



HAL
open science

Restoring mitochondrial Ca^{2+} uptake in metabolic cardiomyopathy: A new promising target to treat atrial fibrillation

Mathieu Panel, J. Fauconnier

► **To cite this version:**

Mathieu Panel, J. Fauconnier. Restoring mitochondrial Ca^{2+} uptake in metabolic cardiomyopathy: A new promising target to treat atrial fibrillation. Archives of cardiovascular diseases, 2023, 10.1016/j.acvd.2023.10.004 . hal-04281097

HAL Id: hal-04281097

<https://hal.science/hal-04281097>

Submitted on 13 Nov 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Restoring mitochondrial Ca²⁺ uptake in metabolic cardiomyopathy:

A new promising target to treat atrial fibrillation

Mathieu Panel*, Jérémy Fauconnier

PhyMedExp, Inserm, CNRS, University of Montpellier, Montpellier, France

Keywords :

Metabolic cardiomyopathy Atrial fibrillation Metabolic syndrome Mitochondria Calcium

Abbreviations:

ATP, adenosine triphosphate; Ca²⁺, calcium; MCUC, mitochondrial calcium uniporter complex; NCX, sodium/calcium exchanger; PDH, pyruvate dehydrogenase; RyR2, ryanodine receptors.

This editorial refers to “Enhanced Mitochondrial Calcium Uptake Suppresses Atrial Fibrillation Associated With Metabolic Syndrome” by Fossier, Panel et al., published in the Journal of the American College of Cardiology [1].

***Corresponding author:**

PhyMedExp, Inserm U1046, CNRS UMR 9214, CHU Arnaud de Villeneuve, Bâtiment Crastes de Paulet, 371, avenue du doyen Gaston Giraud, 34295 Montpellier CEDEX, France

.E-mail address: mathieu.panel@inserm.fr (M. Panel).

--

1. Atrial fibrillation pathophysiology in metabolic disorders

Changing dietary habits, often imposed by social and economic contexts, have led to a dramatic worldwide increase in overweight and obesity over the past 50 years. Cardiovascular complications are the leading cause of death in obesity and diabetes. Metabolic syndrome, which accompanies the development of obesity and precedes type 2 diabetes, increases the incidence and burden of heart failure and arrhythmias and the risk of sudden cardiac death. Among these cardiovascular complications, atrial fibrillation is the most common sustained arrhythmia, with a 20% higher risk in patients with metabolic syndrome [2]. The mechanisms under-lying the initiation and promotion of atrial fibrillation, especially in metabolic syndrome, are poorly understood, and atrial fibrillation tends to be the common endpoint of multifactorial alterations, combining atrial tissue remodelling and cellular defects [3].

At the cellular level, it is now accepted that the shortening of the action potential as well as altered calcium (Ca^{2+}) cycling predispose to ectopic activity and re-entry [3]. At each cardiac cycle, the action potential triggers the opening of L-type Ca^{2+} channels and subsequent Ca^{2+} entry into the cell, which in turn activates the ryanodine receptors (RyR2) embedded in the sarcoplasmic reticulum membrane. The synchronized opening of RyR2 induces a massive cytosolic release of Ca^{2+} from the sarcoplasmic reticulum, which triggers cell contraction in the presence of adenosine triphosphate (ATP). During relaxation, Ca^{2+} is mainly pumped back into the sarcoplasmic reticulum through the Ca^{2+} -ATPase (SERCA2a) and partially extruded from the cardiomyocyte by the sodium-calcium exchanger (NCX). In addition, mitochondria were suggested to participate in the shaping of cytosolic Ca^{2+} by taking up Ca^{2+} , although this remains debated [4]. Several mechanisms underlie the pathological beat-to-beat remodelling of the excitation–contraction coupling contributing to the initiation and maintenance of atrial fibrillation [3]. Disturbances in Ca^{2+} cycling, coined as “alternans”, arise from alterations in the L-type Ca^{2+} channel and NCX activity, which will translate into a reduction in action potential duration, and/or from a reduced Ca^{2+} sequestration by the sarcoplasmic reticulum due to a lower SERCA2a activity. In addition, this Ca^{2+} mishandling is worsened by the production of reactive oxygen species, which oxidizes RyR2, thereby destabilizing the channel closed state and increasing its open probability. This “leaky” RyR2 can trigger premature Ca^{2+} release responsible for after-depolarizations and subsequent ectopic activity [5]. Besides, recent evidence suggests that impaired metabolic supply and mitochondrial function are arrhythmogenic substrates in the context of obesity and diabetes [6,7]. These dysregulations in both cellular Ca^{2+} handling and energy production directly point towards the mitochondrion as a central player in atrial fibrillation, especially because mitochondrial Ca^{2+} is considered the masterpiece in the dynamic control of myocardial energy production (Fig. 1).

