Ministero della Salute

Agenzia Nazionale per i Servizi Sanitari Regionali

Rapid HTA Report

Transcatheter implantable devices for mitral valve repair in adults with chronic mitral valve regurgitation

October 2015

RIHTA
Rete Italiana Health Technology Assessment

agena.s. AGENZIA NAZIONALE PER I SERVIZI SANITARI REGIONALI

This report should be cited as:

Migliore A, Corio M, Perrini MR, Rivoiro C, Jefferson T. Transcatheter implantable devices for mitral valve repair in adults with chronic mitral valve regurgitation: rapid HTA report. Agenas, Agenzia nazionale per i servizi sanitari regionali. Rome, October 2015.

Contributions

Authors

Chiara Rivoiro, Mirella Corio, Antonio Migliore, Maria Rosaria Perrini, Tom Jefferson

Agenas – Agenzia Nazionale per i Servizi Sanitari Regionali.

Corresponding author

Chiara Rivoiro (rivoiro@agenas.it)

External Reviewer

Philippe Primo Caimmi, MD, MSC, Phd, University of A. Avogadro School of Medicine;

San Gaudenzio Clinic Novara (Policlinico di Monza) Department of cardiac surgery.

Acknowledgements

Authors and Agenas would like to thank Maurizio D'Amico, Division of Cardiology, Azienda Ospedaliero Universitaria Città della Salute e della Scienza, Torino (Italy).

Declaration of conflict of interest and privacy

Authors, Clinical expert and External Reviewer declare that they will not receive benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

Index

Foreword

This document is based on two linked but separate methodological approaches. The first is the EUnetHTA Relative Effectiveness Assessment (REA) Model [EUnetHTA REA 2013] based on 4 domains or viewpoints collecting several questions, known as assessment elements (AE). The REA is a self-standing EUnetHTA Core Model® (CM) [EUnetHTA CM]. The second approach is that of Agenas Model which is based on the EUnetHTA CM® for medical and surgical interventions application [EUnetHTA CM® 2.0], adapted to suit production of HTA documents in the Italian context. In this document both approaches co-exist and the total of domains investigated is six, four from the REA and two from the Agenas Model (Appendix 1).

Readers can relate text to the relevant assessment elements reported in full in Appendix 2 and linked in the text by an identification number (ID) made of letters and numbers.

Data and material from the REA Model [EUnetHTA REA 2013] are clearly referenced as such throughout the document.

Prefazione

Il presente documento si basa su due approcci metodologici correlati ma distinti. Il primo è l'EUnetHTA Relative Effectiveness Assessment (REA) Model [EUnetHTA REA 2013], basato su 4 domini che comprendono una serie di quesiti, noti come elementi di valutazione (Assessment Elements, AE). Il REA è un modello a se stante rispetto all'EUnetHTA Core Model® (CM) [EUnetHTA CM]. Il secondo approccio è il Modello Agenas che si basa sull'EUnetHTA CM® (versione per interventi medico-chirurgici) [EUnetHTA CM® 2.0] adattato per la produzione di documenti HTA nel contesto italiano. In questo documento i due approcci metodologici coesistono e il totale dei domini indagati è sei: quattro provenienti dal modello REA e due provenienti dal modello Agenas (Appendice 1).

I lettori possono identificare e reperire nel testo gli elementi di valutazione (AE) contraddistinti da numeri e lettere e spiegati integralmente nell'Appendice 2.

Dati e materiale provenienti dal modello REA sono chiaramente citati in tutto il testo con lo specifico riferimento bibliografico [EUnetHTA REA 2013].

Sommario

In Europa, l'insufficienza mitralica è tra i più frequenti disturbi valvolari con indicazioni chirurgiche, seconda solo alla stenosi della valvola aortica. La prevalenza del rigurgito mitralico moderato o severo è inferiore all'1% nella popolazione di età inferiore ai 50 anni, mentre sale all'11% nelle persone oltre i 70 anni. L'insufficienza mitralica di grado moderato o severo è frequente nelle persone affette da scompenso cardiaco, raggiungendo un tasso di incidenza del 40% nei casi di scompenso cardiaco grave.

Le opzioni terapeutiche attuali per il trattamento del rigurgito mitralico associato o meno a scompenso cardiaco, prevedono, a seconda della gravità del quadro clinico interventi farmacologici, riparazione chirurgica o sostituzione della valvola mitralica, impianto di dispositivi di assistenza ventricolare, trapianto cardiaco e terapia di resincronizzazione cardiaca.

La riparazione percutanea transcatetere della valvola mitralica potrebbe rappresentare un'alternativa al trattamento chirurgico tradizionale, in una popolazione selezionata di pazienti considerati ad alto rischio o non candidabili per l'intervento cardiochirurgico, in particolare per le comorbilità presenti, età avanzata o severa disfunzione ventricolare sinistra. Due dispositivi impiantabili transcatetere per il trattamento del rigurgito mitralico sono stati identificati sul mercato italiano: un sistema di anuloplastica transcatetere, CARILLON® Mitral Contour System® (Cardiac Dimensions, Inc.) e un sistema transcatetere per la riparazione dei lembi valvolari, MitraClip® System (Abbott Vascular).

Il presente report di valutazione è stato sviluppato per rispondere al quesito se, in pazienti adulti con rigurgito mitralico cronico primario o secondario, che sono ad alto rischio chirurgico o non candidabili all'intervento chirurgico, la riparazione percutanea transcatetere della valvola mitrale sia più efficace, sicura e costo-efficace rispetto al trattamento farmacologico (se indicato) con o senza terapia di resincronizzazione cardiaca.

Le evidenze disponibili ad oggi non consentono di formulare indicazioni definitive riguardo l'efficacia e la sicurezza relativa dei sistemi impiantabili transcatetere (CARILLON® Mitral Contour System® e MitraClip® System) nelle persone adulte affette da rigurgito mitralico cronico di grado moderato-severo o severo rispetto alla terapia convenzionale. Gli studi effettuati e quelli in corso utilizzano CARILLON® Mitral Contour System® in particolare per il rigurgito mitralico cronico funzionale, mentre MitraClip® System è usato sia per il rigurgito mitralico cronico degenerativo che funzionale. I dati derivanti dalle poche analisi economiche ad oggi disponibili indicano che i due dispositivi analizzati sembrano essere costo efficaci rispetto al trattamento medico ottimale, in pazienti adulti affetti da rigurgito mitralico cronico di grado moderato-severo o severo e ad alto rischio chirurgico o non candidabili per l'intervento chirurgico.

L'utilizzo di CARILLON® Mitral Contour System® è ancora ad uno stadio precoce, con un basso livello di diffusione (circa 300 gli impianti effettuati in tutta Europa, 3 in Italia), mentre sono circa 23.000 gli impianti effettuati con Mitraclip® a livello internazionale (dei quali circa 1.500 in Italia). Sono necessari studi comparativi con follow-up di durata adeguata al fine di chiarire il profilo di rischio/beneficio di entrambi i dispositivi analizzati. Gli studi in corso potranno apportare evidenze utili a stabilire se CARILLON® Mitral Contour System® e MitraClip® System siano più efficaci e sicuri rispetto alle altre opzioni di trattamento esistenti.

Sintesi in Italiano

In Europa, l'insufficienza mitralica è tra i più frequenti disturbi valvolari con indicazioni chirurgiche, seconda solo alla stenosi della valvola aortica. La prevalenza del rigurgito mitralico moderato o severo è inferiore all'1% nella popolazione di età inferiore ai 50 anni, mentre sale all'11% nelle persone oltre i 70 anni. L'insufficienza mitralica di grado moderato o severo è frequente nelle persone affette da scompenso cardiaco, raggiungendo un tasso di incidenza del 40% nei casi di scompenso cardiaco grave.

L'insufficienza mitralica può essere primaria o degenerativa, essendo causata da affezioni che colpiscono direttamente l'apparato valvolare (lembi valvolari, anulus, corde tendinee, muscoli papillari) ma anche secondaria o funzionale, ovvero causata da alterazioni della geometria e della funzionalità del ventricolo sinistro (in particolare a seguito di cardiomiopatie ischemiche o dilatative).

Le opzioni terapeutiche attuali per il trattamento del rigurgito mitralico associato o meno a scompenso cardiaco, prevedono, a seconda della gravità del quadro clinico, interventi farmacologici, riparazione chirurgica o sostituzione della valvola mitralica, impianto di dispositivi di assistenza ventricolare, trapianto cardiaco e terapia di resincronizzazione cardiaca.

Secondo le Linee Guida vigenti, la chirurgia rappresenta l'opzione terapeutica di prima scelta per i pazienti con insufficienza mitralica cronica, severa, prediligendo ove possibile, la riparazione alla sostituzione della valvola.

La riparazione transcatetere della valvola mitralica potrebbe rappresentare un'alternativa al trattamento chirurgico tradizionale, in una popolazione selezionata di pazienti considerati ad alto rischio o non candidabili per l'intervento cardiochirurgico, in particolare per le comorbilità presenti, età avanzata o severa disfunzione ventricolare sinistra. Due dispositivi impiantabili transcatetere per il trattamento del rigurgito mitralico sono stati identificati sul mercato italiano: un sistema di anuloplastica transcatetere, CARILLON® Mitral Contour System® (Cardiac Dimensions, Inc.) e un sistema transcatetere per la riparazione dei lembi valvolari, MitraClip® System (Abbott Vascular).

CARILLON® Mitral Contour System® è stato ideato per il trattamento del rigurgito mitralico cronico funzionale ed è costituito da un impianto metallico posizionato nel seno coronarico o nella grande vena cardiaca attraverso un catetere inserito dalla vena giugulare. Obiettivo dell'impianto è ridurre la dilatazione anulare e di conseguenza il rigurgito mitralico attraverso la rimodulazione della geometria anulare. L'intervento può essere eseguito in anestesia generale o sedazione cosciente. La decisione rispetto all'utilizzo di CARILLON® Mitral Contour System® è di competenza di cardiologi esperti in cardiologia interventistica, ecocardiografia e trattamento dello scompenso cardiaco.

Il sistema MitraClip® è stato ideato per la riparazione della valvola mitralica insufficiente in pazienti affetti da rigurgito mitralico di grado severo, di origine funzionale o degenerativa, non candidabili alla chirurgia convenzionale. La scelta sull'utilizzo del Mitraclip®, come da indicazioni presenti anche nelle recenti Linee Guida europee [Vahanian et al. 2012], deve essere concordata da un "*heart team*", costituito da esperti in patologie valvolari, ovvero cardiologi, cardiochirurghi, esperti dello scompenso cardiaco e di immagini radiologiche, anestesisti e, se necessario, da specialisti di terapia intensiva e medici di medicina generale o geriatri che hanno in carico il paziente.

La procedura di impianto viene eseguita in anestesia generale con intubazione endotracheale. Il sistema è costituito da una clip metallica introdotta attraverso la vena femorale che viene inserita sui lembi valvolari in modo da creare un doppio orifizio valvolare per ridurre il reflusso di sangue da atrio sinistro a ventricolo sinistro.

L'uso del sistema Carillon® è possibile in Europa dal 2011 (negli Stati Uniti non ha ricevuto l'approvazione dell'ente regolatorio, la Food and Drug Administration - FDA), mentre MitraClip® ha ricevuto il marchio CE nel 2008 e l'approvazione della FDA nel 2013. I dati forniti dai produttori indicano che ad oggi sono circa 300 gli impianti di Carillon® effettuati in tutta Europa (dei quali 3 in Italia), mentre sono circa 23.000 gli impianti di Mitraclip® a livello internazionale (dei quali circa 1.500 in Italia).

Il presente report è stato sviluppato al fine di rispondere a due quesiti principali:

a) se, nel caso di pazienti adulti con rigurgito mitralico cronico di origine degenerativa, ad alto rischio chirurgico o non candidabili all'intervento chirurgico, affetti o meno da scompenso cardiaco, il trattamento con MitraClip® System fosse più efficace, sicuro e costo-efficace rispetto alla terapia medica standard, con o senza trattamento farmacologico per scompenso cardiaco;

b) se, nel caso invece di pazienti adulti con rigurgito mitralico cronico di origine funzionale, ad alto rischio chirurgico o non candidabili all'intervento chirurgico, l'intervento con MitraClip® System fosse più efficace, sicuro e costo-efficace rispetto al trattamento farmacologico standard (con o senza terapia di resincronizzazione cardiaca) e se l'intervento con CARILLON® Mitral Contour System® nella stessa tipologia di pazienti, fosse più efficace, sicuro e costo-efficace rispetto alla terapia farmacologica (con o senza terapia resincronizzazione cardiaca).

Ricerche bibliografiche sistematiche sono state svolte al fine di reperire in prima istanza studi di sintesi (report di HTA e revisioni sistematiche); solo nel caso di indisponibilità di studi di sintesi, si sono ricercati studi primari.

Sebbene l'unico studio comparativo relativo all'uso di CARILLON® Mitral Contour System®, TITAN [Siminiak et al. 2012], riporti risultati preliminari positivi, è necessario sottolineare alcune criticità: in primo luogo il gruppo di confronto è stato derivato dal gruppo di pazienti sottoposti all'impianto ma che, per ragioni cliniche (compromissione coronarica transitoria, riduzione del rigurgito mitralico inferiore ad 1 grado), hanno subito la rimozione in acuto del dispositivo impiantato. L'impatto di tale procedura sul gruppo di confronto relativamente agli outcome considerati non è stato valutato. Inoltre, il tasso di mortalità non correlata al dispositivo nella popolazione trattata ha causato l'impossibilità di proseguire il follow-up a 12 mesi e a 24 mesi, rispettivamente per il 30,5% e per il 47,2% dei soggetti arruolati.

Non esistono evidenze robuste da studi comparativi circa l'utilizzo di MitraClip® System in pazienti ad alto rischio chirurgico con rigurgito mitralico cronico di grado moderato-severo e severo rispetto alla terapia convenzionale (nessuno trattamento o terapia farmacologica). Piccoli studi comparativi, serie di casi e registri nazionali che riportano risultati favorevoli all'uso di MitraClip® System hanno guidato la scelta di alcune istituzioni nel raccomandare la procedura in popolazioni selezionate di pazienti: pazienti con rigurgito mitralico di tipo degenerativo, sintomatici nonostante il trattamento medico ottimale e non candidabili per l'intervento chirurgico. [HAS 2015]. Anche le più recenti linee guida europee, sebbene riconoscano un livello di evidenza di tipo "C" (derivante da opinione di esperti e/o da piccoli studi, studi retrospettivi o registri) sostengono che "*MitraClip® System sia da considerare nei casi di pazienti sintomatici con rigurgito mitralico cronico severo secondario, non rispondenti alla terapia medica (compresa la terapia di resincronizzazione cardiaca ove indicata), che rispondano a criteri ecocardiografici di eleggibilità, che siano considerati ad alto rischio chirurgico o non candidabili per l'intervento chirurgico da un team composto da cardiologi e cardiochirurghi e che abbiano un'aspettativa di vita superiore ad un anno*" [Vahanian et al. 2012].

Le evidenze disponibili ad oggi non consentono di formulare indicazioni definitive riguardo l'efficacia e la sicurezza relativa dei due dispositivi impiantabili oggetto della valutazione (CARILLON® Mitral Contour System® e MitraClip® System) in adulti affetti da rigurgito mitralico cronico di grado moderato-severo o severo rispetto alla terapia convenzionale. Gli studi effettuati e quelli in corso utilizzano CARILLON® Mitral Contour System® in particolare per il rigurgito mitralico cronico funzionale, mentre MitraClip® System è utilizzato sia per il rigurgito mitralico cronico degenerativo che funzionale.

Mentre l'utilizzo di CARILLON® Mitral Contour System® è da considerarsi ancora in uno stadio iniziale, caratterizzato da un basso livello di diffusione, è da specificare che MitraClip® System è stato impiantato in circa 23.000 pazienti nel mondo, nonostante non siano disponibili prove definitive derivanti da studi comparativi sulla sua efficacia rispetto al comparatore diretto, ovvero la terapia medica ottimale.

Come sottolineato da molti autori, sono necessari studi comparativi con follow-up più estesi al fine di chiarire il profilo di rischio/beneficio di entrambi i dispositivi analizzati. Gli studi in corso potranno presto apportare evidenze utili a stabilire se CARILLON® Mitral Contour System® e MitraClip® siano più efficaci e sicuri rispetto alle altre possibilità terapeutiche esistenti.

Abstract

Mitral regurgitation (MR) is the second most frequent valve disease requiring surgery in Europe. The prevalence of clinically meaningful MR (equal or more than moderate) in individuals younger than 50 years is less than 1% and around 11% in those aged 70 or more. The prevalence of hemodynamically relevant MR in patients affected by heart failure ranges from 13 to 40%, according to different studies.

Medical and surgical therapies are available to treat people with MR. The treatment of choice for most people with severe chronic MR is surgical repair or replacement of the mitral valve (MV).

Catheter-based interventions have been developed to correct MR percutaneously. The two implantable devices for transcatheter MV repair identified on the Italian market and assessed in the present report are: the CARILLON® Mitral Contour System® (Cardiac Dimensions) and the MitraClip® System (Abbott Vascular).

The scope of the present assessment was to answer the question if in adults with chronic primary (degenerative) or secondary (functional) MR who are at high surgical risk or non-surgical candidates, transcatheter MV repair by implantable device is more effective, safe and cost-effective than pharmacological treatment (when indicated) with/without cardiac resynchronisation therapy (CRT).

The available evidence did not allow any final statement to be reached on the relative effectiveness of transcatheter implantable devices for MV repair (CARILLON® Mitral Contour System® and MitraClip® System) in adults with moderate-to-severe and severe chronic MR. The only comparative study on the use of the CARILLON® Mitral Contour System® showed critical methodological issues and incomplete follow-up. No comparative evidence was found on the use of the MitraClip® System in high surgical risk patients with moderate-to-severe and severe MR vs standard care (either no treatment or pharmacological therapy).

The two economic studies (one for CARILLON® Mitral Contour System® and one for MitraClip® System) included in the analysis showed that, in patients with moderate to severe and severe MR at high surgical risk or not eligible for surgery, the two devices are cost-effective compared to conventional/optimal medical treatment. Even if of good quality, the evidence is to be considered still scarce.

Levels of diffusion of the two devices in Italy were found remarkably different with only 3 implants performed using CARILLON® Mitral Contour System® (which is still at an early stage with about 300 implants performed in Europe), and 1,500 implants MitraClip® (23,000 implants worldwide).

The present assessment should be updated when results from ongoing comparative studies become available: one study is ongoing for CARILLON® Mitral Contour System® (NCT02325830

due in July 2017) while four relevant studies are ongoing for MitraClip® System (NCT02444286 due in January 2017, NCT01920698 due in October 2017, NCT02444338 due in September 2019, and NCT01626079 due in 2020).

Introduction

The present assessment is an adaptation to the Italian context of a Pilot Rapid Assessment elaborated within the activities of the EUnetHTA Joint Action 2 Work Package 5 Strand B (JA2 WP5-B) and developed according to the EUnetHTA Model for Rapid Relative Effectiveness Assessment (REA) [EUnetHTA REA, 2013]. The final deliverable is the WP5-B 5th Pilot and is available on the EUnetHTA JA2 website [EUnetHTA JA2 Pilot SB-15].

The present assessment was developed in domains, following the structure defined within the EUnetHTA Network. Such domains represent the various aspects of the assessment of health technologies. Each of the domains contains a series of research questions (named Assessment Elements, AEs) identified by a capital letter and number. However, as the present assessment belongs to the Italian national HTA programme, some integrations and changes were believed necessary. In particular, two models were used:

- The EUnetHTA Core Model® "Rapid Assessment of pharmaceuticals and other technologies" v.3.0 [EUnetHTA REA 2013].
- The Agenas Model (see Appendix 1 for a full description).

The present assessment investigates six domains, 4 from the EUnetHTA REA Model and 2 from the Agenas Model. In this way, for the selected domains, the AEs used are coming from:

- TEC: AEs identified within the WP5-B 5th Pilot;
- CUR: AEs identified within the WP5-B 5th Pilot;
- EFF and SAF: AEs identified within the WP5-B 5th Pilot;
- REG: AEs from the Agenas Model;
- ECO: AEs from the Agenas Model.

Given their transferability, the results from TEC, EFF, and SAF domains were imported from the WP5-B 5th Pilot to the national report: if any, variations were clearly reported in the text. Contextualisation to the national setting was performed for CUR domain's findings, while two further domains were developed *de novo*, using Agenas Model: "Regulatory aspects" (REG) and "Costs and economic evaluation" (ECO).

This assessment addresses the research question whether, specifically in adults with chronic primary or secondary mitral regurgitation (MR) who are at high surgical risk or non-surgical candidates, transcatheter mitral valve (MV) repair is more effective, safe and cost-effective than pharmacological treatment (when indicated) with/without cardiac resynchronisation therapy (CRT).

Two different transcatheter MV repair systems for treatment of MR were identified on the Italian market: the CARILLON® Mitral Contour System® (Cardiac Dimensions, Inc.) for transcatheter annuloplasty and the MitraClip® System (Abbott Vascular) for transcatheter leaflet repair. Standard medical care (with or without pharmacological treatment for HF) was chosen as comparator for both the devices.

1. Report's objectives: policy and research questions

A rapid HTA report was developed to answer the following:

Policy Question: What is the impact of transcatheter MV repair in adults with chronic MR in terms of effectiveness, safety and economic aspects?

Research Question: In adults with chronic primary or secondary MR who are at high surgical risk or non-surgical candidates, is transcatheter MV repair more effective, safe and cost-effective than pharmacological treatment (when indicated) with/without cardiac resynchronisation therapy (CRT)?

The following domains were developed within the present rapid HTA report:

1. Health problem and current use of technology (CUR)
2. Description and technical characteristics of technology (TEC)
3. Regulatory aspects (REG)
4. Clinical effectiveness (EFF)
5. Safety (SAF)
6. Costs and economic evaluation (ECO)

For each investigated domain, the selected Assessment Elements (AEs) are listed in Appendix 2.

2. Health problem and current use of technology

Methods

The AEs of this domain were :

Assessment Element ID	Research question
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What are the symptoms and the burden of disease or health condition for the patient?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

All the AEs of the present domain were addressed in the 5th Pilot produced within EUnetHTA JA2 WP5-B activities [EUnetHTA JA2 Pilot SB-15].

Methods are described within the mentioned document that can be downloaded in full-text. Transferable information provided within the mentioned report has been re-structured according to the Agenas template for HTA documents. Non-transferable information has been contextualised by further investigations.

Health problem was reported in a descriptive summary defined by international and national literature (e.g., reviews articles, epidemiological studies and eventually disease registers). Experts' advice clarified the ICD-9-CM coding (International classification of the diseases – 9th Edition) and current state of the disease management in Italy.

A survey was developed based on two procedural steps:

1. According to the Agenas HTA procedures handbook [Agenas 2014], a questionnaire was sent to manufacturers to collect information about the device and data about the regional level of diffusion related to the devices known as CARILLON® Mitral Contour System® and MitraClip® System.
2. Based on activity data provided by manufacturers, seven Italian Regions were identified for the contextual analysis (CUR and ECO domains; see Chapter 2 and 7). A questionnaire was sent to the seven Regions which overall performed more than 80% of procedures

using the CARILLON® Mitral Contour System® and the MitraClip® System in the last 3 years for which data were available (2012, 2013, and 2014) (see Appendix 3 for full text).

Results

The MV directs blood flow from the left atrium into the left ventricle. MR occurs when the MV does not close properly, allowing blood to flow backwards from the ventricle to the atrium. MR is sometimes referred to as mitral incompetence or mitral insufficiency. MR can be acute (leaflet perforation, chordal rupture, rupture of the papillary muscle due to myocardial infarction) or chronic (long-term disorder associated with valvular or ventricular pathology) and, according to the aetiology, primary (degenerative) or secondary (functional) [EUnetHTA JA2 Pilot SB-15].

Primary MR, often named degenerative MR (DMR), covers all aetiologies in which intrinsic lesions affect one or several components of the MV apparatus. Reduced incidence of rheumatic fever and increased lifespan in industrialised countries have progressively changed the distribution of aetiologies, with degenerative MR now being the most common [Iung et al. 2003; Nkomo et al. 2006] (A0002).

In secondary MR or, as it is also termed, functional MR (FMR), valve leaflets and chordae are structurally normal and MR results from geometrical distortion of the subvalvular apparatus, secondary to left ventricular (LV) enlargement and remodelling due to idiopathic cardiomyopathy or coronary-artery diseases.

In patients with chronic MR, the regurgitation causes left ventricular volume overload that over time induces ventricular remodelling with eccentric hypertrophy, triggering a well-known vicious circle in which MR leads to further MR [Zile et al. 1993]. The phenomenon is initially compensated for by an increase in stroke volume. Progressively, the excessive chamber dilatation is not compensated by adequate hypertrophy, with decreased myocardial contractility and efficiency [Maisano et al. 2014]. Progressive myocardial degeneration may finally lead to irreversible dysfunction and end-stage heart failure (HF) [Beeri et al. 2007]. MR that cannot be managed conservatively may require surgical valve repair or replacement [NICE 2009] (A0004).

According to ICD-9-CM, MR could be identified in hospital discharges records (SDO) with the following codes:

- 394.9 Other and not specified mitral valve diseases
- 394.1 Rheumatic mitral valve insufficiency
- 424.0 Mitral valve disorders.

Epidemiology

The absolute prevalence in specific age groups and comprehensive burden of different specific valve diseases are unknown [Nkomo et al. 2006]. In Europe, MR is the second most frequent

valve disease requiring surgery, after the aortic valve [Vahanian et al. 2012]. Epidemiology studies have demonstrated that the prevalence of MR increases in an aging population. The Framingham study [Singh et al. 1999] showed that the prevalence of clinically meaningful MR (equal or more than moderate) in individuals younger than 50 years is less than 1%, while it becomes 11% over the age of 70 years.

The most common cause of MR in patients undergoing surgery in western countries is degenerative disease (60–70% of cases), followed by ischemic, functional (20%), endocarditis (2–5%), rheumatic (2–5%), and other miscellaneous types [Enriquez-Sarano et al. 2009]. With an aging population and increased prevalence of heart failure in the western countries, functional MR (FMR) is probably becoming more common [Maisano et al. 2014]. The prevalence of hemodynamically relevant FMR in patients affected by heart failure ranges from 13% to 40%, according to different studies [Allen et al. 2008].

The EuroHeart Survey of the European Society of Cardiology [Nieminen et al. 2006] showed that MR (of any grade) is present in 80% of HF patients, and that in 50% of them MR is greater than moderate. In HF patients aged at least 70 years, 89% had MR of any grade, and in 42% of them MR was moderate to severe. This finding was confirmed by another Italian multicentre study [Cioffi et al. 2005]. No specific data about incidence and prevalence of MR in Italian population were retrieved (A0023).

The known risk factors for developing chronic MR are age, hypertension, low body mass index, coronary systolic blood pressure, increased left atrium size and LV diastolic diameter, low left ventricular ejection fraction (LVEF), and female gender [EUnetHTA JA2 Pilot SB-15]. In addition to HF being a complication of MR, it is a major risk factor for the development of MR, having been detected in 56% of patients with LVEF < 40% and clinical HF (70% mild, 30% moderate/severe) in a US cohort [EUnetHTA JA2 Pilot SB-15] (A0003).

Diagnosis

The European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) guidelines identified the gold standard pathway to diagnose a heart valve disease [Vahanian et al. 2012]. When symptoms of chronic MR occur, they often develop gradually and may include: cough, fatigue, exhaustion, and light-headedness, rapid breathing, sensation of feeling the heart beat (palpitations) or a rapid heartbeat, shortness of breath (dyspnoea) that increases with activity and when lying down (orthopnoea), excessive urination at night [Otto et al. 2007; Nishimura et al. 2014].

Severe symptoms may prevent patients from performing everyday tasks and simple activities, such as getting out of bed. The inability to perform activities of daily of living and be independent

can lead to feelings of loss of independence, distress, and depression [EUnetHTA JA2 Pilot SB-15] (A0005).

In the evaluation of the suspect valve disease, the following tests are indicated, relating to the clinical presentation:

- Clinical examination;
- Chest x-ray;
- Electrocardiogram (ECG);
- Echocardiogram (trans-thoracic and trans-oesophageal);
- Other non-invasive investigations: stress testing, exercise ECG; exercise echocardiography; other stress tests; cardiac magnetic resonance; computed tomography; fluoroscopy; radionuclide angiography; biomarkers;
- Invasive investigations (coronary angiography, cardiac catheterisation).

In particular, for chronic MR, echocardiography is the principal investigation and must include an assessment of severity, mechanisms, reparability and consequences [Baumgartner et al. 2009].

After that, assessing the comorbidity is also mandatory: the most frequently encountered comorbidities are peripheral atherosclerosis, renal and hepatic dysfunction, and chronic obstructive pulmonary disease [Vahanian et al. 2012].

As ESC and EACTS guidelines stressed, the most important step is the risk stratification of single patient affected by MV regurgitation [Rosenhek et al. 2012]. Different evaluation scales are proposed and used to assess individual risk-benefit of the specific treatment option. Also operative mortality can be estimated by various multivariable scoring systems using combinations of risk factors [Rankin et al. 2006]. The two most widely used scores are the EuroSCORE (European System for Cardiac Operative Risk Evaluation) [Rabbani et al. 2014] and the STS (Society of Thoracic Surgeons) score [Vahanian et al. 2012] (A00024).

Prognosis

The annual mortality rate in patients with significant DMR varies from 1 to 9% [Maisano et al. 2014]. In asymptomatic severe chronic MR, the reported estimated five-year rate of death from any cause is 22%, death from cardiac causes is 14%, and the rate of cardiac events is 33%. Studies reported also different incidence of sudden death in asymptomatic patients and since the risk of death or major adverse events is proportional to the severity of the regurgitation, surgical treatment is now recommended even in asymptomatic patients when the effective regurgitant orifice is larger than 40 mm^2 [Enriquez-Sarano et al. 2005].The impact of valve surgery on survival remains unclear [Vahanian et al. 2012] (A0004).

Management

The new American College of Cardiology and American Heart Association (ACC-AHA) Guidelines for the Management of Patients with Valvular Heart Disease [Nishimura et al. 2014] and the Guidelines on the management of valvular heart disease (version 2012) of the ESC-EACTS [Vahanian et al. 2012] represent the gold standard for the care pathway of people affected by MR.

