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Electrode Catheters with Gold tip for radiofrequency ablation in cardiac arrhythmias

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Methods

Agenas is a public body. Its mission is to promote innovation and development within the Italian national healthcare service and provide an Early Awareness and Alert (EAA) service by Horizon Scanning (HS) activities in the field of new and emerging health technologies.
A full description of the methods used for the production of the present HS report can be found at www.agenas.it.

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Limitations

This report is based on information available when the searches were made and does not contain data on subsequent developments or improvements of the evaluated technology. The observations made on effectiveness, safety or cost-effectiveness of the technology evaluated in the report are to be considered current, but may change as more evidence becomes available if an update of the documents commissioned.

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Declaration of Conflict of Interest

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers or distributors of the devices assessed in this document.

Massimo Grimaldi declares that in the last three years he has been a consultant for the Biosense Webster. He declares to have worked for Medtronic, Biosense Webster, Boehringher Ingheleim, Daichi Sankyo, Pfizer-Bristoll, Bayer. He declares to have received an allowance from Biosense Webster. He declares that congressional expenses have been paid by Biosense Webster, Boehringher Ingheleim, Daichi Sankyo, Pfizer-Bristoll, Bayer, Dompé, Bruno Faramceutici. He declares to have participated in conferences organized by sponsors.

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Name of the technology/procedure: **Electrode Catheters with Gold tip for radiofrequency ablation in cardiac arrhythmias**

Target population

Patients, of both genders and no age limitation, affected by cardiac arrhythmias that can be treated with radiofrequency ablation, such as Atrioventricular re-entrant tachycardias associated with the Accessory Pathways, Paroxysmal and Persistent Atrial Fibrillation, Atrial Flutter, AV Nodal Re-entry Tachycardia, Atrial Tachycardia, Ventricular arrhythmias.

Description of the procedure and technology

Cardiac ablation with radiofrequency (RF) energy is the standard treatment of most arrhythmias refractory to medical therapy [Scheinman M, 2003]. Radiofrequency catheter ablation has been established as a second line treatment option in patients with symptomatic persistent atrial fibrillation [Fuster V, 2006]. It is also being used in patients for treatment of supraventricular and ventricular tachycardia associated with heart diseases. RF current heats tissue via resistive heating of a thin rim of tissue that is in direct contact with the ablation tip catheter. Deeper tissue heating is the result of passive thermal conduction from this small area of volume heating. Radiofrequency energy is delivered through the tip electrode of the ablation catheter. Catheters reaches the cardiac chambers through the femoral vein or artery. The right spot for delivery of radiofrequency pulses is localized by electrophysiological techniques and frequently by complex mapping systems. Correct positioning in the right place is the cornerstone of a successful ablation.

The transmission of radiofrequency current in the cardiac tissue creates increases temperature leading to tissue necrosis. Transcatheter ablation has shown to be highly successful for ablation of arrhythmogenic tissue located within a few millimetres of the ablation electrode, such as accessory AV pathways (Wolff-Parkinson-White syndrome) and slow atrio-ventricular nodal pathway.

Depending on the tissue depth, in atrial flutter, atrial fibrillation and ventricular arrhythmias ablation, partly deeper and wider lesions can be needed to achieve a transmural lesion. In these fields 4 mm non-irrigated tip catheters often generate lesions too small and the arrhythmogenic tissue may not be fully destroyed increasing the risk of arrhythmias recurrences [Kuck KH, 1991; Morady F, 1993]. For any given electrode size, radiofrequency lesion size is a function of radiofrequency power level, exposure time [Wittkampf FHM, 1989] and contact force. At higher power, however, the exposure time is frequently limited by an excessive temperature increase at the electrode-tissue interface that may exceed 100°C [Haines DE, 1990] leading to blood charring and steam pop phenomenon. Blood charring may provoke microembolization; steam pop may provoke cardiac tamponade. Steam pop phenomenon is related to increase in tissue temperature over 100°C transforming the tissue liquid in steam up to small explosions in the tissue [Avitall B, 1992].

Two approaches have been used to prevent an excessive temperature increase. In ”temperature control mode”, a thermal sensor is used in the ablation electrode to monitor tip-electrode temperature.

An alternative approach, is to irrigate the ablation electrode with saline. Convective cooling maintains a low electrode-tissue interface temperature and prevents excessive temperature in the tip electrode and at the electrode-tissue interface [Wittkampf FH, 1988; Huang SKS, 1989]. An irrigated electrode may be capable of delivering higher radiofrequency power leading to deeper lesions. This approach reduces the risk of blood charring but doesn't cancel the risk of steam pop that may happen in the tissue at 3-5 mm deep.
Irrigated tip electrode catheters are the most frequently used for the ablation in the left cardiac chambers due to low risk of charring and embolization.
Although platinum-iridium electrodes have been the standard for most RF ablation catheters, some manufactures introduced gold tips. Gold has excellent electrical conductive properties, as well as a more than four times greater thermal conductivity than platinum (300 versus 70 W/m °K), although both materials have similar heat capacities (130 and 135 J/kg °K) [Issa Z, 2012; Balázs T, 2013; Linhart M, 2012].
The amount of radiofrequency energy transmitted by the electrode into the tissue is related to distance between the tip electrode and the tissue. The amount of energy increases exponentially as the distance decreases. In order to understand the true amount of radiofrequency transmitted to the tissue and to reduce the risk of perforation, contact force sensors have been introduced into the catheters [Reddy VY, 2015]. Other technological features are valuable to get optimal outcomes in terms of safety and efficacy in transcatheter ablation. Catheters with optimal flexibility, torqueability, tip irrigation and temperature monitoring may improve the outcomes. Beyond the technical features, transcatheter ablation remains an extremely operator-dependent procedure. The expertise of the operator, the team he works with and the workflow are crucial to guarantee the patient optimal results in terms of efficacy and safety.

Clinical importance and burden of disease

An arrhythmia is defined as any rhythm that is not normal sinus rhythm with normal atrioventricular conduction. At present, cardiac arrhythmias for which radiofrequency ablation is indicated are Atrioventricular re-entrant tachycardia associated with the Accessory Pathways (i.e.: Wolff-Parkinson-White syndrome - WPW), Paroxysmal and Persistent Atrial Fibrillation, Atrial Flutter, AV Nodal Reentry Tachycardia, Atrial Tachycardia, Ventricular arrhythmias.

