# UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

# SCUOLA DI DOTTORATO

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Tesi di Dottorato

***"Studio della fisiopatologia della cardiomiopatia ipertrofica: rivalutazione del ruolo delle tecniche di indagine cardiologiche nella diagnosi e nelle decisioni terapeutiche; ruolo, timing ed outcomes del trattamento chirurgico sul profilo aritmico dei pazienti con forma ostruttiva."***


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# 1. Introduction

## 1.1 Definition of Hypertrophic Cardiomyopathy and Epidemiology

Hypertrophic cardiomyopathy (HCM) was described for the first time in 1958 by Dr Teare as a rare disease affecting young adults and causing asymmetrical left ventricular hypertrophy (1). Shortly after, Dr Braunwald focused his attention on the study of this condition which was considered to idiopathically cause a hemodynamically significant subaortic stenosis (2,3). Already at that time the variability of the clinical presentation of this disease was clear and its association with arrhythmic events as ventricular malignant arrhythmias and atrial fibrillation (AF) leading to sudden cardiac death was just becoming evident. Over time, the ability to diagnose this condition grew exponentially as did the therapeutical options available for its treatment.

Today it is known that HCM is a monogenic disease inherited with autosomal dominant transmission and prevalence data from echocardiographic studies estimate this condition affecting about 0.2% of the general population (1:500 subjects) (4). Nonetheless, this estimation only takes into consideration the morphologic expression of myocardial hypertrophy whereas recent data suggest that up to 0.6% of the population may carry pathogenically mutated genes and that the actual prevalence of HCM may be greater than previously thought (5).

The clinical history of the disease may vary among different families and even within the same family in a way that is difficult to predict and that is still beyond our complete comprehension (6). However, the growing understanding of HCM has transformed this condition from a rare and untreatable affliction with unfavorable outcome into a treatable disease with normalized life expectancy.

## 1.2 Etiology and Pathophysiology

Mutations of sarcomere-protein-encoding genes account for about 60% of HCM cases and the most common pathogenic mutations involve genes encoding for the myosin-binding protein C (MYBPC3) and the β-myosin heavy chain (MYH7). Some of the genes less commonly involved in the etiopathogenesis of HCM are those encoding for α-tropomyosin, cardiac troponin C and I, actin, myosin essential and regulatory light chain

proteins (7–9). Nonetheless, often clinical presentation may be widely variable as genetic mutations are expressed with incomplete penetrance.

In a minority of patients, multiple mutations may affect the genes encoding for sarcomere proteins related to this disease, these cases appear to be associated with precocious development of HCM and with a more aggressive clinical course (10).

Moreover, not all the known genetic mutations are associated with the clinical finding of HCM, in fact some genetic variants are classified as likely-pathogenetic, non-pathogenetic and variants of-unknown-significance (VUS).

Of the remaining 40% of HCM cases, 30% do not show any genetic background whereas 10% represent the so-called "phenocopies", conditions of cardiac hypertrophy associated with either metabolic disorders, mitochondrial diseases, neuromuscular diseases or other syndromes (11).

Among the most common phenocopies there are:

- HCM phenocopies related to metabolic disorders: frequently X-linked or inherited with autosomal recessive transmission, the most common of which is the Anderson-Fabry disease caused by a mutation of the gene encoding α-galactosidase A.

  Danon disease on the other hand is a glycogen storage disease due to the deficiency of LAMP2 protein.

  Some mitochondrial diseases are caused by mutation in mitochondrial DNA of genes encoding for proteins that belong to the respiratory chains.

  Amyloidosis is a disease of protein misfolding and metabolism which often causes multi-organ deposit of the mutated protein which is insoluble and at a cardiac level causes thickening of heart walls.
- HCM phenocopies due to congenital malformation syndromes: generally cause the development of the hypertrophic phenotype during childhood. The most frequent syndromes are Noonan, Costello and LEOPARD syndromes.
- HCM phenocopies due to neurodegenerative hereditary disease: such as Friedreich ataxia, which causes neurological, endocrinological disorders associated to various degrees of myocardial hypertrophy.

The Hypertrophic Cardiomyopathy phenotype may be extremely variable as the quantity and location of hypertrophied muscle does not follow specific patterns. The most common type of HCM is determined by an asymmetrical thickening of the basal and middle portions of the interventricular septum which ends protruding in the Left Ventricular Outflow Tract (LVOT). In a smaller proportion of patients the hypertrophy is located at the middle portions of the ventricular walls and is associated with hypertrophied papillary muscles, this form is called "midventricular" HCM and is associated with intraventricular obstruction and with increased intraventricular pressure, which is evident especially towards the apex of the left ventricle (LV). The continuous pressure overload of the ventricular apex often causes the thinning of its walls and the formation of an LV aneurysm, a scarred and extremely pro-arrhythmic deformation of the LV apex.

Midventricular HCM makes up for about 10% of all cases of HCM and, on one hand it presents different clinical features from the more common, basal phenotype. On the other hand, the surgical treatment of such patients requires a different approach and has different outcomes, so surgical studies on basal-HCM generally exclude patients with a midventricular obstructive phenotype.

Clinicopathologic studies found that common histologic features are fibrotic replacement of myocardial tissue, small vessels disease and multiple stages of myocardial ischemia in absence of obstructive coronary artery disease (12) together with cellular disarray and increased extra-cellular collagen matrix.

HCM is also often accompanied by recurring anatomic anomalies of the mitral valve anatomy and sub-valvular apparatus: the valve's leaflet are frequently elongated, especially the anterior, and its chordae may be redundant or extremely fibrotic and stiff or even sometimes the papillary muscles may have direct insertion into one of the valve's leaflets.

The cellular disarray together with the microvascular disfunction cause a chronic inflammatory damage which determines substitution of the myocardial tissue with extracellular matrix and causes progressive intra myocardial fibrosis. This process has two consequences: on one hand it determines diastolic dysfunction, anomalous relaxation of the myocardial tissue in the diastolic phase of the cardiac cycle, and on the other hand it

alters the conducive capacities of the myocardium, thus creating a pro-arrhythmic substrate.

During the natural history of the disease, the Left Ventricle Ejection Fraction (LVEF) is frequently and for long time supra-normal however, left ventricular systolic dysfunction may occur in the late stages of the disease due to extreme loss of contractile tissue and extended myocardial fibrosis (13).

The Left Ventricle Outflow Tract (LVOT) obstruction is a key feature in the pathophysiological mechanism of this disease, it is present in about two thirds of all cases and usually is determined by the interaction of two components: a fixed component, the hypertrophied and stiff LV which also has a smaller cavity than normal; and a dynamic component which is caused by the systolic anterior motion (SAM) of the anterior leaflet of the mitral valve (14,15).

### 1.3 Diagnosis

The diagnosis of HCM is based on clinical findings and echocardiographic or cardiac magnetic resonance (CMR) imaging is paramount. It is defined HCM a condition where the cardiac walls present a thickness ≥ 15 mm in at least 1 cardiac segment that may not be explained by cardiac overload (13). In first degree relative of a patient affected by HCM the presence of cardiac wall thickness ≥ 13 mm is considered sufficient to confirm the diagnosis (13). In the pediatric population HCM is defined by wall thickness ≥2 standard deviations (SD) the age and sex-adjusted predicted value (16).

