CARDIAC MONITORS FOR THE DETECTION OF ATRIAL FIBRILLATION AMONG PATIENTS DIAGNOSED WITH A CRYPTOGENIC STROKE

Effectiveness, cost-effectiveness and budget impact of external loop recorders (ELR), and implantable loop recorders (ICMs) for British Columbia.

HEALTH TECHNOLOGY ASSESSMENT REPORT

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List of Abbreviations

BC	British Columbia
BCCSS	BC Clinical and Support Services
BCPSQC	BC Patient Safety & Quality Council
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CUA	Cost Utility Analysis
ELR	External Loop Recorder
FHA	Fraser Health Authority
HCP	Health Care Providers
HTA	Health Technology Assessment
HTAO	Health Technology Assessment Office
ICER	Incremental Cost-Effectiveness Ratio
ICM	Implantable Cardiac Monitor also know as Implantable Loop Recorder
IHA	Interior Health Authority
ILR	Implantable Loop Recorder (aka ICM)
Imp ICM	Implantable loop recorders or cardiac monitors
Ins ICM	Insertable loop recorders or cardiac monitors
MOH	Ministry of Health
NHA	Northern Health Authority
NIHR	National Institute for Health Research (United Kingdom)
OR	Operating Room
PVN	Patient Voices Network
PHAC	Public Health Agency of Canada
PHC	Providence Health Care
PHSA	Provincial Health Service Authority
PPV	Positive Predictive Value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality Adjust Life-Years
RR	Risk Ratio
SAE	Serious Adverse Event
VCH	Vancouver Coastal Health
VCHA	Vancouver Coastal Health Authority
VIHA	Vancouver Island Health Authority

Executive Summary

The purpose of this health technology assessment (HTA) is to summarize the available evidence on cardiac monitors, including external loop recorders (ELR), and implantable loop recorders also known as implantable cardiac monitors (ICMs) for the purpose of diagnosing atrial fibrillation (AF) in patients who have recently experienced a cryptogenic stroke or transient ischemic attack (TIA) experiencing symptomatic or asymptomatic AF. The purpose of detecting AF among patients who have experienced a cryptogenic stroke is to offer effective treatment (e.g., oral anticoagulant therapy) to prevent a recurrent stroke. ICMs are separated into two categories: implantable (Imp ICM) and insertable (Ins ICM), with very different costs and logistics for monitoring. This report includes the results of a jurisdictional scan to determine ICM use across Canadian provinces and territories, a summary of key stakeholder perspectives, a summary of patient experience, evidence on efficacy, safety, and cost-effectiveness of ELR and both types of ICM in comparison to available alternatives and budget impact for British Columbia.

Jurisdictional scan: Among provinces who responded to the HTA request, Saskatchewan, Quebec, Newfoundland and Labrador, and Prince Edward Island provide differing degrees of coverage for the use of ICMs and for different clinical indications. Saskatchewan, Quebec and Prince Edward Island provide coverage for patients who have had a cryptogenic stroke. Newfoundland and Labrador provide coverage for ICMs for additional clinical indications but cryptogenic stroke is not one of them. Ontario and the Northwest territories currently do not publicly fund ICMs.

Key stakeholder: All stakeholders agree unanimously that this technology should be provided as an insured service in BC; however, it was discussed that in order to ensure the success of this technology, proper MSP codes and payment schedules must be created to support the long-term follow-up and remote care required for ICMs. It was agreed upon by all stakeholders that the use of ICM would provide an enormous potential for prevention of recurrent stroke and death in patients who have already experienced an occurrence of cryptogenic stroke.

Patient experience: patients stated that the decision to receive ICM was relatively simple as the possible benefits of the technology were perceived to be significantly greater than possible side-effects or unintended consequences, given the relative simplicity of the ICM procedure and low complication rates.

For individuals who had received an ICM, the procedure was described to be a quick, simple, and painless process. Patients described very little wait time in receiving an ICM, with a range of 1 to 2 weeks of wait-time. Patients generally stated very positive feelings about their experience with an ICM. By receiving an ICM, patients felt a sense of comfort and protection knowing that they were monitored, and described a decreased mental burden in wondering why they had experienced a cryptogenic stroke, and whether they would be likely to experience another episode.

Assessment of evidence: Two RCTs were included in this clinical effectiveness analysis. EMBRACE was an RCT with 572 cryptogenic stroke patients randomized to receive ELR or one additional monitoring period with 24-hour Holter. The primary outcome, detection of AF lasting longer than 30 seconds after a 30-day monitoring period, was observed in 16.1% patients in the

ELR arm compared with 3.2% in the control arm. EMBRACE had high risk of performance bias, detection bias and reporting bias.

CRYSTAL-AF was an RCT with 441 cryptogenic stroke patients comparing an implantable loop recorder (ICM arm) to the standard of care (control arm). In total, 221 patients were randomized to ICM arm and 220 patients were randomized to control arm. For the primary outcome, patients who received ICM had a significantly higher detection rate of AF during the first 6 months of monitoring, the hazard ratio of detection was 6.4 [95% CI, 1.9-21.7, p<0.001]. Patients in the ICM arm had a consistently higher detection rate of AF in the subsequent period beginning at 6 months and up to 36 months when compared with the control arm. At 36 months, 30% of patients in ICM arm were estimated to have AF detection compared with 3% in control arm. However, the attrition rate was high after the first 6 months in the RCT. At 36 months, only 10% of patients remained in the RCT, which created a large difference between the estimated detection rate and the observed rate at 36 months. CRYSTAL-AF was judged as high risk of bias in performance bias, detection bias, and attrition bias. The below-recommended level of monitoring in the control arm could also lead to a greater difference in detection rate between the treatment arms.

The diagnostic yield data from the RCT was heterogeneous in term of method and baseline characteristics therefore could not be combined. The data from CRYSTAL-AF was chosen as input parameter for the economic model because of longer monitoring period and more generalizable to other diagnostic strategies that had no data.

Economic analysis for British Columbia: The purpose of the economic analysis was to evaluate the cost-effectiveness of outpatient cardiac monitoring devices for the detection of atrial fibrillation (AF) in discharged patients with a recent history of cryptogenic stroke for the BC population.

A Markov model was created for outcomes of testing for AF to estimate the costs and health outcomes, including quality-adjusted life years (QALYs) and clinical outcomes, associated with multiple diagnostic strategies compared with a strategy of no testing over a 20-year time horizon in BC, as the average life-expectancy of stroke patients is on average 11.4years. Seven diagnostic strategies were compared with no further testing, as follows:

0. No testing (standard comparator)
1. ELR followed by Imp ICM
2. ELR followed by Ins ICM placed in procedure room in hospital settings
3. ELR followed by Ins ICM placed in procedure room in physicians’ office settings
4. ELR only (i.e., ELR followed by no further testing)
5. Imp ICM only (i.e., Imp ICM followed by no further testing)
6. Ins ICM placed in procedure room in hospital settings only (i.e., Ins ICM followed by no further testing)
7. Ins ICM placed in procedure room in physicians’ office settings only (i.e., Ins ICM followed by no further testing)

Incorporating the best available evidence into the economic model, offering cardiac monitoring to cryptogenic stroke patients in BC (with any of the strategies considered in this report) compared with no further investigation for AF and using conventional thresholds for cost-effectiveness (up to $50,000 per QALY gained), none of the strategies would be deemed cost-effective (focusing on the base-case results and assumptions). The ICERs ranged from $183,312 per QALY (ELR followed by implantable ICM) to $324,282 per QALY (directly using insertable ICMs placed in procedure rooms in hospital facilities). This is a result of fairly important incremental costs ($[redacted] per patient) and modest gains in survival (0.09 to 0.11 per patient) and quality of life (0.07 to 0.08 per patient) over a 20-year time horizon. These results are mainly driven by the assumptions around monitoring frequency and costs post-implant. Strategies which combine ELR with either implantable or insertable ICMs, or using ICMs directly as the first-line device, virtually offer the same benefits in survival and QALY.

Results were most sensitive to AF prevalence among the cryptogenic stroke population, OAC adherence, length of monitoring post implant, and the assumed physician's/technician's fees for follow-up monitoring. There is a moderate degree of uncertainty in the model. The diagnostic yield was obtained from a previous study comparing implantable device with the ELR. Both implantable and insertable devices have more robust evidence on the effect of cardiac monitoring either used as a first-line device or in combination with ELR. There is considerable uncertainty regarding the fees associated with ICM monitoring post-implant and no data on the frequency of data readings for both ICM types. The frequency of readings will directly impact monitoring costs not only because each reading incurs a fee for service under the current funding system, but also because the frequency of reading impacts the number of patients diagnosed with AF. The choice of insertable devices, albeit clinically more feasible, has higher financial implications associated with the incremental cost of implantation, monitoring fees and expenses related to device explantation. Adoption of implantable or insertable devices further requires a policy dialogue and clinical consideration around funding models for post-monitoring of ICMs.

Budget Impact for British Columbia: Chapter 7 demonstrated that monitoring patients discharged with a history of cryptogenic stroke with non-invasive cardiac monitoring first (ELRs), followed by ICMs inserted in a procedure room at the physicians' office, compared to the status quo (no further monitoring), can result in 1,140 undiscounted life-years and 943 undiscounted QALYs gained at the population level for the 10 years following this policy implementation (Strategy 3 in Chapter 6). These benefits are driven by avoiding approximately 282 deaths and 179 moderate to severe recurrent strokes among the cryptogenic stroke population diagnosed with AF.

Under this policy, the BC health care system will need to accommodate 17,294 4-week ELR tests and 16,627 ICM devices. The overall incremental cost is estimated to be approximately $254.4 million over 10 years. This represents an additional 10% over the expected budget to provide healthcare for this patient population without cardiac monitoring. Costs associated with implantation/explantation of the ICMs (5.3%) and their monitoring (2.3%) are the largest contributors to the budget impact, and are expected to increase progressively as more patients are kept alive and undertake cardiac monitoring overtime.

The policy around monitoring post ICM implant monitoring is perhaps the most critical piece to be discussed in a broad context, before incorporating this technology, specifically with regards to clinical data management (transmission, readings, stewardship, etc.), pricing and funding models for post-implantation monitoring, and accountability for the clinical findings. Changes in the assumptions made with respect to these parameters play a significant role in the benefits and budget impact estimates. The current estimates assumed that patients will have, on average, 6 data readings per year, under a fee for service model, with the same monitoring fees as currently charged for pacemaker monitoring.

Chapter 1 Background and Problem

1.1 Purpose of this health technology assessment (HTA)

The purpose of this health technology assessment (HTA) is to summarize the available evidence on cardiac monitors, including external loop recorders (ELR), and implantable loop recorders also known as implantable cardiac monitors (ICMs) for the purpose of diagnosing atrial fibrillation (AF) in patients who have recently experienced a cryptogenic stroke or transient ischemic attack (TIA) experiencing symptomatic or asymptomatic AF. ICMs are separated into two categories: implantable (Imp ICM) and insertable (Ins ICM), with very different costs and logistics for monitoring. This report includes evidence on efficacy, safety, and cost-effectiveness of ELR and both types of ICM in comparison to available. In addition, perspectives from key stakeholders were sought.

1.2 Policy question and research objectives

1.2.1 Primary policy question or decision problem to be answered by this HTA

- Are cardiac monitors an effective tool to help diagnose underlying AF in patients with cryptogenic stroke or TIA when compared with standard care?
- If yes, which diagnostic strategy is the most cost-effective and what will be the budget impact of using cardiac monitors to diagnose AF in patients with cryptogenic stroke or TIA in British Columbia (BC)?

1.2.2 Primary research questions to be answered by this HTA

- What are the underlying causes of cryptogenic stroke and TIA?

- What is the annual incidence of cryptogenic stroke and TIA in BC?
- How are eligible candidates for this technology determined, and what is the size of this population in BC?
- What is the potential complication if AF is left untreated and their burden to the healthcare system?
- What is the current standard of care to diagnose AF in patients with cryptogenic stroke or TIA? And its limitations?
- What are the different kinds of cardiac monitors? And how they are used to diagnose AF in patients with cryptogenic stroke or TIA? What are the various options of diagnostic strategy involving cardiac monitors?
- Once diagnosed, what is the current treatment option for AF in BC?
- What are stakeholder perspectives in the current standard of care to diagnose AF in patients with cryptogenic stroke or TIA in BC? What are the important points of policy change and potential implementation issues in BC?
- What is the patient experience with the standard of care to diagnose AF in patients with cryptogenic stroke or TIA in BC?
- What are the example models of public provision of cardiac monitors in similar publicly funded health systems (e.g. Australia, Ontario, United Kingdom (UK))?
- What is the current evidence on the clinical effectiveness of ELRs, and both types of ICMs (Imp ICM and Ins ICM) used to diagnose AF in patients with cryptogenic stroke or TIA when compared with standard care?

- What are the relative cost-effectiveness and budget impact for the public health care system by using various diagnostic strategies for AF that involve cardiac monitors for patients with cryptogenic stroke or TIA when compared with the status quo? What would be the impact for the different health authorities from a budget impact perspective?

1.3 Background information

1.3.1 Disease burden in BC and potential causes of cryptogenic stroke and TIA

There are two main types of stroke, hemorrhagic and ischemic.[1] An ischemic stroke is caused by hypoperfusion to one or more areas of the brain due to an obstruction in the supplying blood vessel.[1] Similar to an ischemic stroke, a TIA, which is sometime referred to as "mini-stroke", is a blockage of blood flow to the brain.[2] A TIA produces similar symptoms to a stroke however, they typically resolve after a period of time and usually do not result in permanent disability.[2] A hemorrhagic stroke is caused by a rupture of blood vessels in the brain. Intracranial hemorrhage is referring to bleeding in the brain that may or may not involve a rupture of blood vessel. For the purpose of this HTA, the term "stroke" refers to an ischemic stroke and the term "intracranial hemorrhage (ICH)" refers to a hemorrhagic stroke and intracranial hemorrhage.

In Canada, stroke is the leading cause of adult neurological disability and the third leading cause of death. [3] Approximately 60% of stroke survivors in Canada experience some degree of disability after a stroke.[4] However, the Oxford Vascular Study reported that the mean utility of patients who had a cryptogenic stroke was 0.7, which was similar to the mean utility of minor stroke patients. This finding suggested that most cryptogenic stroke patients that would require long term ECG monitoring were likely to have experienced a minor stroke during their index event. [5] The modified Rankin scale (mRS) is commonly used to categorize the level of disability a patient experiences after a stroke [6], which affects both the patient's quality of life and life expectancy (Table 1.1).[5]

Table 1.1 Disability levels after stroke and corresponding quality of life and life expectancy

mRS score	Disability level [6]	EQ-5D utility[5]	Life expectancy at 70 years of age (in years) [4]
No stroke	-	0.85	16.3
0-2	Minor stroke - no disability to minor disability - patients can perform daily tasks without assistance	0.73	11.4
3-4	Moderate stroke - moderate disability - patients require assistance with daily tasks or unable to live independently	0.5	
5	Severe stroke - severe disability - patients are bedridden and incontinent.	0.13	

AF can only cause an ischemic stroke or TIA. Ischemic stroke caused by AF is more likely to be fatal compared with non-AF strokes (25% vs 14%). [7]

The incidence of primary stroke among non-AF individuals is approximately 3.1 per 1,000 person-years. The incidence of primary stroke among individuals with AF but without oral anticoagulant treatment is estimated to be 4- to 5-times higher.[8]

Even in the absence of post-stroke complications, stroke patients, over the long term, may still be at higher risk of recurrent cardiovascular events.[9] The incidence of recurrent stroke among non-AF patients is approximately 71.5 per 1,000 person-years compared with 108 per 1,000 person-years among AF patients.[10, 11] Preventing recurrent stroke is one of the main goals after a primary stroke and lead to further investigation of AF with cardiac monitors. Individuals diagnosed with AF may be prescribed oral anticoagulant treatment to lower their risk of stroke.

In BC, during the fiscal year 2017-2018, [redacted] experienced [redacted] ischemic strokes or TIAs which required hospitalization and resulted [redacted] deaths.[12] Among patients who were hospitalized, the average length of stay (LOS) was 15 days in neurology ward.[13] The total number of strokes and TIAs requiring hospitalization has increased between 2013/2014 and 2017/2018, and less than 1% had access to ELRs within 6 months after the stroke (Table 1.2).[12]

Table 1.2: Number of patients hospitalized due to ischemic stroke and TIA, cases of stroke & TIA, number of death due to stroke or TIA in BC, and number of ELRs performed in those stroke cases [12]

Fiscal Year	Unique Person	Stroke Cases	Deaths	ELR
2013/2014	[redacted]	[redacted]	[redacted]	[redacted]
2014/2015	[redacted]	[redacted]	[redacted]	[redacted]
2015/2016	[redacted]	[redacted]	[redacted]	[redacted]
2016/2017	[redacted]	[redacted]	[redacted]	[redacted]
2017/2018	[redacted]	[redacted]	[redacted]	[redacted]

Source: Incident cases from DAD and Death counts from Vital Stats records. Ischemic & Tia Stroke ICD10=163 & I64 & G45 (Tia). Exclude brain injury/trauma ICD10 (S02, S06) & rehabilitation care Z50. ELR: Stroke patients who billed MSP fee for service (33062, 33069, and 33092) within 6 months after the stroke date. Deaths: Number for deaths from Ischemic and Tia stroke.

In Canada, the acute hospitalization costs (i.e., in the first 30 days after stroke event) were estimated at $16,200 for patients with minor stroke, and $55,000 for a severe stroke. [14-16] Additionally, the annual health care costs for case management after the event were estimated at $18,400 for patients with minor stroke, and $30,900 for severe stroke including hospitalization, physician services, rehabilitation services, diagnostics, and medications. [14, 15]

It is clinically important to determine the cause of the stroke in order to properly treat and lower the risk of subsequent strokes. While the cause of ICH can often be determined in the hospital, the cause of ischemic stroke can be difficult to determine despite advances in diagnostic technologies. Ischemic stroke can be caused by the obstruction of a blood vessel which can develop locally or can be an embolus that travels from another part of the cardiovascular system.[17] Ischemic stroke caused by an embolus with unidentified origin is called a cryptogenic stroke.[17, 18] In addition, due to the transient nature of TIA, the cause of TIA is often difficult to identify. For the purpose of this HTA, we used the term cryptogenic stroke to refer to both cryptogenic stroke and TIA; and stroke patients to refer to both ischemic stroke and TIA patients. There are no standard criteria to define cryptogenic stroke. According to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria, cryptogenic stroke is defined as [18]:

- No arterial stenosis (>50%) or occlusion coupled with non-lacunar infarct on imaging
- No clinical lacunar syndrome if imaging shows no infarct or small (<1.5 cm) subcortical infarct
- No major-risk or medium-risk cardioembolic sources

Potential causes of cryptogenic stroke include mitral or aortic valvular disease, cancer, arteriogenic emboli, genetic causes and atrial fibrillation (AF).[18] When the standard workup does not identify the cause of stroke, AF is increasingly recognized as a common underlying cause of cryptogenic stroke. [17, 18] Most patients that fit into this TOAST criteria and did not receive an AF diagnosis after standard workup, would be asymptomatic. Due to the asymptomatic and episodic nature of some AF, diagnosis can be challenging. It is estimated that cryptogenic stroke accounts for 10% to 40% of all ischemic stroke.[17, 19] Assuming 25% (mean of the above estimates from the literature) of strokes are cryptogenic after the standard workup, it is estimated that in BC during the 2017/18 fiscal year, [redacted] ischemic stroke and TIA survivors would be potential candidates for further monitoring with either ELR or ICM.[12]

1.3.2 The diagnostic strategy for post stroke patients with suspected atrial fibrillation (AF)

AF is a type of abnormal heart rhythm characterized by a rapid and unsynchronized beating of the upper chambers of the heart.[20] As a result, the risk of forming a blood clot in the heart is higher than normal. The blood clot can then travel to the brain and cause a stroke. For this reason, patients with AF have a significantly increased risk of stroke and mortality associated with stroke.[20] AF can be episodic and asymptomatic.

Electrocardiogram (ECG) is the most common tool used to diagnose AF. During an episode of AF, a patient's ECG will exhibit a distinct fibrillatory pattern which can be used to diagnose AF. The duration of the fibrillatory episode is also considered in the ECG interpretation. The diagnostic cut-off of AF duration can vary among clinicians. Some specialists argue that an episode of AF lasting ≥30 seconds is sufficient for an AF diagnosis. However, others argue that the AF episode should last at least 2 minutes before a clear diagnosis can be made. [20]

During a patient's hospital stay for acute stroke treatment, their ECG is being continuously monitored using cardiac telemetry. If AF is not detected in hospital, the patient may be referred to outpatient specialist care. Other tests, such as brain imaging, ultrasound and blood work would be performed in order to rule out other causes of ischemic stroke, such as large artery atherosclerotic stenosis, lacunar stroke or non-AF cardiogenic embolism. [18] If the previous methods have not being conclusive for other causes, a Holter monitor may be considered to establish a baseline risk assessment. [21] The Holter monitor is a portable ECG monitor used in an out-patient setting. It continuously records heart rate within the monitoring period, typically 24 to 48 hours. Newer Holter monitors are able to record up to 14 days, however, since the patients need to remove the monitor before showering, compliance during the monitoring period may be an issue. [22] Skin irritation is a common complaint that may affect compliance. In addition, continuous monitoring provided by a Holter monitor might not be necessary for ambulatory patients, as compare to episodic recording provided by other cardiac monitors (e.g. ELR, ICM), as the majority of the heart beat recorded are likely to be normal rhythm.[22] Data from the Holter monitor are downloaded when the patient returns to the clinic. Episodic AF can be difficult to diagnose because the arrhythmic pattern of AF may not present during the patient's hospital stay for stroke treatment or during 24-48 hour Holter monitoring after discharge in outpatient clinic. Long-term cardiac monitoring maybe required to diagnose episodic AF in cryptogenic stroke patients.

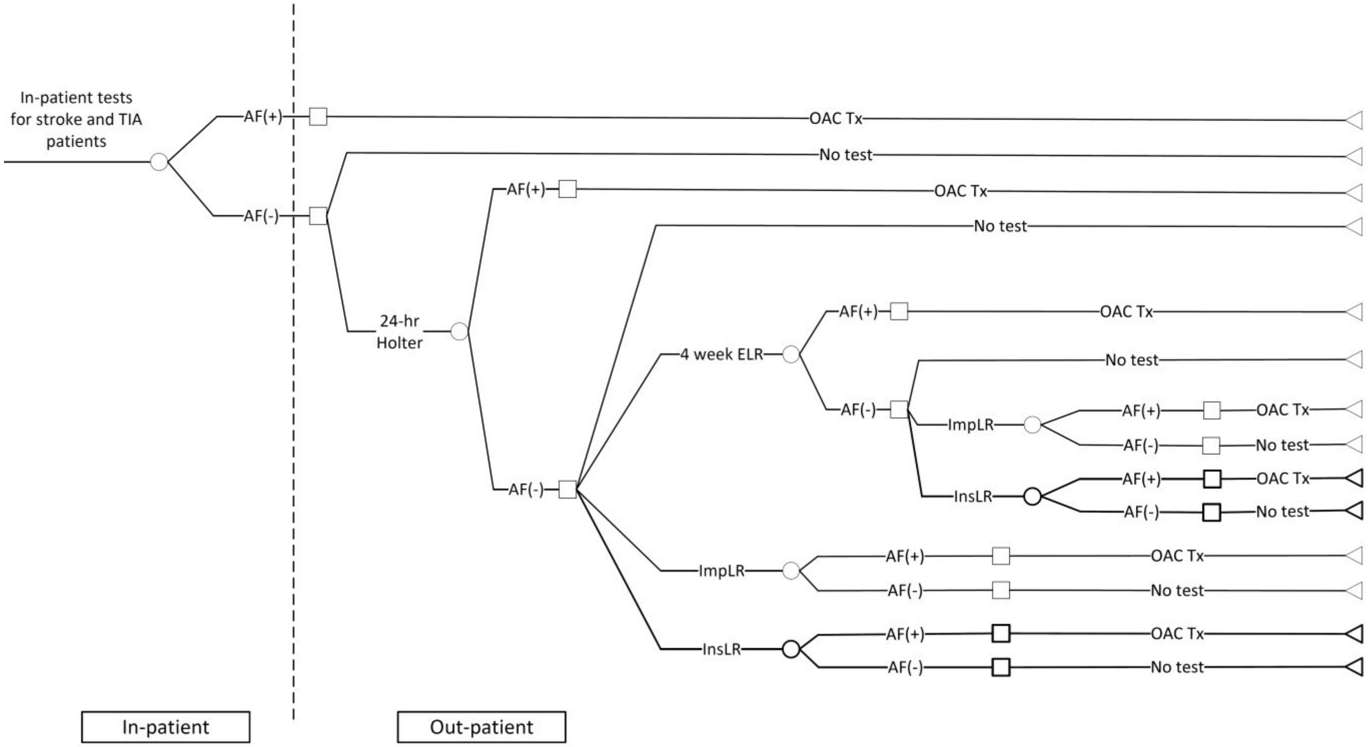
In episodic AF, the detection rate is correlated to the duration of monitoring. In a study that measured heart rhythm using both 24-hour Holter monitor and ELR, the detection rate increased as the duration of monitoring increased.[23] According to BC guideline on "Ambulatory ECG monitoring" [21], the choice of device depends on several factors:

- the type and frequency of patient's symptom(s);

- the ability of the patient (e.g., to activate a device while having symptoms, to fill out a diary); and
- the accessibility of the device

The decision tree for diagnosing AF in cryptogenic stroke can be found below in Figure 1.1

Figure 1.1 The diagnostic pathway of AF in cryptogenic stroke or TIA


In-patient tests for stroke and TIA patients
AF(+)
OAC Tx
AF(-)
No test
AF(+)
OAC Tx
No test
24-hr Holter
AF(+)
OAC Tx
4 week ELR
No test
AF(-)
ImpLR
AF(+)
OAC Tx
AF(-)
No test
InsLR
AF(+)
OAC Tx
AF(-)
No test
AF(-)
ImpLR
AF(+)
OAC Tx
AF(-)
No test
InsLR
AF(+)
OAC Tx
AF(-)
No test
In-patient
Out-patient

AF: atrial fibrillation; ELR: external loop recorder; ImpLR: Implantable loop recorder; InsLR: Insertable loop recorder; OAC Tx: oral anticoagulant treatment

The diagnostic pathway does not include cardiac monitors classified as external event recorders. According to key stakeholder interviews, the external cardiac monitors currently available in BC are external event recorders (EVR) which do not have an automatic AF episode detection feature and require the patient to trigger recording during a suspected episode of AF (i.e.; when they perceive the symptoms). Due to the asymptomatic nature of AF in a significant number of cryptogenic stroke patients, an EVR is not suitable as an alternative in this case. Besides, In BC, there is currently a 2-month waitlist to receive an EVR. A summary of the possible options for cardiac monitoring devices in BC can be found in Table 1.3.

Table 1.3: Cardiac monitors available in BC (not necessarily covered by the public health system) [21]

Device	Duration of monitoring	Device characteristics
Holter monitor	Typically 24 hours can be up to 2 weeks	An external device that is worn constantly, with **continuous** recording which is retrieved and interpreted once the device is returned. Only suitable for patients with symptoms or asymptomatic AF episodes occurring within the monitoring period, or when establishing risk/response to therapy.
Event Recorder	Up to 2 week	An external device that is worn constantly, with memory loop recording capability which can **record an episode** upon patient activation, whereby the data is stored in the device. There is no built-in Auto-detect function to record asymptomatic AF episodes. Data needs to be downloaded when the device is returned.
External loop recorder	Up to 1 month	An external device that is worn constantly, with memory loop recording capability which can **record an episode** automatically triggered by a built-in algorithm that allows the device to store data for asymptomatic arrhythmias or patient activation, whereby the data is stored in the device. Data can be downloaded when the device is returned.
Implantable cardiac monitor	Up to 3-4 years	The device is subcutaneously implanted, with a memory loop recording capability which can **record an episode** and store data either after patient activation or by Auto-detect algorithm during an AF episode. In some older models, data must be downloaded at the clinic. However, newer models allow data to be transmitted from the patient’s home.

1.3.3 Treatment for cryptogenic stroke and AF

After a cryptogenic stroke, according to the BC[24] and AHA[25] guidelines all patients should be offered antiplatelet treatment. Antiplatelet, including aspirin (ASA), are drugs that prevents the formation of blood clots which are effective in reducing the risk of recurrent ischemic stroke. [Ref] However, in AF patients with prior stroke, antiplatelet treatment did not reduce the risk of recurrent stroke or death when compared with no treatment. [26] Instead, oral anticoagulant (OAC) is more effective in treating patients with AF because it decreases the risk of recurrent stroke and death when compared with antiplatelet alone or no treatment. [26] Warfarin is a commonly use OAC and is recommended by BC guideline. [24] In a meta-analysis, warfarin reduced the risk of recurrent stroke by 39% (RR 0.61 (95% CI 0.48-0.78)). [27] When the patient cannot tolerate warfarin, a non-vitamin K oral anticoagulant, such as apixaban, dabigatran, edoxaban or rivaroxaban can be considered. In several RCTs, the non-vitamin K oral anticoagulant showed similar risk reduction in stroke prevention when compared with warfarin but may require less dose adjustment. [28-30] It is important to consider the risk of OAC therapy before initiation because not all post-stroke patients might benefit from OAC therapy.[31, 32] OAC by the nature of it’s mechanism of action, might also increase of bleeding. [24, 33] Therefore, it is important to weigh the individual benefit of stroke reduction and risk of bleeding in each patient before initiating OAC.

The list of available OAC in Canada according to the Canadian Pharmacist Association can be found in Table 1.11. Patients with other co-morbidities, such as hypertension or diabetes, should also continue with any appropriate treatment. This HTA included warfarin, apixaban, rivaroxaban and dabigatran as OAC options.

Table 1.4: Oral anticoagulant treatments available in Canada [34]

Drug name	Dosage	Common adverse event	Comments
warfarin	Oral: Dose to maintain INR between 2 and 3 for most cerebrovascular indications; for stroke prevention in certain high-risk patients with mechanical heart valves, maintain INR between 2.5 and 3.5	Bleeding. Skin necrosis.	Warfarin is the preferred anticoagulant (extensive published experience). Warfarin anticoagulants are contraindicated in pregnancy.
acenocoumarol	Oral: Dose to maintain INR between 2 and 3 for most cerebrovascular indications; for stroke prevention in certain high-risk patients with mechanical heart valves, maintain INR between 2.5 and 3.5	Bleeding.	Warfarin is the preferred anticoagulant (extensive published experience). Warfarin anticoagulants are contraindicated in pregnancy.
apixaban	Usual: 5 mg twice daily oral If serum creatinine >133 mmol/L and patient either >80 years of age or ≤60 kg: 2.5 mg BID PO	Bleeding.	Not recommended when ClCr <15 mL/min or in patients undergoing dialysis.
dabigatran	Usual: 150 mg twice daily oral Patients with increased bleeding risk or >80 years of age: 110 mg BID PO	Bleeding, gastric intolerance.	Contraindicated when ClCr <30 mL/min.
edoxaban	60 mg daily oral If ClCr 30–50 mL/min or patient ≤60 kg: 30 mg daily PO	Bleeding.	Not recommended when ClCr <30 mL/min.
rivaroxaban	20 mg daily oral Use 15 mg daily PO if ClCr 30–49 mL/min	Bleeding.	Not recommended when ClCr <30 mL/min.

Note: ClCr= Creatinine Clearance; INR= Prothrombin time international normalized ratio; PO= by mouth.

1.3.4 Description of External Loop Recorders (ELR)

External monitoring, using ELR with automatic detection of AF episodes for up to 30 days, may be suitable for patients experiencing symptoms (e.g. palpitation, fatigue) weekly or monthly, as well to detect asymptomatic AF episodes occurring within this period.[21] An ELR is a non-invasive and re-usable cardiac monitor that patients can wear around their waist or as a necklace with two to three lead attach to the chest. An ELR does not continuously record the patient's ECG, rather, it only records the ECG during an AF episode. The ECG recording may be initiated by the patient (due experiencing of symptoms such as palpitation, fatigue) or triggered by the automatic AF detection feature of the device. The patient will have to visit the clinic 3 times in this 30-day window, the first to receive the external monitor, the second time to replace the battery of the device (typically 14-18 days from time of set-up), and third, at the 30-day completion mark to return the device. During the 2nd and 3rd visit to the clinic, the data will be downloaded, transferred, and analyzed. One advantage of the ELR compared with the Holter monitor is that it may be easily removed prior to showering and can be reconnected afterwards.[22] However, the constant removal and reconnection of the device can lead to inaccurate ECG recording. The main limitation of ELR is skin irritation from the electrodes causing patients to remove the recorder and causing incomplete data collection. In addition, patients report that the device is uncomfortable during sleep.[22]

Some of the stakeholders interviewed for this report believe ELRs should be incorporated into the diagnostic pathway, and if adopted, it would come as a first line test, especially for symptomatic patients. The advantage of ELR is its non-surgical nature. Patients who want to opt out or not suitable for surgery can use ELR. The arguments were that this would offer a more ethical approach in providing a less invasive and costly monitoring alternative, before suggesting ICMs. If ELR monitoring does not detect AF among post-stroke patients, ICM monitoring would be offered subsequently.

However, an existing counter argument suggests that for low burden or asymptomatic patients, AF is unlikely to be detected during the relatively short monitoring periods associated with Holter monitors, and perhaps, with even the new ELR devices (such as Spiderflash-T) which can offer extended 30-day monitoring. Among patients experiencing symptoms less than once a month or those who are asymptomatic, an ICM may then be a more suitable option for monitoring as a first line test. For a more descriptive explanation of this issue, please refer to section 3.3.1 Access to treatment/ Clinical Pathway.

