SOCIETA' ITALIANA DI CARGIOLOGIA INVASIVA (SICI-GISE)
CLINICAL RESEARCH

STUDY TITLE

GIse registry Of Transcatheter treatment of mitral valve regurgitaTiOn (GIOTTO)

Study Number: GISE/01/2014/GIOTTO

Registry under the auspices of Società Italiana di Cardiologia Invasiva (SICI-GISE)

Revision: **1.0**

Date: **November 2014**

Co-Primary Investigators:
Dr. Francesco Bedogni (Istituto Clinico S. Ambrogio, IRCCS San Donato)
Prof. Corrado Tamburino (Ospedale Ferrarotto Alessi Catania)
Dr. Arturo Giordano (Clinica Pineta Grande - Unita' Operativa di Cardiologia Invasiva, Caserta)

Protocol Authors:
Dr. Francesco Bedogni (Istituto Clinico S. Ambrogio, IRCCS San Donato)
Dr. Luca Testa (Istituto Clinico S. Ambrogio, IRCCS San Donato)

Protocol Approval

Sponsor	Sponsor Società Italiana di Cardiologia Interventistica (SICI-GISE)	 Signature President Prof. Sergio Berti	Date 15/12/2014

Compliance Statement

This registry will be conducted in accordance with this Clinical Investigational Plan, the Declaration of Helsinki, applicable sections in ISO 14155:2011 and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations applicable to registries must always be followed. The conduct of the registry will be approved by the appropriate Ethics Committee (EC) of the respective clinical site and as specified by Italian regulations.

Revision History

History of Revisions				
Revision	Description of Change	Prepared By	Title	Date
01	Document issue	Dr Luca testa	CO-PI Istituto Clinico S. Ambrogio, IRCCS San Donato	November 2014

PROTOCOL SIGNATURES PAGE

Prior to participation in the G8 clinical study, as the site Principal Investigator (PI) I understand that I must obtain written approval from my Ethics Committee, and provide a copy of it to the Co-ordinating Co-Principal Investigators (CCPI) or designee, along with the Ethics Committee approved Informed Consent Form prior to the first enrolment at my study site. As the site Principal Investigator, I must also:

- Conduct the study in accordance with the study protocol, the signed Investigator Agreement, the Declaration of Helsinki, Good Clinical Practices, international harmonized standards for clinical investigation of medical devices (ISO 14155, Clinical investigation of medical devices for human subjects – Good Clinical Practice), and applicable laws and regulations and ensure that all study personnel are appropriately trained prior to any study activities.

- Ensure that the study is not commenced until all necessary approvals have been obtained.

- Ensure that written informed consent is obtained from each subject prior to any data collection; using the most recent Ethics Committee approved Patient Information and Consent Form.

- Provide all required data and reports and agree to source document verification of study data with patient's medical records by the CCPIs or designee and any regulatory authorities.

- Allow the CCPIs or its designees, as well as regulatory representatives, to inspect and copy any documents pertaining to this clinical investigation according to the national data protection laws.

- Ensure that the members of the investigation site team participating in the conduct of the clinical investigation are qualified by education, training or experience to perform their tasks and this shall be documented appropriately.

Investigator's Signatures

I have read and understood the contents of the G8 clinical protocol and agree to abide by the requirements set forth in this document.

Participating Center

(print)_____

Interventional Cardiologist: Co-Principal Investigator

(print):_____

Date: _____

Signature:_____

Sommario

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1 PROTOCOL SYNOPSIS

Study Title:	GIOTTO (GIse registry Of Transcatheter treatment of mitral valve regurgitaTiOn)
Study Sponsor:	Società Italiana di Cardiologia Interventistica (GISE)
Device Name:	MitraClip® System,
Device Description:	In Italy, the MitraClip® system is CE marked approved for treatment of mitral regurgitation (MR). MitraClip is used for both degenerative MR (DMR) and functional MR (FMR). This less-invasive mitral valve repair therapy is adapted from the open surgical double-orifice technique, and increases the options for select MR patients, may reduce the symptoms of heart failure (HF), and may improve quality of life.
Study Rationale:	The current state of the art management of severe mitral regurgitation is surgical mitral valve repair, either with open chest surgery or mini-thoracotomy. However, standard surgical approaches requiring cardiopulmonary bypass are suitable for patients with low or moderate surgical risk, thus many patients are denied surgery because of unfavorable risk-benefit balance. The EuroHeart Survey

	conducted by the ESC showed that one half of patients with severe mitral regurgitation were denied surgical treatment because they were felt to be at too high risk for surgery by the referring physician. Such patients are usually elderly and have co-morbidities. Thus, there is a need for novel devices enabling interventional cardiologists and cardiothoracic surgeons to perform mitral repair in a minimally-invasive fashion and possibly without cardiopulmonary bypass. The landmark EVEREST II trial randomized 279 patients with grade 3/4 MR in a 2:1 fashion to MitraClip® or surgical repair/replacement showing a lower major adverse event rate at 30-days in the MitraClip® group (15.0% vs. 48%; superiority p<0.001), mainly driven by the need for blood transfusion with surgery, and the primary efficacy endpoint of freedom from the combined outcome of death, new surgery for mitral valve dysfunction or the occurrence of >2+ MR was achieved in 55% vs. 73% (non-inferiority p=0.007). However, this study has included a highly selected patient cohort in which patients with significant surgical risk have been excluded. More recently, Multinational (ACCESS-EU, EVEREST-High Risk) and national registries (TRAMI, SWISS) have shown safety and efficacy in the real world experience. Patients currently treated are high risk, elderly, with comorbidities and mainly affected by FMR. There is need for an Italian registry, since Italy has produced the second largest volume of transcatheter mitral procedures in the world after Germany. The present registry is designed to collect real world

	clinical data on early and long-term outcomes following percutaneous mitral regurgitation therapy in consecutive patients undergoing transcatheter procedures in Hospitals linked to the GISE database. The main objective is to achieve demographic and outcome data and identify predictors of clinical success, according to real-world Italian data. In addition the registry is designed to obtain health economic data to support reimbursement strategies in Italy. The study is focusing on MITRACLIP therapy since this is the leading method for treatment currently in Italy.
Study Design:	single arm, observational study, multicentre, retrospective and prospective
Study Objectives:	To collect real world data in order to evaluate safety and efficacy of MitraClip® since the device introduction in Italy. A dedicated web-based CRF will be constructed including demographic, clinical and outcome data. A section on health economics information (resource consumption in hospital and in the year after the procedure) will be added to the clinical evaluation.
Sample Size:	All consecutive patients undergone/ undergoing a transcatheter mitral valve repair, with Mitraclip device, will be enrolled to reach a number of about 500 patients in about 30 hospitals. There is no prespecified end of enrolment date. Data analysis will be conducted at the end of follow-up oeriod of the last enrolled patient. . Additional data analysis will be done according to specific topics, approved

	by the scientific board of GISE and or on Ethic Committees requests.
Population:	Patients undergoing/undergone a transcatheter mitral valve repair procedure in hospitals linked to the GISE network. More specifically Patients from the investigators' general Mitraclip treatment patient population will be eligible to be enrolled in this Registry. Patients should meet all the inclusion criteria and none of the exclusion criteria. Retrospective enrolments are allowed if available data are in line with the Study requirements and the patients can give their consent to be enrolled in the study informed consent process.
Study Duration:	First Patient is expected Q1 2015. End of the enrolment after 18 months. End of the study after further five years.
Study Follow-Up:	Hospital discharge, 1, 6, 12 months post-procedure, and yearly thereafter as per clinical standard practice.
Inclusion Criteria:	1. Symptomatic severe (4+) MR, or >3+ MR and NYHA > II 2. Mitral valve anatomy should be suitable for MitraClip or other percutaneous devices 3. Signed (by subject or legal representative) and dated approved subject informed consent form prior to any study related procedure

Exclusion Criteria:	1. Valve anatomy is unsuitable for MitraClip therapy 2. Currently participating in the study of an investigational drug or device

2 INTRODUCTION

2.1 Mitral valve: crossroads of the left ventricle

The mitral valve is anatomically and functionally integrated in the left heart (figure 1). Consequently, any left ventricular geometrical and functional alterations can induce mitral regurgitation (MR). Vice versa, mitral regurgitation could determine organic and functional alterations of the left ventricle. As a consequence, the anatomo-functional integrity of the mitral valve is fundamental to preserve left ventricular function. In fact, the mitral apparatus plays a structural role in maintaining the physiological function and geometry of the left ventricle, in addition to its well-known hemodynamic role (prevention of reflux in systole from the left ventricle to the left atrium). The deleterious effect of valve replacement without chordal apparatus preservation is well known: the interruption of the mitro-ventricular continuity is associated with left ventricular dilatation and contractile dysfunction (1-3).

In patients with chronic MR, the reflux causes volume overload that over time induces ventricular remodeling with eccentric hypertrophy triggering a well-known vicious circle in which MR begets MR (4). The phenomenon is initially compensatory: it is needed to maintain cardiac antegrade flow by an increase of stroke volume. Progressively, the excessive chamber dilatation is not compensated by adequate hypertrophy and the ventricular chamber assumes an unfavorable geometry that affects contractility and energetic efficiency. At the same time, the ongoing hemodynamic stimulus induces cellular and subcellular degeneration with progressive and, in extreme cases, even irreversible damages(5). A similar fate is reserved to the left atrium, which initially enlarges as compensatory mechanism, but, over time, undergoes geometrical and cellular degeneration with development of an anatomical substrate that favors arrhythmias (6). The left atrial enlargement is associated with poor prognosis (7). The atrial function is also important in delaying symptoms and the onset of pulmonary hypertension of patients with chronic MR.

2.2 Organic and functional mitral regurgitation

Mitral regurgitation can be caused by several diseases, which determine a variety of anatomo-functional settings. The identification of the underlying mechanism is a critical step in the decision-making process for the treatment of patients with MR, because it affects the type of therapy and when indicated, the timing of surgery. The main classification involves the differentiation between organic (also called primary) and functional (also called secondary) MR. In primary MR, regurgitation is secondary to anatomical changes of one or more components of the mitral apparatus. Typical organic MR includes degenerative (mitral valve prolapse), post-rheumatic and post-endocarditis etiologies. Functional MR (FMR) is characterized by valvular dysfunction in the absence of anatomical lesions. In this case, MR is secondary to ventricular remodeling, either global or regional. Several components of the mitral apparatus may be involved with geometrical and functional changes. Most commonly, ventricular remodeling induces an apical and lateral displacement of the papillary muscles with valve tethering and mitral ring dilatation; the combination of these two components generates a geometry unfavorable for leaflet coaptation.