Medical and surgical therapies are available to treat people with MR. The treatment of choice for most people with severe chronic MR is surgical repair or replacement of the MV. However, in some cases, surgical treatment may be delayed or deferred due to the presence of other medical conditions that increase the risk of surgery [Vahanian et al. 2012] (A0025). For the scope of the present assessment the following specific target population was considered: adults with moderate-to-severe and severe DMR or FMR who are at high surgical risk or are non-surgical candidates (A0007).

Catheter-based interventions have been developed to correct MR percutaneously. Preliminary data suggest a potential clinical benefit of percutaneous treatment of MR [Feldman et al. 2011; Maisano et al. 2012; Maisano et al. 2013]. However, there is lack of evidence from properly designed randomised, controlled, multicentre clinical trials that could clarify data about target population, effectiveness, cost-effectiveness of the existing devices for percutaneous treatment of MR. Following this lack of evidence, the Italian Federation of Cardiology published the Italian consensus statement on transcatheter treatment of chronic MR with MitraClip® System [Maisano et al. 2014].

The two devices for transcatheter MV repair identified on the Italian market and assessed in the present report are:

- CARILLON® Mitral Contour System® (Cardiac Dimensions);
- MitraClip® System (Abbott Vascular).

Data from manufactures on the number of devices implanted worldwide are reported in 5th WP5-B Pilot [EUnetHTA JA2 Pilot SB-15]. For the Italian context, the manufacturers reported that 3 patients were treated between January 2012 and December 2014 with the CARILLON® Mitral Contour System® , while patients treated with MitraClip® System were 1,398 (Table 2.1) (A0011). Since most of the regions selected for the survey did not return the questionnaire (only one responder), specific data regarding treatment of MR with the MitraClip® System in the Italian public health service are lacking. Moreover, since no national explicit guidelines are available on the ICD-9-CM code for the different transcatheter MR repair interventions, the Italian regions adopt the codes heterogeneously (A0011).

Tab. 2.1 Number of MitraClip® Systems used in Italy (years 2012-2014).

Geographic areas*	Number (%)
North	638 (45.6%)
Centre	244 (17.4%)
South	516 (37%)

Source: Agenas analysis based on manufacturers data.

** The geographic areas are those defined by the Italian Institute of Statistics (ISTAT) for all Italian social and demographical studies.*

From June 2015, the GIse registry Of Transcatheter treatment of MV regurgitaTiOn (GIOTTO) [GISE 2015], coordinated by the SICI-GISE (Società italiana di cardiologia invasiva), collect retrospective and prospective demographic, clinical and outcome data of patients treated in Italy with the MitraClip® system.

Conclusions

MR is a complex condition with two different aetiologies in patients with a *plethora* of comorbidities. Specific epidemiological data on the target population size in Italy were not found. Management of symptomatic MR include surgical repair or replacement of the MV. In adults with moderate-to-severe and severe DMR or FMR who are at high surgical risk or are non-surgical candidates, catheter-based interventions could be an option to correct MR percutaneously. The 2 devices considered in the present assessment have distinct utilisation rates in Italy: while very small number of patients were treated in Italy with CARILLON® Mitral Contour System®, the MitraClip® System has been implanted over a thousand of patients from 2012 to 2014.

3. Description and technical characteristics of technology

Methods

The AEs of this domain were:

Assessment Element ID	Research question
B0001	What are the technologies and what are the comparators?
B0002	What are the claimed benefits of the technologies in relation to the comparators?
B0004	Who administers the technologies and the comparators, and in what context and level of care are they provided?
B0008	What kind of special premises are needed for the technologies and the comparators?
B0009	What supplies are needed for the technologies and the comparators?

All the AEs of the present domain were addressed in the 5th Pilot produced within EUnetHTA JA2 WP5-B activities [EUnetHTA JA2 Pilot SB-15]. Methods are described within the mentioned document that can be downloaded in full-text. Information provided within the mentioned report has been re-structured according to the Agenas template for HTA documents. No new searches have been performed and no new evidence has been considered.

Results

The present assessment focuses on the two systems for transcatheter MV repair for MR identified on the Italian market: CARILLON® Mitral Contour System® (Cardiac Dimensions, Inc.) for transcatheter annuloplasty and MitraClip® System (Abbott Vascular) for transcatheter leaflet repair (Table 3.1).

Comparators were chosen based on CE mark, specific indications, information in published clinical guidelines for treatment of MR [Nishimura et al. 2014; Vahanian et al. 2012], EUnetHTA guidelines [EUnetHTA guidelines], and were amended following comments from dedicated reviewers and external experts. Standard medical care (with or without pharmacological treatment for HF) was chosen as comparator for both the devices. The presence of an implanted cardiac resynchronisation therapy (CRT) device was not considered an exclusion criterion. Surgery was not the claimed comparator for any of the devices and is not an option considering the population assessed (patients suffering of MR, with or without HF, who are at high surgical risk or are non-surgical candidates). Standard medical care mainly consists in medical management, provided by cardiologists in the setting of secondary care, targeted to relieve symptoms but not able to reverse the underlying pathology of MR, so disease progression is not prevented. There is no evidence to support the use of angiotensin-converting-enzyme (ACE)

inhibitors, beta-blockers, spironolactone, diuretics, aldosterone antagonists, and nitrates in chronic MR without HF, and these agents are, therefore, not recommended in this group of patients [EUnetHTA JA2 Pilot SB-15]. When HF has developed, ACE inhibitors are beneficial and should be considered in patients with advanced MR and severe symptoms who are not suitable for surgery or when residual symptoms persist following surgery. Beta-blockers and spironolactone should also be considered for relief of symptoms because no medicine is indicated for MR. These drugs are approved in all European countries [De Bonis et al. 2015; McMurray et al. 2012; Nishimura et al. 2014; Vahanian et al. 2012; Yancy et al. 2013] (B0001).

Table 3.1: Transcatheter MV repair systems available on the Italian market. All the devices listed in the table are CE marked and registered within the Italian National Medical Devices Inventory (Repertorio Dispositivi Medici – RDM).

Device name	Manufacturer	CE mark	FDA status	RDM registration number(s)
Carillon Mitral Contour System	Cardiac Dimensions, Inc.	Aug-2011	-	628454, 627001, 628540
MitraClip System	Abbott Vascular	Mar-2008	Oct-2013*	55220, 294642, 81618, 233783, 357446, 16323, 81587, 55263, 81493

Source: *Data from the RDM database. Devices are listed in alphabetical order by device name.*

** "for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for MV surgery by a heart team, which includes a cardiac surgeon experienced in MV surgery and a cardiologist experienced in MV disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation."*

CARILLON® Mitral Contour System® (Cardiac Dimensions, Inc.)

The CARILLON® Mitral Contour System® is a percutaneous mitral annuloplasty device designed to treat FMR. It consists of a metallic implant intended for permanent placement in the coronary sinus or great cardiac vein, and a catheter-based delivery system consisting of a custom curved delivery catheter with a handle assembly. The metallic implant is attached to the handle assembly and delivered through the catheter to the coronary vein along the posterolateral aspect of the mitral annulus (B0001). The implant is designed to re-shape the mitral annulus in order to reduce annular dilation and therefore reduce MR (B0002).

According to the information provided by the manufacturer, the adoption of CARILLON® Mitral Contour System® requires hospitals to have expertise in the areas of interventional cardiology, echocardiography, and HF. Cardiologists typically make recommendations regarding the application of CARILLON® Mitral Contour System®, provide information to potential patients and their family members, and perform the procedure within a catheterisation laboratory. As a fully implantable, non-active, non-electronic device, once the device is in place, there is no management indications for patients or their caregivers (B0004).

The procedure is performed within secondary healthcare setting (both public and private), and typically takes 40 minutes. Real-time echocardiography and angiography can be conducted during the procedure to help evaluate efficacy and safety aspects of the procedure. Since the device is placed in the venous system (right side of the heart), blood thinners or anticoagulants are typically not required. The procedure can be conducted using conscious sedation or general anaesthetic. The device can be recaptured and effectively repositioned if necessary (B0004).

The CARILLON® Mitral Contour System® can be used in a catheterisation laboratory utilising standard catheterisation techniques. The implantable device is deployed via percutaneous means with access via the jugular vein, with the device being delivered into the coronary sinus or great cardiac vein. The delivery catheter used for device deployment is 9F (0.3 mm). No trans-septal puncture is required. The device is deployed under fluoroscopic guidance. Echocardiography may also be used during the procedure as a diagnostic tool (either transoesophageal echocardiography - TOE, or transthoracic echocardiography - TTE). The procedure can be performed under general anaesthetic or conscious sedation (B0008).

In the packaging itself, both the CARILLON® delivery catheter and CARILLON® handle assembly are provided. If an additional implant procedure attempt is planned, the implant procedure should be repeated with a new delivery catheter, handle assembly, and implant as all components of the CARILLON® Mitral Contour System® are single use only. There are approximately 30 different device sizes (lengths and anchor diameters) that allow the placement of the device in a variety of different patients' anatomies [EUnetHTA JA2 Pilot SB-15] (B0009).

MitraClip® System (Abbott Vascular)

The MitraClip® System is a transcatheter therapeutic approach for the reconstruction the insufficient MV in patients with severe DMR or FMR who are not considered suitable candidates for conventional MV surgery. A metallic clip is delivered to the heart through the femoral vein, after trans-septal puncture is performed, and is implanted on the valve leaflets to create a double orifice valve, replicating the edge-to-edge surgical procedure introduced by Alfieri [De Bonis et al. 2010] (B0001). The system is designed to allow the creation of a double-orifice valve to decrease the backflow of blood (therefore reducing MR) and allow the heart to pump blood more efficiently (B0002).

According to the information provided by the manufacturer, the decision to use the MitraClip® System is aligned with the European guidelines [Vahanian et al. 2012] and the latest position statement from the ESC Working Groups on Cardiovascular Surgery and Valvular Heart Disease [De Bonis et al. 2015], and is usually made by a "*heart team*" (B0004) – a multidisciplinary group with a particular expertise in valvular heart disease, including cardiologists, cardiac surgeons,

imaging specialists, HF specialists, anaesthetists, and, if needed, general practitioners, geriatricians, or intensive care specialists.

The procedure is performed within secondary healthcare, in both public and private settings, while the patient is under general anaesthesia (so that TOE can be performed safely in order to visualise the MV leaflets). Transfemoral transvenous access is obtained and trans-septal puncture is performed at the interatrial fossa, to position the steerable guide catheter in the left atrium. The clip delivery system is then introduced through the guide catheter to orient the clip perpendicular to the valve leaflets' line of coaptation. The valve leaflets are grasped between the corresponding arm and gripped resulting in the creation of a double-orifice valve. MR is assessed throughout the entire procedure using real-time TOE (2D and/or 3D) to confirm optimal positioning and sufficient reduction in MR. The procedure does not require cardiac arrest or cardiopulmonary bypass, thereby permitting a real-time evaluation of the impact of the clip implantation on MR. If reduction in MR is not sufficient, the clip can be taken safely off the leaflets, repositioned, and re-implanted, or can be removed completely according to the implanting physician's judgement [EUnetHTA JA2 Pilot SB-15] (B0004).

The MitraClip® System can be used in a standard catheterisation laboratory or in a hybrid room with the following equipment: fluoroscopy; general anaesthesia; slave monitors (one for fluoroscopy, one for echocardiography); echocardiography machine equipped with TOE probe; sterile system preparation station. The MitraClip® device should be implanted with sterile techniques using echocardiography (e.g., TOE and TTE) and fluoroscopy. The procedure is usually performed under general anaesthetic (B0008).

The MitraClip® System consists of 2 major parts: the clip delivery system, which includes the implantable clip, a steerable sleeve and a delivery catheter; and the steerable guide catheter, which includes a dilator. Several accessories are used in conjunction with the MitraClip® delivery system including: a stabiliser, a lift, a silicone pad, a support plate, and fasteners (B0009).

Conclusions

The two technologies considered in the present assessment address the treatment of MR: while the CARILLON® Mitral Contour System® only addresses MR of functional aetiology (FMR), the MitraClip® System addresses both aetiologies, degenerative (DMR) and functional. Different access strategies have been implemented: jugular vein for the CARILLON® Mitral Contour System®, femoral vein for the MitraClip® System.

The two systems provide the intended anatomical effect by acting on different structures of the MV: the CARILLON® Mitral Contour System® only addresses FMR by re-shaping annulus geometry from the coronary sinus; the MitraClip® System is designed to reduce MR by clipping

the leaflets of the MV to each other, thereby replicating the suture placed in the Alfieri technique, and addresses both DMR and FMR. The two procedures are performed within secondary healthcare, in the setting of a standard catheterisation laboratory, while the patient is under general anaesthesia or even under conscious sedation, in the case of the CARILLON® Mitral Contour System®.

The decision on the use of the CARILLON® Mitral Contour System® is typically taken by a cardiologist having expertise in the areas of interventional cardiology, echocardiography, and HF management while, for the use of the MitraClip® System, the decision is usually made using the "*heart team approach*".

4. Regulatory aspects

Methods

The AEs of this domain were:

Assessment Element ID	Research question
A0020	For which indications has the technology received marketing authorisation or CE marking?
A0021	What is the reimbursement status of the technology?

All the AEs of the present domain belong to the Agenas Model but were found substantially equivalent with those within the REA Model (see Appendix 2). The AEs were addressed in the 5th Pilot produced within EUnetHTA JA2 WP5-B within the domain "Description and technical characteristics of technology" [EUnetHTA JA2 Pilot SB-15].

Methods are described within the mentioned document that can be downloaded in full-text. Information provided within the mentioned report has been re-structured according to the Agenas template for HTA documents and supplemented using data from a manufacturers' survey performed independently by Agenas to gather information on the reimbursement status of the technology across the Italian Regions.

Results

CARILLON® Mitral Contour System® (Cardiac Dimensions, Inc.)

CARILLON® Mitral Contour System® obtained the CE mark in August 2011 with the indication for use in patients with FMR (Table 4.1). The use of CARILLON® Mitral Contour System® is contraindicated in patients with existing devices in the coronary sinus or great cardiac vein and in patients who have had a MV replacement or a mitral annuloplasty ring implant (A0020).

Detailed information about the reimbursement of the technology across the Italian regions has not been provided by the manufacturer (A0021).

MitraClip® System (Abbott Vascular)

The MitraClip® System obtained the CE mark in March 2008 as intended for the reconstruction of the insufficient MV through tissue approximation (Table 4.1). Patients with the following conditions should not be treated with the MitraClip System: i) Patients who cannot tolerate procedural anticoagulation or post procedural anti-platelet regimen; ii) Active endocarditis of the MV; iii) Rheumatic MV disease; iv) Evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus. The manufacturer recommends the procedure to be performed when an

experienced heart team has determined that reduction of MR to ≤ 2+ is expected following implantation (A0020).

The current Italian reimbursement system does not have a specific code for the MitraClip procedure. Different DRG codes are used in different regions: DRG 518 *"Percutaneous interventions on cardiovascular system without stent insertion"* in Lombardia, DRG 105 *"Cardiac valve and other major cardiothoracic procedures w/o cardiac catheterisation"* in Emilia Romagna, and DRG 108 *"Other intervention on cardiac valves"* in Veneto. No official decrees have been issued in all the other regions where the procedure is performed. (A0021).

Table 4.1: Transcatheter implantable device for mitral valve repair available on the Italian market presented together with their approval status in Europe and USA. All the devices listed in table are registered within the Italian National Medical Devices Inventory (Repertorio Dispositivi Medici – RDM).

Region	Approval	Indication(s)	Date
CARILLON® Mitral Contour System®			
Europe	CE mark	*The Carillon® Mitral Contour System® is indicated for use in patients with functional mitral regurgitation.*	August 2011
USA	FDA approval	-	-
MitraClip® System			
Europe	CE Mark	*The MitraClip® System is intended for reconstruction of the insufficient mitral valve through tissue approximation.*	March 2008
USA	FDA approval	*This device is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in MV surgery and a cardiologist experienced in MV disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.*	October 2013

Source: *Data from the RDM database. Devices are listed in alphabetical order by device name.*

Conclusions

The two systems are available in the European market under the CE mark regulation. The MitraClip® System is also available in the USA. Differences have been noticed between indications for use in Europe and the USA, being CE mark indications much broader than those defined by the FDA (only a specific subset of DMR patients).

Across Europe [EUnetHTA JA2 Pilot SB-15], as well as across the Italian regions, the two technologies are differently reimbursed. In Italy differences in reimbursement are related to the coding procedure.

5. Clinical effectiveness

Methods

The AEs of this domain were:

Assessment Element ID	Research question
D0001	What are the expected beneficial effects of the technologies on mortality?
D0003	What are the effect of the technologies on the mortality due to causes other than the target disease?
D0005	How do the technologies impact on symptoms and severity of chronic MR?
D0006	How do the technologies affect progression (or recurrence) of chronic MR?
D0011	What are the effects of the technologies on patients' body functions?
D0016	How does the use of the technologies affect activities of daily living?
D0012	What are the effects of the technologies on generic HRQoL?
D0013	What are the effects of the technologies on disease-specific QoL?
D0017	Was the use of the technologies worthwhile?

All the AEs of the present domain were addressed in the 5th Pilot produced within EUnetHTA JA2 WP5-B activities [EUnetHTA JA2 Pilot SB-15]. Methods are described within the mentioned document that can be downloaded in full-text. Information provided within the mentioned report has been re-structured according to the Agenas template for HTA documents. No new searches have been performed and no new evidence has been considered. According to Agenas's assessment needs, the analysis was limited to two of the three devices considered within the EUnetHTA 5th Pilot (i.e., the CARILLON® Mitral Contour System® and the MitraClip® System).

Evidence analysis for the present domain was structured according to the PICO defined in Table 5.1. Literature searches were performed in the following databases: Ovid MEDLINE, Embase, Cochrane Library, CINAHL, CRD databases (DARE, NHS EED, HTA). In addition, the following clinical trials databases were searched to identify ongoing studies on the two devices included in the assessment: ClincalTrials.gov, ISRCTN, EU Clinical Trials Register, metaRegister of Controlled Trials (mRCT), International Clinical Trials Registry Platform (ICTRP) (Appendix 4).

Analysis of secondary and primary studies was performed, for each device, in two different phases: secondary studies (i.e. HTA reports and systematic reviews published in peer-reviewed journals) were screened as a first step and then, only where secondary studies were not available, primary studies were considered for inclusion.

Secondary studies were retrieved in full-text version. A cross-reference search was also performed. To allow a broader overview, searches were extended to include HTA reports

published in non-English languages but having a summary in English. HTA reports were extracted and tabulated in ascending chronological order. Only the most recent reports were discussed qualitatively. Systematic reviews were assessed according to year of publication, time range, scope, and population to identify the most recent review that overlapped with the scope of the present assessment. Searches from such reviews were then extended to include May 2015, to identify further, more recent, primary studies fulfilling the inclusion criteria of the present assessment. The R-AMSTAR tool [Kung et al. 2010] was designated for quality assessment of systematic reviews while the criteria from the Cochrane Handbook for Systematic Reviews of Interventions [Higgins et al. 2011] were chosen to assess the methodological quality of RCTs and CCTs.

Table 5.1: Table describing the population, the intervention, the comparisons, and the outcomes relevant for effectiveness and safety assessment together with the eligible study designs. Adapted from [EUnetHTA Rapid assessment PILOT ID: SB-15].

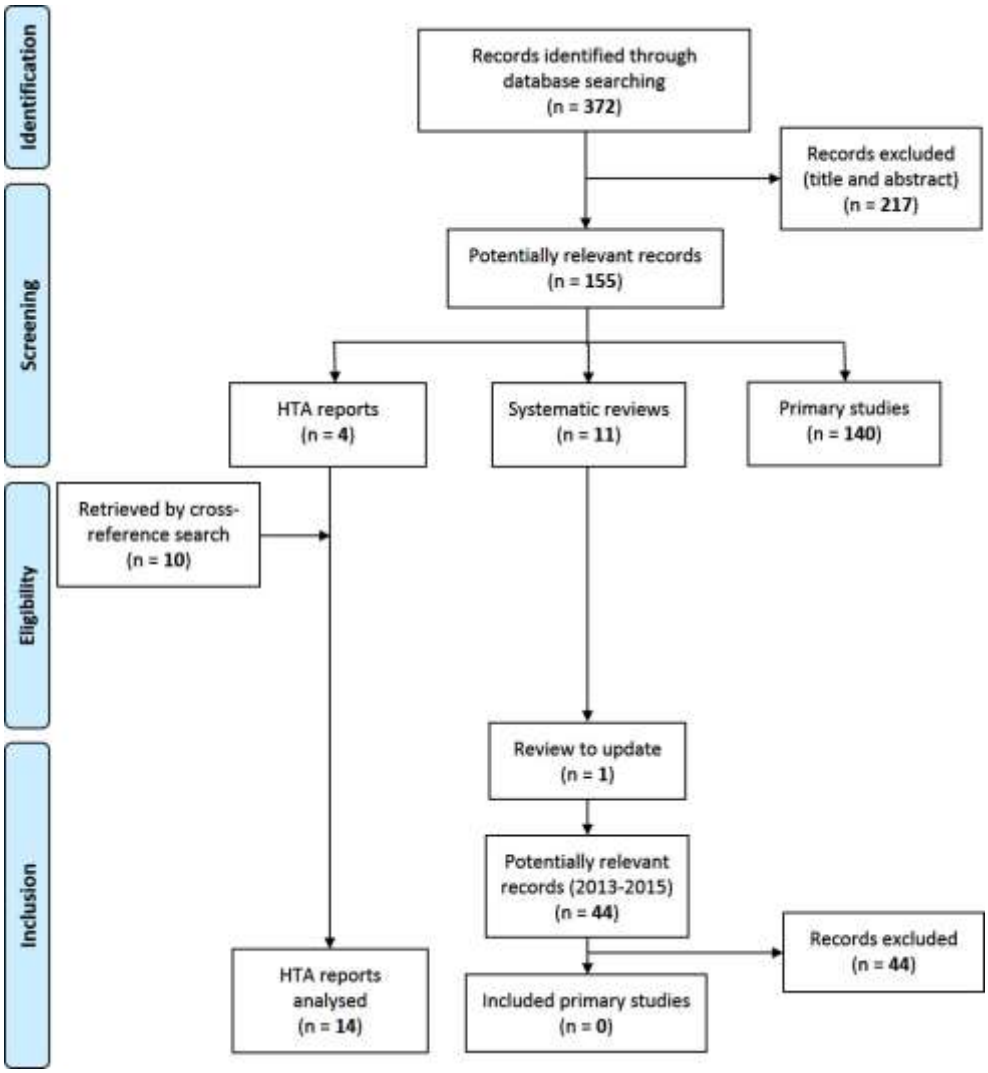
Population	Adults with moderate-to-severe and severe degenerative mitral regurgitation (DMR) or functional mitral regurgitation (FMR) who are at high surgical risk or non-surgical candidates. *ICD-10-CM code for the indication: I34.0 mitral (valve) insufficiency.*
Intervention	Transcatheter MV repair by device implantation for mitral regurgitation. Two systems will be considered within the present assessment: • CARILLON® Mitral Contour System® for annulus repair; • MitraClip® System for leaflet repair; *Both the interventions are proposed to treat the condition.*
Comparison	High surgical risk or non-surgical candidates, with or without heart failure (HF), presenting with DMR: ▪ MitraClip® System vs standard medical care (with or without HF pharmacological therapy). High surgical risk or non-surgical candidates presenting with FMR: ▪ MitraClip® System vs pharmacological therapy (with or without CRT); ▪ CARILLON® Mitral Contour System® vs pharmacological therapy (with or without CRT).
Outcomes	Primary effectiveness outcomes: mortality (all-cause), cardiovascular mortality, need for cardiac transplantation, NYHA functional status improvement, freedom from NYHA class ≥ 3, improvements in the 6-minutes walk test (6MWT) score, reduction in hospitalisation rate, cardiovascular hospitalisation, need for MV surgery, quality of life (any measure). Secondary effectiveness outcomes: improvements in echocardiographic outcomes (e.g. reduction in ventricular volumes, improvement in LVEF), procedural success rate. Safety outcomes: durability of the device, short- and long-term AEs (device-related as well as procedure-related): i) Any AE; ii) serious AEs; iii) most frequent AEs
Study design	Systematic reviews, Health Technology Assessment (HTA) reports, randomised controlled trials (RCT), controlled clinical trials (CCT).

Key: *6MWT = 6-minutes walk test; CRT = cardiac resynchronization therapy; DMR = degenerative mitral regurgitation; FMR = functional mitral regurgitation; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; vs = versus.*

Results

The search produced 372 records. The reference list was screened by title and abstract to identify potentially relevant studies. Among the 155 potentially relevant studies, 15 were secondary studies (i.e. HTA reports and systematic reviews published in peer-reviewed journals), whereas 140 were primary studies. A cross-reference search identified further 10 HTA reports [EUnetHTA JA2 Pilot SB-15].

Figure 5.1: Flow-chart of the studies for effectiveness assessment according to PRISMA. Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.



A total of 14 HTA reports were identified. Among these were 3 updated versions of previous reports and 1 horizon scanning report without any literature review, leaving 10 HTA reports for

full-text analysis and extraction (Table 5.2). Three reports focused on the CARILLON® Mitral Contour System®, and the rest focused on the MitraClip® System. Links to the full-text documents are provided in bibliography.

A total of 11 systematic reviews were identified, all of which were on the MitraClip® System. The review by Munkholm-Larsen et al. [Munkholm-Larsen et al. 2014] was selected for update within the present assessment, on the basis of year of searches, time range, scope, and population. Primary studies in the period 2013–2015 were screened to identify new evidence on the use of the MitraClip®. As no new comparative studies were found among the 44 records identified, no further studies were included within the present assessment. Therefore, for the MitraClip® system, assessment elements were answered using the findings from the review by Munkholm-Larsen et al. [Munkholm-Larsen et al. 2014].

To find evidence on CARILLON® Mitral Contour System®, the whole list of primary studies was screened. One comparative study on the use of CARILLON® Mitral Contour System® was identified [Siminiak et al. 2012], but it did not meet the inclusion criteria of the present assessment because no formal surgical risk assessment was performed on the study population. In light of the scarcity of studies, and although not used for any quantitative analysis, the study was described briefly and used to attempt answer the assessment elements for CARILLON® Mitral Contour System®.

Description of available evidence on CARILLON® Mitral Contour System®

Secondary studies

CARILLON was assessed by the The National Institute for Health and Care Excellence (NICE, UK) in 2010 [NICE 2010], by Health Policy Advisory Committee on Technology (HealthPACT, Australia) in 2012 (update of an earlier assessment) [HealthPACT, 2012], and by the National Health Committee (NHC, New Zealand) in 2013 [NHC 2013]. The evidence of safety and efficacy, based only on a few case series, was judged inadequate for quality and quantity from the 3 institutions; 2 of them recommended this procedure should be used only in a research context [NICE 2010; NHC 2013] [EUnetHTA JA2 Pilot SB-15].

Primary studies

No new studies have been identified on the use of CARILLON® Mitral Contour System®. The study mentioned in the most recent HTA report [NHC 2013] presented the results of the TITAN trial [Siminiak et al. 2012]: a prospective, non-randomised, non-blinded, multicentre study designed on the basis of an earlier feasibility study (CARILLON Mitral Annuloplasty Device European Union Study - AMADEUS [Schofer et al. 2009]) to assess safety and functional changes

at 24 months. The population was composed of 53 patients with dilated ischaemic or non-ischaemic cardiomyopathy, at least moderate (2+) FMR; LVEF < 40%, NYHA class II–IV, 6MWT 150–450 m, and stable HF medication regimen. Of those 53 patients, 36 underwent permanent device implantation, and 17 had the device implanted and acutely recaptured due to clinical indications (i.e. 8 due to transient coronary compromise and 9 due to < 1 Grade MR reduction). Two groups were then observed: patients with a permanent implant (at 1, 6, 12, and 24 months) and patients with a recaptured implant (comparison group; followed at 1, 6, and 12 months). Follow-up at 12 months was not completed for all patients; depending on the outcome measure, up to 25 patients in the implanted group were followed and up to 8 in the comparison group. This was also related to the mortality in this sick patient population that was judged to be not device related. Follow-up at 24 months was limited to 19 patients in the implanted group (only for patients who had paired data at both 6 and 12 months). Echocardiographic measures assessed changes in FMR and cardiac structure.

The 30-day mortality rate was 1.9% (1/53; from the non-implanted group), while the 1-year mortality rate was 22.2% (8/36) in the implanted group and 23.5% (4/17) in the comparison group (D0001) (D0003).

The symptoms and severity of FMR were assessed, in both groups, by NYHA classification. At baseline, NYHA class was 3.1 ± 0.23 in the implanted group (36 patients) and 2.9 ± 0.24 in the non-implanted group (17 patients) ($p = 0.105$). The implanted group was reassessed at 12 months and showed improvement in NYHA class from baseline to 2.1 ± 0.64 (25 patients). The improvement was maintained at the 24-month visit with NYHA class of 2.1 ± 0.74 (19 patients) ($p < 0.001$) (D0005).

FMR progression and changes in cardiac structure by echocardiographic measures were also reported. A statistically significant difference was noted between the two groups, with a continued decrease of FMR for up to 12 months noted in the implanted group: in 25 implanted patients, FMR reduction at 12 months ranged from 3 grades for 3 patients, 2 grades for 5 patients, 1 grade for 12 patients, and less than one grade for 5 patients. Statistically significant reduction of LV size was noted in the implanted group, compared with continued enlargement in the comparison group: the mean reduction in LV end-systolic volume was 19% at 12 months. Eight of 25 patients had a > 10% reduction in LV end-systolic volume at 12 months. The echocardiographic assessment also included the assessment of regurgitant volume, effective regurgitant orifice (ERO) area, vena contracta, FMR jet area relative to left-atrial area, and annular septal–lateral diameter: in the implanted group, all the measures were statistically significantly reduced from baseline at the 12-month follow-up (D0006).

