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CLINICAL RESEARCH
Arrhythmias

Long QT syndrome: importance of reassessing arrhythmic risk after treatment initiation

Veronica Dusi [1], Federica Dagradi [2], Carla Spazzolini [2], Lia Crotti [2,3], Paolo Cerea [2], Fulvio L.F. Giovenzana [2], Giulia Musu [2], Matteo Pedrazzini [2], Margherita Torchio [2], and Peter J. Schwartz [2]*

[1]Department of Medical Sciences, University of Turin, Turin, Italy; [2]Center for Cardiac Arrhythmias of Genetic Origin and Laboratory of Cardiovascular Genetics, Istituto Auxologico Italiano, IRCCS, Via Pier Lombardo, 22, 20135 Milan, Italy; and [3]Department of Medicine and Surgery, University of Milano-Bicocca, Milano, Italy

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See the editorial comment for this article 'Risk scores in congenital long QT syndrome: friend or foe?', by A.A.M. Wilde and C. van der Werf, https://doi.org/10.1093/eurheartj/ehae408.

Abstract

Background and Aims Risk scores are proposed for genetic arrhythmias. Having proposed in 2010 one such score (M-FACT) for the long QT syndrome (LQTS), this study aims to test whether adherence to its suggestions would be appropriate.

Methods LQT1/2/3 and genotype-negative patients without aborted cardiac arrest (ACA) before diagnosis or cardiac events (CEs) below age 1 were included in the study, focusing on an M-FACT score ≥2 (intermediate/high risk), either at presentation (static) or during follow-up (dynamic), previously associated with 40% risk of implantable cardioverter defibrillator (ICD) shocks within 4 years.

Results Overall, 946 patients (26 ± 19 years at diagnosis, 51% female) were included. Beta-blocker (βB) therapy in 94% of them reduced the rate of those with a QTc ≥500 ms from 18% to 12% ($P < .001$). During 7 ± 6 years of follow-up, none died; 4% had CEs, including 0.4% with ACA. A static M-FACT ≥2 was present in 110 patients, of whom 106 received βBs. In 49/106 patients with persistent dynamic M-FACT ≥2, further therapeutic optimization (left cardiac sympathetic denervation in 55%, mexiletine in 31%, and ICD at 27%) resulted in just 7 (14%) patients with CEs (no ACA), with no CEs in the remaining 57. Additionally, 32 patients developed a dynamic M-FACT ≥2 but, after therapeutic optimization, only 3 (9%) had CEs. According to an M-FACT score ≥2, a total of 142 patients should have received an ICD, but only 22/142 (15%) were implanted, with shocks reported in 3.

Conclusions Beta-blockers often shorten QTc, thus changing risk scores and ICD indications for primary prevention. Yearly risk reassessment with therapy optimization leads to fewer ICD implants (3%) without increasing life-threatening events.

* Corresponding author. Tel: +390 2619113408, Fax: +390 2619113411, Email: p.schwartz@auxologico.it, peter.schwartz@unipv.it

Structured Graphical Abstract

Key Question

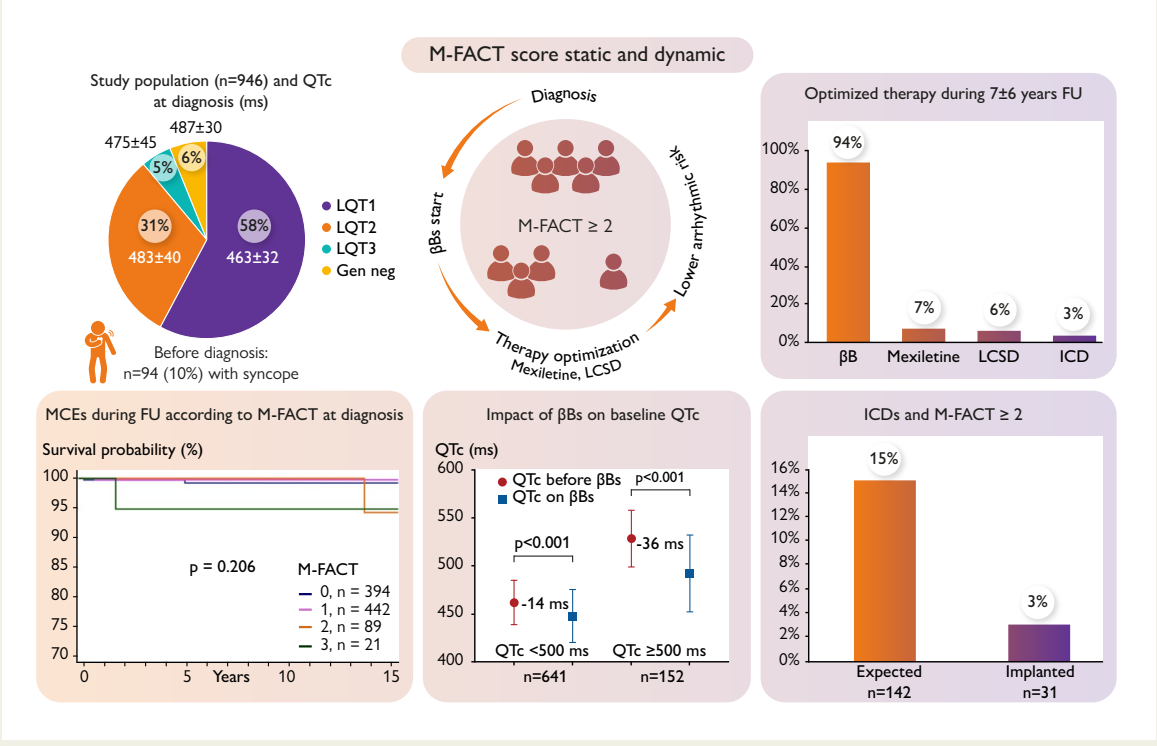
Does an M-FACT score ≥2 in long QT syndrome (LQTS), previously proposed as a cut-off for the implant of the implantable cardioverter defibrillator (ICD), effectively identify high-risk patients? Can therapy modify parameters critical for risk assessment, thus reducing the predicted arrhythmic risk? Does dynamic risk reassessment outperform a single assessment at first visit?

