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Rapid HTA report

Epicardial clip for the left atrial appendage closure

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Nicola Signore declares that in the last 3 years he has worked for Bioflow III Italia, for the SICI-GISE, for the TRILOGY ACS STUDY H7T-MC-TABY. He declares to have participated in the Medical Company committee. He declares to have participated in conferences sponsored by Terumo Italia Srl, Astrazeneca Spa, Eli-Lilly Italy Spa, Menarini and to have participated in meetings organized by Philips Volcano, Astrazeneca Spa, Bayer Spa, Servier, Abbott, Daichi Sankyo.

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Attached - Appendices to the Rapid HTA Report: Epicardial clip for the left atrial appendage closure

Abstract

Background: Atrial fibrillation (AF) is related to a high risk of stroke. The main role in etiopathogenesis is played by the left atrial appendage closure (LAA). As many as 95% of thrombi in non valvular AF are located into the LAA. Prevention of stroke consists in anticoagulation therapy which, however, has its limits and risks. The epicardial clip for LAA closure (LAAC) is a technology in expansion that represents an alternative to oral anticoagulants (OA) in the prevention of stroke.

Aim: To assess effectiveness, safety and costs of epicardial clip closure of the LAA in patients with AF or with diagnosis of LAA thrombosis (with or without AF).

Methods: We carried out a rapid HTA report on current use, technical aspects, effectiveness, safety, and costs of the AtriClip system (AtriCure, Inc.). A systematic literature review was performed relative to effectiveness, safety, economic evaluations, and a cost analysis domains. We collected information from national medical devices databases, clinical experts, and industry.

Results: The AtriClip system offers different device models to perform the closure of the LAA by three surgical approaches: sternotomy (AtriClip Standard, Long, and FLEX), thoracotomy (AtriClip PRO) or thoracoscopy (AtriClip PRO2). The estimated annual number of AtriClip used was relatively small. From 2011 to first half of 2017, the total national volumes of AtriClip devices used were very low (around 160 units) showing a constant trend until 2015. Starting from 2016, the increase in use is proportionally attributable to Lombardia Region. About 85% of all AtriClip devices are used in four centers relative to four Regions (Piemonte, Veneto, Lombardia, and Toscana). The evidence regarding the effectiveness and safety of AtriClip for LAAC is limited. Only case series studies were identified and these are considered evidence of low quality. Efficacy of LAA exclusion varied from 95.7% to 100%. No reported stroke or cerebrovascular event was associated to the LAAC, no thrombi in the left atrium or on the endocardial side of the closed LAA was found. No clip migration or structural deterioration was found. None of the reported adverse events seemed to be related to the clip implantation. We found no economic studies on the AtriClip system. In the explored time frame, the Italian purchased unit cost ranged from € 1,452.53 to € 4,139.20 (all AtriClip models). The Italian cost and volume data shows differences in expenditure along years and between the national areas, probably related to the surgical procedure approach used for LAAC.

Conclusion: The AtriClip system is available on the Italian market since 2009 and all models are CE-marked and FDA-approved. All studies, included in this report, concluded that epicardial clip closure of the LAA is a promising technique. However, these data come from relatively small observational studies and do not allow final statements to support the use of the technology.

Outcomes need to be confirmed by sufficiently powered studies with longer follow-up focusing on stroke/AF prevention via LAAC.

Sintesi in italiano

La fibrillazione atriale (FA) è una alterazione del ritmo cardiaco che può determinare ristagno di sangue nell'atrio con conseguente formazione di trombi e rischio di ictus. La FA è l'aritmia più comune con una prevalenza in aumento a causa del progressivo invecchiamento della popolazione e del miglioramento della diagnosi di FA silente. Circa il 20% degli ictus sono imputabili ai pazienti affetti da FA e la FA stessa aumenta di 5 volte il rischio di ictus. La stima della prevalenza della AF è di circa il 2-3% negli adulti con età pari o superiore a 20 anni, con una maggiore prevalenza nelle persone anziane, in pazienti ipertesi, con insufficienza cardiaca, malattia coronarica (CAD), cardiopatia valvolare, obesità, diabete mellito o malattia renale cronica (CKD) [ESC Guidelines 2016; Gavino C, 2016]. Un ruolo rilevante nell'eziopatogenesi è svolto dall'auricola atriale sinistra (LAA). Nei pazienti affetti da FA non valvolare circa il 95% dei trombi è localizzato nella LAA. La base del trattamento di FA, prima della cardioversione al ritmo sinusale, è la prevenzione delle complicanze tromboemboliche con terapia anticoagulante orale (OAT), mentre l'esclusione dell'appendice atriale sinistra (LAAC) può essere considerata in pazienti con controindicazioni all'OAT a lungo termine, in pazienti sottoposti a chirurgia cardiaca o a chirurgia toracoscopica della FA [Linee guida ESC, 2016], pazienti sottoposti a cardiocirurgia con o senza ablazione con FA permanente, persistente o parossistica e a pazienti sottoposti ad ablazione epicardica con FA mediante intervento di sternotomia (procedura Maze).

Fin dagli anni '40 viene praticata la chiusura della LAA come profilassi del tromboembolismo in pazienti affetti da patologia mitralica. Nel corso degli anni, si sono sviluppate tecniche alternative per la LAAC che prevedono l'approccio chirurgico mininvasivo (anche attraverso dispositivi medici specificamente progettati) o l'approccio percutaneo utilizzando appositi dispositivi medici.

Per quanto riguarda l'approccio chirurgico, negli anni '90, la resezione della LAA è stata reintrodotta come parte integrante nella procedura chirurgica di ablazione della FA [Gavino C, 2016] ed è eseguita con diverse tecniche che ne prevedono l'escissione o la sutura o la chiusura utilizzando anche dispositivi medici specificamente progettati. La diffusione, nell'ultimo decennio, di un dispositivo a clip per l'occlusione/esclusione della LAA per via epicardica ha sollecitato la necessità di effettuare una valutazione del suddetto dispositivo analizzandone i vari aspetti e implicazioni d'utilizzo. La valutazione è stata, quindi, sviluppata attraverso un documento di Health technology assesement (HTA) seguendo il Manuale delle procedure di Agenas [Agenas, 2014], rispettando le procedure delineate nel Piano di prevenzione e trasparenza della corruzione (2017-2019) dell'Agenzia [Agenas, 2017] e seguendo le indicazioni dell'adattamento Agenas al Core Model® per "Procedure mediche e chirurgiche" versione 2.0 [EUnetHTA JA2, 2013].

La tecnologia oggetto di studio, nel presente documento, è il sistema AtriClip (AtriCure, Inc.) che consente di eseguire la chiusura dell'auricola in concomitanza di altri interventi cardiaci o come procedura isolata, per mezzo di un approccio toracoscopico. La parte principale del sistema AtriClip è una clip composta da due molle in nitinol unite da due barre parallele in titanio rivestito con tessuto in poliestere. La clip è pre-caricata su un applicatore che ne consente il rilascio una volta effettuato il posizionamento. Il produttore ha sviluppato diversi modelli del sistema AtriClip con applicatori specifici per diverse esigenze di approccio chirurgico: approccio sternotomico (modelli AtriClip Standard, AtriClip Long e AtriClip FLEX); approccio toracotomico (modello AtriClip PRO); approccio toracoscopico (modello AtriClip PRO2).

La procedura è di competenza del cardiocirurgo e viene eseguita con il paziente in anestesia generale. Una volta raggiunto il sito di applicazione secondo l'approccio ritenuto più idoneo, la clip viene posizionata alla base dell'auricola. L'ecocardiografia transesofagea viene effettuata durante tutta la procedura per confermare la completa chiusura dell'auricola e, quando il posizionamento è ritenuto corretto, la clip viene chiusa permanentemente e sganciata dall'applicatore.

Il sistema AtriClip è un dispositivo medico di Classe III commercializzato in Europa dal 2009. Tutti i modelli hanno anche ricevuto l'approvazione FDA. Le indicazioni d'uso definiscono automaticamente l'approccio chirurgico per il quale lo specifico modello è stato progettato, sternotomia, toracotomia o toracosopia.

In Italia, se la chiusura chirurgica dell'auricola viene effettuata in concomitanza con altre procedure cardiotoraciche, il rimborso della procedura viene effettuato attraverso il DRG dell'intervento principale. Generalmente la tariffa collegata alla procedura di LAAC viene identificata con il codice DRG 108: "Altre procedure cardiotoraciche".

L'analisi dei consumi, desunti dalla banca dati del *Flusso consumi* dei dispositivi medici del Nuovo sistema informativo sanitario (NSIS) identifica, a livello nazionale, 163 dispositivi AtriClip consumati nel periodo fra 2011 e il primo semestre del 2017 (i dati relativi al 2017 sono provvisori e non ancora consolidati).

In Italia, fino al 2015 il consumo annuale del dispositivo AtriClip si attesta su valori molto bassi (circa 15 dispositivi all'anno) mostrando un andamento tendenzialmente costante. A partire dal 2016, si registra un aumento degli acquisti proporzionalmente attribuibile alla Regione Lombardia. Nel periodo in esame, solo 9 Regioni e Province Autonome (su 21) hanno acquistato almeno un dispositivo AtriClip, ma solo tre regioni hanno utilizzato la tecnologia continuamente nell'intero arco temporale (Toscana, Veneto e Lombardia). Nel periodo esplorato, il dispositivo AtriClip più utilizzato è stato AtriClip PRO (49%), seguito da AtriClip per sternotomia (43%) e PRO2 (8%). Tuttavia, la modesta percentuale di AtriClip PRO2 esprime un valore rilevante perché concentrato

solo nel primo semestre del 2017 (dato non consolidato). A partire dal 2016 la diminuzione di consumo di AtriClip per l'approccio chirurgico sternotomico (AtriClip LONG, Standard e FLEX) si è verificata contemporaneamente all'aumento di consumo di AtriClip per l'approccio toracotomico (AtriClip PRO). Dal 2016, le strutture pubbliche italiane hanno utilizzato quasi esclusivamente i modelli per l'approccio chirurgico di toracotomia e toracosopia. Nel periodo osservato, solo 15 strutture pubbliche hanno utilizzato almeno uno dei 163 dispositivi AtriClip con una considerevole variabilità di consumo per struttura (range 1-63). La maggior parte degli ospedali (n=11) ha utilizzato meno di 10 dispositivi e 5 di essi hanno utilizzato solo 1 dispositivo. L'uso del sistema AtriClip è, quindi, concentrato in 4 strutture che hanno consumato l'85% dell'intero volume.

L'efficacia clinica e la sicurezza del dispositivo AtriClip sono state indagate mediante revisione sistematica della letteratura scientifica pubblicata nei database Medline/Pubmed, Embase e Cochrane Library e ClinicalTrials.gov, includendo report HTA, revisioni sistematiche, studi clinici randomizzati (RCT), studi clinici controllati e studi osservazionali a partire da gennaio 2009, corrispondente all'anno di approvazione del primo dispositivo AtriClip.

La popolazione target eleggibile è stata considerata in base ad uno dei seguenti criteri: pazienti con FA valvolare o non valvolare (VFA o NVFA) con alto rischio tromboembolico (punteggio CHA₂DS₂-VASc ≥ 2) e incompatibile con il trattamento anticoagulante a lungo termine; pazienti sottoposti a chirurgia cardiaca o chirurgia toracoscopica per il trattamento della FA; pazienti con diagnosi (mediante imaging cardiaco: eco, angio TC, RM) di trombosi nella LAA (LAAT) con o senza FA; pazienti con LAAT in procedure di chirurgia cardiaca con o senza ablazione epicardica. Il processo di screening della ricerca bibliografica non ha individuato report HTA, revisioni sistematiche o RCT che soddisfacessero i criteri di inclusione. Abbiamo quindi valutato studi osservazionali non comparativi includendo tre studi principali (range pazienti arruolati 40-155 pazienti) [Kurfirst 2017, Ailawadi 2011, Emmert 2014] e due studi che hanno arruolato rispettivamente 22 e 24 pazienti [Alqaqa 2016, Ad 2015]. I tre studi principali riguardavano: uno studio prospettico su singolo centro comprendente 155 pazienti [Kurfirst 2017] sottoposti a chiusura della LAA con AtriClip effettuata tramite sternotomia, toracotomia o toracosopia con follow up a 3 mesi; uno studio prospettico multicentrico [Ailawadi 2011] (studio EXCLUDE) con follow-up a 12 mesi comprendente 71 pazienti sottoposti a chirurgia cardiaca elettiva con concomitante chiusura della LAA con AtriClip tramite sternotomia mediana con o senza bypass cardiopolmonare; uno studio prospettico 'first in-man' trial [Emmert 2014] per LAA Clip System con follow-up di 36 mesi comprendente 40 pazienti sottoposti a chirurgia cardiaca elettiva e procedura di ablazione concomitante. Questi studi riportano un tasso di occlusione della LAA completa dal 95,7% al 100%. I tassi di mortalità ospedaliera, riportati negli studi, variano dal 8,4% al 10% ma sembrano non essere correlati all'intervento chirurgico di chiusura della LAA

mediante il sistema AtriClip né ad eventi avversi. I due studi con minor numero di pazienti riguardavano: uno studio retrospettivo [Alqaqa 2016] su 22 pazienti sottoposti a chiusura della LAA tramite un approccio mini-toracotomico in concomitanza di chirurgia mini-invasiva della valvola mitralica e uno studio retrospettivo [AD 2015] con 24 pazienti arruolati e sottoposti a chiusura della LAA tramite mini-toracotomia destra. La ricerca su clinicaltrials.gov ha identificato due studi in corso (*ATLAS* studio clinico randomizzato con arruolamento stimato di 2000 pazienti e primi risultati disponibili nel 2019 e il *Registro LAAC* coorte prospettica osservazionale con arruolamento stimato di 3000 pazienti e conclusione nel 2026), tre trials non randomizzati conclusi (*EXCLUDE* con 70 pazienti e *Safety and Effectiveness of Left Atrial Appendage Occlusion* con 36 pazienti) e due studi sospesi o ritirati (*AtriCure Minimally Invasive Surgical Ablation for Atrial Fibrillation/RESTORE IIB* ritirato prima dell'arruolamento e *DEEP Pivotal* sospeso). Le pubblicazioni relative ai trial non randomizzati conclusi sono state incluse nell'analisi. La ricerca delle revisioni Cochrane ha identificato solo un protocollo di ricerca il cui obiettivo è la *Valutazione dell'efficacia clinica e della sicurezza LAAC comparata alla terapia orale anticoagulante per la prevenzione dell'ictus in persone con la fibrillazione atriale non valvolare*. Le evidenze trovate sostengono che la chiusura della LAA con il sistema AtriClip sia una tecnica promettente, tuttavia esse derivano da studi osservazionali con un basso livello qualitativo delle prove a supporto delle stesse [Grade 2004]. Gli studi non sono comparabili variando nell'accesso chirurgico (sternotomia, toracotomia o mini-toracotomia) e nel dispositivo utilizzato (AtriClip e AtriClip PRO). Inoltre, non tutti gli studi riportano dati sulle terapie anticoagulanti e sullo stato della FA post chiusura della LAA.

La valutazione dell'ambito economico è stata effettuata utilizzando sia le informazioni presenti in letteratura, sia le informazioni desunte dal flusso informativo NSIS. In particolare, utilizzando la medesima strategia di ricerca effettuata per l'analisi di efficacia e sicurezza del dispositivo oggetto di valutazione, sono stati ricercati tutti gli studi di valutazione economica aventi come obiettivo la comparazione dell'utilizzo dei dispositivi AtriClip, per l'approccio chirurgico della LAAC con l'OAT. Dati di costo sono stati reperiti utilizzando anche il *Flusso Consumi* del NSIS e le informazioni fornite dal distributore per l'Italia che ha risposto ad un questionario redatto ad hoc.

L'analisi della letteratura non ha rilevato nessuno studio di valutazione economica su nessuno dei modelli AtriClip.

Partendo dai volumi di consumo individuati dal *Flusso Consumi*, sono stati considerati i costi medi dei dispositivi AtriClip consumati dalle strutture sanitarie pubbliche che hanno imputato le informazioni nel sistema del Ministero della Salute. Sono stati calcolati i costi medi (IVA inclusa) di tutti i modelli AtriClip, dei singoli modelli e dei modelli AtriClip accorpati per procedura chirurgica (sternotomia, toracotomia e toracosopia) per Regione.