Functional changes in exercise performance were observed by the 6MWT. Scores (distance walked, in metres) were reported at baseline and at 1, 6, and 12 months for both groups. In the

implanted group, 6MWT scores were 302.5 ± 74 m at baseline (36 patients), 397.9 ± 152 m at 1 month (32 patients), 429.9 ± 209 m at 6 months (27 patients), and 406.0 ± 180 m at 12 months (23 patients). In the comparison group, 6MWT scores were 337.9 ± 83 m at baseline (17 patients), 351.0 ± 98 m at 1 month (14 patients), 322.2 ± 105 m at 6 months (10 patients), and 348.1 ± 138 m at 12 months (8 patients). There was a statistically significant difference between the 2 groups (p = 0.005) (D0011).

The assessment of changes in performing activities of daily living (e.g. dressing, showering, walking, doing housework) at baseline and at follow-up intervals was not reported separately in the study, but it is included within the tool used to assess quality of life (QoL) (i.e. the Kansas City Cardiomyopathy Questionnaire) (D0016). Scores were reported at baseline and at 1, 6, and 12 months for both groups. In the implanted group, scores were 43.0 ± 18 at baseline (36 patients), 64.6 ± 19 at 1 month (31 patients), 63.4 ± 23 at 6 months (28 patients), and 61.2 ± 26 at 12 months (24 patients). In the comparison group, scores were 40.4 ± 19 at baseline (17 patients), 47.5 ± 25 at 1 month (14 patients), 49.6 ± 22 at 6 months (10 patients), and 51.0 ± 19 at 12 months (7 patients). There was a statistically significant difference between the two groups (p = 0.001) (D0012) (D0013).

Patient satisfaction after the procedure was not assessed in the study (D0017).

Description of available evidence on MitraClip® System

Secondary studies

MitraClip was assessed by 8 different institutions, from 2009 to 2015 (Table 5.2). In Europe, recommendations from the earliest assessments [HTA Stockholm 2012; NICE 2009] were restrictive in use because of the lack of comparative studies with adequate comparators and low quality observational studies. The latest report, published by Haute Autorité de Santé (HAS) in April 2015 [HAS 2015], considered the series from the EVEREST II HRR study and a further 9 non-comparative cohort studies. HAS highlighted the following critical issues: implanted patients have multiple aetiologies of MR with heterogeneous baseline characteristics and therapeutic strategies that are not identical; complications at 1 year of follow-up are not systematically described in the studies; evidence is limited to small numbers and short follow-up periods; efficacy cannot be assessed by type of MR; the definition of "high surgical risk" varies depending on the study; the learning curve of the technique is not considered in the studies. Despite these issues – but in line with the latest ESC-EACTS and AHA-ACC Guidelines – HAS recommended the use of the MitraClip® System in patients with severe DMR who are symptomatic despite optimal medical treatment, ineligible for surgery, and meet the echocardiographic eligibility criteria. The lack of alternatives for this population and the potential benefit of the MitraClip® System was

considered crucial by HAS. They stated that, for other indications (e.g., FMR or mixed aetiologies) and/or for patients at lower surgical risk, the role of the MitraClip® System remains undetermined.

The review by Munkholm-Larsen et al. [Munkholm-Larsen et al. 2014] was focused on the assessment of safety, success rate, clinical efficacy, and survival outcomes of the MitraClip® System implantation in managing patients with severe DMR and/or FMR and high surgical risk candidates. The review covered the time frame from January 2000 to March 2013. All 12 studies included were prospective observational studies from specialised tertiary referral centres (no comparative studies were identified). The review did not identify any RCTs comparing the MitraClip® vs non-surgical therapies. Only 3/12 studies involved multiple centres [Auricchio et al. 2011; Surder et al. 2013; Whitlow et al. 2012], and only 3/12 studies had 100 or more patients (n = 202 [Treede et al. 2012]; n = 117 [Paranskaya et al. 2013]; and n = 100 [Surder et al. 2013]); the rest of the studies included fewer than 100 patients (range 16–85). Most of the studies (7/12) had a median follow-up of 1 year; 3/12 studies had a median follow-up of 6 months, and only one study reported outcomes beyond 12 months. Immediate procedural success ranged from 72% to 100%; 30-day mortality ranged from 0% to 7.8%. One-year survival ranged from 75% to 90%. The authors of the review highlighted a series of issues: 1) DMR and FMR are often combined (in 9/12 included studies); 2) data on long-term outcomes and durability of device beyond 3 years are limited; 3) inclusion and exclusion criteria, patient selection, and the definition of high risk varied significantly between the included studies; 4) the available literature on high surgical risk patients is of low quality, with the majority being either registries or observational studies. They concluded that *"before further convincing evidence becomes available, the use of MitraClip® implantation should be considered only within the boundaries of clinical trials with special arrangements for clinical governance, consent, and audit or research. MitraClip® interventions should only take place in centres with appropriate cardiothoracic surgical support to manage the potential intraoperative complications"* [Munkholm-Larsen et al. 2014].

Primary studies

No new primary studies fulfilling the inclusion criteria defined in the present assessment were identified by updating the review by Munkholm-Larsen et al. [Munkholm-Larsen et al. 2014]. Assessment elements were developed using findings from the review by Munkholm-Larsen et al. [Munkholm-Larsen et al. 2014].

Survival at 1 year was reported by 6 of the 12 included studies and ranged from 75% to 90%. Long-term survival was not available (D0001) (D0003).

Symptoms and severity of MR were assessed by NYHA classification. A reduction (early, at 6 months or at 12 months of follow-up) in the number of patients in NYHA class III/IV was reported in 9 of the 11 studies that provided information on this outcome. Five of the included studies reported data at 12 months showing a reduction in the proportion of patients in NYHA class II/IV from 98% to 35%, from 88% to 27%, from 94% to 11%, from 98% to 22%, and from 90% to 26% respectively (D0005).

After the MitraClip® System implantation, reduction of MR Grade to ≤ 2+ was shown in all 11 studies that reported this outcome, and ranged from 73% to 100% of patients. In the studies that reported from 6 to 12 months of follow-up, 61–99% of patients presented an MR Grade ≤ 2+. LV volume, as well as LV diameter, showed a reduction from baseline in all 6 studies that reported this outcome. LVEF was reported as improved or unchanged from baseline in 6 studies (D0006).

Only 3 of the 12 included studies assessed functional status in exercise performance by the 6MWT, showing improvements for up to 6 months of follow-up: 194 ± 44 m to 300 ± 70 m ($p < 0.01$) [Pleger et al. 2011]; 171 ± 99 to 339 ± 134 m ($p < 0.001$) [Ihlemann et al. 2011]; and 300 ± 108 m to 339 ± 120 m ($p = 0.02$) [Van den Branden et al. 2012] (D0011).

Changes in performing activities of daily living (e.g. dressing, showering, walking, doing housework) were reported by a general QoL assessment in only 2 of the included studies. This dimension is included within the 2 tools used in the studies: the Short-form (SF)-36 Health Survey Quality of Life Questionnaire and the Minnesota Questionnaire (D0016). The SF-36 Health Survey Quality of Life Questionnaire showed improvements in the physical component from a baseline score of 31.6 ± 9.1 to 37.0 ± 9.7 at 1 month and 36.5 ± 10.6 at 12 months of follow-up ($p = 0.01$). The Minnesota Questionnaire also showed statistically significant improvement from 56.5 ± 21.9 pre-intervention to 39.4 ± 20.5 at 6 months of follow-up ($p < 0.001$) (D0012) (D0013).

Patient satisfaction after the procedure was not assessed in any of the 12 included studies (D0017).

Assessment of methodological quality

As no comparative studies fulfilling the inclusion criteria of the present assessment were identified, methodological quality was only assessed for the only review included [Munkholm-Larsen et al. 2014]. Final R-AMSTAR score was 30/44 indicating that the review can be considered of good quality (see Appendix 5).

Ongoing studies and upcoming evidence

Searches on clinical trials databases allowed to identify the ongoing studies of the two devices assessed (Table 5.3, Table 5.4).

For CARILLON® Mitral Contour System®, one study was identified: the REDUCE FMR (NCT02325830). The study plans to enrol 180 patients and provide results by July 2017. It is a prospective, multicentre, randomised, double-blind study aimed to assess the safety and efficacy of CARILLON® Mitral Contour System® in treating FMR associated with HF, compared to a randomised control group that is medically managed according to HF guidelines. REDUCE FMR does not state to formally assess the surgical risk of the candidates but set a LVEF ≤ 40% among the inclusion criteria. Results from REDUCE FMR are anticipated, as they may be helpful to answer the research questions of the present assessment and provide further information for defining the role of the procedure within the clinical pathway (Table 5.3).

For the MitraClip® System, several studies are ongoing and will, in the near future, be crucial for defining clear indications of this therapy and identifying criteria to select the population that may benefit most from the procedure (Table 5.4). For the present assessment, 4 studies are particularly relevant because they do not consider any surgical option as comparator:

- The RESHAPE-HF1-FU study (NCT02444286) is an observational cohort aimed to enrol 42 FMR patients in NYHA class III/IV with chronic HF, who had previously participated in the RESHAPE-HF trial. The MitraClip® System outcomes will be compared with outcomes from optimal standard of care therapy. Results are expected in January 2017.
- In October 2017, results from the MITRA-FR trial (NCT01920698) are expected to be available. MITRA-FR is a multicentre, randomised study comparing treatment with the MitraClip® implantation in addition to optimal standard medical therapy vs optimal medical therapy alone in 288 patients with severe FMR.
- Another multicentre, randomised trial (NCT02444338) is expected to be completed by September 2019; 380 patients with chronic HF and clinically significant FMR (NYHA class II–IV) will be randomised to the MitraClip® System plus optimal standard of care therapy or standard of care therapy alone.
- The largest trial, the COAPT multicentre, randomised study (NCT01626079), will be completed in 2020 and expects to enrol 430 symptomatic HF subjects, treated with the standard of care, who have been deemed by the site's local heart team as being unsuitable for MV surgery. Percutaneous MV repair using the MitraClip® System will be compared to no intervention (non-surgical management based on standard hospital clinical practice).

Another ongoing study that deserves to be mentioned despite the surgical comparator (reconstructive MV surgery) is the MATTERHORN trial (NCT02371512), aimed to assess MV repair with the MitraClip® System in the context of a multicentre, randomised study enrolling 210 high surgical risk patients with clinically significant MR of primarily functional pathology. Results are expected by December 2017.

Table 5.2: Assessment reports on the two devices considered in the present analysis (CARILLON® Mitral Contour System® and MitraClip® System); ascending chronological order.

Year	Institution	Country	Title	Device	Population assessed	Studies considered for recommendations (n = number of patients)	Recommendations
2009	NICE	UK	Percutaneous MV leaflet repair for MR	MitraClip®	Patients with MR	1 case series (n = 107)	*"Evidence on the safety and efficacy of percutaneous MV leaflet repair for MR is currently inadequate in quality and quantity. Therefore, this procedure should only be used:* ▪ *with special arrangements for clinical governance, consent and research for patients who are well enough for surgical MV leaflet repair to treat their MR, or* ▪ *in the context of research for patients who are not well enough for surgical MV leaflet repair to treat their MR"*
2010	NICE	UK	Percutaneous MV annuloplasty	CARILLON® Mitral Contour System®	Patients with MR	1 case series (n = 48)	*"Current evidence on the safety and efficacy of percutaneous MV annuloplasty is inadequate in quality and quantity. Therefore this procedure should only be used in the context of research, which should clearly describe patient selection, concomitant medical therapies and safety outcomes. Both objective measurements and clinical outcomes should be reported"*
2012 (2010 update)	HealthPACT	Australia	CARILLLON® mitral contour system® for mitral regurgitation	CARILLON® Mitral Contour System®	Patients with FMR	1 comparative study (n = 53); 1 case series (n = 14)	*"The evidence base for the Carillon mitral contour system is limited, and there is still uncertainty around the uptake of this and other comparator technologies for the treatment of MV disease in Australian clinical practice. Therefore, HealthPACT have recommended that no further assessment of this technology is warranted."*
2012 (2011 update)	LBI-HTA	Austria	Percutaneous repair of mitral regurgitation with the MitraClip®	MitraClip®	Patients with moderate-to-severe or severe MR. Patients eligible for surgery as well as for those at high surgical risk	1 RCT (n = 279); 1 uncontrolled before-after study (n = 107)	*"Overall, the available evidence is currently insufficient to assess the efficacy and safety of MitraClip in comparison to the respective standard therapy for patients with MR. Therefore, the inclusion into the hospital benefit catalogue is not recommended, either for operable or for inoperable patients"*
2012	HTA Centre of Stockholm County Council	Sweden	MitraClip® for the treatment of severe mitral insufficiency*	MitraClip®	Patients with severe mitral insufficiency.	1 RCT (n = 279); 11 observational uncontrolled (n = 31– 202)	*"Without any study with an adequate control group and due to low quality of the assessed observational studies … the questions could not be answered whether intervention with MitraClip, compared with medical treatment of patients with severe mitral insufficiency, results in improved quality of life*

							and heart function or reduced hospitalisation and mortality. More research is necessary for further evaluation of MitraClip."
2013	FDA**	USA	MitraClip® Clip Delivery System – SSED	MitraClip®	The intended population for these studies was patients with significant symptomatic MR (≥ 3+) of either FMR or DMR aetiology that were determined to be too high risk to undergo MV surgery based upon the STS predicted procedural mortality replacement score or judgment of a cardiothoracic surgeon	1 single-arm registry (n = 78); 2 continued access registries (n = 581; n = 272) *Final recommendations were based on a cohort of 127 patients determined to be at prohibitive risk for surgical mortality*	*"In conclusion, … the data support that for the percutaneous reduction of significant symptomatic MR (≥ 3+) due to primary abnormality of the mitral apparatus (DMR) in patients who have been determined to be at prohibitive risk for MV surgery by a heart team … and in whom existing comorbidities would not preclude the expected benefit from reduction of the MR, the probable benefits outweigh the probable risk"*
2013	NHC	New Zealand	Percutaneous interventions for MR	CARILLON® Mitral Contour System®; MitraClip®	Patients with MR	CARILLON® Mitral Contour System®: 3 case series (n = 9; n= 48; n = 53) MitraClip®: 1 RCT (n = 279); 11 others (n = NR)	*On CARILLON® Mitral Contour System®:* *"The Australia New Zealand Horizon Scanning Network review in the same year also found a lack of high quality evidence supporting the device. What evidence there is suggests the approach risks coronary artery compression, mitral annulus calcification, and has a relatively high device insertion failure rate"* *On MitraClip®:* *"Current evidence suggests the procedure is safe, but less effective than surgery, cost-ineffective, and potentially significantly cost increasing. Accordingly, it is recommended that the procedure is not publicly funded in New Zealand. This is consistent with MSAC's recent decision in Australia"*
2014	BCBS	USA	Percutaneous MV repair	MitraClip®	Patients with DMR considered at high risk of surgical mortality	5 case series (n = 15–127)	*"The evidence for evaluating the MitraClip in patients with degenerative MR who are at high surgical risk is limited to case series.* *Based on the uncertainty of the mortality outcomes of patients receiving MitraClip compared with their natural history, no conclusion can be reached about the device's effect on net health outcomes"*
2014 (2012 update)	MSAC	Australia	The reduction of severe MR through tissue approximation using transvenous/ transseptal techniques	MitraClip®	Patients considered to be high risk for surgery and currently treated by medical management	20 non-comparative series (n = NR)	*"After considering the strength of the available evidence in relation to safety, effectiveness and cost-effectiveness, MSAC did not support public funding for the reduction of MR through tissue approximation using transvenous/ transseptal techniques because of uncertain*

							comparative safety, effectiveness and cost-effectiveness due to limited direct comparative data"
2015	HAS	France	Assessment of an edge-to-edge MV repair clip and its implantation	MitraClip®	Patients with mitral insufficiency	1 single-arm registry (n = 78); 9 non-comparative series (n = 51–1002)	*"In the current state of knowledge, HAS recommends limiting implantations of the MitraClip device to patients with severe degenerative mitral insufficiency which is symptomatic despite optimal medical treatment, who are not eligible for valve replacement or repair surgery and who meet the echocardiographic eligibility criteria. In this indication, HAS believes that there is no alternative and that the need is not covered. In this indication, the improvement in treatment is substantial in relation to the lack of alternatives.* *In the other indications (functional or mixed mitral insufficiency) and/or for lower surgical risks, the role of the MitraClip edge-to-edge MV repair clip in the therapeutic strategy remains undetermined"*

Key: *BCBS = Blue Cross Blue Shield Association; DMR = degenerative mitral regurgitation; FDA = US Food and Drug Administration; FMR = functional mitral regurgitation; HAS = Haute Autorité de Santé; HealthPACT = Health Policy Advisory Committee on Technology; LBI-HTA = Ludwig Boltzmann Institute for Health Technology Assessment; MR = mitral regurgitation; MSAC = Medical Services Advisory Committee; NHC= National Health Committee; NICE = The National Institute for Health and Care Excellence; NR = not reported; RCT = randomised controlled trial; SSED = Summary of Safety and Effectiveness Data; STS = The Society for Thoracic Surgeons.*

**Title translated from the original language.*

***Summary of safety and effectiveness data (SSED).*

Table 5.3: Ongoing studies on CARILLON® Mitral Contour System®.

Study Id.	Estimated completion date [status]	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02325830 REDUCE FMR	Jul 2017 [recruiting]	Interventional. Multicentre randomised with parallel assignment.	180	Percutaneous MV repair with CARILLON Mitral Contour System	No Intervention (medical management according to heart failure guidelines)	Diagnosis of dilated ischemic or non-ischemic cardiomyopathy; Functional MR: 2+ (Moderate), 3+ (Moderate/Severe), or 4+ (Severe); New York Heart Association (NYHA) II, III, or IV Six Minute Walk distance of at least 150 meters and no farther than 450 meters Left Ventricular Ejection Fraction ≤ 40% LV end diastolic dimension (LVEDD) > 55mm or LVEDD/Body Surface Area (BSA) > 3.0cm/m^2 Stable heart failure medication regimen for at least three (3) months prior to index procedure.	***Primary outcomes:*** Change in regurgitant volume associated with the CARILLON device relative to the Control population (at 12 months). ***Secondary outcomes:*** https://clinicaltrials.gov/ct2/show/NCT02325830

Source: *https://clinicaltrials.gov (accessed on 21st May 2015).*

Table 5.4: Ongoing studies on the MitraClip® System.

Study Id.	Estimated completion date [status]	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT01626079 COAPT	Aug 2020 [recruiting]	Interventional. Multicentre randomised with parallel assignment.	430	Percutaneous MV repair using MitraClip System	No Intervention (non-surgical management based on standard hospital clinical practice).	Symptomatic heart failure subjects who are treated per standard of care and who have been determined by the site's local heart team as not appropriate for MV surgery.	***Primary outcomes:*** Composite of Single Leaflet Device Attachment (SLDA), device embolizations, endocarditis requiring surgery, Echocardiography Core Laboratory confirmed mitral stenosis requiring surgery, LVAD implant, heart transplant, and any device related complications requiring non-elective cardiovascular surgery (12 months); Recurrent heart failure (HF) hospitalizations (24 months). ***Secondary outcomes:*** https://clinicaltrials.gov/ct2/show/NCT01626079
NCT02444338	Sep 2019 [recruiting]	Interventional. Multi-centre randomised.	380	MitraClip device plus optimal standard of care therapy	Standard of care therapy	Patients with chronic heart failure and clinically significant functional MR (NYHA II to NYHA IV).	***Primary outcomes:*** Cardiovascular death. ***Secondary outcomes:*** https://clinicaltrials.gov/ct2/show/NCT02444338
NCT02371512 MATTERHORN	Dec 2017 [recruiting]	Interventional. Multi-centre randomised with parallel assignment.	210	Valve repair with the MitraClip system	Reconstructive MV surgery	Advanced insufficiency of functional or ischemic origin in patients with moderate-to-severe MR of primarily functional pathology and reduced left ventricular function considered to be at high surgical risk.	***Primary outcomes:*** Composite of death, rehospitalisation for heart failure, reintervention (repeat operation or repeat intervention), assist device implantation and stroke (whatever is first) (12 months) ***Secondary outcomes:*** https://clinicaltrials.gov/ct2/show/NCT02371512
NCT02033811	Jan 2020	Observational	200	percutaneous MV repair	NA	Patients undergoing percutaneous MV repair	***Primary outcomes:***

MitraClip® Registry	[recruiting]	(Patient Registry). Cohort study.		(PMVR) with the MitraClip® system		(PMVR) with the MitraClip® system.	Major cardiac adverse events (30 days). ***Secondary outcomes:*** https://clinicaltrials.gov/ct2/show/NCT02033811
NCT01920698 MITRA-FR	Oct 2017 [recruiting]	Interventional. Multi-centre randomised with parallel assignment.	288	Percutaneous MitraClip device implantation in addition to optimal standard medical therapy	Optimal medical therapy alone	Patients with severe FMR.	***Primary outcomes:*** All-cause mortality and unplanned hospitalizations for heart failure (12 months). ***Secondary outcomes:*** https://clinicaltrials.gov/ct2/show/NCT01920698
NCT02444286 RESHAPE-HF1-FU	Jan 2017 [recruiting]	Observational. Cohort study	42	MitraClip device plus optimal standard of care therapy	Optimal standard of care therapy alone	Follow-up of patients treated for clinically significant FMR with New York Heart Association (NYHA) Functional Class III or IV chronic heart failure, former participants in the RESHAPE-HF Trial.	***Primary outcomes:*** Cardiovascular death (24 months). ***Secondary outcomes:*** https://clinicaltrials.gov/ct2/show/NCT02444286

Source: *https://clinicaltrials.gov (accessed on 21st May 2015).*

Key: *6MWT: Six minutes walk test; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVAD: left-ventricular assist device; MI: myocardial infarction; MR: mitral regurgitation; NA = not applicable.*

Afternote: on 6th August 2016, a new study on MitraClip has been added, the HiRiDe trial (NCT02534155). HiRiDe is a two-arm, multi-centre, randomised prospective study comparing MitraClip® to surgical therapy in high and intermediate risk DMR patients. The study aims to assess 30-day safety superiority and 12-month efficacy non-inferiority of the MitraClip®. The overall rate of serious adverse events and device-related serious adverse events will be assessed up to 12 months while the MR severity reduction will be assessed at 6 and 12 months in both groups. The study is currently recruiting 294 patients and will be completed within September 2017.

Conclusions

The available evidence did not allow any final statement to be reached on the relative effectiveness of the transcatheter implantable devices for MV repair in adults with moderate-to-severe and severe chronic MR. In past and oncoming studies the CARILLON® Mitral Contour System® use is essentially addressed to ischaemic and not ischaemic FMR while the MitraClip® System is addressed to FMR and prolapsing MR.

Despite the promising results showed by the only comparative study on the use of the CARILLON® Mitral Contour System®, the TITAN trial [Siminiak et al. 2012], some critical issues can be highlighted: the comparison group was created by implanting and acutely recapturing the device for clinical indications in a subgroup of the initially enrolled patients. How this procedure impacted on the outcomes observed in the comparison group is unknown. Moreover, the non-device-related mortality in this sick patient population affected the number of patients followed at 12 and 24 months; in the implanted group, follow-up was not feasible for 30.5% and 47.2% of patients at 12 and 24 months, respectively.

There is a lack of comparative evidence on the use of the MitraClip® System in high surgical risk patients with moderate-to-severe and severe MR vs standard care (either no treatment or pharmacological therapy). However, positive results from small comparative series (the EVEREST II HRR study enrolled only 78 patients and compared the outcomes with a retrospective cohort of 36 patients receiving medical therapy or surgery), case series, and national registries led some institutions to recommend the procedure in a specific subset of the potential population (patients with severe DMR who are symptomatic despite optimal medical treatment, and are ineligible for surgery [HAS 2015]). The latest European guidelines, even recognising an evidence level of "C" *(consensus of opinion of the experts and/or small studies, retrospective studies, registries)* give the same recommendations (*"may be considered in patients with symptomatic severe secondary MR despite optimal medical therapy – including CRT if indicated, who fulfil the echo criteria of eligibility, are judged inoperable or at high surgical risk by a team of cardiologists and cardiac surgeons, and who have a life expectancy greater than 1 year"*) [Vahanian et al. 2012]. It is not possible to make any conclusion, based on current evidence for patients with FMR.

As recognised by most of the authors, comparative analyses with adequate duration of follow-up are necessary to clarify the benefits–harms ratio of the 2 procedures.

CARILLON® Mitral Contour System® can be considered still at an early stage of development and shows small levels of diffusion. On the contrary, the MitraClip® System counts about

23,000 patients implanted worldwide before results from studies comparing this therapy to its claimed comparator (i.e., optimal medical therapy) have been published.

Mentioned ongoing studies on the CARILLON® Mitral Contour System® and the MitraClip® System will, in the near future, help to determine whether they are more effective and/or safe than the comparators.

6. Safety

Methods

The AEs of this domain were:

Assessment Element ID	Research question
C0008	How safe are the technologies in relation to the comparators: - What is the frequency of adverse events (AdvEs; any) of transcatheter MV repair (technology and procedure) in relation to comparators? - What is the frequency of serious AdvEs of transcatheter MV repair (technology and procedure) in relation to comparators? - What is the frequency of serious AdvEs leading to death for transcatheter MV repair (technology and procedure) in relation to comparators? - What are the most frequent AdvEs of transcatheter MV repair (technology and procedure) in relation to comparators?
C0004	Which aspects may affect the frequency and/or severity of harms?
C0005	Which patient groups are more likely to be harmed by the use of the technologies?
C0007	Are the technologies and comparators associated with user-dependent harms?

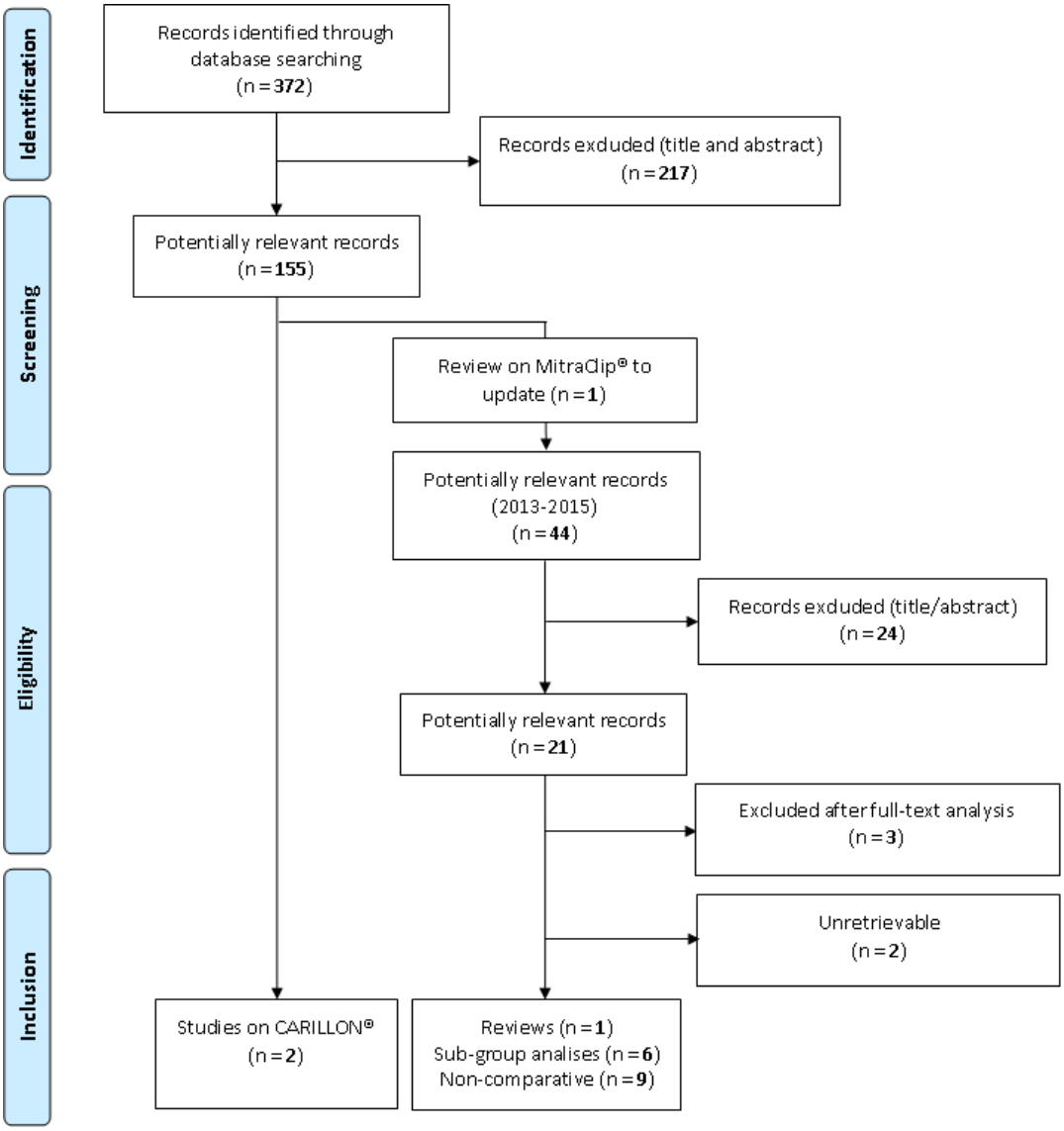
The present domain has been developed using methods and results of the 5th Pilot produced within EUnetHTA JA2 WP5-B activities [EUnetHTA JA2 Pilot SB-15].

Evidence analysis for Safety domain has been structured according to the PICO defined in Table 5.1 with the exception for the study design criteria. Other than the designs considered for Clinical Effectiveness analysis, case series and medical devices adverse events registries were also considered. Literature searches for safety evidence were conducted together with the ones for clinical effectiveness and reported in the Appendix 4. Two reviewers (MC and AM) independently screened the title and/or abstracts of all the records to identify those potentially relevant for the analysis. Differences were solved through discussion and disagreements were managed by involving a third reviewer (MRP). The full text of identified records were retrieved and analysed to include those that met predefined inclusion criteria. Included studied were analysed and safety data were extracted by one reviewer and checked by the other for the analysis of safety profile of the two devices assessed. The R-AMSTAR tool, developed by Kung et al. at the UCLA School of Dentistry, Los Angeles, California, was used for systematic reviews; the criteria from the Cochrane Handbook for Systematic Reviews of Interventions [Higgins et al. 2011] were chosen to assess the methodological quality of RCTs and CCTs and the 18-items checklist developed by the IHE (Canada) was used for case series and cohort studies [Moga et al. 2012].

