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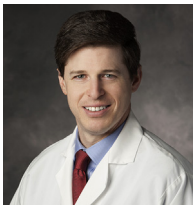
EDITORS' PAGE




Cardiac Amyloidosis

The "Tipping Point" Has Been Reached

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The tipping point is that magic moment when an idea, trend, or social behavior crosses a threshold, tips, and spreads like wildfire.
—Claire Dederrer (1)

"Of all areas, why amyloidosis?" This was the near-universal reaction I (R.W.) received when I told my colleagues that I wanted to focus my time, upon completion of fellowship, on amyloidosis. My rationale was simple. Amyloidosis felt like the only disease in the field of heart failure that we could diagnose but do little about—and that seemed like an opportunity. Amyloidosis was a disease which touched on multiple organ systems—and that appealed to my broader love of internal medicine. Most of all, amyloidosis felt significantly underdiagnosed, the classic "the more you look for it, the more you'll find it" disease—and that suggested the possibility for growth.

Subsequently, I worked with others to establish an Amyloid Center at Stanford University. It was a fortuitous time to enter the field, just before everything was about to change. Only a small community of physicians and scientists around the world focused on this neglected disease—a wonderful group of people, united by an interest in and passion for a disease that most physicians thought was one they would hear about in medical school but would *never* diagnose an actual patient with.

And yet, in a remarkably short period of time, a trickle of patients became a torrent. How did this happen in such a short time? It was a classic "tipping point" scenario—one that peaked over the last 5 years. Like many shifts in medicine, it resulted from a series of independent, but ultimately complementary, and near-simultaneous advances.

In the field of amyloid light-chain (AL) amyloidosis, once the only question was "high-dose alkylator or low-dose alkylator?" However, newer chemotherapies, targeted therapies, and immunotherapies were developed with dramatic improvements in outcomes. The most important advance was the immunotherapy daratumumab, which led to the first ever drug approval for AL amyloidosis in early 2021 (2). All of a sudden, complete or near-complete control of the clonal process leading to light chain amyloid deposition seemed achievable for most patients—a fantasy just 10-15 years earlier.

But nothing matched the evolution of transthyretin (ATTR) amyloidosis from the "disease I've never heard of" to "now that I know what to look for, I'm diagnosing multiple patients per year" territory for many clinicians. This occurred for 2 primary reasons:

1. Clinical trials began, backed by robust science. Even the availability of trials raised the stakes for making a diagnosis. Once the landmark ATTR-ACT (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy) trial reported an overwhelmingly positive result (3), the race to make a diagnosis was on. Suddenly, there was much which could be done for patients if a diagnosis was made, and amyloidosis specialists, physician organizations, advocacy groups, and pharmaceutical companies now had the motivation and resources to educate the medical community about the disease.
2. Simultaneously—and coincidentally from a timing perspective—bone scintigraphy (technetium pyrophosphate or "PYP" scans) was proven to be a reliable method of making a noninvasive diagnosis of ATTR cardiac amyloidosis for most patients (4). This simple, inexpensive, widely available test meant that no longer was endomyocardial biopsy required—opening up a realistic

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diagnostic path for most patients where none had existed before.

Two more ATTR amyloidosis therapies were approved for the less common form of the disease characterized by a hereditary polyneuropathy (5,6); though a rarer disease, the improvement in patient outcomes was monumental. Several more promising therapies for ATTR cardiac amyloidosis are in Phase 3 clinical trials, and for each, anything but a positive result would, at this point, seem like a genuine surprise. And it's not only late-phase clinical trials that are leading to excitement—the first ever trial of CRISPR-Cas9 gene editing technology to be conducted in humans was reported with great enthusiasm earlier this summer (7). What disease was targeted in the trial? ATTR amyloidosis!

This brings us to *JACC: CardioOncology*. At our first editorial board meeting, we discussed one of the *Journal's* fundamental objectives—to serve as the scientific and clinical home for amyloid. To us, this means covering all things cardiac amyloidosis, AL and ATTR included. We want to serve the entire community. And then the submissions came in (8,9). And they kept coming (10-12). And they came some more (13-15). It soon became clear that the time was perfect for a special issue entirely focused on amyloidosis, with the goal of stimulating and invigorating science through high-quality amyloidosis original research and advancing clinical care through state-of-the-art reviews and evidence-based primers. Our brightest hopes were realized over the coming months, as we received one superb submission after another—manuscripts that have turned into the special issue we present to you here. I (B.K.) express my sincerest, heartfelt appreciation and gratitude to both Drs Ron Witteles and Dan Lenihan, who served as associate editors for many of these manuscripts. Without their support and expertise, and the incisive and diligent work of our many collaborative authors and our many reviewers, this issue would not be possible. Thank you.

To clinicians and scientists: never has there been a better time to learn about this fascinating disease for which so much has changed. To trainees: consider devoting at least part of your career to a field that embodies the intersection of science and clinical care—a field that is by definition as multidisciplinary as cardio-oncology itself. To all of our community: We hope you enjoy this special issue as much as we have truly enjoyed putting it together, and we hope it will equip you with the necessary knowledge to advance the clinical care of your patients.

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