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# Left Cardiac Sympathetic Denervation for Long QT Syndrome: 50 Years' Experience Provides Guidance for Management

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## Abstract

### Objectives

This study sought to report our single-center experience with left cardiac sympathetic denervation (LCSD) for long QT syndrome (LQTS) since 1973.

### Background

LCSD is still underutilized because clinicians are often uncertain whether to use it versus an implantable cardioverter-defibrillator (ICD).

### Methods

We performed LCSD in 125 patients with LQTS (58% women, mean QT interval corrected for frequency [QTc]  $527 \pm 60$  ms, 90% on beta blockers) with a follow-up of  $12.9 \pm 10.3$  years. They were retrospectively divided into 4 groups according to the clinical/genetic status: very high risk ( $n = 18$ , symptomatic in the first year of life or with highly malignant genetics), with aborted cardiac arrest (ACA) ( $n = 31$ ), with syncope and/or ICD shocks on beta blockers ( $n = 45$ ), in primary prevention ( $n = 31$ ).

### Results

After LCSD, 17% in the very high risk group remained asymptomatic, compared with 52%, 47%, and 97% in the other 3 groups ( $P < 0.0001$ ), with an overall 86% decrease in the mean yearly cardiac event rate ( $P < 0.0001$ ). Among 45 patients with only syncope/ICD shocks before LCSD, none had ACA/sudden death as first symptom after LCSD and a 6-month post-LCSD QTc  $< 500$  ms predicted excellent outcome. Patients with a QTc  $\geq 500$  ms have a 50% chance of shortening it by an average of 60 ms. LCSD results are not affected by common genotypes.

### Conclusions

We provide definitive evidence for the long-term efficacy of LCSD in LQTS. The degree of antiarrhythmic protection is influenced by patient's specificity and amount of QTc shortening. This novel approach to the analysis of the outcome allows cardiologists to rationally decide and tailor their management strategies to the individual features of their patients.

### Key Words

cardiac sympathetic denervation  
genetics  
implantable cardioverter-defibrillator  
long QT syndrome  
sudden death  
sympathetic nervous system

### Abbreviations and Acronyms

ACA, aborted cardiac arrest  
BB, beta-blocker  
CALM, calmodulin  
CE, cardiac event  
CI, confidence interval  
ECG, electrocardiogram  
ICD, implantable cardioverter-defibrillator  
IQR, interquartile range  
JLN, Jervell Lange-Nielsen  
LCSD, left cardiac sympathetic denervation  
LQTS, long QT syndrome  
MCEs, major cardiac events  
QTc, QT interval corrected for frequency  
RCSD, right cardiac sympathetic denervation  
SD, sudden death  
TdP, Torsades de Pointes  
VATS, video-assisted thoracoscopic surgery  
VF, ventricular fibrillation

Fifty years have elapsed since Arthur Moss performed the first left cardiac sympathetic denervation (LCSD) in a patient with the long QT syndrome (LQTS) (1), based on the experiments in dogs by Yanowitz et al. (2). We followed with the second such case on March 25, 1973 (3), having shown in cats that left stellate ganglion stimulation besides prolonging the QT interval was also triggering T wave alternans, a rare phenomenon that we had identified as typical for LQTS (4). Despite the extremely positive outcome of these pioneering interventions, as both patients became and remained completely asymptomatic for more than 40 years, cardiologists showed modest enthusiasm for this approach. Indeed, until the early 2000s, one of us (P.J.S.), remained the lonely standard-bearer of the procedure. In the years between the late 1970s and the late 1990s, either patients were coming, from all over the world, to our centers in Milan and in Pavia, or we (with our surgeon A.O.) were traveling to even far away countries to operate. Then, when in 2005 Mike Ackerman started to operate on his patients (5), and especially when the thoracoscopic approach facilitated the surgical procedure, at long last it was accepted, also because of 2 large multicenter reports (6,7), that LCSD has a major positive impact on the management of these patients. This was recognized by the guidelines only in 2017 (8), despite nonuniform opinions among experts about the timing of LCSD and ICD implantation in different groups of patients (9). Here, we review our single-center experience with LCSD for LQTS since 1973 (10). The progress made during the past 15 years is now allowing us to analyze the data in a more sophisticated way, no longer naively mixing all comers but integrating the recent understanding that the probability of therapeutic success varies greatly among different subgroups of patients with LQTS. This approach, largely new for LQTS, now provides answers to the critical questions facing a cardiologist who needs to assess whether his or her patient with LQTS is likely to benefit from LCSD and to what extent.

## **Methods**

### **Study population**

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

We analyzed the data of 125 consecutive patients with LQTS, partially previously reported (6,7) (Supplemental Figure 1) in whom, between 1973 and 2020, we had performed LCSD. We are still directly following most of these patients; for the others, follow-up data were obtained by direct contact with primary physicians. We regarded as lost to follow-up the only patient, living abroad, for whom we lost information within 1 year from surgery. Although our own approach to clinical management has been very consistent according to different time periods, patients living abroad (41%, from Europe, Russia, South Africa, China) were managed according to the local prevailing attitudes.

Patients were considered symptomatic if they had experienced at least 1 cardiac event (CE), ie, arrhythmic syncope, aborted cardiac arrest (ACA), or ICD appropriate shocks. Major cardiac events (MCEs) included sudden death (SD), ACA, and ICD shocks. Based on the intention-to-treat principle, CEs occurring after LCSD during brief periods of noncompliance were nevertheless included in the event count.

Over the years we realized that there are specific subgroups of patients who not only are at extremely high risk but who also respond poorly to traditional therapies and, for the most part, are alive just because they have been implanted with an ICD. These groups include symptomatic patients with the Jervell and Lange-Nielsen syndrome (JLN) (11), with the Timothy syndrome (caused

by pathogenic CACNA1C sequence variants) (12), with calmodulin (CALM) pathogenic sequence variants (13,14), or with cardiac events in the first year of life (15,16). Accordingly, our study population was retrospectively divided into 4 groups according to the baseline clinical/genetic features: very high risk patients (n = 18, patients with either symptoms in the first year of life or high risk features including CALM, CACNA1C, JLN, and recurrences on beta-blockers [BB]); patients with previous ACA (n = 31); patients with previous syncope and/or ICD shock on BB or previous syncope and intolerance/refusal to BB (n = 45); and patients with LCSD in primary prevention (n = 31, ie, patients still asymptomatic or with syncope off treatment but deemed to be at high risk based on a combination of factors such as QT interval corrected for frequency [QTc] >500 ms at resting electrocardiogram [ECG] and/or on Holter ECG recordings, T wave alternans, intolerance to BB, prolonged sinus pauses, bizarre repolarization, recognized as dangerous patterns by clinical experience [17]).

### **Surgical procedures**

The interventions were performed over a 47-year period (1973–2020) by 3 surgeons operating at our centers in Milan and Pavia, as well as abroad.

LCSD involves resection of the lower half of the left stellate ganglion, together with the thoracic ganglia from T2 to T4. It provides adequate cardiac denervation with no or minimal Horner's syndrome because most of the sympathetic fibers directed to the ocular region usually cross the upper portion of the left stellate ganglion and are thus spared. The procedures were performed with the supraclavicular approach until 2014 (18) (n = 94), then by using video-assisted thoracoscopic surgery (VATS) including the robotic technique when appropriate (n = 31) (19).