Moreover, there is an assumption that without an increased investment in acquiring new ELRs argued to have a comparable clinical efficacy to the ICM within the initial 30-day of monitoring (such as the Spiderflash-T); ELRs would face the same wait-time as EVRs (two months), followed by an additional wait-time for ICMs for those patients that will require both tests, prolonging their wait-time for an AF diagnosis, and leaving patients at risk of recurrent strokes that could be prevented with a change in their treatment. ELR use has been initiated in research settings in BC and currently concentrated to the Spiderflash-T model, with some jurisdictions even adopting the use of Spiderflash-T within routine clinical practice. However, due to some limitations in the implementation of the Spiderflash-T model, other jurisdictions are currently exploring the integration of other cardiac monitors such as the CardioSTAT model (Table 1.5). For more information regarding the use and limitations of the Spiderflash-T ELR, please refer to section 3.3.8 Risk for successful implementation (financial, human resource, stakeholders & other).

BC has purchased some ELRs that have been in use in some health authorities (Table 1.5). The estimated cost of a 4-week ELR test in the BC context is approximately [redacted] as deduced via a costing exercise conducted with multiple stakeholders. Details of the cost components and assumptions can be found in Appendix A, and includes costs associated with the re-usable device, and the personnel and physician fees necessary to interpret the data gathered during the ELR test. The regulatory status of the ELR devices with Health Canada and other technical details can be found in Table 1.6. Implementations issues with the ELR models will be further explored in the stakeholder interviews section of this report.

Table 1.5. BC historical procurement data of ELRs*[35]

	Units Acquired				**Price per Unit**
	2015	2016	2017	2018	
Spiderflash T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: ELR= External Loop Recorder

[redacted]

Table 1.6: Device information of available long-term Cardiac Monitors (limited to those previously procured in BC)

Device	External, Implantable or insertable	Health Canada license #	Issue date	Manufacturer	Duration of monitoring	Remote monitoring	Method of data transfer	Placement location	Placement personnel
External Loop Recorder									
Spider Flash-T (AFIB) auto-triggered event recorder	External	80700	September 18, 2009	Microport	30 days	No	Office download	Office	Technician
Insertable ICM									
Reveal LINQ insertable cardiac monitor	Insertable	92969	March 10, 2014	Medtronic	3 years	Yes	via in-home device over cell signal or office download	Minimally invasive procedure room at physician's office	1 EP, 1 RN, 1 TECH
St. Jude Medical Confirm Rx Insertable Cardiac Monitor	Insertable	99364	July 5, 2017	St. Jude Medical	3 years	Yes	Via cell phone or tablet app/ office download		
Implantable ICM									
Reveal XT insertable cardiac monitor	Implantable	76093	January 24, 2008	Medtronic	3 years	No	Office download	Cath lab or Operating room or Procedure room	If in OR & procedure room, 1 EP, 1 ANES, 1 TECH, 2 RN
St. Jude Medical Confirm Cardiac Monitor (not Rx)	Implantable	78855	January 19, 2009	St. Jude Medical	3 years	No	Office download		
Biomonitor 2 Monitor	Implantable	98054	November 21, 2016	Biotronik	4 years	Yes	Via home monitoring device through cell signal		If in Cath lab, 1 EP and 2 RNs

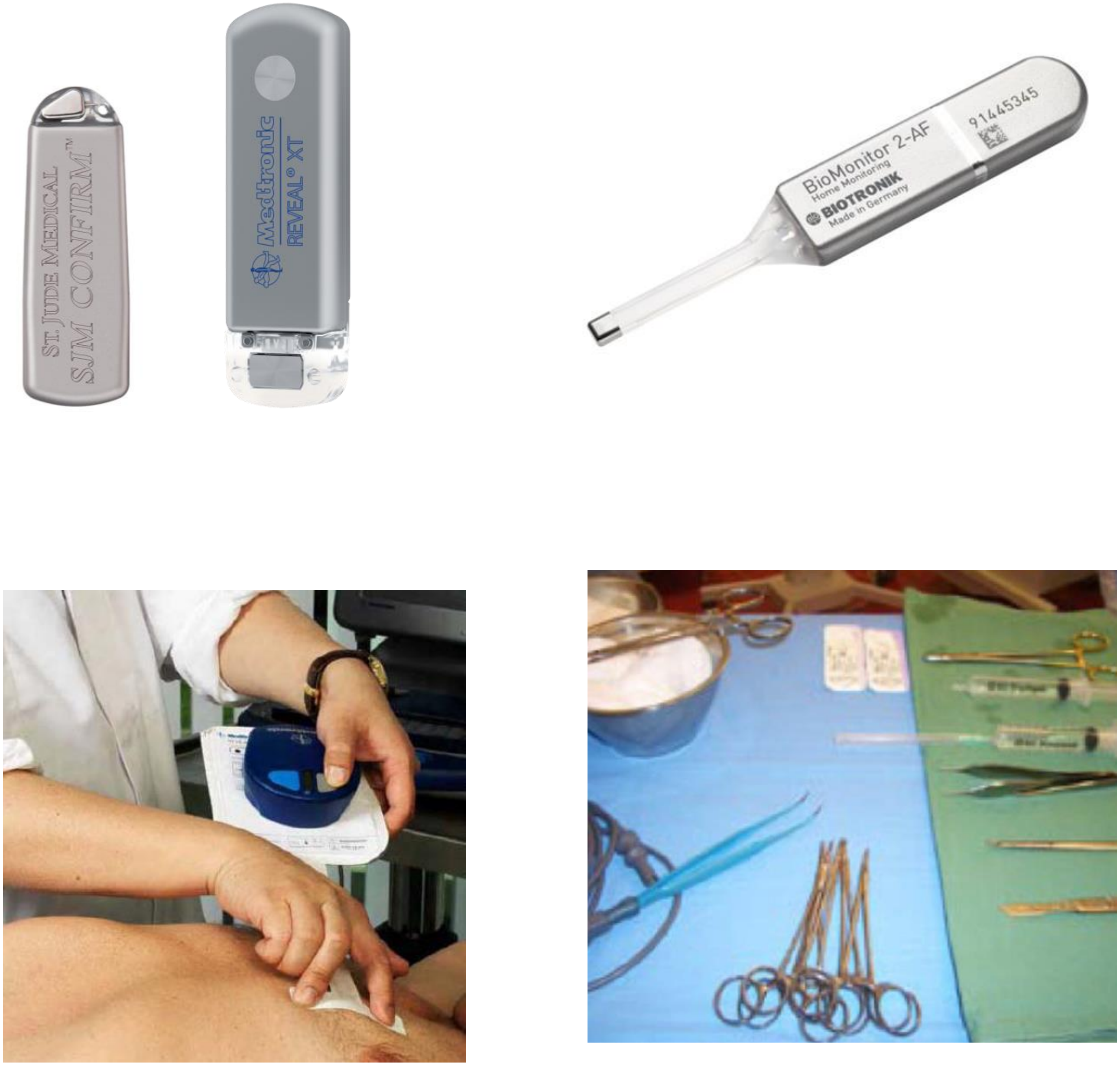
Note: ANES= Anesthesiologist; EP= electrophysiologist; OR= operating room; RN= nurse; TECH= technician

1.3.5 Description of Implantable Cardiac Monitors (ICMs)

An ICM is a cardiac monitoring device that is placed underneath the skin near the heart. Similar to the ELRs, the ECG is only recorded during a suspected episode of AF, either manually activated by the patient or triggered by the automatic AF detection feature of the device. Once inserted, the ICM requires minimal maintenance from the patient. The longevity of the ICM battery is approximately three to four years depending on the manufacturer.

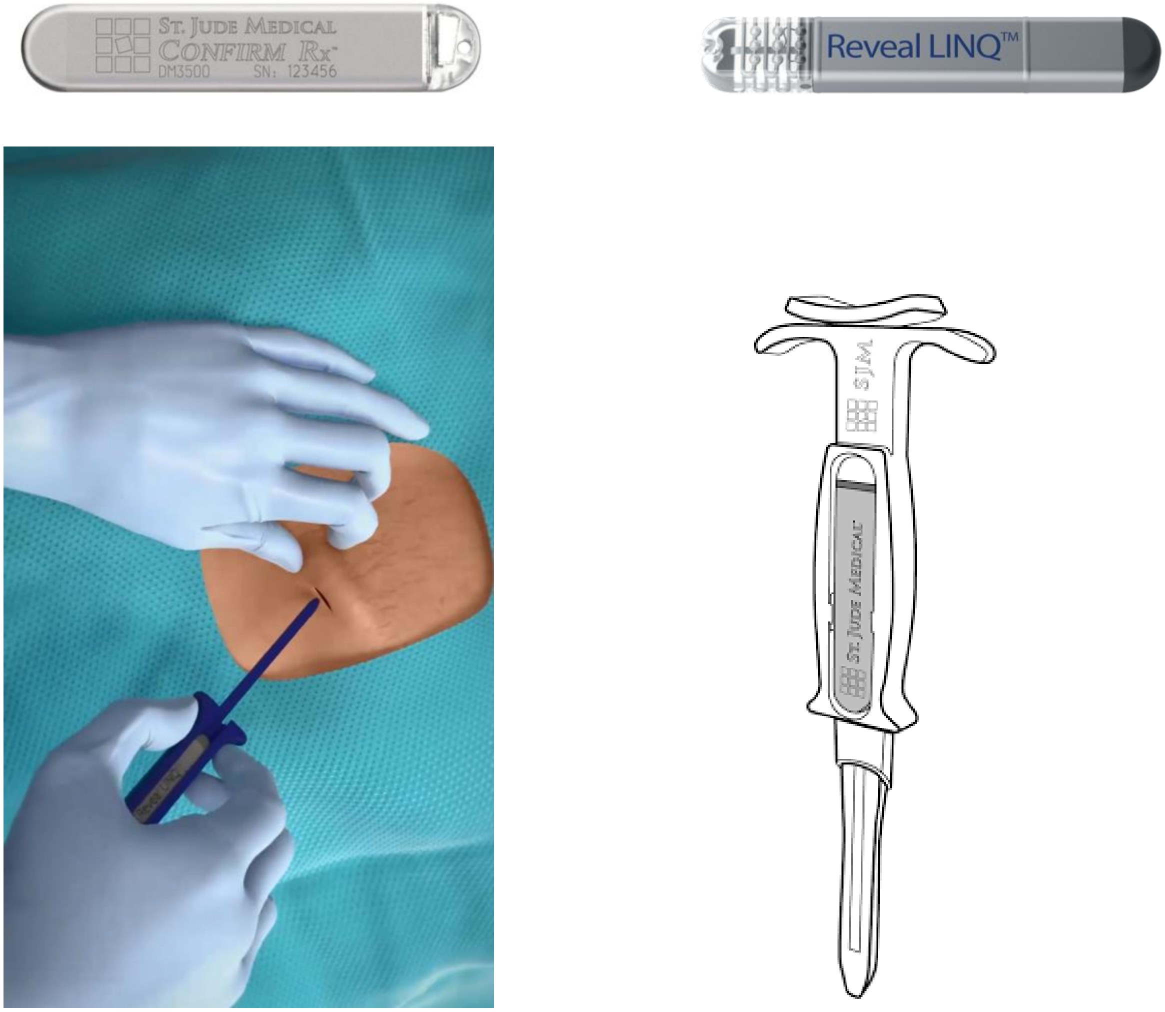
There are two main types of ICM included in this review, implantable (Imp ICM) and insertable (Ins ICM). The two main differences between the two types of devices are the placement procedure and the data transmission (whether the device has an automatic transmission ability). The implantable devices (Figure 1.2) require a placement procedure in a surgically clean environment such as a catheterization laboratory (Cath lab) or operating room (similar to pacemaker battery replacement procedures). The device is approximately the size of a large flash drive. According to key stakeholders interviewed for this report, in BC there is currently a six to eight-week wait time for a Cath lab or operating room. The insertable devices (Figure 1.3) can be placed with an insertion tool in a minimally invasive procedure room in a physician's office. [38] The device is approximately the size of an AAA battery. In both cases, regional anesthesia is needed (usually performed by the physician performing the placement) and the procedure takes on average 15-20 minutes. According to key stakeholders interviewed for this report, there is currently a 2-week wait time for this type of procedure. Once in place, both implantable and insertable ICMs provide a similar type of monitoring in patients with cryptogenic stroke.

Figure 1.2: Implantable ICMs (or Imp ICM)


ST. JUDE MEDICAL
SJM CONFIRM™
Medtronic
REVEAL® XT
BioMonitor 2-AF
Home Monitoring
BIOTRONIK
Made in Germany
91445345

Note: Top images from the left to the right: St Jude Medical, Medtronic, and Biotronik models. Larger in size, usually the size of a USB flash drive. Bottom images: surgical instruments required for implantation (left) and programmer to set the device after implant (right)[39-41]

Figure 1.3: Insertable ICMs (or Ins ICM)


St. Jude Medical
Confirm Rx
DM3500
SN: 123456
Reveal LINQ™
SJM
St. Jude Medical

Note: Top images from the left to the right: St Jude Medical and Medtronic models. Smaller in size, usually the size of an AAA battery. Bottom images: insertion procedure with insertion tool from Medtronic Reveal LINQ (left) and insertion tool from St. Jude Medical Confirm RX (right) [39-41]

Remote monitoring is an advanced feature offered through some models of ICM. It allows the patient's data to be transmitted remotely, preventing the patient from attending the clinic in-person. The remote monitoring feature of ICM can potentially help patients from remote communities to gain access to specialist service without traveling long distances. However, if AF is diagnosed, patients without local access to specialist services will need to make several visits to their specialist for initiation of treatment.

Among the implantable models (Imp ICM), Biomonitor 2 has remote monitoring capability via cellular signal. The patient's data can be downloaded via a home monitoring device. The clinician has real-time access to the information through the internet.[40] For older monitors like Reveal XT or St. Jude Medical Confirm, the data is usually downloaded during the clinic visit; however, the Medtronic Reveal XT has the capability to be linked to a mobile app, which will then permit patients to send in their data remotely (there is still no automatic transmission option). The St. Jude Medical Confirm ICM does not have remote monitoring capability.

Among the insertable models (Ins ICM), Medtronic Reveal LINQ has the ability to automatically transmit data remotely through cellular signals to a central database, whereby the data can be accessed at the device clinic via the Carelink Network and programmer set up by Medtronic.[39] A small portable home monitor is required for remote transmission of data, called the MyCareLink Patient Monitor. If the patient does not have access to the home monitor, the data cannot be automatically transmitted, and must instead, be downloaded during a clinic visit.[39] St Jude Medical Confirm Rx device can also transmit data remotely through a cell phone or tablet app and thus has remote monitoring capabilities. [41] The data can also be download during a clinic visit.

The regulatory status of the implantable models of ICM (Medtronic, St. Jude Medical (currently Abbott) and Biotronik), insertable models of ICM (Medtronic and St. Jude Medical), and other technical details can be found in Table 1.6.

The costs associated with various ICM devices historically purchased in BC are displayed in Table 1.7. The total cost associated with ICMs should account for the cost of the device as well as different health system resources (i.e.; location, personnel, fees) involved in the different types of procedures utilized to implant these devices, the monitoring costs to interpret the long-term data collected by these devices, and explantation of the device at the time of the AF diagnosis or at the end of their battery life, whichever occurs first.

Table 1.7 BC historical procurement data of ICMs [35]

Historical Purchase volume & spending per device	2015		2016		2017		2018		Device Purchase Price (2019)
	Unit #	Spending/Device	Unit #	Spending/Device	Unit #	Spending/Device	Unit #	Spending/Device	
[redacted]									

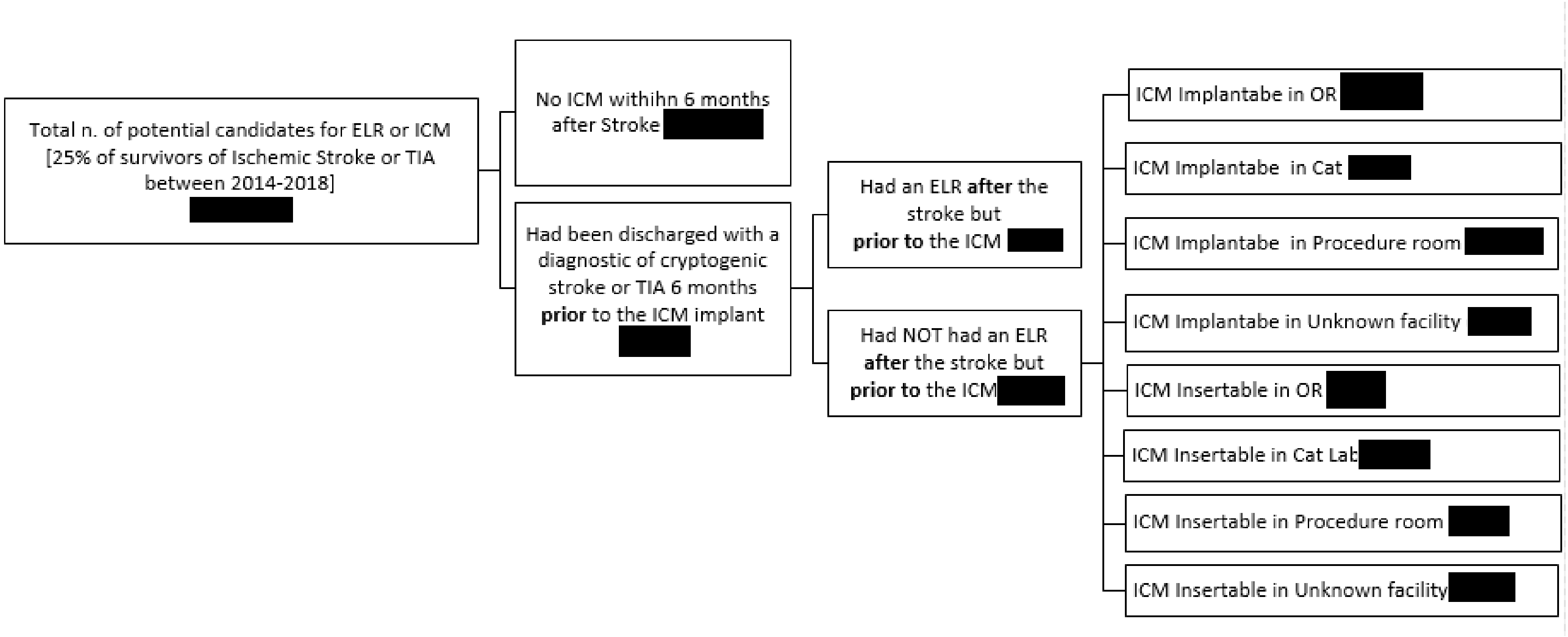
1.3.6 Technology Potential for Illness and Injury prevention: *End goal of cardiac monitoring for post-stroke patients, downstream costs of ICM implantation and current patterns of utilization in BC*

Among patients who have experienced a cryptogenic stroke, ICM may provide a significant opportunity to detect AF, and therefore initiate appropriate therapy preventing subsequent stroke and death. Stakeholders interviewed for this report have indicated that a lack of availability to such diagnostic devices, and therefore the inability to properly diagnose and initiate treatment for these patients, would have severe consequences for patients. Furthermore, stakeholders have indicated that there are significant monetary considerations for the health care system in regards to the high cost of downstream care and long-term care management for patients experiencing another stroke or other adverse events, as delays in patient access to cardiac monitoring (ELR or ICM) may lead to delays in AF diagnosis. Delays in AF diagnosis may lead to an increased risk of recurrent stroke and death as patients will not be receiving the most effective treatment for their underlying condition. Therefore, the purpose of offering timely access to cardiac monitoring to this post stroke patient population is to optimize their treatment by offering oral anticoagulant (OAC) therapy, and consequently, improve survival and other clinical outcomes (e.g.; stroke recurrence, adverse events).

Neither ELRs nor ICMs are broadly covered by the public health system. Some health authorities provide access to those technologies either under research protocols or special programs financed under their global budget. Using BC administrative data combined with the BC ICM registry, during 2014 to 2018 [42], among all the cases that could be classified as cryptogenic stroke (assuming 25% of the Ischemic stroke and TIA cases), [redacted] access to ICMs. Those who received ICM did not have ELR prior to ICMs. (Figure 1.4). Note that the number of ELRs identified through the administrative database was based on MSP fees for that could also be used for EVRs. Although the data may be overestimating the number of ELR tests, the data provide a general idea of the proportion of patients for whom their physicians have tried to access non-invasive tests prior to pursuing ICMs.

Among those who had access to ICM devices, 84% of them had the implantable models, and 15% had the insertable models. Among patients who received the implantable models, 28% had their device placement performed in an OR, 13% had their device placement performed in a Cath Lab, 18% had their device placement performed in a procedure room, and 42% had no information on the type of facility used for device placement. Among patients who received the insertable devices, 69% had their device placement performed in an OR, 23% had their device placement performed in a procedure room, and 8% had no information on the type of facility used for device placement. No insertion of insertable ICM in a Cath lab among cryptogenic stroke patients was identified in the administrative databases (Figure 1.4). In the event of a provincial policy change for the incorporation of this technology, key stakeholders perspective seemed to be unanimous that the placement of insertable devices should move to a minimally invasive procedure room in a physician's office, for optimization of hospital resources.[38]

Figure 1.4 Cryptogenic stroke population in BC and the use of cardiac monitoring technologies and facilities used for implantation [42]


Total n. of potential candidates for ELR or ICM [25% of survivors of Ischemic Stroke or TIA between 2014-2018] [redacted]
No ICM withihn 6 months after Stroke [redacted]
Had been discharged with a diagnostic of cryptogenic stroke or TIA 6 months **prior** to the ICM implant [redacted]
Had an ELR **after** the stroke but **prior to** the ICM [redacted]
Had NOT had an ELR **after** the stroke but **prior to** the ICM [redacted]
ICM Implantabe in OR [redacted]
ICM Implantabe in Cat [redacted]
ICM Implantabe in Procedure room [redacted]
ICM Implantabe in Unknown facility [redacted]
ICM Insertable in OR [redacted]
ICM Insertable in Cat Lab [redacted]
ICM Insertable in Procedure room [redacted]
ICM Insertable in Unknown facility [redacted]

The majority of ICMs used in cryptogenic stroke patients up to date have been performed within Fraser Health authority (64%), and in OR or procedure room (Table 1.8 and Table 1.9).

Table 1.8 ICM among cryptogenic stroke by health authority [42]

Health Authority	[redacted]
01 Interior	[redacted]
02 Fraser	[redacted]
03 Vancouver Coastal	[redacted]
04 Vancouver Island	[redacted]
05 Northern	[redacted]
Provincial Total	[redacted]

Table 1.9 Facility type used for ICM implantation in cryptogenic stroke by health authority [42]

Health Authority	Facility type	[redacted]
01 Interior	Unknown	[redacted]
02 Fraser	Unknown	[redacted]
	Cath Lab	[redacted]
	OR	[redacted]
	Procedure Room	[redacted]
03 Vancouver Coastal	Unknown	[redacted]
	Cath Lab	[redacted]
	OR	[redacted]
	Procedure Room	[redacted]
04 Vancouver Island	Cath Lab	[redacted]
	OR	[redacted]

Note: facility type unknown due missing data in for this field in the registry.

It should be noted; however, that these volumes may be different than the ICMs acquired through the procurement services (Table 1.7) due to a number of reasons unrelated to this HTA (e.g.; direct acquisition by the services, donations, research protocols financed through other resources, utilization in other patient populations (i.e.; syncope)).

The costs of the implant procedure (beyond the device costs) according to the type of facility chosen for device placement are displayed in Table 1.10. Costs were estimated by means of a costing exercise with multiple key stakeholder interviews, and data triangulation with the Health Technology Assessment Office (HTAO) available databases (DAD, MSP, Pharmacare). Details of the cost components and assumptions can be found in Appendix B.

Table 1.10 Procedure costs for the implant of ICMs by device type

Device Type	Facility type	Device Costs	Hospital Costs	MSP fees	Anesthesia fees (MSP)	Total Costs
Implantable	OR	[redacted]	[redacted]	[redacted]	[redacted]	$3,193.18
	Procedure Room	[redacted]	[redacted]	[redacted]	[redacted]	$2,830.42
	Cath Lab	[redacted]	[redacted]	[redacted]	[redacted]	$3,661.52
Insertable	Procedure Room	[redacted]	[redacted]	[redacted]	[redacted]	$5,017.27
	Office	[redacted]	[redacted]	[redacted]	[redacted]	$4,795.67
Explantation	CIHI	[redacted]	[redacted]	[redacted]	[redacted]	$5,009.20

Data collected by the ICM must be analyzed by technicians and electrophysiologists in order to diagnose AF. The estimated costs of monitoring those patients after the implant are displayed in Table 1.11, by device type. The costs were estimated by means of a costing exercise with multiple key stakeholder interviews and data triangulation with the Health

Technology Assessment Office (HTAO) available databases (DAD, MSP, Pharmacare). Details of the cost components and assumptions can be found in Appendix C.

Table 1.11 Monitoring costs, per patient, per year

Device Type	MSP fees	Hospital Costs	Total Costs
Implantable	[redacted]	[redacted]	[redacted]
Insertable	[redacted]	[redacted]	[redacted]

Once an AF diagnosis is made by ELR or ICM monitoring, the clinician can suggest changes to the patient's treatment plan (described in the next section), and cardiac monitoring is no longer required for the purpose of AF detection. If the patient had an ICM implanted (of any type), usually, it would be recommended to have the device explanted at the time of the AF diagnosis, or at the end of their battery life (up to 3 years). If AF was not detected during the ICM battery life, AF is unlikely to be the underlying cause of the primary stroke and further investigation for AF would be discontinued.[36] The cost of the explantation procedure was estimated [redacted] (Table 1.10). Details of the cost components and assumptions for the explantation can be found in Appendix D .

1.3.7 New alternative technologies on the horizon

There are new technologies on the horizon for AF detection such as handheld device and smartphone apps.[43] However, these technologies require patients to pick up and activate the device during an episode; therefore these technologies are not relevant to our mostly asymptomatic cryptogenic stroke population. Another new technology is the Zio patch, which allows 24-hour continuous recording for 14 days and can be worn in the shower.[43] The Zio patch is single use patch-like device that is water resistant. The Zio patch works like a Holter monitor and once the monitoring period is completed, the device is returned to the manufacturer for data retrieval. A report is generated by the manufacturer and is returned to the clinic for interpretation. No new loop recorders were identified. Upcoming RCT are summarize in Table 1.12. The list is a result of a general scan of the clinicaltrials.gov website. Other technologies not on the list, such as non-invasive monitoring by patches, necklace, sticks, bras, and belts, can potentially be the subject of an HTA in the future.

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Table 1.12: Upcoming clinical study for AF detection devices[43]

Study	Study design	Population	Study intervention	Primary outcomes	Expected completion
NCT03197090 (DETECT-AF Trial)	Randomized controlled trial	1,600 patients admitted to internal medicine department	Randomized to Zenicor intermittent ECG while in hospital versus routine care	Newly detected AF after 6 months	5/2018
NCT00846924 (EMBRACE)	Randomized controlled trial	564 patients with recent ischemic stroke or TIA of undetermined cause (within 6 months)	Randomized to 30 day ambulatory cardiac event monitor (AccuHeart Electrode Belt, Braemar ER 910AF) versus 24 h Holter monitor	Detection of ≥1 episode of AF or atrial flutter ≥30 s, as assessed at 90 day follow-up	6/2018
NCT02392754 (SCREEN-AF)	Randomized controlled trial	822 patients aged ≥75 years with history of hypertension and without known AF	Randomized to 2 week continuous ZIO XT ECG monitor and home BP monitor with automatic AF detection capability to be used twice daily at baseline and again at 3 months versus routine care	New diagnosis of ECG confirmed AF or atrial flutter after 6 months	12/2018
NCT01593553 (STROKESTOP study)	Randomized controlled trial	7,173 participants aged 75-76 years living in region of Stockholm or Halland	Randomized to intermittent Zenicor ECG (≥2 times/day) for 14 days and anticoagulation if AF is detected versus routine care	Ischemic or hemorrhagic stroke, systemic embolism, major bleeding leading to hospital admission, or death from any cause after 5 years	3/2019
NCT02522364 (POAF-ILR)	Randomized controlled trial	150 patients with transient postoperative AF after cardiac surgery	Randomized to BioMonitor ILR implantation versus routine care including ECG Holter examination at 3 and 6 months after discharge	AF ≥5 min	12/2019
NCT02036450 (LOOP study)	Randomized controlled trial	6,000 participants with risk factors for stroke	Randomized to ILR (REVEAL LINQ) implantation and anticoagulation if AF ≥6 min is detected versus routine care	Time to stroke or peripheral embolic episode after 3 years of follow-up	1/2020
NCT02506244 (mSToPS)	Randomized controlled trial	2,274 participants at increased risk for AF	Randomized to ZIO XT patch monitoring for first and last 2 weeks of first 4 month monitoring period (immediate monitoring) versus first and last 2 weeks of study months 4-8 (delayed monitoring)	Incidence of newly diagnosed AF at end of first 4 month monitoring period	9/2020

Study	Study design	Population	Study intervention	Primary outcomes	Expected completion
NCT03515057 (VITAL-AF Study)	Randomized controlled trial	35,000 patients aged ≥65 years visiting primary care clinic	Randomized to AliveCor KardiaMobile single lead ECG versus screening or routine care	Incident AF during study period	10/2020
NCT02743416 (STROKESTOP II study)	Randomized controlled trial	8,000 participants aged 75/76 years residing in Stockholm	Randomized to AF screening (if NT-proBNP >125 ng/L (high risk group), intermittent Zenicor-ECG twice daily for 2 weeks; if NT-proBNP <125 ng/L (low risk group), Zenicor-ECG once) versus routine care	Incidence of stroke in low risk group compared with control group after 5 years	4/2023
NCT03274401 (SAFE-PE Study)	Randomized controlled trial	800 patients with recent pulmonary embolism (within 3 months) and risk factors for AF	Randomized to Zenicor intermittent ECG (≥2 times/day) for 2 weeks and prolonged anticoagulation therapy if AF is detected versus routine care	Mortality in screening arm compared with control arm after 5 years	9/2027
NCT02893215 (Silence Study)	Prospective cohort study	1,622 patients with type 2 diabetes, heart failure, and risk factors for AF	Zenicor intermittent ECG (4 times/day) for 2 weeks	No of participants with silent AF after 14 days	9/2020
NCT02507986 (MOBILE-AF)	Multicenter randomized trial	200 adult patients who had an episode of symptomatic Transient ischemic attack (TIA) or episode of ischemic stroke.	A single lead ECG device or a 7-Day Holter Monitor	Percentage of detected atrial fibrillation [Time Frame: 1 year of follow-up]	7/2020
NCT03301662 (TEASE)	Prospective cohort study	100 adult patients with a clinically confirmed diagnosis of ischemic stroke.	Chest and thumb- ECG	Cumulative incidence of atrial arrhythmia at 28 days.	10/2019
NCT02937077 (NOR-FIB)	Prospective cohort study	500 adult cryptogenic stroke patients (18-80 years old)	Revel LINQ for 6 months, single arm	Atrial fibrillation detection rate in 6 months	12/2020

AF=atrial fibrillation; BP=blood pressure; ECG=electrocardiography; NT-proBNP=N-terminal pro b-type natriuretic peptide; TIA=transient ischemic attack.

1.3.8 Policy problem

BC faces a discrepancy in access and public coverage of cardiac monitoring technologies across health authorities. This discrepancy not only affects patients' timely access to appropriate treatment (for those with AF), but also resource allocation and planning for those health authorities that chose to provide these technologies under their global budget.

Insertable ICMs do not require a Cath lab or an operating room for insertion, rather they can be inserted at any physician's office where there is an existing procedure room adhering to aseptic procedures. Therefore, by providing an alternative diagnostic tool to investigate AF, it is believed that ICM insertions in an office setting will help decrease existing wait-times; and thus, may help optimize treatment, prevent secondary strokes, and improve survival and quality of life for this patient population.

Alternatively, key stakeholders are also debating whether to improve the capacity to less invasive cardiac monitors (ELR) before recommending implantable options, as they may provide a more ethical and cost-effective approach for a policy change, and provide resource reallocation opportunities to expand access to cardiac monitors.

Therefore, this assessment aims to understand the impact for patients and health authorities, in use of the above-mentioned strategies including combined alternatives of ELR and ICM, to expand access to cardiac monitors for patients post cryptogenic stroke.

1.4 Structure of report

A Canadian jurisdictional scan is provided in the next section, followed by Stakeholder perspectives outlined in the next two sections. The report will continue with an assessment of the clinical and economic evidence presented in detail in chapters 4 and 5. The economic model is found in the next section (chapter 6) and is followed by the budget impact (chapter 7).

Chapter 2 Jurisdictional Scan

Summary

Communication with provincial stakeholders was established via CADTH liaison officers and the BC Ministry of Health's intergovernmental relations network. Responses were received from Saskatchewan, Ontario, Quebec, Newfoundland and Labrador, Northwest Territories, and Prince Edward Island.

Currently, among the provinces who have responded to the HTA request, Saskatchewan, Quebec, Newfoundland and Labrador, and Prince Edward Island provide different degrees of coverage for the use of ICMs and for different clinical indications. Saskatchewan, Quebec and Prince Edward Island provide coverage for patients who have had a cryptogenic stroke. Newfoundland and Labrador, provide coverage for ICMs for additional clinical indications but cryptogenic stroke is not one of them.

Ontario and the Northwest territories currently do not offer publicly funded ICMs.