The most common form of primary MR is degenerative disease. This pathology is probably linked to a genetic etiology and is characterized by chordal rupture or elongation and onset of prolapse or flail of one or both leaflets. There are two main variants: the myxomatous and the fibroelastic degeneration (8). The first is characterized by redundancy of tissue that appears myxomatous at histopathological examination (figure 2). At gross anatomy, the valve shows multiple injuries often with chordal thickening and rupture associated with elongation. Almost invariably, the annulus is severely dilated. Myxomatous degeneration most commonly affects younger patients. Surgical repair is often very complex in this contest and must be performed by experienced surgeons, because of coexisting lesions that require an integrated approach including several reparative techniques. On the contrary, fibroelastic degeneration is typical of the elderly population; it is characterized by isolated lesions, without redundancy of tissue. The annulus is often normal or only mildly dilated. Leaflet tissue is more fragile, and looks translucid at gross examination.

Functional MR may be secondary to ischemic or idiopathic dilated cardiomyopathy. In the early stages of post-ischemic disease it is not uncommon to observe regional ventricular remodeling with no or minimal annular dilatation and eccentric location of the regurgitant jet (9). In patients with idiopathic dilated cardiomyopathy, more often global remodeling of the left ventricle is associated with a more symmetric pattern. In this setting, the tethering forces on the left ventricle are evenly distributed and the regurgitation jet is central. Furthermore, the ring is more dilated as a consequence of global remodeling of the left ventricle (10). In the advanced stage of post-ischemic and idiopathic dilated cardiomyopathy, the anatomo-functional presentation could be often indistinguishable.

2.3 Epidemiology and natural history of patients with MR

2.3.1 Epidemiology of mitral regurgitation

Epidemiology studies have demonstrated that the prevalence of MR increases with aging of the population. The Framingham study (11) showed that the prevalence of clinically meaningful MR (equal or more than moderate) in individuals younger than 50 years is less than 1%, while it becomes 11% over the age of 70 years. More recently, these data have been confirmed by Nkomo (12) in a population-based study.

The most common etiology of MR in patients undergoing surgery in Western countries is degenerative disease (60-70% of cases), followed by ischemic, functional (20%), endocarditis (2-5%), rheumatic (2 -5%), and other miscellaneous types (13). However, these data may not reflect the true prevalence of the disease in the population, but rather the referral pattern of patients with surgical indication. With aging population and increased prevalence of heart failure in the western countries, FMR is probably becoming more common. The prevalence of hemodynamically relevant FMR in patients affected by heart failure ranges from 13% to 40%, according to different studies(14). The EuroHeart Survey of the European Society of Cardiology showed that MR (of any grade) is present in 80% of heart failure patients and in 50% of them MR is greater than moderate(15). In a large cohort of American centers, moderate or severe MR was present in 29% of patients with heart failure (16). In the Italian registry IN-HF outcomes, carried out in 61 centers on 3755 outpatients, 3103 patients were in NYHA class III-IV or NYHA II with hospitalization due to heart failure in the

previous year(17). An echocardiography evaluation was available in 1190 of these patients: data showed the presence of moderate or severe MR in 13% of cases. In heart failure patients aged ≥ 70 years, 89% had any-grade MR and in 42% of them MR was moderate to severe. This finding was confirmed by another Italian multicenter study (18). In patients hospitalized for heart failure, moderate to severe MR seems to be present in a high percentage of cases (~ 74%) (19). Reversibility of functional MR according to volume status must also be considered. In the ESCAPE trial, therapy guided by pulmonary artery catheterization during hospitalization improved MR more than therapy guided clinically by evidence of systemic venous congestion. However, this early reduction did not translate into improved outcomes at follow-up, when volume status reverted toward baseline(20).

2.3.2 Natural history

There are few prospective studies on the natural history of MR. Most data come from observational studies (21-24). The natural history and clinical outcomes in patients treated with medical therapy or surgery are different in functional and degenerative etiology.

Old studies on natural history of degenerative MR reported 5-year survival ranging from 27 to 97%. This variability could be attributed to case mix and especially to the different severity of the lesions. In more recent studies, it has been clearly demonstrated that patients with significant MR (e.g. in the presence of flail) have lower survival compared to the general population. The annual mortality rate in patients with significant degenerative MR varies from 1% to 9%, (7,21,22,25-27). The mortality is higher in patients with left ventricular dilatation and in symptomatic patients (NYHA III-IV)(27). The incidence of sudden death in completely asymptomatic patients could be also underestimated. There is clear evidence that the risk of death or other major adverse events associated with mitral valve disease is proportional to the grade of regurgitation (25). According to these data, the indication to surgical treatment is suggested even in asymptomatic patients when ERO (Effective Regurgitant Orifice) is greater than 40 mm^2. As far as FMR is concerned, observational studies have shown an increased mortality in patients with congestive heart failure (CHF) in presence of significant MR (28). The degree of MR is proportionally associated with mortality (29). However, the relationship of mortality with the presence of MR and the degree of severity may be not so relevant in patients in advanced stage of heart failure (NYHA Class III-IV) as shown by Redfield (30). This consideration was later confirmed in 469 patients in whom functional MR was proven to be an independent determinant of death or heart transplantation only in those with less severe heart failure and a lower risk profile (31). Concerning the impact of functional MR on health economics, data from the IN-HF outcome study showed that re-hospitalization for heart failure is significantly more frequent in patients with moderate-severe MR than in those with no or not significant MR(17).

2.4 Conventional treatment of MR

2.4.1 Pharmacological therapy

Various intravenous or oral vasodilators (nitroprusside, ACE-inhibitors, hydralazine and isosorbide dinitrate) in conjunction with loop diuretics may reduce MR in selected patients (32,33) by decreasing the load on the left ventricle (34).

The results of anti-apoptotic agents and the inhibition of fibrosis by neurohormonal antagonists (ACE inhibitors, angiotensin receptor blockers, beta-blockers, aldosterone antagonists) have been well described for CHF. However, there is only modest evidence that the inhibition of the renin-angiotensin system provides advantages beyond the vasodilation per se in patients with severe MR (29,35). According to experimental and in-vivo data, beta-blockers might attenuate left ventricle remodeling in case of severe MR.

However, there is no conclusive evidence that neurohormonal antagonists may specifically improve clinical outcomes when severe ventricular dysfunction is already present.

Intravenous positive inotropes reduce MR. In an echocardiography series, 61% of patients with left ventricular ejection fraction <50% had an improvement in the degree of MR during dobutamine stress echocardiography (36). However, inotropic agents are not suitable for chronic use and play a limited role in the management of MR outside in-hospital setting.

2.4.2 Ventricular resynchronization therapy

Cardiac resynchronization therapy (CRT) may reduce functional MR both acutely and chronically in selected patients (37,38). Such an effect on MR disappears when the CRT is turned off.

The reduction of MR with CRT is due to several effects. First, improvement of ventricular contraction immediately after CRT can significantly increase the closing force of the valve (37,39,40) reducing MR in the initial part of the systole. Secondly, reverse remodeling of the left ventricle and changes in the geometry of the mitral apparatus may further reduce MR. Indeed, these changes positively impact on systolic regurgitation by reducing of the tethering forces on the mitral leaflets. This effect is clearly observed in the medium-term and long-term ($\geq$ 6 months) follow-up after CRT (37,39). Finally, reduction of left ventricle intraventricular dyssynchrony has been shown to decrease MR, even though it is not known in which part of systole this effect occurs (39). Recently, the Cleveland Clinic group has shown in a series of 266 patients implanted with CRT that most of the MR improvement is seen in the first days after intervention. The process of reverse remodeling of the left ventricle occurs late after implantation and is not accompanied by further improvement of regurgitation. They also showed that patients with significant MR before CRT exhibit a greater reverse remodeling. The authors also reported a significantly higher adverse event rate in patients with residual MR greater than 2+ following CRT treatment(figure 3) (41).

In general, the indication to CRT is given in patients with moderate to severe symptoms of heart failure despite optimal pharmacological therapy, a concomitant reduced ejection fraction and a wide (> 120 msec) QRS complex. In these patients, the presence of significant functional MR may represent a further reason to implant CRT. Sitges et al. showed that among non-responders (on the basis of clinical or echocardiography evaluation) no MR reduction was observed in the majority of them(42). Unfortunately, it is difficult to predict which patients can effectively respond to CRT. It was suggested that patients with larger mitral valve tenting area (> 3.8 cm^2) or with an extended infarcted area may benefit less from CRT (42,43). Moreover, although CRT reduces MR, residual regurgitation persists in most cases(44,45).

2.4.3 Surgical treatment of degenerative MR

The factors taken in account in the current US and European guidelines for MR surgical treatment include symptoms, left ejection fraction, end-diastolic ventricular dimensions, atrial fibrillation and pulmonary hypertension (46,47).

Indeed, the annual mortality rate in untreated highly symptomatic patients in NYHA functional class III-IV is 36% (27) and the functional class (NYHA) is an independent predictor of mortality and postoperative ventricular dysfunction (24).The most important predictor of outcome in patients undergoing surgery is left ventricular function (24,48), which correlates with postoperative performance, functional class and survival (49,50).

The pre-operative end-diastolic diameter (<45 mm) is a predictor of ventricular dysfunction in the postoperative period (51). An indexed value of end-systolic volume equal or superior to 50 ml/m^2 is inversely correlated with postoperative ventricular function and survival (48).

Late outcomes are also influenced by preservation of left atrial function. One third of medical treated MR patients develops atrial fibrillation (27) and this is associated with an increase in mortality and morbidity.

Pulmonary hypertension is associated with increased post-operative early mortality, a higher recurrence of symptoms and a lower long-term survival (52). Pulmonary hypertension is considered a marker of diastolic dysfunction and MR severity is associated with lower post-operative left ventricular function (53).

Excellent results obtained with surgical repair in degenerative disease induced several groups to perform early surgery, especially in high-volume centers experienced in mitral repair (54). Indeed, advanced age and comorbidities increase significantly the operative risk (55) and decrease the probability of repair (56). If mitral valve repair is performed before the onset of symptoms and left ventricular dysfunction, life expectancy is similar to that of the general population (51). The current evidence indicates that reparative surgery with optimal hemodynamic result is superior to medical treatment alone in terms of survival and freedom from major adverse cardiac events (25)More than 30 years ago, Carpentier described the basic rules for mitral repair: preserve the movement of the leaflets, restore a large area of coaptation and remodel the annulus (57). Currently, the nature and combination of various reparative techniques are dictated by the location of the lesions through a detailed collection of echocardiography and anatomical preoperative and intraoperative information.

It is fundamental to distinguish, in the context of type II lesions, the presence or absence of sufficient tissue for repair. The posterior leaflet prolapse can be treated by triangular or quadrangular resection and concomitant annular plication.

In contrast, Barlow's disease requires a more extended quadrangular resection associated with correction of the height of the leaflets through sliding-plasty. This consists in the resection of the leaflet base after quadrangular resection with subsequent repositioning and translation to the native annulus,(figure 4).Nowadays, many surgeons prefer to avoid resections ("respect rather than resect") implanting neochords on the free edge of the leaflets (figure5). This technique can be applied to prolapsing segments or flail caused by rupture or elongation of mitral chords (58). As an alternative, prolapse can be treated by chordal transfer (59).