### **Statistical analysis**

Continuous variables are presented as mean  $\pm$  SD or median (interquartile range [IQR]) and categorical variables as percentages. Continuous variables are compared with Student's *t*-test or Mann-Whitney *U* test, as appropriate. Absolute and relative frequencies are reported for categorical variables and compared by the Fisher exact test or the chi-square test, as appropriate. Number of events >50 for a given patient was counted as 50. Incidence rates for both any CE and for MCE were computed before and after LCSD by dividing the total number of cardiac events by the total amount of observation time of patients and expressed as the average number (with 95% confidence interval [CI]) of events per patient per year of follow-up. The effect of LCSD on event count was assessed by the incidence rate ratio from a negative binomial regression using generalized estimating equations and expressed as percentage change in the rate of events when event rates are compared after and before LCSD. Robust SEs were computed to account for inpatient correlation over time.

Cumulative event-free survival was calculated using Kaplan-Meier curves and compared in subgroups by log-rank test. For this analysis, time was calculated to the first CE or MCE post LCSD and data are displayed as cumulative event-free survival. The prognostic roles of preoperative QTc (<500 or  $\geq$ 500 ms), QTc at discharge, and QTc at 6 months after LCSD were evaluated by a Cox model. Hazard ratio (HR) and its 95% CI were computed while controlling for age at surgery, sex, the presence of preoperative ACA, and of recurrences on BBs. A *P* value <0.05 was considered statistically significant.

Computations and images were carried out using IBM SPSS Statistics version 27.0, Medcalc Statistical Software version 20, and GraphPad Prism (version 8.0.0).

## Results

Table 1 shows the main characteristics of the 125 patients who underwent LCSD, also according to the 4 predefined study subgroups (see Methods).

### Clinical history before LCSD

Most patients (n = 102, 82%) were symptomatic before surgery, including 42 (34%) with a previous ACA and 81 (72%) with recurrences despite BB therapy. A median of 7 CEs per patient (IQR: 3-20) was observed from the sentinel event to LCSD, with a median yearly rate of 1.58 CEs (95% CI: 1.49-1.77). Onset of symptoms occurred in childhood (younger than age 8) in 51 patients, including 11 (11%) who had their sentinel event in the first year of life. Median age at surgery was 16 years (IQR: 10-27 years). Overall, 99 patients (79%) were genotyped: 43 LQT2, 24 LQT1, and 10 LQT3. Nine patients had very severe genotypes including 5 JLN, 1 Timothy syndrome caused by a CACNA1C pathogenic variant, and 3 CALM1 pathogenic variants. Six patients had >1 pathogenic variant and 7 were genotype negative.

Thirteen patients (10%) were not on BBs before LCSD, mostly because of severe bradycardia, hypotension, or asthma, or refusal. The type of BB was known in 106 (95%) of 112 patients: most (88%) were on propranolol (63%) or on nadolol (25%), whereas 13 (12%) were on  $\beta$ 1-selective BB. Twelve patients (10%) were also on mexiletine.

Six patients (5%) had a pacemaker implanted before LCSD for sinus bradycardia to allow full-dose BB. Fifteen patients (12%) received an ICD: 9 after an ACA, 6 because of syncopal episodes despite BB. Among them, 12 (80%) suffered multiple appropriate ICD shocks before LCSD (median 14, IQR: 5-51). Within the 4 study subgroups the most frequent indications for LCSD were previous syncope/ICD shocks on BB or previous syncope and intolerance/refusal to BB (n = 45). The mean QTc of patients with ACA and of those with syncope/ICD shock were extremely long and similar ( $537 \pm 65$  vs  $530 \pm 51$  ms;  $P = 0.80$ ). LQT1 and LQT2 patients were equally represented among those with ACA, whereas in primary prevention there were more LQT2 than LQT1 (64% vs 23%;  $P = 0.001$ ). Of the 31 patients in primary prevention, 23 (74%) were asymptomatic before LCSD with a QTc of  $490 \pm 40$  ms.

### Clinical history after LCSD

Clinical history after LCSD is shown in Table 2. The mean follow-up after surgery was  $12.9 \pm 10.3$  years (median 10.5 years, IQR: 4.3-18.9 years), ranging from 1 to 46 years.

### Morbidity/mortality

After LCSD and based on the intention-to-treat analysis, 70 (56%) of 125 patients remained totally asymptomatic, whereas 55 had CEs. Syncope only occurred in 23 patients (18%) and MCEs occurred in 32 patients (26%), including 5 cases of SD (4%) and 14 patients (11%) with ACA. The median time elapsed from LCSD to first CE was 20 months (IQR: 7-52 months) for any CE, 129 months (IQR: 24-205 months) for MCEs, and 103 months (IQR: 36-160 months) for SD. The percentage of asymptomatic patients after LCSD ranged from 97% among those who underwent LCSD as primary prevention to 17% in the very high risk group, being approximately 50% in the other 2 groups ( $P < 0.0001$ ), whereas the percentage of patients with MCEs ranged from 0% to 78% across groups ( $P < 0.0001$ ). Overall, the incidence of CEs and of MCEs among the 94 patients who underwent LCSD as secondary prevention was 57% (n = 54) and 34% (n = 32) respectively during a mean follow-up of  $15.0 \pm 10.5$  years (median 13.3 years, IQR 6-21.2 years). None of the 23 patients who were asymptomatic before LCSD had CEs during a mean follow-up of  $6.3 \pm 7.1$  years (median 4.2 years, IQR: 1.0-7.4 years).

There were 5 SDs (2 in the very high risk subgroup). Among the 18 very high risk patients the overall incidence of SD was 11%, but it reached 33% among the 6 patients without an ICD. The other 3 patients with SD were in the subgroup with previous syncope/ICD shock (n = 45) with an incidence of 7% (none of them had an ICD); however, 2 of them had completely stopped taking BB despite continuation of syncopal episodes until SD. Importantly, among the 5 patients with SD, the lethal episode was *always* preceded by at least 2 CEs after LCSD (median 3, IQR: 2-9).

Overall, among the 44 patients without ICD at the time of their first CE after LCSD, 37 (84%) had a syncope as first CE, 7 (16%) had an ACA (3 in the very high risk group, 4 in the group with previous ACA), none had SD. Notably, 23 (100%) of 23 of those in the group with syncope before LCSD had a syncope as first CE after LCSD, as opposed to 8 (67%) of 12 in the group with previous ACA and 5 (63%) of 8 in the very high risk group (*P* between groups = 0.01).

Figure 1 shows the change in clinical status that followed LCSD over a mean period of  $13.0 \pm 10.5$  years among patients on treatment and after the exclusion of the very high risk group.

### **Right cardiac sympathetic denervation (RCSD)**

Five patients (1 with previous ACA, 4 in the very high risk group, including 1 CALM and 1 Timothy syndrome) underwent RCSD because of MCE recurrences after LCSD (median time elapsed between LCSD and RCSD: 36 days, range 21-292 days). Among them, 3 had a very favorable response (complete suppression of MCEs in 1 case, >85% reduction in the other 2). In the fourth case MCEs were completely suppressed for 3 years until the patient died in her sleep. In the fifth patient, with Timothy syndrome, multiple ICD shocks recurred leading to heart transplantation 3 years after RCSD. Notably, 4 of these 5 patients had either single or dual-chamber pacing when they underwent RCSD. Among the 3 responders to RCSD, 1 received atrial pacing a few months after RCSD with significant reduction in syncopal episodes caused by Torsades de Pointes (TdP). The only patient who died suddenly, in 1995, after 3 uneventful years following RCSD, did not have any pacing backup nor ICD.

### **Event-free survival**

Long-term cumulative event-free survival across groups was analyzed as both “intention to treat” (n = 125) (Supplemental Figure 2) and “on-treatment” (n = 122) (Figure 2), after the exclusion of the 3 patients (2 SD) with complete interruption of their prescribed BB after LCSD, despite multiple CE recurrences after LCSD. All these 3 patients were in the group with previous syncope/ICD shock, and all had a QTc before LCSD  $\geq 500$  ms.

