European Commission

Directorate General for Communications Networks, Content and Technology
Sustainable and Secure Society - Health and Well-being

H2020 PHC-30-2015 689617
Research and Innovation Action

Work Package: WP4

Digital Patient Definition, Data Collection

Deliverable: D4.4

Literature and Guidelines Report

Version: 1v5

Date: 30-Apr-17

DOCUMENT INFORMATION

IST Project Num	H2020 PHC-30-2015 689617	**Acronym**	EurValve
Full title	Personalised Decision Support for Heart Valve Disease		
Project URL	http://www.eurvalve.eu		
EU Project officer	Carmen LAPLAZA SANTOS (CNECT/H/01)		

Work package	**Number**	4	**Title**	Digital Patient Definition, Data Collection
Deliverable	**Number**	4.4	**Title**	Literature and Guidelines Report

Date of delivery	**Contractual**	30-Apr-17	**Actual**	30-Apr-17
Status	Version 1v5		Final ☑	
Nature	Prototype ☐ Report ☑ Dissemination ☐ Other ☐			
Dissemination Level	Public (PU) ☑ Consortium (CO) ☐		Restricted to other Programme Participants (PP) ☐ Restricted to specified group (RE) ☐	

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Abstract (for dissemination)	The EurValve project combines multiple complex modelling components to develop a comprehensive, clinically-compliant decision-support system (DSS) that will assist clinicians with the complex task of optimising intervention in the dominant two conditions within valvular heart disease, namely aortic stenosis and mitral regurgitation. The aim of WP 4 is to collect the data on which the project depends. As part of WP 4, a literature search has been performed. This report presents results of this literature search.
Keywords	Heart valves, interventions, clinical decisions, literature, guidelines

VERSION LOG

Issue Date	Version	Author	Change
30-Jan-17	1v0	Iris Verel	First version of text and rules on aortic stenosis
15-Mar-17	1v1	Herman ter Horst	Revision and extension of text
12-Apr17	1v2	Iris Verel	Further rules on aortic stenosis added. Text and rules on mitral regurgitation added
26-Apr-17	1v3	Iris Verel, Herman ter Horst	Comments from Sheffield processed
28-Apr-17	1v4	Herman ter Horst	Final edits
30-Apr-17	1v5	PMO	Submission version

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1 INTRODUCTION

The aim of EurValve is to develop and deploy a modelling-based decision support system for aortic and mitral valve disease that introduces simulation into the comparison of effects and risks when alternative treatment strategies are being assessed. Clinical diagnosis and interventional planning for valve disease will be facilitated by interpreting and exploiting all available information, from personal clinical data, population data, clinical guidelines and simulations. The decision support system will take into account a broad range of available information, including in particular the results from computational models, the purposes of which are to offer a more effective characterisation of the disease state and to predict the effects of intervention.

This document reports on results obtained in Task 4.3. This task is part of WP (Work package) 4, the aim of which is to collect the data on which the project depends. These data include clinical information from each patient, and population and epidemiological data that are used for both data inference and data and model interpretation. Some of these data are patient-specific, for example, medical images, patient records, disease-relevant measurements, and pervasive monitoring data (Task 4.4). Others are more general, for example data from the published literature (Task 4.3) and population data. Medical images are required by Task 3.2 to determine patient anatomy. Patient records, disease-relevant measurements and pervasive monitoring data are used by Task 3.1 for machine learning and by Task 3.3 for flow simulations. Data from the literature and population data will be used in conjunction with the machine learning system and for flow simulation.

The purpose of Task 4.3 is to identify relevant literature to facilitate the population of those data fields that are necessary for the execution of the model in situations where the parameters required have not been measured on the individual patient, and to identify literature relevant to the interpretation of measured and computed data in the context of diagnosis, prognosis, and decision support. The set of reference publications used in this context has been primarily selected from clinical guidelines, reviews, meta-analyses, and multi-centre clinical trials. Meaningful knowledge/rules have also been extracted from the literature.

1.1 Relationship to other Tasks

The purpose of Task 3.1 is to develop and provide a machine learning module to infer data that are not directly available for the patient but which are required for the execution of computational mechanistic physiological models to provide personalised information relevant for decision support. In addition to using patient data for learning required computational model parameters, Task 3.1 also intends to incorporate as part of the learning process, where possible and useful, information obtained from the literature. To this end, Task 3.1 interacts with Task 4.3 on Literature Data. To illustrate the potential use of information from the literature, it is important to note that it is often emphasised (specifically in clinical guidelines for management of valvular heart disease (VHD) (Joint Task Force on the Management of VHD of the ESC and the EATCS, 2012) (Nishimura, et al., 2014)) that, since there are relatively large numbers of elderly VHD patients, comorbidities often play a role. The specific pattern of comorbidities influences the risks that need to be assessed in clinical decision making. As there are many different possible patterns of comorbidity, it would be hard to proceed by relying on data alone: we do not expect to find datasets with significant numbers of patients for many relevant comorbidity patterns.

EurValve is developing a comprehensive DSS, incorporating patient-specific data wherever possible, to provide as fully-tailored a recommendation as can be computed, and key to the DSS design is the initial definition of the matching comprehensive dataset (the digital patient definition) that informs the modelling and decision engine. The purpose of Task 4.1 is to identify all data that might be important to support the decision process for patients presenting with aortic or mitral valve disease, and to define the operations on these data to underpin the decision support mechanism. The use of literature data, collected in Task 4.3, has been part of the identification process for data that need to be part of the digital patient definition.

The primary aim of WP5 is to design and implement the decision support system, including case-based reasoning, and to define the strategy for integration within the EurValve infrastructure. WP5 relies on Task 4.3 to be able to refer to relevant publications.

The purpose of Task 6.2 is to operate on the enhanced data provided by the study cohort, to develop new knowledge for integration into the DSS workflow. This task will provide information that is relevant to clinicians and to the DSS in the management of heart valve patients, based on learning from data and literature, using inputs from Task 4.3.

1.2 Scope of this document

This report summarises information from the literature that is relevant for interventional decision making for valvular heart disease and, in line with the focus of EurValve, it considers both aortic stenosis and mitral regurgitation. It should be emphasised that the report does not provide what is commonly known in the medical literature as a systematic review. Instead, the purpose of the literature review reported here has been to develop a possible way of arriving at semi-structured summaries of key conclusions with respect to interventions on heart valves, together with many nontrivial examples of such conclusions from the most recently published literature. As the literature is evolving rapidly, it is of interest to have such a semi-structured way of capturing key conclusions in a way that readily facilitates updates as new literature appears.

This report does not describe how the information retrieved from the literature will be used in decision support, this work occurs later in the project. The semi-structured method employed to summarise conclusions from the literature is used to explore forming a bridge between the original literature, which is stated in unstructured, natural language, and decision support systems, which need a structured, procedural way of arriving at their recommendations.

2 SET UP OF THE LITERATURE SEARCH

In order to identify and collect relevant literature data, the following data sources have been used: medical textbooks, guidelines relating to valvular heart disease (VHD), and journal papers. The first source of information, medical textbooks, provides a basic understanding of valvular heart disease, although some of the medical knowledge provided tends to be not up to date. To circumvent this, nowadays, medical textbooks often come with an online version that is regularly updated and there are online reference tools available.

Guidelines are specifically written to assist clinicians in their decision process and are updated every few years. They are based on clinical consensus and extensive reviews of literature. Journal articles provide the most recent insights and the most detailed information relating to accomplishments in intervention techniques, risk stratification and influences on disease outcome, but may provide conflicting information. To complement these sources of knowledge, interviews with clinicians have been conducted to gather information on daily clinical practice.

The remainder of this report presents the results of the literature search.

3 MEDICAL TEXTBOOKS

Medical textbooks serve as authoritative resources for students at all levels, for physicians-in-training, and for practitioners of medicine. The established texts are written by authors who are highly accomplished and recognised in their respective disciplines. A downside is that these books try to cover a broad medical topic in thousands of pages of text and figures. Also, by the time the authors have written their contributions and the book is published, perhaps a year or two have elapsed. For instance, medical textbooks tend to have little information on the intervention Transcatheter Aortic Valve Implantation (TAVI), since this is a relatively new technique that is still researched heavily. The medical textbooks mentioned below are considered to be widely-used reference works with a special emphasis on cardiology and heart valve disease (Table 1). All of these texts refer to the *ESC/EACTS Guidelines* and *AHA/ACC Guidelines* (see Section 4) for current information on valvular heart disease diagnosis and treatment, and often contain figures reproduced from the Guidelines.

Book Title	Editors	Edition
Harrison's Principles of Internal Medicine (Kasper, 2015)	D.L. Kasper, A.S. Fauci, S.L. Hauser, D.L. Longo, J.L. Jameson, J. Loscalzo	19th
Current Medical Diagnosis & Treatment (Papadakis & McPhee, 2016)	M.A. Papadakis, S.J. McPhee	55th
Braunwald's Heart Disease, a textbook of Cardiovascular Medicine (Mann, Zipes, Libby, & Bonow, 2015)	D.L. Mann, D.P. Zipes, P. Libby, R.O. Bonow, E. Braunwald	10th
Valvular Heart Disease, a companion to Braunwald's Heart Disease (Otto & Bonow, 2014)	C. Otto, R. Bonow	4th
***Pathophysiology* of Heart Disease (Lilly, 2011)**	L.S. Lilly	5th

Table 1: List of common medical textbooks

We have deliberately refrained from organising the information presented from textbooks in a structured way. Instead, we have selected sequences of quotes from these textbooks that combine to establish an environment of understanding. The quotes provided below should therefore be viewed as describing background and context for the information from journal articles presented later in this report. By way of illustration, for aortic stenosis, textbooks place more emphasis on surgery than on TAVI, but in a later section we will see that recent journal articles have moved the emphasis towards TAVI.

Harrison's Principles of Internal Medicine (Kasper, 2015) presents the classic pathophysiologic basis of clinical medicine and details the methods and tools that are currently available for the assessment of symptoms and the effective management of diseases. The print edition is available in two volumes. Volume 1 focuses on the foundations of medicine and the understanding and assessment of cardinal disease manifestations; Volume 2 focuses on specific diseases, by system including a section on disorders of the cardiovascular system with four sub-sections on the different valve diseases (Part 10, section 4). This textbook is also available as an eBook on multiple platforms and as an updated online edition.

The following topics concerning **aortic stenosis** (AS) are covered in *Harrison's Principles of Internal Medicine* (Kasper, 2015): Etiology and pathogenesis, bicuspid aortic valve disease, natural history, medical treatment, surgical treatment, percutaneous aortic balloon

valvuloplasty (PABV), and transcatheter aortic valve replacement (TAVR). The following statements can be found in this book:

> "Based on data obtained at post-mortem examination in patients before surgical treatment became widely available, symptoms had existed for <4 years in >80% of patients who died with AS."
> For this reason, "operation is indicated in patients with severe AS who are symptomatic, those who exhibit LV systolic dysfunction (EF<50%), and those with bicuspid aortic valve disease (BAV) and an aneurysmal root or ascending aorta (maximal dimension >5.5cm). (..) Patients with asymptomatic moderate or severe AS who are referred for coronary artery bypass grafting (CABG) surgery should have AVR. In patients without heart failure, the operative risk of AVR is approximately 2% but increases as a function of age and the need for concomitant aortic surgery or coronary revascularization with bypass grafting."
> "In patients with low-flow, low-gradient severe AS with reduced LVEF, the perioperative mortality risk is high (15-20%)."
> "Because many patients with calcific AS are elderly, particular attention must be directed to the adequacy of hepatic, renal, and pulmonary function before AVR is recommended. Age alone is not a contraindication to AVR for AS."
> "The 10-year survival rate of older adult patients with AVR is approximately 60%."

The following topics concerning **mitral regurgitation** (MR) are covered in *Harrison's Principles of Internal Medicine* (Kasper, 2015): Etiology, pathophysiology, medical treatment, surgical treatment, transcatheter mitral valve repair, and mitral valve prolapse. The following statements can be found in this book (see the first paragraph of Section 4.2 for explanation of some terminology relating to mitral regurgitation):

> "Fatigue, exertional dyspnea, and orthopnea are the most prominent complaints in patients with chronic severe MR. Palpations are common and may signify the onset of AF."
> "In the selection of patients with chronic, non-ischemic, primary or organic, severe MR for surgical treatment, the often slowly progressive nature of the condition must be balanced against the immediate and long-term risks associated with operation. These risks are significantly lower for primary valve repair than for valve replacement."
> "The surgical management of patients with functional, ischemic MR is more complicated and most often involves simultaneous coronary artery revascularization."
> "A transcatheter approach to the treatment of either organic or functional MR may be feasible in selected patients with appropriate anatomy. The proper role of currently available techniques remains under active investigation."
> "Most patients [with MVP, Mitral Valve Prolapse] are asymptomatic and remain so for their entire lives. However, in North America, MVP is now the most common cause of isolated severe MR requiring surgical treatment."

