Arrhythmogenic Disorders of Genetic Origin

Sudden Cardiac Death in Hypertrophic Cardiomyopathy

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Introduction
Hypertrophic cardiomyopathy (HCM) is a common disorder of cardiac muscle associated with sudden cardiac death (SCD). HCM is defined by increased left ventricular wall thickness or mass, in the absence of abnormal loading conditions to account for the observed abnormality. In most adults, the disease is inherited as an autosomal dominant trait and is caused by mutations in cardiac sarcomere protein genes. Histologically, HCM is characterized by myocardial disarray, fibrosis, and small vessel disease. Macroscopically, the hypertrophy is typically asymmetrical and 25% of patients have resting left ventricular outflow tract obstruction (LVOTO).

SCD in HCM is caused mainly by ventricular arrhythmias that can be effectively treated by implantable cardioverter defibrillator (ICD) therapy. Identification of patients at high risk is a cornerstone of management and research during the past 4 decades has recognized a number of phenotypic characteristics that can be used to identify those patients who might benefit from an ICD.

Genetics and Pathogenesis
In infants and children, HCM is often associated with syndromes (eg Noonan’s syndrome, LEOPARD syndrome) and metabolic diseases (eg, glycogen storage diseases). In adults and adolescents, HCM is primarily caused by mutations in cardiac sarcomeric protein genes, and is inherited in an autosomal dominant manner. Mutations in these genes can be found in ≈60% of patients, and MYBPC3 and MYH7 mutations account for the majority of cases. Genotype–phenotype correlations are weak, with significant interfamily and intrafamily phenotypic variability. Exactly how HCM develops as a consequence of sarcomere protein gene mutations is not known.

Sudden Cardiac Death and Underlying Mechanisms
Existing data indicate that most patients with HCM die from cardiac causes, but this may reflect referral bias from centers reporting on mortality in HCM. Although the data do not exist, based on prevalence of 1/500, it is likely that most patients with HCM remain undiagnosed during life. Because of this, it is not possible to be sure of the mode of death in the general, unselected HCM population.

In published series, SCD is the most common cause of death in HCM and often affects young and frequently asymptomatic patients. The annual SCD rate is <1%, but within the general population with HCM there are subgroups with much higher incidence. SCD in HCM is mediated primarily by ventricular fibrillation. The central role of ventricular arrhythmias in the pathogenesis of SCD in HCM is supported by the observation that HCM patients treated with ICD receive appropriate therapies. Systematic analysis of stored electrograms shows that the majority of ventricular arrhythmias occur while in normal sinus rhythm and are precipitated by premature ventricular complexes. In addition, data from chance electrographic recordings have shown that ventricular fibrillation can be precipitated by runs of ventricular tachycardia, rapid atrial fibrillation (AF), or accelerated atrioventricular conduction. In addition to ventricular fibrillation, asystole and pulseless electric activity have both been reported in association with SCD. High-grade atrioventricular block may also have a role, but its contribution to the burden of SCD is unknown.

There are several potential mechanisms for ventricular arrhythmias. Intraventricular dispersion of conduction, attributed to variable cardiomyocyte size, fibrosis and disarray provides alternative conduction pathways promoting re-entry. Intercalated discs are disrupted, and the smooth conduction of action potentials between cardiomyocytes can be disturbed promoting arrhythmias. Studies in transgenic mice have highlighted the importance of increased myofilament Ca sensitivity, which causes shorter effective refractory periods and increased dispersion of repolarisation capable of generating functional reentry. Abnormal Ca handling also inhibits physiological proteolytic degradation pathways and result in persistence of Ca handling proteins, which may ultimately lead to electrophysiological dysfunction.

SCD in HCM has been linked with physical exertion. A vicious cycle of increasing myocardial ischemia, caused by diastolic dysfunction, LVOTO, systemic hypotension, and decreased stroke volume, has been suggested, but SCD can occur at rest or sleep, when metabolic demands are low. The exact triggers of ventricular arrhythmias remain unclear.

Risk Factors of SCD in HCM
Various phenotypic characteristics have been linked with SCD and are currently used to identify patients at risk. These risk factors were first noted in small, comparative observational studies, and then re-examined in larger studies with multivariable survival analysis using the Cox proportional hazards model. The online-only Data Supplement is available at http://circcep.ahajournals.org/lookup/suppl/doi:10.1161/CIRCEP.111.962043/-/DC1.