When looking at the on-treatment analysis (Figure 2), survival free from any CE at 10 and at 15 years was 97% and 97% in patients in primary prevention, 49% and 42% in patients with syncope/ICD shock, 60% and 45% in patients with ACA, and 15% and 8% in the very high risk group (*P* < 0.0001). Survival free from MCEs at 10 and at 15 years was 100% and 100% in patients in primary prevention, 87% and 74% in patients with syncope/ICD shock, 78% and 69% in patients with ACA, 35% and 9% in the very high risk group (*P* < 0.0001).

An additional survival analysis for ACA/SD (Figure 3) in patients with either no ICD at the time of their first MCE or without ICD shocks during follow-up (n = 108) shows a 79% survival free from ACA/SD at 15 years for both patients with previous syncope on BB and patients with previous ACA.

### **Number of events**

In the secondary prevention group (n = 94), the mean yearly rate of CEs per patient decreased by 86% from 1.66 (95% CI: 1.57-1.75) before LCSD to 0.26 (95% CI: 0.23-0.28) after LCSD (*P* < 0.001).

Among the 31 patients with a history of ACA, the mean yearly rate of MCEs declined by 80% from 0.63 (95% CI: 0.54-0.72) before LCSD to 0.13 (95% CI: 0.10-0.16) after LCSD ( $P = 0.03$ ). Among the 18 patients in the very high risk group, a significant 75% reduction in the mean yearly rate of CEs was observed, from 2.1 (95% CI: 1.8-2.3) to 0.48 (95% CI: 0.39-0.58) ( $P = 0.01$ ), whereas for MCEs the decrease from 0.68 (95% CI: 0.56-0.83) to 0.44 (95% CI: 0.36-0.54) was nonsignificant ( $P = 0.19$ ). Importantly for the quality of life, among the 10 patients with recurrent ICD shocks before LCSD and not belonging to the very high risk group, the number of shocks was dramatically reduced by more than 90% from 24 (IQR 10-47) to 1.0 (IQR 0-3);  $P = 0.002$ , during a mean follow-up post LCSD of  $6.4 \pm 2.8$  years.

### **LCSD as monotherapy**

Twelve patients (none with either pacing or ICD backup at LCSD), including 4 in primary prevention, 4 with previous syncope, and 4 with previous ACA, were treated with LCSD as monotherapy for a mean of  $18 \pm 12$  years because of BB intolerance/refusal. Among them, none had MCEs during follow-up, 2 (both with previous ACA) had syncopal episodes only.

### **LCSD and QT interval**

At baseline, the mean QTc was  $527 \pm 60$  ms, including 9 (7%) patients with a normal QTc ( $\leq 440$  ms) and 83 (66%) with a QTc  $\geq 500$  ms. For 98 patients, QTc values were available both at hospital discharge and at 6 months after LCSD. Overall, QTc shortened by  $16 \pm 24$  ms ( $P < 0.0001$ ) at discharge and by  $26 \pm 35$  ms ( $P < 0.0001$ ) at 6 months. Figure 4 shows the degree of shortening observed at discharge and at 6 months after surgery according to baseline QTc ( $< 500$  ms,  $\geq 500$  ms,  $\geq 550$  ms). Thus, QTc shortens after LCSD and the effect, often visible already at discharge, is clearly manifest at 6 months of follow-up.

Given the special relevance of QTc shortening for those patients with a markedly prolonged QT interval (QTc  $\geq 500$  ms), we focused on this subgroup. Among them, 69 had available QTc values before and after surgery and 37 (54%) of 69 shortened the QTc by  $\geq 30$  ms after LCSD; the mean QTc reduction in these 37 was  $64 \pm 24$  ms. Overall, after LCSD the QTc of 23 (33%) of 69 patients was shortened to  $< 500$  ms.

After age at surgery, sex, preoperative ACA, and recurrence on BB were accounted for, both a preoperative QTc  $\geq 500$  ms (HR: 3.17; 95% CI: 1.55-6.5;  $P = 0.001$ ) and a QTc  $\geq 500$  ms at discharge (HR: 2.54; 95% CI: 1.26-5.14;  $P = 0.01$ ) were independent predictors of CEs. After the exclusion of the 12 patients with CEs (9 with MCEs) in the first 6 months after LCSD, in the remaining 89 patients the persistence of a QTc  $\geq 500$  ms at 6 months after LCSD was associated with a major increase in adjusted risk for any CE (HR: 4.2; 95% CI: 1.86-9.55;  $P = 0.005$ ).

Finally, we focused on the 42 patients on treatment with history of syncope/ICD shock. Within these patients, those with a QTc  $< 500$  ms at 6 months postsurgery had a strikingly better event-free survival at 15 years than those with a QTc  $\geq 500$  ms (80% vs 9%;  $P = 0.0001$ ) and none had MCEs (Figure 5). Thus, if LCSD brings QTc below 500 ms, a significantly better prognosis can be expected.

### **Genotype and LCSD**

After exclusion of the very high risk group, we assessed the impact of genotype in the 45 symptomatic patients with adequate numbers (18 LQT1, 27 LQT2): their mean yearly rate of CEs after LCSD dropped similarly by 95% and by 86%, respectively. Details are provided in the Supplemental Material. Among the 22 asymptomatic patients (4 LQT1, 16 LQT2, 2 LQT3) none

had recurrences during follow-up. Thus, the protective effect of LCSD is not influenced by common genotypes.

### **Surgical complications**

No major complications occurred after LCSD. Minor complications are detailed in Supplemental Table 1. A permanent ptosis of the left eyelid was observed in 3 (2.4%) of 125 patients but required surgery only in 1. Transient neuropathic pain despite prophylactic administration of gabapentin occurred in 11 patients, all after VATS-LCSD (35% of VATS), and with one exception always resolved within 3 months.

### **Discussion**

The present findings allow novel conclusions about the impact of LCSD in the management of patients with LQTS because of their unique strength in terms of the unprecedented length of the follow-up, of the consistency in the extent of denervation and of the overall clinical management, of the clinically guided approach to the analysis of the QTc changes, and of the identification of the groups more and less likely to be adequately protected.

This almost 50 years of single-center experience (10), in which the clinical issues related to patients with LQTS and the personally conducted experimental research designed to understand the mechanisms of action of RCSD and LCSD could be jointly examined, has borne fruit.

Indeed, the present results, besides providing much-needed answers to critical questions by clinical cardiologists whenever they face a patient with LQTS deemed not to be fully protected by the current treatment, move the field forward and should have an impact on future guidelines.

The need to distinguish between patients

Even though we had realized rather soon that, for instance, patients with a history of syncope were at higher risk for recurrences (20), for too long most analyses on therapeutic efficacy kept including everyone, thus favoring quantity over quality. Only in 2009 did it become evident how lumping together the few subjects with events in the first year of life with those who had become symptomatic later in life was profoundly misleading, because this subgroup responds poorly to any treatment and should not be used to predict the outcome of therapy in the rest of the LQTS population (15,16). The naïveté of that approach had led to the widespread misconception that patients with LQT3 were not benefiting from BB, fully corrected once the follow-up of patients with events in the first year of life was kept separate from that of all other patients (21). It was based on these and similar considerations that we identified subgroups more or less likely to benefit from LCSD, as this concept helps the clinicians in what should be a “nonautomatic choice” of the best therapy for patients not fully protected by BB (Central Illustration). A correct risk stratification of patients with LQTS requires grasping that they are far from being a homogeneous group, and therefore require a highly personalized approach (22). Our present approach to risk stratification is based not so much on systematic data analysis but more on the recognition of patterns associated with higher arrhythmic risk, which represents the integration of repeated observations and long-term clinical experience.

