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Managing long QT syndrome patients, cooking, and common sense

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This essay stems from a controversial recommendation present in the 2022 European Guidelines which indicated the appropriateness of considering an implantable cardioverter defibrillator (ICD) implant even for still asymptomatic long QT syndrome (LQTS) patients deemed to be at high risk by the 1-2-3 LQTS score based on QTc and genotype calculated prior to the institution of therapy. As 15 years ago, we also had proposed, but never used, a risk score called M-FACT to identify patients at high risk of an appropriate ICD shock, we felt the responsibility of assessing what would have happened to our patients if we had rigorously used that score. We performed a study recently published in the *European Heart Journal* which brought to general attention two concepts important for clinical management. One is that all LQTS patients should be seen at least once a year for a reassessment of arrhythmic risk based on standard electrocardiogram, 12-lead 24 h Holter recording and an exercise stress test. The other is that, based on these yearly visits, we perform 'therapy optimization' by adding to the standard β-blocker therapy either left cardiac sympathetic denervation or mexiletine or an ICD implant. On almost 1000 LQTS patients, all genotyped, this dynamic approach was accompanied by not a single death, few events, and out of 142 patients who should have received an ICD based on the score, only 22 did and only 3 had an ICD shock. These data and concepts call for a reconsideration of the recommendation made by the guidelines.

When the 2022 European Guidelines on sudden cardiac death were published,[1] their recommendations concerning the long QT syndrome (LQTS) elicited two distinct reactions among cardiologists. Some were relieved, others were concerned. The first group was glad that finally they received clear guidance: already in the initial visit(s) and before initiating therapy, if QTc and genotype were available, it was possible to know whether or not an implantable cardioverter defibrillator (ICD) was indicated. The two parameters would indicate the path ahead, and it would have become easy to select the therapeutic option even with limited experience with LQTS patients. Furthermore, their choices were going to be protected by the large umbrella provided by the Guidelines. The second group was concerned that by allowing a risk score, never mind which one, to guide therapeutic choices important for the quality of life of their patients might have resulted in implanting an excessive and unjustified number of ICDs.

As members of the second group, we will share our initial concerns and describe our subsequent actions which led us to perform a study aimed at assessing

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whether or not a risk score might have been useful to implement correct medical choices.

Concerns and action

In a review published with Corrado and Link, in the same year of the 2022 Guidelines, the following considerations had been made in relationship to risk stratification for channelopathies and cardiomyopathies.[2] We had noted that 'to assist the clinician in the risk assessment, algorithms have been developed which result in risk scores, often designed as electronic calculators, whose clinical utility remains to be established'. A critical point follows the fact that, given that the arrhythmic substrate may worsen over time according to late or progressive phenotypic expression, it may not be sufficient to perform risk stratification for sudden cardiac death in patients with genetic arrhythmias at their initial evaluation but it might be necessary to reassess it on a regular basis during follow-up. Most important in our view was that the effect of treatment is not generally considered by risk scores. In other words, the baseline arrhythmic risk is evaluated to predict future malignant events, without accounting for changes in the risk resulting from proper treatment either present at the time of first evaluation or subsequently started during follow-up. For example, pharmacological treatment with β-blockers could significantly modify the basal arrhythmic risk of patients with channelopathies such as LQTS and thus alter the predictive power of risk scores. We specifically wrote that 'Failure to adjust for the effects of treatment may cause risk scores to overestimate the predicted risk and lead to inappropriate therapy including ICD implantation'.[2]

During the revision of our submitted manuscript, one reviewer smartly asked what had happened with 'the risk score proposed by Schwartz *et al.* in 2010?'. We all had forgotten about it because in our clinical practice we never used that risk score, but it was true that we had published it. In the largest study on LQTS patients implanted with ICDs, we had indeed proposed a scoring system designed to predict the probability of appropriate ICD shocks.[3] In that score, which we called M-FACT, 1 point each was assigned to an aborted cardiac arrest (ACA), syncope on β-blockers, age <20, and a QTc between 500 and 550 ms; 2 points to a QTc > 550 ms. Based on our 2010 article, patients without ACA but with an M-FACT score ≥2 had an incidence of ICD shocks of 40% at 4 years of follow-up, compared to a rate below 5% for the patients with a score <2. Overall, the data suggested as appropriate to implant an ICD in LQTS patients with an M-FACT score ≥2.