The LVOT obstruction is generally evaluated using continuous wave (CW) Doppler across the LVOT, if obstruction is present it shows a typical waveform. HCM is considered obstructive if the peak gradient evaluated with CW-Doppler is ≥30 mmHg and the gradient is deemed hemodynamically significant if it is ≥50 mmHg.

It is of great importance to collect all anamnestic data available, specifically all information regarding family history of SCD, heart failure (HF), heart transplantation, implantable cardioverter defibrillator (ICD) placements. Age at diagnosis may orient towards specific scenarios as metabolic disorders and genetic syndromes are more common during childhood, sarcomere genes mutation generally become clinically evident during the adult life whereas amyloidosis is most frequent during old age (17).

Typical electrocardiographic (ECG) findings include increased precordial QRS voltage, indicative of LV hypertrophy, anomalies of the ST-T segment and deep, inverted T-waves in the lateral leads. However, up to 10% of the cases may present with a normal ECG.
CMR has developed increasing importance both for the assessment of hypertrophy and for tissue characterization and fibrosis quantification. After paramagnetic contrast medium intravenous infusion, late gadolinium enhancement (LGE), indicative of myocardial fibrosis, may be quantified with important clinical and prognostic implications (18).
Genetic screening is strongly recommended in all patients diagnosed with HCM and if a pathological genetic mutation is identified it is recommended to extend the genetic testing to all first-degree relatives (19).

### 1.4 Clinical Course

HCM is usually asymptomatic during the first phase of the disease and until young adulthood.
Dyspnea is the first symptom to occur followed by chest pain which is also typical of this disease. These symptoms may present themselves at rest but most frequently they appear during exertion or after eating as both condition determine an increase in the LVOT obstruction and gradient (7). Ischemic suffering of the myocardium is due to discrepancy between the increased myocardial demand of oxygen and the reduced supply secondary to altered microvascular circulation (12).
In HCM patients, syncope generally takes place during intense physical activity, it may be caused by either sustained tachyarrhythmias, typically ventricular, or by increased LVOT gradient and subsequent inefficient hemodynamics. In some cases, although less frequent, bradycardias or altered vascular reflexes may cause syncope.
Palpitations are commonly secondary to supraventricular or ventricular ectopic beats, but they may be also due to sustained tachycardias (20).
The diastolic dysfunction, which is variably present in all cases, and the systolic dysfunction of the most advanced forms of HCM, invariably determine the occurrence of the typical symptoms of heart failure, the first of which is exertional dyspnea.
It has been demonstrated that the diastolic dysfunction together with increased LV filling pressure and left atrial (LA) enlargement determine a progressive increase in pulmonary

pressure which was estimated to be directly associated with the clinical severity of the disease (21).

The progressive development of LV enlargement and systolic dysfunction are signs of the terminal phase of the disease.

During these stages right heart catheterization (RHC) and Cardiopulmonary Exercise Testing (CPET) are recommended as they may give useful information especially if the patient is candidate to heart transplantation (22).

The clinical course of the disease is extremely variable, and it is not infrequent that the first sign of disease may be cardiac arrest. Some patients live asymptomatically all their lives to develop exertional dyspnea during old age whereas for others the first signs of the disease appear together with an episode of supraventricular arrhythmia, typically atrial fibrillation (AF).

The natural story of the obstructive disease evolves either towards heart failure or to SCD and annual mortality for HCM is estimated to be around 3% (11).

### 1.5 Medical Therapy

Beta-blockers are strongly recommended for the medical management of HCM because of their negative inotropic and chronotropic effect: nadolol, metoprolol and atenolol are the preferred molecules due to their pharmacokinetics. When beta-blockers are contraindicated the use of non-dihydropyridine calcium channel blockers may be considered whereas dihydropyridines are contraindicated due to their vasodilating activity which may exacerbate or aggravate LVOT obstruction (23)(24).

Disopyramide can be used in association with beta-blockers to reduce LVOT obstruction and it has shown to increase functional capacity and at the same time to reduce the arrhythmic burden (25–27). However, the positive effects of this drug tends to reduce over time and sometimes it can cause relevant anti-cholinergic side-effects.

Vasodilators are generally contraindicated in patients with HCM, especially those with an obstructive physiology, however the use of angiotensin converting enzyme-inhibitors (ACE-i) or angiotensin receptor blockers (ARB) is recommended in the advanced stages of the disease, when the systolic dysfunction becomes evident.

In late years a new molecule has become available for the treatment of HCM patients with obstructive physiology: Macavamten. It is a selective inhibitor of cardiac myosin ATPase which acts by limiting the interaction between cardiac actin and myosin and thus reduces myocardial contractility. Its effects have been studied in the EXPLORER-HCM trial, a double blinded randomized controlled trial that showed safety and efficacy compared with placebo after 30 weeks of treatment (28). Another recent double blinded randomized trial, MAVERICK-HCM confirmed the reduction of LVOT gradient and symptoms after 16 weeks of treatment with Mavacamten. However, this study also found a significant, though reversible, reduction of LVEF in up to 8% of treated patients (29).

# 2. Arrhythmic Spectrum

## 2.1 Supraventricular Arrhythmias

It was estimated that symptomatic AF occurs in about 20% of all HCM patients while the burden of asymptomatic supraventricular arrhythmias remains unexplored although it is probably significant (30,31). LA dilatation and atrial myopathy are involved in the occurrence of AF, which is up to 4-fold more common in HCM patients than in the general population (32), multiple mechanisms concur to the genesis of negative atrial remodeling: LV diastolic dysfunction, LVOT obstruction and SAM determine variable degrees of chronic pressure and volume overload that, over time, cause a dimensional increase even in patients without arrhythmic events (33).

Furthermore, HCM patients with AF show an increased rate of adverse events as death, secondary to embolic cerebral events and hospitalizations for heart failure (34). In fact, stroke is an important determinant of morbidity and mortality and it is estimated to have an incidence of 0.8%/year in patients younger than 40 years and of 1.9%/year in older patients. For this reason, long-term oral anticoagulation is mandatory in all patients with HCM who develop AF (33).

On the other hand, the lack of atrial hemodynamic contribution to diastolic ventricular filling, in the context of stiff ventricles such as those with HCM, is responsible for hemodynamic functional deterioration and worsening of heart failure symptoms and mortality (35).

The association between AF and SCD is still debates, some studies reported absence of any significant association between them (30,36) however a large recent meta-analysis found in AF an independent predictor of death and ICD appropriate discharges (37).

On the treatment side, the most recent guidelines on the management of HCM suggest that rhythm control should preferred to rate control whenever feasible (38).

Class III antiarrhythmics as amiodarone and sotalol are the first-choice drugs, however care must be taken especially in long-term duration of anti-arrhythmic therapy due to the frequent side-effects of these medications (33).

Furthermore, there is some evidence that the combination of disopyramide and beta-blockers may be effective in preventing arrhythmic relapses however whether this effect is maintained over time is still unclear (39).

Class 1c antiarrhythmic drugs are contraindicated in HCM as they have shown to increase the probability of malignant arrhythmic events.

