European Heart Journal - Digital Health (2024) **5**, 505–506
https://doi.org/10.1093/ehjdh/ztae053

EDITORIAL
Artificial intelligence (machine learning, deep learning)

Artificial intelligence–empowered treatment decision-making in patients with aortic stenosis via early detection of cardiac amyloidosis

Joana M. Ribeiro [1,2,*], Rutger Jan Nuis[2], and Peter P.T. de Jaegere[2,*]

[1]Unidade de Intervenção e Diagnóstico Cardiovascular, Unidade Local de Saúde da Região de Aveiro, Avenida Artur Ravara n° 35, 3810-164 Aveiro, Portugal; and [2]Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, 's-Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands

Online publish-ahead-of-print 22 August 2024

It is said that beauty lies in the eyes of the beholder. What is more appealing than a simple, universally available solution to a vexing problem that affects so many patients in terms of prognosis and quality of life and, hence, relevant clinically and from a societal perspective?

In the present issue of the European Heart Journal—Digital Health, Pereyra Pietri *et al.*[1] report their findings of the prediction of cardiac amyloidosis (CA) in patients with aortic stenosis (AoS) who underwent transcatheter aortic valve replacement (TAVR) using an artificial intelligence (AI) electrocardiogram (ECG) model. They found that out of the 1426 patients (mean age 81 ± 9 years, 58% male), 349 (24%) had high CA probability on the pre-procedure ECG. Of note, and not unexpectedly, after multivariable adjustment, a high probability of CA was associated with increased all-cause mortality [hazard ratio (HR) 1.4, 95% confidence interval (CI) 1.0–2.0] and heart failure hospitalizations (HR 1.6, 95% CI 1.1–2.2) at 1 year.

The importance of this study and findings are two-fold: a clinically easy to implement method for virtually all patients referred for aortic valve replacement to assess response to treatment (i.e. TAVR) and—if findings are proven to be repeatable in a broader range of patients including those of/in different geographic regions—their proposal may have a sizable impact on the refinement of patient selection and, hence, treatment decision-making, thereby avoiding inappropriate use of TAVR (utility vs. futility). As rightfully pointed out by the authors, in case of doubts of the ECG analysis, it may serve to initiate further diagnostic evaluation for CA.

The pathophysiologic response to an increased afterload such as in patients with AoS and/or arterial hypertension consists of left ventricular (LV) myocardial changes in cardiac structure, function, and morphology (remodelling). Typically, the cardiomyocytes increase in size (myocyte hypertrophy) with consequent LV hypertrophy (LVH; i.e. increase in cardiac mass) to maintain LV wall stress within normal limits and preserve cardiac function. This is initially a reversible adaptive process but may progress to irreversible changes with loss of cardiac function and death due to—among others—the deposition of collagen in the extracellular matrix, which is the hallmark of myocardial fibrosis.[2] The genetic and molecular mechanisms governing these processes remain poorly understood. They have an insidious onset preceding clinical manifestations and are associated with a dismal prognosis.[2]

A high prevalence of CA (up to 16%) has been reported in patients who underwent TAVR, more than those who underwent surgical aortic valve replacement (SAVR).[3,4] This is not surprising since transthyretin CA (ATTR) [more than amyloid light (AL) chain CA] is also linked to ageing and inflammation of the myocardium and aortic valve.[3] As such, the combination of AoS and age could cyclically potentiate one another.[3,4]

In clinical practice, echocardiography may readily detect structural and functional cardiac alterations and identify potential causes such as AoS and/or arterial hypertension. However, it cannot reveal the underlying histochemical myocardial changes for which more sophisticated and less accessible diagnostic tools are needed (e.g. magnetic resonance imaging).

Given the rising prevalence of AoS along with the increase in life expectancy, it is impractical to screen all AoS patients for concomitant CA. Moreover, screening patients with clinical 'red flags' may not improve the detection of CA.[5] Artificial intelligence has shown to augment and improve the diagnostic cascade in multiple diseases. More particularly, in AoS, deep learning–enhanced ECG analysis and the digital stethoscope (and possibly a combination of both) have been proposed to facilitate disease detection in early stages while optimizing health resources.[2,6,7]

The work done by Pereyra Pietri *et al.*[1] is a welcome addition to this end. The results are encouraging as an algorithm as the one employed by the authors, embedded in the electronic health records that could serve as a cost-effective, simple, and innocuous (non-invasive, radiation-free) tool to pinpoint individuals at a heightened risk of CA. As mentioned above, it may improve TAVR outcomes by refining patient selection and treatment decision-making and, henceforth, cost/effectiveness via more appropriate use of human and material resource. Detection of the AoS before (silent) irreversible myocardial damage occurs would offer a remarkable advantage, since the efficacy of TAVR is dependent on a timely intervention.