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hazards model with SCD as the end point (composite of actual SCD, aborted SCD +/- appropriate ICD shocks).

Ideally, the SCD end point in clinical studies should encompass all deaths caused by ventricular arrhythmias (and even bradycardias) that can be prevented by an ICD. However, not all arrhythmic deaths are sudden and not all sudden deaths are arrhythmic, and consequently accurate classification is challenging. Most HCM studies have used a modified Cardiac Arrhythmia Suppression Trial definition of SCD: death of cardiac origin, occurring unexpectedly within 1 hour of the onset of new symptoms or a death that was unwitnessed and unexpected, unless a specific noncardiac cause of death found. The temporal characteristics of death are thus used to extrapolate not only its cardiac origin, but also its arrhythmic nature. More recent studies have considered appropriate ICD therapies as SCD surrogates (7% to 38% of SCD end points). However, not all treated ventricular arrhythmias would have resulted in SCD, and the incidence of ICD therapies depends on pharmacological treatment and device programming, and thus appropriate shocks are unsatisfactory SCD surrogates.

The difficulties in diagnosing SCD, the use of appropriate ICD therapies as SCD surrogates, and challenges in coding cardiac phenotype accurately, influence the outcomes of clinical studies as discussed below.

1. Nonsustained ventricular tachycardia
Fortuitous electrocardiographic recordings captured complex ventricular arrhythmias responsible for SCD. Nonsustained ventricular tachycardia (NSVT) is common on Holter monitoring, but is brief (<10 beats), infrequent (<5 runs in 24 hours), and generally asymptomatic. NSVT is more common with increasing hypertrophy, which probably reflects increased fibrosis and disarray.

Two small comparative studies from tertiary referral centers demonstrated that NSVT was more common in SCD patients. The subsequent survival studies, which examined the relation of NSVT and SCD, are summarized in detail in the online-only Data Supplement. The prevalence of NSVT in these studies ranged between 17% and 32%, but the definition of NSVT was not uniform. All studies that demonstrated a significant association between NSVT and SCD defined NSVT as ≥3 consecutive ventricular beats at a rate of ≥120 beats/minute lasting <30 seconds. In a recent systematic review, the average reported hazard ratio (HR) for NSVT (irrespective of definition) was 2.89 (95% confidence interval [CI], 2.2–3.6).

The abovementioned studies used variable inclusion criteria, which may have lead to selection bias; in some studies, not all patients had Holter tapes, whereas in others, having a Holter was a prerequisite. The duration of monitoring has also been variable (24-hour monitoring was used in 4 studies, 24- to 48-hour monitoring in 2 studies, 48-hour monitoring another study), but NSVT was not indexed to Holter monitoring duration.

Even though the prevalence of NSVT increases with age, the risk of SCD associated with NSVT may be lower in older patients. Monserrat et al showed that NSVT in patients aged ≤30 years was associated with a 4-fold increase in the risk of SCD (univariable HR, 4.35; 95% CI, 1.54–12.28; P=0.006), but there was no effect in older patients (univariable HR, 2.16; 95% CI, 0.82–5.69; P=0.1). Exercise-induced ventricular arrhythmias, present in 1% to 2% of patients with HCM, are also independently associated with SCD (multivariable HR, 3.14; 95% CI, 1.29–7.61; P=0.01).

2. Severe left ventricular hypertrophy
Severe left ventricular hypertrophy (LVH) may contribute to SCD because of its deleterious effects on myocardial architecture, myocardial oxygen demand, coronary vascular resistance, and capillary density. LVH is associated with increasing prevalence of NSVT and exercise-induced ventricular arrhythmias.

All studies investigating the prognostic value of LVH used echocardiography to quantify its severity. This wall thickness is measured in the parasternal short-axis plane at the level of the mitral valve, papillary muscles, and apex. Most studies have used maximum wall thickness (MWT), defined as the greatest thickness in any single segment of the left ventricle as a measure of the severity of hypertrophy.