In particolare, dal 2011 al primo semestre 2017, nove regioni italiane hanno imputato nel sistema il costo (IVA inclusa) di uno dei modelli AtriClip, con un range regionale che varia da € 1.452,53 a € 4.139,20 (per quelle regioni che hanno imputato il costo per più due anni), fatta eccezione per la Toscana che mostra nel primo semestre del 2017 un costo medio più elevato che negli anni precedenti. Analizzando i costi dei singoli modelli consumati, il modello Standard di AtriClip ha subito un decremento dal 2014, mentre l'AtriClip Flex (consumato a partire dal 2016) ha subito un leggero aumento nel primo semestre del 2017. L'AtriClip PRO invece non ha subito modifiche di costo rilevanti, mentre AtriClip PRO2 è stato rilevato solo per il primo semestre del 2017 ed è il modello che ha il costo medio più alto di tutti i modelli AtriClip (€ 4.139,20). Anche accorpando i dispositivi AtriClip per l'approccio chirurgico utilizzato non si rilevano variabilità sostanziali nel costo medio nel corso degli anni.

Infine, la spesa pubblica annuale sostenuta varia da € 19.623 nel 2012 a € 38.126 nel 2014. Nel 2016 si registra un incremento della spesa pari a più del doppio rispetto all'anno precedente (€70.858 nel 2016 e €33.029 nel 2015) e un aumento ancora più significativo nel solo primo semestre del 2017 (€ 102.096).

A partire dal 2011 il 58% della spesa è attribuibile all'AtriClip PRO (41%) e ad AtriClip PRO2 che ha assorbito il 17% del totale della spesa di tutti gli anni solo nel primo semestre del 2017 (anno di commercializzazione in Italia).

Conclusioni

La FA è l'aritmia più comune e la sua prevalenza è in aumento a causa del progressivo invecchiamento della popolazione e di una migliore rilevazione della FA asintomatica. La scelta del trattamento della FA, prima della cardioversione al ritmo sinusale, è finalizzata alla prevenzione delle complicanze tromboemboliche con OAT e la combinazione con LAAC può essere considerata in pazienti con controindicazioni per il trattamento anticoagulante a lungo termine o in pazienti sottoposti a chirurgia cardiaca o chirurgia FA toracoscopica [ESC Guidelines, 2016]. Il LAAC con chirurgia minivasiva potrebbe essere un'ulteriore opzione per prevenire eventi tromboembolici nei pazienti con alto rischio emorragico e non rispondenti al trattamento standard.

L'utilizzo dei dispositivi AtriClip nelle strutture sanitarie pubbliche italiane dal 2011 al primo semestre del 2017 si attesta su un numero relativamente basso di device utilizzati (circa 160). L'analisi dei volumi ha mostrato che i modelli AtriClip per sternotomia (Standard, Long e FLEX) sono stati prevalentemente utilizzati fino al 2015, quando l'utilizzo della tecnologia era indicato solo in concomitanza con altri interventi cardiocirurgici. Nel 2013, il modello AtriClip per toracotomia (AtriClip PRO) è entrato nel mercato italiano e si è via via sostituito ai precedenti

modelli diventando prevalente nel 2016 (più del 55% dei casi). In Italia nel 2017, è entrato in commercio il modello AtriClip per toracosopia (AtriClip PRO2) e, sebbene in valore assoluto i numeri siano di modesta entità è diventato il secondo dispositivo AtriClip utilizzato (circa il 30% dei casi) durante il primo semestre dello stesso anno. Tuttavia, nel servizio sanitario pubblico nazionale, l'85% di utilizzo di AtriClip, sulla base dei dati disponibili, risulta avvenire in solo 4 strutture in quattro regioni (Piemonte, Veneto, Lombardia e Toscana).

Da un punto di vista economico, l'utilizzo dei dispositivi AtriClip deve tenere in considerazione la variabilità dei prezzi dei vari modelli messi in relazione ai differenti approcci chirurgici per i quali sono destinati, in special modo per il modello AtriClip PRO2 unico modello indicato per l'utilizzo nella LAAC in toracosopia senza la combinazione con un altro intervento cardiocirurgico.

Il tasso di successo delle varie tecniche di chiusura dell'auricola è molto variabile. Il sistema AtriClip potrebbe rappresentare un approccio interessante poiché permette di eseguire la procedura in tempi relativamente brevi. La base delle prove di efficacia e sicurezza disponibili sembra mostrare un potenziale beneficio dell'uso del clipping con AtriClip. Tuttavia, le evidenze sono limitate a studi non randomizzati e per lo più non comparativi. La randomizzazione è fondamentale in casi in cui i pazienti e le variabili di contesto giocano un ruolo fondamentale perché consente il confronto di tutte le situazioni comparabili.

Per poter confermare i dati evidenziati sulla LAAC con il sistema AtriClip riportati in questo report, sono necessari studi più ampi, con follow-up più lunghi e che riportano dati stratificati per procedura concomitante, tipo di accesso e dispositivo per la prevenzione dell'ictus e FA. Studi randomizzati comparativi e multicentrici ben disegnati con valutazioni a lungo termine dovrebbero essere condotti a fianco di valutazioni economiche prospettiche per consentire che la scelta sia basata su prove di buona qualità.

Il modello più innovativo è ovviamente AtriClip PRO2, che, grazie all'approccio minimamente invasivo potrebbe essere potenzialmente il concorrente dei diversi occlusori endocardici già presenti sul mercato. Tuttavia, tali dispositivi endocardici sono in uso clinico da diversi anni e le raccomandazioni per il loro uso sono state emesse nell'ambito di linee guida internazionali di recente pubblicazione, mentre AtriClip PRO2 è stato introdotto solo recentemente sul mercato ed assume quindi le caratteristiche di una tecnologia emergente su cui non è stata rintracciata letteratura scientifica.

Introduction

The present rapid HTA report was carried out following the Agenas' Manual of Procedures [Agenas, 2014] and the procedures outlined in the Agency's Corruption Prevention and Transparency Plan (2017-2019) [Agenas, 2017].

This document was developed following the EUnetHTA Core Model[®] application for "Medical and surgical procedures" version 2.0. The Core Model is divided into domains representing each a specific area of technology impact to be assessed. Each domain contains a series of research questions or Assessment Elements (AEs) identified by a capital letter and number (e.g., A0001). To test the Core Model applicability, an adapted model was elaborated by Agenas (see Appendix 1 for a full description). The use of the Core Model is mirrored in the structure of this report, where each chapter corresponds to a domain and reports the AEs considered for the assessment.

The topic of this HTA is a clip device for left atrial appendage closure (LAAC). Atrial fibrillation (AF) is related to a high risk of stroke. The main role in etiopathogenesis is played by the LAA. As many as 95% of thrombi in non valvular AF are located into the LAA. Prevention of stroke then consists in permanent anticoagulation which, however, has its limits and risks. The epicardial clip for LAAC is a technique in diffusion that needs to be assessed as alternative prevention of stroke.

1. Report's objectives: policy and research questions

This rapid HTA report has been developed to answer the following questions:

Policy question: What is the impact of epicardial clip closure of LAA in patients with AF or with diagnosis of LAA thrombosis (LAAT) with or without AF?

Research question: What are the effects of epicardial clip closure of the LAA in patients with AF or with diagnosis of LAAT (with or without AF) in terms of effectiveness, safety and costs?

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

- Health problem and current use of technology (CUR).
- Description of technology (TEC) and regulatory aspects (REG).
- Clinical effectiveness (EFF) and safety (SAF).
- Costs and economic evaluation (ECO).

For each investigated domain, the selected AEs are listed in Appendix 2

2. Health problem and current use of technology

2.1 Methods

We selected the following AEs:

Assessment Element ID	Research question
A0001a	For which health condition is the technology proposed?
A0001b	Which group of patients represents the target population for the technology?
A0001c	For what purposes is the technology used?
A0002	What is the health condition in the scope of this assessment?
A0003	What are the known risk factors for the health condition?
A0004	What is the natural course of the health condition?
A0005	What are the symptoms for the patient at different stages of the health condition?
A0006	What are the statistics of incidence, prevalence, morbidity, and mortality of the health condition?
A0011	What is the diffusion of the technology in Italy?
B0001b	What is(are) the comparator(s)?
B0005b	In what context and level of care is the comparator used?
G0009a	Who decides which people are eligible for the technology?
G0009b	On what basis is the eligibility for the technology decided?

2.1.1 Health problem

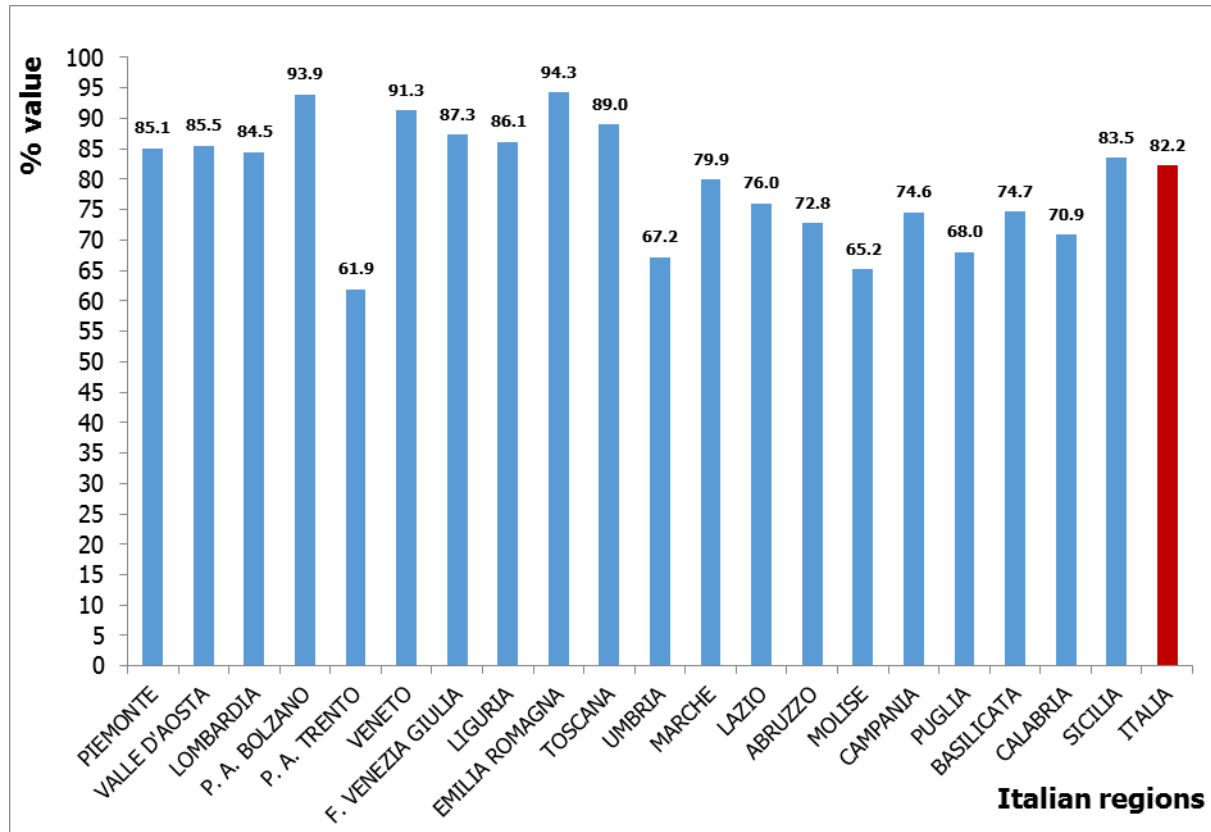
Health problem was reported in a descriptive summary defined by international and national literature review: in particular, we searched for review articles, epidemiological studies and disease registers. Informal interviews with collaborating clinical experts were also carried out to clarify the current management of disease in Italy.

2.1.2 Current use of technology

We identified the New Health Information System (NSIS), held by the Ministry of Health, as the official data source. Among the broad set of information contained in the NSIS, we selected the "Data bank for monitoring consumption of medical device directly used by Italian NHS" (*Flusso consumi*) for our investigations. This data bank, regulated by the Decree of the Ministry of Health of 11th June 2010, contains data on medical devices consumption and expenditure by the Italian regions. The database is fed by the Regions that gather data from public health care providers in their territory. At present, the database is not yet fed homogeneously and coverage rates, broken down by Italian regions, are shown in figure 2.1. Since every medical device is identified with a

number of registration (RDN code) it is possible getting the amount of a single medical devices used.

Figure 2.1: "Flusso consumi" database coverage rates, broken down by regions (2014)



Source: extracted from Ministero della Salute, 2015

With the aim of identifying the consumption of AtriClip systems assessed in this report (in terms of number of devices used) in Italian public health structures from 2011 to first half of 2017 (last data available), we extracted data related to the volume of AtriClip devices using the National Classification of Medical Devices (CND) code associated to this kind of devices: "HA3010201 - SURGICAL CLIPS, NOT ABSORBABLE, OPEN-SURGERY". The searches were carried out in November 2017.

We identified the current use of AtriClip system using RDN code reported in the Italian National Medical Devices Inventory and Database (Banca Dati e Repertorio Dispositivi Medici – BD/RDM) listed below (for more details see chapter 3 - table 3.1). We made simple descriptive analysis broken down by types of surgical procedures:

- *Sternotomy approach:* AtriClip models indicated for the occlusion of the LAA under direct visualisation, in conjunction with other open cardiac surgical procedures, i.e., AtriClip Long (ID-BD/RDM: 239689; 239813; 239815; 239816), AtriClip Standard (ID-BD/RDM: 533430; 533449; 533451; 533453) and AtriClip FLEX (ID-BD/RDM: 1403062; 1403066; 1403067; 1403068);

- *Thoracotomy approach:* AtriClip model indicated for the occlusion of the LAA under direct visualisation in conjunction with other open cardiac surgical procedures in minimally invasive procedure, i.e., AtriClip PRO (ID-BD/RDM: 863395; 863474; 863475; 863476);
- *Thoracoscopy approach:* AtriClip model indicated for the occlusion of the heart's LAA without restrictions, i.e., AtriClip PRO2 (ID-BD/RDM: 1501191; 1501376; 1501380; 1501388).

2.2 Results

2.2.1 Health problem

Health condition, treatment options and target population (A0001a- A0001c , A0002, A0003, A0005, A0006)

AF is a quivering or irregular heartbeat (arrhythmia) that can lead to blood clots into the atrial chambers with increasing risk for stroke, heart failure and other heart-related complications. AF is the most common arrhythmia and its prevalence is increasing due to the progressive aging of the population and better detection of silent AF. About 20% of strokes are attributable to AF and AF patients are at 5-fold increased risk of stroke. Estimates suggest an AF prevalence of approximately 2-3% in adults aged 20 years or older, with greater prevalence in older persons and in patients with conditions such as hypertension, heart failure, coronary artery disease (CAD), valvular heart disease, obesity, diabetes mellitus, or chronic kidney disease (CKD) [ESC Guidelines 2016; Gavino C, 2016]. Pulse rate is sensitive, but not specific, for diagnosis, and suspected atrial fibrillation should be confirmed with 12-lead electrocardiography [Gutierrez,2016]. The CHADS2 and the CHA2DS2-VASc scoring systems assess the risk of stroke, with a score of 2 or greater indicating a need for anticoagulation; the HAS-BLED score estimates the risk of bleeding. Scores of 3 or greater indicate high risk [Gutierrez,2016]. .

The mainstay of treatment of AF, before the effective cardioversion to sinus rhythm, is the prevention of thromboembolic complications with oral anticoagulation therapy (OAT) and the combining with left atrial appendage closure (LAAC) may be considered in patients with contraindications for long-term anticoagulant treatment or in patients undergoing cardiac surgery or thoracoscopic AF surgery [ESC Guidelines, 2016].

Selection of therapy should be individualized based on risks and potential benefits, cost, and patient preference: warfarin, dabigatran, factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban), and aspirin are options for stroke prevention; left atrial appendage obliteration is an option for reducing stroke risk (two implantable devices used to occlude the appendage, the Watchman and the Amplatzer Cardiac Plug, appear to be as effective as warfarin in preventing

stroke, but they are invasive), another percutaneous approach to occlusion, wherein the left atrium is closed off using the Lariat, is also available, but data on its long-term effectiveness and safety are still limited; surgical treatments for atrial fibrillation are reserved for patients who are undergoing cardiac surgery for other reasons [Gutierrez, 2016].

