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Subcutaneouscardiac Rhythm Monitors: A Comprehensive Review

Gaurav Aggarwal[1], Saurabh Aggarwal[2], Venkata Alla[3], Bharat Narasimhan[4], Kyungmoo Ryu[5], Courtney Jeffery[6], Dhanunjaya Lakkireddy[6]

[1]Department of Medicine, Jersey City Medical Center, Jersey City, NJ
[2]Department of Cardiology, Unitypoint Clinic, Des Moines, IA
[3]Division of Cardiology, Department of Medicine, Creighton University School of Medicine, Omaha, NE
[4]Department of Medicine, St Luke's Roosevelt Hospital at Icahn School of Medicine, New York, NY
[5]Abbott, Sylmar, CA
[6]The Kansas City Heart Rhythm Institution and Research Foundation, Overland Park, KS

Abstract

Subcutaneous loop recorders (SCRMs) are subcutaneous electronic devices which have revolutionized the field of arrhythmia detection. They have become increasingly appealing due to advances such as miniaturization of device, longer battery life, bluetooth capabilities and relatively simple implantation technique without the need for complex surgical suites. They can be implanted in the office, patient bedside without the need to go to the operating room. One of the most common indications for their implantation is detection of atrial fibrillation (AF) after a cryptogenic stroke. They have also been utilized for assessing the success of rhythm control strategies such post pulmonary venous isolation. More recently studies have assessed the utility of SCRMs for detecting silent AF in at risk populations such as patients with sleep apnea or those on hemodialys is. In this paper, we review the evolution of SCRMs, the clinical studies assessing their value for different indications, their role incurrent clinical practice and future avenues in the era of smart wearable devices like apple watch etc.

Introduction

Healthcare providers frequently use electrocardiography (ECG) and 24-48-hour external Holter monitorsto detectcardiac arrhythmias. Devices like event monitors, mobile telemetry monitors or external loop recorders increase the odds of detecting arrhythmias by further prolonging the duration of monitoring[1].Subcutaneouscardiac rhythm monitors (SCRMs) or subcutaneous loop recorders (ILRs) are small electronic devices that have been increasingly used to monitor cardiac rhythm for prolonged durations. Common indications for SCRM sinclude detection of occult atrial fibrillation (AF) in patients with a stroke of uncertain etiology, otherwise called cryptogenic stroke, monitoring success of rhythm control strategy in the management of AF,[2] arrhythmia detection in patients with unexplained syncope and in patients with infrequent but disabling palpitations. In this article, we review the current literature on SCRMs and future avenues for research.

Evolution of SCRMs:

Subcutaneous cardiac monitoring devices with a continuous cardiac rhythm monitoring capability for an extended time period were initially developed in the 1990s. The development of the cardiac monitoring devices started with the original cardiac monitor that was a pacemaker-size device (53 x 60 x 8 mm or 26 cubic centimeters) with two electrodes on the device can (Figure 1a, Cardiac Monitor, Model 1033[9], Medtronic, Minneapolis, MN). In late 1990s and early 2000s, a set of downsized subcutaneous cardiac monitors with additional capabilities, such as increased battery longevity, larger memory capacity for stored electrograms and events, MR-conditional and remote monitoring emerged. Medtronic Reveal, Medtronic Reveal Plus, Medtronic Reveal DX, Medtronic Reveal XT, St. Jude Medical Confirm, Biotronik Biomonitor, Biotronik Biomonitor 2, Boston Scientific LUX-Dx and Transoma Sleuthare some such examples that revolutionized the long-term clinical management of the patients receiving cardiac monitors with a streamlined outpatient implant procedure and accurate and reliable detection of arrhythmic events during the monitoring duration (Figure 1B).

The currently used cardiac monitors are further miniaturized (1.2 – 1.9cc) with an "insertable" mechanism for implantation by uniquely designed insertions tools. The insertion takes only a few minutes, and patients can be continuously monitored, with device data uploading to the remote care network for remote review by clinicians. The insertable cardiac devices are MR-conditional and last more than 2 years once inserted. Figure 2 illustrates the currently available "insertable" cardiac monitors with respective insertion tools and transmitters. The basic

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Corresponding Author
Dhanunjaya Lakkireddy MD
The Kansas City Heart Rhythm Institution and Research Foundation
HCA Midwest Health Second Floor, 5100 W 110th St Overland Park, KS 66211, USA.