Atrioventricular re-entrant tachycardia associated with Accessory Pathways

Atrioventricular re-entrant tachycardia (AVRT) is an arrhythmia in re-entrant tachycardia in which the accessory pathway is necessary for initiation and maintenance of the tachycardia. The two major types of this arrhythmia in people with an AV accessory pathway are orthodromic AVRT and antidromic AVRT.
Orthodromic AVRT comprises 90 to 95 percent of the re-entrant tachycardias associated with the WPW syndrome. The ECG during orthodromic AVRT typically shows a regular ventricular rate ranging from 150 to 250 or higher bpm. Antidromic AVRT is the least common arrhythmia associated with WPW syndrome, occurring in only 5 to 10 percent of patients. The ECG during antidromic AVRT typically shows a regular ventricular rate ranging from 150 to 250 or higher bpm, wide QRS complexes, with an RP interval that is usually more than one-half the tachycardia RR interval, and a constant RP interval. The prevalence of the WPW syndrome varies from setting to setting, 2.5/1000 in healthy aviation personnel [Smith RF, 1964], and 0.7/1000 in people aged 6 to 20 years [Fitzsimmons P, 2001].
The majority of patients with the WPW pattern on their ECG will remain asymptomatic. However, a small percentage of patients with the WPW pattern will develop arrhythmias as a part of the WPW syndrome. The clinical manifestation of WPW when an arrhythmia will occur may include: palpitations, dizziness, syncope, pre-syncope, chest pain or sudden cardiac death.

Atrioventricular nodal re-entrant tachycardia

Atrioventricular nodal re-entrant tachycardia is characterized by a regular supraventricular tachycardia that results from the formation of a re-entry circuit confined to the AV node and perinodal atrial tissue [Ganz LI

and Friedman PL,1995; Ferguson JD and DiMarco JP, 2003; Liuba I, 2006]. Epidemiologically, atrioventricular nodal re-entrant tachycardia is the most common among the supraventricular paroxysmal re-entry tachyarrhythmias accounting for nearly two-thirds of the paroxysmal supraventricular tachycardia. The disease is most common in women [Ganz LI and Friedman PL, 1995; Ferguson JD and DiMarco JP, 2003; Liuba I, 2006] and usually it is not associated with organic heart disease and can be presented at any age. In the 2/3 of the cases, the first manifestation begins after the first 20 years of life while the average age of onset occurs in the third or fourth decade of life. The severity of clinical manifestations depends on the age of the patient, the duration and frequency of tachycardia, and the presence or absence of associated heart disease [Goyal R, 1996]. Clinical manifestations are characterized by palpitations, presyncope, syncope, angina that can evolve in heart failure.

Atrial tachycardia

Atrial tachycardia (AT) is a regular atrial rhythm originating outside of the sinus node at a constant rate of >100 bpm [Saoudi N, 2001]. In contrast to macroreentrant atrial arrhythmias or atrial fibrillation, which involve multiple sites or larger circuits, atrial tachycardia arises from a single site within the left or right atrium.
Focal atrial tachycardias are usually paroxysmal and self-limited but in some occasions the arrhythmia may be continuously present from the onset. This last condition is known as incessant AT and it may induce left ventricular dysfunction [Chen SA,1998; Medi C, 2009].
Incidence of focal atrial tachycardia is relatively low and the disease accounts for between 5 and 15 percent of arrhythmias in adults undergoing study for paroxysmal supraventricular tachycardia [Chen SA,1994]. The disease is equally distributed between men and women.

Paroxysmal atrial fibrillation

Atrial fibrillation (AF) is a cardiac arrhythmia characterized by a complete irregularity of the electrical activation of the atria where normal atrial contractions are replaced by chaotic movements completely ineffective for the propulsion of the blood thus making the heart rhythm completely irregular.
Paroxysmal atrial fibrillation is defined as an episode of AF terminating spontaneously or within 7 days after a medical intervention [January CT, 2014]. The frequency of episodes of paroxysm by AF is uncertain. Recent studies indicate that most of these episodes are asymptomatic [Page RL,1994, Israel CW, 2004] even in those episodes in which paroxysm lasts more than 48 hours [Israel CW, 2004]. The natural history of subjects with paroxysmal AF is characterized by continuous but variable episodes of paroxysm. When untreated, the incidence of at least one episode of paroxysm is may raise to 70% within the first year [Coplen SE, 1990] but may reach 90% within the first 4 years from diagnosis [Rostagno C, 1995].
Therapeutic decisions in paroxysmal AF should take into account the duration and the presence or absence of the symptoms occurring during the episode. Transcatheter ablation of atrial fibrillation is considered to be a more effective approach to pharmacological treatments [Calkins H, 2009]. Currently its use is increasing for the prevention of paroxysmal episodes in subjects with paroxysmal AF and is considered second-line therapy when pharmacological treatments have no effect. It may be first line therapy in patients with normal heart that prefer avoid anti-arrhythmic drugs.

Atrial flutter

Atrial flutter is a supraventricular tachyarrhythmia characterized by a rapid atrial activation (200-350 bpm) and is regulated with a corresponding ventricular activation frequency of about 120 to 130 beats per minute. Atrial flutter has an incidence 2-5 times higher in males than women. It is difficult for such arrhythmia to develop into a healthy heart because it is generally secondary to pathologies such as atrial dilatation (mitralic and tricuspidal valvulopathies) or inflammatory processes (eg COPD), infiltrative or secondary to surgery or iatrogenic (eg Flecainide or propafenone) [Fosmoe RJ, 1960; Garson A, 1985; Granada J, 2000].
Since data on the incidence of atrial flutter in the general population are not entirely clear because the existing data derive from hospitalizations, and because in some circumstances arrhythmia may progress to atrial fibrillation. According to some US data, the incidence of atrial flutter is 5 per 100,000 in patients under

the age of 50 reaching the estimate of 587 per 100,000 in the ultra-eighteen [Granada J, 2000]. The dominant symptom is palpitation with sudden onset and sudden angina, anxiety, syncope, cardio-cirrhosis.