The target population includes also patients at high risk and patients undergoing cardiac surgery with or without ablation having permanent, persistent or paroxysmal AF and patients undergoing stand-alone AF epicardial ablation through sternotomy surgery (Maze operation) [Gavino C, 2016]. Systemic embolization threatens patients with AF. The risk is enhanced at the time of cardioversion. Transesophageal echocardiography (TEE) prior to cardioversion to screen for left atrial thrombus (LAT), a marker of high risk for embolization, is recommended for many patients with AF. [Malik 2014] reported that LAT is not an uncommon finding of AF patients prior to cardioversion. The current practice of TEE examination may be justified since neither clinical nor routine 2D echo examinations reliably identify LAT.

Into this general picture, the minimally invasive surgical LA closure offers a further option for preventing thromboembolic events in non-responder AF ablation patients with high haemorrhagic risk.

Clinical course and prognosis (A0004)

Anticoagulation therapy reduces the risk of thromboembolic events by two-thirds in patients with AF. The prevalence of left atrial thrombus (LAT) in AF patients with anticoagulation therapy has not been fully investigated. In the study of Shota Fukuda [Shota Fukuda, 2011] LAT was observed in 13 (8.8%) of 148 patients with sub-therapeutic anticoagulation, and in 3 (3.6%) of 83 patients with sufficient anticoagulation. The presence of LAT was associated with higher CHADS₂ score, decreased LA volume changes and the presence of spontaneous echocardiographic contrast (SEC) in patients with sub-therapeutic anticoagulation. Patients with LAT after sufficient anticoagulation were male with permanent AF who had decreased left ventricular systolic and diastolic function and dilated LA on TTE and SEC, and reduced appendage flow velocity on TEE. Patients with LAT had worse cardiovascular outcomes compared with those without LAT ($p = 0.02$). A univariate risk factor associated with worse cardiovascular outcomes, which was observed in 8.8% of patients with sub-therapeutic anticoagulation and 3.6% of patients with sufficient anticoagulation. The EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot) [Lip, 2014] provides systematic collection of contemporary data regarding the management and treatment of 3119 subjects with AF from 9 member countries of European Society of Cardiology (ESC). In this analysis, they report the development of symptoms, use of antithrombotic therapy and rate vs. rhythm strategies, as well as determinants of mortality and/or stroke/transient ischaemic attack (TIA)/peripheral embolism during 1-year follow-up. At the follow-up, patients

were frequently asymptomatic (76.8%), but symptoms are nevertheless common among paroxysmal and persistent AF patients, especially palpitations, fatigue, and shortness of breath. Oral anticoagulant (OAC) use remains high, 78% overall at follow-up, and of those on vitamin K antagonist (VKA), 84% remained on VKA during the follow-up, while of those on non-VKA oral anticoagulant (NOAC) at baseline, 86% remained on NOAC, 11.8% changed to a VKA and 1.1% to antiplatelet therapy. Digitalis was commonly used in paroxysmal AF patients. Of rhythm control interventions, electrical cardioversion was performed in 9.7%, pharmacological cardioversion in 5.1%, and catheter ablation in 4.4% of patients. Despite good adherence to anticoagulation, 1-year mortality was high (5.7%), most deaths were cardiovascular (70%). Hospital readmissions were common, especially for atrial tachyarrhythmias and heart failure. On multivariate analysis, independent baseline predictors for mortality and/or stroke/TIA/peripheral embolism were age, AF as primary presentation, previous TIA, chronic kidney disease, chronic heart failure, malignancy, and minor bleeding. Independent predictors of mortality were age, chronic kidney disease, AF as primary presentation, prior TIA, chronic obstructive pulmonary disease, malignancy, minor bleeding, and diuretic use. Statin use was predictive of lower mortality. Overall OAC use remained high, although persistence with therapy may be problematic. Nonetheless, continued OAC use was more common than in prior reports. Despite the high prescription of OAC, 1-year mortality and morbidity remain high in AF patients, particularly from heart failure and hospitalizations. Left atrial appendage obliteration is an option for reducing stroke risk.

Management of treatment (B0001b, B0005b, G0009a, G0009b)

In patients with non-valvular AF, a LAA thrombus is a major source of systemic embolisation. Currently, the standard treatment of an established LAA thrombus is a period of therapeutic anticoagulation with warfarin. Novel oral anticoagulants (NOAC) are increasingly used; however, their efficacy is unknown. The current American Heart Association/American College of Cardiology guideline recommends that if a thrombus is identified on a TOE before cardioversion, the procedure should be postponed, followed by a 3- week or longer period of anticoagulation. However, LAA thrombi may persist in up to 20% of patients after a 4-week or longer duration of adequate anticoagulation. Failure of anticoagulation therapy is likely multifactorial, including both pharmacological and non-pharmacological factors (e.g. CHA₂DS₂-VASc score, left atrium size, duration of therapy). Currently, there is no specific recommendation on how to avoid persistence of LAA thrombi. Rivaroxaban, a selective, direct inhibitor of factor Xa, has emerged as a NOAC with relatively predictable pharmacokinetic and pharmacodynamic profiles. Case reports have demonstrated complete resolution of LAA thrombi within 7–42 days of rivaroxaban therapy 10–15 mg daily. It is suggested that rivaroxaban may have a direct effect of resolving established LAA thrombi. Similar to dabigatran failure, rivaroxaban failure in the setting of warfarin success may be

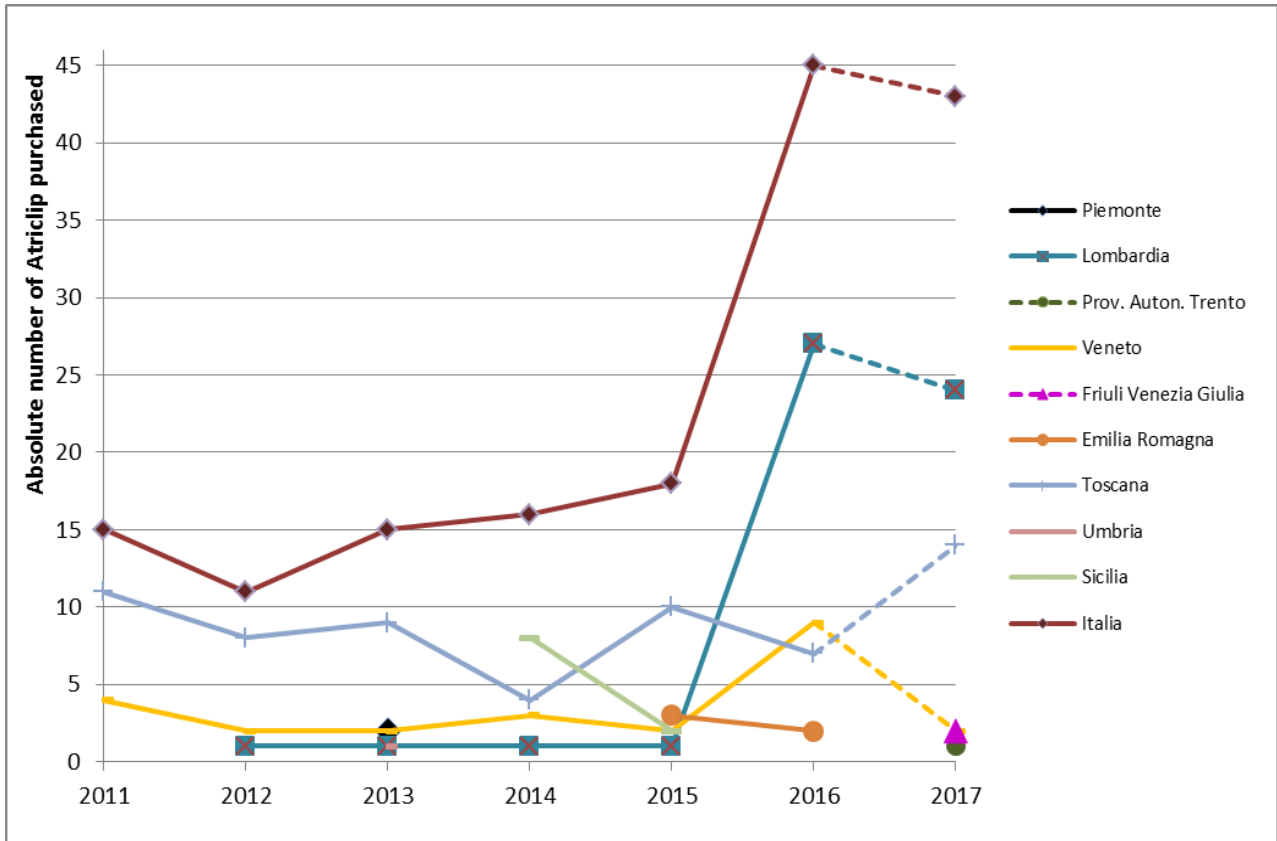
explained by (i) action on a single clotting factor or (ii) fluctuating and uncertain intensity of anticoagulation. Unlike warfarin, there are no studies documenting the rate of persistent LAA thrombi following anticoagulation with a NOAC. Serial TOE to document its resolution are warranted before cardioversion or catheter ablation of AF [Jaber, 2000]. The efficacy of rivaroxaban in this setting remains to be answered in a large-scale study, such as the upcoming X-TRA trial [Lip, 2015].

2.2.2 Current use of technology

(A0011) In the seven years between 2011 and first half of 2017, the analysis showed that 163 events matched the BD/RDM registration numbers listed in the tables 3.1 (Chapter 3). The estimated annual number of AtriClip systems used was relatively small. In the period under review, only 9 Regions and Autonomous Provinces (out of 21) used at least one AtriClip device but only 3 regions used the technology continuously every year (Toscana, Veneto, and Lombardia). Figure 2.2 shows the trend of device use across the Italian Regions from 2011 to first half of 2017. From 2011 to 2015, the annual national volumes of AtriClip devices used were very low (around 15 units per year) showing a constant trend. Starting from 2016, the increase in use is proportionally attributable to Lombardia Region.

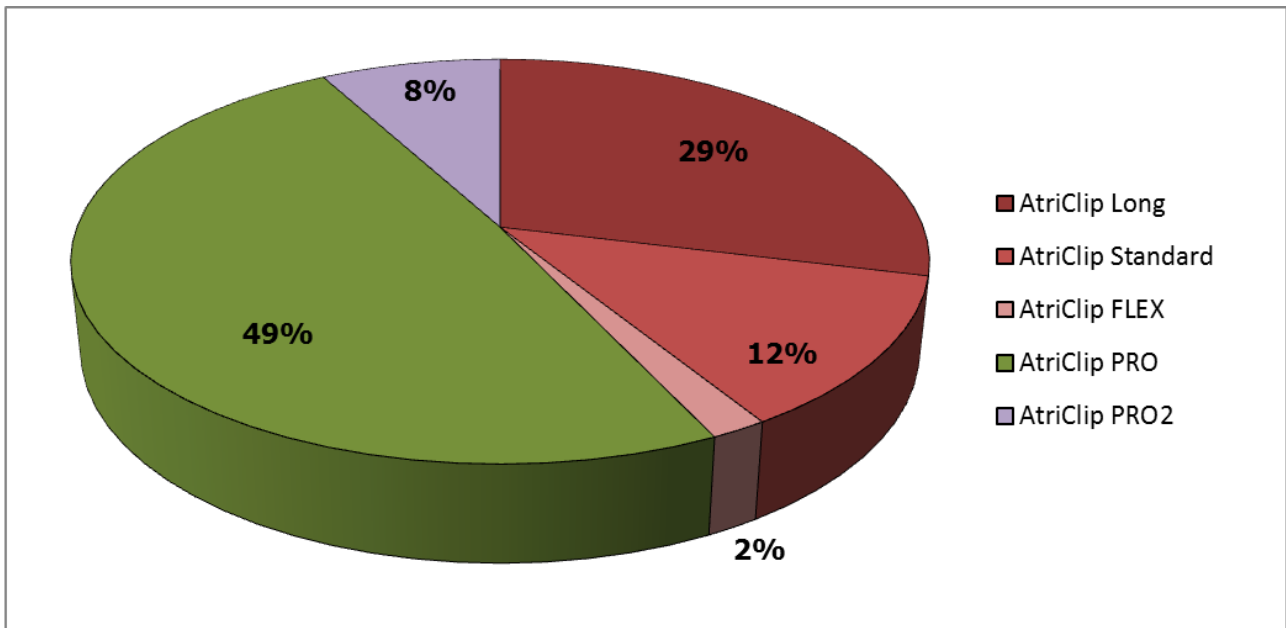
In the explored period, the most frequent AtriClip device used was AtriClip PRO (49%) followed by AtriClip for sternotomy (43%) and AtriClip PRO2 (8%). However, the lower percentage of AtriClip PRO2 has an important weight because the data refers only to the first half of 2017 (fig. 2.3). From 2016, the Italian public hospitals used almost only the models for thoracotomy and thoracoscopy surgical approach (more than 90% - fig. 2.4). In figure 2.5 we can see how in 2016 the decrease of the AtriClip Long, Standard and FLEX occurred at the same time as the increase of AtriClip PRO.

Figure 2.2: Number of AtriClip devices used from 2011 to 2017* across the Italian Regions



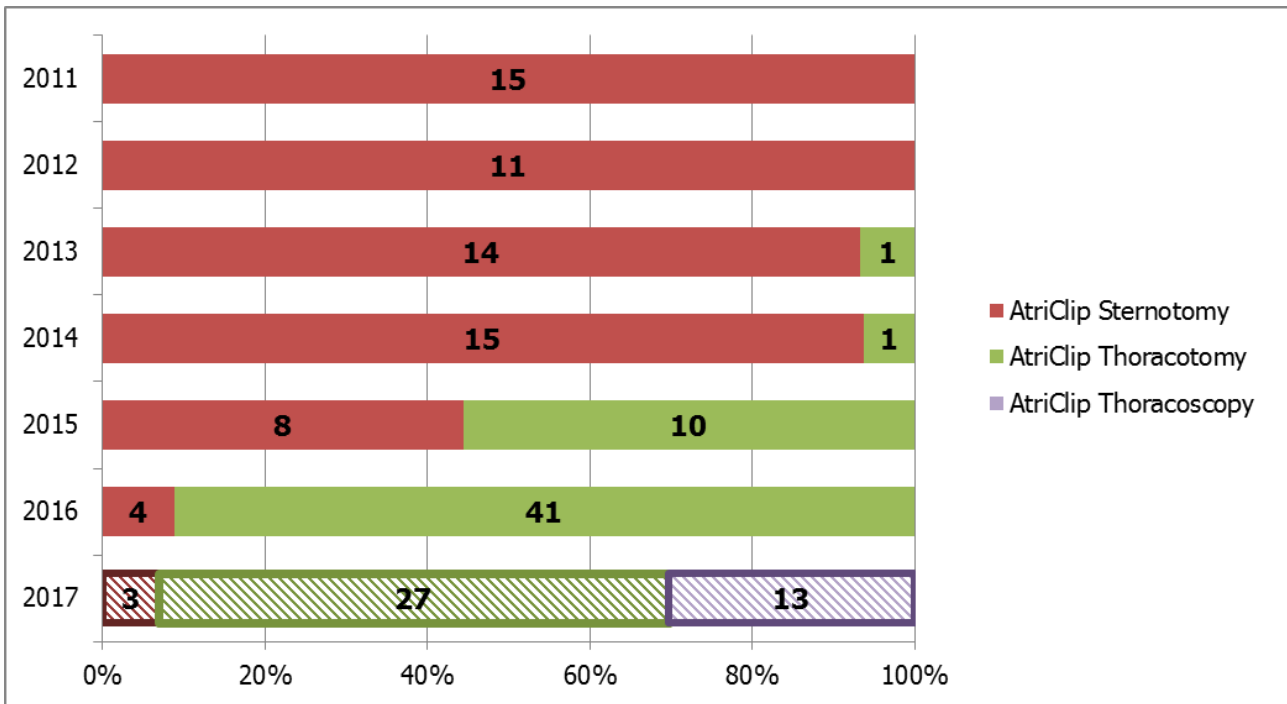
Source: Agenas analysis based on "Flusso consumi – CNS029" 2011 – 2017 (* first half of 2017)

Figure 2.3: AtriClip devices used in Italy broken down by model type (2011- 2017*)