It has been demonstrated that transcatheter AF ablation is a feasible and safe in HCM patients and that it efficaciously reduces the rate of AF reoccurrences. Large atria frequently show extra-pulmonary vein firings (40) which require longer procedure and additional ablation lines (40,41) whereas smaller LA have better outcomes (42).

Given the heavy burden of AF on HCM patients, surgical ablation of AF has been successfully practiced during HOCM surgery with a significant reduction of postoperative arrhythmic relapses both at short and long-term (43).

Recent observations showed that, in HOCM patients, the relief of LVOT obstruction may, by itself, reduce the postoperative AF burden by 30% compared to non-operated patients (44).

### 2.2 Ventricular Arrhythmic Burden

HCM is the most frequent cause of SCD in young patients and athletes (45) and ventricular arrhythmias constitute a heavy burden for HCM patient and an important treatment target. The natural history of HCM has been changed since the introduction of ICDs given their demonstrated effects as life-saving devices (38,45). Secondary prevention of malignant ventricular arrhythmias or cardiac arrest constitutes a class I recommendation to ICD implantation whereas, as of today there is still some debate about in ventricular arrhythmic risk estimation strategies for primary prevention ICD implants. Conversely, the role of medical antiarrhythmic therapy in the context of SCD prevention is extremely limited (38,45).

The main recognized risk factors are family history of SCD, severe LV wall thickness ($\geq$ 30mm), unexplained syncope and registered episodes of non-sustained ventricular tachycardia (38,45).

Important is also the role of other risk factors such as age, LA dimensions, LVOT obstruction and gradient, reduced LV systolic function, CMR-evaluated areas of late gadolinium enhancement > 15% of total LV mass and LV apical aneurysms (46).

European guidelines recommend to use the validated HCM risk-SCD calculator (47,48) at least annually in all patients aged > 16 years whereas a specific model is recommended for the pediatric population, HCM Risk-Kids (49,50).

Conversely, American scientific societies recommend assessment of single risk factors and indicate the presence ≥1 of them as enough evidence to consider ICD positioning (45) also in the pediatric subgroup. Nevertheless, Experts agree that in all cases personalized clinical evaluation and shared decision-making, taking care also of the patients' point of views, are essential to achieve the best preventive practice.

The first generation of ICDs had epicardial leads implanted via thoracotomy, these devices have been progressively substituted by transvenous devices, with intracavitary leads, which today are considered the gold standard of SCD prevention and have the greatest quantity of supporting data. Subcutaneous devices have been introduced in recent years and are supported by growing experience and literature suggesting that they are safe and efficient alternatives to transvenous devices especially in patient without need for cardiac pacing (51).

The most frequent complications related to this technology are, in order of frequency, inappropriate shocks, lead ruptures and infections with a cumulative rate of about 2%/year.

Relief of LOVT obstruction after septal myectomy has shown to impact significantly the ventricular arrhythmic burden of HOCM patients, specifically the risk of SCD and appropriate ICD discharges has been demonstrated to be significantly lowered by surgery and to be inferior in surgically managed patient than in a medically managed population (52–57),

### 2.3.1 **Bradyarrhythmias and Conduction Disturbances**

Bradycardias are a rare finding in the natural history of HCM, in fact when atrio-ventricular conduction disturbances are found in the context of a hypertrophic phenotype, phenocopies such as Anderson-Fabry disease, sarcoidosis, Danon disease, amyloidosis and PRKAG2 cardiomyopathy should always be suspected assessed (38). The prevalence of diseased

atrio-ventricular (AV) conduction system in sarcomeric HCM is attested in <20% of the patients and correlates with the age of the population; intra-ventricular (IV) conduction disturbances is even rarer.

However, septal reduction therapies carry a significant risk of iatrogenic IV and AV blocks. Specifically, data from large registries found that septal myectomy is associated with the postoperative development of left bundle branch block in 50-100% of the cases whereas, in specialized tertiary care centers, the risk of post-surgical complete AV block is around 2-3% (58).

Conversely, after alcohol septal ablation (ASA) the rate of complete AV block is around 10-33% depending on volume of ethanol injected and number of septal perforator arteries ablated (58,59).

In all cases, it is demonstrated that the need for continuous pacing is associated with an increase in morbidity and mortality in the post-surgical HCM population (60).

# 3. Septal Reduction Therapies

## 3.1 Septal Myectomy

Surgical septal myectomy was invented by Dr Morrow during the 1970s and, since then has been showing to reduce symptoms and to improve survival and functional capacity of all patients with significant LVOT obstruction and severe exertional dyspnea despite medical therapy (61,62). . This technique was refined by Dr Messmer in 1994 extending the myectomy and introducing mobilization of malattached papillary muscle (63).

Today this surgery is reserved to those patients who show a pressure gradient across the LVOT ≥50 mmHg, estimated with CW Doppler during echocardiography, and are symptomatic with exertional dyspnea NYHA class ≥ III or ≥ II in the presence of other ancillary indices of severity of the disease.

As midventricular obstructive HCM present specific clinical, anatomical and technical surgical features, patients with midventricular HCM are generally excluded from the surgical studies on the relief of LVOT obstruction which is typical of the "basal" obstructive HCM phenotype.

Morrow's septal myectomy is executed on cardio-pulmonary extracorporeal circulation with an approach that requires median sternotomy. In most cases the surgical procedure is conducted through a longitudinal aortotomy and through the native aortic valve (61,64,65). A portion of the interventricular septum is excised with an incision that is started below the aortic annular plane, in between the right and left coronary cusps, and goes into the mid portion of the interventricular septum in a trapezoid shape with a wider base towards mid-ventricular level.

However, even in basal HOCM there are more components to LVOT obstruction than just septal hypertrophy. In fact, anomalous fibromuscular bundles and abnormalities of the mitral subvalvular apparatus as fibrous chordae are common findings that often concur to the genesis of the obstruction and as such require proper treatment (64,65).

From a pathophysiological standpoint, these structural features determine anterior displacement and rotation of mitral valve coaptation which is thought to be the cause of progressive fibrosis and retraction of mitral valve's secondary chordae. Secondary chordae retraction is then associated with slack primary chordae that during the systolic phase of

the cardiac cycle protrude into the LVOT causing the systolic anterior motion (SAM) of the anterior mitral leaflet.

Following the growing understanding of HOCM pathophysiology surgical techniques have been implemented to address all components of LVOT obstruction with a tailored approach (65).

Septal myectomy has shown to be effective in >90% of the treated patients to reduce the gradient at the LV outflow with a 30-days observed mortality of 3-4% in tertiary care centers (66).

The most common surgical complications of septal myectomy include injuries to the cardiac conduction system, iatrogenic ventricular septal defect (VSD) and iatrogenic aortic valve regurgitation.

Surgical intervention on the mitral valve, in the forms of either repair or replacement, is described in up to 20% of the cases of septal myectomy and related to significant mitral valve regurgitation due to degenerated valve leaflets and subvalvular apparatus (67). Whenever possible, the valve repair is preferable to valve replacement and the most commonly used and described techniques are: anterior mitral leaflet's plication and anterior leaflet repair with patch augmentation (68).