At this point, we felt to bear the responsibility of assessing whether the use of our own score would have resulted in correct medical decisions and, accordingly, we analysed the clinical outcome in our cohort of LQTS patients without a history of ACA. We focused on what had happened to the patients who, either at diagnosis or during follow-up, had an M-FACT score ≥2, which should have almost automatically led to an ICD implantation.

From theory to reality

The details of our study have been recently published,[4] and here, it will be sufficient to recap the main points. The interested reader will find the answers to possible questions in the actual publication.

The study population included 946 LQTS patients, all genotyped. There were 547 LQT1 (58%), 297 LQT2 (31%), and 48 LQT3 (5%). Half of the patients were probands, and the other half was made of family members. A syncope before diagnosis or β-blockers initiation had occurred in 10% of the patients whereas a QTc ≥ 500 ms was present at the first evaluation in 18%. The bottom line was that 106 patients (12%) had an M-FACT score ≥2.

Here comes a first critical point: namely that—by longstanding rule of our group—we see most, if not all, of our patients once a year, and every year we reassess their risk by always performing a standard electrocardiogram (ECG), a 12-lead 24-h Holter recording, and an exercise stress test. And here comes the second critical point: namely that, if we regard the risk of the individual patient still high or higher, we perform 'therapeutic optimization'. By this term, we refer to the addition to β-blockers of either left cardiac sympathetic denervation (LCSD),[5-7] mexiletine (which we proposed in 1995 for LQT3,[8] and which we now use also for LQT2[9]), or ICD implant.[3] In this study, we defined the M-FACT score calculated at every visit. The initial one was named 'static M-FACT', and the subsequent ones 'dynamic M-FACT'. *Figure 1* depicts the post-diagnosis evolution of the 106 patients with a static M-FACT ≥ 2. Once β-blocker therapy was initiated, QTc was shortened in 57 of them so that their dynamic M-FACT score became <2. Interestingly, and clinically relevant, the patients who had cardiac events (CEs) during follow-up were those with modest QTc shortening (−14 ± 28 ms) on β-blocker therapy whereas those who had greater QTc shortening (−45 ± 33 ms) remained fully asymptomatic (*Figure 2*).

In the group still at M-FACT > 2, we performed LCSD[5-7] in 55%, added mexiletine[8] in 31%, and implanted an ICD in 27%. Within this very high-risk group, seven patients (14%) had cardiac events: one had an ICD shock and six had syncope. Following β-blocker initiation 57 of the 106 patients lowered their M-FACT score to below two points, suggesting a decreased risk. Nonetheless, we thought that some of them needed further protection, and we performed LCSD in 7%, added mexiletine in 17%, and implanted an ICD in one patient (2%). None of these 57 patients suffered a single cardiac event.

Very importantly, and a clear sign of the value of regular control visits, 32 patients who had an M-FACT score <2 at the initial visit evolved to a dynamic score ≥2 during follow-up and required therapeutic optimization: LCSD in 19%, mexiletine in 28%, and an ICD in 25%. During the follow-up, two patients had an ICD shock and one had syncope. During a mean follow-up of 10 years, not a single patient died.