2.1 Objectives

The objective of the jurisdictional scan was to outline policies from across Canada regarding the use of implantable cardiac monitors, whether they have been publicly funded, and the current state of technology use internationally.

2.2 Methods

Two methods were used to address the objectives. First, standardized emails were sent to relevant stakeholders in each province by the CADTH liaison officers. In addition, the BC Ministry of Health, using the intergovernmental relations network, contacted other provincial Ministries of Health. If the email recipient felt that they did not have the necessary expertise to respond, they were asked to forward the request to a knowledgeable colleague. A snowball sampling scheme was used to refer the team to any other stakeholders other than those previously recommended. Follow-up with responders was completed as necessary. If individual interviews with stakeholders in other provinces were required, these were conducted by the UBC researchers and incorporated in this report. The standardized email requested response to three questions:

(1) Is your province currently using ICM, and if yes, to what capacity?

(2) If ICM is offered, what are the clinical eligibility criteria for receiving an ICM?

(3) If your province uses ICM, can you share more information regarding:

  a) What are the criteria/policy/protocol in place in your province in order for patients to qualify for the coverage by the public health system for each technology?
  b) Other than evidence of clinical effectiveness, what factors influence the decision on whether to use an ICM (i.e. cost, patient preference, convenience, availability in your jurisdiction, other barriers)?
  c) Have you measured/seen results of clinical or cost-effectiveness of the use of ICM in your jurisdiction? If yes, are you able to share any data/information with us?

2.3 Results

2.3.1 Jurisdictional Surveys and Interviews

Email responses were received from Saskatchewan, Ontario, Quebec, Manitoba, Newfoundland and Labrador, Northwest Territories, Nunavut and Prince Edward Island. If the email recipient felt that they did not have the necessary expertise to respond, they were asked to forward the request to a knowledgeable colleague. No responses were received from the province of Alberta, Manitoba, Nova Scotia, and New Brunswick.

2.3.1.1 Saskatchewan

In Saskatchewan, responses were received from Saskatoon and Regina.

Saskatoon

In Saskatoon, ICMs are being implanted in the Electrophysiology Laboratory. All ICMs must be ordered and approved by a Cardiac Electrophysiologist (EP). There are no specific clinical criteria; therefore, qualifying to receive an ICM is under the EP's discretion. Due to the high cost of the ICMs, they are being ordered conservatively; however, as output demand for long term non-invasive monitoring increases and in consideration of the limited and sometimes ineffective function of non-invasive monitors (ELRs), ICMs are being used with increasing frequency.

Saskatoon has found that on an individual basis, there have been clinical findings showing that ICMs have been very effective in identifying AF in patients with an occurrence of Cryptogenic Stroke, and also in other clinical areas such as identifying arrhythmias in infrequent palpitations, unexplained syncope, and AF research.

Regina

In Regina, ICM are also implanted in the EP lab, where in the last fiscal year, [redacted] implants have been conducted. Clinical criteria specified for ICM implants include: Syncope

NYD, Cryptogenic Stroke, Symptomatic Palpitations Not Yet Diagnosed (NYD), and Atrial Fibrillation (though not as often observed as the other clinical indications). All approved implants are qualified by coverage by the public healthcare system.

When ICM was first introduced, a number of patients who had received an ICM very quickly showed abnormalities that helped diagnose their condition within 1 week, thus rendering the ICM unnecessary as now a therapeutic device was required (such as a pacemaker). Given this finding, a policy was implanted that in order to qualify to receive an ICM, patients currently must have received an external loop recorder for a month period before qualifying for an ICM, and thus, eliminating the need for ICM for patients who are symptomatic enough to be captured via an external loop recorder.

Regina has not collected any data on the cost-effectiveness of the use of ICM or the downstream treatment outcomes of those who have received an ICM.

2.3.1.2 Ontario

Ontario has indicated that they do not fund or track the use of ICMs within their program area.

2.3.1.3 Quebec

In Quebec, ICMs are currently publicly funded. From May 1st, 2017 to April 30th 2018, a total of [redacted] devices have been implanted in University centers and regional centers, respectively. The primary clinical indication for ICM implants are stated to be for the investigation of syncope NDA, whereby Holter monitoring, cardio memo, and an event monitor (specifically King of Hearts) testing have all shown to be inconclusive, and that the eligibility criteria to receive an ICM are based only on clinical indications. ICM use is only approved under the circumstance that a diagnosis could not be established by using any other diagnostic tools or devices.

Currently, no studies have been conducted to investigate the clinical outcomes and downstream clinical effectiveness for ICMs.

2.3.1.4 Manitoba

Manitoba has indicated that ICM is used fairly regularly, with the decision for implant based on a case-by-case basis by an Electrophysiologist, who will decide whether to go for a conventional ILR or an ICM. Typically, patients who are younger, patients with a diagnosis that might require more urgent turn-around, patients with high-risk presentations, and patients who would highly prefer an ICM as compared to an ILR will receive the ICM. Coverage of ICM is provided under the umbrella of ILRs as determined by the physician. No specific criteria/policy is currently in place. There is also no current available data assessing the clinical or cost-effectiveness of the use of ICMs in Manitoba.

2.3.1.5 Newfoundland and Labrador

In Newfoundland and Labrador, although ICM is implanted for some clinical indications, from a neurology perspective, cryptogenic stroke is not included within the criteria for ICM approval. Currently, standard secondary stroke prevention management is provided to the Cryptogenic Stroke patient group.

Currently, the province engages in 24 or 48 hours Holter monitoring; however, 2-week monitoring via an event recorder (which can be triggered by the patient when they feel symptomatic) is not available. While not yet approved, 30-day external monitoring is under investigation and consideration.

2.3.1.6 Northwest Territories

ICMs are currently not offered in the Northwest Territories (NWT). If a patient from NWT may require this technology, a referral is made to other jurisdictions that may offer ICMs, whereby the clinical criteria would be specified by the provider/facility.

2.3.1.7 Prince Edward Island

ICMs are currently in use in Prince Edward Island; however, use of this technology is rather limited. The Medtronic Reveal XT and the Medtronic Reveal LINQ have been stated to be implanted in the OR and device clinic, respectively. Clinical eligibility are not stated to be formally defined. Given a high clinical suspicion for cardiac syncope or atrial arrhythmia (atrial fibrillation or atrial flutter), which has not been captured on prolonged non-invasive ambulatory ECG monitoring (loop recorder), an implantable ICM is implanted. A typical patient profile would include a young individual with an occurrence of Cryptogenic Stroke. Other factors under consideration for ICM implants include the patient’s willingness for frequent trips to the clinic, more so in the case of the Medtronic Reveal XT (which does not have an automatic data transfer option), but also for follow-up appointment for the Medtronic Reveal LINQ.

Currently, no studies have been conducted to investigate the clinical outcomes and downstream clinical effectiveness for ICMs.

2.3.2 Published HTAs

The CRD, NICE AHRQ, Health Quality Ontario and the Alberta HTA database were searched for relevant HTA reports. The keywords “cryptogenic stroke”, “cardiac monitor”, “loop recorder”, “implantable cardiac” and “stroke” were used as search terms. Two relevant reports were found, a NICE evidence summary published in 2018 and one HTA report from CADTH published in 2016. The NICE evidence summary included relevant RCT and non-RCT on the topic of implantable cardiac monitor. The NICE evidence summary included search update as in February 2018, was used as cross-reference source. The CADTH report in 2016 was used as an example for our search strategy and an inspiration to our model structure. The result of the CADTH report is summarized in chapter 5.

Chapter 3 Key Stakeholders Perspectives

Summary

During the period of June to December 2018, we conducted phone and email interviews with 34 key stakeholders. . Personnel from all BC health authorities were interviewed. The participants included individuals with experience or knowledge of ICM and professionals working in the field of stroke prevention and management, and cardiology.

All stakeholders agree unanimously that this technology should be provided a an insured service in BC; however, it was discussed that in order to ensure the success of this technology, proper MSP codes and payment schedules must be created to support the long-term follow-up and remote care required for ICMs. It was agreed upon by all stakeholders that the use of ICM would provide an enormous potential for prevention of recurrent stroke and death in patients who have already experienced an occurrence of Cryptogenic Stroke.

3.1 Objective

The objectives of the stakeholder engagement were to:

1. Understand the BC experience with ICM implants/insertions for patients with an occurrence of Cryptogenic Stroke
2. Understand the burden of Cryptogenic Stroke in BC
3. Understand the patterns of care and capacity in BC for the management of care for patients with an occurrence of a Cryptogenic stroke, and the clinical pathway used to aid diagnosis

3.2 Methods

During the period of June to December 2018, we conducted phone and email interviews with 35 key stakeholders:

Key stakeholders were recruited through referral and snowball sampling, having been identified as having knowledge about available ICM technologies, and being qualified to answer the questions related to the ICM procedure, effectiveness of the technology, and the current clinical pathway for patients with an occurrence of Cryptogenic Stroke. Personnel from all BC health authorities were interviewed. The participants included individuals with experience or knowledge of ICM and professionals working in the field of stroke prevention and management, and cardiology.

Feedback was summarized, aggregated, and anonymized so that no personally identifiable information was included.

A semi-structured interview guide was developed for the interviews, whereby different questions were identified as appropriate for the specific role of each stakeholder. This guide evolved as questions were refined to reflect what had been learned from previous interviews.

All completed interviews were imported into software (NVivo, QSR International, version 11) for aggregate qualitative analysis. Interviews were coded according to the interview guide to derive common themes and to summarize findings.

3.3 Findings

During the time period of June to December 2018, we conducted phone and email interviews with 35 key stakeholders:

- 15 cardiologists, electrophysiologists, and stroke neurologists
- 11 HCP specializing in follow-up care for an ICM or ELR
    - 6 cardiology technicians
    - 3 nurses working in the device clinic
    - 2 device clinic supervisors
- 5 provincial and health authority stakeholders

- 1 Infection Control Practitioner
- 3 manufacturer representatives (Medtronic, Abbott, and Biotronik)

Sampling incorporated stakeholder perspectives from both rural and urban centres, integrating the perspectives of higher level managers, physicians focusing in this area, technologists providing one-on-one care to patients, and the manufacturers of ICMs. Personnel interviewed included individuals from all BC health authorities.

3.3.1 Access to treatment/ Clinical Pathway

All Stakeholders agreed that the current access to ICM implants/insertions in the province are not equitable for patients, as there is no provincial coverage for both the cost of purchasing the device, as well as the physician and technical fees required for the management of care of patients with an ICM, requiring continuous follow-up in the three year period from receiving the ICM, similar to remote monitoring.

Currently, the ICM is funded through the global pacemaker budget, which is stated to not be feasible in the long-term as the need for ICM insertions increase, given that the budget cannot absorb the costs of this additional testing. In addition, it has been discussed by physicians, that some physicians may feel less incentivized to follow-up a patient with an ICM implant as there is limited funding under the MSP fee code reimbursement for long-term follow-up. Physicians at present are utilizing the MSP fee codes set out for a pacemaker procedure, which is similar enough in nature; however, the use of this fee code does not take into account frequent follow-up and chart review for patients who have consistently (often monthly) reports from the automatic transmission enabled by the ICM remote capabilities.

Within the current system, ICMs are typically offered to asymptomatic patients who have had an occurrence of a Cryptogenic Stroke; and who have not been diagnosed via the use of other diagnostic devices such as a 24/hr Holter monitor, 2-week event monitor, or extended 30-day external loop recorders. However, it has been discussed that the use of a 24 hour Holter monitor and a 2-week event monitor bear very little clinical significance, as these tests are often inconclusive and do not have the capability to detect symptoms due to a) lack of clinical clarity in the data recorded, and b) limitations of recording for a short-time period, which does not provide enough time to capture symptoms for a patient who may be asymptomatic and experiencing infrequent episodes. More so, it was discussed that even without considering the low clinical efficacy of these two devices, in fact health authorities have very limited access to these technologies, often having to enlist patient in waiting lists for a period of 2-3 months.

In respect to the difficulties in procuring other diagnostic devices, and even if obtained, the lack of clinical confidence for the above mentioned devices, many physicians have changed the clinical pathway to immediately order an ICM for patients with a high clinical acuity and risk factors, which can secure appropriate follow-up care both in a timely fashion (currently there is a 1-2 week waiting period), as well a high confidence in the clinical data recorded by the ICM.

However, it was discussed by some physicians, both electrophysiologist and stroke neurologists, that although they understand the rationale behind this decision (considering the current lack of access and availability of a 24 hour Holter monitors and 2-weeke event monitors), it is not financially and clinically responsible to offer an ICM to patients as the first diagnostic option, given the high cost of the ICM for the public healthcare system. Instead, some physicians have discussed the use of 30-day external mentoring devices, namely a device called the Spiderflash-T, which are better suited as the first line of therapy (by prevention), as the Spiderflash-T device is believed to have: a) a much lower purchase cost as compared to the ICM, b) provide the same clinical clarity for data recorded as the ICM, c) is less invasive than an ICM as it is not implanted/inserted, and d) can be used for patients who are believed to be symptomatic enough to be caught in a 30-day window, so that the number of patients finally refereed to an ICM will be drastically lower; which in turn, leads to increased cost-savings for the system.

It should be noted that some physicians believe that ICM should be offered as the first line of therapy for some patients who may have shown clinical indications to receive an ICM directly, given the urgency of their need for the device, and how often they are thought to be experiencing episodes (low likelihood that they would not be captured in the 30-day window). However, other physicians inherently disagree with this statement and believe that extended loop recorders must be used as the first line of therapy for all patients before qualifying for an ICM.

3.3.2 How many providers will be using the technology?

While the focus of this HTA is in regards to the use of ICM in patients with an occurrence of Cryptogenic Stroke, it was discussed by many physicians that the scope of use for ICM is expanding to provide long-term cardiac monitoring for a range of underlying conditions. Therefore, in consideration of the high prevalence of chronic cardiac conditions, this technology is thought is expected to be widely used in all health authorities throughout the province.

3.3.3 Cost for patients

There are no considerable costs for the patient. Recovery time for the ICM procedure is approximately 1-2 weeks, with patients returning to usual activities within 2-3 days. Patients will expect 3-4 follow-up appointments within the year from the time of receiving an ICM.

3.3.4 Perspectives on patient experiences (reported by clinicians or service providers)

Stakeholder shave described patients who have had an occurrence of Cryptogenic stroke to display a high level of anxiety, as healthcare providers cannot offer an explanation of the possible cause of this episode; and therefore, have stated that patients are mostly quite eager to receive an ICM in hopes of confirming a diagnosis leading to specific therapeutic action (receiving a pacemaker, or medications that reduce the risk of recurrent stroke).

3.3.1 Technology potential for improving health in marginalized and disadvantaged populations

It has been discussed by stakeholder that the remote monitoring feature of ICM can potentially help patients from remote communities to gain access to specialist service without traveling long distances. In addition, given the increasingly simple procedure required for an

ICM insertion (Medtronic Reveal LINQ), it is believe that ICM can be available in a decentralized manner, in which all hospitals will have the ability to provide ICM within their own centres. However, if AF is diagnosed, patients without local access to specialist services will need to make several visits to their specialist for initiation of treatment, as well 3-4 yearly follow-up appointments to review data measured by the ICM.

3.3.2 Non-health benefits (autonomy, convenience, comfort and confidence)

As mentioned previously, the use of ICM offers considerable insurance to patients who are at risk of a recurrent stroke, and thus, in receiving an ICM, experience a significant sense of relief and control over their health and life, and optimistic in being able to avoid the detrimental effects of recurrent stroke or other adverse events.

3.3.3 Perspectives on providing the technology as an insured service in BC

All stakeholders agree unanimously that this technology should be provided a an insured service in BC; however, it was discussed that in order to ensure the success of this technology, proper MSP codes and payment schedules must be created to support the long-term follow-up and remote care required from specialist, and more so the device clinic cardiac technologist who are having to review monthly updates from the automatic transmission of data form the ICM, and that separate provincial funding (apart from pacemakers) is provided for the use of ICM given the cost of this technology.

3.3.4 Description of the costs of technology and other costs

It was discussed that while the manufacturer (main manufacturer being Medtronic), provides both training and help in the set-up of ICM capabilities within hospitals, considerable time and resources must be invested in training the technologist in how the ICM operates, how to educate the patients, and how to read the automatic transmission of reports receiving from ICM (how to decipher an “actual event” from those triggered by the automatic function or the patient themselves), and also, in setting up the Carelink network to gain access to automatic transmission, and how to review the alerts that are transmitted automatically.

3.3.5 Sector cost considerations

Given the existing provincial systems in place for the use of pacemakers within all urban and rural centers in BC, stakeholders do not anticipate a major sector shift for the organization and planning of how to make ICMs available provincially; but rather, they are focused on the absolute need for a sector shift in the MSP reimbursement funding for remote long-term monitoring for both the physician, and more so the technologist who will arguably experience a dramatic increase in workload in increased use of ICMs provincially (given that with the automatic transmission of data, this data must be reviewed by both technologist and physicians on a monthly basis).

3.3.6 Environmental impact

The manufacturer (Medtronic) has taken responsibility for the disposal of ICMs upon explantation, and the hospital / device clinics will follow similar procedures to disposal of any waste in a pacemaker procedure. The environmental impact would be similar to other cardiac devices like pacemakers, and their volume would depend on the size of the eligible population by the policy implementation.

3.3.7 Capacity for providing the technology in BC and other implementation considerations

As previously discussed, given the extensive existing network for pacemaker insertions in BC, providing ICM in a decentralized manner is not considered to be difficult; however, it is in the follow-up and review of the automatic transmissions that the question of specialty training to review the automatic reports (both by trained technologist and an electrophysiologist) should be considered. More so, as mentioned previously, the biggest barrier for stakeholders have been the lack of funding to provide ICM (given that the current funding is derived from the global pacemaker budget), and the follow-up reimbursement fee codes for physicians and technicians. In addition to this, currently, there is an internal disagreement between physicians advocating for the use of ICM, to either be used as the first-line of therapy (prevention as therapy) by some stakeholders, while other physicians agree to the use of the ICM, but only as a second-line therapeutic tool after having first received a 30-day external monitor. In implementing this technology, the current clinical pathway and indications may wish to be reviewed.

Moreover, although training of technologist to both set up the ICM, educate the patients, and review the automatic transmissions are not described to be very difficult, it has been stated to be rather time consuming, and so, resources should be allocated to build this capacity in a decentralized manner (within different device clinics throughout the province).

Lastly, in implementation of the Insertable ICM (Medtronic Reveal LINQ) in office settings (as is the goal for any future implants, given that there are considered to be significant cost savings in avoiding insertable ICM (LINQ) implants in the OR or the Cath lab), infection control considerations will have to be integrated into the costs for providing this technology provincially. It was discussed by an infection control practitioner, that for the functioning of the room, they would expect all the subcutaneous devices be inserted with aseptic technique, and that they would also require infrastructure for hand hygiene and disposal of sharps. As well, the rooms should be cleaned after each procedure to ensure no blood or bodily fluids are left on surfaces, and etc. Please refer to Appendix E Infection Control Requirements for ICM Procedure for an example of specific guidelines used.

3.3.8 Risk for successful implementation (financial, human resource, stakeholders & other)

It was discussed by some stakeholders that in fact the set-up of the Carelink network and programmer (installed at the device clinic to allow automatic transmission of data from the patient to the clinic) to have taken a considerable amount of time (approximately a 1 year period). Given the extensive time required for this set-up, it was described that not all hospitals within the different health authorities have been able to complete this set-up, and so, although receiving an insertable ICM (Medtronic Reveal LINQ), follow-up procedures similar to non-automatic transmission of data must be followed (similar to the Medtronic Reveal XT). Thus, it is crucial that in implementation of this technology, all centers offering the Medtronic Reveal LINQ have the ability to set-up the Carelink network at their own centres, or partner with another centre to take on their patient load for follow-up of automatic transmissions.

More so, it was discussed by some stakeholders that despite receiving the ICM and the MyCareLink patient monitor (used to transmit data to the device clinic), older patients with limited numeracy and computer skills have had a lot of trouble in setting up their patient monitor (it has been reported that some have never even turned on the device when they have been discharged, thus rendering the technology useless). It has also been mentioned that such older patients may also experience difficulty in sending automatic transmissions when they are feeling symptomatic (patient activation ability of the ICM), or in the case of the ICM Medtronic Reveal XT, where automatic transmission is available via use of an app. Therefore, it has been suggested that in implementation of this technology, older patients with difficulty in computer/numeracy skills be offered guidance and aid in setting up their device at home, and reviewing automatic remote monitoring capabilities of the patient-activated component of the ICM.

Furthermore, a major risk discussed was regarding the increased work flow caused by the automatic transmission of the insertable cardiac monitors (Medtronic Reveal LINQ). It was stated by technicians, that with the insertable ICM, not only would technicians (and EPs/ or cardiologists) review and sign off on monthly reports automatically generated by the device, but they would also have to investigate any patient activated occurrences, which have been described to occur on average 4 times a year for each patient (in addition to the monthly reports), and in some cases even more times if the patient does not fully understand the use of the patient-activator. As well, it was discussed that the clinic will also receive automatic alerts if the device has registered an "event" in reference to the specifications by which it has been programmed; however, often times, the technicians describe having to look over this data and filtering through "false events" registered. As can be imagined, despite the wonderful benefits of automatic transmission for patient safety and quality of care, this imposes a major shift in the work plan of technicians, and adds considerable work burden to the device clinic monitoring such patients.

Lastly, another major risk factor was discussed; however, in regards to the extended 30-day loop recorder rather than the ICM. In consideration of the effectiveness of the discussed 30-day extended loop recorder, called the Spiderflash-T, VCH, VIHA and FHA have reported experience with this technology either through research funding/projects, or within clinical practice. While VCH and VIHA have spoken very positively about the ease of use of Spiderflash-T (in regards to its clear recording, ability to yield a confident diagnosis, and simple set-up cesses), FHA has had a negative experience with this technology, [redacted] This was due to restrictions in where the data is required to be stored [redacted]

[redacted] was not permitted by the safety and privacy policies at FHA. Given the above finding, although all interviewees have discussed very positive feedback in regards to the use of Spiderflash-T, FHA has had to initiate a process to look elsewhere for other options that may work within their IT infrastructure, given limitations to absorb ICM costs within their global pacemaker budget, and the price point set out for the ICM devices. Thus, if the purchasing of 30-day external loop recorders are to be considered, an investigation must be launched to look at the feasibility of implementing Spiderflash-T devices provincially, and whether there are any alternatives technologies that can be used instead. Currently, stakeholders have discussed the investigation of other diagnostic devices such as CardioSTAT, which is considered by some stakeholders to be one of the next viable alternatives to Spiderflash-T.

3.3.9 Conclusion

All stakeholders agree unanimously that this technology should be provided as an insured service in BC; however, it was discussed that in order to ensure the success of this technology, proper MSP codes and payment schedules must be created to support the long-term follow-up and remote care required for ICMs. It was agreed upon by all stakeholders that the use of ICM would provide an enormous potential for prevention of recurrent stroke and death in patients who have already experienced an occurrence of Cryptogenic Stroke.

Chapter 4 Patient Experience

Summary

The decision to receive ICM was stated to be a relatively simple decision for patients as the possible benefits of this technology are discussed to significantly higher than possible side-effects or unintended consequences, given the relative simplicity of the ICM procedure and low rates of complications, and the overall risk of a recurring stroke or other adverse events with patients who had previously experienced a Cryptogenic Stroke.

For individuals who had received an insertable ICM, the procedure was described to be a quick, simple, and painless process. Patients described very little wait time in receiving an ICM, with a range of 1 to 2 weeks of wait-time.

4.1 Objective

To gain an understanding of the outcomes important to patients in order to guide the evaluation of the clinical literature and health policy.

This chapter will be divided into 3 subsections:

I. Patient experience from the Literature
II. Patient Experience Specific to BC (PE conducted in BC)
III. Patient Experience report received from manufacturer

Each section will include methods, results, and summary to clarify process of data procurement and findings from each of the 3 methods of data collection stated above.

4.2 Patient experience from literature

A rapid review of qualitative studies was conducted by CADTH on behalf of the HTA Office from the BC Ministry of Health to aid in meeting the overall objectives of this HTA. The methods and results below are a direct excerpt from the CADTH rapid review report. The full report, which includes all in-text references used in the writing below (within the CADTH report) can be found in the *Supplementary Material titled: Cardiac Monitors - Patient Engagement Rapid Review.*

4.2.1 Methods

The CADTH rapid response review described patients' perspectives of and experiences with cardiac monitors for stroke, atrial fibrillation, and heart failure. A limited literature search was conducted on key resources including Medline in Ovid, CINAHL, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limited retrieval to qualitative studies. The search was also limited to English language published between January 1, 2013 and August 17, 2018. Summary of findings

The research question guiding this review was:

- How do patients experience, make decisions around, and live with outpatient cardiac monitors for the diagnosis of stroke, atrial fibrillation, and/or heart failure?

4.2.2 Results

In this section, we describe patients' experiences and perspectives living with and making decisions surrounding cardiac monitors, as represented in the primary literature. This section is grouped under three categories: Information Acquisition, Patient Engagement, and

Usability and Functionality of Cardiac Monitoring Devices. Each of these categories contain multiple themes that identify patients’ perspectives on cardiac monitors and explain how patients navigate through challenges living with and adjusting to cardiac monitoring devices in their daily lives.

Information Acquisition

Information was a common theme embedded in patients’ expressions and experiences of cardiac monitoring. Patients desired more information in general and more information that is timely, accurate, reliable, and relevant to their cardiac condition. Patients also described how the information provided to them by care providers should take into account their unique medical needs and integrate their preferences for care. In this section, two themes are discussed: (1) *uncertainty/lack of information* and (2) *need for more information*.

Uncertainty/lack of information

Patients described regularly experiencing uncertainty in different aspects of the cardiac monitoring process. Some patients felt that they did not have the right type or amount of information to manage their cardiac condition effectively and use their monitoring device accurately.[24,25,28,29,32] This realization, without adequate support from care providers, increased the uncertainty in patients with regards to how to monitor their cardiac condition appropriately.[25,28]

In multiple studies, patients identified different sources and causes of uncertainty. Patients experienced uncertainty from unexplainable symptoms that confused their care providers, discrepancies between what they experienced as symptoms and what is measured by the device, waiting for the monitoring device to collect sufficient data to establish a baseline for their assessment, lack of regular communication with a clinic, and unmet expectations of care.[24,25,27,28,32] For some patients, there was a link between uncertainty in cardiac monitoring and the lack of adequate information about their cardiac condition. These patients reported that they had minimal information about what cardiac monitoring may reveal[28] and how to interpret monitoring data.[27] One patient stated: "…the uncertainty is the worst part. It can eat you up from the inside, because you are in a position where all you can do is wait for an attack or episode to happen before you can get any diagnosis or indication of what is wrong with you.[28] For this patient, uncertainty challenges their identity and personal understanding of their cardiac condition. If uncertainty is not identified, appraised, and managed appropriately, it can affect all aspects of patients' lives, reducing their motivation and commitment to self-monitoring and self-management.

As a way to mitigate uncertainty, patients in three studies expressed a desire for accurate and reliable information about their cardiac condition at an appropriate time and using delivery methods tailored to their circumstances.[25,28,31] These patients suggested that information be provided in a way that acknowledges different learning styles, avoids medical jargon, uses plain language, and explains key terms in educational materials.[25,29]

Need for more information

Patients in multiple studies reported a general need for more information about how to use their cardiac device, treatment options while using a cardiac monitor, and the distinct aspects of the cardiac monitoring process.[25-31] For some patients, the need for information was fueled by the emotional distress they experienced from uncertainty and lack of adequate information.[25] Patients described a need for information regarding device accuracy and reliability;[25] clarity about the purpose of cardiac monitoring devices;[25,28] how to communicate with care providers about their symptoms;[31] how to interpret monitoring data;[29] how to connect with local organizations and groups that support patients who use cardiac monitors;[29] and information about treatment options, medications, and adverse drug reactions.[25,29-31]

Over time, as patients engaged in managing their cardiac condition and using monitoring devices, their information needs evolved.[27] Patients' need for information was motivated by their comfort and satisfaction with the information they have accumulated and the knowledge gaps that remain in understanding their cardiac condition and the device. For some patients, the strong need for more information decreased when they became overwhelmed with the amount of information provided to them.[31] Instead of more information, a collaborative discussion about cardiac monitoring with care providers supported these patients to reflect on and organize the information already acquired, which enhanced the sense of trust and rapport between patient and care provider. For some patients, this may be achieved through affirmation and regular communication with the care provider immediately after experiencing symptoms.[26,28,31,32]

Patient Engagement

Patient engagement in treatment and device decision-making were central topics raised by patients in the included studies. Patients expressed both positive and negative experiences associated with their engagement in health care, which was linked to how they perceived their personal responsibilities in managing their health through monitoring and their relationship with care providers. In this section, the following themes are discussed: *personal responsibilities of self-management,* and *the relationship between patients and their care providers*.

Personal responsibilities of self-management

The start of cardiac self-monitoring presents a change in the day-to-day routine for many patients. For some, this change was so significant that it affected their personal and social identity. Patients recognized that new personal responsibilities will follow the onset of cardiac monitoring. However, patients' response to these responsibilities depended on their daily routine and social location; whereas some patients found these new responsibilities unproblematic and easy to integrate into their lives, other patients experienced higher stress and frustration[26,28,32] associated with an increased burden of using additional technology in daily life.[26] For some patients, new responsibilities were embraced[26,28,29,32] and the device increased their sense of self-efficacy in managing their cardiac health;[27-30] for others, the same responsibilities spurred confusion and concerns about keeping up with these responsibilities in a busy life.[26,28,29,32] Patients with high information needs may need additional support when identifying and adjusting to new responsibilities pertaining to cardiac monitoring.

The responsibilities that patients reported include: constantly monitoring their cardiac data;[27,29] integrating the device into daily routine activities;[27] being informed about their cardiac condition, treatment options, and how to use the device accurately;[30] maintaining comprehensive documentation of their symptom experience and medication history;[28] knowing when to seek professional help; [27] evaluating personal health goals;[29] using past experiences with technology to solve the problems with cardiac monitors;[27] transmitting data from the cardiac monitor to a clinic when symptoms are experienced;[28] calling the clinic to substantiate the device data with their personal experience of symptoms;[27,28] ensuring that the equipment is safe and secure when traveling between places;[28] and mentioning all relevant information to care providers during a medical consultation.[27,28]

The relationship between patient and their care providers

The patient-care provider relationship was central to patients' experiences associated with cardiac self-monitoring. Patients using a cardiac monitoring device reported that they felt more engaged in medical consultations because the device allowed discussions to be focused on monitoring data and tailored to their unique medical needs [27-29] However, some patients found that care providers overemphasized device data in medical consultations,[28] which gave the impression that patients' experiential knowledge living with their cardiac condition and using the device was not relevant to their self-management.[31] These patients expected individualized and tailored care to their unique medical condition that could only be achieved through a co-reflection on both what is felt by the patient and what is detected by the device.[25,27,28]

Care providers' initiative to engage patients in health decision-making was perceived by patients as being positive and motivational.[25,27,31] Collaborative decision-making, in particular, increased patients' feelings of involvement, cooperation, and connection with care providers.[31] Furthermore, continuous communication with care providers and medical staff, either in-person or through the device, was perceived as the focal point of shared decision-making by some patients because it provided ongoing support to acquire a deeper understanding of their cardiac condition and maintain positive self-management behaviours.[27,28] Moreover, useful, relevant, and regular communication with care providers and medical staff contributed to the sense of relief and reassurance that has been commonly reported by patients using cardiac monitors.[25,28,29,31,32]

Some patients expressed a need for more regular communication with the clinic[26,28,29] and between different care providers involved in the management of their cardiac condition and the data collected by a cardiac monitor.[25] Patients reported concerns about their interactions with care providers and medical staff. In general, patients described that they were provided inadequate information from their care provider about their cardiac condition, treatment, and device management.[24-26,28,32] In two studies, patients reported that feedback and advice by their care provider were unclear or inconsistent.[28,32] As a result, patients experienced hopelessness, uncertainty, and feeling unappreciated by their care provider.[28,31,32] In the beginning of their treatment and management, patients expected sympathy and timely feedback from care providers.[28] However, due to a perceived lack of adequate, relevant, and consistent communication, some patients came to no longer expect comfort and patient-centred care. In many cases, this was reported to be due to the lack of time and resources available to the care provider to address patients' personal and social needs.[28] Some patients perceived no news as good news and that care providers will only contact patients if it is absolutely necessary.[27,28] For others, no news increased uncertainty in whether they are using the device correctly or whether care providers are actually monitoring their data. The latter group of patients experienced greater uncertainty in device use and self-management, which lead to disengagement, hopelessness, and despair in self-monitoring.

Usability and Functionality of Cardiac Monitoring Devices

This section describes the perspectives of patients pertaining to the usability and functionality of cardiac monitoring devices. The following themes are discussed: *learning to use cardiac monitoring devices*, *living with cardiac devices, managing the discrepancy between what is felt and detected,* and *perceived benefits and disadvantages of using the device*.