Ventricular ectopies

Ventricular ectopies are very frequent in general population. Rarely they can provoke palpitations or left ventricular dysfunction. When the ventricular ectopies are symptomatic or cause of tachicardiomyopathy a treatment is needed. The antiarrhythmic drugs represent the first line therapy but, when the arrhythmia arises from the right ventricle outflow tract, transcatheter ablation is preferred over drugs.

Ventricular tachycardia

The number of patients suffering from Ventricular Tachycardia is quickly increasing due to the aging population and the growing number of implanted defibrillators. It is characterized by a regular ventricular rhythm originating usually from damaged myocardial tissue.

Products, manufacturers, distributors and approval

Only AlCath® Gold tip catheters manufactured by VascoMed GmbH (Binzen Germany) are available on the Italian market. AlCath® Gold tip catheters are classified according the Classificazione Nazionale dei Dispositivi Medici (CND) under the class “C020301 Elettrocateteri per ablazione a radiofrequenza di foci aritmogeni” and are registered within the Italian National medical device database (RDM) with the numbers reported in Tab. 1 since 2008 (information provided by the manufacturer).
AlCath® Gold tip catheters can be irrigated and non-irrigated. The irrigated catheters use saline solution and are connected to an irrigation pump. The same catheters are available in platinum-iridium (AlCath®) also. The first AlCath® gold tip catheter received CE mark in 2006 (information provided by the manufacturer). Models and characteristics of the gold tip catheters non irrigated are reported in the Tab. 1,

Tab. 1. Alcath® gold tip catheters non irrigated.

Model	AlCath® TC LT Gold fullCircle	AlCath® TC Gold FullCircle
Registration number (BD/RDM)	134229	134229
Tip electrode type	Non-irrigated	Non-irrigated
Tip electrode size	8 mm	4 mm

and the gold tip catheters irrigated are listed and described in Tab. 2.

Tab. 2. Alcath® gold tip catheters irrigated.

Model	AlCath® Flux Gold eXtra	AlCath® TC Flux eXtra Gold FullCircle	AlCath® Flutter LT Gold FullCircle	AlCath® Force*
Registration number (BD/RDM)	907434	378885, 378890, 378891, 378892, 378893	907454	1462102, 1462120, 1462121, 1462122, 1462123
Tip electrode type	Irrigated. 12 holes	Irrigated. 12 holes	Irrigated. 12 holes	Irrigated. 12 holes. Integrated with force sensor
Tip electrode size	3,5 mm	3,5 mm	8 mm	3,5 mm

** CE mark of AlCath® Force expired on 26/06/2018. This information was confirmed by manufacturer.*

The main differences among gold tip catheters, non-irrigated and irrigated, are the availability of different sizes of the ablation electrode tip and other catheter specific properties, such as working length and curve configurations.". The 8 mm tip catheter is often used to perform atrial flutter ablation. The irrigated 3.5 mm tip catheters provide deeper lesions and reduce the risk of clot formation; these catheters are therefore often used in left atrium and ventricle. All AlCath® catheters are provided with a thermal sensor integrated in the catheter tip for monitoring temperature and avoiding tissue overheating. As all ablation catheters, AlCath® catheters with gold tip must be connected to a radiofrequency generator. Irrigated catheters must also be connected to an irrigation pump. Movements of the distal catheter handle are translated 1:1 into a deflection of the catheter tip in all AlCath® catheters.

Product name [Manufacturer]	Distributor	CE Mark	BD/RDM	FDA
AlCath® [VascoMed GmbH, Binzen Germany]*	BIOTRONIK SE & CO. KG	☑	☑	☐

**All products reported in Tables 1-2*

Setting

The gold tip catheter is used in a hospital setting in electrophysiology operating rooms during the cardiac ablation procedure with radiofrequency. The electrophysiology operating room must be equipped with C-arm fluoroscopic X-ray system and polygraph to read intracardiac electrograms (IEGMs); the operating room could also be equipped with mapping systems that locate, the catheter in the space through the magnetic and/or electrical systems. To perform this procedure the hospital should be equipped with cardiology and arrhythmology departments.

☐ Home	☑ Hospital	☐ Outpatient
☐ Accident and Emergency	☐ Other:	

Roll out in Italy

To identify the diffusion of the technology in Italy we consulted different sources as "*flusso consumi* - NSIS database" of Ministry of Health (MoH) and data from manufacturer. We also performed a regional survey.
On the 28th of July 2017 we sent an *ad hoc* request to HTA regional referees to gather data of purchased quantities, in 2015 and 2016, and their relative median price, related to both catheters, gold and platinum-iridium, for radiofrequency ablation therapy to compare any difference in use and prices. There were 19 participants. In this paragraph we report the context analysis regarding the use of technology while in the "Cost of the technology/procedure" paragraph we illustrate the cost analysis context.
We received 11 answers and only one of these was not included in our analysis because referred to data from local health trust (and not regional), with a final result of 10 answers.
The data gathered did not allow an in-depth analysis owing to their limited comparability (purchase vs. use data, different details provided).
The analysis showed that gold tip catheters represent only around 5.5% (188 in 2015 and 225 in 2016) of the

total catheters purchased and used. For each technology (gold and platinum-iridium) resulted a slight increase of the quantities in 2016 respect to 2015.
From the analysis of *flusso consumi* (NSIS database - MoH) we got the amount of a single medical device used (gold tip catheters), since in the database every medical device is identified with a registration number (RDM code) (Tab. 3). A constant trend of use of the technology, in both years, with 350 gold tip catheters in 2015 and 363 in 2016 was evident. The same analysis for platinum-iridium catheters was problematic due to high number of manufacturers of these technologies.
The manufacturer (consulted in August 2017, after a public call) stated that 75 Public Hospitals and 20 Private Hospitals use the electrode catheters with gold tip, with more than 3.000 catheters used in Italy from 2008.

Tab.3. Gold tip catheters used in Italy, in 2015 and 2016.