Key Finding

Of 946 patients with LQTS, none died during 7±6 year follow-up. Beta-blockers, often accompanied by mexiletine and left cardiac sympathetic denervation, shortened QTc, a parameter pivotal for risk stratification, thus voiding its predictive value. Dynamic risk assessment with timely therapeutic optimization significantly decreased the number of ICDs which would have been implanted based on baseline M-FACT score without enhancing risk of life-threatening events.

Take Home Message

In LQTS patients a single risk prediction made at diagnosis, prior to therapeutic optimization, is likely to overestimate risk and to result in unnecessary ICD implantations, with a negative impact on quality of life.



Genotype, QTc, and history of arrhythmic events at diagnosis are reported for the whole study population. Kaplan–Meier curves of major cardiac event-free survival during follow-up (FU) are depicted by the static M-FACT score. In the central, upper panel, there is a schematic representation of the evolution over the time of an M-FACT score ≥2, from a static presentation at diagnosis through a dynamic change during FU on beta-blockers (βBs), along with therapy intensification, which leads to a lower number of patients with an intermediate/high level of risk. In the central, lower panel, the impact of βBs on QTc according to the baseline value is shown. On the right, top, the frequency of βB use and of all incremental therapeutic measures implemented during FU is shown; on the right, bottom, the percentage of implantable cardioverter defibrillators actually implanted in the long QT syndrome cohort is plotted against the one expected according to a static M-FACT score ≥2. LCSD, left cardiac sympathetic denervation.

Keywords Channelopathies • Long QT syndrome • Risk scores • Ventricular arrhythmias • Sudden cardiac death

Introduction

Life-threatening arrhythmias of genetic origin, whether caused by cardiomyopathies or by channelopathies, often haunt clinical cardiologists, because a wrong therapeutic decision may carry devastating consequences for both patients and physicians. The main cause of grief is represented by the fact that aborted cardiac arrest (ACA) and sudden cardiac death (SCD) can be the first manifestations of the disease.[1] The problem does not involve patients presenting after a cardiac arrest, because there is a general consensus that most of them need protection in the form of an implantable cardioverter defibrillator (ICD; secondary prevention).[2,3] In contrast, indications for prophylactic device implantation in patients without life-threatening ventricular tachyarrhythmias (primary prevention) are often less certain[4,5] and can daunt

practicing cardiologists. Recently, to assist clinicians in risk assessment, several algorithms have been developed that result in risk scores, often designed as electronic calculators,[6–9] whose clinical utility, at least for the long QT syndrome (LQTS), remains to be established.

In 2010, in the largest study focused on patients with LQTS implanted with an ICD, we proposed a scoring system, called M-FACT, designed to predict the probability of appropriate ICD shocks based on pre-implantation clinical features.[10] Having recently raised concerns about the possibility that a passive acceptance of published risk scores based on the initial clinical presentation might overestimate the predicted risk and lead to inappropriate therapy, including excessive recommendation for ICD implants,[11] it became an ethical responsibility to assess whether or not the use of our own proposed score in LQTS would have led to correct medical choices.

Accordingly, we analysed the clinical outcome in our cohort of patients with LQTS without a history of ACA before diagnosis or of cardiac events (CEs) in the first year of life.[12] We considered as clinically relevant questions what will happen to patients with syncope on beta-blocker (βB) therapy and the relevance of genotypes during follow-up. Our main focus was on the actual risk of ACA/SCD in patients with an intermediate/high level of risk, i.e. those with, either at diagnosis or during follow-up, an M-FACT score ≥2 that we had previously proposed as a cut-off for ICD implantation[10] and assessed whether or not using the M-FACT risk score in patients with LQTS might lead to a significant overuse of ICDs compared with expert-driven treatment based on static and dynamic risk assessments. The results were disturbing and carried significant clinical implications.

Methods

The M-FACT score

The understanding of the present study requires a clear description of the M-FACT score, which was developed as a score assigned at the time of ICD implant to predict the likelihood of a patient receiving appropriate ICD shocks based on four pre-implantation clinical variables that were identified as independent predictors of outcome in a multivariable analysis.[10] On this basis, we assigned 1 point each to cardiac arrest, syncope on βBs, age <20, and a QTc between 500 and 550 ms; 2 points to a QTc >550 ms. In addition, just for previously symptomatic patients, we assigned 'minus 1 point' for the absence of CEs on βBs for at least 10 years. Based on our own 2010 data,[10] patients with no history of ACA but an M-FACT ≥2 had an incidence of ICD shocks at 4 years at a rate of ∼40%, compared with a rate of below 5% among those with an M-FACT <2, thus suggesting the need for an ICD in patients with an M-FACT ≥2.

Study population

Inclusion criteria

We focused on patients with LQTS clinically evaluated between 1971 and 2023, who were found to be genotype-positive for variants (pathogenic, likely pathogenic, or variants of undetermined significance) in the *KCNQ1*, *KCNH2*, or *SCN5A* genes, or to be genotype negative-phenotype positive, who had been followed up for at least 1 year after diagnosis or after our first visit and consistently managed at our center. Patients with the Jervell and Lange-Nielsen (J-LN) syndrome ($n = 6$),[13] those with a history of ACA before diagnosis/initiation of βB therapy ($n = 25$), and/or with CEs in the first year of life ($n = 3$)[12] were excluded, leading to a final population of 946 patients.

Event adjudication

Cardiac events included arrhythmic syncope, appropriate ICD shocks, ACA, and SCD. Documented episodes of asymptomatic self-terminating polymorphic ventricular tachycardia [torsades de pointes (TdP)], lasting at least for 10 beats, were considered as CEs and included in the syncope group. Major CEs (MCEs) were defined as SCD, ACA, and appropriate ICD shocks.