Learning to use cardiac monitoring devices

Four articles discussed patients' experiences with learning to use a cardiac monitoring device.[26,27,29,32] Upon first exposure to the device, patients and family are required to manage different physical components of the device,[28] ensure that it is measuring and transmitting data to the clinic accurately,[27] and integrate the device into daily routine activities.[29] Learning to use the device may take time for some patients and require support from the clinic, family, and friends.[29] Over time, as patients engaged with the technology, they felt more competent and confident with using cardiac devices to monitor their health.[29] One study differentiated between three categories of users based on technological proficiency: 1) novice with limited or no experience using technology; 2) competent with some experience using technology for work or leisure; and 3) expert who guides others to use technology for work or leisure.[29] Although the learning curve may depend on the severity of patients' medical condition and their personal circumstances,[29] technological proficiency and support from family, friends, and the clinic enabled patients to quickly overcome the learning curve and adjust to using the cardiac monitoring device in daily routine.[27]

Living with cardiac devices

Five studies discussed patients' experiences living with cardiac monitoring devices.[24,27-29,32] Patients described that they were using these devices as a form of "intermittent self-assessment" or a method for continuous self-monitoring.[29] Other patients used the device to adopt and maintain healthy behaviours,[29] establish and evaluate exercise and weight loss goals,[27] gauge when they need medical attention,[29] to support their transition into community care,[29] and augment health care decision-making.[27]

Patients derived a sense of safety, relief, reassurance, and confidence from using a cardiac device because of the perception that they are being constantly monitored by their health care team.[28,29] Patients in one article desired for a "double-check" by their care providers to determine whether or not they are using the device correctly; this "double-check" improved patient reassurance and confidence in the cardiac monitoring device.[32] One patient mentioned: "I'm quite happy doing it at home, although I think in the very near future I'll make an appointment with either my GP or practice nurse, to take a reading on site, just to make sure that it's actually performing accurately. I don't believe, for one minute, it's not, but I think a double check would be in order…".[32] This patient, although confident in using the device himself, still desired a double check from his care provider. Other patients were uncertain and concerned about whether their health data was actually being monitored by care providers.[32]

For some patients, uncertainty was reduced from continuous communication and feedback through the device system[25,27-29,31,32] However, patients in three articles expressed a strong need for ongoing support from the clinic and care providers in the form of physical assistance, continuous reminders, and technological guidance.[26,29,32]

In two instances, patients reported using the device less frequently. First, when patients were communicating with their clinic or care provider regularly, either to establish a baseline for their cardiac condition or to re-evaluate their self-management plan, some patients did not fully understand the purpose or benefits of using the device and perceived the monitoring device as redundant.[29] Second, some patients stopped using the device after receiving normal readings on multiple occasions.[25,29] For these patients, using the device was linked to its ability to provide timely, accurate, and useful feedback about their cardiac condition.

Managing the discrepancy between what is felt and what is detected

Each patient understands and appraises their medical condition differently depending on their lived experiences with symptoms, engagement with activities of daily living, and general well-being.[27] However, these experiences may conflict with the device when experiences do not appear to match with the data collected. In two articles, patients expressed concerns about the discrepancies between what they experienced as symptoms and what the device detected as symptoms.[27,28] One article differentiated this discrepancy into three situations: 1) a patient experiences a symptom and the device measures the symptom; 2) a patient experiences a symptom, but the device does not detect it; and 3) the device detects a symptom, but the patient does not experience it.[28]

Consistency between what is felt and what is detected was expressed as an important concern by patients in two articles.[27,28] On the one hand, if there was a consistency between what patients felt and what the device detected, then patients reported positive coping to symptoms.[28] However, inconsistency caused frustration, discouragement, uncertainty, and dissonance about their medical condition.[28]

For some patients, the experience of symptoms was so important to their identity and understanding of cardiac condition that they questioned or ignored the medical advice and feedback from care providers if the advice was not congruent with what they expected or experienced.[27] These patients developed their own normal range of cardiac measures based on their experiential knowledge and used the cardiac monitoring device to only maintain physiological indicators rather than adjust lifestyle behaviours.[27] Other patients understood that any significant change in health is a combination of what is experienced and what is detected by the cardiac device. These patients recommended that all discussions with care providers about device data should combine both personal experience and device data, allowing both the patient and care provider to increase their shared understanding of the patients' unique medical needs and thereby provide tailored feedback to improve their health.[28]

Perceived benefits and disadvantages of using cardiac monitoring devices

In the studies that discussed cardiac monitoring devices, the reported benefits to device use outnumbered the reported disadvantages. The disadvantages that were mentioned by patients were embedded in their negative experiences associated with using technology in general and accessing the health care system. For some patients, the disadvantages to device use decreased and benefits became more salient as patients engaged with the technology over time.[29]

Relief and reassurance were central motivations for patients in all included studies. Patients both sought and derived relief from using a cardiac monitoring device. In some instances, patients described the monitoring device as a "safety net" because it provided them with accurate, reliable, and automatic information to monitor their health.[26,28,29,32] For some patients, reassurance was related to the view that a care provider is monitoring their cardiac condition at a distance.[26,29] These patients perceived self-monitoring as a way to relegate the need to be constantly vigilant about their health to care providers, which improved their quality of life and reduced some of the burdens associated with managing a heart condition.[26] One patient expressed that: "It actually relaxed me to know that I have this [the device], that it would help if something happened…if I had another heart attack they would know about it right away and I would know about it right away too. They could monitor it. That does relax me a lot, knowing that there's something there that's going to help me if I need it."[26] Constant communication with care providers either in-person or through the device system increased feelings of relief and reassurance to use the device because patients felt a stronger connection with their care providers at far distances, communication supported reflection and understanding of the cardiac condition, patients felt that they had up-to-date information about their cardiac condition, and communication increased motivation for establishing healthy lifestyle behaviours.[26-29] This was especially important for patients in rural and remote areas who found that communication through the device in the form of reminder messages to check monitoring data humanized the technology for them.[26,29] Accuracy and reliability of the device was also viewed as central to the functionality of device. If the device was viewed as inaccurate or unreliable, then patients did not perceive it as a safety net.[32]

In terms of using their devices, multiple patients described pacemakers and mobile-health monitoring devices as easy-to-use.[26,29,32] In one study, patients reported no barriers to setup and installation.[26] Although not mentioned in all included studies, patients in two studies agreed that using the device is convenient to them because it reduces the number of appointments they need to attend, avoided unnecessary hospital visits, decreased the traveling time to clinics, and increased freedom and flexibility in monitoring their cardiac condition.[26,32]

4.2.3 Summary of Findings

The onset of cardiac monitor use accompanies many life changes and new personal responsibilities. For some patients, these responsibilities can spur motivation to engage in self-management and health care decision-making. For other patients, new responsibilities can create confusion and uncertainty about how to use their device and communicate with care providers about cardiac self-management. Embedded in these experiences are patients' expressions of uncertainty and the need for more accurate and timely information about the cardiac monitoring process. Although patients participating in the included studies mentioned more positive than negative experiences to using cardiac monitors, negative experiences were described that stem from uncertainty in how to use the device, treatment options while using a cardiac monitor, available community supports, and the perceived accuracy and reliability of cardiac monitors. As patients engaged with cardiac monitors over time, the benefits to using cardiac devices outweighed the disadvantages. Providing information on cardiac self-management and using monitoring devices may support patients' ongoing reflection and understanding of their cardiac condition. Information that is provided in a timely and appropriate manner may motivate patients to engage in their own health care decision-making, which they perceived as a central component to maintaining self-management behaviours. However, some patients experienced barriers to using the device, many of which were due to their health literacy status and technological proficiency. These patients requested additional support either through the system or through in-person to use the device. When such support was provided, patients felt relief, reassurance, and confidence, which enabled them to integrate cardiac monitoring into their daily routine.

4.3 Patient experience specific to BC

4.3.1 Methods

Patient recruitment was initiated via 3 sources: the Patient Voices Network (PVN), which is administered by the BC Patient Safety & Quality Council (BCPSQC) Patient & Public Engagement network, the BC Support Unit newsletter and bulletin, and direct patient engagement requests to specific physicians providing ICMs. The PVN invitation was published on the BCPSQC website for a period of approximately 3 months. However, there was no expressed interest in participating in this patient engagement initiative from any patients collaborating with the PVN network, nor from the BC Support Unit patient network. Therefore, all participants were recruited via direct referral by physicians to patients who had recently received an ICM, and had agreed to partake in our HTA project. Upon referral, patients were contacted by the research coordinator for this event, and provided with the UBC research team's contact information. Upon being contacted, the UBC research team provided patients with a consent form, approved by the University Of British Columbia Board Of Ethics, agreeing to partake in the HTA. Phone interviews were conducted with all patients agreeing to partake in the project.

4.3.2 Participants

Due to a limited number of ICM implants conducted with partnering physicians agreeing to provide us with direct patient referrals, only 3 patient interviews were conducted with patients who have had an occurrence of a Cryptogenic Stroke, 2 of whom were male and 1 female. Of the two male participants, one was 35 years of age, and the other 81 years of age. The female participant was 76 years old.

It should be noted, that due to the small number of participants recruited, the HTA team was regrettably not able to conduct a meaningful gender analysis on the collected qualitative data; however, the authors highly recommend the readers to consider significant gender differences affecting rates of stroke occurrence, and the impact of stroke on women versus men. In example, in the 2018 Stroke Report released by the Heart and Stroke Foundation of Canada, it is described that: "The #1 cause of premature death in women in Canada is heart disease and Stroke, 59% of all deaths from stroke in Canada are women, and that 2/3 of all heart disease and stroke clinical research focuses on men”[44]. Please refer to the *Supplementary material for the full 2018 report from the Heart and Stroke Foundation of Canada, titled Lives disrupted: The impact of stroke on women.*

4.3.3 Summary of Interviews

All conducted interviews were then transferred to the software NVivo for aggregate qualitative analysis. Interviews were coded according to the interview guide, to derive common themes and messages (nodes) stated throughout. Upon coding all interviews under the established nodes, sub-group analysis was conducted to examine difference in gender and age. However, of course, it is recognized that there are major limitations in the interpretations of findings from this sample, given the excessively small number of patients interviewed, and the existence of sampling bias for direct referral to patients agreeing to be interviewed. The purpose of these interviews is to gain an understanding of the BC patient experience, and although limited in its comprehensiveness, can still provide useful insights for the evaluation the technology under consideration.

4.3.3.1 Decision to receive ICM

The decision to receive ICM was stated to be a relatively simple decision for patients, as the possible benefits of this technology are discussed to be significantly higher than possible side-effects or unintended consequences, given the relative simplicity of the ICM procedure and low rates of complications, and the overall risk of a recurring stroke or other adverse events with patients who had previously experienced a Cryptogenic Stroke.

4.3.3.2 Experience with ICM

Patients generally stated very positive feelings about their experience with an ICM, and discussed that it was actually a great relief to receive the ICM. By receiving an ICM, patients felt a sense of comfort and protection knowing that they were monitored, and described a decreased mental burden in wondering why they had experienced a Cryptogenic Stroke, and whether they would be likely to experience another episode, “It’s amazing how you know that at all times, no matter what you are doing, they are looking at your heart to see how it’s doing in different situations, it’s really a relief so you can prevent another stroke or something worse”.

Insertable ICM

For individuals who had received an insertable ICM, the procedure was described to be a quick, simple, and painless process. Patients described very little wait time in receiving an ICM, with a range of 1 to 2 weeks of wait-time. It was mentioned that the patients were in fact rather surprised that the procedure was done in an “ordinary” room, and the general ease of the procedure, “We were in and out, it was very fast”. Patients stated that they felt minor discomfort for a week after the procedure, “it was more a throbbing pain that was only a 2 out of 10, then kind of like a soreness”, after which time they hardly felt the ICM at all. In fact, they found that the aesthetic appearance of the ICM was much better than they had previously envisioned, due to the small size of the device. Patients reported no problems with exercise, or any other activities with the device.

Implantable ICM

For the female participant who had received an implantable device, it was mentioned that due to the larger size of the device in comparison to the patient's smaller physical figure, in fact the procedure was “extremely painful”. It was stated that the device was implanted in an operating room and was in general an uncomfortable experience, followed by a 2-week recovery period in which time the incision was rather painful. However, it was mentioned that approximately after 3-4 weeks of recovery, the patient could hardly feel the device at all. The only discomfort from this point forward was in an instance where the patient may have been engaging in chest muscle exercises. This patient stated that the explantation procedure was much more tolerable, driven mainly by the belief that a more adequate dose of local anesthesia was used.

4.3.3.3 Follow-up care for ICM

Patients described different experiences with receiving the instructions to allow them to automatically transmit their data to the device clinic. While one patient described receiving some education about the device at the time of their implant, the other patients described receiving the information for how to set up the automatic transmission function about a week after their procedure date. These patients stated that any additional information was passed along during a follow-up appointment at the device clinic, to first check their incision for rate of recovery and any infections, and then to explain how to set up their automatic transmission from home.

For the younger patient, it was described that this set-up was extremely easy with very clear instructions; however, for an older patient with admittedly limited computer skills, they described that they were rather confused about how to set up the device. It was mentioned that at the device clinic, not a lot of information was given regarding how to properly set up the device at home, and instead were referred to a video from the manufacturer guiding the steps to how to set up the device. It was also mentioned that if the patient's children had not been there to set up the device, it would have been very difficult to set up the automatic function to transmit the data.

For one patient, it was described that only after 7 days after receiving the insertable ICM (Medtronic Reveal LINQ), they had been successfully diagnosed. The patient was very content regarding this finding, and was increasingly impressed with the time to diagnosis; however, it was mentioned by the patent that, "the diagnosis was so fast that I got a pacemaker even before the scar from the ICM had time to heal".

4.3.4 Conclusion

The decision to receive ICM was stated to be a relatively simple decision for patients, as the possible benefits of this technology are discussed to significantly higher than possible side-effects or unintended consequences, given the relative simplicity of the ICM procedure and low rates of complications.

For individuals who had received an insertable ICM, the procedure was described to be a quick, simple, and painless process. Patients described very little wait time in receiving an ICM, with a range of 1 to 2 weeks of wait-time.

Patients generally stated very positive feelings about their experience with an ICM. By receiving an ICM, patients felt a sense of comfort and protection knowing that they were monitored, and described a decreased mental burden in wondering why they had experienced a Cryptogenic Stroke, and whether they would be likely to experience another episode.

4.4 Patient Experience Report received from manufacturer (Medtronic)

Given the limited number of participants recruited for patients with direct experience with an ICM implant/insertion in BC, Medtronic Company has agreed to share their own internal report for the use of ICMs in the Canadian context, and the patient experience with this technology. While this report is in fact very useful in understanding the patient experience, the *authors must warn the readers that they are not aware of the methods used to create this document, and as well, the existence of conflicts of interests within the report findings.*

The methods and results below are a direct excerpt from the report received by the nufacturer. [redacted]

4.4.1 Methods:

[redacted].

4.4.2 Results:

[redacted]

[redacted].

[redacted]

[redacted]

4.4.3 Summary of findings

[redacted]

[redacted]

Chapter 5 Assessment of Evidence

Summary

Two RCTs were included in this clinical effectiveness analysis related to diagnostic strategy 4 and 5. EMBRACE was an RCT with 572 cryptogenic stroke patients randomized to receive ELR or one more round of 24-hour Holter. The primary outcome, after a 30-day monitoring period, 16.1% patients in the ELR arm had an AF episode lasting longer than 30 seconds as compared with 3.2% in the control arm. EMBRACE had high risk of performance bias, detection bias and reporting bias.

CRYSTAL-AF was an RCT with 441 cryptogenic stroke patients comparing an implantable ICM (ICM arm) to the standard of care (control arm). In total, 221 patients were randomized to ICM arm and 220 patients were randomized to control arm. For the primary outcome, patients who received ICM had a significantly higher detection rate of AF during the first 6 months of monitoring, the hazard ratio of detection was 6.4 [95% CI, 1.9-21.7, p<0.001]. This result was the same as the CADTH HTA report. Patients in the ICM arm had a consistently higher detection rate of AF in the subsequent period since the first 6 months up to 36 months when compared with the control arm. At 36 months, 30% of patients in ICM arm were estimated to have AF detection compared with 3% in control arm. However, the attrition rate was high after the first 6 months in the RCT. At 36 months, only 10% of patients remained in the RCT, which created a large difference between the estimated detection rate and the observed rate at 36 months. CRYSTAL-AF was judged as high risk of bias in performance bias, detection bias, and attrition bias. The below-recommended level of monitoring in the control arm could also lead to a greater difference in detection rate between the treatment arms.

The diagnostic yield data from the RCT was heterogeneous in term of method and baseline characteristics therefore could not be combined. The data from CRYSTAL-AF was chosen as input parameter for the economic model because of longer monitoring period and more generalizable to other diagnostic strategies that had no data.

5.1 Objectives

To assess the safety and clinical effectiveness of external loop recorder (ELR), implantable ICM (Imp ICM) and insertable ICM (Ins ICM) alone or in combination as diagnostic strategy, in the detection of atrial fibrillation in patients who recently experienced a cryptogenic stroke or TIA when compared with standard of care.

The diagnostic strategies of interest included:

0. Do not receiving any ELR, Imp ICM or Ins ICM as control arm
1. First receiving an ELR for a month of monitoring and then an Imp ICM in operating room and monitor for up to 36 months
2. First receiving an ELR for a month of monitoring and, then an Ins ICM in a Cath lab and monitor for up to 36 months
3. First receiving an ELR for a month of monitoring and then an Ins ICM in a minimally invasive procedure room in a hospital setting and monitor for up to 36 months
4. Receive an ELR for a month of monitoring only
5. Receive only an Imp ICM in operating room and monitor for up to 36 months
6. Receive only an Ins ICM in a Cath lab and monitor for up to 36 months
7. Receive only an Ins ICM in a minimally invasive procedure room in physician office settings and monitor for up to 36 months

5.2 Methods

5.2.1 Inclusion criteria.

Table 5.1 defines the patient population, inclusion criteria and outcomes of interest.

Table 5.1. Inclusion criteria

Patient Population	Intervention	Appropriate Comparators	Outcomes
Adults who experienced a recent cryptogenic stroke or TIA	ELR, Imp ICM or Ins ICM alone or in any combination of interest	Patient not receiving an ELR, Imp ICM or Ins ICM. But patient may receive a Holter or event recorder.	Clinical outcomes • Proportion of patients diagnosed with AF post stroke or TIA • All-cause mortality • Risk of recurrent stroke • Any adverse events
			Economic outcomes Costs of implementation, quality-adjusted life years (QALYs), out-of-pocket expenses (patients and caregivers), difference in management strategy, productivity, ICER, PSA

Note: AF= atrial fibrillation; ICER= incremental cost effectiveness ratio; OR= operating room; TIA= transient ischemic attack

Study design

For the purposes of this project, we followed the 2011 report on the hierarchy of evidence from the Centre for Evidence-based Medicine at the University of Oxford.[45] We first searched for any systematic review of randomized controlled trials (RCTs) (level 1). If the amount of evidence was deemed insufficient at this level, we searched for randomized trials (level 2). If again the amount of evidence was deemed insufficient at this level, we searched for nonrandomized studies (level 3). Lower levels of evidence were considered hypothesis-generating and determined to be insufficient for policy decision-making.

5.2.2 Exclusion criteria

Non-English-language publications; abstract/conference proceedings; letters and commentaries; quality of life reported without utilities or QALY.

5.2.3 Literature search overview

Initial scoping searches were done in June 2018 using MEDLINE (Ovid) to assess the volume and type of literature relating to the objectives. The scoping search also informed the development of the final search strategies. The search strategies were developed by an information specialist, with input from the reviewers. The strategies were designed to capture generic terms for ischemic stroke, atrial fibrillation, and cardiac implants. Since CADTH published an HTA report with similar research objectives in 2016, we limited our search from 2016 to present. [19] In addition, the NICE evidence summary in 2018 was used as a cross-reference. [46] Published articles were identified in MEDLINE and Embase through Ovid. Search results were imported into Endnote and Microsoft Excel for screening. An update search was performed in January 2019 with the same search strategies. The search is considered up to date as of Jan 21, 2019. The search strategies can be found in (Appendix F).

Relevant articles were identified during screening. Articles retrieved for full-text reading were separated by the type of publication (i.e., systematic reviews, randomized trials, and nonrandomized comparative studies). Economic studies were also sorted out for detailed reading at this point in the process.

5.2.4 Study selection and data extraction

One reviewer screened titles, abstracts, and then full texts following a specified protocol. The study flow was summarized using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

A reviewer extracted all the data for clinical outcomes, while another reviewer extracted all the data from economic analyses. Data were cross-checked for errors by the two reviewers. Any discrepancy was resolved by discussion.

5.2.5 Quality assessment

The systematic reviews and RCTs were critically appraised using an adapted Cochrane checklist for critical appraisal. [47] A risk of bias table for included studies was generated. Nonrandomized studies were critically appraised with the Downs and Black checklist recommended by the Cochrane Collaboration. [48]

5.2.6 Data synthesis

Cochrane Review Manager Software, RevMan 5.3.5, was used to synthesize data for clinical outcomes. [49] Dichotomous outcomes were analyzed by using risk ratio (RR) or odds ratio. When we found a statistically significant RR or odds ratio we also calculated risk difference (RD) and number needed to treat for the outcome (NNT) when possible. The results of economic studies were presented in descriptive tables.

5.2.7 Subgroup analysis

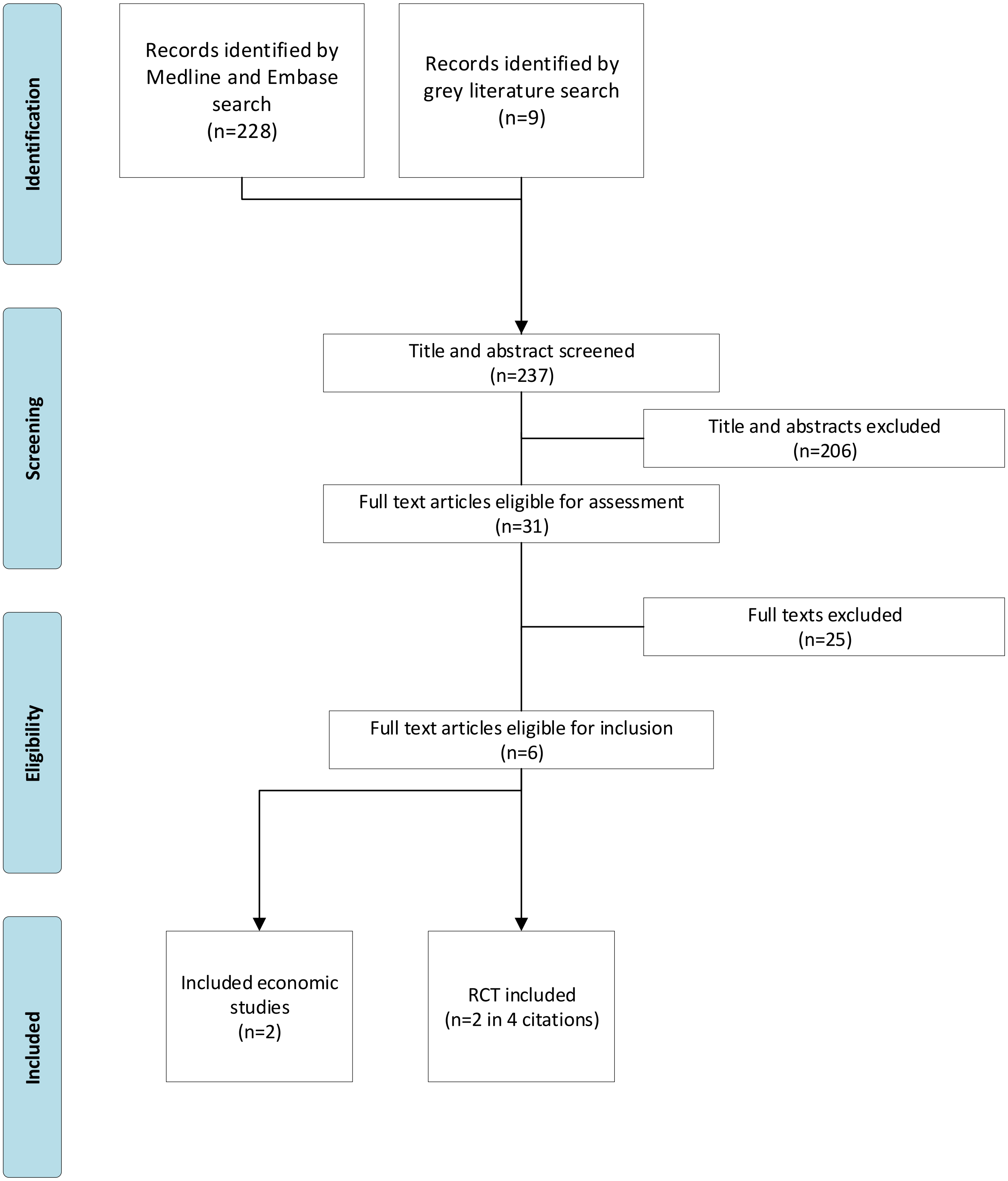
If possible, compare the insertable ICM to an implantable ICM.

5.3 Clinical effectiveness

5.3.1 Search results

MEDLINE and Embase identified 185 citations from 2016 to June 2018. From the 237 citations, 31 was extracted for full-text review. The CADTH report and NICE summary added eight citations for full-text review.[19, 46] Out of the 31 full-text articles, 25 was excluded with reason, two RCTs from four articles, among which three articles related [50-52] to the same RCT (CRYSTAL-AF) were included for clinical review and one article was included for economic review. In addition, the CADTH HTA, found by jurisdictional scan, was also included in the economic literature review.[19] The complete flow diagram can be found below.

Figure 5.1: PRISMA flow diagram of study selection


Identification
Records identified by Medline and Embase search (n=228)
Records identified by grey literature search (n=9)
Screening
Title and abstract screened (n=237)
Title and abstracts excluded (n=206)
Full text articles eligible for assessment (n=31)
Eligibility
Full texts excluded (n=25)
Full text articles eligible for inclusion (n=6)
Included
Included economic studies (n=2)
RCT included (n=2 in 4 citations)

5.3.2 Description of included studies

No study examining combination diagnostic strategies (strategy 1, 2, 3) or Ins ICM (strategy 6 and 7) was identified. One RCT (EMBRACE) comparing ELR alone with standard of care (strategy 4) and one RCT (CRYSTAL-AF) published in three articles comparing Imp ICM alone (strategy 5) with standard of care were included in the clinical review. [23, 50-52]

EMBRACE Trial[23]

EMBRACE was an open label RCT that randomized patients to receive an ELR for 30 days or one additional round of 24-hour Holter monitoring. Patients age 55 or older without atrial fibrillation, and had had an ischemic stroke or TIA of undetermined cause (according to TOAST) within the previous six months were eligible to enroll. The ELR used in the RCT was Braemer ER910AF Cardiac Event Monitor, which had since been discontinued. In total, 287 patients were randomized to ELR and 285 patients randomized to the control arm. The average age of randomized patients was 72.5; on average, patients received their randomized intervention 75 days after the index event. The primary outcome was the detection of one or more episodes of ECG-documented atrial fibrillation or flutter lasting 30 seconds or longer within 90 days follow-up (with 30-days wearing ELR) after randomization.

CRYSTAL-AF Trial[50-52]

CRYSTAL-AF trial was a RCT. Patients age 40 and older who had a stroke or TIA diagnosis within the past 90 days that was cryptogenic in nature were eligible for enrollment. Stroke was classified as cryptogenic when the cause of stroke remained unknown after extensive testing. Extensive testing included 12-lead ECG, 24 hours or more of ECG monitoring, transesophageal echocardiography, screening for thrombophilic states (in patients <55 years of age), and MRA, CTA, or catheter angiography of the head and neck.

Eligible patients were randomized to receive an implantable ICM (ICM arm) or standard care (control arm) in a 1:1 ratio. In total, 221 patients were randomized to ICM arm and 220 patients randomized to control arm. The average age of patients was 61.5. Of the 221 patients randomized to ICM arm, 208 (94.1%) received the device (Reveal XT) on average 38.1 days after the index event. Patients randomized to the control arm underwent an assessment at the discretion of the site investigators. In the first 6 months, 65 patients (29.5%) received 88 conventional ECG, 17 patients (7.7%) received 24-hour Holter monitoring and one patient (0.5%) received an external event monitor. The detection rate of AF at 6-month was the primary outcome of the RCT. Secondary outcomes included the AF detection rate at 12 months, the incidence of recurrent stroke or TIA, change in oral anticoagulation and antiarrhythmic drugs, quality of life, economic and disease burden, the role of patient assistant device in the time of AF diagnosis in subjects implanted with Reveal XT.

Reveal XT was an implantable ICM which required to be placed in an operating room. A newer version of cardiac monitors, insertable ICM, which can be inserted in a minimally invasive procedure room at a doctor’s office was included in the scope of this review. However, no RCT between insertable ICM and standard care was identified. In consultation with our clinical advisor and the manufacturer, both affirmed that the only difference between the implantable ICM model (Reveal XT) and the insertable ICM model (Reveal LINQ) were the insertion procedure and the way the data is transmitted for interpretation. Once the devices are in the patient's body, both function in a similar way recognizing the arrhythmias. Therefore, the clinical advisors deemed reasonable to assume the clinical effectiveness of the insertable ICM to be the same as implantable ICM in the economic model, but keeping the distinction in the procedure and data transmission. For other detail about the RCT, please refer to Appendix G.

5.3.3 Description of excluded studies

A list of citations excluded at full-text screening and the reason for exclusion is located in Appendix H. The main reasons for exclusion were that the citation was being single arm study and review protocol. In the present of RCT, all single-arm studies were excluded from the clinical review as described by the procedure in section 5.2.1.

5.3.4 Quality assessment

EMBRACE Trial[23]

The quality of EMBRACE was assessed using a modified version of the Cochrane risk of bias tool. [53] EMBRACE was an open label RCT. Due to its open label nature, the RCT has a high risk of performance bias and detection bias. The risk can be mitigated by blinded assessment, which was not the case in EMBRACE. EMBRACE has low risk of attrition bias due to low drop-out. For a RCT that only last for 90 days, all-cause mortality and recurrent stroke might not reported. However, the quality of life of patients going under the test should have been reported as the device itself might have caused the quality of life to change. This important patients-centered outcome was not included in the trial design. Therefore, EMBRACE has high risk of reporting bias. EMBRACE have high risk of bias in three of six bias categories.

CRYSTAL-AF Trial[51]

The quality of CRYSTAL-AF was assessed using a modified version of the Cochrane risk of bias tool. [53] Due to the unblinded nature of the RCT, the RCT had a high risk of performance risk and detection risk. It was common for RCT involving a surgical procedure to not be blinded to patients and investigator, however, a blinded assessment committee would help mitigate the risk of detection bias. CRYSTAL-AF trial had low attrition during the first 6 months which was the stopping point of the primary outcome. However, the attrition rate increased after 6 months; which at 36 months, only 10% of patients remained in the RCT. Overall, the RCT was rated high risk in three out of six categories of biases for RCT.

The details of critical appraisal can be found in Appendix I.

5.3.5 The proportion of AF detected

EMBRACE[23]

The primary outcome was the detection of one or more episodes of AF or flutter lasting 30 seconds or longer within 90 days after randomization. The primary outcome was detected in

45 of 280 patients (16.1%) in the intervention group, as compared with 9 of 277 (3.2%) in the control group.

CRYSTAL-AF[51]

The definition of AF according to the RCT was an episode of irregular heart rhythm, without detectable P waves, lasting more than 30 seconds. [51] The proportion of patients with AF detection in each intervention arm by time period can be found in the table below. It is interesting to note that the 30% detection rate was an estimation using the Kaplan-Meier analysis. At 36 months, 42 out of 221 patients was diagnosed with AF. The Kaplan-Meier analysis took into account the AF patients who dropped out and therefore not detected. That was why the estimated detection rate was higher than the observed detection rate. According to this diagnostic yield, four cryptogenic stroke patients would have to be monitored for 3 years to diagnose one AF patient.

Table 5.2: Proportion of randomized patients with AF detection [50, 51]

	ICM arm	Control arm
1 month	3.7%	0.5%
6 months	8.9%	1.4%
12 months	12.4%	2.0%
24 months	21.1%	3.0%
36 months	30.0%	3.0%

The hazard ratio of detection was 6.4 [95% CI, 1.9-21.7, p<0.001] at 6 months.

5.3.6 All-cause mortality

All-cause mortality was not reported in EMBRACE. [23] At 6 months, three patients (1.4%) in the ICM arm and two patients (0.9%) in the control arm died in CRYSTAL-AF. [51]

5.3.7 Recurrent stroke

Recurrent stroke was not reported in EMBRACE. [23] At 12 months, the proportion of patients in CRYSTAL-AF who had a recurrent stroke was 7.1% in the ICM arm and 9.1% in the control arm. The hazard ratio of recurrent stroke was 0.68 [95% CI, 0.35-1.32, p=0.25]. [54] At 36 months, 20/221 (9.0%) in ICM arm and 24/220 (10.9%) in the control arm had a recurrent stroke or TIA. [50]

5.3.8 EQ-5D

Quality of life was not reported in EMBRACE.[23] The mean (SD) EQ-5D value at 12 months was 78.9 (15.6) and 76.3 (16.2) in the ICM arm and control arm respectively (p=0.11) in CRYSTAL-AF. [54]

5.3.9 Withdrawal due to an adverse event and intervention related adverse event

Withdrawal due to adverse event was not reported in EMBRACE.[23]

At 36 months, among the 208 patients who received ICM, five (2.4%) were removed due to infection or pocket erosion. [50, 51] The most common adverse event related to ICM were infections (1.4%), pain (1.4%), and irritation or inflammation (1.9%). [51]

5.3.10 Limitations

The studies demonstrated that a proportion of cryptogenic patients had AF. This suggested that having AF might be associated with higher risk of stroke, but did not indicate a causal relationship. In another word, showing a portion of cryptogenic stroke patients had AF did not suggest that AF caused the strokes. There was also no evidence showing that the detection of AF were linked to reduction of recurrent stroke. The logic between detection of AF and risk of recurrent stroke was linked by the assumption that portion of AF patients would initiate OAC treatment which shown to reduce recurrent stroke. If the patients did not initiate OAC treatment, there would be no reduction of recurrent stroke.