Medical device name	RDM code	2015	2016
AlCath® TC LT Gold fullCircle AlCath® TC Gold FullCircle	134229	168	178
AlCath® Flux Gold eXtra	907434	68	41
AlCath® TC Flux eXtra Gold FullCircle	378885	0	0
	378890	0	1
	378891	5	43
	378892	16	10
	378893	14	9
AlCath® Flutter LT Gold FullCircle	907454	79	81
AlCath® Force*	1462102	0	0
	1462120	0	0
	1462121	0	0
	1462122	0	0
	1462123	0	0
TOTAL		**350**	**363**

Data elaborated by Agenas (Source NSIS database – Italian MoH)
** CE mark of AlCath® Force expired on 26/06/2018. This information was confirmed by manufacturer.*

☐ Pre-marketing	☐ On the market for 1-6 months	☐ On the market for 7-12 months
☑ On the market for more than 12 months	☐ Not identified	

Comparators

The comparators for irrigated and non-irrigated gold tip catheters are irrigated and non-irrigated catheters in platinum-iridium respectively.

Effectiveness and safety

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

The following PICOD (Population, Interventions, Comparator, Outcomes, Design of studies) structure was defined for this project:

- Population: subjects with cardiac arrhythmias that require radiofrequency ablation.
- Intervention: (irrigated or non-irrigated) radiofrequency ablation with use of gold-tip electrode catheters.
- Comparator: (irrigated or non-irrigated) radiofrequency ablation with use of platinum-iridium-tip electrode catheters.
- Outcomes: Ablation acute success; Thromboembolic events; Silent Cerebral Lesions (after atrial fibrillation ablation); Arrhythmia recurrence; Pericardial effusion; Tamponade; AV block; Re-hospitalization.
- Design of studies: HTA reports, systematic reviews, and randomized controlled trials (RCTs).

Electronic searches were performed on Medline/PubMed, Embase, the Cochrane Library and *clinicaltrial.gov* following a search strategy based on the above listed PICOD. In particular, we searched the literature available in the period from January 2007 to August 2017, in English language. Two review authors independently assessed titles and abstracts of all retrieved citations according to the defined inclusion criteria. The methodological quality of each included study was assessed in accordance with the criteria established by the Cochrane tool for assessing risk of bias [Higgins JPT, 2011]. The following domains for the risk of bias were considered: i) Random sequence generation and allocation concealment (selection bias); ii) Blinding of participants and personnel (performance bias); iii) Blinding of outcome assessors (detection bias); iv) Incomplete outcome data (attrition bias); v) Selective reporting (reporting bias). Where a sufficient number of primary studies was identified, a meta-analysis was performed. Dichotomous outcomes results were expressed as risk ratio (RRs) with 95% confidence intervals (CIs). Analysis was performed according to the intention-to-treat principle. Heterogeneity was evaluated using a Chi-square test with N-1 degrees of freedom, with an alpha of 0.10 used for statistical significance and with the I^2 test [Higgins JPT, 2011]. Review Manager (Revman 5.3) was used for data synthesis. Data were pooled using both the random-effects model and the fixed-effect model to ensure robustness.

Our systematic searches identified 76 records from the three electronic databases. After removing duplicates, the title/abstract screening allowed the identification of 12 potentially eligible studies. After the exclusion of four studies with reasons (see Appendix 1), eight publications of five trials remained for inclusion [Sacher FM, 2007; Stuhlinger MC, 2008; Kardos AC, 2009; Lewalter TC, 2011; Linhart MI, 2012] (See Appendix 2). Three were secondary publications of the AURUM 8 trial [Lewalter TL, 2012; Lickfett LE, 2013; Lewalter TC, 2017]. These three studies evaluated differences in clinical and echocardiographic parameters between paroxysmal and persistent atrial flutter in the AURUM 8 study [Lickfett LE, 2013], a post hoc comparison of procedural data within subgroups of participants [Lewalter TL, 2012] and optimal combination of ablation settings leading to the highest procedural efficacy [Lewalter TC, 2017].

Description of trials

The five trials included were published between 2007 and 2012 in the following countries: Germany (n=3) [Stuhlinger 2008, Lewalter 2011, Linhart 2012], France (n=1) [Sacher 2007], and the Netherlands (n=1) [Kardos 2009]. Overall 845 participants were included (range 30 to 462) and the arrhythmias for which RF were applied were: atrial fibrillation (n=2; participants 100) [Sacher 2007, Linhart 2012]; atrial flutter (n=2; participants 493) [Kardos 2009, Lewalter 2011]; and atrio-ventricular nodal reciprocating tachycardia (AVNRT) (n=1; participants 252) [Stuhlinger 2008]. The mean age ranged from 57 to 66 years whereas, men were dominant in the atrial fibrillation or atrial flutter population ranging from 65% to 83% whereas in the trial

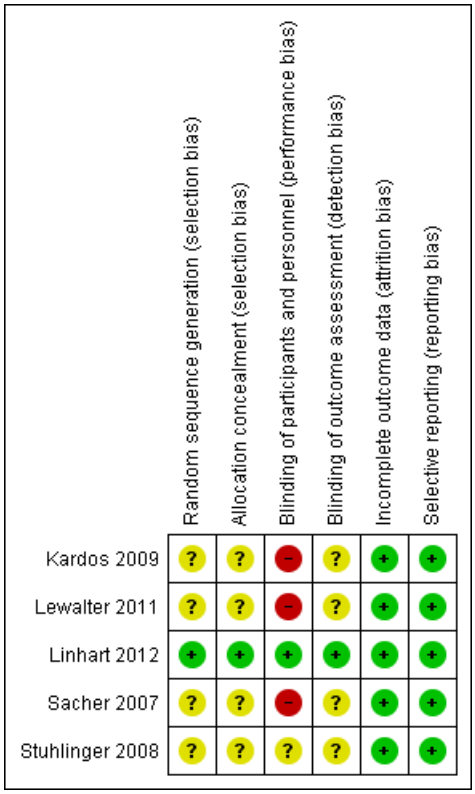
with AVNRT the percentage of males was lower (35%).
In terms of interventions all the studies compared gold-tip catheter with platinum-iridium. Three trials used 8mm-tip catheter [Sacher 2007, Kardos 2009, Lewalter 2011], one used 4mm-tip [Stuhlinger 2008], and one used 5mm[1] irrigated tip [Linhart 2012]. Three trials used irrigated catheters [Sacher 2007, Kardos 2009, Linhart 2012].
The primary outcomes were bidirectional isthmus block within 20 minutes of application for Sacher [Sacher 2007]; mean increase of power or temperature as a function of time during RF ablation for Stuhlinger [Stuhlinger 2008]; procedural success, duration of fluoroscopic exposure as well as procedural duration for Kardos [Kardos 2009]; reduction of the cumulative RF application duration time to bidirectional cavotricuspid isthmus block for Lewalter [Lewalter 2011]; and the temperature generated at the catheter tip for Linhart [Linhart 2012]. All the studies reported acute success rate. The secondary outcomes of the studies included procedural complications and other outcomes that are described in Appendix 3 Table 1. Follow-up time was 6 months in two studies [Kardos 2009, Lewalter 2011], 9 months in one study [Sacher 2007] and unclear in two [Stuhlinger 2008, Linhart 2012].
However, it must be noted that subjects with ventricular tachycardia, for whom the gold tip device should be ideal due to its ability to perform deeper and wider lesions, were not considered in the included studies.