### **Mechanism(s) of action of LCSD**

The mechanisms of action underlying the effects of LCSD have been reviewed often (23). Here we simply list them: LCSD prevents the release of norepinephrine in the ventricles from the left-sided cardiac nerves, it raises the threshold for ventricular fibrillation (VF) (24), it increases ventricular

refractoriness (25), it does not impair left ventricular performance given the persistence of right cardiac sympathetic nerves (26), for the same reason it does not decrease heart rate (26), and it reflexly increases cardiac vagal efferent activity (27). Furthermore, as this is a preganglionic denervation, it is not followed by reinnervation nor by post-denervation supersensitivity (28). An aspect often missed is that a significant difference between BB and LCSD is that the latter also prevents alpha-adrenergic-mediated increases in the heterogeneity of repolarization, caused by early and delayed afterdepolarizations (29).

## **The impact of LCSD on arrhythmic events**

### **Secondary prevention**

Most patients (n = 94, 75%) underwent LCSD as secondary prevention because of either recurrence on BBs or BB intolerance/refusal. In this high-risk population, we confirmed the overall good antiarrhythmic protection provided by LCSD, especially on MCEs, as already reported but with a strikingly shorter follow-up (6,7). Indeed, during a mean follow-up of 15 years, there was an 86% reduction in the mean annual rate of CEs; 43% of patients remained asymptomatic and 66% had no MCEs. These percentages become 49% and 76%, respectively, after the exclusion of the 18 patients in the high-risk group. Notably, at variance with our previous reports, here we included ICD appropriate shocks among the MCEs: 14 (15%) of 94 patients suffered ICD shocks only, representing almost half of the patients with MCEs during follow-up. Even though this approach is largely used among ICD recipients, ICD shocks are not equivalent of ACA/SD, rather they largely outnumber them because of appropriate but unnecessary ICD shocks delivered on potentially self-limiting ventricular arrhythmias (30). This is likely the case for patients with LQTS after LCSD, which is primarily an antifibrillatory intervention in structurally normal hearts, as it increases VF threshold (24) and thus prevents the deterioration of TdP into VF. Indeed, the degree of protection provided by LCSD against MCEs was consistently greater than that provided against syncope. Importantly, among the patients with previous “syncope/ICD shock only” before LCSD, none had either CEs in the first 6 months after LCSD or an MCE as their first symptom after LCSD, and a QTc <500 ms at 6 months after surgery was associated with an excellent outcome (100% survival free from MCEs).

### **Secondary prevention in the “very high risk” subgroup**

At significant variance with our previous reports, we now identified a very high risk subgroup of patients, defined by CEs in the first year of life and/or by highly malignant genotypes with recurrences on BB, unlikely to be fully protected by any treatment. As expected, after LCSD, these patients had a much poorer outcome compared with the other patients in secondary prevention, thus mandating an ICD implant. Nonetheless, even in this subgroup, we observed a significant reduction of CEs after LCSD. This strongly suggests that LCSD should always be considered at the time of ICD implantation to reduce the subsequent number of ICD shocks and to improve quality of life (31,32). Some of these patients additionally required RCSD, which further reduced the arrhythmic burden.

Among the patients who also underwent RCSD, the possible need of a pacemaker has become evident. This is because the sympathetic control of heart rate is exerted primarily by the right cardiac sympathetic nerves, as proposed by Langley in 1892 (33) and confirmed in anesthetized (34,35) and conscious (26) animals. Thus, a pause-dependent initiation of TdP (36) may become more likely after RCSD, an arrhythmogenic mechanism specifically related to LQTS.

### **Primary prevention**

The patients who underwent LCSD as primary prevention reflect the recent and progressive extension of our indication for LCSD, confirmed by their shorter follow-up. We have always been cautious before proposing surgery for asymptomatic patients. This was, in part, the consequence of the historic role of our group in the development of LCSD as an integral component of the therapeutic armamentarium for LQTS (3) because we probably tried to avoid being labeled as biased advocates of LCSD. The present results, with the inherent limitation of any intervention in primary prevention, indicate that LCSD is a very reasonable option, because no patients suffered MCEs after surgery and 1 patient only suffered a single syncopal episode. Admittedly, in these cases it is not possible to demonstrate a benefit from the intervention; however, the observation that patients regarded as “nonprotected by the current therapy” did very well postsurgery is reassuring. Notably, the Mayo Clinic group, which has performed LCSD in LQTS since 2005, included patients in primary prevention since the beginning, with similar results (37).

### **Surgical extension**

The sympathetic fibers innervating the heart pass through the lower half of the stellate ganglia (T1) and through the thoracic ganglia from T2 to T4 (34). This is what dictates the extent of surgery and, indeed, as repeatedly confirmed, the removal of these 4 ganglia has always produced clear protection. In our previous large studies (6,7,38), whenever denervation was incomplete, either because of sparing the stellate ganglion or because T4 was not removed, there was a clear increase in therapeutic failures. Further evidence supporting this experience-based concept has just come by the Mayo Clinic group, which reported that among 15 patients referred for recurrences after LCSD performed elsewhere, 3 patients (20%) had a re-do LCSD performed instead of a sequential RCSD because of incomplete resection with the first intervention (39). An intact stellate ganglion was found in all 3 cases. We and the other 2 groups worldwide with a major experience in cardiac sympathetic denervation believe that the extent of denervation described previously is essential for therapeutic success (39,40). Thus, we find no scientific justification for “simpler approaches” that leave intact the stellate ganglia (41, 42, 43).

We regard as inappropriate to perform bilateral cardiac sympathetic denervation in patients with LQTS at outset (42,43), without assessing first whether LCSD has failed to prevent recurrences. Given the proarrhythmic potential of bradycardia and of sinus pauses in LQTS, the role of right-sided nerves in preserving the sympathetic control of heart rate (26) should be kept in mind.

### **LCSD and the QT interval**

We established long ago (20,44) that the longer the QTc, the higher is the risk for arrhythmic events. Already the first large studies on LCSD in LQTS had shown that a variable degree of QT shortening was following denervation (6,7), but that was all; now, a more sophisticated approach has obtained more accurate quantitative information of direct clinical impact.

We focused on the 69 patients with a markedly prolonged QTc ( $\geq 500$  ms) because it is mostly within this group that shortening matters and, by recognizing the inherent measurement errors, we distinguished between patients shortening their QTc by  $< 30$  ms or  $> 30$  ms. More than half of these patients ( $n = 37$ ) shortened their QTc by  $\geq 30$  ms, and their mean decrease was 64 ms. Thus, when contemplating LCSD for patients with LQTS with a QTc  $\geq 500$  ms, an additional consideration should

be that they have more than a 50/50 chance of shortening their QTc by 60 ms on average, unquestionably a clinically relevant change.

### **Genotype and LCSD**

The present data show that common genotypes do not have an impact on the probability of success of LCSD, which should be implemented based on a clinical evaluation independent of the genotype.

### **Our recommendations for LCSD**

Following our 1975 recommendation (3), BB are the cornerstone of LQTS therapy. Much more heterogeneous is the management of patients with LQTS regarded as at higher risk because of arrhythmia recurrence on BBs, BB intolerance, or the persistence of a high-risk pattern on BBs. The choice to recommend either LCSD or ICD is often made based on personal preference, availability of competent surgeons, or of a defensive medicine approach instead of basing it on actual results and on cost-benefit for the individual patient.

