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A STUDY ON THE PREVALENCE OF RISK FACTORS OF DRUG-INDUCED QTC PROLONGATION AMONG PATIENTS IN INTENSIVE CARE UNIT

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ABSTRACT: Sudden cardiac death (SCD) is the most common cause of mortality among cardiovascular etiologies. Drug-induced Long-QT syndrome (diLQTS) is a prominent occurrence in Intensive Care Units (ICUs), often progressing to Torsades de Pointes (TdP), resulting in SCD. A prospective observational cross-sectional study was conducted to determine the prevalence of risk factors for diLQTS and to identify patients at risk for it in ICUs using the Tisdale score. Patients were recruited based on the selection criteria, and data on their demographics, laboratory and ECG assessments and administered medications were obtained from their case files. The prevalence of risk factors was calculated and the risk for diLQTS among the patients was assessed using the Tisdale score. Among 150 patients recruited, 51% and 49% were male and female, respectively, mostly aged >65 years (38%). QTc-prolongation was prevalent in 46% of patients. The prevalence of risk factors among the patients was: 35.33% aged ≥68 years, 40% females, 42% hypokalemic, 14% with acute MI, 28% with heart failure, 4% with sepsis, 24.66% prescribed with loop-diuretics, and 68% administered ≥2 QT-prolonging agents. The prevalence of patients with high, moderate and low risk for diLQTS was found to be 31.33%, 40% and 28.66%, respectively. Advanced age, hypokalemia, and longer QTc interval at admission were significantly associated with QTc prolongation. Conclusively, QTc prolongation was prevalent among the patients admitted to ICUs with a high prevalence of the risk factors for diLQTS. Medication administration should be monitored for these patients for safety and optimal therapeutic outcomes.

INTRODUCTION: Sudden Cardiac Death (SCD) is a condition where mortality occurs due to paroxysmal cardiac abnormalities and is one of the most common causes of death among cardiovascular etiologies.

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The causes for SCD range from structural cardiac abnormalities such as coronary artery disease (CAD) in the elderly to electrophysiological anomalies like primary cardiac dysrhythmias among the young population, both of which may be attributed to acquired or inherited causes, of which Ventricular Fibrillation (VF) contributes about 50% to the mortality, where the survival rates are low due to its sudden onset in outpatients where it is challenging to resuscitate stat [1]. Prolonged QT interval is one such parameter that can predispose a person to SCD. Long QT Syndrome (LQTS) is a cardiac channelopathy characterized by prolonged

QTc interval beyond 450ms in men and beyond 460ms in women, which, if left unattended, may lead to Torsades de Pointes (TdP) [2]. The ACCF/AHA scientific statement quotes a QTc interval of >500 ms, or an elevation of QTc >60 ms from the pre-drug baseline post-drug administration, as warning signals that warrant prompt management and correction [1]. LQTS can either be congenital, including up to 17 different types based on the underlying mutation, or acquired, which can be either due to underlying pathologies such as electrolyte imbalances, cardiac dysrhythmias, infections, *etc*., or drug-induced, the latter contributing to a larger proportion of the incidences [3]. The Arizona Centre for Education and Research on Therapeutics (AZCERT) has listed around 296 drugs with the potential to cause TdP, categorised as known, possible, and conditional risk for causing TdP [4].

Among inpatients, a large proportion of them is treated with a multifaceted therapeutic approach due to multiple comorbid conditions, predisposing them to polypharmacy [5, 6]. Most of the medications administered to stabilize the patients, such as antiarrhythmics, antipsychotics, antibiotics, and antihistamines, have the tendency to cause QTc prolongation, either as an adverse effect or through interaction with concomitantly administered medications. As a result, most patients admitted to hospitals are inherently at risk for drug-induced long QT syndrome (diLQTS) [6, 7].