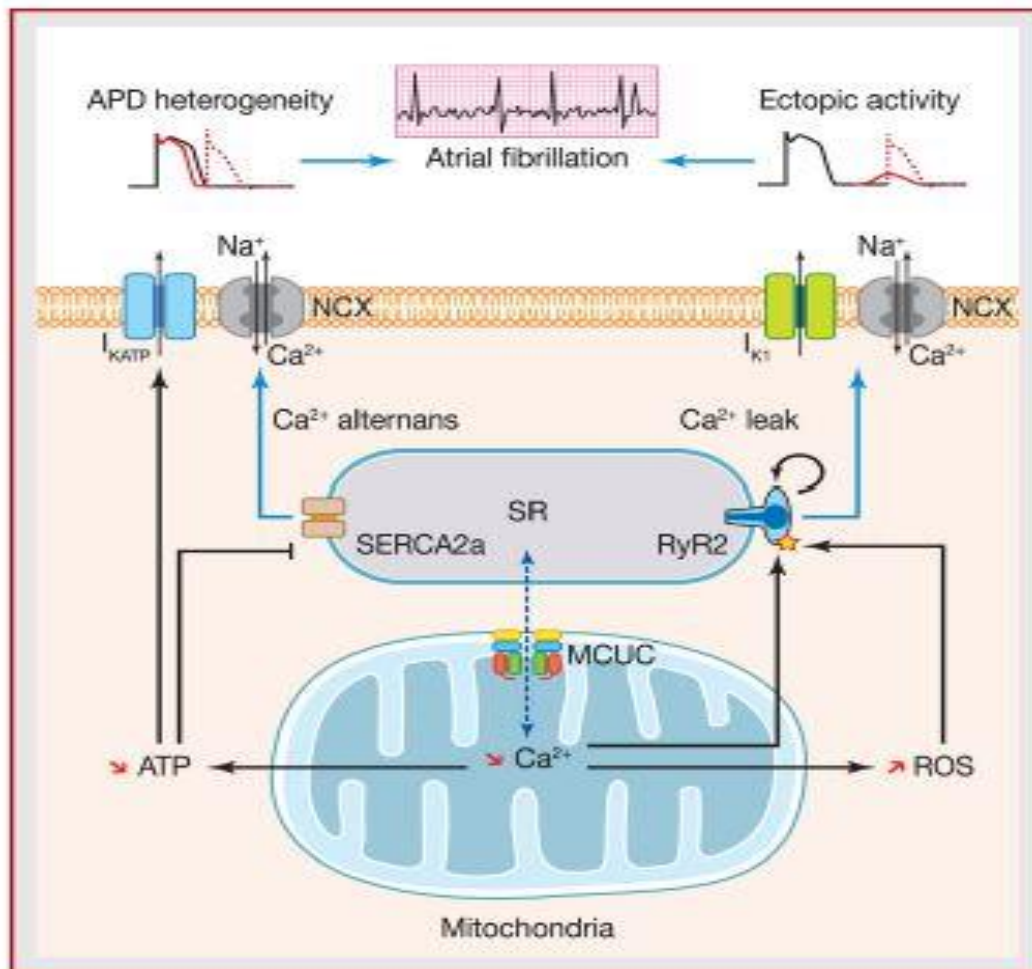


Fig. 1. Mitochondria as a central player in atrial fibrillation. The reduced mitochondrial calcium (Ca^{2+}) uptake decreases the dynamic adenosine triphosphate (ATP) synthesis, which induces a beat-to-beat action potential duration (APD) heterogeneity due to oscillations of ATP-sensitive potassium current (I_{KATP}) activation and cytosolic Ca^{2+} alternans. Concomitantly, the lower mitochondrial Ca^{2+} uptake, in synergy with production of reactive oxygen species (ROS), increases sarcoplasmic reticulum Ca^{2+} leak, which triggers ectopic action potential. Both APD heterogeneity and ectopic action potential are the substratum for the triggering and maintenance of atrial fibrillation. NCX: sodium/calcium exchanger; RyR2: ryanodine receptor.