Patient management

Patients are usually evaluated with a resting electrocardiogram (ECG), an exercise stress test, and a 24 h 12-lead ECG Holter recording at least once a year. After the first evaluation, when βBs are prescribed, more visits are generally planned to optimize βB dosage. Patients deemed to be at high risk based on a combination of factors such as symptoms on βBs, QTc ≥500 ms at resting ECG or on Holter ECG recordings or exercise stress recovery, T-wave alternans,[14] intolerance to βBs, prolonged sinus pauses, bizarre repolarization, all recognized as dangerous patterns by clinical experience, receive treatment intensification with mexiletine and/or left cardiac sympathetic denervation (LCSD) at first, and, more rarely, an ICD, depending on patient characteristics and according to our flow chart.[15]

M-FACT score calculation

The M-FACT score was calculated at the time of diagnosis ('static M-FACT score') and then during follow-up ('dynamic M-FACT score'). Our main objective was to assess the outcome of patients with an M-FACT ≥2, either static or dynamic, used as a proxy for any patient with LQTS presenting with similar features at the initial visit or during follow-up, and thus requiring a therapeutic decision. We used the same scoring system prospectively in the entire population. Among patients with an M-FACT score <2 at diagnosis, we identified those who reached a dynamic M-FACT score ≥2 during follow-up, as this represents the first time when the responsible physician is faced with the crucial question of whether his/her patient is sufficiently protected by the sole βB therapy or whether additional therapeutic measures, particularly an ICD implantation, are needed for the prevention of MCEs.

QT interval was measured on the resting ECG in Leads DII and V5; QTc was calculated according to Bazett[16] and the longest value was used.

For the purpose of the M-FACT score calculation, in those patients initially diagnosed and managed elsewhere who came to our centre without a documented ECG, we had to use the QTc values reported on their medical charts for the baseline assessment. In the subsequent follow-up, we used the ECGs directly measured by us. For the analysis of the effect of βBs on ECG parameters, to guarantee consistency and reproducibility of the measurements, we included only those patients with an available, directly measurable, 12-lead ECG both before and, for greater comparability, at 12–18 months after they started βBs. We also evaluated the outcome of the entire population to identify significant and independent predictors of CEs during follow-up, including genotype. Finally, we assessed the outcome of patients with a syncopal episode on βBs independently of the M-FACT score.

Statistical analysis

Categorical variables are presented as counts and percentages and compared between groups by using Fisher's exact test or a χ^2 test, as appropriate, and continuous variables are presented as mean ± standard deviation. The McNemar test was used for the comparison of paired nominal data. Paired continuous variables were compared using a paired *t*-test or a Wilcoxon signed rank test, as appropriate. Unpaired continuous variables were compared using an unpaired *t*-test or a Mann–Whitney test, as appropriate.

Upon treatment, the cumulative event-free survival rate was calculated using the Kaplan–Meier method with the log-rank test for comparison by the M-FACT score. For this analysis, time was calculated since the diagnosis/start of βB therapy. A Cox-proportional hazard regression model was built to estimate the hazard ratio (HR) for the association between the main clinical and genetic characteristics of interest at diagnosis and the occurrence of the first CE during follow-up in the overall population. Harrell's *C*-index was reported to assess the adequacy of risk prediction.

Table 1 General characteristics of the study population

	LQT1	LQT2	LQT3	Negative genetics	Total
Genotype	547 (58)	297 (31)	48 (5)	54 (6)	946 (100)
Female	311 (57)	127 (43)	23 (48)	22 (41)	483 (51)
Proband status	250 (46)	129 (43)	25 (52)	38 (70)	442 (47)
Age at diagnosis (years)	27 ± 20	26 ± 18	22 ± 17	26 ± 17	26 ± 19
Syncope before diagnosis/βB start	43 (8)	38 (13)	8 (17)	5 (9)	94 (10)
QTc at diagnosis	463 ± 32	483 ± 40	475 ± 45	487 ± 30	471 ± 37
QTc at diagnosis ≥500 ms	55 (10)	82 (28)	11 (23)	22 (40)	170 (18)
FU after diagnosis, years (mean ± SD)	6.2 ± 5.6	7.5 ± 8.6	10.5 ± 9.2	6.6 ± 5.5	7.0 ± 6.0
On βBs	514 (94)	283 (95)	43 (90)	53 (98)	893 (94)
On propranolol, mg/kg/die	131 (26), 2.0 ± 0.3	63 (22), 2.1 ± 0.5	12 (28), 2.1 ± 0.3	13 (25), 2.1 ± 0.4	219 (25), 2.1 ± 0.4
On nadolol, mg/kg/die	371 (72), 1.0 ± 0.2	215 (76), 1.0 ± 0.3	29 (67), 1.0 ± 0.2	40 (75), 1.0 ± 0.2	655 (73), 1.0 ± 0.2
On β1-selective βB	12 (2)	5 (2)	2 (5)	0	19 (2)
QTc on βB ≥500 ms	32 (6)	61 (22)	7 (16)	8 (15)	108 (12)
CEs on βB	14 (3)	15 (5)	2 (5)	2 (4)	33 (4)
ACA on βB	2 (0.4)	1 (0.4)	1 (2)	0 (0)	4 (0.4)
ACA on βBs among patients with QTc at diagnosis ≥500 ms	1 (2)	1 (0.4)	0 (0)	0 (0)	2 (0.2)
ACA on βBs among patients with QTc at diagnosis <500 ms	1 (0.2)	0 (0)	1 (8)	0 (0)	2 (0.2)
Syncope on βB	12 (2)	14 (5)	1 (2)	2 (4)	29 (3)
Syncope on βB in previously asymptomatic patients ($n = 852$)	5 (1)	5 (2)	0 (0)	1 (2)	11 (1)
Syncope on βB in previously symptomatic patients ($n = 94$)	7 (16)	9 (24)	1 (13)	1 (20)	18 (19)
PM	1 (0.2)	1 (0.3)	0 (0)	0 (0)	2 (0.2)
ICD	9 (2)	15 (5)	6 (13)	1 (2)	31 (3)
LCSD	15 (3)	31 (10)	6 (13)	6 (11)	58 (6)
RCSD	0 (0)	1 (0.3)	0 (0)	0 (0)	1 (0.1)
Mexiletine at last FU	4 (0.7)	44 (15)	7 (15)	8 (15)	63 (7)
SCD during FU	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

ACA, aborted cardiac arrest; CEs, cardiac events; FU, follow-up; ICD, implantable cardioverter defibrillator; LCSD, left cardiac sympathetic denervation; PM, pacemaker; RCSD, right cardiac sympathetic denervation; SCD, sudden cardiac death; SD, standard deviation.