The present findings, together with those by the Mayo Clinic group (37), should help to define and upgrade the role of LCSD in future guidelines, especially in reference to the delicate matter of ICD indication and timing. Our data, with an unprecedented follow-up duration, demonstrate that patients with a syncopal episode on BB (with the sole exclusion of those defined here as “at very high risk”) can be initially managed with LCSD and then re-assessed 6 months after surgery for the possible need of an ICD, which could be avoided when the QTc is <500 ms. For those with a QTc  $\geq$ 500 ms, the decision should take into account that none of the patients with syncopal episodes on BBs before LCSD had an ACA or SD as first symptom after LCSD. The recurrence of syncopal episodes on treatment after LCSD should prompt treatment intensification (RCSD  $\pm$  pacemaker  $\pm$  mexiletine), with possible consideration for ICD implantation. As to asymptomatic patients or patients with syncope off treatment with a common genotype or negative genetic analysis and a high-risk pattern, the present data and those by the Mayo Clinic (37) strongly suggest that LCSD should always be performed first, combined, if necessary, with mexiletine to further shorten the QT interval (45, 46, 47). The risk/benefit ratio of an ICD in these patients appears to be against implantation (48).

There are laudable efforts (49,50) to provide a risk estimate at diagnosis and off therapy, with the objective to identify candidates for ICD implant in primary prevention. As in medicine any risk is greatly reduced by effective therapies, before jumping from diagnosis to ICD, especially in youngsters, common sense would require reassessing risk “on optimal therapy.” The present data show that, for LQTS patients at high risk but without previous ACA, optimal management is represented by the combination of BB and LCSD.

Finally, the evidence of the strong, albeit not absolute, protection afforded by LCSD should force cardiologists to provide their patients with a full disclosure of the treatment options available, regardless of their personal views. When dealing with patients with LQTS at risk for lethal arrhythmias, to deny at-risk patients their right to complete information about the advantages and disadvantages of LCSD can carry medico-legal consequences (51).

### **Conclusions**

The present findings, supported by an extremely long follow-up, go beyond anything published before on the role of LCSD for LQTS because for the first time they “talk” to the cardiologist who faces his or her patients with LQTS not fully protected by BB and help him or her to make the

therapeutic choice based on “who the patient is.” The recognition of the heterogeneity of patients with LQTS, based on their specific history (events in the first year of life, or not), on their specific ECG ( $QTc < 500$  ms or  $\geq 500$  ms), on their specific LQTS-causing genes, now allows to decide when to use LCSD, when to use it in addition to BBs or as a complement to an ICD (to reduce the probability of shocks while having the ICD as a safety net). Even a relatively gross intervention such as cutting nerves to prevent lethal arrhythmias (52) can now enter the “precision medicine” era (22).

## Perspectives

**COMPETENCY IN MEDICAL KNOWLEDGE:** LCSD provides a clear and long-term antifibrillatory protection in patients with LQTS. A new approach to the data analysis allows recognition that this protection is not uniform as it varies according to the arrhythmic risk of the individual patients, and this facilitates a more personalized clinical management with different layers of interventions. The degree of QT shortening at 6 months postoperative also provides information on residual arrhythmic risk.

**TRANSLATIONAL OUTLOOK:** The number of centers performing LCSD is growing but this effective procedure, which has a positive effect on quality of life, remains underutilized with too many patients being offered only  $\beta$ B and ICD implantation. The present data are expected to have a profound impact on the guidelines for the management of patients with LQTS.

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**Table 1.** Baseline Characteristics of the Study Population

	<b>All Patients (N = 125)</b>	<b>Very High Risk Patients (n = 18)</b>	<b>Previous ACA (n = 31)</b>	<b>Previous Syncope/ICD Shock on <math>\beta</math>B/<math>\beta</math>B Intolerance (n = 45)</b>	<b>Primary Prevention (n = 31)</b>
<b>Female</b>	73 (58)	8 (44)	21 (68)	32 (71)	12 (39)
<b>Genotype known</b>	99 (79)	15 (83)	21 (68)	31 (69)	31 (100)
<b>LQT1</b>	24 (25)	2 (13)	8 (38)	7 (23)	7 (23)
<b>LQT2</b>	43 (44)	0 (0)	8 (38)	15 (48)	20 (64)
<b>LQT3</b>	10 (10)	3 (20)	2 (9)	2 (6)	3 (10)
<b>JLN/CALM/CACNA1C</b>	9 (9)	5/3/1 (50)	-	-	-
<b>&gt;1 pathogenic variant</b>	6 (6)	0 (0)	2 (9)	4 (13)	0 (0)
<b>Negative genetic analysis</b>	7 (7)	1 (7)	1 (5)	4 (12)	1 (3)
<b>Genotype unknown</b>	27 (21)	3 (17)	9 (30)	14 (31)	0 (0)
<b>Symptomatic before LCSD</b>	102 (82)	18 (100)	31 (100)	45 (100)	8 (26)
<b>Age at first symptom, y</b>	7 (2-14)	0.5 (0.5-1)	8 (5-13)	9 (4-19)	13 (10-22)
<b>Symptoms in first year of life</b>	11 (9)	11 (61)	-	-	-
<b>Type of first symptom</b>					
<b>ACA</b>	16 (13)	7 (39)	7 (23)	-	0 (0)
<b>Syncope</b>	86 (69)	11 (61)	24 (77)	45 (100)	8 (26)
<b>Previous ACA</b>	42 (34)	11 (61)	31 (100)	-	0 (0)
<b><math>\beta</math>B</b>	112 (90)	18 (100)	27 (87)	40 (89)	27 (87)
<b>Number of CEs</b>	5 (1-13.5)	10 (5-30)	9 (4-30)	6 (3-13)	0 (0-1)
<b>&gt;1 ACA</b>	17 (14)	9 (50)	8 (26)	-	-
<b>Recurrences on <math>\beta</math>B (patients on <math>\beta</math>B)</b>	81 (72)	18 (100)	24 (89)	40 (100)	0 (0)
<b>PM</b>	6 (5)	0 (0)	1 (3)	5 (11)	0 (0)
<b>ICD</b>	15 (12)	7 (39)	4 (13)	4 (9)	0 (0)
<b>Mexiletine</b>	12 (10)	5 (28)	3 (10)	2 (4)	2 (6)
<b>QTc, ms</b>	527 $\pm$ 60	553 $\pm$ 83	537 $\pm$ 65	530 $\pm$ 51	498 $\pm$ 41
<b>&lt;500 ms</b>	42 (34)	4 (22)	10 (32)	11 (24)	16 (52)
<b><math>\geq</math>500 to &lt;550 ms</b>	40 (32)	4 (22)	7 (23)	18 (40)	13 (42)

	<b>All Patients (N = 125)</b>	<b>Very High Risk Patients (n = 18)</b>	<b>Previous ACA (n = 31)</b>	<b>Previous Syncope/ICD Shock on <math>\beta</math>B/<math>\beta</math>B Intolerance (n = 45)</b>	<b>Primary Prevention (n = 31)</b>
<b><math>\geq 550</math> ms</b>	43 (34)	10 (56)	14 (45)	16 (36)	2 (6)
<b>Mean age at LCSD, y</b>	20 $\pm$ 15	9 $\pm$ 8	20 $\pm$ 11	19 $\pm$ 13	28 $\pm$ 19
<b>Mean time from first MCE to LCSD, y</b>	8.0 $\pm$ 8.1	8.3 $\pm$ 8.3	10.0 $\pm$ 10.5	6.9 $\pm$ 6.1	6.2 $\pm$ 5.3

Values are n (%) or median (IQR).