The edge-to-edge technique introduced by Alfieri (60) has been successfully described in cases of important myxomatous degeneration (Barlow's disease) and bileaflet prolapse, usually in combination with annuloplasty (figure 6).

In surgical mitral repair, annuloplasty plays a very important role and is routinely carried out. The aim of annuloplasty is to restore the normal ratio between annular diameters and preserve an adequate mobility of the leaflets (61). Currently, several prosthetic annular models are available, rigid and flexible, complete and incomplete. Lack of annuloplasty has been associated with reduced durability of repair, although some evidence suggests that annuloplasty could be avoided in selected patients(62) (63)

Operative mortality rate and complications after mitral repair surgery are extremely low. The American Society of Thoracic Surgery Database collected data from more than 15,000 patients who underwent isolated mitral valve surgery from 2001 to 2011. According to the database, hospital mortality is below 2% for repair, compared to 4-10% for valve replacement (55). Some authors emphasize the impact of the volume of interventions on mortality, indicating a mortality of 3% in low-volume centers as compared to 1% in high-volume centers (54).

Major neurological events occur in 1% of cases (64). Mitral repair also reduces morbidity if compared to mitral valve replacement (reduced incidence of endocarditis, thromboembolic events and bleeding associated with chronic anticoagulant therapy needed for mechanical prostheses). On long-term, quality of life in patients undergoing mitral repair is comparable to that of the general population (65).

On the other hand, in elderly patients with comorbidities the operative risk increases (55), the chances of repair decrease (25) and the quality of life does not improve significantly (66).

2.4.4 Surgical treatment of functional MR

The indications for FMR are still debated.

The indication for treatment of stand-alone FMR is not supported by general consensus, while it is well accepted that patients with indication to surgical myocardial revascularization (CABG) with concomitant moderate-to-severe functional ischemic mitral regurgitation (IMR) should also undergo correction of MR (67-70).

Before choosing a combined procedure (CABG + IMR correction), the ratio between heart failure progression due to IMR on one hand and the increased surgical risk of concomitant mitral valve surgery on the other should be carefully evaluated. The perioperative mortality risk of a combined procedure has been reported to be 6-15% compared to 3-5% of isolated CABG (67,68,71-75). The latest evidence recommends early treatment, since the excessive length of heart failure history before corrective surgery inversely correlates with the likelihood of reverse ventricular remodeling (76).

Before the introduction of undersized annuloplasty, mitral replacement with biological or mechanical prostheses was the procedure of choice in patients with functional MR. If performed with removal of subvalvular apparatus this intervention could cause a sudden fall

of postoperative ventricular function (77), whereas preservation of such apparatus has been shown to preserve it (78).

Bolling first reported the idea to restore leaflet coaptation in functional MR by the implantation of an undersized annuloplasty ring (79,80). The rationale of undersized annuloplasty is to reduce the septo-lateral dimension of the mitral valve; MAS associated with CABG is the most common procedure performed to correct this condition.

Despite there are no randomized trials comparing annuloplasty to replacement, two retrospective studies demonstrated the efficacy of both treatments in eliminating MR in the early postoperative phase (68,69). Mortality rate is lower in mitral repair (68,69). However, in high-risk patients Gillinov showed similar 5-year survival in patients treated with repair or replacement (68). Despite annuloplasty does not treat the cause of MR, it is a simple, reproducible and effective technique for eliminating regurgitation (75,81,82). The current opinion is that the undersized annuloplasty is associated with lower mortality and is therefore preferable than replacement (72). Appropriate annular size reduction is fundamental to efficiently enhance coaptation(83). On the other hand, excessive ring reduction has been associated with development of functional mitral valve stenosis (84). Annuloplasty can be performed with various types of ring (rigid, semi-rigid or flexible, complete or incomplete), although an objective evidence of the superiority of a model over another has never been reported (83,85). Currently, specific anatomically-designed rings are available. The peculiar tridimensional structure of these devices may reduce the distance between papillary muscles (e.g. Geoform (86), Edwards LifeSciences, Irvine, CA, USA) or correct the asymmetric tethering (eg Carpentier-McCarthy-Adams (87) IMR ETlogix, Edwards LifeSciences, Irvine, CA, USA).

Although the edge-to-edge technique in association with a ring has shown to improve durability and efficacy of annuloplasty alone (88,89), literature results are conflicting(90). Indeed, while some authors described a rate of IMR recurrence after surgery of 30% at 1 year (91), others have shown the edge-to-edge technique to be more effective than isolated annuloplasty in terms of clinical outcomes and hemodynamic reverse remodeling (92). On the other hand, the efficacy of the surgical edge-to-edge technique *without* annuloplasty for the treatment of functional MR is still debated(93-95).

Indeed, data on surgical outcomes following isolated annuloplasty are also conflicting. Different studies showed a high rate of recurrence or persistence of IMR after undersized annuloplasty. According to a few series, 6 months after the procedure up to 15-30% of patients may have residual or recurrent moderate to severe MR(83,96,97).

According to other authors the recurrence of moderate to severe regurgitation may be as high as 70% after 5 years (96). The reason for this failure may be that annuloplasty does not reduce the tethering forces (83,96). On the contrary, posterior leaflet tethering is increased in some patients after annuloplasty. Another factor potentially related to recurrent MR is the persistence of moderate residual MR immediately after the intervention. In this case, progressive remodeling and ventricular dilation could induce increasing degree of MR (96). The presence of persistent or recurrent regurgitation decreases event-free survival at 3 years.The 30-day mortality of undersized annuloplasty in FMR is high, about 6-15% (67,68,71-75). The post-operative recovery is long, and extended length of stay is frequently reported. In patients with significant ventricular dilatation, long-term mortality increases and there is no reverse remodeling despite the absence of MR (75). The baseline ventricular size

represents one of the predictors of reverse remodeling (81). An end-diastolic diameter >65 mm or an end-systolic diameter over 51 mm inversely correlates with reverse remodeling. Due to high mortality at short and long term, long length of hospital stay, high percentage of residual MR and reduced chance of reverse remodeling, the indication of this intervention should be carefully evaluated in elderly patients with comorbidities. Moreover, there are no studies showing an improvement in the quality of life in these patients.

2.5 MitraClip Treatment

MitraClip is a device developed by Evalve and acquired by Abbott Vascular (figure 7), which reproduces the edge-to-edge surgical technique introduced into clinical practice by Alfieri (60,88,89,98,99). The surgical technique consists in suturing the free margins of both mitral leaflets at the origin of regurgitation, under direct vision with extracorporeal circulation and cardioplegic arrest. In the case of percutaneous treatment, the leaflets are joined by applying a clip under echocardiograpy guidance on the beating heart (figure 8).

Compared to the surgical edge-to-edge procedure, the percutaneous MitraClip implant offers the advantage of a reduced trauma. Of note, it also allows real time assessment of the hemodynamic effects of the clip implant by online echocardiography. In case the result is suboptimal, the clip can be repositioned or additional clips can be implanted.

The edge-to-edge surgical experience has proven to be effective and versatile. Versatility is a characteristic retained also by the percutaneous device. In fact, MitraClip implant can be performed eather in degenerative or functional MR .

The percutaneous technique was introduced in 2003 (100) and, up to now, more than 7000 patients have been treated with this device all over the world. The majority of cases has been performed in Europe. Moreover, MitraClip therapy has been evaluated in several trials and registries.

The EVEREST study (Endovascular Valve Edge-to-edge REpair of mitral regurgitation STudy) comprises a series of trials (101-115), including the first randomized controlled trial in which the percutaneous approach was compared to surgical treatment in selected patients with MR (mainly with degenerative etiology). The study results showed that after one year surgery is superior to percutaneous treatment in terms of efficacy (measured as freedom from recurrence of MR and survival), whereas the percutaneous strategy was associated with reduced blood transfusions rates (102). In a post-hoc analysis, the MitraClip therapy has proven to be non inferior to surgery in terms of effectiveness in three subgroups of patients: patients older than 70 years, those with left ventricular dysfunction and those with functional MR.

The value of the randomized cohort of EVEREST is limited because it involved only operable patients affected mainly by degenerative MR. This subset of patients does not correspond to the subjects currently undergoing MitraClip treatment in clinical practice, who in most cases have functional MR, are elderly and mostly inoperable or at high surgical risk. Furthermore, the study started when the technical experience was in a very early stage and the results were strongly influenced by the learning curve; moreover, the results of the surgical cohort were suboptimal, with in-hospital mortality approaching 6%, a value that compares unfavourably

with the hospital mortality of 1.2% for this type of intervention reported in the STS database. Despite important limitations further outlined below, the EVEREST randomized controlled trial is an important milestone in the field of percutaneous treatment of MR. First of all, this is the first study that has adjudicated both surgical and percutaneous outcomes from an independent core-lab. Secondly, since the EVEREST is the first core-lab study on MitraClip therapy, three-year durability data are available (figure 9). They demonstrated that the degree of MR reduction obtained one year after the procedure remains stable over time (Feldman, ACC 2012, Chicago personal communication). At landmark analysis, it became evident that the eventual failure of the procedure occurs mainly in the first 6 months after implantation. After this time, patients who require surgical revision after MitraClip are rare and their number is not significantly different from that observed in the cohort randomized to surgical treatment. These data are crucial as they suggest two conclusions. First, failure of the percutaneous treatment occurs in the first few months after implantation and is potentially preventable with better patient selection and improved implantation technique. Second, in patients with acceptable one-year result, the hemodynamic benefit of the procedure appears to be stable over time. The durability of the MitraClip was questioned because of previous experiences with the surgical edge-to-edge approach. Indeed, absence of an annuloplasty system has been associated with a lower durability of the repair. Despite convincing surgical data about better results of concomitant edge-to-edge and annuloplasty, EVEREST data suggest that the absence of annuloplasty is not associated with reduced durability.

The EVEREST study has limitations that should be taken into account. Indeed, treated patients were quite healthy, with a low mean age and good EF. These patients do not represent the population of patients currently undergoing MitraClip in the real world. Indeed, most of them are elderly, with comorbidities and decreased left ventricular function. Moreover, in the majority of cases, the MitraClip is used in functional rather than in degenerative mitral valve disease. Another limitation of the EVEREST randomized trial is that the surgical outcomes were worse than expected and there was a high rate of replacement over repair. This may be due to several factors, including surgical experience of the participating centers and clinical characteristics of the patients enrolled in the study. Due to these limitations, additional controlled randomized trials focusing on the current indications for MitraClip therapy are needed.

To fill the gap between the evidence from the randomized trial and that emerging from current practice, unbiased analysis of real-world post-market registries could provide preliminary information.