Results

Among 372 records identified by the literature search, 18 studies (1 secondary study and 17 primary studies) were included to assess the safety of the CARILLON® Mitral Contour System® and the MitraClip® System. The inclusion process is graphically represented as a PRISMA flow diagram in Figure 6.1.

Figure 6.1: Flow-chart of the studies for safety assessment according to PRISMA. Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.



Secondary studies

One systematic review on the MitraClip® System was included in the assessment of safety, which was the most recently published systematic review that met the inclusion criteria. The review was updated within the present assessment [Munkholm-Larsen et al. 2014].

In regards to CARILLON® Mitral Contour System® the same secondary studies used in the Clinical Effectiveness domain were assessed for inclusion in Safety domain; the justification for their exclusion is explained in detail in the chapter on Clinical Effectiveness (see Chapter 5).

Primary studies

The studies screened for their inclusion in the safety analysis were the same as those considered in the Clinical Effectiveness domain, but they did not meet the inclusion criteria for the present assessment [EUnetHTA JA2 Pilot SB-15]. Additional cohort, case series, and registry studies were reviewed to see whether they met the criteria for inclusion in the Safety domain.

The included systematic review on the MitraClip® System [Munkholm-Larsen et al. 2014] was updated; so primary studies published from 2013 to 2015 were screened to identify new evidence on the use of the MitraClip® System. In total, 44 studies were identified as potentially relevant, 15 of which were included [Alegria-Barrero et al. 2014; Armoiry et al. 2013; Attizzani et al. 2015; Bozdag-Turan et al. 2014; Braun et al. 2014; Glower et al. 2014; Hellhammer et al. 2014; Hellhammer et al. 2015; Koifman et al. 2014; Reichenspurner et al. 2013; Rudolph et al. 2014; Toggweiler et al. 2014; Vandendriessche et al. 2014; Wiebe et al. 2014; Yeo et al. 2014].

All 155 potentially relevant records were screened to identify evidence for CARILLON® Mitral Contour System®. Two studies were included [Schofer et al. 2009; Siminiak et al. 2012].

In conclusion, 17 primary studies were included for safety assessment.

All included studies were prospective, cohort studies in which all patients underwent the procedure with the CARILLON® Mitral Contour System® or the MitraClip® System. Ten studies assessing the MitraClip® device were analyses of registries. Subgroups analyses assessing safety and clinical outcomes in groups of patients with different clinical characteristics were performed in 8 studies (all on the MitraClip® System). Ten studies were multicentre (2 studies on CARILLON® Mitral Contour System®; 8 studies on MitraClip® System) and one study was from a single centre.

Safety results reported in the included studies were extracted and tabulated; a narrative description is provided below.

Description of available evidence on CARILLON® Mitral Contour System®

Primary studies

In the prospective, multicentre, single-arm study by Schofer et al. [Schofer et al. 2009], patients with dilated ischaemic or non-ischaemic cardiomyopathy and moderate-to-severe FMR were included. Thirty of the 48 patients enrolled into the AMADEUS study received the CARILLON® Mitral Contour System® device. No implantation was attempted in 5 patients for varying clinical reasons and the implant was recaptured in 13 patients. Safety was evaluated according to the 30-day rate of MAEs (Major Adverse Events) defined as the composite endpoint of death, MI, cardiac perforation requiring catheter-based or surgical intervention, device embolisation, or the occurrence of surgery or percutaneous coronary intervention related to device failure. Safety outcomes were measured as the number of AdvEs in the total intention-to-treat patient population (46 patients; 2 patients withdrew from the study before the 30-day follow-up). Six patients experienced a total of 7 MAEs including one patient who was dead at 30-day of follow-up. Durability of the device was not assessed (see Table 6.1).

The study by Siminiak et al. [Siminiak et al. 2012] presented results of the TITAN trial designed on the basis of the previously described feasibility study [Schofer et al. 2009]. The detailed description of the study is reported in the Clinical Effectiveness section (see Section 4.2) [EUnetHTA JA2 Pilot SB-15]. Safety was defined as the 30-day composite of death, MI, cardiac perforation, device embolisation, or surgery for device failure. The safety findings at the 30-day and 12-month follow-up referred to the overall intent-to-treat population (53 patients) without distinguishing between intervention or comparison groups, except for the death endpoint that was estimated either for the implanted cohort (36 patients) or for the comparison cohort (17 patients). The only safety data at 24 months refers to the number of deaths in the implanted cohort [EUnetHTA JA2 Pilot SB-15]. All safety endpoints were measured as ratio of number of AEs and intent-to-treat population. Safety findings are reported in Table 6.1; the 30-day MAE rate in the overall intent-to-treat population was 1.9%. At 12 months there were 8 deaths in the implanted group (22.2%) and 4 deaths in the device recaptured group (23.5%). Between 12 and 24 months further, 3 not device related deaths occurred.

Table 6.1: Safety findings from included primary studies – CARILLON® *Mitral Contour System®*

Study [ref.]	Number of patients	Follow up	Main safety findings		Limitations of the study (as acknowledged by study authors)	Authors' conclusions
			Safety results	***n/N (%)***		
Schofer et al. (AMADEUS trial) [Schofer, 2009]	48 patients	30 days	*Death*	*1/46 (2.2)*	*First-in-human feasibility and safety trial, lack of a randomised, blinded control group.*	*"Percutaneous reduction in FMR with a novel coronary sinus–based mitral annuloplasty device is feasible in patients with heart failure, is associated with a low rate of major adverse events, and is associated with improvement in quality of life and exercise tolerance. Further studies are required to define the long-term efficacy of the therapy, optimal timing for intervention, and effects on survival."*
			Myocardial infarction§	*3/46 (6.5)*		
			Cardiac perforation necessitating catheter based or surgical intervention§	*3/46 (6.5)*		
			Device embolization	*0/46 (0)*		
			Device failure requiring surgical or percutaneous coronary intervention	*0/46 (0)*		
			Total major adverse events	*7/46 (15.2)*		
Siminiak et al. (TITAN Trial) [Siminiak, 2012]	53 *(36 permanent, group A; 17 recaptured, group B)*	30 days; 12 months; 24 months	*Death (30 days)*	*A: 0/36 (0)* *B: 1/17 (16)*	*Lack of a randomised and blinded comparator.*	*"This study demonstrates that percutaneous CS-based mitral annuloplasty can significantly and safely reduce FMR severity in HF patients, resulting in significant LV reverse remodelling over 12 months and improved measures of clinical outcome over 24 months. The lack of a randomized and blinded comparator remains the primary limitation of the study. As such, a randomized trial comparing intervention with a medically managed control group is warranted."*
			Death (12 months)	*A: 8/36 (22.2)* *B: 4/17 (23.5)*		
			Death (24 months)*	*A: 3/n.r. (n.a.)* *B: n.a.*		
			Myocardial infarction *(30 days)* *(12 months)*	 *0/53 (0)* *2/53 (4)*		
			Cardiac perforation *(30 days)* *(12 months)*	 *0/53 (0)* *0/53 (0)*		
			Device embolization *(30 days)* *(12 months)*	 *0/53 (0)* *0/53 (0)*		
			Surgery due to device *(30 days)* *(12 months)*	 *0/53 (0)* *0/53 (0)*		
			Overall MAE rate *(30 days)* *(12 months)*	 *1/53 (1.9)* *14/53 (26.4)*		

§: not specified if the adverse event is caused by the procedure or by the device.
**Safety data at 24 months follow up refer only to the intervention group.*

Key: *FMR, functional mitral regurgitation; MAE, Major Adverse Events; n.r., not reported; n.a., not applicable; CS, coronary sinus; HF, heart failure; LV, left ventricular.*

Although the study by Siminiak [Siminiak et al. 2012] assessed the safety outcomes in 2 cohorts of patients, one with successfully implanted with CARILLON® Mitral Contour System® and one with patients in whom the implanted device was recaptured for clinical indications, the evidence available is not sufficient to assess the safety of CARILLON® Mitral Contour System® in comparison with pharmacological therapy (with or without CRT) exhaustively [EUnetHTA JA2 Pilot SB-15]. All safety findings reported refer to the overall intention-to-treat population without distinguishing between the intervention and comparator cohorts, except for the endpoint "death" measured at 30 days and 12 months of follow-up. The incidence of deaths was lower in the implanted group at 30 days, with 0% (0/36 patients) vs 6% (1/17 patients), as well as at 12 months, with 22.2% (8/36) vs 23.5% (4/17 patients). However, the different safety findings in the 2 groups were not statistically analysed because of the small number of complications that occurred at 30-days' follow-up (C0008). Available evidence on this novel device did not address specifically the aspects that may affect the frequency and/or severity of harms. However, one study [Schofer et al. 2009] reported that two MAEs (CS perforations) occurred early in the study (first and fourth patient) confirming that there is a learning curve to access the CS. Therefore, risks associated with this therapy are expected to decrease with improved procedural skills and experience. In addition, careful assessment of coronary arterial flow is important to successfully recapture or reposition the system when a compromised coronary artery was observed (C0004). Hence the analysis of the available evidence [Schofer et al., 2009] showed that there is a learning curve for accessing the CS safely; careful management of high surgical risk patients and acquisition of procedural skills are necessary to lower the risks associated with this device. Furthermore, experience-based skills related to the assessment of coronary arterial flow are crucial for recapturing and repositioning the device successfully and safely.

No other evidence was found to answer the research question (C0007). The available evidence did not allow to identify possible patient groups more likely to be harmed by using CARILLON® Mitral Contour System®. The cohort size in the 2 included studies was small (range 48–53 patients) and seemed to overlap. In addition, subgroup analyses were not undertaken. One study [Schofer et al. 2009] pointed out that neither demographic nor echocardiographic parameters were clearly predictive of procedural success. Instead, the procedural steps of placing the device further distal in the CS/GCV and applying more traction to plicate more tissue were associated with procedural success (C0005).

Description of available evidence on MitraClip® System

Secondary studies

One systematic review [Munkholm-Larsen et al. 2014] met the inclusion criteria; it included 12 prospective observational studies assessing the MitraClip® System in high surgical risk patients with significant MR. No RCTs were identified. With the exception of 3 studies that had 202, 117, and 100 patients, respectively, all other studies included fewer than 100 patients (range 16–85). Seven studies had a median follow-up of 1 year. Three studies had a median follow-up of 6 months. Only 1 study reported outcomes beyond 12 months. Safety outcomes across studies following implantation of the MitraClip® System for high surgical risk patients, included 30-day mortality, cerebrovascular accident, need for early mitral surgery, cardiac tamponade, trans-septal complications, partial clip detachment and transfusion of ≥ 2 units of packed red blood cells. The implantation of the MitraClip® System is an option for managing selected high surgical risk patients with severe MR.

Primary studies

In the non-comparative study by Alegria-Barrero et al. [Alegria-Barrero et al. 2014], 43 consecutive patients with severe DMR or FMR (MR 3+ or 4+) and high surgical risk (as defined by logEuroSCORE) ineligible for conventional MV repair underwent the MitraClip® System implantation. MAEs at 12 months were defined as a composite of cardiovascular mortality, MI, unplanned cardiac surgery, transfusion of more than 2 U of blood, and hospitalisation for HF [EUnetHTA JA2 Pilot SB-15]. Forty of the 43 patients enrolled were successfully implanted (overall procedural success of 93%) with 21 receiving one clip (group 1) and 19 receiving more than one clip (group 2). MAEs occurred in 5 patients of forty (12%) with successful clip implantation. One patient in group 2 with previous MV repair underwent surgical bailout MV repair after the MitraClip® implantation was unable to reduce the degree of MR. No other MAEs peri-procedurally nor 30-day mortality were recorded. Three patients in group 2 and 1 patient in group 1 died at 12 months follow-up because of HF related to dilated cardiomyopathy (all patients had FMR). Safety findings are reported in Table 6.2.

In the multicentre cohort study by Armoiry et al. [Armoiry et al. 2013], short- and mid-term safety and efficacy results in 62 patients with FMR (73.8%), DMR (23.0%) or mixed MR (3.2%) who underwent a MitraClip® System procedure in 7 French centres between 2010 and 2012 were reported. All patients were judged ineligible for surgery or at high surgical risk by a heart team. Patient data were collected and recorded in a multicentre national registry. Safety was evaluated and described by the occurrence of in-hospital deaths, in-hospital surgical MV repairs, and other non-fatal AdvEs, as well as by the proportion of per procedural blood

transfusions. In-hospital events were events occurring during the hospital stay for the MitraClip® System procedure. The 6-month survival rate was also estimated [EUnetHTA JA2 Pilot SB-15]. In-hospital death occurred in 2 patients with FMR (3.2%). Two other surgical MV repairs were required after the MitraClip® procedure (patients with FMR). Other non-fatal AdvEs were observed in 7 patients (11.3%): 1 clip was implanted in the wrong position in the subvalvular apparatus, 1 deep venous thrombosis, 1 bleeding at puncture site, 1 new-onset atrial arrhythmia, 1 acute febrile respiratory illness, 1 false aneurysm at venous puncture site and 1 tamponade. Peri-procedural blood transfusion was necessary in 5 patients (8.1%). No cases of stroke or myocardial infarction were reported. After 6 months, the survival rate was 83.1% (see Table 6.2).

In the non-comparative, non-randomized study by Attizzani et al. [Attizzani et al. 2015], 171 patients with severe MR (3+ or 4+) at high surgical risk (as judged by an interdisciplinary medical team) undergoing the MitraClip® implantation in 1 Italian centre (University hospital) between 2008 and 2013 as part of the ongoing GRASP (Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation) registry were investigated. The primary safety endpoint was the incidence of MAEs at 30 days defined as the composite of death, MI, reoperation for failed the MitraClip® implantation, non-elective cardiovascular surgery for AdvEs, stroke, renal failure, deep wound infection, mechanical ventilation for > 48 h, gastrointestinal complication requiring surgery, new onset of permanent atrial fibrillation (AF), septicaemia, and transfusion of 2 U of blood. In this study patients were divided in 2 groups: 78 patients that did not fulfill echocardiographic eligibility criteria of EVEREST I and II studies formed the investigational group (i.e. $EVEREST_{OFF}$ group) whereas 93 patients meeting these criteria represented the control group (i.e. $EVEREST_{ON}$ group). Thirty-day follow-up data were available for all enrolled patients. MAEs were reported in 8 patients, 2 patients (2.6%) in the $EVEREST_{OFF}$ group and 6 (6.5%) in the $EVEREST_{ON}$ group ($p = 0.204$) including 1 death (1.3%) in the first group and 2 deaths (2.2%) in the latter one ($p = 0.566$). At 12 months, follow-up data from 154 patients (90%) were available and safety data related to the number of deaths and MV surgery were reported. No surgical valve repair intervention was required while 11 (15.7%) patients died in the $EVEREST_{OFF}$ group and 9 (10.7%) in the $EVEREST_{ON}$ group ($p = 0.358$) as reported in Table 6.2.

The single-centre study by Bozdag-Turan et al. [Bozdag-Turan et al. 2014], investigated a cohort of 121 patients with severe MR (≥ 3+) at high surgical risk according to logEuroSCORE and the STS mortality risk calculation, undergoing the MitraClip® implantation. Clinical data and outcomes of patients were collected and recorded in a prospective single-centre registry.

Evaluation of the clinical and safety endpoint was carried out at the 12-month follow-up. In particular, data concerning re-interventions and major adverse cardiac and cerebrovascular events (MACCE) were reported [EUnetHTA JA2 Pilot SB-15]. This study reported that 38 patients (31.4%) experienced a MACCE 12 months after the procedure while 9 patients (7.4%) underwent MV surgery. During the follow-up period 28 patients died, 4 of them at 30 days after the procedure. No patient died during the procedure despite the high surgical risk level. Patients were allocated to 2 groups according to their left ventricular functionality (patients with LVEF ≤30 and patients with LVEF >30), and a stratified analysis of the outcomes was performed (see Table 6.2).

In the study by Braun et al. [Braun et al. 2014], 119 patients, with symptomatic MR at high surgical risk or who declined surgery, were enrolled to undergo percutaneous edge-to-edge repair of MV with the MitraClip® System between 2009 and 2012. The outcomes of patients with DMR (n = 72) compared to patients with FMR (n = 47) were analysed. In both groups, more than 50% of patients did not meet the eligibility criteria of the EVEREST II trial representing a real-world sample. In terms of safety, data on MV re-intervention and death after 12 months following MitraClip® implantation were recorded [EUnetHTA JA2 Pilot SB-15]. In this study outcome data were available for 113 patients (95%) at follow-up. Ten patients (all from DMR group) underwent conventional mitral surgery while 5 patients (4 from DMR group and 1 from FMR group) underwent second clipping. No procedural death was observed. However, 2 patients died within a few days after successful clipping (1 from FMR group while it is not clear if the other patient was from FMR or DMR group. Two patients experienced complications related to the procedure: gastrointestinal bleeding occurred in 1 patient with DMR and myocardial infarction in 1 patient with FMR. Safety findings are reported in Table 6.2.

The study by Glower et al. [Glower et al. 2014] was a prospective, multicentre evaluation of the safety and effectiveness of the MitraClip® System in 351 patients with symptomatic MR (MR grades 3+ to 4+) at high surgical risk (≥ 12%, estimated using the STS calculator or by a surgeon co-investigator according to pre-specified criteria) with 12-months' follow-up. Analyses included patient data from both the EVEREST II prospective registries of high surgical risk patients: EVEREST II HRR and REALISM HR [EUnetHTA JA2 Pilot SB-15]. Among 351 patients enrolled in both the EVEREST II HRR and REALISM HR, 342 patients (97.4%) had 30-day follow-up and 327 patients (93.2%) had 1-year follow-up. Death occurred in 4.8% (17/351) patients at 30 days with no death related to a device malfunction. MAEs occurred in 66 patients of 351 (18.8%) mostly consisting of blood transfusions ≥2 U occurring in 13.4% of

patients (47/351). Nine strokes were reported none of which was due to device or air embolization. Major vascular complications were infrequent, occurring in 12 patients (3.4%). At 1 year 80 patients had died (22.8%), MAE rate was 37.6% (132/351), with the most common event being blood transfusions (79 patients among 351, 22.5%), and 3 additional strokes occurred. The rate of device-related complications was low through 12 months: single-leaflet device attachment occurred in 8 patients, with most (6) in the early phase (<30 days); MV surgery occurred in 3 patients while a second MitraClip procedure was performed in 4 patients during 30 days after the first procedure. No device embolization occurred. See Table 6.2.

A study by Hellhammer et al. [Hellhammer et al. 2014] reported on a sub-analysis of the MitraClip® Registry (NCT02033811) concerning high surgical risk patients with diabetes mellitus. Among 58 patients with symptomatic severe and moderate-to-severe MR enrolled, 19 (32.8%) had diabetes mellitus II. Primary safety endpoints comprised clip implantation, in-hospital complications, and 30-day mortality [EUnetHTA JA2 Pilot SB-15]. The authors reported that MitraClip has been implanted successfully in all 19 patients with diabetes (100%) and in 38 of 39 no diabetic patients (97.4%). In-hospital complications occurred in 10 patients (1 with diabetes mellitus II and 9 non-diabetic patients). No patient died in the diabetes group while 1 death occurred in the non-diabetes group during 30 days after the procedure. No death was reported in either group during 3 months after the implantation procedure. Thus, due to a low mortality (at 30 days and 3 months) and few overall complications, the safety of the procedure was demonstrated even in the diabetes patients group. Safety findings are reported in Table 6.2.

Another study by Hellhammer et al. [Hellhammer et al. 2015] aimed to assess the impact of anaemia on peri-procedural MACCE and mortality in patients undergoing treatment of severe MR using the MitraClip® System. A total of 80 patients were included in the study, all of whom were at high surgical risk (logEuroSCORE ≥ 20% or pre-existing conditions). Anaemia was assessed at baseline and 2 groups were defined: 41 (51.3%) patients presented with anaemia, whereas 39 (48.7%) had normal erythrocyte levels. As reported in Table 6.2, mortality at 30 days did not show a statistically significant difference (2.4% in patients with anaemia and 5.1% in patients without anaemia; p = 0.611). Groups did not differ in terms of in-hospital complication rates. MACCE rate (including death, myocardial infarction, stroke, and procedure related re-operation) was 4.9% (n = 2) and 5.1% (n = 2) in the two groups (p = 0.959). The need for preoperative and postoperative transfusion did not differ between groups.

The study by Koifman et al. [Koifman et al. 2014] reported a single-centre experience in Israel. From 2011, 20 high surgical risk patients with at least moderate-to-severe MR with HF symptoms were considered eligible for the MitraClip® implantation [EUnetHTA JA2 Pilot SB-15]. The procedure was halted in 1 patient due to inability to achieve MR reduction, leaving 19 patients successfully implanted. Patients were discharged at a mean of 2.8 ± 3.5 days post-implantation, 13 (65%) were discharged on the day after the procedure, but a number of patients had longer hospitalisation periods. Notably, 4 patients were hospitalised for more than 5 days (2 patients developed fever; 1 patient had a large femoral artery pseudo-aneurysm; 1 patient continued to suffer from intractable HF and thrombocytopenia and died following a massive stroke 2 weeks after clip implantation). Among 18 patients with successful reduction of MR surviving to discharge, 2 patients died, 1 due to HF 7 months post-procedure and the other to non-cardiac causes 6 months post-procedure (see Table 6.2).

The study by Reichenspurner et al. [Reichenspurner et al.2013] reported on the results of a sub-group of patients within the MitraClip Therapy Economic and Clinical Outcomes Study Europe (ACCESS-EU) study, a post-approval study designed to gain information on the use of the MitraClip® System in the EU with respect to health economics and clinical care, and to provide further evidence on the safety and effectiveness of the MitraClip® in a real-world setting. The subgroup limited to moderate-to-severe (MR 3+) or severe (MR 4+) DMR patients consisted of 117 of the overall 567 patients in the ACCESS-EU study. Those patients were then stratified according to LogEuroSCORE of high and low surgical risk [EUnetHTA JA2 Pilot SB-15]. The authors reported that within 30 days, the overall incidence of AEs was 17.9% (21/117), with 27.3% (9/33) and 14.3% (12/84) for high- and low-risk subgroups, respectively. This included 3 patients requiring valve re-intervention. Mortality at 30 days was 6.0% (7/117) with 9.1% (3/33) and 4.8% (4/84) for high- and low-risk subgroups, respectively. Causes of death were classified as cardiac in 42.9% (3/7) of cases as determined by the sites. At 12 months, the overall incidence of AdvEs in the entire cohort was 41.0% (48 of 117). This included 13 patients undergoing repeated valve intervention. Mortality at 12 months was 17.1% (20 of 117) for the entire cohort and 24.2% (8/33) and 14.3% (12/84) for high-risk and low-risk subgroups, respectively. Causes of death were classified as cardiac in 45% (9/20) cases as determined by the sites. Safety findings are reported in Table 6.2.

The study by Rudolph et al. [Rudolph et al. 2014] presented a subgroup analysis of patients from the German TRAMI registry (only prospectively enrolled), stratified by NYHA functional class. Among the 803 patients enrolled, 143 (17.8%) had NYHA class IV, 572 (71.2%) NYHA class III, and 88 (11.0%) NYHA class I or II. As reported in Table 6.2 with only 1 fatal event

observed, procedural mortality was judged as very low, with no differences between groups. The number of transfusions/severe bleeding increased significantly with NYHA functional class (NYHA IV, 13.6% vs NYHA III, 6.3% vs NYHA I/II, 3.4%; $p < 0.01$), as did the number of transient ischaemic attacks (NYHA IV, 3.6% vs NYHA III, 0.5% vs NYHA I/II, 0.0%; $p < 0.01$). Moreover, duration of ventilation and intensive care unit stay were longer in patients with high NYHA class. A higher percentage of patients in NYHA IV required ≥3 days until mobilisation (NYHA IV, 11.7% vs NYHA III, 6.4% vs NYHA I/II, 2.3%; $p < 0.05$). Patients in NYHA class IV were less frequently discharged (80.0% vs 90.4% vs 95.3%; $p < 0.001$). In-hospital mortality did not differ between groups.

The study by Toggweiler et al. [Toggweiler et al. 2014] reported on 74 patients included in the Swiss MitraSWISS registry between 2009 and 2011. All patients had moderate-to-severe (MR 3+) or severe (MR 4+) FMR and DMR and were considered at high surgical risk defined by a logEuroSCORE > 15% and/or additional surgical risk factors [EUnetHTA JA2 Pilot SB-15]. The authors reported intra-procedural complications in 3 patients (4%) making clip implantation unfeasible. Six patients (8%) had bleeding requiring transfusion, and 1 (1%) patient had a pericardial tamponade after rupture of the left atrium. No strokes occurred at 2 years post-procedure. Overall, in-hospital mortality was 4.1% (3/74). At 2 years, partial clip detachment had occurred in 7 (10%) patients (within the first 30 days in 4 patients; between 30 days and 1 year in 2 patients; 1 patient had clip detachment 2 years post procedure). In 5/7 (71%) patients, partial clip detachment resulted in 3+ or 4+ MR and the procedure was repeated in 5 patients, whereas the remaining 2 were treated medically. The re-do procedure reduced MR to moderate in 2/5 (40%) patients while the remaining 3 patients had persistent moderate-to-severe or severe MR. Safety findings are reported in Table 6.2.

The study by Vandendriessche et al. [Vandendriesscheet al. 2014] reported on the prospective Belgian registry aimed to collect data on the use of the MitraClip® System in high surgical risk patients with HF and severe MR. A total of 41 patients were treated from 2010 to 2013. All patients had FMR and cardiomyopathy or annular dilatation; one patient presented with mixed aetiology [EUnetHTA JA2 Pilot SB-15]. In-hospital MAEs occurred in 5 patients (12%). One in-hospital death due to intracranial bleeding was observed, 2 additional major bleeding (1 requiring urgent surgery), and 2 patients needed to undergo urgent cardiac surgery (see Table 6.2).

The study by Wiebe et al. [Wiebe et al. 2014] reported on the non-randomised German TRAMI Registry, fed by 15 centres retrospectively from 2009 to 2010 and prospectively up to 2013.

Outcomes of a total of 1,002 patients were reported. Baseline echocardiographic data indicated 627 patients with FMR, however, it is noteworthy that the missing data rate for this criterion was 13%. A clustered analysis by surgical risk assessed on the logEuroSCORE (high risk if ≥ 20) indicated 557 patients (55.6%) were at high surgical risk [EUnetHTA JA2 Pilot SB-15]. In-hospital MACCE rate (including mortality, stroke, and myocardial infarction) was 4.9% (27/546) in high surgical risk patients. The major in-hospital complications rate was 19.4% (108/557) while the minor in-hospital complications rate was 13.8% (77/557). Other complications were observed in 17.8% of cases (97/546). Days at Intensive Care Unit ranged from 1–2 while the mean hospital stay was 10 days (6–17). Safety findings are reported in Table 6.2.

The study by Yeo et al. [Yeo et al. 2014] reported on the MitraClip® Asia-Pacific Registry (MARS). The data were collected retrospectively. The series comprised high surgical risk DMR patients and symptomatic FMR patients treated from 2011 to 2013 in 5 countries. A total of 142 patients were observed [EUnetHTA JA2 Pilot SB-15]. As reported in Table 6.2, 30-day mortality rate was 5.6% (n = 8), of which 4.2% (n = 6) was in-patient mortality. The 30-day MAE rate was 12.7% (18/142). One patient (0.7%) underwent a MV reoperation, 5 patients (3.5%) had blood transfusion of ≥ 2 U, 2 patients (1.4%) developed sepsis, 1 patient (0.7%) had prolonged intubation, and 1 patient (0.7%) was readmitted for HF. No cases of device embolization were observed. No statistically significant difference was observed in MAE rate between FMR (6.2%, 7/76) and DMR (15.4%, 10/65) patients (p = 0.306).