The diagnostic yield was heterogeneous between the two RCTs. The EMBRACE trial identified 16.1% patients in the ELR arm with AF during the first 30-day of monitoring. In comparison, CRYSTAL-AF trial identified 3.7% in the ICM arm during the first 30-days of monitoring. The difference could be due the baseline differences in the RCTs. Patients in EMBRACE were older which could lead to a higher prevalence of AF. In addition, the patients in CRYSTAL-AF received a transesophageal echocardiogram before randomization, this could help identified some of the higher burden patients who already have a blood clot in the wall of the heart chamber. Due to the heterogeneity in method and baseline characteristics, the result from the RCTs cannot be combined. This mean that this assessment solely rely on data from CRYSTAL-AF. Sensitivity analyses explore scenarios of a higher yield or higher burden leading to faster diagnosis in chapter 6 and appendix N to address uncertainty around this data.

EMBRACE

EMBRACE used a model of ELR that had been discontinued. Whether the result could be replicated in other types of ELR was uncertain. The rate of detection for a 30-day monitoring technology was higher than CRYSTAL-AF. This could due to the older population in EMBRACE which could have a higher prevalence of AF and more frequent AF episode. The prevalence of AF was hard to determine due to the shorter period of monitoring.

CRYSTAL-AF

Less than half of the patients randomized to the control arm received some sort of testing in the first 6 months. Therefore, the difference in detection rate between arms might be partly due to the lack of monitoring in the control arm. The majority of patients who received some monitoring in the control arm received conventional ECG, a snapshot of ECG at the moment of test, which was unlikely to capture intermittent AF unless patients were having an episode during the test. This standard of care did not meet the two-week out-patient monitoring recommended by Canadian guideline.[3]

In the CRYSTAL-AF trial, the ICM used was Reveal XT. It was an implantable ICM which required to be implanted in an operation room clean environment. The newer version, which was referred to as insertable ICM, generally served the same purpose but required a simpler procedure for insertion in a minimally invasive room at the doctor’s office.

High attrition rate also contributed to a large difference between the estimated detection rate and actually detection rate after 12 months of follow up. Since the number was an estimate, not an actual observation, this contribution to the level of uncertainty in this outcome.

5.3.11 Diagnostic yield data for the economic model

Since the diagnostic yield is the pivotal input of the economic model, choosing the best quality diagnostic yield data is important. Both EMBRACE and CRYSTAL-AF provided the diagnostic yield.[23, 51] To avoid heterogeneity between RCT affecting the data, data from CRYSTAL-AF was chosen as the input parameter for the diagnostic yield of all the diagnostic strategies according to the amount of monitoring time. There were several reasons in choosing CRYSTAL-AF over EMBRACE as the input parameter:

1. The data from the two RCTs was too heterogeneous to be combined.
2. EMBRACE used a model of ELR that has been discontinued. Whether the result could be generalized to other ELR is not certain.
3. CRYSTAL-AF provided monthly diagnostic yield for 36 months while EMBRACE only provided data for the first month of monitoring.

A sensitivity analysis was included for a higher yield with data from Asithumbi 2018.[55] Asithumbi 2018 is a retrospective review of 234 cryptogenic stroke patients that provided monthly yield data. The first month diagnostic yield in Asithumbi 2018 was similar to EMBRACE.

5.3.12 Overall summary of clinical effectiveness

- Two RCTs were included in this clinical effectiveness analysis. EMBRACE was an RCT with 572 cryptogenic stroke patients randomized to receive ELR or one more round of 24-hour Holter.
    - The primary outcome, after a 30-day monitoring period, 16.1% patients in the ELR arm had an AF episode lasting longer than 30 seconds compared with 3.2% in the control arm.
    - EMBRACE had high risk of performance bias, detection bias and reporting bias.
- CRYSTAL-AF was an RCT with 441 cryptogenic stroke patients comparing an implantable ICM (ICM arm) to the standard of care (control arm). In total, 221 patients were randomized to ICM arm and 220 patients were randomized to control arm.
    - For the primary outcome, patients who received ICM had a significantly higher detection rate of AF during the first 6 months of monitoring, the hazard ratio of detection was 6.4 [95% CI, 1.9-21.7, p<0.001]. This result was the same as the CADTH HTA report. [19]
    - Patients in the ICM arm had a consistently higher detection rate of AF in the subsequent period since the first 6 months up to 36 months when compared with the control arm. At 36 months, 30% of patients in ICM arm were estimated to have AF detection compared with 3% in control arm. However, the attrition rate was high after the first 6 months in the RCT. At 36 months, only 10% of

patients remained in the RCT, which created a large difference between the estimate detection rate and the actual observed rate at 36 months.

    - CRYSTAL-AF was judged as high risk of bias in performance bias, detection bias, and attrition bias. The below-recommended level of monitoring in the control arm could also lead to a greater difference in detection rate between the treatment arms.

- The diagnostic yield data from the RCT was heterogeneous in term of method and baseline characteristics, therefore could not be combined. The data from CRYSTAL-AF was chosen as input parameter for the economic model because of longer monitoring period and more generalizable to other diagnostic strategies that had no data.

5.4 Literature review of cost-effectiveness data

The purpose of the economic literature review is to summarize relevant economic studies that examine the cost-effectiveness of ICM compare with the standard of care.

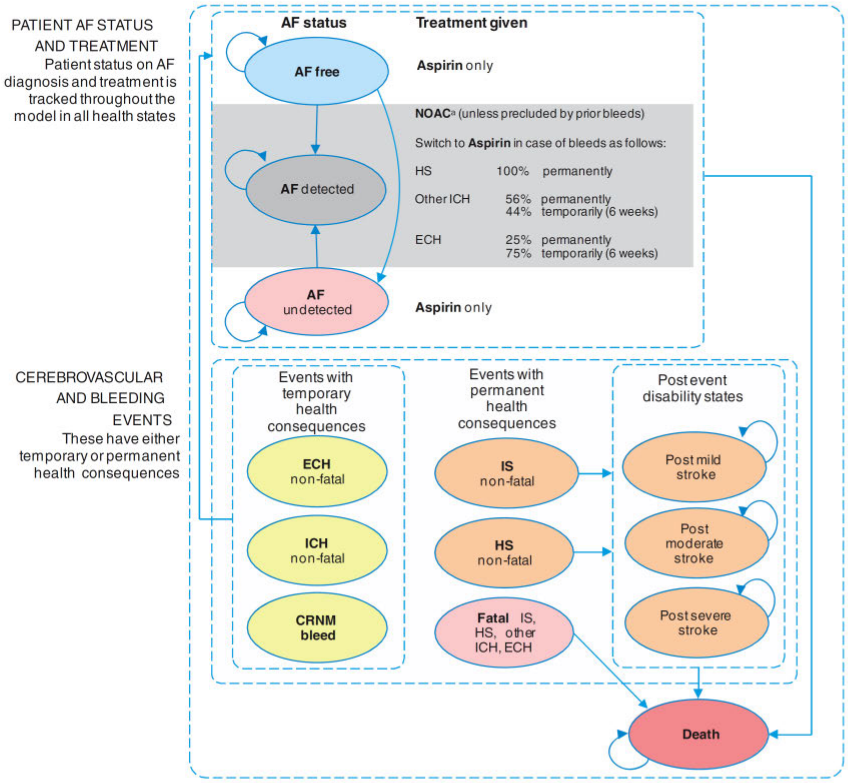
5.4.1 Description of included studies

Our search identified two economic analyses comparing ICM with the standard of care.[19, 56] Detailed about the included studies can be found in Appendix J.

Diamantopoulos 2016 developed a Markov model with 14 states: 3 AF detection states, 9 event states, and death.[56] The model structure can be found in Figure 5.2. The primary purpose of the study was to estimate the cost-effectiveness of ICM compared with standard of care which included conventional ECG, Holter monitoring and external loop recorder over a lifetime horizon in cryptogenic stroke patients. The analysis is presented from the perspective of the UK healthcare system in unknown year British pound. The study was funded by Medtronic, which is making of Reveal XT and Reveal LINQ.

Cost and quality-adjusted life year (QALY) were presented. From the UK perspective, the estimated incremental cost-effective ratio (ICER) was £17,175 per QALY gained when compared with standard of care. The detail result can be found in Appendix K.

Figure 5.2: Diamantopoulos 2016 Markov model[56]

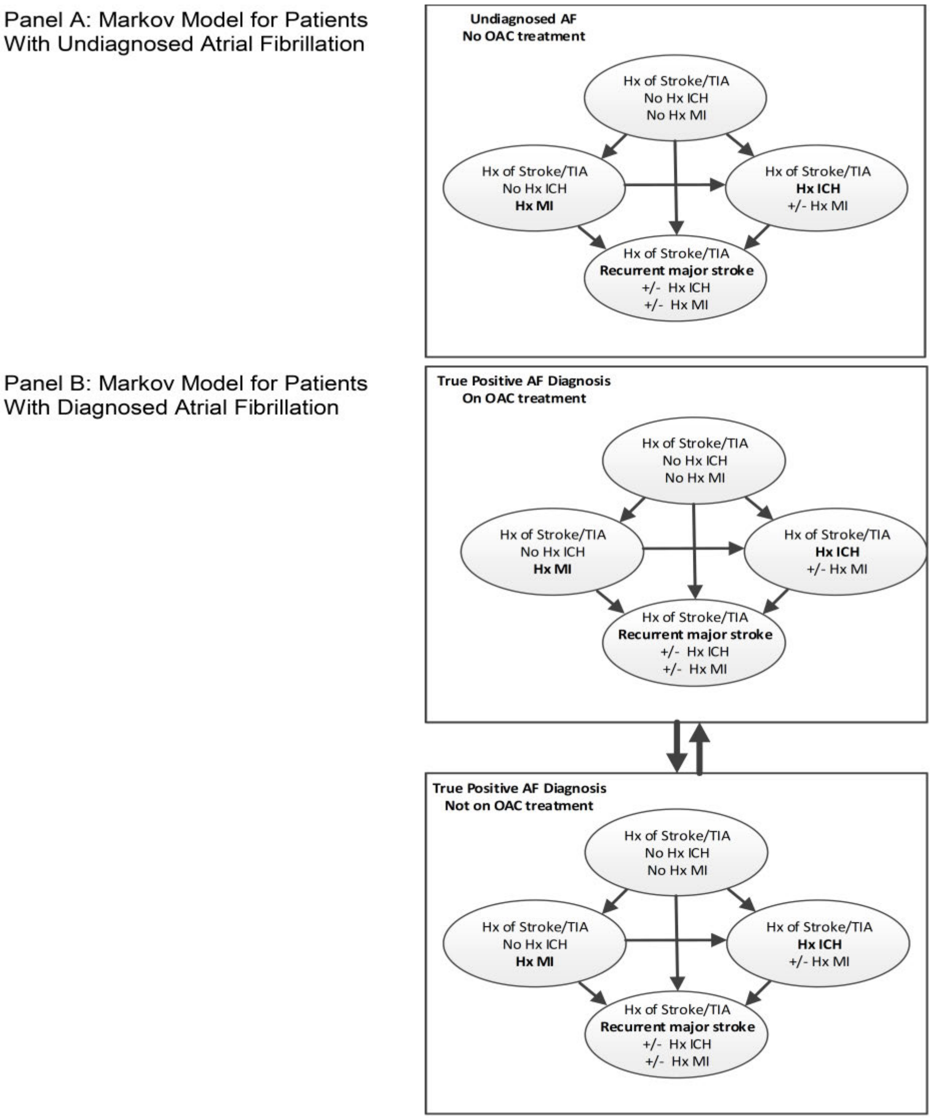

PATIENT AF STATUS AND TREATMENT
Patient status on AF diagnosis and treatment is tracked throughout the model in all health states
AF status
Treatment given
AF free
Aspirin only
NOACa (unless precluded by prior bleeds)
Switch to Aspirin in case of bleeds as follows:
HS 100% permanently
Other ICH 56% permanently 44% temporarily (6 weeks)
ECH 25% permanently 75% temporarily (6 weeks)
AF detected
AF undetected
Aspirin only
CEREBROVASCULAR AND BLEEDING EVENTS
These have either temporary or permanent health consequences
Events with temporary health consequences
ECH non-fatal
ICH non-fatal
CRNM bleed
Events with permanent health consequences
IS non-fatal
HS non-fatal
Fatal IS, HS, other ICH, ECH
Post event disability states
Post mild stroke
Post moderate stroke
Post severe stroke
Death

Note. AF: atrial fibrillation; NOAC: non-vitamin-K oral anticoagulants; HS: hemorrhagic stroke; ICH: intracranial hemorrhage; CRNM: clinically relevant non-major; ECH: extracranial hemorrhage; IS: ischemic stroke.
[a]NOACs are administered in base-case analysis, warfarin is substituted in sensitivity analysis.

CADTH published an HTA report in 2016 examined various cardiac monitoring strategies. One of the strategies they examined comparing ICM with the standard of care with included conventional ECG, Holter monitoring and external loop recorder.[19] The authors developed a Markov model with two panels each contain 4 states. The model diagram can be found in Figure 5.3. The primary purpose of this analysis was to estimate the cost-effectiveness of ICM compared with standard care over a lifetime time horizon in cryptogenic stroke patients from a Canadian perspective.

Cost and QALY were presented. The ICER of ICM compared with standard of care in cryptogenic stroke patients was CAD$414,732/QALY if warfarin was used as OAC, CAD$273,815/QALY if apixaban was used as OAC, CAD$420,062 per QALY gained if dabigatran was used as OAC and CAD$390,578 per QALY gained if rivaroxaban was used as OAC. Detailed results can be found in Appendix K.

Figure 5.3: CADTH Markov model [19]


Panel A: Markov Model for Patients With Undiagnosed Atrial Fibrillation

Panel B: Markov Model for Patients With Diagnosed Atrial Fibrillation

Undiagnosed AF
No OAC treatment
Hx of Stroke/TIA No Hx ICH No Hx MI
Hx of Stroke/TIA No Hx ICH Hx MI
Hx of Stroke/TIA Hx ICH +/- Hx MI
Hx of Stroke/TIA Recurrent major stroke +/- Hx ICH +/- Hx MI
True Positive AF Diagnosis
On OAC treatment
Hx of Stroke/TIA No Hx ICH No Hx MI
Hx of Stroke/TIA No Hx ICH Hx MI
Hx of Stroke/TIA Hx ICH +/- Hx MI
Hx of Stroke/TIA Recurrent major stroke +/- Hx ICH +/- Hx MI
True Positive AF Diagnosis
Not on OAC treatment
Hx of Stroke/TIA No Hx ICH No Hx MI
Hx of Stroke/TIA No Hx ICH Hx MI
Hx of Stroke/TIA Hx ICH +/- Hx MI
Hx of Stroke/TIA Recurrent major stroke +/- Hx ICH +/- Hx MI

AF = atrial fibrillation; Hx = history; ICH = intracerebral hemorrhage; MI = myocardial infarction; OAC = oral anticoagulant; TIA = transient ischemic attack.

5.4.2 Quality of reporting

Quality of reporting using CHEERS was applied to all studies (n=2) that reported CEA (model-based and study-based). [57] Please see Appendix J for detail assessment. Overall, both studies had good reporting. Diamantoupoulos 2016 reported 21 out of 21 items and CADTH report reported 18 out of 21 items.

5.4.3 Overall summary of cost-effectiveness and discussion

Diamantoupoulos 2016 found that using ICM is cost-effective with £17,175 per QALY gained. However, CADTH found that ICM was not cost-effective and none of the ICER was below $100,000 per QALY gained. One of the main difference is the difference in QALY gain. Diamantoupoulos 2016 report a 0.15 QALY gain between the intervention arms, while CADTH reported a 0.015 QALY gain. The difference in QALY gain contributed greatly to the differences in cost per QALY gained.

All of the economic analyses compared the Reveal XT with the standard of care and assumed no waiting period for patients in either arm. Following their example would ignore the issue that the current 2-month waiting period in BC for ICM could have a profound clinical impact as recurrent strokes or death might occur during the waiting period. Eliminating the waiting period could affect the clinical effectiveness of treating cryptogenic stroke patients. The BC economic analysis aims to examine the impact of the currently existing waiting period as well as using different combination of monitoring strategies on the cost-effectiveness of monitoring for AF in cryptogenic stroke patients in BC.

Chapter 6 Economic Analysis for British Columbia

Summary

The goal of cardiac monitoring among patients with a cryptogenic stroke is to identify patients with AF, to then offer them OAC therapy, which can decrease their risk of a recurrent stroke. Therefore, under the assumption that AF diagnostic will lead to treatment decisions, and incorporating the best available evidence into the economic model, offering cardiac monitoring to cryptogenic stroke patients in BC (with any of the strategies considered in this report) compared with no further investigation for AF, using conventional thresholds for cost-effectiveness (up to $50,000 per QALY gained), none of the strategies would be deemed cost-effective as they result in modest gains in survival and quality of life at the population level (focusing on the base-case results and assumptions).

The ICERs ranged from $183,312 per QALY (ELR followed by implantable ICM) to $324,282 per QALY (directly using insertable ICMs placed in procedure rooms in hospital facilities). This is a result of fairly important incremental costs [redacted] *average per patient implanted) and modest gains in survival (0.09 to 0.11 average per patient implanted) and quality of life (0.07 to 0.08 average per patient) over a 20-year time horizon. These results are mainly driven by the assumptions around monitoring frequency and costs post-implant. Strategies which combine ELR with either implantable or insertable ICMs, or using ICMs directly as the first-line device, virtually offer the same benefits in survival and QALY.*

Results were most sensitive to AF prevalence among the cryptogenic stroke population, OAC adherence, length of monitoring post implant, and the assumed physician's/technician's fees for follow-up monitoring. There is a moderate degree of uncertainty in the model. The diagnostic yield was obtained from a previous study comparing implantable device with the ELR. Both implantable and insertable devices have more robust evidence on the effect of cardiac monitoring either used as a first-line device or in combination with ELR. There is considerable uncertainty regarding the fees associated with ICM monitoring post-implant and no data on the frequency of data readings for both ICM types. The frequency of readings will directly impact monitoring costs not only because each reading incurs a fee for service under the current funding system, but also because the frequency of reading impacts the number of patients diagnosed with AF. The choice of insertable devices, albeit clinically more feasible, has higher financial implications associated with the incremental cost of implantation, monitoring fees and expenses related to device explantation. Adoption of implantable or insertable devices further requires a policy dialogue and clinical consideration around funding models for post-monitoring of ICMs.

6.1 Objectives

To evaluate the cost-effectiveness of outpatient cardiac monitoring devices for the detection of Atrial Fibrillation (AF) in discharged patients with a recent history of cryptogenic stroke for the BC population.

6.2 Methods

A Markov model was created for outcomes of testing for AF to estimate the costs and health outcomes, including quality-adjusted life years (QALYs) and clinical outcomes, associated with multiple diagnostic strategies compared with a strategy of no testing over a 20-year time horizon in BC.

6.2.1 Target population and subgroups

The BC population was stratified into three age subgroups (60 years, 70 years, and 80 years and over). To generate population-based results, subgroup-specific results were weighted averaged, with the weights being the BC distribution of stroke patients within each subgroup.

6.2.2 Setting and location

The public healthcare system in BC, covering the entire population of the province, in the reference year of 2017/2018.

6.2.3 Study perspective

The economic analysis was conducted from the publicly funded health system perspective. Out-of-pocket expenses and productivity loss were not included.

6.2.4 Comparators

The diagnostic pathway options involve a non-invasive cardiac monitor as first-line test (i.e.; External Loop Recorder-ELR), followed by Implantable Cardiac Monitor (ICM) for patients who remained undiagnosed (second-line test); or ICMs directly used as first-line test for a number of reasons (i.e.; no ELRs provided in their health authority, patients are virtually asymptomatic, patients live in remote areas with difficulty to travel to access ELRs, etc.). Neither ELRs, nor ICMs are largely funded in BC ([redacted] of the potential eligible population) resulting in different access to those technologies across health authorities (i.e.; some patients have access to ICMs under special cases funded from global budget, some patients have access to ELR and/or ICM under clinical studies, some don't have access to either one, etc.). All other workup for cardioembolic stroke (i.e., in hospital, 24h Holter) were assumed to be done prior to the decision problem. Therefore, this model only included either ELR or ICM alone as first-line tests, or a combination of both technologies compared to no further testing, allowing for investment or disinvestment considerations to be made in the context of BC.

In this study, another relevant aspect for key stakeholders is the type of facility where the ICM devices are implanted, which affect wait times for the technologies (and consequently the expected effectiveness of each technology in terms of AF detection and treatment) and adverse events while waiting to receive the diagnostic device. Therefore, three alternatives of ICMs were included: i) Implantable ICMs placed in hospital facilities (Imp ICM), ii) Insertable ICMs placed in procedure rooms in hospital facilities (Ins ICM proc. room in hospital), and iii) Insertable ICMs placed in procedure rooms in the physician’s office (Ins ICM proc. room in office) and adhering to aseptic procedures. Altogether, a combination of seven diagnostic strategies were compared with no further testing, as follows:

0. No testing (standard comparator)
1. ELR followed by Imp ICM
2. ELR followed by Ins ICM placed in procedure room in hospital settings
3. ELR followed by Ins ICM placed in procedure room in physicians’ office settings
4. ELR only (i.e., ELR followed by no further testing)
5. Imp ICM only (i.e., Imp ICM followed by no further testing)
6. Ins ICM placed in procedure room in hospital settings only (i.e., Ins ICM followed by no further testing)
7. Ins ICM placed in procedure room in physicians’ office settings only (i.e., Ins ICM followed by no further testing)

For insertable ICMs, according to the stakeholder’s interviews, the most sensible policy change would be to incorporate this technology with their insertion being performed exclusively in the doctor’s office. This way the health system could free up resources in the hospital facilities (OR rooms, procedure rooms) as these new devices do not require to be inserted in those facility types, and decrease wait times. Therefore, one of the strategies (strategy 7) assumed 100% of the insertable ICMs are placed in the doctor’s office. However, a strategy mimicking the current pattern of utilization (strategy 6) is also included and assumed they are placed 100% in procedure rooms. According to the ICM registry, no insertable ICMs in the cryptogenic stroke population has historically been placed in Cath Labs and therefore, this option was not included.

6.2.5 Time horizon

The evidence indicates that the mean life expectancy for patients with cryptogenic stroke at 70 years of age is 11.4.[4] Therefore, a 20-year time horizon was used in the base-case analysis. Additionally, a 10-year time horizon was investigated in the sensitivity analyses.

6.2.6 Discount rate

Consistent with CADTH guidelines, a discount rate of 1.5% was applied to both costs and outcomes. [58] Alternative values of 0% and 3% were explored in sensitivity analyses.

6.2.7 Currency, price date, and conversion

All costs were inflated to 2018 Canadian dollars using the annual health and personal care Consumer Price Index for BC [59].

6.2.8 Choice of health outcomes

The primary outcome of interest was quality-adjusted life years (QALY), which captures both the length and quality of life associated with different outcomes during cardiac monitoring for AF. Secondary outcomes of interest include life-years gained, number of adverse events (AE), and device-related wait times. These outcomes were included based on the perceived importance to patients and relevance to the health care system.

Post cryptogenic stroke patients can experience AE related to the stroke prevention therapies (or the lack of) such as recurrent stroke (minor, moderate or severe), myocardial infarction (MI) and intra-cranial hemorrhage (ICH). These AE are relevant for this technology assessment because their rates are affected by the treatment decisions made based on the diagnosis of AF, which in turn is affected by whether the patients undergo any of the included diagnostic strategies, and the respective diagnostic yield and wait times of the different diagnostic strategies.

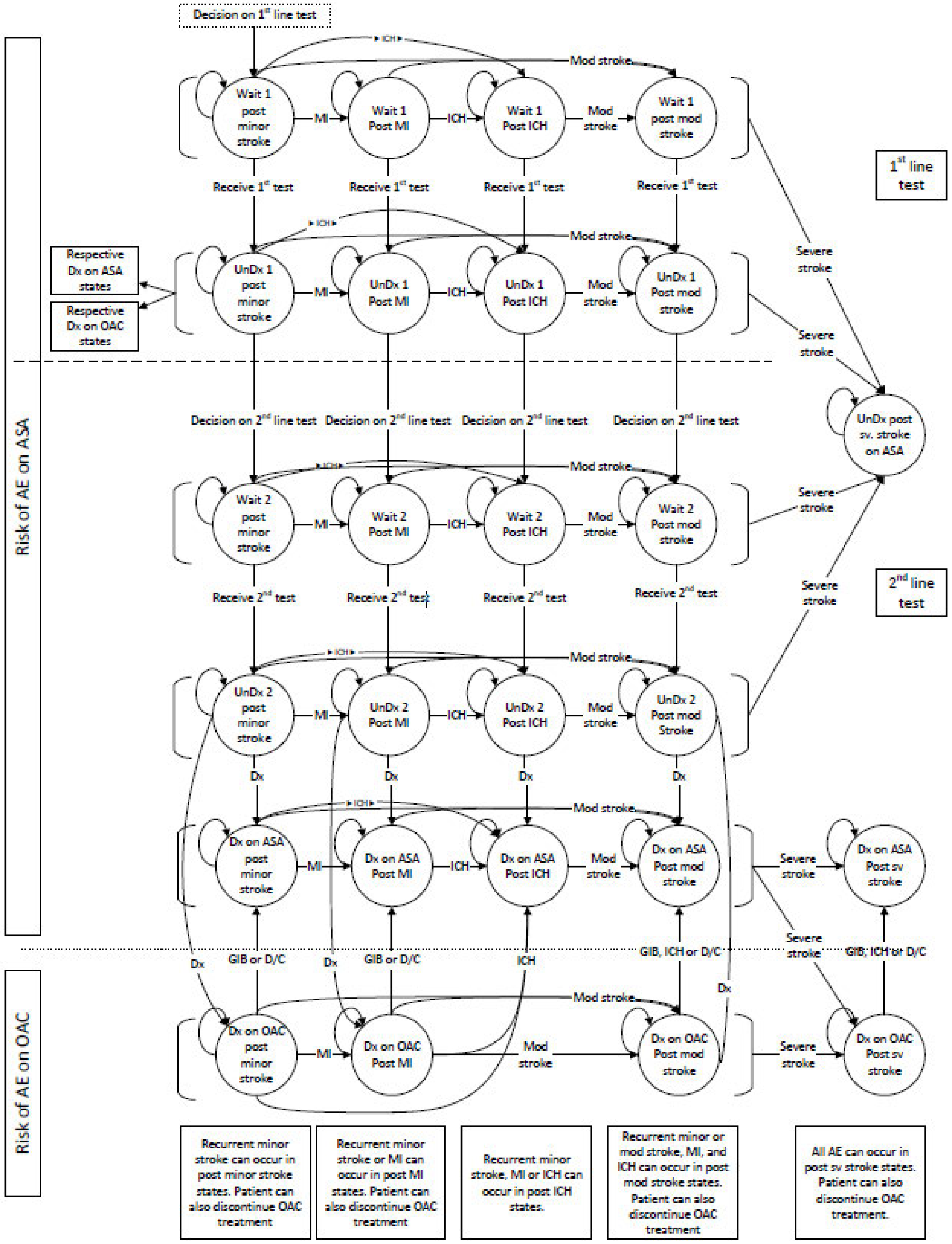
6.2.9 Model structure

To date, previous economic models have evaluated ICM devices as a first-line test strategy (compared with a strategy of no testing) in discharged patients with a recent history of stroke or TIA. In consultation with clinical experts for this project (BC-based cardiologist and neurologist), we learned about the sequential testing and ethical concerns about choosing invasive strategies as a first-line test. In our model, patients undergo a first-line test (except in the comparator arm where there is no test), and, if ELR was the chosen first-line test, a considerable number of patients (those who remained undiagnosed) transition to receive a second-line test. Those who had ICMs chosen as the first-line test do not undergo to a second-line test, but remain monitored up to an AF diagnosis or until the end on the ICM battery life.

In the clinical practice, the choice of first- and second-line tests are affected by the wait-times, which are driven by delays in booking hospital facilities (operation room, Cath Lab, procedure room) limited availability of the technologies, and provider's preferences. The sequential testing and wait-times were not factored into the previous economic analyses. Therefore, a new state-transition Markov model (developed in TreeAge PRO 2018) for sequential testing comparing multiple options was built.

Figure 6.1 provides the overall structure of the Markov model, and each circle in the model represents a Markov state. The model included 42 states (of which 8 are tunnel states). The model represents wait states for the first- and second-line devices, transition from undiagnosed to diagnosed condition, types of stroke prevention therapy the patients may be receiving (acetylsalicylic acid (ASA) to represent antiplatelet therapy or oral anticoagulant-OAC) before or after and AF diagnosis, AE related to the stroke prevention therapy and/or underlying AF condition, and their respectively mortality. The cycle length was biweekly.

Figure 6.1 Markov model structure and health states


Decision on 1st line test
ICH
Mod stroke
Wait 1 post minor stroke
MI
Wait 1 Post MI
ICH
Wait 1 Post ICH
Mod stroke
Wait 1 post mod stroke
Receive 1st test
Receive 1st test
Receive 1st test
Receive 1st test
1st line test
ICH
Mod stroke
Respective Dx on ASA states
Respective Dx on OAC states
UnDx 1 post minor stroke
MI
UnDx 1 Post MI
ICH
UnDx 1 Post ICH
Mod stroke
UnDx 1 Post mod stroke
Severe stroke
Severe stroke
Risk of AE on ASA
Decision on 2nd line test
Decision on 2nd line test
Decision on 2nd line test
Decision on 2nd line test
UnDx post sv. stroke on ASA
ICH
Mod stroke
Wait 2 post minor stroke
MI
Wait 2 Post MI
ICH
Wait 2 Post ICH
Mod stroke
Wait 2 Post mod stroke
Severe stroke
Receive 2nd test
Receive 2nd test
Receive 2nd test
Receive 2nd test
Severe stroke
2nd line test
ICH
Mod stroke
UnDx 2 post minor stroke
MI
UnDx 2 Post MI
ICH
UnDx 2 Post ICH
Mod stroke
UnDx 2 Post mod Stroke
Dx
Dx
Dx
Dx
ICH
Mod stroke
Dx on ASA post minor stroke
MI
Dx on ASA Post MI
ICH
Dx on ASA Post ICH
Mod stroke
Dx on ASA Post mod stroke
Severe stroke
Dx on ASA Post sv stroke
Dx
GIB or D/C
Dx
GIB or D/C
ICH
GIB, ICH or D/C
Severe stroke
GIB, ICH or D/C
Dx
Mod stroke
Risk of AE on OAC
Dx on OAC post minor stroke
MI
Dx on OAC Post MI
Mod stroke
Dx on OAC Post mod stroke
Severe stroke
Dx on OAC Post sv stroke

Recurrent minor stroke can occur in post minor stroke states. Patient can also discontinue OAC treatment

Recurrent minor stroke or MI can occur in post MI states. Patient can also discontinue OAC treatment

Recurrent minor stroke, MI or ICH can occur in post ICH states.

Recurrent minor or mod stroke, MI, and ICH can occur in post mod stroke states. Patient can also discontinue OAC treatment

All AE can occur in post sv stroke states. Patient can also discontinue OAC treatment.

Note: The figure represents wait states for the first- and second-line devices, transition from undiagnosed to diagnosed with AF, and whether on acetylsalicylic acid (ASA) or oral anticoagulant (OAC), and progression through the multiple adverse events relevant to this population or death. The upper section (first 2 rows) refers to progression while waiting or under the first-line test; followed by (3rd and 4th rows) progression while waiting or under the second-line test (if any), and then (last 2 rows) by progression after an AF diagnosis reflecting adherence to ASA or OAC therapies. The arrows representing a downward transition represents a progression in the diagnostic pathway, and the arrows representing a transition horizontally to the right, represents the occurrence of adverse events hierarchically displayed based on their quality of life post event (the further to the right side of the image the worse the quality of life). Patients experiencing adverse events transition into the respective post-event states. Because GIB and recurrent minor stroke could be temporary events, they result in cost and disutility without transitioning out from the primary state. There is no upward or leftward transitions in the model (no coming back), and once patients transition to a state with lower utility value, they can only remain in that state, or move to states with similar or worse quality of life. Abbreviations: No AE = No adverse events; UnDx = Undiagnosed; Dx = Diagnosed.

All patients enter the model under ASA therapy in "*Wait 1 post minor stroke*" state and remain there until an AE occurs, or die, whichever happens first. Patients who complete the wait without any AE and receive the test, immediately move to the undiagnosed state (UnDx post minor stroke). Patients experiencing an AE during the wait period transition into their respective post AE states ("Wait 1 post MI", "Wait 1 post ICH", "post Severe Stroke on ASA", or "post Severe Stroke on OAC") Patients in the post AE states are still at risk of AEs and can continue transition to another post AE state (with worsen quality of life), return to the same post AE state they were in, die, or receive the test and immediately move to one of the undiagnosed states ("UnDx post MI", "UnDx post ICH", "UnDx post moderate Stroke") whichever happens first.

Patients who survive the wait and received the test remain in the undiagnosed states ("UnDx post minor stroke", "UnDx post MI", "UnDx post ICH", "UnDx post moderate stroke") until they die, have an AE, are diagnosed with AF, or complete the monitoring time undiagnosed and enter the second wait time for the second-line test (for the ELR + ICM strategy only), whichever happens first. In the same way, patients who experience an AE after the test, transition to their respective post AE states (“UnDx post MI”, “UnDx post ICH”, “UnDx post moderate stroke”, “UnDx post Severe Stroke on ASA”) Patients in the post AE states are still at risk of AEs and can continue to transition to another post AE state (with worse quality of life) or return to the same post AE state they were in, as described above.