Initial comparative studies examining the prognostic value of LVH provided conflicting results. This relationship was further examined in more than 10 larger survival studies, summarized in detail in the online-only Data Supplement. Six studies showed a significant association between severe hypertrophy and SCD, and in a recent systematic review, the average hazard ratio for severe hypertrophy (irrespective of definition) was 3.1 (95% CI, 1.81–4.4). The use of MWT has a number of limitations. All studies have coded MWT as a binary or ordinal variable rather than a continuous variable. MWT ≥30 mm has been almost universally used to signify severe hypertrophy, but this cut-off is not based on any specific biological properties conferred by this particular wall thickness. MWT measurements are subject to observer variability, and limited echocardiographic windows may prevent adequate assessment of all myocardial segments. Furthermore, the thickness of a single myocardial segment may not adequately represent the true burden of hypertrophy; a MWT of 20 mm in a patient with exclusively apical HCM is not the equivalent of a MWT of 20 mm in a patient who has hypertrophy involving all myocardial segments. This limitation can be overcome by alternative assessments of LVH severity such as the Wigle scoring system, and a single study reported a significant association of increasing Wigle scores and SCD.

3. Systolic blood pressure (SBP) response to exercise
SCD in HCM has been associated with physical exertion, and the hemodynamic responses to exercise have been investigated in search of a pathophysiological link with SCD.

Exercise is associated with a physiological increase in sympathetic activity, a reduction in vagal tone, and redistribution of blood from visceral organs to exercising muscles. There is a physiological increase in SBP by approximately 7 to 10 mm Hg per metabolic equivalent, with the peak SBP achieved at maximum workload. Exercise-induced hypertension (in the absence of antihypertensive and β-blocker treatment, orthostatic hypotension, and significant bradycardia) is rare and is associated with cardiac pathology.
A blunted systolic blood pressure response to exercise (SBPRE) was first noted in a study of 6 patients with HCM in 1970, and subsequently examined in 129 patients who underwent a maximal symptom-limited treadmill exercise test. Approximately, one-third of patients exhibited an abnormal SBPRE, which was associated with a younger age and a family history of SCD (FHSCD), but not LVOTO or severe hypertrophy. The exact mechanism behind exercise-induced hypotension is unclear, but hemodynamic studies suggest that in the majority of cases, an inappropriate drop in systemic vascular resistance, despite an appropriate increase in cardiac output is responsible.

The prognostic importance of abnormal SBPRE was subsequently examined by Sadoul et al in a study of 161 primary prevention HCM patients aged ≤40 years. In this study, abnormal SBPRE was defined as a failure of the SBP to rise by ≥20 mm Hg during exercise, or by a fall of >20 mm Hg from the peak SBP recorded. In a comparative analysis, SCD was more common in those with an abnormal SBPRE (15% versus 3%; P<0.009). A number of survival studies, using variable definitions for abnormal SBPRE, failed to show a clear association with SCD, and are summarized in detail in the online-only Data Supplement. 

In a recent systematic review, the average reported hazard ratio for abnormal SBPRE (irrespective of definition) was 1.3 (95% CI, 0.64–1.96). Four studies have considered the impact of sex on SBPRE, as women have a lower incidence of SCD in affected relatives, and McKenna et al subsequently demonstrated that FHSCD was more common in families of patients with HCM.

The effects of a FHSCD as a predictor of SCD were examined using survival analysis in 11 subsequent studies, summarized in detail in the online-only Data Supplement. Four studies, with different definitions for FHSCD, have shown a significant association with SCD. In a systematic review, the average hazard ratio of FHSCD (irrespective of definition) was 1.27 (95% CI, 1.16–1.38).

Determining the cause of death in family members is often problematic. Witnesses’ accounts, death certificates, and postmortem examinations are not always available, and their interpretation depends on the expertise of the treating physician or pathologist. Most studies have used as age cut-off 40 to 50 years and have considered only multiple first-degree relatives. The prognostic value of SCD in second-degree relatives has not been examined.

The effect of FHSCD on SCD is related to the genetic nature of the disease. Affected relatives share the same genetic defect and to some degree have similar environmental exposures. Troponin T mutations have been associated with a high incidence of SCD, despite milder hypertrophy. Other specific mutations are associated with adverse prognosis, but there is significant intrafamily and interfamilial variation, and the strength of the genotype-phenotype correlation is not strong enough to warrant recommendation in risk prognostication.