Table 6.2: Safety findings from included primary studies – MitraClip® System

Study [ref.]	Number of patients	Follow up	Main safety findings		Limitations of the study (as acknowledged by study authors)	Authors' conclusions
			Safety outcomes reported	***n/N (%)***		
Alegria-Barrero et al. [Alegria-Barrero, 2014]	43 *(40 successfully implanted: 21 with 1 clip, group A; 19 with ≥2 clips, group B)*	30 days;12 months	*Mortality rate at 12 months*	*A: 1/21 (4.7)* *B: 3/19 (15.8)*	*Relatively small number of patients recruited.*	*"MitraClip® was shown to be a safe treatment for patients with severe functional and degenerative MR"*
			Major procedural complications	*A: 0/21 (0)* *B: 1/19 (5.3)*		
Armoiry et al. [Armoiry, 2013]	62	In-hospital	*In-hospital mortality rate*	*2/62 (3.2)*	*Missing data corresponding to variables not reported from each centre; mid-term follow-up data available for a limited number of patients.*	*"The preliminary data of our registry are encouraging in terms both efficacy and safety and may solve the unmet need in patients who are ineligible for conventional surgery". However "randomized control trials are mandatory to confirm these preliminary data"*
			Surgical MV repairs after the MitraClip procedure	*2/62 (3.2)*		
			Other non-fatal AEs (wrong clip positioning, deep venous thrombosis, bleeding at puncture site, new-onset of atrial arrhythmia, acute febrile respiratory illness, false aneurysm at venous puncture site and tamponade)	*7/62 (11.3)*		
			Procedural blood transfusion	*5/62 (8.1)*		
			Stroke	*0/62 (0)*		
			Myocardial infarction	*0/62 (0)*		
Attizzani et al. [Attizzani, 2015]	171 *(78 not fulfilling echocardiographic eligibility criteria of EVEREST I and II studies, $EVEREST_{OFF}$ group; 93 meeting these criteria, $EVEREST_{ON}$ group)*	30 days; 12 months	*MAEs (including death) at 30 days (P=0.204)*	*$EVEREST_{OFF}$: 2/78 (2.6)* *$EVEREST_{ON}$: 6/93 (6.5)*	*No randomized control group, small sample size with limited follow-up, 12 month follow up echocardiographic parameters could have been influenced by survival bias, 12 month follow-up data were available for 90% of enrolled patients, study setting was a centre performing high volume of Mitraclip implantation per year.*	*"Favorable safety rates previously demonstrated for this relatively novel procedure could be reproduced in more complex settings"* suggesting *"a potential room for expanding the indication of MitraClip® implantation in high risk surgical patients beyond the EVEREST studies' eligibility criteria; nevertheless, additional research with longer follow-up an larger sample sizes are mandatory before any formal recommendation"*
			Mortality rate at 30 days (P=0.566)	*$EVEREST_{OFF}$: 1/78 (1.3)* *$EVEREST_{ON}$: 2/93 (2.2)*		
			Mortality rate at 12 months (P=0.358)	*$EVEREST_{OFF}$: 11/70 (15.7)* *$EVEREST_{ON}$: 9/84 (10.7)*		
			Surgery for MV dysfunction at 12 months (P=n.r.)	*$EVEREST_{OFF}$: 0* *$EVEREST_{ON}$: 0*		
Bozdag-Turan et al.	121 *(38 with EF≤30; 83 with*	12 months	*MACCE at 12 months (P=0.38)*	*EF≤30: 14/38 (36.8)* *EF>30: 24/83 (28.9)*	*N.r.*	*"Percutaneous edge- to-edge repair could be safely performed with good*

[Bozdag-Turan, 2014]	*EF>30)*			*All: 38/121(31.4)*		*clinical and echocardiographic results in surgical high risk patients with or without severe impaired systolic left ventricular function"*
			Mortality rate 12 months (P=0.051)	*EF≤30: 13/38 (34.2)* *EF>30: 15/83 (18.1)* *All: 28/121(23.1)*		
			Myocardial infarction at 12 months (P=0.18)	*EF≤30: 2/38 (5.3)* *EF>30: 1/83 (1.2)* *All: 3/121(3.4)*		
			Cerebro-vascular accident at 12 months (P=n.r.)	*EF≤30: 0/38 (0)* *EF>30: 0/83 (0)* *All: 0/121(0)*		
			Major bleeding at 12 months (P=0.13)	*EF≤30: 4/38 (10.5)* *EF>30: 3/83 (3.6)* *All: 7/121(5.8)*		
			MV surgery total at 12 months (P=0.035)	*EF≤30: 0/38 (0)* *EF>30: 9/83 (10.8)* *All: 9/121(7.4)*		
Braun et al. [Braun, 2014]	119 *(72 with DMR, 47 with FMR)*	12 months	*Conventional mitral surgery after Mitraclip procedure at 12 months*	*DMR: 10/n.c.* *FMR: 0/n.c.*	*Relatively small patient population, lack of follow-up data, subjectivity of echocardiographic MR quantification after clip implantation.*	*"Percutaneous edge- to-edge repair of MV is feasible in patients with degenerative as well as functional MR". However "Randomized controlled trial comparing MitraClip® therapy in high risk patients to medical therapy as well as MV surgery are necessary to clarify the future role of this novel method".*
			Second MV clipping at 12 months	*DMR: 4/n.c.* *FMR: 1/n.c.*		
			Procedural deaths	*DMR: 0/n.c.* *FMR: 0/n.c.*		
			Post-procedural deaths	*DMR:1/n.c.* *FMR: 1/n.c.*		
			Procedure related complications	*DMR: 1/n.c.* *FMR: 1/n.c.*		
Glower et al. [Glower, 2014]	351 *(105 with DMR and 246 with FMR)*	30 days; 1 year	*Mortality rate at 30 days*	*All: 17/351 (4.8)* *DMR: 7/105 (6.7)* *FMR: 10/246 (4.1)*	*Patient group was narrowly defined, short term data, no surgical or medical control group, possibly placebo effect due to medical therapy prior to device implantation.*	*"MV device is feasible and relatively safe and is effective (…) in this high-risk group of patients who are unlikely to receive surgery and essentially have no other option to reduce MR".*
			MAEs at 30 days	*All: 66/351 (18.8)* *DMR: 19/105 (18.1)* *FMR: 47/246 (19.1)*		
			*Stroke at 30 days**	*All: 9/351 (2.6)*		
			Major bleeding complications at 30 days	*DMR: 19/105 (18.1)* *FMR: 47/246 (19.1)*		
			*Blood transfusions ≥2U at 30 days**	*All: 47/351 (13.4)*		
			Mortality rate at 1 year	*All: 80/351 (22.8)* *DMR: 25/105 (23.8)* *FMR: 55/246 (22.4)*		
			MAEs at 1 year	*All: 132/351 (37.6)* *DMR: 38/105 (36.2)*		

				FMR: 94/246 (38.2)		
			*Stroke at 1 year**	*All: 12/351 (3.4)*		
			*Blood transfusions ≥2U at 1 year**	*All: 79 /351 (22.5)*		
			*Single leaflet device attachment rate (device related complication) at 1 year**	*All: 8/351 (2.28)*		
			*MV surgery (device related complication) at 1 year**	*All: 3/351 (0.9)*		
			*Second Mitraclip procedure (device related complication) at 1 year**	*All: 4/351 (1.1)*		
			*Mitraclip embolization (device related complication) at 1 year**	*All: 0/351 (0)*		
			*MV stenosis (device related complication) at 1 year**	*All: 3/351 (0.9)*		
Hellhammer et al. [Hellhammer, 2014]	58 *(19 with diabetes mellitus II, 39 without diabetes mellitus II)*	30 days; 3 months	*Mortality rate at 30 days (P=0.672)*	*Diabetes: 0/19 (0)* *No diabetes: 1/39 (2.6)*	*Short follow-up, small size population, no randomized study.*	*"MitraClip® system is safe and event rates are low." However "a prospective randomized study with more patients and longer follow follow-up time was necessary".*
			Successful clip implantation rate (P=0.672)	*Diabetes: 19/19 (100)* *No diabetes: 38/39 (97.4)*		
			In-hospital complications (MACCE, peripher vascular complications, stroke, pacemaker damage, sepsis, ventilation>24 h, acute kidney injury stage III, major bleeding)	*Diabetes: 1/19 (5.3)* *No diabetes: 9/39 (23.1)*		
			MV surgery (P=0.672)	*Diabetes: 0/19 (0)* *No diabetes: 1/39 (2.6)*		
Hellhammer et al. [Hellhammer, 2015]	80 *(41 with anaemia, group A; 39 with normal erythrocyte levels, group B)*	Up to 12 months	*Mortality rate at 30 days (P = 0.611)*	*A: 1/41 (2.4)* *B: 2/39 (5.1)*	*Limited number of patients and unequal follow-up times.*	*"MV repair with the MitraClip® system can be performed safely and efficiently in patients with anemia. Anemia does not affect clinical outcome and quality of life in patients undergoing MV repair."*
			MACCE rate (including death, myocardial infarction, stroke, and procedure related re-operation; P = 0.959)	*A: 2/41 (4.9)* *B: 2/39 (5.1)*		
Koifman et al. [Koifman, 2014]	20	231 days (mean)	*Abortion of the procedure*	*1/20 (5)*	*Small sample size and relatively short follow-up duration.*	*"MV repair using the MitraClip® percutaneous technique is feasible and safe in high risk, mainly inoperable, highly symptomatic patients with significant MR."*
			Patients hospitalised for more than 5 days	*4/20 (20)*		
			Mortality at 7 months	*2/20 (10)*		
Reichenspurner et al. [Reichenspurner,	117 *(33 high surgical risk, group A; 84*	30 days; 12 months	*Adverse events rate at 30 days*	*21/117 (17.9)* *A: 9/33 (27.3)* *B: 12/84 (14.3)*	*Lack of a protocol for patient selection and determination of*	*"Primarily for DMR patients who are inoperable or at exceedingly high risk for surgical MVR, MitraClip®*

2013]	*low surgical risk, group B)*		*Mortality rate at 30 days*	*7/117 (6.0)* *A: 3/33 (9.1)* *B: 4/84 (4.8)*	*aetiology.*	*therapy represents an attractive and less-invasive treatment option. The majority of patients thus treated benefit significantly regarding the severity of MR as well as clinically, regarding NYHA functional class and improvements in physical capacities and quality of life."*
			Adverse events rate at 12 months	*48/117 (41.0)*		
			Mortality rate at 12 months	*20/117 (17.1)* *A: 8/33 (24.2)* *B: 12/84 (14.3)*		
Rudolph et al. [Rudolph, 2014]	803 *(143 NYHA class IV, 572 NYHA class III, 88 NYHA class I or II)*	30 days	*Mortality* *Procedural (P = 0.59)* *At 30 days (P < 0.05)*	*Procedural* *1/803 (0.1) – NYHA III* *At 30 days* *NYHA IV: 11/137 (8.0)* *NYHA III: 17/526 (3.2)* *NYHA I/II: 4/83 (4.8)*	*Inhomogeneous population (but still reflecting real-life practice) and need of randomised studies to clarify the real therapeutic value and optimal time point of MitraClip implantation in severely diseased group of patients (e.g., those in NYHA IV).*	*"Our data indicate that percutaneous MV repair with the MitraClip® is feasible and safe, and leads to relevant clinical improvement even in critically ill, not fully recompensated patients, but is associated with an elevated 30-day mortality. The decision to perform the procedure in this group of patients has therefore to be individualized. While awaiting further studies addressing this topic, aggressive medical management of acute HF should be considered prior to MitraClip® therapy in this patient group."*
			Transfusions/severe bleeding *Procedural (P < 0.01)* *At 30 days (P = 0.19)*	*Procedural* *NYHA IV: 19/140 (13.6)* *NYHA III: 35/554 (6.3)* *NYHA I/II: 3/87 (3.4)* *At 30 days:* *NYHA IV: 15/98 (15.3)* *NYHA III: 38/387 (9.8)* *NYHA I/II: 4/57 (7.0)*		
			Transient ischaemic attacks (TIA) *Procedural (P < 0.01)* *At 30 days (P < 0.01)*	*Procedural* *NYHA IV: 5/140 (3.6)* *NYHA III:3/555 (0.5)* *NYHA I/II: 0/88 (0)* *At 30 days* *NYHA IV: 6/91 (6.6)* *NYHA III: 5/380 (1.3)* *NYHA I/II: 0/55 (0)*		
			≥3 days until mobilisation (P < 0.05)	*NYHA IV: 16/137 (11.7)* *NYHA III: 35/546 (6.4)* *NYHA I/II: 2/88 (2.3)*		
Toggweiler et al. [Toggweiler, 2014]	74	2 years	*Intra-procedural complications making procedure unfeasible*	*3/74 (4)*	*Low number of patients and limited experience of the centres.*	*"In the light of these results, the definition of procedural success may need to be re-evaluated. In future, improved patient selection, experience and maybe concomitant utilisation with nonsurgical mitral annuloplasty devices may lead to even better outcomes and a wider*
			Bleeding requiring transfusion	*6/74 (8)*		
			Pericardial tamponade after rupture of the left atrium	*1/74 (1)*		
			Strokes at 24 months	*0/74 (0)*		
			In-hospital mortality	*3/74 (4)*		
			Partial clip detachment at 24 months	*7/74 (10)*		

			Repeated procedure due to persistent 3+ or 4+ MR	*5/74 (6.8)*		*application of the MitraClip® procedure."*
Vandendriessche et al. [Vandendriessche, 2014]	41	Up to 12 months	*In-hospital MAEs (death, additional major bleeding need to undergo urgent cardiac surgery).*	*5/41 (12)*	*Small sample size.*	*"In the light of these results, the definition of procedural success may need to be re-evaluated. In future, improved patient selection, experience and maybe concomitant utilisation with nonsurgical mitral annuloplasty devices may lead to even better outcomes and a wider application of the MitraClip® procedure."*
Wiebe et al. [Wiebe, 2014]	557	72 days (median)	*In-hospital MACCE rate (mortality, stroke, and myocardial infarction)*	*27/546 (4.9)*	*Inadequacy of the logEuroSCORE in reflecting decisions based on valve morphology or aetiology of MR, and absence of post-procedural results and longer terms durability data.*	*"Percutaneous MV repair with the MitraClip® system is feasible in patients with a logEuroSCORE ≥ 20. Procedural results were similar, despite a significant higher intra-hospital MACCE rate compared to patients with lower predicted cardiac operative risk. Although mortality was four times higher than in patients with a logEuroSCORE < 20, mortality in high risk patients was lower than predicted by the logEuroSCORE. In patients with a logEuroSCORE ≥ 20, moderate residual MV regurgitation is more frequent."*
			Major in-hospital complications rate	*108/557 (19.4)*		
			Minor in-hospital complications rate	*77/557 (13.8)*		
			Other complications rate	*97/546 (17.8)*		
Yeo et al. [Yeo et al., 2014]	142	Up to 30 days	*Mortality rate at 30 days*	*8/142 (5.6)*	*Non-comparative nature of the study and short duration of follow-up.*	*"MitraClip® therapy is a safe and efficacious therapeutic option for patients with either FMR or DMR. In the Asia-Pacific region. The significant proportion of DMR. In comparison to the commercial experience in Europe, deserves further examination."*
			In-hospital mortality rate	*6/142 (4.2)*		
			MAE rate at 30 days	*18/142 (12.7)*		
			Patients underwent MV reoperation	*1/142 (0.7)*		
			Blood transfusion of ≥2 units	*5/142 (3.5)*		
			Sepsis	*2/142 (1.4)*		
			Prolonged intubation	*1/142 (0.7)*		
			Patients readmitted for HF	*1/142 (0.7)*		

**Data are reported for all patients without distinguishing between DMR and FMR patients.*

Key: *AEs, adverse events; MAE, major adverse events; n.r., not reported; n.c., not clear; EF, Ejection fraction; DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; MV, MV; NYHA, New York Heart Association; HF, heart failure; MACCE, major adverse cardiac and cerebrovascular events; MR, mitral regurgitation; Tot, total.*

Given the lack of studies on the MitraClip® System with proper comparisons, an assessment of safety could not be performed in relation to the comparators defined. The largest series referred to the combined cohort from the EVEREST II HRR and the REALISM HR studies [Glower et al. 2014], and to the German TRAMI register [Wiebe et al. 2014]. For the 351 high surgical risk patients in the EVEREST II HRR and REALISM HR [Glower et al. 2014], safety outcomes were reported at 30 days and 12 months. Mortality rate at 30 days was 4.8% (17/351) with no death related to device malfunctions. The MAE rate was 18.8% (66/351) with blood transfusion ≥ 2 units being the most frequent event occurring at a rate of 13.4% (47/351). None of the reported strokes (9/351) was due to device or air embolisation. Major vascular complications were experienced in 12 (3.4) patients. The mortality rate at 12 months was 22.8% (80/351). The MAE rate was 37.6% (132/351), with the most common event being blood transfusion (22.5%; 79/351), and 3 additional strokes occurred (12/351). Events of single-leaflet device attachment, listed as the most frequent device-related complication, occurred at a rate of 2.3% (8/351), mostly in the early phase. A second MitraClip® procedure was necessary in 1.1% of patients (4/351) only within 30 days after the initial procedure. MV surgery was performed in 0.9% of patients (3/351). No events of device embolisation occurred. For the 557 high surgical risk patients in the TRAMI register [Wiebe, 2014], safety outcomes were reported at in-hospital (mean hospital stay: 10 days; 6–17) and post-discharge follow-up (307 patients; mean: 75 days; 42.0–172.0). In-hospital mortality rate was 4.3% (24/554). Four events of stroke were reported (0.7%) and no event of myocardial infarction. MAE rate was 19.4% (108/557) with transfusion or severe bleeding as the most frequent events occurring at a rate of 13.7% (75/546). Major vascular complications were experienced in 2.2% of patients (12/546). Respiratory insufficiency and psycho syndrome for 3 or more days, both listed among MAEs, were observed in 3.5% (19/547) and 2.4% (13/546) of patients, respectively. Mortality rate at post-discharge follow-up was 13.4% (41/307). Rate of MACCE was 13.4% (41/307) while 38.6% of patients (103/267) experienced re-hospitalization for cardiac, cardiovascular, and other reasons. Device-related complications were reported: partial detachment of the clip from one of the leaflets was seen in 2% of patients. Procedural complications rate was 8.9% (49/550) (C0008). Subgroup analyses on specific populations were performed in the included studies. In particular, the impact of type II diabetes mellitus [Hellhammer et al. 2014], anaemia [Hellhammer et al. 2015], and NYHA class [Rudolph et al. 2014] were studied. No significant differences in terms of safety and effectiveness emerged from the study on diabetic patients [Hellhammer et al. 2014] even though only short-term (3 months) results for a small population (19 with type II diabetes and 39 with no diabetes) were

presented. Similarly, peri-procedural MACCE and 1-year survival did not differ between patients with anaemia (n = 41) and those without anaemia (n = 39) [Hellhammer et al. 2015]. In the other comparison [Rudolph et al. 2014], while in-hospital MACCE and re-hospitalisation rates were similar between groups in different NYHA classes, the 30-day mortality rate was significantly higher in NYHA class IV patients: 8.0% in NYHA IV (11/137), 3.2% in NYHA III (17/526), and 4.8% in NYHA II/I (4/83) ($p < 0.05$) (C0005). The available evidence showed that patient selection and organisational settings have been identified as aspects affecting frequency and severity of harms. Frailty of patients, in particular NYHA class IV, has been associated with higher mortality rates [Rudolph, 2014]. A learning curve effect has been documented previously [Schillinger et al. 2011]. It is likely that high-volume centres, with a proper heart team experienced in patient selection and with the specific technology, are able to perform the procedure with the lowest harm rate for the patients [Ledwoch et al. 2014] (C0004). In particular effects of a learning curve have not been addressed in any of the studies included for the present safety analysis (C0007). One of the studies [Wiebe et al. 2014] referenced a previous study in which a learning curve effect was acknowledged and significant differences between the earliest and latest procedures were observed [Schillinger et al. 2011]. In the series of 75 patients, the median total procedure time (total time from puncture to closure of the femoral vein) decreased from 180 min to 95 min ($p = 0.0001$); the median device time (total time from insertion of the SGC until removal of the clip delivery) decreased from 105 min to 55 min ($p = 0.002$); safety events decreased from 16 to 3 ($p = 0.0003$); acute procedural success (clip successfully placed and MR Grade ≤ 2+ at discharge) increased from 80% to 92% ($p = 0.46$). At 6 months, completeness of MV repair (MR ≤ 2+) was 89.4% for the latest patients and 65.0% for the earliest ($p = 0.03$) [Schillinger et al. 2011]. The manufacturer, Abbott Vascular, highlighted a more recent analysis from the German MV Registry (496 patients in 10 centres) that investigates the impact of the learning curve on procedural success and complications [Ledwoch et al. 2014]. The analysis, which is limited to centres performing at least 50 procedures per year, showed that a learning curve does not appear to significantly affect acute MR reduction in-hospital and 30-day mortality.

Assessment of methodological quality

Methodological quality of case series was assessed by the IHE 18-items checklist (according to the tool, quality is rated as "acceptable" if the study has 14 or more positive answers). Both the studies on CARILLON® Mitral Contour System® were rated of "acceptable quality" as scored 16 "Yes" [Schofer et al. 2009] and 14 "Yes" [Siminiak et al. 2012] respectively (see

Appendix 5). Among the 15 studies on the MitraClip® System, 8 resulted to be of "acceptable quality" whereas 7 studies were not (see Appendix 5).

Conclusions

The evidence of safety for CARILLON® Mitral Contour System® is still limited to small series, and little can be concluded on the transferability of the results. Available data are encouraging and the technology has been acknowledged to be relatively safe within the studies identified. However, the fact that the effects of a learning curve have not been explored is an issue that should be considered carefully.

Safety data related to the MitraClip® System were retrieved from large series and registries that, overall, showed comparable rates. Studies' results acknowledge that percutaneous MV repair with MitraClip® System is a feasible and safe treatment for patients with FMR and DMR who are at high surgical risk or non-surgical candidates. However, as recognised by most of the authors, comparative analyses with adequate follow-ups are deemed necessary to clarify the benefits/harms ratio of the procedure. Effects of a learning curve have been acknowledged in a series of 75 patients [Schillinger et al. 2011] while the analysis of 496 procedures in 10 centres performing at least 50 procedures per year, showed that a learning curve does not appear to significantly affect acute MR reduction, in-hospital and 30-day mortality [Ledwoch et al. 2014].

7. Costs and economic evaluation

Methods

The AEs of this domain were:

Assessment Element ID	Research question
E0001	Can you identify what types of resources are used when delivering the assessed technologies and their comparators (resource-use identification)?
E0002	Can you quantify what amounts of resources are used when delivering the assessed technologies and their comparators (resource-use measurement)?
E0009	What were the measured and/or estimated unit costs of the resources used by the assessed technologies and their comparator(s)?
E0005	What is (are) the measured and/or estimated health-related outcome(s) of the assessed technologies and their comparator(s)?
E0006	What are the estimated differences in costs and outcomes between the technologies and their comparator(s)?
E0010	What are the uncertainties surrounding the inputs and economic evaluation(s) of the technologies and their comparator(s)?
E0012	To what extent can the model estimates of inputs, outcomes, or economic evaluation(s) be considered as providing valid descriptions of the technologies and their comparator(s)?
D0023	How does the technologies modify the use of resources?
G0007	What are the likely budget impacts of implementing the technologies being compared?

The present domain has been developed using the Agenas Model, an adaptation of the EUnetHTA Core Model® (Appendix 1) since economic aspects are not investigated in the EUnetHTA REA Model.

To analyse the economic implications of using the transcatheter implantable devices for MV repair in adults with chronic MR, a systematic review of economic evidence and a context analysis were performed.

Systematic searches were conducted to identify economic studies focused on transcatheter implantable devices for MV repair in adults with moderate-to-severe and severe DMR or FMR at high surgical risk or non-surgical candidates. Literature searches have been performed in the following databases: PubMed, Embase, Cochrane Library (EED and HTA database), CINHAL. All searches were performed limiting the results to English language sources published between 2005 and the time of searches (May 2015). The keywords used for the searches of effectiveness and safety were combined with the following: cost utility, cost-effectiveness, cost minimization, cost analysis, cost-allocation, cost consequences analysis, economic evaluation, economic analysis,

economic aspect, economic assessment, ICER, health care cost, budget impact analysis. The search strategy is reported in the Appendix 6. Two reviewers (MC and MRP) screened the records by title and abstract. Disagreements were solved by discussion with a third party (TJ). Potentially relevant studies were retrieved in full-text and reconsidered for actual inclusion in the review of economic evidence. Data extraction was conducted independently on pre-defined extraction tables. Methodological quality of economic studies was assessed by using the "Checklist for economic evaluations of health problems" [Drummond et al. 1996].

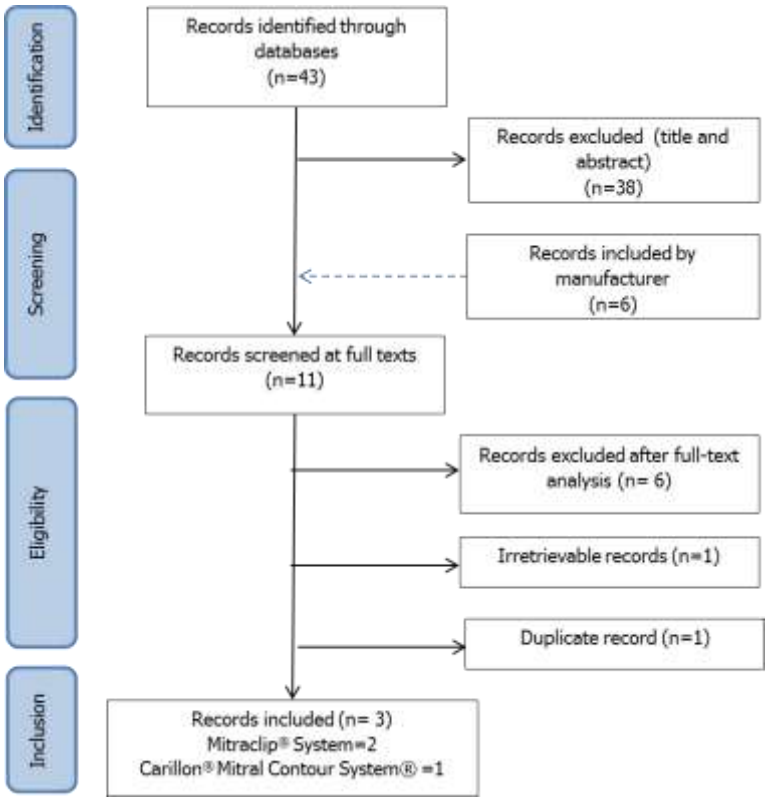
The economic aspects within the context analysis were described using data from the questionnaire-based survey presented in Chapter 2. The questionnaire was aimed at collecting the main economic information to identify, quantify and economically measure the resources used when preforming transcatheter MV repair with the identified technologies (CARILLON® Mitral Contour System® and MitraClip® System). In the 3rd part of the questionnaire (Economic research) the regions were asked to provide the following economic data:

- Cases and details of treatment (e.g., total number of procedures performed using the assessed technology in the target population, setting of treatment, number of patients with peri-procedural complications, distinguishing between FMR and DMR patients when relevant);
- Resources used: number of devices purchased and actually used, average purchase price of the device and the additional equipment/materials necessary for the technology to be used;
- Human resources (clinical staff/personnel) necessary for carrying out the device related procedure and their training;
- Further resources used in the pre-procedural, peri-procedural and post-procedural phases (e.g., disposables, drugs, medications, average length of stay).

Results

Among 43 records identified by the literature search, 3 studies were included to assess the costs and economic effects of the two devices. Six studies, regarding exclusively the Italian context, were identified and provided by manufacturer (Abbott Vascular); none of them was included (one was a duplicate, one was an unpublished presentation and four did not meet our inclusion criteria - see in Appendix 7 the excluded studies with the reason for exclusion). The inclusion process is graphically represented as a PRISMA flow diagram in Figure 7.1.

Figure 7.1: Flow-chart of the studies for costs and economic assessment according to PRISMA. Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.



Three studies were included: one on the CARILLON® Mitral Contour System® [Borisenko et al 2015] and two on the MitraClip® System [Cameron et al. 2014; Mealing et al. 2013]. All included studies were cost-utility studies and one of them performed also a cost-effectiveness analysis; one compared the CARILLON® Mitral Contour System® versus optimal medical treatment (OMT) and the others the MitraClip® System with standard care and conventional medical management (CMM). All the studies developed a Markov model to evaluate the cost-effectiveness of the CARILLON® Mitral Contour System® or the MitraClip® System versus OMT. However, for the study by Cameron et al. [Cameron et al. 2014] only the cost-analysis was considered, since the comparator group comprised a mix of patients with the majority of which (86%) medically managed and the rest (14%) who underwent MV surgery. One of the three included studies was conducted in Canada [Cameron et al. 2014] and the other two in Europe: Germany [Borisenko et al. 2015] and UK [Mealing et al. 2013]. All studies were funded completely or partially by the manufacturer via a consultancy agreement between manufacturer and research group. Competing interest was declared in all studies (see Table 7.1).

Table 7.1: General information of the included economic studies.

Study	Country	Objective	Patients	Intervention	Comparator	Economic analysis/Modelling	Model outputs	Time horizon	Perspective	Funding	Disclosure
Borisenko O et al. 2015	Germany	To determine the cost-effectiveness of PMVR using the Carillon Mitral Contour System in German setting	Patients with congestive heart failure and moderate to severe FMR with normal QRS interval, inoperable	Carillon Contour System	Optimal medical treatment	CUA/ Decision tree and after Markov model	- ICER - QALY	Time horizon of decision tree: 1 month Time horizon at base-case (Markov model): 10 years	German statutory health insurance	Sponsored by Cardiac Dimensions Inc.	Declared
Cameron HL et al. 2014	Canada	To evaluate the cost-effectiveness of MitraClip therapy compared with standard of care	Patients with significant MR at high risk for mitral valve surgery	MitraClip system	Standard care	CEA and CUA/Markov model	- Incremental cost per LY gained - Incremental cost per QALY gained	Time horizon: lifetime	Canadian healthcare payer	Consultancy agreement between Cornerstone Research Group, Inc. and Abbott Vascular	Declared
Mealing S et al. 2013	UK	To evaluate the cost-effectiveness of MitraClip therapy compared with conventional medical management	Patients with severe MR, for whom surgery is not an option due to high operative risk	MitraClip system	Conventional medical management	CUA/Markov model	- ICER - QALY	Short-term: 30 days Long term:5 years	UK NHS	Consultancy agreement between Oxford Outcomes Ltd. and Abbott Vascular	Declared

***Key**: FMR, functional mitral regurgitation; MR, mitral regurgitation; CUA, cost-utility analysis; CEA, cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year; NHS, National Health System.*

Description of available evidence on CARILLON® Mitral Contour System®

The study by Borisenko et al. [Borisenko et al. 2015] developed a cost-utility analysis to assess the cost-effectiveness of CARILLON® Mitral Contour System® versus OMT in patients with congestive HF and moderate to severe FMR with normal QRS interval ineligible to surgery.

The analysis was performed from a Germany statutory health insurance perspective. Two models were developed for the CUA analysis: a decision tree for short term (30 days) and a Markov model for a long time horizon (10-years).

The results of model are presented as an ICER and benefits expressed in terms of QALYs.

The following cost and resources types (E0001) were used:

- Procedure of implant;
- CARILLON® device;
- Hospitalisation;
- Extra-days of hospitalisation;
- Routine management.

The amount of resources used when performing the CARILLON® Mitral Contour System® procedure and OMT were not reported (E0002) while the relative unit costs (E0009) were collected and tabulated below (see Table 7.2). However the study reported the overall costs associated to CARILLON® Mitral Contour System® to be equal to €36,785 compared to €18,944 of OMT at 10 year follow up.

Efficacy data used to populate the model were derived from the TITAN trial [Siminiack et al. 2012] and other publications [Cowper et al. 2004; Ford et al. 2012].

Over 10 years, the life years gained (LYG) using the CARILLON® device were 5.87 compared to 4.46 in OMT group while the QALYs were 4.06 and 2.91 respectively. Therefore the percutaneous MV repair provided significant benefits to patients compared to OMT (E0005).

The cost-effectiveness ratio was €15,533 per QALY gained for the base-case analysis (E0006) as reported in Table 7.3. One-way and probabilistic sensitivity analyses were performed. From the one-way sensitivity analysis the most sensitive variables were: CARILLON® device cost, age of the patients, probability unsuccessfully annuloplasty, severity of FMR at baseline. At lifetime horizon the procedure with the CARILLON® device resulted more cost-effective with ICER equal to €7,914/QALY (E0010).