A two-tailed *P*-value <.05 was considered as statistically significant. Computations and images were recorded using IBM SPSS Statistics version 27.0, MedCalc Statistical Software version 20.

Results

Study population

Table 1 summarizes the general characteristics of the 946 LQTS genotyped patients (483 females, 51%): 547 LQT1 (58%), 297 LQT2 (31%), 48 LQT3 (5%), and 54 (6%) genotype-negative patients, with a mean age at diagnosis of 26 ± 19 years. Most patients were diagnosed after the year 2000. Almost half ($n = 442$, 47%) were probands, with a similar proportion across LQT1, LQT2, and LQT3, but the proportion was higher among genotype-negative patients (70%). Among them, 94 (10%) had a syncope before diagnosis/initiation of βB therapy. Overall, 170 patients (18%) had QTc values ≥500 ms at the first evaluation.

Most patients ($n = 893$, 94%) were started on βB therapy, mostly nadolol (73%) or propranolol (25%), leading to a clear reduction in the number of those with a QTc ≥500 ms over follow-up (from

Table 2 Impact of beta-blocker therapy on heart rate and QTc

	n	Baseline HR	HR on βB	Baseline QTc	QTc on βB	ΔQTc
LQT1	443	74 ± 20	60 ± 16*	467 ± 31	450 ± 31*	−17 ± 24
LQT2	267	74 ± 19	60 ± 14*	487 ± 41	467 ± 39*	−20 ± 29
LQT3	36	70 ± 13	61 ± 11*	469 ± 34	455 ± 37*	−14 ± 26
Genotype negative	47	76 ± 18	60 ± 14*	487 ± 28	460 ± 24*	−28 ± 26
Total	793	74 ± 19	60 ± 15*	475 ± 36	457 ± 35*	−18 ± 27
All patients ≥500 ms	152	75 ± 19	62 ± 15*	528 ± 29	492 ± 40*	−36 ± 34
All patients <500 ms	641	74 ± 20	60 ± 15*	462 ± 23	448 ± 27*	−14 ± 22**
LQT1 ≥500 ms	49	71 ± 15	62 ± 18*	523 ± 28	486 ± 45*	−37 ± 34
LQT1 <500 ms	394	75 ± 20	60 ± 15*	460 ± 23	446 ± 25*	−14 ± 22**
LQT2 ≥500 ms	78	76 ± 21	61 ± 14*	536 ± 31	501 ± 35*	−35 ± 33
LQT2 <500 ms	188	72 ± 18	60 ± 14*	466 ± 22	453 ± 30*	−13 ± 25**
LQT3 ≥500 ms	5	67 ± 9	60 ± 10	525 ± 25	508 ± 40	−18± 56
LQT3 <500 ms	31	69 ± 15	60 ± 12*	460 ± 26	446 ± 29*	−13 ± 20
Genotype negative ≥500 ms	19	71 ± 13	61 ± 17*	512 ± 13	468 ± 27*	−44 ± 29
Genotype negative <500 ms	28	75 ± 16	59 ± 11*	471 ± 25	454 ± 21*	−17 ± 19**

Data refer to patients with a 12-lead ECG both before and within 18 months from βB therapy initiation.
*$P < 0.05$ before and on βB.
**$P < 0.05$ comparing the QTc change within the same genotype and according to baseline QTc.

164/893, 18% to 108/893, 12%; −34%, $P < .001$) across all genotypes (*Table 1*).

Table 2 shows the effect of βB therapy on heart rate and QTc. In the overall population on βB therapy with available ECG data ($n = 793$), resting heart rate was reduced from 74 ± 19 to 60 ± 15 b.p.m. ($P < .0001$), while QTc shortened from 475 ± 36 to 457 ± 35 ms ($P < .0001$, mean reduction −18 ± 27 ms), without significant differences across genotypes. The amount of QTc shortening on βBs was more pronounced among those with a QTc ≥500 ms (−36 ± 34 vs. −14 ± 22 ms, $P < .0001$; *Figure 1*).

On βB therapy, 33 (4%) patients had CEs, including 5 MCEs (ACA in 4, ICD shock in 1); 69% of them were already symptomatic before therapy initiation. During a mean follow-up of 7 ± 6 years after diagnosis, 31 patients (3%) received an ICD and 63 (7%) patients started mexiletine. LCSD was performed in 58 patients (6%) followed by right cardiac sympathetic denervation in 1.

Importantly, there was not a single case of SCD in the entire cohort of patients with LQTS followed at our centre over more than 35 years. Among the 31 patients implanted with an ICD, shocks on βBs during follow-up occurred in 3 patients (10%), all implanted in secondary prevention. None of these 31 had electrical storms.

Supplementary data online, *Figure S1* shows the survival free from MCEs and from any CEs in the entire population. Survival free from MCEs at 5, 10, and 15 years was 99.5%, 99.5%, and 98.5%, respectively. Survival free from any CEs at 5, 10, and 15 years was 97%, 95%, and 93%, respectively.

In the overall population (see Supplementary data online, *Table S1*), only two independent predictors of CEs during follow-up were identified; namely, syncope before diagnosis [HR 7.58, 95% confidence interval (CI) 3.55–16.18, $P < .001$] and QTc ≥500 ms at presentation

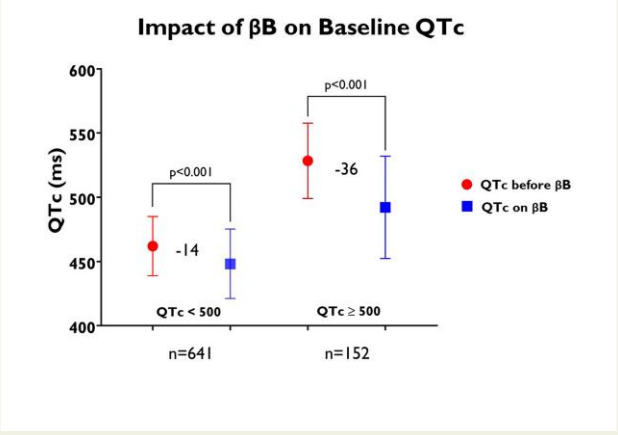


Figure 1 Impact of beta-blocker therapy on QTc according to baseline QTc. The effect of beta-blockers on QTc was assessed, for greater comparability, in all patients with a 12-lead electrocardiogram available before and within 18 months of beta-blocker initiation

(HR 3.13, 95% CI 1.5–6.99, $P = .002$). Within the limitation of few patients with CEs ($n = 33$), genotype was not associated with outcome. The model has a good predictive performance power (*c*-statistic 0.86, 95% CI 0.80–0.93, $P < .001$).