The high risk registry (HRR) enrolled patients who had clinical or anatomical exclusion criteria for the MitraClip arm of the EVEREST randomized trial. The outcomes were compared with a control group represented by patients who were not treated because of anatomical contraindications to the implant. Compared to the control group, the 30-day mortality of patients treated with MitraClip was similar, while the survival at 1 year of follow-up was higher (although without statistically significant difference, figure 10)(116)

The HRR is the first study that demonstrated a prognostic benefit in high-risk patients treated with the MitraClip. Moreover,, it is noteworthy that it showed a benefit in terms of health economics: the group of patients treated with the MitraClip showed a decreased number of hospitalizations (reduced by a factor of 55% as compared to the year before implantation) with a documented benefit observed in both the degenerative and functional MR groups (figure 11). Unfortunatly, in this registry the comparator group was inadequate due to the

fact that more than 50% of comparative patients presented problems of screening. In addition, risk assessement was augmented by less rigourous “up assignement” (117)

The ACCESS-EU registry is a prospective, observational, multicenter post-market trial. The registry collected data from 567 patients treated in 14 high-volume centers in Europe. The study had two phases: phase I completed the enrollment on April 2011 and phase II was initiated in September 2011 and finished in 2012. The main difference between the two phases is that in phase II ultrasound data were evaluated by a single core lab, while in phase I outcomes were adjudicated by individual centers.

The ACCESS registry offers a snapshot of the characteristics of patients who currently undergo the procedure in the real word: mainly elderly patients with comorbidities, high surgical risk and a high prevalence of functional mitral regurgitation (figure 12). The mean age of patients was 74 ± 10 years, with a prevalence of male gender (64%). The patients had several comorbidities, with an average surgical risk of 23 ± 18 % estimated by the logistic EuroSCORE. The etiology of MR was functional in 77% of patients, equally distributed between idiopathic and post-ischemic forms. The majority of patients were severely symptomatic (NYHA class III-IV in 85% of cases) and an ejection fraction less than 40% was present in 53% of them. Procedural success rate was 99.6%, with only 2 patients out of 566 in whom it was not possible to implant a clip. In 60% of cases, a single clip was deployed (340 patients), in 37% two clips (208 patients) and in 3% (16 patients) three or four clips. The mean procedural time was 117 ± 69 minutes. The mean lengh of stay in ICU was 2.5 ± 6.5 days and the overall mean hospitalization was 7.7 ± 8.2 days. Mortality at 30 days was 3.4%. This mortality rate is notable low, especially if we consider that the majority of patients were at high surgical risk and affected by MR secondary to chronic heart failure. There were the following in-hospital adverse events: stroke (4 patients, 0.7%), acute myocardial infarction (4 patients, 0.7%), renal failure (24 patients, 4.2%), respiratory insufficiency (4 patients, 0.7%), cardiac arrest requiring resuscitation (10 patients, 1.8%), cardiac tamponade (6 patients, 1.1%) and bleeding (21 patients, 3.7%). In 80% of the cases, patients were discharged home, with no need of rehabilitative or home care.

At one year, there were no cases of embolization of the clip, while in 27 (4.8%) cases there was a partial clip detachment (single leaflet attachment, SLA). In 10 of these cases, SLA was treated with the implantation of an additional clip. Thirty-six (6.3%) patients with recurrent MR required surgery within 12 months after the procedure, while 19 (3.4%) required a second MitraClip procedure. At 12 months, the survival rate was 82% and 79% of patients showed residual MR less than or equal to 2+ (figure 13). Although this degree of reduction is lower than that observed after surgical repair, the persistence of a MR grade less than or equal to mild to moderate could be a reasonable therapeutic target in patients at high surgical risk. Obviously, this should not be an acceptable target for low-risk patients, for whom surgery remains the first choice.

In addition to the efficacy in reducing regurgitation, the ACCESS registry demonstrated remarkable clinical effictiveness: one year after the procedure, 71% of patients are in NYHA functional class I or II (figure 14). At one year from the index procedure, most patients have an improvement in quality of life (with a mean reduction of Minnesota Living with Heart Failure Questionnaire of -13.5±20.5 points, from 41 to 28) and a gain in functional capacity (mean increase of 59±120 meters from baseline at the six-minute walking test).

In conclusion, the ACCESS registry showed that patients currently treated in Europe are different from those originally enrolled in the EVEREST study: they are older, with more comorbidities, and more frequently their MR has a functional etiology. Despite the risk profile of these patients is higher as compared to the EVEREST trial population, the procedure remains safe and effective, with satisfactory results 6 months after treatment. Although the ACCESS-EU results currently available are limited to one year of follow-up, we know from the EVEREST II trial that the hemodynamic results obtained at 6 months remain stable over time (up to 3 years after the procedure), since the risk of failure tends to run out within 6 months from implantation. Undoubtedly, the data from the registry are insufficient to fully assess the exact clinical role of the procedure. However, randomized trials in which the MitraClip will be compared to standard medical therapy has began enrollment in 2013 and will increase our knowledge regarding this issue.

2.6 Study Patient selection Mitraclip Treatment

2.6.1 Clinical Guidelines

The recent guidelines of the European Society of Cardiology consider the MitraClip as a potential therapeutic intervention in selected patients affected by severe symptomatic mitral regurgitation in case they are at high surgical risk or inoperable (118). The class assigned to this indication is IIb (evidence C), due to the lack of results from adequate randomized trials designed to guide treatment decisions in the real world. Compared to the reccommendations for surgical treatment in degenerative MR, the role of MitraClip in these patients is confined to very high risk patients otherwise inoperable. In the case of isolated FMR, MitraClip has received the same reccomendation level and class of surgery. Registries and observational data have shown that the MitraClip implantation is effective in about 70-80% of patients, with limited periprocedural risk, certainly lower than that of surgery, expecially in elderly patients with comorbidities or severe left ventricular dysfunction.

The screening selection process for Mitraclip implantation has to be reserved to expert centers owning an integrated multidisciplinary structure (Heart Team) including interventional cardiologists, cardiac surgeons, echocardiographists, anesthesiologists and heart failure specialists. The presence of surgeons in the decision-making process is essential to characterize the individual risk and to evaluate alternative therapeutic strategies, in the case of either functional or degenerative MR. The centers performing the MitraClip intervention must also have experience in treating patients with heart failure and have to be in connection with a regional hospital network (experienced with heart failure treatment) in order to monitor medical therapy and follow-up of patients implanted. The integration and coordination between hospital and territory is essential particularly for the treatment of patients at higher risk.

In the decision flow-chart, we identify three fundamental sequential steps: the indication for treatment of MR, the evaluation of surgical risk and the feasibility of the transcatheter procedure. All these steps are extremely critical and require specific experience and a multi-disciplinary approach to provide a decision free from biases and to offer a patient-individualized therapy option.

Specifically, since in low-risk patients surgical repair intervention is known to be associated with a favorable prognostic impact (in degenerative pathology), it remains the treatment of choice in the majority of patients.

Based on the available data, and in view of the limited experience which may underestimate potential downsides, the current indications for MitraClip therapy should be limited to the treatment of symptomatic patients with MR refractory to medical therapy and deemed at high surgical risk or inoperable by surgeons proficient in mitral valve surgery and working in istitutions with a high-volume mitral surgical programs. These indications are in agreement with those outlined in the recent European Society of Cardiology guidelines (47,119)

In selected candidates, the MitraClip procedure appears to be associated with an improvement of life quality, a chance for reverse left ventricular remodeling, an increase of functional capacity and a reduction of hospitalizations. Therefore, MitraClip therapy may play a significant role in the field of non-pharmacological therapy of heart failure and mitral valve disease.

3 CLINICAL STUDY DESIGN & METHODOLOGY

3.1 Clinical Study Overview

Single arm, multi-center, retrospective and prospective study collecting clinical and health economic data from patients undergone/undergoing treatment with the MitraClip® in Hospitals linked to the GISE registry. Patients are selected upon clinical conditions and severity of MR.

3.2 Study Objectives

To collect real world data in order to further evaluate safety and efficacy of MitraClip®. A dedicated web-based CRF will be constructed including demographic, clinical and outcome data. A section on health economics information (resource consumption in hospital and in the year after the procedure) will be added to the clinical evaluation.

3.3 Study Endpoints

Safety endpoints: collection of safety data (MACCE and mortality) at 30days from the index procedure.

Efficacy endpoints:

- collection of early (<30d) efficacy: reduction of MR, device success, procedural resource utilization (refer to the CRF).
- collection of long-term (6m, 1y) efficacy data including survival, freedom from recurrent MR, and other health economic data (refer to the CRF)

3.3.1 Safety and Efficacy Data Analysis

The safety and efficacy endpoints of the transcatheter procedures will be assessed by monitoring the patient's clinical status accordingly to the clinical investigational plan and by recording the echocardiographic parameters. Safety assessments will consist of recording of all adverse events, and regular monitoring of hematology and blood chemistry parameters and vital signs. These parameters are evaluated during the patient's follow-up visits.

Follow-up analysis will include both safety and efficacy analyses mentioned above, at each of the post-procedure intervals. Overall mortality rate will be determined at the end of the study.

3.4 Study Design

Giotto is an observational, multicenter retrospective/prospective study aimed to collect data on the Mitraclip treatment in the real world clinical environment. The study will involve all

the sites where the Mitraclip treatment is included in the standard practice and meeting the eligibility criteria detailed in section 3.7.

3.5 The MitraClip System®

3.5.1 Intended Use

The MitraClip® System is intended for reconstruction of the insufficient mitral valve through tissue approximation.

3.5.2 General Description

The MitraClip system consists of two parts: 1) the Clip Delivery System and 2) the Steerable Guide Catheter.

The Clip Delivery System consists of three major components: 1) the Delivery Catheter 2) the Steerable Sleeve and 3) the MitraClip device. The Clip Delivery System is introduced into the body through a Steerable Guide Catheter which includes a dilator. The Clip Delivery System and Steerable Guide Catheter constitute the MitraClip® System.

The Clip Delivery System is used to advance and manipulate the implantable MitraClip® device for proper positioning and placement on the mitral valve leaflets. The system is designed to deploy the implant in a way that requires multiple steps to ensure safe delivery of the device.

The MitraClip® device is a single sized, percutaneously implanted mechanical Clip. The MitraClip® device grasps and coapts the mitral valve leaflets resulting in fixed approximation of the mitral leaflets throughout the cardiac cycle. The MitraClip® device is placed without the need for arresting the heart or cardiopulmonary bypass. The implantable MitraClip® device is fabricated with metal alloys and polyester fabric (Clip cover) that are commonly used in cardiovascular implants.

The MitraClip® device arms can be adjusted to any position from fully opened, fully inverted and fully closed. These positions are designed to allow the MitraClip® device to grasp and approximate the leaflets of the mitral valve using the controls on the delivery catheter handle. The MitraClip® device can be locked and unlocked and repeatedly opened and closed. The Gripper can be raised or lowered repeatedly.

The procedure is performed in the cardiac catheterization laboratory with echocardiographic and fluoroscopic guidance while the patient is under general anesthesia. To access the left heart, standard transseptal catheterization is performed by the interventional cardiologist. The Guide Catheter is then percutaneously inserted into the femoral vein. The Delivery Catheter is then inserted into the Guide and the Clip is positioned above the mitral valve. Manipulation of the steering mechanism on the handles of the Guide and Delivery Catheter positions the Clip on the mitral valve. The Clip is actuated (i.e., opened and closed, locked, deployed) through manipulation of levers on the handle of the Delivery Catheter.