Description of available evidence on MitraClip® System

In the study by Mealing et al. [Mealing et al. 2013], the authors developed a decision analytic model with a lifetime horizon to assess the cost-effectiveness of the MitraClip® System versus CMM in patients with severe MR (degenerative or functional) at high surgical risk or otherwise

not eligible for surgery. The analysis was performed from a UK NHS perspective. For the cost-effectiveness analysis, two interlinked Markov models were developed for the post-procedure period: the short-term model (time horizon 30 days and time unit 1 day) and the long-term model (time horizon 5 years and time unit 1 month). The results of model are presented as an ICER and Benefits expressed in terms of QALYs.

The following cost and resources types (E0001) were used:

- Drug cost and other resource obtained from British National Formulary and National Service Schedule of Reference Costs;
- Hospitalisation costs, calculated using weighted averages of the events;
- Total cost of the MitraClip® System provided by the manufacturer (£20,000);
- Estimates of background medication: based on expert opinion and assumed constant across both treatment options.

The amount of resources used when performing the MitraClip® procedure and CMM were not reported (E0002) as well as the relative unit costs (E0009) (see Table 7.2). However the study reported the overall costs associated to the MitraClip® System to be GBP£31,593 compared to GBP£4,610 of CMM at 5 year follow up.

The mortality rate and other clinical events estimates were derived from the EVEREST II HRS. The lifetime survival estimated using the Weibull function in the MitraClip® System and CMM arms was 5.1 and 1.9 years respectively. Over a 5 year follow-up, the MitraClip® patients gained a QALY of 1.84 compared to 0.62 in patients treated with CMM (E0005).

The cost-effectiveness ratio was GBP£22,153 per QALY gained considering a 5-year time horizon (E0006). A probabilistic sensitivity analysis and deterministic analyses were performed. From the univariate deterministic analyses the model resulted to be most sensitive to time horizon, the MitraClip® procedure cost, utility decrements associated with NYHA II parameters; so the model was run on longer time horizons. The ICER resulted to be lower with a longer time horizon, in particular it was GBP£13,664 at 10-years, GBP£11,921 at 15-years, and GBP£11,451 at 20-years (E0010) (Table 7.3).

The study by Cameron et al. [Cameron et al 2014] is a cost-effectiveness analysis of the MitraClip® System implantation versus standard care in patients with significant MR at high surgical risk. The analysis was performed from the Canadian healthcare payer perspective. Since the comparator (standard care) did not meet our inclusion criteria we considered only the cost data. The authors collected all costs and resource consumptions of the MitraClip® treatment for each phase: pre-procedural, peri-procedural, post-procedural and at follow-up.

The cost and resources types reported in Table 7.2 were used (E0001):

- The MitraClip® device;
- Pre-procedural (clinical and surgical consultations, diagnostic tests);
- Peri-procedural (staff, diagnostic tests, disposables, vascular closure device, medications);
- In-hospital care (ICU, cardiac ward);
- The MitraClip® System complications, adverse events and disease management.

The amount of resources used when performing the MitraClip® procedure were reported in Table 7.2 (E0002) as well as the relative unit costs (E0009). The total cost associated to the MitraClip® System was CND$62,510.

Table 7.2: Resource-use information.

Study	Resource-use identification [E0001]	Resource-use measurement [E0002]	Resource-use valuation [E0009]		Currency/year
			Intervention	**Comparator**	
Borisenko O et al. 2015	Procedure of Implant 2) Carillon device 3) Hospitalization - hospitalization cost in intensive care unit - hospitalization cost in coronary care unit - hospitalization cost with CABG performed - hospitalization cost with PTCA - hospitalization cost with heart transplantation performed - hospitalization cost with no procedure 4) Extra days (hospitalization) in case of vessel perforation 5) Routine management (NYHA Class I, II, II, IV)	Not reported	Carillon (€) 1) 4844; 2) 18,000; 3) - 5004; - 5004; - 15,056; - 3793; - 86,337; - 2740. 4) 1998;	*OMM (€)* 5) NYHA I: 495; NYHA II: 874; NYHA III 864; NYHA IV: 929.	€/2013
Cameron HL et al. 2014	1) MitraClip device 2) Pre-procedural - Cardiology consultation - Cardiac surgery consultation - TEE - TTE - Chest x-ray - Electrocardiogram - Laboratory evaluations 3) Peri-procedural implantation - Anesthesiologist - Respiratory Therapist - Cardiologist - TEE - TTE - Disposables - Vascular closure device - Medications 4) In-hospital care - Intensive care unit - Cardiac ward 5) Mitraclip complications - Major vascular complication - Major bleeding complicaton - Non-cerebral thromboembolism 6) Adverse events - MIA - Major stroke - Renal failure - Mechanical ventilation>48h - GI complication requiring surgery - Septicemia - Blood transfusion (≥2 units of blood) 7) Disease management - HF clinic visit - Repeat cardiology consultation - TTE	1) 1 2) 1 visit for both consultation; 1 test for each diagnostic test; 228 units for laboratory. 3) 2 fees for cardiologist and 1 fee for both other professionals; 1 test for TEE and TTE; 1 set of disposables; 3 vascular closure devices; 1 dose of medications. 4) 2.2 days for ICU and 1.7 days for cardiac ward; 5) 1 physical unit for all complications; 6) 1 physical unit for all adverse events; 7) 0.25 for HF clinic visit and TTE; 0.17 for repeat cardiology consultation; 0.08 for laboratory evaluations.	MitraClip system ($CDN) 1) 30,000 2) - 157 - 90.3 - 258.40 - 148.65 - 23.58 - 11.05 - 0.517 3) - 637 - 108.96 - 1,618.50 - 285.40 - 148.65 - 175 - 325 - 2.86 4) - 1,440/day; - 492/day 5) - 5,233 - 7,118 - 7,142 6) - 7,700 - 6,890 - 6,493 - 2,888 - 5,832 - 13,047 - 535.51 7) - 157.88 - 105.25 - 148.65	Standard care Not pertinent	$CND/2013

	- Laboratory evaluations		- 29.47		
Mealing S et al. 2013	Drug cost and other resource 2. Hospitalization costs 3. MitraClip delivery system 4. MitraClip procedure 5. Background medication	Not reported	MitraClip system Not reported	CMM Not reported	GBP£/2011

Key: *CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; NYHA, New York Heart Association; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; MIA, myocardial infarction; HF, heart failure.*

Table 7.3: Effectiveness, costs and cost-effectiveness results

Study	Cost results		Efficacy results [E0005]		Discount rate	Differences in costs and results [E0006]	Sensitivity analysis [E0010]	Sensitivity analysis results	Conclusion
	Intervention	Comparator	Intervention	Comparator					
Borisenko O et al. 2015	Total cost: €36,785	Total cost: €18,944	- LYG: 5.87 - QALY gained: 4.06	- LYG: 4.46 - QALY gained: 2.91	3% per year	ICER: €15,533/QALY	- One-way sensitivity analysis - Probabilistic sensitivity analysis (Monte Carlo simulations)	- One-way sensitivity analysis: stable. The most sensitive variables: cost of the Carillon system, age of the patient, probability of unsuccessful annuloplasty, presence of severe FMR at baseline. Lifetime horizon analysis: - Incremental cost €19,539; - incremental life-years gained: 3.23; - QALY gained 2.47. Lifetime horizon: PMVR was more cost-effective over lifetime with ICER of €7,914/QALY;	When compared with optimal medical treatment, PMVR using the Carillon® Mitral Contour System® may be cost-effective in inoperable patients with congestive heart failure who have moderate to severe FMR.
Cameron HL et al. 2014	Total cost: CND$62,510	No extracted since the study comparator did not fit inclusion criteria			5% per year	No extracted since the study comparator did not fit inclusion criteria			While results from clinical studies demonstrate that the MitraClip device can successfully reduce the degree of MR and improve QoL in patients not considered to be suitable candidates for MV surgery, and for whom there are no other treatment options, the results of this analysis demonstrate that MitraClip therapy also offers a cost-effective option for these patients.
Mealing S et al. 2013	Cost: - Time horizon 2 years: GBP£28,725 - Time horizon 5 years: GBP£31,593	Cost: - Time horizon 2 years: GBP£3,156 - Time horizon 5 years: GBP£4,610	Lifetime survival: 5.1 years QALY: - Time horizon 2 years: 0.92 - Time horizon 5 years: 1.84	Lifetime survival: 1.9 years QALY: - Time horizon 2 years: 0.43 - Time horizon 5 years: 0.62	3.5% per year	Incremental QALY: - Time horizon 2 years: 0.48 - Time horizon 5 years: 1.22 Incremental cost: - Time horizon 2 years: GBP£25,565 - Time horizon 5 years: GBP£26,989 ICER per QALY: - Time horizon 2 years: GBP£52,947 - Time horizon 5 years: GBP£22,153	- Probabilistic sensitivity analysis - Deterministic analyses	- Univariate Deterministic sensitivity analysis: Model most sensitive: time horizon, utility decrements associated with NYHA II, Cost of MitraClip procedure. - Time horizon analysis: * ICER at 10 years: GBP£13,664; * ICER at 15 years: GBP£11,921; * ICER at 20 years: GBP£11,451.	MitraClip represents a cost-effective treatment option compared to medical management over a 10-year time frame at conventional reimbursement thresholds.

Key: *LYG, life year gained; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; PMVR, percutaneous MV repair; FMR, functional mitral regurgitation; QoL, quality of life; MV, mitral valve; NYHA, New York Heart Association.*

Assessment of methodological quality

The quality assessment of the economic studies was performed using the checklist developed by Drummond et al. 1996 (Appendix 8).

Only two studies were assessed [Borisenko et al. 2015; Mealing et al. 2013]; the study by Cameron et al. [Cameron et al. 2014] was not assessed because only cost data were considered.

The methodological quality was judged to be high for both studies, with respectively 26 and 25 "Yes" for Borisenko et al. and Mealing et al. [Borisenko et al. 2015; Mealing et al. 2013] (E0012).

Contextual analysis

The questionnaire-based survey to the manufacturers (Cardiac Dimension Inc. and Abbott Vascular) showed that in the time frame observed, 2012-2014, a very small number of procedures was performed with CARILLON® Mitral Contour System® and for this reason the use of the device was not investigated further. The analysis was then performed only for the MitraClip® System, according to the regional volumes of activity provided by the manufacturer. More than 80% of the MitraClip® procedures were performed in seven regions. Questionnaires were sent by mail to those regions (2nd July 2015; remind done on 3rd September 2015). Due to the low response rate (14.28%; only one responder) and the low level of activity represented (only 4% of the procedures) further analyses were believed not representative and then not performed.

Conclusions

The evidence available showed that, in patients with moderate to severe and severe MR at high surgical risk or not eligible for surgery, the use of CARILLON® Mitral Contour System® or MitraClip® System seems to be cost-effective compared to OMT/CMM. However, the available economic evidence is thin, even if recently published. Among the ongoing clinical trials (Table 5.4), two studies planned to collect also health economic data and one study aims to perform a cost-effectiveness analysis:

- The COAPT Trial (NCT01626079) aims to test the null hypothesis that there is no difference between MitraClip® System and standard hospital clinical practice in terms of safety and effectiveness, for the treatment of moderate-to-severe or severe FMR in symptomatic HF subjects who have been determined by the site's local heart team

as not appropriate for MV surgery. One of the "Other Outcome Measures" includes economic data collected in the 5 year follow-up.

- The NCT02444338 trial is designed to provide additional evidence regarding appropriate recommendations for use of the MitraClip® System compared to optimal standard of care therapy in patients with chronic HF and clinically significant FMR. Additionally, the trial will collect evidence regarding health economics of the MitraClip® System for use in this patient population.
- The MITRA-FR (NCT01920698) compares the safety, the efficacy and the cost-effectiveness of two therapeutic strategies (optimal standard of care therapy alone versus percutaneous MitraClip® procedure plus optimal standard of care therapy) in patients with severe secondary MR. Cost-effectiveness of each therapeutic strategy will be assessed by the evaluation of medical costs linked to the pathology (hospitalisations, consultations, and external medical costs) and compared in the 2 groups during the first 12 months of follow up.

Further full economic evaluations alongside clinical trials aimed to collect and investigate not only costs' data but also the cost-effectiveness of both devices are recommended.

8. Discussion

Two technologies for percutaneous treatment of MR available on the Italian market were assessed in the present report. In past and ongoing studies, the CARILLON® Mitral Contour System® has been used in FMR patients, while the MitraClip® System has been used for both FMR and DMR aetiologies. The devices have different access: the jugular vein for the CARILLON® Mitral Contour System®, and the femoral vein for the MitraClip® System. The two procedures are performed within secondary healthcare in a standard catheterisation laboratory, while the patient is under general anaesthesia or even under conscious sedation (CARILLON® Mitral Contour System®).

The decision to use of the CARILLON® Mitral Contour System® is typically taken by a cardiologist having expertise in the areas of interventional cardiology, echocardiography, and HF management while, for the MitraClip® System the decision is usually made using the *"heart team approach*".

Across Europe [EUnetHTA JA2 Pilot SB-15], as well as across the Italian regions, the two technologies are reimbursed with different strategies. In Italy, differences in reimbursement are related to procedure coding (no procedure-specific codes are available).

Levels of diffusion of the two devices in Italy during 2012-2014 were found remarkably different: with only 3 implants performed, the CARILLON® Mitral Contour System® is still at an early stage (about 300 implants performed in Europe) while 1,500 implants have been performed using the MitraClip® System (23,000 implants worldwide).

As reported in international literature, CARILLON was assessed by 3 international HTA institutions: the National Institute for Health and Care Excellence (NICE, UK) in 2010 [NICE 2010], the Health Policy Advisory Committee on Technology (HealthPACT, Australia) in 2012 [HealthPACT, 2012], and the National Health Committee (NHC, New Zealand) in 2013 [NHC 2013]. The evidence of safety and effectiveness, based only on a few case series, was considered inadequate in quality and quantity by the 3 institutions. Two of them recommended that the procedure should be used only in the context of research [NICE 2010; NHC 2013]. Despite the existence of a comparative study on the use of CARILLON® Mitral Contour System®, it's important to note that the comparison group was created by implanting and acutely recapturing the device for clinical indications in a subgroup of the initially enrolled patients. It is unclear how this procedure impacted on the outcomes observed in the comparison group. The non-device-related mortality in this sick patient population affected the number of patients followed at 12 and 24 months as in the implanted group, follow-up was not feasible for 30.5% and 47.2% patients at 12 and 24

months, respectively. The ongoing REDUCE FMR study aims to assess the safety and efficacy of CARILLON® Mitral Contour System® in treating FMR associated with HF, compared to a randomised control group that is medically managed according to HF guidelines. The study does not formally assess the surgical risk of the candidates, but sets a LVEF ≤ 40% as an inclusion criterion. Results from REDUCE FMR are anticipated as they may answer the research questions posed in the present assessment and may provide further information for defining the role of the procedure within the clinical pathway.

The MitraClip® System was assessed by 8 different institutions, from 2009 to 2015 (Table 5.2). In Europe, recommendations from the earliest assessments [NICE 2009; HTA Stockholm 2012] were restrictive in use because of the lack of comparative studies with adequate comparators and low quality observational studies. The latest report, published by Haute Autorité de Santé (HAS) in April 2015 [HAS 2015], considered the series from the EVEREST II HRR study and a further 9 non-comparative cohort studies. HAS highlighted the following critical issues:

- implanted patients have multiple aetiologies of MR with heterogeneous baseline characteristics and therapeutic strategies that are not identical;
- complications at 1 year of follow-up are not systematically described in the studies;
- evidence is limited to small numbers and short follow-up periods;
- efficacy cannot be assessed by type of MR;
- the definition of "high surgical risk" varies depending on the study;
- the learning curve of the technique is not considered in the studies.

Despite these issues – but in line with the latest ESC-EACTS and AHA-ACC Guidelines – HAS recommended the use of the MitraClip® System in patients with severe DMR who are symptomatic despite optimal medical treatment, ineligible for surgery, and meet the echocardiographic eligibility criteria. The lack of alternatives for this population and the potential benefit of the MitraClip® System was considered crucial by HAS. They stated that, for other indications (e.g., FMR or mixed aetiologies) and/or for patients at lower surgical risk, the role of the MitraClip® System remains undetermined.

The review by Munkholm-Larsen et al. [Munkholm-Larsen et al. 2014] was focused on the assessment of safety, success rate, clinical efficacy, and survival outcomes of the MitraClip® System implantation in managing patients with severe DMR and/or FMR and high surgical risk candidates. The review covered the time frame from January 2000 to March 2013. All 12 studies included were prospective observational studies from specialised tertiary referral centres (no comparative studies were identified). The review did not identify any RCTs

comparing the MitraClip® vs non-surgical therapies. The authors of the review highlighted a series of issues:

1) DMR and FMR are often combined (in 9/12 included studies);
2) Data on long-term outcomes and durability of device beyond 3 years are limited;
3) Inclusion and exclusion criteria, patient selection, and the definition of high risk varied significantly between the included studies;
4) The available literature on high surgical risk patients is of low quality, with the majority being either registries or observational studies.

They concluded that "*before further convincing evidence becomes available, the use of MitraClip® implantation should be considered only within the boundaries of clinical trials with special arrangements for clinical governance, consent, and audit or research. MitraClip® interventions should only take place in centres with appropriate cardiothoracic surgical support to manage the potential intraoperative complications*" [Munkholm-Larsen et al. 2014].

No new primary studies fulfilling the inclusion criteria defined in the present assessment were identified by updating the review by Munkholm-Larsen et al. [Munkholm-Larsen et al. 2014], which was rated as good quality according to the R-AMSTAR scale.

Available evidence does not allow any final statement on the relative effectiveness of transcatheter implantable devices for MV repair (the CARILLON® Mitral Contour System® and the MitraClip® System) in adults with moderate-to-severe and severe chronic MR compared with standard management. Comparative analyses with adequate durations of follow-up are necessary to clarify the benefits–harms ratio of the two procedures in selected clinical conditions. Ongoing studies will help, in the near future, to determine whether they are more effective and/or safe than the comparators.

As for clinical effectiveness, the evidence of safety for CARILLON® Mitral Contour System® is still limited to small series, and little can be concluded on the transferability of the results. Available data are encouraging and the technology has been acknowledged to be relatively safe within the studies identified. However, the fact that the effects of a learning curve have not been explored is an issue that should be considered carefully. Safety data related to the MitraClip® System were retrieved from large series and registries that, overall, showed that percutaneous MV repair with MitraClip® is a feasible and safe treatment for patients with FMR and DMR who are at high surgical risk or non-surgical candidates. However, as recognised by most of the authors, comparative analyses with adequate follow-up are deemed necessary to clarify the benefits/harms ratio of the procedure. Effects of a learning

curve have been acknowledged in a series of 75 patients [Schillinger et al. 2011] while the analysis of 496 procedures in 10 centres performing at least 50 procedures per year, showed that a learning curve does not appear to significantly affect acute MR reduction, in-hospital and 30-day mortality [Ledwoch et al. 2014]. Scarce evidence available show that the devices assessed (CARILLON® Mitral Contour System® and MitraClip® System) for patients with moderate to severe and severe MR at high surgical risk or not eligible for surgery seem to be cost-effective compared to CMM/OMT.

During the production of the present report, a new study providing a comparative review of the evidence on MitraClip® and medical therapy effectiveness was published [Gonzalez et al. 2015]. The study was identified during the public consultation phase, following a reviewer's comment. The study presented findings from a literature review conducted in February 2013 in which 30 primary studies, 29 observational studies and 1 RCT were included. Most of the studies (16 out of 30) involved less than 50 participants. Study quality, assessed by the review authors using the Downs and Black adapted checklist, was in all cases rated as "good" or "very good". The authors highlighted three key issues related to available evidence: i) Limited evidence addressing the incremental benefits of MitraClip® over medical therapy has been produced; ii) Updated literature on medical therapy in high-risk patients, which could enable a comparative exercise is scarce; iii) Quantification of incremental benefits in medical technologies should take into account the methodological distinctions that medical devices' accurate valuation requires. The review authors concluded that "*A relevant message derived from the results in this review is that despite a wide corpus of evidence on the safety and short-term effectiveness of MitraClip produced in recent years, such evidence is still inconclusive as to whether MitraClip should be systematically preferred over medical therapy in treating high-risk patients in real practice settings*." This is in agreement with the conclusion of the present national report.

9. Recommendations

The present assessment needs to be updated when results from ongoing comparative studies are made available. In particular, for the CARILLON® Mitral Contour System®, the REDUCE FMR study (NCT02325830) due in July 2017, while four studies are awaited for the MitraClip® System: the RESHAPE-HF1-FU study (NCT02444286) due in January 2017, the MITRA-FR trial (NCT01920698) due in October 2017, study NCT02444338 due in September 2019, and the COAPT study (NCT01626079) due in 2020. Another ongoing study may be relevant as it has a surgical comparator, the MATTERHORN trial (NCT02371512), assessing MV repair with the MitraClip® System in high surgical risk patients with clinically significant MR of primarily functional pathology (results are expected by December 2017).

On the basis of these considerations, the two implantable devices for transcatheter MV repair assessed in the present report should be used in well identified centres, with appropriate cardiological and cardiothoracic surgical expertise. All professionals who implanted such devices should collect all the relevant data in a specific registry or research setting.

Further full economic evaluations alongside comparative, randomised controlled trials are needed to determine the relative effectiveness, safety profile and economic impact of both CARILLON® Mitral Contour System® and MitraClip® System.

10. Funding

The production of this rapid HTA report was made possible by financial contributions from the Italian Ministry of Health and Agenas. Agenas takes the sole responsibility for the final form and content of this rapid HTA report. The views expressed herein do not necessarily represent the views of the Italian Ministry of Health or any regional government.

11. Competing interests declaration

The Authors declare that they will not receive either benefits or harms from the publication of this report. None of the Authors has or has held shares, consultancies or personal relationships with any of the manufacturers of the devices assessed in this report.

Bibliography

EUnetHTA REA 2013 Model. HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals,2013. Available from: https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf

EUnetHTA CM. EUnetHTA Core Model®. Avilable from: http://www.eunethta.eu/hta-core-model.

EUnetHTA Core Model 2.0. EUnetHTA Core Model for medical and surgical interventions 2.0. Available from: http://www.eunethta.eu/outputs/hta-core-model-medical-and-surgical-interventions-10r

Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012 Oct;42(4):S1-44.

Siminiak T, Wu JC, Haude M, Hoppe UC, Sadowski J, Lipiecki J, et al. Treatment of functional mitral regurgitation by percutaneous annuloplasty: results of the TITAN Trial. Eur J Heart Fail 2012;14(8):931-8.

HAS 2015. Haute Autorité de Santé. Rapports d'évaluation des technologies de santé. MITRACLIP - Clip de réparation mitrale bord à bord et son acte d'implantation. April 2015. Available from: http://www.has-sante.fr/portail/jcms/c_2028913/fr/rapport-d-evaluation-mitraclip

EUnetHTA JA2 Pilot SB-15. EUnetHTA Joint Action 2 Work Package 5 Strand B 5th Pilot SB-15 "Transcatheter implantable devices for MV repair in adults with chronic MV regurgitation". Available from: http://www.eunethta.eu/news/5th-pilot-rapid-assessment-wp5-ja2-strand-b-transcatheter-implantable-devices-mitral-valve-repa

Agenas 2014. Manual of HTA procedure. Available from: http://www.agenas.it/images/agenas/hta/Manuale_procedure_HTA.pdf

Iung B, Baron G, Butchart EG et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231 –1243. 2.

Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005 –1011.

Zile MR, Tomita M, Ishihara K et al. Changes in diastolic function during development and correction of chronic LV volume overload produced by mitral regurgitation. Circ Res. 1993 May;72(5):1110-23.

Maisano F, Alamanni F, Alfieri O, et al. Transcatheter treatment of chronic mitral regurgitation with the MitraClipsystem: an Italian consensus statement. J Cardiovasc Med (Hagerstown) 2014 Mar;15(3):173-88.

Beeri R, Yosefy C, Guerrero JL et al. Early repair of moderate ischemic mitral regurgitation reverses left ventricular remodeling: a functional and molecular study. Circulation 2007 Sep 11;116(11 Suppl):I288-93.

NICE 2009. National Institute for Health and Care Excellence interventional procedure guidance 309. Percutaneous mitral valve leaflet repair for mitral regurgitation. August 2009. Available from: http://www.nice.org.uk/guidance/ipg309

Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol 1999 Mar 15;83(6):897-902. Erratum in: Am J Cardiol 1999 Nov 1;84(9):1143.

Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. Lancet 2009; 373:1382–1394.

Allen LA, Felker GM. Advances in the surgical treatment of heart failure. Curr Opin Cardiol 2008; 23:249–253.

Nieminen MS, Brutsaert D, Dickstein K,et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006 Nov;27(22):2725-36.

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

Otto CM, Bonow RO. Valvular heart disease. In: Libby P, Bonow RO, Mann DL, Zipes DP, editors. , eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*8th ed.Philadelphia, PA: WB Saunders 2007:1625-1712.

Nishimura RA, Otto CM, Bonow RO, Carabello BA et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Am Coll Cardiol 2014 Jun 10;63(22):2438-88.

Baumgartner H, Hung J, Bermejo J et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. Eur J Echocardiogr 2009;10:1– 25.

Rosenhek R. Almanac 2011: valvular heart disease. The national society journals present selected research that has driven recent advances in clinical cardiology. Rev Port Cardiol 2012 Apr;31(4):337-50.

Rankin JS, Hammill BG, Ferguson TB Jr.et al. Determinants of operative mortality in valvular heart surgery. J Thorac Cardiovasc Surg 2006;131:547 – 557.

Rabbani MS, Qadir I, Ahmed Y, et al. Heart valve surgery: EuroSCORE vs. EuroSCORE II vs. Society of Thoracic Surgeons score. Heart Int 2014 Sep24;9(2):53-8.

Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. N Engl J Med 2005; 352:875–883.

Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 2011; 364:1395–1406.

Maisano F, Taramasso M, Cioni M, et al. Review of the MitraClip clinical evidence. Miner Cardioangiol 2012; 60:85–93. 3.

Maisano F, Franzen O, Baldus S, et al. Percutaneous mitral valve interventions in the real world: early and one year results from the ACCESS-EU, a prospective, multicenter, non-randomized post-approval study of the MitraClip(R) therapy in Europe. J Am Coll Cardiol 2013; 62:1052–1061.

GISE 2015. GIse registry Of Transcatheter treatment of MV regurgitaTiOn (GIOTTO). Available from: http://www.gise.it/news/1515/registro_giotto

De Bonis M, Al-Attar N, Antunes M,et al. Surgical and interventional management of mitral valve regurgitation: a position statement from the European Society of Cardiology Working Groups on Cardiovascular Surgery and Valvular Heart Disease. Eur Heart J 2015 Jul 7.

McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012 Aug;14(8):803-69.

Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240–e327.

EuneHTA guidelines. Available from: https://eunethta.fedimbo.belgium.be/eunethta-guidelines.

De Bonis M, Alfieri O. The edge-to-edge technique for mitral valve repair. HSR Proc Intensive Care Cardiovasc Anesth 2010;2(1):7-17.

Kung J, Chiappelli F, Cajulis OO, et al. From Systematic Reviews to Clinical Recommendations for Evidence-Based Health Care: Validation of Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) for Grading of Clinical Relevance. The Open Dentistry Journal 2010;4, 84-91).

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011. Available from www.cochrane-handbook.org.

Munkholm-Larsen S, Wan B, Tian DH et al. A systematic review on the safety and efficacy of percutaneous edge-to-edge mitral valve repair with the MitraClip system for high surgical risk candidates. Heart 2014;100(6):473-8.

NICE 2010. National Institute for Health and Care Excellence interventional procedure guidance 352. Percutaneous mitral valve annuloplasty. July 2010. www.nice.org.uk/ipg352.

HealthPACT 2012. Technology Brief: Update. Carillon Mitral Contour System for Mitral Regurgitation. February 2012 https://www.health.qld.gov.au/healthpact/docs/briefs/WP089.pdf

NHC 2013. National Health Committee. Percutaneous Interventions for Mitral Regurgitation - Technology Note. July 2013 http://nhc.health.govt.nz/system/files/documents/publications/percutaneous-interventions-for-mrt.pdf

Schofer J, Siminiak T, Haude M, et al. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. Circulation 2009;120(4):326-33.

HTA Stockholm 2012. Stockholms läns landsting - Gotland. MitraClip vid behandling av svår mitralisinsufficiens. May 2012. Available from: http://www.vardgivarguiden.se/Global/04_Utbildning%20och%20utveckling/HTA/HTA_Rapport_MitraClip_2012_5.pdf

Auricchio A, Schillinger W, Meyer S, et al. Correction of mitral regurgitation in nonresponders to cardiac resynchronization therapy by MitraClip improves symptoms and promotes reverse remodeling. J Am Coll Cardiol 2011;58:2183–9.

Surder D, Pedrazzini G, Gaemperli O, et al. Predictors for efficacy of percutaneous mitral valve repair using the MitraClip system: the results of the MitraSwiss registry. Heart 2013;99:1034–40.

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

Treede H, Schirmer J, Rudolph V, et al. A heart team's perspective on interventional mitral valve repair: percutaneous clip implantation as an important adjunct to a surgical mitral valve program for treatment of high-risk patients. J Thorac Cardiovasc Surg 2012;143:78–84.

Paranskaya L, D'Ancona G, Bozdag-Turan I, et al. Residual mitral valve regurgitation after percutaneous mitral valve repair with the mitraclip(R) system is a risk factor for adverse one-year outcome. Catheter Cardiovasc Interv 2013;81:609–17.

Pleger ST, Mereles D, Schulz-Schonhagen M, Krumsdorf U, Chorianopoulos E, Rottbauer W, et al. Acute safety and 30-day outcome after percutaneous edge-to-edge repair of mitral regurgitation in very high-risk patients. Am J Cardiol 2011;108:1478-82.

Ihlemann N, Franzen O, Jørgensen E, et al. Promising results after percutaneous mitral valve repair. Dan Med Bull. 2011;58:A4299.