Risk of bias

Appropriate randomisation process and allocation concealment methods were used in only one study [Linhart 2012]. In the remaining four trials no clear description was provided regarding sequence generation and allocation concealment [Sacher 2007, Stuhlinger 2008, Kardos 2009, Lewalter 2011]. Hence, we cannot conclude whether the studies were free from selection bias. In terms of performance bias no mention of blinding was identified in the studies, however, since we judged acute success rate as an objective outcome we did not consider the potential bias as serious. In terms of detection bias, only one study [Linhart 2012] reported about blinding of the outcome assessor while the remaining trials did not report sufficient description to make a judgement. No concern of attrition bias were reported as all the subjects were included in the final analysis without taking into account any cross-over. All the outcomes relevant to the present assessment were considered in this study and there was no evidence of reporting bias.

[1] *The manufacturer declared in the Public consultation phase that the device "Electrode catheter 5mm tip" is not more used in clinical practice.*

Fig. 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

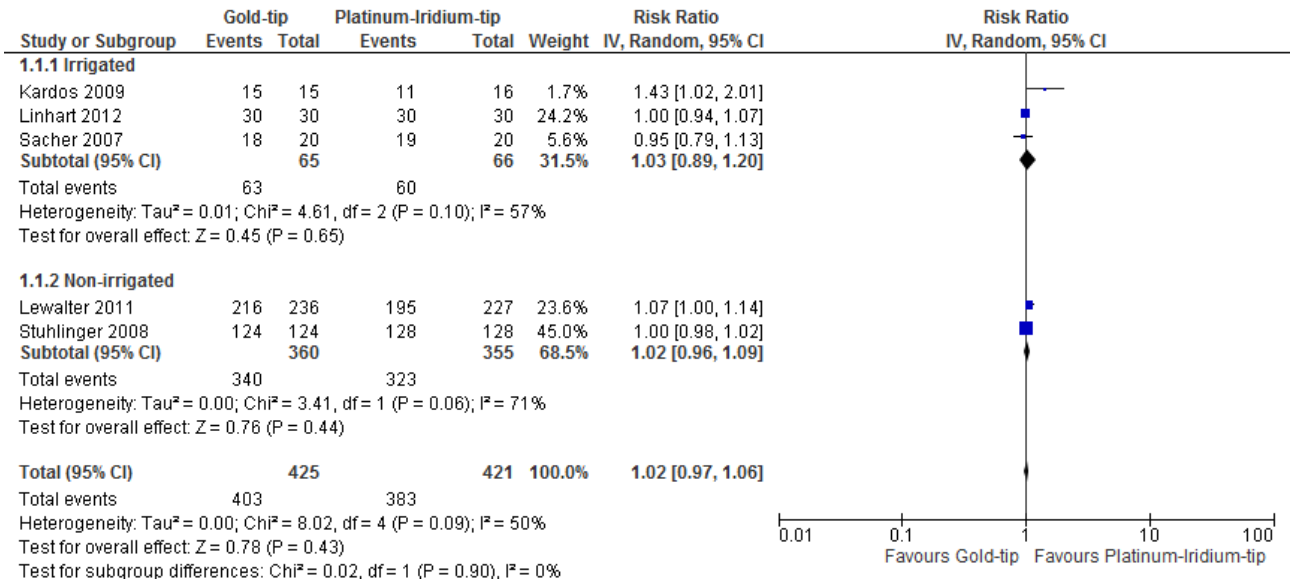


Findings

Ablation acute success

All the trials reported this outcome. The proportion of success was 95% in the Gold-tip group and 92% in the Platinum-iridium group. There was no statistical difference between the groups (RR 1.02, 95%CI 0.97 to 1.06; I^2 =50%) Subgroup analysis between trials that used irrigated devices and non-irrigated devices were also performed. Test for subgroup differences did not show significant difference. (**Fig. 2**).

Fig 2. Forest plot of comparison: Gold-tip vs Platinum Iridium, outcome: Ablation acute success.



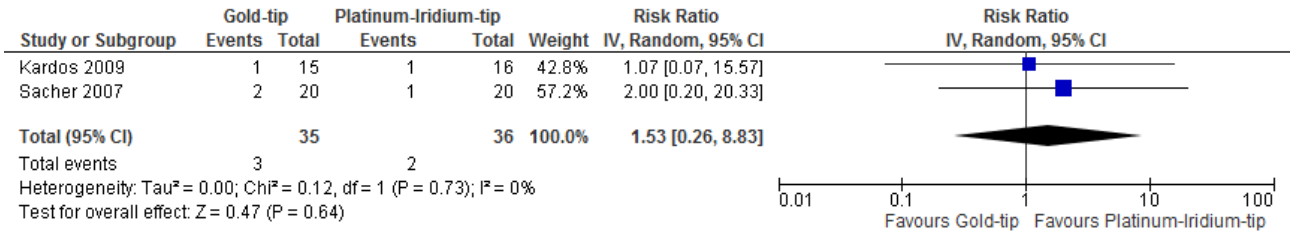
Thromboembolic events

Only two trials reported thromboembolic events. Only one event was reported in the platinum-iridium group in the Lewalter 2011's trial. No evidence of difference was detected.