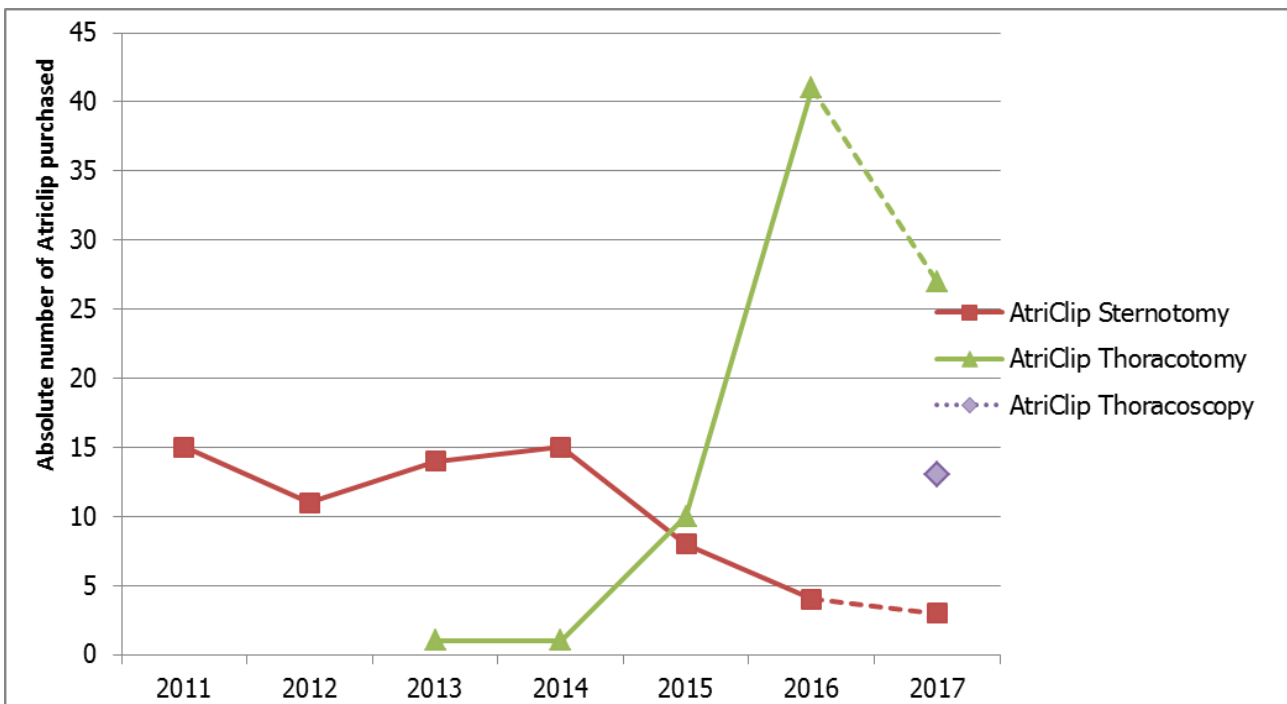
Source: Agenas analysis based on "Flusso consumi – CNS029" 2011 – 2017 (* first half of 2017)

Figure 2.4.: Number of AtriClip devices used in Italy broken down by year and type of surgical approach*



Source: Agenas analysis based on "Flusso consumi – CNS029" 2011 – 2017 (* first half of 2017)

Figure 2.5: Number of AtriClip devices used from 2011 to 2017* broken down by type of surgical approach*

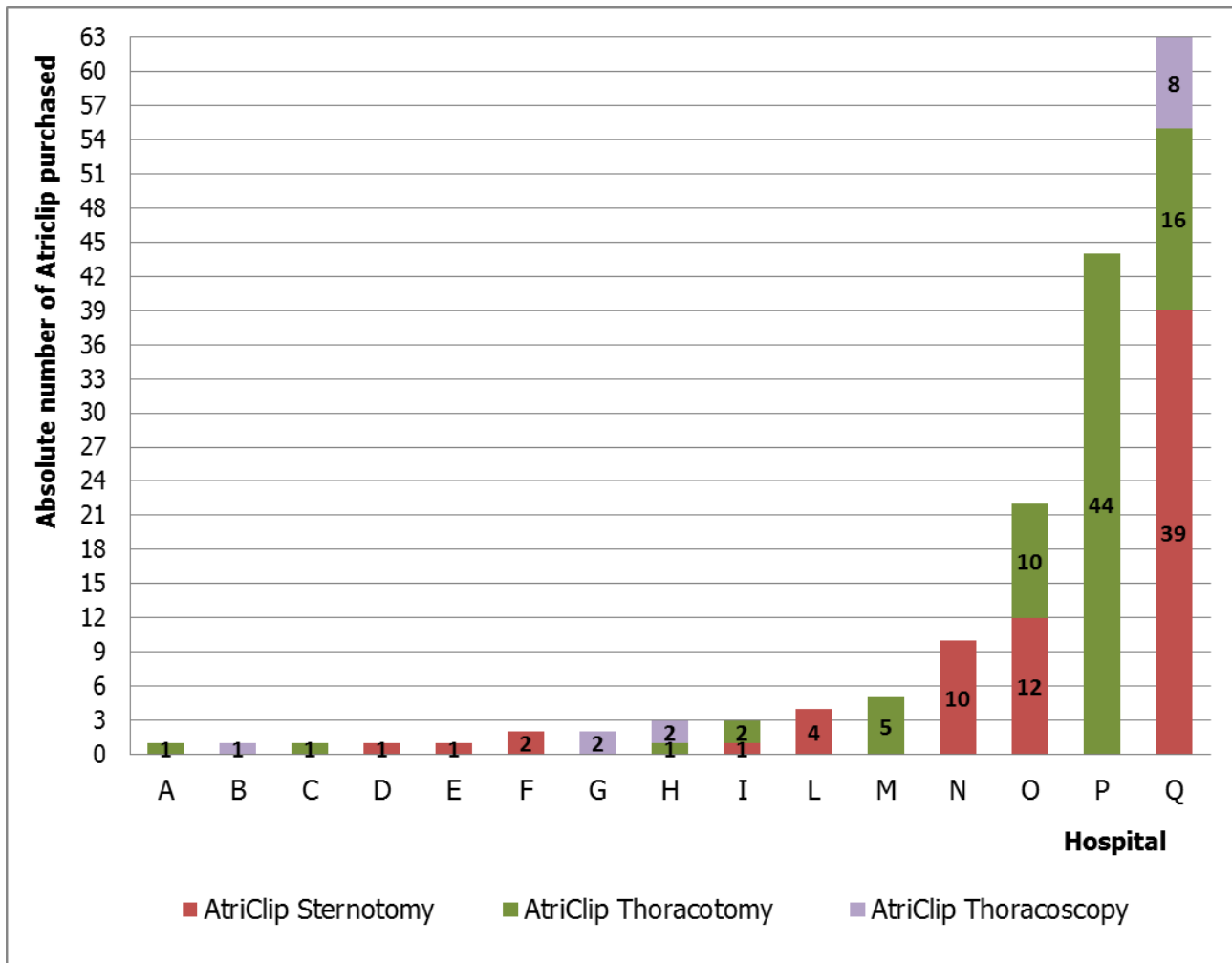


Source: Agenas analysis based on "Flusso consumi – CNS029" 2011 – 2017 (* first half of 2017)

Between 2011 and 2017, 163 AtriClip devices were used in 15 Italian public hospitals only. In the same period, as shown by the bar chart (Figure 2.6), the number of devices per hospital ranged

from 1 to 63. Most hospitals (n=11) used less than 10 devices, and 5 of them used only one device. The use of the AtriClip system is localised in 4 hospitals which used 85% of the total volume.

Figure 2.6: Number of AtriClip devices used from 2011 to 2017* broken down by hospital and type of surgical approach



Source: Agenas analysis based on "Flusso consumi – CNS029" 2011 – 2017 (* first half of 2017)

2.3 Discussion of results

AF is the most common arrhythmia and its prevalence is increasing due to the progressive aging of the population and better detection of silent AF. The mainstay of treatment of AF, before the effective cardioversion to sinus rhythm, is the prevention of thromboembolic complications with OAT and the combining with left LAAC may be considered in patients with contra-indications for long-term anticoagulant treatment or in patients undergoing cardiac surgery or thoracoscopic AF

surgery. The minimally invasive surgical LAAC could be a further option for preventing thromboembolic events in non-responders to standard treatment of AF with high haemorrhagic risk [ESC Guidelines, 2016].

The analysis of the volumes of use of AtriClip devices in the Italian public health structures from 2011 to 2017 showed that the AtriClip models for sternotomy (Standard, Long, and FLEX) were largely prevalent until 2015 when the technology was used only in combination with major cardiac procedures. In 2013, the AtriClip model for thoracotomy (AtriClip PRO) entered the Italian market and the number of devices for such approach became prevalent in 2016 (>55% of cases) with a huge increase of the total number of AtriClip procedures (more than three-fold). In 2017, the AtriClip model for thoracoscopy (AtriClip PRO2) became available in the Italian market and it is now the second device for number of procedures per year. The large majority of all the device is used in four centres across four Regions (Piemonte, Veneto, Lombardia and Toscana). The use of the AtriClip model for thoracoscopy overcame in first half of 2017 the one of AtriClip model for sternotomy (provisional data).

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3. Description of technology and regulatory aspects

3.1 Methods

3.1.1 Description of technology

Assessment Element ID	Research question
B0001	What is this technology?
B0003	What is the phase of development of the technology?
B0004	How is the technology used?
B0005	In which setting and level of care is the technology used?
B0007	Does the technology require additional/special equipment/tools or accommodation?
B0009	What disposables and supplies are needed to use the technology?
F0001	F0001a: Is the technology new/innovative? F0001b: Is the technology an add-on, a replacement or a modification of the standard mode of care?

All the AEs selected within the TEC domain were developed. The technology and its technical characteristics were presented by using information gathered by a structured questionnaire sent to the manufacturers (as described in Appendix – 3) supplemented by *ad hoc* internet searches on manufacturers' websites, brochures, instructions for use (IFU) documents, and regulatory bodies' databases.

3.1.2 Regulatory aspects

Assessment Element ID	Research question
A0020	What is the marketing authorisation status of the technology?
A0021	What is the reimbursement status of the technology across the country?

All the AEs selected within the REG domain were developed. The regulatory status of the identified devices (CE marking and FDA approvals) was described by using information gathered by a structured questionnaire sent to the manufacturers (as described in Appendix – 3) supplemented by *ad hoc* internet searches on regulatory bodies' websites and databases, and manufacturers' press releases.

3.2 Results

3.2.1 Description of technology

The surgical occlusion of the LAA has been performed for many decades and with different techniques, including excision, stapler removal and running sutures, and medical devices specifically designed [Chatterjee S, 2011].

The technology assessed in the present report is the AtriClip system, manufactured by AtriCure, Inc., and allows to perform the closure of LAA in concomitance with other open-chest heart interventions or as a stand-alone (i.e., isolated) thoracoscopic procedure for AF ablation. The main part of the AtriClip system is a self-closing external clip (Gillinov-Cosgrove™ clip) available in different sizes (35 mm, 40 mm, 45 mm and 50 mm), consisting of two nitinol springs joined by two titanium parallel rods covered with polyester fabric (Dacron). The clip is connected to an applier tool from which is released once complete closure of LAA is achieved (B0001).

The manufacturer developed different applier systems resulting in specific models for specific needs (Table 3.1). Following the indications for use (IFU), the different AtriClip models can be grouped according the types of surgical approach [IFU P000645.M; IFU P000858.D; IFU P001090.C]:

- *Sternotomy approach*: the AtriClip models indicated for the occlusion of the LAA under direct visualisation, in conjunction with other open cardiac surgical procedures, i.e., AtriClip Standard, AtriClip Long, and AtriClip FLEX.
- *Thoracotomy approach*: the AtriClip model indicated for the occlusion of the LAA under direct visualisation in conjunction with other open cardiac surgical procedures in mininvasive procedure, i.e., AtriClip PRO.
- *Thoracoscopy approach*: the AtriClip model indicated for the occlusion of the heart's LAA (without further restrictions), i.e., AtriClip PRO2.

A new model, AtriClip PRO•V, has been launched in September 2017 in the United States only. The new device presents an open-ended clip and should enable easier navigation and placement when used during minimally-invasive surgery (MIS) procedures. At the time of writing (November 2017), the device does not have the CE mark and is not registered within the Italian National Medical Devices Inventory and Database (B0003).

Table 3.1: AtriClip models registered within the Italian National Medical Devices Inventory and Database (Banca Dati e Repertorio Dispositivi Medici – BD/RDM). All the devices listed in the table are CE marked

Manufacturer	Device name	BD/RDM registration number(s)	Main technical features	Surgical approach
AtriCure, Inc.	AtriClip standard	533430 533449 533451 533453	<ul style="list-style-type: none"> ▪ Fixed head articulation ▪ Plunger grip ▪ Stiff shaft (6 mm) 	Sternotomy
	AtriClip Long	239689 239813 239815 239816	<ul style="list-style-type: none"> ▪ Head articulation $\pm 90^\circ$ lateral ▪ Malleable shaft (25 cm) 	Sternotomy
	AtriClip FLEX	1403062 1403066 1403067 1403068	<ul style="list-style-type: none"> ▪ 45-60 degree head articulation ▪ Plunger grip ▪ Malleable shaft (6mm) 	Sternotomy
	AtriClip PRO	863395 863474 863475 863476	<ul style="list-style-type: none"> ▪ Head articulation 180° * ▪ Thumb control ▪ Malleable shaft (25 mm) 	Thoracotomy
	AtriClip PRO2	1501191 1501376 1501380 1501388	<ul style="list-style-type: none"> ▪ Quick deploy feature ▪ Head articulation $\geq 30^\circ$ ** ▪ Rigid shaft (25 mm) 	Thoracoscopy

* side-to-side.

** side-to-side and up-&-down with lock feature.

Source: Data from BD/RDM database (accessed on 13th September 2017) and manufacturer.

The procedure is performed under general anaesthesia, within the operating room, by cardiac surgeons (B0005). Once the application site has been reached, by full or partial sternotomy, single or multiple thoracotomy or thoracoscopic access, the clip is placed mechanically through the applier at the base of the LAA avoiding the circumflex and pulmonary arteries. If the location of the clip is not satisfactory, the clip can be repositioned before deployment. Once the clip is in optimal position, it is closed and released from the applier tool (automatically for AtriClip PRO2, manually for other models). Complete closure of LAA is confirmed by transoesophageal echocardiography (TEE) (B0004).

Equipment, tools, disposables, and supplies needed for the procedure are no different from those normally available within the operating room during cardiothoracic procedures (B0007).

The AtriClip system is provided "ready-to-use", with the clip pre-loaded on the applier tool, but a specific malleable sizing tool is necessary to define the proper size of the clip and is provided by the manufacturer (Table 3.2) (B0009).

Table 3.2: Accessories of the AtriClip system registered within the Italian National Medical Devices Inventory and Database (Banca Dati e Repertorio Dispositivi Medici – BD/RDM). All the devices listed in the table are CE marked

Manufacturer	Device name	BD/RDM registration number(s)	Description
AtriCure, Inc.	AtriClip selection guide	562608	Malleable sizing tool

Source: Data from BD/RDM database (accessed on 13th September 2017) and manufacturer.

Different techniques to perform surgical closure of LAA have been proposed during the past decades. Success rate of these techniques varies widely (0-73%) [Kurfirst V, 2017]. The AtriClip system, may represent an interesting approach for the closure of the LAA since it performs both mechanical and electrical isolation of the LAA in relatively short time and by a simple procedure. The most innovative model is obviously the AtriClip PRO2, which allows a minimally invasive approach (i.e., thoracoscopic) and, for isolated LAA closure procedures, could be the direct competitor of the different endocardiac LAA occluders already on the market (F0001). However, endocardiac devices are in clinical use since several years and recommendations for their use have been issued within the most recent guidelines while AtriClip PRO2 has been only recently introduced on the market and it is then an emerging technology.

3.2.2 Regulatory aspects

Approval

AtriClip system is a Risk Class III medical device marketed in Europe since 2009. All the different models are also approved by the FDA (Table 3.3) (A0020). Indications, contraindications, and warnings for the use of the different models are presented in Table 3.4.

Like all medical devices, AtriClip system requires registration to the Italian National Medical Devices Inventory and Database (Banca Dati e Repertorio Dispositivi Medici – BD/RDM) to be purchased by NHS's hospitals.

Reimbursement

In Italy, before that AtriClip PRO2 came into the market, surgical LAA closure was concomitant to other cardiothoracic surgical procedures. In these cases, the DRG of the main intervention is typically used for the reimbursement. The DRG code 108 – "Other cardiothoracic procedures" is one of the codes that can be typically linked to the procedure [Regione Veneto 2015]. The national fee linked to DRG 108 is € 16,419 [DM 18/12/2012]. Some variability across Regions may exists (A0021).