Current Medical Diagnosis and Treatment (Papadakis & McPhee, 2016) emphasises the practical features of clinical diagnosis and patient management in all fields of internal medicine and in specialties of interest to primary care practitioners and to subspecialists who provide general care. An online version of the book provides full electronic access to *Current Medical Diagnosis and Treatment* plus expanded basic science information and additional chapters. It is updated throughout the year and includes an expanded, dedicated Media Gallery as well as access to Diagnosaurus with 1000+ differential diagnoses. One chapter is dedicated to Heart Disease (chapter 10).

The following topics concerning **aortic stenosis** are covered in *Current Medical Diagnosis and Treatment* (Papadakis & McPhee, 2016): General considerations, clinical findings, prognosis & treatment, and when to refer. Table 10-2 describes typical findings, used for differential diagnosis, of each native valve lesion, including aortic stenosis. The following statements can be found in this book:

> "Valve intervention is warranted in all patients who have symptomatic severe aortic stenosis. (..) Asymptomatic patients with severe aortic stenosis (aortic valve area less than 1.0 cm^2) should generally undergo intervention according to the following guidelines: (1) they are undergoing other cardiac surgery (i.e., CABG), (2) there is evidence for a reduced LVEF (less than 50%), (3) when the mean gradient exceeds 55 mm Hg, (4) when there is failure of the BP to rise more than 20 mm Hg with exercise, (5) when there is severe valvular calcium, or (6) when there is rapid rise in the peak aortic gradient (more than 0.3 m/sec/year). (..) Following the onset of heart failure, angina, or syncope, the prognosis without surgery is poor (50% 3-year mortality rate)."
>
> "Around one-third to one-half of all patients with AS have significant coronary artery disease (CAD) (..). With the advent of transcatheter valve replacement, the procedure is being used in patients for whom surgery is not an option. For this reason, a Heart Team approach is mandatory and factors, such as frailty and anatomic features, such as a calcified aorta, vascular access, etc. can effect decision making."
>
> "The interventional options in patients with aortic valve stenosis are variable and depend on the patient's lifestyle and age. (..) In young and adolescent patients, percutaneous balloon valvuloplasty still has a small role.
>
> "Middle-aged adults generally can tolerate the anticoagulation therapy necessary for the use of mechanical AVR, so many undergo AVR with a bileaflet mechanical valve."
>
> "In older patients, bioprosthetic (either porcine or bovine pericardial) valves with a life expectancy of about 10-15 years are routinely used instead of mechanical valves to avoid need for anticoagulation."
>
> "The use of TAVR has grown dramatically, with over 75,000 implants reported."
>
> "All of the professional societies stress the importance of a Heart Valve Team when considering aortic stenosis intervention. This is critically important because many patients referred for TAVR have serious comorbid conditions that will not improve with alleviation of the aortic stenosis."

The following topics concerning **mitral regurgitation** are covered in *Current Medical Diagnosis and Treatment* (Papadakis & McPhee, 2016): General considerations, clinical findings, treatment & prognosis, when to refer, and mitral valve prolapse syndrome. Table 10-2 describes typical findings, used for differential diagnosis, of each native valve lesion, including mitral regurgitation. The following statements can be found in this book:

> "B-type natriuretic peptide (BNP) is useful in the early identification of LV dysfunction in the presence of mitral regurgitation, and asymptomatic patients with BNP values greater than 105 pg/mL are at higher risk for developing heart failure."
>
> "There may also be a role for cardiac resynchronization therapy with biventricular pacemaker insertion, which has been found to reduce mitral regurgitation due to cardiomyopathy in many patients."
>
> "There are several ongoing trials of percutaneous approaches to reducing mitral regurgitation. These approaches include the use of a mitral clip device to create a double

orifice mitral valve, various coronary catheter devices to reduce the mitral annular area, and devices to reduce the septal-lateral ventricular size and consequent mitral orifice size."

Braunwald's Heart Disease (Mann, Zipes, Libby, & Bonow, 2015) covers the entire spectrum of cardiovascular medicine, highlighting the latest advances in basic, translational, and clinical science, with an emphasis on conveying how this information informs both the prevention and the treatment, of cardiovascular disease. It contains a chapter on valvular heart disease and text on guidelines, management of valvular heart disease (Part VIII, Chapter 63). *Braunwald's Heart Disease* is part of a learning platform that includes a family of companion texts, which provide detailed expert content for the subspecialist across a broad range of cardiovascular conditions. One of these companion texts focuses on *Valvular Heart Disease* (Otto & Bonow, 2014) in particular. In order to provide a "living textbook", the print version of *Braunwald's Heart Disease* and its companion texts, is complemented by an online version that contains audio, video, and additionally written content not available in the textbook. The online version of *Heart Disease* is updated frequently with the results of late-breaking clinical trials, reviews of important research publications, and updates on clinical practice authored by leaders in the field.

The following topics concerning **aortic stenosis** are covered in *Braunwald's Heart Disease* (Mann, Zipes, Libby, & Bonow, 2015): Causes and pathology, pathophysiology, disease course, surgical treatment, transcatheter aortic valve implantation, and results. The following statements can be found in this book:

"The severity of outflow tract obstruction gradually increases over 10 to 15 years, so the clinical course includes a long latent period during which stenosis severity is only mild to moderate and clinical outcomes are similar to those for age-matched normal patients."
"Risk factors associated with a higher mortality rate include a high New York Heart Association (NYHA) functional class, impairment of LV function, advanced age, and the presence of associated coronary artery disease. The 30-day mortality rate also is significantly related to the number of AVR procedures performed at each hospital. The 10-year survival rate of hospital survivors in surgically treated patients is approximately 85%. Risk factors for late death include higher preoperative NYHA functional class, advanced age, concomitant untreated coronary artery disease, preoperative impaired LV function, preoperative ventricular arrhythmias, and associated significant aortic regurgitation (AR)."
"Surgical risk and postoperative morbidity are related to the higher prevalence of comorbid conditions in older patients, rather than to age per se."

The following topics concerning **mitral regurgitation** are covered in *Braunwald's Heart Disease* (Mann, Zipes, Libby, & Bonow, 2015): Causes and pathology, pathophysiology, disease course, surgical treatment of primary mitral regurgitation, surgical treatment of secondary mitral regurgitation, transcatheter treatment of secondary mitral regurgitation, and mitral valve prolapse. The following statements can be found in this book:

"Some degree of MR is found in approximately 30% of patients with coronary artery disease who are being considered for CABG."
"In asymptomatic patients with severe [primary] MR, the rate of progression to symptoms, LV dysfunction, pulmonary hypertension or AF is 30% to 40% at 5 years."
"Moreover, long-term survival after successful surgical repair of primary degenerative MR is reduced in patients with even mild preoperative symptoms compared with those who

undergo surgery when asymptomatic. These considerations have prompted recommendations for earlier surgery in patients who are candidates for repair, especially in the setting of flail leaflets. (..) However, the recommendation for mitral valve repair in asymptomatic patients should be considered only for those with severe MR who are referred to centres in which the surgical experience indicates a high degree of certainty of successful mitral valve repair."

"Preoperative AF is an independent predictor of reduced long-term survival after mitral valve surgery for chronic MR."

"What is less clear is whether secondary MR, once established, contributes to progression of LV dysfunction and plays a causative role in the observed worse outcomes. Thus whether secondary MR should be a target for surgical or device intervention remains uncertain."

"In patients with functional MR, the primary problem is disease of the LV myocardium, and prognosis is strongly influenced by the degree of LV dysfunction. Mitral valve repair or replacement in these latter patients has a less beneficial effect on long-term outcome, particularly in those with ischemic MR, than in patients with degenerative MR. In the absence of a prospective randomized trial powered to address clinical outcomes, retrospective data have failed to show a survival benefit of mitral valve surgery for ischemic MR."

The following topics concerning **aortic stenosis** are covered in *Valvular Heart Disease, a Companion to Braunwald's Heart Disease* (Otto & Bonow, 2014): Cellular and molecular basis of calcific aortic valve disease, clinical and genetic risk factors for calcific valve disease, aortic stenosis, surgical approach to diseases of the aortic valve and the aortic root, and transcatheter aortic valve implantation. The following statements can be found in this book:

"Calcification in stenotic valves is often associated with increases in osteogenic signalling and the presence of osteoblast-like and osteoclast-like cells, but can also occur in the absence of bone-related cells."

"In the development of novel therapeutic approaches to slow or potentially halt progression of valvular dysfunction in fibrocalcific aortic valve disease, it is likely that successful interventions will need to target both calcification and fibrosis in the stenotic aortic valve."

"To date, no lifestyle modifications or medical therapies have been shown to slow calcific aortic valve disease initiation or progression, and the mainstays of therapy remain careful observation and timely procedural intervention with surgical or transcutaneous aortic valve replacement at the onset of valve-related symptoms. Calcific aortic valve disease is one of the most common indications for cardiac surgery, with approximately 75,000 aortic valve replacement procedures performed annually in the United States."

"Thus far, the body of evidence suggests strong associations between many traditional cardiovascular risk factors and calcific aortic valve disease, especially in its early stages."

"Risk factors for the subsequent development of valve calcification were age, male gender, total cholesterol, and smoking."

"What is more surprising is that early-stage calcific aortic valve disease, prior to hemodynamic perturbations, is also associated with an increased risk of cardiovascular events."

"In adults with symptomatic aortic stenosis, predictors of survival are transaortic velocity or gradient, functional status, LV systolic function, comorbid disease, and gender."

"About 50% of adults undergoing valve replacement for aortic stenosis have significant coronary artery disease."

> "The assessment of the interventional risk is particularly important in elderly patients. Objective parameters to assess interventional risk and thus to predict the risk of surgery and to identify high-risk patients who would benefit from percutaneous procedures are needed. In that regard, reliable risk scores that predict surgical mortality would be helpful. The EuroSCORE, still widely used in Europe, was not developed for this specific patient group, has major limitations, and frequently overestimates the 30-day mortality."
>
> "TAVI is technically feasible in most patients with aortic stenosis. Evaluation should identify patients in whom a significant improvement in quality and duration of life is likely and avoid unnecessary intervention in patients in whom the procedure can be performed but benefit is unlikely. For this reason evaluation of neurocognitive functioning, frailty, functional status, mobility, and social support is important in patient selection."

A separate chapter is dedicated to risk assessment for valvular heart disease. This chapter describes risk scores, How risk algorithms are constructed, Limitations of risk algorithms, Use of risk algorithms, What can be predicted, Available risk algorithms for aortic stenosis, and Risk algorithms in transcatheter aortic valve implantation - see for a summary, Section 5 in this document.

The following topics concerning **mitral regurgitation** are covered in *Valvular Heart Disease, a Companion to Braunwald's Heart Disease* (Otto & Bonow, 2014): Myxomatous mitral valve disease, secondary mitral regurgitation, mitral regurgitation: timing of surgery, mitral valve repair and replacement, transcatheter mitral valve repair and replacement, and intraoperative echocardiography for mitral valve surgery. The following statements can be found in this book:

> "Mitral valve prolapse (MVP) occurs in 2.4% of the population and is the leading cause of mitral regurgitation in developing countries."
>
> "Despite the risk of complications, MVP appears to have an excellent prognosis. When patients with severe MR from MVP undergo repair surgery at an appropriate time, there is considerable evidence that their survival is as good as, if not better than, that of a control population without MVP. This is not necessarily true if a mitral valve replacement is performed or if MR has led to LV dysfunction."
>
> "Although MVP is equally prevalent in men and women, men are much more likely to experience significant complications. (..) The reasons that men are more likely to present with a complicated course are unknown."
>
> "It is well known that patients with hemodynamically significant primary MR are at risk for development of atrial fibrillation (..). However, it has only been recently recognized that atrial fibrillation can lead to MR in patients with anatomically normal mitral valves. (..) This concept is not universally accepted."
>
> "MR is often thought to be a bystander consequence of ischemic heart disease, and its clinical importance is overlooked. (..) , the presence of MR increases mortality twofold in the setting of MI, in chronic heart failure, and even after coronary revascularization, and even a mild degree of MR in the setting of ischemic heart disease affects survival negatively."
>
> "Medical therapy can be aimed at reducing MR in the short term and inducing LV reverse remodelling over the long term."
>
> "The data examination of the role of mitral valve repair at the time of CABG have been conflicting. If the role of mitral valve repair with CABG is unclear, the indication for mitral valve repair along with CABG in patients with severely reduced EF (<30%) is even murkier."