As the approach to treat LQTS is not very reliable, prevention of it is the cornerstone modality to be adapted at any hospital setup, which can be effectively done by using risk assessment tools, which help to assess the risk of developing diLQTS or drug-induced TdP and enable optimization of therapeutic regimen accordingly [7]. Many risk assessment tools have been introduced and implemented in hospital setups, including QT nomogram, MedSafety scan CDS, Hincapie-Castillo model for predicting severe QTc prolongation, Bindraban risk-assessment score, *etc* [8-12]. However, their low specificity and sensitivity, in addition to the requirement of complex laboratory procedures to identify the presence of risk factors for QTc prolongation, thereby levying additional charges to the patients, limited their implementation into regular practice to the required extent [8]. Patients admitted to the ICU often have multiple comorbid conditions associated with electrolyte imbalances and infections, necessitating multiple antibiotics and electrolyte infusions to attain homeostasis at larger doses, most of which have a greater tendency to cause QTc prolongation [13]. With already existing pathologic conditions, such as sepsis, diabetes mellitus, congestive cardiac failure or myocardial infarction (MI), in addition to advanced age, which predispose the patients to channelopathies and thereby to LQTS, the use of 1 or more QTc prolonging agents may potentiate the risk of Tdp and subsequent SCD exponentially [14]. A prospective observational study conducted by Tien M H Ng *et al.* to determine the incidence and predictors of drug-induced QTc prolongation in ICU patients showed that 48% of the patients administered with QT-prolonging agents developed QTc prolongation [15].

The credibility of the aforesaid risk-assessment tools is questionable in critical care setup, making prevention of diLQTS in these patients even more challenging. The Tisdale risk assessment score is one such tool specifically designed and validated for use in intensive care set up to assess the risk of diLQTS in critically-ill patients.[16] This tool provides a quantified measure of risk by considering various risk factors for QTc prolongation that are prevalently present in critically ill patients without the requirement of any additional biochemical assessments other than those required for the evaluation and diagnosis of the patient, making it feasible and economical to use in regular practice in a critical care setup.

The tool considers the risk factors of advanced age (>68 years), female gender, use of loop diuretics, hypokalemia, admission QTc≥450ms, acute MI, heart failure, sepsis, use of 1 QTc prolonging agents and use of 2 or more QTc prolonging agent. Scores have been provided to the individual risk factors based on the weightage of their role in causing QTc prolongation, making up the final score of 21 points. Based on this, the patients are stratified into low-risk (score<7), moderate-risk (score 7-10) and high-risk (>10) categories for developing diLQTS **Table 1** [16, 17]. This enables the healthcare providers to take preventive measures, either in the form of regular cardiac monitoring, withdrawal of any QTc prolonging agent and

replacement of it with its therapeutic alternative, or early initiation of medication such as magnesium sulphate prophylactically to prevent the progression of QTc prolongation to TdP [18, 19].

TABLE 1: TISDALE RISK ASSESSMENT SCORE

Risk Factor	Score
Age ≥68 years	1
Female gender	1
Use of loop diuretic	1
Serum K^+ ≥3.5 mmol/L	2
Admission QTc interval ≥450ms	2
Acute MI	2
Heart Failure	3
1 QTc prolonging agent	3
Sepsis	3
≥2 QTc prolonging agents	3
Total Score	21
Low-risk: <7; Moderate-risk: 7-10; High-risk: >10	

With an increased proportion of patients being admitted into the critical care units and a rise in the incidence and prevalence of risk factors for QTc prolongation among them, it is the need of the hour to emphasize the importance of prevention and management of diLQTS and the consequences of it if left untreated. Risk assessment is the first and foremost modality to preventing diLQTS. This study provides insight into the prevalence of the risk factors for QTc prolongation as considered by the Tisdale risk-assessment score among critically ill patients, along with the influence of individual risk factors as included in the Tisdale risk-assessment score on the QTc interval of the patients and the reliability of the said score in effective risk assessment.

MATERIALS AND METHODS:

Study Design: The study was a case-control observational study conducted between January 2021 to December 2021 at a Tertiary Care Hospital in Bangalore to determine the prevalence of risk factors of drug-induced QT prolongation in an ICU setting. The study was approved by the Scientific and Ethics Committee of the institution and informed consent was taken from participants before recruiting them into the study.

Eligibility Criteria: The study involved patients admitted to ICU who were aged above 18 years and to whom QT-prolonging agents were prescribed. Patients with congenital QT-prolongation, implanted pacemakers, those with admission QTc interval greater than 500ms, and those admitted for elective surgery were excluded from the study to eliminate confounding. Patients who were unwilling to consent were also excluded from the study.