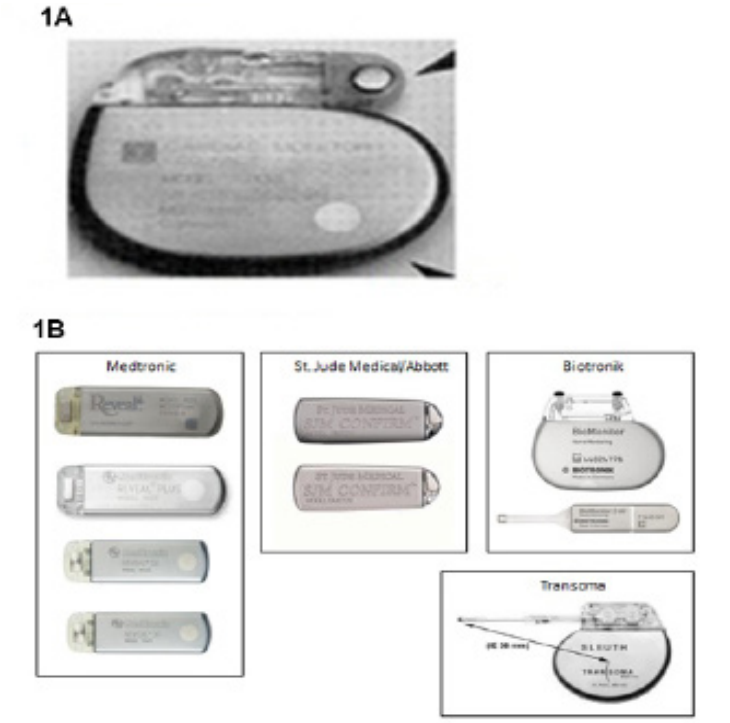

Figure 1A & 1B: **Evolution of SCRMs., 1A : Evolution of SCRMs., 1B : Various implantable cardiac monitors.**

operation of the typical cardiac monitor is illustrated in Figure 3. Similar to other cardiac subcutaneous devices, cardiac electrograms recorded from bipolarly configured electrodes located at each end of the device (typically >35mm) are amplified and filtered through analog circuitry. Based on electrogram analysis, rhythm adjudication will log and store the events of interest (e.g., pause, bradycardia, tachycardia, AF) in the device's memory. Stored episodes and electrograms will be transmitted to the device manufactures' remote care network at a scheduled time interval or instantaneously via either radiofrequency based bedside monitor (Medtronic and Biotronik) or low energy Bluetooth based wireless communication using patient's smartphone (Abbott/St. Jude Medical Confirm Rx/Boston Scientific Lux-Dx/ Medtronic Linq II).

Available SCRMs:

SCRMs, also called insertable cardiac monitors (ICMs),[3] appeal to healthcare providers and patients alike due to the recent advances in miniaturization and remote monitoring4. Latest SCRMs are "injectable" devices implanted with the help of 'kits' supplied by the manufacturer with battery liferanging from 2-4 years. The devices are small, inconspicuous and do not interfere with daily activities. As opposed to those with external monitors, patients with SCRMs don't have to take any precautions while swimming or bathing. SCRMs are more patient friendly and suitable for patients with allergy to electrode material used in external monitors. All devices are MRI compatible. The currently approved indications for ILR implantation are listed in Table 1.

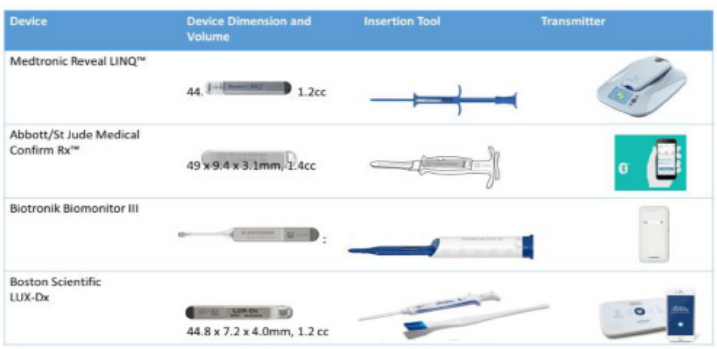

Figure 2: **Currently available SCRMs in the United States.**

Reveal-XT (Medtronic, Minneapolis, USA) was one of the earliest commercially launched SCRMs that had a separate memory for automatic recordings and patient activated recordings. It has now been replaced in clinical practice with the Reveal-LINQ SCRM, which is currently the smallest SCRM available on the market. The device and recordings are monitored using "CARELINK" remote monitoring. The battery life is about 3 years and the patients are given hotspots like pacemaker remote monitoring boxes which can be plugged next to their bed-stand for wireless monitoring and transmission.

Confirm RX (Abbott St Jude Medical, Minneapolis, USA) is another device currently on the market5. The battery life for this device is estimated at 2 years. It is monitored remotely by the "MERLIN" system. Patients can send symptom recordings through an app on the smartphone. Patients who do not have a smartphone are provided a dummy smartphone with the app by the manufacturer. Biomonitor 3 (Biotronic SE & Co, Berlin, Germany) is a recently launched SCRMdevice6. It is the company's third generation device. It is the biggest in size compared to all SCRMs and has the longest battery life of about 4 years. The "SMART" algorithm allows to save the first, longest and the last episode of every arrhythmia and is monitored by "HOME MONITORING" system provided for remote monitoring. These patients get a hotspot which can be kept next to the patient's bed-stand for wireless transmissions. Patients can also record symptoms and check device status with a smartphone app.

Although there are numerous SCRMs available, there are no published studies that compare them. However, performing such studies is challenging given the need for a large sample size and associated costs.