ACA = aborted cardiac arrest;  $\beta$ B =  $\beta$ -blockers; CALM = calmodulin; CE = cardiac events;

ICD = implantable cardioverter-defibrillator; IQR = interquartile range; JLN = Jervell and Lange-

Nielsen; LCSD = left cardiac sympathetic denervation; LQT = long QT; MCE = major cardiac events;

PM = pacemaker; QTc = QT interval corrected for frequency.

**Table 2.** Clinical History After LCSD

	<b>All (N = 125)</b>	<b>Very High Risk Patients (n = 18)</b>	<b>Previous ACA (n = 31)</b>	<b>Previous Syncope/ICD Shock on <math>\beta</math>B or With Intolerance to <math>\beta</math>B (n = 45)</b>	<b>Primary Prevention (n = 31)</b>
<b>Follow-up, y</b>	12.9 $\pm$ 10.3	12.6 $\pm$ 10.1	16.7 $\pm$ 10.6	14.3 $\pm$ 9.6	6.4 $\pm$ 6.6
<b>Person-y</b>	1,610	227	500	643	196
<b>Any CE</b>	55 (44)	15 (83)	15 (48)	24 (53)	1 (3)
<b>ACA/SD/ICD shock</b>	32 (26)	14 (78)	8 (26)	10 (22)	0(0)
<b>SD</b>	5 (4)	2 (11)	0 (0)	3 (7)	0 (0)
<b>ACA</b>	13 (10)	3 (17)	5 (16)	5 (11)	0 (0)
<b>ICD shock only (no ACA or SD)</b>	14 (11)	9 (50)	3 (10)	2 (4)	0 (0)
<b>Heart transplant for refractory VAs</b>	1 (1)	1 (6)	0 (0)	0 (0)	0 (0)
<b>Noncardiac death</b>	6 (5)	2 (11)	3 (10)	1 (2)	0 (0)
<b>Syncopal episodes only</b>	23 (18)	1 (6)	7 (23)	14 (32)	1 (3)

	<b>All (N = 125)</b>	<b>Very High Risk Patients (n = 18)</b>	<b>Previous ACA (n = 31)</b>	<b>Previous Syncope/ICD Shock on <math>\beta</math>B or With Intolerance to <math>\beta</math>B (n = 45)</b>	<b>Primary Prevention (n = 31)</b>
<b>1 syncope only</b>	8 (6)	1 (6)	2 (7)	4 (9)	0 (0)
<b>Syncope as first CE<sup>a</sup></b>	37/44 (84)	5/8 (63)	8/12 (67)	23/23 (100)	1/1 (100)
<b>ACA as first CE<sup>a</sup></b>	7/44 (16)	3/8 (27)	4/12 (33)	0/23 (0)	0/1 (0)
<b>SD as first CE<sup>a</sup></b>	0/44 (0)	0/8 (0)	0/12 (0)	0/23 (0)	0/1 (0)
<b>RCSD</b>	5 (4)	4 (22)	1 (3)	0 (0)	0 (0)
<b>Implantable loop recorder</b>	4 (1)	0 (0)	1 (3)	0 (0)	3 (10)
<b>PM</b>	7 (6)	1 (6)	1 (3)	0 (0)	0 (0)
<b>PM at last follow- up</b>	10 (8)	3 (17)	2 (6)	0 (0)	0 (0)
<b>ICD</b>	28 (22)	5 (28)	11 (35)	9 (20)	3 (10)
<b>ICD at last follow- up</b>	43 (34)	12 (67)	15 (48)	13 (29)	3 (10)
<b>Dual-chamber ICD at last follow-up</b>	20 (16)	4 (22)	7 (23)	9 (20)	3 (10)
<b>Mexiletine</b>	9 (7)	2 (11)	0 (0)	1 (2)	2 (6)
<b>Mexiletine at last follow-up</b>	20 (16)	6 (33)	3 (10)	3 (7)	7 (23)

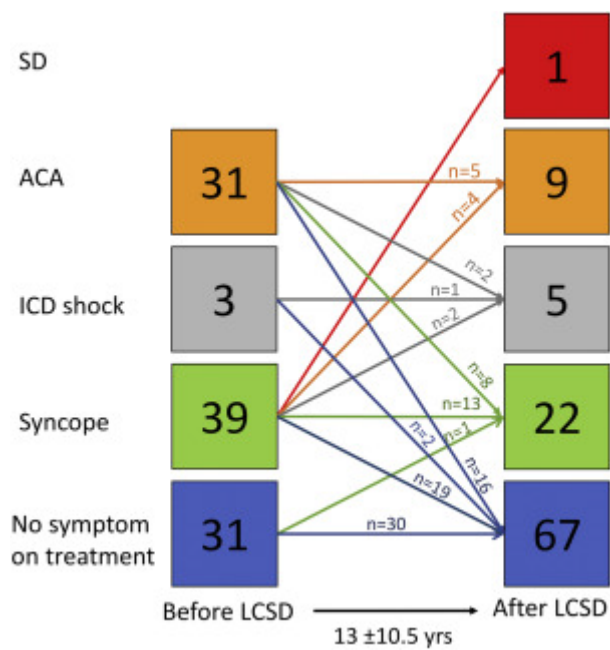
Values are n (%) or n/N (%), unless otherwise noted.

ACA = aborted cardiac arrest; CE = cardiac events; ICD = implantable cardioverter-defibrillator;  
LCSD = left cardiac sympathetic denervation; MCE = major cardiac events; PM = pacemaker;  
RCSD = right cardiac sympathetic denervation; SD = sudden death; VAs = ventricular arrhythmias.

<sup>a</sup>Among those with CEs after LCSD and no ICD at the time of first CE.

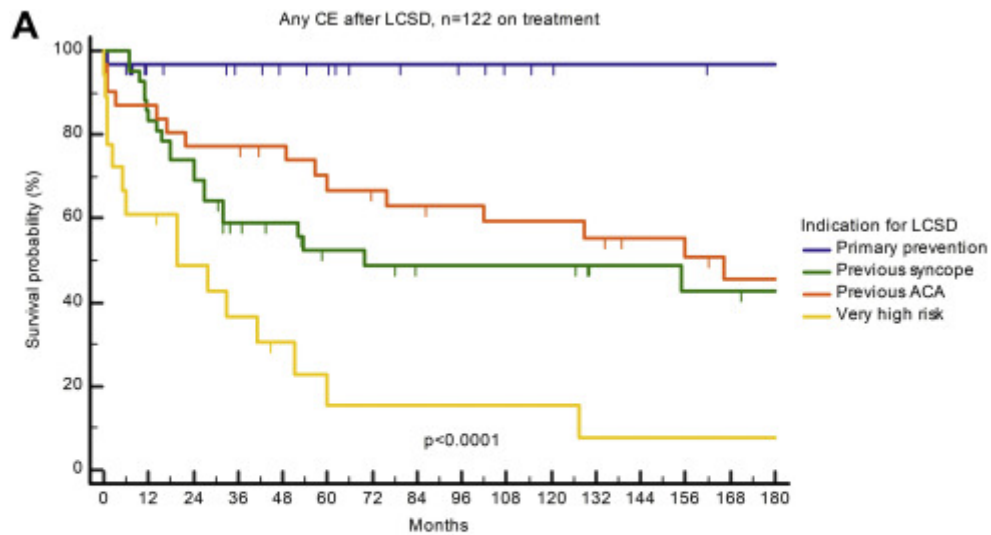
**Figure 1.** Changes in Symptoms Category After LCSD

On treatment analysis (n = 104) showing the effect of LCSD on patients' status (assessed categorically based on the most severe symptom) excluding the very high risk group. The figure shows the number of patients within each group before and after LCSD. The **numbers in the squares** represent the patients within each symptom group. The **numbers over the rows** represent the number of patients who either change status or remain in the same one. LCSD = left cardiac sympathetic denervation