Table 3.3: Approval details of AtriClip system (all models available on the Italian market)

Manufacturer	Device name	CE mark	FDA approvals
AtriCure, Inc.	AtriClip (<i>standard</i>)	Oct-2009	Jun-2010
	AtriClip Long	Oct-2009	Jun-2010
	AtriClip FLEX	Sep-2014	Aug-2014
	AtriClip PRO	Dec-2012	Aug-2012
	AtriClip PRO2	Jun-2016	Apr-2016

Source: Data from BD/RDM database (accessed on 13th September 2017), manufacturer and FDA database.

Table 3.4: Indications for use, contraindications, and warnings for the AtriClip system models

AtriClip (standard) AtriClip Long AtriClip FLEX	AtriClip PRO	AtriClip PRO2
Indications		
The AtriClip™ LAA Exclusion System is indicated for open occlusion of the heart's left atrial appendage.	The AtriClip™ LAA Exclusion System is indicated for the occlusion of the heart's left atrial appendage, under direct visualization, in conjunction with other open cardiac surgical procedures. Direct visualization, in this context, requires that the surgeon is able to see the heart directly, without assistance from a camera, endoscope, etc., or any other viewing technology. This includes procedures performed by sternotomy (full or partial) as well as thoracotomy (single or multiple).	The AtriClip LAA Exclusion System is indicated for the occlusion of the heart's left atrial appendage.
Contraindications		
<ol style="list-style-type: none"> 1. Do not use this device as a contraceptive tubal occlusion device. 2. Do not use this device if the patient has a known allergy to Nitinol (nickel titanium alloy). 		
Warnings		
<ol style="list-style-type: none"> 1. Do not attempt to reposition or remove the Clip after deployment. This may result in tissue damage or tearing. 2. Use this device only as intended. 3. Do not use on tissue which, in the opinion of the surgeon, would not be able to tolerate conventional suture materials or conventional closure techniques (such as surgical stapling). 4. Carefully evaluate Clip position, tissue thickness, and tissue width prior to Clip deployment. To determine appropriate Clip size, refer to the Cosgrove-Gillinov™ Selection Guide Instructions for Use. Failure to correctly size or deploy the Clip may result in: tissue trauma, dehiscence, tissue tearing, displacement and/or lack of desired homeostasis. 5. Do not use on a LAA less than 29mm in width and 1.0mm wall thickness. 6. Do not use on a LAA greater than 50mm when tissue is uncompressed. 7. Do not use this device if the patient has sensitivity to Nickel (nickel titanium alloy). 		

Source: IFU documents for the European market.

3.3 Discussion of results

The AtriClip system offers different device models to perform the closure of the LAA by three surgical approaches: sternotomy (AtriClip Standard, Long, and FLEX), thoracotomy (AtriClip PRO) or thoracoscopy (AtriClip PRO2). The procedure needs to be performed by cardiac surgeons, in a surgical theatre, under general anaesthesia and can be concomitant to other cardiothoracic interventions or isolated. No additional tools are required other than a sizing tool to properly select the clip size.

The AtriClip system is available on the Italian market since 2009 and the four models are all CE-marked and FDA-approved. When performed in concomitance to other cardiothoracic procedures or as isolated surgical intervention, the surgical closure of the LAA is typically reimbursed within the generic DRG 108 - *Other cardiothoracic procedures*.

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Instructions for use document P001090.C. Available at <https://www.atricure.com/download-asset-file/8477> (accessed on 11th April 2017).

Kurfirst V, Mokráček A, Canádyová J, Frána R, Zeman P. Epicardial clip occlusion of the left atrial appendage during cardiac surgery provides optimal surgical results and long-term stability. *Interact Cardiovasc Thorac Surg*. 2017 Jul 1;25(1):37-40.

Regione Veneto. Decreto n. 85 del 8 aprile 2015: Linee d'indirizzo regionali della chiusura dell'auricola sinistra per la prevenzione del tromboembolismo arterioso nella fibrillazione atriale. https://www.regione.veneto.it/c/document_library/get_file?uuid=2e7db51a-9b70-4d7b-8274-573fd4e08a19&groupId=10793 (accessed on 13th September 2017).

DM 18/12/2012. <http://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=45074&page=newsett> (accessed on 13th September 2017).

4. Clinical effectiveness and safety

The following AEs within the EFF and SAF domains were selected for this report:

Assessment Element ID	Research question
Effectiveness	
D0001*	What is the expected beneficial effect of epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment on all-cause mortality?
D0002*	What is the expected beneficial effect of epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment on disease-specific mortality?
D0005*	<p><i>D0005a:</i> How does epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment affect symptom frequency of the target condition?</p> <p><i>D0005b:</i> How does epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment affect symptom severity of the target condition?</p> <p><i>D0005c:</i> How does epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment affect symptom duration of the target condition?</p>
D0006	<p><i>D0006a:</i> How does epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment affect the progression of the target condition?</p> <p><i>D0006b:</i> How does epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment affect the recurrence of the target condition?</p>
D0012*	What is the effect of epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment on generic health-related quality of life?
D0015*	What is the effect of epicardial clip closure of the LAA in patients with AF with or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment on return to previous living conditions?
D0018	Do differences in acceptability predict the overall uptake of epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment?
Safety	
C0001	What harms are associated with the use of epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment?
C0002*	Are the harms related to the exposure to epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment?
C0005*	Are there susceptible patient groups that are more likely to be harmed through the use

	of epicardial clip closure of the LAA in patients with AF or with diagnosis of LAA thrombosis (LAAT) with or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment?
C0007*	Are there applications or maintenance procedures of epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment which may increase the risk of harmful events?
C0060*	How does the safety profile of epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment vary between different generations, approved versions or products?
C0061*	Can different organizational settings increase or decrease harms of epicardial clip closure of the LAA in patients with AF or with diagnosis of LAA thrombosis (LAAT) with or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment?
C0062*	Is there a requirement for specific training, use of a protocol or available guideline for epicardial clip closure of the LAA in patients with AF or with diagnosis of LAA thrombosis (LAAT) with or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment which may reduce the occurrence or severity of the harm in patients?
C0063*	Is there a requirement for specific training, use of a protocol or available guideline for epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant treatment which may reduce the occurrence or severity of the harm in professionals?
F0003*	Is the epicardial clip closure of the LAA in patients with AF or without AF in patients with high thromboembolic risk (score CHA2DS2-VASc ≥ 2) and unsuitable for long term anticoagulant used for other indications (extended use) or other purposes, e.g., in combination with other technologies (unintended use) that may have harms in addition to those following from the intended use?

* AE within the protocol and for which no evidence was found.

4.1 Methods

Clinical effectiveness and safety of AtriClip device were investigated through a literature search fulfilling defined criteria for Population, Interventions, Comparator, Outcomes and Design of studies (Table 4.1 PICOD) on the following data bases: Medline/Pubmed, Embase, Cochrane Library and ClinicalTrials.gov. Search data was performed on 19 of June 2017 and includes relevant literature from January 2009 on since the approval of the first AtriClip device (Appendix 4). Additional hand-searching was performed.

Table 4.1: Population, Interventions, Comparator, Outcomes and Design of studies

Population	Patients with valvular or non-valvular atrial fibrillation (VAF or NVAf) with high thromboembolic risk (score CHA ₂ DS ₂ -VASc ≥ 2) and unsuitable for long term anticoagulant treatment, patients undergoing cardiac surgery or thoracoscopic stand-alone AF surgery. In addition, patients with diagnosis (by mean of cardiac imaging: echo, angioTC, MRI) of LAA thrombosis (LAAT) with or without AF; patients with LAAT within heart surgery procedures with or without epicardial ablation.	
Intervention	Closure of LAA by epicardial clip.	
Comparator	OAT.*	
Outcomes	<p><i>Effectiveness outcomes:</i></p> <ul style="list-style-type: none"> • Non-fatal or fatal stroke (ischaemic/haemorrhagic) or systemic embolism • Death • LAA Exclusion confirmed at the longest follow up confirmed by transoesophageal echocardiography (TEE) • Health-related quality of life and disability (secondary outcome) 	<p><i>Safety outcomes:</i></p> <ul style="list-style-type: none"> • Clips system complications (Clip migration) (surgical outcome) • Clip occlusion failure (leakage) (surgical outcome) • Clip procedure-related adverse events (revision for bleeding, leakage, clot formation) (surgical outcome) • transient ischaemic attack (TIA), • cerebrovascular accident (CVA), • intensive care unit (ICU) stay (days) • Hospital stay (days) • Systemic embolism
Design of studies	HTA reports, systematic reviews, randomized controlled trials (RCTs). If they are not available, we will consider whether to include other types of study.	

*The comparator was confined only to OAT since percutaneous approach is the first alternative option after contraindications to OAT.

Two authors independently assessed titles and abstracts of all retrieved citations according to the defined inclusion criteria PICOD. A standardized data extraction sheet was used and quality assessment of included literature was performed with the Quality Assessment Tool for Case Series Studies developed by National Lung Heart Blood Institute (NLHBI https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case_series). However, observational studies are considered of low grade for supporting evidence [Grade 2004]. Efficacy and safety assessment elements (AE) are inserted within the text wherever it was possible to address the specific AE.

4.2 Results

4.2.1 Selection process for studies identification

From the literature search screening process (Fig. 4. 1), no HTA reports, systematic reviews or RCT were found that satisfied our PICOD. We used EndNote X7.2 to manage retrieved articles. We therefore evaluated full text for studies with no controls and included three major studies (40-155

patients) and two smaller studies (22-24 patients) [Kurfirst 2017, Ailawadi 2011, Emmert 2014, Alqaqa 2016, Ad 2015] (Table 4.2).

A complete list of included, excluded (with motivation) or not retrieved articles from full text screening process in relation to the PICOD, is in Appendix 5. Technical articles, case reports and poster abstracts were excluded a priori. Data extraction from included studies are in Appendix 6. Quality of included case series studies, although considered of low grade for supporting evidence [Grade 2004] has been assessed and is in Appendix 7.

Following is a description of included articles Clinical trial.gov and Cochrane reviews search results

Figure 4.1 Flow-chart of the studies according to PRISMA

(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.

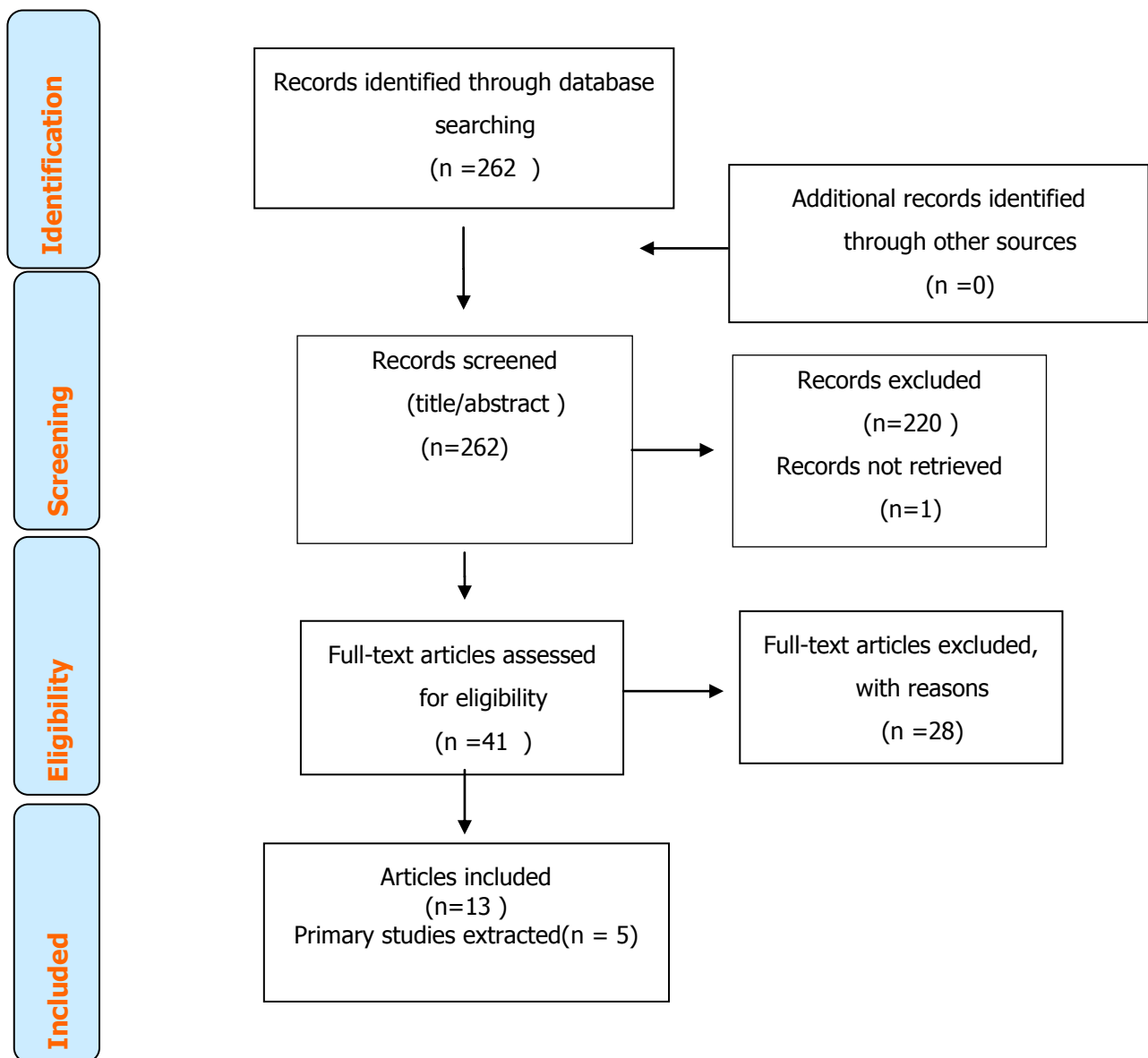


Table 4.2 Studies included and extracted*

Article	Population/intervention	Follow up
Kurfirist 2017*	155 patients AtriClip/AtriClip-PRO via sternotomy, thoracotomy or thoracoscopic	12 months
Ailawadi 2011	71 patients (EXCLUDE trial) AtriClip via sternotomy	12 months (Image only up to 3 months)
Emmert 2014 *	40 patients AtriClip via open surgery	36 months
Alqaqa 2016	22 patients via mini-torachotomy AtriClip (Pro?)	No out patient follow up
Ad 2015	24 patients mini-torachotomiy AtriClip Pro	Mean follow-up of 12.3 months
All studies conclude LAA closure with AtriClip device is safe with high success rates. No adverse event is reported to be related to clip implantation. No clip migration or deterioration has been reported.		

*For these studies multiple references were found and are listed in the description of each study and in the Appendix 5; only the most up-dated reference for each study is here included

4.2.2 Description of included studies and clinical trials.

Case series studies

(D0006, C0001) Study: **Kurfirist V, Mokráček A, Čanádyová J, et al. Effectivity of left atrial appendage occlusion with AtriClip in 155 consecutive patients - Single center study. Cor et Vasa 2017 doi: 10.1016/j.crvasa.2017.05.015¹**

This single center study includes 155 patients undergoing cardiac surgery procedures [CABG 32 (20.6%), valve procedure 39 (25.2%), combined procedure 6 (3.9%), Thoracoscopic AF ablation + AtriClip 71 (45.8%) and AtriClip as a lone procedure 7 (4.5%)] with epicardial AtriClip exclusion of the LAA placed via a sternotomy, thoracotomy or from a thoracoscopic approach. Follow-up to assess LAA closure: was performed by TEE/CT 1- to 3-month postoperatively. Perioperative success rate of clip implantation: complete LAA occlusion 152 (98.0%), LAA leak 0 (0%), LAA residual stump >1 cm 3 (1.9%). Revised for bleeding: 10 patients (6.4%) but none of the revisions were due to clip implantation (all on-pump procedure). Four patients had a transitory ischemic attacks (no thrombi in the left atrium or on the endocardial side of the closed LAA) and 2 patients cerebrovascular attack (no thrombi was found in the left atrium or endocardial side of the closed LAA in one patient, in the other patient the event occurred 1 month after discontinuation of NOAC). ICU stay varied from (days) 4.1 to 3.8, hospital stay (days) from 12.1 to 5.2. Hospital mortality was 8.4% (all in the group with high preoperative EuroSCORE). No clip migration or structural deterioration was found. Anticoagulant therapies at follow up: Antiaggregation usage 62 (43.7%), Warfarin usage 55 (38.7%), NOAC usage 20 (14.1%) and LMWH usage 5 (3.5%). Limitations reported: single center observational study without any control group. Authors conclude that

¹ This study has previous publications [Kurfirist 2017 Interactive; Mokraceck 2015; Kurfirist 2014; Mokraceck 2017 (full text not retrieved)], we extracted the most recent and checked previous article for related issues.

