Improving treatment planning in cardiac intervention

Financial support by the Dutch Heart Foundation, Pfizer B.V., Boehringer Ingelheim B.V., Servier Nederland Farma B.V., ChipSoft Nederland B.V., and FEops, for the publication of this thesis is gratefully acknowledged

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The crucial role of the Heart Team

Optimalisatie van de behandelstrategie bij cardiale interventies

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. H. R.B.M. Kummeling, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 1 november 2018 des middags te 2.30 uur

door

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geboren op 2 februari 1988 te Bodø, Noorwegen

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Take one step to the side and its all absurd

-Leonard Cohen

In this thesis, challenges associated with interventions in cardiac disease are discussed. In the age of personalized medicine and informed decision making the role of adequate treatment planning is steadily increasing. Novel techniques and insights are developed at a rapid pace and contribute to improved procedural success rates and patient safety. Despite a multitude of advancements in recent years, peri-procedural challenges are still at large and need to be addressed. As a result, the importance of the multidisciplinary heart team is growing and cannot be exonerated from clinical practice. New techniques, multidisciplinary approaches, and computer-based simulations are developing and are inseparable from the future. New insights present with new challenges, but new challenges may also provide new insights.

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General Introduction

PART ONE - MITRAL REGURGITATION

Epidemiology of valvular disease

Valvular heart disease is one of the leading causes of cardiac mortality and morbidity worldwide, with a prevalence of moderate to severe valve disease of 2.5% in the general population. With increasing age, prevalence increases exponentially (13% above age 75), mostly of degenerative origin(in developing countries)(Figure 1)[1]. In contrast, valvular disease in developing countries is mainly caused by rheumatic disease[2]. Among patients with moderate to severe valve disease, aortic and mitral valve disease are diagnosed most frequently, with the highest prevalence for aortic stenosis (AS)[3] and mitral regurgitation (MR)[1].

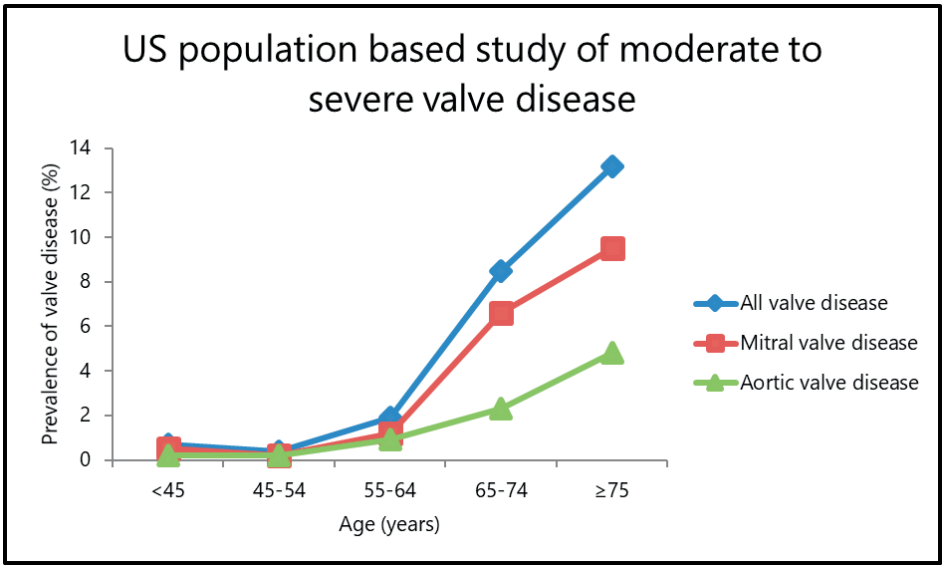


Figure 1. US population based study of moderate to severe valve disease. Adapted from Nkomo et al. Burden of Valvular Heart Diseases: a Population-Based Study. Lancet 2006; 368: 1005-11.

Diagnosis of valvular pathology

Although physical examination may be suggestive of valvular disease; diagnosis, degree of severity, and feasibility of repair rely on echocardiographic analysis. Initial assessment of severity, function, and dimensions are performed using trans-thoracic echocardiography (TTE), while trans-esophageal echocardiography (TOE) usually assesses the mechanism of the valvular pathology and feasibility of potential intervention. Despite advancements in echocardiographic techniques, the diagnosis of valvular disease severity remains challenging and is largely dependent on quality of acquired images and a combination of qualitative, semiquantitative, and quantitative parameters. Therefore, grading of severity is prone to subjective interpretation and subsequent misdiagnosis. In addition, due to logistical and time constraints, not all param-

eters may be included in routine clinical practice, i.e. effective regurgitant orifice area (EROA), or proximal isovelocity surface area (PISA)[4,5].

Decisions regarding choice of therapy and timing of intervention are ideally discussed in the heart team, a multidisciplinary team consisting of at least a cardiologist and a cardiothoracic surgeon. Indeed, the implementation of a heart team at cardiothoracic centers has been incorporated in the most recent European Guidelines[6].

The indication for medical treatment and/or surgical intervention is largely based on the presence of several clinical and echocardiographic parameters, such as symptomatic signs of cardiac decompensation, new-onset arrhythmias, or deterioration of left-or right ventricular function. In secondary valve disease, i.e. functional MR due to annular dilation, an initial medicinal approach may be preferred if a consequent reverse remodeling and improvement in valvular disease is anticipated. In primary (organic) valve disease medicinal treatment may alleviate symptoms, however surgical intervention may be the only therapeutic option.

Naturally, the risks of surgical intervention need to be weighed against the benefits. Factors such as comorbidity, feasibility of repair, and prognosis bring considerable weight to the balancing scale and need to be considered. Although surgical repair or replacement are the preferred standard of care, alternative options are available for patients that are deemed unfit for surgery, i.e. patients with significant comorbidities or those at high surgical risk[6]. For example, percutaneous catheter based intervention through balloon aortic/mitral/pulmonic[7] valvotomy, transcatheter aortic valve replacement[8] (TAVI), or MitraClip[9] placement are widely accepted alternatives to traditional surgery and are part of routine practice at most cardiothoracic centers[10].

MitraClip therapy for mitral regurgitation

Percutaneous edge-to-edge repair with the MitraClip system (Abbott Vascular Structural, Menlo Park, California, USA) is based on the edge-to-edge technique developed by Alfieri in the 90's and is applied both in functional and organic MR[11,12]. Following venous access, the catheter is advanced through the inferior vena cava to the right atrium and a transseptal puncture is performed to reach the left atrium. The clip is lowered past the mitral valve into the left ventricle. After grasping both valve leaflets the clip is closed, creating a double orifice and a subsequent reduction in MR[13]. Although no convincing benefit in terms of survival has yet been demonstrated, the MitraClip has been shown to be safe and improve clinical outcome in patients with moderate to severe MR[9,14]. In the EVEREST II study, 12-month survival in MitraClip patients was slightly superior to a control group (76% versus 55%, p=0.047), and a marked improvement was seen in left ventricular (LV) reverse remodeling, New York Heart Association (NYHA) heart failure class, and Quality of life[14].

Procedural success rates are dependent on several factors, including center expertise, individual patient characteristics, and advancements in technology. In particular, location of clip placement and number of clips to be placed are important factors that determine residual MR and may therefore have a significant impact on clinical improvement and cost effectiveness.

PART TWO – CARCINOID HEART DISEASE

Background carcinoid heart disease

Neuroendocrine tumors (NET) are rare malignancies with an incidence of 5 per 100,000 per year[15]. Approximately 40-60% of patients present themselves with local or distant metastases at diagnosis[16,17]. Carcinoid syndrome, characterized by flushing, diarrhea and/or wheezing, is caused by tumor overproduction of vasoactive substances in the systemic circulation, particularly serotonin[18]. Approximately 20% of patients will develop cardiac manifestations, known as carcinoid heart disease (CAHD)[19]. CAHD is characterized by the formation of plaque-like deposits on the endocardium of valve leaflets, cardiac chambers, and the intima of the aorta and pulmonary arteries[20]. Serotonin is thought to be inactivated in the lungs, resulting in primarily right-sided complications[21]. Clinical signs of CAHD consist primarily of right sided decompensation due to severe tricuspid/pulmonic regurgitation (figure 2), increasing right ventricular dimensions, and deteriorating right ventricular function.

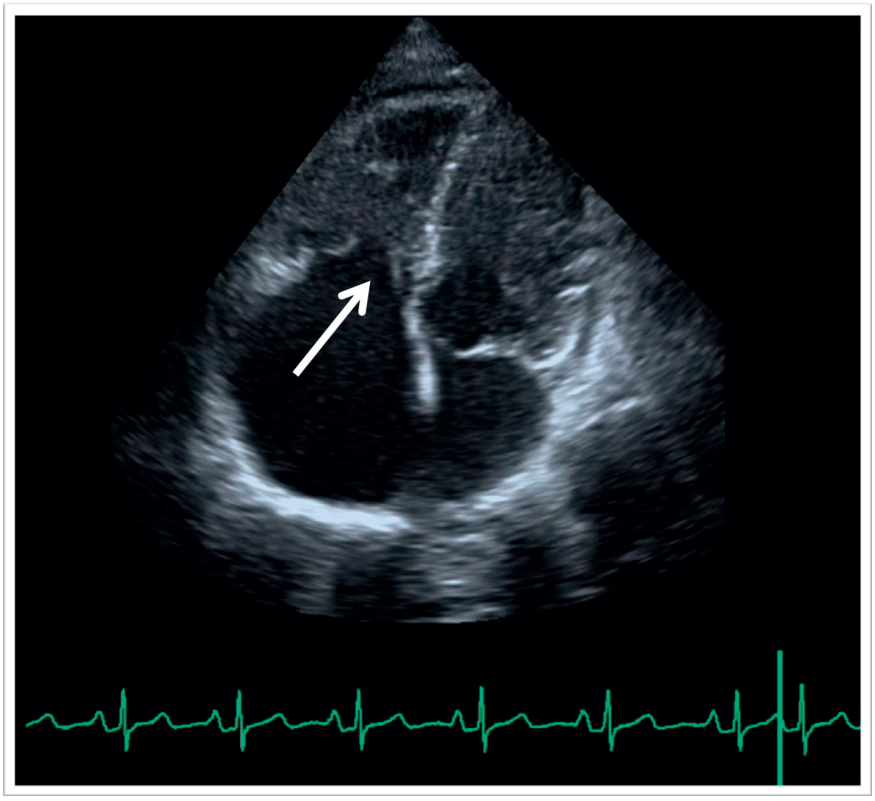


Figure 2. Characteristic restrictive movement of medial leaflet (white arrow) during systole, resulting in severe central tricuspid regurgitation.

Sporadically, left-sided involvement is seen in patients with a patent foramen ovale, bronchial NET, or excessively high serotonin concentrations[22]. Although rare, intramyocardial metastases may occur occasionally.

First-line treatment for NETs consists of a somatostatin analogue, such as octreotide and lanreotide, and aims at decreasing hormonal secretion and subsequent prevention of carcinoid crisis. Progression free survival has been shown, however a significant effect on overall survival is yet to be demonstrated[23,24]. In patients with inoperable or metastatic NET, peptide receptor radionuclide therapy has shown promising results[25].

In spite of earlier screening and advancements in medical therapy, the only therapeutic option for CAHD patients is surgical intervention. Although the perioperative 30-day mortality has decreased drastically over the years and has recently been estimated below 5%[26], the benefit of surgery should be weighed against the risks. Cardiac surgery has been associated with a mortality risk reduction of 0.48, although data from this study should be interpreted in light of a non-randomized study design with significant limitations[27].

Decisions with regards to timing of intervention and choice of intervention (bioprosthesis or mechanoprosthesis) ought to be made in a dedicated heart team. Here, a multidisciplinary approach is required to tackle challenges that present themselves with such a complex and rare disease.

PART THREE - ANTICOAGULATION AND THROMBOLYSIS

Anticoagulant bridging

Patients with a mechanical heart valve (MHV) require life-long administration of vitamin K antagonists (VKA) to prevent thromboembolic complications[28,29]. During a subsequent invasive procedure, VKA administration may be temporarily ceased to reduce peri-operative bleeding risk[30]. In patients with a high risk of thrombo-embolic complications, the time period with sub-therapeutic INR levels, also known as the anticoagulation gap, is ideally bridged with a short-acting heparin. Although in most cases therapeutic doses of heparin are administered before and after the procedure, different bridging regimens exist. These include, but are not limited to: low-dose heparin bridging, post-procedure only bridging, and early transition off heparin bridging[31].

There are two strategies for heparin bridging; unfractionated heparin (UFH) and low-molecular-weight-heparin (LMWH). Both strategies are associated with distinct biochemical[32,33], financial[34] and logistical profiles. For example, UFH is administered intravenously and requires continuous monitoring of activated partial thromboplastin time (aPTT). LMWH is administered subcutaneously and usually does not require monitoring of anti-Xa levels (except in patients with poor renal function or in patients with severe obesity). Conclusive evidence regarding the ideal bridging strategy is scarce and studies are often observational and/or single-arm[35–38]. As

a result, international guidelines are conflicting. European Guidelines (ESC) are in favor of the use of UFH only while American (ACC/AHA) guidelines advocate the use of either[6,39]. Future studies comparing UFH with LMWH are needed to fully elucidate the ideal heparinoid strategy.

With regards to atrial fibrillation, the risk of thrombosis is dependent on the presence of additional risk factors, such as hypertension, sex, and old age. Traditionally, risk stratification was performed using the $Chads_2$ score, which has recently been replaced by the updated Cha_2ds_2-Vasc score. As is the case with mechanical heart valves, the need to bridge with heparin is dependent on the thrombo-embolic risk, and thus on the Cha_2ds_2-Vasc score. European guidelines have not adapted a cut-off point, leaving the peri-procedural anticoagulant strategy in patients with atrial fibrillation subject to debate[40].

Ultrasound-assisted catheter directed thrombolysis in pulmonary embolism

Pulmonary embolism (PE) is associated with considerable morbidity and mortality with an overall crude mortality rate of approximately 15% at 3 months after diagnosis[41]. High-risk PE are defined as patients in shock or hypotension (<90 mmHg systolic) with signs of right ventricular (RV) dysfunction on an imaging test (increased end-diastolic RV-LV diameter; hypokinesia of the free RV wall, increased velocity of the TR jet)[42]. Standard treatment of patients with acute high risk PE consists of intravenous anticoagulation with UFH and systemic thrombolysis (ST)[42,43]. In patients with a contraindication for ST, or in those where ST has failed, surgical pulmonary embolectomy is recommended[44,45]. Contraindications for ST include, but are not limited to, structural intracranial disease, active bleeding, previous intracranial bleeding, ischemic stroke within 3 months, recent brain or spinal surgery, bleeding diathesis[45,46]. As an alternative to pulmonary embolectomy percutaneous catheter-directed treatment should be considered in centers with adequate expertise[42]. In intermediate-high-risk patients (no shock/hypotension but RV dysfunction and raised cardiac biomarkers) percutaneous catheter-directed treatment may be considered if the anticipated risk of bleeding under ST is high[42,47]. Percutaneous catheter-directed treatment refers to ultrasound-assisted catheter-directed thrombolysis (USAT). In this method, a side-hole drug infusion catheter is placed through the thrombus after which ultrasound causes separation of fibrin fibres and increases the permeability for thrombolytic drugs. In addition, acoustic streaming form ultrasound pressure waves enhances drug penetration. Next, the thrombolytic drug binds with plasminogen receptor sites[48–50]. As a result, a considerably lower dosage of thrombolytic medication may be administered, which may be of significant benefit in patients with a high bleeding risk.

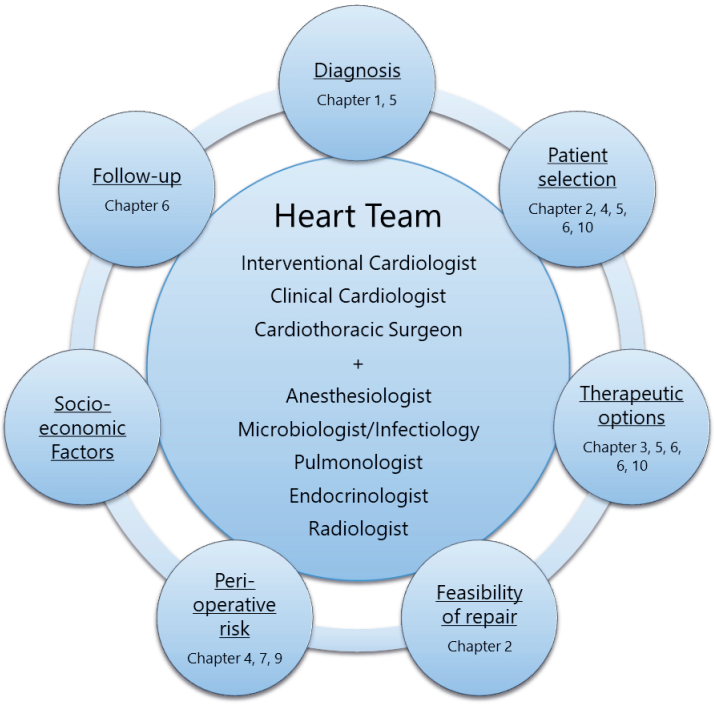
THE HEART TEAM

Throughout this thesis the significance of a multidisciplinary heart team will frequently be reiterated. In fact, the European Society of Cardiology has incorporated the heart team into the most recent guidelines[10]. The concept of a multidisciplinary board is not new and has already been implemented in oncological care and in the field of organ transplantation, however the heart team is relatively new and the precincts have to be established. Although the added value of such a heart team is intuitive, there are some concerns, and adoption of such a heart team has been met with varying enthusiasm[51]. Regardless of the acceptance of a heart team in cardiothoracic centers, a true definition of "heart team" is lacking. Attendance ranges from two clinicians to many multidisciplinary professionals, and the exact tasks to be discussed are undefined. Furthermore, the improvement in clinical outcomes is poorly investigated, especially in valvular disease. It has been demonstrated that patients with multivessel disease treated in a center without a heart team were less likely to receive appropriate guideline-based intervention, which underscored the importance of such a multidisciplinary approach[52]. It seems reasonable to extrapolate these results to the field of valvular disease, although studies quantifying the added value of the heart team in valvular disease are needed. The potential benefits of a heart team have been outlined before[53], and an overview is presented in the table below.

Potential Benefits of a Multidisciplinary Heart Team
Shared decision making between medical professionals
Higher procedural success rates
Less complications
Greater adherence to guidelines
Improved knowledge/education for physicians and patients
Faster time to decision
Improved cost-effectiveness

To achieve these goals, a clear-cut definition of the valvular heart team is needed. This thesis contains a conceptual model (below) which may serve as a cornerstone.

The core of the team should consist of a clinical cardiologist with valvular expertise, an interventional cardiologist, and a cardiothoracic surgeon. If required, additional attendance of for example an electrophysiologist, a cardiologist with expertise in congenital disease, or any other medical specialty (anesthesiologist, microbiologist etc.) is recommended. The task of the heart team is 7-fold, and consist of diagnosis, adequate patient selection, discussion of therapeutic options, feasibility of repair, peri-operative risk, soci-economic factors, and follow-up. It is imperative that the treating, or referring, physician is involved in this process to allow for a thorough assessment of both socio-economic factors and a plan for follow-up. In this thesis, the chapters are (in)directly related to one of these tasks and thus contribute to the optimization of this concept.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Interventional Cardiologist
Clinical Cardiologist
Cardiothoracic Surgeon
+
Anesthesiologist
Microbiologist/Infectiology
Pulmonologist
Endocrinologist
Radiologist

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Thesis Outline

PART ONE: MITRAL REGURGITATION

Mitral regurgitation

Grading of valve severity is partly based on semi-quantitative measures. As a result, determining degree of mitral regurgitation is challenging and European guidelines provide no clear algorithm. In **chapter 1** a pragmatic scoring index to be used in clinical practice is presented to determine severity of mitral regurgitation. Screening for valvular heart disease in at-risk patients may decrease mortality and morbidity. Patients with severe symptomatic mitral valve regurgitation that are deemed unfit for traditional mitral valve repair or replacement may be eligible for percutaneous repair with the MitraClip system. Identifying the patients in which MitraClip treatment may be beneficial remains challenging. In **chapter 2** a proof-of-concept is presented where a virtual representation of the mitral valve, including clip placement, is projected using trans-esophageal echocardiographic (TOE) images. In patients unfit for TOE, options are limited. In **chapter 3** however a successful MitraClip placed using trans-thoracic echocardiography is presented.

Although MitraClip placement is associated with considerable improvement in quality of life, the procedure is not without risk. Access to the left atrium requires a transseptal puncture, the resulting iatrogenic atrial septum defect has been linked to complications. In **chapter 4** the available literature on this matter has been reviewed and recommendations have been made in which patients closure of the defect should be considered.

PART TWO: CARCINOID HEART DISEASE

Carcinoid heart disease

The cardiac manifestations of a neuroendocrine tumor are associated with high mortality and morbidity. The only curative treatment consists of valvular surgery, although little evidence exists on survival and quality of life. **Chapter 5** presents a guide for screening and referral for carcinoid heart disease. In **chapter 6** an illustrative case report is presented of a patient with carcinoid heart disease and recurrent carcinoid heart disease merely 18 months after valve surgery with a bioprosthesis. This case report highlights the crucial role of a multidisciplinary heart team in the management of carcinoid heart disease.

PART THREE: ANTICOAGULATION AND THROMBOLYSIS

Anticoagulant bridging

In anticipation of an invasive procedure with a high bleeding risk, patients with a mechanical heart valve have to temporarily discontinue oral anticoagulation and are usually bridged with

either intravenous unfractionated heparin of low-molecular-weight heparin. European and American guidelines are inconclusive, bridging strategy is therefore often left to the attending physician's discretion. In **chapter 8**7bridging with either strategy has retrospectively been reviewed in a multicenter study. The outcome of this study has changed the bridging protocol at our center. **Chapter 8** contains a reply to a letter to the editor regarding the bridging study in chapter 8. In this letter, a reply is offered which aims to explain the relatively high incidence of bleeding in our study. **Chapter 9** contains the updated and practical protocol in close harmony with the multidisciplinary anticoagulant committee, that is used in the UMCU and can be adopted elsewhere.

Local ultrasound facilitated thrombolysis

Patients with an acute high risk pulmonary embolism carry a poor prognosis and immediate intervention with systemic thrombolysis is desirable. A new catheter based procedure with localized thrombolysis may serve as future alternative to systemic thrombolysis. In **chapter 10** the first experience of local thrombolysis was retrospectively analyzed.

Part One

Mitral Regurgitation

Chapter 1

An easy- to- use scoring index to determine severity of mitral regurgitation by 2D echocardiography in clinical practice

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Echocardiography 2017; 34: 1275-1283

ABSTRACT

Purpose: Mitral regurgitation (MR) grading by two- dimensional transthoracic echocardiography is challenging, but important to determine the best treatment strategy in patients with MR. Current guidelines advocate an integrative approach, although no recommendation is provided on how to do so. An easy-to-use index will be helpful for standardized and reproducible MR grading.

Methods: Eleven echocardiographic parameters were retrospectively evaluated in 145 patients with moderate or severe MR. Parameters were scored positive or negative for severe MR, where expert panel consensus reading was considered as the reference standard. Logistic regression was performed, and adjusted coefficients were used to create a risk score for severe MR per patient (*ROSE-index*). The best cutoff with corresponding predictive values was determined.

Results: Eighty- two percent of all parameters could be determined. Multivariable analysis revealed five parameters that remained significant predictors for severe MR: morphology, jet characteristics, vena contracta, systolic reversal, and left ventricular dimensions. With different weighing, a total score of 8 could be obtained. Median total *ROSE-index* score for moderate (2.0) and severe MR (5.0) did significantly differ. The cutoff score (≥4) revealed sensitivity 0.84 and specificity 0.83 to diagnose severe MR. Negative predictive value was 100% for score 0 and 1; score 6–8 showed a 100% positive predictive value. Inter- and intra-observer agreements were excellent (*K*- values >0.80).

Conclusion: Here, we propose an easy-to-use tool for integrated analysis of guideline parameters to assess MR severity. Using this so-called *ROSE-index* revealed reliable and reproducible assessment of severe MR (cutoff≥4) that may be helpful for clinical decision making.

Keywords
2D transthoracic echocardiography, easy-to-use, mitral regurgitation, semiquantitative index

INTRODUCTION

Mitral regurgitation (MR) is frequently diagnosed, representing 32% of the native left-sided valve disease.(1) Its prevalence increases significantly with age; at present nearly 10% of people over 75-years have significant leakage of the mitral valve (MV).(2) Structural deficiencies in the MV apparatus (organic MR) or secondary changes induced by abnormal ventricular size and deformation (functional MR) contribute to the valvular regurgitation.(3-5) The definitive therapy is usually surgical intervention, notwithstanding advances in catheter-based approaches.(6;7) Surgery is indicated in patients with *severe* MR and symptoms, and timely intervention is pivotal to prevent complications including heart failure, arrhythmia, and sudden cardiac death. Thus, it is of utmost importance to accurately determine the severity of MR.(3;6-9) Due to its relatively low costs and extensive availability two-dimensional (2D) transthoracic echocardiography (TTE) still is the key imaging modality for *diagnosing* MR. However, differentiating moderate from severe MR remains challenging in the absence of a clear definition of the MR severity and its quantification.(10-12) Accurate quantification not only prevents undergrading of patients with identified severe MR as having non-severe MR (13), it also prevents referral of patients to surgical centers for severe MR by echocardiography that reveal non-severe MR on advanced evaluation, for example, by trans-esophageal echocardiography (TEE) or cardiac magnetic resonance (CMR).(14)

Unfortunately, a semiquantitative estimation of MR mainly based on visual analysis of jet characteristic is still used in daily practice(8;15;16), despite the fact that previous studies have shown the inaccuracy and lack of reproducibility of this method(17-20). Quantitative assessment of MR, such as the proximal isovelocity surface area (PISA) method and calculation of the effective regurgitant orifice (ERO) area by 2D and Doppler, avoids subjective interpretation and therefore is preferable.(6;10;12;21;22) Nevertheless, these methods are widely used as research tools, but sparsely applied in routine evaluation due to the time consuming aspect, technical limitations, and operator dependency.(21;23-25) Recognized echocardiographic signs and corresponding cut-off values of MR severity are theoretically based, or known predictors of postoperative outcome in patients with severe MR. Given the different strengths and weaknesses of these individual methods to assess severity, the current guidelines recommend an integration of multiple echo parameters to incorporate advantages of each variable while limiting the effect of technical and measurement errors. It includes the evaluation of valve morphology, jet characteristics, vena contracta (VC) and related effective regurgitant orifice (ERO), regurgitant volume and/or fraction, MV inflow pattern, pulmonary venous inflow, systolic pulmonary artery pressure (SPAP), and left atrial and/or ventricle consequences.(6;10;12) However, no algorithm or recommendation is provided on how to do so. In our experience physicians are aware of the additional value of an integrative approach, though they are limited by the lack of a practical tool to correctly interpret the echocardiographic results within an acceptable timeframe for daily practice.

In this retrospective study we performed a cross-sectional analysis of the recommended echo parameters for MR grading in 145 patients to: 1) develop a practical scoring index to determine MR severity using the current guidelines (referred to as the ROSE-index: mitral RegurgitatiOn Severity grading by an Easy-to-use index), and 2) compare the ROSE-index with an expert's semi-quantitative evaluation of MR severity (reference standard). We hypothesized that the ROSE-index will be more accurate and less time intensive than currently used grading methods, thereby stimulating the use of an integrative approach. This may improve MR grading for clinical decision making, follow-up and research purposes.

MATERIALS AND METHODS

Study population

We retrospectively analyzed the 2DTTE data of 145 patients that were referred to the University Medical Center Utrecht for the evaluation of moderate or severe MR. Figure 1 depicts the flowchart of the study design.

Echocardiographic examination

Standardized 2DTTE examination was performed in all subjects utilizing multiple parasternal and apical views with the patient in the left lateral position. Examinations were performed with Philips 5500 or Philips iE33 (Philips Medical Systems, Andover, MA, USA) echocardiography machines. All datasets were archived on the hospital server as video loops and freeze frames in a digital format (DICOM). Offline analysis was performed using Xcelera software. In our echo laboratory, the routine assessment of MR grade is performed by a member of the experienced team of sonographers, and supervised by the expert team of cardiologists. This semiqualitative consensus reading by the expert team was used as the reference standard for MR severity.

Subsequently, as much as possible parameters as recommended by the current guidelines were scored, focused on the following 11 parameters: MV morphology, regurgitation jet characteristics, VC, MV inflow (E- wave), ratio of the time- velocity integral (TVI) over the MV and aortic valve (TVI MV/AoV), ERO, regurgitant volume, left atrial volume indexed (LAVI), left ventricular (LV) dimensions, systolic reversal (SR), and SPAP. In Table 1, the definitions and cutoff values for severe MR are depicted. Two- dimensional TTE measurements were obtained in accordance with the guidelines of the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI)(5,6,9,11,21,22). In Online Resource 1 (Data S1), a detailed description of the echocardiographic examination methods is given.

Total index score per patient

Cutoff values of the quantitative parameters (see Table 1) were used to score each parameter negative (0) or positive (1) for severe MR. In three qualitative variables, the cutoff was based on a composite outcome of several subanalyses (each scored 0 or 1 for severe MR):

- MV morphology composed of the subparameters (1) flail leaflet, (2) papillary muscle rupture, (3) annular dilatation (end-diastolic diameter >3.5 cm), (4) tethering (positive for severe MR when tethering area >2.5 cm^2 and/or coaptation distance ≥1 cm), (5) rheumatic etiology, (6) cleft presence (defined as a visual discontinuity of the leaflet from the free edge of the mitral ring, resulting in a degree of regurgitation), and (7) (previous) endocarditis. Valve morphology was considered to be positive (score 1) if (at least) one of the above was present;
- regurgitation jet characteristics was scored 1 if one of the following sub parameters scored positive for severe MR: the presence of a swirling jet, jet reaching the left atrial posterior wall, and jet to left atrial surface ratio (positive score when jet covers >40% of the left atrial surface);
- LV dimension was scored positive if: (1) left ventricular end systolic dimension (LVESD) ≥45 mm in organic MR (≥40 mm in case of flail leaflet), or (2) left ventricular end-diastolic dimension (LVEDD) >65 mm in functional MR.

To assess the total *ROSE-index* score*,* each score per variable was multiplied by the contribution of that variable (indicated by the coefficients per variable after multivariable analysis).

Statistical analysis

Statistical analysis was performed using SPSS software version 21.0 (SPSS, IBM Corporation, Armonk, NY, USA) and the R language environment (R Core Team 2015, version 3.2.1). Multiple imputation was performed using the Multivariate Imputation by Chained Equations (mice) package and modeling, internal validation, and calibration with the Regression Modeling Strategies (rms) package (23,24). All analyses in this study are according to the most recent reporting guidelines (TRIPOD statement)(25). Continues values were expressed as mean±SD and compared with the unpaired Student's *t* test for normally distributed data. Skewed variables were depicted as median with interquartile range (IQR), and compared using the Mann-Whitney *U* test. Categorical data were described using frequencies and percentages, with comparative evaluations performed via the chi- square or Fisher's exact test. A two- tailed *P*- value <0.05 was regarded as statistically significant. Missing data were considered at random and therefore eligible for multiple imputations. The mice package was used to create 20 imputed datasets(23). The imputation procedure was performed with all predictors and the outcome used in the modeling steps included. Using univariable and multivariable logistic regression, the coefficients (β's) and corresponding odds radios (ORs) with 95% confidence intervals (95% CIs) were calculated.

Table 1 Cutoff values for severe mitral regurgitation per parameter as defined by the current guidelines(5,6).

Parameter	Cut-off values based on the guidelines
1. Valve morphology[a]	
annular dilatation	3.5 cm
2. Jet characteristics[b]	-
3. VC	0.70 cm
4. ERO	
organic MR	0.40 cm^2
functional MR	0.20 cm^2
5. Regurgitant volume	
organic MR	60 ml
functional MR	30 ml
MV inflow pattern	
6. MV TVI and AoV TVI ratio	1.4
7. E-wave	150 cm/sec
8. Systolic flow in pulmonary veins	Systolic reversal
9. SPAP	50 mmHg
10. LAVI	60 ml/m^2
11. LV dimensions	
organic MR (LVESD)	4.5 cm[c]
functional MR (LVEDD)	6.5 cm

VC: vena contracta, ERO: effective regurgitant orifice, MR: mitral regurgitation, MV: mitral valve, TVI: time-velocity integral, AoV: aortic valve; SPAP: systolic pulmonary artery pressure, LAVI: left atrial volume index, LV: left ventricular; LVESD: left ventricular end systolic dimension, LVEDD: left ventricular diastolic dimension.

[a]Predictive of severe MR in case of: annular dilatation, flail leaflet, papillary muscle rupture, large tethering area or coaptation distance, rheumatic etiology, cleft (visual discontinuity of the leaflet from the free edge of the mitral ring, resulting in regurgitation), and (previous) endocarditis.

[b]Including both central and eccentric (impinging on the lateral wall or the interatrial septum) jets, and predictive of severe MR in case of: swirling type, reaching the left atrial posterior wall, and jet to left atrial surface ratio >40%.

[c]4.0 cm for flail leaflet

To obtain the *ROSE-index*, a backward stepwise approach was adopted starting with all 11 guideline based parameters included(26). In Online Resource 2 (Data S1), a detailed description is given. For the calculation of the total *ROSE-index* score, the coefficients of the parameters that were retained in the final model were simplified by rounding them to their nearest integer. The total *ROSE-index* score per patient was used in a receiver operating characteristic (ROC) and two-by-two table analysis for assessing the best cutoff value to determine severe MR. Resulting predictive values were calculated. The observed and predicted probabilities of severe MR per patients were evaluated. To test inter- observer variability, all images were analyzed by two observers that independently and blinded to the clinical data reviewed the echocardiographic images and scored as much as possible parameters from the *ROSE-index*. One observer repeated the measurements in 50 randomly selected cases at two different time points (6 months' time difference) to assess intra- observer variability. Inter- observer and intra- observer agreements using the five-parameter scoring index were determined by linear weighted Kappa statistics for the clinical diagnosis (MR severity), and Bland- Altman plots for total MR severity index score.

The *K*- values <0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80, and >0.80 were considered to represent slight, fair, moderate, substantial, and excellent agreement, respectively(27). The hypothesis of equal median total *ROSE-index* score was tested by the Wilcoxon signed rank test, while the differences in MR severity were tested by the McNemar's test. Comparisons were considered significant in the presence of a *P*-value <0.05.