### 3.2 Alcohol Septal Ablation

ASA is a percutaneous technique that targets the hypertrophic interventricular septum by inducing a iatrogenic myocardial infarction with ethanol injection in one or more septal perforator branches of left anterior descending (LAD) coronary artery. This treatment is generally reserved to older patients who are excluded from septal myectomy. Young age and moderate hypertrophy are considered a contraindication to the procedure (69) and in expert centers this technique has shown safety and adequate resolution of LVOT obstruction even in patients at high surgical risk (70). Its complete effects are typically assessable only 3 to 6 months after the procedure and in 15-20% of patients a second ASA procedure may be necessary.

The most common complication of this technique is conduction system damage with a permanent pacemaker implantation rate ranging between 10 and 33%, as previously mentioned (58,59). Other possible complications include large myocardial infarctions,

generally due to iatrogenic damage of LAD coronary artery or to technical errors in the ethanol injection technique (71).

### 3.3 Heart Transplantation

Heart transplantation represents the last therapeutical resort in the treatment algorithm of HOCM patients. It is generally reserved for those with advanced-stage systolic dysfunction and evolution to a dilated hypokinetic cardiomyopathy, generally young patients with heart failure refractory to medical therapy (72).

The use of ventricular assistance devices (VAD) as bridge to transplantation has been described in this population, however its applicability is reduced by the small dimensions of the ventricular cavity in the hypertrophic phenotype and so it is applicable mostly to patients who develop LV dilatation (73).

# 4. Long Term Outcomes and Arrhythmic Burden after Septal Myectomy

## 4.1 Objective of the study

Objective of the present study was to assess the long-term clinical outcomes of patients treated with septal myectomy for the relief of LVOT obstruction and specifically, to assess the association between pre-operatory clinical and echocardiographic variables and adverse events in order to individuate potential predictors of success and failure to be used as therapeutic targets.

## 4.2 Methods

### 4.2.1 Study population

439 consecutive patients were treated between June 2013 and December 2019; they received surgical treatment of Basal Hypertrophic Obstructive Cardiomyopathy (HOCM) at the tertiary care center "Policlinico di Monza" to relieve the symptoms deriving from severe LVOT obstruction which were not controlled by optimized medical therapy.

Data from this population are the preliminary results obtained during long-term follow-up after Septal Myectomy and Chordal Cutting.

The diagnosis of HOCM was based on clinical features including the echocardiographic finding, in the absence of other potentially causative factors, of severe left ventricular hypertrophy (left ventricular wall thickness ≥15 mm) together with evidence of obstruction of the LVOT to blood output represented by a pressure gradient ≥ 30 mmHg which could be estimated echographically either in basal conditions or evoked by the Valsava maneuver. In case of severely symptomatic patients who did not show LVOT gradient under basal conditions, post-prandial echocardiography and exercise echocardiography were performed to try to evoke a significant pressure gradient. Surgical indication was given when the pressure gradient across LVOT, in basal conditions or evoked, was found ≥ 50 mmHg.

All therapeutical decision regarding the medical and surgical management of the patients were shared by a multidisciplinary team made of cardiac surgeon, cardiologist, radiologist

and cardiothoracic anesthesiologist and were based on the results of the following assessments:

- Clinical visit was aimed at appraising the presence of heart failure symptoms, graded using the New York Heart Association (NYHA) scale, and at collecting the patient's family history of HCM and SCD and personal history of syncope, supraventricular arrhythmias, relevant comorbidities and medications in use.
- Electrocardiography (ECG) was performed at each stage of preliminary evaluation and post-operative follow up to assess heart rhythm, heart rate, atrio-ventricular and intra-ventricular conduction and repolarization abnormalities.
- Trans-thoracic echocardiography was conducted and analyzed in all patients who accessed to our facilities by a member of the internal medical team specialized in cardiomyopathies at baseline and at each follow up visit.
- ECG-Holter monitoring was deemed necessary to ascertain the presence of supraventricular and ventricular arrhythmias, it was performed at the time of baseline evaluation evaluation, at 3-4 months after surgery and annually thereafter.
- Cardiac Magnetic Resonance (CMR) was performed to study the morphological and functional status of hypertrophic hearts as well as to investigate myocardial tissue characteristics and the presence of late gadolinium enhancement (LGE), indicative of myocardial fibrosis. CMR was also used in the planning of the surgical procedures.
- Exercise-echocardiography and cardiopulmonary exercise testing were required pre-operatively only in some patients. They were also used in the follow-up phase of the study in selected patients.
- Left Heart Catheterization, left ventricle angiography, aortography and coronary angiography were performed pre-operatively in all patients to assess coronary anatomy and exclude concomitant coronary artery disease but also to study invasively the LV anatomy, the LVOT obstruction and the pressure gradient between the LV and the Aorta.
- Right Heart Catheterization was performed in selected cases when significant pulmonary hypertension was suspected (echocardiographically estimated systolic pulmonary artery pressure $\geq$ 50 mmHg).

### 4.2.2 Surgical Procedure

The operative procedure has been described previously (64,65,74) and the surgical act was planned based on pre-operative CMR, when available (75). Transesophageal echocardiography (TEE) was conducted at the beginning of surgery to assess the morphology of the left ventricle and of the mitral valve and then, on cardiopulmonary bypass, septal myectomy was performed through a longitudinal aortotomy. After septal myectomy, the subvalvular mitral apparatus was analyzed and anomalous chordae or fibromuscular bundles, if present, were excised and/or dissected. Finally, the ventricular face of the anterior leaflet of the mitral valve was inspected and fibrotic secondary chordae were resected. Once off extracorporeal circulation TEE was repeated to ascertain the success of surgery as well as to exclude potential acute complications.

### 4.2.3 Long Term Follow-up and Outcomes

Follow up visits and echocardiography were performed in the great majority of patients at 3-6 moths after surgery and annually thereafter. However, hospital access was limited for patients coming from distant regions of Italy and especially during the Covid19 pandemic. Thus, all patients also received telephonic follow-up checkups.

All events that took place within the first 30 days from surgery were excluded from the analysis as the objective of this study was to evaluate the long-term effects of surgical treatment of HOCM.

The primary outcome of this study was a composite of all-cause mortality, resuscitated cardiac arrest, appropriate ICD discharge, hospitalizations for heart failure and stroke.

Left atrial remodeling was then evaluated and specifically its relation to clinical status, heart failure symptom and supraventricular arrhythmias.

Thirdly, long-term ventricular arrhythmic burden after LVOT obstruction correction was studied as well as the postoperative incidence of bradyarrhythmias.

### 4.2.4 Statistical analysis

The statistical analysis was performed using all data available at the date of October 8$^{th}$ 2022. Continuous variables are presented as either mean ± standard deviation or median. They were compared using the Student t-test or analysis of variance (for parametric

variables) or the Mann-Whitney test (for non-parametric variables). Categorical data are expressed as the percentage frequency and compared using the $\chi 2$ test. Association between variables was assessed using linear or logistic regression models for continuous and categorical variables respectively. Hazard ratios (HRs) and their corresponding 95% confidence intervals were derived from Cox proportional hazards models. Additionally, cumulative event rates over time were generated using the Kaplan-Meier method, and differences in outcome event curves were assessed with the log-rank test. The statistical analysis was carried out using Stata/MP 18.0 (StataCorp). A probability value of less than 0.05 was deemed statistically significant.