Arrhythmia recurrence

Arrhythmia recurrence was reported by only two studies. These studies used both irrigated devices. The proportion of events was 9% in the gold-tip group compared to 6% of platinum-iridium group, with no evidence of difference between the groups (RR 1.53, 95% 0.26 to 8.83). (**Fig.3**)

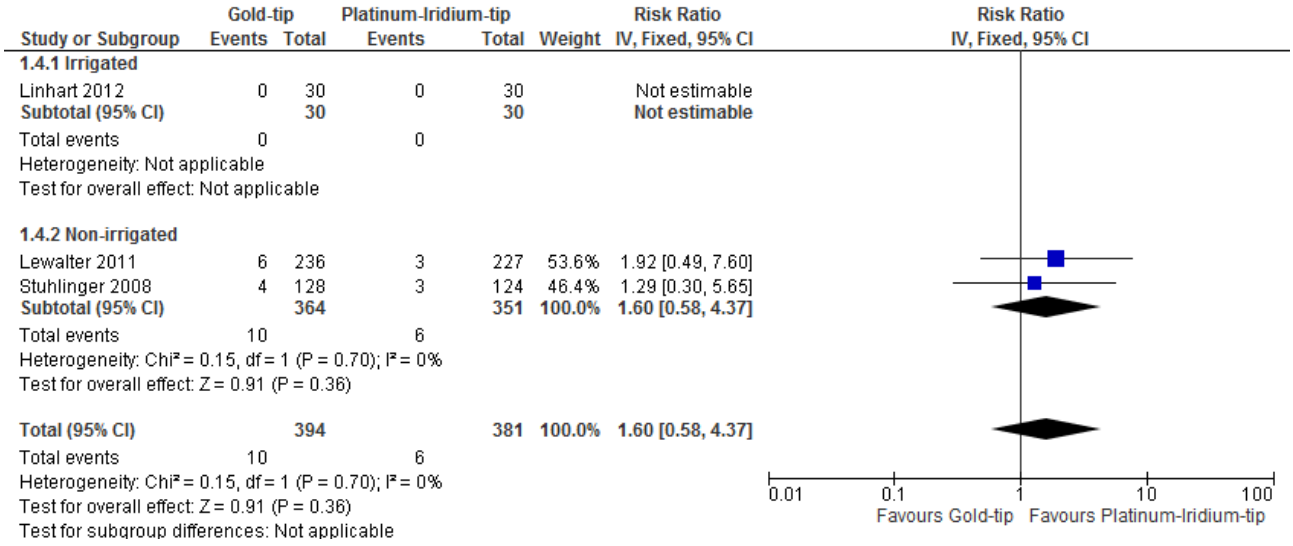
Fig. 3. Forest plot of comparison: Gold-tip vs Platinum Iridium, outcome: Arrhythmia recurrence.



AV block

AV block was reported by three trials [Stuhlinger 2008, Lewalter 2011, Linhart 2012]. In Linhart 2012 that evaluated irrigated devices no event occurred in none of the groups. In the studies that evaluated non-irrigated catheters the rates of AV block were 3% subjects and 2% subjects in the gold and platinum groups respectively. No evidence of difference was observed between the two groups.(**Fig.4**)

Fig. x4. Forest plot of comparison: Gold-tip vs Platinum Iridium, outcome: AV block.



Outcomes not evaluated

The following outcomes were not evaluated by any of the included study: silent cerebral lesions, pericardial effusion, tamponade, and re-hospitalization. In the study by Linhart 2011, pericardial effusion was evaluated as part of the "periprocedural complications" that were defined as one or more of the following: aneurysm or major hematoma following puncture of right femoral vein, pericardial effusion, phrenic nerve palsy, atrioesophageal fistula, symptomatic pulmonary vein stenosis, or stroke. The authors stated that no

procedural complication occurred.

Potential benefits to patients

There was no difference in clinical outcomes between the gold tip catheter and the platinum-iridium tip catheter in the ablation procedure with radiofrequency for cardiac arrhythmias.

☐ Mortality reduction or increased survival	☐ Reduction of the morbidity	☐ Improved quality of life (patient/users)
☐ Improved patient monitoring	☐ Other:	☑ Not identified

Cost of the technology/procedure

To analyse the economic aspects, related to the technology object of this report, we carried out a research of the available evidence and, for the context data, we performed a regional survey and contacted the manufacturers through an ad hoc questionnaire sent by e-mail.
Electronic searches to find economic evaluations and cost analysis on electrode catheters with gold tip for radiofrequency ablation in cardiac arrhythmias and their related procedure were performed on bibliographic databases (Pubmed, Embase and Cochrane Library) in August 2017. No economic studies and cost analysis were available from our research. This result was confirmed also by the manufacturer.
In order to investigate the cost of gold tip catheters and platinum-iridium catheters for ablation therapy, we carried out a regional survey to gather data of medium price of quantities purchased, in 2015 and 2016. We received 11 answers and only one of these was not included in our analysis because it contained local data, with a final result of 10 answers.
The 10 answers showed differences of median prices. These differences were linked to the different characteristics of catheters, as length of the tip and type of catheters (irrigated and non-irrigated), but different formats used by regional referees and different level of information provided did not allow us to manage the answers in homogenous clusters and perform a rigorous analysis.
Due to the limits described, we report the minimum and maximum of the weighted average prices, for both technologies, without the difference between irrigated and no irrigated catheters. Except for catheters with particular characteristics, as contact force measurement, the comparison between gold tip catheters and platinum–iridium catheters showed similar values for minimum weighted average price (Tab 4). We identified a higher value of the maximum weighted average price of platinum-iridium catheter. However, the maximum price (of Euro 2,440) regarded a small amount of catheters purchased, while the remaining catheters registered a maximum value similar of gold tip. The broader variability of prices is perhaps due to the larger amount of platinum-iridium catheters purchased. The cost of the specific equipment/tools required for gold tip catheters use is not considered in our analysis because it's the same as the comparator.