AtriClip epicardial exclusion with of the LAA appears to be a reproducible and safe surgical method with a high success rate confirmed by clip stability, complete occlusion of the LAA, and absence of any AF-related thromboembolic events. No funding was provided for this work and none of the authors reported a conflict of interest regarding this paper. Quality evaluation was fair.

(D0006, C0001) Study: **Ailawadi G, Gerdisch MW, Harvey RL, et al. Exclusion of the left atrial appendage with a novel device: Early results of a multicenter trial. Journal of Thoracic and Cardiovascular Surgery 2011;142(5):1002-09.e1. doi: 10.1016/j.jtcvs.2011.07.052**

This is a non-randomized, prospective multicenter trial designed to assess the safety and efficacy , investigational exemption device study (EXCLUDE trial). 71 patients undergoing elective cardiac surgery [coronary artery bypass grafting (CABG) 77,5%, valve repair or replacement, surgical Maze procedures (ablative or cut-and-sew),or atrial septal defect repair] with stroke score greater than 2 were eligible for concomitant AtriClip (Atricure Inc, Westchester, Ohio. 35, 40, 45, and 50 mm) via median sternotomy on or off cardiopulmonary bypass. Intraprocedural successful left atrial appendage exclusion was confirmed 95.7%. Although significant adverse events occurred in 48.6%,(most common events included postoperative hemorrhage, pleural effusion, heart block and congestive heart failure).there were no adverse events related to the device and no perioperative mortality. At 3-month follow-up (98.4%) had successful left atrial appendage exclusion by TEE/CT imaging. At 12-month follow-up, 19 patients (29.7%) remained on chronic anticoagulation with warfarin. Limitations reported: short-term imaging follow-up of only 3 months, although clinical follow-up extends to 12 months; relatively small cohort of patients. The authors concluded that safe and atraumatic exclusion of the left atrial appendage can be performed during open cardiac surgery with the AtriClip device with greater than 95% success. Funding was provided by Atricure Inc, and authors have nothing to disclose with regard to commercial support. Quality evaluation was fair.

(D0006) Study: **Emmert MY, Puippe G, Baumuller S, et al. Safe, effective and durable epicardial left atrial appendage clip occlusion in patients with atrial fibrillation undergoing cardiac surgery: first long-term results from a prospective device trial. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2014;45(1):126-31. doi: 10.1093/ejcts/ezt204 [published Online First: 2013/05/10]²**

² This study has previous publications [Emmert 2013; Starck 2012; Salzberg 2010 Journal of thoracic...; Salzberg 2011 (full text not retrieved)], we extracted the most recent and checked previous article for related issues.

Forty patients with AF were enrolled in this prospective 'first-in-man' trial for LAA Clip System (AtriClip, Atricure, Dayton, OH, USA. 35, 40, 45 and 50 mm) with elective cardiac surgery and concomitant ablation procedure with mean CHA2DS-VASC score of close to 4. Serial imagery workup was reported at baseline, 3-, 12-, 24- and 36-month follow-up. Early mortality was 10% due to non-device-related reasons, clips were found to be stable showing no secondary dislocation 36 months after surgery. No intracardial thrombi were seen, none of the LAA was reperfused and in regard to LAA stump, none of the patients demonstrated a residual neck >1 cm. Apart from one unrelated transient ischaemic attack (2.7%) (TIA) that occurred 2 years after surgery in a patient with carotid plaque, no other strokes and/or neurological events demonstrated in any of the studied patients during follow-up. No of the other adverse event (myocardial infarction 1 (2.7%), heart failure 1 (2.7%), arrhythmia 1 (2.7%), endocarditis 1 (2.7%), renal failure 1 (2.7%), liver failure (2.7%), pneumonia 2 (5.2%), malignancy 1 (2.7%) was related to their best knowledge to LAA closure.

At 3 years, 22 patients were in sinus rhythm (22 of 32, 68.8%) and of the 10 in AF (10 of 32, 31.2%), only 3 (3 of 10, 30.0%) were still being anticoagulated with warfarin. Limitations reported the need of further data in a stroke-prevention scenario. The authors concluded that concomitant epicardial LAA occlusion using AtriClip device is 100% effective, safe and durable in the long term and that it is applicable regardless of LAA morphology. This research was funded by an unrestricted research grant from Atricure. One of the authors is a consultant for Atricure and has received speaker fees. Quality evaluation was fair.

(D0006,C0001) Study: **Alqaqa A, Martin S, Hamdan A, et al. Concomitant Left Atrial Appendage Clipping During Minimally Invasive Mitral Valve Surgery: Technically Feasible and Safe. Journal of atrial fibrillation 2016;9(1):1407. doi: 10.4022/jafib.1407 [published Online First: 2016/12/03]**

This small study (22 patients) used only preexisting post-operative records. The objective was to examine the safety and feasibility of epicardial clipping (AtriClip® LAA Exclusion System (Cincinnati, Ohio, AtriCure®) of the LAA via a mini-thoracotomy approach during minimally invasive mitral valve surgery. Eight(36%) had mitral valve replacement and the rest had mitral repair surgery. Five(23%) patients needed blood product transfusion during the surgery. Two patients had re-operation to evacuate chest wall hematoma, both underwent annuloplasty surgery. No clip related bleeding was observed and no perioperative mortality was recorded. Limitation reported: small retrospective study not powered to evaluate stroke prevention, no outpatient follow up was done. The authors concluded that during minimally invasive mitral valve surgery, concomitant exclusion of the left atrial appendage using AtriClip(R) can be performed rapidly and safely. Funding was not reported, authors reported no disclosure of conflict. Quality evaluation was good.

(D0006, C0001) Study: **Ad N, Massimiano PS, Shuman DJ, et al. New Approach to Exclude the Left Atrial Appendage During Minimally Invasive Cryothermic Surgical Ablation. Innovations (Philadelphia, Pa) 2015;10(5):323-7. doi: 10.1097/imi.000000000000179 [published Online First: 2015/11/03]**

This study assessed the safety and efficacy of applying the AtriClip PRO (AtriCure, Inc, West Chester, OH USA) and exclude the LAA through right minithoracotomy and transverse sinus. 24 patients were enrolled. The procedural success rate was 95%. Nine minimally invasive mitral valve repairs were combined with surgical ablation; the rest were isolated right minithoracotomy Cox maze procedures. There was no remaining LAA neck in 71% of the patients. No strokes or TIAs, no acute renal failure, no pneumonia, no operative deaths were reported, only two readmissions within 30 days (8%), which were unrelated to LAA closure. Median length of stay was 5.5 days. Limitations reported: small, retrospective case series; study conducted in a center with in-depth experience in both surgical ablation and management of the LAA making results maybe not generalizable to less experienced centers. The authors concluded that this new approach is safe and effective and should offer a superior and consistent early and long-term solution compared with the current approach of endocardial stitch closure. Funding is not reported; one author is consultant and coowner of Left Atrial Appendage Occlusion, the other authors declare no conflict of interest. Quality evaluation was fair.

From the specific search on Cochrane reviews we found a methodological protocol for a Cochrane Review

[<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012385/full?refreshCitedByCounter=true>

Last updated 08 November 2017] with the following objective: "To assess the clinical effectiveness and safety of left atrial appendage closure compared with oral anticoagulation for preventing stroke in people with non-valvular atrial fibrillation (NVAf).

Trials from Clinicaltrial.gov database

Clinicaltrial.gov trial search identified (Table 4.3) two ongoing studies (one randomized-parallel assignment trial (*ATLAS*) and one observational prospective cohort (LAAO Registry)), three completed Non-Randomized-Single Group Assignment trials (*EXCLUDE*, *Safety and Effectiveness of Left Atrial Appendage Occlusion* and *Stroke Feasibility Study*) and two withdrawn or suspended trials (*AtriCure Minimally Invasive Surgical Ablation for Atrial Fibrillation/RESTORE IIB* withdrawn prior to recruitment and *DEEP Pivotal* suspended).

ATLAS is the only ongoing RCT of interest to this report for the comparator (OAT) and intervention (AtriClip) although the population is restricted to patients scheduled for any non-mechanical valve and/or CABG (structural heart) procedure where direct access to the LAA is

expected. Primary outcome measure should be available in 2019. Estimate enrollment for this study is of 2000 patients. LAAO Registry study, with an estimate enrollment of 3000 patients, is a prospective cohort that will provide data on stroke and will be concluded in 2026.

The non randomized completed studies available publications relative to *EXCLUDE* (70 patients) and *Safety and Effectiveness of Left Atrial Appendage Occlusion* (36 patients) trials are among the included studies. The *Stroke Feasibility Study* (11 patients) has no publication available.

Table 4.3 Trials (ongoing, completed and not) www.clinicaltrials.gov

TRIAL	STATUS
Ongoing	
<p>AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures (ATLAS) (ATLAS) : ClinicalTrials.gov Identifier NCT02701062 https://www.clinicaltrials.gov/ct2/show/record/NCT02701062?term=atriclip https://www.atricure.com/clinical-trials-patients</p> <p>Description: Patients without a documented history of AF but who present with a CHA2DS2- VASc of => 2 and HASBLED of => 2 and will undergo a valve or CABG (structural heart) procedure with direct visual access to the LAA will be eligible to participate based upon the inclusion and exclusion criteria defined in this protocol. Up to 2000 patients will enroll at up to 40 sites and will be randomized 2:1 (2 with AtriClip to 1 without AtriClip. Subjects who not develop Post-operative Atrial Fibrillation (POAF) will be followed for 30 days for safety. Subjects who develop POAF and receive the AtriClip will be followed for 365 days post index procedure.</p> <p>Study Design: Randomized, Parallel Assignment, Open Label</p> <p>Sponsor: AtriCure, Inc.</p>	<p>This study is currently recruiting participants.</p> <p>First Posted: March 8, 2016 Last Update Posted: September 15, 2017</p> <p>Estimated Primary Outcome measure Completion Date November 2019</p>
<p>Left Atrial Appendage Occlusion Registry (LAAO Registry) This study is currently recruiting participants. See Contacts and Locations: ClinicalTrials.gov Identifier: NCT02699957 https://clinicaltrials.gov/ct2/show/study/NCT02699957</p> <p>Description: The Left Atrial Appendage Occlusion Registry (LAAO Registry™) is designed to assess the prevalence, demographics, management, and outcomes of patients undergoing percutaneous and epicardial based left atrial appendage occlusion procedures to reduce the risk of stroke. The primary aims of the LAAO Registry are to optimize the outcomes and management of patients through the implementation of evidence-based guideline recommendations in clinical practice, facilitate efforts to improve the quality and safety for patients undergoing percutaneous and epicardial based left atrial appendage procedures, investigate novel quality improvement methods and provide risk-adjusted assessment of patients for comparison with nationwide NCDR data. The secondary purpose of the LAAO Registry is to serve as a rich source of clinical data to support assessments of short- and long-term safety, comparative and cost effectiveness research, and as a scalable data infrastructure for post market studies.</p> <p>Study design: Observational Model Cohort Prospective Target Follow-Up Duration: 2 Years</p>	<p>This study is currently recruiting participants</p> <p>First Posted: March 7, 2016 Last Update Posted: June 28, 2017</p> <p>Estimated Primary Completion Date: January 2026 (Final data collection date for primary outcome measure)</p>

<p>Sponsor: American College of Cardiology</p>	
<p>Completed</p>	
<p>AtriCure Exclusion of the LAA in Patients Undergoing Concomitant Cardiac Surgery (EXCLUDE): ClinicalTrials.gov Identifier NCT00779857</p>	<p>This study has been completed.</p>
<p>Description: Prospective, non-randomized trial to evaluate the safety and efficacy of the LAA Exclusion Device (Clip) for the exclusion of the LAA via epicardial tissue approximation.</p>	<p>First Posted: October 24, 2008 Last Update Posted: June 4, 2013</p>
<p>Study Design: Non-Randomized, Single Group Assignment, Open Label Number of patients: 70</p>	
<p>Publication:[Ailawadi 2011] Ailawadi G, Gerdisch MW, Harvey RL, Hooker RL, Damiano RJ Jr, Salamon T, Mack MJ. Exclusion of the left atrial appendage with a novel device: early results of a multicenter trial. J Thorac Cardiovasc Surg. 2011 Nov;142(5):1002-9, 1009.e1. doi: 10.1016/j.jtcvs.2011.07.052. Epub 2011 Sep 8.</p>	
<p>Sponsor: AtriCure, Inc.</p>	
<p>Safety and Effectiveness of Left Atrial Appendage Occlusion: ClinicalTrials.gov Identifier NCT00567515 https://ClinicalTrials.gov/show/NCT00567515.</p>	<p>This study has been completed.</p>
<p>Description: This study is to evaluate acute and long-term safety and effectiveness of Left atrial appendage occlusion (LAA)with the AtriCure LAA Occlusion System. This device will be applied in patients with atrial fibrillation (AF), paroxysmal, persistent and permanent, undergoing cardiac surgery with a concomitant Maze/Ablation procedure.</p>	<p>First Posted: December 5, 2007 Last Update Posted: February 13, 2013</p>
<p>Publications: [Emmert 2014] [Salzberg 2010]</p> <p>Emmert MY, Puippe G, Baumüller S, Alkadhi H, Landmesser U, Plass A, Bettex D, Scherman J, Grünenfelder J, Genoni M, Falk V, Salzberg SP. Safe, effective and durable epicardial left atrial appendage clip occlusion in patients with atrial fibrillation undergoing cardiac surgery: first long-term results from a prospective device trial. Eur J Cardiothorac Surg. 2014 Jan;45(1):126-31. doi: 10.1093/ejcts/ezt204. Epub 2013 May 8.</p> <p>Salzberg SP, Plass A, Emmert MY, Desbiolles L, Alkadhi H, Grünenfelder J, Genoni M. Left atrial appendage clip occlusion: early clinical results. J Thorac Cardiovasc Surg. 2010 May;139(5):1269-74. doi: 10.1016/j.jtcvs.2009.06.033. Epub 2009 Nov 1.</p>	
<p>Study Design: Single Group Assignment, Open Label Number of patients: 36</p>	
<p>Sponsor: AtriCure, Inc.</p>	
<p>Stroke Feasibility Study: ClinicalTrials.gov Identifier NCT01997905 https://ClinicalTrials.gov/show/NCT01997905.</p>	<p>This study has been completed.</p>
<p>Description: This is a feasibility study to assess the safety and efficacy of the AtriCure AtriClip</p>	<p>First Posted: November 28, 2013 Last Update Posted:</p>

<p>when placed via Minimally Invasive Surgical Deployment to the Left Atrial Appendage. The purpose is for evaluation of Stroke Prevention in Patients with Non-Valvular Atrial Fibrillation who are unable to take Oral Anticoagulants.</p> <p>Study Design: Single Group Assignment, Open Label Number of patients: 11</p> <p>Sponsor: AtriCure, Inc.</p>	<p>December 14, 2016</p>
Withdrawn or suspended	
<p>AtriCure Minimally Invasive Surgical Ablation for Atrial Fibrillation/RESTORE IIB: ClinicalTrials.gov Identifier NCT00571779</p> <p>https://ClinicalTrials.gov/show/NCT00571779.</p> <p>Description: Feasibility study arm to evaluate the safety of adding the left atrial linear connecting lesions of the Cox-Maze lesion set to the current RESTORE SR II IDE study procedure of performing pulmonary vein isolation, selected left atrial autonomic ganglionated plexi (GP) ablation, and optional left atrial appendage (LAA) excision/exclusion on a beating heart for patients with permanent or persistent Atrial Fibrillation (AF).</p> <p>Sponsor: AtriCure, Inc.</p>	<p>This study has been withdrawn prior to enrollment.</p> <p>First Posted: December 12, 2007 Last Update Posted: February 21, 2011</p>
<p>Pivotal Study Of A Dual Epicardial & Endocardial Procedure (DEEP) Approach (DEEP Pivotal): ClinicalTrials.gov Identifier NCT02393885</p> <p>https://www.clinicaltrials.gov/ct2/show/record/NCT02393885?term=atricure</p> <p>https://www.atricure.com/clinical-trials-patients</p> <p>Description: The objective of this study is to establish the safety and effectiveness of a dual epicardial and endocardial ablation procedure for patients presenting with Persistent Atrial Fibrillation or Longstanding Persistent Atrial Fibrillation utilizing the AtriCure Bipolar System and AtriClip® PRO LAA Exclusion System in an endoscopic or open ablation procedure, followed by an endocardial mapping and ablation procedure utilizing commercially available RF based, irrigated, power controlled, ablation catheters for endocardial lesions. The endocardial procedure will be staged to occur after 90 days post epicardial surgical procedure.</p> <p>Study Design: Single Group Assignment, Open Label</p> <p>Sponsor: AtriCure, Inc.</p>	<p>This study has suspended participant recruitment. First Posted: March 20, 2015 Last Update Posted: June 22, 2017</p> <p>Note: no reason is reported for the suspension</p>

4.3 Discussion of results

The evidence found is only from case series studies. These vary in the access (sternotomy, thoracotomy or mini-thoracotomy) and in the device (AtriClip PRO and AtriClip) used. Thus, they are not comparable. LAA Exclusion (confirmed by transoesophageal echocardiography TEE) data from included studies varies from 95,7% to 100%. No reported stroke or cerebrovascular event

data was associated (to their best knowledge) to the LAA clipping for no thrombi in the left atrium or on the endocardial side of the closed LAA was found. Hospital mortality varied from 8,4 to 10% and was not associated to LAA clipping intervention. No Health-related quality of life and disability data was reported . No clip migration or structural deterioration was found. None of the reported adverse events seems to be related, to their best knowledge, to the clip implantation. The three major studies report data on anti-coagulant therapies at different follow up which shows at 12 months patients remaining on anticoagulants in 29,7-43,7% up to roughly 3% at three year follow up in one study [. One of the included studies report on AF status at 3 year follow up with 31,2% of patients having AF. All studies were supported by TEE/CT imaging and presence of thrombus in LAA was a reason for exclusion. All studies included in this report conclude the LAA epicardial clipping is a promising technique. These data come from relatively small observational studies and are therefore considered of low grade for supporting evidence and need to be confirmed by larger studies with longer follow up that focus on stroke/AF prevention via LAA closure. Stratification of results by concomitant procedure, type of access and device is necessary.