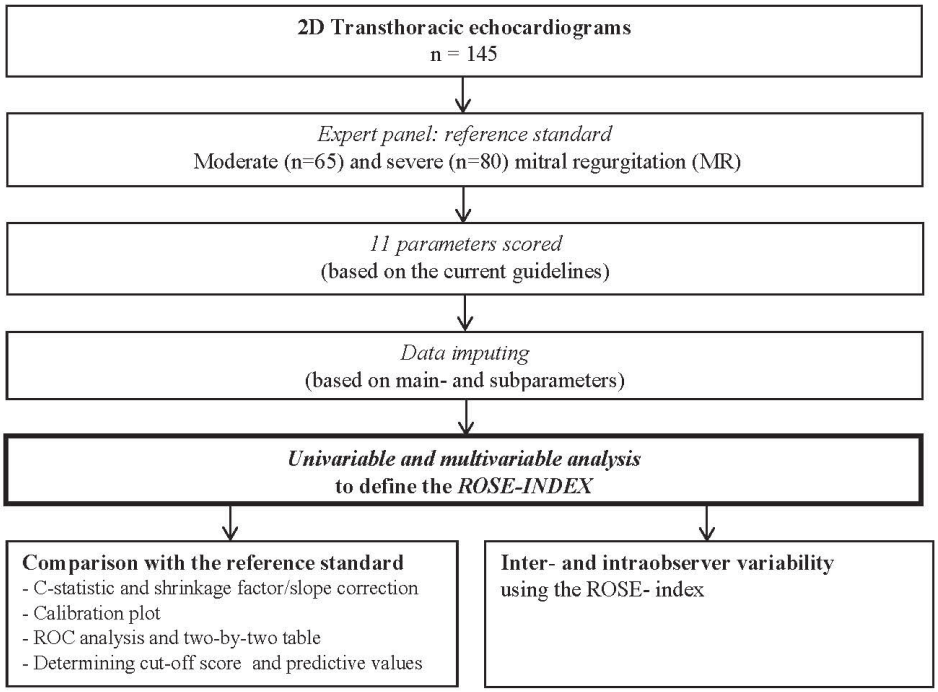

Figure 1 Flowchart of the study design

RESULTS

Patient characteristics

Based on our reference standard, 80 (55%) subjects were classified as having severe MR and 65 (45%) as having moderate MR. Baseline characteristics are depicted in Table 2. Additional echocardiographic results are depicted in Online Resource 3 (Data S1). A significant difference was seen between the numbers of male patients in the moderate vs severe MR group (42% vs 61%, respectively). Data revealed an equal distribution of organic and functional MR when comparing MR severity (*P*=0.173). Functional MR resulted from cardiomyopathy and ischemic LV dysfunction in both 27 patients (31%). Of all organic MR patients, degenerative MV disease was diagnosed in 27 (47%), annulus calcification in 9 (16%), rheumatic valve disease in 6 (10%),

and endocarditis in 11 (19%) patients. MV flail leaflet was seen in 9 (16%) organic MR patients. Except from the LV ejection fraction (EF), all echo parameters showed a significant difference in mean or median between moderate and severe MR, with higher values in severe MR. Concomitant severe TR was more frequently seen in the severe MR group (17.5% vs 1.5%, respectively, *P*=0.002). Significant MS was not diagnosed. When comparing differences in rhythm during echocardiography, there was no significant difference in the presence of atrial fibrillation (AF) between subgroups (18 (28%) moderate and 12 (15%) severe MR patients, *P*=0.067).

Determination and scoring of parameters

We were able to score a median of 9.0 (IQR 8.0–10.0) parameters per patient of the 11 parameters as recommended by the guidelines. Table 3 shows the percentage scored per parameter in the overall population. Valve morphology, jet characteristics, LAVI, and LV dimensions could be determined in more than 90% of the subjects, whereas the pulmonary flow patterns could be evaluated in 60% and ERO in only 43% of the analyzed echocardiograms. Comparison of severe and moderate MR patients showed no significant difference in the percentages scored per parameter. All variables did significantly differ in the percentages of positive scored parameters when comparing the subgroups. MV- inflow, regurgitant volume, LAVI, LV dimensions, and pulmonary pressure scored positive in <50% of the patients with severe MR. On the contrary, MV- inflow and SR showed a 100% negative score in the moderate MR subgroup.

Table 2 Baseline characteristics

	Moderate MR, n=65	Severe MR, n=80	p-value
Age (mean ±SD)	60.9 (18.0)	59.6 (16.6)	0.636
Gender, *male* (n, %)	27 (41.5)	49 (61.3)	*0.018*
BSA (mean ±SD)	1.9 (0.2)	1.9 (0.2)	0.725
Etiology (n, %)			0.173
organic	43 (66.2)	44 (55.0)	
functional	22 (33.8)	36 (45.0)	
Mitral stenosis (mean ±SD)	4 (6.2)	1 (1.3)	0.174
Significant mitral stenosis	0 (0)	0 (0)	
Other severe valve disease (n, %)			
AoS	1 (1.5)	7 (8.8)	0.074
TR	1 (1.5)	14 (17.5)	*0.002*
AR	1 (1.5)	2 (2.5)	1.000
Rhythm (n, %)			
Sinus rhythm	47 (72)	68 (85)	0.067

MR: mitral regurgitation, BSA: body surface area, AoS: aortic stenosis, TR: tricuspid regurgitation, AR: aortic regurgitation

Logistic regression model

Each of the echocardiographic parameters was used as an univariate predictor of severe MR. In Table 4, these parameters are depicted with corrected OR's that remained significant predictors (*P*- value<0.25) for severe MR after multivariable analysis, including their simplified coefficients

(corrected with a shrinkage factor of 0.82 after internal validation, and rounded to their nearest integer). Multiple regressions showed that the following variables need to be evaluated for reliable MR grading: MV morphology, jet characteristics, VC, SR, and LV dimensions. The *ROSE-index* score was calculated by adding the value for each of these individual parameters following the formula:

ROSE-index score=(valve morphology*1)+(jet characteristics*2)+(vena contracta*2)+(systolic reversal*2)+(LV dimensions*1).

The maximum score was 8 based on the five parameters with corresponding coefficients. The final model is also shown in Online Resource 4 (Data S1).

Internal validation and predictive values

Based on the implemented data, there was a significant difference (P<0.0001) in median total *ROSE-index* score for moderate vs severe MR (based on the most optimal imputed database, see Figure 2). The discriminative ability (of all 20 imputed datasets) showed a pooled C- statistic of 0.91, and shrinkage factor of 0.85. The calibration of the *ROSE-index* revealed no apparent over- or underestimation at the entire range of predicted probabilities (Figure 3). ROC- analysis of the total *ROSE-index* score per patient (based on the most optimal implemented dataset) showed a best cutoff score of ≥4 to determine severe MR with sensitivity 0.84, specificity 0.83, positive predictive value 0.86, and negative predictive value 0.81 (Table 5). A score of 0 or 1 was always related to nonsevere MR (100% NPV), whereas a score of ≥6 was only seen in patients with severe MR (100% PPV)(Figure 2). One of three patients that showed score 2 or 3 was diagnosed with severe MR (observed predicted probability 32%, calculated probability 28%). The number of patients with score 2 or 3 was 41 (28%).

Inter- observer and intra- observer variability

Inter- observer variability showed an excellent agreement between both observers regarding the clinical diagnosis (K=0.86, 95% CI 0.82–0.90), with no significant inter- observer variability (P=0.75). In 10 patients (6.9%), there was a change in clinical diagnosis when comparing the results of observer 1 and 2. Median (IQR) total *ROSE-index* score did not significantly differ between both observers (both median score 3.0, IQR 2.0–5.0, P=0.721) and the Bland- Altman analysis showed a strong correlation (r=.84, P<0.0001). The median difference in total *ROSE-index* score by observer 1 and observer 2 was 0.0 (IQR −1.0 to 1.0). Intra- observer variability also showed a strong correlation between acquisition 1 and acquisition 2 regarding total *ROSE-index* score (r=.90 (P<0.0001) including a median difference of 0.0, IQR 0.0–0.0) and excellent agreement for the clinical diagnosis (K=0.84, 95% CI 0.75–0.93) demonstrating diagnostic stability and a low intra- observer variability (P=1.00). In three of 50 patients (6.0%), there was a change in clinical diagnosis when comparing the results of both acquisitions.

Tables are depicted in Online Resource 5 (Data S1).

Table 3 Number scored per parameter in the total population (n=145), severe mitral regurgitation subgroup (n=80), and moderate mitral regurgitation subgroup (n=65), and percentage of the scored parameters that is positive for severe mitral regurgitation following the cutoff values as defined by the current guidelines, in patients with severe and moderate mitral regurgitation, respectively(5,6)

Parameter	Scored per parameter	% of scored parameters that is positive for severe MR		
	total	*severe MR*	*moderate MR*	*p-value*
Morphology, n (%)	141 (97.2)	78.2	33.3	0.000
Jet, n (%)	140 (96.6)	93.4	48.4	0.000
E-wave, n (%)	106 (73.1)	23.3	0	0.000
Ratio TVI MV/AoV, n (%)	128 (88.3)	70.4	31.6	0.000
Vena contracta, n (%)	124 (85.5)	61.8	8.9	0.000
ERO, n (%)	63 (43.4)	52.9	17.2	0.003
Regurgitant volume, n (%)	124 (85.5)	43.5	9.1	0.000
LAVI, n (%)	140 (96.6)	41	19.4	0.006
LV dimensions, n (%)	132 (91.0)	42.5	20.3	0.007
Systolic reversal, n (%)	87 (60.0)	55.6	0	0.000
SPAP, n (%)	117 (80.7)	40	21.2	0.029

MR: mitral regurgitation, TVI: time-velocity integral, MV: mitral valve, AoV: aortic valve, ERO: effective regurgitant orifice, LAVI: left atrial volume index, LV: left ventricular, SPAP: systolic pulmonary artery pressure.
The median (IQR) number of parameters scored in severe mitral regurgitation is 9.0 (8.0-10.0), and in moderate mitral regurgitation 9.0 (9.0-10.0), P=0.968.

DISCUSSION

In the present study, an easy- to- use scoring index was determined and validated based on daily clinical echocardiograms of moderate or severe MR, which (1) correctly determined MR severity in 83% using only five of the 11 echocardiographic parameters as recommended by the current guidelines, and (2) proved to be reliable and reproducible. This so- called *ROSE-index* can serve as an easy- to- use tool for integrated analysis of guideline parameters, and thus aid both clinicians and researchers to determine MR severity.

The MR severity model

Based on a two- by- two table revealing the lowest percentage of patients that were misdiagnosed by the *ROSE-index* (Table 5), a cutoff score ≥4 was considered to indicate severe MR. Of the patients with score <4, only scores 0 or 1 were always related to moderate MR, whereas patients with index score 2 or 3 had, respectively, a 22% and 38% calculated predicted probability to be misdiagnosed. Awareness in these subjects is recommended, and extra evaluation using stress echocardiography or CMR imaging may be of additional value to unveil the true severity. Among patients with score ≥4, 14% were classified incorrectly. However, due to pre- operative

diagnostics (TEE, evaluation in a heart valve team), we expect these misclassified patients will be correctly reclassified in a later phase, as is currently also the case in daily practice in often a higher percentage of patients.

Table 4 Univariable and multivariable analysis, including corrected coefficient and contribution to the risk score of the parameters in the *ROSE-index*

Parameter	Univariable OR, 95%CI	p-value	Multivariable OR, 95%CI*	p-value	Corrected OR, 95%CI (slope 0.82)	Corrected coefficient
Morphology	6.86 (3.22-14.64)	<0.0001	2.68 (0.78-9.15)	0.11	2.31 (0.81-6.57)	0.8377027[a]
Jet	9.95 (3.89-25.44)	<0.0001	13.57 (2.41-76.37)	0.004	9.18 (2.12-39.89)	2.21756[b]
E-wave	3.00 (0.98-9.22)	0.05	NS	NS	NS	-
MV TVI/AoV TVI ratio	4.42 (2.04-9.56)	0.0002	NS	NS	NS	-
Vena contracta	11.59 (3.91-34.37)	<0.0001	11.16 (2.41-51.76)	0.003	7.78 (2.11-28.66)	2.051082[c]
ERO	3.56 (0.96-13.22)	0.06	NS	NS	NS	-
Regurgitant volume	4.99 (1.86-13.38)	0.002	NS	NS	NS	-
Systolic reversal	22.14 (4.31-113.65)	0.0004	13.67 (1.91-97.87)	0.01	9.24 (1.73-49.25)	2.223508[d]
SPAP	1.95 (0.85-4.47)	0.11	NS	NS	NS	-
LAVI	2.69 (1.23-5.86)	0.01	NS	NS	NS	-
LV dimensions	2.95 (1.33-6.53)	0.008	2.67 (0.72-9.92)	0.14	2.31 (0.76-7.04)	0.8360791[e]

MV=mitral valve; TVI=time- velocity integral; AoV=aortic valve; ERO=effective regurgitant orifice; SPAP=systolic pulmonary artery pressure; LAVI=left atrial volume index; LV=left ventricular; NS=not significant.

*Rule=Wald *P*<0.25, all factors included at first step multivariable analysis.

a. Contribution to risk score: 1

b. Contribution to risk score: 2

c. Contribution to risk score: 2

d. Contribution to risk score: 2

e. Contribution to risk score: 1

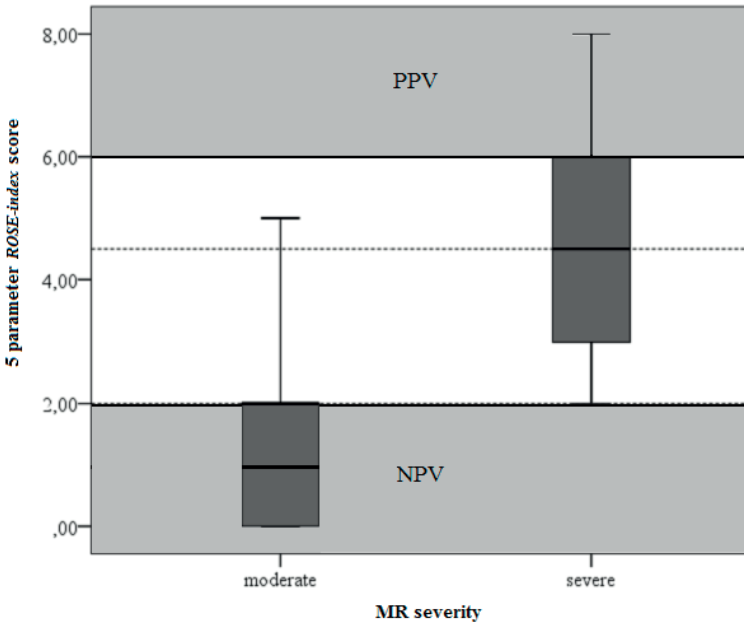

Figure 2 Box plots (dark grey color) of the total *ROSE-index* score (vertical axis) in moderate (n=65) and severe (n=80) mitral regurgitation patients (based on the most optimal imputed database). The 100% positive predictive value (PPV, score>5) and 100% negative predictive value (NPV, score<2) are depicted in the light gray color. The median (IQR) total score in moderate mitral regurgitation is 2.0 (0.5–3.0), and in severe mitral regurgitation 5.0 (4.0–7.0), *P*<0.0001

Parameters in the index

The parameters MV morphology and LV dimensions were frequently scored (>90%) in our study, and they are known to be related to the clinical outcome of patients with MR (28,29) However, their poor specificity for severe MR results in a lower contribution of these parameters to the *ROSE-index*. VC was the only quantitative measurement included in the scientific index after regression analysis. Despite thetechnical difficulties in obtaining VC(30), it was determined in 86% of the study population with high specificity (negative score in >90% of patients with moderate MR). This confirms the concept that the VC is less susceptible to physiologic loading conditions, hence may be more feasible, accurate, and appropriate as screening tool(30–32). In particular, the quantitative ERO measurement was sparsely evaluated.

Our data therefore confirm that this parameter has not been widely accepted as a part of routine echo examination, due to its known limitations(18–20). One would expect regurgitant volume (calculated using the PISA method) to be under- evaluated as well; however, assessment can also be performed using standardized methods for calculation of flow. Nevertheless, both parameters were not significantly related to the MR severity in our multivariable analysis. Thus, despite studies revealing validity and utility of ERO and related parameters in a research setting(33,34), our study confirms the results showing variable feasibility in a clinical

setting(20,35,36). As in the study of Quader et al.(37), we showed that E-wave velocity was not sensitive enough to exclude severe MR, therefore not useful as a screening tool. Regarding the qualitative measurements, both jet characteristics and SR contributed more to the final score. In accordance with previous studies, color flow imaging was highly sensitive and therefore of value despite its low specificity(15,19,38). The systolic flow reversal was important due to its known high specificity rate(39).

Reproducibility

The inter- and intra- observer variability for both clinical diagnosis and *ROSE index* score showed an excellent agreement. A change in clinical diagnosis was seen in 6.9% of the patients when comparing results of observer 1 vs 2. As would happen in clinical practice, consensus reading was performed in these 10 cases that the observers disagreed on, resulting in a final revised change of clinical diagnosis in 3% of the patients. Reason for MR severity revision was most often due to poor echo images. As this reflects daily practice, the index is useful for clinical decision making, as consensus reading is usually implemented in most cardiology practices.

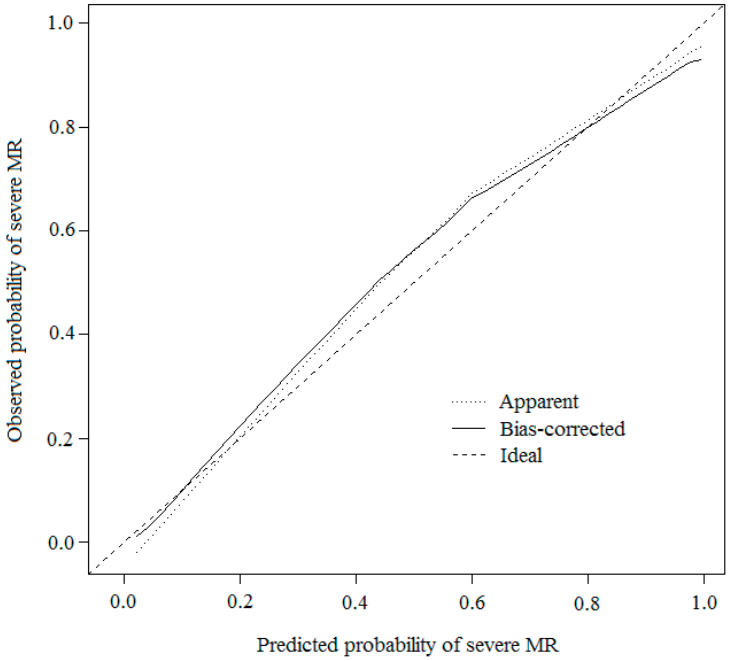

Figure 3 Observed vs predicted probability of the outcome severe mitral regurgitation for the *ROSE-index*

Previous scoring indexes

Two earlier studies in literature used a scoring index based on the guidelines(36,40). In the retrospective study of Thomas et al.(40),MR grading was performed using six echo parameters that were frequently applied. Although the authors stated their MR Index may be easy to use, it included three quantitative measurements (PISA, SPAP, LA dimension), and the venous flow pattern parameter; all known to be more difficult to apply. Moreover, each parameter was scored on a difficult four point scale. The reference standards used were the qualitative grading by an expert and the regurgitant fraction. In contrast, we used expert reading as a reference standard as it is most frequently used and previously proved reliable(8,40,41). Regurgitant fraction was excluded in our study due to technical issues in a retrospective study. Our index is superior for distinguishing moderate from severe MR, whereas the MR Index by Thomas et al. mainly differentiated mild from severe MR. A second prospective study of Thomas et al.(41) in 62 patients reported a sensitivity (82%), specificity (98%), and PPV (93%) for the MR Index of ≥2.2 to detect severe MR. These values correspond with the results of our study.

Table 5 Two- by- two table based on the best cutoff value of *the ROSE-index* score with corresponding area under the curve (AUC) of 0.91 (based on the most optimal imputed database)

***ROSE-index* score=(valve morphology*1)+(jet characteristics*2)+(VC* 2)+(systolic reversal*2)+(LV dimensions*1)**			
	severe MR	***moderate MR***	**total**
score ≥4	67	11	78
score <4	13	54	67
total	80	65	145

MR: mitral regurgitation.
Cut-off value for severe MR (score ≥4) according to the MR severity index: sensitivity 0.84, specificity 0.83, positive predictive value 0.86, negative predictive value 0.81

Langer et al.(36) used the same MR Index in their retrospective study in 177 patients, although they simplified it by only assessing the PISA radius, VC, CW Doppler signal, and MV- inflow. The aim of their study was to compare the echo grading system with left ventriculography; however, almost all patients had MR grade ≤3. A few other articles described algorithms for distinguishing severe from nonsevere MR, although none of these step- by- step approaches were analyzed in a retrospective or prospective study(42–44).

Clinical implications

Current practice for the management of MR is aimed at early detection and reliable surveillance of significant MR. Our five- parameter *ROSE-index* may aid the treating physician how to use the integrated approach as recommended by the guidelines(5,6).Scores 0 and 1 always indicate moderate MR; score ≥4 is related to severe MR. mPatients with index score 2 or 3 need evaluation in a heart valve team(45), and cross- checking with the clinical assess-

ment and hemodynamic consequences, for example, by stress echocardiography remains important(46,47). Furthermore, we foresee three- dimensional (3D) echocardiography and/or CMR imaging techniques to gain a more important role in MR grading in the nearby future, although technical limitations and time- consuming processing still prevent it from becoming widely adopted into daily practice at the present(44,48,49).

Limitations

This concerns a retrospective study with its inherent limitations. As the reference standard, we used semiqualitative echocardiographic grading by an expert panel. Although this has been previously used as a reference standard and proved reliable in other studies(8,40,41), the evaluation by various experts is difficult to standardize and may cause variability in classification. Furthermore, only patients with moderate or severe MR were evaluated, and consequently, our findings may

not be extrapolated to lower grades of MR severity. Also the exact value of the *ROSE-index* score in patients with AF needs to be further investigated. Finally, the utility of our current scoring index needs further validation in prospective and longitudinal studies.

CONCLUSION

Our semiquantitative *ROSE-index* is an easy- to- use scoring index to determine severity of mitral regurgitation by two- dimensional trans-thoracic echocardiography in clinical practice and for research purposes. In contrast to current guideline recommendations involving 11 parameters, this five- parameter grading index is relatively simple and less time- consuming without a loss of accuracy. Consensus reading in

a multidisciplinary heart valve team, with cross- checking against the hemodynamic consequences of mitral regurgitation, remains necessary in one of four patients.

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MATERIALS AND METHODS

Two-dimensional TTE measurements were obtained in accordance with the guidelines of the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI).(10;12;26;27) In order to determine annular dilatation, MV annular dimensions in the apical 4- and 2-chamber views were averaged. Analysis of jet characteristics was done in the parasternal long-axis and apical 4- and 2-chamber views. We evaluated the density of the MR related CW signal using the continuous wave (CW) Doppler across the MV. The VC was imaged in the parasternal long-axis or apical 4-chamber view and measured as the narrowest part of the regurgitant jet. The PISA radius was only assessed in the apical four-chamber when a magnified view with optimized Nyquist range (15-40 cm/s) was available. Regurgitant volume and ERO were obtained using the standard formulas.(10;12;26) In absence of the PISA we calculated the regurgitant volume following the formula: regurgitant volume = LV inflow - LV stroke volume. LV stroke volume and ejection fraction (EF) were measured as recommended by the guidelines, preferably by the biplane method of discs.(27) Pulmonary venous flow pattern was evaluated based on the Doppler signal in the right or left upper pulmonary vein. Reversal of the pulmonary flow was related to severe MR. While AF and elevated LA pressure can blunt forward systolic pulmonary vein flow, it was considered as 'not applicable' in these patient subgroups. Pulse waved (PW) Doppler was used to obtain the maximum of the E-wave in the apical 4-chamber view. Mitral and aortic TVI ratio were determined using the corresponding PW signals in the 3- or 4-chamber view. Also the MV-inflow peak velocity (Ewave) measurements were not determined in case of AF. We determined SPAP by summing the gradient across the tricuspid valve and the right atrial pressure. Left atrial volume (using the 2- and 4-chamber views) was corrected for BSA to assess LAVI. We measured the LV end-systolic and -diastolic diameters in the long parasternal view. In case of atrial fibrillation, an averaged value was determined (eye-balling).

RESULTS

Table 1. Echocardiographic characteristics

Echo parameter	Moderate MR, n=65	Severe MR, n=80	p-value
MV annular dimension (cm)	3.3 (0.4)	3.6 (0.5)	*0.000*
Tethering area (cm2)	0.76 (0.74)	1.16 (1.07)	*0.011*
Coaptation height (cm)	0.41 (0.37)	0.58 (0.53)	*0.027*
VC (cm)	0.42 (0.16)	0.70 (0.21)	*0.000*
ERO (cm2)	0.16 (0.08)	0.29 (0.17)	*0.000*
Regurgitant volume (ml)	22.7 (12.1)	40.7 (24.3)	*0.000*
E-wave (cm/sec)	100.3 (35.8)	122.0 (31.3)	*0.000*
TVI MV / TVI aorta ratio	1.3 (0.5)	1.8 (0.6)	*0.000*
SPAP (mmHg)	37.8 (13.5)	45.5 (16.7)	*0.005*
LAVI (mL/m2)	48.6 (18.3)	62.4 (36.8)	*0.001*
LVEDD (cm)	5.8 (1,1)	5.0 (1.7)	*0.000*
LVESD (cm)	4.2 (1.4)	6.5 (1.2)	*0.010*
LV EF (%)	41.1 (13.1)	40.8 (16.7)	0.837

Table 2. Inter- (a) and intra-observer (b) comparison of the MR severity index, based on clinical diagnosis

a.

		Observer 1		
Observer 2		*Severe MR*	*Moderate MR*	*Total*
	Severe MR	58	4	62 (43%)
	Moderate MR	6	77	83 (57%)
	Total	64 (44%)	81 (56%)	

MR: mitral regurgitation
Linear weighted kappa = 0.86 (95% CI 0.82-0.90) based on the analysis of 145 patients

b.

		Observer 1, acquisition 1		
Observer 1, acquisition 2		*Severe MR*	*Moderate MR*	*Total*
	Severe MR	11	2	13 (26%)
	Moderate MR	1	36	37 (74%)
	Total	12 (24%)	38 (76%)	

MR: mitral regurgitation
Linear weighted kappa = 0.84 (95% CI 0.75-0.93) based on the analysis of 50 patients

Chapter 2

Trans-esophageal echocardiography based computational simulation of the mitral valve for MitraClip placement

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Chamuleau SAJ, Voskuil M, Kraaijeveld AO

Submitted

ABSTRACT

Aims

Percutaneous edge-to-edge repair with the MitraClip system is an established alternative to traditional surgical repair in patients with severe mitral regurgitation. Procedural success is dependent on ideal clip location and number of clips to be placed. In this study, a computer-based model was created and applied to virtually simulate mitral valve closure after virtual MitraClip placement.

Methods and results

A 3-dimensional computer-based reconstruction of the mitral valve was made using trans-oesophageal echocardiography images of two patients with severe mitral regurgitation. Virtual placement of one or more MitraClips resulted in a residual mitral regurgitation which corresponded with the true situation.

Conclusions

Pre-procedural computer-based simulation of MitraClip placement is a promising step towards improving treatment planning and hence procedural success rates, safety, and cost-effectiveness.

INTRODUCTION

Patients with severe functional and/or organic mitral regurgitation (MR) deemed unfit for traditional surgical mitral valve (MV) repair or MV replacement may be eligible for percutaneous edge-to-edge repair with the MitraClip system (Abbott Vascular Structural, Menlo Park, California, USA)[1]. MitraClip therapy has been shown to effectively reduce MR, with low rates of peri-operative morbidity and mortality[2]. Success rates are dependent on individual patient characteristics, operator expertise/experience, and technical advancements. Procedural challenges such as optimal clip location placement, and ideal number of clips to be placed are performed using trial and error and are susceptible to procedural inefficacy resulting in residual MR or mitral stenosis.

In this study a patient-specific 3-dimensional reconstruction (FEops, Ghent, Belgium) of the MV of two patients allowed for anatomical assessment in an interactive fashion. Computational simulation demonstrated deformation of the MV leaflets across the cardiac cycle, which corresponded well with true 3D trans-oesophageal echocardiography (TOE) images.

Subsequently, virtual placement of one or more MitraClips may provide insight into expected residual MR and hence increase procedural treatment planning and cost-effectiveness, and will be of value for educational purposes.

METHODS

A 3-dimensional model of the mitral valve is produced based on 3-dimensional TOE (Figure 1A). Image acquisition requires 3 to 4 heartbeat interpolation under ventilator breath hold with a target framerate of 20-25 frames per beat and full visualization of the annulus and leaflets. Images are exported using Qlab (Philips) and the 4-dimensional (3-dimensional + time) DICOM stack of images are imported into 3D Slicer, a platform for medical image analysis and visualization[3]. Manual segmentation (red and blue dots) of the annulus (Figure 1B) and both valve leaflets (Figure 1C) is performed in the mid-diastolic frame.

Next, a template mesh registration of the leaflet pointcloud was performed (Figure 2A), which was subsequently used to virtually add chordae (Figure 2B). Annular displacement boundary conditions (Figure 2C) were defined based on true annulus position in diastole (blue) and systole (red). The finite-element surface mesh geometry and boundary conditions were generated in pyFormex (an open-source Python-based framework for processing complex 3D geometries) and includes anterior (gray) and posterior leaflets (brown), and marginal chordae and their papillary muscle attachments. The finite model (Figure 2D) is shown in surgical view and only the leaflets are shown.

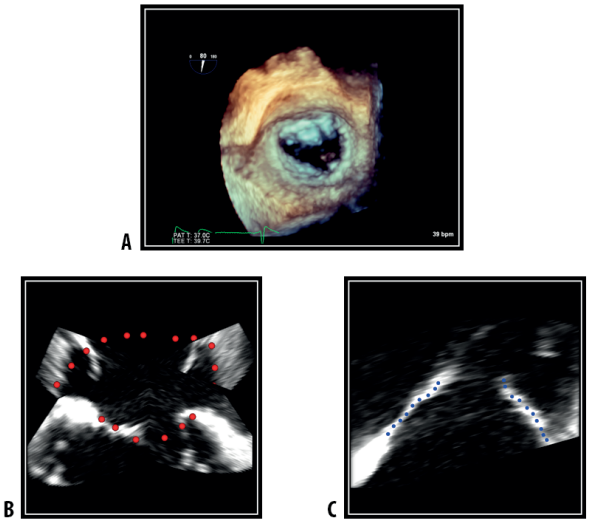

Figure 1. TOE image tracing
A) 3-dimensional trans-oesophageal echocardiography image of mitral valve in surgical view. B) Manual segmentation of annulus (red dotted line) and valve leaflets (C) (blue dotted line).

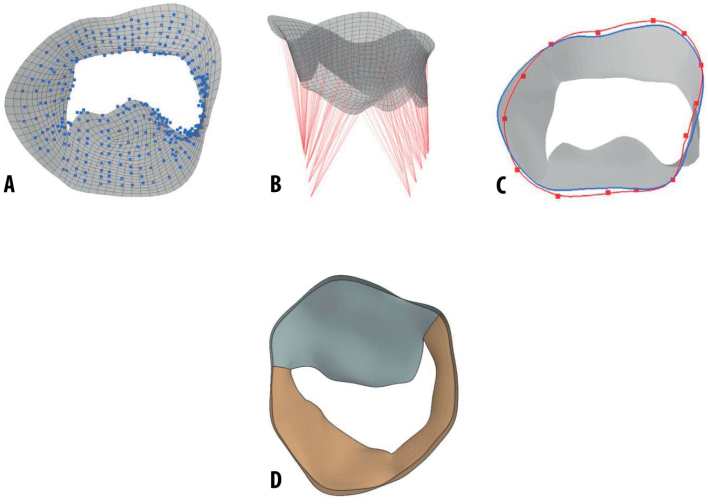

Figure 2. Simulation pre-processing
A) Template mesh registration of the leaflet pointcloud. B) Virtual addition of chordae. C) Determination of annular displacement boundary conditions, based on true annulus position in diastole (blue) and systole (red). D) Finite model shown in surgical view with anterior (gray) and posterior (brown) leaflets.

RESULTS

Two patients (Figure 3) with grade 4 MR were analyzed. The mechanism of MR was in both cases caused by annular dilation and retraction of one, or both valve leaflets. Mid-diastolic models for both patients are shown on the left in Figure 3. Systolic closure (right) of the mitral valve was simulated under a pressure load (120 mmHg, or 0.016 MPa) using ABAQUS/Explicit (Dassault Systèmes, Providence, USA). In both patients retraction of the posterior valve leaflet can be seen with resulting MR.

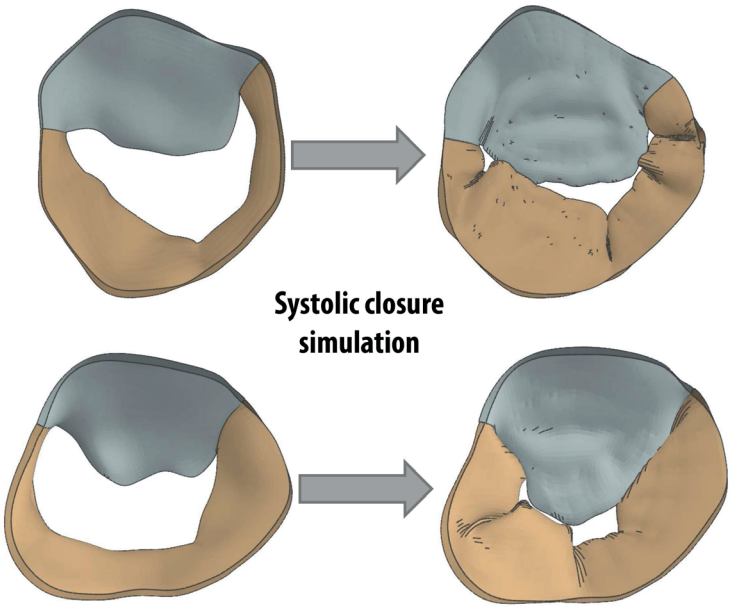

Figure 3. Systolic closure simulation
Mid-diastolic models for both patients (left). Systolic closure (right) of the mitral valve was simulated under a pressure load. In both patients retraction of the posterior valve leaflet can be seen with resulting mitral regurgitation.

The simulated leaflet position (purple lines) derived from the systolic closure model of both patients (top and bottom) was compared with true TOE imaging (Figure 4A). In (Figure 4B) a color plot is displayed showing the distance in millimeters between the simulated systolic mitral valve in and the true systolic mitral valve contours traced from TOE images. The average distance error for patient 1 (left) was 0.9 mm, while the average error for patient 2 (right) was 0.7 mm. Largest distance error (maximum 5 mm, red) was observed in folds between scallops, and commissures.

A Mitraclip was virtually added to the model grasping the anterior and posterior leaflets together (Figure 5A). Mitraclip location was estimated based on the true post-clip 3-dimensional TOE images. In both patients (top and bottom), systolic closure with the MitraClip (2 clips in patient 1, top) was simulated (Figure 5B).