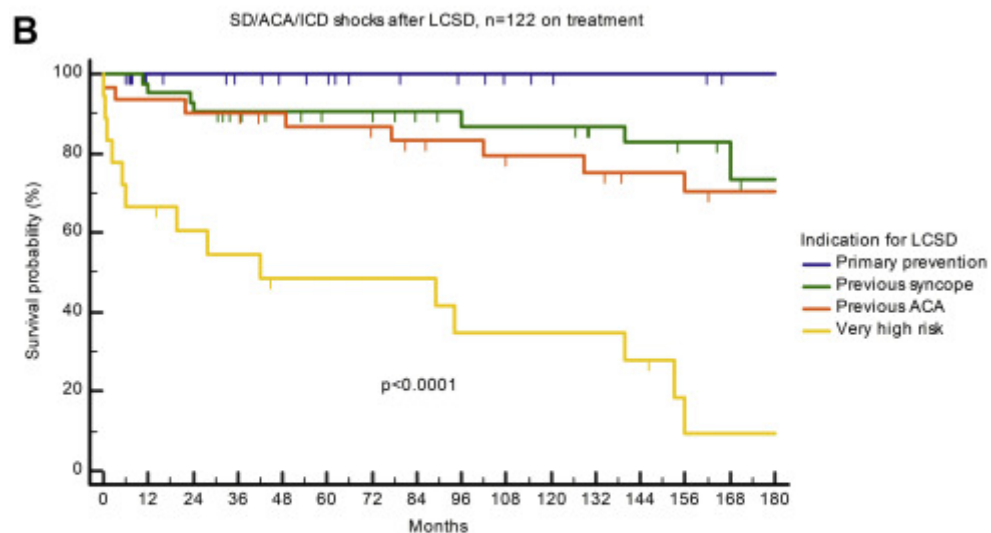
**Figure 2.** Survival Free From CEs After LCSD According to Subgroups

On treatment Kaplan-Meier curves (n = 122) of cumulative survival to a first cardiac event (CE) **(A)** and to a first major cardiac event (MCE) **(B)** after LCSD and according to subgroups. Numbers under the curves are patients at risk. LCSD = left cardiac sympathetic denervation.



Number at risk

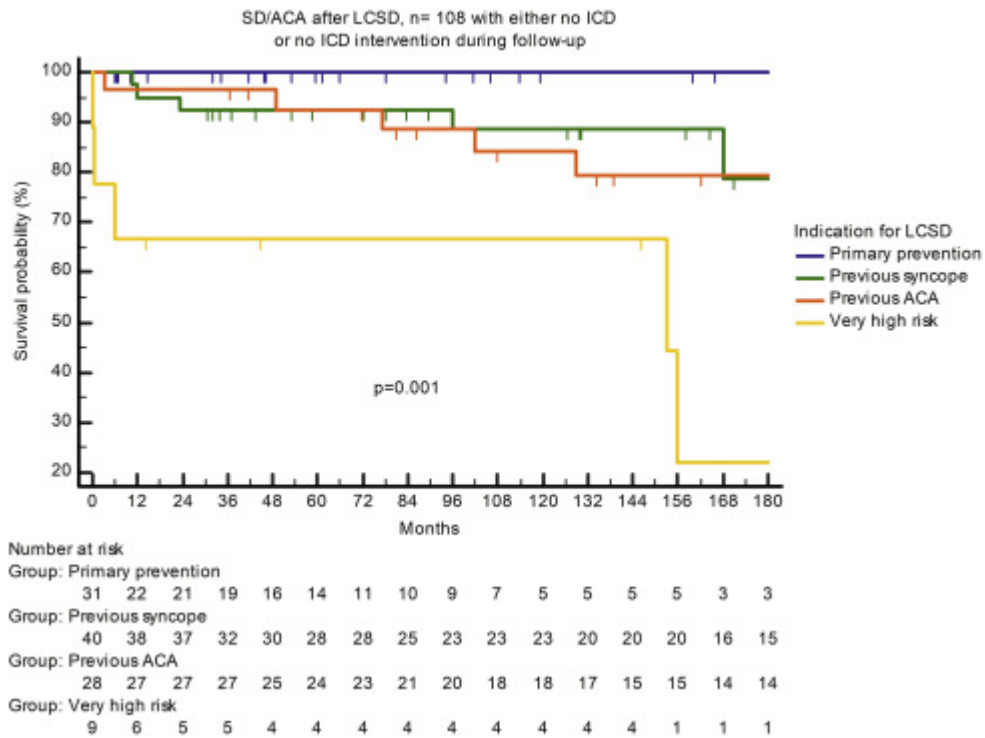
Group: Primary prevention	31	21	20	18	15	14	10	9	8	6	5	4	4	4	3	3
Group: Previous syncope	42	35	29	20	18	14	13	11	11	11	11	8	8	7	7	6
Group: Previous ACA	31	27	24	24	22	19	18	17	16	15	15	14	12	11	9	9
Group: Very high risk	18	11	8	6	4	2	2	2	2	2	2	1	1	1	1	1



Number at risk

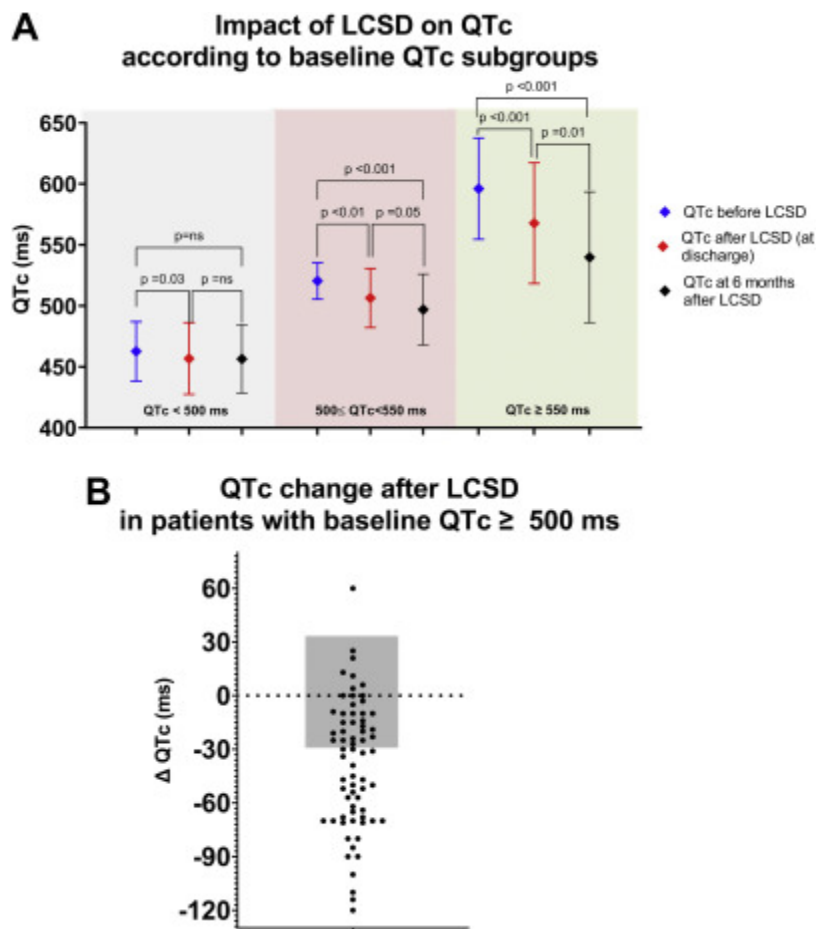
Group: Primary prevention	31	22	21	19	16	15	11	10	9	7	6	5	5	5	3	3
Group: Previous syncope	42	40	38	33	31	29	28	26	24	24	24	21	20	19	16	15
Group: Previous ACA	31	29	28	28	26	25	24	22	21	19	19	18	16	15	14	14
Group: Very high risk	18	12	10	9	7	7	7	7	5	5	5	5	4	1	1	1

**Figure 3.** Survival Free From CEs After LCSD According to ICD Presence or Interventions  
 On treatment Kaplan-Meier curves of cumulative survival free from ACA/SD in patients with either no ICD at the time of their first ACA/SD after LCSD or no ICD interventions during follow-up.  
 ACA = aborted cardiac arrest; ICD = implantable cardioverter-defibrillator; LCSD = left cardiac sympathetic denervation; SD = sudden death.