Linq II (Medtronic, Minneapolis, USA) is one of the latest devices available claiming 4.5 years of longevity. It also has the lowest published rate of false positive AF (4.7%)[7]. It can also detect PVCs which could

Table 1: **Current indications for subcutaneous loop recorders**

Recommended indications: **1. Patients with cryptogenic stroke in whom reasonable workup including electrocardiogram, Holter and mobile telemetry monitors, routine transthoracic and/or transesophageal echocardiograms, carotid duplex and hypercoagulable workup has not revealed a diagnosis** **2. Patients with unexplained syncope which is too infrequent to be caught on a Holter or event monitor**
Reasonable indications: **1. Patients with palpitations that are too infrequent to be caught on a Holter or event monitor and cardiac arrhythmia is strongly suspected based on clinical presentation** **2. Patients with atrial fibrillation who undergo ablation to monitor for recurrence**
Other indications where more data are needed: **1. Patients at high risk for arrhythmias like those with sleep apnea, hemodialysis or history of cardiac especially mitral valve surgeries** **2. Patients with stroke where a cause has been identified already for example those with patent foramen ovale**

Table 2: Studies evaluating role of subcutaneous loop recorders in patients with cryptogenic stroke

Study name	Year	Number of patients (n)	Arrhythmia characteristics	Median follow up	Outcome
Glotzer et al (MOST trial)	2003	312	Patients with PPM detected AR≥220 bpm for at least 5 min	27 months	HR for death or non-fatal stroke 2.79 (95% CI 1.51-5.15, p=0.001)
Dion et al	2010	24	Patients with CS with AF ≥30 sec	14.5 months	No patient had significant AF during fu
Healey et al (ASSERT trial)	2012	2580	PPM or ICD detected AR ≥190 bpm for at least 6 min	2.5 years	HR for ischemic stroke or systemic embolism 2.49 (95% CI 1.28-4.85, p=0.007)
Etgen et al	2013	22	Patients with CS and AF duration≥6 minutes	1 year	27.3% patients had AF during fu
Cotter et al	2013	51	Patients with CS and AF≥ 2 min	229± 116 days	25.5% patients had AF during fu
Ritter et al	2013	60	Patients with CS and AF≥ 2 min	1 year	17% patients had AF during fu
Rojo-Martinez et al	2013	101	Patients with CS and AF≥ 2 min	281±212 days	33.7% patients had AF during fu
Christensen et al (SURPRISE study)	2014	85	Patients with CS and AF≥ 2 min	569±310 days	16.1% patients had AF during fu
Sanna et al (CRYSTAL-AF trial)	2014	221	Patients with CS and AF≥ 30 sec	1 year	12.4% patients had AF during fu
Brachman et al (CRYSTAL-AF trial)	2016	221	Patients with CS and AF≥ 30 sec	3 years	30.0% patients had AF during fu
Toni et al (SAFFO study)	2016	424	Patients with athero-embolic or lacunar stroke	1 year	Ongoing with results expected in 2021

HR – hazard ratio, CI – confidence interval, AF – atrial fibrillation, CS – cryptogenic stroke
Bpm – beats per minute, Min – minutes, Fu – follow up

be helpful in detecting high-risk patients. Patients can utilize their smartphones for the mobile application to transfer data, log their symptoms and to monitor device status[8]. Patients who do not want to or cannot use mobile phones, there is a Bluetooth home communicator as an alternative for transferring data. It is also the first device with an option for remote programming which might help reducing patient office visits.

Lux-Dx (Boston Scientific, Marlborough, Massachusetts)is also one of the latest entries into the SCRM market[9]. It features a dual-stage algorithm to automatically detect and verify data before sending it. It also features remote programming like Linq II so that cardiologists can make adjustments to the device without calling the patients into the office. Bench testing for the device showed 53% reduction in false posiitves. It claims around 3 years of battery life.

Implant considerations:

Manufacturers supply an insertion kit which contains the device, a blade and an insertion tool. The device is usually inserted in the third to fifth intercostal space, just to the left of sternal border. The device can be either implanted vertically and parallel to the sternum, or at a 45° angle to the sternum10. The diagonal approach can maximize the output signal as this would be parallel to both atrial and ventricular depolarization vectors[2]. Other implantation sites reported include left axillary location or a horizontal implant in the sixth or seventh intercostal space.

The supplies are arranged on a Mayo stand prior to implantation (Figure 4). Pre-procedure antibiotics can be given, especially in higher risk patients like those with immunosuppression. The parasternal region between 3rd and 5th intercostal space is identified and shaved. Full aseptic precautions are employed to minimize pocket infections. After washing hands thoroughly as in the caseof any device implant, the implanting provider wears a sterile gown and gloves. The previously identified area is cleaned with betadine or chlorhexidine and patient is covered with a sterile drape. Only a small area of chest should remain exposed where SCRM is to be inserted. Usually 5-10 ml of 2% lidocaine is given subcutaneously for local anesthesia. Lidocaine with epinephrine is also useful reduce risk of skin bleeding as many of these patients could be on anti-coagulation. Using less amount oflocal anesthetic will cause patient discomfort but a large amount candampen the initial output signals. A pocket is made with the blade and SCRM is inserted with the help of insertion tool. The technique for insertion differs slightly between different SCRM brands. The pocket should be of accurate size to avoid device movement which causes artifactif pocket is bigger, and risk for erosion is higher when pocket is smaller. Once the SCRMhas been inserted, it should be checked for good signal strength by connecting it wirelessly to the remote monitor. This is an important step to reduce false detections. If signal is unsatisfactory, then the device can be adjusted or re-implanted for better signal strength. Once adequacy of signal is verified (usually R waves more than 0.3 mV), the incision can be closed with absorbable suture. Though skin staple is used in some institutes, this appears to be less preferred. Skin glue or dermabond is also being used in some centers which avoids suture removal or staple removal later. Finally, a medium sized band-aid or transparent bandage is applied. The procedure takes about 20-30 minutes. A trained technician explains the monitoring techniqueand safety precautions to the patient and the family. Pain control strategy is individualized but most patients do well with 3-5 days of acetaminophen or non-steroidal medications. It is recommended to keep the insertion site dry for a week, until patients come back to the clinic for a site check. The site should be checked visually for any signs of infection like erythema or drainage. If the insertion site is healed, then the staples or non-absorbable sutures are removed.

