More Evidence on an Abominable Pairing
Atrial Fibrillation and Kidney Disease

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In the past 5 years we have experienced a surge in scientific activity related to exploring various aspects linking atrial fibrillation and kidney disease. Previously an understudied topic with available findings derived mostly from small and underpowered samples that were often of limited generalizability, important insights have now been made in large and mostly generalizable cohorts. First, these findings included the realization that the prevalence of atrial fibrillation increased monotonically with impaired kidney function, both and independently, with reduced estimated glomerular filtration rate (eGFR) and with increased urine albumin excretion.2 Patients with end-stage renal disease requiring dialysis had a particularly high prevalence of diagnosed atrial fibrillation exceeding 10%, with >17% of those older than 65 years of age being diagnosed with this most common of arrhythmias.2 Then, not surprisingly, it was also found that the incidence of atrial fibrillation increased with reduced kidney function, again with older patients initiating dialysis for end-stage renal disease in the United States having a particularly high incidence at 148 new cases diagnosed per 1000 person-years of observation.4 Outcomes in patients with atrial fibrillation and kidney disease were found to be particularly poor, with dialysis patients having been diagnosed with atrial fibrillation experiencing a 1-year mortality of almost 40%, twice the rate of otherwise similar patients without atrial fibrillation.2

A detailed and differentiated review of the issue of antithrombotic treatment in patients with kidney disease was recently provided by Capodanno and Angiolillo.6 The current issue of Circulation contains an interesting study by Bansal et al,7 who focused on one possible association between kidney disease and atrial fibrillation that had previously not garnered much attention. The investigators examined the alternative hypothesis whether, in patients with relatively advanced kidney disease, incident atrial fibrillation was associated with increased subsequent risk of faster kidney function decline compared with otherwise similar patients who were not diagnosed with atrial fibrillation. Thus, it was investigated whether the reverse of the previously shown association of existing kidney dysfunction with subsequent incidence of atrial fibrillation was also present, for a possible bidirectional relationship. Bansal’s study builds on the evidence already generated using the Niigata Preventive Medicine Study,8 in which Watanabe and et al described that patients with incident atrial fibrillation who had relatively preserved kidney function, indicated by an eGFR ≥60 mL/min/1.73 m2 and absence of dipstick-detectable proteinuria, developed more advanced kidney dysfunction at significantly higher rates: new atrial fibrillation was independently associated with a 80% higher adjusted rate of developing eGFR <60 mL/min/1.73 m2 (while also requiring a decline in eGFR of at least 10 mL/min/1.73 m2 above the normal age-related decrease over 10 years) and a 116% higher adjusted rate of developing any proteinuria that could be detected by urine dipstick testing.8

Bansal and colleagues extend this work from the Niigata Study to a large and, for the purpose of this research, mostly generalizable source of data, from a large, close-panel health maintenance organization in Northern California. The organizational features of this health care delivery system are important for their research in that it contains comprehensive data on (almost) all healthcare encounters by their members, of which laboratory measurements and diagnosis codes (electrocardiograms would be even better) are most relevant to this research. Reliable capture of their cohort-restricting feature, reduced eGFR (< 60 mL/min/1.73 m2) on ≥2 occasions, and study exposure, time-dependent presence of atrial fibrillation, were crucial elements and can be considered credibly ascertained. In contrast to Watanabe’s work, whose outcome focused on kidney function decline, the current study ascertained incident end-stage renal disease requiring initiation of dialysis or receipt of a kidney transplant as the main outcome of study, which can be considered a hard study end point, both of high relevance to patients, caregivers, and providers. The study is further strengthened by the reliable capture of a limited but relevant set of important comorbid
conditions, biometric parameters including blood pressure, serum hemoglobin, and dipstick proteinuria measurements, and use of several cardiovascular medications.