Tab. 4: Minimum and maximum medium price range from analysis of regional data.

Medium price	Gold Tip		Platinum-Iridium Tip	
	2015	2016	2015	2016
Min (€)	488,00	488,00	366,00	472,00
Max (€)	1.525,00	1.525,00	2.440,00	2.440,00

This range of medium prices was confirmed by the manufacturer who declared that "*the price of gold tip catheters is at the same level of competitor platinum-iridium tip catheters"*. The manufacturer indicated in the questionnaire a list price, for gold tip catheter, as following reported:

- Gold tip 4mm: € 1,500
- Gold tip 8mm: € 1,700
- Gold tip irrigated: € 2,295
- Gold tip contact force *(CE mark expired on 26/06/2018)*: € 4,000

The cost of the procedure is not listed in Italy as a specific reimbursement for ablation performed with the technology object of this assessment.

☐ Increased costs compared to alternative treatments	☐ Increased costs due to increased demand	☐ Increased costs due to the required investments
☐ New costs	☐ Other: Reduction of costs linked to the reduction of re-intervention rate	☑ Not identified

Potential structural and organisational impact

Structural impact

There are no differences between the gold tip and platinum-iridium tip catheters on structural impact.

☐ Increase in requirement of instruments	☐ Always be used	☐ Can be used only under specific circumstances
☐ Decrease in requirement of instruments	☐ Other:	☑ Not identified

Organisational impact

There are no differences between the gold tip and platinum iridium tip catheters on organisational impact.

☐ Increase in the number of procedures	☐ Re-organisation required	☐ Training required for users
☐ Reduction in the number of procedures	☐ Other:	☑ Not identified

Conclusions

We identified five trials involving 845 subjects that evaluated the effect of gold tip catheter compared to platinum-iridium tip catheter for the treatment of several types of arrhythmias. The overall quality of the

evidence was low. In addition, it must be noted that subjects ventricular tachycardia, for whom the gold tip device should be ideal due to its ability to perform deeper and wider lesions, were not considered in the included studies. The results indicated that the two interventions provide similar effects in terms of ablation success rate; the events related to arrhythmia recurrence, thromboembolic events, AV block were rare in both groups under comparison and were not evaluated by all the included studies. In conclusion, there is no evidence of difference between Gold tip and platinum-iridium tip in terms of efficacy and safety. We performed also subgroup analysis based on the use of irrigation or not and we found that the effect treatment are substantially the same for the primary outcome. In addition, it must be noted that Linhart 2012 used 5-mm irrigated catheters that are no longer used in clinical practice. The exclusion of this study in a sensitivity analysis does not change our conclusion.
No economic evidence was available. From the context cost analysis in the regional survey, albeit in presence of limitations, we found similar costs for both technologies, even though the quantities purchased in the years investigated are different, with a predominance of platinum-iridium tip catheters, that influenced the maximum medium price.
From of the organizational and structural impact points of view no difference has emerged between the technologies.

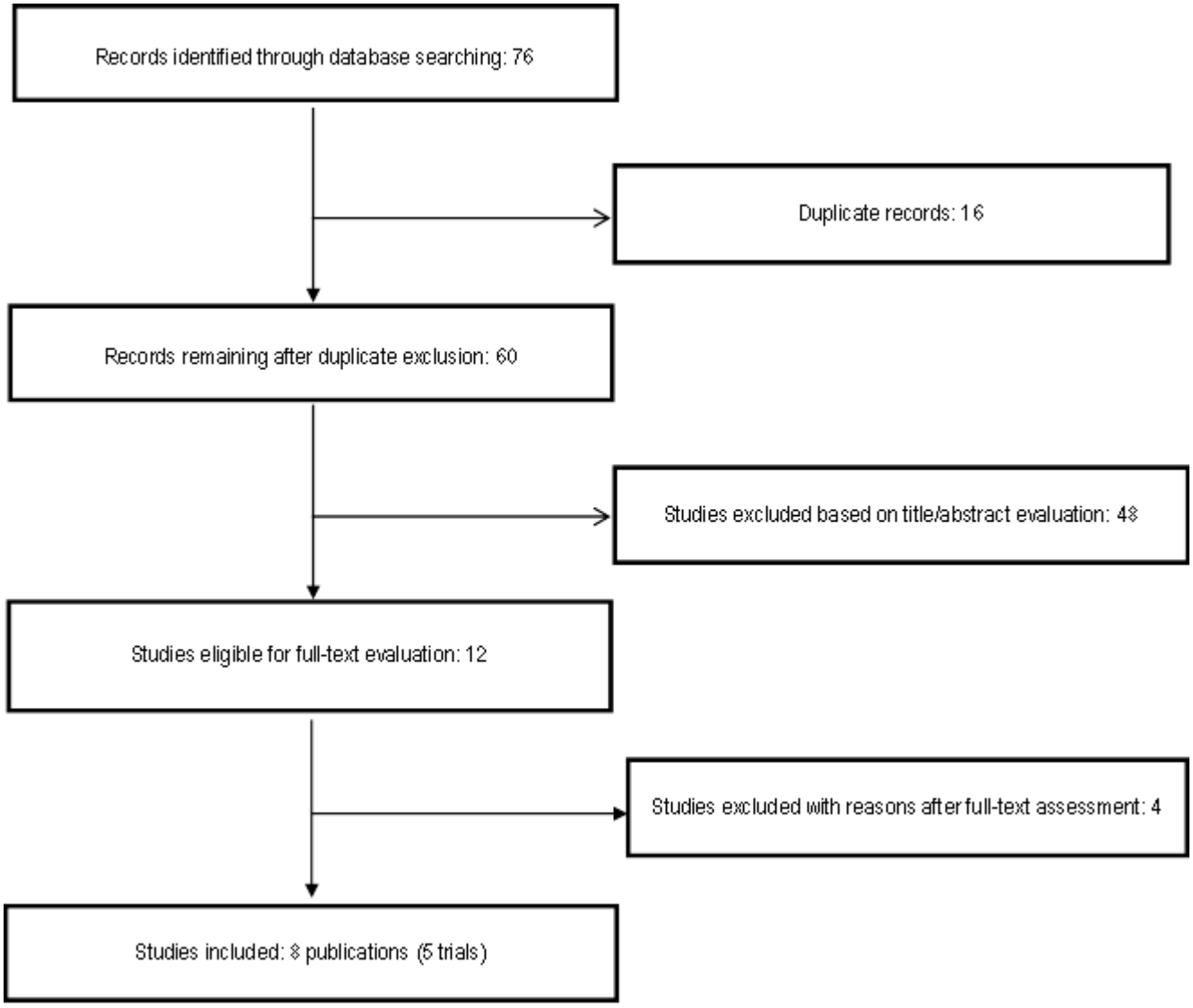
Future prospects

We are not aware of new electrode catheter models for radiofrequency ablation in cardiac arrhythmias.