Definitions:

Drug-induced QTc Prolongation: A QTc interval greater than 500ms after administering QT-prolonging agents was considered drug-induced QTc prolongation.

Hypokalemia: A serum potassium level equal to or less than 3.5mmol/L was considered hypokalemia.

Study Outcomes: The primary outcome was the prevalence of risk factors of QT-prolongation. The secondary outcome included the association between the risk factors and QT-prolongation and the percentage of patients falling under each risk category for developing QTc prolongation.

Data Collection Procedure: A sample size of 150 was calculated considering the confidence interval and expected prevalence derived from similar studies. Patients were recruited per the inclusion criteria, and relevant details such as demographics, past medical and medication history, pre-existing medical conditions, and laboratory data, including serum potassium levels, were collected. Reports of 12 lead ECGs were collected and QTc was calculated using Bazzett's formula, which was used to assess whether a patient had been exposed to prolonged cardiac activity due to drug therapy. Medications with evidence for causing QTc prolongation as an adverse effect being administered to the patients were identified by utilizing the Arizona Centre for Education and Research on Therapeutics Database (AZCERT). A self-designed data collection form was used to document the study subjects' relevant demographic and clinical data in real-time. In case of missing variables, the data of the pertaining patient was not considered for statistical analysis. The treating physicians were blinded to prevent bias.

Statistical Analysis: Data collected was assessed with Tisdale Risk-Assessment Score to determine the risk of development of drug-induced QTc prolongation. The statistical analysis was performed by using SPSS software ver. 17.0 and Epi-info software ver. 7.2.4.0. The distribution of characteristics was described using percentages.

The association of the individual risk factors with the QTc interval was determined using Binary Logistic regression and expressed as odds ratios. Statistical significance for the association between risk factors and QTc prolongation was considered if a p-value of <0.05 was obtained for a Confidence Interval of 95% for obtained odds ratio, considering a maximum of 5% error.

RESULTS: A total of 252 patients were screened, out of which 83 were excluded due to non-compliance with the inclusion criteria. The relevant data were collected from the remaining patients. Due to incomplete or missing data, the information from 19 patients was not considered for statistical analysis **Fig. 1.**