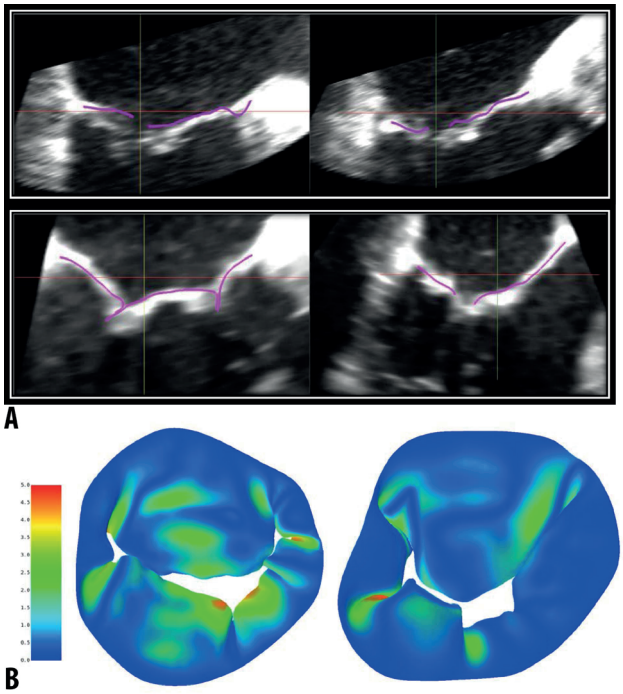

Figure 4. Qualitative and quantitative comparison with true echocardiographic imaging
A) Simulated leaflet position (purple lines) derived from the systolic closure model of both patients (top and bottom), compared with true trans-oesophageal echocardiography (TOE) imaging. B) Color plot showing distance (millimeters) between simulated systolic mitral valve and true systolic mitral valve contours traced from TOE images.

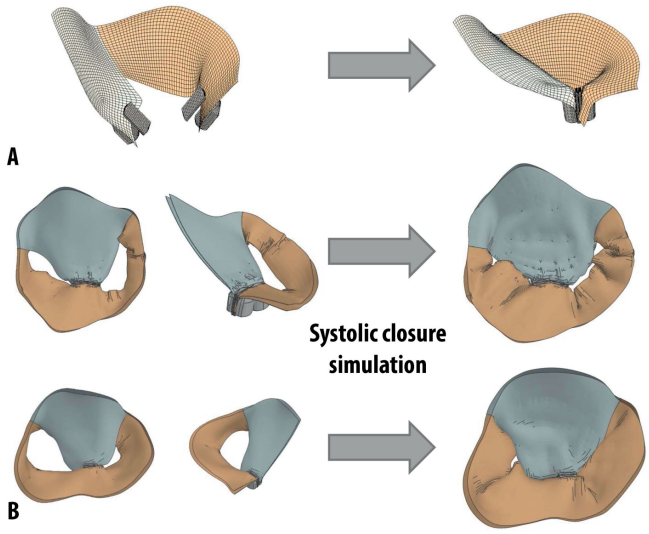

Figure 5 Mitraclip simulation
A) Virtual MitraClip addition. B) Systolic closure simulation.

Patient 1 (Figure 5, top) shows a small residual MR at A3-P3, which coincides with a grade 1 residual MR in the true position (Figure 6A). Likewise, patient 2 (Figure 5, bottom) shows a negligible commissural residual MR, which coincides with the insignificant MR in the true position (Figure 6B). The Mitraclip causes an artifact in the post-procedural TOE images making a quantitative comparison (colorplot, as seen in Figure 4b) inaccurate.

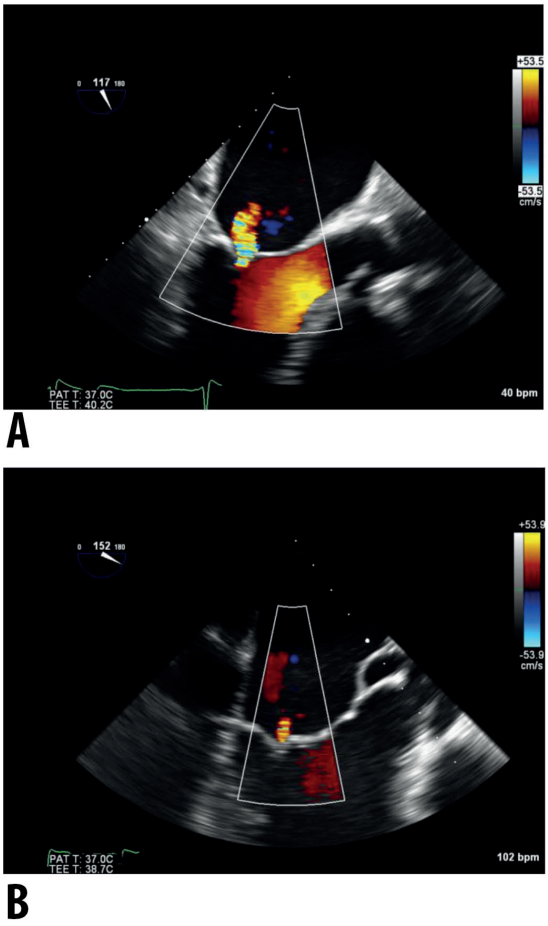

Figure 6 True residual MR
Trans-oesophageal echocardiography color Doppler images of residual mitral regurgitation of patient 1 (A) and patient 2 (B).

Figure 6 shows TOE color Doppler images of residual MR of both patients. Patient 1 (Figure 6A) shows a grade 1 residual MR at A3-P3. Patient 2 (Figure 6B) shows an insignificant residual MR.

DISCUSSION AND LIMITATIONS

In this study, a proof-of-concept was demonstrated of a computer-based simulation of the MV, including MitraClip, in two patients with severe MR. Using this software, pre- and post-procedural TOE images were used to successfully create a model which can be seen as representation of true conditions. A high level of agreement was observed between the computer simulated model and the true leaflet positions, as seen in the color plot. The average error for both patients was 0.7 and 0.9 mm respectively, with a maximum error of 5 mm in folds between scallops. Fine-tuning of technical aspects with more patient data is likely to reduce average error. Qualitative assessment of the location of the residual MR coincided well with the true residual MR as seen in the Color Doppler images.

To date, no publications of a virtual creation of a computer based model of the mitral valve using TOE are available. However, using computed tomography, magnetic resonance imaging, and ultrasound a few studies have demonstrated creation of a mesh model of the left ventricular endocardium[4] and aortic root[5,6]. Although technical improvements are to be made, these computer-based pre-procedural assessments of individual patient data mark a new frontier in personalized medicine.

In a clinical setting, pre-procedural virtual MitraClip placement may be of benefit for several reasons. Firstly, the mechanism of the MR may be visualized more easily in a 3-dimensional fashion. Secondly, the feasibility of clip placement may be assessed by analyzing valve movement/length, and coaptation area. Finally, an estimation of clip(s) location can be made with subsequent residual MR, a significant step forward compared with the trial-and-error aspect in the actual procedure.

The technique outlined in this article is susceptible to limitations. Simulation is highly dependent on TOE image quality and image acquisition should ideally be performed by an experienced operator. Furthermore, segmentation of the annulus and valve leaflets is performed manually, leaving software simulation subject to human error.

CONCLUSION

The method described here represents the first step towards a new innovative technique where virtual simulation of the mitral valve and subsequent MitraClip placement may be performed prior to the actual procedure. The ideal number of clips to be placed and their ideal location may be determined on beforehand, which may greatly improve procedural planning, result rates, safety, and cost-effectiveness. In future studies, multi-patient analysis of the predictive value will reveal the potential of this model.

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RELATIONSHIP WITH THE INDUSTRY:

This study was funded by: Abbott Vascular Netherlands, Heerlen, the Netherlands.
Abbott was not involved in the collection, analysis, or interpretation of the data, nor where they involved in the preparation, review, or approval of the manuscript.

Conflict of interest:

Matthieu de Beule is the CEO of FEops
Sander de Bock is an employee at FEops
The other authors have no conflict of interest

Abbreviations

MR	Mitral Regurgitation
MV	Mitral Valve
TOE	Trans-oesophageal echocardiography

Chapter 3

Trans-thoracic echocardiography guided MitraClip placement under conscious sedation

Hart EA, Teske AJ, Voskuil M, Stella PR, Chamuleau SAJ, Kraaijeveld AO

Journal of American College of Cardiology: Cardiovascular Interventions
2017; 10(3): e27-e29

We report a case of a 77-year old male patient with a history of atrial fibrillation, ischemic dilating cardiomyopathy (left ventricular ejection fraction <20%), severe mitral regurgitation (MR) and a cured esophageal adenocarcinoma. He had symptomatic heart failure NYHA class III/IV. The heart team deemed the patient unfit for conventional surgery and MitraClip (Abbott Vascular, Menlo Park, California) placement was recommended. Transcatheter MitraClip placement is traditionally performed using trans-esophageal echocardiography (TEE). However, the history of esophagectomy left the patient unfit for TEE-guided MitraClip placement due to a significant stenosis at the esophagogastric junction and a blind pouch (Figure 1A).

To the best of our knowledge, we demonstrate the first ever successful treatment of severe MR through trans-thoracic echocardiography-guided MitraClip placement without general anesthesia.

Pre-procedurally, trans-thoracic echocardiography revealed severe grade 4/4 MR (Figure 1B) due to left ventricular dilation with retraction and displacement of the posterior (P1-P3) valve leaflet and retraction of the anterior (A1-A3) leaflet, resulting in malcoaptation. The effective regurgitant orifice was 0.80cm^2, with a regurgitant volume of 80ml/beat and pulmonary vein systolic reversal. Adequate image acquisition in supine position including 3-dimensional images images (Online Video 1) was assessed pre-procedurally. During the procedure, trans-thoracic echocardiography was performed in supine position with the patient under conscious sedation. Transseptal puncture was guided by the 4- and 5-chamber apical view (Figure 1C), with careful assessment of needle position in relation to the aorta using the parasternal short axis view. Positioning of the MitraClip guide wire/catheter (Figure 1D) and subsequent introduction of the clip within the left ventricle was performed in the 2-, 3- and 4 chamber apical view (Figures 1E and 1F). Two clips were successfully placed (Online Videos 2 and 3), 1 clip joining scallops at A3-P3 and one at A2-P2 (Figures 1G and 1H). MR was reduced to grade 2 (Figure 1I) with an effective regurgitant orifice of 0.20cm^2 with a regurgitant volume of 24ml per beat and partial restore of pulmonary vein systolic flow. Mean pressure gradient was 4.6 mm Hg at 96 beats per minute. The postoperative course was uneventful.

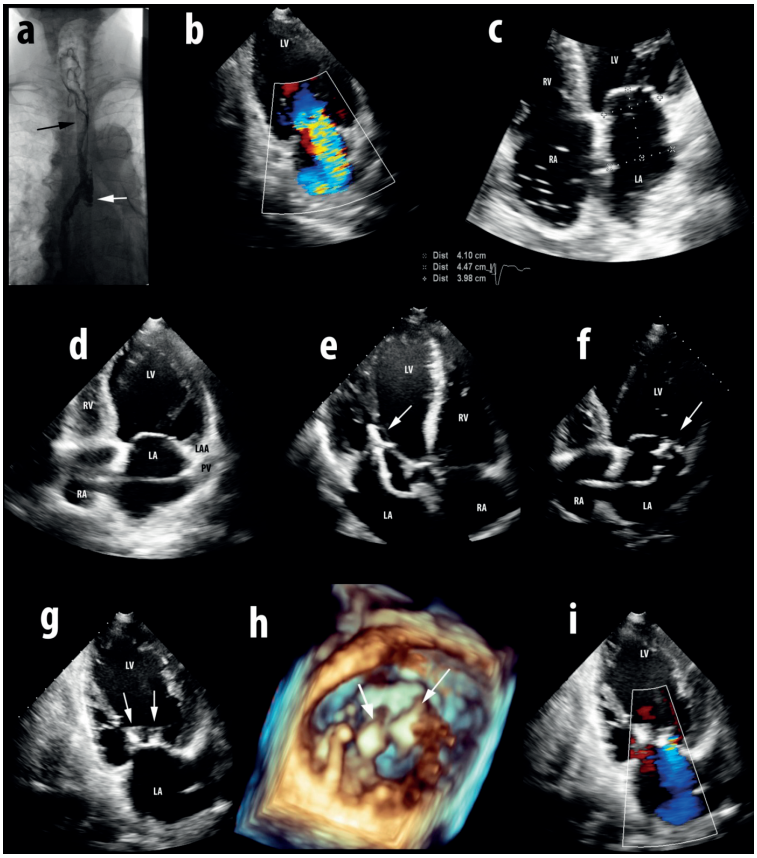

Figure 1 MitraClip Placement Guided by Transthoracic Echocardiography

A) Angiogram of esophagus showing stenosis (black arrow) and blind pouch (white arrow) B)2-chamber view showing pre-procedural severe mitral regurgitation (Online Video 1). C) Measurement of correct height for atrial septum puncture. D) Guide wire extending into pulmonary vein. E, F) A 4-chamber introduction of Mitraclip (white arrow) (Online Videos 2 and 3). G) Mitraclips in situ (white arrows). H) A 3-dimensional view with MitraClips in situ (white arrows). I) A 2-chamber post-procedure moderate mitral regurgitation.

LA = Left atrium; LAA = Left atrial appendage; LV = Left ventricle; PV = Pulmonary vein; RA = Right atrium; RV = Right ventricle.

Chapter 4

Hemodynamic and functional consequences of the iatrogenic atrial septal defect following Mitraclip therapy

Hart EA, Zwart K, Teske AJ, Voskuil M, Stella PR,
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Netherlands Heart Journal 2017; 25:137-142

ABSTRACT

Percutaneous MitraClip placement for treatment of severe mitral regurgitation in high surgical risk patients is a commonly performed procedure and requires a transseptal puncture to reach the left atrium. The resulting iatrogenic atrial septal defect (iASD) is not routinely closed, yet the hemodynamic and functional consequences of a persisting defect are not fully understood. Despite positive effects such as acute left atrial pressure relief, persisting iASD's are associated with negative consequences, namely significant bidirectional shunting and subsequent worse clinical outcome. Percutaneous closure of the iASD may therefore be desirable in selected cases. In this review we discuss the available literature on this matter.

INTRODUCTION

Percutaneous mitral valve repair for the treatment of severe mitral regurgitation has become a safe and widely used alternative for mitral valve surgery in high-risk surgical patients[1–4]. Although repair with the MitraClip (Abbott Vascular Structural, Menlo Park, California, USA) is less effective at reducing mitral regurgitation (MR) compared to conventional surgery, the procedure is associated with superior safety and similar improvements in clinical outcome with respect to quality of life, heart failure status and left ventricular function (LVF)[5].

The MitraClip guiding catheter (24 French) is commonly introduced via the right femoral vein and requires a transseptal puncture to access the left atrium, leaving an iatrogenic atrial septal defect (iASD). Manipulation of the catheter allows the system to grip the mitral valve leaflets, subsequently effectively reducing the regurgitant orifice[6] (figure 1).

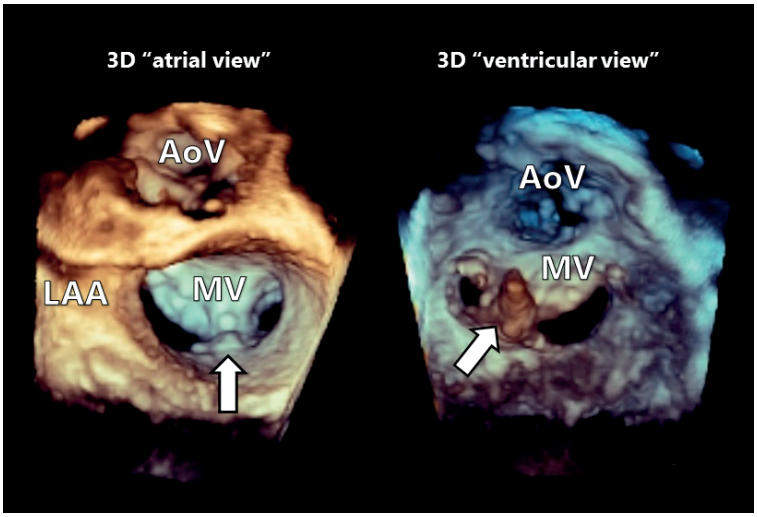

Fig. 1 3D atrial view (left) and 3D ventricular view (right) of MitraClip in situ (arrows)

A complete overview of the MitraClip procedure is described by Feldman et al.[1]. Other percutaneous procedures (7-14 French) requiring transseptal punctures, such as pulmonary vein isolation , left atrial appendage closure, and percutaneous balloon mitral valvuloplasty likewise result in an iASD and persistant shunting has been reported[7–9]. The hemodynamic consequences in these procedures are thought to be minimal and therefore closure of the iASD is not routinely performed. As iASD size increases exponentially with catheter size[10], the iASD following the MitraClip procedure (Figure 2) might induce hemodynamic significant shunting, although little is known on this subject.

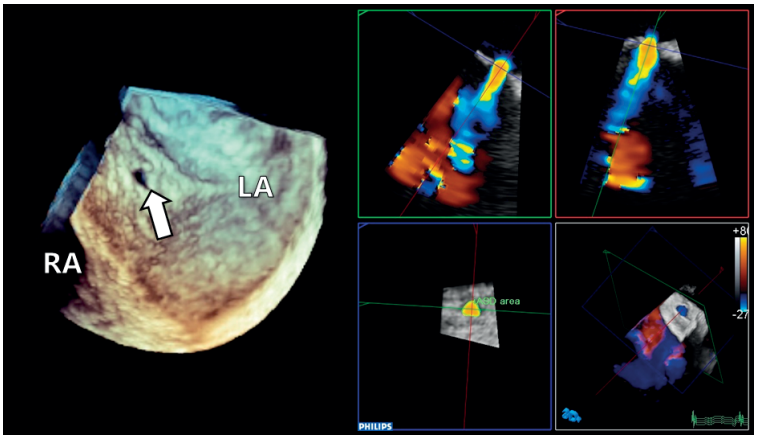

Fig. 2 3D view of iatrogenic atrial septum defect (left) and display of shunt using color Doppler (right)

For example, atrial septum defects with long term left-to-right shunting are associated with right ventricular (RV) dilatation, ultimately leading to RV failure, pulmonary hypertension, and arrhythmias[11–14]. In this review we discuss the aspects of the iASD after MitraClip placement and focus on 1) the prevalence, 2) hemodynamic consequences, 3) case report publications, and finally 4) individual risk assessment.

A pubmed search was performed on May 12th 2016, identifying studies related to the iASD following MitraClip therapy. Search terms used were: ((atrial septal defect) OR ASD OR (septal defect)) AND (mitraclip OR (mitral clipping) OR (mitral valve clips) OR (mitral valve repair) OR (mitral repair)). The search yielded 869 hits. We included relevant case reports, articles reporting on the prevalence of iASD following MitraClip procedure, and articles discussing hemodynamic consequences of the iASD. After cross-checking references we found four papers reporting on the prevalence[13,15–17], four papers assessing the hemodynamic consequences[13,15,16,18], and four papers reporting on a total of seven case reports[16,19–21].

Prevalence

The prevalence of the iASD has been investigated in several studies (Table 1).

Table 1 Prevalence of iASD following MitraClip therapy

Study	Method	N	Prevalence of iASD		
			1 month	6 months	12 months
Smith et al. 2012[15]	TTE	30	43%	27%	27%
Ussia et al. 2014[16]	TTE	28	81%	n/a	n/a
Saitoh et al. 2012[17]	TOE	11	82%	n/a	n/a
Schueler et al. 2015[13]	TOE	66	n/a	50%	n/a

iASD: iatrogenic atrial septal defect; TTE: Transthoracic echocardiography; TOE: Transoesopheagal echocardiography

Smith et al. reported a 1-month prevalence of 43% (average diameter 6.0mm ±2.3mm), and 27% (6.6mm ±3.1mm) at 12 months, identified using color flow Doppler in the apical four chamber or subcostal view on trans-thoracic echocardiography (TTE)[15]. Ussia et al. (TTE) and Saitoh et al. (trans-oesopheagal echocardiography (TOE)) recorded a significantly higher prevalence of 81% (average diameter 4.5mm ±3.1mm) and 82%, respectively, after one month while Schueler et al. observed a 50% prevalence using TOE and color Doppler at 6 months with a maximal diameter of 4.3 mm ±1.7mm and minimal diameter of 3.8mm ±2.1 mm[13,16,17].

Various studies have reported on iASD prevalence following non-MitraClip procedures (i.e. ablation procedures[7,22–24], LAA[25], and PBMV[9,26–29]). McGinty et al. grouped iASD incidence from these studies and found an average iASD prevalence of >35% immediately following the procedure, 20% at 1-6 month follow-up, and >10% at 6 months[30]. A direct correlation between catheter size, iASD diameter, and prevalence[10,16] may explain the higher iASD prevalence following MitraClip placement compared with non-MitraClip procedures.

Predisposing factors for the long-term prevalence of iASDs have been suggested and include residual high transmitral gradient, left-ventricular (LV) hypertrophy, increased left atrial (LA) pressure from residual MR (MR grade 2.7 ±1.1 for iASD versus 1.5 ±0.9 for non-iASD)[15], duration of the procedure[7,15,16,27], and mitral valve calcification[9,28].

Hemodynamic consequences

We identified four studies assessing hemodynamic and functional consequences of the iASD following MitraClip placement (Table 2).

Table 2 Hemodynamic and functional consequences of iASD

Study	N	Effect	Conclusion
Hoffman et al. 2014[18]	28	Positive	Immediate volume and pressure relief left atrium
Smith et al. 2012[15]	30	Neutral	iASDs are not hemodynamically significant
Ussia et al. 2014[16]	28	Negative	Three (11%) patients developed negative hemodynamic consequences, requiring closure of the iASD
Schueler et al. 2015[13]	66	Negative	Persistent iASDs are associated with worse clinical outcome and increased mortality rates

iASD: iatrogenic atrial septal defect

Hoffman et al. included 28 high-risk or inoperable patients with symptomatic mitral regurgitation[18]. TOE was used to measure the velocity-time integral across the iASD and the iASD area (0.19cm^2 ±0.05) immediately following guiding catheter withdrawal, which allowed for the calculation of the shunt volume (14±6 ml/beat). Invasive LA pressure measurements showed a reduction from 17±8 mm Hg to 15±8 mmHg upon catheter withdrawal, contributing to LV preload reduction. The authors concluded that the iASD resulted in immediate volume and pressure relief of the left atrium. Unless the patient suffers from pulmonary hypertension this effect may prove to be beneficial, although long-term effects were not assessed in this study.

Smith et al. reviewed the echocardiographic features and predictors of iASD following MitraClip placement in 30 patients[15]. Using TTE, RV size, LA volume and tricuspid/mitral regurgitation were quantified in both iASD and non-iASD patients at 12 month follow-up. No significant differences were found in right heart midventricular diameter or LA volume, although the prevalence of an iASD was associated with a relatively high LA volume index (51.4±14mL) at 12 months. Compared with non-iASD patients, there was a significantly higher average tricuspid regurgitation (TR) grade (1.1±0.6 for non-iASD versus 2.1±1.8 for iASD) and persistent MR grade (1.5±0.9 for non-ASD versus 2.7±1.1 for iASD) at 12 months. In conclusion, the authors stated that although the iASD does not appear to be hemodynamically significant, it is associated with relatively high LA pressures, suggestive of a causative role of high LA pressures in the persistence of the iASD.

Ussia et al. assessed the iASD in 28 patients following MitraClip repair[16]. Three patients deteriorated hemodynamically, 2 of which immediately following the procedure, and required iASD closure after which immediate improvement occurred; these cases are described later in this review. The authors suggested the following 3 steps to be taken to aid in the early recognition of potential iASD complications: 1) 3D-TEE assessment of iASD shape and diameter (laceration or diameter >8mm may impair spontaneous closure), 2) postprocedural atrial pressure and O^2 saturation measurement through Swan-Ganz catherization to assess shunt significance, and 3) detection of new supraventricular arrhythmia's which may indicate hemodynamic deterioration.

The study performed by Schueler et al. prospectively followed 66 patients for 6 months following MitraClip implantation and compared clinical outcomes between persistent iASD patients (n=33) versus non-iASD patients (n=33) at follow-up[13]. Apart from a slightly larger basal (5.1±0.8 cm for iASD versus 4.6±0.8 cm for non-iASD p=0.01) and midventricular (3.7±0.8 cm for iASD versus 3.3±0.7 cm for non-iASD p=0.03) RV diameter, no differences in baseline criteria between the two groups were observed. During follow-up, the iASD group showed worsening of systolic pulmonary artery pressure (PAP) post clip placement (+1.6 mmHg versus -10.9 mmHg for non-iASD, p=0.02) and a larger portion of patients remained within New York Heart Association (NYHA) class >II heart failure. At follow-up, the iASD group showed a significant reduction in LA volume (162.5±63.3 mL to 139.1±47.6 mL) suggestive of a positive influence of the iASD. However, the iASD group presented with higher levels of N-terminal pro-brain natriuretic peptide (6667.3±7363.9 ng/dl vs. 4835.9±6681.7 ng/dl for non-iASD, p=0.05) and less improvement in the 6-minute walk test (20.8 ± 107.4 m vs. 114.6 ± 116.4 m, p=0.001). Furthermore, a persisting iASD was associated with a higher all-cause mortality rate at 6 months (16.6% versus 3.3%, p=0.05). Cause of death was not reported and numbers were relatively small, these findings should therefore be interpreted with caution. Furthermore, as stated by the authors, it is unknown whether a persisting iASD is the cause or effect of worse clinical outcomes. Future studies should investigate the exact mechanism behind iASD persistence and subsequently analyze long-term clinical outcomes.

Case studies

We identified 4 case reports describing a total of 7 patients. Huntgeburth et al. described two 70+ year old patients with functional MR grade 4+, severely impaired EF (30-35%), renal impairment and pulmonary disease[19]. These initially stable patients rapidly deteriorated following successfull MitraClip placement. Echocardiographic imaging revealed a bidirectional shunt, predominantly left-to-right, in the first patient. Acute right heart failure and cardiogenic shock prompted iASD closure with an Amplatzer device, after which the patient showed immediate hemodynamic improvement. The second patient presented with impaired LV function (left ventricular ejection fraction (LVEF) of 30%), chronic obstructive pulmonary disease, and an enlarged right heart chamber with compression of the LV. The patient experienced severe right-to-left shunting with a subsequent decline in oxygen saturation in merely hours following the procedure, which was resolved after percutaneous iASD closure. The authors highlighted the need for postinterventional screening for relevant shunt volumes and 24 hour availability for emergency iASD closure.

Ussia et al. described three patients with NYHA class III/IV heart failure undergoing MitraClip placement experiencing hemodynamic deterioration[16]. All 3 patients showed a final MR grade reduction of at least 2 and iASD size ranged from 0.65 to 1 cm. One patient showed showed significant left-to-right shunting eventually leading to the development of right-sided heart failure (15 days post-procedure). The second patient presented with severly impaired LVEF (20%) and a systolic PAP of 30mmHg. Following withdrawal of the catheter the patient immediately developed bronchospasms and pulmonary hypertension with a systolic PAP of 50mmHg and a bidirectional shunt was detected. The third patient presented with pulmonary hypertension (systolic PAP 65 mmHg) and after catheter withdrawal systolic pulmonary pressure increased, right-sided chamber enlargement was observed and a left-to-right shunt was detected, eventually leading to cardiorespiratory arrest. All 3 cases were resolved through percutaneous closure with either an Amplatzer or Figulla Occluder.

Likewise, Losi et al. reported on a 54-year old patient with chronic heart failure (NYHA class IV), poor LVEF, increased systolic PAP (70 mm Hg), and high grade functional MR[20]. Immediately following the procedure the patient experienced a significant drop in the partial pressure arterial oxygen/fraction of inspired oxygen (PaO^2/FiO^2)ratio from 160 to 80, indicative of right-to-left shunting. Closure of the septal defect with an Amplatzer device normalized the PaO^2/FiO^2 ratio to 180. The authors suggested a possible role for the PaO^2/FiO^2 ratio as guidance in identifying a clinically significant shunt.

Finally, Chandraprakasam and Satpathy described the case of a 88-year old female with NYHA class IV heart failure, right ventricular systolic pressure of 60 mmHg, and severe MR undergoing succesfull MitraClip placement[21]. Following the procedure she experienced persistent hypoxemia (O^2 saturation 85%) despite adequate end expiratory values and a FiO^2 of 100%. TOE revealed a predominantly right-to-left shunt. The defect was closed with an Amplatzer device after which the patient improved significantly.

Although rare, these 7 case reports highlight possible consequences of a persisting iASD. The need for iASD closure, and in which patients this may be beneficial, remains an important discussion. In 4 of these cases, right-to-left shunting was detected, indicative of significantly elevated right heart sided pressures. Profylactic closure of the defect should be considered in this patient group, although the suitability of these patients for the MitraClip procedure may altogether be questioned.

Risk assessment

Complications related to the iASD are relatively rare and profylactic closure of the defect in all patients may therefore not be a desirable addition to clinical care. Closure of the defect is a permanent solution and prevents any future transseptal procedures. Furthermore, in the acute phase following clip implantation the iASD may initiate left-to-right shunting which may reduce LA pressure and LV preload, a potentially beneficial effect. Indeed the effect of deliberate trans-catheter creation of an intracardiac shunt has recently been analysed in non-MitraClip heart failure patients. The resulting left-to-right shunt in patients with preserved[31] or reduced[32] LVEF showed a marked decrease in pulmonary capillary wedge pressure in both groups and an improvement in NYHA heart failure class and quality of life score[32].

On the other hand, a careful selection of at risk patients and subsequent closure of the defect in these patients may be beneficial. Patients with marked pulmonary hypertension with right-to-left shunting are at risk of developing significant hypoxia and iASD closure should be considered. Furthermore, patients with poor RV function, pulmonary hypertension and/or significant left-to-right shunting may profit from closure as well. Exact cut-off values for pulmonary hypertension, RV function and left-to-right shunting volume indicating the need for iASD closure are unknown but are of interest for future research. As suggested by others, post-procedural hemodynamic monitoring by right heart catheterization, TOE assessment of shunting and defect size[16], and transient balloon occlusion[14] may aid in selecting these at risk patients.

CONCLUSION

MitraClip patients are most often high-risk surgical patients and represent a unique and relatively vulnerable population. Although closure of the iASD following catheter-based interventions is not routinely performed, the possible consequences of an iASD following MitraClip therapy are still not fully understood. Studies have reported both positive and negative effects of the iASD. Therefore, prospective studies analyzing the role of iASD closure are needed to fully understand the mechanism and impact of the iASD and to identify patients in which closure may be beneficial.

FUNDING

None

Conflicts of Interest: E.A. Hart, K. Zwart, A.J. Teske, M. Voskuil, P.R. Stella, S.A.J. Chamuleau and A.O. Kraaijeveld declare that they have no competing interests.

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Part Two

Carcinoid Heart Disease

Chapter 5

Carcinoid heart disease: a guide for screening and timing of surgical intervention

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Netherlands Heart Journal 2017; 25(9): 471-478

ABSTRACT

The cardiac manifestations of a neuroendocrine tumour are referred to as carcinoid heart disease (CaHD) and are associated with a poor prognosis. Surgical intervention is the only proven therapeutic option and may prolong survival and quality of life. No consensus has been reached internationally with regard to screening for CaHD and the optimal timing for surgery. Although limited evidence is available on this matter, a trend towards early surgery and subsequent reduced mortality has been observed. In this review we provide an overview of the current understanding and propose a protocol to guide cardiologists in the screening for CaHD and the timing of referral to a specialised surgical centre.

INTRODUCTION

Neuroendocrine tumours

Well-differentiated neuroendocrine tumours (NETs) are rare malignancies, occurring in 5.25 per 100,000 people per year [1]. The majority of NETs develop in the small intestine, particularly in the ileum, and in the bronchopulmonary system. Less frequently NETs arise from other sites within the gastrointestinal tract, including colon, rectum and stomach [2]. Some of these tumours, in particular small intestinal NETs, secrete various vasoactive substances, including serotonin (5-hydroxytryptamine; 5-HT), tachykinins, prostaglandins, histamine, and kallikrein. Typically, the liver inactivates these substances when released into the portal circulation. However, when a serotonin-producing NET metastasises to the liver, direct access to the systemic circulation may result in carcinoid syndrome. Carcinoid syndrome is characterised by episodic cutaneous flushing, hypotension, gut hypermotility with diarrhoea, and bronchospasms [3–5].

Carcinoid heart disease

Patients with carcinoid syndrome are at risk to develop carcinoid heart disease (CaHD), also known as Hedinger syndrome. Since the introduction of somatostatin analogues, the incidence of CaHD has dropped from over 50% [6] to approximately 20% in patients with carcinoid syndrome [7]. CaHD is most likely caused by the paraneoplastic effects of vasoactive substances excreted by the tumour, particularly serotonin [5,7,8]. Although patients with CaHD are often asymptomatic in the early stages of the disease [9], signs of right heart failure are associated with disease progression.

The disease is characterised by plaque-like deposits of fibrous tissue involving the endocardium of the valve leaflets, cardiac chambers, and less frequently the intima of the pulmonary arteries and aorta [10]. Primarily the right side of the heart is affected, due to thickening and retraction of the tricuspid and pulmonary valve leaflets, with subsequent regurgitation and/or stenosis. Left-sided valve involvement occurs in less than 10% of patients with CaHD and is commonly observed in patients with a right-to-left shunt (e.g. patent foramen ovale) and elevated right heart-sided pressures, bronchial NETs or severe carcinoid syndrome with high amounts of vasoactive substances [6]. Sporadically, left-sided valvular disease is present in the absence of right-sided valve involvement [11,12]. There is no clear explanation for the predominant right-sided valve involvement. Vasoactive substances excreted by the tumour are thought to be largely inactivated within the pulmonary circulation [13].

The presence of CaHD has a detrimental effect on the prognosis of NET patients and therefore early diagnosis and treatment, if possible, are of major importance [6,14]. More specifically, the cause of death in CaHD patients is attributable to cardiac involvement in almost half of the cases [15].

In this review we present two case studies illustrating typical CaHD presentations. Next, we provide an overview of the current understandings and guidelines regarding CaHD. Addition-

ally, a step-by-step approach is provided with regards to the screening, diagnosis, and surgical management.

DIAGNOSIS

Biomarkers

Several biochemical markers are useful in the diagnosis of CaHD and are related to disease progression and prognosis. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels are significantly elevated in patients with CaHD compared with those without [16]. Due to its high sensitivity and specificity for the detection of CaHD in NET patients (92% and 91%, respectively), NT-proBNP may be useful as a screening test [16,17]. Moreover, NT-proBNP levels are correlated with disease progression and survival [18].

High levels of chromogranin-A, a neuroendocrine secretory protein, are associated with the development of CaHD in NET patients [19] and with worse survival, especially when NT-proBNP levels are elevated.

5-Hydroxyindoleacetic acid (5-HIAA) is a metabolite of serotonin and its urinary excretion directly correlates with serotonin production. Urinary 5-HIAA levels are significantly higher in NET patients with CaHD than in those without, and higher levels are associated with progression of cardiac involvement [9,13]. Although specificity is low, suggesting the development and progression of CaHD is co-dependent on other factors [20], aggressive treatment to decrease 5-HIAA levels is advisable.

Imaging

Echocardiographic assessment is the gold standard for the detection of CaHD [21]. Two-dimensional and three-dimensional visualisation of fibrous plaques of the endocardium should be performed, as well as evaluation of wall thickness, wall motion abnormalities and right and left ventricular dimensions and function [21,22]. More recently, the use of strain imaging (i.e. tissue Doppler imaging) has emerged as a helpful tool in the detection of early right ventricular (RV) dysfunction [23] and identification of high-risk patients [24].

Analysis of the pulmonary and tricuspid valve may reveal leaflet thickening with retraction and reduced mobility resulting in severe regurgitation, stenosis, or both [21,22].