Multiple mutations are also not uncommon. Whether genetic information improves risk stratification for SCD over and above phenotypic markers is not known.

5. Syncope

Syncope, a temporary loss of consciousness secondary to transient, global cerebral hypoperfusion is a challenging clinical diagnosis. There are multiple causes of syncope in HCM: atrial fibrillation, supraventricular tachycardias, bradyarrhythmias, sustained ventricular arrhythmias, abnormal vascular responses, exercise-related LVOTO, mitral regurgitation, and ischemia, neurally mediated syncope (vasovagal, situational, and carotid sinus syncope), and orthostatic hypotension. Once the diagnosis of syncope is reached, identifying the cause relies primarily on historical data provided by patients and witnesses.

The association of syncope and SCD was first noted in a comparative study, and then subsequently examined in 11 studies using survival analysis (summarized in detail in the online-only Data Supplement). Five of these studies have shown a significant association with SCD, and in a systematic review, the average hazard ratio of unexplained syncope (irrespective of definition) was 2.68 (95% CI, 0.97–4.38). In the majority of these studies, the prognostic significance of unexplained syncope was examined, but this has been poorly defined as unexplained loss of consciousness. Spirito et al in 2009 defined unexplained as syncope “of unknown origin, when it occurred in circumstances not clearly consistent with a neurally mediated event, ie, without apparent explanation at rest or during ordinary daily activities, or during an intense effort”. Furthermore, different frequencies of syncopal episodes, with various time cut-offs, have been used to code unexplained syncope in these studies. The variable definitions, in addition to the diagnostic difficulties, account for the variability seen in the association of syncope and SCD.

6. Left ventricular outflow tract obstruction

LVOTO is caused by systolic anterior movement of the mitral valve into the outflow tract, which creates a physical barrier impeding the flow of blood from the ventricle to the aorta during systole. LVOTO can mediate SCD either by causing severe reduction in cardiac output leading to electromechanical dissociation or by precipitating ventricular...
arrrhythmias though myocardial ischemia caused by increased left ventricular end-diastolic pressure.1

LVOTO is routinely quantified using pulsed and continuous wave Doppler echocardiography. Even though a gradient of ≥30 mm Hg indicates LVOTO, only gradients ≥50 mm Hg are thought to be clinically significant, as with less severe LVOTO, the majority of stroke volume is ejected prior to the onset of systolic anterior movement of the mitral valve.1 Assessment of gradients should be done both at rest and on provocation (e.g., Valsalva), in view of the dynamic nature of LVOTO.1 Peak-to-peak systolic gradients obtained from invasive hemodynamic studies are not interchangeable with the maximum instantaneous gradients determined by continuous Doppler.

Studies investigating the relation of LVOTO and SCD are summarized in detail in the online-only Data Supplement.38,39,43,52,53,55,56,58,59 All but one study32 used Doppler echocardiography under resting conditions, with and without provocation.38,39,53,55,59 Five studies reported a significant association between SCD and LVOTO.39,52,56,59,81 Numerous smaller studies with fewer SCD events were negative.38,43,53,55 LVOTO measurements are prone to biological, as well as observer variability, which have the potential to dilute the true effect of LVOTO on SCD. In addition, the proportion of patients treated with septal reduction therapy varies in each study, and such treatments may reduce the risk of SCD and weaken the association.82,83

7. AF and left atrial size
AF and left atrial size may indirectly reflect the risk of SCD, as they may both relate to atrial remodeling secondary to increasing ventricular fibrosis which, in turn, makes the myocardium more susceptible to arrhythmias.84 Hardason et al85 was the first to report the association with SCD. The effect of paroxysmal, persistent, or chronic AF as a predictor of SCD was examined in 5 studies using survival analysis.43,52,53,58,59 The one study that found a significant association between AF and SCD considered only chronic AF as a risk factor.44 Left atrial diameter, quantified with echocardiography has also been explored as a risk factor of SCD in HCM in 4 studies which used survival analysis.42,43,52,53. Even though left atrial size was associated with SCD in a single study,42 the multivariable analysis did not include other established risk factors, such as NSVT, making interpretation problematic.