SCRMs wereinitially implanted predominantly by electrophysiologists, though non-invasive and invasive cardiologists, and general practitioners have been implanting them increasingly. In some organizations, nurses, and advanced practice practitionersimplant SCRM with significant cost reductions[11,12]. SCRMs were initially implanted in the hospital setting only, mostly in the electrophysiology lab. Current data suggests that SCRMs can be safely implanted even in the office setting. In a non-randomized study (Reveal LINQ In-Office) performed by Rogers et al, SCRM implantation in a non-hospital setting was performed in 65 patients with low complication rate and only 3% of patients requiring device explant[13]. The same authors then conducted a randomized study of 521 patients RIO-2 (Reveal LINQ In-Office-2) and showed that the overall complication rates were similar in patients who underwent SCRM implant in hospital versus office environment[14]. In this study, the implanting providers described

Table 3: Guidelines for current indications for SCRM implantation

Condition / Guideline	Class	Level of Evidence	Recommendations
Atrial Fibrillation			
2019 AHA/ACC/ HRS Atrial fibrillation guidelines	I	B-NR	In patients with cardiac subcutaneous electronic devices (pacemakers or implanted cardioverter-defibrillators), the presence of recorded atrial high-rate episodes (AHREs) should prompt further evaluation to document clinically relevant to AF to guide treatment decisions (S7.12-1-S7.12-5).
	IIa*	B-R	In patients with cryptogenic stroke (i.e., stroke of unknown cause) in whom external ambulatory monitoring is inconclusive, implantation of SCRM (loop recorder) is reasonable to optimize detection of silent AF (S7.12-6).
2020 ESC Atrial Fibrillation guidelines	IIa	B	In selected stroke patients (elderly, CV risk factors, indices of LA remodelling etc), additional ECG monitoring by long-term non-invasive ECG monitor insertable cardiac monitors should be considered, to document AF.
Syncope			
2009 ESC syncope Guidelines	I	B	SCRM is indicated in an early phase evaluation in patients with recurrent syncope of uncertain origin, absence of high risk criteria and a high likelihood of recurrence within the battery longevity of the device
	I	B	SCRM is indicated in High risk patients in whom a comprehensive evaluation did not demonstrate a cause of syncope or lead to a specific treatment.
	IIa	B	SCRM should be considered to assess the contribution of bradycardia before embarking on cardiac pacing in patients with suspected or certain reflex syncope presenting with frequent or traumatic syncopal episodes.
Cryptogenic Stroke			
Canadian Stroke Best Practice Recommendations: Acute Inpatient Stroke Care Guidelines, Update 2015		C S B P R Evidence Level B	Prolonged cardiac monitoring (up to 30 days) is recommended to assess for paroxysmal atrial fibrillation if cardioembolic mechanism suspected and no evidence of atrial fibrillation on 24-48 hour ECG monitoring
Ventricular arrhythmia / Sudden Cardiac death			
ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death	I	B	SCRMs are useful in patients with sporadic symptoms suspected to be related to arrhythmias such as syncope when a symptom-rhythm correlation cannot be established by conventional diagnostic techniques
	I	C-EO	The choice of a specific cardiac monitor should be determined on the basis of the frequency and nature of syncope events
	IIa	B-R	To evaluate selected ambulatory patients with syncope of suspected arrhythmic etiology, an subcutaneous cardiac monitor can be useful.

the office location to be 'very convenient' and associated with less delays. The patients also had a 'positive experience' more often in the office setting.

SCRMs for cryptogenic stroke:

Stroke is one of the leading causes of morbidity and mortality in the United States[15]. Patients are deemed to have acryptogenic stroke if a cause is not readily identified after routine initial workup.[16] Almost a third of all ischemic strokes are ultimately labelled as cryptogenic and almost a quarter are associated with occult AF[17]. AF remains subclinical in majority of patients and can be missed by rhythm monitoring for short duration. Detection of occult AF and subsequent initiation of anticoagulation can significantly reduce the risk of a recurrent stroke[18,19].

One of the first observational study to evaluate the role of SCRMs in patients with cryptogenic stroke was performed by Dion et al. who prospectively enrolled 24 patients aged≤75 years who had a cryptogenic stroke within the previous 4 months[20]. No sustained arrhythmias were detected after a follow up of 14 months. The major limitation of the study was its small sample size. In contrast,Etgen et al. found subclinical AF of ≥ 6 minutes duration in 17 (27%) of the 65 patients with cryptogenic stroke after one year of monitoring[21]. Cotter et al studied 51 patients with cryptogenic strokeand found subclinical AF in a quarter (25.5%) of patients after a mean follow up of 8 months with median time to detection 48 days[22]. Several other investigators found that SCRMs detected AF of ≥2 minutes duration in 17%-33% of patients with cryptogenic stroke[23–25] with detection times ranging from 60-109 days.