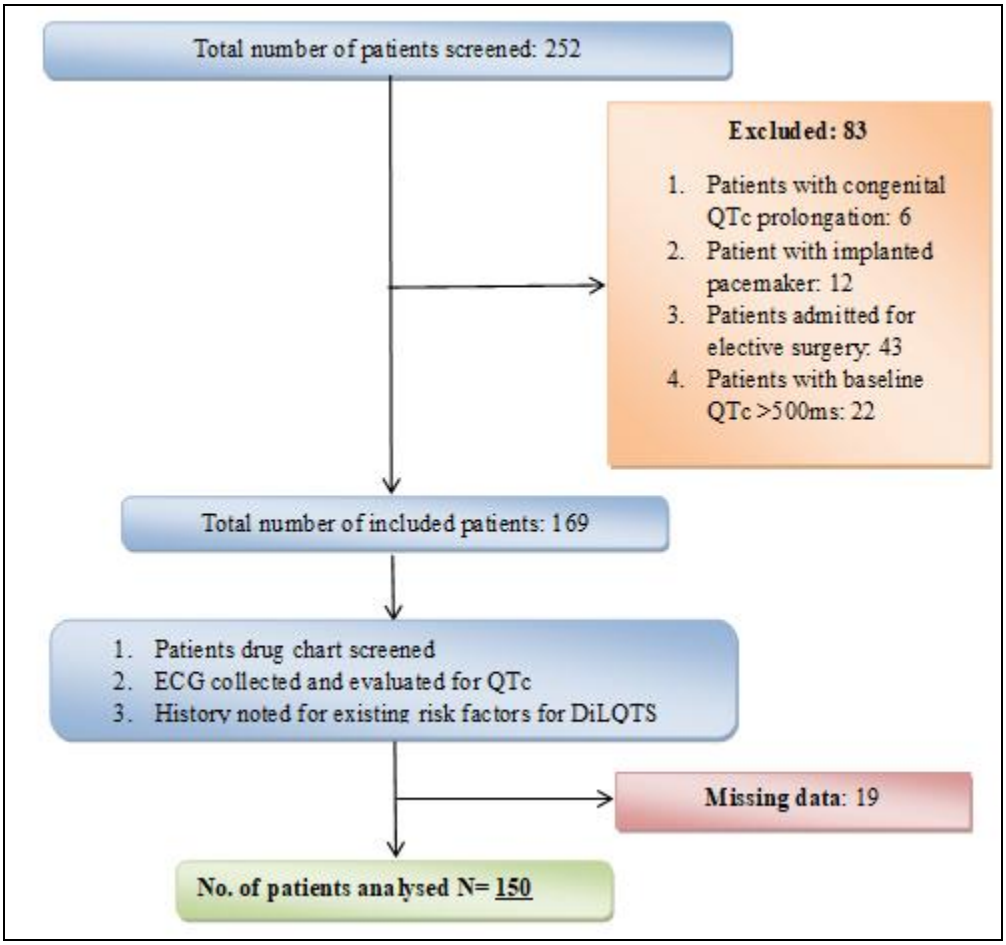

FIG. 1: FLOW CHART DEPICTING PARTICIPANTS AT VARIOUS STAGES OF THE STUDY

Out of the remaining 150 patients, 69 patients (46%) were found to have developed QTc prolongation. Among the enrolled patients, 38% of the patients were aged above 65 years, representing the majority population, followed by patients belonging to the age groups of 56-65 years. Among the patients who had QTc prolongation,. 52.17% were aged above 65 years (p=0.014) **Table 2.** Among the patients who developed QTc prolongation, 50.72% were men, and 49.27% were women (p=0.096). Among the various comorbid conditions, cardiovascular disorders (56%) and endocrine disorders (43.33%) were found to be prevalent among the subjects. Among those with QTc prolongation, 69.56% and 46.37% of the patients had cardiovascular and endocrine disorders, respectively, the former being statistically significant (p=0.002) and the latter being statistically insignificant (p=0.48). 20.28% and 18.84% of the patients with QTc prolongation had neurological (p=0.01) and infectious (p=0.007) disorders, respectively. The patients' systolic and diastolic blood pressures were examined and categorized based on the JNC 8 classification. Among the enrolled patients, 60% were prehypertensive, followed by 14% and 5.33% patients in stage 1 and stage 2 HTN, respectively. A significant association between elevated systolic blood pressure and prolongation in QTc interval was observed in **Table 2.**

TABLE 2: BASELINE CHARACTERISTICS

Characteristics	All (N=150)	With QTc Prolongation (N=69)	Without QTc Prolongation (N=81)	P-value
Age (in years)				
18-30, n (%)	14 (9.33)	4 (5.79)	10 (12.33)	0.014*
31-45, n (%)	22 (14.66)	7 (10.14)	15 (18.51)	0.014*
46-55, n (%)	28 (18.66)	9 (13.04)	19 (23.45)	0.014*
56-65, n (%)	29 (19.33)	13 (18.84)	16 (19.75)	0.014*
>65, n (%)	57 (38)	36 (52.17)	21 (25.92)	0.014*
Gender				
Male, n (%)	87 (58)	35 (50.72)	52 (64.19)	0.096
Female, n (%)	63 (42)	34 (49.27)	29 (35.8)	0.096
BMI				
<18.5, n (%)	3 (2)	1 (1.44)	2 (2.46)	0.96
18.5-24.9, n (%)	94 (62.7)	44 (63.7)	50 (61.7)	0.96
25-29.9, n (%)	49 (32.7)	22 (31.88)	27 (33.33)	0.96
≥30, n (%)	4 (22.7)	2 (2.89)	2 (2.46)	0.96
Comorbidities				
Cardiovascular, n (%)	84 (56)	48 (69.56)	36 (44.44)	0.002*
Neurological, n (%)	19 (12.66)	14 (20.28)	5 (6.17)	0.01*
Endocrine, n (%)	65 (43.33)	32 (46.37)	33 (40.74)	0.48
Hepatic, n (%)	8 (5.33)	4 (5.79)	4 (4.93)	0.81
Renal, n (%)	11 (7.33)	6 (8.69)	5 (6.17)	0.55
Infections, n (%)	17 (11.33)	13 (18.84)	4 (4.93)	0.007*
Blood Pressure				
Systolic blood pressure, mmHg, n (%)				
<120	31 (20.66)	9 (13.04)	22 (27.16)	0.006*
120-139	90 (60)	39 (56.52)	51 (62.96)	0.006*
140-159	21 (14)	16 (23.18)	5 (6.17)	0.006*
≥160	8 (5.33)	5 (7.24)	3 (3.70)	0.006*
Diastolic blood pressure, mmHg, n (%)				
<80	34 (22.66)	14 (20.28)	20 (24.69)	0.16
80-89	76 (50.66)	29 (42.02)	47 (58.02)	0.16
90-99	28 (18.66)	16 (23.18)	12 (14.81)	0.16
≥100	12 (8)	10 (14.49)	2 (2.46)	0.16