M-FACT at diagnosis and outcome

Supplementary data online, *Table S2* summarizes the distribution of all 946 patients with LQTS into groups according to static M-FACT

Table 3 General features of patients with long QT syndrome with an M-FACT score ≥2

	Static score ≥2 (*n* = 106)	Dynamic score ≥2 (*n* = 32)
M-FACT=0 at diagnosis		4 (12)
M-FACT=1 at diagnosis		28 (88)
LQT1	31 (29)	11(34)
LQT2	57 (54)	17 (53)
LQT3	6 (6)	2 (6)
Genotype negative	12 (11)	2 (6)
Syncope before diagnosis	31 (29)	7 (22)
Proband status	86 (78)	20 (63)
Age at diagnosis	17 ± 17	14 ± 13
QTc at diagnosis	535 ± 33	490 ± 23
QTc on βB	493 ± 43	495 ± 36
Components of the score		
Age <20 years[a]	92 (87)	23(72)
QTc[b], ms	535 ± 33	513 ± 36
QTc ≥500 ms[b]	106 (100)	24 (75)
QTc ≥550 ms[b]	34 (32)	5 (16)
Symptoms on βB		12 (38)
Follow-up post-diagnosis, years	9 ± 8	11 ± 8

[a]Age <20 at diagnosis for static M-FACT and upon achievement of a dynamic M-FACT score ≥2 in the second group.
[b]QTc off therapy for static M-FACT and on βB for dynamic M-FACT.

(i.e. at diagnosis) with the corresponding prevalence of MCEs and CEs during follow-up. Most patients (*n* = 836, 88%) scored 0–1 at diagnosis, the remaining 110 (12%) presented with an M-FACT ≥2. While MCEs were too uncommon to appreciate any difference between score groups, the frequency of any CEs during follow-up significantly increased from 2% in patients with an M-FACT of 0–1 to 14% among patients with an M-FACT ≥2 (11% in M-FACT =2 and 24% in M-FACT =3, *P* < .001 across groups).

Supplementary data online, *Figure S2* shows the survival free from MCEs and from any CEs in the entire population according to the M-FACT score at diagnosis. Static M-FACT was significantly associated with CEs, but not with the rare incidence of MCEs. Among patients with a static M-FACT ≥2, survival free from MCEs at 5, 10, and 15 years was 99%, 99%, and 95%, respectively; survival free from any CEs at 5, 10, and 15 years was 88%, 84%, and 80%, respectively.

Characteristics and outcome of patients with M-FACT ≥2

A total of 110 patients presented with a static M-FACT ≥2. As 4 of them refused to take βBs, we analysed the remaining 106 on optimal treatment after diagnosis. Their general features and distribution per genotype are reported in *Table 3*.

At diagnosis, all these patients had a QTc ≥500 ms (mean QTc 535 ± 33 ms), including 34 with a QTc ≥550 ms. During a mean follow-up of 9 ± 8 years on βB, 52 (49%) maintained a QTc ≥500 ms, including 12 (11%) with a QTc ≥550 ms. *Figure 2* summarizes the post-diagnosis evolution of these 106 patients. While 57 patients (54%) lowered their M-FACT below 2, the rest (*n* = 49, 46%) maintained a dynamic M-FACT ≥2: 15/49 (31%), because of a first CE on βBs (13 syncope and 2 ACA), the remaining because of persisting QTc values ≥500 ms on βBs. After therapeutic optimization (LCSD in 27, 55%, mexiletine in 15, 31%, and ICD in 13, 27%), only 7/49 patients (14%) had recurrences (6 syncope, 1 ICD shock). Among the remaining 57/106 (54%, bottom of *Figure 2*) patients with a dynamic M-FACT <2 on βBs (age >20 or QTc <500 ms on βBs), none suffered CEs on βBs. Nonetheless, some of them received further therapeutic optimization triggered by our clinical risk assessment (LCSD in 4, 7%, mexiletine in 10, 17%, and ICD in 1, 2%). Intriguingly, within the 100 patients with a static M-FACT score ≥2 and with an ECG recorded within 18 months of βB therapy, those with breakthrough CEs had a significantly lesser QTc shortening (−14 ± 28 ms vs. −45 ± 33 ms, *P* < .01; Supplementary data online, *Figure S3*), despite an identical baseline QTc (536 ± 22 and 536 ± 34 ms).

A dynamic M-FACT ≥2 was subsequently developed in an additional 32 patients (*Table 3*) with an M-FACT <2 at diagnosis (4, 12% with an M-FACT of 0 and 28, 88%, with an M-FACT of 1). The main reason (17/32, 53%) for a dynamic M-FACT ≥2 on βBs was the combination of age <20 and QTc ≥500 ms, while 12 patients reached a dynamic M-FACT ≥2 due to symptoms on βBs (in 5 cases associated with a QTc ≥500 ms), in 2 cases represented by ACA. Therapeutic optimization in these patients was achieved through mexiletine in 9 (28%), ICD in 8 (25%), and LCSD in 6 (19%); only 3/32 (9%) had recurrences after optimization (syncope in 2, ICD shock in 1; *Figure 3*).