More than 206,000 individuals with eGFR < 60 mL/min/1.73 m² but without end-stage renal disease and free of previously diagnosed atrial fibrillation were identified and included in the cohort. The unadjusted analysis showed that person-time spent with atrial fibrillation was associated with a small but significant 18% increment in the rate of incident end-stage renal disease. However, adjustment for the measured potential confounders, some of which were time-dependent, yielded an almost 4-times larger estimate of association, suggesting that person-time spent after diagnosis of atrial fibrillation was associated with a 67% higher rate of end-stage renal disease when taking into account other relevant factors. Although this finding is qualitatively and quantitatively consistent with the study by Watanabe et al.⁸ (in which atrial fibrillation was associated with an increased incidence of the eGFR end point by 80% and the proteinuria end point by 116% in adjusted analyses), the strong confounding toward the null, removed by multivariable adjustment, is striking, unusual, and should require further consideration.

If an unadjusted estimate of an association toward higher risk among exposed individuals increases after multivariable adjustment, it usually means that exposed individuals were systematically healthier compared with unexposed individuals on some or all of the observed potential confounders of the association. This means that patients (or rather, person-time spent) with reduced eGFR and atrial fibrillation must have been healthier than patients (or person-time spent) without atrial fibrillation. This seems a bit counterintuitive given what we know about risk factors for atrial fibrillation, although we learn that younger age was associated with an increased risk of incident atrial fibrillation in the study cohort. (This may perhaps be an indication of informative censoring in that older patients with chronic kidney disease who are more likely to die have less opportunity to experience atrial fibrillation, death and, perhaps, outmigration from the health care system being competing risks.) In a cohort study with time-invariant exposure one can usually glean any differences between exposed and unexposed individuals from a typical table 1. Unfortunately, such information is not available in studies with time-varying exposure, as is the case here. It would have been useful, however, to provide additional estimates of the association from models that included only single or more restricted sets of potential confounders to understand which factors (jointly) drove this relatively large underestimation of the association in unadjusted comparison.

What are the possible explanations for this increased incidence of end-stage renal disease in patients with reduced eGFR who developed atrial fibrillation? Residual confounding is certainly a possibility, as acknowledged by the authors, but given the direction of the confounding by already observed characteristics, it does not seem that one needs to be concerned about missing information on severity of comorbidities whose presence was only ascertained. One possible candidate, however, is rate of decline of kidney function, which has evolved as an independent risk factor for a number of cardiovascular outcomes, independent of the level of eGFR.⁹,¹⁰ It is conceivable that patients with faster declines in their kidney function experience a higher risk of developing atrial fibrillation, and that atrial fibrillation actually does not contribute to their already hastened eGFR trajectory toward end-stage renal disease.

Assuming that atrial fibrillation is in fact a cause of accelerated kidney function decline and increased risk of end-stage renal disease, a number of potential causative factors or mechanisms come to mind and warrant further investigation, including systemic inflammation, profibrotic, and hemodynamic factors. The latter is supported by an interesting observation of improved kidney function in patients whose atrial fibrillation was ablated successfully, compared with patients whose arrhythmia persisted after such intervention.¹¹ Finally, medications required to manage atrial fibrillation remain possible sources for accelerated kidney function decline. Specifically, warfarin has been shown to contribute to structural kidney damage and kidney function impairment, especially in patients with already reduced eGFR and those with high achieved international normalized ratios.¹² Bansal and colleagues provide no information on the use of oral anticoagulation in the study patients with atrial fibrillation or on its association with incident end-stage renal disease. Further investigation regarding the renal safety of oral anticoagulation, especially in patients at high renal risk, is warranted.

In their conclusion, Bansal and coworkers suggest that more evidence is needed to understand the possible causes (if causal) of accelerated kidney function decline in patients with (new) atrial fibrillation. Although I do not disagree, the entirety of the available evidence seems to suggest strongly that we need to prevent atrial fibrillation from occurring in the first place in patients with kidney disease, as the optimal management is ill defined and the outcomes are abysmal. Primary prevention is where, in my opinion, the lever should be anchored. The totality of the growing evidence indicates clearly that we need to prioritize efforts toward identifying ways to dissociate the abominable bidirectional relationship between kidney disease and atrial fibrillation.

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References


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