Van den Branden BJ, Swaans MJ, Post MC et al. Percutaneous edge-to-edge mitral valve repair in high-surgical-risk patients: do we hit the target? JACC Cardiovasc Interv 2012;5:105-11.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Moga C, Guo B, Schopflocher D, Harstall C. Development of a quality appraisal tool for case series studies using a modified Deplhi technique. Methodology Paper. Edmonton AB: Institute of Health Economics, 2012.

Alegria-Barrero E, Chan PH, Foin N et al. Concept of the central clip: when to use one or two MitraClips(R). EuroIntervention 2014; 9(10):1217-24.

Armoiry X, Brochet E, Lefevre T et al. Initial French experience of percutaneous mitral valve repair with the MitraClip: a multicentre national registry. Arch Cardiovasc Dis 2013; 106(5):287-94.

Attizzani G.F., Ohno Y., Capodanno D. et al. Extended use of percutaneous edge-to-edge mitral valve repair beyond EVEREST (Endovascular Valve Edge-to-Edge Repair) criteria: 30-Day and 12-month clinical and echocardiographic outcomes from the GRASP (getting reduction of mitral insufficiency by percutaneous clip implantation) registry. JACC Cardiovasc Interventions 2015; 8(1):74-82.

Bozdag-Turan I, Paranskaya L, Birkemeyer R et al. Percutaneous mitral repair with the MitraClip system in patients with mild-to-moderate and severe heart failure: a single-centre experience. Cardiovasc Ther 2014; 32(2):66-73.

Braun D, Lesevic H, Orban M et al. Percutaneous edge-to-edge repair of the mitral valve in patients with degenerative versus functional mitral regurgitation. Catheter Cardiovasc Interv 2014; 84(1):137-46.

Glower DD, Kar S, Trento A et al. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. J Am Coll Cardiol 2014; 64(2):172-81.

Hellhammer K, Balzer J, Zeus T et al. Percutaneous mitral valve repair using the MitraClip(R) system in patients with anemia. Int J Cardiol 2015; 184:399-404.

Hellhammer K., Zeus T., Balzer J. et al. Safety and efficacy of percutaneous mitral valve repair using the MitraClip® system in patients with diabetes mellitus. PLoS ONE 2014; 9(11).

Koifman E, Fefer P, Hay I, Feinberg M, Maor E, Guetta V. MitraClip implantation for high risk patients with severe mitral regurgitation: the Sheba experience. Isr Med Assoc J 2014; 16(2):91-5.

Reichenspurner H, Schillinger W, Baldus S, Hausleiter J, Butter C, Schäefer U, et al. Clinical outcomes through 12 months in patients with degenerative mitral regurgitation treated with the MitraClip(R) device in the ACCESS-EUrope Phase I trial. Eur J Cardiothorac Surg 2013; 44(4):e280-8.

Rudolph V, Huntgeburth M, Von Bardeleben RS et al. Clinical outcome of critically ill, not fully recompensated, patients undergoing MitraClip therapy. Eur J Heart Fail 2014; 16(11):1223-9.

Toggweiler S, Zuber M, Surder D, et al. Two-year outcomes after percutaneous mitral valve repair with the MitraClip system: durability of the procedure and predictors of outcome. Open Heart 2014; 1(1):e000056.

Vandendriessche T, Kotrc M, Tijskens M, et al. Percutaneous mitral valve repair in high-risk patients: initial experience with the Mitraclip system in Belgium. Acta Cardiol 2014; 69(3):265-70.

Wiebe J, Franke J, Lubos E, et al. Percutaneous mitral valve repair with the MitraClip system according to the predicted risk by the logistic EuroSCORE: preliminary results from the German Transcatheter Mitral Valve Interventions (TRAMI) Registry. Catheter Cardiovasc Interv 2014; 84(4):591-8.

Yeo KK, Yap J, Yamen E, et al. EuroIntervention: Percutaneous mitral valve repair with the MitraClip: Early results from the MitraClip Asia-Pacific Registry(MARS). 10 edition. Vol. 5. 2014.

Schillinger W, Athanasiou T, Weicken N, et al. Impact of the learning curve on outcomes after percutaneous mitral valve repair with MitraClip and lessons learned after the first 75 consecutive patients. Eur J Heart Fail 2011;13:1331–1339.

Ledwoch J, Franke J, Baldus S, et al. Impact of the learning curve on outcome after transcatheter mitral valve repair: results from the German Mitral Valve Registry. Clin Res Cardiol 2014 Nov;103(11):930-7.

Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 1996;313:275–83.

Borisenko O, Haude M, Hoppe UC, et al. Cost-utility analysis of percutaneous mitral valve repair in inoperable patients with functional mitral regurgitation in German settings. BMC Cardiovasc Disord 2015;15(1):43.

Cameron HL, Bernard LM, Garmo VS, et al. A Canadian cost-effectiveness analysis of transcatheter mitral valve repair with the MitraClip system in high surgical risk patients with significant mitral regurgitation. J Med Econ 2014;17(8):599-615.

Mealing S, Feldman T, Eaton J, et al. EVEREST II high risk study based UK cost-effectiveness analysis of MitraClip(R) in patients with severe mitral regurgitation ineligible for conventional repair/replacement surgery. J Med Econ 2013;16(11):1317-26.

Cowper PA, DeLong ER, Whellan DJ,et al. Economic effects of beta-blocker therapy in patients with heart failure. Am J Med 2004;116(2):104–11.

Ford E, Adams J, Graves N. Development of an economic model to assess the cost-effectiveness of hawthorn extract as an adjunct treatment for heart failure in Australia. BMJ Open 2012;2:e001094.

Gonzalez FM, Finch AP, Armeni P, et al. Comparative effectiveness of Mitraclip plus medical therapy versus medical therapy alone in high-risk surgical patients: a comprehensive review. Expert Rev Med Devices 2015 Jul;12(4):471-85.

List of acronyms and abbreviations

6MWT: 6-minute walk test

ACC: American College of Cardiology

ACCESS-EU: MitraClip Therapy Economic and Clinical Outcomes Study Europe

ACE: Angiotensin-converting-enzyme

AdvE: Adeverse event

AE: Assessment element

AF: Atrial fibrillation

AMADEUS: CARILLON Mitral Annuloplasty Device European Union Study

CCT: Comparative controlled trial

CE: Conformité Européene

CINHAL: Cumulative Index to Nursing and Allied Health Literature

COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation

CRD: Centre for Reviews and Dissemination

CRT: Cardiac resynchronisation therapy

DMR: Degenerative mitral regurgitation

ERO: Effective regurgitant orifice

ESC-EACTS: European Society of Cardiology–-European Association for Cardio-Thoracic Surgery

EU: European Union

EVEREST II HRR: Endovascular Valve Edge-to-Edge Repair Study II High Risk Registry

FDA: United States Food and Drug Administration

FMR: Functional mitral regurgitation

HAS: Haute Autorité de Santé

HealthPACT: Health Policy Advisory Committee on Technology

HF: Heart failure

HTA: Health Technology Assessment

ICD: International Statistical Classification of Diseases and Related Health Problems

IHE: Institute of Health Economics

ISRCTN: International Standard Randomised Controlled Trial Number

LA: Left atrial

LBI HTA: Ludwig Boltzmann Institute for Health Technology Assessment

LVAD: Left Ventricular assist device

LV: Left ventricular

LVEF: Left ventricular ejection fraction

MACCE: Major cardiac and cerebrovascular events

MAE: Major adverse event

MATTERHORN: Multicenter, Randomized, Controlled Study to Assess Mitral Valve Reconstruction for Advanced Reconstruction for Advanced Insufficiency of Functional or Ischemic Origin

MeSH: Medical Subject Headings

MI: Myocardial infarction

MR: Mitral regurgitation

MSAC: Medical Services Advisory Committee

MV: Mitral valve

NHC: National Health Committee

NHS: National Health Service

NICE: The National Institute for Health and Care Excellence

NR: Not reported

NYHA: New York Heart Association

QoL: Quality of life

R-AMSTAR: Revised Assessment of Multiple Systematic Reviews

RCT: Randomised controlled trial

REA: Relative Effectiveness Assessment

REALISM: Real World Expanded Multicenter Study of the MitraClip® System

REDUCE: FMR CARILLON® Mitral Contour System® for Reducing Functional Mitral Regurgitation

RESHAPE-HF: Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation

RESHAPE HF1-FU: Observational Study of Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation – Follow Up of the Former Participants in the RESHAPE-HF trial

STS: The Society for Thoracic Surgeons

SF-36: Short-form 36 Health Survey

SGC: Steerable guide catheter

STS: The Society for Thoracic Surgeons

TOE: Transoesophageal echocardiography

TITAN: Transcatheter Implantation of Carillon Mitral Annuloplasty Device

TMVR: Transcatheter mitral valve repair

TRAMI: Transcatheter Mitral Valve Interventions

U: Unit

Appendix 1 – The Agenas adaptation of the EUnetHTA Core Model®

Health Technology Assessment (HTA) is the multidisciplinary evaluation of one or more health interventions in their context of use. Since 2006 Agenas has been involved in the EU HTA network EUnetHTA (http://www.eunethta.eu/contactus/all/356/all). EUnetHTA's main aim is to increase collaboration and avoid inefficiencies and duplications by using shared, standardised and agreed methods. These in a continuous development cycle. One of the methods produced and used is the HTA Core Model® [EUnetHTA CM]. The idea behind the Model is the provision of a standard method for HTA evidence synthesis, structuring and presenting in a standard format to facilitate its use by network agencies and others.

The Core Model is divided into domains which represent the various aspects of the assessment of health technologies' research. Each domain contains a series of research questions or Assessment Elements (AEs). Ver 2.0 of the EUnetHTA Core Model is divided into domains:

1. Health problem and current use of technology (CUR)
2. Description and technical characteristics of technology (TEC)
3. Safety (SAF)
4. Clinical effectiveness (EFF)
5. Costs and economic evaluation (ECO)
6. Ethical analysis (ETH)
7. Organisational aspects (ORG)
8. Social aspects (SOC)
9. Legal aspects (LEG)

While using the Core Model in both Joint Actions 1 and 2 with the European Commission, Agenas identified some recurring common problems with the Core Model requiring further development work if the Model were to be used in the production of Health Technology Assessment reports in Italy.

The problems are mainly AE repetition, partial or complete overlap of AE content and likely answers, as well as lack of definition and clarity.

As a consequence Agenas undertook its own review of the Model to streamline its use and increase its relevance to everyday work of both HTA doers and HTA users. The Model basis for the review was version 2.0, medical and surgical intervention application.

The review process included a visual inspection of the 104 AEs with linked clarifications to identify any likely overlaps. The second phase consisted in grouping all AEs related to a unique concept (such as informed consent, technology and comparator(s) descriptions, regulatory information, mortality as a burden of illness measure, mortality as an outcome measure) into the likeliest domain of relevance. Agenas also attempted to link some of the

text of each AE's clarification note more closely with the AE and corrected any English syntax problems. In addition a single AE containing multiple questions was divided into sub questions. All original AE identifiers were maintained to denote the origin of the AE. To make identification of the information quicker and unpack some domains, Agenas also introduced two new domains REG or Regulatory Information and HAZ or Environmental Hazard for the assessment of possible harms not directly caused to the technology's recipient.

Agenas started using its Core Model adaptation for the 2014-2015 crop of Agenas HTA reports. Although some Agenas HTA reports are adaptations to Italy of up to date reports produced elsewhere or updates of previous Agenas work. In these cases the Agenas Core Model adaptation use will be partial. Agenas plans to evaluate and develop the Model further.

Appendix 2 – List of selected Assessment Elements (AEs)

Domain: Health problem and current use of technology (CUR)

A0002: What is the disease or health condition in the scope of this assessment?

Clarification: Use the target condition and ICD codes defined in the scope of the project and consider adding details such as: description of anatomical site, disease aetiology and pathophysiology, types of disease or classification according to origin, subtype, severity, stages, or risk level, and different manifestations of the condition. The following properties of the target condition are defined in separate assessment elements: risk factors (A0003), natural course (A0004), symptoms (A0005), and burden of disease for the society (A0006).

A0003: What are the known risk factors for the disease or health condition?

Clarification: Describing risk factors is especially important when they suggest possibilities for primary and secondary prevention. This information may affect the choice of comparator or the appraisal of the overall value of the technology under assessment. The risk factors for acquiring the condition, and the risk factors for relapses or worsening of the condition should be reported here, separately. The prevalence of the various risk factors might differ in different geographic areas and among different sub-populations.

A0004: What is the natural course of the disease or health condition?

Clarification: This assessment element should provide information on the prognosis and course of the health condition when untreated. This information is relevant for appraising the overall value of the technology. It may also guide the assessment of the predicted value or effectiveness of the technology, as technologies may work differently at different stages or severity grades of the disease, and there may be a relationship between earlier intervention and better prognosis. This element should also provide information on the time lag between the onset of disease and the symptoms or other findings that eventually trigger the need of diagnostics and care.

A0005 What are the symptoms and the burden of disease or health condition for the patient?

Clarification: This element should describe the patient's relevant symptoms before intervention with the technology, their severity and whether they are persistent, intermittent, or undulating taking into account different stages of the disease. Patients' perceptions of the burden of the disease are not always in line with the clinical seriousness of the disease or its societal burden.

A0006 What are the consequences of the disease or health condition for the society?

Clarification: Describe consequences and burden of the disease or health condition by providing information on prevalence or incidence of the disease that is prevented or treated by using the technology; disease-specific mortality and disability, life years lost, and/or disability-adjusted life years, quality of life, QALYs.

A0024 How is the disease or health condition currently diagnosed according to published guidelines and in practice?

Clarification: The effectiveness of an intervention may vary in differently diagnosed populations. A sensitive test tends to have low specificity such that there are several people who do not have the condition among the test-positive population. The effectiveness of an intervention in that population may be lower than in a population examined with a less sensitive test (but with more true positive cases). It is important to point out possible discrepancies between guidelines and actual practice

A0025 How is the disease or health condition currently managed according to published guidelines and in practice?

Clarification: It is important to describe whether the technology is an add-on or a replacement for the existing management options, and what the other evidence -based alternatives are. Are there differences in the treatment of diseases at their different stages? Identification of practice variations may imply differences in the quality of health care. Deviation from evidence -based guidelines may suggest over/under use of the technology

A0007 What is the target population in this assessment?

Clarification: Relevant for all assessments: both safety and effectiveness depend largely on the subpopulation towards which the intervention is targeted. The technology may be used for all patients with the condition, or only those in the early stages, or at a specific severity level, or for those at moderate risk of having the condition. Personalised medicine divides the target population into even smaller units when targeting the intervention to specific subgroups based on e.g. genetic profile. Use the target population defined in the scope of the project, and consider adding further details and description of who defined the selected subgroups and why. Point out e.g. if certain populations should be excluded from the analysis?

A0023 How many people belong to the target population?

Clarification: This information can be used to give an idea of the resource requirements in general for implementing the technology. Estimates of incidence and prevalence should be provided. Estimates of likely relevant increases or decreases in the size of the target population in the future should also be included.

A0011 How much are the technologies utilised?

Clarification: Provide national estimates for current and future utilisation rates for the indication under assessment, for both the technology under assessment and its comparators. Variations in utilisation reflect market access, sales figures, actual usage in hospital level and adherence to the use of the technology by both professionals and patients. Data on current and previous utilisation reflect the phase of the technology (experimental, emerging, established or obsolete). This also has implications for the availability of evidence and the level of uncertainties. Specific to Screening Technologies (2.0) What is the current rate of screening adherence?

Domain: Description and technical characteristics of technology (TEC)

B0001 What is the technology and the comparator(s)?

Clarification: This is relevant in all assessments. Use the descriptions of the technology and comparator(s) defined in that scope and elaborate them here in more detail. Technology may include a single device, a questionnaire, imaging or sequence of technologies. The HTA may address one or several similar technologies. Describe separately for the technology and the comparator: the type of device, technique, procedure or therapy; its biological rationale and mechanism of action, and also, describe how the technology differs from its predecessors, and the various current modifications or different manufacturers' products, especially if the dissimilarities affect performance.

B0002 What is the claimed benefit of the technology in relation to the comparators?

Clarification: This issue is especially relevant in new technologies with uncertain expectations and claims of benefit. Describe the following aspects:

- How is it expected to be an improvement over previous /existing technologies used for the same health problem?
- The expressed objectives for the implementation of the technology in health care; what are the claimed objectives e.g. increased safety, health benefit, accuracy or patient compliance, and whether it is intended to replace or to supplement existing technologies.

B0004 Who administers the technology and the comparators and in what context and level of care are they provided?

Clarification: This issue should be answered in case there is a relevant difference between the technology and the comparator. Describe the following aspects:

- Which professionals (nurses, doctors, and other professionals) apply and make decisions about starting or stopping the use of the technology?

- Do the patients themselves, or their carers, administer the technology?
- Who can select the patients, make referrals, decide to initiate the use of the technology, or interpret the outcome?
- Are there certain criteria (skills, function, training requirements) for the patients or professionals who will administer the technology?
Describe the level of care in which the technology is used: self care, primary care, secondary and tertiary care. If secondary or tertiary care, describe whether it is intended to be used in the outpatient or inpatient setting. Its role in the management pathway can be as a replacement, an add-on or for triage.

B0008 What kind of special premises are needed for the technology and the comparator (s)?

Clarification: This issue should be answered in case there is a relevant difference between the technology and the comparator. Many technologies require purpose-built premises, such as radiation-secured areas, Faraday cages, dressing rooms for the patient, or specific premises for storage and reconstitution of chemotherapy pharmaceuticals equipped with fume cupboards.Typical premises in primary or secondary care may differ markedly from country to country. A clear description of necessary facilities is needed instead of general statement (e.g. to be used in hospitals only).

B0009 What supplies are needed for the technology and the comparator(s)?

Clarification: This issue should be answered in case there is a relevant difference between the technology and the comparator. Examples are syringes, needles, pharmaceuticals and contrast agents, fluids, bandages and tests to identify patients eligible for treatment.

Domain: Regulatory aspects (REG)

A0020: For which indications has the technology received marketing authorisation or CE marking?

Clarification: There are both international and national market authorisation systems. An overview of the status withregard to key processes, e.g. CE marking, EMA/FDA approval is recommended. Also information on national data and ananalysis of possible discrepancies can be highly useful.

Potentially equivalent to A0020 within the WP5 REA Model.

A0021: What is the reimbursement status of the technology?

Clarification: Information on national reimbursement status from different countries for the technology. Notice that reimbursement status may differ for different purposes: e.g. treatment vs. prevention. Information on full coverage, co-payments, coverage under special circumstances/conditional coverage is useful.

Potentially equivalent to A0021 within the WP5 REA Model.

Domain: Safety (SAF)

C0008: How safe is the technology in relation to the comparator(s)?

Clarification: Here one should identify and describe the direct harms of the use and the administration of the technology and the comparator(s). Highlight the differences in the most important risks (i.e. the most severe and frequent harms) of the technology and its comparator. Consider:

- What is the frequency of serious AEs in participants group(s) treated with the technology and the comparator(s) under assessment?
- What are the most severe AEs in participants group(s) treated with the technology and the comparator(s) under assessment?

- What is the frequency of AEs lead to discontinuation in participants group(s) treated with the technology and the comparator(s) under assessment?
- What is the frequency of deaths in participants group(s) treated with the technology under assessment?
- What is the frequency of unexpected AEs in participants and comparison groups?
- What are the most frequent AEs in participants group(s) treated with the technology and the comparator (s) under assessment?

C0004: How does the frequency or severity of harms change over time or in different settings?

Clarification: This issue is especially relevant for new or evolving technologies where there are considerable uncertainties in the safety evidence, and in technologies with steep learning curves. How does the safety profile of the technology vary between different generations, approved versions or products? Is there evidence that harms increase or decrease in different organizational settings?

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of the technology?

Clarification: Typically, people with comorbidities and co-medication, pregnancy, intolerances, or specific genetic profiles, elderly people, children and immunosuppressed patients. Are there any relevant contra-indications or interactions with other technologies?

C0007: Are the technology and comparator(s) associated with user-dependent harms?

Clarification: Describe here what is known of the harms caused by the properties or behaviour of professionals, patients or other individuals who apply or maintain the technology. Is there e.g. a noteworthy risk of malfunction of a device, due to deficient user training or personal attitude; or a risk of errors related to reconstitution, dosage, administration, or storage of medicines, that may have serious consequences; or, is there a risk of addiction? Describe what is known of the learning curve, intra- or inter-observer variation in interpretation of outcomes, errors or other user-dependent concerns in the quality of care. For further information see Endpoint used in REA of pharmaceuticals – Safety

Domain: Clinical effectiveness (EFF)

D0001: What is the expected beneficial effect of the technology on mortality?

Clarification: Report the results both in absolute terms and relative to the comparator. Mortality is the preferred, objective endpoint for assessments of life- threatening conditions. Overall mortality and disease-specific mortality are distinguished. Several methods are used to adjust mortality rates and survival curves, e.g. relative survival (observed versus expected survival), which can be quite misleading; and hazard ratio (derived from a statistical method comparing the median survivals in the two groups). Note that progression-free survival is not a mortality endpoint; it describes the time from the beginning of an intervention until a patient shows signs of disease progression. Overall mortality refers to all-cause mortality. It is expressed either as mortality rates (incidence in given population, at given time point and usually risk standardized), or survival (number of people alive for a given period after an intervention). Disease-specific mortality is a proportion of the all-cause mortality. It should be noted that even if a given treatment reduces one type of death, it could increase the risk of dying from another cause, to an equal or greater extent. Disease-specific mortality is typically presented as rates and as age- and risk- adjusted measures such as hazard ratio. It is a frequently used endpoint in screening trials, where it is considered to be subject to bias. Supplement with relevant data if differences can be expected for specific subgroups.
Specific to Diagnostic Technologies: In diagnostic and screening technologies this issue refers to the expected beneficial effect of the test - treatment – chain.
Specific to Screening Technologies: In diagnostic and screening technologies this issue refers to the expected beneficial effect of the test - treatment - chain, With screening tests one should consider the effects of lead time bias, length time bias and selection bias to the mortality.

D0003: What is the effect of the technology on the mortality due to causes other than the target disease?

Clarification: Report the results both in absolute terms and relative to the comparator. This issue includes all unintended, either positive or negative effects of the technology on mortality. There may be e.g. decrease of mortality of another disease observed or suspected; or increased mortality due to accidents or hazardous medical interventions after false positive or incidental test results. Supplement with relevant data if differences can be expected for specific subgroups.
Specific to Diagnostic Technologies In diagnostic and screening technologies this issue refers to the expected beneficial effect of the test-treatment-chain, Specific to Screening Technologies In diagnostic and screening technologies this issue refers to the expected beneficial effect of the test-treatment-chain, With screening tests one should consider the effects of lead time bias, length time bias and selection bias to the mortality.

D0005: How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?

Clarification: Report the results both in absolute terms and relative to the comparator. Describe the efficacy and effectiveness of the technology on relevant disease outcomes (symptoms and findings). Outcomes such as function, quality of life and patient satisfaction are reported in other assessment elements of this domain. Report changes in severity, frequency and recurrence of symptoms and findings. Supplement with relevant data if differences can be expected for specific subgroups. See also guideline Endpoints used in REA of pharmaceutical.

D0006: How does the technology affect progression (or recurrence) of the disease or health condition?

Clarification: Report the results both in absolute terms and relative to the comparator. Report here efficacy and effectiveness outcomes such as complete cure, progression-free survival, time-to-event (next stage of disease, relapse. Describe here the duration of treatment effect on symptoms and findings: permanent, short term, long term, intermittent, undulating. Supplement with relevant data if differences can be expected for specific subgroups.

D0011: What is the effect of the technology on patients' body functions?

Clarification: Report the results both in absolute terms and relative to the comparator. International classification of function proposes the following categories for body functions: mental, sensory and pain, voice and speech, cardiac, respiratory and immune functions, genitourinary and reproductive functions, movement-related, and skin functions. Report the results both in absolute terms and relative to the comparator. Supplement with relevant data if differences can be expected for specific subgroups.

D0016: How does the use of the technology affect activities of daily living?

Clarification: Report the results both in absolute terms and relative to the comparator. Supplement with relevant data if differences can be expected for specific subgroups. Activities of Daily Living (ADL) is used in rehabilitation as an umbrella term relating to self care, comprising those activities or tasks that people undertake routinely in their every day life. The activities can be subdivided into personal care and domestic and community activities.

D0012: What is the effect of the technology on generic health-related quality of life?

Clarification: Report the results both in absolute terms and relative to the comparator. Supplement with relevant data if differences can be expected for specific subgroups. Health related quality of life (HRQL) is typically measured with self- or interviewer -administered questionnaires to measure cross-sectional differences in quality of life between patients at a point in time (discriminative instruments) or longitudinal changes in HRQL within patients during a period of time (evaluative instruments). Two basic approaches to quality - of -life measurement are available: generic instruments that provide a summary of HRQL; and specific instruments that focus on problems associated with single disease states, patient groups, or areas of function. Generic instruments include health profiles and instruments that generate health utilities. Each approach has its strengths and weaknesses and may be suitable for different circumstances

D0013: What is the effect of the technology on disease-specific quality of life?

Clarification: Report the results both in absolute terms and relative to the comparator. Supplement with relevant data if differences can be expected for specific subgroups. Health related quality of life (HRQL) is typically measured with self- or interviewer -administered questionnaires to measure cross-sectional differences in quality of life between patients at a point in time (discriminative instruments) or longitudinal changes in HRQL within patients during a period of time (evaluative instruments). Two basic approaches to quality - of -life measurement are available: generic instruments that provide a summary of HRQL; and specific instruments that focus on problems associated with single disease states, patient groups, or areas of function. Generic instruments include health profiles and instruments that generate health utilities. Each approach has its strengths and weaknesses and may be suitable for different circumstances

D0017: Was the use of the technology worthwhile?

Clarification: Describe patients' overall perception of the value of the intervention and their satisfaction with the treatment. For further information see Guidelines on Endpoints used in REA of pharmaceuticals: http://www.eunethta.eu/outputs/methodological-guideline-rea-pharmaceuticals-surrogate-endpoints

Domain: Costs and economic evaluation (ECO)

E0001: Can you identify what types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?

Clarification: Report the resource items taken into account in the analysis of the assessed technology and its comparator(s), the reasons for their inclusion as well as the sources of information used when identifying these. It must be included the resources related to the use of the technology and/or resources due to the use of technology. It is relevant the analysis perspective for the identification of resources. Providing the results in tabular form is recommended (e.g. length of stay in hospital).

E0002: Can you quantify what amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?

Clarification: Report the quantify of resource required to estimate overall costs (e.g. 5 days of stay in hospital (E0009). Include the appropriate values, ranges, probability distributions as well as all references used. Providing the results in tabular form is recommended. Report the methods and data source(s) used to measure resource use associated with the technologies.

E0009: What were the measured and/or estimated unit costs of the resources used by the assessed technology and its comparator(s)?

Clarification: For each technology report mean values of estimated costs and, where possible, information concerning distributions surrounding these estimates. Cost estimates from different viewpoints can be reported here (e.g., patient, hospital, societal). In addition, reporting disease-stage-specific cost estimates and costs estimated using varied discount rates. Providing the results in tabular form is recommended.

E0005: What is (are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s)?

Clarification: For each technology report mean values of estimated effects and, where possible, information concerning distributions surrounding these estimates. It is suggested that estimates are expressed both in natural units, whenever possible, and in alternative forms, such as QALYs. Report the methods and data source(s) used to estimate the outcomes associated with the technologies.

E0006: What are the estimated differences in costs and outcomes between the technology and its comparator(s)?

Clarification: There are numerous ways of calculating or comparing the differences in the costs and effects of the assessed technology and its comparator(s); typically, one or more of the following approaches are used when

reporting the results of health-economic evaluations: - listing the costs and outcomes of each technology in tabular form - an incremental cost-effectiveness ratio (ICER) - an incremental cost effectiveness plane or efficiency frontier - the net monetary benefit (NMB) and/or net health benefit (NHB).

E0010: What are the uncertainties surrounding the inputs and economic evaluation(s) of the technology and its comparator(s)?

Clarification: The effects of uncertainty should be reported separately for parameter values, assumptions and analytical methods used in the analysis, whenever possible. For example: - deterministic sensitivity analysis in tabular form or using a Tornado diagram - probabilistic sensitivity analysis, e.g., in the form of a CEAC - value-of-information analysis. The methods used in the sensitivity analysis should be reported in detail here.

E0012 : To what extent can the model estimates of inputs, outcomes, or economic evaluation(s) be considered as providing valid descriptions of the technology and its comparator(s)?

Clarification: It would be valuable to report any of the numerous ways of assessing to what extent the estimates for the technologies can be considered valid, For example: - How well the model predicts health effects - Whether model includes all aspects of resource use and costs considered important - Estimates of the potential direction and/or potential magnitude of bias induced - An attempt to identify key factors that could compromise the validity of the model. The process of validation and the types of validation addressed in the model should be reported here.

D0023: How does the technology modify the use of resources?

Clarification: This item aims to take into account the amount of resources resulting from organizational impact produced by the introduction of technology. Itisbased on results of ORG domain.

G0007: What are the likely budget impacts of implementing the technologies being compared?

Whenever a technology is introduced, there will be an impact on health care budgets. Budget impact analysis attempts to examine the likely impact of introducing a technology on financial outlays from, e.g., the perspective of different payers. Different payers include: government-level institutions; regions; municipalities; employers; insurance companies and patients/participants. The relevant perspective from which to estimate budget impact may change during different phases of the management process Budget impact analysis provides data to inform an assessment of the affordability of a technology. It also provides a service planning tool to inform decisions about taking the technology into use.

Appendix 3 – Questionnaire-based survey

QUESTIONARIO Rapid HTA Report

"Riparazione transcatetere della valvola mitrale negli adulti con rigurgito mitralico cronico"

Premessa

Nell'ambito dell'assessment sulla procedura di "Riparazione transcatetere della valvola mitrale per il rigurgito mitralico primario e/o secondario" Agenas ha condotto una ricerca al fine di identificare i dispositivi commerciali in uso in Italia per pazienti adulti ad alto rischio chirurgico o non candidabili alla chirurgia.