### 4.3 Results

#### 4.3.1 Demographic and Baseline Characteristics

439 consecutive patients underwent cardiac surgery to relieve LVOT obstruction between 2013 and 2019. 92.1% of the 439 patients were contacted for follow up. Among them 2 patients had died during index hospitalization within 30 days from surgery, 1 because of respiratory insufficiency and the other patient for pericardial tamponade. 1 other patient could not be weaned from cardiopulmonary bypass after surgery and so was assisted with extracorporeal membrane oxygenation (ECMO) and was given urgent heart transplantation. Therefore, the final population of this study comprised 401 patients.

The baseline characteristics are summarized in Table 1, the mean age of the patients at the time of surgery was 50.5 years and 42% were women, all patients were symptomatic with effort dyspnea, NYHA class was II in 22.2% of the cases and III-IV in 77.7%. 61 patients (15%) had a history of unexplained syncope, 11 (3%) had survived a malignant ventricular arrhythmia and 94 subjects (23%) had history of atrial fibrillation. At the moment of inclusion in this study, 50 patients had been already implanted with an ICD. Almost one third of the baseline population had arterial hypertension.

At baseline mean LVEF was 65%, the mean thickness of the interventricular septum was 22 mm and the mean LVOT gradient at rest was 67.5 mmHg (Echocardiographic baseline characteristics are summarized in Table 2.).

341 patients (85%) underwent septal myectomy as described previously whereas 60 (15%) patients also received other concomitant cardiac procedures: mitral valve replacement

(MVR) was performed in 24 (5.9%) patients, 22 (5.5%) patients received concomitant coronary artery bypass graft (CABG) and 3 (0.75%) received aortic valve replacement (AVR), as summarized in Table 3.

### 4.3.2 Long Term Follow-Up

Mean duration of follow up was 57 months and relevant clinical data were collected from all 401 patients (Table 4.). Echocardiographic data were collected only for those patients reaching our Center and so were available in 216 cases (54%), these patients had a mean clinical follow up duration of 56 months (Table 5.).

16 patients (4%) died during follow up, 5 people due to advanced heart failure refractory to medical therapy whereas 11 patients died for other reasons: 3 patients developed malignant cancer, 3 had Covid19 pneumonia leading to fatal respiratory failure, 2 patients died subsequently to ischemic stroke, 1 patient died of acute kidney failure, 1 of acute pulmonary embolism and 1 of acute aortic dissection.

78 patients (19.4%) were hospitalized of which 14 (3.5%) had acutely decompensated heart failure, 17 (4.2%) patient underwent re-do cardiac surgery or transcatheter procedures, 16 (4%) patients were implanted with ICD and 12 (3%) with permanent PM, 7 patients had an acute cerebral-vascular event, 4 patients experienced an appropriate ICD discharge, 3 patients were hospitalized for Covid19 Pneumonia, 1 patient developed acute kidney failure, 1 had acute pulmonary embolism, 1 had acute aortic dissection and 1 patient showed superficial wound infection which was managed medically.

87 (21.7%) patients had at least 1 episode of AF during follow up, in 54 cases there was a pre-operative history of supraventricular arrhythmias whereas AF was newly diagnosed in 33 cases. 40 patients with pre-operative history of AF did not develop new episodes after surgery.

81.8% of patients who were contacted for follow up had a functional NYHA class I and 15.8% had class II NYHA symptoms.

### 4.3.3 Outcomes and Survival Analysis

During the follow up, 38 (9.5%) patients met the primary endpoint of death, resuscitated cardiac arrest, appropriate ICD discharge, hospitalizations for heart failure and stroke. Specifically, 16 patients died, 6 patients experienced ventricular malignant arrhythmias (2 were resuscitated from cardiac arrest and 4 received appropriate ICD discharges), 9 patients were hospitalized for acutely decompensated heart failure and 7 patients had a cerebral-vascular event. The 1-year and 3-year rates of composite endpoint were respectively 2.5% and 4.5%.

As shown in Table 6, survival analysis with Cox Proportionate Hazard model found that preoperative AF predicts the composite outcome (HR 2.26, CI 1.2-4.4; $p = 0.015$) whereas no association was found between the primary endpoint and the other variables studied. The Kaplan Meier curve showing the difference in survival between groups divided on the basis of preoperative AF is reported in Figure 1.

### 4.3.4 Left Atrial Remodeling

Follow-up echocardiographic data of left atrial dimensions was available for 216 patients. From the analysis conducted on these data it was possible to assess that also in this subgroup of patients the presence of AF before surgery was predictive of the composite outcome (HR 4.11, CI 1.3-12.7; $p = 0.014$). We also noted that there was a significant association between indexed left atrial volume (LAVi) and preoperative AF (OR 1.03, CI 1.02-1.05; $p = 0.001$) and a significant reduction in LAVi (-7 ml/m2; $p = 0.001$) and in NYHA class (z= 24; $p > 0.001$) after surgery.

However, using Cox Proportionate Hazard model no association was found between either preoperatory LAVi and the composite outcome nor between the difference of pre- and post-operative LAVi (DeltaLAVi) and the composite outcome.

On the other hand, the reduction in the LAVi dimensions (DeltaLAVi) was found significantly associated with the postoperative occurrence of AF (OR 1.02, CI 1.01 – 1.04; $p = 0.03$).

Also, DeltaLAVi was found associated with both postoperative NYHA class (coeff. -0.025; $p = 0.025$) and with the reduction observed between preoperative and postoperative NYHA class (DeltaNYHA) (coeff. 0.05; $p = 0.039$) as shown in Figure 2.

### 4.3.5 Postoperative Arrhythmic Burden:

During pre-surgical work-up the risk of ventricular malignant arrhythmias was evaluated for all patients using the HCM risk-SCD score as suggested by current European guidelines (38,47,48) and mean baseline SCD risk was found to be 3.98±2.56%. Then the patients were divided into 3 groups based on the predicted risk of malignant arrhythmias: 266 (66.3%) patients had calculated risk < 4% at 5 years; 69 (17.2%) patients had a risk between 4 and 6%; 66 (16.4%) patients had >6% risk at 5 years as shown in Table 8.

At the end of the follow up 6 arrhythmic events had been registered with a cumulative rate of 1.5% at 57 months: 2 patients suffered from resuscitated cardiac arrests for which they later received an ICD for secondary prevention; in 4 other cases there were appropriate ICD discharges.

No differences were found in event rates among the different predicted-risk groups ($\chi 2 = 2.31$; $p = 0.31$), as there were no differences based on preoperative NYHA functional class ($\chi 2 = 1.03$; $p = 0.59$) or preoperative presence of AF ($\chi 2 = 0.11$; $p = 0.74$). The Kaplan Meier curve showing no differences in survival free from ventricular arrhythmias between predicted-SCD risk groups is reported in Figure 3.

During the follow up 28 patients received cardiac implantable electronic devices (CIEDs), 12 permanent pacemakers were implanted for bradyarrhythmias and 16 ICDs, only 2 of which were secondary prevention implantations. As for the remaining 14 ICDs, no data available suggest major ventricular arrhythmic events explaining the implantations so it is reasonable to believe that these devices were implanted on the basis of the decision of the single clinician. The cumulative rate of CIEDs implantation at 5 years was 6.9% at 57 months.