Further enlightening data should be available from the two ongoing clinical trials (ATLAS to be concluded in 2019 with a restricted co-intervention population and LAAO Registry to be concluded in 2026) and from the ongoing Cochrane review "Left atrial appendage closure versus oral anticoagulation for preventing stroke in people with atrial fibrillation".

Agenas' model AEs that were not answered in this report due to lack of available evidence reflect some of the need of further research and can be found at the beginning of this chapter.

Bibliography

See APPENDIX 5.

5. Cost and economic evaluation

5.1 Methods

We selected the following AEs:

Assessment Element ID	Research question
E0001	Can you identify what types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?
E0002	Can you quantify what amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?
E0009	What were the measured and/or estimated unit costs of the resources used by the assessed technology and its comparator(s)?
E0005	What is(are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s)?
E0006	What are the estimated differences in costs and outcomes between the technology and its comparator(s)?
E0010	What are the uncertainties surrounding the inputs and economic evaluation(s) of the technology and its comparator(s)?

We answered only at E0009 AE since there were no data useful to other AEs originally selected.

In order to answer cost and economic research questions we carried out a systematic review on the Italian and international scientific literature to identify and analyze the economic studies for the AtriClip system (all models) in patient populations identified in PICOD (see table 4.1)

Four databases including Pubmed/Embase, Cochrane library (EED database - HTA database), Clinicaltrial.gov and DARE were searched on 19th June 2017. The search strategy was the same for effectiveness and safety domain (see Appendix 4). We included all types of economic analysis: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), cost-consequences analysis (CCA) and cost-minimization analysis (CMA) comparing the use of AtriClip versus OAT. When more papers referred to the same economic analysis or model, only the papers with more recent data and the most complete reports were included.

One author (SP) screened the title or abstract (if available) of studies yielded from literature searches. Difficulty in screening process were resolved through discussion with another author (EA). The full-texts of potential eligible studies were investigated to select studies to be included in the analysis, according to the inclusion criteria stated above. We used EndNote X7.2 to manage retrieved studies. We also searched for information related to research question E0009 (only device cost) through the same national database (Flusso consumi) used for Current Use analysis (see Chapter 2). We also used information from manufacturer collected by structured questionnaire (as described in Appendix – 3). All results were reported for all the AtriClip models individually and considering the surgical approach (as described in Chapter 3).

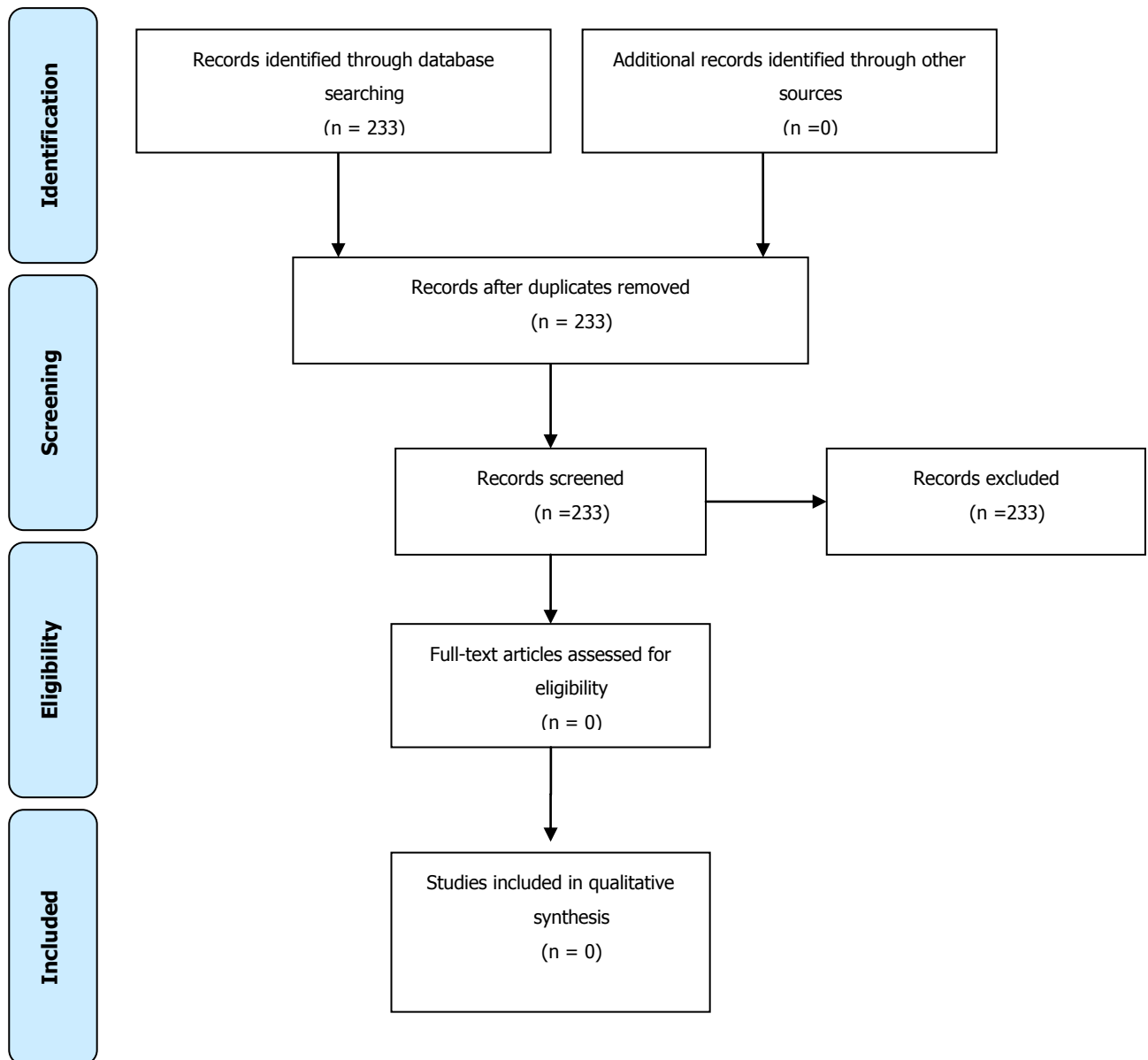
5.2 Results

5.2.1 Economic literature review

We did not find any economic study regarding the AtriClip system. The flow chart of the selection process from literature is reported in Figure 5.1.

Figure 5.1: Prisma flow chart for identification of included studies

(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. doi:10.1371/journal.pmed1000097)



5.2.2 Costs from Italian database "Flusso Consumi"

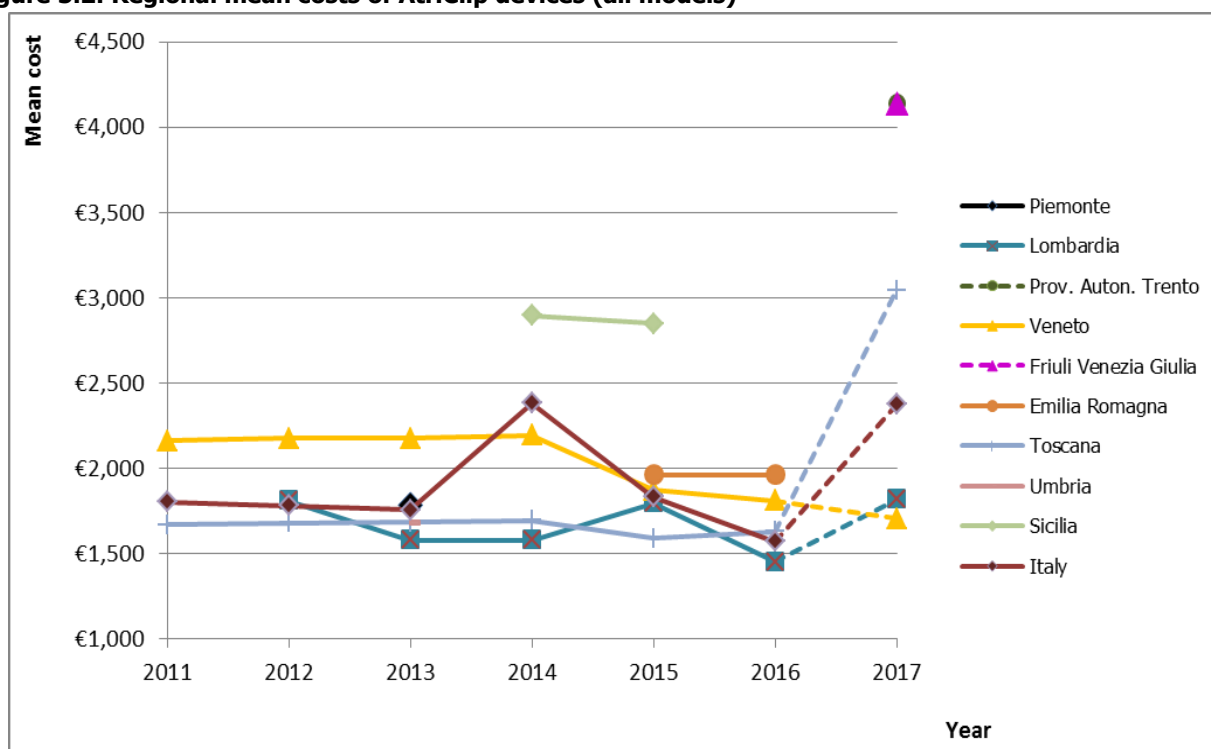
In order to gather information on the cost of AtriClip devices (E0009), we searched data from 2011 to 2017 (where 2017 refers to the first half of the year only). As stated in Chapter 2, the AtriClip devices have been bought in nine regions from 2011. Table 5.1 shows the mean values of the purchase cost of all the AtriClip models. Considering all years (2011-2017) and without stratifying by model or surgical approach, the purchase cost ranges from € 1,452.53 to € 4,139.20 (E0009). The trend of the mean price of the AtriClip devices across the nine Italian Regions is presented in Figure 5.2. The figure shows a sufficiently linear trend in the purchase cost, with higher values for Friuli Venezia Giulia, even though values are referred to a single year, and Sicily (referred to two years only), while for the first half of 2017, values referred to Toscana show an increase. No relevant variations occurred in the remaining Regions over the years as confirmed by the national mean value.

Table 5.1: Mean cost of AtriClip devices across the Regions (all models)

Italian Region	2011	2012	2013	2014	2015	2016	2017*
Piemonte			€ 1,786.05				
Lombardia		€ 1,812.58	€ 1,580.80	€ 1,580.80	€ 1,797.12	€ 1,452.53	€ 1,817.23
Prov. Auton. Trento							€ 4,139.20
Veneto	€ 2,163.00	€ 2,178.00	€ 2,178.00	€ 2,196.00	€ 1,872.00	€ 1,811.91	€ 1,705.60
Friuli Venezia Giulia							€ 4,139.20
Emilia Romagna					€ 1,963.52	€ 1,963.52	
Toscana	€ 1,672.11	€ 1,681.90	€ 1,683.75	€ 1,695.80	€ 1,590.16	€ 1,629.48	€ 3,046.75
Umbria			€ 1,681.90				
Sicilia				€ 2,896.76	€ 2,848.28		
Italy	€ 1,803.01	€ 1,783.98	€ 1,756.31	€ 2,382.88	€ 1,834.99	€ 1,574.64	€ 2,374.34

Source: Agenas analysis based on "Flusso consumi – CNS021" 2011 – 2017 (* first half of 2017)

Figure 5.2: Regional mean costs of AtriClip devices (all models)



Source: Agenas analysis based on "Flusso consumi – CNS021" 2011 – 2017 (* first half of 2017)

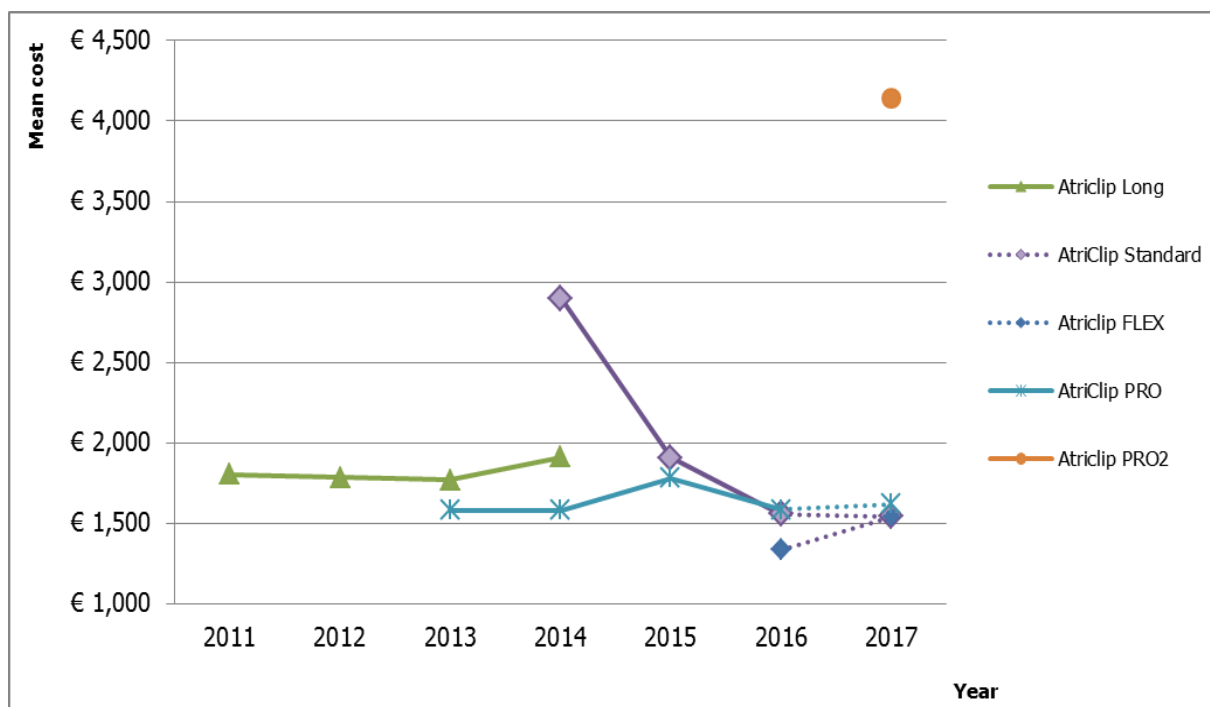
In more detail, we considered purchase costs of the AtriClip models in order to analyse their values and trend in the Italian NHS and understand which model generated variability in costs. Table 5.2 and Figure 5.3 show that AtriClip Long was sold until 2014 and its price was almost constant over the four years (from 2011 to 2014). AtriClip Standard was purchased from 2014 and it underwent a relevant decrease, in terms of mean purchasing value, from 2015 (approximately €1,000 less from 2014 to 2015). On the other hand, AtriClip FLEX was purchased only in 2016 and 2017 (first half) with a moderate price increase in 2017. Regarding AtriClip PRO, purchased since 2013, there are no changes over the years, while for the newly released AtriClip PRO2, in the first half of 2017, the average purchase cost by the NHS was over the national mean value (€ 4,139) (E0009).