The first randomized study to assess the utility of SCRMs in patients with cryptogenic stroke was the CRYSTAL-AF (Cryptogenic Stroke and Underlying AF) study[23]. This study randomized 441 patients aged ≥40 years to either SCRM implantation or conventional monitoring strategy. After a mean follow up of 6 months, AF was detected in 8.9% in patients with SCRM compared to 1.4% of patients with conventional strategy (hazard ratio (HR) 6.4, 95% confidence interval (CI) 1.9 to 21.7, p<0.001). After 12 months, AF was detected in 12.4% of patients with SCRM versus 2% of the patients with control group (HR 7.3, 95% CI 2.6 to 20.8, p<0.001). The median time for detection was 84 days in the SCRM group. About 79% of these patients had asymptomatic AF which is higher than 60-70% reported prevalence of asymptomatic AF[24,25].The device was found to be safe with only 5 (2.4%) device infections needing explant and 96.6% of patients still had the SCRM inserted after 12 months. Potential reasons for the lower 1-year detection rate in this study compared to the prior observational studies could be the younger age of the study population and lower prevalence of hypertension. Significant differences in detection of subclinical AFpersisted at 3 years (30.0% with SCRM vs 3.0% in control arm, HR 8.8, 95% CI 3.5 to 22.2, p<0.001)[26]. In a recent study, Milstein et al analyzed data from 343 consecutive patients who underwent SCRM implantation for cryptogenic stroke[27]. During first 30 days, only 5% of the patients had AF compared to 21% patients at 1 year. Hence, the authors proposed directly proceeding with SCRM implant prior to hospital discharge in patients with cryptogenic stroke.

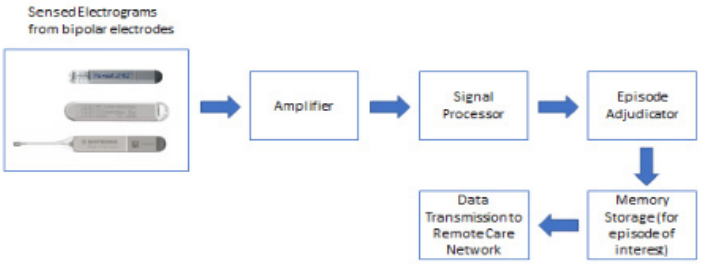

Figure 3: Basic operation of SCRMs

Table 4: Advantages and Disadvantages of different modes on cardiac rhythm monitoring

	Advantages	Disadvantages	Indications
Holter Monitoring	*Low Cost *Continuous monitoring	Limited to 24-48h (<2 weeks) Intrusive *No remote monitoring capability	*Daily/near daily symptoms *Analysis of AHRE burden *Assessment of PVC burden * Diagnosis of inappropriate sinus tachycardia
Event Recorders	*Relatively longer duration – upto 1 month. *Comfortable – intermittent use	*Intermittent monitoring limited to events. *No record of asymptomatic events or arrhythmia *Disabling symptoms or loss of consciousness precludes device activation by the patient. *Selective sequence recording	*3-4episodes/month *Assessment of cardiac etiology of syncope or palpitations.
External loop recorder	*Relatively longer duration – upto 1 month. *Automatic event detection. No patient activation required.	*Device storage is limiting *Selective sequence recording	*3-4episodes/month *Assessment of cardiac etiology of syncope or palpitations.
Subcutaneous cardiac rhythm monitor	*Duration upto 4.5 years *Automatic event detection. No patient activation required.	*Relatively more expensive *Minimally invasive surgery involved. *Selective sequence recording	*Monthly symptoms (Infrequent) * Cryptogenic stroke – assessment for AF. * AHRE burden analysis
Commercially available devices (Smartwatches/ Fitness bands)	*Widely available and non-intrusive *Real time user alerts	*Lack of sufficient validation data on performance. *False positive / clinically insignificant alerts to user contributes to undue anxiety.	*Assessment of cardiac etiology of syncope or palpitations. * AHRE burden analysis * Diagnosis of inappropriate sinus tachycardia

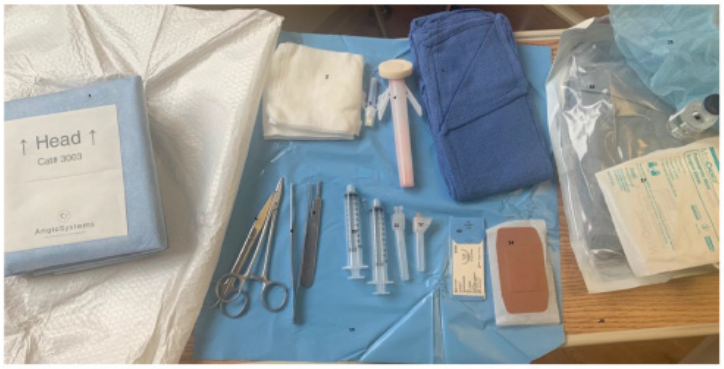

Figure 4: Equipment needed for implantation

Legend:
1 Sterile patient drape
2 4x4 gauze pieces
3 Skin glue
4 Chlorhexidine prep
5 Sterile towels
6 Medium scissors
7 Needle holder
8 Forceps
9 Blade holder
10 10 ml syringes x2
11 22 gauge needle to draw anesthetic
12 26 gauge needle to inject anesthetic
13 Silk suture
14 Skin bandage
15 surgeon hat
16 Surgeon sterile gown
17 Sterile gloves
18 2% Lidocaine with/out epinephrine
19 Sterile drape for tabletop
20 Mayo stand

A meta-analysis of 16 studies, 3 randomized and 13 observational, found significantly higher odds of AF detection with SCRM compared to conventional strategy (OR 4.54, 95% CI 2.92 to 7.06, p <0.00001). Another meta-analysis of 11 studies (a mix of randomized, observational and registry data) also found a 5.7-fold increased detection of AF in patients with SCRM compared to conventional monitoring in patients with cryptogenic stroke[28]. A large multicenter, randomized, controlled, open label trial, Detection of Silent AF after Ischemic Stroke (SAFFO) is currently enrolling patients ≥65 years of age with ischemic or lacunar stroke and randomizing to SCRM versus standard monitoring[29].