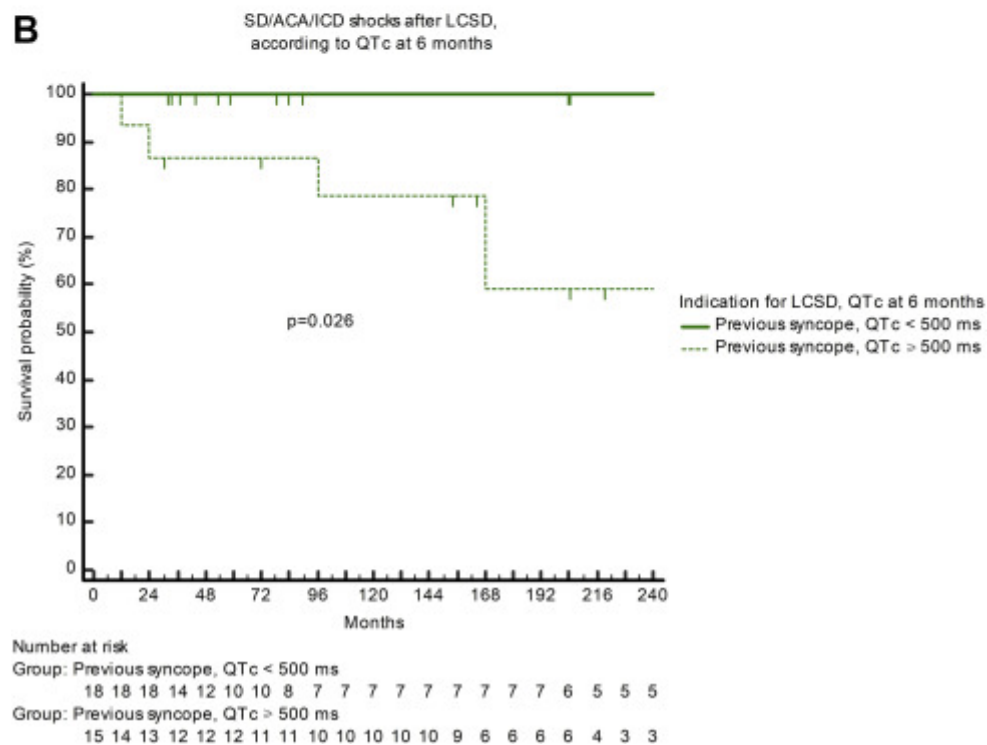
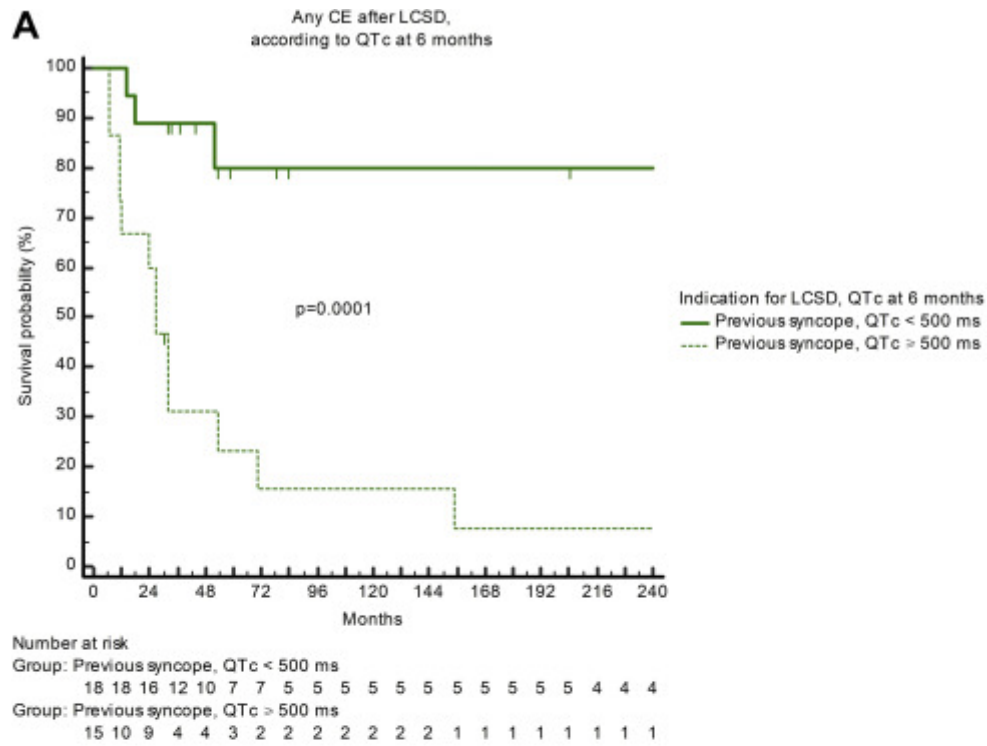
**Figure 4.** Impact of LCSD on QTc

**(A)** Impact of LCSD on QTc according to baseline QTc subgroups (QTc <500 ms, 500 ≤QTc <550 ms, QTc ≥550 ms). **Bars** represent the SD; **dots** represent the mean. **(B)** ΔQTc before versus after LCSD in patients with baseline QTc ≥500 ms. Each **dot** represents a patient, and the **gray zone** includes ΔQTc between -30 and +30 ms. LCSD = left cardiac sympathetic denervation; QTc = QT interval corrected for frequency.



**Figure 5.** Survival Free From Cardiac Events After LCSD in Patients With Previous Syncope/ICD Shock According to QTc at 6 Months

On treatment Kaplan-Meier curves of cumulative survival to a CE **(A)** and to an MCE **(B)** after LCSD in patients with previous syncope/ICD shock according to post-LCSD QTc <500 ms or ≥500 ms. Numbers under the curves are patients at risk. Abbreviations as in Figures 1, 3, and 4.



**Central Illustration.** Flowchart Summarizing Our General Approach to Patients With Long QT Syndrome Apparently Not Protected by Beta-Blockers

Based on findings and concepts present in the text and on our clinical experience, this flowchart shows an outline of what we regard as a “reasonable approach” to the management of patients with LQTS looking as not protected by  $\beta$ B. As every clinical flowchart, it cannot take into consideration the many specificities of individual patients. Accordingly, it should not be regarded as a formal recommendation, as clinical decisions must be taken after careful assessment of each single patient. Rather, it represents a sort of road map offering possible solutions for the practicing cardiologist. ACA = aborted cardiac arrest; BB = beta blocker; CALM = calmodulin; ICD = implantable cardioverter-defibrillator; JLN = Jervell and Lange-Nielsen; LCSD = left cardiac sympathetic denervation; LQTS = long QT syndrome; PM = pacemaker; QTc = QT interval corrected for frequency; RCSD = right cardiac sympathetic denervation.