2. Mitochondrial Ca²⁺-dysregulation as an arrhythmogenic substrate

During each heartbeat, mitochondria take up a fraction of the cytosolic Ca²⁺-released by the sarcoplasmic reticulum. Ca²⁺-enters mitochondria through the voltage-dependent anion channel and the mitochondrial Ca²⁺-uniporter complex (MCUC), located in the outer and inner membrane, respectively. Inside mitochondria, Ca²⁺-stimulates several key steps of the oxidative metabolism, which increases the ATP production to meet the myocardial energetic requirement. More specifically, Ca²⁺-promotes activation of the pyruvate dehydrogenase (PDH) by inducing its dephosphorylation. PDH allows the pyruvate issued from glycolysis to enter the Krebs' cycle, thus supplying the mitochondrial respiratory chain with more electron donors NADH and FADH₂ as the cardiac work-load increases. Montaigne's group previously demonstrated that preoperative mitochondrial dysfunction of the atrial myocardium, evidenced as a decreased mitochondrial respiratory chain activity, is associated with the occurrence of atrial fibrillation after cardiac surgery in patients with metabolic syndrome, identifying for the first time the mitochondrion as a key player in the pathogenesis of atrial fibrillation [7]. To go further, focusing on the mitochondrial Ca²⁺-dynamics in these metabolic syndrome patients, we identified a new arrhythmogenic mechanism underlying the development of atrial fibrillation. We demonstrated a down regulation of the dynamic mitochondrial Ca²⁺-uptake in atrial tissue from patients with metabolic syndrome, which was associated with a sustained reduction in mitochondrial Ca²⁺-content as evidenced by the increased phosphorylation of PDH. These data explain the decreased carbohydrate-driven mitochondrial respiration described by Montaigne et al. [7]. The reduction in Ca²⁺-uptake was associated with a structural remodelling of the MCUC, evidenced by an overexpression of the gatekeeper subunit MICU1, highlighting a new post-translational regulation of this protein complex in cardiac bioenergetics and diseases.

Such a decrease in the dynamic mitochondrial Ca²⁺-uptake is susceptible to promote fluctuations in ATP synthesis. This would have several effects on excitation–contraction coupling. First, activation of the ATP-dependent potassium channel will shorten the action potential and decrease refractory periods, causing reentrant arrhythmia [8]. Concomitantly, this can lead to alterations in Ca²⁺-cycling as: 1) the metabolic oscillations would affect the ATP-dependent Ca²⁺-reuptake through SERCA2a, which would in turn alter the RyR2 activity by increasing the Ca²⁺-induced Ca²⁺-release process and propagation of the local Ca²⁺-release [9] and; 2) the beat-to-beat fluctuations in sarcoplasmic reticulum Ca²⁺-content can induce alternans in sarcoplasmic reticulum Ca²⁺-release that activate the NCX and the inward rectifying potassium current I_{K1}, resulting in action potential heterogeneity [10,11].

Moreover, changes in metabolic supply and fluctuation in the mitochondrial respiration rate may increase reactive oxygen species production and subsequent RyR2 oxidation, favouring ectopic activity (Fig. 1). Therefore, the correction of mitochondrial Ca²⁺-uptake appears to be an attractive strategy to counteract most of the cellular defects observed in atrial fibrillation.