Impact of therapies on the M-FACT score

As a consequence of the QTc shortening induced by βB therapy (*Figure 1*), in 93/793 patients (12%), βBs caused an M-FACT reduction of at least 1 point at the first visit after therapy implementation. When therapy optimization was performed with mexiletine in 63 patients, the M-FACT score was reduced by ≥1 point in 23 (37%), with a mean QTc shortening of 49 ± 25 ms, from 527 ± 20 to 479 ± 19 ms, while it increased in none. Following LCSD, performed in 58 patients, the M-FACT score was reduced by 1 point in 20 (35%), with a mean a QTc shortening of 49 ± 24 ms, from 553 ± 39 to 504 ± 31 ms, while it increased in none. Among the 19 patients with LCSD and mexiletine, the combined therapeutic intensification led to an M-FACT score reduction of at least 1 point in 10 (53%) through a QTc shortening.

M-FACT and implantable cardioverter defibrillator

Overall, 31 (3%) patients received an ICD: 15 (48%) as primary prevention, 12 (39%) after syncopal episodes on βBs, and 4 (13%) after an ACA on βBs. Notably, our group implanted only 14/31 (45%) ICDs, including 7 as primary prevention; the others were implanted before referral to our centre.

Based on static M-FACT ≥2 at diagnosis, 110 should have been implanted with an ICD. However, only nine (8%) did actually receive it during follow-up. Looking at all patients with an M-FACT ≥2 (static or dynamic), 142 patients would have been implanted by rigidly following the 2010 indications.[10] In reality, only 22 of these 142 patients (15%) received an ICD, with shocks during follow-up in 3 of them (14%), all with either ACA or syncope on βBs. Importantly, among the 804

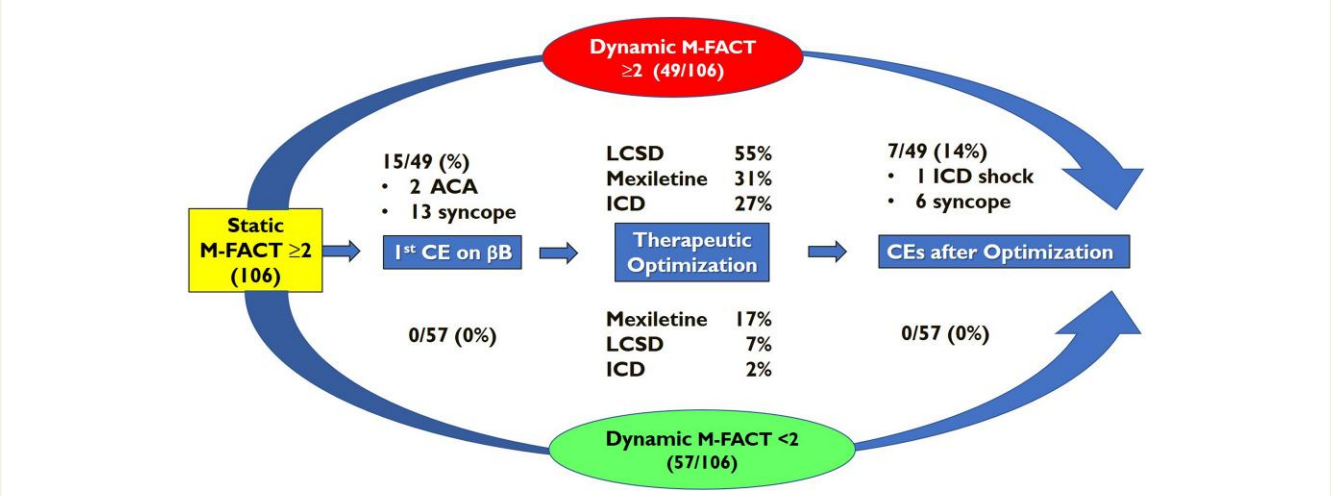


Figure 2 Evolution of the 106 patients with long QT syndrome on beta-blockers with a static M-FACT ≥2 at presentation during a mean follow-up of 9 ± 8 years. Post-diagnosis cardiac events on beta-blockers conferring the score one more point, additional therapeutic interventions, and cardiac events occurring 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 <2 (lower half). Changes in QTc on beta-blockers (<500/550> ms) and in patient age (<20> years) also contributed to any further shift of dynamic M-FACT

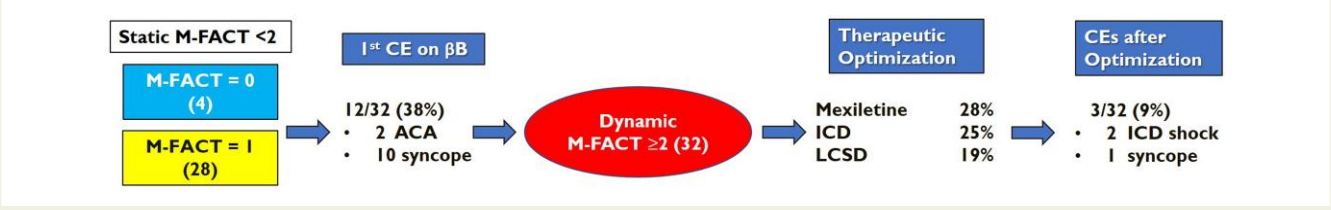


Figure 3 Evolution of the 32 patients with long QT syndrome who developed a dynamic M-FACT ≥2 during follow-up. Their static M-FACT <2 is shown on the left, along with cardiac events on beta-blockers conferring the score one more point, additional therapeutic interventions, and cardiac events occurring despite therapy optimization. Changes in QTc on beta-blockers (<500/550> ms) and in patient age (<20> years) also contributed to any further shift of dynamic M-FACT

patients with an M-FACT of 0–1, and therefore theoretically at low risk, an ICD was implanted in 9 (1%).

Patients with syncope on beta-blockers

Independently of the M-FACT score, a syncope on βB therapy occurred in 29/893 patients (3%) (*Table 4*); most ($n = 18$, 62%) had a QTc ≥500 ms on βB. Seven of these 29 patients (24%) were referred from other centres after their event: none was taking propranolol or nadolol at the target dose and with proper compliance, and all had already received an ICD. Among the 22 patients followed at our centre since diagnosis, therapeutic intensification was achieved by LCSD in 17 (77%), ICD in 5 (23%), and mexiletine in 3 (14%). At 13 ± 10 years after the first syncope on βB, 0/29 patients had either SCD or ACA, 1/29 (3%) had appropriate ICD shocks on atenolol, and 8/29 patients (28%) suffered repeated syncope. Following LCSD, 7/17 (41%) patients still had recurrences, just a single episode in 4, and 3/7, all with QTc values persisting over 500 ms, received an ICD.