'It's not by chance', says the chef

The zero mortality in our large cohort (we have not lost a single patient in the last 35 years) does not depend solely on our almost blanket use of nadolol and propranolol—the only two β-blockers truly effective[10]—but it is largely due to the therapy intensification (with LCSD, mexiletine, and ICDs) which is the logical consequence of our yearly visits. We do not wait for breakthrough events to recognize that a patient presents signs which, based on our experience,

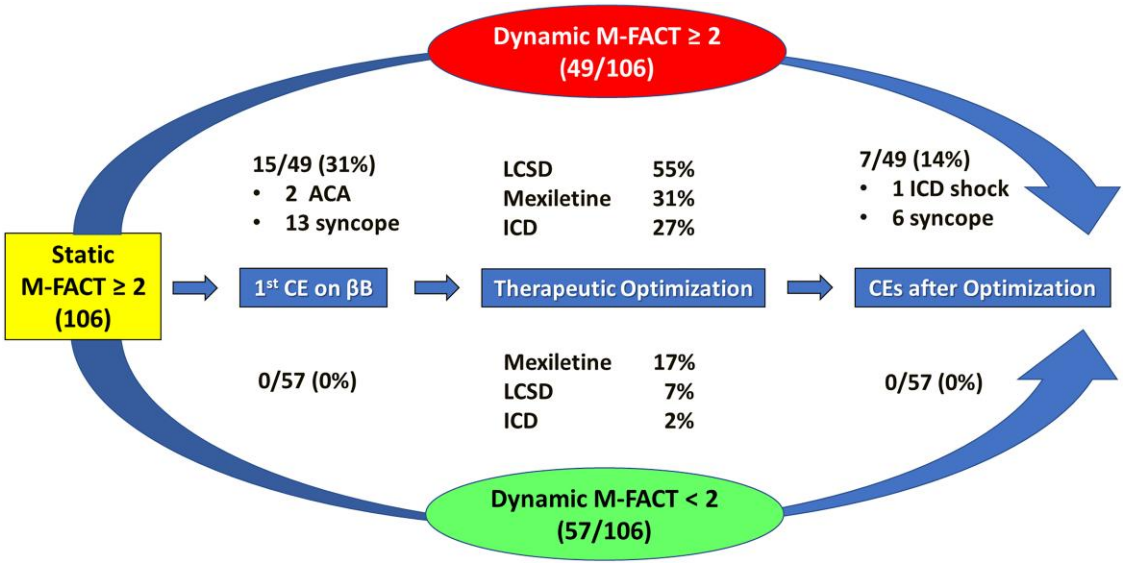

Figure 1 Evolution of the 106 long QT syndrome patients on β-blockers with a static M-FACT ≥ 2 at presentation during a mean follow-up of 9 ± 8 years. Post-diagnosis CEs on β-blockers conferring the score 1 more point, additional therapeutic interventions and CEs occurring despite therapy optimization are shown for patients maintaining or increasing the static score up to a dynamic M-FACT ≥ 2 (upper half) and for those lowering the score to <2 (lower half). Changes in QTc on β-blockers (<500/550> ms) and in patient age (<20> years) also contributed to any further shift of dynamic M-FACT (from Ref. 4 with permission).

