

VIEWPOINT

# Calmodulinopathies

## The Need for a Registry

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### ABSTRACT

Calmodulinopathies are very rare genetic disorders associated with a high risk for sudden cardiac death. Disease-causing variants in 1 of the 3 identical *CALM* genes cause severe forms of long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, or idiopathic ventricular fibrillation, and there are many unanswered questions concerning management and underlying mechanisms. What is currently known depends largely on the initial publications from the ICamR (International Calmodulinopathy Registry). However, progress is delayed because the accrual of patients in ICamR is slow. As we did long ago for long QT syndrome, this is a call for action, requesting doctors all over the world to enroll even their isolated cases in the Registry. This is the only way to obtain, for an adequate number of patients, the data necessary to define the spectrum of clinical manifestations and the genotype-phenotype correlation essential for an improved risk stratification and best therapeutic management.

If you are willing to contribute, please contact us. (JACC Clin Electrophysiol. 2025;11:2791-2794)

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Rare diseases are an unending source of problems. They are difficult to diagnose (“*never seen one before*”), they tend to be serious and often lethal, and they are difficult to manage (“*this is my first case, there is nothing in the guidelines*”).<sup>1</sup> Although this is all true, there is a way out, because we have faced these problems before, and we have learned.

Fifty years ago, the knowledge about the long QT syndrome (for which the acronym “LQTS” was created in 1975<sup>2</sup>) was extremely limited. There was a smorgasbord of therapies, a clear sign that no one knew what to do, and just a handful of patients were treated with  $\beta$ -blockers. What was available in the literature until then was just a small number of case reports, without any insight on the nature of what

appeared to be a highly lethal disorder. A 1975 publication<sup>2</sup> broke the spell by forcefully proposing 2 therapeutic interventions:  $\beta$ -blockers as the main therapy for all patients, and left cardiac sympathetic denervation for those not fully protected by  $\beta$ -blockers. As still very little was known, Arthur Moss and Peter Schwartz, together with Richard Crampton, established the International Registry for the Long QT Syndrome in 1979,<sup>3</sup> with the objectives to learn more about the underlying mechanisms, the natural history of the disease, and the response to therapy. However, the progress was slow because the number of patients enrolled in the Registry was growing piecemeal.

To address that problem, more than 40 years ago, in 1983 to be precise, one of us (P.J.S.), with the

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

support of the European Society of Cardiology, published a short paper inviting cardiologists from all over the world to enroll their patients in the LQTS Registry.<sup>4</sup> It was stated that “A *valid assessment of therapeutic efficacy in an uncommon disease cannot be based on ‘personal experience’; cooperative efforts are necessary.*” After mentioning the existence of the International LQTS Registry, it was also written that “*Over 200 patients have already been enrolled, but many more are needed to draw meaningful and valid conclusions.*”

That paper triggered a major response, and large numbers of LQTS patients were rapidly enrolled. The Registry was a success beyond any expectation, not only providing full answers to our original questions, but also allowing the identification of the LQTS-causing genes—it was the Registry that, with its large pedigrees of clearly affected and non-affected individuals, provided molecular biologists and geneticists the material essential for their discoveries.<sup>3</sup>

Another example of the important findings obtained through Registries is what has happened with catecholaminergic polymorphic ventricular tachycardia.<sup>5,6</sup> History often repeats itself, and nowadays, when confronted with life-threatening arrhythmias in a child with a calmodulin variant, we face the same problems of 50 years ago with LQTS.

Three reports, published between 2012 and 2014, unexpectedly linked calmodulin mutations to catecholaminergic polymorphic ventricular tachycardia,<sup>7</sup> to LQTS with a strikingly high mortality in infancy,<sup>8</sup> and to idiopathic ventricular fibrillation.<sup>9</sup> This “calmodulin explosion” made clear that variants on the 3 identical calmodulin genes (*CALM1*, *CALM2*, and *CALM3*) were causing extremely severe phenotypes with a high incidence of sudden cardiac death before age 5 years.

Calmodulin, a protein critically involved in the regulation of all major cardiac ion channels and the most important cellular calcium sensor, plays a key role in preserving cardiac electrical stability. It has the unique feature of being encoded by 3 genes in 3 different chromosomes all characterized by their extreme conservation. Indeed, *CALM* variants are poorly tolerated and cause severe clinical phenotypes, often associated with increased risk for life-threatening arrhythmias.<sup>10</sup>

In 2015, to address the same issues we had in the past with LQTS, we created the ICamR (International Calmodulinopathy Registry) with the support of European Research Network GUARD-Heart. The first report, based on 70 patients, appeared in 2019<sup>11</sup> and the second in 2024,<sup>12</sup> with data on 140 patients. There