Appendix 1. List of excluded studies with reasons

Study ID	Reason for exclusion
Lewalter 2005	The comparison between Gold and Platinum tip electrode ablation catheter was in vitro.
Collins 2006	Patients with typical atrial flutter were randomised to radiofrequency ablation or cryoablation.
Muntean 2012	This study evaluated a magnetically guided irrigated gold-tip catheter for ablation of AF. No comparator was used
De Greef 2016	A single arm study (GOLD-Precision) that evaluated the incidence of asymptomatic cerebral embolism after pulmonary vein isolation using a new gold multi-electrode radiofrequency ablation catheter. Controls were used from another study (the ERACE study)

Appendix 2. Study screening process



Appendix 3: Secondary outcomes of the studies included procedural complications and other outcomes

Study ID (country)	Objective	Study design	Participants		Outcomes		Follow up	Funding
			Intervention group/ Gold-Tip	*Control group/ Platinum*	*Primary*	*Secondary*		
Sacher 2007 (France)	To assess the clinical efficacy of irrigated 8-mm gold-tip catheter with "standard" 8-mm Platinum-Iridium tip (Pt tip) catheters for the ablation of cavotricuspid isthmus-dependent atrial flutter	RCT	Number: 20 Age: 66 (SD 10) Male: 16 (80%) Prior AF 9 (45%)	Number: 20 Age: 64 (SD 11) Male: 16 (80%) Prior AF 9 (50%)	Bidirectional isthmus block within 20 minutes	- Procedural parameters - Procedural complications	9 ± 2 months (median 8: range 5–12)	Gold-tip catheters were provided by Biotronik
Stuhlinger 2008 (Germany)	To analyse differences in the rise of temperature or power as a function of time during RF ablation between gold catheters and standard platinum–iridium tip for patients with atrio-ventricular nodal reciprocating tachycardia (AVNRT)*.	RCT	Number: 128 Age: 57.2 (18.3–85.9) Male: 31% Duration of symptoms (yr): 7.6 (3.2–15.9)	Number: 124 Age: 52.7 (18.5–80.3) Male: 39% Duration of symptoms 8.1 (3.62–20.9)	mean increase of power as a function of time (dP/dt) until reaching 95% of maximum.	-RF ablation time -cumulative duration of ablation -No. of ablations per patient", -temperature (min, max, power, time)	- Unclear	Not reported

Kardos 2009 (The Netherlands)	To test the maximum voltage guided technique of cavotricuspid isthmus (CTI) ablation using two irrigated 8-mm tip catheters containing gold or platinum-iridium for patients with atrial flutter.	RCT	Number: 15 (atrial flutter) Age: 66 ± 11 Men: 80% Recurrence of atrial flutter: 1	Number: 16 (atrial flutter) Age: 69 ± 12 Men: 60% Recurrence of atrial flutter: 1	(a) procedural success (b) duration of fluoroscopic exposure (c) procedural duration.	(a) number of RF lesions, (b) total duration of RF delivery (c) number of AF recurrences up to 6 months of follow-up	6 months	Not funded
Lewalter 2011 (Germany)	To compare the clinical efficacy of standard 8 mm platinum-Iridium tip catheter and 8 mm gold-tip catheters in the ablation of the cavotricuspid isthmus -dependent atrial flutter.	RCT (AURUM 8) NCT00326001	Number: 236 Age: 66+10 Male: 81%	Number: 227 Age: 66+11 Male: 85%	Reduce the cumulative RF application duration time to bidirectional CTI block	(a) increase ablation success rate; (b) deliver more power; (c) decrease the number of RF applications; and reduce (d) the incidence of charring/ coagulum/thrombus formation (e) fluoroscopy time (f) procedure duration (g) procedure-related complications, and (h) arrhythmia recurrence	6 months	Some of the authors reported sponsorship from Biotronik. The study was sponsored by Deutsche Stiftung fur Herzforschung (not for profit institution)

Linhart 2012 (Germany)	To investigate the procedural parameters tip temperature, delivered power and cooling flow requirements of the irrigated Gold vs platinum iridium tip catheter in pulmonary vein isolation and cavotricuspid isthmus ablation for patients with atrial fibrillation.	RCT	irrigated gold tip Participants: 30 Age: 61.8±9.2 Male: 67%	irrigated Pt tip Participants: 30 Age: 61.8±10.3 Male: 63%	The temperature generated at the catheter tip.	Periprocedural complications defined as (one or more of the following): (i) aneurysm (ii) major hematoma (iii) pericardial effusion (iv) phrenic nerve palsy (v) atrioesophageal fistula (vi) symptomatic pulmonary vein stenosis (vii) stroke.	- Unclear	Some author received honoraria from Biotronik. Sponsorship for the study: unclear

Evidence searches

Searches of the databases were carried out from January 2007 to August 2017 using the following keywords to indicate:

- ***the technology:*** *Electrode Catheters with Gold tip*
- ***the pathology:*** *Cardiac arrhythmias*

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Glossary

AT: Atrial tachycardia

AVRT: Atrioventricular re-entrant tachycardia

BD/RDM: Medical device Repertory

ECG: Electrocardiogram

EU: European Union

FDA: Food and Drug Administration

IDE: Investigational device exemption

SD: Standard deviation

WPW: Wolff-Parkinson-White