## 4.4 Discussion

This study collected the data from the numerous population referring to the largest tertiary care center in Italy for the surgical relief of HOCM to evaluate arrhythmic long term outcomes and individuate predictors of success after myectomy but also to appraise potential markers that may indicate the need to anticipate the timing of invasive treatment.

All baseline data were collected retrospectively from the database of the Center for the treatment of Hypertrophic Cardiomyopathy of the Policlinico di Monza, whereas clinical follow up data were collected prospectively during clinical visits or telephone check-ups.
As the aim of this study was to assess the long-term results of successful surgical treatment of HOCM all adverse events taking place within 30 days from surgery or during index hospitalization were censored.
The long-term overall survival rate was 96% at 57 months with 90.5% of patients surviving free of primary composite endpoint. NYHA functional class was significantly improved after surgery and remained stable in time until last follow up with 81.8% of the patients in NYHA class I and 15.8% in NYHA class II.
In our analysis the Cox Proportionate Hazard model found that the preoperative presence of AF predicted the primary endpoint and was also associated to patients' clinical status and symptoms.
AF is an established risk factor and disease modifier in the natural course of HOCM, and LA dilatation plays a critical role in its development. Progressive stretching of the atrial tissue results in the formation of fibrotic patches within the myocardium which create a conducive environment for micro-reentrant circuits, substrate for this arrhythmia (33).
Left ventricular diastolic dysfunction, LVOT obstruction and systolic anterior motion (SAM) of mitral valve's anterior leaflet are three structural conditions which, by causing pressure and volume overload of the LA chamber, contribute to this process. Additionally, LA enlargement is influenced by various other factors, including age and body-mass index (BMI) (76,77).
As a result, individuals with HCM have a higher likelihood of developing AF, which is up to four times more common among these patients than in the general population and tends to occur at a younger age (32).
From the analysis of the echocardiographic data available it appears clear that surgery determines a positive remodeling of the LA, this is significantly associated with improved postoperative symptoms, heart compensation and reduced occurrence of AF.
As in the general HCM population LA dimensions and AF occurrence are independent predictors of adverse events and HCM-related mortality (34,37,78–80), there is reason to believe that the positive remodeling observed after surgery may be associated with a

survival benefit. From the analysis of the echocardiographic data available, our study failed to show significant association between the positive atrial remodeling and the few adverse events registered although a significant correlation was observed between preoperative atrial dimensions and preoperative burden of AF as well as between the quality of postoperative LA remodeling and postoperative occurrence of AF and functional class.

This finding supports the idea that, in experienced centers, increased atrial dimensions may be used as an indicator to anticipate surgery also in patients with mild symptoms (class NYHA II) (81).

As for SCD risk estimation, there exist varying opinions between European and American scientific organizations regarding the assessment strategy. While certain risk factors are acknowledged as significant by both societies, there are differences in the interpretation of others. Nonetheless, experts concur that identifying high-risk individuals and recommending ICD placement is a complex and sensitive issue because although ICD implantation is potentially lifesaving, it may also have troubling complications (38,45).

In the present population only 6 malignant ventricular arrhythmias were registered postoperatively with a cumulative rate of 1.5% at 57 months (0.3%/year). The observed rate did not differ among the predicted risk groups and was significantly inferior to the rate calculated by the HCM risk-SCD score pre-operatively.

Therefore, if on one hand the HCM risk-SCD score is not applicable after myectomy on the other hand it certainly serves at indicating that even in those patients with predicted high-risk, surgical intervention may significantly mitigate such risk to an extent that has not yet been measured but appears beyond significant. In fact, it has already been shown in previous papers that surgical myectomy reduces the incidence of ventricular malignant arrythmias in treated patients (52–57,82) and this study confirms this idea with its long-term observations and shows how SCD-risk is made more homogeneous across different risk groups by myectomy.

However, as myectomy does not bestow complete immunity from SCD, all patients who meet the criteria for SCD primary prevention should be treated with ICD implantation nonetheless (38).

It is known from the literature that all septal reduction therapies carry an intrinsic risk of bradyarrhythmias and specifically of complete Atrio-Ventricular Block (AVB). Septal

myectomy is associated with the development of left bundle branch block in 50-100% of the cases although a detrimental effect of this condition on patients' outcomes has never been demonstrated. Complete AVB on the other hand is a much less frequent complication as in high volume centers it occurs in 2-3% of the cases after surgery (58,83) but necessitates the implantation of a permanent pacemaker and the need for continuous pacing has a demonstrated negative impact on long-term survival (84).

In our population, 12 (3%) patients were implanted with permanent pacemakers due to the development of significant bradycardias. However, since the occurrence of such events was diluted along the follow up time it appears likely that septal myectomy may be only a concurring factor in their determination.

On the other hand, 16 (4%) patients received an ICD during the investigated time and only in 2 cases the implantation followed a significant ventricular arrhythmia. Moreover, there is no evidence suggesting that the remaining 14 devices were implanted for secondary SCD prevention as there is no evidence of their activation to prevent SCD. Thus, the most likely explanation remains that these devices have been implanted following the decision of each single patient's caring physician. The cumulative rate of CIEDs implantation at 5 years was 6.9% at 57 months.

Finally, given the evidence provided by this study it seems coherent to hypothesize that an earlier surgical management of HOCM that considers LA enlargement and AF occurrence as landmarks of advanced disease to be avoided, may reduce LA negative remodeling, and prevent or at least delay the occurrence of AF with positive impact on patients' prognosis and symptoms. At the same time, the positive effect of septal myectomy on SCD and the low rate of postoperative ventricular arrhythmic events need to be further studied to fully understand whether myectomy may reduce the need for ICD implantations and their rate of appropriate discharges.

### 4.5 Limitations

The present study was monocentric in nature and the analysis was based on data collected both in a retrospective and a prospective fashion.

As the Policlinico di Monza is a tertiary care center, referral bias may affect the quality of the data.

The follow up visits were limited by the geographical distance from the home regions of some patients and by the Covid19 pandemic which reduced access to healthcare facilities and to transportation.

### 4.6 Conclusions

The analysis of the data collected over a large temporal window at the Policlinico di Monza showed that in HOCM patients AF has a significant impact also on those who undergo surgical relief of LVOT obstruction and predicts long-term postoperative outcomes.

LA enlargement was associated with the occurrence of AF and with the development and evolution of symptoms of heart failure. LA postoperative positive remodeling was associated with reduced AF postoperative occurrence and improved patients' functional status.

The observed rate of postoperative ventricular malignant arrhythmia was extremely low and the events were not associated with either preoperative or postoperative AF.