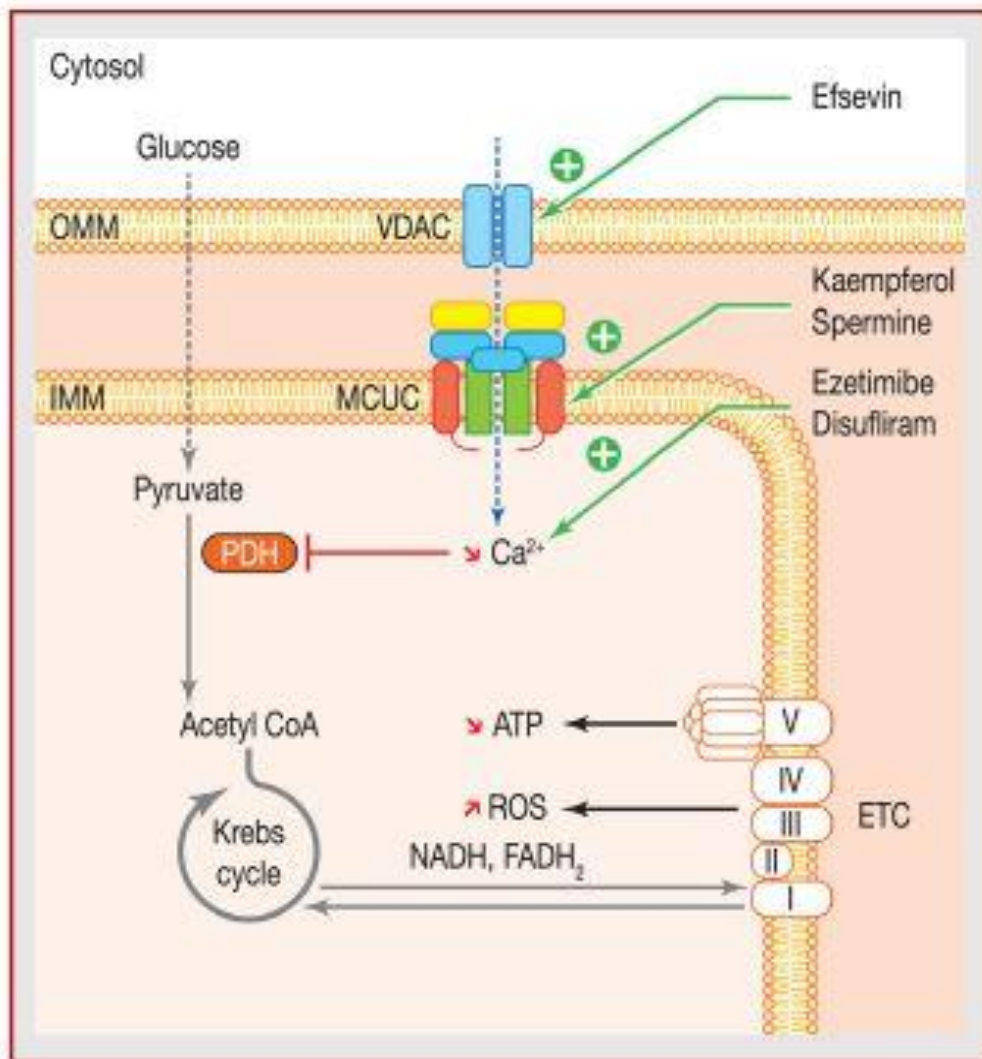


Fig. 2. Mitochondrial calcium (Ca^{2+}) uptake as a target to prevent metabolic syndrome-induced atrial fibrillation. The decrease in mitochondrial Ca^{2+} uptake impairs adenosine triphosphate (ATP) production by limiting the conversion of pyruvate to acetyl CoA and subsequent Krebs cycle activity. Fluctuations in the electron transport chain supply increase production of reactive oxygen species (ROS). By restoring the Ca^{2+} -mediated dynamic ATP production, the pharmacological modulation of mitochondrial Ca^{2+} uptake alleviates the dysregulation of cellular Ca^{2+} handling underlying atrial fibrillation. ETC: electron transport chain; FADH_2 : flavin adenine dinucleotide; IMM: inner mitochondrial membrane; NADH_2 : reduced nicotinamide adenine dinucleotide; OMM: outer mitochondrial membrane; PDH: pyruvate dehydrogenase; voltage-dependent anion channel.