The presence of a patent foramen ovale may be detected through bubble or saline-contrast echocardiography. Myocardial carcinoid metastases are rare (4%) [6], primarily intramyocardial, and may be the only manifestation of CaHD [10]. On echocardiography these tumours can be identified by their homogeneous aspect and clearly defined contours.

RV size, function (ejection fraction) and regurgitant volumes are more accurately assessed using cardiac magnetic resonance (CMR) imaging. CMR imaging may therefore be a helpful tool when transthoracic echocardiography (TTE) is insufficient. Additionally, CMR imaging allows for

careful assessment of myocardial tissue and may therefore aid in the detection of fibrous plaques and myocardial metastases [22,25]. The typical features of CaHD are summarised in Table 1.

Table 1. Typical characteristics of carcinoid heart disease

Ø	Significant tricuspid regurgitation
Ø	Mixed pulmonary regurgitation and stenosis
Ø	Concomitant left-sided valve involvement (<10%), primarily in patients with persistent foramen ovale, bronchial carcinoid or severe carcinoid syndrome
Ø	Pathognomonic fibrous plaques on echocardiography involving the endocardium of valve leaflets and cardiac chambers
Ø	Intramyocardial metastases

Below, two typical CaHD cases are described with significant tricuspid regurgitation and intramyocardial metastases, respectively.

Case report 1

A 47-year-old male with hepatic metastases of a NET of the ileum presented with progressive complaints of dyspnoea and hepatomegaly. TTE revealed severe tricuspid regurgitation with marked leaflet thickening, restriction of all three leaflets (Fig. 1), and a characteristic dagger-shaped jet on continuous wave Doppler (Fig. 1). Further assessment showed moderate RV dilation with mild RV dysfunction, mild pulmonary regurgitation, and mild mitral regurgitation based on leaflet thickening and retraction of the posterior leaflet. A patent foramen ovale was detected. Left ventricular (LV) function was normal. In anticipation of carcinoid progression of valve dysfunction the patient underwent successful tricuspid, mitral, and pulmonary valve replacement with bioprosthetic valves. The foramen ovale was closed. Postoperatively the RV function normalised and the tricuspid regurgitation was categorised as mild. Shortly thereafter the patient underwent successful resection of the primary tumour. Four months later the patient is in relatively good condition without signs of right heart decompensation and will be seen in the outpatient clinic for TTE in 3 months.

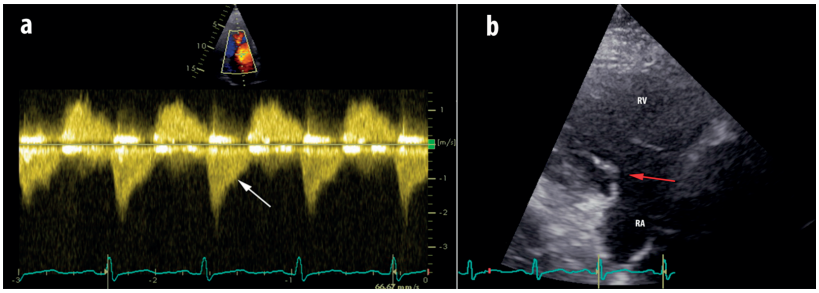

Fig. 1 a) Characteristic 'dagger' shaped jet on continuous wave Doppler b) Parasternal view of RV inflow tract showing thickening and retraction of tricuspid leaflets (arrow) during systole. *RV* right ventricle; *RA* right atrium

Case report 2

A 74-year-old male with hepatic metastases of a NET of unknown origin was admitted to hospital with thoracic pain, suspicious for acute coronary syndrome, and fever. Electrocardiography revealed marked ST elevations in leads II, III, AVF, V2-V6, and negative T waves in the precordial leads. Further diagnosis ruled out myocardial ischaemia. No clinical signs of heart failure were present and TTE showed no valvular abnormalities. CMR imaging revealed two apical intramyocardial lesions (Fig 2). The patient was diagnosed with pericarditis secondary to the intramyocardial carcinoid metastases. No surgical options were available. To date the patient has started on peptide receptor radionuclide therapy (PRRT) and will be seen in the cardiology outpatient clinic every 6 months.

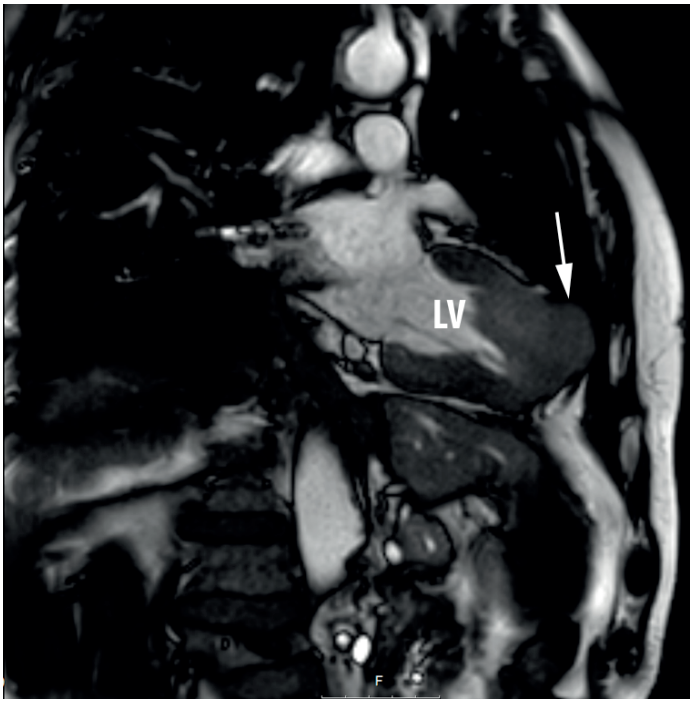

Fig. 2 CMR image of one of the two apical intramyocardial lesions (arrow). *LV* left ventricle

Management

NET patients with CaHD have a significantly decreased life expectancy compared with patients without cardiac involvement [6,14]. Therefore, early detection and treatment is crucial in preventing right heart failure and improving prognosis. The management of CaHD can be divided into three components: medical therapy, non-cardiac interventions, and cardiac interventions.

Medical therapy

The main goals in the treatment of patients with carcinoid syndrome are prolongation of progression-free survival, symptom control and subsequent improvement in quality of life. Somatostatin analogues inhibit hormone hypersecretion by binding to somatostatin receptors present on the majority of NET cells [26]. Octreotide [27] and lanreotide [28] have been shown to prolong progression-free survival; however, a significant effect on overall survival has not been demonstrated. In patients with carcinoid syndrome refractory to somatostatin analogues, the novel therapeutic agents telotristat and pasireotide have shown promising results for symptom control [29,30].

In patients with inoperable or metastatic NETs, PRRT with radiolabelled somatostatin analogues may prove to be beneficial. [31]. PRRT allows for targeted delivery to tumour cells and its effect has been analysed in several large studies [32–34].

More recently, everolimus [35], a mechanistic target of rapamycin (mTOR) inhibitor, and sunitinib [36], an oral vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor, were approved by the US *Food and Drug Administration (FDA)* for the treatment of advanced pancreatic NETs in 2011 [31]. Despite prolongation of progression-free survival, no increase in overall survival was recorded.

In rapidly progressing pancreatic NETs with a high tumour burden, or in patients with non-pancreatic NETs without other treatment options, chemotherapy is indicated [31,37], despite the absence of studies showing a beneficial effect on overall survival. Alkylating agents such as streptozocin and temozolomide have been FDA approved although their use is limited due to their toxicity [31]. Temozolomide is deemed less toxic than streptozocin and has shown promising antitumour activity when administered in combination with capecitabine, a prodrug of 5-fluorouracil [31,37].

NON-CARDIAC INTERVENTIONS

Metastatic disease can be a contraindication for surgical resection of the primary tumour. In contrast, resection of hepatic metastases seems to decrease the risk of cardiac progression and improve prognosis [22]. However, hepatic surgery carries a significant risk of extensive periprocedural bleeding in patients with CaHD, due to the elevated pressures in portal and transhepatic circulation secondary to tricuspid regurgitation. Therefore, cardiac valve surgery is chronologically preferred over hepatic surgery in these patients [22]. Following valve replacement, hepatic resection can be performed relatively safely and is associated with similar outcomes when compared with NET patients without cardiac involvement [38]. Hepatic intra-arterial therapies such as transarterial chemoembolisation and bland embolisation, and selective internal radiotherapy with yttrium-90 microspheres may serve as an alternative to hepatic resection and is predominantly indicated in patients with hepatic metastases [31]. These

techniques may induce tumour regression and achieve symptom control. However, limited evidence is available on these interventions and a favourable effect on the progression of CaHD has hence not been demonstrated.

CARDIAC INTERVENTIONS

Upon onset of New York Heart Association (NYHA) heart failure class III or IV symptoms in patients with CaHD, 2-year survival has been recorded as low as 10% [39]. Valve replacement is the only effective treatment option for symptomatic CaHD patients and is associated with symptomatic improvement [20,40] and increased survival [20,39–44]. Recently, 200 CaHD patients (of which 87 underwent cardiac surgery) were analysed and all-cause mortality was assessed [41]. The average age was 63 years and the majority of patients were in NYHA class II or III. Predictors of 10-year all-cause mortality by multivariate Cox proportional hazard analysis were age, urinary 5-HIAA excretion, moderate or severe RV dilation, and cardiac surgery. Cardiac surgery was associated with a risk reduction of 0.48 (95% CI 0.31 to 0.73, $p<0.001$). However, these data should be interpreted in light of the non-randomised study design with patients diagnosed in a large time frame from 1981-2000. Importantly, the percentage of patients who underwent cardiac surgery has increased over the years. It is therefore conceivable that the beneficial effect of surgery is influenced by other factors, such as improved medication, experience, and patient selection. A more recent study analysed outcomes after surgical valve replacement in 19 patients [42]. The mean age was 56 years and the average NYHA class was III. A 5-year survival rate of 43% was found. No predictors for mortality were identified although preoperative 5-HIAA levels were lower in patients who were still alive during data analysis than in those who died (not significant). In a similar study short- and long-term outcomes of CaHD following valve replacement were retrospectively assessed [39]. In total 195 patients were analysed. The mean age was 61 years and 70% of the patients were classified in NYHA class III and IV. All patients underwent tricuspid valve replacement, and 81% pulmonary valve replacement. Survival rates at 1, 5, and 10 years were 69%, 35%, and 24%, respectively. Univariate predictors of overall mortality included age, preoperative creatinine, NYHA class, use of loop diuretics, preoperative chemotherapy, ascites, diabetes mellitus, tobacco use, left-sided valve disease, and right-sided heart size and function.

Patients who are ineligible for cardiac surgery may benefit from pulmonary balloon valvuloplasty. Case studies have been reported where balloon valvuloplasty was performed with major clinical improvements afterwards [45,46], although relapsing stenosis poses a significant threat [47]. Therefore, surgery should be preferred.

Perioperative care

Tumour catecholamine release is catalysed by emotional stress, hypercapnia, hypothermia, and hypotension [48]. Furthermore, perioperative vasoactive medications such as epinephrine, norepinephrine, and dopamine are frequently administered to maintain adequate circulation [49], yet are known to provoke carcinoid crisis [48,49]. Therefore these substances should be administered with caution. At the same time, at the onset of marked hypotension it is difficult to differentiate between carcinoid crisis and the haemodynamic consequences of RV failure. Furthermore, the postoperative course of these patients may also be complicated by bleeding and acute renal dysfunction [50]. Hence the perioperative anaesthetic management of a NET patient with carcinoid syndrome is challenging and requires optimal monitoring. Table 2 provides an overview of the perioperative steps to be taken in anticipation of a carcinoid crisis during surgery.

Table 2. Perioperative and hypotension management of cardiac surgery in NET patients

Perioperative management
Ø Discontinue ACEi
Ø 500 g octreotide bolus i.v. preoperatively + i.v. octreotide pump 2000 g/24 hours
Ø Stop octreotide after detubation if patient is hemodynamically stable
Hypotension
Ø NaCl 0.9%
Ø 500-1000 g octeotride bolus + octeotride pump 50-200 g/hour
Ø Inotropes with caution. Only norepinephrine or dopamine
ACEi, Angiotensin converting enzyme inhibitor; i.v., intravenously

ACEi angiotensin converting enzyme inhibitor; *iv* intravenously

SCREENING AND FOLLOW-UP

Due to the complexity and rarity of CaHD, patients should be treated in a specialised centre by a multidisciplinary team involving the oncologist, endocrinologist, gastroenterologist, cardiologist, and abdominal and cardiothoracic surgeons [14,51,52]. With regards to the indications of screening for CaHD, no consensus has been reached. The UK and Ireland Neuroendocrine Tumour Society (UKINETS) guidelines recommend that all patients with midgut NETs and all patients with carcinoid syndrome should be screened for CaHD, which may include measuring NT-proBNP or echocardiography [52]. Others suggest echocardiography should only be performed in patients with carcinoid syndrome [52] or with elevated NT-proBNP-[51] or 5-HIAA levels [52]. European Neuroendocrine Society (ENETS) guidelines recommend echocardiographic screening only in patients with carcinoid syndrome or if urinary 5-HIAA and/or chromogranin A are elevated [19]. An algorithm for the screening for CaHD in patients with metastatic NET with or without carcinoid syndrome has been proposed by others, suggesting annual clinical

assessment, TTE and NT-proBNP measurement [25]. In the case of uncertain RV function and suspicion of extracardiac involvement, CMR imaging is recommended. If there is uncertainty regarding valve morphology, transoesophageal echocardiography should be performed. Referral to a cardiologist is recommended on the presence of any of the following criteria: 1) moderate-severe tricuspid/pulmonary regurgitation or stenosis, 2) right heart dilation, 3) RV functional impairment, 4) extracardiac involvement, 5) abnormal tissue Doppler imaging with significantly raised NT-proBNP. In the absence of these criteria TTE should be repeated every 6-12 months. Upon diagnosis of CaHD, the ENETS recommends regular (annual) echocardiographic screening to assess deterioration in heart function [19,53].

Here, we propose a protocol to be used as guidance in the screening for CaHD and the referral process (Fig. 3).

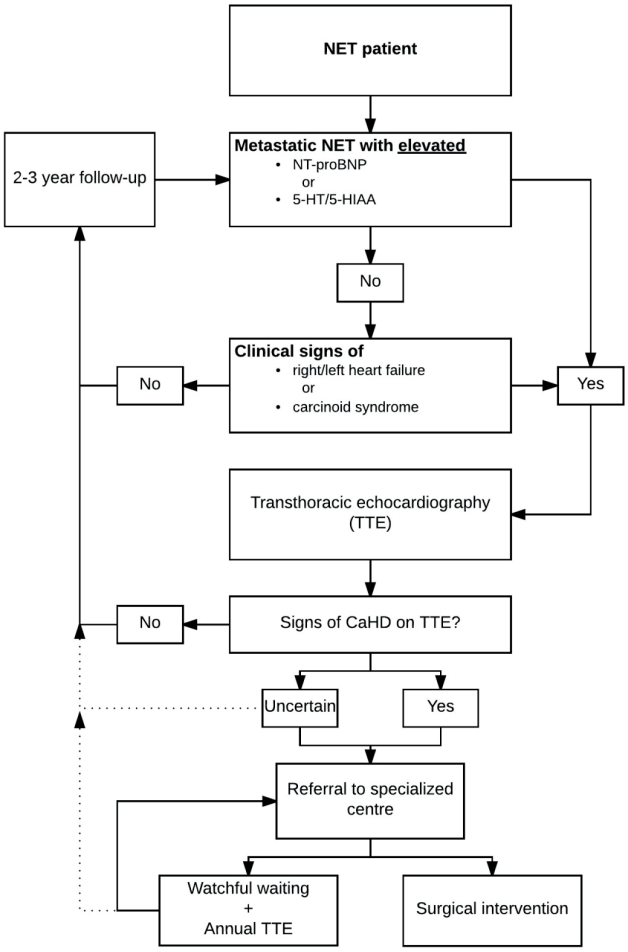

Fig. 3 Proposed protocol for screening and referral in CaHD patients. Level of Evidence V

NET neuroendocrine tumour; *NT-proBNP* N-terminal pro b-type natriuretic peptide; *5-HT* 5-hydroxytryptamine; *5-HIAA* 5-hydroxyindoleacetic acid; *CaHD*, carcinoid heart disease

In this protocol a liberal screening and referral strategy is implemented to prevent diagnostic and therapeutic delay. Metastatic NET patients with elevated NT-proBNP or serotonin (5-HT/5-HIAA) levels should be assessed with TTE. In the absence of metastatic disease or normal biomarkers, TTE should be performed if clinical signs of right/left heart failure or carcinoid syndrome are present. In the case of confirmed CaHD on TTE, referral to a specialised centre is recommended. A multidisciplinary analysis may either result in surgical intervention, or watchful waiting. In case of the latter, annual TTE is recommended, which may be performed in a non-specialised centre. NET patients without confirmed CaHD on TTE, without clinical signs of right heart failure/carcinoid syndrome or without elevated biomarkers, should be assessed by a cardiologist every 2-3 years.

PATIENT SELECTION AND TIMING OF CARDIAC INTERVENTION

Conventionally, valve replacement in CaHD patients has been reserved for patients with symptomatic right heart failure, due to high rates of perioperative mortality in a vulnerable population [53]. However, perioperative mortality has decreased significantly over time [54] and early postoperative mortality has been recorded as low as 10% [41–43], even in patients with NYHA class III and with symptoms of right heart failure [42]. Importantly, 30-day mortality following cardiac surgery has been recorded and a significant decrease from the time period before 1990 (20%) until 2010-2012 (below 5%, Fig. 4) has been observed [39,40].

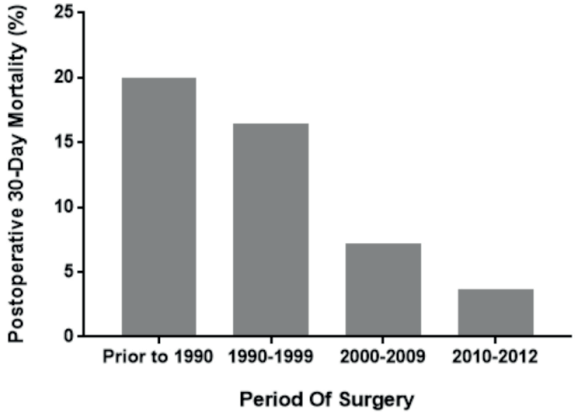

Fig. 4 Postoperative 30-day mortality of CaHD patients according to surgical era, adapted from Connolly et al. [39,40]

This may be explained by a more liberal approach to surgery in recent eras, where both symptomatic and asymptomatic patients with right-sided dysfunction were referred for surgery, as opposed to mainly symptomatic patients. However, other factors may play a role as well, such as improved patient selection, increased experience, progress in oncological management, and advances in surgical techniques [39].

Obviously, the risks of intervention should be weighed against the benefits. The dramatic decrease in perioperative mortality over time raises the question whether a more liberal/ less stringent approach to surgical treatment is indicated. Interestingly, one study found no relation between asymptomatic surgical intervention and long-term survival in multivariate analysis, although this could be explained by the influence of the comorbid malignancy, which may independently affect survival[39]. Despite the decrease in perioperative mortality over time and a trend towards earlier (asymptomatic) surgical intervention [39,41], limited evidence is available in favour of surgery in asymptomatic patients. Valve replacement in asymptomatic and mildly symptomatic patients (NYHA class I or II) has shown to be associated with a higher postoperative survival rate when compared with severely symptomatic patients (NYHA class III or IV), which advocates early surgical intervention [41]; however, these results should be interpreted with caution as confounding by indication cannot be excluded. Moreover, in this study none of the patients in NYHA class II died in the early postoperative phase. In the absence of clear signs or symptoms of right heart failure, it is challenging to determine which patients ought to be considered for surgery [52]. Biomarkers, and recent echocardiographic techniques such as RV strain assessment may prove to be useful in the early detection of RV dysfunction in these patients [23,54].

CONCLUSION

CaHD has a detrimental effect on prognosis in NET patients. Despite the risks associated with surgery in this population, cardiac intervention has been shown to prolong survival and to increase quality of life. Over time, a trend towards earlier intervention in asymptomatic patients with signs of CaHD has been observed, with increased survival rates and lower perioperative mortality. Although consensus with regards to timing of surgery has not been reached, routine cardiac screening including clinical assessment, biomarkers, and echocardiographic parameters may aid in determining the optimal timing of referral to a specialised centre and subsequent surgical intervention.

Funding: None
Conflict of Interest: None declared

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Chapter 6

Lessons learned from a single case report regarding carcinoid heart disease; the importance of a dedicated multidisciplinary heart team

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van Leeuwaarde RS, Chamuleau SAJ

Submitted

ABSTRACT

Carcinoid heart disease (CaHD) is a complex disorder with considerable morbidity and mortality. Timing of screening and surgical intervention is subject to debate and requires a multidisciplinary approach by a cardiologist, cardiothoracic surgeon, and additional medical specialties. Patients with CaHD should ideally be discussed by a dedicated heart team in a cardiothoracic center. The case report in this article describes a patient with CaHD, subject to two rare complications during follow up. As seen in this case, the treatment of patients with CaHD is not limited to treatment, but requires a thorough, multidisciplinary follow-up.

Keywords: Carcinoid heart disease; heart team; tricuspid valve

Funding: None
Disclosure of interest:
The authors report no conflict of interest

CARCINOID HEART DISEASE

The cardiac manifestations of a neuroendocrine tumor (NET) are known as carcinoid heart disease (CaHD) and occur in up to 20% of NET patients with carcinoid syndrome [1]. Carcinoid syndrome, characterized by episodic flushing, wheezing, hypotension and/or diarrhea, is caused by the excretion of vasoactive substances, particularly serotonin[2]. It is currently unclear which patient characteristics are associated with development of CaHD and it has been shown that prognosis is poor once patients present with symptomatic CaHD [3–5]. Plaque-like deposits on particularly the tricuspid and pulmonary valve may lead to significant stenosis and/or regurgitation, and consequently right ventricular dilation, reduced function, right-sided decompensation and subsequent hospitalization [6,7]. Although left-sided involvement is rare due to alleged serotonin inactivation in the lungs, it has been reported especially in patients with a patent foramen ovale, a bronchial NET, or high circulating concentrations of vasoactive substances[8]. Over the years significant advancements have been made in the medical therapy for NETs. Currently, peptide receptor radionuclide therapy with radiolabeled somatostatin analogues is now considered the best second line treatment in patients with progressive metastatic NET[9].

Patients with CaHD represent a population with a rare and complex disorder in which standard treatment strategies have not been established. Early screening, diagnosis and treatment are crucial in prolonging survival and increasing quality of life [10,11].

The typical characteristics of CaHD are displayed in Table 1.

Table 1. Typical characteristics of carcinoid heart disease (CaHD)

Severe tricuspid regurgitation and/or stenosis
Pulmonary regurgitation and/or stenosis
Left-sided valvular disease (<10%)
Typical fibrous plaques on valve leaflets and/or endocardium
Intramyocardial metastases

THE HEART TEAM

The role of a multidisciplinary heart team in deciding treatment strategy in patients with valvular heart disease has increased significantly over the years. In fact, the recommendation of implementing a heart team in cardiothoracic surgery centers has been incorporated in the most recent European guidelines [12,13]. Indeed, complex decisions such as choice of intervention, choice of prosthesis, surgical risk, and even diagnosis should be discussed by a dedicated cardiologist with valvular expertise and a cardiothoracic surgeon. Additional attendance of an electrophysiologist, pathologist, pulmonologist and/or microbiologist may prove beneficial.

The only curative treatment for valvular carcinoid disease is surgery. Although studies suggest prolonged survival after valvular surgery, no clear benefit other than improvement in

quality of life has been shown as results are inevitably influenced by confounding factors such as improved experience, surgical techniques, medical treatment, and patient selection [4,5]. Importantly however, perioperative risk has drastically decreased over the years with a current 30-day post-operative mortality of less than 5% [5].

If valve replacement is recommended, the choice of prosthetic valve type requires careful consideration. A bioprosthesis may be favored over a mechanical valve for the following reasons: 1) a bioprosthesis does not necessitate lifelong anticoagulation, a significant advantage for patients with secondary hepatic coagulopathies or those who will undergo surgery or receive chemotherapy, and 2) bioprostheses have shown a trend towards better survival compared to mechanical prostheses, albeit not statistically significant[5]. Although recurrent carcinoid heart disease has been reported on explanted bioprostheses after 8 years[5] and 18 months[14], it is uncommon.

On the other hand, the lifespan of a bioprosthesis is significantly shorter than that of a mechanical valve. In relatively young patients this may pose a problem as replacement of a prosthesis is associated with considerable risk. In CaHD patients however, this may not be a factor as the expected patient survival regrettably rarely exceeds survival of the prosthesis itself[5].

Peri-procedural anesthetic management is essential in CaHD patients undergoing surgery. In addition to stress and hypotension, carcinoid crisis (flushing, hypotension, bronchospasms) may be provoked by perioperative vasoactive medication, such as dopamine, epinephrine, and norepinephrine[15]. Prevention of carcinoid crisis is facilitated by preoperative octreotide administration and hence requires adequate supervision by an anesthesiologist and endocrinologist[10].

Early referral to a dedicated heart team in a cardiothoracic center is of importance to prevent therapeutic delay[10]. Even in asymptomatic patients, surgery should be considered as New York Heart Association (NYHA) heart failure class is inversely correlated with postoperative- and long-term survival [4,5].

Importantly, involvement of the heart team in the post-operative course is crucial. Due to the complexity of the disorder, patients often find themselves in unchartered territory and treatment of complications requires a multidisciplinary approach. Complications of cardiac surgery for carcinoid heart disease include, but are not limited to, atrioventricular conduction disorders requiring pacemaker implantation, arrhythmias, carcinoid crisis, and acute renal failure[16].

The multidisciplinary aspect of the CaHD heart team is highlighted in Figure 1.

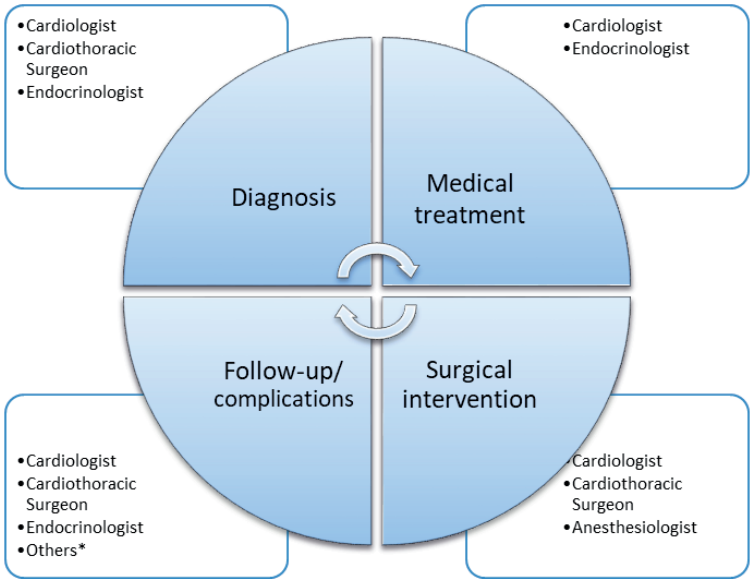

Fig. 1. The ideal multidisciplinary heart team in carcinoid heart disease. * relevant medical specialties including, but not limited to, microbiologist, pulmonologist, pathologist, nephrologist

CASE REPORT

The following case report describes treatment and post-operative course of a patient with CaHD that underwent right-sided heart valve replacement. Decisions regarding type of prostheses, concomitant mitral valve surgery, and pacemaker lead positioning were discussed in the heart team and highlight the importance of a multidisciplinary approach, during diagnosis, treatment, and follow-up.

A 45-year-old female with no prior medical history was diagnosed in 2014 with a small intestine NET with hepatic metastases. The primary tumor was deemed irresectable and the patient was medically treated with a long acting somatostatin analogue. Echocardiographic analysis revealed moderate valvular disease characterized by moderate tricuspid- and mitral insufficiency. A patent foramen ovale was observed. She was referred to the Utrecht Medical Centre for cardiac follow-up. At the beginning of 2016, both trans-thoracic echocardiography (TTE) and trans-esophageal echocardiography (TEE) revealed progression of carcinoid heart disease with severe tricuspid regurgitation based on restrictive movement of all leaflets and malcoaptation (Figure 2).

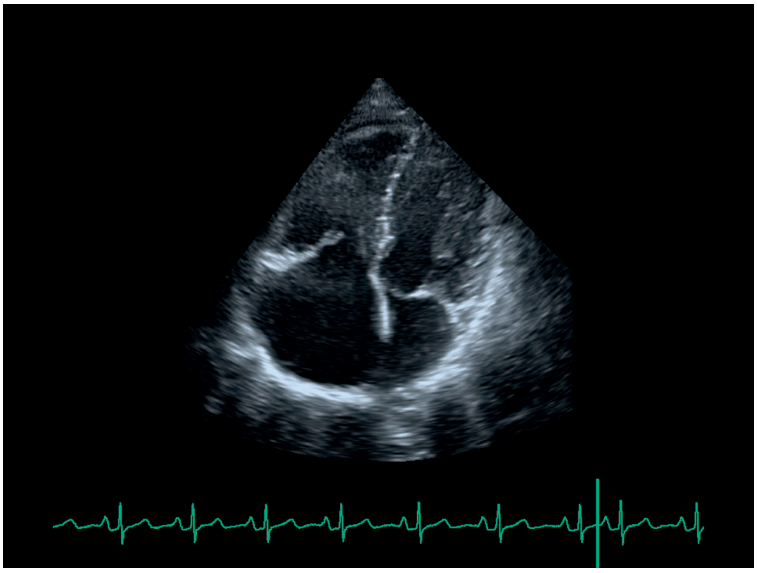

Fig 2. Trans-thoracic 4-chamber view during systole showing severe dilation of the right ventricle and right atrium, restrictive movement of tricuspid leaflets with malcoaptation.

The right ventricle and right atrium were severely dilated. Right-and left ventricular function were normal with moderate mitral- and pulmonic regurgitation. She was discussed in the heart team by a cardiologist with expertise in valvular disease, and a cardiothoracic surgeon. Valve replacement was recommended, prompted by progression of right ventricular dilation and laboratory values indicative of cardiac decompensation (right ventricular diameter 49 mm, B-type natriuretic peptide 46 pmol/L). In May 2016 she underwent both tricuspid- and pulmonic valve replacement with a Perimount bioprosthesis. The patent foramen ovale was closed, no surgery was performed on the mitral valve because of mild regurgitation and a normal aspect of the leaflets. Postoperatively she developed a 3rd degree atrioventricular block for which a 2-chamber pacemaker system was implanted. After heart team consultation with an electrophysiologist, the ventricular lead was implanted in a posterolateral branch of the coronary sinus to avoid a course through the tricuspid bioprosthesis, a standard position for chronic resynchronization therapy patients.

After a couple months the patient presented with dyspnea on mild exertion. Echocardiography revealed normal function of the right sided bioprostheses. Surprisingly, severe MR was detected, based on restriction of the posterior valve leaflet. Remarkable asynchrony was observed with an abnormal contraction pattern of the posterior leaflet, and an abnormal regional strain pattern, confirmed by a cardiologist with expertise in deformation imaging (Figure 3a). It seemed the severe MR was based on reverse asynchrony due to the ventricular lead pacing the papillary muscle of the posterior valve leaflet. Temporarily switching off the pacemaker revealed a reduction of MR to moderate and significant normalization of posterior valve leaflet contraction pattern. A new left ventricular lead was implanted anteriorly in the great cardiac

vein. Hereafter, the MR was reduced to mild/moderate and strain patterns normalized (Figure 3b).

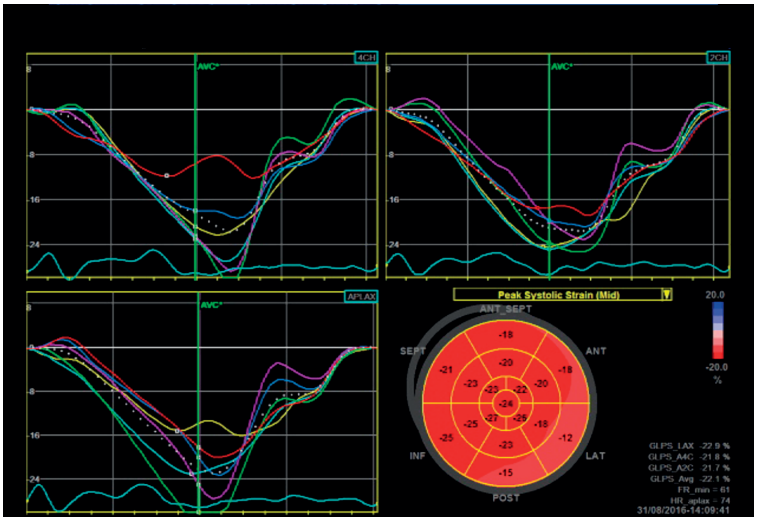

Fig 3a. Abnormal posterolateral strain pattern coinciding with pacemaker lead position.

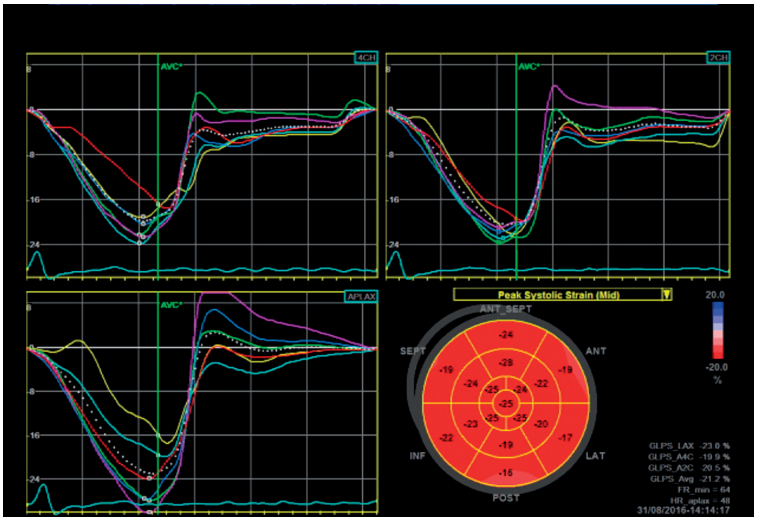

Fig 3b. Normalization of deformation imaging pattern in the posterolateral region.

A year later, in June 2017 she was re-admitted after routine follow-up presentation in the cardiology outpatient clinic with clinical signs of right-sided decompensation. Echocardiography revealed severe TR and moderate pulmonic regurgitation with abnormal thickening of the valves. After presentation in the heart team she underwent successful mechanical heart valve replacement of both right-sided valves. Macro- and microscopic inspection of the valves

revealed extensive fibrosis highly suggestive of recurrent CaHD (Figure 5). Although recurrent CaHD within 18 months has been reported [14], it is rare. Upon diagnosis of recurrent CaHD both bioprostheses were successfully replaced with a mechanical heart valve. The post-operative course was uneventful.