# Tables and Figures

| Table 1. Baseline characteristics of the study population | Total = 401 |
|---|---|
| Age, y | 50.5±13.9 |
| Female sex, n (%) | 168 (42) |
| NYHA class, n (%) | |
| -I | 0 |
| -II | 89 (22.2) |
| -III | 274 (68.3) |
| -IV | 38 (9.4) |
| Syncope, n (%) | 61 (15) |
| Family History of HCM, n (%) | 61 (15) |
| Previous Ventricular Malignant Arrhythmias, n (%) | 11 (3) |
| HCM risk-SCD score, % | 3.98±2.56 |
| Previous ICD implantation, n (%) | 50 (12.5) |
| History of AF, n (%) | 94(23%) |
| paroxysmal % | 64 |
| persistent % | 28 |
| permanent % | 8 |
| Hypertension, n (%) | 119 (30) |
| Coronary Artery Disease, n (%) | 29 (7) |

**Table 1. Baseline characteristics of the study population. NYHA = New York Heart Association; HCM = Hypertrophic Cardiomyopathy; ICD = Implantable Cardioverter Defibrillator; AF = Atrial Fibrillation.**

| Table 2. Baseline Echocardiographic Data | Total = 401 |
|---|---|
| Left Ventricle Ejection Fraction, % | 65±7 |
| Interventricular Septum Thickness, mm | 22±5 |
| Mitral Regurgitation, 1-4 + | 2.1±1.1 |
| Left Ventriclular Outflow Tract basal gradient, mmHg | 67.5±36 |
| Left Atrial diameter, mm | 45±8 |

**Table 2. Baseline Echocardiographic Data.**

| Table 3. Surgery Data | Total = 401 |
|---|---|
| Septal myectomy + chordal cutting | 341 (85) |
| Septal myectomy + AVR | 3 (0.75) |
| Septal myectomy + MVR | 24 (5.9) |
| Septal myectomy + MVRepair (Annular Ring) | 11 (2.7) |
| Septal myectomy + CABG | 22 (5.5) |

**Table 3. Surgery Data. AVR = Aortic Valve Replacement; MVR = Mitral Valve Replacement; MVRepair = Mitral Valve Repair; CABG = Coronary Artery Bypass Graft.**

| Table 4. Long Term Clinical Outcomes | Total = 401 |
|---|---|
| Mean Follow up time, months | 57.1±18.7 |
| | |
| Death, n (%) | 16 (4) |
| -Heart Failure, n (%) | 5 (1.2) |
| -Other, n (%) | 11 (2.7) |
| --Covid19 Pneumonia, n | 3 |
| --Cancer, n | 3 |
| --Stroke, n | 2 |
| --Acute Kidney Failure, n | 1 |
| --Pulmonary Embolism, n | 1 |
| --Aortic Dissection, n | 1 |
| | |
| Hospital Re-admissions, n (%) | 78 (19.4) |
| -Heart Failure, n (%) | 14 (3.5) |
| -Other, n (%) | 64 (16) |
| --Re-operation, n (%) | 17 (4.2) |
| ----Mitral Valve Replacement, n | 6 |
| ----Mitral + Aortic Valve Replacement, n | 5 |
| ----Heart Transplantation, n | 2 |
| ----Mitral Valve Repair (right thoracotomy), n | 1 |
| ----Mitral Transcatheter Edge-to-Edge Repair, n | 1 |
| ----Percutaneous Paravalvular Leak Closure, n | 1 |
| ----Left Ventricle Pseudoaneurysm, n | 1 |
| --Implantable Cardioverter Defibrillator implantation, n (%) | 16 (4) |
| --Permanent pacemaker implantation, n (%) | 12 (3) |
| --Cerebrovascular Event, n | 7 |
| --Appropriate ICD discharge, n | 4 |
| --Covid19 Pneumonia, n | 3 |
| --Inppropriate ICD discharge, n | 1 |
| --Aortic Dissection, n | 1 |
| --Pulmonary Embolism, n | 1 |
| --Acute Kidney Failure, n | 1 |
| --Sternal Complications, n | 1 |
| | |
| Atrial Fibrillation, n (%) | 87 (21.7) |
| -with previous history of AF | 54 (13.5) |
| -without previous history of AF | 33 (8.2) |
| Preoperative History of AF but no postoperative episodes | 40 (10%) |
| | |
| NYHA Class, n (%) | (n = 385) |
| -I | 315 (81.8) |
| -II | 61 (15.8) |
| -III | 9 (2.3) |
| -IV | 0 |

**Table 4. Long Term Clinical Outcomes. ICD = Implantable Cardioverter Defibrillator NYHA = New York Heart Association.**

| Table 5. Long-term Echocardiographic Data | Total = 216 |
|---|---|
| Left Ventricle Ejection Fraction, % | 59±6 |
| Interventricular Septum Thickness, mm | 18±4 |
| Mitral Regurgitation, 1-4 + | 0.9±2.3 |
| Left Ventriclular Outflow Tract basal gradient, mmHg | 8.6±6 |
| Left Atrial diameter, mm | 41±10 |

**Table 5. Long-term Echocardiographic Data.**

| Table 6. Cox Proportional Hazard Model | HR | *P* Value |
|---|---|---|
| Clinical Follow-Up Data | - | - |
| Sex | 0.63 (0.3-1.2) | 0.166 |
| AF pre-op. | 2.26 (1.2-4.4) | 0.015 |
| Hypertension | 1.67 (0.9-3.2) | 0.125 |
| PM/ICD pre-op. | 1.22 (0.4-3.2) | 0.682 |
| Concomitant procedures | 1.80 (0.8-3.9) | 0.130 |

**Table 6. Cox Proportional Hazard Model.**

| Table 7. Cox Proportional Hazard Model | HR | *P* Value |
|---|---|---|
| Echocardiography Follow-Up Data | - | - |
| AF pre-op. | 4.11 (1.3-12.7) | 0.014 |
| LAVi preop | 0.98 (0.9-1.1) | 0.326 |
| DeltaLAVi | 0.99 (0.99-1.01) | 0.876 |

**Table 7. Cox Proportional Hazard Model.**

| Table 8. HCM risk-SCD | n. | % |
|---|---|---|
| Groups | - | - |
| >6% | 66 | 16,4 |
| 4%-6% | 69 | 17,2 |
| <4% | 266 | 66,3 |