"..patients with asymptomatic primary MR were prospectively followed. (..) Independent determinants of survival were age, presence of diabetes, but also the regurgitant orifice (ROA), which provides a quantitative measure of severity of MR."
"It is important to determine etiology of chronic MR when one is considering timing of operation. Different surgical techniques are performed on the basis of valve morphology and underlying etiologies, and the performance of these different surgical techniques has important implications such as when a particular operation should be performed. (..) there is a higher chance of successful repair with degenerative MR, than with other etiologies of primary MR. (..) The surgical approach to ischemic MR remains controversial. Thus, the optimal indication and therapy for patients with functional [non-ischemic secondary] MR remains unknown."
"If the decision to proceed with mitral valve replacement is made, a chordal sparing approach should be employed to preserve chordal-ventricular-annular continuity, which is important to preserve long-term LV shape and performance."
"The complexity of the mitral valve apparatus and the myriad causes of MR have caused the field of transcatheter mitral valve repair and replacement to develop more slowly than treatments for other valve diseases."

Pathophysiology of Heart Disease (Lilly, 2011) is a comprehensive introduction to diseases of the cardiovascular system. The introductory chapters of the book review basic cardiac anatomy and physiology, and describe the tools needed for understanding clinical aspects of subsequently presented material. The remainder of the text addresses the major groups of cardiovascular diseases, including valvular heart disease.

The following topics concerning **aortic stenosis** are covered in *Pathophysiology of Heart Disease* (Lilly, 2011): Etiology, pathology, pathophysiology, clinical manifestations and evaluation, natural history and treatment, and mitral valve prolapse. The following statement can be found in this book:

"The effect of aortic valve replacement on the natural history of aortic stenosis is dramatic, as the 10-year survival rate rises to approximately 60%".
The following topics concerning **mitral regurgitation** are covered in *Pathophysiology of Heart Disease* (Lilly, 2011): Etiology, pathophysiology, clinical manifestations and evaluation, natural history and treatment, and mitral valve prolapse. The following statement can be found in this book:
"Because chronic MR produces continuous left ventricular volume overload, it can slowly result in left ventricular contractile impairment and, ultimately, heart failure. Mitral valve surgery should be performed before this deterioration occurs."
"The operative mortality rate is approximately 2% to 4% for mitral valve repair and 5% to 7% for mitral replacement. These rates are higher if concurrent coronary artery bypass grafting is performed."
"The clinical course of MVP is most often benign. Treatment consists of reassurance about the usually good prognosis and monitoring for the development of progressive MR".

4 CURRENT GUIDELINES

Guidelines summarise and evaluate all evidence available on a particular issue at the time of their writing, with the aim of assisting physicians in selecting the best management strategies for an individual patient with a given condition, taking into account the impact on outcome, as well as the risk-benefit-ratio of particular diagnostic or therapeutic means. Guidelines are based on clinical consensus and are intended to assist clinicians in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases. Guidelines are not substitutes for, but are complementary to, textbooks.

Two guidelines are of importance for VHD management and here we refer to the latest versions of these guidelines.

Guidelines on the management of valvular heart disease (version 2012) (Joint Task Force on the Management of VHD of the ESC and the EATCS, 2012) is issued by The European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) (from now on called *ESC/EACTS Guidelines* in this document). These guidelines focus on acquired VHD, are oriented towards management, and do not deal with endocarditis or congenital valve disease, including pulmonary valve disease, since specific guidelines have been produced by the ESC on these topics.

2014 AHA/ACC Guidelines for the Management of patients With Valvular Heart Disease (Nishimura, et al., 2014) is issued by the American College of Cardiology (ACC) and the American Heart Association (AHA) (from now on called *AHA/ACC Guidelines* in this document). The focus of these guidelines is diagnosis and management of adult patients with VHD. Management of patients with congenital heart disease and infants and children with valve disease are not addressed. The aim is to provide the clinician with concise, evidence-based, contemporary recommendations together with supporting documentation.

Both *ESC/EACTS Guidelines* and *AHA/ACC Guidelines* point out that "due to the lack of evidence-based data in the field of VHD, current recommendations are largely based on expert consensus" (citation from *ESC/EACTS Guidelines*). For this reason, we have also conducted interviews with the clinical partners within the EurValve consortium in order to obtain in depth understanding of considerations taken into account by cardiologists when treating VHD patients.

As stated in both the *ESC/EACTS* and *AHA/ACC Guidelines*, decision-making is complex, since VHD is often seen at an older age and, as a consequence, there is a higher frequency of comorbidity, contributing to increased risk of intervention. Although the importance of the influence of comorbidities on the outcome is emphasised in the guidelines, these comorbidities and their implications are not taken into account in detail in the recommendations provided. For this reason, in searching the journals, our focus has especially been on comorbidities and outcome.

The *ESC/EACTS Guidelines* recommend that decision-making ideally should be made by a 'heart team' with a particular expertise in VHD, including cardiologists, cardiac surgeons, imaging specialists, anaesthetists and, if needed, general practitioners, geriatricians, or intensive care specialists. Two central questions that need to be answered during decision-making by this heart team are whether the patient with VHD should be treated, and if yes, which type of intervention should be chosen. The *ESC/EACTS Guidelines* provide decision

trees for each pathology of interest, and of specific importance in the context of EurValve, one for aortic stenosis (AS, figure 1) and one for primary mitral regurgitation (MR, figure 2). In each decision tree, a hierarchical combination of steps is defined and recommendations are proposed among medical therapy, open surgical repair/replacement or trans-catheter intervention.

4.1 Aortic stenosis

For aortic stenosis, the answer to the first question, to treat or not, is based on the presence of severe disease with symptoms. The definition of severe AS is based on natural history studies of patients with un-operated AS, which show that the prognosis is poor once there is a peak aortic valve velocity of > 4 m/s, corresponding to a mean aortic valve gradient > 40 mmHg. These findings are expressed in the *ESC/EACTS Guidelines*, in which clear echocardiographic criteria for the definition of severe AS are given (Table 2). An exception to these rules applies to a small subset of patients with low volume flow rate due to left ventricular (LV) dysfunction and to patients in which serial testing shows an increase in aortic velocity of 0.3 m/s or greater per year.

The determination of presence of symptoms is more difficult since AS is a gradually progressive disease and many patients do not recognise early symptoms or unconsciously reduce their activities to alleviate symptoms. Also, the symptoms are non-specific such as exertional shortness of breath, angina, dizziness or syncope. According to clinical experience, most patients with severe AS also reveal symptoms when carefully questioned.

Parameter	Aortic stenosis
Valve area (cm2)	< 1.0
Indexed valve area (cm2/m2 BSA)	< 0.6
Mean gradient (mmHg)	> 40
Maximum jet velocity (m/s)	> 4.0
Velocity ratio	< 0.25

Table 2: ESC/EACTS Guidelines, echocardiographic criteria for the definition of severe aortic stenosis

The second question, which type of intervention to use, is more difficult to answer for AS. This decision mostly relies on the heart team, as indicated in the ESC/EACTS decision tree (Figure 1). Some considerations that are taken into account are operative mortality estimation, as provided by the risk scoring systems EuroSCORE (European System for Cardiac Operative Risk Evaluation) and the STS (Society of Thoracic Surgeons) score - see also Section 5, the presence of comorbidities, and cognitive and functional capacities (frailty) of the patient. For instance, as exemplified by this citation from the *ESC/EACTS Guidelines*: “TAVI is recommended in patients with severe symptomatic AS who are, according to the Heart Team, considered unsuitable for conventional surgery because of severe comorbidities”.

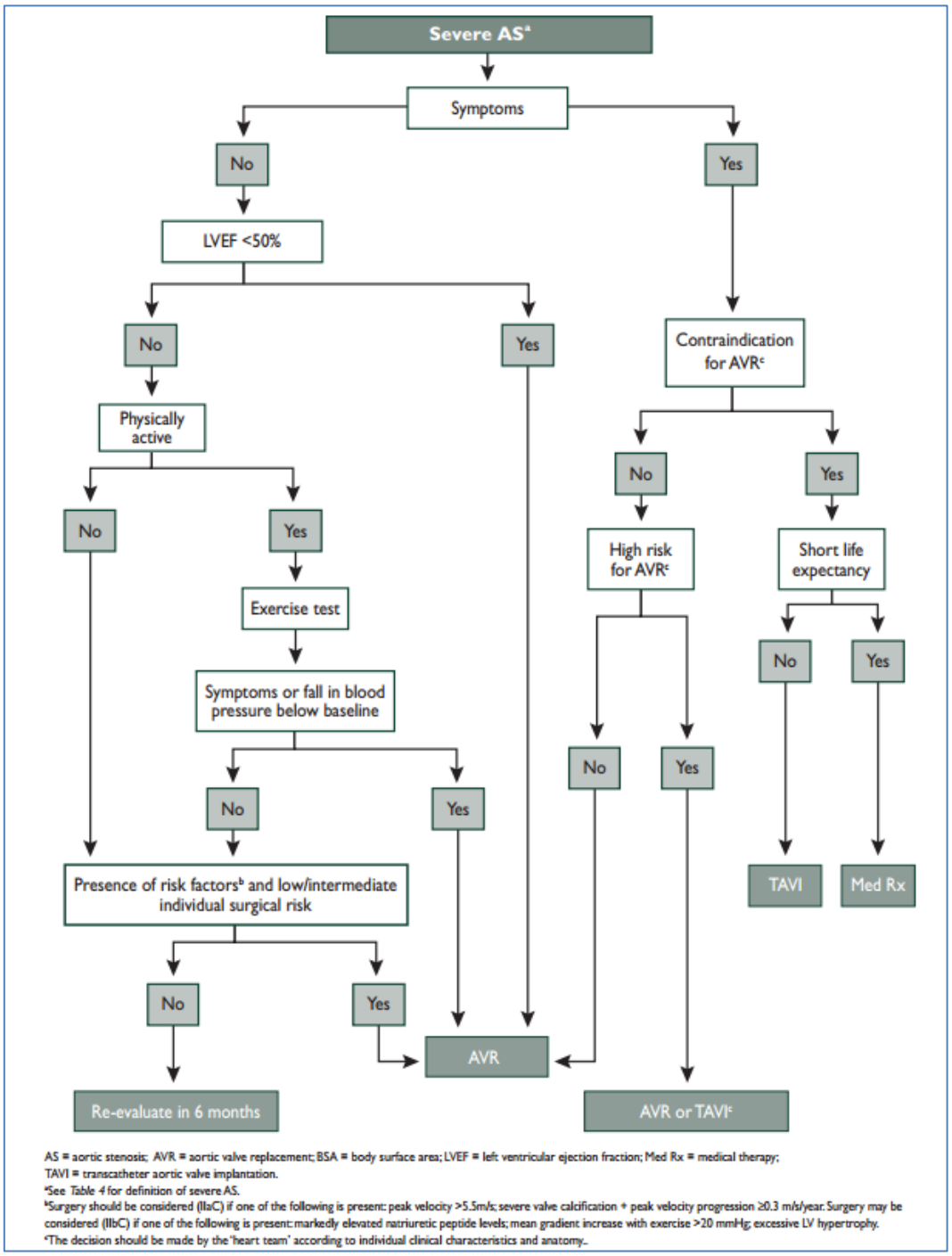


Figure 1: ECS/EACTS guidelines, management of severe aortic stenosis

4.2 Mitral regurgitation

For mitral regurgitation, it is important to distinguish between primary and secondary mitral regurgitation, as these conditions have different implications for intervention.

> Primary MR, also called organic or intrinsic MR, covers all aetiologies in which intrinsic lesions affect one or several components of the valve (leaflets, chordae tendineae, papillary muscles, annulus). Damage can be sudden, causing acute primary MR, or gradual resulting in chronic primary MR, also called degenerative mitral regurgitation.
>
> In secondary MR, also called 'functional mitral regurgitation', valve leaflets and chordae are structurally normal and mitral regurgitation results from geometrical distortion of the subvalvular apparatus, secondary to left ventricular dysfunction. Severe left ventricular dysfunction is caused by either coronary artery disease (CAD), related myocardial infarction ('ischemic chronic secondary mitral regurgitation'), or idiopathic myocardial disease ('non-ischemic chronic secondary mitral regurgitation').