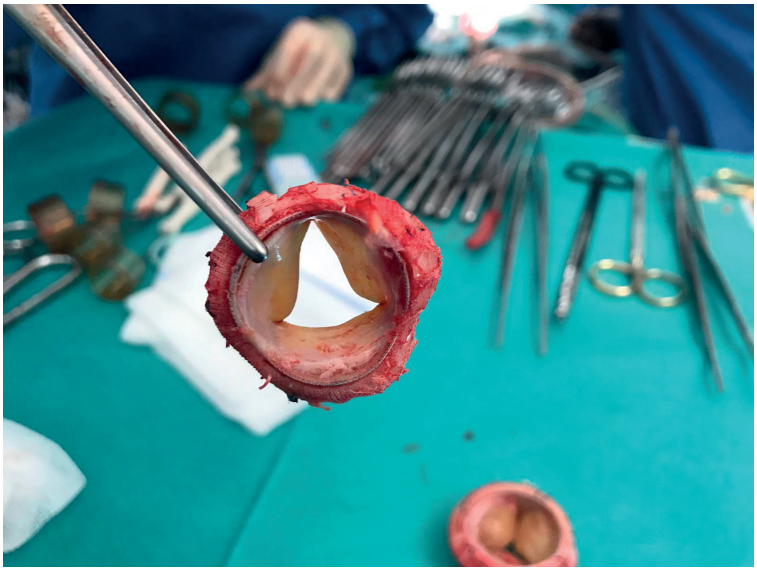

Fig 4. Extensive white connective tissue along annulus of tricuspid bioprosthesis, suggestive of recurrent carcinoid disease.

CONCLUSION

Patients with CAHD represent a vulnerable population with a rare condition. The ideal treatment strategy with regards to timing of surgery, choice of bioprostheses, and possible complications is subject to debate and requires a multidisciplinary approach. The case report in this article highlights the notion that the role of the heart team is not limited to diagnosis and choice of intervention, but requires a thorough coverage of the postoperative course. The low risk of recurrent CaHD on the bioprostheses was carefully weighed against the advantage of the absence of lifelong anticoagulation. Unfortunately, recurrence of CaHD on the bioprestheses prompted a change of course. The particular diagnosis asynchrony by pacing of the papillary muscle and reversing it by changing left ventricular pacing position was reached through multidisciplinary consultation in the heart team of an electrophysiologist and a cardiologist with echocardiographic expertise. To ensure optimal treatment all patients with CAHD should, regardless of disease progression, be discussed in a dedicated multidisciplinary heart team at a cardiothoracic surgery center.

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Part Three

Anticoagulation and thrombolysis

Chapter 7

Anticoagulant Bridging in Left-Sided Mechanical Heart Valve Patients

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International Journal of Cardiology 2017; 232: 121-126

ABSTRACT

Background

In preparation for an invasive procedure with a high bleeding risk, patients with a mechanical heart valve temporarily have to discontinue their anticoagulant therapy and are usually bridged with either intravenous unfractionated heparin (UFH) or subcutaneous low-molecular-weight heparin (LMWH). In this study we retrospectively analyzed the safety of UFH versus LMWH as bridging strategy in left-sided mechanical heart valve patients.

Methods

We performed a retrospective multicenter study in four surgical centers in the Netherlands. Patients with a mechanical heart valve implantation bridged from January 2010 until January 2015 were included. The cumulative incidence of adverse events in the 30 days following the procedure was recorded. Main outcomes were bleeding according to International Society on Thrombosis and Haemostasis (ISTH) criteria, symptomatic thromboembolism, and mortality.

Results

In total, 238 (174 aortic, 42 mitral, 22 aortic + mitral) bridging episodes were included. The incidence of bleeding was 29 (35%) events in the UFH group versus 60 (39%) events in the LMWH group (p=0.50). Incidences of thromboembolism were 2 (2.4%) versus 1 (0.6%). The incidence of death was 1 (1.2%) patient in the UFH group versus 3 (1.9%) patients in the LMWH group. More than 50% of bleeding complications were categorized as a major bleeding.

Conclusions

Bridging anticoagulation in patients with aortic and mitral mechanical valves is associated with considerable risk, but no difference was apparent between UFH and LMWH strategy. The rate of thromboembolism and death was low with either strategy and the vast majority of adverse events were bleedings.

BACKGROUND

Patients with mechanical heart valves (MHV) are at increased risk of developing thromboembolic complications and require life-long administration of oral anticoagulants, i.e. vitamin K antagonists (VKA)[1-6]. In anticipation of an invasive procedure with a considerable bleeding risk, a temporary interruption of oral anticoagulation (OAC) may be required to reduce the increased periprocedural risk of bleeding[6-8]. In doing so, a fine balance must be reached between the risk of bleeding and the risk of developing thromboembolic complications. The VKA is stopped several days prior to the procedure to allow the effect to wane off[3, 7]. During this time window consisting of sub therapeutic International Normalized Ratio (INR) levels, anticoagulation is continued using a short-acting heparin until and after the procedure[6, 8-9]. If considered safe by the surgeon, the VKA is resumed shortly after the procedure and heparin is continued until a stable INR has been reached.

There are two strategies for heparin bridging; administration of intravenous unfractionated heparin (UFH), and subcutaneous low-molecular-weight heparin (LMWH)[6, 9-10]. While both strategies reduce the risk of valve thrombus formation[11], they have distinct biomedical, financial[12-13], and logistical profiles. UFH is administered intravenously according to a nomogram and hence requires peri-procedural hospital admission and continuous monitoring of activated partial thromboplastin time (aPTT)[6, 14]. In contrast, LMWH is administered subcutaneously once or twice daily in an outpatient setting and usually does not require continuous blood monitoring of anti-Xa levels[6, 15-16].

Convincing evidence regarding the ideal heparinoid strategy is terms of efficacy and safety has not been established. As a result, no consensus regarding bridging strategy has been reached internationally. Current European Society of Cardiology (ESC) guidelines state that "*UFH remains the only approved heparin treatment in patients with mechanical prostheses; intravenous administration should be favored over the subcutaneous route (recommendation class IIa, level of evidence C)*"[9]. In contrast, American College of Cardiology/American Heart Association (ACC/AHA) guidelines advocate the use of either; "*bridging anticoagulation with either intravenous UFH or sub- cutaneous LMWH is recommended during the time interval when the INR is subtherapeutic preoperatively in patients who are undergoing invasive or surgical procedures with a 1) mechanical aortic valve replacement (AVR) and any thromboembolic risk factor, 2) older generation mechanical AVR, or 3) mechanical mitral valve replacement (MVR). (Level of Evidence: C)*"[10]. Subsequently, hospital based protocols are frequently inconsistent with one another and the use of either UFH or LMWH is often left to the individual practitioner's discretion.

In this retrospective study we analyzed the clinical application of anticoagulant bridging in left sided MHV patients. In doing so, we assessed the safety and efficacy of UFH versus LMWH based on the cumulative incidence of adverse events, i.e. bleeding, thromboembolism, and death.

METHODS

Data Collection

Patients from 4 major surgical centers in the Netherlands with a mechanical AVR and/or MVR, bridged within the same hospital in the time period from January 1st 2010 until January 1st 2015 were included. Patients were included using databases provided by the participating hospitals and, where possible, the Dutch Thrombosis Center, Saltro. Bridging episodes were identified by scanning written patient documentation between January 2010 and January 2015. In case of uncertainty regarding bridging strategy, the medication list was consulted to identify any switch in anticoagulant medication, or laboratory measurements indicative of UFH strategy-specific aPTT values. Patients receiving sequential therapy (first UFH then LMWH, or vice versa) were included in an intention-to-treat analysis.

Patients with an incomplete bridging strategy, defined as no written documentation of anticoagulant bridging or no evidence of bridging in the patient's medication list or laboratory results, were excluded.

Subsequently patient records were searched for demographics, relevant comorbidities/ risk factors for thromboembolic complications (atrial fibrillation, heart failure, diabetes mellitus, hypertension, malignancy, history of thrombosis) and bleeding (hypertension, history of bleeding), laboratory results, echocardiographic parameters (left ventricular ejection fraction, mitral valve stenosis, left atrial dimensions), medication history, details regarding the procedure, and adverse events.

Bridging protocols across participating centers were based on ESC or ACC/AHA guidelines. The UFH protocol consisted of cessation of anticoagulant therapy 3 (acenocoumarol) or 5 (fenprocoumon) days prior to the procedure. To monitor UFH efficiency, aPTT measurements were conducted every 6 hours with subsequent heparin pump adjustments. LMWH dosages were given once or twice daily, adjusted according to body weight.

Adverse events were scored by two independent researchers (S.C. and J.W.), blinded to the bridging strategy. Any discrepancies were resolved by a third researcher (T.M.). Thromboembolic events were identified through written documentation and results from imaging. Bleeding was scored according to the International Society on Thrombosis and Haemostasis (ISTH) criteria[17-18]. The study protocol was reviewed and approved by the Medical Ethical Committee of the University Medical Center Utrecht.

Definitions

Definitions of adverse events are shown in the Supplemental Data Table 1. Any type of invasive procedure requiring anticoagulant bridging was included, estimated procedural bleeding risk was determined using bleeding risks reported earlier[19-20]. According to ISTH criteria, a major bleeding classification requires overt bleeding. In this study, we included a sub-category of patients that met criteria for a major bleeding yet in whom no overt bleeding was observed. High-

risk MHVs were defined as mechanical mitral valves or aortic mitral valves with >1 risk factor for thrombosis (Atrial fibrillation/flutter, left ventricular ejection fraction <35%, mitral stenosis, hypercoagulability, left atrial dilatation >50mm, spontaneous contrast visible on echocardiography, previous thromboembolic event, older generation MHV (ball-in-cage, monoleaflet)).

Statistical analysis

Patients were stratified by bridging strategy for comparison of baseline characteristics. Continuous variables are expressed as mean ± standard deviation and compared using a Mann-Whitney U Test. Categorical variables are shown as numbers and percentages. Univariate analysis was performed using the Pearson chi-squared test or Fisher's exact test where appropriate. Differences were considered significant at a p-value < 0.05. All statistical analyses were performed using IBM SPSS Statistics Version 20.

RESULTS

The study population consisted of 176 left-sided MHV patients that underwent a total of 238 bridging episodes. The baseline characteristics stratified by bridging strategy are outlined in Table 1.

Table 1 Baseline characteristics

	UFH (n = 84)	**LMWH (n = 154)**	**P-value**
	Mean	Mean	
Age (years)	61.4 ±11.7	62.3 ±10.6	0.47
Male sex (n (%))	52 (62)	102 (66)	0.57
Body mass index (kg/m²)	25.8 ±4.8	27.2 ±5.0	0.03
Pre-procedural laboratory results			
INR	1.76 ±0.74	1.47 ±0.59	<0.01
Hemoglobin (mmol/L)	7.4 ±1.2	7.8 ±1.3	<0.01
Thrombocyte count (x10^9/L)	250 ±102	273 ±91	0.06
Creatinine (µmol/L)	115 ±118	120 ±153	0.69
Location of prosthesis			<0.001
Aortic n (%)	39 (46)	135 (88)	
Aortic ≤1 risk factor*	39 (46)	125 (81)	
Aortic >1 risk factor*	0 (0)	10 (6.5)	
Mitral n (%)	29 (35)	13 (8)	
Aortic and mitral n (%)	16 (19)	6 (4)	
High risk valve§	45 (54)	29 (19)	

Table 1 Baseline characteristics (*continued*)

	UFH (n = 84)	LMWH (n = 154)	P-value
	Mean	Mean	
Estimated procedural bleeding risk by location of prosthesis			
Aortic			0.17
High n (%)	17 (20)	43 (28)	
Low n (%)	22 (26)	92 (60)	
Mitral			0.66
High n (%)	5 (6.0)	3 (1.9)	
Low n (%)	24 (29)	10 (6.5)	
Aortic and mitral			0.26
High n (%)	2 (2.3)	2 (1.3)	
Low n (%)	14 (17)	4 (3)	
Vitamin K antagonist			0.60
Acenocoumarol n (%)	56 (67)	98 (64)	
Fenprocoumon n (%)	27 (33)	55 (36)	
Comorbidity/risk factors			
Hypertension n (%)	31 (37)	56 (36)	1.00
Atrial fibrillation n (%)	30 (36)	26 (17)	<0.01
CHA_2DS_2-VASc score	2.1 ±1.6	2.8 ±1.7	0.09
Malignancy n (%)	4 (4.8)	5 (3.2)	0.72
Diabetes mellitus n (%)	9 (11)	26 (17)	0.20
Heart failure n (%)	16 (19)	10 (6.5)	<0.01
History of arterial/venous thrombosis n (%)	13 (15)	41 (27)	0.05
LVEF < 35% n (%)	6 (18)	4 (8.0)	0.31
Mitral valve stenosis n (%)	3 (8.9)	0 (0)	0.07
Left atrial dilation > 50mm n (%)	4 (12)	9 (18)	0.55
History of bleeding n (%)	22 (26)	37 (24)	0.71
Other medication			
NSAID n (%)	4 (4.7)	13 (8.4)	0.43
Antiplatelet drug n (%)	10 (12)	17 (11)	0.84
Corticosteroid n (%)	7 (8.2)	15 (9.7)	0.72
SSRI n (%)	1 (1.2)	2 (1.3)	1.00

MHV, mechanical heart valve; UFH, Unfractionated Heparin; LMWH, Low Molecular Weight Heparin; n, number of bridging episodes; INR, International Normalized Ratio; LVEF, left ventricular ejection fraction; NSAID, Non-steroidal anti-inflammatory drug; SSRI, selective serotonin re-uptake inhibitor.

*Atrial fibrillation/flutter, left ventricular ejection fraction <35%, mitral stenosis, hypercoagulability, left atrial dilatation >50mm, spontaneous contrast visible on echocardiography, previous thromboembolic event, older generation MHV (ball-in-cage, monoleaflet)

§ mitral valve and/or aortic valve with >1 risk factor for thromboembolic complications

The groups were comparable with respect to age, sex, thrombocyte count, creatinine level, bleeding risk, type of vitamin K antagonist, and medication. Furthermore, the prevalence of hypertension, malignancy, diabetes mellitus, and a history of arterial/venous thrombosis did not differ between the groups.

Mechanical aortic valves were primarily bridged with LMWH. High-risk mechanical heart valves were mostly bridged with UFH (61% versus 39% for LMWH). The prevalence of atrial fibrillation ($p<0.01$) and heart failure ($p<0.01$) was significantly higher in the UFH group compared to the LMWH group, although average CHA_2DS_2-VASc score was similar. The pre-procedural INR level was higher ($p<0.01$) and the hemoglobin level was lower ($p<0.01$) in the UFH group compared to the LMWH group. At baseline no difference was found in thrombocyte count. Follow-up on thrombocyte count was available in 110 bridging episodes (46%). In total, 1 patient the UFH group (1.2%) developed a >50% drop from baseline in thrombocyte count, compared to 5 patients (3.2%) in the LMWH group. No specific laboratory analysis for heparin-induced thrombocytopenia was available.

In total 44 out of 176 patients (25%) were bridged more than once in the 5-year time period. Nine (5.1%) of these patients underwent a different bridging strategy (UFH or LMWH) during the second or third bridging episode. Missing values were recorded as follows: body mass index (UFH 17; LMWH 40), INR (UFH 12; LMWH 27), hemoglobin (UFH 8; LMWH 48), thrombocyte count (UFH 9; LMWH 64), creatinine (UFH 3; LMWH 15), vitamin K antagonist (UFH 1; LMWH 1), LVEF (UFH 50; LMWH 104), mitral valve stenosis (UFH 50; LMWH 104), left atrial dilation > 50mm (UFH 50; LMWH 104).

Incidence of adverse events

In Table 2 the cumulative incidences of major adverse events (major bleeding, thromboembolism, and death) within 30 days following the procedure are displayed.

Table 2 Adverse events

	UFH (n=84)	**LMWH (n=154)**	**P-value**
	n (%)	n (%)	
Major bleeding†	16 (19)	29 (19)	0.97
Thromboembolism	2 (2.4)	1 (0.6)	0.29
Death	1 (1.2)	3 (1.9)	1.00
Total major adverse events	**19 (23)**	**33 (21)**	**0.83**

Incidence of major adverse events (major bleeding, thromboembolism, death) within 30 days following the procedure in MHV patients bridged with UFH and LMWH. Numbers are based on bridging episodes.
† Scored using the International Society on Thrombosis and Haemostasis (ISTH) criteria. MHV, Mechanical heart valve; UFH, Unfractionated Heparin; LMWH, Low Molecular Weight Heparin

No statistically significant differences between the groups were observed. In total, 19 procedures (23%) bridged with UFH experienced an adverse event compared to 33 procedures

(21%) bridged with LMWH (p=0.83). With regards to bleeding, a major bleeding occurred in 19% of patients in both bridging groups.

A clinically relevant non-major bleeding (CRNMB) occurred in 9.5 and 13% of patients for UFH and LMWH respectively. A minor bleeding was observed in 1.2 and 4.5%, and a major bleeding without overt bleeding in 4.8 and 2.6%. Four patients died, 1 of which was bridged with UFH and 3 with LMWH. A thromboembolic event occurred in 2 patients bridged with UFH and in 1 patient bridged with LMWH.

All thromboembolic complications were preceded by a bleeding event. Treatment of these bleeding events included correction of the anticoagulant therapy. Three-out-of four deaths were bleeding related. In these patients the bleeding episode and thromboembolism or death were recorded as two independent adverse events.

Evaluation of bleeding events

Among bleeding events, in retrospect 45 (51%) were judged as a major bleeding, 28 (31%) a CRNMB, and 8 (9%) a minor bleeding. Eight (9%) events were judged as a major bleeding without overt bleeding.

Major bleedings are outlined in the Supplemental Data Table 2. Among major bleedings, 16 (36%) were bridged with UFH versus 29 (64%) with LWMH. The majority of procedures were of high bleeding risk. Nearly one-quarter (24%) of all major bleedings in the LMWH group consisted of macroscopic hematuria, while no hematuria was seen in the UFH group. In the UFH group 25% developed a wound hematoma versus 14% in the LMWH group. One patient developed a bleeding prior to the invasive procedure. This patient, set to receive a total hip replacement, developed a thigh hematoma upon initiation of UFH therapy on day -1.

Evaluation of deaths and thromboembolic events

Description of deaths and thromboembolic complications are depicted in the Supplemental Data Table 3. In total, 4 patients died within 30 days following the procedure. Only 1 patient died within the first five days after the procedure. Bleeding as a direct or indirect cause of death was observed in 3 patients; 1 patient died from respiratory exhaustion on day 24 as a complication following pocket hematoma drainage, 1 patient died on day 30 from a subarachnoid bleeding, and 1 patient died from cardiac tamponade on day 4. The fourth patient succumbed to terminal renal insufficiency and metabolic acidosis on day 20. Although criteria for a major bleeding (no overt bleeding) were not reached, this patient experienced a 2.8 mmol/L drop in hemoglobin in the 14 days following the procedure.

Three patients experienced a thromboembolic complication. Two of the patients had an aortic MHV with no additional risk factors for thrombosis; one patient had an aortic MHV and a mitral MHV. All three patients experienced a bleeding prior to the thromboembolism. In one of

these patients (post-renal transplantation) UFH was temporarily ceased as a result of a (major) bleeding on day 13, after which UFH was restarted on day 15. Peripheral arterial embolisms were observed on day 17. One patient (UFH) underwent pacemaker implantation and was diagnosed with macroscopic hematuria (CRNMB) on day 6 and a mitral valve thrombus on day 23. The third patient was admitted for transurethral renal stone removal and was bridged with enoxaparin. After VKA resumption this patient developed macroscopic hematuria on day 6, after which the VKA was again replaced with enoxaparin. No correction of anticoagulation was recorded. An ischemic lacunar stroke was diagnosed on day 13.

Definite conclusions following sub-analysis have to be drawn with caution considering the relatively small sample size, however a sub-analysis with only high-risk MHVs showed no statistical difference between the two strategies.

Similarly, no statistical difference was found in the incidence of any adverse event with respect to VKA choice, other comorbidities (i.e. heart failure, hypertension, atrial fibrillation), laboratory values, and procedural bleeding risk (data not shown). Combining the major bleeding without overt bleeding group with the major bleeding group did not change the outcome (p=0.67).

DISCUSSION

In this retrospective multicenter study we provided insight into the clinical application of anticoagulant bridging with MHV patients in the Netherlands. We compared the safety of UFH versus LMWH among 176 MHV patients undergoing 238 bridging episodes. No statistical difference was found in the cumulative incidence of adverse events.

High-risk MHVs were mostly bridged with UFH, however choice of strategy was inconsistent not only between participating centers but also between practitioners within a center. This is in line with the lack of consensus in national and international guidelines, and highlights the need for a universal strategy. A discrepancy was observed between the incidence of heart failure in both groups, and the incidence of reduced ejection fraction. Unfortunately LVEF status was associated with a relatively large number of missing data which made it difficult to reach statistical significance. Furthermore, it is conceivable that some patients were diagnosed with heart failure with a preserved ejection fraction.

The safety of UFH and LMWH as bridging strategy has been reported previously (Table 3). However, it is difficult to compare these findings to our study since these studies were observational, small, single-arm, or did not differentiate between different VKA indications, i.e. mechanical valve or atrial fibrillation.

Table 3 Major bleeding, thromboembolic complications and death in MHV patients following anticoagulant bridging

Study	MHV	Strategy	Major Bleeding (%)	Thromboembolism* (%)	Death (%)
Schulman et al.[21] 2015	185	LMWH	11	0	n/a
Pengo et al.[22] 2009	190	LMWH	1.2[§]	0.1	n/a
Daniels et al. [23] 2009	99	UFH	6.1	3.1	[#]
	243	LMWH	3.7	0.8	
Bui et al.[24] 2009	62	LMWH	3.2	0	0
Spyropoulos et al.[25] 2008	68	UFH	8.8	1.5	1.5
	165	LMWH	4.2	0.6	0.6
Jaffer et al.[26] 2005	19	LMWH	0	0	n/a
Spyropoulos et al.[27] 2004	48	LMWH	4.2	0	n/a
Douketis et al.[19] 2004	215	LMWH	0.9	0.6	n/a
Kovacs et al.[28] 2004	112	LMWH	7.1	3.6	0
Ferreira et al.[29] 2003	82	LMWH	1.2	0	n/a

* arterial thromboembolism

[#] 1 death, bridging strategy unknown

[§] including other vitamin K antagonist indications

MHV, mechanical heart valve; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin

In these studies, thromboembolic rates were low, ranging from 0 to 3.6%. This is comparable to our findings. However, the incidence of bleeding was considerably higher in our study. We found that major bleeding occurred in 19% of all bridging episodes, while major bleeding rates in previous studies ranged from 0 to 11%[19, 21-29]. Bleeding criteria were similar, however Spyropoulos et al. employed a stricter ≥3 g/dl (1.86 mmol/L) hemoglobin drop criterion, compared to the ≥2 g/dl (1.24 mmol/L) hemoglobin drop criterion in our study. Additionally, subjective interpretation of a “visible” or “overt” bleeding may play a role. Although incidences of death have been infrequently reported in earlier studies, our death rates were in accordance with previous findings[24, 25, 28].

On average, heparin therapy was continued following the procedure for an average of 7.1 days (±6.5 days). The majority of bleeding events occurred in the first 10 days following the procedure (data not shown). These results are in accordance with Daniels et al. who reported the majority of major bleedings at 0-12 days following the procedure[23]. Hence, a patient seems to be most at risk of developing significant bleeding during the time period in which dual anticoagulation with VKA and heparin is administered.

Approximately half of the bleedings in our study were scored as a major bleeding, a clinically important complication. In fact, nearly one-out-of five patients in this study developed a major bleeding. Furthermore, all three thromboembolic complications were preceded by a bleeding event. In these cases bleeding was corrected by either switching or temporarily discontinuing anticoagulant medication, leaving the patients potentially at risk of developing

a thromboembolism. A direct relation between correction of bleeding and the development of a thromboembolic complication cannot be excluded. Finally, three-out-of-four deaths were bleeding related, while no death was related to thromboembolism.

From these results, anticoagulant bridging may successfully protect patients from developing thromboembolic complications, regardless of heparin strategy. However, the question arises whether in protecting patients from a thromboembolic event, the goal has been surpassed and patients are in fact exposed to a potentially bigger threat: bleeding. The necessity to bridge patients at risk for thromboembolic complications has been challenged in earlier reports[4, 30]. To extrapolate these results to patients with MHVs, randomized trials such as the PERIOP2 (NCT00432796) comparing bridging versus no bridging are needed.

Surprisingly the majority of adverse events, including bleeding, were associated with sub-therapeutic aPTT values (data not shown). Despite the use of a nomogram, aPTT values are known to fluctuate extensively and stable aPTT values within one patient are rare [14]. Perhaps correction of sub- or supra-therapeutic aPTT levels may have triggered temporary pro-hemorrhagic or pro-thrombotic states leading to bleeding and thrombo-embolic complications, respectively.

Limitations

These results should be interpreted in light of the retrospective, non-randomized study design. Hence, the presence of missing data was inevitable. For example, individual bleeding risk and thrombocyte count were missing in a significant number of cases, as well as echocardiographic parameters. We acknowledge the presence of significant baseline differences due to the lack of randomization. Patients at higher thrombo-embolic risk (high risk valves, atrial fibrillation, heart failure) were mostly bridged with UFH, leading to confounding by indication. The observed events of death and thrombo-embolism in the UFH group may therefore be influenced by these additional risk factors.

Furthermore, adverse events occurring at another medical center not participating in this study or at the general physician's practice were missed, leading to an underestimation of adverse events. Finally, the four participating centers share the status of a specialized heart center, hence any referral for an invasive procedure may introduce inclusion bias.

Bridging protocol

Unstable aPTT values for UFH combined with both logistic and financial advantages over UFH, makes LMWH a more feasible strategy. With regards to safety, a comparison between the two strategies in terms of thromboembolism and death may be subject to debate. However, it seems as though bleeding risks were similar between the two strategies. In light of these findings and based on the results from earlier studies/guidelines we have developed an in-house protocol as guidance for MHV patients undergoing an invasive procedure (Figure 1).

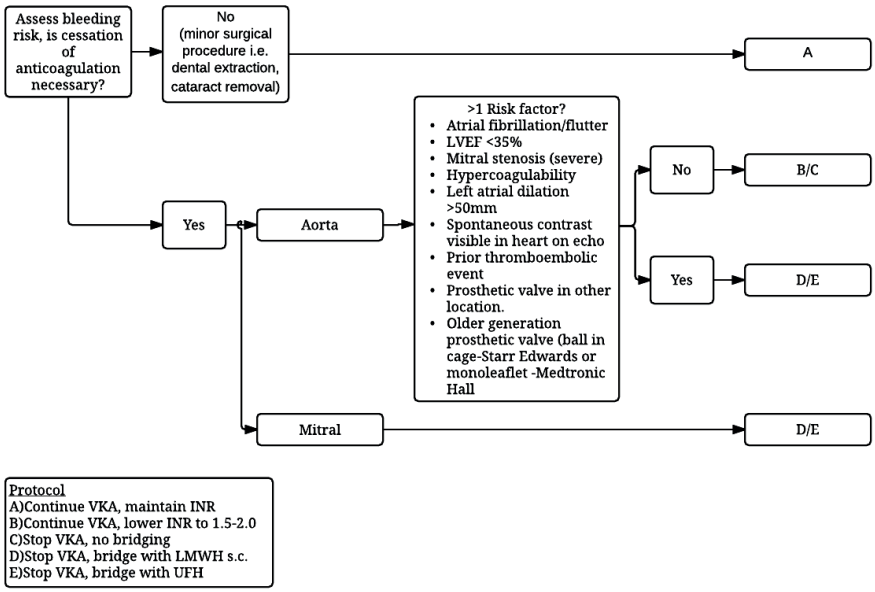

Figure 1 Bridging protocol for mechanical heart valve patients
LVEF, Left ventricular ejection fraction; VKA, Vitamin K antagonist; LMWH, Low-molecular-weight heparin; UFH, Unfractionated Heparin

Here we propose anticoagulant bridging with high-risk MHVs should be applied based on a patient's individual risk profile and may be left to the physician's discretion. Importantly, we suggest that all mechanical heart valves may be bridged with LMWH, which contradicts European guidelines. Options A-C are not assessed in this study but are based on ACC/AHA guidelines [10].

CONCLUSIONS

With regards to bridging strategy, no difference was found in the 30-day incidence of adverse events between UFH and LMWH. Furthermore, the incidence of bleeding was considerably higher than the incidence of thromboembolism or death. Prospective studies are needed to confirm our results and to fully elucidate the role of anticoagulant bridging in anticipation of an invasive procedure.

FUNDING

None

CONFLICT OF INTEREST

The authors report no relationship that could be constructed as a conflict of interest.

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SUPPLEMENTAL DATA

Supplemental data 1 Definition of adverse events

Bleeding	
Major Bleeding (ISTH)	Overt bleeding and: - fall in hemoglobin concentration ≥20 g/L (1.24mmol/L) or -blood transfusion of 2 or more units of packed red blood cells or -intraocular, intracerebral or retroperitoneal hemorrhage.
Clinically relevant non-major bleeding (ISTH)	Not meeting criteria for major bleeding, but needing medical intervention, temporary cessation of medical therapy, contact with a physician, or any discomfort such as pain or impairment in daily life
Minor Bleeding (ISTH)	Other bleeding events not meeting criteria for major bleeding or clinically relevant non-major bleeding
Major Bleeding w/o overt bleeding (Non-ISTH)	Meeting criteria for major bleeding without overt bleeding
Thromboembolism	Stroke, TIA, amaurosis fugax, peripheral arterial embolism, prosthetic valve thrombosis, unstable angina or myocardial infarction.

ISTH, International Society on Thrombosis and Haemostasis, TIA, Transient Ischemic Attack

Supplemental Data 2 Major Bleeding events

Major Bleeding						
Sex	**Age (years)**	**MHV location**	**Bridging strategy**	**Procedural bleeding risk[22,29]**	**Time of diagnosis (days*)**	**Description**
Male	58	Aortic	UFH	High	10	Intra-abdominal bleeding
Male	55	Aortic	UFH	High	8	Intra-abdominal bleeding
Male	67	Aortic	UFH	Low	-1	Thigh hematoma
Female	74	Aortic	UFH	High	16	Muscle bleeding
Male	64	Mitral	UFH	Low	2	Unknown location
Female	47	Mitral	UFH	Low	5	Subfascial hip hematoma
Male	70	Mitral	UFH	Low	4	Wound hematoma
Female	69	Aortic + Mitral	UFH	High	3	Unknown location
Female	73	Aortic + Mitral	UFH	Low	0	Wound hematoma
Female	74	Aortic	UFH	High	2	Breast hematoma
Female	33	Mitral	UFH	Low	6	Post-tonsillectomy bleed
Male	52	Aortic	UFH	Low	3	Rectal blood loss
Male	81	Mitral	UFH	Low	5	Wound hematoma
Male	70	Mitral	UFH	Low	29	Subarachnoid hemorrhage
Female	72	Aortic	UFH	Low	4	Two packed cells
Female	71	Mitral	UFH	Low	5	Wound hematoma
Male	64	Aortic	LMWH	High	3	Hematuria
Male	87	Aortic	LMWH	High	9	Hematuria
Female	66	Aortic	LMWH	High	6	Intestinal bleeding

Supplemental Data 2 Major Bleeding events (*continued*)

Major Bleeding						
Sex	**Age (years)**	**MHV location**	**Bridging strategy**	**Procedural bleeding risk[22,29]**	**Time of diagnosis (days*)**	**Description**
Male	52	Aortic	LMWH	High	1	Epi- and subdural hematoma
Male	67	Aortic	LMWH	High	4	Cardiac tamponade
Male	55	Aortic	LMWH	Low	6	Unknown location
Male	68	Aortic	LMWH	High	19	Wound hematoma
Female	71	Aortic	LMWH	High	6	Intra-abdominal bleeding
Female	72	Aortic	LMWH	High	0	Unknown location (Hb decrease)
Male	72	Aortic	LMWH	High	3	Hematuria
Male	64	Mitral	LMWH	Low	7	Haemarthros
Female	55	Mitral	LMWH	Low	1	Two packed cells
Male	69	Aortic + Mitral	LMWH	Low	6	Thigh hematoma
Male	68	Aortic	LMWH	High	3	Rectal blood loss
Male	62	Aortic	LMWH	High	1	Hematuria
Female	75	Aortic	LMWH	Low	7	Rectus sheath hematoma
Male	66	Aortic	LMWH	High	4	Hematuria
Male	67	Aortic	LMWH	High	5	Hematuria
Male	68	Aortic	LMWH	High	5	Hematuria
Female	32	Aortic	LMWH	High	3	Wound hematoma
Female	54	Mitral	LMWH	Low	1	Intra-abdominal bleeding
Male	66	Aortic	LMWH	Low	3	Wound hematoma
Male	64	Aortic	LMWH	Low	1	Hematemesis
Female	59	Aortic	LMWH	Low	9	Wound hematoma
Male	76	Aortic	LMWH	Low	10	Shoulder hematoma
Male	68	Aortic	LMWH	Low	2	Intra-ocular bleeding
Male	75	Aortic	LMWH	High	1	Unknown location (Hb decrease)
Female	74	Aortic	LMWH	Low	11	Extra-peritoneal bleeding
Female	73	Aortic + Mitral	LMWH	Low	1	Two packed cells

*following the procedure

MHV, Mechanical heart valve; UFH, Unfractionated heparin; LMWH, Low-molecular-weight heparin

Supplemental Data 3 Description of deaths and thromboembolic complications

Death							
Sex	**Age (years)**	**MHV location**	**Bridging strategy**	**Procedure**	**Time of death (days*)**	**Cause of death**	**Bleeding**
Male	70	Mitral	UFH	Colonoscopy without biopsy	30	Subarachnoid bleeding	Yes
Female	68	Mitral	LMWH	Above-knee amputation	20	Renal insufficiency	No
Male	76	Aortic	LMWH	ICD placement	24	Respiratory exhaustion#	Yes
Male	67	Aortic	LMWH	Re-Bentall	4	Cardiac tamponade	Yes
Thromboembolism							
Sex	**Age (years)**	**MHV location**	**Bridging strategy**	**Procedure**	**Time of diagnosis (days*)**	**Type of thromboembolism**	
Male	55	Aortic	UFH	Renal transplantation	17	Peripheral arterial embolism	
Female	57	Aortic + Mitral	UFH	Pacemaker implantation	23	Mitral prosthetic valve thrombosis	
Male	82	Aortic	LMWH	Transurethral renal stone removal	13	Lacunar stroke	

*following the procedure

MHV, Mechanical heart valve; UFH, Unfractionated heparin; LMWH, Low-molecular-weight heparin

Supplemental data 4 aPTT values adverse events UFH

	Below target range*, n (%)	**Within target range*, n (%)**	**Above target range*, n (%)**
Major Bleeding n=337	194 (58)	94 (28)	49 (5)
Thromboembolism n=105	70 (67)	24 (23)	11 (10)
Death n=17	8 (47)	5 (29)	4(24)
Based on 459 aPTT values			

* aPTT therapeutic range: 60-90 seconds or heparin ratio 2.0-2.5

n, number of aPTT measurements; aPTT, activated partial thromboplastin time; CRNMB, clinically relevant non-major bleeding

Chapter 8

Reply to Letter to the Editor "Bridging anticoagulation in patients with mechanical heart valves"

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International Journal of Cardiology 2017; 236: 399

We thank Dr. Özlek et al. for their remarks concerning our recent article and appreciate the recognition of the importance of the current trial. We acknowledge that the major bleeding rate in our study is substantially higher compared to previous studies. Several factors may have played a role.