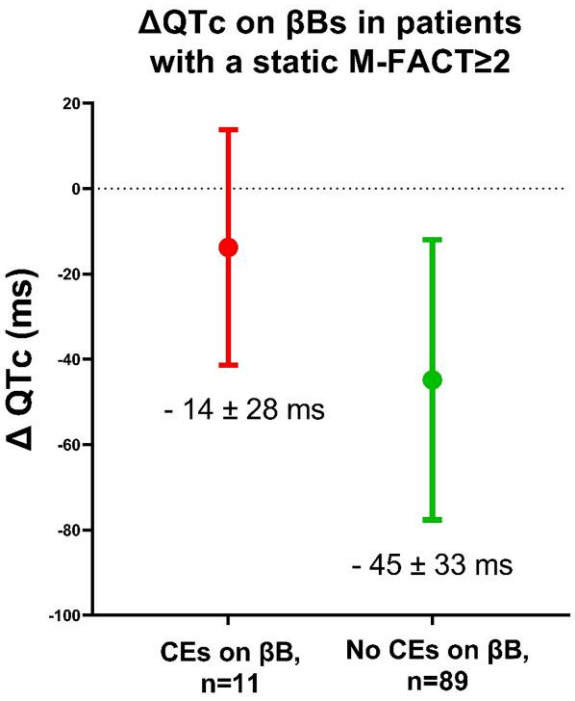

Figure 2 QTc change on β-blockers in patients with a static M-FACT ≥ 2 with or without CEs on therapy ($n = 100$ with available ECG within 18 months of β-blockers therapy initiation). Patients with CEs had a significantly lesser QTc shortening (from 536 ± 22 to 522 ± 26, −14 ± 28, $P = 0.09$) compared to those without CE (from 536 ± 34 to 491 ± 44, −45 ± 33, $P < 0.001$, P-value for the comparison between the two groups <0.01). Bars show mean with standard deviation (from Ref. 4 with permission).

we interpret as pointing to an increased risk. These signs include T-wave alternans, long pauses, and bizarre ECG changes. This proactive approach allows us to adopt early on the necessary preventing measures which contribute to excellent event free survival of our LQTS patients.

Every good chef, when preparing a special sauce, will—from time to time—dip a fork in the sauce, take it to his/her mouth, and then, if necessary, will add salt, pepper, or other spices, to make it perfect. Taking good care of LQTS patients and high-quality cooking are indeed very much alike. As you should not light the gas under the pot and walk away, by the same token you should not initiate a treatment for a patient and then forget about him/her. Constant reassessment together with being ready to add other ingredients is key to both quality cooking and careful patient's management.

If we had blindly trusted the M-FACT score we would have implanted with an ICD the 142 patients who, initially or during follow-up, manifested a score ≥2. By the constant risk reassessment and by the 'yearly optimization', we implanted only 22 patients without a single sudden death in the entire cohort of 946 patients. Moreover, 9 patients who had a score <2 at the initial visit received an ICD during follow-up because they manifested patterns indicating to us that they were at high risk.

We need to clarify that the M-FACT score was not our real target. We used it as a proxy for all the risk scores that assume that it is possible to assess whether or not an LQTS patient should be implanted with an ICD before having initiated therapy. Indeed, to return to the 2022 Guidelines,[1] we believe that their very rapid adoption of one such score, specifically the 1-2-3 risk score recently proposed,[11,12] was a bit naïve and potentially misleading for many cardiologists without clear personal experience with LQTS.

That's not all

A few additional considerations appear to be in order.

As our study[4] was provocative and dared to challenge the European Guidelines, the *European Heart Journal*

correctly invited two recognized experts, Arthur Wilde and Christian van der Werf, to write an editorial about it. As they expressed their opinion in a clear and unambiguous way,[13] the best we can do is to share with the readers some of their statements verbatim.

> 'The value of developing and using a risk score in untreated LQTS patients, who by all guidelines should at least receive β-blocker therapy, is limited. It is, therefore, simply wrong to place the 1-2-3 LQTS risk score so prominently in the ESC Guidelines. … Dusi et al. nicely show the importance of a dynamic score to identify patients in whom the QTc and associated risk changes during follow-up'.

Quite recently, we have been involved in a study jointly performed with the largest American centre for LQTS, the one led by Dr Ackerman at the Mayo Clinic, on almost 3000 LQTS patients, which examined what happened to the almost 300 patients who met the 2022 European Guidelines-based recommendation for implanting an ICD.[14] Most of them were treated effectively without an ICD. Thus, while in the past we had written that 'most patients with LQTS do not need and should not receive an ICD'[6] we can now add that an ICD may not be necessary even among patients with LQTS who should receive one according to the guidelines.

Our present view could probably be summarized along the following lines. The patients affected by LQTS represent a moving target, their risk needs to be reassessed on a regular basis in order to evaluate the possible need for therapy optimization. Guidelines should be careful before making recommendations that might lead to almost automatic therapeutic decisions bypassing the time honoured careful medical assessment of the individual patients. In this regard, in our opinion the 2022 European Guidelines need to be corrected and updated. Finally, LQTS is a very uncommon life-threatening disease, which should be handled by experts, not by amateurs.

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Data availability

Data available upon reasonable request to the corresponding author.

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