For chronic primary MR, the answer to the first question, to treat or not, is based on the presence of severe disease with symptoms, such as decreased exercise tolerance and exertional dyspnea. The *ESC/EACTS Guidelines* also proposes treatment for asymptomatic patients with severe disease, although this is controversial as "there are no randomized trials to support any particular course of action". Eligible asymptomatic patients are patients with signs of left ventricular dysfunction, new onset atrial fibrillation, high systolic pulmonary arterial pressure, or high likelihood of durable repair as can be seen in Figure 2. In the absence of symptoms, the estimated 5-year rate of death from any cause has been reported to be 22%.

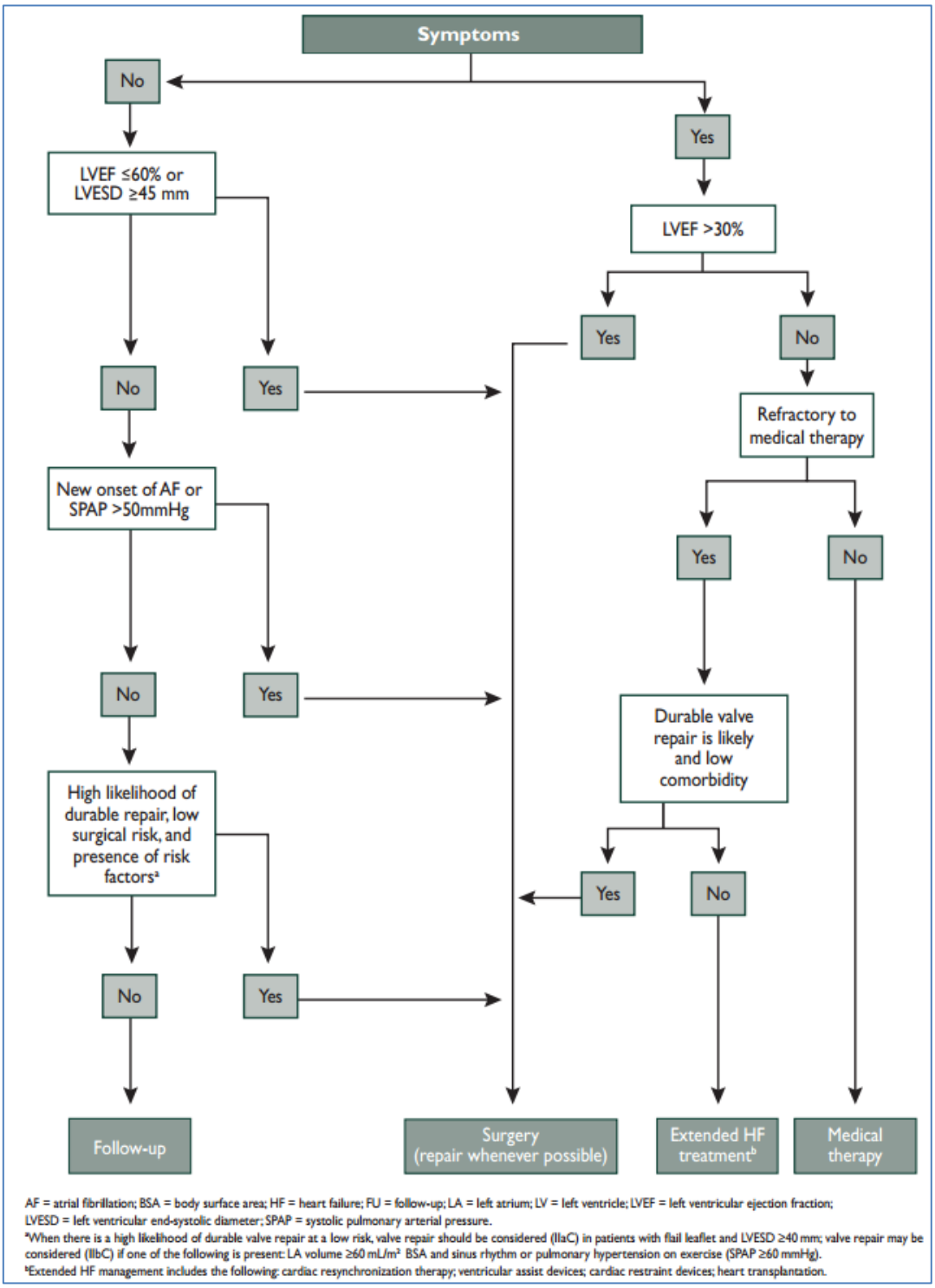
To determine severity of MR, several echocardiographic methods can be used, which can give qualitative, semi-quantitative or quantitative measurements (Table 3). As stated in the *ESC/EACTS Guidelines*, "all quantitative evaluations have limitations. In particular, they combine a number of measurements and are highly sensitive to errors of measurement, and are highly operator dependent; therefore, their use requires experience and integration of a number of measurements, rather than reliance on a single parameter."

The preferred answer to the second question, which intervention to use, is surgery. Alternatives, in case of high surgical risk or inoperability, are catheter-based interventions or medical therapy. The only percutaneous intervention that has been evaluated is the edge-to-edge procedure (MitraClip), but this procedure reduces MR less effectively, and recurrence or worsening of MR is more likely to occur compared to surgery. There is no evidence to use medical therapy in chronic MR without heart failure. When heart failure has developed, ACE inhibitors are beneficial and should be considered in patients with advanced MR and severe symptoms.

Parameter	Mitral regurgitation
Qualitative	
Valve morphology	Flail leaflet/ruptured papillary muscle/large coaptation defect
Colour flow regurgitant jet	Very large central jet or eccentric jet adhering, swirling, and reaching the posterior wall of the left atrium
Continuous wave signal of regurgitant jet	Dense/triangular
Other	Large flow convergence zone
Semiquantitative	
Vena contracta width (mm)	≥7 (>8 biplane)
Upstream vein flow	Systolic pulmonary vein flow reversal
Inflow	E-wave dominant≥1.5 m/s
Other	Time-velocity integral mitral/ time-velocity integral aortic >1.4
Quantitative	
Effective regurgitant orifice area (mm2)	Primary ≥40; Secondary ≥20
Regurgitant volume (ml/beat)	Primary ≥60; Secondary ≥30
+ enlargement of cardiac chambers	Primary: left ventricle, left atrium

Table 3: ESC/EACTS Guidelines, echocardiographic criteria for the definition of severe mitral regurgitation

For secondary MR, it is more difficult to find the answer to the first question, to treat or not, and the second question, which intervention to use, since "the heterogeneous data regarding secondary mitral regurgitation result in less evidence-based management than in primary mitral regurgitation" as stated in the *ESC/EACTS Guidelines*. Severe MR should be corrected at the time of bypass surgery. Otherwise, indications for isolated mitral valve surgery are questionable and optimal medical treatment is thought to be currently the best option. Medical therapy should be given to all patients with secondary MR in line with the guidelines on the management of heart failure (Ponikowski, et al., 2016). Patients with symptomatic severe secondary MR may be considered for percutaneous MitraClip procedure despite optimal medical therapy.



AF = atrial fibrillation; BSA = body surface area; HF = heart failure; FU = follow-up; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; SPAP = systolic pulmonary arterial pressure.
[a]When there is a high likelihood of durable valve repair at a low risk, valve repair should be considered (IIaC) in patients with flail leaflet and LVESD ≥40 mm; valve repair may be considered (IIbC) if one of the following is present: LA volume ≥60 mL/m² BSA and sinus rhythm or pulmonary hypertension on exercise (SPAP ≥60 mmHg).
[b]Extended HF management includes the following: cardiac resynchronization therapy; ventricular assist devices; cardiac restraint devices; heart transplantation.

Figure 2: ECS/EACTS guidelines, management of severe chronic primary mitral regurgitation

5 RISK SCORES

As described in both the *ESC/EACTS* and *AHA/ACC Guidelines*, "the decision to intervene, as well as the type of intervention for a patient with severe VHD, should be based on an individual risk-benefit analysis" (citation from *AHA/ACC Guidelines*). One important risk of the procedure is operative mortality. This can be estimated by various multivariable scoring systems using combinations of risk factors. The two most widely-used scores are the EuroSCORE (www.euroscore.org/calc.html) and the STS predicted risk of mortality score (http://209.220.160.181/STSWebRiskCalc261/). The latter has the advantage of being specific to VHD since it was developed with data originating from aortic valve surgery only, while the EuroSCORE II was based on all cardiac operations. However, despite its focus on VHD, the STS score is considered less easy to use since it consists of 24 variables, while the EuroSCORE II consists of 18 variables. Lists of the variables used in these risk scores can be found in Annex 3. The STS score makes a distinction between the following procedure types: coronary artery bypass only, aortic valve replacement, mitral valve replacement only, mitral valve repair, aortic replacement + CABG, mitral valve replacement + CABG, and mitral valve repair + CABG. EuroSCORE II does not make this distinction. In addition to operative mortality, the STS risk score provides an estimate of important complications such as prolonged hospitalisation, stroke, respiratory failure, mediastinitis, renal failure, and reoperation.

There are several important limitations to these scores that need to be taken into account when using them for risk adjustment. We give a summary of information from *Valvular Heart Disease, a Companion to Braunwald's Heart Disease*.

Firstly, risk algorithms are accurate only for the population and in the time frame in which they are developed and validated. For instance, the most recent version of the EuroSCORE, EuroSCORE II, was derived from data from patients operated on in 2010 and from 43 countries worldwide. The STS models were developed using database records for surgical procedures taking place between 2002-2006 in the United States. To ensure high calibration for the current study cohort and thus to adjust for time frame, coefficients of each model are re-estimated using the current 3-year study sample of the STS database.

Secondly, risk adjustment loses accuracy at the extremes of the population studied, where there are too few patients upon which to build a statistically valid model. This is true for instance for high-risk patients, resulting in an overestimation of the operative risk for these patients.

Thirdly, risk algorithms cannot reliably be applied directly to populations and treatments other than those in which they were developed. The implication is that although both surgical aortic valve replacement and TAVI are used in treating patients with AS, aortic valve replacement risk algorithms are based on "surgical" outcomes and therefore may not be directly applicable to TAVI.

Fourthly, risk algorithms cannot account for variables not collected or analysed. This lack of accounting can be caused by three things: (1) infrequent occurrence resulting in the fact that the impact cannot be measured (e.g. porcelain aorta), or (2) the factor cannot be accurately measured, or (3) the factor was previously not known to be causal. For the latter reason the STS models have now been updated to include multiple potential risk factors not previously collected, such as previous radiation exposure, liver disease, and frailty as measured by gait speed. Despite this update, still several comorbidities are not taken into account.

6 JOURNAL LITERATURE DATA COLLECTION

6.1 Database search

Journal literature published in English in the database Scopus, complemented with data from PubMed, has been searched and reviewed. The latest versions of the *ESC/EACTS Guidelines* were published in 2012 and of the *AHA/ACC Guidelines* in 2014. In this literature review, emphasis has been put on the most recent published articles going back to approximately 2013. Note that more recent literature often builds upon the foundation of older publications. Moreover, literature published before this time is reviewed by the guidelines. The focus in our literature search has been on comorbidities and outcome, since comorbidities were pointed out in the guidelines as being influential on outcome, but were not addressed in detail in these guidelines as was already mentioned in Section 4.

Using “aortic stenosis” as a search term in Scopus, the number of retrievals exceeds 16,000 documents. Limiting the search to the years 2013-2016 still provides more than 4,000 document results. Using “mitral regurgitation” as a search term in Scopus, the number of retrievals exceeds 14,000, while limiting to the years 2013-2016 provided approximately 3,000 results. To make the search results more specific, the search term “outcome” was added, and separate searches were performed in combination with comorbidities. In our search for papers on AS we started with the following comorbidities: age, frailty, MR, diabetes, COPD / lung disease, porcelain aorta, renal failure, and previous CABG. Comorbidities that were used in the journal literature search, are based on patient risk factors used as input in the STS risk score and the EuroSCORE II, and on information gathered in clinical interviews.