Thus, among patients with syncope despite βBs, by performing LCSD, one can expect at least half of them to become asymptomatic.

Discussion

The main finding of the present study is that a risk score developed to predict device shocks in patients with LQTS who already had an ICD, albeit correctly estimated on the basis of data available in 2010,[10] if implemented today on a broader LQTS population would inappropriately lead to an excessive and unnecessary number of ICD implants (*Structured Graphical Abstract*). This unabashed reappraisal of our own previous data carries major clinical implications. On one hand, it is a clear reminder that the implementation of effective therapies (βB, LCSD, and possibly mexiletine) is by definition likely to lower the baseline arrhythmic risk and thereby reduce the need for ICDs. On the other hand, it calls for caution before jumping from the clinical presentation at the time of diagnosis to a rigid risk assessment which would lead, more likely than not, to a possibly unnecessary ICD implant, paradoxically leaving unprotected those patients whose risk might increase over time.

Concerns were recently expressed[11] for the growing push to use electronic risk calculators and risk scores that would allegedly allow to predict risk already at the initial baseline evaluation. As these

Table 4 Characteristics and outcome of patients with syncope on beta-blockers

Syncope on βB, $n = 29$	n (%)
Female	20 (69)
LQT1/LQT2/LQT3/genotype negative	12/14/1/2 (42/48/3/7)
Syncopal episodes before diagnosis	17 (59)
Age at first CE	16 ± 13
QTc ≥500 ms on βBs	18 (62)
On propranolol/nadolol at the target dose and compliant before syncope on βB	22 (76)
On mexiletine at last FU	3 (10)
LCSD at last FU	17 (59)
ICD at last FU	12 (41)
ICD implanted by our group	5 (42)
FU after first syncope on βB (years)	13 ± 10
ACA during FU	0 (0)
ICD shock during FU	1 (3)
Recurrence of syncope on βB	8 (28)

ACA, aborted cardiac arrest; CE, cardiac events; FU, follow-up; ICD, implantable cardioverter defibrillator; LCSD, left cardiac sympathetic denervation.

algorithms do not account for changes in the arrhythmic risk resulting from effective treatment, their predictive power, at least for LQTS, is likely to be altered once the patients are properly managed. This is why their supine acceptance by cardiologists without specific expertise in LQTS, or in other arrhythmogenic disorders of genetic origin, could have serious consequences.

Lastly, the data in the patients who had a syncope while taking βBs indicate that, when therapy is properly optimized, the risk of ACA is modest or minimal and may not automatically require an ICD implant.

The origin of the M-FACT score

The original submission in 2010 of our manuscript[10] had not mentioned a risk score. We had simply indicated that at univariate analysis, a prior ACA, CEs despite therapy, a markedly prolonged QTc and younger age at implantation appeared to be potentially useful risk stratifiers to predict the probability of appropriate therapies from the ICD, thus allowing the identification of those patients expected to benefit most from the implantation. A multivariate Cox model identified all four selected variables as independent predictors of future appropriate shocks. Then, a clever reviewer suggested developing a score (the reviewer went as far as to suggest the acronym M-FACT!) based on the number of these risk factors when coexisting in the same patient. Understandably, we gratefully followed the reviewer's suggestion, and the M-FACT score was thus published. Relevantly, an M-FACT score ≥2 was associated with a 40% risk of experiencing a first appropriate shock within 4 years of implant.

On this basis, for example, an asymptomatic 15-year-old patient with LQTS with a QTc of 530 ms would probably be implanted by a physician who, without further considerations, would passively follow what had been published. In our practice, we never followed the possible indications from the M-FACT score because our management decisions always reflect the overall assessment that we make, and readjust at each yearly visit, by incorporating all facets of the clinical presentation and integrating them with our personal experience with LQTS.[17] As we recently criticized the flurry of novel risk calculators,[11] we felt the responsibility to quantitatively assess the value and limits of the risk score that we had previously proposed and left in the literature without further warnings for the cardiologists with more limited experience.

Implantable cardioverter defibrillator shocks vs. major cardiac events

As previously stated, the M-FACT score was specifically developed to predict ICD shocks in patients with LQTS who already have an ICD. Implantable cardioverter defibrillator shocks are not surrogates for ACA/SCD; rather, they largely outnumber them because of appropriate but unnecessary shocks delivered on potentially self-limiting ventricular arrhythmias[11,18] that would have otherwise just resulted in syncopal or pre-syncopal episodes in patients without an ICD. Notably, the probability for a polymorphic ventricular tachycardia such as the TdP to degenerate into ventricular fibrillation (VF) is greatly influenced by the ongoing pharmacological and non-pharmacological therapy concurring to increase the VF threshold. More refined is the anti-arrhythmic prophylaxis, lower is the risk of TdP degeneration into VF. This is particularly true for LCSD, which is primarily an anti-fibrillatory intervention in structurally normal hearts[19] and is one reason for the different outcomes between centres using[15,20,21] or not using/under-using LCSD.[22] The importance of distinguishing the underlying arrhythmias leading to ICD interventions has been stressed by a multinational collaboration, including 864 patients with arrhythmogenic right ventricular cardiomyopathy.[23]

Considerations on management

For age at diagnosis, distribution across genotypes, baseline QTc and, approximately, the percentage of patients with syncope before diagnosis, our population is similar to other large LQTS cohorts reported worldwide.[22,24,25] Importantly, almost 95% of our patients were on βB therapy with propranolol or nadolol, as opposed to 84%[25] and especially 68%[22] of patients on βB therapy in recently reported large LQTS cohorts.

The percentage of patients with CEs on βB therapy was very low: 4% overall, ranging from 3% in LQT1 to 5% in both LQT2 and LQT3, and it was mostly represented by syncopal episodes and never by SCD. Less than 1% of patients ($n = 4$) had an ACA on βB therapy. Although most patients had always been followed by us and were therefore treated uniformly with nadolol or propranolol at the target dose, a minority came to us already on βB therapy, sometimes under-dosed or with the less effective β1-selective atenolol and metoprolol.[26] Indeed, 1 of 4 ACA and 6 of 29 syncope, theoretically 'on βB therapy', occurred among this minority treated suboptimally.