Patients diagnosed with AF at any cycle after receiving a test transition into their respectively diagnosed state according to their treatment decisions. Those AF diagnosed patients who chose to adhere to OAC transition to the Dx on OAC states (“Dx on OAC minor stroke”, “Dx on OAC post MI”, “Dx on OAC post moderate Stroke”, “Dx on OAC post Severe Stroke”) Those not adherent to a change in therapy transition to the Dx on ASA states (Dx on ASA minor stroke”, “Dx on ASA post MI”, “Dx on ASA post ICH”, “Dx on ASA post moderate Stroke”, “Dx on ASA post Severe Stroke”)

After AF diagnostic, patients remain at risk for AEs and can continue to transition horizontally to the right to another post AE state (with worse quality of life), or return to the same state they were in, as described above. The only exception is for the patients who transitioned to the post Severe Stroke states. Patients in the “Dx post Severe Stroke on OAC” state can die or experience an ICH or GIB and transition to the “Dx post Severe Stroke on ASA” state, whichever happens first. However, any patients who had a severe stroke (regardless of having or not an AF diagnosis, or being on OAC or ASA therapy), did not receive any further testing (or monitoring) and remained in the post-severe stroke states until they died.

6.2.10 Parameter sources and assumptions

Input parameters for the model were sourced from the literature review (reported in Chapter 5), and administrative data analysis from the Ministry of Health (Data discharge abstract (DAD), Medical Services Plan [MSP], Stroke Registry, and PHSA ICM registry) to tailor the cost-effectiveness analysis to the BC context, to the extent possible.

6.2.10.1 Baseline stroke severity and age distribution of post cryptogenic stroke patients

The Oxford Vascular Study reported that the mean utility of patients who had a cryptogenic stroke was 0.7[5], which is similar to the mean utility of minor stroke patients (Table 1.1). This finding suggested that most cryptogenic stroke patients that would require long term ECG monitoring were likely to have experienced a minor stroke during their index event. Therefore, it was assumed all patients enter the model in the "*Wait 1 post minor stroke*" state.

The age distribution assumed was of the ischemic stroke +TIA patients in BC in the reference year of 2017/2018 (Table 6.1), limited to the age groups included in this analysis. [12]

Table 6.1 Stroke patients by age group, BC 2017/18 [12]

Age group	Patients	%	Rescaled for 60+ age group (%)
Under 60 years	[redacted]	[redacted]	[redacted]
60 – 69 years	[redacted]	[redacted]	[redacted]
70 – 79 years	[redacted]	[redacted]	[redacted]
80+ years	[redacted]	[redacted]	[redacted]
All ages	[redacted]	[redacted]	[redacted]

Source of stroke data and diagnosis: Incident cases from DAD.
Ischemic & Tia Stroke ICD10=163 & I64 & G45 (Tia)
Exclude brain injury/trauma ICD10 (S02, S06) & rehabilitation care Z50
ELR: Stroke patients who billed MSP fee for service (33062, 33069, and 33092)

6.2.10.2 The prevalence of AF among cryptogenic stroke patients

Patients subject to the present decision analysis are those who survived a recent history of ischemic stroke or TIA and no prior diagnosis of AF. The model used a 27.23% prevalence of AF among the cryptogenic population [19], and patients were artificially placed into two groups prior to entering the model (disease and no disease) to have their risk of AE and probabilities of being diagnosed with AF by any test adjusted accordingly. Alternative values were explored in sensitivity analyses.

6.2.10.3 Utilization of OAC, treatment discontinuation and effect of OAC on AE risks

After a cryptogenic stroke, according to the guidelines, all patients are offered antiplatelet therapy, assumed to be ASA therapy. Therefore, all patients are assumed to enter the model under ASA as the standard therapy. Upon AF diagnosis, patients were prescribed OAC therapy for stroke prevention and the proportion of patients who changed their therapy from ASA to OAC was assumed from Huisman 2017. [60] This is a study on a global registry of AF patients and estimated 78.3% were taking at least one type of OAC. However, there are many OAC drugs available with different risks of AE. Weitz 2015, which was a Canadian study [61] examined the trends of OAC prescription in Canada between 2008 and 2014, showed the number of warfarin prescription had been in the decline since 2010 while the prescription of non-vitamin K OAC, particularly rivaroxaban, had been on the rise. Since the patient population in the model was likely to be under the care of a neurologist or cardiologist, the average prescription proportion of different types of OAC from neurologist and cardiologist from Weitz

2015 was used in the model. According to Weitz 2015, approximately 45% patients receive Warfarin, 29% receive Dabigatran, 23% receive Rivaroxaban and 3% receive Apixaban.[61]

In the model, patients taking OAC could discontinue treatment at any time and transition to their respective states under ASA treatment (Dx post minor stroke, Dx post MI, Dx post moderate stroke, Dx post severe stroke). The percentage of patients who had considered stopping OAC was assumed from a published local survey done in BC and used as the annual probability of discontinuing OAC treatment.[62] The study was chosen because it was a BC study with data for each individual OAC. It was likely that not all patients who had considered stopping OAC would eventually discontinue but the overall annual probability (17%) of discontinuation was similar to the number CADTH used in their model.[19] Therefore, we used this number (17%) as more conservative estimate of discontinuation. However, in the real world, patients could switch to another OAC or restart OAC after a period of time. The probability of switching or restarting OAC after discontinuation was not included in the model due to the lack of data. Instead, the scenario with no withdrawal of OAC treatment was explored as a sensitivity analysis.

Patients entering the model could experience AE such as, recurrent stroke (minor, moderate or severe), myocardial infarction (MI), intra-cranial hemorrhage (ICH) and major GI bleed in each cycle, under both stroke prevention therapies (ASA or OAC). All the input parameters used to calculate the probabilities of AE are displayed in Table 6.2

Table 6.2: Rate of adverse events

Risk group	Therapy	Parameter	Mean	Lower bound (95% CI)	Upper bound (95% CI)	Source/ Method/ Assumptions
Non-AF patients	ASA	Annual rate of MI	0.0060	0.0056	0.0066	Soliman 2014 [63]
		Annual rate of ICH	0.0029	0.0023	0.0050	CADTH [19]
		Annual rate of recurrent stroke	0.0715	0.0420	0.1340	Calculated Stroke rate in non-AF patients (Gage 2004 [10]) * HR of stroke in non-AF patients on ASA (Mohan2009 [11])
		Annual rate of GIB	0.0373	0.0058	0.0490	An 2015 [64]
AF patients	ASA	Annual rate of MI	0.0120	0.0096	0.0149	Soliman 2014 [63]
		Annual rate of ICH	0.0029	0.0023	0.0050	CADTH [19]
		Annual rate of recurrent stroke	0.1080	NA	NA	Gage 2004 [10] (and validated against, SRAF 2007[65])
		Annual rate of GIB	0.0373	0.0058	0.0490	An 2015 [64]
	Warfarin	Annual rate of MI	0.0115	NA	NA	Calculated Annual rate of MI in AF patients on ASA therapy (Soliman 2014 [63]) * HR of MI in AF patients on OAC therapy (CADTH [19])
		Annual rate of ICH	0.0066	NA	NA	Calculated Annual rate of ICH in AF patients on ASA therapy * HR of ICH in AF patients on OAC therapy (CADTH [19])
		Annual rate of recurrent stroke	0.0529	NA	NA	Calculated Annual rate of recurrent stroke in AF patients on ASA therapy (Gage 2004 [10]) * OR of stroke in AF patients on OAC therapy (Saxena 2004 [66])
		Annual rate of GIB	0.0634	NA	NA	Calculated Annual rate of GIB in AF patients on ASA therapy (An 2015 [64]) * OR of GIB in AF patients on OAC therapy (Hart 2007 [27])
	Apixaban	Annual rate of MI	0.0101	NA	NA	Calculated Annual rate of MI in AF patients on Warfarin (calculated) * HR of MI in AF patients on Apixaban (Granger 2011[67])
		Annual rate of ICH	0.0024	NA	NA	Calculated Annual rate of ICH in AF patients on Warfarin (calculated) * HR of ICH in AF patients on Apixaban (Easton 2012 [28])

Risk group	Therapy	Parameter	Mean	Lower bound (95% CI)	Upper bound (95% CI)	Source/ Method/ Assumptions
AF Patients		Annual rate of recurrent stroke	0.0455	NA	NA	Calculated Annual rate of recurrent stroke in AF patients on Warfarin (calculated) * HR of stroke in AF patients on Apixaban (Easton 2012 [28])
		Annual rate of GIB	0.0463	NA	NA	Calculated Annual rate of GIB in AF patients on Warfarin (calculated) * HR of GIB in AF patients on Apixaban (Easton 2012 [28])
	Rivaroxaban	Annual rate of MI	0.0130	NA	NA	Calculated Annual rate of MI in AF patients on Warfarin (calculated) * HR of MI in AF patients on Rivaroxaban (Hankey 2012 [30])
		Annual rate of ICH	0.0048	NA	NA	Calculated Annual rate of ICH in AF patients on Warfarin (calculated) * HR of ICH in AF patients on Rivaroxaban (Hankey 2012 [30])
		Annual rate of recurrent stroke	0.0545	NA	NA	Calculated Annual rate of recurrent stroke in AF patients on Warfarin (calculated) * HR of stroke in AF patients on Rivaroxaban (Hankey 2012 [30])
		Annual rate of GIB	0.0615	NA	NA	Calculated Annual rate of GIB in AF patients on Warfarin (calculated) * HR of GIB in AF patients on Rivaroxaban (Hankey 2012 [30])
	Dabigatran	Annual rate of MI	0.0181	NA	NA	Calculated Annual rate of MI in AF patients on Warfarin (calculated) * RR of MI in AF patients on Dabigatran (Diener 2010 [29])
		Annual rate of ICH	0.0018	NA	NA	Calculated Annual rate of ICH in AF patients on Warfarin (calculated) * RR of ICH in AF patients on Dabigatran (Diener 2010 [29])
		Annual rate of recurrent stroke	0.0529	NA	NA	Calculated Annual rate of recurrent stroke in AF patients on Warfarin (calculated) * RR of stroke in AF patients on Dabigatran (Diener 2010 [29])
		Annual rate of GIB	0.0812	NA	NA	Calculated Annual rate of GIB in AF patients on Warfarin (calculated) * RR of GIB in AF patients on Dabigatran (Diener 2010 [29])

Risk group	Therapy	Parameter	Mean	Lower bound (95% CI)	Upper bound (95% CI)	Source/ Method/ Assumptions
AF or non-AF Patients	On ASA or OAC therapy	Proportion of severe stroke	0.0520	0.0518	0.0522	Krueger 2012[4] Assumed as the distribution of all recurrent strokes happening after entering the model.
		Proportion of moderate stroke	0.4050	0.4047	0.4053	Calculated Annual rate of GIB in AF patients on Warfarin (calculated) * RR of GIB in AF patients on Dabigatran (Diener 2010 [29])
		Proportion of minor stroke	0.5420	0.5417	0.5423	

Footnote: AF = Arterial fibrillation; ASA = acetylsalicylic acid; GIB=GI bleed; ICH=intracranial hemorrhage; NA = not available; OAC = oral anticoagulant; CI: confidence interval

In terms of OAC treatment effect on the risks of AE, a Cochrane systematic review [66] examined the effect of warfarin against ASA on AF patients with a history of stroke, and estimated the odds ratio of recurrent stroke was 0.49 (95% CI 0.33-0.72) from two RCTs that included 1371 patients. This odds ratio was applied to the annual rate of recurrent stroke in AF patients taking ASA (0.1080) to obtain the annual rate of recurrent stroke in AF patients taking warfarin (0.1080*0.49=0.0529). The effects of non-vitamin K OACs were estimated from a subgroup of pivotal RCTs using the same manner of calculation.[28-30]

The annual rate of recurrent stroke in AF patients taking antiplatelet drugs was estimated from Gage 2004[10] and SRAF 2007.[65] Gage 2004[10] was a retrospective analysis of 2,580 non-valvular AF patients receiving aspirin in several multicentre clinical trials. SRAF 2007[65] was a systematic review that examined the independent risk factors for stroke in patients with AF. Both found that the risk of recurrent stroke was around 10% per year (or 10.8 per 100 patient-year). It is important to note that these are the risk of recurrent stroke, not the first stroke. The rate of the first stroke in AF patients was 1.89 per 100 patient-year, which is much lower than the rate of recurrent stroke according to a systematic review.[68]

The distribution of stroke severity for those recurrent strokes occurring after the patients enter the simulation model was assumed the same as distribution among survivors obtained from a large Canadian study (Kreuger 2012).[4] Kreuger 2012 was a cost avoidance study on the optimal stroke care pathway in Canada and obtained the data of stroke severity from Canadian Stroke Audit in 2008-2009.[4] The proportion of stroke survivors according to each modified ranking score (mRS) score in 2008/2009 in Canada is displayed in the Table 6.3, and is in line with the definitions commonly used by other studies and supported by our clinical advisors.[4, 56]

Table 6.3 Distribution of stroke survivors in Canada in 2008-2009. [4]

mRS score	Disability level [6]	Proportion (%) [4]
0-2	Minor stroke - no disability to minor disability - patients can perform daily tasks without assistance	54.2%
3-4	Moderate stroke - moderate disability - patients require assistance with daily tasks or unable to live independently	40.5%
5	Severe stroke - severe disability - patients are bedridden and incontinent.	5.2%

GIB could occur when patients taking ASA or OAC. When patients were taking ASA, an event of GIB would incur cost to treat and disutility. Because the history of GIB was not tracked in the model, it was a limitation which would lead to some patients having history of GIB while taking ASA were given an option to receive OAC at diagnosis. However, in our model, not 100% of patients diagnosed would initiate OAC. Therefore, the impact of this limitation was mitigated. If patients taking OAC experienced a GIB, 100% of the OAC patients was switched to ASA in the model. If a patient had a history of ICH, the patient would be assumed to continue ASA therapy after an AF diagnostic due to the increased risk of bleeding from OAC. The different level of severity in ICH was not included in our model because of the low rate of ICH that it was unlikely to have a significant impact on the outcomes. Therefore, the average rate of ICH across all severities was assumed. Additionally, all patients under OAC who subsequently experienced ICH were switched back to ASA therapy. Other technology related complication (such as pocket erosion) was not modelled due to lack of adequate data on time to event and event rate between ICM devices.

6.2.10.4 Mortality

In each cycle, patients could either die from background mortality or from the acute AE (i.e. 30-day mortality). Mortality risks were applied in the model, in a stepwise process by the end of each cycle. First, the background mortality was applied to all the patients alive on the different states. Second, the AE mortality was applied only to those patients experiencing an AE within the cycle.

The background mortality for each state was adjusted according to the history of AE by multiplying the age-specific background mortality in BC (from Stats Canada 2014-2016 [69], Appendix L) by the hazard ratio of death following an specific AE (Table 6.4). For example, the annual background mortality probability for a 70-year-old person in BC was 1.4%, therefore the annual probability of dying for a 70-year-old in the post minor stroke state was 1.4% * HR 1.9, which is equal to 2.7%. For patients in the AF disease group in the model, an additional hazard ratio of 1.4 was applied to the adjusted background mortality, regardless if their AF have been diagnosed or not by any test.

Table 6.4 One-year hazard ratio of death after specific AEs.

Parameter	Mean	Low bound (95% CI)	Upper bound (95% CI)	Source
Post minor stroke	1.99	1.82	2.17	Bronnum-Hansen 2001[70]
Post moderate stroke	3.40	3.11	3.71	Diamentoupoulos 2016 [56], Bronnum-Hansen 2001[70]
Post severe stroke	9.69	8.86	10.57	
Post MI	1.99	1.82	2.17	Kammersgaard 2006 [71], Bronnum-Hansen 2001 [70]
Post ICH	2.20	NA	NA	Fogelholm 2005 [72]
AF+	1.40	1.10	1.70	Kammersgaard 2006 [71]

Footnote: AF= atrial fibrillation; ICH=intracranial hemorrhage; MI=myocardial infarction, NA= Not available

The 30-day mortality after various adverse events was different between AF and non-AF patients as well as the type of stroke prevention therapy the patients were receiving. The probability of 30-day mortality according to disease and treatment status can be found in Table 6.5. The average ICH mortality rate across all severity was assumed for all ICH events. Elwood 2016 was a systematic review that examined the risk of fatal bleeding associated with aspirin.[73] This study found that the rate of fatal bleed when taking aspirin was very low (3.5/10,000 patients taking aspirin). In addition, it also found that aspirin was associated with lower risk of fatal bleed (rate ratio 0.45 95% CI (0.25-0.8)). However, the analysis had a high degree of heterogeneity. Therefore, as a conservative approach, the model assumed the risk of 30-day mortality of GIB when taking aspirin to be zero. The probability of death during implantation and explanation of devices was not modelled due to lack of data. All probabilities were adjusted for cycle length (2 weeks).

Table 6.5 30-day mortality after AE

Risk group	Therapy	Probability of death 30 days after	Value	Low value	High value	Source
Non-AF	ASA	MI	0.0760	0.0650	0.1600	CADTH[19]
		ICH	0.3100	0.2500	0.4200	
		Recurrent stroke	0.2800	0.1200	0.3500	
AF	ASA	MI	0.1100	0.0700	0.2700	
		ICH	0.3100	0.2500	0.4200	
		Recurrent stroke	0.3900	0.1300	0.6000	
	OAC	MI	0.1100	0.0700	0.2700	
		ICH	0.4400	0.2800	0.7100	
		Recurrent stroke	0.2700	0.1200	0.3400	
		GIB on warfarin	0.0710	0.0509	0.0911	Charlton 2018 [74]
		GIB on apixaban	0.0355	0.0210	0.0500	Charlton 2018 [74], Hylek 2014 [75]
		GIB on rivaroxaban	0.0497	0.0000	0.1025	Charlton 2018 [74]
		GIB on dabigatran	0.0639	0.0000	0.1025	Charlton 2018 [74]

Footnote: AF = Arterial fibrillation; ASA = acetylsalicylic acid; GIB=GI bleed; ICH=intracranial hemorrhage; NA = Not available; OAC = oral anticoagulant

6.2.10.5 The wait times

According to key stakeholder interviews (refer to Chapter 3), the choice of test, device and facility where to perform the minimally invasive procedures affect the wait times for patients to have the cardiac monitoring started. For the base-case, the wait-time before receiving monitoring devices was assumed to be 8 weeks for ELR, 8 weeks for implantable loop recorder, 4 weeks for insertable loop recorder inserted in hospital facility, and 2 weeks for insertable loop recorder inserted in a physicians' office (Stakeholder interview) The wait times for ICM was assumed the same regardless if they are used as first- or second line test. All patients assumed to receive the respective device immediately after the wait period. Sensitivity analyses were performed to investigate whether the costs-effectiveness ratio of the different strategies would change if there would be virtually no resource constrains and the patients would have access to either monitoring technology as they needed (assumed a 2-week wait time across all technologies simultaneously regardless of 1st or 2nd line tests).

6.2.10.6 Diagnostic performance of different technologies

The evaluation of diagnostic technologies takes into account four performance characteristics including true positive, false negative, false positive, and true negative probabilities. Instead of applying the test sensitivity, previous economic studies mainly relied on the diagnostic yield as the primary performance outcome.[19] The diagnostic yield is defined as the proportion of patients in whom the cardiac monitoring technique yield a definitive diagnosis out of the total number of patients that have received the diagnostic procedure. This approach to modeling diagnostic yield was chosen because direct estimation of sensitivity (i.e. individual with the condition will be detected) and specificity is nearly impossible for ICM devices due to a lack of criterion standard ("gold-standard")technology for evaluating the presence of AF. In this context, true and false positive rates can be elicited because these cases are adjudicated by physicians in the clinical practice.

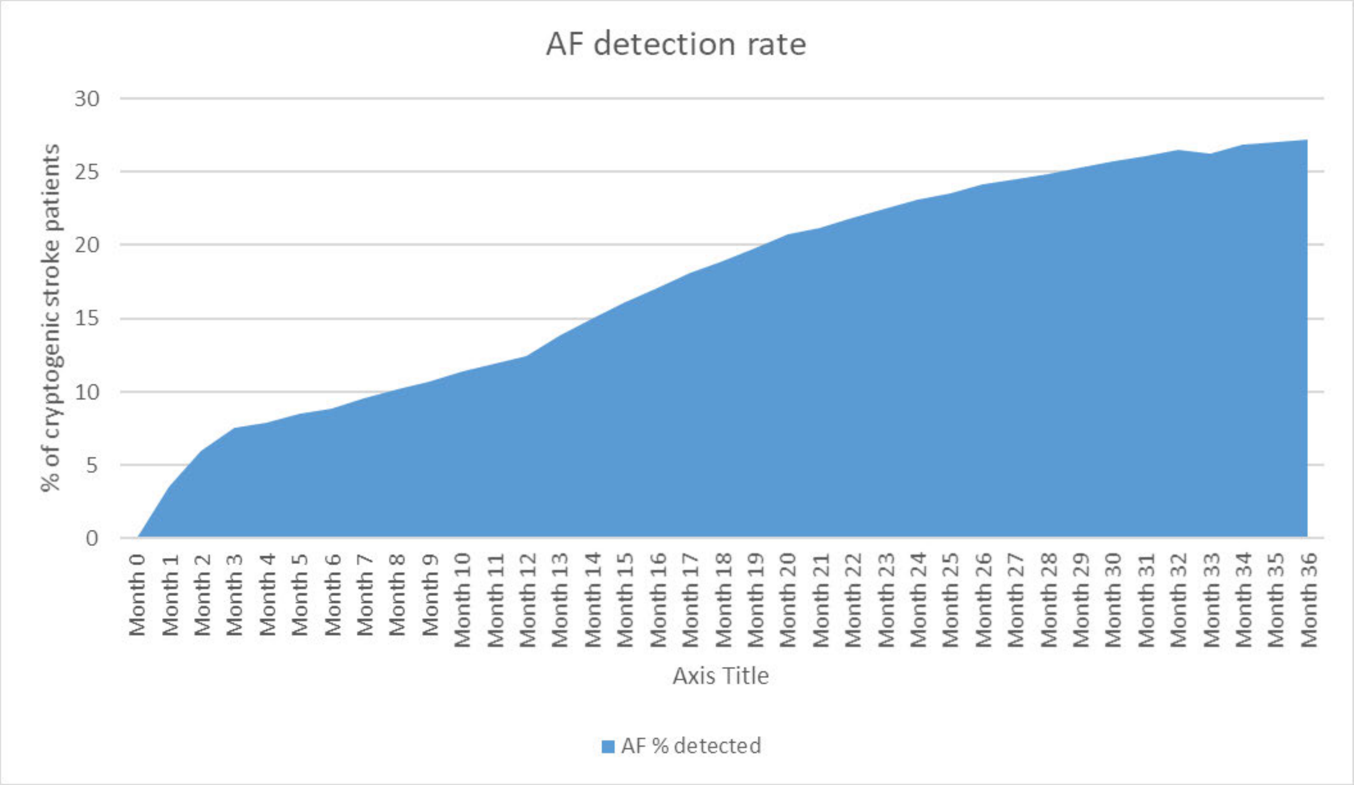
6.2.10.6.1 Duration of monitoring and diagnostic yield of ELRs

The maximum period of monitoring was assumed to be one month for an ELR. Previous study reported that 30 days of ELR would result in a diagnostic yield of 3.5% among all cryptogenic stroke patients (or 13% among AF patients).[19] The probability of being diagnosed among those in the AF group was calculated as 7.5% in a biweekly cycle (i.e., multiplying diagnostic yield with AF prevalence and dividing by 2), so that 13% of patients would be diagnosed with AF in the disease group over a period of one month after receiving the test. In the non-disease group, after receiving ELR, the probability of being diagnosed with AF was assumed zero.

6.2.10.6.2 Duration of monitoring and diagnostic yield of ICM devices

The maximum period of monitoring was assumed to be 36 months for both implantable and insertable ICMs. ICMs were assumed to be explanted immediately after AF diagnosis or after 36 months of monitoring for those patients remaining undiagnosed. Figure 6.2 shows the cumulative proportion of all cryptogenic patients being diagnosed with AF over time .[19] The diagnostic yield was only available for implantable ICMs because there is no clinical studies investigating diagnostic yield using the insertable models. The diagnostic yield for insertable ICMs was assumed to be similar to the implantable ICMs because according to the manufacturer and interviewed clinicians, they only differ on the method of implantation and data transmission, but not in the monitoring capabilities.

Figure 6.2: Diagnostic yield of ICMs among all cryptogenic stroke patients submitted to cardiac monitoring [19]



After patients receive an ICM of any model, AF diagnosis is not instantaneous. Instead, they depend on the frequency of data transmission (by either clinic visits, or remote transmission), the frequency of data readings by the technicians, and the frequency of AF diagnosis by the electrophysiologists. The differences in those frequencies between implantable and insertable models were based on the assumptions gathered during stakeholder interviews to elicit the monitoring practices in BC and the monitoring costs for both models (Table 1.11, Appendix C).

In order to mimic their average frequency of data transmission and readings, patients on implantable ICMs were assumed to have their AF diagnosis occurring in the model every two months, and patients on insertable ICMs were assumed to have their AF diagnosis occurring in the model every month. Therefore, the probability of AF diagnosis was applied every 4 cycles for implantable ICM, and every 2 cycles for insertable ICMs, using their respective cumulative diagnostic yield for those time periods. Although the diagnostic yield was assumed to be similar between implantable and insertable ICMs, fewer patients were expected to be diagnosed on implantable ICM as a results of their higher risk of death (due adverse events) accumulated over waiting times for the implant and longer periods in between data readings.

The probability of being diagnosed with AF was applied only to the disease group in the model and adjusted for the assumed prevalence of AF among cryptogenic stroke population (See section 6.2.10.2). The cumulative proportion of diagnosed AF patients in each month after receiving and ICM can be found in Table 6.6. Therefore, in the disease group, all patients were assumed to be diagnosed with AF at the end of 36 months. In the no disease group, the probability of being diagnosed with AF was assumed zero.

Table 6.6: Diagnostic yield of ICMs among cryptogenic stroke patients with underlying AF [19]

Month	**Implantable ICM (%)**	**Insertable ICM (%)**	**Month**	**Implantable ICM (%)**	**Insertable ICM (%)**
1	13.00	13.00	19	72.64	72.64
2	Skip	22.03	20	Skip	76.02
3	Skip	27.69	21	Skip	77.67
4	29.09	29.09	22	80.50	80.50
5	Skip	31.33	23	Skip	82.74
6	Skip	32.43	24	Skip	84.69
7	35.26	35.26	25	86.38	86.38
8	Skip	37.20	26	Skip	88.62
9	Skip	39.44	27	Skip	90.01
10	41.98	41.98	28	91.41	91.41
11	Skip	43.92	29	Skip	92.80
12	Skip	45.61	30	Skip	94.45
13	50.97	50.97	31	95.59	95.59
14	Skip	54.90	32	Skip	97.50
15	Skip	59.13	33	Skip	96.40
16	62.80	62.80	34	98.64	98.64
17	Skip	66.43	35	Skip	99.16
19	Skip	69.56	36	100.00	100.00

Footnote: AF = Arterial fibrillation; ICM = insertable cardiac monitors

6.2.10.7 Utilities

All post cryptogenic stroke patients were assumed to enter the model with history of minor stroke (i.e. utility of 0.73). The utilities of post-stroke states were obtained from the Oxford Vascular Study.[5] The Oxford Vascular Study was a large observational study of the stroke patients in Oxfordshire, UK. It also evaluated the long-term utility of stroke patients using EQ-5D, as recommended by NICE. It was chosen because the utility of minor, moderate, and severe stroke was reported in the same population which would preserve consistency. The utility of post minor stroke state was similar to the Canadian National Population Health Survey in 1994 and U.S. Medical Expenditure Panel Survey.[76, 77] The utilities of post MI and post ICH states were obtained from CADTH.[19] Patients with history of multiple events were assumed to stay in the health state with the worse utility. For example, patients in the post severe stroke state could still experience an MI, which incur treatment costs and temporary disutility, and if still alive, they would remain in the severe stroke state surviving with lower utility values compared to those in the post MI states who did not experienced a recurrent stroke.

The acute disutility (30 days) of recurrent stroke was also obtained from the Oxford Vascular Study [5] and found to be the same across the different stroke severity. The disutility of MI, ICH, and GIB were obtained from the CADTH report.[19] No disutility was incurred for OAC treatment because not all OAC available in BC was studied, and the study that compared warfarin and aspirin did not find a significant difference in utility between warfarin and aspirin therapy.[78] Disutility from implantation and/or explanation of ICMs were not modelled due to lack of evidence in the existing literature. All utility and disutility values applied in the model are listed in Table 6.7.

Table 6.7: Utility and disutility values applied to events and health states

Category	States or adverse event	Value	Low value	High value	Source
Utility of states	Post minor stroke	0.73	0.72	0.74	OXVAS [5]
	Post moderate stroke	0.5	0.46	0.54	
	Post severe stroke	0.13	0.07	0.19	
	Post MI	0.65	0.50	0.90	CADTH[19]
	Post ICH	0.62	0.32	0.68	
Acute disutility of adverse events (30-day)	GIB	-0.03	-0.05	-0.01	
	Recurrent stroke (minor, moderate and severe)	-0.15	-0.23	-0.07	OXVAS [5]
	MI	-0.01	-0.02	0.00	CADTH [19]
	ICH	-0.05	-0.15	-0.02	

Footnote: AF = Arterial fibrillation; ASA = acetylsalicylic acid; GIB=GI bleed; ICH=intracranial hemorrhage; NA = Not available; OAC = oral anticoagulant

6.2.10.8 Costs

All final input parameter for costs incurring in the model are reported in Table 6.8.

Table 6.8 Health care costs of health states, adverse events and OAC treatment

Baseline age-specific healthcare expenditure per year (cost of being alive in a health state)*				
Parameter	**Base-case**	**Low value**	**High value**	**Source**
Ages 60 – 69 years	$11,168	$9,580	$16,499	Calculated from CIHI [79]
Ages 70 – 79 years	$11,746	$10,112	$17,564	
Ages 80 + years	$12,492	$9,580	$17,031	
Patients with AF (multiplier)	1.1	1.0	1.2	Wolf PA et al. 1998 [80]
Healthcare expenditure associated with medical history per year (cost of being alive in a health state) *				
Minor stroke	$19,586	$9,687	$32,892	Singh 2013 [14], Mittmann 2012[15]
Moderate stroke	$26,239	$14,636	$49,444	Calculated Average costs of minor and severe stroke
Severe stroke	$32,892	$19,586	$65,997	Singh 2013 [14], Mittmann 2012[15]
MI	$19,586	$9,687	$32,892	
ICH	$19,586	$9,687	$32,892	

Healthcare expenditure associated with adverse events (30 days cost of an event) *				
Minor stroke	$17,244	$7,451	$38,321	Singh 2013 [14], Mittmann 2012[15], CIHI 2015[16]
Moderate stroke	$37,895	$22,886	$59,078	
Severe stroke	$58,545	$38,321	$79,835	
MI	$19,586	$9,580	$39,385	
ICH	$38,321	$17,244	$58,545	
GIB	$10,618	$5,322	$13,838	Singh 2013 [14], CIHI 2015[16]
Annual costs of AF treatment (OAC drugs + **plus monitoring costs) * [£]**				
Warfarin	$422	$293	$692	ODB 2015[81], Ontario drug 2015[81], Coyle 2013.[82]
Dabigatran	$1,371	$1,171	$1,597	
Rivaroxaban	$1,232	$1,064	$1,490	
Apixaban	$1,371	$1,171	$1,597	

* All costs were inflated to 2018 Canadian dollars using the annual health and personal care Consumer Price Index for BC [59]; [£] Ontario drug prices were cross-checked with BC costs and deemed very similar. Small differences are unlikely to change the direction of the results. Therefore, Ontario costs were assumed as the input parameter.

Baseline age-specific costs are related to the Canadian public sector health care costs including expenditure on hospitals, physician care, nursing homes, and drugs. [16] All patients enter the model with the medical history of minor stroke, therefore they have relatively higher baseline costs. The biweekly costs were calculated as the proportional sum of 'Baseline age-specific healthcare expenditure' and 'Healthcare expenditure associated with medical history" (sum of both annual costs, divided by 26 cycles). These costs were inflated by 1.1 multiplier in the disease group (to reflect higher than average costs) after patients are diagnosed with AF. [80] These costs were applied at the beginning of each cycle assuming that patients would incur these costs before dying. The cost of ASA treatment was assumed to be included in the 'Healthcare expenditure associated with medical history' for all patients with the history of minor stroke. The cost of OAC treatment are discontinued for patients who discontinue therapy in any cycle. The estimated costs of acute adverse events (30-day) are assumed to be the same regardless of year of occurrence in the model. The costs of events are applied for each AE to patients experiencing the AE assuming those who died also incurred the cost of AE.

The one-time device costs of the cardiac monitors (Table 6.9) and device-related monitoring costs (Table 6.10) are applied to all patients according to the choice of first-line and second-line testing. In strategies 1-4 (with ELR as the first line test), the one-time costs of ELR are applied to all patients alive by the end of the wait 1 states (post minor stroke, post MI, post ICH, and post moderate stroke) immediately before receiving the ELR test and entering the undiagnosed states.