**Table 8. Preoperative HCM risk-SCD.**

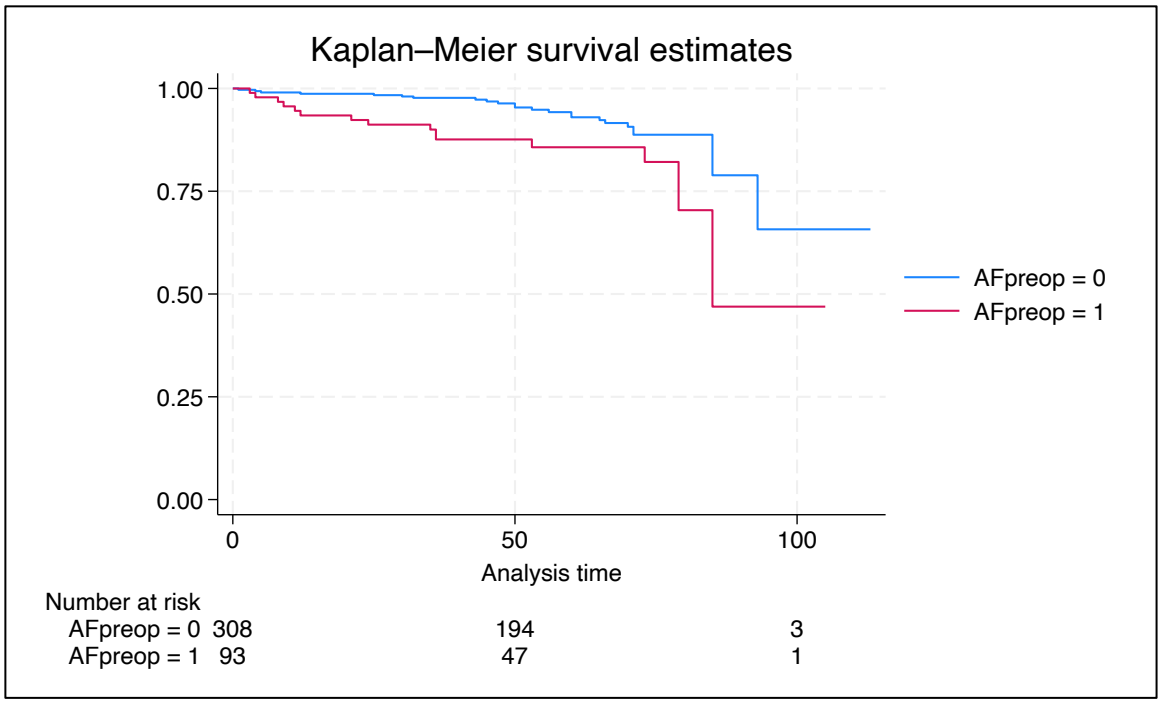


**Figure 1. Kaplan-Meier curve of survival free from composite endpoint.**
**[composite of all-cause mortality, resuscitated cardiac arrest, appropriate ICD discharge, hospitalizations for heart failure and stroke]**

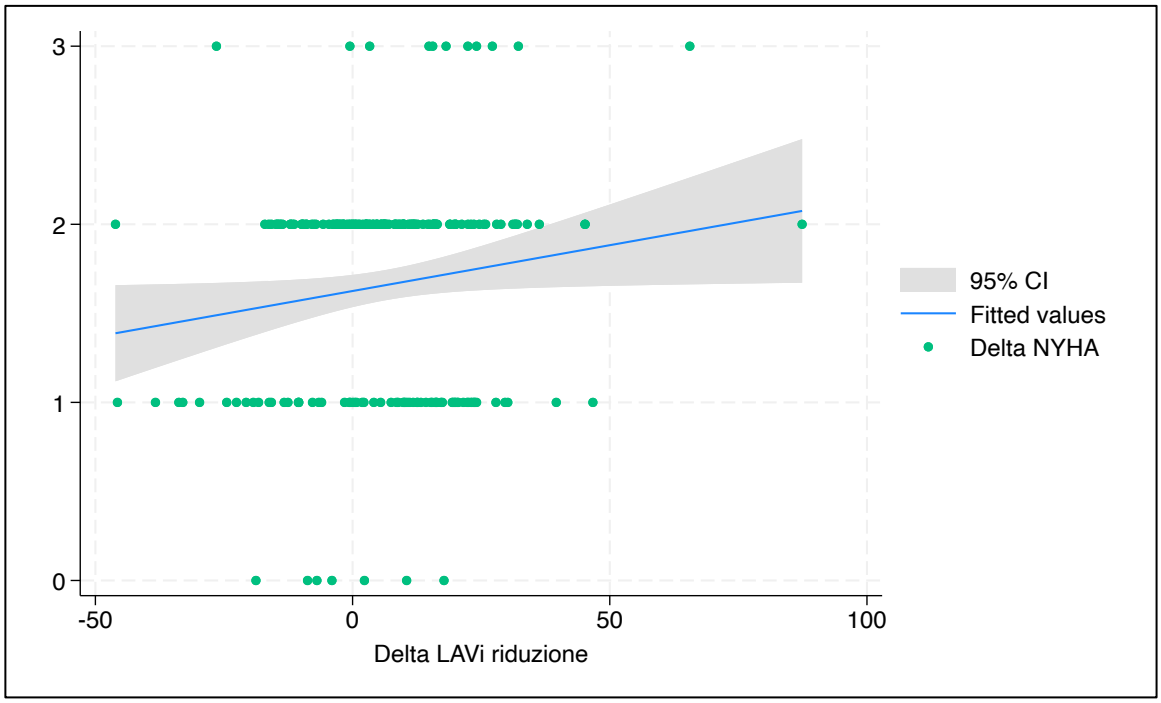


**Figure 2. Linear relation between DeltaLAVi and Delta NYHA.**

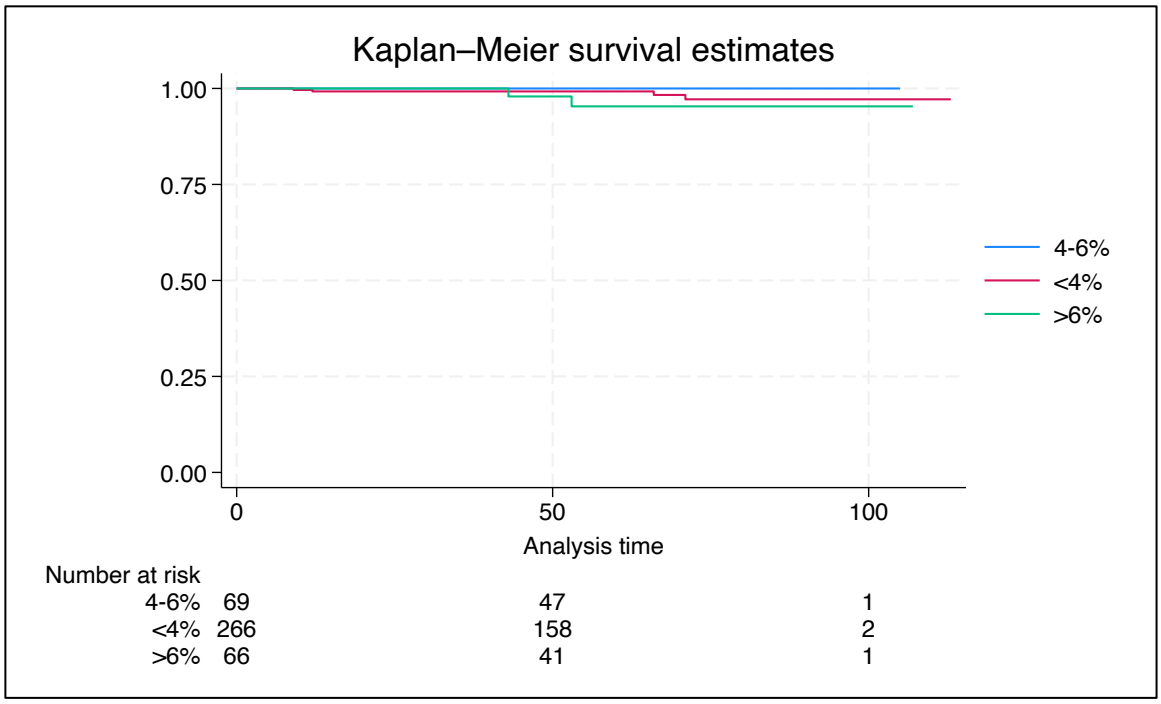


**Figure 3. Kaplan-Meier curve of survival free ventricular malignant arrhythmias.**

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