Another consideration important for its impact on correct management is that the zero mortality in our cohort depends on something else, besides full-dose βB therapy, and specifically on the broader use of 'therapy intensification'. We did not just wait for breakthrough events on βB therapy, but we also added LCSD,[15,20,27] mexiletine,[28–31] and even ICDs in primary prevention, whenever during the yearly control visits we observed signs that we usually interpret as alerting to increased arrhythmic risk, such as markedly prolonged QTc values on 12-lead 24 h Holter ECG, typically at night-time, large beat-to-beat variability of both RR

intervals, and duration/morphology of ventricular repolarization, all pointing to high electrical instability.

This vigilant approach, active in the early adoption of further preventive measures, clearly contributed to the excellent event-free survival, particularly from SCD and ACA, observed in our patients despite the very low use of ICD (3%), mostly implanted in secondary prevention and/or by other centres before referral to us. The very low usage of ICD, the lowest reported among worldwide referral LQTS centres,[22,25] gave us the unique opportunity to assess the risk of life-threatening CEs in an optimally treated LQTS population with an almost null impact of unnecessary ICD shocks.

Impact of management on the M-FACT score

The present data clearly indicate that in patients with LQTS without prior ACA and with an M-FACT ≥2, treated with optimal therapy (correct βBs plus, if necessary, LCSD and/or mexiletine) the risk of SCD is essentially zero. They reinforce the evidence that patients with common genotypes (i.e. with the exclusion of mutations causing calmodulinopathy[32] or J-LN) and a first syncopal episode on correct βB therapy should not necessarily all undergo ICD implantation, as recommended by recent guidelines,[3] but could be initially managed with LCSD.[15,20,21,27] Indeed, 'optimal therapy' can profoundly modify the prognosis suggested by 'risk scores', especially if they are not accompanied by proper clinical management, implemented with common sense, by cardiologists with specific expertise in LQTS.

Besides its direct impact on the prevention of arrhythmic episodes, our high βB usage was associated with a significant reduction in the number of patients with markedly prolonged QTc values (≥500 ms) during follow-up. When we examined the impact of βBs on QTc without the confounding effect of other therapies and age changes, by limiting the analyses to the first ECG on βBs within 18 months of therapy initiation, we found a mean QTc shortening of ∼20 ms with a range between 14 and 36 ms according to baseline QTc (*Figure 1*). The unpredicted finding of an apparent association between the degree of QT shortening on βB therapy and breakthrough CEs (see Supplementary data online, *Figure S3*) merits further investigation. Incidentally, independently of the implications for arrhythmic scores, this represents the largest study on the impact of βBs on QTc.

It follows that, once on therapy, a parameter contributing importantly to our own risk score (QTc) was strikingly modified, and the risk was no longer the same. It is evident that if we had relied on an M-FACT score ≥2, we would have in all likelihood implanted with an ICD 142 patients, mostly young. With our approach, which we might call 'yearly optimization', the total number of ICDs implanted in this group was 22 without a single sudden death in the entire cohort of 946 patients. This approach carried another benefit. Indeed, 9 patients out of 804 with an M-FACT <2 (both static and dynamic), but who manifested during follow-up patterns indicating high risk despite therapy optimization, received an ICD. If the initial assessment had not been re-evaluated during follow-up, they would have remained at risk for life-threatening arrhythmias. Nonetheless, the original M-FACT score remains useful because, as shown in Supplementary data online, *Figure S2*, the static score is associated with the risk of syncopal episodes. Therefore, the M-FACT score could help non-experts decide when referral and 'therapy intensification' might be warranted. The main message of the present study is to avoid jumping from a static evaluation to ICD implantation before having considered the impact of βBs and of treatment intensification, if necessary.

The fact that, 15 years after diagnosis, survival free from MCEs and from any CEs was 99% and 93%, respectively, cannot be dismissed or belittled and should be presented to the families when informing them about the impact of different management strategies.

Limitations and strengths

Whereas the original M-FACT score was developed to assess the probability of appropriate ICD shocks in patients already implanted, the current study was based on patients not yet implanted; this might appear as a limitation, but it is not. To verify whether or not it is appropriate to implant patients with LQTS with an ICD based on their clinical presentation, which was our objective, it is essential that patients do not already have an ICD. The M-FACT score was not our target; rather it was a tool to explore the appropriateness of medical decisions based on a static or even dynamic risk assessment of the patients, not contemplating all the available therapeutic options (and their effects) before an ICD implant.

Ours is a single-centre study. This is a strength, because it avoids the major limitation of multicentre studies, in which patients are treated differently by different doctors with different degrees of expertise and with different approaches, and where, not infrequently, there is no access to LCSD. In contrast, the uniformity of the approach at a centre with a recognized long-standing expertise provides a clear indication of what the outcome can be if patients receive truly optimal treatment. In the present case, with data from almost 1000 patients, it is evident that a constantly reviewed risk assessment leads to a most satisfactory outcome without affecting quality of life.

Caution is necessary before extrapolating our conclusions to risk calculators proposed for other genetic disorders in which therapy does not always modify the parameters determining risk, as is probably the case for hypertrophic cardiomyopathy.[6]

Conclusions

Our data conclusively show that following the M-FACT score literally would have been detrimental for the patients, as it would have led to many unnecessary ICD implants in young patients and might have missed the identification of patients whose risk increased during follow-up. The inescapable conclusion is that to decide what might be the arrhythmic risk for patients with LQTS before starting therapy is not justifiable based on the present data on a large cohort of patients managed in a centre with long-standing experience. To assume that other risk scores to assess risk at the time of diagnosis, such as the 1–2–3 risk score recently proposed[8] and immediately adopted by some guidelines,[3] would not suffer the same limitations and weaknesses of the M-FACT score looks like wishful thinking.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

Data are available upon reasonable request to the corresponding author.

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Ethical Approval

This retrospective analysis of our clinical reports was approved by the Ethics Committee of the Istituto Auxologico Italiano number 051806.

Pre-registered Clinical Trial Number

None supplied.

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