Artificial intelligence has the potential to refine the diagnosis–treatment pathway in a patient-centred fashion, by offering a unique

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal – Digital Health* or of the European Society of Cardiology.

* Corresponding authors. Tel: +351234378376, Email: joanamsbgribeiro@gmail.com (J.M.R.); Tel: +31107035656, Email: p.dejaegere@erasmusmc.nl (P.P.T.d.J.)

understanding of patient–disease–treatment relationship. In both AoS and CA, disease progression is often unpredictable, ranging from fast-progressing malignant phenotypes to more benign forms characterized by extended asymptomatic periods and a more favourable prognosis. The disease course will be dependent on disease-specific (e.g. bi- vs. tricuspid aortic valve morphology; ATTR vs. AL CA) and patient-specific characteristics (e.g. age, cardiovascular risk factors, and chronic kidney disease) and their interaction (i.e. patient–disease interaction). Adding to this complexity, treatment decisions must consider not only the identification of the specific phenotype of each patient and their position within the disease progression timeline but also on how the particularities of patient and disease will shape the response to a given treatment (e.g. annular size, location of the atrioventricular node, and wild-type vs. familial ATTR CA)—i.e. patient–disease–treatment interaction. On this matter, the identification of AS-CA patients before valve intervention is particularly relevant as such patients may experience better outcomes after TAVR than after SAVR.[8] Pereyra Pietri *et al.*[1] already demonstrated the prognostic relevance of their AI algorithm in AS patients; if further studies confirm adequate diagnostic accuracy, along with prospective data supporting clinical feasibility and cost-effectiveness, the team of Pereyra Pietri *et al*. would be taking a major step in optimizing combined AS-CA management. They would accurately identify patients at high risk of CA and adverse outcomes, facilitating timely and appropriate treatment that could benefit these individuals.

It is true that beauty lies in the eyes of the beholder, but also in those who are radiating beauty.

Funding: The authors received no funding for this work.

Conflict of interest: none declared.

References

1. Pereyra Pietri M, Farina JM, Mahmoud AK, Scalia IG, Galasso F, Killian ME, *et al.* The prognostic value of artificial intelligence to predict cardiac amyloidosis in patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J Digit Health* 2024;**5**:295–302.
2. Nuis RJ, Ribeiro JM, Lopez-Jimenez F, Vahanian A, de Jaegere PPT. Treatment decision in aortic stenosis—look at the valve but do not forget the ventricle. *SN Compr Clin Med* 2023;**5**.
3. Bonelli A, Paris S, Nardi M, Henein MY, Agricola E, Troise G, *et al.* Aortic valve stenosis and cardiac amyloidosis: a misleading association. *J Clin Med* 2021;**10**:4234.
4. Jaiswal V, Agrawal V, Khulbe Y, Hanif M, Huang H, Hameed M, *et al.* Cardiac amyloidosis and aortic stenosis: a state-of-the-art review. *Eur Heart J Open* 2023;**3**:oead106.
5. Jakstaite AM, Vogel JK, Luedike P, Jánosi RA, Carpinteiro A, Rischpler C, *et al.* Screening for occult transthyretin amyloidosis in patients with severe aortic stenosis and amyloid red flags. *J Clin Med* 2024;**13**:671.
6. Cohen-Shelly M, Attia ZI, Friedman PA, Ito S, Essayagh BA, Ko W-Y, *et al.* Electrocardiogram screening for aortic valve stenosis using artificial intelligence. *Eur Heart J* 2021;**42**:2885.
7. Chorba JS, Shapiro AM, Le L, Maidens J, Prince J, Pham S, *et al.* Deep learning algorithm for automated cardiac murmur detection via a digital stethoscope platform. *J Am Heart Assoc* 2021;**10**:e019905.
8. Ternacle J, Krapf L, Mohty D, Magne J, Nguyen A, Galat A, *et al.* Aortic stenosis and cardiac amyloidosis: JACC review topic of the week. *J Am Coll Cardiol* 2019;**74**:2638–2651.