For further information and details, please refer to the device Instructions For Use.

3.6 Risk Benefit Analysis

Giotto study meets the definition no sponsor observational clinical trial. Participation in this style of clinical study represents no additional risk and carries no additional benefit to the subjects who decide to participate. Risks associated with Mitraclip treatment are detailed within the Mitraclip Instructions For Use. The subjects will be enrolled after being selected by the site for the Mitraclip treatment as per clinical standard practice. Patients would be exposed to these risks regardless of whether they participate in this study.

3.7 Site Selection Criteria

The selection criteria for the participating sites are as follows:

- Sites will be linked to the GISE network.
- Sites have the Mitraclip treatment as clinical standard procedure
- Sites must have adequate facilities and equipment to treat and evaluate the subjects according to the existing guideline and Mitraclip IFU and staff with adequate experience, in the Mitraclip device implantation technique.
- The Principal Investigator must understand and agree to this Protocol and accept Investigator responsibility
- Principal Investigator agrees to obtain the approval from the site EC to conduct the Giotto study.

3.8 Patient Screening and Enrollment

Any subject who already received or deemed suitable and selected by the site to receive the Mitraclip treatment, in accordance with all applicable device Instructions For Use, should be considered for entry into this study.

Eligibility will be documented on the inclusion/exclusion criteria sheet. Subjects who meet the eligibility criteria and have signed and dated the Informed Consent Form and actually undergone / undergo a Mitraclip implant procedure are considered enrolled in the study.
The date the subject signed the informed consent form must be documented in the subject's medical record. Eligibility will be decided by the site co-PIs.

3.8.1 Inclusion Criteria

A subject may be enrolled in the study if all of the following general inclusion criteria are met, and no exclusion criteria are met:

1. Patients who are eligible for Mitraclip device according to current national and international guidelines (and their future revisions) and per investigator evaluation;

2. Patients who are willing and capable of providing informed consent, participating in all Follow-ups associated with this clinical investigation at an approved clinical investigational center;

More specifically patients inclusion criteria are in line with the indications for use detailed in the IFU in particular, patients have to meet the following inclusions criteria

1. Symptomatic severe (4+) MR, or 3+ MR and NYHA > II

2. Mitral valve anatomy should be suitable for MitraClip

3. Signed (by subject or legal representative) and dated approved subject informed consent form prior to any study related data collection

3.8.2 Exclusion Criteria

The patients exclusions criteria are as follows:

1. Valve anatomy is unsuitable for MitraClip therapy as per the indication in the Mitraclip IFU

2. Currently participating in the study of an investigational drug or device

3. The subject is unable or not willing to complete follow-up visits and examination for the duration of the study.

3.8.3 Informed Consent

The Clinical Investigator will obtain the standard informed consent to undergo a Mitraclip treatment Procedure in line with the hospital's standard practice. In addition, written informed consent and Authorization to Use and Disclose Health Information must be obtained from a potential subject after the patient has been identified as a suitable candidate for the Mitraclip treatment according to the standard clinical practice of the site or after the Mitraclip Procedure, in case of retrospective patients.

This consent must be obtained for each subject in advance of any entries being made onto the eCRF (electronic case report forni). Failure to comply with this consenting process may result in exclusion of the Clinical Investigator from the study.

The subject (or the subject's legal representative) must sign the Ethical Committee approved informed consent prior to enrollment. Failure to provide informed consent renders the subject ineligible for the study. If all Inclusion criteria are met and no Exclusion criteria are present,

informed consent is documented. Once the informed consent will be signed, a new record in the electronic CRF will be generated and a new patient ID number will be assigned.

3.8.4 Enrolment

Any subject deemed suitable to receive a Mitraclip system, in accordance with applicable Mitraclip Instructions for Use, should be considered for entry into this study.

The Clinical Investigator must exclude any subjects with existing conditions that would compromise their participation and follow-up in this study.

3.8.5 Patient Withdrawal

The Principal Investigators should discuss reasons for study withdrawal with the patient. All study patients may be withdrawn from the study by willingness of the patient or physician judgment at any time, accordingly to the terms specified in the Informed Consent. Should a subject withdraw or is withdrawn, every effort must be made to complete and report the observations as thoroughly as possible. It should be understood that an excessive rate of withdrawals could render the study difficult to interpret. Hence, unnecessary withdrawal of subjects should be avoided. Patients who withdraw or are withdrawn from the study should:

- Have the reason(s) for their withdrawal recorded;
- Be seen by an investigator and all final assessments should be performed and recorded;
- Be asked about the presence of any AEs. If an ongoing AE is present, the patient should be followed up until satisfactory clinical resolution of the event is achieved;
- In the event of pregnancy, the subject should be monitored until conclusion of the pregnancy and the outcome of pregnancy reported to the CCPIs monitor.

In either event, the Clinical Investigator will clearly and promptly document the date and reason(s) for the subject' s withdrawal from this study within e-CRF.

3.9 Adverse Event Reporting

Adverse Events reporting will be managed according to the existing regulation on Medical Devices Clinical trials and to the GISE Internal Procedures

Please see in Annex I the rules for the Adverse Events Reporting and forms.

The procedure provides guidance on the types of events that should be recorded in the e-CRF system and the classification of the events. In addition the procedure provides indications on events reportability with particular reference to those which require immediate reporting to GISE.

Where applicable, it is the Clinical Investigator's responsibility to inform the ethics committee of any adverse events related to the device, and all unexpected study related serious adverse events.

3.10 Study Procedures and Follow-Up Visits

The study follow-up visits and related procedures are summarized in the Table below.

Table 1: Schedule of Study Procedures and Follow-Up Visits

Procedure	**Baseline**	**Procedure**	**Discharge**	**30 days**	**6 months**	**12 months and following annual FU up to 5 years**
Visit Number	1	2	3	4	5	6
Range	Up to -30 days	0	0	+/- 5 days	+/-14 days	+/-14 days
Subject Enrollment Log	X					
Inclusion/Exclusion	X					
Informed Consent	X					
Demographics	X					
Medical History	X					
Physical exam and vital signs	X		X	X	X	X
Blood Tests	X		X	X	X	X
Adverse Events	X	X	X	X	X	X
Cardiac Medication Profile	X		X	X	X	X
12-Lead ECG (within 24 hours of procedure)	X		X	X	X	X

Procedure	Baseline	Procedure	Discharge	30 days	6 months	12 months and following annual FU up to 5 years
Mitral Regurgitation Assessment by TTE	X		X	X	X	X
Mitral Regurgitation Assessment by TEE	X	X				
X ray		X	X			
NYHA Functional Class	X			X	X	X
Mitral Regurgitation Treatment		X				
QoL Measures	X			X	X	X

3.10.1 Visit 1: Baseline

Participants will be recruited from the Investigators' patient population undergoing Mitraclip Treatment. The investigators will obtain signed patient's informed consent prior to enrolling the patient into the study.

Within seven (7) days of the procedure, all patients must have a history, brief physical exam including vital signs and documentation of concomitant medications, complete blood count (CBC), plasma free hemoglobin, blood urea nitrogen (BUN), serum creatinine, creatine kinase (CK) and CK-MB, 12-lead ECG (ECG should be done within 24 hours prior to the procedure) and an assessment of NYHA functional status. A serum pregnancy test for females with childbearing potential must be completed within seven days prior to the procedure. In addition, within 30 days of the procedure, all patients must undergo a Baseline transthoracic echocardiogram (TTE). Patients usually require a transesophageal (TEE) echocardiogram be performed prior to treatment to confirm the patient's eligibility for enrollment into the study regarding the presence of intracardiac mass, thrombus or vegetation. This echocardiogram should be performed within 3 days of the procedure and may be performed on the day of the procedure immediately preceding initiation of the

treatment. Quality of Life measures will be collected including the following: six-minutes walking test (6MWT), Minnesota Living with Heart Failure questionnarie (MLHFQ). .

Baseline activated clotting time (ACT) will be determined following venous access for the endovascular procedure and following hospital standard practice for surgery. ACT and heparin administration (or alternative anticoagulation therapy) should be recorded throughout the procedure. Documentation of a final ACT level, before leaving the catheterization laboratory, is left to the Investigator's discretion. All ACTs will be recorded in the medical record for source documentation purposes.

3.10.2 Visit 2: Procedure

The day of the surgery shall be considered Day 0 of the Trial. The procedures to be completed at this visit are:

- Ensure that the patient informed consent has been signed, dated and filed.
- Ensure that the patient continues to meet the qualifications to participate in the trial.
- Record any adverse events during the procedure.

3.10.3 MitraClip Procedure

Patients will be prepared for the procedure as per the institution's standard practice for an invasive percutaneous endovascular procedure and transesophageal echocardiography.

Procedure need to be performed according to Existing guidelines, Mitraclip Instructions For Use and site standard practice.

3.10.4 Visit 3: Hospital Discharge

The patients should be monitored during the pre-hospital discharge period. All patients will receive standard post-procedure care as judged appropriate by the Principal Investigator.

On the day of discharge from the hospital, the following information will be recorded:

- Blood draws performed according to hospital standard practices.
- 12-Lead ECG per hospital standard practice
- TTE Echocardiography
- Brief physical exam including vital signs and documentation of concomitant medications

- Short-term anti-coagulation therapy, antibiotic therapy, and endocarditis prophylaxis per the protocol. Anti-coagulation therapy for surgical patients should follow hospital standard practice.

- Documentation of medical procedures and events by referring physicians, including internists as well as cardiologists, family members, neighbors.

- Any planned long absences from the area should be recorded to facilitate the continued ability to contact a study subject.

3.10.5 Visit 4: 30 Day Follow-Up

At 30 day from the procedure, the following information will be recorded:

- TTE Echocardiography

- Brief physical exam including vital signs and documentation of concomitant medications

- Short-term anti-coagulation therapy, antibiotic therapy, and endocarditis prophylaxis per the protocol. Anti-coagulation therapy for surgical patients should follow hospital standard practice.

- Documentation of medical procedures and events by referring physicians, including internists as well as cardiologists, family members, neighbors.

- Any planned long absences from the area should be recorded to facilitate the continued ability to contact a study subject.

- Quality of Life measures (6MWT, MLHFQ).

3.10.6 Visit 5: 6 Month Follow-Up

At the 6 month Follow-Up visit, , the following information will be recorded:

- TTE Echocardiography

- Brief physical exam including vital signs and documentation of concomitant medications

- Short-term anti-coagulation therapy, antibiotic therapy, and endocarditis prophylaxis per the protocol. Anti-coagulation therapy for surgical patients should follow hospital standard practice.

- Documentation of medical procedures and events by referring physicians, including internists as well as cardiologists, family members, neighbors.

- Any planned long absences from the area should be recorded to facilitate the continued ability to contact a study subject.

- Quality of Life measures (6MWT, MLHFQ).