Documents that were most recent, describing clinical studies with at least 200 included patients, and in journals with at least an impact factor of 3, were selected for review. Due to the more complex and heterogeneous nature of mitral valve disease, study cohorts are smaller compared to those in AS studies, resulting in fewer articles with at least 200 included patients. Articles, referenced in these selected documents as being important in the field, were also reviewed. In addition, recent and relevant meta-analyses or systematic reviews were used to gather useful references. We included impact factor (IF) in the search although it can be debated whether the impact factor of a journal is a useful criterion. For older papers, number of citations seems to be a stronger criterion than journal impact factor. However, since we focused on recent papers number of citations did not seem appropriate.

We have also used lists of common chronic diseases to determine comorbidities that could influence AS or MR intervention. Lists of often occurring chronic diseases are published, for instance, by the World Health Organisation (described as non-communicable diseases) and Centers for Disease Control and Prevention. Goodman et al. described in 2012 a list of 20 common chronic conditions (Goodman, Posner, Huang, Parekh, & Koh, 2012), developed by a working group on multiple chronic conditions within the US Department of Human Health Services (HHS). These common chronic conditions have been used as search terms in combination with the search terms “aortic stenosis” or “mitral regurgitation” and “outcome” (Table 4 and Table 5). High hit rates imply a connection between the chronic condition and the outcome of AS or MR intervention. In our journal search, not only the terms in the table of chronic diseases were used but also synonyms.

Chronic disease	Scopus hits	Main reason(s) for hits
hypertension / high blood pressure	587	Hypertension is associated with AS progression.
congestive heart failure	201	Congestive heart failure development can be caused by advanced AS. Intervention of AS can cause heart failure.
coronary artery disease / ischemic heart disease	453	There is a high concomitance of coronary artery disease and AS. Coronary artery disease is a predictor of adverse outcome after AS intervention.
cardiac arrhythmias	113	Cardiac arrhythmias can be caused by intervention of AS.
hyperlipidemia	32	Hyperlipidemia is correlated with hypertension and hypertension is associated with AS progression. Hyperlipidemia is listed in the clinical profiles of study cohort patients.
stroke / cerebrovascular disease	1115	There is a high frequency of pre-existing cerebrovascular disease in AS patients. Intervention of AS can cause stroke.
arthritis	11	
asthma	5	
autism spectrum disorder	1	
cancer (all except non-melanoma skin)	53	Previous chest radiation due to cancer can cause VHD. Occurrence of simultaneous treatment of cancer and AS.
chronic kidney disease	86	Chronic kidney disease correlates with lower survival rate after intervention of AS.
chronic obstructive pulmonary disease	79	Chronic obstructive pulmonary disease correlates with lower survival rate after intervention of AS; “chronic lung disease” has 145 hits (also used).
dementia (including Alzheimer's)	6	
depression	33	Also hits from e.g. respiratory depression and ventricular depression.
diabetes	202	There is a correlation between diabetes and higher BMI. Higher BMI correlates with higher survival rate of patients with AS after intervention. Diabetes correlates with lower survival rate after intervention of AS.
hepatitis	9	
HIV	1	
osteoporosis	14	
schizophrenia	0	
substance abuse disorders (drug and alcohol)	0	

Table 4: List of 20 most common chronic conditions and search results in Scopus in combination with aortic stenosis

Chronic disease	Scopus hits	Main reason(s) for hits
hypertension / high blood pressure	485	Valvular heart disease is a common cause of pulmonary hypertension and pulmonary hypertension is a predictor of deterioration of disease.
congestive heart failure	352	Hospitalisation for congestive heart failure can be a clinical endpoint in MR studies. MR is associated with worse outcome in patients with congestive heart failure.
coronary artery disease / ischemic heart disease	484	There is a high coexistence of coronary artery disease and MR.
cardiac arrhythmias	134	Cardiac arrhythmias can occur after MR intervention.
hyperlipidemia	13	
stroke / cerebrovascular disease	800	Intervention of MR can lead to stroke.
arthritis	13	
asthma	3	
autism spectrum disorder	0	
cancer (all except non-melanoma skin)	50	Cardiac complications can occur after treatment of cancer with radiotherapy.
chronic kidney disease	60	Chronic kidney disease leads to worse clinical outcomes after percutaneous MR intervention and reduction in MR severity after percutaneous intervention is associated with improved renal function.
chronic obstructive pulmonary disease	35	
dementia (including Alzheimer's)	0	
depression	17	
diabetes	118	Patients with diabetes often have (mild) MR. Diabetes is a predictor of long-term mortality after surgery and a predictor of MR progression after valve repair.
hepatitis	0	
HIV	1	
osteoporosis	2	
schizophrenia	0	
substance abuse disorders (drug and alcohol)	2	

Table 5. List of 20 most common chronic conditions and search results in Scopus in combination with mitral regurgitation

6.2 Data Management

Collected journal literature data was stored in the management system Zotero and annotated. Zotero is a free tool to collect, organise, cite and share research sources. It offers a searchable interface to which PDF, image, audio and video files can be added. Notes were added to each document summarising the content.

7 RULES

Using the journal literature that has been collected in the data management system, rules were compiled. See Annex 1 for the rules for aortic stenosis, Annex 2 for the rules for mitral regurgitation, and Annex 3 for the list of papers used to compile these rules.

These rules on AS and MR give a semi-structured description of major conclusions drawn in the journal documents. The rule-structure was composed, and stabilised during the first months of the literature search. The rules consist of the following components, which include text:

Intervention: the main interventions in AS are surgical aortic valve replacement (SAVR), transcatheter aortic valve implantation (TAVI) or medical therapy (conservative). The main interventions in MR are surgery, either repair or replacement, medical therapy or percutaneous mitral valve repair, usually MitraClip.

Factor: a factor can be a comorbidity or any other condition or status of a patient that is relevant for the clinical decision due to the influence it has on the outcome of an intervention.

Rule: a rule describes how and to what extent a certain factor influences the outcome of an intervention. A rule is formulated as follows:

IF **factor**, **intervention** THEN **outcome** higher/lower/same.

The outcome mentioned in a rule can for example be one of the following:

- mortality at 30 days
- mortality at 1 year
- survival
- quality of life
- stroke
- major bleeding
- major vascular complications
- myocardial infarction
- heart failure
- permanent pacemaker
- acute kidney failure
- valve-related complications
- rehospitalisation
- re-intervention

Occurrence: describes how often a factor occurs in different population groups. For instance, it can describe the occurrence of the factor in the study population of patients undergoing aortic valve intervention as described in the reference, in the population of patients undergoing aortic valve intervention in general, or how often the factor occurs in the general population.

Evidence: information on the level of evidence is provided based on several characteristics, such as the publication type (meta-analyses, systemic review, or study description), type of

study (randomised vs nonrandomised, prospective vs retrospective, multi-centre vs single centre), size of the study cohort, and journal impact factor.

Reference on which the rule is based.

The rules have been grouped into **classes** based on the factor concerned. For instance, classes can be comorbidities such as frailty and diabetes, but also rules about high surgical mortality risk have been grouped into a class.

Another example of a class into which rules have been grouped concerns advanced age: people of 90 years and older, called nonagenarians. Although, based on age, this group of patients is thought to be at increased risk for morbidity and mortality after TAVI, the rules composed from the literature show that nonagenarians can have good outcomes after TAVI with risk of stroke, aortic valve re-intervention, or myocardial infarction and mortality risk at 1-year after TAVI that is no different from patients younger than 90 years.

Another class concerns diabetes. For AS, the rules show that there is a disagreement in the journal literature about whether diabetes is associated with increased mortality after TAVI. Since study cohorts differ in population characteristics, and different parameters were measured, it is possible that only a certain subset of diabetes patients is at higher risk of mortality.

In some cases, the evidence presented in the rules obtained from journal papers is contradictory. There does not seem to be a method of deciding in such situations which rule is most likely to be true and therefore useful. It is clear that care should be exercised with the use of a rule obtained from the literature when it is contradicted by another rule. Moreover, a rule that is not contradicted by another rule could become contradicted by a new publication that is published later. There are however also cases where conclusions that seem to be contradictory are actually stated to hold for different groups of patients.

Amongst the rules presented for aortic stenosis there are more statements about TAVI than about SAVR. This reflects our search criteria focusing on recent papers: in recent years, research has placed relatively more emphasis on TAVI, which was set up in the 2000s and continues to undergo improvements. For the same reason the current risk scores place more weight on the evidence from SAVR than from TAVI, and the guidelines similarly give more guidance with respect to SAVR. We did not systematically search for evidential basis on SAVR in the older literature, but some of that older evidence is also captured in textbooks from which quotes were given in Section 3.

Even though the rules based on recent literature put much focus on TAVI, they still seem to be useful in connection with the decision regarding surgery versus TAVI. For a long time the situation was that if an intervention for AS was indicated, the intervention would be surgery. When TAVI was initiated, it at first became an intervention that was considered suitable only for the oldest patients or for the patients with the highest risk. As TAVI and experience with TAVI has developed, so TAVI has become suitable for larger patient groups. The most recent literature provides evidence for deciding current suitability of TAVI as an alternative for surgery.

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9 List of Key Words/Abbreviations

ACC	American college of cardiology
ACE inhibitor	Angiotensin-converting enzyme inhibitor
AF	Atrial fibrillation
AHA	American heart association
AR	Aortic regurgitation
AS	Aortic stenosis
AVR	Aortic valve replacement (either by surgical or transcatheter approach)
BAV	Bicuspid aortic valve disease
BMI	Body mass index
BSA	Body surface area
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCS	Canadian Cardiovascular Society grading of angina
COPD	Chronic obstructive pulmonary disease
DSS	Decision support system
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
EuroSCORE	European system for cardiac operative risk evaluation
IF	Impact factor
LV	Left ventricle
METs	Metabolic equivalents
MI	Myocardial infarction
MR	Mitral regurgitation
MVP	Mitral valve prolapse
NYHA	New York Heart Association
PABV	Percutaneous aortic balloon valvuloplasty
PCI	Percutaneous coronary intervention
RASI	Renin-angiotensin system inhibitors
ROA	Regurgitant orifice area
SAVR	Surgical aortic valve replacement
STS	Society of Thoracic Surgeons
TAVI	Transcatheter aortic valve implantation
TAVR	Transcatheter aortic valve replacement
VHD	Valvular heart disease
WP	Work package

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ANNEX 1 RULES DISTILLED FROM LITERATURE CONCERNING AORTIC STENOSIS

1.1 Class: Mitral regurgitation

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
TAVI	moderate to severe mitral regurgitation, concomitant with aortic stenosis	IF moderate to severe mitral regurgitation is present at time of TAVI, THEN a higher early and late mortality is seen.	Approximately 20% of patients undergoing TAVI have moderate to severe mitral regurgitation. 1.7% of the US population have mitral regurgitation, while mitral regurgitation occurs for 9.3% in persons 75 years of age or older.	Journal IF 16.5 and 4.0 Meta-analysis literature, more than fifteen studies.	Nombela-Franco, JACC 63, 2643(2014). Boerlage-van Dijk, Int.J.Cardiol. 204, 95 (2016).

1.2 Class: Age, 90 years or older

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
TAVI	age 90 years or older, with aortic stenosis	IF the patient is 90 years or older and undergoes TAVI, THEN although recovery is slower, TAVI improves long term quality of life (1-year time point) to the same degree in nonagenarians as in patients < 90 years old.	16% of patients undergoing TAVI in the U.S. are 90 years or older.	Journal IF 16.5 Large (>3.500 patients), multi-center study in the US.	Arsalan, JACC 67, 1387(2016).
TAVI	age 90 years or older, with aortic stenosis	IF the patient is 90 years or older and undergoes TAVI, THEN rate of stroke, aortic valve reintervention, or myocardial infarction at 30-days and 1-year after TAVI is not different from patients < 90 years old.	16% of patients undergoing TAVI in the U.S. are 90 years or older.	Journal IF 16.5 Large (>3.500 patients), multi-center study in the US.	Arsalan, JACC 67, 1387(2016).
TAVI	age 90 years or older, with aortic stenosis	IF the patient is 90 years or older and undergoes TAVI, THEN 30-day and 1-year mortality rates are significantly higher among nonagenarians. However, nonagenarians have a higher Predicted Risk of Operative Mortality score, and therefore have similar ratios of observed to expected 30-day death.	16% of patients undergoing TAVI in the U.S. are 90 years or older.	Journal IF 16.5 Large (>3.500 patients), multi-center study in the US.	Arsalan, JACC 67, 1387(2016).
TAVI	age 90 years or older, with severe aortic stenosis	IF the patient is 90 years or older and undergoes TAVI, THEN 1-year mortality rates are similar to younger populations. Although nonagenarians had a higher STS score, they had a healthier clinical profile compared to younger patients, concerning diabetes, hyperlipidemia, prior coronary artery bypass and mean body mass index.	16% of patients undergoing TAVI in the U.S. are 90 years or older.	Journal IF 4.5 Medium (> 200, < 1000 patients), single center study in the US.	Escárcega, Am.Heart.J. 173, 118 (2016).

