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EDITORIAL COMMENT

# Learning From Trials

## Time to Look More Closely at the Kidneys in ATTR Amyloidosis?*

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Systemic transthyretin amyloidosis (ATTR) is an emerging cause of cardiomyopathy and heart failure, particularly in elderly people. Validation of noninvasive diagnostic approaches coupled with the unrelenting development of targeted therapies has recently revolutionized the management of this disease, improving early recognition and translating into improved outcomes.[1] Although cardiologists may only seldom encounter patients affected by the dominantly inherited form of ATTR, wild-type transthyretin amyloidosis (ATTR-wt) cardiomyopathy is no longer considered a rare disease, particularly in men over 80 years of age.[2] Treatment of ATTR presently exploits 2 potentially complementary therapeutic strategies: stabilization of the transthyretin (TTR) quaternary structure by small-molecule ligands such as tafamidis and reduction of circulating TTR concentrations by means of RNA-based gene-silencing drugs. Importantly, both these disease-modifying approaches have been originally validated in patients with hereditary transthyretin amyloidosis (ATTRv) according to neurologic outcome measures.[3,4]

Tafamidis is the first drug investigated in ATTR-ACT (ATTR cardiomyopathy. In the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial), treatment with tafamidis significantly reduced all-cause mortality and cardiovascular-related hospitalizations compared with placebo over 30 months, further corroborating tetramer stabilization as a key therapeutic target.[4] Presently, tafamidis is the only approved therapy for ATTR-wt cardiomyopathy and for patients with ATTRv cardiomyopathy in the absence of polyneuropathy. However, a rapid evolution of the therapeutic landscape for ATTR cardiomyopathy is to come based on the positive results of both the novel TTR stabilizer acoramidis[5] and the RNA interference agent patisiran[6] and when considering the significant number of ongoing studies in this setting.[1]

The disease is well recognized as a systemic disease, but renal involvement has not been addressed so far in clinical trials for ATTR. Amyloid-related kidney damage usually manifests with proteinuria evolving to nephrotic syndrome and progressive development of chronic kidney disease (CKD). This pattern of kidney dysfunction is typically observed in light chain (AL) amyloidosis and AA (reactive) amyloidosis because of massive glomerular and vascular amyloid deposition, leading to dialysis when left untreated.[7] Similarly, in ATTR, renal involvement is observed in up to 30% of patients with an early onset phenotype associated with the Val50Met (V50M) variant, even before neurologic involvement.[8] In ATTR-wt and non-V50M ATTRv, significant urinary abnormalities are not generally observed. However, recent studies suggest that kidney involvement might be more prevalent in ATTRv patients than previously assessed. In 3 large series including late onset, non-V50M patients, CKD consistently developed in 30% of cases, and 20% presented with significant proteinuria.[9-11] Pathological characterization of renal biopsies from patients with ATTRv demonstrates a higher frequency of

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tubulointerstitial deposits, particularly in the medulla, compared to AL and reactive amyloidosis.[10] Importantly, massive glomerular deposits also are found in patients with no measurable proteinuria, overall supporting progressive CKD in the absence of urinary abnormalities as a clinical manifestation of ATTR amyloid involvement.[10] However, renal biopsy is rarely performed, and a decline in kidney function is largely attributed to cardiorenal syndrome in the context of amyloid cardiomyopathy and heart failure.[12] Overall, renal involvement in ATTR has been poorly characterized, and renal outcome measures have not been included, even as exploratory endpoints, in any phase 3 clinical trial to date.

In this issue of *JACC: CardioOncology*, Sperry et al[13] report a post hoc analysis from the ATTR-ACT trial investigating the impact of tafamidis (at pooled doses of 20 mg/d and 80 mg/d) on renal function after 30 months of treatment compared with placebo. The endpoint of the analysis was a composite and included all-cause death, dialysis, renal transplant, or a decline in the estimated glomerular filtration rate (eGFR) of at least 30% of the baseline value. Overall, this endpoint favored tafamidis. The decrease in eGFR was the driving force of this composite assessment, being observed in 66% and 65% of patients who reached the endpoint in the tafamidis and the placebo arm, respectively. Death was second in frequency (32% in the treatment arm and 33% in the control arm), whereas the number of patients progressing to dialysis or requiring renal transplant was negligible. Time to the composite endpoint demonstrated divergence of curves after at least 1 year of treatment. Considering the baseline characteristics of the study population, including 55% of patients with National Amyloidosis Centre stages II and III, the authors postulate that the treatment effect might be mostly related to a slower progression of cardiorenal syndrome.

Despite its post hoc design and the lack of validated endpoints for ATTR, this study broadens the available information on the clinical effects of tafamidis and suggests its possible beneficial impact on long-term outcomes. Additionally, it fuels new interest on the role of renal amyloid deposits on CKD in patients with ATTR, in addition to the contributions of age, cardiac dysfunction, and treatments targeting the renin-angiotensin-aldosterone system.

Dissecting the specific renal effect of treatment is difficult. When assessing renal outcomes in AL amyloidosis, death is considered a possible source of "interference" and is accounted for by censoring patients who died or by a competing risk model. Moreover, in a study including a significant proportion of subjects suffering from ATTRv, characterized by decreasing muscle mass that can cause falsely normal creatinine levels, eGFR may itself be subject to "interference." Our ability to monitor ATTR and assess the efficacy of disease-modifying therapies is moving forward slowly.

The scenario is strikingly different in AL amyloidosis. In this disease, the response criteria that consistently predict survival were validated 20 years ago[14,15] and transformed individual patient management and the design of clinical trials. AL amyloidosis usually progresses at a faster pace than ATTR if left untreated, but several effective chemo/immunotherapy approaches are now available that can quickly and profoundly suppress the production of the amyloid light chain. This translates into relatively rapid improvement of organ involvement within months and can eventually lead to complete recovery. These differences are probably caused by different disease mechanisms, with direct organ toxicity of the circulating amyloid precursor having a dominant role in AL amyloidosis. In ATTR, improvements induced by disease-modifying therapies are less easily appreciable, and we lack validated treatment endpoints.

With these considerations in mind, how can we improve our ability to assess treatment efficacy in ATTR? The identification and validation of the response criteria will be challenging in this disease until new treatments become available that will be able to reverse the for now apparently inexorable decline in cardiac function. In the current setting of slow-action treatment for ATTR-CM, research should focus on progression rather than response criteria that predict death and can be delayed by treatment in a relatively short time. Only large, international studies with long follow-up may be able to reach this goal.

In conclusion, by providing a nephrologic perspective, the present study calls for better characterization of renal dysfunction and damage in ATTR. To advance this area of research and clinical care, investigators and clinicians should seek to identify a unifying definition of renal involvement, possibly based on validated thresholds for proteinuria and alternative equations including cystatin C to better account for muscle wasting.

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