* Statistically significant association, *i.e.*, p-value<0.05.

Azithromycin and furosemide were found to be administered to 4.34% and 30.43% of the patients with QTc prolongation, respectively, and showed significant association with prolonged QTc interval. Out of the 5 commonly observed QT-prolonging drug interactions, the interaction of ondansetron with tramadol and with metronidazole was observed in 39.5% and 35.6% of the patients respectively, among whom 50% and 42.85% of the patients were found to have a prolonged QTc interval, respectively **Table 3.**

TABLE 3: COMMONLY ADMINISTERED QTC PROLONGING AGENTS

Drug	All (N=150)	With QTc Prolongation (N=69)	Without QTc Prolongation (N=81)	P-value
Known risk of TdP				
Escitalopram	4 (2.66)	2 (2.89)	2 (2.46)	0.87
Domperidone	5 (3.33)	2 (2.89)	3 (3.70)	0.78
Ondansetron	69 (46)	34 (49.27)	35 (43.20)	0.45
Clarithromycin	4 (2.66)	3 (4.34)	1 (1.23)	0.23
Azithromycin	3 (2)	3 (4.34)	0 (0)	0.05*
Ciprofloxacin	5 (3.33)	3 (4.34)	2 (2.46)	0.52
Possible risk of TdP				
Ofloxacin	4 (2.66)	2 (2.89)	2 (2.46)	0.87
Tramadol	26 (17.33)	12 (17.39)	14 (17.28)	0.98
Levetiracetam	8 (5.33)	5 (7.24)	3 (3.70)	0.33
Conditional risk of TdP				
Pantoprazole	116 (77.33)	57 (82.60)	59 (72.83)	0.15
Metronidazole	30 (20)	11 (15.94)	19 (23.45)	0.25

Piperacillin/ Tazobactam	29 (19.33)	11 (15.94)	18 (22.22)	0.33
Furosemide	32 (21.33)	21 (30.43)	11 (13.58)	0.012*

* Statistically significant association, *i.e.,* p-value<0.05.

When assessed with the Tisdale risk assessment score, 35.33% of the patients were ≥68 years and 24.66% of the patients were administered loop diuretics. 42% of the patients had serum potassium levels ≤3.5 mmol/L, and 14% and 28% presented with acute MI and heart failure, respectively. Among the patients with QTc prolongation, 72.46% were administered with 2 or more QT-prolonging agents, and the factor showed a positive association with prolonged QT interval [OR=1.46 (0.73-2.95 at 95% CI); p=0.610], followed by 63.76% of them having a serum potassium level of 3.5 mmol/L or less, depicting the statistically significant positive association between hypokalaemia and QTc prolongation [OR=5.74 (2.82-11.69) at 95%CI); p<0.001]. About 50.72% and 49.27% of the patients with QTc prolongation were aged more than 68 years or equal to it and were female, respectively, both showing a positive association with QTc prolongation, the former being statistically significant [OR=3.603 (1.78-7.29 at 95% CI); p=0.006] and the latter being insignificant [OR=1.65 (0.86-3.17 at 95% CI); p=0.231]. Approximately 37.7% of them had admission QTc ≥450 ms, showing a significant association with the development of QTc prolongation [OR= 3.14 (1.38-7.42 at 95% CI); p=0.02]. All other risk factors positively associated with QTc interval prolongation were not statistically significant. Approximately 31.33% of patients were under the high-risk category for drug-induced QTc prolongation, 40% were categorized as moderate-risk, and 28.66% were classified under the low-risk category for the condition **Table 4.**