Firstly, different criteria of major bleeding were used across studies. In our study, bleeding was scored according to International Society on Thrombosis and Haemostasis (ISTH) criteria. In some of the previous studies more stringent criteria were applied. For example, Spyropoulos et al. employed a ≥3 g/dL instead of ≥2 g/dL (ISTH) post-procedural hemoglobin drop[1]. Biteker et al. did not record hemoglobin drop but scored major bleedings based on medical urgency, i.e. fatal or life-threatening bleeding, bleeding at a critical site, or requiring acute medical intervention[2]. In doing so, patients with a significant hemoglobin drop without requiring immediate medical intervention were not recorded. Additionally, across studies the subjective interpretation of an overt bleeding may have differed. In our study, bleedings were assessed by two independent researchers blinded to bridging strategy. Any disagreement was resolved by a third study member.

It is conceivable that there may have been differences in bridging regimen across studies. For example, the time in which dual anticoagulation was administered (both vitamin K antagonist and heparin) was considerably longer in our study (7.1 ± 6.5 days) compared to Daniels et al. (3.0 (±2.4) – 6.3 (±5.7) days)[3]. Perhaps the more aggressive anticoagulant strategy increased post-procedural bleeding risk.

Finally, patient populations varied across the different studies. Daniels performed risk stratification prior to the procedure by including a third low-risk group in which the INR was temporarily lowered, without heparin bridging. In our study, these potentially lower-risk patients were nonetheless bridged with heparin. More importantly some, studies excluded cardiac- [2,4-5] or vascular [2,4] surgery, which are considered procedures with a high periprocedural bleeding risk. Daniels et al. included only patients referred to the Thrombosis Center for periprocedural anticoagulation management, leaving the study subject to referral bias[3]. As stated by the authors, it is therefore possible that patients with an increased risk of thrombosis, or bleeding, were not included in their analysis. We attempted to eliminate the referral bias by also including these high risk patients.

In conclusion, we believe that the discrepancy with earlier reports may be partially explained by differences in bleeding assessment, bridging protocol and patients included in the analyses. We feel that our study closely resembles daily clinical practice and underlines the importance of a patient tailored approach to bridging in patients with mechanical heart valves.

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Chapter 9

Peri-procedureel Antistollingbeleid bij Vitamine K Antagonisten; een Multidisciplinair Protocol.

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Submitted

INTRODUCTIE

Bij patiënten met een verhoogd risico op trombose worden vaak ter preventie van trombo-embolische complicaties levenslang vitamine K antagonisten (VKA) voorgeschreven. Bij VKA's zal een verhoogde International Normalized Ratio (INR) waarde worden nagestreefd en is continue monitoring via de trombosedienst noodzakelijk. Indien een patiënt een chirurgische ingreep zal ondergaan zal peroperatief worden overwogen de VKA tijdelijk te staken om zo het operatieve bloedingsrisico te verlagen[1]. Dit is afhankelijk van het type ingreep. Zo kan bijvoorbeeld bij een ingreep met een laag risico op bloeding worden overwogen om de VKA te continueren en de streef INR te handhaven of aan te passen[2]. Bij een hoog bloedingsrisico zal de VKA tijdelijk gestopt moeten worden. De periode met een sub-therapeutisch INR kan indien gewenst overbrugd ("bridging") worden met een kortwerkende heparine[1–3]. Op deze manier is de periode met sub-therapeutische INR waarden zo kort mogelijk; de kortwerkende heparine kan immers enkele uren voor de ingreep worden gestopt. Ten aanzien van VKA's kan er gekozen worden uit twee strategieën; intraveneuze ongefractioneerde heparine (un-fractionated heparin (UFH)) of subcutane therapeutische laag-moleculair-gewicht heparine (low-molecular-weight-heparin(LMWH)). Beide strategieën gaan gepaard met een verschillend financieel en logistiek profiel. Zo is bij UFH continue monitoring noodzakelijk van de heparine ratio, en daarbij aanpassing van de heparine pomp, terwijl dit bij LMWH niet het geval is. Daarbij kan LMWH poliklinisch worden toegediend, terwijl bij UFH ziekenhuis opname vereist is. Daar staat tegenover dat LMWH geen goed antidotum heeft en dat er bij LMWH een relatieve contra-indicatie bestaat bij patiënten met een slechte nierfunctie of morbide obesitas.

Helaas zijn er bij gebrek aan overtuigende studies geen eenduidige richtlijnen met betrekking tot de juiste strategie, met als gevolg dat het peri-operatieve beleid zowel in Nederland als internationaal verschillend wordt toegepast. In dit artikel geven wij een overzicht van de meest recente standpunten van de Europese (European Society of Cardiology[4,5]), Amerikaanse (American College of Cardiology/American Heart Association[6,7]), en Nederlandse (Federatie Medisch Specialisten[8] en Nederlandse Internisten Vereniging (NIV)[9]) richtlijnen. De richtlijnen van de NIV en de Federatie Medisch Specialisten zullen veelal overeenkomen aangezien de NIV richtlijnen worden ondersteund door de Federatie Medisch Specialisten. Ondanks de belangrijke en steeds meer prominente rol van direct werkende orale anticoagulantia (DOAC) in het antistollingsbeleid zullen deze in dit artikel niet worden besproken.

Dit artikel bevat een pragmatisch peri-procedureel VKA antistollingsprotocol (Figuur 1) samengesteld door de multidisciplinaire antistollingscommissie in het Universitair Medisch Centrum Utrecht. Ten opzichte van reeds eerder verschenen overbruggingsschema's [3,10,11] bevat dit protocol een aantal aanpassingen, met name op het gebied van VKA overbrugging bij atriumfibrilleren en mechanische kunstkleppen. Deze aanpassing zijn als volgt:

1) Overbruggen bij atriumfibrilleren vanaf een CHA_2DS_2-VASc score (in plaats van $CHADS_2$ score) van 8 óf indien er sprake is van reumatisch kleplijden of een CVA/TIA in de afgelopen 6 maanden.
2) Mechanische kunstkleppen kunnen worden overbrugd met LMWH in plaats van UFH.

Deze aanpassingen zijn onder andere gebaseerd op vernieuwde inzichten door recente studies, in combinatie met klinische ervaringen in ons centrum, en worden hieronder uiteengezet.

BLOEDINGSRISICO

Ten eerste dient het peri-operatieve bloedingsrisico bepaald te worden. Bij een hoog risico procedure bedreigt een bloeding het leven, orgaan, of het operatieresultaat en zal tot irreversibele schade leiden. Indien het risico wordt ingeschat als laag kan de VKA gecontinueerd worden. Bij handhaving van de streef INR is overbrugging uiteraard niet noodzakelijk. Indien de streef INR wordt aangepast (bijvoorbeeld naar INR 1,5-2,0) dient de keuze tot wel/niet overbruggen zorgvuldig worden overwogen. Men bevindt zich hier namelijk in een grijs gebied waarbij een tijdelijke verlaging van de streef INR bij patiënten met een laag risico op trombose geen gevaar vormt terwijl dit wel zo is bij patiënten met een hoog risico op trombose. Het is bijvoorbeeld mogelijk dat iemand met een hoog risico op trombo-embolische complicaties (mitralis kunstklep en meerdere risicofactoren) een relatief kleine ingreep zal ondergaan; in deze situatie is slechts het tijdelijk verlagen van de INR zonder extra maatregelen niet gewenst. Het juiste beleid is in deze gevallen niet goed te standaardiseren en zal per patiënt moeten worden beoordeeld.

Bij een ingreep met een hoog bloedingsrisico zal de ingreep zonder antistolling moeten plaatsvinden. De noodzaak tot overbruggen en de daarop volgende overbruggingsstrategie is afhankelijk van het risico op trombo-embolische complicaties en dus afhankelijk van de indicatie.

INDICATIE VOOR ANTISTOLLING

Mechanische kunstklep

De ideale overbruggingstrategie bij kunstkleppen is onbekend. Europese richtlijnen adviseren bij gebrek aan overtuigend bewijs mechanische kunstkleppen te overbruggen met UFH[4]. Amerikaanse richtlijnen laten echter ruimte voor het gebruik van zowel UFH als LMWH[6]. Beide adviezen vallen onder Level of Evidence C en zijn gebaseerd op meerdere observationele studies[12,13]. Bij deze studies wordt geen verschil aangetoond tussen de twee strategieën in de cumulatieve incidentie van zowel trombo-embolische complicaties als bloedingen, echter beschouwt men deze resultaten in de Europese richtlijnen niet als voldoende om het gebruik

van LMWH toe te staan. Nederlandse richtlijnen tonen geen bezwaar tegen het overbruggen met LMWH en onderstrepen nogmaals de logistieke en farmacokinetische voordelen van LMWH ten opzichte van UFH[8,9].

Recent vergeleek een Nederlandse studie retrospectief UFH met LMWH in vier chirurgische centra in Nederland[14]. Deze studie toonde geen verschil in de incidentie van trombo-embolische complicaties (respectievelijk 2,4% en 0,6%), mortaliteit (1,2% en 1,9%) of ernstige bloedingen (19% en 19%). Helaas zijn er geen gerandomiseerde studies beschikbaar. In het protocol in dit artikel heeft gezien de financiële en logistieke voordelen van LMWH over UFH plus de sterke suggestie van een vergelijkbaar risicoprofiel LMWH vervangen UFH als overbruggingsstrategie.

Biologische kunstklep

In de eerste 3 maanden na implantatie van een biologische kunstklep bestaat er een verhoogde kans op trombo-embolische complicaties, tot 10% binnen 90 dagen bij een biologische mitralisklep en tot 3.6% bij een aortaklep[15]. Europese en Amerikaanse richtlijnen adviseren derhalve een VKA voor te schrijven gedurende de eerste 3 maanden voor zowel een mitralis/tricuspidalis klep (klasse IIa indicatie), als een aortaklep (klasse IIb indicatie)[6,16]. Over de noodzaak tot overbruggen met heparine is weinig bekend en in internationale richtlijnen wordt geen duidelijk advies gegeven. Indien er ten tijde van de procedure nog steeds een indicatie voor VKA gebruik bestaat adviseren wij te overbruggen met LMWH.

Atriumfibrilleren

De noodzaak tot overbruggen bij atriumfibrilleren is afhankelijk van het jaarlijkse risico op trombose. Dit wordt berekend door middel van de CHA_2DS_2-VASc score[17] (Tabel 1) (voorheen de $CHADS_2$[18] score). Deze score wordt bepaald aan de hand van een aantal factoren: hartfalen, hypertensie, leeftijd, diabetes mellitus, geslacht, doorgemaakte ischemisch CVA, en vaatlijden. In de meest recente Europese richtlijnen [4] wordt geen afkapwaarde voor overbrugging aanbevolen maar wordt gerefereerd naar de BRIDGE trial, een grote gerandomiseerde studie waar overbruggen met therapeutisch LMWH werd vergeleken met niet overbruggen bij patiënten met atriumfibrilleren[19]. Deze studie toonde geen verschil tussen de twee strategieën met betrekking tot het aantal trombo-embolische complicaties (bridging: 0,3%, no bridging: 0,4%). Het aantal bloedingen was echter significant hoger in de overbruggingsgroep (bridging 3,2%, no bridging 1,3%). Afgaand op deze resultaten zou overbruggen bij atriumfibrilleren dus overbodig zijn. Helaas is een van de beperkingen van de studie dat het aantal patiënten met een hoger risico op trombo-embolische complicaties ondervertegenwoordigd is. Het aantal patiënten in deze studie met een $CHADS_2$ score van 4 of hoger (jaarlijks risico op trombo-embolische complicaties van ≥8,5%) was namelijk ongeveer 14%. Bij deze groep wordt daarom nog steeds geadviseerd om te overbruggen (met LMWH), het is immers niet uitgesloten dat patiënten met een hogere $CHADS_2$ score toch baat hebben bij overbruggen.

Helaas kan de (verouderde) $CHADS_2$ score niet nauwkeurig één op één worden vertaald naar de huidige CHA_2DS_2-VASc score. Een $CHADS_2$ score van 4 komt overeen met een jaarlijks risico op trombose van 8,5%. Vertaald naar de CHA_2DS_2-VASc score komt men hier uit op een score ongeveer tussen 5 en 6, waarbij een score van 6 correleert met een jaarlijks risico op trombose van 9,8%. Een American College of Cardiology (ACC) expert consensus paper uit 2017 hanteert een CHA_2DS_2-VASc score van 4 waarbij wordt geadviseerd om bij een score hoger dan 4 te overbruggen met LMWH[20]. Het argument is hierbij dat bij een CHA_2DS_2-VASc score van 4 of lager het risico op trombose relatief laag is, namelijk <5% op jaarbasis, en dat men relatief veilig de vitamine K antagonist tijdelijk kan staken zonder te overbruggen. Nederlandse richtlijnen hanteren een afkapwaarde van 7 waarbij een CHA_2DS_2-VASc score van 0-7 als laag risico wordt beschouwd. Bij deze groep wordt overbruggen met LMWH niet noodzakelijk geacht[8,9].

Daarbij wordt wel in de richtlijnen van de Federatie Medisch Specialisten nadrukkelijk onderscheid gemaakt tussen patiënten met reumatische hartziekte en/of een CVA/TIA in de voorgeschiedenis (<6 maanden)[8]. Indien dit het geval is dient te worden overbrugd met LMWH, ongeacht de CHA_2DS_2-VASc score. Zo niet is deze keuze afhankelijk van de CHA_2DS_2-VASc score en adviseren wij te handelen conform de richtlijnen, namelijk overbruggen bij een CHA_2DS_2-VASc score van 8 of hoger.

Tabel 1 [17]

	Risicofactor	Score
C	Congestief Hartfalen	1
H	Hypertensie	1
A_2	Leeftijd (Age) ≥75 jaar	2
D	Diabetes Mellitus	1
S_2	Doorgemaakte trombo-embolische complicatie (incl. CVA/TIA) (Stroke)	2
V	Vaatlijden (Vascular disease)	1
A	Leeftijd 65-74 jaar (Age)	1
S_c	Geslacht (Sex)	1

CHA_2DS_2-VASc score	Jaarlijks risico op ischemisch CVA
0	0%
1	1,3%
2	2,2%
3	3,2%
4	4,0%
5	6,7%
6	9,8%
7	9,6%
8	6,7%*
9	15,2%*

*gebaseerd op relatief laag patiënten aantal

CVA= Cerebrovasculair accident, TIA= Transient ischemic attack

Veneuze trombo-embolie

Bij veneuze trombo-embolische complicaties, zoals bij een diep veneuze trombose (DVT) of bij longembolieën is de overbruggingsstrategie afhankelijk van het risico op recidief. Naar mate de tijd verstrijkt wordt dit risico kleiner. Het risico op recidief (indien geen antistolling) is dan ook het grootst in de eerste maanden na een DVT/longembolie, namelijk tot 50% in de eerste maand (zonder antistolling) en tot 10% (met antistolling) in de eerste 3 maanden[1]. De Nederlandse richtlijnen adviseren te overbruggen met therapeutische LMWH bij patiënten met een maandelijks recidiefkans van meer dan 10% (hoog risico)[8,9]. Indien een patiënt zich bevindt in de eerste 3 maanden na een event adviseren wij dan ook te overbruggen met LMWH. Indien de ingreep plaatsvindt langer dan 3 maanden na het event, en de patiënt gebruikt nog steeds een VKA, hoeft niet te worden overbrugd en kan indien gewenst de VKA tijdelijk worden gestopt.

Mitralisklepstenose/CVA/Arteriële trombo-embolie

Indien er een indicatie bestaat voor orale antistolling bij mitralisklepstenose[4], CVA, of arteriële trombo-embolie adviseren wij te overbruggen met LMWH. In de literatuur is weinig bekend over de ideale overbruggingsstrategie bij deze indicaties, wij adviseren te kiezen voor de optie met de laagste kans op trombo-embolische complicaties, namelijk overbruggen met therapeutische LMWH.

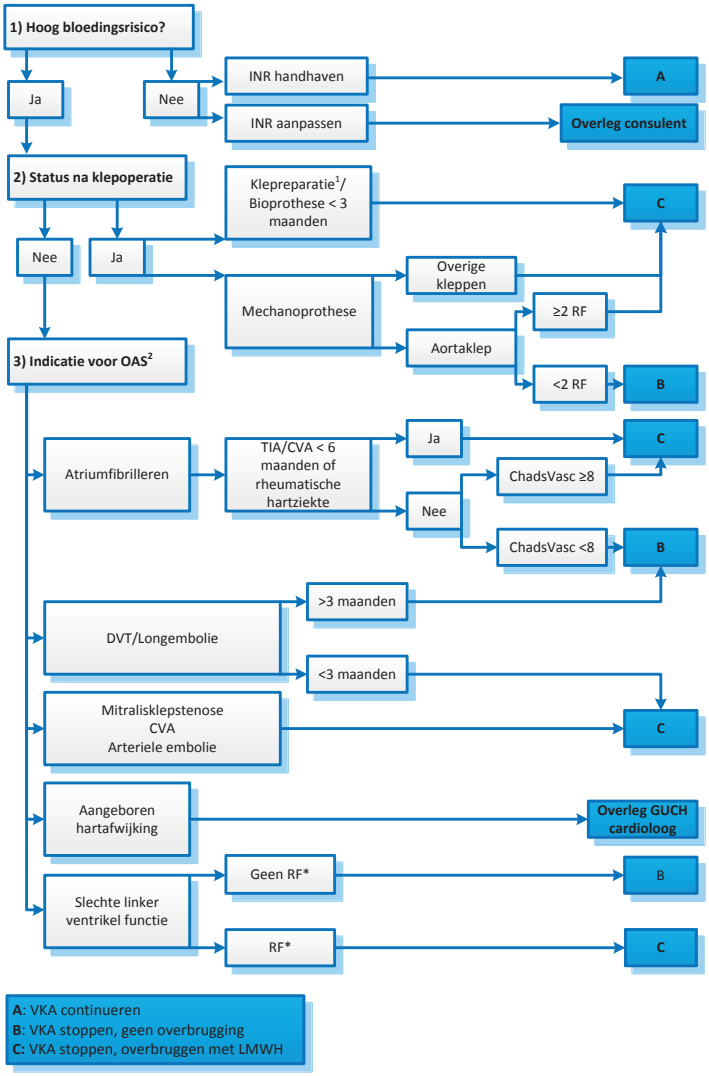
Aangeboren hartafwijkingen

Het risico op trombose bij patiënten met een aangeboren hartafwijking is niet goed te standaardiseren en is afhankelijk van meerdere factoren. In sommige gevallen volstaat tijdelijk stoppen met de VKA, terwijl bij patiënten met complexe kleppathologie overbrugging met LMWH of UFH noodzakelijk kan zijn. Indien de indicatie voor een VKA wordt bepaald door een aangeboren hartafwijking adviseren wij om het perioperatieve antistollingsbeleid altijd te overleggen met een grown-up-with-congenital-heart disease (GUCH) cardioloog.

Slechte linker ventrikel functie

Ten aanzien van de wetenschappelijke onderbouwing bij antistolling en overbrugging bij patiënten met een slechte linker ventrikel functie (LVF) is wederom weinig over bekend en is men afhankelijk van expert opinion. Indien er een antistollingsindicatie bestaat in het kader van een slechte LVF is het perioperatieve antistolling beleid afhankelijk van de aanwezigheid van bijkomstige trombo-embolische risicofactoren[21,22]. Tabel 2 geeft een overzicht van enkele risicofactoren. Het is uiteraard vanzelfsprekend dat het hier gaat om extra risicofactoren naast de slechte LVF, dit is immers reeds één van de risicofactoren. Wij adviseren om geen overbrugging toe te passen met LMWH of UFH indien er naast de slechte LVF géén bijkomende risicofactoren zijn. Indien dit wel zo is dient te worden overbrugd met LMWH.

In Figuur 1 worden de adviezen t.a.v. de peri-procedurele antistolling bij VKA samengevat. Dit protocol is gebaseerd op nationale en internationale richtlijnen, recente studies, ervaringen in ons centrum, en is samengesteld door de antistollingscommissie in het Universitair Medisch Centrum Utrecht.



Figuur 1 [8,14]

VKA=Vitamine K antagonist, INR=International Normalized Ratio, LMWH=Low-molecular weight heparin, OAS=Orale Antistolling, TIA= Transient ischemic attack, CVA= Cerebrovasculair accident, DVT= Diep veneuze trombose, RF=Risicofactoren (Zie Tabel 2), GUCH=Grown up with congenital heart disease, ChadsVasc = zie Tabel 1

[1]Inclusief plaatsen ring/patches/(neo)chordae

[2]Indien er meerdere indicaties zijn à kiezen voor strategie met minste risico op trombose (C kiezen boven B)

*Extra risicofactoren naast slechte linker ventrikel functie

In Figuur 1 dienen 3 vragen gesteld worden; 1) is er sprake van een hoog bloedingsrisico, 2)heeft de patiënt een klepoperatie ondergaan, en 3) zijn er nog overige antistollingsindicaties? Indien er sprake is van een laag bloedingsrisico kan de VKA worden gecontinueerd. Bij het tijdelijk verlagen van de streef INR (>1,5) dient te worden overlegd met het behandelend specialisme (overleg consulent). In het vervolg van de Figuur wordt de overbruggingsstrategie bepaalt op basis van het risico op trombo-embolische complicaties.

Tabel 2

Risicofactoren voor trombo-embolische complicaties (naast mechanische kunstklep of slechte linkerventrikel functie)
Atriumfibrilleren/flutter
Linkerventrikel ejectiefractie (LVEF) <35%
Aneurysma cordis
Spontaan contrast zichtbaar in het hart (echo), en/of trombus in LV
Mitralisklepstenose (matig/ernstig)
Hypercoagulabiliteit (maligniteit/sepsis)
Linker atrium dilatatie (>50mm)
Trombo-embolische event in de voorgeschiedenis (incl. TIA/CVA)
Kunstklep in andere positie dan aortaklep
Oude generatie kunstklep (dus: geen bi-leaflet klep), bijvoorbeeld ball-in-cage (Starr Edwards) of mono-leaflet klep (Medtronic Hall)

CONCLUSIE

Bij patiënten met een indicatie voor een VKA die een invasieve ingreep ondergaan is een afweging tussen het bloedingsrisico en het risico op trombo-embolische complicaties van cruciaal belang. Een praktisch perioperatief antistollingsprotocol, zoals in Figuur 1, kan nuttig zijn.

Toekomstige studies zullen ongetwijfeld voor aanvullingen zorgen ten aanzien van het ideale perioperatieve antistollingsbeleid. In dit protocol is al reeds een verandering toegepast ten opzichte van de Europese richtlijnen, namelijk overbrugging van mechanische kunstkleppen met LMWH in plaats van UFH. Ten aanzien van atriumfibrilleren hebben wij een duidelijke CHA_2DS_2-VASc afkapwaarde gekozen en volgen wij de huidige Nederlandse richtlijnen.

Het gebruik van UFH kan worden toegepast in uitzonderingssituaties, bijvoorbeeld bij patiënten met een aangeboren hartafwijking of bij complexe kleppathologie.

Zelfs bij het gebruik van LMWH zullen mogelijk veranderingen optreden in de nabije toekomst. Zo heeft een recente observationele studie aangetoond dat bij overbrugging bij mechanische kunstkleppen met LMWH in een profylactische dosering in plaats van een therapeutische dosering het aantal bloedingen laag was (1,3%) terwijl er geen trombo-embolische complicaties optraden[23]. Uiteraard zal dit resultaat moeten worden bevestigd door middel van

een gerandomiseerde studie met adequate populatiegrootte waarbij er direct werd vergeleken met therapeutische doseringen. Als men dit resultaat extrapoleert is het niet ondenkbaar dat er in de toekomst niet meer met heparine wordt overbrugd. Recent toonde een grote meta-analyse geen verschil in de incidentie van trombo-embolische complicaties bij patiënten die werden overbrugd versus patiënten die niet werden overbrugd[24]. Het aantal bloedingen was significant hoger in de overbrugging groep. Eén van de meerdere grote beperkingen van deze analyse is echter dat er geen duidelijk onderscheid werd gemaakt tussen de verschillende indicaties voor VKA gebruik en daarbij ook het individuele risicoprofiel.

Een focused update in 2017 van de American Heart Association heeft de noodzaak tot overbruggen met hoog risico patiënten (inclusief mechanische kunstkleppen) verlaagd van een klasse I (is recommended) indicatie naar IIa (is reasonable)[25]. De uitkomst van een gerandomiseerde studie met patiënten met een hoog risico op trombose (mechanische kunstklep en/of atriumfibrilleren met hoge CHA_2DS_2-VASc score) waarbij LMWH overbrugging wordt vergeleken met niet-overbruggen zou zeer interessant zijn.

Dit overzichtsartikel bevat een pragmatisch antistolling protocol voor patiënten met orale antistolling in de vorm van een VKA, toepasbaar in de kliniek. Hierbij wordt rekening gehouden met zowel het bloedingsrisico als het risico op trombo-embolische complicaties. Het protocol is samengesteld door de antistollingcommissie in het UMC Utrecht en is onder andere gebaseerd op de huidige Europese, Amerikaanse en Nederlandse richtlijnen, en bevat relevante literatuur op dit gebied.

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Chapter 10

Local ultrasound-facilitated thrombolysis in pulmonary embolism: first Dutch experience and comparison with systemic thrombolysis.

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In preparation

ABBREVIATIONS

AZN	St. Antonius Hospital, Nieuwegein
CI	Confidence interval
CTPA	Computed tomographic pulmonary angiography
DOAC	Direct oral anticoagulant
ECMO	Extracorporeal membrane oxygenation
EKOS	EkoSonic Endovascular system (EKOS Corporation; Bothell, WA, USA)
EMC	Erasmus Medical Center Rotterdam
ESC	European Society of Cardiology
ISTH	International Society on Thrombosis and Haemostasis
IQR	Interquartile range
LMWH	Low-molecular-weight heparin
OR	Odds ratio
PE	Pulmonary embolism
RR	Risk ratio
RV	Right ventricle
ST	Systemic thrombolysis
UMCU	University Medical Center Utrecht
USAT	Ultrasound-assisted catheter-directed thrombolysis
VCF	Vena cava filter
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
VUMC	VU University Medical Center

ABSTRACT

Objectives: To describe pulmonary embolism (PE) patients who underwent ultrasound-facilitated catheter-directed thrombolysis (USAT) and to compare outcomes of USAT and systemic thrombolysis (ST) in high-risk patients.

Background: ST is an effective treatment for hemodynamically unstable, high-risk PE, but is associated with bleeding complications. USAT, using a lower dose of thrombolytic, possibly reduces bleeding complications.

Methods: All patients who underwent USAT for PE in the Netherlands from 2010-2017 and patients undergoing ST for PE from 2007-2017 in the UMC Utrecht were identified. Characteristics and outcomes of USAT patients were compared to ST patients. Primary outcomes were major (including intracranial and fatal) bleeding and all-cause mortality after 1 month. Secondary outcomes were all-cause mortality and recurrent venous thromboembolism (VTE) within 3 months.

Results: 44 patients (33 high-risk PE) underwent USAT. Major bleeding occurred in 14 patients (32%; 95%CI 20-47), including 2 intracranial and 4 fatal bleeding. All-cause mortality after 1 month was 42% (95%CI 28-57). Comparing high-risk PE patients treated with USAT (n=33) and ST (n=53), a higher incidence of major bleeding was observed (37% versus 28%, p = 0.43) including 1 versus 5 intracranial bleeds. All-cause mortality after 1 month was 48% versus 59%, p = 0.37; recurrent VTE 0% versus 3%, p = 0.20. Heterogeneity in presentation and bleeding risk factors appears to be associated with differences in outcomes in multivariate regression analysis.

Conclusions: Major bleeding occurred more often in USAT patients whereas intracranial bleeds were more frequent in ST patients. Further research is required to guide patient selection.

INTRODUCTION

Acute pulmonary embolism (PE) is a common cardiovascular disease that can result in significant morbidity and death. PE patients with hemodynamic shock or hypotension are classified as high-risk, those with right ventricular (RV) dysfunction and/or myocardial injury as intermediate-risk and patients without those signs as low risk of mortality[1]. In the high-risk group, approximately 5% of all PE patients, an in-hospital mortality of 25-65% is found, depending on clinical presentation and timely availability of treatment[1-3]. Systemic thrombolysis (ST) is currently standard of care in high-risk patients (European Society of Cardiology (ESC) Guideline on Pulmonary Embolism level of evidence I-B)[1-4]. It has been shown to restore pulmonary perfusion more rapidly compared to standard anticoagulation therapy alone, thereby improving RV function and reducing mortality[5-8]. However, ST carries a 20% risk of major bleeding, including a 2-3% risk of intracranial hemorrhage[1,4,9-10]. Consequently, risk factors for bleeding are considered (relative) contraindications for this treatment[8,11]. In intermediate-risk patients, ST compared with anticoagulation is associated with a decrease in mortality or hemodynamic decompensation within seven days from 6% to 3%[1,4]. This comes at the expense of an increased risk of major bleeding, both extracranial and intracranial, from 1% to 6% and 0% to 2%, respectively[1,4]. Thrombolytic therapy is thus not routinely recommended in intermediate-risk patients, but should be considered if rapid clinical deterioration occurs[1,4].

The high incidence of bleeding in patients treated with ST is thought to be related to the dose of thrombolytic agent. Therefore, different attempts have been made to reduce the dose and to administer the thrombolytic agent locally using catheter-based approaches. Ultrasound-facilitated, catheter-directed local thrombolysis (USAT) using the EkoSonic Endovascular system (EKOS Corporation; Bothell, WA, USA) is currently the most studied technique. With this catheter, ultrasound is used to drive a low dose of thrombolytic agent directly into plasminogen receptor sites within the thrombus and separate fibrin strands more efficiently, thereby increasing the number of available plasminogen activator receptor sites[12-13]. Previous studies on USAT and other local thrombolytic interventions for PE did show a reduction of pulmonary artery pressure and improved echocardiographic parameters such as right ventricle/left ventricle ratio. However, these studies were single-arm with a short follow-up and mainly included patients with intermediate-risk PE[14-15]. These include retrospective studies comparing USAT and ST, and studies comparing thrombolytic interventions with anticoagulation[16-22]. Currently, no randomized controlled trial comparing USAT with ST has been performed. Meanwhile, in high-risk patients in whom ST is contraindicated or has failed, ESC guidelines recommend surgical embolectomy or, alternatively, USAT[1]. However, there is great variation between hospitals in the use of this technique.

The aim of this retrospective study was to describe characteristics and outcomes of all patients treated with USAT for acute PE in the Netherlands, to provide insight into the current use and

outcomes of USAT. Furthermore, we aimed to assess potential differences in the incidence of major bleeding and mortality between USAT and ST to provide points of departure in guiding proper patient selection.

MATERIALS AND METHODS

Study population

This retrospective study was conducted at University Medical Center Utrecht (Utrecht, the Netherlands), St. Antonius hospital (Nieuwegein, the Netherlands), Erasmus Medical Center (Rotterdam, the Netherlands) and VU University Medical Center (Amsterdam, the Netherlands). We included all patients that underwent USAT for acute PE in the Netherlands since its introduction in 2010 until July 2017. Patients were identified from a database maintained by interventional cardiologists performing USAT, by searching radiology reports on 'thrombectomy, 'fibrinolysis', 'pulmonary arteries', 'thoracic arteries' and 'EKOS' and by using software implemented in the local electronic medical record. Demographic data, patient related factors and clinical information were extracted.

PE was diagnosed with computed tomographic pulmonary angiography (CTPA) or, when considered unsafe, echocardiography (RV overload) or high suspicion on clinical grounds. High-risk PE was defined as PE with hemodynamic shock or hypotension (systolic blood pressure <100 mmHg or a decline of >40 mmHg), intermediate-risk PE was defined as PE with signs of RV dysfunction and/or elevated cardiac biomarkers[1]. Shock is defined as the presence of hypotension or other signs of reduced tissue perfusion (altered mental state, oliguria, clammy and pale skin, hyperlactatemia). The presence of RV dysfunction or dilatation (dilated, enlarged or decompensated RV, right heart strain, RV failure or dysfunction) was extracted from echocardiography and CTPA reports as noted by performing physician. Bleeding risk factors are based on ACCP and ESC guidelines[1,23]. Major bleeding risk factors include recent hemorrhagic stroke, surgery, trauma, head injury, gastrointestinal bleeding, central nervous system malignancies and active bleeding. Minor bleeding risk factors are recent transient ischemic attack, current therapeutic anticoagulation, pregnancy, traumatic resuscitation, refractory hypertension, end stage liver disease, infectious endocarditis and active stomach ulcer.

Furthermore, from 2007 to March 2017, all patients undergoing ST for high-risk PE in the UMC Utrecht were identified by searching patient files on thrombolysis, PE, CTPA and synonyms. We excluded all ST patients <16 years, patients who received interventional therapy in addition to ST, and patients in whom follow-up data were not available. Characteristics and outcomes of these patients were compared to those of high-risk PE patients treated with USAT.

This study was not subject to the Medical Research Involving Human Subjects Act and was approved by the Medical Research Ethics Committee before data acquisition.

Thrombolysis

In all participating hospitals, ST is administered in high-risk PE patients without major contraindications for systemic thrombolytic therapy, according to guidelines[1]. Generally accepted major contraindications are abovementioned major bleeding risk factors. In 2010, USAT for PE was performed for the first time in the Netherlands at the VU University Medical Center. Since 2014, in four Dutch hospitals. USAT is considered in patients with high-risk PE and contraindications for ST that are hemodynamically unstable, but whose condition is otherwise stable enough to be transported to the catheterization laboratory. However, local protocols vary regarding combination with other therapies, including extracorporeal membrane oxygenation (ECMO), thrombus aspiration and ST.

Generally, when a patients' condition deteriorates despite treatment with USAT, either ST or local interventions are used. Because this only concerns a limited number of patients, treatment decisions are made on an individual basis.

USAT was performed by either experienced interventional cardiologists (Utrecht) or interventional radiologists (Nieuwegein, Rotterdam, Amsterdam). Venous access was obtained via the femoral or internal jugular vein. In case of unilateral PE, one EKOS-catheter was placed through the thrombus in the pulmonary artery, and 24 mg of Alteplase was locally administered for 24 hours. In case of bilateral PE, two EKOS-catheters were placed, one on each side, and 12 mg of Alteplase was administered per catheter for 12 hours. ST consisted of an intravenous bolus of 10 mg followed by the infusion of 90 mg Alteplase in 2 hours. Heparin was administered according to predefined protocols. In one hospital (Utrecht), an intravenous bolus of heparin of 5000 IE or 80 IE per kilogram body weight is administered before USAT, and continuous infusion is started after USAT with a target aPTT of 2-2.5. In the other hospitals (Nieuwegein, Rotterdam, Amsterdam) heparin is administered concomitantly, based on a target aPTT level of 2.5-3, and continued afterwards. If no bleeding had occurred within 24-48 hours after thrombolysis, standard anticoagulation therapy consisting of direct oral anticoagulants (DOAC), low molecular weight heparin (LMWH) or a vitamin K antagonist (VKA) was started.