Furthermore, available data suggests that device detected atrial high rate events (AHREs) are associated with excess risk of thromboembolism and stroke. One of the first studies to suggest this was a subgroup analysis of MOST (Atrial Diagnostics Ancillary Study of the Mode Selection) study which randomized patients with sinus node dysfunction to either DDDR versus VVIR pacing modes[30]. In the study, AHREs defined as atrial rate >220 beats per minute (bpm) lasting ≥5 minutes wereassociated with a 6-fold increased risk of AF and a more than 2-fold increase in both total mortality and stroke[31]. Similarly, in the ASSERT study (Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial),atrial tachyarrhythmias defined as atrial rates (AR)>190 bpm for ≥6 minutes were associated with a 5.5-fold increased risk of AF and more than 2-fold risk of ischemic stroke or systemic embolism[32].

While a number of consensus groups and professional societies recommend prolonged cardiac rhythm monitoring of patients with cryptogenic stroke, they do not recommend a duration. SCRMs have not yet been included as a standard recommended procedure in any of these guidelines. The most recent 2017 ISHNE/HRS guideline on ambulatory ECG monitoring and the 2020 ESC/EHRA/ESO guidelines for management of AF favor extended cardiac rhythm monitoring though they do not specify the duration for monitoring[33,34]. The only guideline that suggests a duration of monitoring is the 2014 AHA/ASA guideline on prevention of stroke in patients with prior stroke or TIA which recommends 30-day cardiac rhythm monitoring within first 6 months of index event[35]. However, large outcome studies are needed to confirm or refute the benefit of SCRMs in patients with cryptogenic stroke. Whether detection of AF in patients with cryptogenic stroke leads to reduction in incidence of future strokes remains to be seen. Additionally, more studies are needed to address the potential concern for increased bleeding as more patients are started on anticoagulation after detection of a brief subclinical AF episode.

SCRMs for AF detection in patients at risk of AF other than those with cryptogenic stroke:

AF, is the most common cardiac arrhythmiaand35SCRMs have been increasingly used in patients at high risk for AF, other than patients with cryptogenic stroke. Multiple studies have found AF even in patients with TIA or stroke from a known cause. Among patients with any stroke, Rabinstein et al. found AF in 14% patients with 3-week ambulatory ECG monitoring while Grond et al in a larger study of 1135 patients with any stroke or a TIA reported silent AF in 4.3% after 72-hour Holter monitoring[36,37]. The ongoing STROKE-AF (Stroke of Known Cause and Underlying AF) is a multicenter, randomized

Table 5: Future areas of research in the field of subcutaneouscardiac rhythm monitors

1. Threshold duration for SCRM- detected atrial fibrillation to initiate anticoagulation which will maximize the benefit to risk ratio
2. Determining whether patients who have other identified risk factors for stroke on initial workup will benefit from SCRM implant to look for occult atrial fibrillation
3. Improving the SCRM algorithms to reduce the burden of false readings
4. Determining whether administration of antibiotics pre-implant is cost effective in reducing device infections
5. Determining the optimal site of implant for best possible signal and concomitantly reducing false readings
6. Determining the optimal amount of local anesthetic and post implant pain control strategies
7. Cost-effectiveness of SCRMs in patients with different indications for best selection of patients
8. Implantation of SCRM for detection of arrhythmias in high-risk populations

controlled trial that aims to compare detection of AF using an SCRM versus standard therapy in patients with a recent stroke presumed to be due to large vessel cervical or intracranial atherosclerosis, or small vessel disease[38].

The ongoing LOOP study will shed light on the clinical impact of SCRM on stroke reduction by screening patients for occult AF and initiating anticoagulation[39]. In the recently published sub-study analysis of 597 patients enrolled in the LOOP study,[40] AF was found in 35% of patients after 40 months with cumulative incidence for episodes lasting ≥6 minutes, ≥5.5 hours and ≥24 hours being 33.8%, 16.1% and 5.7% respectively. Notably, despite the high prevalence of AF, overall burden was low at 0.13% , only 16% of patients progressedto having 24 hour episodes and the vast majority (90%) remained asymptomatic[41]. SCRMs have also been used to monitor the success of rhythm control strategy in patients undergoing percutaneous or surgical ablation and can be particularly important when making decisions regarding cessation of anticoagulation[42–44].