3.10.7 Visit 6 and following yearly FU: 12 Month Follow-Up

At the 12 month Follow-Up visit, the following information will be recorded:

- Blood draws performed according to hospital standard practices.

- 12-Lead ECG per hospital standard practice

- TTE Echocardiography

- Brief physical exam including vital signs and documentation of concomitant medications

- Short-term anti-coagulation therapy, antibiotic therapy, and endocarditis prophylaxis per the protocol. Anti-coagulation therapy for surgical patients should follow hospital standard practice.

- Documentation of medical procedures and events by referring physicians, including internists as well as cardiologists, family members, neighbors.

- Any planned long absences from the area should be recorded to facilitate the continued ability to contact a study subject.

- Quality of Life measures (6MWT, MLHFQ).

3.11 Statistics and Data Management

Statistical Overview

The data will be reviewed by a Data Safety and Monitoring Board.

The Data Safety and Monitoring Board will be also responsible for:

- Determining whether information collected are sufficient to address the objectives
- Recommending modifications to the statistical analysis plan to address additional research questions based on review of the data

9.2 Analysis Population

All patients who are successfully registered will be included in the analysis.

9.3 Sample Size Calculations and Assumptions

Being this an observational registry aiming at quantifying effect estimates without direct comparisons to literature benchmarks, we proceeded without a formal power analysis. As the main analysis is a pooled analysis of all included patients, an overall and comprehensive analysis is planned as the primary analytical approach to reflect real-world patients and practice.

.9.4 Statistical Analyses

Continuous endpoints will be summarized by presenting the total number of patients, mean, standard deviation, median, minimum, and maximum. Tabulation of categorical parameters will include counts and percentages. The outcomes will be summarized as both a discrete and a continuous variable using the method described above. Survival analysis will be performed with the Kaplan-Meier method. Statistical inference will be based on the computation of 95% confidence intervals using the adjusted Wald method. Additional analyses will involve key subgroups defined according to baseline and and procedural features, with statistical significance set at the 5% 2-tailed level. Specifically, Student t, Fisher exact, and log-rank tests will be used for such bivariate analyses, whereas multivariable linear regression, logistic regression, and Cox proportional hazard analyses will be used to adjust for confounders.

3.12 Reports and Publications

Interim reports will be prepared as deemed necessary throughout the course of this study. GISE will have the ownership of and full access to the full set of data. Every participating center will be owner and have access restricted to the patients enrolled in that specific center.

3.13 Investigators Responsibilities

Approving the protocol by signing the signature page, the Principal Investigator (PI) of the site is responsible of the correct implementation of the Clinical Protocol.

PI will conduct the study in accordance with the Declaration of Helsinki, Good Clinical Practices, international harmonized standards for clinical investigation of medical devices (ISO 14155, Clinical investigation of medical devices for human subjects – Good Clinical Practice), and applicable laws and regulations.

PI will ensure that all study personnel are appropriately trained prior to any study activities.

PI will be responsible to obtain the EC approval to conduct the Giotto Study.

The PI will be responsible to obtain the Patient Informed Consent according to study procedures detailed in the specific paragraph and using the most recent Ethics Committee approved Patient Information and Consent Form. No patient data will be collected before the ICF signature

The PI will be responsible to provide all the required data and reports, including source document of study data contained patient's medical records, in case of inspection by the CCPIs or designee and any regulatory authorities.

PI will be responsible of the research team qualification, selection and training on the study procedures (Study Protocol). PI is responsible to document the training or experience of the team.

PI will be responsible for the maintenance of the confidentiality of enrolled subject data in accordance with the provisions of Law Decree nr 196, June 30th 2003 and following amendment, transposition of the EU Data Protection Directive 95/46/EC or locaL equivalent legislation. Data protection consent will be obtained from subjects as part of the informed consent process.

3.14 Sponsor Responsibilities

GISE, as study sponsor, will be responsible of access and maintenance of the electronic data capture system and for training to the sites.

GISE will be responsible for the maintenance of the confidentiality of subject data in accordance with the provisions of Law Decree nr 196, June 30th 2003 and following amendment, transposition of the EU Data Protection Directive 95/46/EC or local equivalent legislation. Data protection consent will be obtained from subjects as part of the informed consent process.

3.15 Research Ethics Committee Approval

If required by the Local Ethics Committee, study approval need to be obtained before any patient is enrolled in the Giotto Study.

In case of absence of a requirement for such Ethics Committee review and approval the local PI will provide to Gise documented evidence in order to obtain authorization to start the study at the site and access to the e-CRF system.

Prior to the initiation of this clinical study, the Clinical Investigator must submit the Giotto Clinical Study Protocol and any other documents as may be required to the Competent Local Research Ethics Committee for review and approval. The Committee will be requested to provide a letter documenting approval of this clinical study, in conformity to the existing regulation.

Any significant study amendment must be notified to the Research Ethics Committees approving the original clinical investigation plan. Where appropriate, the Co-ordinating Clinical Investigator must notify the Multi Research Ethics Committee of the discovery of any adverse events relating to the device and unexpected study related serious adverse events. The Principal Clinical Investigator must notify the Local Research Ethics Committee adverse events in conformity to the Procedures detailed in the Annex I and to the local EC requirements.

3.16 Good Clinical Practices

This study will be conducted in accordance with the principles of ISO 14155:2011, Clinical investigation of medical devices for human subjects -- Good clinical Practice.

This study will be conducted in accordance with the relevant articles of the latest version of the Declaration of Helsinki.

3.16.1 Clinical Study Amendments

Any Significant study amendment will be notified, if required, to the Ethics Committees of the sites participating to the Study. If it was necessary to obtain Ethics Committee approval in advance of the start of the study, the Research Ethics Committee will be informed or be requested to approve any amendments in accordance with their procedures.

3.17 Financial Agreement

No personal payments will be made to any of the Clinical Investigators or study teams. Costs of the Study will be covered by GISE, as study sponsor. No financial agreement will be made with the clinical site due to the no profit feature of the Study.

3.18 Clinical Study Termination

In case of early termination will be necessary, the procedures will defined on an individual study site basis after review and consultation by both parties and local EC, if required. In terminating the clinical study or an individual site, GISE and the Clinical Investigator will guarantee an appropriate consideration to the protection of the subject's interests. All the documentation will be archived according to the existing regulation and any bodies who have approved the study (e.g. research ethics committees) will be informed as per local requirements.

4 Confidentiality and Study Data Protection

All information and data concerning subjects or their participation in this trial will be considered confidential.

All data used in the analysis and reporting of this evaluation will not bear identifiable reference to the subjects.

The investigator must ensure that the subject's anonymity will be maintained and that the confidentiality of records and documents that could identify subjects will be protected, respecting the privacy of and confidentiality rules in accordance with applicable regulatory requirements.

- Subjects must be identified only by their assigned study number and initial on all CRFs and other records and documents.

- The investigator will keep a Patient Identification List with complete identification information (name, address, contact number, IC#) on each subject.

The subject should also be informed about the use of his/her health information collected during the study (study data).

5 Study Documentation and Record Archiving

The investigators must maintain adequate and accurate records to document the conduct of the study and substantiate the study data. These documents include those required by applicable regulations, and the patients' source documents, as described below.

5.1.1 Regulatory Documents

Regulatory documents are those documents that individually and collectively permit evaluation of the study compliance with applicable regulations and the quality of the data produced. These documents include:

- Signed protocol and amendments

- Sample e-CRFs

- EC Approval letter, including a dated list of EC membership and members' affiliation

- Informed consent form

- CV of investigator and co-investigator(s)

- Correspondences with EC

- Interim reports to EC

- Other appropriate documents in accordance with EC local Requirements and GCP guidelines

These documents will be filed in an Investigator Study File. This file shall be used to facilitate and ensure filing of all relevant regulatory documents during and after the study. The investigator will be responsible for keeping the Investigator's Study File updated and ensuring that all required documents are filed.

5.1.2 Source Data

Source data are original hospital records, clinical charts, patient identification list/enrolment log, original laboratory report, memoranda, pharmacy dispensing records, recorded data from automated instruments, transcriptions certified after verification as being accurate, microfiches, photographic negatives, microfilm, magnetic or electronic media, x-rays, subject's files, and records kept at pharmacy, at the laboratories and medico-technical departments involved in the study. The investigator must maintain source documents for each patient in the study. All information recorded on the e-CRFs must be traceable to these source documents.

5.1.3 Retention of Study Documents

The investigator shall arrange for the retention of all study documents and records, including subject records, e-CRFs, signed informed consent forms and the patient identification list for at least the number of years required by the local regulations after completion or discontinuation of the study. GISE will retain the database records and the study documentation for at least 5 years after the end of the study.

5.2 Case Report Form (e-CRF)

5.2.1 Data Collection

For the purpose of this study Gise will provide access to an electronic data capture system. The electronic Capture System is compliant with existing national regulation in term of data protection, and clinical data compliance.

Electronic CRF will be provided. Gise guarantees technical support dedicated to the users of e-CRF, for any kind of problem or enquiry. All investigational centers must have a secure internet connection to comply with e-CRF requirements. The investigator must ensure that the clinical data required by the clinical investigation plan are carefully reported in the eCRF. He/she must also check that the data reported in the e-CRF correspond to those in the official files. Data must be entered into e-CRFs in English by the designated site personnel as soon as possible after a subject visit, data manager will have access to data recorded.

The investigator or his/her authorized designees will review the e-CRF for accuracy and completeness.

5.3 Study Monitoring

Considering the observational feature of the Giotto, study the monitoring activity will be conducted only on remote basis.

The data manager and monitors will verify on routinely base the patients e-CRF in order to verify missing data and/or inconsistencies. In case of problems in the data the data manager will contact the PI requiring verification of the missing or inconsistent data. The data manager may require copy of the data source in order to verify the single data. In presence of multiple and unresolved data inconsistencies at the single site the Sponsor will evaluate the opportunity of monitoring visit to source data verification.

6 REFERENCES

1. Sarris GE, Cahill PD, Hansen DE, Derby GC, Miller DC. Restoration of left ventricular systolic performance after reattachment of the mitral chordae tendineae. The importance of valvular-ventricular interaction. J Thorac Cardiovasc Surg 1988;95:969-79.

2. Westaby S. Preservation of left ventricular function in mitral valve surgery. Heart 1996;75:326-9.

3. Yun KL, Sintek CF, Miller DC et al. Randomized trial comparing partial versus complete chordal-sparing mitral valve replacement: effects on left ventricular volume and function. J Thorac Cardiovasc Surg 2002;123:707-14.

4. Zile MR, Tomita M, Ishihara K et al. Changes in diastolic function during development and correction of chronic LV volume overload produced by mitral regurgitation. Circulation 1993;87:1378-88.

5. Beeri R, Yosefy C, Guerrero JL et al. Early repair of moderate ischemic mitral regurgitation reverses left ventricular remodeling: a functional and molecular study. Circulation 2007;116:I288-93.