8. Age
Even though SCD can occur at any age, early studies from tertiary referral centres suggested that there was a higher incidence in adolescence and early adulthood.72,85,86 Despite these early observations, the effect of age on the risk of SCD has been investigated only in a limited number of more recent survival studies.42,52,53,59 Only the largest study by Spirito et al42 found a significant reduction in SCD risk with increasing age. However, this study42 did not include other more established risk factors (e.g., NSVT) in the multivariable analysis, and firm conclusions cannot be drawn.

9. New York Heart Association (NYHA) functional class
Functional limitation in HCM is often secondary to LVOTO, diastolic dysfunction, cardiac ischemia, adverse remodeling, and atrial arrhythmias.34 SCD has been reported across all functional classes,7,40 and none of the studies examining the relation of NYHA functional class and SCD using survival analysis reported a significant association33,52,53,58,59. This may relate to the low interobserver concordance of NYHA classification.87

10. Sex
Male patients have more fibrosis on histological examination,2 and experience exercise-induced ventricular arrhythmias more than their female counterparts.36 There is conflicting data about a sex difference in the prevalence of LVOTO,38,58,59 severity of LVH,41,43,81 and incidence of SCD.7,85 None of the 3 studies which used survival analysis showed a significant association between sex and SCD.52,58,59

11. Invasive electrophysiological studies
Programmed electric stimulation has no value in risk stratification, as inducing ventricular arrhythmias predominantly reflects the aggressiveness of the stimulation protocol, and not the arrhythmogenic potential of the myocardium.88,89 Increased fractionation of paced right ventricular electrograms has been linked with SCD in patients with HCM.28,29,90 The invasive nature in a mostly asymptomatic population and the expertise required make it unlikely that fractionation analysis will become a routine risk-stratification test.

12. Late gadolinium enhancement
Late gadolinium enhancement in cardiac magnetic resonance studies reflects the presence of extracellular myocardial collagen deposition.91 The presence of late gadolinium enhancement is associated with impaired systolic function and the aggregation of risk factors for SCD, in particular NSVT.92,93 In a recent study of 217 patients with HCM, the presence and extent of late gadolinium enhancement was associated with cardiovascular morbidity and mortality, but was not associated with SCD in a multivariable model.94

13. Systolic function
Implantation of ICD in HCM patients with systolic dysfunction has been advocated by some investigators who have suggested that systolic impairment should be considered as another risk factor for SCD.95,96 This is based on the observation that HCM patients with impaired systolic function received appropriate ICD therapies at a rate similar to previously reported HCM patients with aborted SCD.96 However, the value of systolic function as a predictor of SCD has not been examined in an unselected HCM cohort.

Prevention of SCD: Antiarrhythmic Treatment and ICD
The class III antiarrhythmic amiodarone has been used to prevent sustained ventricular arrhythmias and SCD in HCM patients with NSVT.97 However, its effectiveness is limited, as SCD still occurs in amiodarone-treated patients.98 Currently, the ICD is the gold standard treatment for both the primary and secondary prevention of SCD in HCM. Data published to date show that SCD is rare in ICD recipients, and they receive appropriate device therapies that terminate potentially life-threatening ventricular arrhythmias.10–18 However, ICD implantation in HCM is associated with
considerable morbidity, secondary to inappropriate shocks and implant-related complications (Figure).\textsuperscript{18} Moreover, a substantial number of ICD recipients have a poor quality of life and psychological status, with significant occupational and lifestyle restrictions.\textsuperscript{99,100} ICD therapy is also expensive and requires lifelong medical surveillance.

**Clinical Guidelines**

Even though ICD therapy for the secondary prevention of SCD is uncontroversial, selection of patients for primary prevention ICD implantation is challenging because of the extensive heterogeneity of the disease.\textsuperscript{34,35,101,102} An ideal risk-stratification strategy should be able to accurately distinguish patients with HCM at sufficiently high risk of SCD to justify the risks of ICD implantation.