SCRMs for unexplained syncope:

Syncope accounts for about 1-2% of emergency department visits and 6% of hospital admissions with an annual cost of $1.7 billion in the United States alone[45]. Various guidelines have been published for evaluation and management of patients presenting with syncope[46]. An unexplained syncope is defined as syncope for which the cause is undetermined after a thorough history, physical examination including orthostatic vital signs and ECG[47]. SCRMs have been shown to be important diagnostic tools for evaluation of unexplained syncope particularly when a dysrhythmia is suspected. One of the first randomized studies to evaluate the role of SCRMs in patients with syncope was the RAST (Randomized Assessment of Syncope Trial) study which randomized 60 patients to SCRM versus conventional monitoring[48]. After a mean follow up of 10.5 months, SCRMgroupwas significantly more likely to have a diagnosis (55% in SCRM vs 19% in conventional group). Theinvestigators alsodemonstrated that prolonged monitoring with SCRM was more cost effective than conventional monitoring[49]. Similarly, Edvardsson et al.in a study of 650 patients with unexplained syncopereported that 78% of patients (n=170) who had recurrent episode (only 218 of 650 pts) had received a diagnosis from ICRM and 51% of those patients received pacemaker[50]. In another study, patients in the SCRM-guided strategy who underwent permanent pacemaker implantation were 57% less likely to have a syncopal spell during follow up[51]. A number of other investigators have demonstrated similar success of SCRM guided strategy in identifying prolonged pauses or asystole needing pacemaker even in those with alternative diagnosis such as postural orthostatic tachycardia syndrome (POTS).[52,53] Current guidelines on the indications for SCRM implantation are listed in Table 3.

SCRMs for infrequent palpitations:

Palpitations are one of the most common reasons for visit to the primary care physician or emergency department[54]. They can be infrequent, sometimes with patients being symptom free for months. Such infrequent episodes may be missed by traditional ambulatory ECG monitors. For a select group of patients with disabling episodes of palpitations that have been missed by Holter and event monitors, SCRM implantation can be considered[55]. However, there are no published studiesregarding use of SCRMs in such patients.

SCRMs for detection of arrhythmias in other high-risk patients:

Dodeja et al retrospectively studied 22 patients with adult congenital heart disease who underwent SCRM implantation[56]. SCRM findings resulted in change in management in 41% of the patients with one-third of events being asymptomatic. In another study evaluating the role of SCRMs inpatients with adult congenital heart disease, SCRMs led to a diagnosis in 59% of the patients with median time to diagnosis being 4.5months[57]. Patients on hemodialysis have also been found to be at high risk of arrhythmias which can be detected with SCRMs[58].In a study of patients on hemodialysis, SCRMs shed light on the causes of sudden death demonstrating the burden of silent arrhythmias in this population[59].A recent study showed the possible benefit of SCRMs in patients with congestive heart failure; 43% of patients hadSCRM guided therapeutic changes[60]. Another group at risk for arrhythmias is patients who have sleep apnea with 20% of patients found to have occult AF[61].

Studies comparingSCRMs and other modes of monitoring:

In the prospective ABACUS (Assessing Arrhythmia Burden After Catheter Ablation for AF Using an Subcutaneous Loop Recorder), Kapa et al demonstrated the superiority of SCRM indetermining the success of AF ablation62. After one year, 60% patients were found to have AF by SCRM compared to 31%with conventional monitoring. In contrast, Podd et al. demonstrated that SCRMis inferior to a permanent pacemaker set at ODO mode(monitoring only) for detecting AG following ablation[63]. Pacemaker group had significantly more AF detection rate (97% vs 55%, p<0.001) and positive predictive value (100% vs 58%, p = 0.03) compared to the SCRM group. In a recently published study, Mamchur et al studied 53 patients with AF were randomized to an SCRM or a noninvasive ambulatory ECG monitoring device[64]. The diagnostic value was comparable between the two groups with no additional diagnostic information after 2 weeks of monitoring. However, the SCRM group was only monitored for 3 months which was a major limitation of this study as detection rates continues to rise with longer monitoring. In a sub-analysis of the LOOP study, various other rhythm monitoring strategies were compared to SCRM and were found to be more sensitive in patients who were older, men and those with higher NT-proBNP values[65]. The diagnostic yield increased with increased number of duration, dispersion and number of screenings. The advantages and disadvantages

of SCRMs compared to other modes of rhythm monitoring are listed in Table 4.

Safety:

SCRMs are associated with low complication rates overall and most complications occur within a few days of implantation. In a study of 540 patients, overall complication rate was 3.3% with majority being implant site infection and implant site pain leading to explant or pocket revision66. In the CRYSTAL-AF study, overall explant rate at 12 months was 3.4% with infection, pain and inflammation at the insertion site being the most common adverse events[23].

Data Management:

While SCRMs provide an invaluable source of diagnostic data, they also can easily overwhelm the staff who have to manage this data. The precise management of SCRM data and alerts is imperative to reduce alarm fatigue and data overload (which can lead to missed abnormal rhythms). There are 2 essential parts to manage SCRM data – the first being how the device is programmed at implant and subsequent visits (based on patient specific needs) and the second is how the alerts are programmed on the websites.

Keeping all alerts and detection criteria for all diagnosis on for all patients can significantly increase the unnecessary data that is received. This can contribute to increased workload burden to the clinic staff and create alarm fatigue. Prior to turning on any alert or detection criteria for a patient, the clinician should always ask the question, "is this going to prompt clinical action for this patient?" If the answer is no, then it is likely that turning that alert on or detection criteria would not provide any contribution to that patient's care and in fact could increase alarm fatigue potentially leading to a true arrhythmia being missed.