6. Everett THt, Verheule S, Wilson EE, Foreman S, Olgin JE. Left atrial dilatation resulting from chronic mitral regurgitation decreases spatiotemporal organization of atrial fibrillation in left atrium. Am J Physiol Heart Circ Physiol 2004;286:H2452-60.

7. Grigioni F, Avierinos JF, Ling LH et al. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. J Am Coll Cardiol 2002;40:84-92.

8. Fornes P, Heudes D, Fuzellier JF, Tixier D, Bruneval P, Carpentier A. Correlation between clinical and histologic patterns of degenerative mitral valve insufficiency: a histomorphometric study of 130 excised segments. Cardiovasc Pathol 1999;8:81-92.

9. Agricola E, Oppizzi M, Maisano F et al. Echocardiographic classification of chronic ischemic mitral regurgitation caused by restricted motion according to tethering pattern. Eur J Echocardiogr 2004;5:326-34.

10. Kwan J, Shiota T, Agler DA et al. Geometric differences of the mitral apparatus between ischemic and dilated cardiomyopathy with significant mitral regurgitation. Circulation 2003;107:1135-1140.

11. Singh JP, Evans JC, Levy D et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (The Framingham Heart Study) (vol 83, pg 897, 1999). Am J Cardiol 1999;84:1143-1143.

12. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005-11.

13. Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. Lancet 2009;373:1382-94.

14. Allen LA, Felker GM. Advances in the surgical treatment of heart failure. Curr Opin Cardiol 2008;23:249-53.

15. Nieminen MS, Brutsaert D, Dickstein K et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006;27:2725-36.

16. Varadarajan P, Sharma S, Heywood JT, Pai RG. High prevalence of clinically silent severe mitral regurgitation in patients with heart failure: role for echocardiography. J Am Soc Echocardiogr 2006;19:1458-61.

17. Maggioni AP GM, Lucci D, et al. on behalf of IN-HF Outcome Investigators. Prevalence and outcomes of patients with chronic HF with moderate-severe mitral regurgitation: data from the IN-HF Outcome database. . Eur J Heart Fail 2012;1 (suppl 1): P1141

18. Cioffi G, Tarantini L, De Feo S et al. Functional mitral regurgitation predicts 1-year mortality in elderly patients with systolic chronic heart failure. Eur J Heart Fail 2005;7:1112-7.

19. Robbins JD, Maniar PB, Cotts W, Parker MA, Bonow RO, Gheorghiade M. Prevalence and severity of mitral regurgitation in chronic systolic heart failure. The American journal of cardiology 2003;91:360-2.

20. Palardy M, Stevenson LW, Tasissa G et al. Reduction in mitral regurgitation during therapy guided by measured filling pressures in the ESCAPE trial. Circ Heart Fail 2009;2:181-8.

21. Rosenhek R, Rader F, Klaar U et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. Circulation 2006;113:2238-44.

22. Rosen SE, Borer JS, Hochreiter C et al. Natural history of the asymptomatic/minimally symptomatic patient with severe mitral regurgitation secondary to mitral valve prolapse and normal right and left ventricular performance. Am J Cardiol 1994;74:374-80.

23. Szymanski C, Levine RA, Tribouilloy C et al. Impact of Mitral Regurgitation on Exercise Capacity and Clinical Outcomes in Patients With Ischemic Left Ventricular Dysfunction. Am J Cardiol 2011.

24. Tribouilloy CM, Enriquez-Sarano M, Schaff HV et al. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. Circulation 1999;99:400-5.

25. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. The New England journal of medicine 2005;352:875-83.

26. Avierinos JF, Gersh BJ, Melton LJ, 3rd et al. Natural history of asymptomatic mitral valve prolapse in the community. Circulation 2002;106:1355-61.

27. Ling LH, EnriquezSarano M, Seward JB et al. Clinical outcome of mitral regurgitation due to flail leaflet. New Engl J Med 1996;335:1417-1423.

28. Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol 2003;91:538-543.

29. Mehra MR, Reyes P, Benitez RM, Zimrin D, Gammie JS. Surgery for severe mitral regurgitation and left ventricular failure: what do we really know? J Card Fail 2008;14:145-50.

30. Patel JB, Borgeson DD, Barnes ME, Rihal CS, Daly RC, Redfield MM. Mitral regurgitation in patients with advanced systolic heart failure. Journal of cardiac failure 2004;10:285-291.

31. Bursi F, Barbieri A, Grigioni F et al. Prognostic implications of functional mitral regurgitation according to the severity of the underlying chronic heart failure: a long-term outcome study. Eur J Heart Fail 2010;12:382-388.

32. Stevenson LW, Bellil D, Grover-McKay M et al. Effects of afterload reduction (diuretics and vasodilators) on left ventricular volume and mitral regurgitation in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1987;60:654-8.

33. Hamilton MA, Stevenson LW, Child JS, Moriguchi JD, Walden J, Woo M. Sustained reduction in valvular regurgitation and atrial volumes with tailored vasodilator therapy in advanced congestive heart failure secondary to dilated (ischemic or idiopathic) cardiomyopathy. Am J Cardiol 1991;67:259-63.

34. Kizilbash AM, Willett DL, Brickner ME, Heinle SK, Grayburn PA. Effects of afterload reduction on vena contracta width in mitral regurgitation. J Am Coll Cardiol 1998;32:427-31.

35. Carabello BA. The current therapy for mitral regurgitation. J Am Coll Cardiol 2008;52:319-326.

36. Heinle SK, Tice FD, Kisslo J. Effect of dobutamine stress echocardiography on mitral regurgitation. J Am Coll Cardiol 1995;25:122-7.

37. Kanzaki H, Bazaz R, Schwartzman D, Dohi K, Sade LE, Gorcsan J. A mechanism for immediate reduction in mitral regurgitation after cardiac resynchronization therapy - Insights from mechanical activation strain mapping. J Am Coll Cardiol 2004;44:1619-1625.

38. Pierard LA, Carabello BA. Ischaemic mitral regurgitation: pathophysiology, outcomes and the conundrum of treatment. Eur Heart J 2010;31:2996-3005.

39. Ypenburg C, Lancellotti P, Tops LF et al. Mechanism of improvement in mitral regurgitation after cardiac resynchronization therapy. Eur Heart J 2008;29:757-765.

40. Breithardt OA, Sinha AM, Schwammenthal E et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. (vol 41, pg 765, 2003). J Am Coll Cardiol 2003;41:1853-1853.

41. Verhaert D, Popovic ZB, De S et al. Impact of Mitral Regurgitation on Reverse Remodeling and Outcome in Patients Undergoing Cardiac Resynchronization Therapy. Circulation-Cardiovascular Imaging 2012;5:21-U49.

42. Sitges M, Vidal B, Delgado V et al. Long-Term Effect of Cardiac Resynchronization Therapy on Functional Mitral Valve Regurgitation. Am J Cardiol 2009;104:383-388.

43. Marsan NA, Westenberg JJ, Ypenburg C et al. Magnetic resonance imaging and response to cardiac resynchronization therapy: relative merits of left ventricular dyssynchrony and scar tissue. Eur Heart J 2009;30:2360-7.

44. Ypenburg C, Lancellotti P, Tops LF et al. Acute effects of initiation and withdrawal of cardiac resynchronization therapy on papillary muscle dyssynchrony and mitral regurgitation. J Am Coll Cardiol 2007;50:2071-7.

45. Ypenburg C, van Bommel RJ, Borleffs CJ et al. Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. J Am Coll Cardiol 2009;53:483-90.

46. Bonow RO, Carabello BA, Chatterjee K et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e1-142.

47. Vahanian A, Alfieri O, Andreotti F et al. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2012.

48. Crawford MH, Souchek J, Oprian CA et al. Determinants of survival and left ventricular performance after mitral valve replacement. Department of Veterans Affairs Cooperative Study on Valvular Heart Disease. Circulation 1990;81:1173-81.

49. Dujardin KS, Seward JB, Orszulak TA et al. Outcome after surgery for mitral regurgitation. Determinants of postoperative morbidity and mortality. Journal of Heart Valve Disease 1997;6:17-21.

50. Enriquez-Sarano M, Tajik AJ, Schaff HV et al. Echocardiographic prediction of left ventricular function after correction of mitral regurgitation: results and clinical implications. J Am Coll Cardiol 1994;24:1536-43.

51. Enriquezsarano M, Tajik AJ, Schaff HV, Orszulak TA, Bailey KR, Frye RL. Echocardiographic Prediction of Survival after Surgical-Correction of Organic Mitral Regurgitation. Circulation 1994;90:830-837.

52. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9-13.

53. Enriquez-Sarano M, Rossi A, Seward JB, Bailey KR, Tajik AJ. Determinants of pulmonary hypertension in left ventricular dysfunction. J Am Coll Cardiol 1997;29:153-9.

54. Gammie JS, O'Brien SM, Griffith BP, Ferguson TB, Peterson ED. Influence of hospital procedural volume on care process and mortality for patients undergoing elective surgery for mitral regurgitation - Response. Circulation 2007;116:E147-E147.

55. Djurkovic-Ivanovic S, Markovic L, Popovic G, Cvetkovic-Pendic D. [Disorders of heart rhythm in patients with mitral valve prolapse detected by continuous electrocardiography]. Srp Arh Celok Lek 1991;119:152-4.

56. Bolling SF, Li S, O'Brien SM, Brennan JM, Prager RL, Gammie JS. Predictors of mitral valve repair: clinical and surgeon factors. The Annals of thoracic surgery 2010;90:1904-11; discussion 1912.

57. Carpentier A. Cardiac valve surgery--the "French correction". J Thorac Cardiovasc Surg 1983;86:323-37.

58. David TE, Bos J, Rakowski H. Mitral valve repair by replacement of chordae tendineae with polytetrafluoroethylene sutures. J Thorac Cardiovasc Surg 1991;101:495-501.

59. Sousa Uva M, Grare P, Jebara V et al. Transposition of chordae in mitral valve repair. Mid-term results. Circulation 1993;88:II35-8.

60. Alfieri O, Maisano F, De Bonis M et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. J Thorac Cardiovasc Surg 2001;122:674-81.

61. Carpentier A. AD, Filsoufi F. . Reconstructive valve Surgery. W.B Saunders. 2010.

62. Barlow CW, Ali ZA, Lim E, Barlow JB, Wells FC. Modified technique for mitral repair without ring annuloplasty. Ann Thorac Surg 2003;75:298-300.

63. Duebener LF, Wendler O, Nikoloudakis N, Georg T, Fries R, Schafers HJ. Mitral-valve repair without annuloplasty rings: results after repair of anterior leaflet versus posterior-leaflet defects using polytetrafluoroethylene sutures for chordal replacement. Eur J Cardiothorac Surg 2000;17:206-12.

64. Savage EB, Ferguson TB, DiSesa VJ. Use of mitral valve repair: Analysis of contemporary United States experience reported to the society of thoracic surgeons national cardiac database. Ann Thorac Surg 2003;75:820-825.