In 2003, the American College of Cardiology (ACC) and European Society of Cardiology (ESC) jointly published a clinical expert consensus document on HCM.\textsuperscript{34} To identify primary prevention patients at high risk of SCD, these guidelines recommend the assessment of 5 major risk factors: NSVT, unexplained syncope, abnormal SBPRE, FHSCD, and extreme LVH.\textsuperscript{34} In the presence of $\geq 2$ major risk factors, the guidelines state that “the risk for SCD is of sufficient magnitude” to justify prophylactic ICD implantation, whereas in patients with a single risk factor “strong consideration should be afforded for a prophylactic ICD”.\textsuperscript{34} Since the publication of the ACC/ESC guidelines in 2003, only 8 new survival studies using unselected cohorts examined SCD,\textsuperscript{38,39,42,54–56,58,81} of which only 3 included the 5 major risk factors in their multivariable statistical analysis.\textsuperscript{38,39,56} The results of the remaining studies are of limited value in the context of the current approach to risk stratification.

Subsequent to the ACC/ESC 2003 guidelines, both the ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias\textsuperscript{101} and the ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities\textsuperscript{102} state that ICD implantation can be effective or is reasonable for patients with HCM who have 1 or more major risk factors for SCD (both class IIa recommendations, level of evidence C). In the ACCF/AHA 2011 guidelines for the diagnosis and treatment of HCM,\textsuperscript{35} ICD implantation is reasonable in patients with FHSCD, MWT $\geq 30$ mm, or recent unexplained syncope, whereas an ICD can be useful in patients with NSVT or abnormal SBPRE in the presence of other established or emerging risk factors (both class IIa indications).\textsuperscript{35} These approaches represent a significant departure from the ACC/ESC 2003 guidelines, which are based on consistent evidence from unselected HCM cohorts that accumulating risk factors reflect a higher risk of SCD, and that individual risk factors in isolation have poor positive predictive value for SCD.\textsuperscript{9,39,41,103} The lack of association between the rate of appropriate ICD shocks and risk factor profile in studies of HCM ICD recipients\textsuperscript{12,17,18} cannot justify the new approaches, as the ICD studies consist of highly selected patients with HCM, and the end point used is an appropriate ICD shock and not SCD per se. The assumption that all appropriate ICD discharges are equivalent to SCD is flawed.\textsuperscript{45} In addition, even though NSVT has the highest effect size on SCD,\textsuperscript{104} particularly in the young, this is not reflected in the ACCF/AHA 2011 guidelines where the value of NSVT as a risk factor has been downgraded.

The major disadvantage of all current risk-stratification strategies\textsuperscript{34,35,101,102} is that they do not provide individualized absolute risks, but rely on relative risk estimates that have limited value in personalized prognostication.\textsuperscript{104} In addition, none of these approaches has been validated temporally or geographically.\textsuperscript{105} Cohorts of primary and secondary prevention patients selected for ICD implantation with the current guidelines have low appropriate shock rates at 4.6%/year (95% CI, 3.1–6.1) with a higher inappropriate shock rate and significant complication rates.\textsuperscript{18} Even though the recent development of a totally subcutaneous ICD may help reduce implant-related complications in the future,\textsuperscript{106,107} risk stratification will also have to improve.

**New Approaches to SCD Risk Stratification**

To overcome the limitations of current clinical guidelines, a clinical risk-prediction model that provides patients and physicians with an individualized absolute risk prediction for

![Figure](image.png)

**Figure.** Inappropriate shocks and implant complications in hypertrophic cardiomyopathy (HCM) patients. The studies shown have not used uniform reporting criteria, and the follow-up periods are variable (mean follow-up period range: 1.7–4.9 years). Begley et al\textsuperscript{12} and Kaski et al\textsuperscript{11} include psychological complications. Primo et al\textsuperscript{15} did not report implant complications.\textsuperscript{10–17}
SCD should be developed. An example of a current risk-prediction model is the CHA2DS2-VASc score, which provides an absolute risk of thromboembolic complications associated with AF. The heterogeneity of HCM would necessitate the use of multiple predictor variables chosen on the basis of the published studies discussed above. The Cox proportional hazards model is well suited for survival data, and can use combinations of predictor values to estimate the absolute risk of an event at a particular time point. Dichotomization of continuous variables, based on arbitrary or statistical criteria, should be avoided to prevent unnatural jumps in predictions. Such a study should have broad inclusion criteria to avoid selection bias, and even though a prospective design is often preferable, retrospective data collection is more practical, as outcomes in HCM are rare. Once developed, it can subsequently be validated externally and an impact study can examine outcomes in patients treated with the prediction model compared with those treated in a conventional manner.

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