Table 6.9 One-time costs related to the different cardiac monitors in BC

Facility type	% of Use	Device Type	Total Costs	Source/Assumptions
ELR (30-day)	100%	Spiderflash	[redacted]	Appendix A Reading and interpretation of results already included
ICMs				
Weighted Costs		**Implantable**	[redacted]	Weighted costs of implantable ICM procedures calculated based on the distribution of facilities used for implantation in the BC administrative data (Figure 1.4) Assumptions for each costs component are detailed in Table 1.10,Table 1.11 and Appendix B
OR	47.62%	Implantable	[redacted]	
Procedure Room in hospital	30.95%	Implantable	[redacted]	
Cath Lab	21.43%	Implantable	[redacted]	
Procedure Room in hospital	100%	Insertable	[redacted]	
Office	100%	Insertable	[redacted]	
OR	100%	Explantation surgery	$5,009	CIHI Patient Cost Estimator

Table 6.10 Monitoring costs of ICM per year per patient

Device Type	Total Costs	Source/Assumptions
Implantable	[redacted]	Assumptions for each costs component are detailed in Table 1.11 and Appendix C
Insertable	[redacted]	

Note: the costs of monitoring were based solely on assumptions from multiple stakeholders' interviews and their experiences (clinicians, technicians, managers, etc.) on the average frequency of data transmission by the patients, average number of clinic visits, average data readings by the technician and electrophysiologists. Currently, there is no data readily available on monitoring practices after the implant in the BC health system. Details in Appendix C.

In all strategies with implantable ICMs (either as first- or second line test), the weighted average cost of implantable ICMs was assumed, based on the utilization of the different facilities for implant across BC. This one-time weighted average cost of the procedure was applied to all patients alive by the end of the wait 1 states for strategy 4 where the implantable ICM is the first-line test (post minor stroke, post MI, post ICH, and post moderate stroke) immediately before receiving the implant and entering the undiagnosed states. In strategy 1, in which the implantable ICM is the second-line test in the diagnostic pathway, these one-time cost of the procedure was applied to all patients alive by the end of the wait 2 states (post minor stroke, post MI, post ICH, and post moderate stroke, for the strategy 4) immediately before they receive the implant and enter the undiagnosed states.

In a similar way, the specific one-time costs of the insertable ICMs were applied to the strategies 2 and 3 as the second-line test, and strategies 5 and 6 as the first-line test.

The implantable and insertable ICM monitoring costs (Table 6.10) are applied at the beginning of every cycle, for 36 months, to patients alive in the undiagnosed states after receiving and ICM, assuming the deaths due adverse event and background mortality occurred by the end of each cycle. All costs were adjusted for cycle length (2-weeks).

In addition, the costs of explanation (Table 6.9) are applied to all patients in the undiagnosed states after receiving an ICM, who had an AF diagnosis and survived (background mortality and AE mortality). This was based on the assumption that those patients who had an AF diagnosis but died before entering the diagnosed states have not gone under explanation. Also, the costs of explanation were applied to all patients in the undiagnosed states still alive at 36 months after receiving and ICM (implantable or insertable).

6.2.11 Analytic methods

For the base-case analysis, outcomes are calculated for the various diagnostic strategies compared to no testing. Relevant wait times are taken into consideration for each of the ICM devices for the first-line and second-line devices, respectively. These wait times are assumed to be known (i.e. no uncertainty), because wait-time is subject to Operation room booking and the availability of the devices. Base-case results are calculated using a deterministic analysis (using mean parameter values). In determining the most efficient strategy, we compared the incremental cost-effectiveness ratio (ICER) against the willingness-to-pay (WTP) of $50,000 per QALY gained. A univariate deterministic sensitivity analysis is conducted to evaluate the effect of changes in key assumptions on the results. Among others, we evaluated change in time horizon, discount, wait-times, AF prevalence, utility values of the patients entering the model, OAC discontinuation, diagnostic yield, cost of ICM devices and cost of patients' monitoring post-implant.

6.3 Results

6.3.1 Total costs and outcomes – population level

The Markov model estimated the costs, quality of life and survival (as a result of disease progression and mortality under various diagnostic strategies) for the BC cryptogenic stroke population. Below, the results of three scenarios are described: no testing (comparator, Strategy 0), ELR followed by implantable ICMs (Strategy 1), and insertable ICMs (only) performed in a procedure room at the physicians' office (Strategy 7)to guide interpretation of the results in Table 6.11 and Table 6.12.

For every 1,000 cryptogenic patients **not undergoing any test (Strategy 0 - comparator),** over the 20-year time horizon after their primary stroke, it is estimated that there will be another 180 moderate strokes, 23 severe strokes, 60 MIs, 24 ICH, and 305 GIB, resulting in 925 deaths. The number of deaths and strokes (moderate and severe) are relatively higher, and the numbers of MI, ICH and GIB are relatively lower compared to if the same patients would undergo AF testing by cardiac monitors. This is consistent to the expected benefit of the AF detection but also the risks these patients are exposed after switching to OAC therapy. Overall, if no test is pursued after the primary stroke, on average, the cryptogenic stroke patients were estimated to live for 7.53 years and have 5.24 QALYs (Table 6.11), over a 20-year time horizon after the primary stroke. These patients were estimated to incur to the health care system a total costs of $ 264,598 per patient over 20 years after the primary stroke (Table 6.12). The total cost includes [redacted] to treat their acute AEs, and [redacted] health care costs that will incur over the life of the survivors (hospitals, physician care, nursing homes, other drugs, etc.).

If these same patients were, instead, further tested with **ELR followed by implantable ICMs (Strategy 1)**, for every 1,000 patients, over the 20-year time horizon after their primary stroke, is estimated that there will be another 175 moderate strokes, 22 severe strokes, 61 MIs, 25 ICH, and 323 GIB, and 924 deaths. On average, these patient population were estimated to live 7.63 years and have 5.33 QALYs (Table 6.11), over a 20-year time horizon after the primary stroke. Regarding the number of tests/devices over the 20-year time horizon, the same 1,000 patients are estimated to receive 985 ELR tests and 936 implantable ICMs. The AF diagnosis was estimated to be confirmed in 33 patients (3.3%) by the ELR, and 218 patients (22%) by the implantable ICMs, and the cumulative wait time across the diagnostic pathway was estimated to be, on average, 4 months per patient. This strategy is estimated to have a total cost of 9,662 per patient over 20 years. The total costs include [redacted] ELR tests, [redacted] ICM implantation, [redacted] monitoring costs of the [redacted] ICM explantation, $[redacted] acute AEs, [redacted] health care costs that will incur over the life of the survivors (hospitals, physician care, nursing homes, other drugs, etc.), [redacted] specifically for OAC drugs (Table 6.12).

Alternatively, if these same patients were, instead, monitored directly with insertable ICMs implanted in a procedure room at the physicians’ office **(Strategy 7)**, for every 1,000 patients, over a 20-year time horizon after their primary stroke, is estimated that there will be another 176 moderate strokes, 23 severe strokes, 62 MIs, 25 ICH, and 326 GIB, and 924 deaths. On average, these patient population were estimated to live 7.62 years and have 5.31 QALYs (Table 6.11), over a 20-year time horizon after the primary stroke. Regarding the number of tests/devices over the 20-year time horizon, the same 1,000 patients are estimated to receive 992 insertable ICMs. The AF diagnosis was estimated to be confirmed in 261 patients (26%) by the insertable ICMs, and the cumulative wait time across the diagnostic pathway was estimated to be, on average, 2 weeks per patient. This strategy is estimated to have a total cost of $286,984 per patient over 20 years. The total costs include [redacted] ICM implantation, [redacted] monitoring costs of the ICM, [redacted] ICM explantation, $[redacted] acute AEs, [redacted] health care costs that will incur over the life of the survivors (hospitals, physician care, nursing homes, other drugs, etc.), and $[redacted] for OAC drugs (Table 6.12).   The results for the other diagnostic strategies are displayed in Table 6.11 and Table 6.12.

Table 6.11 Clinical outcomes at the population level- deterministic analysis under a 20-year time horizon

	Undiscounted outcomes (per 1,000 patients)											Discounted outcomes (per patient)	
	Wait (in months)	**N. MI**	**N. ICH**	**N. GIB**	**N. Moderate stroke**	**N. Severe stroke**	**N. Deaths**	**N. ELR tests**	**N. diagnosed with ELR**	**N. ICM devices**	**N. diagnosed with ICM**	**Total QALYs**	**LY**
No Test (Comparator)	0	60	24	305	180	23	925	-	-	-	-	5.24	7.53
ELR -> Imp ICM (St.1)	4	61	25	323	175	22	924	985	33	936	218	5.33	7.63
ELR -> Ins ICM proc. room in hospital (St.2)	3	61	25	324	175	22	924	985	33	942	223	5.33	7.64
ELR -> Ins ICM proc. room in office (St.3)	2.5	61	25	324	175	22	924	985	33	942	223	5.33	7.64
ELR only (St.4)	2	60	24	307	180	23	925	985	33	-	-	5.25	7.54
Imp ICM ONLY (St.5)	2	62	25	326	176	23	924	-	-	985	255	5.31	7.61
Ins ICM proc. room in hospital Only (St.6)	1	62	25	326	176	23	924	-	-	992	261	5.31	7.62
Ins ICM proc. room in office Only (St.7)	0.5	62	25	326	176	23	924	-	-	992	261	5.31	7.62

Note: MI = Myocardial infarction; ICH = Intracranial hemorrhage; GIB = gastro-intestinal bleed; ELR = External Loop Recorder; ICM = Implantable/insertable cardiac monitor; QALY= Quality adjusted life years; LY = life-years; St1 = ELR followed by implantable ICM; St2 = ELR followed by insertable ICM in procedure room in hospital settings, St3 = ELR followed by insertable ICM in procedure room in physician’s office settings; St4 = ELR only; St5= Implantable ICM only; St6 = Insertable ICM in procedure room in hospital settings only; St7 = Insertable ICM in procedure room in physician’s office setting only;

Table 6.12 Costs at the population level over a 20-year time horizon (deterministic analysis)

	Discounted outcomes (per patient)							
	Cost of ELR	Cost of ICM implantation	Cost of ICM Monitoring	Cost of ICM Explantation	Health Care Costs of surviving	Cost of acute AE	Cost of OAC	Total Costs
No Test (Comparator)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	$264,598
ELR -> Imp ICM (St.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	$279,662
ELR -> Ins ICM proc. room in hospital (St.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	$286,847
ELR -> Ins ICM proc. room in office (St.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	$286,639
ELR only (St.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	$265,862
Imp ICM ONLY (St.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	$279,389
Ins ICM proc. room in hospital Only (St.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	$287,204
Ins ICM proc. room in office Only (St.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	$286,984

Note: ELR = External loop recorder; ICM = Implantable or insertable cardiac monitors; AE = adverse events; OAC – Oral anticoagulants; QALY= Quality adjusted life years; LY = life-years; St1 = ELR followed by implantable ICM; St2 = ELR followed by insertable ICM in procedure room in hospital settings, St3 = ELR followed by insertable ICM in procedure room in physician's office settings; St4 = ELR only; St5= Implantable ICM only; St6 = Insertable ICM in procedure room in hospital settings only; St7 = Insertable ICM in procedure room in physician's office setting only

6.3.2 Incremental costs and outcomes – population level

The results of three scenarios are described below to guide interpretation of the results in Table 6.13 : ELR followed by implantable ICM (Strategy 1), insertable ICMs (only) performed in procedure room at the physicians' office (Strategy 7), and ELR only (Strategy 4), compared to no testing.

Over a 20-year time horizon, compared to no further testing of patients with cryptogenic stroke, if patients undergo cardiac monitoring with **ELR followed by implantable ICM (Strategy 1), it** is estimated to result in an average incremental cost of $15,064 per patient, and result in incremental gains of 0.08 QALYs and 0.11 LY per patient. These results translate to ICERs of $183,312 per QALY and $143,304 per LY gained (Table 6.13). Reminding that these results were generated under the assumptions that the implantable ICM devices available would have on average 6 data readings per patient per year, with the AF cases being diagnosed every 2 months (and consequently offered a changed in stroke prevention therapy to OAC drugs), considering the current wait times in the health system.

Alternatively, if the same patients were to undergo cardiac monitoring directly with an **insertable ICM placed in a procedure room at the physician's office (Strategy 7)** is estimated to result on an average incremental cost of $22,386 per patient, and result on incremental gains of 0.07 QALYs and 0.09 LY per patient. These results translates into ICERs of $321,133 per QALY and $247,336 per LY gained (Table 6.13). Reminding that these results were generated under the assumptions that the insertable ICM devices available would have on average 12 data readings per patient per year, with the AF cases being diagnosed every month (and consequently offered a changed in stroke prevention therapy to OAC drugs).

On the other hand, if the same patients were to undergo cardiac monitoring with **ELR only (Strategy 4)**, is estimated to result on an average incremental cost of $1,264 per patient, and result on incremental gains of 0.01 QALYs and 0.01 LY per patient. These results translates into ICERs of $142,799 per QALY and $109,783 per LY gained (Table 6.13). In spite of this strategy result in the lowest ICERs compared to no testing, it results in virtually no incremental gains in QALYs or LY per patient, and assumed a 8-week wait time for the ELR installation (similar to the current wait times in the Province for EVR testing).

A number of interviewed key stakeholders believed that offering the non-invasive monitoring first and then proceeding to the insertable ICMs placed in the physician's office would be the most ethical diagnostic pathway for the patients, and would free up resources in the operating rooms and procedure rooms across the province, optimizing the health care system resources. This alternative diagnostic strategy, **ELR followed by insertable ICM in a procedure room at the physician's office (Strategy 3)**, is estimated to result in an average incremental cost of $22,041 per patient, and result in incremental gains of 0.08 QALYs and 0.11 LY per patient. These results translate into ICERs of $260,395 per QALY and $203,650 per LY gained (Table 6.13). Note that these results were generated under the assumptions of an 8-week wait time to receive the ELR and, that after the insertable ICM patients would have on average 12 data readings per year, with the AF cases being diagnosed every month (and consequently offered a change in stroke prevention therapy to OAC drugs).

Table 6.13 Incremental cost, benefits and cost-effectiveness of outpatient cardiac monitoring for cryptogenic stroke patients in BC compared to no testing over a 20-year time horizon (results are discounted and expressed per patient)

	ICER/ QALY	ICER/ LY	Incremental costs	Incremental QALYs	Incremental LYs
ELR -> Imp ICM (St.1)	$183,312	$143,304	$15,064	0.08	0.11
ELR -> Ins ICM proc. room in hospital (St.2)	$262,850	$205,570	$22,249	0.08	0.11
ELR -> Ins ICM proc. room in office (St.3)	$260,395	$203,650	$22,041	0.08	0.11
ELR only (St.4)	$142,799	$109,783	$1,264	0.01	0.01
Imp ICM ONLY (St.5)	$220,941	$169,923	$14,791	0.07	0.09
Ins ICM proc. room in hospital Only (St.6)	$324,282	$249,761	$22,606	0.07	0.09
Ins ICM proc. room in office Only (St.7)	$321,133	$247,336	$22,386	0.07	0.09

Note: External loop recorder; ICM = Implantable or insertable cardiac monitors; ICER = Incremental cost-effectiveness ratio; QALYs= Quality adjusted life years; LYs = life-years; St1 = ELR followed by implantable ICM; St2 = ELR followed by insertable ICM in procedure room in hospital settings, St3 = ELR followed by insertable ICM in procedure room in physician's office settings; St4 = ELR only; St5= Implantable ICM only; St6 = Insertable ICM in procedure room in hospital settings only; St7 = Insertable ICM in procedure room in physician's office setting only

6.3.3 Subgroup analysis

Subgroup analysis by age group were conducted (Appendix L). The results were similar to those from the base-case analysis. The diagnostic strategy with ELR has the lowest ICER compared to no testing for all age groups but yield virtually no benefit in QALYs and LYs. The ICERs of the diagnostic strategies using ICMs directly, or combining ELR+ICMs, ranged from $139,806/QALY to $471,523 across age groups and different strategies.

6.3.4 Characterizing uncertainty

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Even under scenarios where several factors are optimized, the resulting ICERs do not become more attractive from a value perspective under the traditionally accepted thresholds of willingness to pay. Furthermore, among all the scenarios tested, the incremental QALY gains of the different cardiac monitoring strategies do not surpass 0.26 over a 20-year time horizon.

6.4 Discussion

The goal of cardiac monitoring among patients with a cryptogenic stroke is to identify patients with AF. Patients identified with AF can then be offered OAC therapy which can decrease their risk of a recurrent stroke. The use of any diagnostic test that does not lead to management of a condition will likely have no impact on the risks a certain condition causes. Therefore, under the assumption that AF diagnostic will lead to treatment decisions, and incorporating the best available evidence into the economic model, offering cardiac monitoring to cryptogenic stroke patients in BC (with any of the strategies considered in this report) compared with no further investigation for AF, using conventional thresholds for cost-effectiveness (up to $50,000 per QALY gained), none of the strategies would be deemed cost-effective (focusing on the base-case results and assumptions), as they result in modest gains in survival and quality of life at the population level.

Offering ELR only (Strategy 4) is associated with the lowest cost (i.e., incremental cost of $1,047) primarily due to the overall low cost associated with the ELR test, and no long term monitoring costs , or explantation costs. The key limitations of this strategy include a poor diagnostic yield, as only 3% patients are confirmed with AF condition; and minimal QALY and LY gains.

Strategies which combine ELR with either implantable or insertable ICMs, or using ICMs directly as the first-line device, virtually offer the same incremental survival (0.09 to 0.11) and QALY gains (0.07 to 0.08) over a 20-year time horizon. However, the ICERs ranged from $183,312 per QALY (ELR followed by implantable ICM, Strategy 1) to $324,282 per QALY (directly using insertable ICMs placed in hospital facilities, Strategy 6). These differences are mainly driven by the monitoring costs considering that approximately 70% of the ICM recipients will not be diagnosed with AF during the 3-years of cardiac monitoring, therefore only incurring monitoring costs but not accruing any benefit of the use of the technology from the assumed effect in change of drugs for stroke prevention.

Key considerations from a policy perspective are revealed through the sensitivity analyses. Some parameters in our analyses are unknown (e.g., AF prevalence) or have not yet been established in BC (e.g., physician fees for reading, frequency of readings, duration of cardiac monitoring).

Testing a combined effect of higher AF prevalence (increased to 50%), increased OAC adherence (increased to 100%) and lower physician and/or technician fees (decreased by 69%) for ICM monitoring, the ICERs for all cardiac monitoring strategies that involve implantable or insertable devices were substantially lower compared with the base-case, however, not yet deemed cost-effective under traditionally accepted willingness to pay thresholds. These factors were found to have the greatest impact in terms of improving survival and quality of life among patients with cryptogenic stroke; a key factor in narrowing the gap between ICERs and WTP threshold. For example, among patients undergoing cardiac monitoring with ELR followed by implantable device (Strategy 1), the ICER is $91,552 per QALY gain (compared with the base-case ICER of $169,119 per QALY gain in the base-case). The ICERs for cardiac monitoring strategies with insertable devices, although substantially lower compared with the base-case, are at least $100,814 per QALY gain. However, these findings should be interpreted with caution.

While the sensitivity analysis for AF prevalence (increased to 50%) decreased the ICER per QALY gained by at least 20%, to date there are no effective methods for identifying cryptogenic stroke patients at high risk for AF.

Improving OAC adherence is critical. The purpose of the cardiac monitoring strategies is to identify patients with AF in order for the patient to receive effective therapy (e.g., OAC) to reduce the risk of recurrent stroke. Downstream benefits associated with AF cardiac monitoring and detection (e.g., LY gains) will not be fully realized if OAC adherence is suboptimal.

Currently, there is no fee code specific to ICM monitoring. Stakeholder interviews revealed that physicians responsible for patients with ICMs use the fee codes associated with pacemaker monitoring. Therefore, there is considerable uncertainty regarding the fees associated with ICM monitoring. Lastly, there is no data on the frequency of data readings for both ICM types. The frequency of readings will directly impact monitoring costs not only because each reading incurs a fee for service but also because the frequency of reading impacts the number of patients diagnosed with AF (i.e., more frequent readings, more patients are diagnosed with AF sooner). Patients diagnosed with AF are offered OAC therapy and therefore incur benefits from stroke prevention and improved survival.

Our analysis has several limitations due to the scarce evidence available (only one trial which used implantable ICM [54]) and the lack of direct comparison between implantable and insertable ICMs. The diagnostic yield estimates came from a previous study that compared an implantable ICM with the ELR strategy. [54] As no clinical studies investigating diagnostic yield for insertable ICM was identified, similar diagnostic yield for implantable and insertable devices was assumed. Different wait times, frequency of readings, cost of device implantation and monitoring costs were applied in the model. In some analyses, despite slightly higher QALYs and LY gains associated with insertable devices, the increased incremental cost resulted in higher ICERs. Our findings raise important policy and clinical questions about the choice of first-line test and/or sequential testing with insertable devices compared with the implantable devices. The latter (either implantable as the first-line device, or in sequential combination after ELR) have lower ICERs but are associated with longer wait times and an in-hospital procedure, and were assumed to have less frequent data readings, consequently taking longer to detect the AF therefore delaying a patient the opportunity to begin OAC therapy and decrease their risk of recurrent stroke.

At the onset of this assessment there was a belief across multiple interviewed key stakeholders that due the lower costs of the facilities utilized for the insertable ICMs, with the possibility for shorter wait times to start the cardiac monitoring, the benefits of this technology would offset any initial higher cost with the insertable devices. However, during the assessment and gathering of information about the post-implant process of monitoring of the different types of ICMs became clear that the differences between ICM types in data transmission capabilities, which in turn can affect the frequency of data readings, and consequently, the frequency of AF diagnosis and associated monitoring costs play a major role in the relative cost-effectiveness of these different cardiac monitoring strategies. The advantages of lower procedure costs of insertable ICM (excluding the device in itself, see Table 1.10) are rapidly counterbalanced by the monitoring costs in any of the strategies with this model (Table 6.12). The policy around post-monitoring is perhaps the most critical piece to be discussed before the incorporation of this technology in a broad context to define frequency of data readings (e.g. anytime the patient transmits the data, monthly, bi-monthly, etc.) which in turn will affect the effectiveness of the technology in diagnosing AF, and the funding models for post-implant monitoring (e.g.; fee for service, payment plan per length of monitoring regardless of number of readings, per patient regardless of number of readings) which in turn will affect their relative cost-effectiveness.

Chapter 7 Budget Impact

Chapter 7 demonstrated that monitoring patients discharged with a history of cryptogenic stroke with non-invasive cardiac monitoring first (ELRs), followed by ICMs inserted in a procedure room at the physicians' office, compared to the status quo (no further monitoring), can result in 1,140 undiscounted life-years and 943 undiscounted QALYs gained at the population level for the 10 years following this policy implementation (Strategy 3 in Chapter 6). These benefits are driven by avoiding approximately 282 deaths and 179 moderate to severe recurrent strokes among the cryptogenic stroke population diagnosed with AF.

Under this policy, the BC health care system will need to accommodate 17,294 4-week ELR tests and 16,627 ICM devices. The overall incremental cost is estimated to be approximately $254.4 million over 10 years. This represents an additional 10% over the expected budget to provide healthcare for this patient population without cardiac monitoring. Costs associated with implantation/explantation of the ICMs (5.3%) and their monitoring (2.3%) are the largest contributors to the budget impact, and are expected to increase progressively as more patients are kept alive and undertake cardiac monitoring overtime.

The policy around monitoring post ICM implant monitoring is perhaps the most critical piece to be discussed in a broad context, before incorporating this technology, specifically with regards to clinical data management (transmission, readings, stewardship, etc.), pricing and funding models for post-implantation monitoring, and accountability for the clinical findings. Changes in the assumptions made with respect to these parameters play a significant role in the benefits and budget impact estimates. The current estimates assumed that patients will have, on average, 6 data readings per year, under a fee for service model, with the same monitoring fees as currently charged for pacemaker monitoring.

7.1 Objectives

To evaluate the budget impact of a policy change in BC to implement ELR and ICMs as the standard outpatient cardiac monitoring devices for the detection of AF among discharged patients with a recent history of cryptogenic stroke, compared with maintaining the status quo of no further tests with long term cardiac monitors.

7.2 Methods

Based on multiple iterations with key stakeholders (i.e. clinical experts, program area leaders, policy analysists, etc.) two scenarios were created to evaluate the budget impact in BC.

The **status quo scenario** assumes that patients who are discharged with a cryptogenic stoke will not undergo further testing with ELR or ICM to detect AF, and their risk of recurrent stroke and ICH are modeled assuming patients begin ASA therapy (standard of care). This assumption was made because ELRs and ICMs are not largely funded in BC ([redacted] of the potentially eligible population, Figure 1.4).

Scenario A assumes 100% of patients discharged with a cryptogenic stroke will have access to further AF investigation-- firstly with non-invasive cardiac monitoring (ELRs), followed by minimally invasive cardiac monitoring (Ins ICMs) placed in procedure room in the physicians' office (and adherent to septic procedures) if no AF is detected during the non-invasive monitoring period. This is equivalent to Strategy 3 in Chapter 6, and it was chosen as the scenario analysis for policy implementation for a number of ethical and logistical reasons, for instance: 1) giving patients and clinicians access to a non-invasive option first before submitting the patients to an invasive procedure; 2) moving the implant of these devices from hospital settings (i.e. operating rooms, Cath labs) to minimally invasive procedure rooms in the physician's office for optimization of the already saturated hospital resources (i.e. wait times for ORs); 3) adopting a technology that allows the patients to transmit their data from home without the need for a clinic visit; 4) minimizing underestimation of the budget necessary for the use of the technologies, should the physicians opt for their use in a large scale, and no mechanisms of patient selection is in place to triage patients.

Our clinical experts have steered us to make some important assumptions regarding technology implementation. As a consequence, Scenario A assumes:

- 100% of the patients found to have AF after cardiac monitoring with either ELRs or ICMs will be **100% adherent to the OAC therapy** (100% initiation and 0% discontinuation). The ultimate purpose of additional cardiac monitoring (ELR and ICM) is to detect AF and therefore change the patient’s therapy from ASA to OAC in order to decrease the risk of recurrent stroke. The risks and benefits of OAC therapy should AF be diagnosed are discussed with the patient prior to initiating ELR and ICM. In medical practice, the clinical experts unanimously agreed that if the patient does not agree to begin and adhere to OAC in the event of an AF diagnosis, further cardiac monitoring (with either ELR or ICMs) will not be pursued.
- Furthermore, in the context of remote cardiac monitoring, regardless of the number of data transmissions the patient’s monitor sends, the diagnosis of AF and change in treatment occurs whenever the data is being read by the clinicians (and the fees for data reading occurs). Scenario A assumes the **data readings are limited to an average of 6 times per year** (only 6 fees charged per year), for the entire battery life of the ICMs (3 years), adjusting the **time of AF diagnosis and treatment change to approximately every 2 months**, under the same **fee-for-service** funding system and **fee prices as the remote monitoring fee for pacemakers**.

In all scenarios, it was assumed that all health care costs, including the cost of the devices, monitoring, adverse events of either therapy (ASA or OAC), and costs of managing a post-stroke patient were paid by the public health care system. It was assumed that the system capacity would accommodate all the projected number of ELRs and ICMs required for the eligible population from 2019 onwards.

The deterministic Markov model utilized in the economic evaluation (Figure 6.1) was also used for the budget impact analysis. However, the model was configured to simulate the dynamic population impact over 10 years (2019 to 2028), based initially on the reference population with cryptogenic stroke in the 2017/2018 fiscal year. It is estimated that cryptogenic stroke accounts for 10% to 40% of all ischemic stroke.[17, 19] Assuming 25% (mean of the estimates from the literature) of strokes are cryptogenic after the standard workup, it is estimated that, in BC, during the 2017/18 fiscal year, 1,355 of the 5,421 ischemic strokes and TIA survivors would have been potential candidates for further monitoring with either ELR or ICM.[12] This eligible population was aggregated in age groups according to the BC age distribution of stroke/TIA (Table 6.1). [12]

The budget impact analysis was conducted for different age groups. To collate age-specific results to generate the overall budget impact during this period, age-specific subgroup weights were assigned based on Statistics Canada's projected population growth and aging data. [83] Incidence of cryptogenic stroke was assumed to remain the same in the BC population.

Every year, a new cohort of patients enter the model from the time of their discharge as a cryptogenic stroke, and thus, the number of ELR tests, ICM implantations, monitoring costs, and recurrent strokes and other adverse events were calculated cumulatively (starting from 2019). Cost of stroke management from prevalent cases of cryptogenic stroke occurring prior to

2019 were not included. As such, the reported cost estimates only pertain to the diagnostic investigation, management and treatments of cases beginning in 2019.

In line with CADTH guidelines, no discounting or inflation was applied in the BIA. Costs were expressed in 2018 Canadian dollars. We assumed no changes in price units during the period (meaning that any nominal change in price in the future would be the same as the rate of inflation).

7.3 Results

7.3.1 Status quo

It is estimated that over the next 10 years, BC is expected to have 17,478 new cases of cryptogenic stroke accounting for population aging and growth. Among these patients, under the status quo scenario in BC (i.e., neither ELR or ICM are publicly funded), it is estimated that 546 MI events, 211 ICH events, 2,710 IGB events and 1,827 moderate to severe recurrent strokes will occur, resulting in 5,169 deaths. These patients are expected to accumulate, over the next 10 years, 73,508 life-years, and 52,125 QALYs overall.

Total health management costs for the cryptogenic stroke population in BC after their first stroke was estimated at $2.6 billion over 10 years (Table 7.1). The annual cost was predicted to accumulate from $49.4 million in 2019 (for the 2019 cohort of patients alone) to $447 million in 2028 (cumulative costs for the cohorts treated from 2019-2027 and still alive). These costs include the cost of treating the acute portion of strokes, MI, ICH and GIB, as well as age-specific average costs to the health system (cost of being alive) after the occurrence of any of the adverse events (Table 6.8).

7.3.2 Scenario A – ELR followed by ICM inserted in the office available to all cryptogenic stroke patients

Applying the assumption in Scenario A, 100% adherence to OAC and data readings limited to an average of 6 per year (to the Strategy 3 from Chapter 6), the cost-effectiveness of ELR+ ICM inserted in the office was estimated to be $126,501/QALY (47% decrease in ICER compared with no further monitoring, Appendix O). The estimated annual costs and budget impact evaluation (compared to the status quo) can be found in Table 7.2.

The estimated total cost of Scenario A over 10 years is $2.8 billion. The annual cost was predicted to accumulate from $59.9 million in 2019 (for the 2019 cohort of patients alone) to $484.4 million in 2028 (cumulative costs for the cohorts treated from 2019-2027 and still alive). Of the total costs, ELR is estimated to cost [redacted], ICM (device plus implantation) is estimated to cost [redacted], monitoring costs associated with ICM is estimated to cost $59.3 million, explantation of ICMs by the end of the battery life or when an AF is diagnosed (whichever occurs first) is estimated to cost $54.8 million, and OAC drugs after an AF diagnosis are estimated to cost [redacted]. In addition, the health management costs associated with the cryptogenic stroke population after their first stroke is estimated to be $2.6 billion. This includes the costs of treating the acute portion of strokes, MI, ICH and GIB, but also age-specific average costs to the health system (cost of being alive) after any of those events occur.

Compared to the status quo, to absorb the demand of the cryptogenic stroke population, the BC health care system will be required to purchase enough ELR re-usable devices to perform 17,294 ELR tests (approximately 109 devices, see distribution by health authority in Appendix A), and 16,627 insertable ICMs for the next 10 years. This translates to between 1,462 and 2,013 ELR tests annually, and between 1,405 and 1,935 ICMs inserted in the office annually, which in turn will generate a battery waste to be managed of approximately 2,000 to 3,000 triple-A batteries per year from the ELRs tests, and between 1,405 and 1,935 of ICM batteries per year, up to 3 years after the policy implementation and continuously after.

The benefits of cardiac monitoring, AF diagnosis, and change to OAC therapy in this population of cryptogenic stroke patients is estimated to avoid 282 deaths (5.5% decrease) and 179 moderate to severe recurrent strokes (9.8% decrease) over the next 10 years, resulting in an incremental survival gain of 1,140 life-years (1.6% increase) and 943 QALYs (1.8% increase). However, it is also estimated that this will result in an additional 396 GIB events (14.6% increase), 24 ICH events (11.1% increase), and 21 MI events (3.9% increase) due to the increased risk associated with patients on OAC therapy, and longer years of survival for these patients.

The overall incremental costs are estimated at approximately $254.4 million, which is equivalent to approximately a 10% increase in the overall budget estimated for the health care management of this patient population after their first stroke. These estimates are compounded by the incremental costs associated with ELR tests ($11.2 million, 0.4% increase), ICM implantation (79.7 million, 3.1% increase), monitoring ($59.3 million, 2.3% increase), ICM explantation ($54.8 million, 2.1% increase), OAC medication (12.4 million, 0.5% increase) and acute and chronic management of adverse events ($37.0 million, 1.4% increase, cost of surviving post adverse event).

Table 7.1 Status quo: total costs for management of cryptogenic stroke patients in BC without further test/cardiac monitoring for AF after discharge, over 10 years (undiscounted).