Outcome assessment

Primary outcomes were all-cause mortality during the first month of follow-up as well as major bleeding, including intracranial hemorrhage and fatal bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH)[23]. Secondary outcomes were all-cause mortality and recurrent VTE after three months of follow-up, objectively confirmed by CTPA, perfusion-scintigraphy, pulmonary angiography, compression ultrasound or phlebography[1]. Mortality outcomes were assessed by data from medical records. All outcomes were evaluated using clinical information as noted in patient files.

Statistical analysis

Baseline characteristics and outcomes were compared between high-risk patients treated with USAT and ST using two-sided chi-square test and Fisher's exact test for categorical variables and two sample unpaired t-tests for continuous variables. Logistic regression was performed with both major bleeding and mortality after one month of follow-up as dependent variables, and different patient related factors and type of treatment as independent variables in separate, univariate analyses. Analyses were repeated after adjusting for confounders as determined by expert opinion and literature, namely age, sex, mechanical ventilation, resuscitation, altered mental status and whether CTPA was performed prior to initiating therapy, and the presence of minor or major bleeding risk factors. All statistical analyses were performed in SPSS version 21 (SPSS Inc., Chicago, Illinois, USA). P-values <0.05 were considered significant.

RESULTS

We identified 48 patients with PE that underwent treatment with USAT (Figure 1), of whom 44 completed at least 1 month of follow-up.

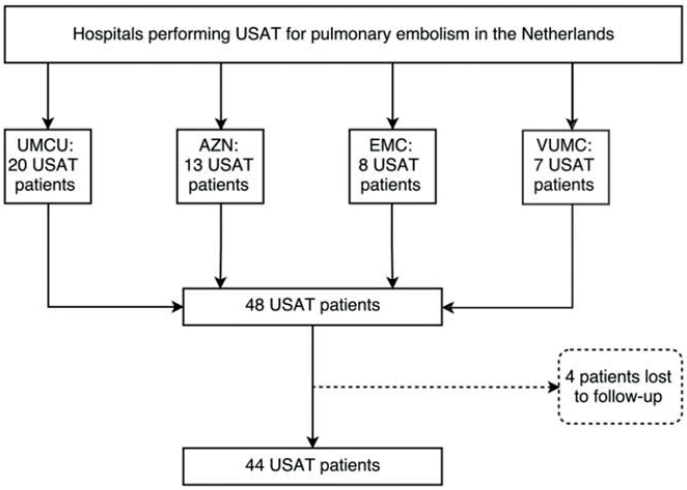

Figure 1. Flowchart of the included patients
Abbreviations: AZN, St. Antonius Hospital Nieuwegein; EMC, Erasmus Medical Center Rotterdam; UMCU, University Medical Center Utrecht; USAT, Ultrasound-facilitated, catheter-directed local thrombolysis; VUMC, VU University Medical Center Amsterdam

Baseline characteristics are shown in Table 1. Most patients presented with high-risk PE (n=33, 75%). RV dysfunction or dilatation was present in almost all patients (98%). 48% needed resuscitation before arrival at the hospital or during hospital admission. Before proceeding to therapy, definitive diagnosis was obtained by CTPA in 84%, and by echocardiography in 11%. In two patients, PE was suspected on clinical grounds (sudden dyspnea and hemodynamic

instability in a patient immobilized after leg surgery), or high pulmonary artery pressures during coronary angiography. USAT was performed bilaterally in 93%. Average dose of thrombolytic agent used in 41 patients treated with Alteplase was 25 mg (SD 11), in 41 patients. Heterogeneity in management of acute PE between participating hospitals mainly consisted of different indications for USAT and combination with other treatment options. In one hospital, USAT was performed in intermediate-risk patients in case of severe RV strain or near respiratory failure. In the other hospitals, USAT was rarely performed in patients without high-risk PE but more often combined with ST or thrombus aspiration, in variable order. Table 2 illustrates the treatment of patients that received additional therapy before or after USAT.

Table 1. Baseline characteristics USAT patients

	n (% of 44)
Demographic data	
Age (years) (median (IQR));	62 (51-71)
>75 years (%)	8 (18)
Female (%)	21 (48)
Patient related factors	
History of VTE	8 (19) ‡
Active malignancy	9 (21) ‡
Therapeutic anticoagulation (VKA, DOAC)	4 (9)
Clinical status	
High risk PE	33 (75)
Intermediate risk PE	11 (25)
Low risk PE	0
Hypotension (SBP <100 mmHg)	26 (63) *
Shock	33 (75)
RV dysfunction or dilatation	41 (98) †
Resuscitation	21 (48)
Mechanical ventilation	17 (40) ‡
Major bleeding risk factors	
1 risk factor	15 (34)
2 or more risk factors	1 (2)
Minor bleeding risk factors	
1 risk factor	9 (20)
2 or more risk factors	1 (2)
Diagnosis confirmed by CTPA	37 (84)

Abbreviations: CTPA, computed tomographic pulmonary angiography; DOAC, direct oral anticoagulants; IQR, interquartile range; PE, pulmonary embolism; SBP, systolic blood pressure; USAT, Ultrasound-facilitated, catheter-directed local thrombolysis; VKA, vitamin K antagonist; VTE, venous thrombo-embolism

* n = 41; † n = 42; ‡ n = 43

Table 2. Additional therapies in USAT patients (all high-risk)

Patient	ST	Thrombus aspiration	VCF	ECMO
1	Full dose	-	Yes	-
2	-	Yes	Yes	-
3	Full dose	Yes	-	Yes
4	Low dose	Yes	-	-
5	Loading dose	Yes	-	-
6	Full dose	Yes	-	-
7	-	Yes	-	Yes
8	-	Yes	-	-
9	-	Yes	-	-
10	Lower dose	-	-	-
11	Lower dose	-	-	-
12	Lower dose	-	-	Yes
13	Lower dose	-	-	-
14	Full dose	-	-	Yes
Total	10	8	2	4

Abbreviations: ECMO, extracorporeal membrane oxygenation; ST, systemic thrombolysis, USAT, ultrasound-facilitated, catheter-directed local thrombolysis; VCF, vena cava filter

Outcomes

Table 3 shows the outcomes of patients treated with USAT. Four patients were lost to follow-up, including one high-risk patient. Fourteen patients (14/44, 32%) suffered major bleeding after USAT, as specified in Table 4. Four patients (4/14, 29%) had >1 major bleed simultaneously. Three of them had epistaxis requiring intervention and, respectively, intra-abdominal bleeding, compartment syndrome and intrathoracic bleeding, the fourth had hematuria and melaena. Four patients died from bleeding (4/44, 9%). One of these patients presented with both high-risk PE and ischemic stroke, which was subject to hemorrhagic transformation after USAT. Another patient developed intermediate-risk PE with respiratory insufficiency six days after a subarachnoid hemorrhage from an aneurysm, that rebled after USAT. Two other patients with fatal bleeding both experienced traumatic resuscitation resulting in multiple rib fractures and died from hypovolemic shock after severe thoracic bleeding and bleeding from access sites.

Table 3. Outcomes of USAT patients

	USAT n (% of 44)
Primary outcomes (after 1 month)	
Major bleeding, including intracranial and fatal bleeding	14 (32)
Intracranial bleeding	2 (5)
Fatal bleeding	4 (9)
All-cause mortality	18 (41)
Secondary outcomes (after 3 months) ‡	
All-cause mortality	18 (42) ‡
Recurrence of VTE	1 (2) ‡
Other outcomes	
Hospital length of stay (median days (IQR)) *	12 (6-18)

Abbreviations: IQR, interquartile range; USAT, Ultrasound-facilitated, catheter-directed local thrombolysis; VTE, venous thrombo-embolism

* Assessed in all patients surviving the first month of follow-up

‡ n = 43

Table 4. Major bleeding in USAT patients

Major bleeding (as defined by the ISTH[23])	n
Access site hematoma	4
Intrathoracic bleeding (hemothorax or chest wall after traumatic resuscitation or surgery)	4
Intraabdominal hematoma	3
Mucosal bleeding (nasal)	2
Bleeding from ECMO cannula site	1
Hematoma on lower arm, causing compartment syndrome	1
Hemorrhagic transformation of ischemic stroke	1
Subarachnoid hemorrhage due to rebleed from aneurysm	1
Gross hematuria	1
Total number of major bleeding episodes in 14 patients with major bleeding	**18**

Abbreviations: ECMO, extracorporeal membrane oxygenation; ISTH, International Society on Thrombosis and Haemostasis USAT, Ultrasound-facilitated, catheter-directed local thrombolysis; VKA, vitamin K antagonist; VTE, venous thrombo-embolism

Fourteen patients (30%) died from causes other than bleeding. Four patients did not respond to USAT (4/44, 9%), of whom one also received ST, and died. Irreversible brain damage, organ failure, heparin-induced thrombocytopenia, sepsis and glioblastoma lead to the death of the other patients. In one patient, echocardiographic signs of recurrent PE were seen after USAT and died despite of the use of additional ST. No other episodes of recurrent VTE were observed. After treatment, 70% that survived the first month of follow-up was discharged home, 17% went to a nursing or rehabilitation facility. Five patients (13%) were transferred to another hospital, of whom four were lost to follow-up.

Of fourteen patients treated with USAT in combination with ST or thrombus aspiration, four patients suffered major bleeding, including one fatal. A higher mortality was seen in patients treated with both USAT and ST compared to patients treated with USAT with or without thrombus aspiration (70% versus 32%, p = 0.34). The incidence of major bleeding was lower in this group (26% versus 30%, p = 0.82).

Eleven patients were treated with USAT for intermediate-risk PE, of whom nine survived. Except for one fatal, intracranial aneurysm rebleed as mentioned, no episodes of major bleeding were observed in these patients.

Systemic thrombolysis

53 patients that underwent ST for high-risk PE in our tertiary center from 2007-2017 were identified. Patients that underwent ST and other therapies were excluded (or, if applicable, analyzed in the USAT group). Table 5 shows the results of a comparison of 53 ST patients and 33 USAT patients with high-risk PE.

Table 5. Systemic thrombolysis compared to USAT in high-risk patients

	ST n (% of 53)	USAT n (% of 33)	p value
Demographic data			
Age (years) (median (IQR));	55 (49-66)	63 (51-71)	0.16
>75 years (%)	8	15	0.30
Female (%)	30 (57)	17 (52)	0.65
Patient related factors			
History of VTE	4 (8)	8 (25) †	0.05
Active malignancy	10 (19)	8 (24)	0.58
Therapeutic anticoagulation (VKA, DOAC)	0	2 (6)	0.14
Clinical status			
Hypotension (SBP <100 mmHg)	50 (94)	29 (88)	0.42
Shock	53 (100)	32 (97)	0.38
RV dysfunction or dilatation	52 (98)	32 (97)	1.00
Resuscitation	38 (72)	20 (61)	0.29
Mechanical ventilation	41 (77)	17 (52)	0.01
Major bleeding risk factors			
1 risk factor	17 (32)	13 (39)	0.49
2 or more risk factors	1 (2)	1 (3)	1.00
Minor bleeding risk factors			
1 risk factor	3 (6)	6 (18)	0.07
2 or more risk factors	1 (2)	1 (3)	0.38
Diagnosis confirmed by CTPA	19 (36)	26 (79)	<0,01

Abbreviations: CTPA, computed tomographic pulmonary angiography; DOAC, direct oral anticoagulants; IQR, interquartile range; PE, pulmonary embolism; SBP, systolic blood pressure; ST, systemic thrombolysis; USAT, Ultrasound-facilitated, catheter-directed local thrombolysis; VKA, vitamin K antagonist; VTE, venous thrombo-embolism

† n = 32

Baseline characteristics are comparable, except for history of VTE, which was more frequent in USAT patients. Additionally, median age of USAT patients appears to be higher, although differences were not statistically significant. Regarding clinical presentation, mechanical ventilation was present in a higher percentage of ST patients (77% versus 50%, p = 0.01). The presence of at least one minor bleeding risk factor was more common in USAT patients (21% vs 6%, p = 0.07). Before initiating therapy, diagnosis was generally confirmed by CTPA in USAT patients, whereas ST was regularly administered when echocardiography was suggestive of PE. Alteplase was used in 86% of ST patients and 91% of USAT patients. Other thrombolytic agents used were Urokinase, Streptokinase, Tenecteplase and a combination of Tenecteplase and Alteplase. Patients undergoing USAT or ST with Alteplase received 27 and 83 mg on average, respectively.

In this study, major bleeding occurred more often in USAT patients (37 vs 28%, p = 0.43), whereas intracranial bleeds were more common in ST patients (9 vs 3%, p = 0.40) (Table 6).

Table 6. Systemic thrombolysis compared to USAT in high-risk patients

	ST n (% of 53)	USAT n (% of 33)	p value
Primary outcomes (after 1 month)			
Major bleeding, including intracranial and fatal bleeding	15 (28)	12 (37)	0.43
Intracranial bleeding	5 (9)	1 (3)	0.40
Fatal bleeding	5 (9)	3 (9)	1.00
All-cause mortality	31 (58)	16 (48)	0.37
Secondary outcomes (after 3 months)			
All-cause mortality	31 (58)	16 (50) †	0.50
Recurrence of VTE	0	1 (3) †	0.20
Hospital length of stay (median days (IQR)) *	7 (5-11)	17 (9-30) †	0.015

Abbreviations: IQR, interquartile range; ST, systemic thrombolysis; USAT, Ultrasound-facilitated, catheter-directed local thrombolysis; VTE, venous thrombo-embolism

* Assessed in all patients surviving the first month of follow-up

† n = 32

Additionally, median days of hospitalization was significantly higher in USAT patients (17 vs 7 days, p = 0.02). Ten patients were treated with varying doses of ST before or after USAT. After excluding those patients and comparing 23 high-risk PE patients treated with USAT only to 53 ST patients, although not statistically significant, a larger difference in all-cause mortality after 1 month of follow-up was found (39% versus 59%, p = 0.13), whereas the comparison of major bleeding was similar, with 39% (9/23) major bleeding in patients treated with USAT only.

Subgroup analysis in the total group of high-risk patients showed that at least one major risk factor for bleeding was present in 56% of patients with major bleeding, and in 75% with fatal bleeding (data not shown). 47% and 19% of patients that presented with at least one major bleeding risk factor suffered major or fatal bleeding, respectively. No significant differences in incidence of bleeding and mortality between USAT and ST patients with at least one major risk factor were found.

Univariate regression analysis showed that need of resuscitation and ventilation, no CTPA prior to initiating therapy, altered mental status and age were associated with mortality in high-risk PE patients and age >75 years, CTPA prior to therapy and mechanical ventilation were selected as relevant confounders in the adjusted analysis. Although not statistically significant, the data suggest that USAT is associated with a lower mortality compared to ST, as shown in Table

Table 7. Determinants of mortality and bleeding: logistic regression analysis

Mortality after 1 month	OR	95% CI	p value	Corresponding RR
Age >75 years	7.8	0.9 to 65.4	0.06	1.9
Sex: female versus male	0.5	0.2 to 1.2	0.11	0.7
Resuscitation	4.0	1.5 to 10.5	0.01	2.2
Mechanical ventilation	9.4	3.2 to 27.4	0.00	3.6
Altered mental status	4.2	1.5 to 11.8	0.01	1.9
CTPA performed prior to initiating therapy	0.3	0.1 to 0.8	0.02	0.6
Treatment: USAT versus ST				
- *Unadjusted analysis*	0.7	0.3 to 1.6	0.37	0.8
- *Adjusted for age >75 years, CTPA prior to therapy, mechanical ventilation*	1.6	0.5 to 5.4	0.46	1.2
Major bleeding				
Age >75 years	5.3	1.2 to 23.3	0.03	2.4
Sex: female versus male	1.1	0.4 to 2.6	0.90	1.1
Resuscitation	2.1	0.7 to 5.9	0.17	1.6
Mechanical ventilation	1.6	0.6 to 4.7	0.35	1.4
Altered mental status	2.1	0.7 to 6.1	0.18	1.8
CTPA performed prior to initiating therapy	1.2	0.5 to 3.0	0.69	1.1
Major bleeding risk factors	3.1	1.2 to 7.9	0.02	2.1
Minor bleeding risk factors	1.5	0.4 to 6.0	0.54	1.3
Treatment: USAT versus ST				
- *Unadjusted analysis*	1.4	0.6 to 3.7	0.43	1.3
- *Adjusted for age >75 years, presence of major bleeding risk factors*	1.2	0.4 to 3.3	0.71	1.1

Abbreviations: CI, confidence interval; OR, odds ratio; RR, risk ratio ST, systemic thrombolysis; USAT, Ultrasound-facilitated, catheter-directed local thrombolysis

In analyses adjusted for age and factors suggestive of a more severe, urgent presentation, an inverse association was found (RR 1.2). Factors associated with major bleeding were age >75 years and the presence of major bleeding risk factor(s) and these were selected as relevant confounders. An unadjusted RR of 1.3 for major bleeding for USAT versus ST corresponds with the observed higher incidence of major bleeding in USAT patients, which was less distinct after adjusting for confounders.

DISCUSSION

This study provides an overview of the use of USAT for PE in the Netherlands. Major bleeding occurred in 32%, of which one third was fatal. This higher incidence compared to the ±10% major bleeding in previous literature may be because of the higher percentage of high-risk patients in our study[15,18-19]. Furthermore, a high percentage in our cohort had major bleeding risk factors and thus major contraindications. All four patients suffering from fatal bleeding after USAT had at least one minor or major risk factor. Two patients suffered from intracranial hemorrhage after USAT, which is rarely described. With a concomitant ischemic stroke, and recent subarachnoid hemorrhage, these patients were at especially high risk for intracranial bleeding. In the present study, 47% of all high-risk PE patients with at least one major bleeding risk factor had a major bleeding. This restates that, especially in the presence of major risk factors, thrombolysis carries a serious risk of major bleeding complications[4,7]. To achieve maximal clinical benefits with minimal bleeding risk, clear risk stratification models for bleeding are warranted.

Due to the need to base treatment decisions on individual factors, some USAT patients were also treated with ST, thrombus aspiration or VCF. In the comparison between high-risk USAT and ST patients, all high-risk PE patients treated with USAT were included, thereby showing the outcomes of the present-day use of USAT. In the ten high-risk USAT patients that were additionally treated with varying doses of ST, a higher all-cause mortality, but less major bleeding was observed compared to patients treated with USAT with or without thrombus aspiration and VCF. This could be related to a more severe clinical presentation, where various attempts at thrombus resolution were made. The lower incidence of major bleeding suggests that USAT is a considerable option in high-risk PE patients if other techniques failed, which is also shown in previous literature[20].

Comparing outcomes of patients treated with USAT and ST, a somewhat lower mortality and higher incidence of major bleeding was observed in USAT patients. The latter could be related to the recommendation by current guidelines to opt for USAT in the presence of major contraindications. However, in one third of ST patients, at least one major contraindication was present as well, possibly because USAT was not available yet throughout the larger part of the inclusion. Furthermore, age >75 years, which was more common in USAT patients, is presumed to predispose for bleeding and mortality according to both our regression analysis and previous literature[4,7,24]. After adjusting for major bleeding risk factors and old age, although not statistically significant, USAT might still be associated with a somewhat higher incidence of major bleeding (RR 1.1). Regression analysis further showed that factors insinuating a more severe presentation, such as resuscitation, mechanical ventilation and the inability to perform a CTPA before initiating therapy, were predictive of mortality. For USAT, patients need to be stable enough to be transported to the catheterization laboratory and may therefore be in a slightly

better clinical condition. This could have led to confounding by indication, in favor of a greater benefit of USAT. After adjusting for age and aforementioned predictors, relative risk suggests that USAT is associated with a higher mortality. However, this was not statistically significant.. . Furthermore, for unknown reasons, in both our study and previous research median length of hospital stay of surviving patients was longer in patients that underwent USAT[17].

A retrospective study comparing USAT and ST found less intracranial hemorrhage, but more procedural bleeding in USAT patients[19]. A lower incidence of intracranial hemorrhage is also observed in our study. Likewise, procedural bleeding is regularly observed in USAT patients. One study comparing USAT with ST showed a substantially reduced mortality in patients treated with USAT, which is hard to interpret considering the difficulty of demonstrating improved efficacy of ST compared to anticoagulation therapy alone on mortality[17]. Regarding clinical benefits of USAT, a previous study comparing USAT and anticoagulation with anticoagulation alone reported its superiority on echocardiographic parameters and mortality[14]. Furthermore, complication rates of USAT and its beneficial effect on pulmonary artery pressures and echocardiographic parameters were shown[15,18,21-22,25-26]. In conclusion, a beneficial effect of USAT is suggested, but the impact on clinically relevant outcomes is understudied. Moreover, this is only based on single-arm studies, retrospective studies and studies comparing different interventions.

The use of heparin during USAT is still understudied. Various regimes are used in other studies on USAT and PE, if mentioned at all. Likewise, different protocols are used in hospitals participating in the present study. In one previous study on different catheter directed therapies, no association between use of heparin and a higher incidence of major bleeding was found[18]. The implications of the heterogeneity in heparin protocols are not clear.

The main strength of the present study is the inclusion of all patients treated with USAT for PE in the Netherlands, with little loss to follow-up, therewith providing a comprehensive view on the use of USAT for PE in our country. It provides more insight into the outcomes of high-risk PE patients based on data from real clinical practice. However, the study population was small and heterogeneous, and the high-risk cohorts were not matched by design. Other noteworthy limitations are predominantly due to the retrospective study design. Information bias could be introduced as data is extracted from electronic patient files as noted by the treating physician. Even though hemodynamic stability is clearly defined, and classification is performed to the best extent possible, misclassification could still lead to an underestimation of effects. As mentioned, differences in treatment protocol and patient selection might have introduced bias. Although all ST patients included were treated in one hospital, the included patients are thought to be a representative sample of the total group. In any case, the decision on type of treatment is made by the treating team of physicians and could be based on numerous other considerations, which could not all be accounted for.

CONCLUSION

A higher incidence of major bleeding was observed in patients treated with USAT. However, USAT was predominantly used in a heterogeneous group of high-risk PE patients with major contraindications to ST. It seems that particular care is needed in older patients and patients with major (intracranial) bleeding risk factors. In terms of efficacy on mortality and incidence of recurrent VTE, USAT seemed non-inferior to ST. Therefore, prospective studies with a large population comparing the two strategies should be performed.

DISCLOSURE OF CONFLICTS OF INTEREST

The authors state that they have no conflict of interest.

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General Discussion and Future Perspectives

In this thesis several aspects of treatment planning have been addressed with the goal of improving efficacy and safety of cardiac interventions in valvular heart disease. More precisely, optimization of the MitraClip procedure, and timing of screening and surgical intervention in patients with carcinoid heart disease (CaHD) were discussed. Furthermore, the periprocedural strategy in patients with oral anticoagulants was assessed, followed by an analysis of the use of ultrasound facilitated thrombolysis for pulmonary embolism.

Diagnosis in mitral regurgitation

In chapter 1 a trans-thoracic echocardiography (TTE) grading index for the degree of mitral regurgitation (MR) is presented. In current guidelines[6,39], 11 parameters are used, however the application and calculation of all parameters is time-consuming and often omitted in clinical practice. For example, calculation of the effective regurgitant orifice (EROA) or proximal isovelocity surface area (PISA) require extensive calculations and are dependent on adequate image acquisition. In clinical practice, determination of the degree of MR severity is often limited to qualitative and quantitative parameters, such as jet characteristics or the presence of pulmonary vein flow reversal or blunting, respectively. Provided the degree of severity may carry significant consequences, such as mitral valve repair or replacement, adequate classification is important. In this scoring index, multivariate analysis successfully identified 5 parameters that remained significant predictors of severe MR. These parameters consisted of the (semi) qualitative and quantitative factors; 1)valve morphology, 2)jet characteristics, 3)vena contracta, 4)systolic reversal, and 5)LV dimensions. These parameters are easily acquired and evaluated and therefore represent an easy-to-use scoring index for clinical practice. Important limitations have to be addressed however. (Semi)qualitative parameters were used as the reference standard. Variations in grading among the reference panel were inevitable. Furthermore, although a reference panel has been accepted as a reliable standard[54], the lack of a golden standard remains of significant importance and can unfortunately not be avoided.

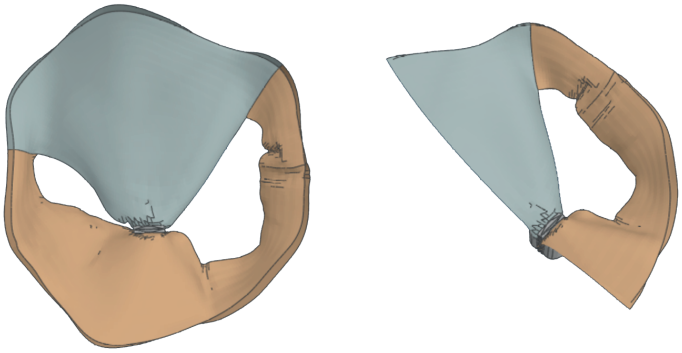
The easy-to-use scoring index using trans-thoracic echocardiography represents a simplified yet accurate step in the diagnosis of severe or moderate MR. Although the use of cardiac magnetic resonance imaging or 3-dimensional imaging allows for a more accurate assessment of MR severity, these procedures are bound by both logistic and financial restrictions and are still not implemented in daily routine practice.

Determining the severity of MR is of importance when deciding treatment options. Although surgery is generally not performed in MR grade 3 or lower, the presence of symptoms may warrant intervention. The indication for surgical intervention in severe primary MR is dependent on the presence of several factors, including reduced ejection fraction or symptoms (Class I indication), and/or atrial fibrillation or pulmonary hypertension (Class IIa indication)[10]. A dilemma arises among a select group of patients which are 1) asymptomatic with no additional Class I or IIa indications, or 2) inoperable or carry high surgical risk. With regards to the first group, no consensus has been reached regarding a surgical or watchful waiting approach. The

Dutch Asymptomatic Mitral Regurgitation (AMR)[55] trial is an ongoing registry which aims to identify the ideal treatment strategy in asymptomatic patients with severe MR.

Percutaneous approaches

Patients with MR deemed unfit for traditional surgery may benefit from a percutaneous approach, which often entails the MitraClip procedure outlined in this thesis. In chapter 2, a proof-of-concept study was presented where trans-esophageal echocardiography (TEE) images of 2 patients with severe MR were used to create a computer-based simulation of the mitral valve. TEE images acquired throughout the cardiac cycle allowed for an accurate simulation of systolic closure. This project was prompted by the growing field of virtual treatment planning, which has already been applied in both the non-cardiac[56] and cardiac field[57,58]. A computer based virtual representation of the mitral valve may not only aid the operator through provision of patient-specific anatomy, but may also predict procedural outcome. Currently, the MitraClip procedure is subject to trial-and-error, and the feasibility of the procedure is prone to the limitations of (2D and 3D) TEE images. More specifically, true residual MR and transvalvular gradient cannot be measured definitively until the clip has irreversibly been released from the delivery system. Prediction of final residual MR is dependent on operator experience and cannot be fully foreseen nor calculated. In the model presented in this study a successful representation of the mitral valve, including MitraClip, was created using TEE imaging.



Residual MR in the model seemed to coincide well with true color Doppler imaging. Although validation in a large patient group needs to performed, this study paves the way to more successful treatment planning. With the future in mind, it is highly desirable to pre-procedurally assess feasibility of the procedure, clip location, number of clips to be placed, and residual MR. Furthermore, addition of a pressure gradient may allow for prediction of resulting gradient across the valve.

The notion of pre-procedural mitral valve reconstruction has recently been investigated by others. In these studies, 3-dimensional TEE imaging and computed tomography were used to

print a silicon replica[59–61], which can be used in surgical training, case planning, and evaluation of interventional techniques.

Pragmatically, MitraClip treatment planning in the future should consist of heart team evaluation of a 3-dimensional computer based simulation/reconstruction of the mitral valve and concomitant virtual MitraClip placement. This may allow for more careful patient selection and predict procedural success rate. After all, the trial-and-error nature of the procedure is outdated and should be resolved.

In chapter 4, the hemodynamic consequences of the iatrogenic atrial septum defect (iASD) following transseptal puncture during the MitraClip procedure were reviewed. Despite the current absence of a recommendation advising prophylactic closure of the defect, a growing concern regarding the harmful effect of the iASD has emerged. Several case reports have been published reporting on significant shunting with severe hemodynamic consequences[62–64] which were resolved after closure of the iASD. Recently, one study showed that the iASD is associated with worse clinical outcome and increased mortality rates compared to patients without a residual iASD, although the causes of death were not elucidated and may be influenced by confounding factors. The transseptal puncture is safely performed in other procedures without post-procedural closure, such as pulmonary vein isolation and left atrial appendage closure. However, the catheter used in these procedures is significantly smaller (7-14 French versus 24 French). It is therefore conceivable that the larger catheter used in the MitraClip procedure creates a larger defect with significant consequences. Interestingly however, not only harmful effects of the iASD have been reported. One study reported immediate volume and pressure relief of the left atrium associated with the defect[65]. Nevertheless, this may be beneficial only in the short term as long term effects were not assessed. Importantly, the prevalence of the iASD at 6 months has been recorded as low as 27% [66], the significance of the defect may therefore be limited.

In spite of the potentially harmful effects of the iASD, routine prophylactic closure of the device should not be implemented into practice. The negative hemodynamic effects are limited and rare, the prevalence at 6 months is low, and prophylactic closure prevents future procedures requiring a transseptal puncture. Nevertheless, closure of the defect may be beneficial in some patients. Patients with marked left-to-right or right-to-left shunting may benefit from closure to prevent right-or left-sided cardiac decompensation. TEE assessment of defect size and shunting, or even transient balloon occlusion may aid in the detection of patients suitable for closure[64,67]. In fact, TEE imaging based qualitative and quantitative evaluation of the iASD are now part of routine practice during the procedure and during follow-up at our center. Future studies assessing factors that may contribute to a hemodynamically significant iASD should be performed to allow a better understanding of this phenomenon.

Although the MitraClip system has been readily applied, the future of interventional treatment for MR is expanding. Examples of promising new techniques include, but are not limited to: coronary sinus anuloplasty[68,69], mitral anuloplasty[70], enhanced coaptation, and chordal repair[71]. Furthermore, the field of transcatheter mitral valve implantation with transapical or transseptal approaches is rapidly evolving with several pre-clinical trials and first-in-man studies underway. Although these techniques seem promising, they are mostly in their infancy and large trials are yet to be performed. Further testing and improvement of imaging guidance are imperative, however needless to say these techniques will be confronted with similar procedural obstacles and difficulties as mentioned in this thesis.

It is not unlikely that future heart team consultations will be presented with an array of interventional possibilities. Although a multitude of techniques can be overwhelming, an array of new possibilities gives the field on interventional cardiology an exciting new dimension. If so, adequate patient selection and treatment planning will become increasingly important. Once again it will be imperative that individual patient characteristics are provided to the heart team to allow for the most optimal treatment choice.

Carcinoid Heart Disease

Carcinoid heart disease (CaHD) is a rare and complex disease that requires a multidisciplinary approach and treatment should be tailored to the individual patient[72]. Early screening for CaHD in patients with a metastatic neuroendocrine tumor (NET), clinical signs of cardiac decompensation, or carcinoid syndrome is imperative. The exact role of biomarkers in this process is subject to debate and monoanalyte biomarkers are limited by varying degrees of sensitivity and specificity. N-terminal pro-brain natriuretic peptide (NT-proBNP) is currently recommended to objectify cardiac involvement[73,74] and may be implemented in clinical practice. Urinary 5-Hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin, directly correlates with serotonin production. However, sensitivity is low, suggesting CaHD development and progression is co-dependent on other factors[75]. Novel biomarkers such as connective tissue growth factor (CTGF/CCN2), activin A, or transforming growth factor-β (TGF-β) are promising, however not clinically available. Furthermore, these monoanalyte markers fail to capture the multiple biochemical pathways of a NET. Future steps consist of the development of a NET multianalyte algorithmic test, which allows for the implementation of multiple biomarkers to explore diagnosis, classification, response to treatment, and prognosis[76,77]. Such efforts have been made (NETest, a multianalyte qRT-PCR assay) and have been regarded as a promising tool for clinical use, however validation in the clinical setting is yet to be performed[77].

With regards to screening, no consensus has been reached when it comes to method of screening and timing of referral. The European Neuroendocrine Tumor Society (ENETS) recommend performing echocardiographic screening when chromogranin A (CgA) or 5-HIAA are elevated[78], despite the varying reported degrees of sensitivity and specificity[76]. Others recommend the use of NT-proBNP[73,79]. In our protocol in chapter 5 we pragmatically recommend

measuring NT-proBNP and/or 5-HIAA in patients with metastatic NET. If biomarkers are elevated or if clinical signs of cardiac decompensation or carcinoid syndrome are present TTE should be performed. If signs of cardiac involvement are present, the patient should be referred to a specialized center for a multidisciplinary approach (heart team).

Currently, the only therapeutic option for CaHD is surgical intervention through valvular replacement, or in rare cases, debulking of solid cardiac metastases. In a particularly vulnerable population, the decisions whether to surgically intervene and the timing of such an intervention are exceptionally challenging. Peri-operative mortality (<5%) has decreased significantly over the years due to improved techniques, experience, and adjuvant medical therapies[26]. Nevertheless, a clear benefit on survival is yet to be demonstrated as the comorbid malignancy partially dictates survival. In fact, 5-year survival is still as low as 35%[26]. Patients presenting with symptomatic cardiac decompensation benefit from surgical intervention as symptomatic relief may account for an increase in quality of life[80]. A true dilemma arises however in those patients with asymptomatic CaHD. Early surgical intervention in asymptomatic patients is associated with superior survival compared with patients in New York Heart Association (NYHA) heart failure class III and IV, however confounding by indication muddles these results[27]. Regardless of the relatively low peri-operative mortality, unnecessary exposure to the risks of surgical intervention in a vulnerable population is not desirable. On the other hand, it may be sensible to perform surgical intervention before the patient deteriorates and peri-operative risk increases. Furthermore, CaHD may limit options for hepatic surgery. In these cases cardiac intervention may be advisable to allow for further NET treatment. Future prospective studies analyzing the role of surgical intervention in asymptomatic patients are of importance.

It is currently unclear which patients with a metastatic NET will develop CaHD and it is unclear which patients will become symptomatic. The use of deformation imaging has been investigated in patients with asymptomatic MR and reduced left ventricular global local strain at baseline was independently associated with mortality[81]. Likewise, it has been shown that patients with an intestinal NET without cardiac involvement may have reduced right ventricular strain[82]. The additional value of strain deformation imaging may therefore be of particular value in the detection of early CaHD. In fact, strain imaging should be part of routine echocardiography in this population to allow for more careful patient selection.

Among patients accepted for valvular surgery, the choice of prosthesis represents a complicated predicament. Although a bioprosthesis has an inferior life-span compared with a mechanoprosthesis, it does allow for freedom from life-long anticoagulation. This is particularly desirable in patients with secondary coagulopathies and in those who will undergo further surgical interventions or chemotherapy. Furthermore, patient survival rarely exceeds valve durability and freedom from reoperation rates for bioprosthesis and mechanoprosthesis at 10 years are both above 80%[26]. However, a bioprosthesis is prone to recurrent carcinoid disease

and early (<18 months) recurrent disease has been reported in literature and in chapter 6[26,83]. It is currently unclear why some patients develop recurrent disease in such an early stage and the detection of biomarkers predictive of CaHD progression could be of interest. Lastly, a trend towards better survival has been recorded in literature, albeit not significant[26].