1.3 Class: Intermediate or low risk

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
TAVI	Intermediate and low risk patients with severe aortic stenosis	IF patients have an intermediate or low STS risk score and undergo TAVI, THEN TAVI is safe and leads to improved outcome	83% of patients with severe aortic stenosis undergoing TAVI are intermediate or low risk STS patients.	Journal IF 3.3 Large (>1.300 patients), multi-center study in Israel.	Barbash, Am.J.Cardiol 116, 1916 (2015).
TAVI vs SAVR	patients with severe aortic stenosis	IF patients are not selected on mortality risk and undergo TAVI, THEN there is no significant difference between TAVI and SAVR for the composite rate of death from any cause, stroke, or myocardial infarction after 1 year.	82% of the patients in this trial were considered low-risk.	Journal IF 16.5 Medium (>200, <1000 patients), multi-center study in Denmark and Sweden	Thyregod, JACC 65, 2184(2015).
TAVI vs SAVR	patients with severe aortic stenosis at intermediate risk	IF intermediate risk (STS 4-8%) patients undergo TAVI, THEN TAVI outcome is similar to surgical aortic-valve replacement with respect to death from any cause or disabling stroke at 2 years (19% with TAVI vs 21% with surgery). Looking only at procedures with transfemoral-access, TAVI resulted in lower rate of death from any cause or disabling stroke compared to surgery (16% vs 20%).		Journal IF 55.9 Large (>2000 patients), multi-center study in US and Canada (partner).	Leon, N.Engl.J. Med. 374, 1609 (2016).
TAVI vs SAVR	patients with severe aortic stenosis at intermediate risk	IF intermediate risk (STS 4-8%) patients undergo TAVI, THEN at 30 days major vascular complications were more frequent after TAVI compared to surgery (7.9% vs 5.0%) and other complications were lower, including life-threatening bleeding (10.4% vs 43.4%), acute kidney injury (1.3% vs 3.1%) and new-onset atrial fibrillation (9.1% vs 26.4%).		Journal IF 55.9 Large (>2000 patients), multi-center study in US and Canada (partner).	Leon, N.Engl.J. Med. 374, 1609 (2016).

1.4 Class: High risk

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
TAVI vs SAVR	high risk (STS score of at least 10%) patients with severe aortic stenosis	IF patients have a high risk score, THEN TAVI has a similar risk of death from any cause at 1 year compared to SAVR (appr. 25%)		Journal IF 55.9 Medium (>200, <1000 patients), multi-center study in US.	Smith, N.Engl.J. Med. 364, 2187(2011).
TAVI vs SAVR	high risk (STS score of at least 10%) patients with severe aortic stenosis	IF patients have a high-risk score, THEN TAVI has a higher risk of major stroke at 1 year and major vascular complications at 30 days compared to SAVR		Journal IF 55.9 Medium (>200, <1000 patients), multi-center study in US.	Smith, N.Engl.J. Med. 364, 2187(2011).
TAVI vs SAVR	high risk (STS score of at least 10%) patients with severe aortic stenosis	IF patients have a high-risk score, THEN SAVR has a higher risk of major bleeding and new-onset atrial fibrillation at 30 days compared to TAVI.		Journal IF 55.9 Medium (>200, <1000 patients), multi-center study in US.	Smith, N.Engl.J. Med. 364, 2187(2011).

1.5 Class: Frailty

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
TAVI	frail patients with high risk or inoperable, with severe aortic stenosis	IF patients have a frailty score more than the median value and undergo TAVI, THEN mortality and poor outcome (including quality of life) are increased 1 year after TAVI.	The prevalence of frailty in patients with severe aortic stenosis ranges from appr. 20-84%. 45% of the patients with high risk or deemed inoperable with severe aortic stenosis were considered frail.	Journal IF 3.3 (Green) Medium (>200, <1000 patients), multi-center study in US. (Green)	Rowe, Open Heart 1, e000033(2014). Green, Am.J.Cardiol 116, 264 (2015). Lindman et al. Clin. Geriatr. Med. 32 (2016)305
TAVI	frail patients with aortic stenosis	IF gait speed (5-m walk) is measured of patients scheduled to undergo TAVI, THEN lower gait speed is correlated with higher mortality risk at 30 days.	The prevalence of frailty in patients with severe aortic stenosis ranges from appr. 20-84%).	Journal IF 6.0 Large (>8000 patients), multi-center trial in US.	Alfredsson, Circulation 133, 1351 (2016). Lindman et al. Clin. Geriatr. Med. 32 (2016)305

1.6 Class: Diabetes

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
TAVI	diabetes mellitus, with severe aortic stenosis	IF patients have a high level of HbA1C (indicating poorly controlled DM) and undergo TAVI, THEN risk of mortality after TAVI is increased. Diabetes mellitus is not associated with increased mortality risk nor with increased complication rates.	41% of the patients with severe aortic stenosis have diabetes mellitus, based on HbA1c levels. Half of these patients are insulin treated. Population: in the US, in 2012, 8.5% of the population had diagnosed diabetes mellitus, 3.3% had undiagnosed diabetes mellitus.	Journal IF 3.3 Medium (>200, <1000 patients), single-center study in Israel.	Chorin, Am.J.Cardiol 116, 1898 (2015). Mozaffarian Circulation 131, e29 (2015).
TAVI	High risk patients with severe aortic stenosis and diabetes mellitus	IF patients have insulin-treated diabetes mellitus and undergo TAVI, THEN midterm all-cause mortality after TAVI is increased. Mortality is not increased in patients with orally treated diabetes mellitus. Other independent predictors of mortality found were chronic lung disease, chronic renal failure, frailty, and alternative access route (transapical /transaortic/ subclavian).	Approximately one third of patients undergoing TAVI have diabetes mellitus, and between a third to half of them have insulin-treated diabetes mellitus.	Journal IF 3.3 Medium (>200, <1000 patients), single-center study in US.	Abramowitz Am.J.Cardiol 117, 1636 (2016).

1.7 Class: COPD / Lung disease

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
TAVI	patients with severe aortic stenosis and COPD	IF patients with severe aortic stenosis undergoing TAVI have COPD, THEN they have increased risk of developing acute kidney injury.	21-23% of patients with severe aortic stenosis develop acute kidney injury after TAVI	Journal IF appr. 2	Koifman, Cath.Cardio vasc.Int. 87, 523(2016).
TAVI	patients with severe aortic stenosis	IF patients with severe aortic stenosis undergoing TAVI develop acute kidney injury, THEN they have increased long-term mortality rates.	21-23% of patients with severe aortic stenosis develop acute kidney injury after TAVI	Journal IF appr. 2	Koifman, Cath.Cardio vasc.Int. 87, 523(2016).
TAVI	patients with symptomatic severe aortic stenosis and COPD	IF patients with severe aortic stenosis undergoing TAVI have COPD, THEN there is a significant association between the severity of COPD and the long-term all-cause mortality.	40% of the patients in the study cohort who underwent TAVI had moderate to very severe COPD.	Journal IF 4.4 Medium (>200, <1000 patients), single-center prospective study in Germany.	Gotzmann, Am.Heart J. 170, 837 (2015).
TAVI	patients with symptomatic severe aortic stenosis and restrictive ventilatory disease	IF patients with severe aortic stenosis undergo TAVI , THEN having restrictive ventilatory disease is an independent predictor of all-cause mortality and 30-day mortality.	25% of the patients in the study cohort who underwent TAVI had restrictive ventilatory disease.	Journal IF 4.4 Medium (>200, <1000 patients), single-center prospective study in Germany.	Gotzmann, Am.Heart J. 170, 837 (2015).
TAVI	patients with symptomatic severe aortic stenosis and oxygen dependency	IF patients with severe aortic stenosis undergo TAVI, THEN having oxygen dependency is an independent predictor of all-cause mortality.	7% of the patients in the study cohort who underwent TAVI had oxygen dependency.	Journal IF 4.4 Medium (>200, <1000 patients), single-center prospective study in Germany.	Gotzmann, Am.Heart J. 170, 837 (2015).
TAVI	patients with symptomatic severe aortic stenosis and chronic lung disease	IF patients with severe aortic stenosis undergoing TAVI have chronic lung disease, THEN clinical improvement after TAVI does not differ significantly from patients without chronic lung disease.	21-43% of patients with aortic stenosis undergoing TAVI have chronic lung disease according to literature (this study cohort: 43%).	Journal IF 16.5 Large (>2500 patients), multi-center study in US.	Dvir, JACC 63, 269 (2014).

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
TAVI vs medical therapy	inoperable patients with symptomatic severe aortic stenosis and chronic lung disease	IF inoperable patients with severe aortic stenosis have chronic lung disease, THEN TAVI is superior to medical therapy.	21-43% of patients with aortic stenosis undergoing TAVI have chronic lung disease according to literature (this study cohort: 43%).	Journal IF 16.5 Large (>2500 patients), multi-center study in US.	Dvir, JACC 63, 269 (2014).
TAVI vs SAVR	high-risk patients with symptomatic severe aortic stenosis and chronic lung disease	IF high-risk patients with severe aortic stenosis have chronic lung disease, THEN TAVI has similar clinical outcomes when compared to SAVR.	21-43% of patients with aortic stenosis undergoing TAVI have chronic lung disease according to literature (this study cohort: 43%).	Journal IF 16.5 Large (>2500 patients), multi-center study in US.	Dvir, JACC 63, 269 (2014).
TAVI	patients with symptomatic severe aortic stenosis and chronic lung disease	IF patients with severe aortic stenosis undergoing TAVI have chronic lung disease, THEN oxygen-dependency, poor mobility (6-min walk < 50m), renal disease, low BMI, higher mean pulmonary artery pressure, and higher aortic valve gradient are independent predictors for 1-year all-cause mortality. Only 50% were alive with good functional status after 1-year follow-up compared to appr. 70% with chronic lung disease and no oxygen-dependency and appr. 75% without chronic lung disease.	21-43% of patients with aortic stenosis undergoing TAVI have chronic lung disease according to literature (this study cohort: 43%).	Journal IF 16.5 Large (>2500 patients), multi-center study in US.	Dvir, JACC 63, 269 (2014).

1.8 Class: STROKE

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
TAVI	patients with aortic stenosis	IF patients undergo TAVI, THEN female sex, chronic kidney disease, enrollment date (low vs. high experience – early or later in study), and new-onset atrial fibrillation are predictors of cerebrovascular events.	Cerebrovascular events post TAVI occur in 1-11% of the cases.	Journal IF 16.5 Meta-analysis literature, sixty four studies.	Auffret, JACC 68, 673(2016).
TAVI	high risk patients with severe aortic stenosis	IF patients undergo TAVI, THEN new-onset atrial fibrillation correlates with higher rates of stroke at two years compared with sinus rhythm.	In the study cohort, 36% of the patients had pre-existing atrial fibrillation.	Journal IF 7.6 Large (>1900 patients), multi-center study mainly in Europe.	Tarantini, JACC: Cardiovasc.I Int. 9, 937 (2016).
TAVI	patients with severe aortic stenosis	IF patients undergo TAVI, THEN the presence of carotid artery stenosis is not associated with all-cause mortality, stroke, myocardial infarction or readmission for heart failure.	In the study cohort, 31% of the patients undergoing TAVI had any degree of carotid artery stenosis.	Journal IF 4.0 Medium (>200, <1000 patients), single-center study in Israel.	Ben-Shoshan, Int.J.Cardiol. 227, 278 (2017).

1.9 Class: Atrial fibrillation

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
TAVI	high risk patients with severe aortic stenosis	IF patients undergo TAVI, THEN pre-existing atrial fibrillation and new-onset atrial fibrillation correlate with worse clinical outcomes compared with patients in sinus rhythm, including all-cause death, cardiac death, and bleeding events. Independent predictors of new-onset atrial fibrillation were age, NYHA class III or IV, nontransfemoral access route, and balloon post-dilation.	In the study cohort, 36% of the patients had pre-existing atrial fibrillation.	Journal IF 7.6 Large (>1900 patients), multi-center study mainly in Europe.	Tarantini, JACC: Cardiovasc.Int. 9, 937 (2016).

