardial infarction population [4]. In all, 413 patients with atrial fibrillation and CKD were compared to 559 patients with atrial fibrillation and normal renal function. It was found that CKD did not significantly impact the relationship between rate controlling agents (beta blocker, calcium channel blocker, or digitalis) versus antiarrhythmic agents (primarily consisted of amiodarone, procainamide, and sotalol accounting for 80% of antiarrhythmic drug use) and 30-day and 1-year mortality outcome. However, confirmatory larger and prospectively randomized clinical trials are needed to address the role of the rate or rhythm controlling agents in patients with atrial fibrillation and CKD, since evidence from clinical trials on rate and rhythm control strategies in atrial fibrillation may not be generalizable to patients with impaired renal function.

The recent trials of direct oral anti-coagulants for thromboembolism prophylaxis in atrial fibrillation are far better with respect to their inclusion of patients with Stage 3 CKD, but again limited data exist among patients with more advanced renal disease (Table 1).

This shortage of robust randomized control trial data ultimately leads to heterogeneous practice patterns in patients with CKD and atrial fibrillation [5]. One must hope that future pivotal trials, such as the soon to be published Catheter Ablation vs. Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA, clinicaltrials.gov/NCT00911508), will at the very least include data regarding baseline renal function and the percentage of patients enrolled with CKD.

Looking beyond atrial fibrillation, lack of CKD acknowledgement and inclusion is seen in other seminal electrophysiology clinical trials of implantable cardioverter-defibrillators (ICDs) for primary prevention of sudden cardiac death and cardiac resynchronization therapy (Table 1.) The European Heart Rhythm Association published a comprehensive position statement on decision-making in patients with CKD and cardiac rhythm disturbances or implantable electrical devices in 2015 [3]. It provides guidance for this unique patient group but is limited due to the imperfect data available

Table 1. Selection of landmark electrophysiology randomized control trials and participant CKD information

Intervention	Trial name	Year	Baseline kidney function	Exclusion criteria	Percentage of patients enrolled with CKD
Rate vs. rhythm control in atrial fibrillation	AFFIRM	2002	Not reported	Dialysis dependence	Unknown
	RACE	2002	Not reported	Not stated	Unknown
	RACE-II (strict vs. lenient rate control)	2011	Not reported	Not stated	Unknown
Direct oral anticoagulants in atrial fibrillation	RE-LY (dabigatran)	2009	Not reported	CrCl <30 mL/min	CrCl <50 mL/min, 19% of total enrollment
	ARISTOTLE (apixiban)	2011	Not reported	Cr >2.5 mg/dL or CrCl <25 mL/min	CrCl <50 mL/min, 17% of total enrollment
	ROCKET AF (rivaroxaban)	2011	Mean CrCl of 67 mL/min, IQR 52–87	CrCl <30 mL/min	CrCl <50 mL/min, 21% of total enrollment
Catheter ablation for atrial fibrillation	CASTLE-AF	2018	Not reported	Dialysis dependence	Unknown
	CABANA	Likely 2018	Pending	Pending	Pending
ICD for primary prevention of SCD	DANISH	2016	Mean eGFR 73 mL/min/1.73 m ² , IQR of 58–92	Dialysis dependence	eGFR <73 mL/min/1.73 m ² , 49% of total enrollment
	SCD-HeFT	2005	Mean serum Cr of 1.1 mg/dL, IQR of 0.9–1.4	Cr >2.5 mg/dL	Unknown
Cardiac resynchronization therapy	CARE-HF	2005	Mean GFR of 60 mL/min/1.73 m ² , IQR of 46–73	Not stated	Unknown
	MADIT-CRT	2009	Mean serum Cr of 1.2 mg/dL	Cr >3.0 mg/dL	Unknown

CrCl, creatinine clearance; CKD, chronic kidney disease; IQR, interquartile range; eGFR, estimated glomerular filtration rate; Cr, creatinine; ICD, implantable cardioverter defibrillator; SCD, sudden cardiac death.

(predominantly registry cohorts and meta-analyses) in patients with CKD and cardiac rhythm disturbances.

A recently published observational study of 5,877 community-based patients with heart failure with reduced ejection fraction and CKD demonstrates that ICD placement was not significantly associated with improved survival but was associated with increased risk for subsequent hospitalization due to heart failure and all-cause hospitalization with mean follow-up of 3.1 years [6]. ICDs have known complications (ICD device infection,

worsening Tricuspid regurgitation from RV lead) that potentially may contribute to higher rates of hospitalization overall. A 2014 meta-analysis similarly demonstrated that among patients with an estimated glomerular filtration rate <60 mL/min/1.73 m², no survival benefit is seen with primary prevention ICDs [7]. These analyses are clear examples why certain electrophysiology interventions may not provide benefit, and in fact may be harmful, to patients with CKD. They also suggest that we must study this high-risk group more extensively. Specific data

on patient outcome and device performance of subcutaneous ICDs are awaited from the EFFORTLESS S-ICD registry, in which CKD was present in 9% of the patients implanted with subcutaneous ICD [8].

Rather than being discouraged by the apparent apathy toward CKD in certain cardiac electrophysiology clinical trials, this should be viewed as an opportunity for increased collaboration among CV and renal clinical trialists. What can begin with retrospective analyses of the pivotal atrial fibrillation trials, with an eye toward possi-

ble CKD subgroups, will hopefully result in future cardiac electrophysiology trials incorporating and reporting outcomes in patients with Stage 3 CKD or higher.

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