Screening, timing of intervention, choice of prosthesis, and the post-operative course are relatively unknown areas that require a multidisciplinary approach. Patients with CaHD should be discussed in a heart team in a cardiothoracic surgery center with expertise in this field. As demonstrated in chapter 6, the additional expertise of an imaging cardiologist and an electrophysiologist specialized in device therapy was of crucial importance.

Currently, a retrospective study on the early-, mid-, and late outcomes after tricuspid valve replacement in CaHD is performed by the Erasmus Medical Center (Rotterdam) in close collaboration with the University Medical Center Utrecht, the Academic Medical Center (Amsterdam), and Leiden University Medical Center. In this study, approximately 50 patients (17 from the UMC Utrecht) will be included with a surgical intervention date ranging from 1972 to 2017. Baseline characteristics and clinical outcomes will be recorded according to recognized guidelines[84], and will include early and later (cardiac) mortality, thrombo-embolic events, bleeding events, re-intervention, other major (cardiac) events, and echocardiographic data. This study will be the second largest cohort to date analyzing the outcomes of tricuspid valve surgery. Mortality associated factors will be identified which will aid in future patient (and prosthesis) selection. Specifically, outcomes regarding type of prosthesis will be of interest considering center preference; one center implants only bioprostheses, one center only mechanoprostheses, and one center both. Furthermore, ideal timing of surgery will be addressed.

Anticoagulant bridging

In chapter 7, a study was performed comparing the safety and efficacy of intravenous unfractionated heparin (UFH) versus subcutaneous low-molecular-weight-heparin (LMWH) as bridging strategy in mechanical heart valve patients using vitamin K antagonists (VKA). This study was of clinical importance considering the discrepancy between European and American guidelines[6,39]. No difference was found between the two strategies in the cumulative incidence of thrombo-embolic complications, mortality, or bleeding. Although the rate of thrombo-embolic complications and mortality were comparable to earlier studies[36–38], our incidence of major bleeding (19% for both USH and LMWH) was much higher. In a reply to a letter to the editor regarding this issue we postulated several explanations. Firstly, different criteria of major bleeding were used with some studies applying more stringent criteria. Secondly, different bridging regiments were employed. In our case, a rather aggressive bridging strategy was used with longer (7.1 ± 6.5 days) post-procedural bridging. Finally, different patient populations may have played a role where our study included more high-risk patients, such as patients undergoing major cardiac or vascular surgery. Although the final results are bound by the limitations of a retrospective

study and lack the power to draw definitive conclusions with regards to the cumulative incidence of thromboembolic complications, the study does underscore several important points. Firstly, this study represents yet another observational study where no difference is found in the safety and efficacy between UFH and LMWH. Secondly, the incidence of bleeding is high. Furthermore, two conclusions can be drawn; 1)thrombo-embolic complications are rare, 2)in today's clinical practice thrombo-embolic complications are efficiently prevented. It is conceivable that reality lies in between. Considering the high incidence of (life-threatening) major bleedings, it is not unthinkable that through anticoagulant bridging the patient is exposed to a potentially bigger threat: bleeding. In the absence of adequately powered prospective trials and no such trial registered in the near future this study, combined with earlier observational studies, represents the best available evidence in this field. Addressing the issue of excessive bleeding, attempts have been made to reduce the risk of bleeding. A recent meta-analysis with a total of 35,944 patients compared bridging (with LMWH or UFH) versus non-bridging in patients using VKA's[85]. Bridging with heparin significantly increased the risk of major bleeding (OR=3.23), while there was no difference in the risk of thrombo-embolic complications (OR=0.99) or mortality (OR=0.71). Although this meta-analysis was bound by major limitations, such as a lack of a sub-analysis of VKA indication, and a high-level heterogeneity, it does provide a backbone for future prospective studies addressing the need to bridge. A less aggressive approach was proposed by a study performed in 2017, which analyzed the effect of prophylactic LMWH instead of therapeutic doses[86]. In this single arm study with 434 bridging episodes, prophylactic doses of LMWH as bridging strategy, resulted in a low incidence of major bleeding (1.3%) and no thrombo-embolic complications. To validate the safety of prophylactic doses of LMWH, a large randomized controlled trial should be performed comparing prophylactic with therapeutic LMWH doses.

In a similar fashion, the ideal bridging strategy among patients with atrial fibrillation is subject to debate. Although consensus has been reached regarding heparinoid strategy (LMWH), the patients in which bridging is indicated remains unclear. European guidelines acknowledge the role of LMWH bridging in selected patients, however no Cha_2ds_2-Vasc cut off score has been implemented[40]. The only large randomized controlled trial to date comparing bridging versus non-bridging in patients with atrial fibrillation, the BRIDGE trial, showed no difference in the incidence of thrombo-embolic complications (0.3% versus 0.4%, p=0.01 for non-inferiority, respectively) while the incidence of bleeding was higher in the bridging group (3.2% versus 1.3, p=0.005 for superiority)[87]. Although these results suggest a non-bridging approach may be safer, one major limitation has to be emphasized. Despite a total sample size of 1884 patients, the number of patients with a higher (≥ 4) $Chads_2$ score was low. A continuing potential benefit by bridging patients at higher risk of thrombo-embolic complications can therefore not be excluded. In chapter 9 a protocol was provided to guide clinicians in deciding optimal peri-procedural anticoagulant strategy for patients with atrial fibrillation on VKA. Here, we chose

a cut-off Cha_2ds_2-Vasc of 7, where patients with a score of 8 should be bridged with LMWH and those below should not. In addition, rheumatic valve disease or a recent (within last 6 months) cerebrovascular accident (CVA) or trans-ischemic attack (TIA) also warrants bridging with LMWH, regardless of Cha_2ds_2-Vasc score. The evidence on this matter is scarce, the chosen cut-off point should be considered Level of Evidence C and may be subject to change in the future. The Cha_2ds_2-Vasc cut-off score of 7 was chosen based on the premise that a score of 7 or lower represents a yearly risk of thrombo-embolic complications of less than 10% (if not on anticoagulation)[88]. An annual risk of more than 10% or a recent CVA/TIA of rheumatic valve disease is commonly considered high risk[89,90] and warrants bridging. Nevertheless, as mentioned before the benefits of bridging should always be weighed against the potential harm. Future studies should assess the role of bridging in patients with a higher thrombo-embolic risk, such as patients with a mechanical valve or a high Cha_2ds_2-Vasc score.

Intuitively a physician may be inclined to “do more” rather than “do less”, especially if traditional treatment dictates the former. However keeping in mind the principle of *primum non nocere*, it is not unlikely that the practice of therapeutic anticoagulant bridging as it exists today may be eliminated form future medical care.

Ultrasound-assisted catheter directed thrombolysis

In chapter 10 an overview was presented of the initial experience of the EkoSonic Endovascular system (EKOS), an ultrasound-assisted catheter directed thrombolysis (USAT) system. The USAT system has been developed as an alternative to systemic thrombolysis (ST) in patients with a pulmonary embolism (PE) and significant contraindications for ST. In particular, life threatening bleeding complications such as intracranial bleedings may be avoided based on the significantly lower administration of thrombolytic medication. Clinical studies have analyzed the effect of USAT, with varying results. The ULTIMA study, performed in 2014, randomized intermediate risk patients either to a UFH + USAT regimen, or UFH alone[47]. UFH + USAT showed a significant reduction in RV/LV ratio compared with UFH alone. No deaths or clinically significant bleedings were recorded. In the SEATTLE study, 150 intermediate risk patients were treated with USAT[91]. A significant reduction in RV/LV ratio was recorded in 25%. 30- Day mortality was 2.7% and the incidence of major bleeding was 11.4%. No intracranial bleedings were observed.

In our retrospective study, 44 patients were included (33 high-risk). Unfortunately, two intracranial bleedings were recorded, although these patients carried a significant risk factor for intracranial bleeding; one patient suffered from a concomitant ischemic stroke, the other patient had recently suffered from a subarachnoid hemorrhage. A comparison with a different cohort consisting of ST patients revealed no significant differences in terms of mortality, bleeding or recurrent thromboembolism. In the ST group 5 intracranial bleedings were recorded, which statistically did not differ from the USAT group. Two of these patients were known with a prior cerebrovascular accident.

It is important to note that the comparison between USAT and ST have to be interpreted with caution as confounding by indication may play a considerable role. After all, USAT is currently seen as an alternative to ST in patients with contraindications[42]. It is highly conceivable that the USAT group consists of a more vulnerable population with a higher a priori risk of bleeding and mortality. Moreover, it is noteworthy that currently USAT is not an option in a resuscitation setting due to logistical time constraints.

The role of USAT in high-risk or intermediate high-risk PE remains unclear. From our study no definite recommendations can be made with regards to preferred thrombolytic treatment. However the added clinical value of USAT remains promising.

In the future, prospective studies comparing USAT with ST are warranted. Randomized studies comparing USAT with standard catheter directed thrombolysis for submassive pulmonary emboli are currently ongoing and are expected to be completed in the next years.

CONCLUSION

In the rising era of informed decision-making and personal medicine, the role of adequate treatment planning will become more crucial. In particular, the central position of the multidisciplinary heart team will continue to grow. To optimally assess treatment options, new technological developments, biomarkers, and advanced imaging techniques (computer-based simulation, deformation imaging, cardiac magnetic resonance imaging) will continuously play a bigger role. This will not only allow for a better patient selection and evaluation of the feasibility of interventions, but it will facilitate a more careful consideration of benefit versus risk. In the end, procedural success rate and patient safety lie at the heart of every treatment.

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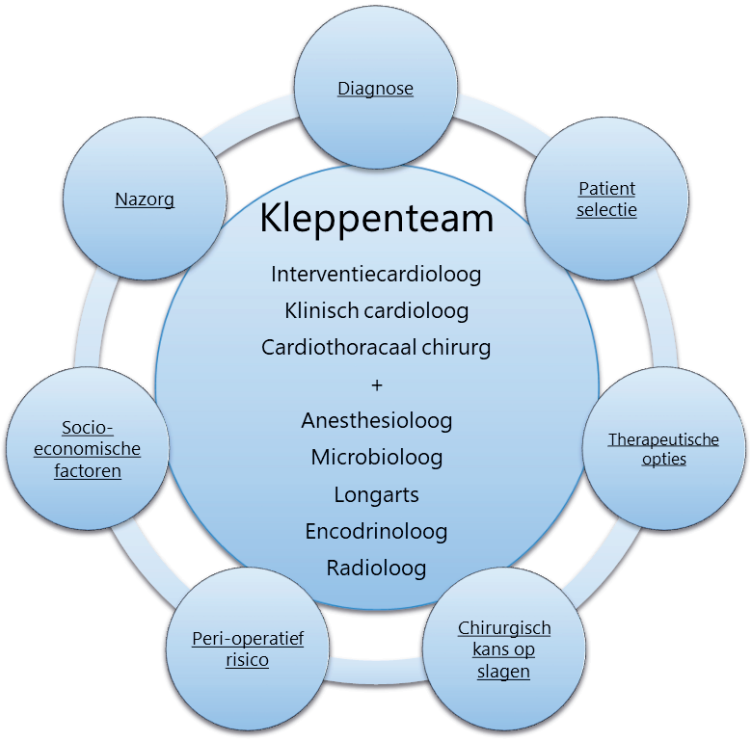
Appendix

NEDERLANDSE SAMENVATTING

Dit proefschrift is opgebouwd uit meerdere klinische studies waarbij het optimaliseren van cardiologische interventies centraal staat. In de huidige kliniek wordt steeds meer nadruk gelegd op de samenwerking tussen arts en patiënt, nieuwe technologische ontwikkelingen, en het multidisciplinaire aspect. Het laatste is vooral zichtbaar door de opkomst van multidisciplinaire "teams" waarbij meerdere specialisaties tot een gezamenlijk behandelplan komen. Deze teams bestaan al enige tijd in bijvoorbeeld de oncologie en de transplantatie geneeskunde. In recente jaren is bij de cardiologie het "hartteam", en in het verlengde daarvan het "kleppenteam", steeds verder ontwikkeld. In dit proefschrift wordt met name de rol van het kleppenteam (valvular heart team) benadrukt, dit is een multidisciplinair panel waar de therapeutische opties van patiënten met kleplijden worden besproken. De samenstelling en taken van het kleppenteam kunnen worden weergegeven in onderstaand model.



In de kern bestaat het kleppenteam uit een interventiecardioloog, klinisch cardioloog, en cardiothoracaal chirurg. Indien gewenst kan de aanwezigheid van overige specialismen van toegevoegde waarde zijn. De taken kunnen worden onderverdeeld in 7 speerpunten, namelijk: diagnose, patiënt selectie, therapeutische opties, chirurgisch kans op slagen, peri-operatief risico, socio-economische factoren, en (klinische) nazorg. Dit proefschrift bevat studies met

als doel deze speerpunten te verbeteren. Dit kan zijn door huidige richtlijnen onder de loep te nemen, technologische en technische vernieuwingen aan te kaarten, en hypotheses te testen. Een overzicht van de studies is hieronder uiteengezet.

Mitraliskleplekkage

In hoofdstuk 1 hebben wij een pragmatisch scoringssysteem gepresenteerd om de gradatie van mitralisklep lekkage te categoriseren bij echocardiografische beeldvorming. In de huidige kliniek zijn er vergaande consequenties gebonden aan de ernst van lekkage; bij een ernstige mitraliskleplekkage kan immers worden geadviseerd om chirurgisch in te grijpen. De Europese richtlijnen hanteren een complex scoringssysteem waarbij 11 parameters worden gebruikt. Helaas kost het meten van al deze parameters veel tijd en is men sterk afhankelijk van beeldkwaliteit. In de praktijk blijkt dat lang niet altijd alle parameters worden toegepast. In ons systeem hebben wij het aantal parameters terug kunnen brengen tot 5, met een acceptabele nauwkeurigheid. Het doel is dat dit systeem makkelijker hanteerbaar is in de praktijk en dus tot efficiëntere besluitvorming zal lijden.

MitraClip procedure

Patiënten met een ernstige mitraliskleplekkage met daarbij klachten, ritmestoornissen, of een verminderde pompfunctie komen in aanmerking voor chirurgisch ingrijpen. Helaas is chirurgie niet altijd mogelijk bij patiënten met veel bijkomstige aandoeningen; het peri-operatieve risico is dan te hoog. Bij deze patiënten bestaat er de mogelijkheid om de lekkage alsnog te behandelen middels de MitraClip procedure. Bij deze procedure wordt via de lies een “clip” ingebracht welke de twee klepbladen op de locatie van de lekkage met elkaar verbindt.

In hoofdstuk 2 hebben wij een studie gepresenteerd waarbij wij echocardiografische beelden hebben gebruikt om een computer simulatie te creëren van de mitralisklep. Met gebruik van dit model hopen wij in de toekomst de MitraClip procedure virtueel te kunnen nabootsen aan de hand van beelden die vooraf zijn genomen, om zo een inschatting te kunnen maken van het uiteindelijke resultaat. Ook kunnen we een inschatting maken bij welke patiënten deze behandeling zinvol is. In het geval van de MitraClip procedure is dit zeer wenselijk aangezien het uiteindelijke resultaat pas na permanente loslating van de clip (los van de catheter) duidelijk is.

Om de MitraClip procedure uit te voeren is adequate beeldvorming nodig in de vorm van een slokdarm echo. Helaas zijn er ook patiënten waarbij dit niet mogelijk is. In hoofdstuk 3 beschrijven wij een procedure waarbij wij als eerste succesvol de MitraClip hebben geplaatst met een uitwendige echo i.p.v. een slokdarmecho.

De MitraClip wordt via de lies ingebracht en wordt zo via de rechter boezem naar de linker boezem geloodst. Hier is echter een punctie nodig van het tussenschot tussen de boezems. Het zogeheten iatrogene atriale septum defect wordt meestal open gelaten daar dit meestal na enige tijd vanzelf sluit. Echter, recent zijn er meerdere case reports verschenen waarbij er ook nadelige effecten van dit defect worden beschreven. Een studie toonde zelfs een verhoogde

kans op overlijden, al zal dit nog moeten worden bevestigd door middel van grote, goed uitgevoerde studies. In hoofdstuk 4 presenteren wij een review waarbij de studies op dit gebied worden doorgenomen. Concluderend zal het profylactisch sluiten van het defect niet nodig zijn, al moet men bij sommige patiënten wel beducht zijn op complicaties en kan het raadzaam zijn om het gat te dichten.

Carcinoide Hartziekte

In het tweede gedeelte van het proefschrift wordt een gecompliceerd ziektebeeld besproken waarbij de cardiale manifestaties tot grote complicaties kunnen lijden. Het gaat hier om carcinoide hartziekte. Het is bekend dat indien een carcinoide tumor metastaseert naar de lever, er een verhoogde kans is op cardiale aantasting. De oorzaak hiervan ligt voornamelijk bij de uitscheiding van serotonine, een neurotransmitter. Serotonine tast met name de hartkleppen in de rechter harthelft aan. Dit kan leiden tot ernstige lekkage en/of stenose. Linkszijdige kleppen worden meestal gespaard, dit is waarschijnlijk om dat de longen serotonine inactiveren en het dus in veel lagere doseringen de linker harthelft bereikt. Het identificeren van de juiste patiënten waarbij aanvullend onderzoek middels echocardiografie nodig is, is moeilijk. Ook het ideale moment van verwijzen naar een chirurgisch centrum is niet vastgesteld. In hoofdstuk 5 geven wij een overzicht van de literatuur op dit gebied en presenteren wij een praktische flowchart voor verwijzing naar een chirurgisch centrum. In hoofdstuk 6 benadrukken wij het belang van het multidisciplinaire kleppenteam in de behandeling van een patiënt met carcinoide hartziekte. In deze casus wordt beschreven hoe een patiënte met carcinoide hartziekte geconfronteerd werd met twee zeldzame gevolgen/complicaties van haar ziekte. Wij beschrijven een pacemaker geinduceerde mitralisklep lekkage, en een zeer snel (1 jaar) recidief van haar carcinoide hartziekte op de nieuwe biologische kunstklep. Zeldzame complicaties bij een ziektebeeld zoals dit dienen te worden behandeld in een multidisciplinair team, in dit geval bestaande uit een cardioloog, cardiothoracaal chirurg, elektrofysioloog, endocrinoloog, patholoog, en oncoloog.

Antistolling en trombolyse

In het derde gedeelte van dit proefschrift wordt het peri-operatieve antistollingsbeleid bij patiënten met een Vitamine K antagonist behandeld. Patiënten met een mechanische kunstklep dienen levenslang antistolling medicatie te gebruiken ter preventie van trombose. Indien een patiënt vervolgens een invasieve ingreep zal ondergaan zal de antistolling (Vitamine K antagonist) tijdelijk moeten worden gestopt om het bloedingsrisico tijdens de operatie zo laag mogelijk te houden. De periode waarin een patiënt geen vitamine K antagonist gebruikt zal bij patiënten met een hoog risico op trombose moeten worden overbrugd met een kort werkende heparine. Er zijn twee overbrugging strategieën; ongefractioneerde heparine (UFH) en laagmoleculair-gewicht-heparine (LMWH). Beide strategieën gaan gepaard met een verschillend logistiek en financieel profiel, in het voordeel van LMWH. Er is op dit moment geen consensus

tussen Europese en Amerikaanse richtlijnen. Volgens de Amerikaanse richtlijnen kan men zowel UFH als LMWH toedienen, maar volgens de Europese richtlijnen is er niet genoeg bewijs om af te stappen van UFH. Men dient dus ten alle tijden te overbruggen met UFH. In hoofdstuk 7 is retrospectief gekeken naar een Nederlandse populatie van patiënten met een mechanische linkszijdige kunstklep, overbrugd met UFH of LMWH. Concluderend was er geen verschil in de incidentie van trombose of ernstige bloedingen. Opvallend genoeg werden veel meer bloedingen geconstateerd dan trombo-embolische complicaties. Dit kan drie dingen betekenen; 1) patiënten worden adequaat beschermd tegen trombose, 2) trombose komt niet zo vaak voor, of 3) een combinatie van de twee voorgaande punten. Men zou zich af kunnen vragen of wij bij het voorkomen van trombose ons doel voorbij streven en de patiënt bloot stellen aan een veel groter gevaar, namelijk bloedingen. Na deze studie is het protocol in het UMC Utrecht aangepast en wordt ruimte gelaten voor overbruggen met LMWH. In hoofdstuk 9 presenteren wij dan ook het nieuwe peri-operatieve antistollingsprotocol zoals het nu wordt gehanteerd in het UMC Utrecht. Hier behandelen wij niet alleen mechanische kunstkleppen, maar ook overige vitamine K antagonist indicaties (boezemfibrilleren, longembolie).

Lokale trombolyse bij longembolieën

In het laatste hoofdstuk van dit proefschrift beschrijven wij een studie waar de eerste ervaring van het UMC Utrecht met lokale trombolyse via een katheter wordt geanalyseerd.

De behandeling bij patiënten met een longembolie met daarbij een hoog risico op overlijden bestaat uit het toedienen van trombolyse. Op deze manier wordt het stolsel opgelost. Echter, er bestaat een hoge kans op complicaties, een bloeding die ergens in het lichaam ontstaat (hersenen) is dan immers niet meer te stoppen en kan tot overlijden leiden. Bij het EKOS systeem beschreven in hoofdstuk 10 wordt een katheter via de lies door het stolsel in de longen gepositioneerd waarna ultrageluid wordt toegepast. Dit verhoogt de permeabiliteit van het stolsel en maakt het stolsel gevoeliger voor het trombolyse medicijn. Op deze manier kan een veel lagere dosering van het middel worden toegediend en neemt het risico op bloedingen af. In onze studie hebben wij de uitkomsten geanalyseerd van een kleine groep patiënten waarbij dit systeem werd toegepast. Concluderend lijkt dit systeem een goed alternatief te zijn voor systemische (algemene) trombolyse bij patiënten met een verhoogde kans op (fatale)bloedingen. Uiteraard zal dit moeten worden bevestigd door middel van grote, gerandomiseerde studies.

DANKWOORD

Professor dr. S.A.J. Chamuleau, beste Steven,

Ik kan mij nog goed herinneren dat ik in een van mijn laatste jaren als student je kamer binnenstapte om te praten over het vak cardiologie. Jouw enthousiasme was besmettelijk. Ik heb toen besloten aan boord te stappen door mij aan te sluiten bij jouw onderzoeksgroep, en ik heb nooit meer achterom gekeken. Ik ben nu in opleiding tot cardioloog en dat heb ik voor het overgrote deel aan jou te danken. Elke stap die we hebben genomen heeft voor mij goed uitgepakt, dus ik neem dan voor lief dat je af en toe de gewoonte hebt om mijn presentatie een kwartier voordat ik op moet helemaal om te gooien. Of dat we bij vrijwel elke bespreking over een manuscript 180 graden draaien en een andere koers varen. Of dat je vraagt of ik een echo workshop van je over wil nemen terwijl ik zelf net een maand kan echoen. Ik neem het niet alleen voor lief, ik vind het prachtig. Je hebt mij vaak in het diepe gegooid, maar daarmee altijd kansen gecreerd. Toch deed je dit altijd omdat je er op vertrouwde dat het goed ging, en het is dat vertrouwen waardoor ik gegroeid ben en waar ik je enorm dankbaar voor ben. Het is voor mij een eer om mijn opleiding onder jouw te hoede te mogen doorlopen. Hoe je met patienten en collega's omgaat is een voorbeeld voor velen, ik kijk er dan ook erg naar uit om het vak van je te leren. Op de tennisbaan zijn gelukkig de rollen omgekeerd, dat zal voor jou helaas wel zo blijven.

Professor dr. P.A.F. Doevendans, beste Pieter,

Het is een eer om onder jou te promoveren, bedankt voor deze kans. Onze meetings waren kleurrijk, met soms een filosofische invalshoek.

Het is echter pas tijdens onze fietstochten dat ik je echt heb leren kennen. Het was een genot en een ware eer om naast je te fietsen tijdens de tochten naar Barcelona en naar Oslo. Ik ken weinig mensen die teleurgesteld zijn als een etappe van 250km er op zit. Wel geruststellend om te zien dat ook bij jou het beste er wel af was in Oslo.

Waar ik nu sta heb ik ook aan jou te danken, bedankt voor het vertrouwen in mij als promovendus en AIOS.

Dr A.O. Kraaijeveld, beste Adriaan,

Toen Steven Chamuleau jou aan mij voorstelde als mijn co-promotor wist ik vrij snel dat het goed zat. Jouw beroemde/beruchte directheid, in combinatie met een toch wat duister (prachtig) gevoel voor humor vormt de basis voor de mooie band die wij hebben. Je hebt een prachtige no-bullshit instelling, maar toch kon ik altijd rekenen op je uitgebreide feedback en had je altijd tijd voor me. Jouw enthousiasme en passie voor de interventiecardiologie heeft gemaakt dat ik onze projecten met veel plezier volbracht. Het is een eer om zometeen ook door jou te worden opgeleid. Ik hoop nog veel met je te mogen samenwerken en ik hoop nog vaak je droom om meer dan 1 game te pakken te mogen verstoren.

Dank je wel **Ingrid** voor al je hulp bij eigenlijk alles wat ik heb gedaan. Als filter van Steven zijn inbox heb je veel van mijn nutteloze vragen aan de professor onder het tapijt gepoetst, maar je had altijd een scherp oog voor echt belangrijke zaken en dan kon ik altijd op je rekenen.

Dr H. Kirkels, beste Hans, bedankt voor de wijze (levens)lessen op de CCU en het vertrouwen in mij als ANIOS/AIOS/promovendus. Ik kijk uit naar de opleiding over een paar jaar.

Graag bedank ik de leden van de leescommissie en oppositie, **Professor dr. R.E.G. Schutgens, Professor dr. M.J. Schalij, dr R.B.A. van den Brink, Professor dr. W.J.L. Suyker, Professor dr. H.A.H. Kaasjager, dr J. Baan.**

Graag bedank ik de **stafleden van de afdeling cardiologie** in het UMCU voor de wijze lessen, reprimandes, en prettige samenwerking in de kliniek.

Verder wil ik ook alle co-auteurs van de hoofdstukken bedanken voor de opmerkingen en suggesties, met name **Ronald Meijer, Michiel Voskuil, Arco Teske, en Jan Westerink.**

En dan komen we bij de prachtige Villa. Waar wanhoop, ongeduld en frustratie dagelijkse kost zijn, maar waar ook in het heden en verleden grootheden hebben gewoond en inspiratie hebben opgedaan, waar toonaangevende papers zijn gepubliceerd en afgewezen, en waar carrieres zijn geboren en verloren. Ik wil alle villijnen en ex-villijnen hartelijk danken voor de academische steun, de humor, en de gedeelde smart. Beginnend met **Sanne**, dank voor je begeleiding tijdens mijn studentenstage en het vertrouwen dat je in mij had tijdens onze cyclosporine review, **Cheyenne** altijd genieten om je maandag morgen te zien om even haarfijn het weekend door te nemen. Ik kijk erg uit naar onze gezamenlijke tijd in het UMC, **Iris** met pijn in mijn hart werd je wreed uit de villa gehaald om ergens anders te zitten. Dank voor je levensadviezen en ik hoop je snel weer te zien, **Thijs** vanaf het begin een vaste kracht in de appendix. Geen idee wat je daar allemaal uitspookt maar ik heb onwijs genoten van onze reisjes naar Warschau en vooral Sofia, waar je bent uitgegroeid tot een legende. Ik hoop nog vaak met je te borrelen, **Mira** bedankt dat je zo keihard bent en je leuke humor. Ik krijg nog 200 euro van je voor de poster prijs. Ook gefeliciteerd dat je nu een celebrity bent in pre-clinical trial land, success! **Chiron en Marijn,** dank voor jullie inzet tijdens het prachtige ESCI congress in Barcelona, veel succes nog! **Remco,** bedankt dat je me in mijn eerste maanden zo hebt geholpen met software issues en dat je altijd klaar stond met een zeer positieve kijk op alles. Dank ook voor de geweldige ESCI reisje, ik heb het gevoel dat je daar altijd piekt. De laatste jaren van onze opleiding gaan grandioos worden, **Thomas** jouw ontspannen kijk op het leven vind ik inspirend. Zelden zo veel gelachen als in de tijd dat ik tegenover je zat in de villa. Vaak zaten we op 1 lijn, vooral als het een heerlijke klaagzang over het leven betrof. Ik weet dat ik je nog vaak ga zien, **Dirk**, aka

de grote organisator, toekomstig president van ESCI, plus nog wat overige lugubere bijnamen. Daar waar jij komt heeft iedereen het naar z'n zin en worden dingen gewoon geregeld. Het was een eer om er bij te mogen zijn op je bruiloft. Je bent een geweldige gozer, ik kijk uit naar onze gezamenlijke opleidingsjaren. **Steven W** ik begrijp nu eindelijk waarom iedereen je een rare snuiter vindt. Grapje natuurlijk. Ik wil je bedanken voor de heerlijke schaakpauzes, zelfspot, en je angstaanjagende pessimism/realisme. Stiekem hoop ik dat je toch in Utrecht gaat solliciteren, je bent een mooie vent en een aanwinst voor het vak, **Odette** dank voor de vele mailtjes die je doorstuurde van krankzinnige journals die een eminent person like you wilden strikken voor een submission, onwijs gelachen. Ik hoop nog vele jaren met je samen te werken in de kliniek!, **Rene** de onbetwiste bourgondische koning van de villa. Wat moet het frustrerend zijn voor je om te weten dat je ondanks het feit dat je slimmer bent dan ik toch volstrekt kansloos bent met schaken. Bedankt voor de heerlijke schaakavondjes waar de dure whiskey niet gespaard werd, ik hoop dat er nog velen volgen.

Als we dan de villa verlaten, belanden we in de afgelegen en vaak vergeten krochten van het UMC, waar geloof het of niet, ook geweldig/dubieus onderzoek wordt gedaan. Dank voor de mooie reisjes, borrels, en overleg **Frebus, Han, Arnoud, Evangeline, Rik, Loek, Mark, Nynke, Max, Janine, Lennart, Bart, Mirthe, Wouter G, David, Laurens (**dank voor je inzet bij de ergo's), **Arjan** (wat is er meneer. Dank voor de mooie dagen in Barcelona!)

Hartelijk dank ook de oud-promovendi, **Wouter v E,** het was een genot om naast je te fietsen tijdens onze tochten. Behalve toen je me bijna doodreed tijdens Trondheim Oslo. Niemand kan de ridiculiteit van het leven zo goed in woorden omzetten als jij. Ik hoop je nog vaak te zien. **Cas** het is prachtig om de interne vooropleiding met jou te doorlopen in het Meander, we zullen elkaar nodig hebben. Dank voor de mooie momenten in de Gouden Koets en in Sofia. Je krijgt de groetjes van **Griezmann**. **Marloes,** dank voor de mooie tijd tijdens onze ANIOS maanden in het UMC, veel samen gelachen. Tot snel! **Peter Paul,** waarschijnlijk weet jij meer van mijn promotie onderwerpen af dan ikzelf. Wel jammer dat je dit jaar zo bar slecht was bij de EK poule. Het is een eer om er bij te zijn op je bruiloft. **Ing Han,** de rust zelve. Dank dat je mij onder je hoede nam tijdens mijn semi-arts stage. Dank ook voor je inzet tijdens borrels, ik kijk erg uit naar onze gezamelijke opleidingsjaren. **Lena,** dank voor de mooie momenten die we samen hadden als ANIOS. Dat jij ontsnapt bent aan de ergo's is mij nog steeds een doorn in het oog.

Geert, dank voor de prachtige fietstochten. Je bent de onbetwiste koprobot. Dank ook voor de samenwerking in de kliniek en alle borrels, **Anne Mieke, Margot, Irene, Manon, Tycho, Stefan, Susanne, Anneke, Christiaan, Evelien, Fatih, Freek, Judith, Marish, Miranda, Sjoukje, Danny**

De studenten met wie ik heb samengewerkt, **Koen en Josephine**, dank voor jullie bijdrage!

Dank je wel **Karen,** de vaste pilaar van de Dutch AMR. Zonder jou stort het hele kaartenhuis in elkaar.

Dank jullie wel, **dames en heren van het echolab/ergo's, verpleging van afdeling B4 en de CCU, personeel van de HCK en het secretariaat.**
Roos, bedankt voor al je hulp bij het opzetten van de hilow, zonder jou was ik nog steeds in conclaaf geweest met de METC. Ben wel blij dat dat rare mickey mouse handje van jou als logo er niet door is gekomen. Met bewondering heb ik mogen aanschouwen hoeveel werk jij in de Dutch AMR hebt gestopt. Ik heb daar enorm veel respect voor. Dank voor je grapjes rondom Erik, het reisje naar Breda, en de koffiepauzes. Het was een enorme eer om paranimf te zijn op je promotie. Dit deed je geweldig, ik hoop dat het mij ook zo vergaat. Ik hoop dat we elkaar nog vaak zullen zien!

Timion, toen jij als student mij hielp bij de hilow viel mij al op met welke nauwkeurigheid je te werk gaat. De degelijkheid en discipline die jij toont op de tennisbaan is terug te zien in je carriere als arts en onderzoeker. Het resultaat is dat we meerdere papers samen hebben gepubliceerd en het is mooi om je achter mij te hebben staan tijdens mijn promotie. Het was ook mooi om de 5-1 tegen Spanje naast je te mogen beleven, net als de vele tenniswedstrijden.

Bas, je bent een goeie fietser, een goeie arts, een goeie onderzoeker, een goeie voetballer, maar vooral een goed mens. Helaas weten veel mensen niet dat je slaap apneus hebt, dat je een raar gevoel voor humor hebt, dat je soms 's nachts werkt, en dat je zogenaamd per ongeluk mensen voorbij fietst omdat je geen zin hebt om te praten. Desondanks zie ik je als een goeie vriend en kijk ik uit naar onze gezamenlijke opleiding. Het is een eer dat je hebt toegezegd om paranimf te zijn, hoop wel dat jij ook een vraag krijgt.

Joris en Emiel, dankzij jullie was de opleiding geneeskunde een waar genot. De mooie momenten in de Alpen, de Pyreneen, Marokko, feestjes, borrels, stadsbieb, en Noorwegen zijn onvergetelijk. Ik ken jullie hoogtepunten. Maar ook jullie vermakelijke dieptepunten en minder heldere momenten. Ik hoop dat er meer komen.

Dank jullie wel voor deze unieke vriendschap, ik hoop dat dit nog maar het begin is.

Mijn broertje en zusje, **Steffen en Sølvi**. Ik was er al toen jullie ter wereld kwamen en heb al jullie fratsen mogen aanschouwen. Ik ben trots op waar jullie staan en wil jullie bedanken voor alle mooie jaren.

Lieve **Hanna,** grote jeu de boules speler, KJ, het begon in San Diego waar ik viel voor jouw lach en je enthousiasme. De tijd daarna was, en is nog steeds, een mooi avontuur. Dank voor je steun en begrip in drukke tijden, bij jou kom ik altijd tot rust. Dit boekje is ook deels van jou.

Mijn ouders, **Harald en Marion,** bedankt voor de onvoorwaardelijke steun, vriendschap, en onuitputtelijke interesse in wat ik uitspook. Jullie zijn altijd een groot voorbeeld voor me geweest. Dankzij jullie heb ik grote delen van de wereld kunnen zien en ben ik uiteindelijk beland waar ik nu ben. Ik hoop nog vaak alles met jullie door te nemen op de Steppingstone.

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