3. Mitochondrial Ca²⁺ and MCUC as new therapeutic targets to treat atrial fibrillation in metabolic disorders

Owing to the lack of target-specific treatment and the significant side-effects of current strategies (anticoagulation, anti-arrhythmic drugs and catheter ablation), treatment of atrial fibrillation remains an unmet clinical need, despite increasing knowledge of the mechanisms underlying its pathogenesis. Consequently, we hypothesized that a pharmacological strategy restoring mitochondrial Ca²⁺ uptake through MCUC-positive modulation would prevent atrial fibrillation. Previous work by Montero et al. identified kaempferol as a potent MCUC agonist, increasing mitochondrial Ca²⁺ uptake through the uniporter complex [12]. Kaempferol, a natural flavonoid found in green leafy vegetables, was shown to be cardioprotective in several preclinical studies reflecting a large variety of cardiac diseases [13]. More specifically, kaempferol reduced cardiac arrhythmias in cellular and animal models of catecholaminergic polymorphic ventricular tachycardia, a genetic disease that is also characterized by altered Ca²⁺ handling [14]. In a mouse model that recapitulated both the clinical and molecular settings of metabolic syndrome and MCUC remodelling, we demonstrated that kaempferol could acutely restore MCUC activity and prevent atrial fibrillation. Thus, these results validate the strategy aimed at treating atrial fibrillation by restoring MCUC function. Other compounds such as efsevin, a voltage-dependent anion channel agonist, or spermine, another MCUC agonist, have been shown to increase mitochondrial Ca²⁺ uptake and reduced Ca²⁺ alternans and arrhythmias [14,15]. However, as for kaempferol, their low affinity and specificity hamper their translational potential. In a more translational effort, the clinically approved drugs disulfiram and ezetimibe, which are also able to increase mitochondrial Ca²⁺ and prevent arrhythmias, could be good candidates to validate this strategy in patients [16]. However, since disulfiram should not be prescribed to patients with heart failure or diabetes, ezetimibe may be the most accessible compound to address this issue. Limited clinical data are already available from a post hoc analysis of a randomized controlled trial comparing placebo with ezetimibe + statin in a population of patients with aortic stenosis [17]. Although ezetimibe did not reduce the incidence of new-onset atrial fibrillation in these patients, its role in preventing atrial fibrillation in other clinical settings warrants further study, particularly to determine whether the MCUC-dependent mechanism of atrial fibrillation exists outside the metabolic syndrome, and its putative role in atrial fibrillation maintenance. In any case, these different drugs might be considered as lead compounds to develop target-specific treatments of atrial fibrillation (Fig. 2) to address the upcoming growth in patients with cardiac arrhythmias [18].

Overall, our work brings the preclinical proof-of-concept that restoring mitochondrial Ca²⁺ homeostasis by directly targeting the MCUC is a novel therapeutic strategy to treat atrial fibrillation and therefore proposes a future antiarrhythmic approach for patients with atrial fibrillation.

Funding

J.F. was supported by the Fondation de France(N°00056858/N°00121055) and by ANR CALMOS (ANR-18-CE17-0003). M.P. was supported by the Fondation Lefoulon-Delalande. Disclosure of interest The authors declare that they have no competing interest.

References

- [1] Fossier L, Panel M, Butruille L, Colombani S, Azria L, Woittrain E, et al. Enhanced mitochondrial calcium uptake suppresses atrial fibrillation associated with metabolic syndrome. *J Am Coll Cardiol* 2022;80:2205–19, <http://dx.doi.org/10.1016/j.jacc.2022.09.041>.
- [2] Schlesinger S, Neuenschwander M, Barbaresko J, Lang A, Maalmi H, Rathmann W, et al. Prediabetes and risk of mortality, diabetes-related complications and comorbidities: umbrella review of meta-analyses of prospective studies. *Diabetologia* 2022;65:275–85, <http://dx.doi.org/10.1007/s00125-021-05592-3>.
- [3] Mason FE, Pronto JRD, Alhussini K, Maack C, Voigt N. Cellular and mitochondrial mechanisms of atrial fibrillation. *Basic Res Cardiol* 2020;115:72, <http://dx.doi.org/10.1007/s00395-020-00827-7>.
- [4] Bertero E, Maack C. Calcium signaling and reactive oxygen species in mitochondria. *Circ Res* 2018;122:1460–78, <http://dx.doi.org/10.1161/CIRCRESAHA.118.310082>.
- [5] Roussel J, Thireau J, Brenner C, Saint N, Scheuermann V, Lacampagne A, et al. Palmitoyl-carnitine increases RyR2 oxidation and sarcoplasmic reticulum Ca²⁺-leak in cardiomyocytes: role of adenine nucleotide translocase. *Biochim Biophys Acta* 2015;1852:749–58, <http://dx.doi.org/10.1016/j.bbadis.2015.01.011>.
- [6] Suffee N, Baptista E, Piquereau J, Ponnaiah M, Doisne N, Ichou F, et al. Impacts of a high fat diet on the metabolic profile and the phenotype of atrial myocardium in mice. *Cardiovasc Res* 2021;118:3126–39, <http://dx.doi.org/10.1093/cvr/cvab367>.
- [7] Montaigne D, Marechal X, Lefebvre P, Modine T, Fayad G, Dehondt H, et al. Mitochondrial dysfunction as an arrhythmogenic substrate: a translational proof-of-concept study in patients with metabolic syndrome in whom post-operative atrial fibrillation develops. *J Am Coll Cardiol* 2013;62:1466–73, <http://dx.doi.org/10.1016/j.jacc.2013.03.061>.
- [8] Akar FG, Aon MA, Tomaselli GF, O'Rourke B. The mitochondrial origin of postischemic arrhythmias. *J Clin Invest* 2005;115:3527–35, <http://dx.doi.org/10.1172/JCI25371>.