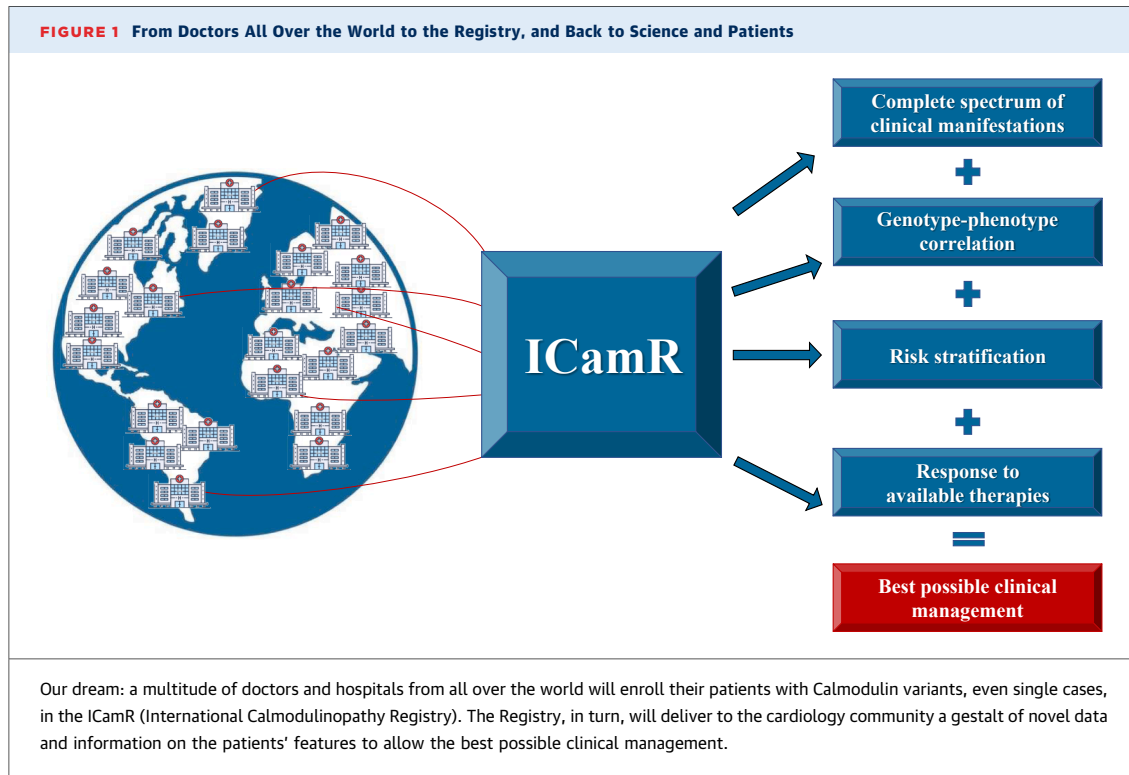
has been progress, but many questions are still unanswered because more patients need to be enrolled.

ICamR has already provided useful information. It has shown the apparent value of triple therapy ( $\beta$ -blockers, mexiletine, and left cardiac sympathetic denervation). It has called attention to the presence of complex phenotypes, notably with neurologic components and/or cardiac structural abnormalities. Impressively, it played a major, and quite positive, role in a notorious trial for infanticide.<sup>13</sup>

A significant increase in the number of patients enrolled in ICamR will allow the registry to address several relevant questions, both scientific and clinical (**Figure 1**). A better understanding of the genotype-phenotype correlation will provide elements for risk stratification as well as clarification of the striking and puzzling distribution of the variants of the patients with life-threatening events, which, in 85% of cases, are located in a specific part of *CALM* genes, namely the EF-hand IV.<sup>10</sup> Larger numbers of patients will also allow clarification of the syndromic aspects, especially the relationship between *CALM* mutations and neurological manifestations, and allow us to assess whether our impression that in some cases, often before age 5 years and without changing therapy, cardiac electrical stability increases together with a impressive reduction of major cardiac events is correct.

All registries face problems. Among the obstacles to the enrollment in ICamR, one certainly is that variants on the calmodulin genes are very rare; another is that most doctors have forgotten their Latin (“*gutta cavat lapidem*” [a drop hollows out a stone]) and may not realize the importance of their every single patients. Progress requires action. Practicing cardiologists need to be aware of the Registry and to realize the importance, for science and for the patients, of a rapid increase in the enrollment of patients in ICamR. Whenever they are informed by the genetic laboratories that one of their patients has a calmodulin variant, they have the opportunity of contributing by contacting us to enroll their patients in the Registry. This would not interfere in any way with their choices of management (although we can usually be of help by providing information and suggestions) and with their right to publish individually their cases, but would significantly increase our ability to understand, sooner rather than later, how to best deal with this very often dramatic disease.

Furthermore, because variant adjudication is often challenging in rare disease, variants of uncertain significance should also be reported because their carefully annotated presence in the Registry will



facilitate their exit from “genetic purgatory.” If patients presenting with features characteristic of a *CALM*-related disease are identified where genetic screening is not available, we would be willing and ready to perform the necessary genetic screening. We will provide information on how to enroll the patients in ICamR, and subsequently, every year we will request a follow-up. The registry does not interfere with any management decision concerning the enrolled patients, who continue to be the responsibility of their attending physician.

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