1.10 Class: Previous CABG

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
TAVI vs SAVR	patients with severe aortic stenosis and previous CABG	IF patients with previous CABG undergo TAVI, THEN perioperative, mid-term all cause and cardiovascular mortality is similar to SAVR.		Journal IF 4.0 Meta-analysis literature, five studies.	Ando, Int.J.Cardiol. 215, 14 (2016).
TAVI vs SAVR	patients with severe aortic stenosis and previous CABG	IF patients with previous CABG undergo TAVI, THEN pacemaker implantation rates are higher and hospital stays are shorter compared to SAVR.		Journal IF 4.0 Meta-analysis literature, five studies.	Ando, Int.J.Cardiol. 215, 14 (2016).

1.11 Class: Coronary artery disease

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
PCI and SAVR	patients with moderate or severe aortic stenosis and significant coronary artery disease	IF patients have moderate to severe aortic stenosis and significant coronary artery disease, THEN combined CABG and AVR is associated with the best outcome at 5 years. In patients in whom combined CABG and AVR is not performed, either percutaneous coronary intervention or AVR significantly improves survival at 5 years as compared to medical therapy.	Aortic stenosis is associated with significant coronary artery disease in up to 50% of the cases. In this study, in 51% of the cases the adopted treatment strategies diverged from the current recommendation in the Guidelines to treat with combined AVR and CABG.	Journal IF 3.2 Medium (>200, <1000 patients), single center study in Belgium	Di Gioia, J.Cardiovasc .Trans.Res. 9, 145 (2016).
PCI and TAVI	patients with aortic stenosis undergoing TAVI	IF patients undergo TAVI and concomitant percutaneous coronary intervention, THEN significantly higher rates of in-hospital mortality and complications: vascular injury requiring surgery, cardiac, respiratory, and infectious, were witnessed compared to patients undergoing TAVI only.	In the study cohort, 66% of the patients undergoing TAVI had coronary artery disease, while 84% of the patients undergoing TAVI and concomitant percutaneous coronary intervention had coronary artery disease.	Journal IF 3.3 Large (>22.000 patients), multi-center study in US	Singh, Am.J.Cardiol 118, 1698 (2016).

1.12 Class: Congestive heart failure

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
SAVR	patients with severe aortic stenosis	IF patients with severe aortic stenosis and left ventricular dysfunction undergo SAVR, THEN preoperative left ventricular end-diastolic diameter of <55 mm was associated with more frequent left ventricular recovery. Left ventricular recovery correlated with better survival and freedom from heart failure in patients with aortic stenosis.	In the study cohort, 26% of the patients with severe aortic stenosis had left ventricular dysfunction.	Journal IF 6.0 Large (>2000 patients), single center study in Canada.	Une, Circulation 132, 741 (2015).

1.13 Class: Renal failure

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
TAVI	high-risk patients with severe aortic stenosis	IF patients undergo TAVI, THEN predictors of 1-year mortality are non-transfemoral access, baseline liver disease and renal failure (high risk, >50%) and cardiovascular conditions such as moderate/severe tricuspid regurgitation, porcelain aorta, atrial fibrillation, coronary artery disease and NYHA functional class III/IV (risk 20-50%).		Journal IF 7.6 Large (>2700 patients), multi-center study in US and Canada (partner).	Schymik, JACC: Cardiovasc.Int. 8, 657 (2015).

1.14 Class: Pacemaker

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
TAVI	high-risk patients with severe aortic stenosis	IF patients undergo TAVI and had no previous pacemaker implantation, THEN left ventricular outflow tract oversizing is associated with permanent pacemaker implantation	TAVI is associated with a higher need for permanent pacemaker implantation compared to surgery, with frequencies varying from 2 to 51%.	journal IF 4.0 Medium (>200, <1000 patients), single center study in The Netherlands.	Rodríguez-Olivares, Int.J.Cardiol. 216, 9 (2016).

1.15 Class: Heart Rate

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
TAVI	inoperable or high-risk patients with severe aortic stenosis	IF patients undergo TAVI, THEN baseline or discharge high resting heart rate was not associated with overall or cardiovascular mortality two years after TAVI	37% of the patients in this study had a high resting heart rate (>77 bpm) before TAVI.	Journal IF 3.9 Medium (>200,<1000 patients), single center study in Switzerland	O'Sullivan, EuroInterv. 12, 490 (2016).
no treatment	patients with asymptomatic mild-to-moderate aortic stenosis	IF patients have asymptomatic mild-to-moderate aortic stenosis, elevated resting heart rate is associated with major cardiovascular events and cardiovascular death		Journal IF 4.0 Large (>1500 patients), multi-center study in Europe.	Greve, Int.J.Cardiol. 180, 122 (2015).

ANNEX 2 RULES DISTILLED FROM LITERATURE CONCERNING MITRAL REGURGITATION

2.1 Class: Degenerative mitral regurgitation

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
surgery repair vs replacement	patients with severe degenerative mitral regurgitation with a flail leaflet	IF patients with degenerative mitral regurgitation with a flail leaflet undergo mitral valve repair surgery, THEN outcome is lower operative mortality, better long-term survival, and fewer valve-related complications compared to mitral valve replacement.	In this study cohort, 89% of the patients underwent mitral valve repair.	Journal IF 6.0 Large (>1900 patients), multi-center study in US and Europe	Lazam, Circulation 135, 422 (2017).
medical therapy	patients with moderate to severe degenerative mitral regurgitation	IF patients with degenerative mitral regurgitation receive medical treatment (conservative management), THEN BNPratio is a powerful, independent, incremental predictor of long-term mortality. After initial surgical treatment BNP activation did not impose excess long-term mortality.	In this study cohort, 58% of the patients received medical treatment while 42% received immediate mitral surgery.	Journal IF 16.5 Large (>1300 patients), multi-center study in US and Europe.	Clavel, JACC 68, 1297 (2016).
surgery	patients with severe organic mitral regurgitation	IF patients undergo surgery, THEN guideline-based indications of symptoms, ejection fraction < 60%, or end-systolic diameter >= 40 mm (class I trigger) and guideline-based indications of atrial fibrillation or pulmonary hypertension (class II clinical complication trigger) is associated with higher postoperative long-term mortality, and heart failure rates, despite low operative risk and high repair rates. Conversely, guideline-based indication of high probability of repair (early class II trigger) is associated with improved survival and low heart failure risk and should be the preferred strategy.	In this study cohort, 53% of patients had one or more class I trigger, 13% had class I with complications trigger, and 34% had early class trigger.	Journal IF 4.2 Large (>1500 patients), multi-center study in US.	Enriquez-Sarano, J.Thorac.Cardiovasc.Surg 150, 50 (2015).

2.2 Class: Pulmonary hypertension - Degenerative mitral regurgitation

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
surgery	patients with significant primary mitral regurgitation and preserved left ventricular ejection fraction	IF patients with grade >=3 primary mitral regurgitation and preserved left ventricular ejection fraction undergo surgery, THEN baseline right ventricular systolic pressure is independently and progressively associated with reduced long-term survival.	In this study cohort, 32% of the patients had right ventricular systolic pressure of 35-50 mm Hg and 15% had higher than 50 mm Hg.	Journal IF 16.5 Large (>1300 patients), single center study in US.	Mentias, JACC 67, 2952(2016).
surgery	patients with degenerative mitral regurgitation	IF patients undergo mitral valve repair surgery, THEN the presence of preoperative pulmonary hypertension increased the risk of early postoperative left ventricular dysfunction by almost twofold.	In the study cohort, 58% of patients were symptomatic, 13% had pulmonary artery systolic pressure > 50 mm Hg, and 38% of patients developed postoperative left ventricular dysfunction.	Journal IF 4.2 Medium (>200, <1000 patients), single center study in US	Varghese, J.Thorac.Cardiovasc.Surg 148, 422 (2014).

2.3 Class: Functional mitral regurgitation

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
MitraClip	patients with ischemic or nonischemic functional mitral regurgitation	IF patients with functional mitral regurgitation undergo MitraClip intervention, THEN acute procedural success is overall high (96%) and inhospital mortality is low (2%) without significant differences between ischemic and non-ischemic etiologies.	72% of patients receiving the MitraClip in this registry had functional mitral regurgitation. 52% of these patients had ischemic MR and 48% had non-ischemic MR.	Journal IF 3.3 Medium (>200, <1000 patients), multi-center study in 8 countries in Europe	Pighi, Am.J.Cardiol 117, 630 (2017).
MitraClip	patients with ischemic or nonischemic functional mitral regurgitation	IF patients with functional mitral regurgitation undergo MitraClip intervention, THEN 1-year mortality and rehospitalization were not significantly different between ischemic and non-ischemic etiologies.	72% of patients receiving the MitraClip in this registry had functional mitral regurgitation. 52% of these patients had ischemic MR and 48% had non-ischemic MR.	Journal IF 3.3 Medium (>200, <1000 patients), multi-center study in 8 countries in Europe	Pighi, Am.J.Cardiol 117, 630 (2017).

2.4 Class: MI - Functional mitral regurgitation

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
medical therapy	patients with myocardial infarction and secondary mitral regurgitation	IF patients with myocardial infarction have secondary mitral regurgitation, THEN use of renin-angiotensin system inhibitors (RASI) was associated with better long-term prognosis. Survival was significantly associated with severity of mitral regurgitation.	In this study cohort, 21% of the patients with myocardial infarction had moderate secondary mitral regurgitation and 10% had severe secondary mitral regurgitation. In patients with moderate or severe secondary mitral regurgitation, 44% received renin-angiotensin system inhibitors.	Journal IF 5.7 Medium (>200, <1000 patients), single center study in Japan	Okura, Heart 102, 694 (2016).

2.5 Class: CABG - Functional mitral regurgitation

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
surgery	patients with ischemic moderate and severe functional mitral regurgitation	IF patients with ischemic mitral regurgitation undergo CABG with or without mitral valve surgery, THEN this is associated with lower mortality than either percutaneous coronary intervention or medical treatment alone.	In this study cohort, 43% of the patients with significant coronary artery disease had mitral regurgitation grade ≥ 2.	Journal IF 6.0 Large (>4900 patients), single center study in US	Castleberry, Circulation 129, 2547 (2014).
surgery	patients with moderate ischemic mitral regurgitation	IF patients with moderate ischemic regurgitation undergo CABG and mitral valve repair, THEN left ventricular reverse remodelling at 2 years, survival, overall adverse events or readmissions are not significantly different from CABG alone while neurologic events and supraventricular arrhythmias were more frequent and moderate or severe residual mitral regurgitation was lower.	Ischemic mitral regurgitation of moderate severity develops in approximately 10% of patients after myocardial infarction.	Journal IF 55.9 Medium (>200, <1000 patients), multi-center study in US and Canada	Michler, N.Engl.J. Med. 374, 1932(2016).

2.6 Class: LV dysfunction – Functional mitral regurgitation

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
surgery	patients with moderate or severe functional mitral regurgitation and severe LV dysfunction	IF patients with functional mitral regurgitation and severe LV dysfunction undergo mitral valve surgery, THEN event-free survival is higher compared to medical therapy.		Journal IF 15.2 Large (>1400 patients), single center study in US	Samad, Eur. Heart J. 36, 2733(2015).

2.7 Class: Coronary artery disease

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
MitraClip	high risk or inoperable patients with (moderate-to-severe and) severe mitral regurgitation and coronary artery disease	IF high risk patients with coronary artery disease undergo MitraClip intervention, THEN at 30-days the composite endpoint of death, myocardial infarction or stroke occurred in 10% of patients and at 1-year follow-up occurred in 30% of patients.	78% of the patients in this trial with mitral regurgitation or cardiac comorbidities had coronary artery disease.	Jjournal IF 4.3 Medium (>200, <1000 patients), multi-center study in Germany	Schwencke, Clin.Res. Cardiol.106, 249(2017).
MitraClip	high risk or inoperable patients with (moderate-to-severe and) severe mitral regurgitation and coronary artery disease	IF high risk patients with coronary artery disease undergo MitraClip intervention, THEN procedural success, defined as post-procedural MR of less than or equal to grade II, is high (98%).	78% of the patients in this trial with mitral regurgitation or cardiac comorbidities had coronary artery disease.	Journal IF 4.3 Medium (>200, <1000 patients), multi-center study in Germany	Schwencke, Clin.Res. Cardiol.106, 249(2017).

