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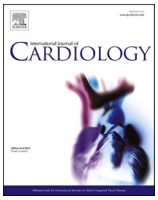

Editorial

Cost-effectiveness of transthyretin cardiac amyloidosis screening and treatment: A Dilemma for the clinician

Professor Claudio Rapezzi, a pioneer in the field of cardiac amyloidosis (CA), used to cite a William Osler's quote: "there are three phases to treatment: diagnosis, diagnosis, and diagnosis". Until recently, when no disease-modifying treatments for transthyretin CA (ATTR-CA) were available, the clinical utility of conclusively diagnosing ATTR-CA might be questioned, as it required the invasive demonstration of amyloid deposits within tissues, without a direct impact on patient management. Thanks to the advances in diagnosis and treatment of ATTR-CA, most patients are now diagnosed through a non-invasive approach, and there is an available therapeutic option: the transthyretin stabilizer tafamidis. The heightened interest in ATTR-CA has led this disease to be recognized as a relatively common etiology of heart failure (HF) with preserved ejection fraction (HFpEF). In light of this, Rapezzi's assertion appears more pertinent than ever: there is an imperative to optimize diagnostic capabilities for addressing ATTR-CA, possibly justifying the feasibility of a systematic screening among patients with specific conditions, such as HFpEF. Accordingly, current HF guidelines strongly advocate for an etiology-driven diagnostic approach to HF [1]. Nevertheless, both national health systems and clinicians struggle with a dilemma due to resource constraints: the cost-effectiveness of systematic screening and treatment.

To investigate this issue, Lau et al. conducted a comprehensive cost-effectiveness analysis in HFpEF patients aged ≥60 years with left ventricular (LV) wall thickness ≥ 12 mm comparing the systematic use of PYP scans, free light chain assessment and immunofixation electrophoresis (universal systematic screening, USS) with the standard of care (SoC) screening for ATTR-CA [2]. This analysis relied on several assumptions from previous studies about the prevalence of ATTR-CA in HFpEF [3], the sensitivity and specificity of different screening approaches, the relative distribution of New York Heart Association (NYHA) functional class, the variation of NYHA class over time, the rate of cardiovascular complications for each NYHA class, and mortality. Most notably, the prevalence of ATTR-CA among HFpEF was estimated based on a systematic screening of ATTR-CA among HFpEF patients ≥60 years with a LV wall thickness ≥ 12 mm leading to a 6.3% rate of ATTR-CA diagnosis compared to 1.3% with the SoC [3]. Screening, treatment costs, and the impact of cardiovascular complications were estimated based on the reimbursement rates in the US healthcare system. Lau et al. demonstrated that the incremental cost-effectiveness ratio (ICER), defined as the incremental costs per Quality-Adjusted Life Year (QALY) gained for USS versus SoC, over an estimated median survival of 7.5 years was $919,509 for each QALY gained. The ICER was even higher when considering a shorter timeframe of 5 years, and was primarily influenced by the age at ATTR-CA diagnosis, the prevalence of ATTR-CA, and tafamidis cost. The US cost of tafamidis should decrease by 84% to 96% to be cost-effective, assuming either a liberal or stringent willingness to pay threshold of $200,000/QALY or $100,000/QALY, respectively [2].

The findings of this study align with previous research on the cost-effectiveness of ATTR-CA screening and tafamidis treatment [4,5], which criticized the current cost of tafamidis for greatly exceeding conventional cost-effectiveness thresholds, making it the "world's most expensive medication for cardiovascular disease" [6]. Due to these high costs, numerous countries, including the UK, currently do not provide reimbursement for tafamidis treatment. However, caution must be exercised in extrapolating these results globally, as all studies conducted so far provide a limited perspective to the American reality, given that costs were estimated based on the US healthcare system. For instance, a PYP scan in the US costs from $3836 to $4689 [2], whereas a bone scintigraphy in Tuscany (Italy) costs €115 (about $125).

A higher prevalence of ATTR-CA improved the cost-effectiveness of a systematic screening. However, the study's estimates relied on a single study on HFpEF patients with LV wall thickness ≥ 12 mm, showing a 6.3% prevalence with systematic ATTR-CA screening [3]. Other studies have reported higher prevalence rates of CA in HFpEF, with a recent meta-analysis estimating an average around 12%, most of them with ATTR-CA [7]. This discrepancy among studies could stem from varying HFpEF definitions and the exclusive inclusion of patients with increased LV wall thickness in certain registries, potentially underestimating the real ATTR-CA prevalence among women [8]. Nonetheless, even assuming a higher prevalence of ATTR-CA among HFpEF, the current expenses associated with the diagnostic algorithm for CA and tafamidis treatment make any systematic screening approach far from being economically feasible. Hence, the imperative for restricting ATTR-CA screening to selected high-risk HFpEF patients, possibly using a combination of biomarkers, red flags, or predictive scores [9].

Additionally, Lau's study likely underestimated the cost of standard treatment for HFpEF, particularly in light of the recent recommendation of sodium-glucose cotransporter-2 inhibitors (SGLT2i) as SoC for HFpEF [1]. It is worth noting that SGLT2i are not recommended for CA, as such patients were excluded from HF trials investigating these drugs. Despite the potential increase in treatment costs, incorporating SGLT2i therapy into the control group could have narrowed the QALY difference between ATTR-CA and non-ATTR-CA groups, potentially leading to a higher estimated ICER. Nevertheless, recent evidence suggests that SGLT2i might confer benefits in ATTR-CA [10]. If SGLT2i were to become the SoC for both HFpEF and CA, it would likely raise treatment-related costs and improve outcomes for both groups. Given these

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considerations, what would be the ultimate impact of tafamidis therapy on prognosis and the global cost-effectiveness of treatment for ATTR-CA remain to be determined in dedicated studies.

In conclusion, years of study on amyloidosis have unveiled that ATTR-CA is a "not-so-rare" [6] treatable disease, prompting clinicians to systematically search for it. In this regard, the approval of tafamidis for ATTR-CA is a significant advance, but its high cost raises concerns about patient access to the treatment. This cost-effectiveness analysis underscores the economic challenges of ATTR-CA systematic screening and treatment, emphasizing the need for more affordable disease-modifying drugs. As we navigate these issues, an effective negotiation between pharmaceutical industries and policymakers is crucial to ensure equitable access to novel therapies without compromising financial sustainability.

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Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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