Table 5.2: Mean cost per each AtriClip model

Product	2011	2012	2013	2014	2015	2016	2017*
AtriClip Long	€ 1,803.01	€ 1,783.98	€ 1,768.84	€ 1,910.17			
AtriClip Standard				€ 2,896.76	€ 1,904.69	€ 1,556.19	€ 1,539.20
AtriClip FLEX						€ 1,331.20	€ 1,539.20
AtriClip PRO			€ 1,580.80	€ 1,580.80	€ 1,779.23	€ 1,581.93	€ 1,617.39
AtriClip PRO2							€ 4,139.20

Source: Agenas analysis based on "Flusso consumi – CNS021" 2011 – 2017 (* first half of 2017)

Figure 5.3: Annual mean cost per each AtriClip model



Source: Agenas analysis based on "Flusso consumi – CNS021" 2011 – 2017 (* first half of 2017)

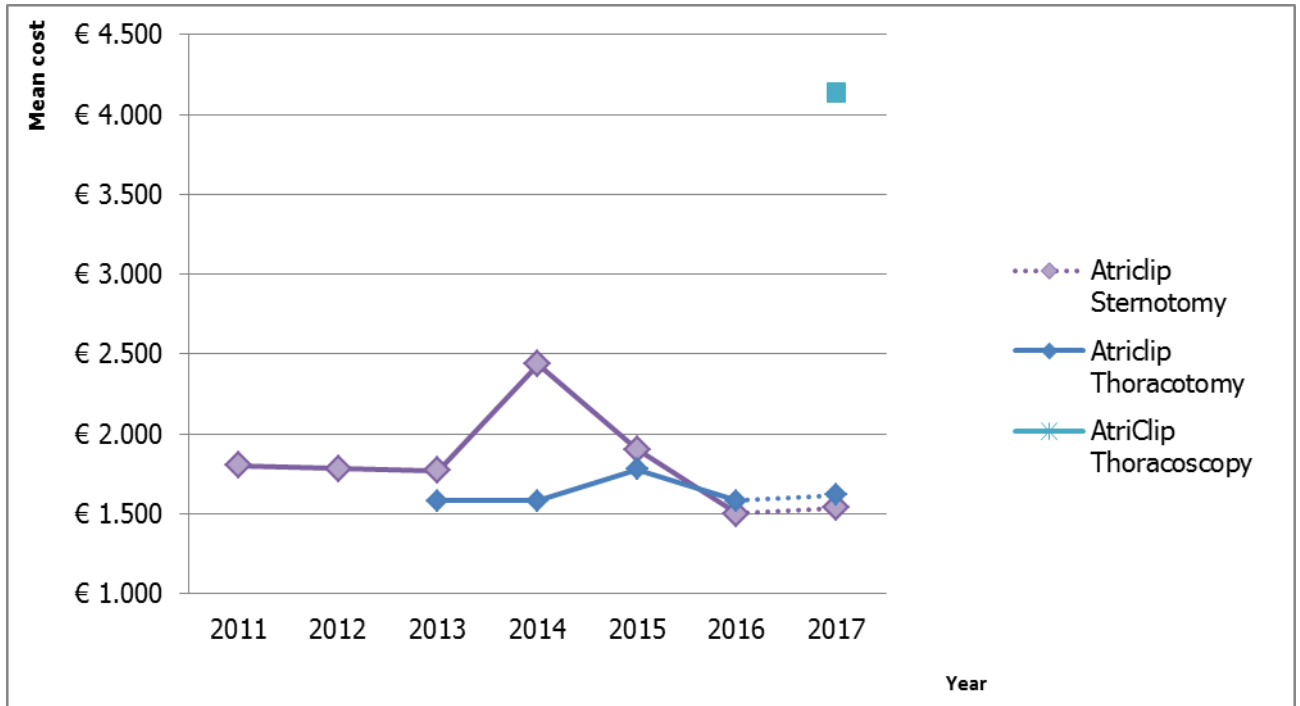
Table 5.3 and Figure 5.4 show the values and trends of mean purchase costs based on surgical approach. We put together AtriClip Standard, Long, and FLEX based on the sternotomic approach (named "AtriClip Sternotomy"), while AtriClip PRO is used in thoracotomy and AtriClip PRO2 for the thoracoscopy. Even combining the devices by surgical approach, the mean cost is constant with no relevant variability (except an increase in 2014). Finally AtriClip PRO2 (thoracoscopic approach) has a single mean value higher than the other devices in the first semester of 2017.

Table 5.3: Mean cost for AtriClip devices broken down by type of surgical approach

AtriClip generation	2011	2012	2013	2014	2015	2016	2017*
AtriClip Sternotomy	€ 1,803.01	€ 1,783.98	€ 1,768.84	€ 2,436.35	€ 1,904.69	€ 1,499.94	€ 1,539.20
AtriClip Thoracotomy			€ 1,580.80	€ 1,580.80	€ 1,779.23	€ 1,581.93	€ 1,617.39
AtriClip Thoracoscopy							€ 4,139.20

Source: Agenas analysis based on "Flusso consumi – CNS021" 2011 – 2017 (* first half of 2017)

Figure 5.4: Mean cost for AtriClip devices broken down by type of surgical approach



Source: Agenas analysis based on "Flusso consumi – CNS021" 2011 – 2017 (* first half of 2017)

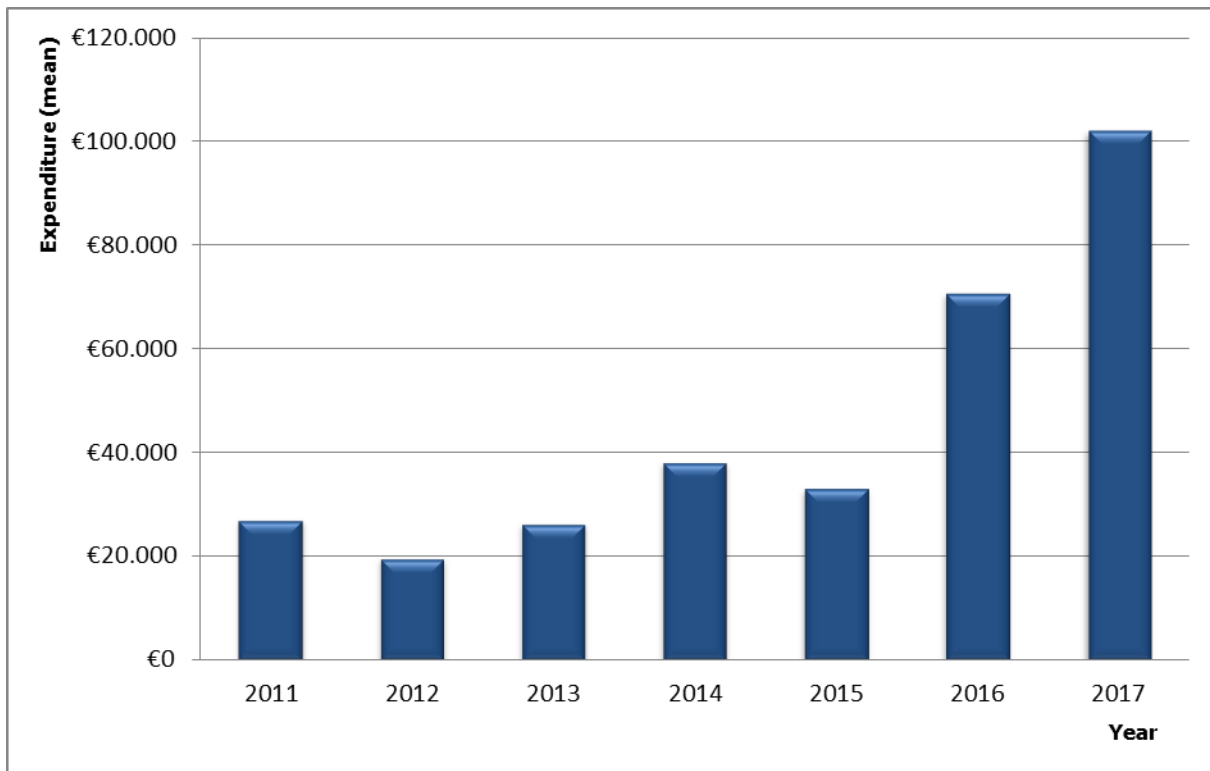
We finally calculated the total of the sustained mean expenditure for each year and then calculated the percentages of expenditure on the total years. This expenditure trend over the years gives us information about the presence and relevance of AtriClip system in the NHS and allow us to calculate future expenditure. Considering the number of AtriClip systems purchased by Italian NHS (Chapter 2) we multiplied them for the mean purchase cost. The results are shown in table 5.4. Up to 2015 the annual public expenditure ranges from € 19,623 in 2012 to € 38,126 in 2014. In 2016, there is an increase of more than twice the previous year (€ 33,029) and an even larger increase in the first half of 2017. Analysing the percentages of spending over the total expenditure (€ 317.125), more than 50% of total expenditure incurred only in 2016 and in the first half of 2017 (figure 5.5). The 58% of the expenditure incurred since 2011 is attributable to AtriClip PRO (41%) and AtriClip PRO2, which in the first semester of 2017 (year of sale to the Italian NHS) absorbs 17% of the total expenditure of all years (figure 5.5).

Table 5.4: Annual expenditure for AtriClip devices (mean)

Year	Expenditure
2011	€ 27,045.18
2012	€ 19,623.78
2013	€ 26,344.58
2014	€ 38,126.08
2015	€ 33,029.84
2016	€ 70,858.98
2017*	€ 102,096.80
Total	€ 317,125.24

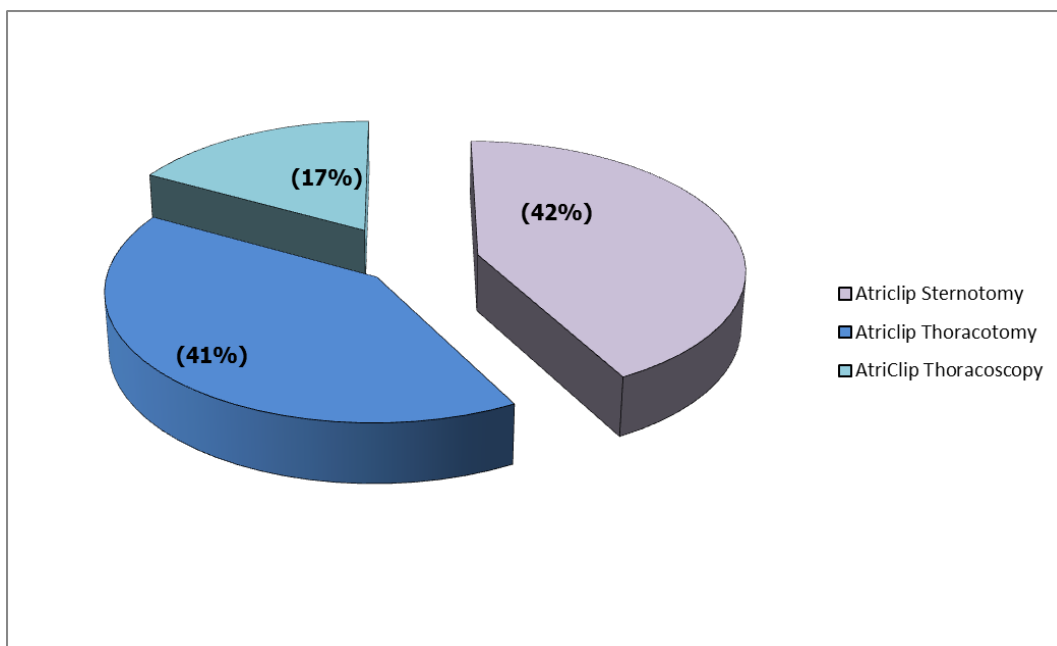
Source: Agenas analysis based on "Flusso consumi – CNS021" 2011 – 2017 (* first half of 2017)

Figure 5.5: Annual expenditure



Source: Agenas analysis based on "Flusso consumi – CNS021" 2011 – 2017 (* first half of 2017)

Figure 5.5: Expenditure for AtriClip devices broken down by type of surgical approach



Source: Agenas analysis based on "Flusso consumi" 2011 – 2017 (* first half of 2017)

5.3 Discussion of results

The 2017 annual expenditure for AtriClip devices in Italy is estimating to be three time greater than 2016. The more expensive AtriClip PRO2 (thoracoscopic procedure), that has been introduced only in 2017, absorbs the 17% of AtriClip expenditure in all years. The absence of economic studies did not allow to extract the information related to the surgical procedure and therefore consider all relevant variables to assess the potential economic impact of these technologies. Economic studies on AtriClip devices should include information on costs of operating room, personnel and hospital stay considering the three different surgical approaches (sternotomy, thoracotomy, thoracoscopy) that could affect the cost of the procedure.

The analysis using Italian cost and volume data from "Flusso Consumi" shows differences in expenditure along years and between the national areas, probably related to the surgical procedure approach used for LAAC.

Considering all these judgments no conclusive information on cost or cost - effectiveness is available up to day.

6. Conclusions

The mainstay of treatment of AF, before the effective cardioversion to sinus rhythm, is the prevention of thromboembolic complications with OAT and the combining with LAAC may be considered in patients with contra-indications for long-term anticoagulant treatment (defects in coagulation, platelet dysfunction or thrombocytopenia, persistent pathologies at risk for spontaneous bleedings, frail or elderly patients) or in patients undergoing cardiac surgery or thoracoscopic AF surgery. The target population includes also patients at high risk for OAT and undergoing cardiac surgery, with or without ablation, having permanent, persistent or paroxysmal AF; patients undergoing stand-alone AF epicardial ablation through sternotomy surgery (Maze operation). The AtriClip system is available on the Italian market since 2009 and the four models are all CE-marked and FDA-approved. When performed in concomitance to other cardiothoracic procedures, the surgical closure of the LAA is reimbursed within the DRG of the main intervention. The analysis of consumption of AtriClip in the Italian public health system showed that AtriClip for sternotomy (Standard, Long, and FLEX) was largely prevalent until 2015 when the technology has been used only in combination with major cardiac operations. In 2013 AtriClip for thoracotomy (AtriClip PRO) has been available in Italy and the number of AtriClip for thoracotomy become prevalent in 2016 (>55% of cases) with a huge increasing of total number of AtriClip devices used (> three time). In 2017, AtriClip for thoracoscopy (AtriClip PRO2) become available in the Italian market and it is now the second device for number of devices per year. Nevertheless the large majority of consumption is concentrated in four centres of four Italian Regions (Piemonte, Veneto, Lombardia, and Toscana). The use of AtriClip for thoracoscopy overcome in 2017 AtriClip for sternotomy. About effectiveness and safety, all studies included in this report concluded that the LAA epicardial clipping is a promising technique and none of the reported adverse events seems to be related, to the best knowledge of authors, to the clip implantation. These data need to be confirmed by larger studies with longer follow-up that focus on stroke/AF prevention via LAA closure. Stratification of results by concomitant procedure, type of access and device is necessary. Agenas' model AEs that were not answered in this report due to lack of available evidence reflect some of the needs for further research. We found no economic studies regarding AtriClip system. No conclusive information on cost/effectiveness is available up to day. The analysis from the Italian database for medical device use shows differences in expenditure along years and between the national areas. The differences can be referred to the number and kind of procedures performed with the different devices. In fact the 2017 annual expenditure for AtriClip (all types) in Italy is estimated to be 3 time greater than 2016, the more expensive AtriClip PRO2, introduced only in 2017, representing the 16% of expenditure.

List of acronyms and abbreviations

AEs: Assessment Elements

AF: Atrial Fibrillation

CND: Classification of Medical Devices

LAA: Left Atrial Appendage

LAAC: Left Atrial Appendage Closure

LAAT: Left Atrial Appendage Thrombosis

LAT: left atrial thrombus

LAT: left atrial thrombus

NSIS: New Health Information System

OAT: oral anticoagulation therapy