65. Heikkinen J, Biancari F, Satta J, Salmela E, Juvonen T, Lepojarvi M. Quality of life after mitral valve repair. Journal of Heart Valve Disease 2005;14:722-726.

66. Maisano F, Vigano G, Calabrese C et al. Quality of Life of elderly patients following valve surgery for chronic organic mitral regurgitation. European Journal of Cardio-Thoracic Surgery 2009;36:261-266.

67. Filsoufi F, Salzberg SP, Adams DH. Current management of ischemic mitral regurgitation. Mount Sinai Journal of Medicine 2005;72:105-115.

68. Gillinov AM, Wierup PN, Blackstone EH et al. Is repair preferable to replacement for ischemic mitral regurgitation? J Thorac Cardiovasc Surg 2001;122:1125-41.

69. Grossi EA, Goldberg JD, LaPietra A et al. Ischemic mitral valve reconstruction and replacement: comparison of long-term survival and complications. J Thorac Cardiovasc Surg 2001;122:1107-24.

70. Miller DC. Ischemic mitral regurgitation redux--to repair or to replace? J Thorac Cardiovasc Surg 2001;122:1059-62.

71. Aklog L, Filsoufi F, Flores KQ et al. Does coronary artery bypass grafting alone correct moderate ischemic mitral regurgitation? Circulation 2001;104:I68-75.

72. Calafiore AM, Di Mauro M, Gallina S et al. Mitral valve surgery for chronic ischemic mitral regurgitation. Ann Thorac Surg 2004;77:1989-1997.

73. Gangemi JJ, Tribble CG, Ross SD, McPherson JA, Kern JA, Kron IL. Does the additive risk of mitral valve repair in patients with ischemic cardiomyopathy prohibit surgical intervention? Annals of surgery 2000;231:710-4.

74. Adams DH, Filsoufi F, Aklog L. Surgical treatment of the ischemic mitral valve. J Heart Valve Dis 2002;11 Suppl 1:S21-5.

75. Braun J, van de Veire NR, Klautz RJ et al. Restrictive mitral annuloplasty cures ischemic mitral regurgitation and heart failure. The Annals of thoracic surgery 2008;85:430-6; discussion 436-7.

76. De Bonis M, Lapenna E, Verzini A et al. Recurrence of mitral regurgitation parallels the absence of left ventricular reverse remodeling after mitral repair in advanced dilated cardiomyopathy. Ann Thorac Surg 2008;85:932-939.

77. David TE, Uden DE, Strauss HD. The importance of the mitral apparatus in left ventricular function after correction of mitral regurgitation. Circulation 1983;68:II76-82.

78. David TE, Armstrong S, Sun Z. Left ventricular function after mitral valve surgery. J Heart Valve Dis 1995;4 Suppl 2:S175-80.

79. Bach DS, Bolling SF. Early improvement in congestive heart failure after correction of secondary mitral regurgitation in end-stage cardiomyopathy. Am Heart J 1995;129:1165-70.

80. Bolling SF, Deeb GM, Brunsting LA, Bach DS. Early outcome of mitral valve reconstruction in patients with end-stage cardiomyopathy. J Thorac Cardiovasc Surg 1995;109:676-82; discussion 682-3.

81. Bax JJ, Braun J, Somer ST et al. Restrictive annuloplasty and coronary revascularization in ischemic mitral regurgitation results in reverse left ventricular remodeling. Circulation 2004;110:Ii103-Ii108.

82. Braun J, Bax JJ, Versteegh MIM et al. Preoperative left ventricular dimensions predict reverse remodeling following restrictive mitral annuloplasty in ischemic mitral regurgitation. European Journal of Cardio-Thoracic Surgery 2005;27:847-853.

83. McGee EC, Gillinov AM, Blackstone EH et al. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2004;128:916-24.

84. Magne J, Senechal M, Mathieu P, Dumesnil JG, Dagenais F, Pibarot P. Restrictive annuloplasty for ischemic mitral regurgitation may induce functional mitral stenosis. J Am Coll Cardiol 2008;51:1692-1701.

85. Borger MA, Alam A, Murphy PM, Doenst T, David TE. Chronic ischemic mitral regurgitation: Repair, replace or rethink? Ann Thorac Surg 2006;81:1153-1161.

86. Spoor MT, Bolling SF. Flexible vs non-flexible mitral valve rings for CHF; Differential durability of repair. Circulation 2005;112:U461-U461.

87. Daimon M, Fukuda S, Adams DH et al. Mitral valve repair with Carpentier-McCarthy-Adams IMR ETlogix annuloplasty ring for ischemic mitral regurgitation - Early echocardiographic results from a multi-center study. Circulation 2006;114:I588-I593.

88. Alfieri O, Lorusso. The double-orifice technique for mitral valve reconstruction: predictors of postoperative outcome - Conference discussion. European Journal of Cardio-Thoracic Surgery 2001;20:589-589.

89. Maisano F, Caldarola A, Blasio A, De Bonis M, La Canna G, Alfieri O. Midterm results of edge-to-edge mitral valve repair without annuloplasty. Journal of Thoracic and Cardiovascular Surgery 2003;126:1987-1997.

90. Bhudia SK, McCarthy PM, Smedira NG, Lam BK, Rajeswaran J, Blackstone EH. Edge-to-edge (Alfieri) mitral repair: results in diverse clinical settings. Ann Thorac Surg 2004;77:1598-606.

91. Bhudia SK, McCarthy PM, Smedira NG, Lam BK, Rajeswaran J, Blackstone EH. Edge-to-edge (Alfieri) mitral repair: Results in diverse clinical settings. Ann Thorac Surg 2004;77:1598-1606.

92. De Bonis M, Lapenna E, La Canna G et al. Mitral valve repair for functional mitral regurgitation in end-stage dilated cardiomyopathy - Role of the "edge-to-edge" technique. Circulation 2005;112:I402-I408.

93. Sartipy U, Albage A, Mattsson E, Lindblom D. Edge-to-edge mitral repair without annuloplasty in combination with surgical ventricular restoration. Ann Thorac Surg 2007;83:1303-9.

94. Bhattacharya S, He Z. Annulus tension of the prolapsed mitral valve corrected by edge-to-edge repair. J Biomech 2012;45:562-8.

95. Maisano F, Vigano G, Blasio A, Colombo A, Calabrese C, Alfieri O. Surgical isolated edge-to-edge mitral valve repair without annuloplasty: clinical proof of the principle for an endovascular approach. EuroIntervention 2006;2:181-6.

96. Hung J, Papakostas L, Tahta SA et al. Mechanism of recurrent ischemic mitral regurgitation after annuloplasty - Continued LV remodeling as a moving target. Circulation 2004;110:Ii85-Ii90.

97. Grossi EA, Bizekis CS, LaPietra A et al. Late results of isolated mitral annuloplasty for "functional" ischemic mitral insufficiency. J Card Surg 2001;16:328-32.

98. Maisano F, Schreuder JJ, Oppizzi R, Fiorani B, Fino C, Alfieri O. The double-orifice technique as a standardized approach to treat mitral regurgitation due to severe myxomatous disease: surgical technique. European Journal of Cardio-Thoracic Surgery 2000;17:201-205.

99. Maisano F, Torracca L, Oppizzi M et al. The edge-to-edge technique: a simplified method to correct mitral insufficiency. European Journal of Cardio-Thoracic Surgery 1998;13:240-245.

100. Condado JA, Acquatella H, Rodriguez L, Whitlow P, Velez-Gimo M, St Goar FG. Percutaneous edge-to-edge mitral valve repair: 2-year follow-up in the first human case. Catheter Cardio Inte 2006;67:323-325.

101. Argenziano M, Skipper E, Heimansohn D et al. Surgical Revision After Percutaneous Mitral Repair With the MitraClip Device. Ann Thorac Surg 2010;89:72-80.

102. Feldman T, Foster E, Glower DD et al. Percutaneous repair or surgery for mitral regurgitation. The New England journal of medicine 2011;364:1395-406.

103. Feldman T, Kar S, Rinaldi M et al. Percutaneous Mitral Repair With the MitraClip System Safety and Midterm Durability in the Initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) Cohort. J Am Coll Cardiol 2009;54:686-694.

104. Feldman T, Wasserman HS, Herrmann HC et al. Percutaneous mitral valve repair using the edge-to-edge technique: Six-month results of the EVEREST phase I clinical trial. J Am Coll Cardiol 2005;46:2134-2140.

105. George JC, Varghese V, Dangas G, Feldman TE. Percutaneous mitral valve repair: lessons from the EVEREST II (Endovascular Valve Edge-to-Edge REpair Study) and beyond. JACC Cardiovasc Interv 2011;4:825-7.

106. Glower D, Ailawadi G, Argenziano M et al. EVEREST II randomized clinical trial: predictors of mitral valve replacement in de novo surgery or after the MitraClip procedure. J Thorac Cardiovasc Surg 2012;143:S60-3.

107. Goldberg SL, Feldman T. Percutaneous mitral valve interventions: overview of new approaches. Curr Cardiol Rep 2010;12:404-12.

108. Herrmann HC, Gertz ZM, Silvestry FE et al. Effects of atrial fibrillation on treatment of mitral regurgitation in the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) randomized trial. J Am Coll Cardiol 2012;59:1312-9.

109. Herrmann HC, Kar S, Siegel R et al. Effect of percutaneous mitral repair with the MitraClip (R) device on mitral valve area and gradient. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2009;4:437-442.

110. Herrmann HC, Rohatgi S, Wasserman HS et al. Mitral valve hemodynamic effects of percutaneous edge-to-edge repair with the MitraClip (TM) device for mitral regurgitation. Catheter Cardio Inte 2006;68:821-828.

111. Ladich E, Michaels MB, Jones RM et al. Pathological healing response of explanted MitraClip devices. Circulation 2011;123:1418-27.

112. Mauri L, Garg P, Massaro JM et al. The EVEREST II Trial: Design and rationale for a randomized study of the evalve mitraclip system compared with mitral valve surgery for mitral regurgitation. Am Heart J 2010;160:23-29.

113. Siegel RJ, Biner S, Rafique AM et al. The acute hemodynamic effects of MitraClip therapy. J Am Coll Cardiol 2011;57:1658-65.

114. Silvestry FE, Rodriguez LL, Herrmann HC et al. Echocardiographic guidance and assessment of percutaneous repair for mitral regurgitation with the evalve MitraClip: Lessons learned from EVEREST I. J Am Soc Echocardiog 2007;20:1131-1140.

115. Whitlow PL, Feldman T, Pedersen WR et al. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. J Am Coll Cardiol 2012;59:130-9.

116. Whitlow PL, Feldman T, Pedersen WR et al. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. J Am Coll Cardiol 2012;59:130-9.

117. Turi ZG, Rosenbloom M. An option for the high-comorbidity patient with mitral regurgitation. J Am Coll Cardiol 2012;59:140-2.

118. Vahanian A, Alfieri O, Andreotti F et al. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart

Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012.

119. McMurray JJ, Adamopoulos S, Anker SD et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847.

Annex I

Adverse events management

Annex I

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