I dispositivi identificati sono:

- MitraClip® System (Abbott Vascular)

- Carillon® Mitral Contour System (Cardiac Dimension Inc)

Il questionario è finalizzato alla raccolta dei dati di attività ed economici, inerenti le procedure realizzate con il dispositivo MitraClip, nel proprio contesto, per gli anni 2012, 2013 e 2014. Il dispositivo Carillon, a causa del numero esiguo di procedure eseguite in Italia, non sarà oggetto di indagine del presente questionario.

Parte 1 di 3

PARTE ANAGRAFICA

Dati identificativi Referente

Nome e Cognome:
Regione:
Città:
Azienda:
Ufficio:
indirizzo e-mail:

Dati identificativi Compilatore

Nome e Cognome:
Azienda:
Ufficio:
indirizzo e-mail:
Numero telefono:

Parte 2 di 3

POPOLAZIONE E PERCORSO CLINICO

La nostra popolazione di riferimento è:

adulti con rigurgito mitralico cronico, primario o secondario, da moderato a grave e grave ad alto rischio chirurgico o non candidabili alla chirurgia.

	2012	2013	2014
Numero di casi di rigurgito mitralico diagnosticati			
- degenerativo/primario (D/P)			
- funzionale /secondario (F/S)			

Numero di casi di rigurgito mitralico trattati			
- degenerativo/primario			
- funzionale /secondario			

	2012		2013		2014	
Distribuzione dei pazienti diagnosticati per età (numero)	**(D/P)**	**(F/S)**	**(D/P)**	**(F/S)**	**(D/P)**	**(F/S)**
18- 50						
51-75						
> 76						
Distribuzione dei pazienti trattati per età (numero)						
18-50						

51-75			
> 76			
Popolazione: adulti con rigurgito mitralico cronico PRIMARIO ad alto rischio chirurgico/non candidabili alla chirurgia			
	2012	2013	2014
Numero di pazienti diagnosticati NON trattati			
Numero di pazienti diagnosticati trattati con TERAPIA FARMACOLOGICA			
Numero di pazienti diagnosticati trattati con Mitraclip			
Numero di pazienti diagnosticati trattati con altro intervento (specificare all'interno della cella indicando anche il numero)			
Popolazione: adulti con rigurgito mitralico cronico SECONDARIO ad alto rischio chirurgico/non candidabili alla chirurgia			
Numero di pazienti diagnosticati trattati solo con TERAPIA FARMACOLOGICA			
Numero di pazienti diagnosticati trattati con TERAPIA FARMACOLOGICA e CRT (Terapia di resincronizzazione cardiaca)			
Numero di pazienti diagnosticati trattati con Mitraclip			
Numero di pazienti diagnosticati trattati con altro intervento (specificare all'interno della cella in cui è riportato il numero)			

Entità del rigurgito mitralico: valutazione ecocardiografica (Rif. Linee guida ASE (Società Americana di Ecocardiografia) e EAE (Associazione Europea di Ecocardiografia)

	2012	2013	2014
Numero di pazienti con rigurgito mitralico moderato (++)			
Numero di pazienti con rigurgito mitralico grave (+++)			

Parte 3 di 3

a) CASI e DETTAGLI DEL TRATTAMENTO

Adulti con rigurgito mitralico cronico PRIMARIO ad alto rischio chirurgico/non candidabili alla chirurgia

Numero totale di procedure con il *Mitraclip System* effettuate per la popolazione di riferimento	2012	2013	2014
Numero di pazienti trattati per tipologia di ricovero			N° pazienti
	Ricovero Ordinario		
	Day-hospital/Day-surgery		
Numero di casi con complicanze intra-procedurali	2012	2013	2014
	Specificare n° e tipologia di complicanza:	**Specificare n° e tipologia di complicanza:**	**Specificare n° e tipologia di complicanza:**

Adulti con rigurgito mitralico cronico SECONDARIO ad alto rischio chirurgico/non candidabili alla chirurgia

	2012	2013	2014
Numero totale di procedure con il *Mitraclip System* effettuate per la popolazione di riferimento			
Numero di pazienti trattati per tipologia di ricovero			N° pazienti
	Ricovero Ordinario		
	Day-hospital/Day-surgery		
Numero di casi con complicanze intra-procedurali	2012	2013	2014
	Specificare n° e tipologia di complicanza:	**Specificare n° e tipologia di complicanza:**	**Specificare n° e tipologia di complicanza:**

RISORSE

Dati Economico-quantitativi

	2012	2013	2014
Quantità acquistata			
Quantità utilizzata			
Prezzo medio di acquisto			

Ulteriore strumentazione (dispositivi) necessari per la procedura

Tipologia di strumentazione	Descrizione/utilizzo della strumentazione	Costo

Formazione del personale

Tipologia Professionalità	Tempo dedicato	Costo della formazione

c) Risorse umane impiegate nella procedura

Medico/Clinico	**Specialità**	
	Numero di unità	
	Tempo (in minuti)	
Anestesista	**Tempo (in minuti)**	
Infermiere	**Tipologia**	
	Numero di unità	
	Tempo (in minuti)	
Altri professionisti	**Tipologia**	
	Numero di unità	
	Tempo (in minuti)	

d) Altre risorse utilizzate per la procedura

Setting	**Sala operatoria (minuti)** **(specificare setting differenti)**		
	Numero di giornate di ricovero (media)		
Preparazione paziente ***(Descrivere brevemente la procedura)***	**Ore**		
	Risorse Umane		
	Test di Laboratorio		
	Esami diagnostici		
Farmaci	**Fase pre-operatoria**		
	Fase Operatoria		
	Fase Post-operatoria		
Materiale monouso utilizzato nella fase intra-operatoria	Descrizione	Numero di unità	Costo per unità

Materiale monouso utilizzato nella fase pre-operatoria e post-operatoria	Descrizione	Numero di unità	Costo per unità

Appendix 4 – Search strategy effectiveness (EFF) and safety (SAF) domain.

Language: English.

PubMed (1st Jan 2005 – 16th May 2015)

"Mitral Valve Insufficiency" MESH term OR [Title/Abstract] "Mitral Valve Incompetence" OR "Failed Mitral valve" OR "Mitral Regurgitation" OR "Mitral Valve Insufficiency" OR "Mitral Valve Regurgitation" OR "Mitral Valve Incompetence" OR "Mitral Insufficiency" OR " mitral valve repair" OR "Mitral Incompetence" OR "leaflets repair" OR "percutaneous edge-to-edge repair" OR " transcatheter edge-to-edge repair" "percutaneous annulus repair" OR "transcatheter annulus repair" OR "transapicalchordal repair" OR "Transcatheter mitral valve" OR "mitral valve repair" OR "transapical mitral valve repair" OR "transapicalchordal replacement" OR " percutaneous chordal repair" OR "transcatheter chordal repair"	AND	(Carillon* AND "annulus repair") OR ("MitraClip System" AND leaflets) OR (NeoChord*" AND chordal) OR neochord OR MitraClip OR Carillon -	AND	"Safety" MESH term OR "Comparative Effectiveness Research" MESH term OR "quality of life" MESH term OR "Return to work" MESH term OR "Patient Satisfaction" MESH term OR "Hospitalization MESH term OR "Patient discharge" MESH term OR Survival Rate MESH term OR Treatment Outcome MESH term OR "Follow-Up Studies" MESH term OR "Quality of life" MESH term [Title/Abstract] "Length of stay OR "Duration of inotropic support" OR "Exercise capacity" OR Safety OR Mortality OR Effectiveness OR "return-to-work" OR "Back-to-Work" OR Complication* OR pain OR "Adverse events" OR "side effects" OR morbility OR survival
"mitral valve" and transcatheter	AND		AND	

EMBASE *(1st Jan 2005 – 17th May 2015)*

'mitral valve repair'/exp EMTREE term OR "mitral valve disease"/exp EMTREE term OR 'mitral valve regurgitation'/exp EMTREE term OR "Mitral Valve Incompetence" OR	AND	'annuloplasty ring'/exp EMTREE term OR 'implantable clip'/exp EMTREE term OR "Transcatheter	AND	EMTREE TERM: 'quality of life'/exp OR EMTREE TERM:"clinical effectiveness" OR EMTREE TERM: "comparative effectiveness" OR EMTREE TERM: 'device safety'/exp OR EMTREE TERM: 'program

"Failed Mitral valve" OR "Mitral Regurgitation" OR "Mitral Valve Insufficiency" OR "Mitral Valve Regurgitation" OR "Mitral Valve Incompetence" OR "Mitral Insufficiency" OR " Miitral valve repair" OR "Mitral Incompetence" OR "leaflets repair" OR "percutaneous edge-to-edge repair" OR " transcatheter edge-to-edge repair" "percutaneous annulus repair" OR "transcatheter annulus repair" OR "transapicalchordal repair" OR "Transcatheter mitral valve" OR "mitral valve repair" OR "transapical mitral valve repair" OR "transapicalchordal replacement" OR " percutaneous chordal repair" OR "transcatheter chordal repair"		mitral valve repair " OR (Carillon AND "annulus repair") OR ("MitraClip System" AND leaflets) OR ("CARILLON Mitral Contour System" AND annulus) OR (NeoChord*" AND DS1000 AND chordal) OR neochord OR MitraClip OR Carillon		effectiveness'/exp OR EMTREE TERM: 'program evaluation'/exp OR EMTREE TERM: 'risk assessment'/exp OR EMTREE TERM: Mortality/exp OR EMTREE TERM: "return-to-work"/exp OR EMTREE TERM: "Back-to-Work"/exp OR EMTREE TERM: 'program acceptability'/exp OR EMTREE TERM: Safety/exp OR EMTREE TERM: 'heart failure'/exp EMTREE TERM: Ventricular Function, Left" OR EMTREE TERM:" Ventricular Dysfunction" OR "Length of stay" OR " "Exercise capacity" OR Complications OR pain OR 'device failure analysis'/exp OR Effectiveness OR "Comparative Effectiveness Research"
"mitral valve" and transcatheter	AND		AND	Survival Rate OR Treatment Outcome OR "Postoperative Complications" "Adverse events" OR "side effects" OR "quality of life" OR QoL OR "Right Ventricular failure"OR survival OR morbility OR effectiveness

Cochrane Library *(1st Jan 2005 – 18th May 2015)*

"Mitral Valve Insufficiency" MESH term OR [Title/Abstract] "Mitral Valve Incompetence" : ti,ab,kw OR "Failed Mitral valve" : ti,ab,kw OR OR "Mitral Regurgitation" : ti,ab,kw OR OR "Mitral Valve Insufficiency" : ti,ab,kw OR "Mitral Valve Regurgitation" : ti,ab,kw OR "Mitral Valve Incompetence" : ti,ab,kw OR	AND	neochord OR MitraClip OR Carillon	AND	MESH descriptor: Safety OR MESH descriptor: Comparative Effectiveness Research OR MESH descriptor: "quality of life" OR MESH descriptor: "Return to work" OR MESH descriptor: "Patient Satisfaction" OR MESH descriptor: "Hospitalization OR MESH descriptor:"Patient discharge" OR MESH descriptor: Survival Rate OR MESH descriptor: Treatment Outcome OR MESH descriptor: "Postoperative Complications" OR MESH descriptor: "Follow-Up Studies" OR MESH descriptor: "Heart Failure" OR

"Mitral Insufficiency" : ti,ab,kw OR " mitral valve repair" : ti,ab,kw OR "Mitral Incompetence" : ti,ab,kw OR "leaflets repair" : ti,ab,kw OR "percutaneous edge-to-edge repair" : ti,ab,kw OR " transcatheter edge-to-edge repair" : ti,ab,kw OR "percutaneous annulus repair" : ti,ab,kw OR "transcatheter annulus repair" : ti,ab,kw OR "transapicalchordal repair" : ti,ab,kw OR "Transcatheter mitral valve" : ti,ab,kw OR "mitral valve repair" : ti,ab,kw OR "transapical mitral valve repair" : ti,ab,kw OR "transapicalchordal replacement" : ti,ab,kw OR " percutaneous chordal repair" : ti,ab,kw OR "transcatheter chordal repair" : ti,ab,kw				MESH descriptor:"Ventricular Function, Left" OR MESH descriptor:" Ventricular Dysfunction "Length of stay " : ti,ab,kw OR "Duration of inotropic support" : ti,ab,kw OR "Exercise capacity" : ti,ab,kw OR Safety:ti,ab,kw OR Mortality:ti,ab,kw OR Effectiveness:ti,ab,kw OR "return-to-work" " : ti,ab,kw OR "Back-to-Work" " : ti,ab,kw OR Complication:ti,ab,kw OR Complications:ti,ab,kw OR pain:ti,ab,kw OR "Adverse events" :ti,ab,kw OR "side effects" :ti,ab,kw OR morbility" : ti,ab,kw OR survival : ti,ab,kw OR morbility: ti,ab,kw OR effectiveness : ti,ab,kw
"mitral valve" and transcatheter" : ti,ab,kw				

Search report – Registered trials

Objective: To identify all the relevant ongoing trials on the three devices assessed within the present project, CARILLON and MitraClip.

Methods:
Searches have been performed on a list of registries and databases defined during the project planning:

- ClincalTrials.gov https://clinicaltrials.gov
- ISRCTN http://www.isrctn.com/
- EU Clinical Trials Register https://www.clinicaltrialsregister.eu
- metaRegister of Controlled Trials (mRCT) www.isrctn.com/page/mrct
- International Clinical Trials Registry Platform (ICTRP) www.who.int/ictrp

Date of searches: 15/05/2015
MeSH: *Mitral Valve Insufficiency; Mitral Incompetence; Mitral Insufficiency; Mitral Regurgitation; Mitral Valve Incompetence; Mitral Valve Regurgitation.*
Keywords: *Mitraclip; Carillon.*
Search limits: Adults, Elderly.
Time limit: None.

Results
Initial number of records: 40

- ClincalTrials.gov: *19 results.*
- ISRCTN: *No results.*
- EU Clinical Trials Register: *No results.*
- metaRegister of Controlled Trials (mRCT)
  The service is under review. Two registries are suggested:
  - The WHO trial search portal for studies worldwide, International Clinical Trials Registry Platform (ICTRP) – *already included in the list of registries to consult.*
  - The UKCTG for studies recruiting in the UK (data pooled from ISRCTN and ClinicalTrials.gov): http://www.ukctg.nihr.ac.uk/default.aspx
    No results.
- International Clinical Trials Registry Platform (ICTRP): *20 results.*

Records excluded (with reason) at first screening: 18 duplicate records; 6 irrelevant endpoint or topic.
Records potentially relevant: 17

Records actually included (after in-deep analysis):7 (see Effectiveness domain, Table 5.3 and 5.4).

Appendix 5 – Quality assessment of Effectiveness (EFF) and Safety (SAF) domain

Quality assessment of systematic reviews (final score calculated from judgments provided by 2 independent assessors).

Munkholm-Larsen et al., 2014	R-AMSTAR items										
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
	4	3.5	4	2.5	3.5	4	2	2	1.5	1	2

Total score*: 30/44

** the R-AMSTAR total score has a range of 11 to 44 where 11 signifies that none of the AMSTAR criteria were satisfied and a score of 44 reveals that all of the criteria of systematic review excellence were verified.*

List of R-AMSTAR items: (1) Was an 'a priori' design provided? (2) Was there duplicate study selection and data extraction?(3) Was a comprehensive literature search performed? (4) Was the status of publication (i.e. grey literature) used as an inclusion criterion? (5) Was a list of studies (included and excluded) provided? (6) Were the characteristics of the included studies provided? (7) Was the scientific quality of the included studies assessed and documented? (8) Was the scientific quality of the included studies used appropriately in formulating conclusions? (9) Were the methods used to combine the findings of studies appropriate? (10) Was the likelihood of publication bias assessed? (11) Was the conflict of interest included?

Adapted from: Kung J, Chiappelli F, Cajulis OO, Avezova R, Kossan G, Chew L, Maida CA. From Systematic Reviews to Clinical Recommendations for Evidence-Based Health Care: Validation of Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) for Grading of Clinical Relevance. The Open Dentistry Journal, 2010, 4, 84-91).

Quality assessment of included primary studies by the IHE 18-items checklist.

The quality is "acceptable" if the study has 14 or more positive answers (i.e. "Yes").

Item #	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	#14	#15	#16	#17	#18	Yes
MitraClip																			
Alegria-Barrero, 2014	Y	Y	N	Y	Y	Y	Y	na	Y	Y	Y	Y	Y	N	N	Y	Y	Y	14
Armoiry, 2013	Y	Y	Y	N	N	Y	Y	na	Y	Y	Y	Y	Y	N	Y	Y	Y	N	13
Attizzani, 2015	Y	Y	N	Y	Y	Y	Y	na	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	15
Bozdag-Turan, 2014	Y	Y	N	Y	N	Y	Y	na	Y	Y	Y	Y	Y	N	N	Y	Y	N	12
Braun, 2014	Y	Y	nr	Y	Y	Y	Y	na	Y	Y	Y	Y	Y	Y	N	Y	Y	N	14
Glower, 2014	Y	Y	Y	Y	N	Y	Y	na	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	15
Hellhammer, 2014	Y	Y	N	Y	N	Y	Y	na	Y	Y	N	Y	Y	Y	N	Y	Y	N	12
Hellhammer, 2015	Y	Y	N	Y	Y	N	Y	na	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	14
Koifman, 2014	Y	Y	N	Y	Y	N	Y	na	Y	Y	Y	Y	Y	Y	N	Y	Y	N	13
Reichenspurner, 2013	Y	Y	Y	Y	Y	N	Y	na	Y	Y	Y	Y	Y	N	N	Y	Y	N	13
Rudolph, 2014	Y	Y	Y	Y	N	N	Y	na	Y	Y	Y	Y	Y	na	N	Y	Y	Y	13
Toggweiler, 2014	Y	Y	Y	Y	Y	N	Y	na	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	16
Vandendriessche, 2014	Y	Y	Y	Y	Y	Y	Y	na	Y	Y	Y	Y	Y	Y	N	Y	Y	N	15
Wiebe, 2014	Y	Y	Y	N	N	N	Y	na	Y	Y	Y	Y	Y	N	N	Y	Y	Y	12
Yeo, 2014	Y	Y	Y	Y	Y	N	Y	na	Y	Y	Y	Y	Y	na	Y	Y	Y	N	14
CARILLON																			
Schofer, 2009	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	16
Siminiak, 2012	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	14

Key: nr= not reported; na= not applicable, Y= Yes, N= No.

Adapted from: Moga C, Guo B, Schopflocher D,Harstall C. Development of a quality appraisal tool for case series studies using a modified Deplhi technique. Methodology Paper. Edmonton AB: Institute of Health Economics, 2012.

List of items: *1. Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction or methods section? 2. Are the characteristics of the participants included in the study described? 3. Were the cases collected in more than one centre? 4. Are the eligibility criteria (inclusion and exclusion criteria) to entry the study explicit and appropriate? 5. Were participants recruited consecutively? 6. Did participants enter the study at a similar point in the disease? 7. Was the intervention clearly described in the study? 8. Were additional interventions (co-interventions) clearly reported in the study? 9. Are the outcome measures clearly defined in the introduction or methodology section? 10. Were relevant outcomes appropriately measured with objective and/or subjective methods? 11. Were outcomes measured before and after intervention? 12. Were the statistical tests used to assess the relevant outcomes appropriate? 13. Was the length of follow-up reported? 14. Was the loss to follow-up reported? 15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes? 16. Are adverse events reported? 17. Are the conclusions of the study supported by results? 18. Are both competing interest and source of support for the study reported?*

Appendix 6 – Search strategy cost and economic evaluation domain (ECO)

PUBMED

19th May 2015

"Mitral Valve Insufficiency" MESH term OR **Search for [Title/Abstract]** "Mitral Valve Incompetence" OR "Failed Mitral valve" OR "Mitral Regurgitation" OR "Mitral Valve Insufficiency" OR "Mitral Valve Regurgitation" OR "Mitral Valve Incompetence" OR "Mitral Insufficiency" OR "mitral valve repair" OR "Mitral Incompetence" OR "leaflets repair" OR "percutaneous edge-to-edge repair" OR "transcatheter edge-to-edge repair" "percutaneous annulus repair" OR	AND	(Carillon* AND "annulus repair") OR ("MitraClip System" AND leaflets) OR MitraClip OR Carillon	AND	Mesh descriptor "Costs and Cost Analysis" OR Mesh descriptor "Economics" OR Mesh descriptor "Cost Allocation" OR Mesh descriptor "Cost-Benefit Analysis" OR Mesh descriptor "Cost of Illness" OR Mesh descriptor "Cost Control" OR Mesh descriptor "Cost Savings" OR Mesh descriptor "Health Care Costs" OR Mesh descriptor "Direct Service Costs" OR Mesh descriptor "Hospital Costs" OR Mesh descriptor "Efficiency", Organizational/economics Cost-effectiveness [Title/Abstract] OR Cost-utility [Title/Abstract] OR Cost–effectiveness [Title/Abstract] OR "resource used" [Title/Abstract] OR "Cost effectiveness analysis" *[Title/Abstract] OR CMA

"transcatheter annulus repair" OR "transapical chordal repair" OR "Transcatheter mitral valve" OR "mitral valve repair" OR "transapical mitral valve repair" OR "transapical chordal replacement" OR "percutaneous chordal repair" OR "transcatheter chordal repair"				(title/abstract) OR "cost effectiveness" (title/abstract) OR CEA (title/abstract) OR "cost utility" (title/abstract) OR CUA (title/abstract) OR CEA [Title/Abstract] "Cost utility analysis" [Title/Abstract] OR "Cost benefit analysis" [Title/Abstract] OR "Cost consequences analysis"*[Title/Abstract] OR
"mitral valve" and transcatheter	AND		AND	"Cost minimization analysis" *[Title/Abstract] OR (economic AND (evaluation OR analysis OR aspect OR assessment)) [Title/Abstract] OR "Budget Impact Analysis" [title/abstract]

27 records

EMBASE

19th May 2015

'mitral valve repair'/exp EMTREE term OR "mitral valve disease"/exp EMTREE term OR 'mitral valve regurgitation'/exp EMTREE term	**AND**	'annuloplasty ring'/exp EMTREE term OR	**AND**	EMTREE TERM: "Economic aspect"/exp OR EMTREE TERM: 'cost analysis'/exp OR

OR "Mitral Valve Incompetence" OR "Failed Mitral valve" OR "Mitral Regurgitation" OR "Mitral Valve Insufficiency" OR "Mitral Valve Regurgitation" OR "Mitral Valve Incompetence" OR "Mitral Insufficiency" OR "Miitral valve repair" OR "Mitral Incompetence" OR "leaflets repair" OR "percutaneous edge-to-edge repair" OR " transcatheter edge-to-edge repair" "percutaneous annulus repair" OR "transcatheter annulus repair" OR "transapical chordal repair" OR "Transcatheter mitral valve" OR		'implantable clip'/exp EMTREE term OR "Transcatheter mitral valve repair " OR (Carillon AND "annulus repair") OR ("MitraClip System" AND leaflets) OR ("CARILLON Mitral Contour System" AND annulus) OR MitraClip OR Carillon		EMTREE TERM: 'cost of illness'/exp OR EMTREE TERM:" economic evaluation"/exp OR EMTREE TERM: 'cost minimization analysis'/exp EMTREE TERM: 'cost effectiveness analysis'/exp EMTREE TERM: 'cost benefit analysis'/exp OR EMTREE TERM: 'cost utility'/exp OR EMTREE TERM: "cost control:/exp OR EMTREE TERM: "cost":/exp OR EMTREE TERM: "health care cost":/exp OR EMTREE TERM: 'hospitalization cost'/exp OR CMA:ab,ti OR CEA:ab,ti OR CUA:ab,ti OR (economic AND ('evaluation'/exp OR 'analysis'/exp OR aspect OR assessment)) OR ('budget impact analysis':ab,ti ORBIA:ab,ti)"

"mitral valve repair" OR "transapical mitral valve repair" OR "transapical chordal replacement" OR "percutaneous chordal repair" OR "transcatheter chordal repair"				OR Cost Analysis/:ab,ti OR "Economics"/:ab,ti OR "Cost Allocation"/:ab,ti OR "Cost-Benefit/:ab,ti OR "Cost Control"/exp OR "Cost Saving"/:ab,ti OR
"mitral valve" and transcatheter	**AND**		**AND**	"Cost-effectiveness"/:ab,ti OR "Cost-utility"/:ab,ti

14 records

COCHRANE LIBRARY
20th May 2015

"Mitral Valve Insufficiency" MESH term OR **Search for [Title/Abstract]** "Mitral Valve Incompetence" : ti,ab,kw OR "Failed Mitral valve" : ti,ab,kw OR OR "Mitral Regurgitation" : ti,ab,kw OR OR	AND	MitraClip OR Carillon	**AND**	Mesh descriptor ""Costs and Cost Analysis" OR Mesh descriptor "Economics" OR Mesh descriptor "Cost Allocation" OR Mesh descriptor "Cost-Benefit Analysis" OR Mesh descriptor "Cost of Illness" OR Mesh descriptor "Cost Control" OR

"Mitral Valve Insufficiency" : ti,ab,kw OR "Mitral Valve Regurgitation" : ti,ab,kw OR "Mitral Valve Incompetence" : ti,ab,kw OR "Mitral Insufficiency" : ti,ab,kw OR "mitral valve repair" : ti,ab,kw OR "Mitral Incompetence" : ti,ab,kw OR "leaflets repair" : ti,ab,kw OR "percutaneous edge-to-edge repair" : ti,ab,kw OR "transcatheter edge-to-edge repair" : ti,ab,kw OR "percutaneous annulus repair" : ti,ab,kw OR "transcatheter annulus repair" : ti,ab,kw OR "transapical chordal repair" : ti,ab,kw OR "Transcatheter mitral valve" : ti,ab,kw OR "mitral valve repair" : ti,ab,kw OR "transapical mitral valve repair" : ti,ab,kw OR "transapical chordal replacement" : ti,ab,kw OR "percutaneous chordal repair" : ti,ab,kw OR				Mesh descriptor "Cost Savings" OR Mesh descriptor "Health Care Costs" OR Mesh descriptor "Direct Service Costs" OR Mesh descriptor "Hospital Costs" OR Cost-effectiveness OR Cost-utility OR Cost – effectiveness OR Cost – utility OR "resource used" OR "Cost effectiveness analysis" * OR CEA OR "Cost utility analysis " OR CUA "Cost benefit analysis" OR CBA "Cost consequences analysis " OR "Cost minimization analysis" OR (economic AND (evaluation OR analysis OR aspect OR assessment)) OR

"transcatheter chordal repair" : ti,ab,kw				"Budget Impact Analysis"
"mitral valve" and transcatheter" : ti,ab,kw				

3 economic studies, 7 trials

CINHAL

20th May 2015

0 record

Appendix 7 – Economic domain (ECO). List of excluded studies with reasons for exclusion

Duplicate (n=1)

Palmieri V, Baldi C, Di Blasi PE, Citro R, Di Lorenzo E, Bellino E, et al. Impact of DRG billing system on health budget consumption in percutaneous treatment of mitral valve regurgitation in heart failure. J Med Econ. 2015;18(2):89-95.

No study design (n=5)

Adamo et al. Effectiveness of MitraClip Therapy in Patients with Refractory Heart Failure - Journal of Interventional Cardiology 28 (1) p. 61-68 2015.

Miniati et al. Hospital-based health technology assessment on the use of mitral clips in the treatment of mitral regurgitation - Technology and healthcare 1(1) 2013.

Palmieri V, Baldi C, Di Blasi PE, Citro R, Di Lorenzo E, Bellino E, et al. Impact of DRG billing system on health budget consumption in percutaneous treatment of mitral valve regurgitation in heart failure. J Med Econ. 2015;18(2):89-95.

Roggeri et al. Difference in resource consumption and costs of patients with chronic heart failure with or without mitral regurgitation. Heart Failure Congress, 2012.

Ussia et al. Quality of life following percutaneous mitral valve repair with the MitraClip System International Journal of Cardiology 155 (2012) 194–200.

Congress presentation (n=1)

Capodanno D. Impatto Della Mitraclip Sulla Sostenibilità Economica Dello Scompenso Cardiaco Con Insufficienza Mitralica - ANMCO Congress 2014.

Irretrievable study (n=1)

H C, L B, V G, J H, A A. A Canadian cost-effectiveness analysis of transcatheter mitral valve repair with the MitraClip System in high surgical risk patients with significant mitral regurgitation (Provisional abstract). Journal of Medical Economics.

Appendix 8 –Quality assessment cost and economic evaluation domain (ECO)

Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 1996;313:275–83

Item	Yes	No	Not Clear	Not appropriate
Study design				
(1) The research question is stated				
(2) The economic importance of the research question is stated				
(3) The viewpoint(s) of the analysis are clearly stated and justified				
(4) The rationale for choosing the alternative programmes or interventions compared is stated				
(5) The alternatives being compared are clearly described				
(6) The form of economic evaluation used is stated				
(7) The choice of form of economic evaluation is justified in relation to the questions addressed				
Data collection				
(8) The source(s) of effectiveness estimates used are stated				
(9) Details of the design and results of effectiveness study are given (if based on a single study)				
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)				
(11) The primary outcome measure(s) for the economic evaluation are clearly stated				
(12) Methods to value health states and other benefits are stated				
(13) Details of the subjects from whom valuations were obtained are given				

(14) Productivity changes (if included) are reported separately				
(15) The relevance of productivity changes to the study question is discussed				
(16) Quantities of resources are reported separately from their unit costs				
(17) Methods for the estimation of quantities and unit costs are described				
(18) Currency and price data are recorded				
(19) Details of currency of price adjustments for inflation or currency conversion are given				
(20) Details of any model used are given				
(21) The choice of model used and the key parameters on which it is based are justified				
Analysis and interpretation of results				
(22) Time horizon of costs and benefits is stated				
(23) The discount rate(s) is stated				
(24) The choice of rate(s) is justified				
(25) An explanation is given if costs or benefits are not discounted				
(26) Details of statistical tests and confidence intervals are given for stochastic data				
(27) The approach to sensitivity analysis is given				
(28) The choice of variables for sensitivity analysis is justified				
(29) The ranges over which the variables are varied are stated				
(30) Relevant alternatives are compared				
(31) Incremental analysis is reported				
(32) Major outcomes are presented in a disaggregated as well as aggregated form				

(33) The answer to the study question is given				
(34) Conclusions follow from the data reported				
(35) Conclusions are accompanied by the appropriate caveats				