The other recommendation to alert management is disabling non-critical alerts. For example, symptomatic episodes that do not coincide with a detected episode and AF in patients with known AF and on anticoagulation. Instead of getting alerted for each episode (which could be hundreds), for these patients it may be better plan to review those episodes and the overall burden every 31 days. If the clinician is constantly reviewing multiple episodes at this time and once again, no clinical action is taken, it is recommended to program the device more aggressively. For example, if the patient has known AF and has had multiple episodes of 6 minutes which have not prompted any change in therapy, consider programming the device to record episodes of AF if they last greater than 6 hours or if the average ventricular rate is 100 bpm or greater.

The most important way to manage data overload is minimizing inappropriate detections. These are most commonly caused by undersensing, oversensing, or when the algorithm misinterprets the rhythm (i.e. calls sinus rhythm with PACs AF).

Frequent undersensing commonly leads to numerous false episodes of pauses and bradycardia. When there are frequent false pause and brady episodes due to undersensing, consider increasing the sensitivity and increasing the detection criteria (i.e. for pause change from 3 sec to 4.5 sec or bradycardia change from 4 beats to 8 beats).

For those practices that have difficulty managing their SCRM data, an option to consider is investment in a software platform or 3rd party vendor to outsource the data management. Some companies provide both the software platform, others provide just the service component, while some provide both as well as allow for a hybrid model to allow the customer to choose how much and which patients they want manged by them. Examples of these vendors include PaceArt Optima (Medtronic), Scottcare, Geneva, Muse, and Pace Mate to name a few. The benefit of using some over the other is that some provide a service component.

Future areas of research:

SCRMs are relatively new in the realm of cardiology compared to other monitoring devices. Table 4 lists the areas for future research with SCRMs. Ischemic strokes can happen even after AF detection and initiation of anticoagulation. In the SURPRISE study, SCRMs detected AFin 18 out of the 85 patients with cryptogenic stroke[67]. However, there were 4 recurrent strokes with 3 of those in patients with diagnosed AF despite being on oral anticoagulation. In the CRYSTAL-AF study after 12 months follow up, even though the rate of use of oral anticoagulants was 14.7% in the ICM group versus 6% in the control group, 7.1% of the patients with SCRMs had a recurrent stroke versus 9.1% patients in the control group[23]. It is therefore obvious that AF is not the sole cause of stroke in a proportion of patients with cryptogenic stroke and SCRM detected AF. Patients who had an ischemic stroke and a positive finding of PFO on echocardiography pose a unique challenge to the clinician to determine whether to close the PFO or evaluate for occultAFor both. A recent study by Scacciatella et al found that SCRMs detectedAF≥5 minutes in a significant number of patients (14.3%) who underwent PFO closure68. There are no published guidelines in this respect.We propose consideration for SCRM implantation and monitoring for at least 6 months before closing the PFO though this approach has not been tested.

False positive readings are an area of huge concern due to the huge burden on device clinics and significant healthcare cost associated with this. In a recent study, the false positive detection rate was found to be 46-86% depending upon indication for implantation, with higher false positive rates for SCRMs implanted for cryptogenic stroke and syncope compared to those implanted for AF surveillance[69]. In the ABACUS study, false positive detection rate for AF with SCRM was 51%[62]. The false positive rate was found to be 31% in the DISCERN study where 50 patients with prior known AF were monitored with SCRM[70]. It is likely that this false positive detection rate is higher in real world practice and can expose patients to excess risk of bleeding from unwarranted anticoagulation. Manufacturers should continue to work on improving algorithms for detection and improving the overall sensitivity and specificity of the devices to address this concern for "data overload"[71]. Triaging the incoming data remains one of the biggest challenges in managing patients with an SCRM. Another related area is reliability of data transmission to a central portal for physician review.

Whether there is a learning curve to implanting an SCRM has also not been studied. The value of peri-implant antibiotics, the optimal amount of anesthetic that should be used during implant and the best regimens for postoperative pain control have not been studied. Another area that needs further study is the optimal site and orientation of implant as different implant sites can have difference in output signals from atrium and ventricle and hence limit sensitivity and/or specificity. The cost effectiveness of SCRMs in various settings also needs to be evaluated so those patients with the most possible benefit

can be selected.

Finally, SCRMs face increasing competition from newer small wearable devices like Apple Watch with Kardiaband (Alivecor Inc) and Fitbit (Fitbit Inc)[72]. Apple watch was found to be better than Fitbit in detecting AF in one study of 40 patients who underwent cardiac surgery[73]. Wasseerlauf et al compared Apple watch with SCRM for detection of AF in 24 patients with prior history of AF[74]. The sensitivity of the watch compared to SCRM was 97.5% with positive predictive value of 40%. However, 3 of the 18 patients with AF>1 hour had AF only when watch was not being worn thus showing the limitation of wearable devices compared to SCRM. In the large Apple Heart Study recruited >400,000 patients, 34% of the patients who returned ECG patches usable for analysis had AF with 84% positive predictive value and no reports of serious app-related adverse events[75]. The future areas of research are listed in Table 5.

Conclusion:

SCRMs facilitate improved arrhythmia detection in patients with unexplained syncope, AF detection in cryptogenic stroke and have become an important part of cardiac diagnostic armamentarium. Technologic advances like device miniaturization and prolonged battery life, decreasing costsand ease of implantation have resulted in increasing use of SCRMs. Future research should focus on improving diagnostic accuracy by minimizingfalse positive detections and defining appropriate patient selection criteria in this era of Apple watch and other smart wearable devices.

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