- [9] Pacher P, Thomas AP, Hajnóczy G. Ca²⁺marks: miniature calcium signals in single mitochondria driven by ryanodine receptors. *Proc Natl Acad Sci U S A* 2002;99:2380–5, <http://dx.doi.org/10.1073/pnas.032423699>.
- [10] Fauconnier J, Meli AC, Thireau J, Roberge S, Shan J, Sassi Y, et al. Ryanodine receptor leak mediated by caspase-8 activation leads to left ventricular injury after myocardial ischemia-reperfusion. *Proc Natl Acad Sci U S A* 2011;108:13258–63, <http://dx.doi.org/10.1073/pnas.1100286108>.
- [11] Fauconnier J, Pasquié J-L, Bideaux P, Lacampagne A, Richard S. Cardiomyocytes hypertrophic status after myocardial infarction determines distinct types of arrhythmia: role of the ryanodine receptor. *Prog Biophys Mol Biol* 2010;103:71–80, <http://dx.doi.org/10.1016/j.pbiomolbio.2010.01.002>.
- [12] Montero M, Lobatón CD, Hernández-Sanmiguel E, Santodomingo J, Vay L, Moreno A, et al. Direct activation of the mitochondrial calcium uniporter by natural plant flavonoids. *Biochem J* 2004;384:19–24, <http://dx.doi.org/10.1042/BJ20040990>.
- [13] Kamisah Y, Jalil J, Yunus NM, Zainalabidin S. Cardioprotective properties of Kaempferol: a review. *Plants (Basel)* 2023;12:2096, <http://dx.doi.org/10.3390/plants12112096>.
- [14] Schweitzer MK, Wilting F, Sedej S, Dreizehnter L, Dupper NJ, Tian Q, et al. Suppression of arrhythmia by enhancing mitochondrial Ca²⁺ uptake in catecholaminergic ventricular tachycardia models. *JACC: Basic to Transl Sci* 2017;2:737–47, <http://dx.doi.org/10.1016/j.jacbts.2017.06.008>.
- [15] Oropeza-Almazan Y, Blatter LA. Mitochondrial calcium uniporter complex activation protects against calcium alternans in atrial myocytes. *Am J Physiol Heart Circ Physiol* 2020;319:H873–81, <http://dx.doi.org/10.1152/ajpheart.00375.2020>.
- [16] Sander P, Feng M, Schweitzer MK, Wilting F, Gutenthaler SM, Arduino DM, et al. Approved drugs ezetimibe and disulfiram enhance mitochondrial Ca²⁺ uptake and suppress cardiac arrhythmogenesis. *Br J Pharmacol* 2021;178:4518–32, <http://dx.doi.org/10.1111/bph.15630>.
- [17] Bang CN, Greve AM, Boman K, Egstrup K, Gohlke-Baerwolf C, Køber L, et al. Effect of lipid lowering on new-onset atrial fibrillation in patients with asymptomatic aortic stenosis: the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. *Am Heart J* 2012;163:690–6, <http://dx.doi.org/10.1016/j.ahj.2012.01.026>.
- [18] Piot O, Boveda S, Defaye P, Klug D, Lacotte J, Marijon E. Prospective evolution of cardiac arrhythmia care: 2030 vision. *Arch Cardiovasc Dis* 2022;115:179–89, <http://dx.doi.org/10.1016/j.acvd.2022.02.008>.