Priority Press MEDNET

ESC 2024: Annual Meeting of the European Society of Cardiology

London, UK / August 30—September 2, 2024

"A hot topic": TTR amyloidosis gets its moment to shine at ESC 2024

London – In transthyretin amyloidosis (ATTR), the liver produces an abnormal transthyretin (TTR) protein, which aggregates into amyloid fibrils that accumulate in peripheral nerves and the heart. Over time, this can lead to progressive cardiomyopathy (ATTR-CM), heart failure (HF), and premature mortality. At the recent meeting of the ESC there was much excitement and enthusiasm about ATTR-CM, largely inspired by the HELIOS-B trial of vutrisiran, an RNA interference (RNAi) agent that, if approved, would become only the second medication indicated for ATTR-CM. This report reviews the most relevant insights from the meeting into the diagnosis and management of ATTR-CM, with expert commentary on their relevance and implications for Canadian clinicians.

Chief Medical Editor: Dr. Léna Coïc, Montréal, Quebec

"Cardiac amyloid is a pretty hot topic!" said Dr Mathew Maurer of Columbia University, New York, at one of the conference's first sessions[1], and the attention and "buzz" continued throughout the meeting. One common thread was the concept that amyloid could be a more common and important driver of cardiovascular (CV) disease than previously recognized. Dr Pablo Garcia-Pavia, Hospital Universitario Puerta de Hierro in Madrid, Spain, showed that the number of new patients with ATTR and other forms of cardiac amyloidosis in his clinic increased from 21 in 2014 to more than 130 in 2023. "This may be due to an increase in knowledge, the availability of new therapies that have fostered an interest in amyloidosis, and advances in cardiac magnetic resonance that allow us to diagnose patients non-invasively," he said. "But the most important factor is a growing recognition that amyloidosis can occur in a wider range of CV scenarios than we previously thought. We're already treating these patients in our clinics, but not necessarily thinking about cardiac amyloidosis."[2]

Dr Garcia-Pavia outlined an algorithm for screening HF patients for ATTR based on clinical and imaging-related "red flags":[2]

- Left ventricular hypertrophy (wall thickness ≥12 mm) PLUS at least one of the following:
  - CV symptoms: HF and/or aortic stenosis in patients under age 65; hypotension or normotension if previously hypertensive; atrioventricular conduction disease
  - Cardiac imaging: subendocardial/transmural late gadolinium enhancement or increased extracellular volume; reduced longitudinal strain with apical sparing; decreased QRS voltage to mass ratio; pseudo Q waves
  - Extracardiac manifestations: sensory involvement or autonomic dysfunction; peripheral neuropathy; proteinuria; skin bruising; bilateral carpal tunnel syndrome; ruptured biceps tendon; possible family history of amyloidosis

Treatment options: real-world and clinical trial data

To date, treatments for ATTR can be classified as either "stabilizers" that bind to abnormal TTR and inhibit its aggregation into amyloid, or "silencers" that use techniques such as RNAi to block protein production in the liver. For the past five years, the stabilizer tafamidis has been the only product indicated in Canada for management of ATTR-CM. Patisiran, an RNAi silencer medication, is indicated for ATTR neuropathy but is not being developed further for ATTR-CM. Vutrisiran, a next-generation RNAi silencer, is also indicated for ATTR neuropathy but not yet for cardiomyopathy.

Tafamidis: Extending the real-world efficacy profile

Dr Marianna Fontana, University College London, UK, reported on all-cause and CV mortality in patients treated with tafamidis in the long-term extension (LTE) of a placebo-controlled phase 3 trial. Outcomes were analyzed based on patients' disease severity and trial medication history (tafamidis throughout, or crossover from placebo to tafamidis). Across all disease stages, the group that received continued tafamidis had numerically lower rates of all-cause and CV mortality compared to those who crossed over. Efficacy was most prominent and occurred earlier in patients with less severe disease, which Dr Fontana said "emphasizes the importance of early disease-modifying treatment in patients with ATTR-CM."[3]

Patisiran: Reinforcing the value of silencers

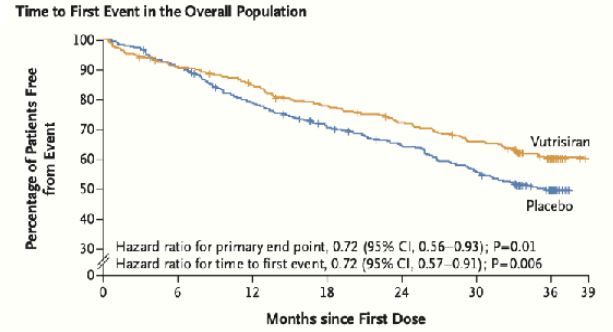
Although a cardiac indication is not being pursued for patisiran, a post-hoc analysis of its key clinical trials provided support for the use of RNAi silencing in ATTR-CM. Dr Olivier Lairez, University Hospital of Toulouse, France, showed that in patients with ATTR-CM or ATTR neuropathy with evidence of cardiac involvement, patients treated with patisiran had better overall survival (hazard HR ratio [HR] 0.587, 95% confidence interval [CI] 0.370–0.932) and lower rates of hospitalization (0.767, 95% CI 0.597–0.985) versus placebo-treated patients. He also highlighted the importance of initiating treatment early; patients who received patisiran throughout the trial and extension had more favourable outcomes than those who crossed over from placebo. Dr Lairez concluded that "we probably should treat the patients early in the process of disease, in order to get the most benefits from the drug."[4]