TABLE 4: RISK FACTORS AND RISK CATEGORY

Risk Factor	All (N=150)	With QTc Prolongation (N=69)	Without QTc Prolongation (N=81)	Odds Ratio	P-value
Age ≥68 years	53 (35.33)	35 (50.72)	18 (22.22)	3.603(1.78-7.29)	0.006*
Female sex	64 (40)	34 (49.27)	30 (37.03)	1.65 (0.86-3.17)	0.231
Loop diuretic	37 (24.66)	24 (34.78)	13 (16.04)	2.79 (1.29-6.04)	0.999
Serum K^+ ≤3.5 mmol/L	63 (42)	44 (63.76)	19 (23.45)	5.74 (2.82-11.69)	<0.001*
Admission QTc≥450ms	39 (26)	26 (37.7)	13 (16)	3.14 (1.38-7.42)	0.003*
Acute MI	21 (14)	14 (20.28)	7 (8.64)	2.69 (1.02-7.11)	0.731
≥ 2 QTc prolonging agents	102 (68)	50 (72.46)	52 (64.14)	1.46 (0.73-2.95)	0.610
Sepsis	6 (4)	5 (7.24)	1 (1.23)	6.25 (0.71-54.85)	0.496
Heart failure	42 (28)	27 (39.13)	15 (18.51)	2.83 (1.35-5.93)	0.312
Risk Category					
High risk (≥11), n (%)	47 (31.33)	40 (85.10)	7 (14.89)	-	-
Moderate risk (7-10), n (%)	60 (40)	25 (41.66)	35 (58.33)	-	-
Low risk (<7), n (%)	43 (28.66)	4 (9.30)	39 (90.69)	-	-

* Statistically significant association i.e., p-value<0.05.

These results suggest that the subjects categorized under the high-risk category as per Tisdale Risk Assessment Score for diLQTS had a higher incidence of QTc prolongation. In comparison, those categorized under the low-risk category had a lower incidence of it.

DISCUSSION: Among the 150 patients recruited in the study, 69 (46%) developed QTc prolongation. Most patients with QTc prolongation presented with cardiovascular and endocrine disorders (69.56% and 46.37%, respectively). A significant association was found between cardiovascular disorders and QTc prolongation (p=0.002), which complies with the fact that existing cardiovascular conditions can potentiate the development of ECG abnormalities.

Although the proportion of patients presenting with underlying infections was low (11.3%), there was a significant association between the presence of infection and QTc interval prolongation (p=0.007). This is likely due to the electrolyte imbalances that occur secondary to infections, leading to the development of QTc prolongation. A significant association between QT-prolonging agents and

QTc prolongation was not established very well, except for azithromycin and furosemide, due to the skewed distribution of drug utilization. Among the factors included in the Tisdale risk assessment score, a significant association was found between advanced age (>68 years), admission QTc >450ms, and hypokalemia. Due to the smaller sample size and the skewed distribution of risk factors among the patients, the association between QTc prolongation and other risk factors could not be established. 85% of patients under the high-risk category for QTc prolongation had longer QTc intervals, while 9% of those in the low-risk category had it. This depicts that the risk assessment score has a considerable positive and negative predictive value, with significant specificity and sensitivity. However, this study does not provide a quantified value for the specificity and sensitivity of the score.

Using the Tisdale risk assessment score in healthcare setup can help identify those at risk of developing drug-induced QTc prolongation and treatment regimens can accordingly be optimized to prevent the patient from developing diLQTS and Torsades de Pointes subsequently. Adapting this risk assessment tool in regular practice is feasible as it utilizes the lab values and factors often monitored in all patients to quantify the risk of developing diLQTS. It does not require the patients to incur additional expenses for additional tests.

CONCLUSION: The study reports that QTc prolongation is prevalent among the patients admitted to the ICUs with a high prevalence of the risk factors for diLQTS, with most ICU patients being at a moderate to high risk for diLQTS when assessed against the Tisdale score. The medication administration should be monitored in these patients for safe medication usage and better therapeutic outcomes.

There is a considerable association between QTc prolongation and the risk factors included in the score. Incorporating the Tisdale score into clinical practice can effectively enhance patient care by stratifying them into risk categories for developing diLQTS and making appropriate therapeutic modifications, which can prevent the development of TdP, reduce the incidence of SCD, and improve patient's therapeutic outcome.

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