2.8 Class: MitraClip

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
MitraClip vs surgery	patients with moderate-to-severe and severe mitral regurgitation	IF patients undergo mitral valve repair (irrespective of intervention, percutaneous or surgery), THEN functional mitral regurgitation and advanced age are important predictors of decreased survival.		Journal IF 16.5 Medium (>200, <1000 patients), multi-center study in US.	Feldman, JACC 66, 2844(2015).
MitraClip vs surgery	patients with moderate-to-severe and severe mitral regurgitation	IF patients undergo percutaneous mitral valve repair with a MitraClip, THEN at 5-year follow-up comparable low rates of surgery for mitral valve dysfunction are found compared to surgery and survival rates are the same.		Journal IF 16.5 Medium (>200, <1000 patients), multi-center study in US.	Feldman, JACC 66, 2844(2015).
MitraClip	patients with moderate-to-severe and severe mitral regurgitation	IF patients undergo percutaneous mitral valve repair with a MitraClip, THEN ischemic functional ethiology, severely dilated ventricles end-systolic volume > 110 mL), or advanced heart failure (NYHA class IV) are independent predictors of all-cause death and rehospitalization for heart failure.	In the study cohort, 45% of the patients had functional ischemic mitral regurgitation.	Journal IF 4.5 Medium (>200, <1000 patients), single center study in Italy.	Capodanno, Am.Heart J. 170, 187 (2015).
MitraClip	patients with severe mitral regurgitation	IF patients undergo MitraClip treatment, THEN predictors of 1-year mortality were NYHA class IV, anaemia, previous aortic valve intervention, serum creatinine ≥1.5 mg/dL, peripheral artery disease, left ventricular ejection fraction, severe tricuspid regurgitation, and procedural failure.	Of patients with severe symptomatic mitral regurgitation, appr. 50% are denied surgical mitral valve intervention. In the study cohort, 71% of the patients had secondary mitral regurgitation.	Journal IF 15.2 Medium (>200, <1000 patients), single center study in Germany.	Puls, Eur.Heart J. 37, 703 (2016).

2.9 Class: Age

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
surgery	patients with mitral regurgitation	IF patients are octogenarians, THEN surgical treatment is associated with high perioperative mortality and poor long-term survival with an uncertain benefit on quality of life.		Journal IF 3.9 Meta-analysis literature, sixteen studies.	Andalib, EuroInterv. 9, 1225 (2014).

2.10 Class: High risk

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
MitraClip vs medical treatment	high-risk patients with moderate to severe or severe mitral regurgitation	IF high-risk patients undergo percutaneous mitral valve repair with a MitraClip, THEN 30-day and 1 year mortality is significantly better compared with medical treatment.	In the study cohort, 70% of the MitraClip high risk patients had functional mitral regurgitation and 30% had degenerative mitral regurgitation.	Journal IF 4.5 Medium (>200, <1000 patients), multi-center study in US.	Velazquez, Am.Heart J. 170, 1050 (2015).
MitraClip vs surgery vs conservative	high-risk patients with moderate to severe or severe mitral regurgitation	IF high-risk patients undergo percutaneous mitral valve repair with a MitraClip, THEN at 3-year follow-up survival rates are similar compared with those undergoing surgery, with both showing survival benefit compared with conservative treatment.		Journal IF 7.6 Medium (>200, <1000 patients), single center study in The Netherlands.	Swaans, JACC: Cardiovasc.Intervent. 7, 875 (2014).
MitraClip	high-risk patients with symptomatic primary mitral regurgitation grade >=3	IF high-risk patients undergo percutaneous mitral valve repair with a MitraClip, THEN procedural success was achieved in appr. 91% of patients and the majority of patients were discharged home with moderate or less mitral regurgitation.	In the study cohort, severe symptoms of heart failure (NYHA class III or IV) were prevalent in 86% of patients and frailty was an indication for the procedure in 57% of patients.	Journal IF 16.5 Medium (>200, <1000 patients), multi-center study in US.	Sorajja, J.Am.Coll. Cardiol. 67, 1129(2016).

2.11 Class: Multiple non-cardiac comorbidities

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
MitraClip	patients with moderate or severe mitral regurgitation and multiple non-cardiac comorbidities	IF patients with 2 or more non-cardiac comorbidities undergo MitraClip intervention, THEN 30-day rate of death of all causes, stroke, and myocardial infarction is higher compared to patients with 1 or none non-cardiac comorbidities.		Journal IF 4.3 Medium (>200, <1000 patients), multi-center study in Germany.	Zuern, Clin.Res. Cardiol. 104, 1044 (2015).

2.12 Class: Renal failure

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
MitraClip	patients with moderate or severe mitral regurgitation and multiple non-cardiac comorbidities	IF patients with 2 or more non-cardiac comorbidities undergo MitraClip intervention, THEN renal failure is an independent predictor of 30-day outcome (death of all causes, stroke, and myocardial infarction).		Journal IF 4.3 Medium (>200, <1000 patients), multi-center study in Germany.	Zuern, Clin.Res. Cardiol. 104, 1044 (2015).

2.13 Class: Chronic kidney disease

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
MitraClip	high-risk patients with symptoms or signs of left ventricular deterioration and mitral regurgitation grade 3 or more	IF patients undergo MitraClip treatment, THEN baseline chronic kidney disease is an independent predictor of worse mortality, surgery for mitral valve dysfunction, or grade >=3 mitral regurgitation.	In the study cohort, 53% of the patients presented with baseline chronic kidney disease.	Journal IF 3.9 Medium (>200, <1000 patients), single center study in Italy.	Ohno, EuroInterv. 11, e1649 (2016).
MitraClip	patients with moderate-severe or severe mitral regurgitation	IF patients undergo MitraClip treatment and have chronic kidney disease, THEN chronic kidney disease severity was strongly associated with worse 1-year survival. Reduction in mitral regurgitation severity after MitraClip repair was associated with small improvement in estimated glomerular filtration rate.	In the study cohort, 43% of the patients had chronic kidney disease stage 3 and 6% had stage 4 or 5.	Journal IF 5.7 Medium (>200, <1000 patients), multi-center study in US.	Wang, Circulation Cardiovasc. Interv. 8, e001349 (2015).

2.14 Class: Diabetes

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
no intervention	patients with type 2 diabetes and mild or moderate-to-severe mitral regurgitation	IF patients with type 2 diabetes have mitral regurgitation, THEN the severity of mitral regurgitation, even if mild, was strongly and progressively associated with an increased risk of both all-cause and cardiovascular mortality.	In the study cohort, 25% of the patients with type 2 diabetes had mild regurgitation and 7% had moderate or severe mitral regurgitation.	Journal IF 5.6 Medium (>200, <1000 patients), single center study in Italy.	Rossi, Am.J.Med. 130, 70 (2017).

2.15 Class: Atrial fibrillation

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
MitraClip	patients with severe mitral regurgitation	IF patients undergo MitraClip intervention, THEN 12-month survival is lower in patients with atrial fibrillation compared to sinus rhythm while the overall cumulative major adverse cardio-cerebrovascular event rate did not differ.	In the study cohort, 48% of the patients had atrial fibrillation.	Journal IF 3.9 Medium (>200, <1000 patients), multi-center study in Germany.	Jabs, EuroInterv. 12, 1697 (2017).
surgery	patients with degenerative mitral regurgitation	IF patients undergo mitral valve repair surgery, THEN a history of atrial fibrillation increased the risk of early postoperative left ventricular dysfunction by almost twofold.	In the study cohort, 58% of patients were symptomatic, 20% had atrial fibrillation, and 38% of patients developed postoperative left ventricular dysfunction.	Journal IF 4.2 Medium (>200, <1000 patients), single center study in US	Varghese, J. Thorac.Cardiovasc.Surg. 148, 422 (2014).

2.16 Class: Hypertrophic obstructive cardiomyopathy

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
surgery	patients with hypertrophic obstructive cardiomyopathy and mitral regurgitation grade 3 or more	IF patients with hypertrophic obstructive cardiomyopathy and mitral regurgitation (not intrinsic) undergo septal myectomy, THEN mitral regurgitation is relieved in most cases (more than 96%) without concomitant mitral regurgitation surgery.	In the study cohort, 58% of the patients who underwent septal myectomy had mitral regurgitation grade 3 or 4.	Journal IF 7.6 Large (>1000 patients), single center study in US.	Hong, JACC 68, 1497 (2016).

2.17 Class: Exercise capacity

INTERVENTION	**FACTOR** relevant for clinical decision	**RULE** for intervention, factor	**OCCURRENCE** of factor in population	level of **EVIDENCE**	**References** Annex 3
surgery or no intervention	patients with asymptomatic degenerative mitral regurgitation grade 3 or more	IF patients undergo exercise echocardiography, THEN lower percentage of age/sex-predicted metabolic equivalents and lower heart rate recovery after exercise were independently associated with adverse long-term clinical outcomes, in addition to known factors like atrial fibrillation, reduced left ventricular ejection fraction, and high resting right ventricular systolic pressure.	In the study cohort, 12% of patients achieved age/sex-predicted metabolic equivalents (METs) of <85%, 18% achieved 86%-100% age/sex-predicted METs, and 70% achieved >100% age/sex-predicted METs. 65% of patients had mitral valve surgery.	Journal IF 6.0 Medium (>200, <1000 patients), single center study in US.	Naji, Circulation 129, 1310 (2014).

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ANNEX 4 VARIABLES USED IN COMMON RISK SCORES

4.1 STS risk model variables

Variable	Unit
Patient age	Value
Sex	Male / Female
Height (cm)	Value
Weight (kg)	Value
Hemo Data-EF Done	Yes / no
Heart Failure within two weeks	Yes / no / unknown
Race documented	Yes / no / patient declined to disclose
Hispanic or latino or Spanish ethnicity	Yes / no / not documented
RF-Renal Fail-Dialysis	Yes / no / unknown
RF-last creat level	Value
Cardiac presentation/symptoms – at time of surgery	Stable angina / unstable angina / angina equivalent / non-ST elevation MI (non-STEMI) / ST elevation MI (STEMI) / other / no symptoms
Cardiac symptoms – at time of surgery	Stable angina / unstable angina / angina equivalent / non-ST elevation MI (non-STEMI) / ST elevation MI (STEMI) / other / no symptoms
Prior MI	Yes / no / unknown
Cardiac Arrhythmia	Yes / no / unknown
RF-chronic lung disease	Mild / moderate / severe / lung disease
RF-cerebrovascular dis	Yes / no / unknown
RF-peripheral arterial disease	Yes / no / unknown
RF-diabetes	Yes / no / unknown
RF-hypertension	Yes / no / unknown

Variable	Unit
RF-immunocompromise	Yes / no / unknown
RF-endocarditis	Yes / no
Coronary anatomy/disease known	Yes / no
status	Elective / urgent / emergent / emergent salvage
resuscitation	Yes-within 1 hour of the start of the procedure / yes-more than 1 hour but less than 24 hours of the start of the procedure – no
Cardiogenic shock	Yes-at the time of the procedure / yes-not at the time of the procedure but within prior 24 hours / no
IABP	Yes / no
Meds-inotropes	Yes / no
Prev cardiac intervent	Yes / no / unknown
VD-mitral	Yes / no
VD-aortic	Yes / no
VD-insuff-tricuspid	Trivial/trace / mild / moderate / severe / none / not documented
VD-insuff-aortic	Trivial/trace / mild / moderate / severe / none / not documented
Incidence	First cardiovascular surgery / first re-op cardiovascular surgery / second re-op cardiovascular surgery / third re-op cardiovascular surgery / fourth or more re-op cardiovascular surgery

4.2 EuroSCORE II risk model variables

Variable	Unit
Age	Years
Gender	Male / female
Renal impairment	Normal (CC >85ml/min) / moderate (CC >50 & <85) / severe (CC <50) / dialysis (regardless of CC)
Extracardiac arteriopathy	Yes / no
Previous cardiac surgery	Yes / no
Chronic lung disease	Yes / no
Active endocarditis	Yes / no
Critical preoperative state	Yes / no
Diabetes on insulin	Yes / no
NYHA	I /II / III / IV
CCS class 4 angina	Yes / no
LV function	Good (LVEF > 50%) / moderate (LVEF 31%-50%) / poor (LVEF 21%-30%) / very poor (LVEF 20% or less)
Recent MI	Yes /no
Pulmonary hypertension	No / moderate (PA systolic 31-55 mmHg)
Urgency	Elective / urgent / emergency / salvage
Weight of the intervention	Isolated CABG / single non-CABG / 2 procedures / 3 procedures
Surgery on thoracic aorta	Yes / no