Vutrisiran: The landmark HELIOS-B trial

One of the most anticipated presentations of the conference was the results of HELIOS-B, a pivotal phase 3 placebo-controlled trial of the RNAi silencer vutrisiran in patients with ATTR-CM and HF. Dr Fontana presented the findings at a "Hot Line" session that highlighted the meeting's most important results, and the study was published simultaneously in the *New England Journal of Medicine*.[5,6]

In HELIOS-B, patients (n=655) were randomized to vutrisiran or placebo for up to three years, followed by an open-label extension. Subjects receiving tafamidis at baseline were allowed to continue; analyses were

Figure 1. **Time to a first event (death from any cause or recurrent cardiovascular event) in the overall study population[5,6]**



No. at Risk (cumulative no. of events)

Vutrisiran	326 (0)	294 (30)	271 (50)	247 (72)	227 (90)	206 (110)	62 (125) 0 (125)
Placebo	328 (0)	295 (31)	253 (70)	221 (96)	199 (115)	172 (142)	52 (159) 0 (159)

Tick marks indicate censored data. CI, confidence interval.
Adapted from: Fontana M et al., N Engl J Med 2024 Aug 30. Online ahead of print.[6]

performed for the overall population (including patients on tafamidis) and the monotherapy population (vutrisiran without tafamidis).[5]

"We're excited to report that vutrisiran met all 10 of the primary and secondary endpoints, demonstrating a treatment effect across a wide range of important and clinically meaningful outcomes in both the overall population and the monotherapy population," said Dr Fontana. On the primary endpoint, a composite outcome of all-cause mortality and recurrent CV events during the double-blind period, vutrisiran was associated with a 28% reduction versus placebo at 36 months in the overall population (Figure 1), and a 33% reduction versus placebo in the monotherapy group (HR 0.672, p=0.0162).[5]

Vutrisiran was also superior to placebo across both the overall and monotherapy populations on the secondary endpoints: changes in the 6-minute walking test and quality-of-life measures at Month 30, stabilization or improvement in HF severity at Month 30, and all-cause mortality through Month 42. On safety endpoints, vutrisiran was well tolerated; the majority of adverse events (AEs) were mild to moderate, and there were no AEs that were observed ≥3% more frequently in the vutrisiran group versus placebo.[5]

Dr Diego Delgado is a clinician investigator at University Health Network in Toronto who led one of the sites for HELIOS-B and is a co-author of the *NEJM* article. Asked to comment on the trial's importance for clinicians in Canada and worldwide, he said, "HELIOS-B is a landmark trial in the field of ATTR-CM. It is going to change practice."[7]

"I've been doing amyloidosis for 25 years, and at the start we didn't have anything to offer to our patients," he explained. "When tafamidis was approved, it changed the way we treat patients, but it only blocks the deposit of the protein that is already being produced, so we are a little bit late in the evolution of the protein." He said that earlier studies of silencers showed signals of potential cardiac benefit, but only in populations with amyloid neuropathy. "So HELIOS-B is the first study showing significant improvement in all-cause mortality and recurrency of CV events in patients with ATTR-CM," he said. He also pointed out that this is the first time a Canadian centre has contributed to a major clinical trial publication in ATTR. "It's great news for Canada to be up there with the European and US centres, because we have amazing amyloid centres all across Canada."[7]

Expert perspective and key takeaways for Canadian clinicians

Asked how the information presented at the meeting might be applied in Canadian clinical practice, Dr Delgado said the first step is more effective patient identification and diagnosis. "We're better than a few years ago, but still very behind in identifying more patients. Amyloid has been considered a rare disease, but in reality it's not that rare – it's only rare because we are not investigating," he said. "We need to improve awareness and education, and to start thinking about amyloidosis as not being rare." He recommended that clinicians should watch for clinical and imaging-related red flags, then trigger the diagnostic algorithm and work in collaboration with Centres of Excellence in amyloidosis to coordinate follow-up and initiation of therapy.

Dr Delgado felt that RNAi and other strategies that treat the source of a pathologic protein are "the future of cardiovascular medicine," but also acknowledged that clinicians may need time to become comfortable using novel therapies. "These drugs are very different from cardiac therapies that we're used to, so they do require some education and knowledge. But it's going to happen," he said. "[RNAi medications] may soon be used in more common conditions like hypertension and that will be part of the learning process – we'll start with a disease that people are more familiar with, and that will evolve into other disciplines."[7]

References:

1. Maurer M, Oral presentation at ESC 2024. August 30–September 2, 2024.
2. Garcia-Pavia P, Oral presentation at ESC 2024. August 30–September 2, 2024.
3. Fontana M, Oral presentation at ESC 2024. August 30–September 2, 2024.
4. Lairez O, Oral presentation at ESC 2024. August 30–September 2, 2024.
5. Fontana M, Hot Line presentation at ESC 2024. August 30–September 2, 2024.
6. Fontana M et al., *N Engl J Med* 2024 Aug 30. Online ahead of print.
7. Delgado D, Interview at ESC 2024. August 30–September 2, 2024.

Mednet Inc. 286 Sanford Ave N, Suite 401, Hamilton ON, L8L 6V4

PP24-100E