		2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2019-2028
	N. annual incident cases of cryptogenic stroke	1,477	1,534	1,593	1,653	1,711	1,775	1,838	1,900	1,962	2,034	17,478
Status Quo	MI event	11	21	31	42	51	61	70	78	87	95	546
	ICH event	4	8	12	16	20	23	27	30	34	37	211
	GIB event	51	104	155	205	253	300	346	390	432	473	2,710
	N. Recurrent strokes (moderate + severe)	35	70	105	138	171	203	233	263	291	318	1,827
	Death	81	170	262	356	455	557	662	767	874	984	5,169
	N. ELR tests	0	0	0	0	0	0	0	0	0	0	0
	N. ICM devices	0	0	0	0	0	0	0	0	0	0	0
	QALYs	1,043	2,054	3,034	3,982	4,897	5,782	6,635	7,455	8,241	9,001	52,125
	LYs	1,439	2,848	4,225	5,568	6,872	8,140	9,369	10,554	11,694	12,798	73,508
	Cost of ELR tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cost of ICM implantation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cost of ICM Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cost of ICM explantation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AE Costs (acute + chronic management)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cost of OAC drugs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total Costs	49.4M	98.2M	146.0M	192.8M	238.5M	282.9M	326.1M	367.8M	408.0M	447.0M	2.6B

Note: costs of patients whose cryptogenic stroke occurred prior to 2019, and are still alive in the health care system, are not include in the cumulative analysis.

Table 7.2 Scenario A: total costs for management of cryptogenic stroke patients in BC with cardiac monitoring for AF after discharge with ELR tests followed by insertable ICMs placed in the physicians' offices, over 10 years (undiscounted).

		2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2019-2028	% change
ELR followed by ICM inserted in physicians' office – Scenario A	MI event	10	21	32	43	53	63	73	82	91	100	567	
	ICH event	4	9	13	18	22	26	30	34	38	41	234	
	GIB event	51	113	174	234	291	346	400	451	500	547	3,106	
	N. Recurrent strokes (moderate + severe)	30	61	92	123	153	182	211	239	266	292	1,648	
	Death	73	155	240	331	425	523	625	730	837	947	4,887	
	N. ELR tests	1,462	1,518	1,576	1,635	1,693	1,757	1,819	1,880	1,941	2,013	17,294	
	N. ICM devices	1,405	1,460	1,515	1,572	1,628	1,689	1,749	1,807	1,866	1,935	16,627	
	QALYs	1,046	2,067	3,063	4,031	4,970	5,881	6,762	7,610	8,425	9,213	53,067	
	LYs	1,442	2,862	4,257	5,624	6,957	8,258	9,521	10,743	11,920	13,062	74,647	
	Cost of ELR tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Cost of ICM implantation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Cost of ICM Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Cost of ICM explantation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	AE Costs (acute + chronic management)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Cost of OAC drugs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Total Costs	59.9M	112.1M	163.3M	216.6M	264.2M	310.9M	356.4M	400.4M	443.0M	484.4M	2.8B	
	Impact to attend demand with ELR and ICM (vs. Status quo)												%
	MI event	-1	0	0	1	2	2	3	4	4	5	21	3.9%
	ICH event	0	0	1	2	2	3	3	4	4	5	24	11.1%
	GIB event	-1	9	19	29	38	46	54	61	68	74	396	14.6%
	N. Recurrent strokes (moderate + severe)	-5	-9	-13	-16	-18	-20	-22	-24	-25	-27	-179	-9.8%
	Death	-8	-15	-22	-26	-30	-33	-36	-37	-37	-37	-282	-5.5%
	N. ELR tests	1,462	1,518	1,576	1,635	1,693	1,757	1,819	1,880	1,941	2,013	17,294	100%
	N. ICM devices	1,405	1,460	1,515	1,572	1,628	1,689	1,749	1,807	1,866	1,935	16,627	100%
	QALYs	3	13	29	49	73	99	126	155	184	212	943	1.8%
	LYs	3	14	33	57	85	117	152	189	226	264	1,140	1.6%

Cost of ELR tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of ICM implantation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of ICM Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of ICM explantation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE Costs (acute + chronic management)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of OAC drugs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Costs	10.5M	14.0M	17.3M	23.7M	25.8M	28.0M	30.3M	32.6M	35.0M	37.4M	254.4M	10.0%

Note: costs of patients whose cryptogenic stroke occurred prior to 2019, and are still alive in the health care system, are not include in the cumulative analysis.

7.4 Discussion

Incorporating the best available evidence for the BC context into a decision-analytic simulation model demonstrated that standardizing the implementation of cardiac monitoring (Scenario A) for AF investigation for patients discharged with a history of cryptogenic stroke with non-invasive cardiac monitoring first (ELRs), followed by ICMs inserted in a procedure room at the physicians' office (Chapter 6, Strategy 3), compared to the status quo (no further monitoring), can result in gains in survival and QALYs over time assuming the majority of AF diagnosed patients will be treated with OAC**.** The incremental benefits result in a gain of 1,140 undiscounted life-years and 943 undiscounted QALYs at the population level for the next 10 years following the implementation of Scenario A. These benefits are driven by avoiding approximately 282 deaths and 179 moderate to severe recurrent strokes among the cryptogenic stroke population diagnosed with AF. The BC health care system will need to accommodate 17,294 4-week ELR tests and 16,627 ICM devices. The overall incremental cost is estimated to be [redacted] over 10 years, which represents [redacted] estimated budget to provide healthcare for this patient population in the absence of cardiac monitoring (i.e., the status quo). Costs associated with implantation/explantation of the ICMs [redacted] and their monitoring [redacted] are the largest contributors to the budget impact. Incremental costs with OAC drugs and other costs to provide healthcare for this patient population represents only [redacted] the budget impact. However, incremental costs are expected to progressively increase as more patients are kept alive and are undertaking cardiac monitoring in the health care system over time.

This economic analysis has several key limitations. Concerns about the quality of the data (single trial with implantable ICM, lack of direct comparison between implantable and insertable ICMs) and assumptions regarding reimbursement of data readings (and time of the AF diagnosis) were previously discussed in the cost-effectiveness analysis; however, it is important to reinforce that the post-ICM implantation process of monitoring the data generated by the ICMs (frequency, ICM monitoring fee, funding model), which in turn can affect the frequency of AF diagnosis and associated monitoring costs significantly impact the estimated benefits and estimated budget impact. The current estimates assume that patients will have, on average, 6 data readings per year, under a fee for service model, applying the pacemaker monitoring fee. It is important to note that the frequency of the data readings are entirely dependent on the frequency of ICM data transmission. The frequency of ICM data transmission may be 1-2 tracings per year, or may occur daily. This represents a huge incremental workload for the clinics and clinicians compared to an in-person visit every 6-12 months to download the ICM data. Currently, there is no readily available data in BC on the frequency of data readings or mechanisms to cap the frequency of data readings after ICM implantation. Under the current fee for service funding mechanism and the current monitoring fees charged, any deviation to the average number of data readings can significantly and progressively inflate the budget impact estimates. From another perspective, other considerations need to be given to the processes limiting the number of data readings. If the data is transmitted automatically, and not immediately read, in the instance of an AF patient not being immediately diagnosed and treated, if a preventable AE occurs (recurrent stroke, death), ethical and legal implications may follow given the availability of the data for the health system to act on. The policy regarding post-monitoring is perhaps the most critical piece to be discussed in a broad context, before the incorporation of this technology, to define ICM data management (transmission, readings, stewardship, etc.), funding models for post-implantation monitoring and accountability for the clinical findings.

Finally, it is important to consider that, without a mechanism to select cryptogenic stroke patients at highest risk for AF prior to ICM implantation, this budget impact assessment reveals that more than 70% of the eligible patients will only generate compounding costs related to ICM (implantation, explantation, monitoring) for the 3 years following the device insertion, without incurring any benefit as these patients will not be diagnosed with AF.

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Appendix E Infection Control Requirements for ICM Procedure

Below are some excerpts from the CSA Z8000 – 18 standards. These standards are intended to be used by all facilities providing health care services, regardless of type, size, location, or range of services.

9.3.3 Technical requirements for procedure rooms

Note: *This Clause sets requirements for all types of procedure rooms. Clause 9.3.3.1 addresses common requirements for procedure rooms and Clause 9.3.3.2 sets additional requirements for procedure rooms where Category III services are provided.*

9.3.3.1 General

9.3.3.1.1

Provisions shall be made for examinations, interviews, preparation, testing, and obtaining vital signs of patients for outpatient surgery or other non-surgical procedures.

9.3.3.1.2

An area for preparation and examination of frozen sections (i.e., cryosection) may be part of the general laboratory if immediate results are obtainable without unnecessary delay in the completion of surgery.

9.3.3.1.3

Appropriate, convenient, and easily accessible locations shall be provided for supplies and cleaned equipment.

9.3.3.1.4

Appropriate holding space shall be provided for soiled equipment that requires cleaning.

9.3.3.1.5

A staff lounge in either a team room or shared in a central area shall be provided.

9.3.3.1.6

Provision should be made for education (i.e., adequate space and audio-visual facilities).

9.3.3.1.7

Consideration should be given to providing a layout where staff workstations and support areas are separated from reception, waiting, and patient care areas.

9.3.3.1.8

Positive distractions (e.g., acoustic, visual, entertainment, or daylight) should be considered, particularly for lengthy procedures or recovery and pain management.

9.3.3.1.9

The ceiling design should be taken into account, especially for areas such as procedure rooms and recovery areas where patients are on their backs for long periods of time.

9.3.3.2 Procedure rooms — Common requirements

9.3.3.2.1

The following requirements shall apply to all procedure rooms (Category II and Category III):

a) Each room shall have a system for emergency communication with the main communication and control station.

b) X-ray film viewers for handling at least four films simultaneously or a PACS workstation (digital image viewers) shall be provided.

c) Perimeter walls, ceiling, and floors, including penetrations, shall be sealed.

d) Medical gas terminal units shall be provided in accordance with Annex F of CSA Z7396.1.

e) A scavenging system for medical gases should be provided, according to the services used.

f) A surgical plume scavenging system shall be provided if electrocautery or laser procedures will be used. See CSA Z305.13.

g) The need to maintain for patient warmth shall be considered in the design (e.g., by providing temperature controls) and provision shall be made for patient warming systems.

h) Direct access to a Stage 2 recovery area shall be provided.

9.3.3.2.2

Lighting shall be adaptable for minimally invasive surgery use, with dimmable spotlights and zoned switching of fluorescent fixtures.

9.3.3.2.3

Procedure rooms shall be designed for visual and acoustical privacy for the patient.

9.3.3.2.4

Station outlets for oxygen and medical vacuum shall be available in the procedure room. See Annex F of CSA Z7396.1.

9.3.3.2.5

A dedicated hand hygiene sink shall be available in the room.

9.3.3.2.6

A system for emergency communication shall be provided.

9.3.3.2.7

Floor covering in the procedure suite shall be monolithic.

9.3.3.3 Procedure rooms — Operative procedure rooms

9.3.3.3.1 General

The following requirements shall apply to all operating rooms where Category III services are provided:

a) Each room shall have a system for emergency communication with the surgical suite control station.

b) X-ray film viewers for handling at least four films simultaneously or a PACS workstation (digital image viewers) shall be provided.

c) Operating room perimeter walls, ceiling, and floors, including penetrations, shall be sealed.

d) Medical gas terminal units shall be provided in accordance with Annex F of CSA Z7396.1.

e) A scavenging system for medical gases shall be provided.

f) A surgical plume scavenging system shall be provided if electrocautery or laser procedures will be used. See CSA Z305.13.

g) Provision shall be made for patient warming systems.

Note: *See CAN/CSA-Z317.2 for requirements regarding temperature controls. Operating rooms are Type I areas in the area classification system used in CAN/CSA-Z317.2.*

h) A central music system shall be provided for each operating and procedure room.

Note: *Patient confidentiality and acoustics are especially important in day surgery and PACU patient areas.*

9.3.7 Infection prevention and control

9.3.7.1 General

Provisions for infection prevention and control in operating rooms and procedure rooms shall include the following:

a) There shall be no floor drains.

b) Laminar flow diffusers shall be provided over the patient, with low level exhaust in corners of the OR.

c) Laminar flow systems in arthroplasty joint replacement surgery operating rooms shall be provided.

d) The design shall specify the flow of supplies and maintain separation between clean and contaminated equipment.

e) Hygiene sinks and supplies shall be immediately outside of an operating room or procedure room.

f) Scrub facilities (scrub sinks) with hands-free operable controls shall be provided adjacent to the entrance of procedure rooms and shall be arranged to minimize incidental splatter on nearby personnel, medical equipment, or supplies.

g) Management of soiled scopes and storage for clean scopes and other equipment shall be in accordance with CAN/CSA-Z314 and infection prevention and control guidelines.

Sections of CSA z317.2-15 Special requirements for heating and ventilation HVAC also apply

6.10.3 Medium level air separation

The following pressure-controlled spaces shall be designed and constructed so that a pressure differential of 2.5 Pa can be maintained in relation to adjacent areas.

Note: *This requirement applies both to room construction (i.e., sufficiently airtight to support a pressure differential) and HVAC system design.*

medical device reprocessing (MDR) and sterile storage;
operative birthing rooms (Caesarean delivery areas);
sterile core/operating rooms/surgery;
interventional or invasive imaging (e.g., angiography, cardiac catheterization, interventional MRI suites);
biomedical waste storage;
autopsy; and other rooms or areas identified by a risk management exercise as needing air separation.

6.11.3 Type I areas

6.11.3.1

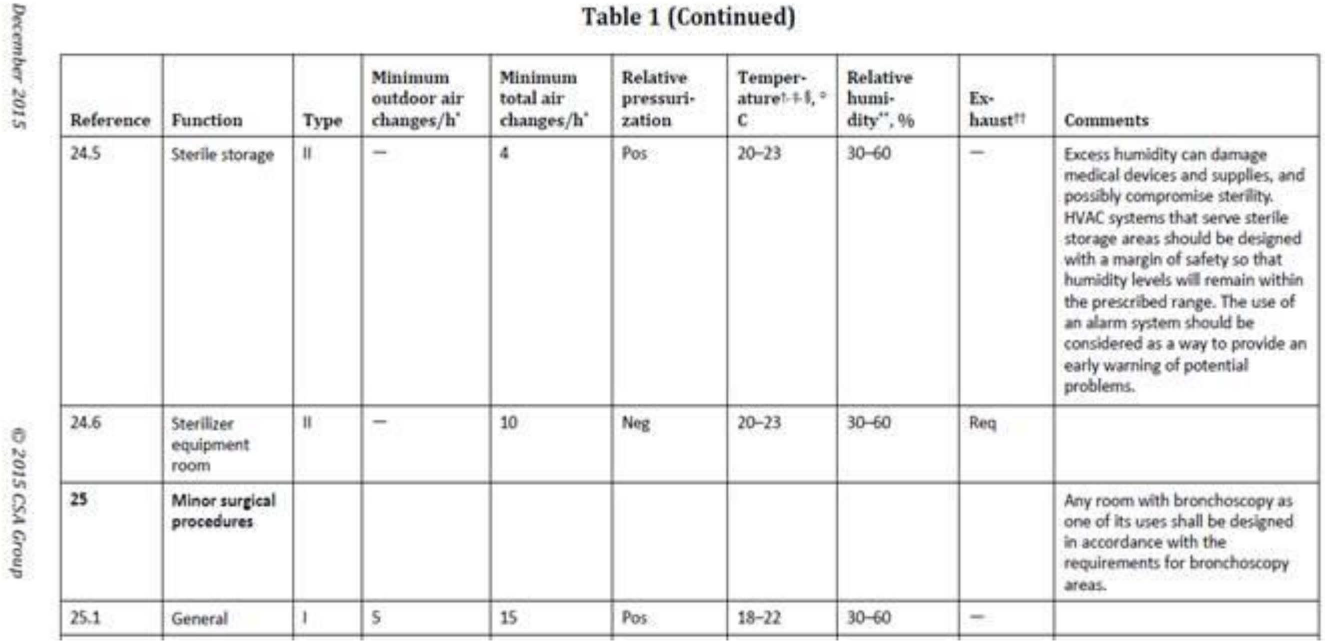
Air shall be supplied from the ceiling in Type I areas. The air supply for operating rooms, delivery rooms, and other rooms used for invasive procedures shall be provided through non-aspirating ceiling outlets near the centre of the work area.

6.11.3.2

Return or exhaust air inlets shall be near the floor level for rooms used for invasive procedures, anaesthetizing locations, or where anaesthesia might be exhaled. Any area in the health care facility where patients are recovering from general anaesthetic (e.g., day surgery) shall have air change rates consistent with those for surgical recovery rooms. Each operating and delivery room shall have at least two return or exhaust air inlets, located remotely from each other. The position of the inlets shall be such that areas without air movement (i.e., dead zones) are minimized. The bottom of ventilation (return/exhaust) openings shall be 75 to 500 mm above the floor. Low-level grille cores shall be provided with one-quarter turn fasteners so that they can be removed for cleaning while leaving the mounting frame in place.

Note: *Operating room supply, exhaust/return grilles, and air boots should be manufactured from material that can be disinfected.*

Table 1 CSA Z317.2-15



December 2015

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Table 1 (Continued)

Reference	Function	Type	Minimum outdoor air changes/h*	Minimum total air changes/h*	Relative pressurization	Temperature†‡§, °C	Relative humidity**, %	Exhaust††	Comments
24.5	Sterile storage	II	—	4	Pos	20–23	30–60	—	Excess humidity can damage medical devices and supplies, and possibly compromise sterility. HVAC systems that serve sterile storage areas should be designed with a margin of safety so that humidity levels will remain within the prescribed range. The use of an alarm system should be considered as a way to provide an early warning of potential problems.
24.6	Sterilizer equipment room	II	—	10	Neg	20–23	30–60	Req	
25	**Minor surgical procedures**								Any room with bronchoscopy as one of its uses shall be designed in accordance with the requirements for bronchoscopy areas.
25.1	General	I	5	15	Pos	18–22	30–60	—	

Appendix F Search Strategies

F.1 MEDLINE

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to May 30, 2018>
Search Strategy:
----
1 Arrhythmias, Cardiac/ (58302)
2 Atrial Fibrillation/ (46611)
3 ((atrial or auricular or atrium or atria) adj2 fibrillation$).tw,kf. (60682)
4 (a-fib or afib).tw,kf. (368)
5 (arrhythmia$ or arrythmia$ or dysrhythmia$ or dysrythmia$ or disrhythmia$ or disrythmia$ or tachyarrhythmia$ or tachyarrythmia$).tw,kf. (89835)
6 or/1-5 [Afib] (173102)

7 stroke/ or brain infarction/ or brain stem infarctions/ or lateral medullary syndrome/ or cerebral infarction/ or dementia, multi-infarct/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or stroke, lacunar/ (114319)
8 Brain Ischemia/ (45553)
9 brain infarction/ or brain stem infarctions/ or lateral medullary syndrome/ or ischemic attack, transient/ (24624)
10 (stroke or strokes or poststroke or apoplex$).tw,kf. (217123)
11 ((cerebrovascular or cerebro-vascular or cerebral or intracerebral or brain or brainstem or subcortical or cortex or ischaemi$ or ischemi$ or intracranial) adj3 (accident or accidents or infarction or infarctions or attack or attacks or insult$ or arrest or failure or insufficiency)).tw,kf. (65139)
12 ((ischaemi$ or ischemi$) adj3 (brain or seizure$ or cerebral)).tw,kf. (44698)
13 (CVA or CVAs or TIA or TIAs).tw,kw. (10353)
14 or/7-13 [Stroke] (321995)

15 6 and 14 [Afib and Stroke] (21143)
16 Electrocardiography/ (181214)
17 Electrocardiography, Ambulatory/ (10162)
18 (electrocardiograph$ or electrocardiogram$ or electro-cardiograph$ or electro-cardiogram$ or electric-cardiogra$ or EKG or EKGs or ECG or ECGs).tw,kf. (128715)
19 ((cardiac or heart or coronary or atrium or auricular or atrial or atria) adj3 monitor$).tw,kf. (11490)
20 ((monitor$ or record$) adj3 device$).tw,kf. (7801)
21 ((detect$ or diagnos$ or screen$ or predict$) and monitor$).ti. (8081)
22 (auto-detect$ or autodetect$ or auto-record$ or autorecord$).tw,kf. (56)
23 ((event or events or postevent$ or loop) adj5 (recorder$ or monitor or monitors or recording or monitoring)).tw,kf. (7251)
24 or/16-23 (264636)

25 and/6,14,24 [Afib & Stroke & Monitoring] (2767)

26 "prostheses and implants"/ or electrodes, implanted/ (61737)
27 Monitoring, Physiologic/ (51250)
28 Monitoring, Ambulatory/ (7422)
29 (monitor$ or record$).tw,kf. (1547477)
30 or/27-29 (1568828)
31 26 and 30 (8447)

32 and/6,14,31 [Afib & Stroke & Implant Monitoring] (33)

33 (implant$ or insert$ or subcutaneous$ or sub-cutaneous$).tw,kf. (719940)
34 internal loop.tw,kf. (623)
35 (ILR or ILRs).tw,kw. (393)
36 (Medtronic and Reveal).mp. (77)
37 or/33-36 [Implants] (720692)

38 and/6,14,24,37 (331)

39 (Cardiac implant$ adj5 (device? or monitor$)).tw,kf. (768)
40 and/6,14,39 [Afib & Stroke & Implant Monitoring] (54)

41 or/32,38,40 [Combined Results] (367)

42 limit 41 to yr="2016 -Current" (125)
43 (2016$ or 2017$ or 2018$).dt. (3006793)
44 41 and 43 (131)
45 42 or 44 (138)

46 limit 45 to English language (134)

F.2 Embase

Database: Embase <1974 to 2018 July 09>
Search Strategy:
----
1 heart arrhythmia/ (116202)
2 atrioventricular junction arrhythmia/ or heart fibrillation/ or heart palpitation/ or heart preexcitation/ (27641)
3 heart atrium arrhythmia/ (5487)
4 atrial fibrillation/ or chronic atrial fibrillation/ or new-onset atrial fibrillation/ or paroxysmal atrial fibrillation/ or permanent atrial fibrillation/ or persistent atrial fibrillation/ (42836)
5 sinus node disease/ or sick sinus syndrome/ or sinus arrest/ or sinus arrhythmia/ or sinus bradycardia/ or sinus tachycardia/ (22502)
6 heart atrium flutter/ (12198)
7 heart supraventricular arrhythmia/ (3395)
8 paroxysmal supraventricular tachycardia/ (2660)
9 supraventricular premature beat/ (2809)
10 supraventricular tachycardia/ or ectopic atrial tachycardia/ or junctional ectopic tachycardia/ (17880)
11 heart atrium fibrillation/ (88956)
12 atrium fibrillation/ (37149)
13 intermittent heart atrium fibrillation/ (2)
14 ((atrial or auricular or atrium or atria) adj2 fibrillation$).tw,kw. (106405)
15 (a-fib or afib).tw,kw. (1222)

16 (arrhythmia$ or arrythmia$ or dysrhythmia$ or dysrythmia$ or disrhythmia$ or disrythmia$ or tachyarrhythmia$ or tachyarrythmia$).tw,kw. (133989)
17 or/1-16 (348353)

18 cerebrovascular accident/ or cardioembolic stroke/ (168984)
19 brain ischemia/ or transient ischemic attack/ (149118)
20 brain infarction/ or brain stem infarction/ or cerebellum infarction/ (49778)
21 (stroke or strokes or poststroke or apoplex$).tw,kw. (345765)
22 ((cerebrovascular or cerebro-vascular or cerebral or intracerebral or brain or brainstem or subcortical or cortex or ischaemi$ or ischemi$ or intracranial) adj3 (accident or accidents or infarction or infarctions or attack or attacks or insult$ or arrest or failure or insufficiency)).tw,kw. (96997)
23 ((ischaemi$ or ischemi$) adj3 (brain or seizure$ or cerebral)).tw,kw. (63550)
24 (CVA or CVAs or TIA or TIAs).tw,kw. (22406)
25 or/18-24 (525217)

26 17 and 25 [Afib and Stroke] (50445)

27 implantable cardiac monitor/ (11855)
28 ((implant$ or insert$ or subcutaneous$ or sub-cutaneous$) adj3 (monitor$ or recorder$)).tw,kw. (4573)
29 insertable cardiac event recorder/ (1)
30 echocardiography/ and implantation/ (3672)
31 or/27-30 (19381)

32 17 and 25 and 31 (586)

33 electrocardiography/ (141793)
34 electrocardiography monitoring/ (8049)
35 electrocardiogram/ (106552)
36 ambulatory electrocardiography/ (177)
37 (electrocardiograph$ or electrocardiogram$ or electro-cardiograph$ or electro-cardiogram$ or electric-cardiogra$ or EKG or EKGs or ECG or ECGs).tw,kw. (180876)
38 ((cardiac or heart or coronary or atrium or auricular or atrial or atria) adj3 monitor$).tw,kw. (17137)
39 ((monitor$ or record$) adj3 device$).tw,kw. (11228)
40 ((detect$ or diagnos$ or screen$ or predict$) and monitor$).ti. (11163)
41 (auto-detect$ or autodetect$ or auto-record$ or autorecord$).tw,kw. (100)
42 ((event or events or postevent$ or loop) adj5 (recorder$ or monitor or monitors or recording or monitoring)).tw,kw. (11318)
43 or/33-42 [Monitoring] (347233)

44 17 and 25 and 43 (6603)

45 (implant$ or insert$ or subcutaneous$ or sub-cutaneous$).tw,kw. (949381)
46 internal loop.tw,kw. (723)
47 (ILR or ILRs).tw,kw. (839)
48 (Medtronic and Reveal).mp. (574)
49 "ILRs Reveal XT"/ (1)
50 or/45-49 (950356)

51 and/17,25,43,50 (899)
52 32 or 51 (1090)

53 limit 52 to yr="2016 -Current" (406)

Appendix G Characteristics of Included Studies

Name	**EMBRACE**	
Methods	Open label multi centre RCT	
Population	Patients were eligible for enrollment if they were 55 years of age or older, did not have known atrial fibrillation, and had had an ischemic stroke or TIA of undetermined cause (according to TOAST) within the previous 6 months, diagnosed by a stroke neurologist after a standard workup, including 12-lead ECG, ambulatory ECG monitoring with the use of a Holter monitor for a minimum of 24 hours, brain and neurovascular imaging, and echocardiography.	
Outcomes	The primary outcome was the detection of one or more episodes of ECG-documented atrial fibrillation or flutter lasting 30 seconds or longer within 90 days after randomization. Secondary outcomes included: • oral anticoagulant use at 90 days, atrial fibrillation lasting 30 seconds or longer that was detected by the study monitor; • atrial fibrillation of any duration that was detected by the study monitor, atrial fibrillation lasting 2.5 minutes or longer (the maximum recording duration per episode) that was detected by the study monitor; • adherence to monitoring; • a switch from antiplatelet to anticoagulant therapy in the period from randomization to 90 days.	
Baseline characteristics	ELR arm (n=286)	Control arm (n=285)
Age, y	72.5±8.5	73.2±8.8
Sex, n (%)		
Male	154 (53.8)	160 (56.1)
Female	132 (46.2)	125 (43.9)
Index event, n (%)		
Stroke	188 (65.7)	172 (60.4)
TIA	98 (34.3)	113 (39.6)
Prior stroke or TIA, n (%)		
Stroke	45 (15.7)	36 (12.6)
TIA	42 (14.7)	46 (16.1)

Score on modified Rankin scale, n (%)		
0–2	274 (95.8)	263 (92.3)
>2	12 (4.2)	22 (7.7)
Score on NIH Stroke Scale		
Hypertension, n (%)	204 (71.3)	191 (67.0)
Diabetes mellitus, n (%)	55 (19.2)	55 (19.3)
Hypercholesterolemia, n (%)	191 (66.8)	177 (62.1)
Current smoker, n (%)	19 (6.6)	24 (8.4)
Coronary artery disease, n (%)	24 (8.4)	23 (8.1)
Coronary bypass surgery, n (%)	29 (10.1)	19 (6.7)

Name	**CRYSTAL-AF**	
Methods	Randomized controlled trial comparing implantable loop recorder to standard of care	
Population	Eligible patients were 40 years of age or older and had received a diagnosis of stroke or TIA, occurring within the previous 90 days, that was supported by consistency between symptoms and findings on brain magnetic resonance imaging or computed tomography The main exclusion criteria were a history of atrial fibrillation or atrial flutter, an indication or contraindication for permanent oral anticoagulant therapy at enrollment, and an indication for a pacemaker or implantable cardioverter–defibrillator	
Outcomes	Primary outcome: AF detection rate in 6 months Secondary outcomes included the AF detection rate at 12 months, incidence of recurrent stroke or TIA, change in oral anticoagulation and antiarrhythmic drugs, quality of life, economic and disease burden, role of Patient Assistant device in the time of AF diagnosis in subjects implanted with Reveal XT	
Baseline characteristics	ICM arm (n=221)	Control arm (n=220)
Age, y	61.6±11.4	61.4±11.3
Sex, n (%)		
Male	142 (64.3%)	138 (62.7%)
Female	79 (35.7%)	82 (37.3%)
Patent foramen ovale (PFO), n (%)	52 (23.5%)	46 (20.9%)
Index event, n (%)		

Stroke	200 (90.5%)	201 (91.4%)
TIA	21 (9.5%)	19 (8.6%)
Prior stroke or TIA, n (%)		
Stroke	37 (16.7%)	28 (12.7%)
TIA	22 (10.0%)	27 (12.3%)
Score on modified Rankin scale, n (%)		
0–2	184 (83.3%)	186 (84.5%)
>2	36 (16.3%)	34 (15.5%)
Score on NIH Stroke Scale	1.6±2.7	1.9±3.8
Hypertension, n (%)	144 (65.2%)	127 (57.7%)
Diabetes mellitus, n (%)	34 (15.4%)	38 (17.3%)
CHADS2 score, n (%)		
2	69 (31.2%)	81 (36.8%)
3	92 (41.6%)	91 (41.4%)
4	50 (22.6%)	34 (15.5%)
5	9 (4.1%)	14 (6.4%)
6	1 (0.5%)	0 (0.0%)
Hypercholesterolemia, n (%)	125 (56.6%)	128 (58.2%)
Current smoker, n (%)	43 (19.5%)	44 (20.0%)
Coronary artery disease, n (%)	16 (7.2%)	9 (4.1%)
Use of antiplatelet agent, n (%)	212 (95.9%)	212 (96.4%)

Appendix H Characteristics of Excluded Studies

Excluded study	Reference
Bernstein 2017	Bernstein RA, Kamel H, Granger CB, Kowal RC, Ziegler PD, Schwamm LH. Stroke of Known Cause and Underlying Atrial Fibrillation (STROKE-AF) randomized trial: Design and rationale. Am Heart J. 2017;190:19-24.
Reason	Protocol
Toni 2016	Toni D, Lorenzano S, Strano S, Investigators ST, Toni D, Strano S, et al. Detection of Silent Atrial Fibrillation aFter Ischemic StrOke (SAFFO) guided by implantable loop recorder: multicentre Italian trial based on stroke unit network with paired cardio-arrhythmology units (Italian Neurocardiology Unit Network). Int J Stroke. 2016;11(3):361-7.
Reason	Protocol
Christensen 2014	Christensen LM, Krieger DW, Hojberg S, Pedersen OD, Karlsen FM, Jacobsen MD, et al. Paroxysmal atrial fibrillation occurs often in cryptogenic ischaemic stroke. Final results from the SURPRISE study. Eur J Neurol. 2014;21(6):884-9.
Reason	Single arm
Conti 2017	Conti S, Reiffel JA, Gersh BJ, Kowey PR, Wachter R, Halperin JL, et al. Baseline Demographics, Safety, and Patient Acceptance of an Insertable Cardiac Monitor for Atrial Fibrillation Screening: The REVEAL-AF Study. J Atr Fibrillation. 2017;9(5):1551.
Reason	Single arm
Cotter 2013	Cotter PE, Martin PJ, Ring L, Warburton EA, Belham M, Pugh PJ. Incidence of atrial fibrillation detected by implantable loop recorders in unexplained stroke. Neurology. 2013;80(17):1546-50.
Reason	Single arm
Diederichsen 2017	Diederichsen SZ, Haugan KJ, Hojberg S, Holst AG, Kober L, Pedersen KB, et al. Complications after implantation of a new-generation insertable cardiac monitor: Results from the LOOP study. Int J Cardiol. 2017;241:229-34.
Reason	Single arm
Dion 2010	Dion F, Saudeau D, Bonnaud I, Friocourt P, Bonneau A, Poret P, et al. Unexpected low prevalence of atrial fibrillation in cryptogenic ischemic stroke: a prospective study. J Interv Card Electrophysiol. 2010;28(2):101-7.
Reason	Single arm
Etgen 2013	Etgen T, Hochreiter M, Mundel M, Freudenberger T. Insertable cardiac event recorder in detection of atrial fibrillation after cryptogenic stroke: an audit report. Stroke. 2013;44(7):2007-9.
Reason	Single arm

Giralt-Steinhauer 2015	Giralt-Steinhauer E, Cuadrado-Godia E, Soriano-Tarraga C, Ois A, Jimenez-Conde J, Rodriguez-Campello A, et al. New-Onset Paroxysmal Atrial Fibrillation Diagnosis in Ischemic Stroke Patients. Eur Neurol. 2015;74(3-4):211-7.
Reason	Single arm
Healey 2017	Healey JS, Alings M, Ha A, Leong-Sit P, Birnie DH, de Graaf JJ, et al. Subclinical Atrial Fibrillation in Older Patients. Circulation. 2017;136(14):1276-83.
Reason	Single arm
Israel 2017	Israel C, Kitsiou A, Kalyani M, Deelawar S, Ejangue LE, Rogalewski A, et al. Detection of atrial fibrillation in patients with embolic stroke of undetermined source by prolonged monitoring with implantable loop recorders. Thromb Haemost. 2017;117(10):1962-9.
Reason	Single arm
Jorfida 2016	Jorfida M, Antolini M, Cerrato E, Caprioli MG, Castagno D, Garrone P, et al. Cryptogenic ischemic stroke and prevalence of asymptomatic atrial fibrillation: a prospective study. J Cardiovasc Med (Hagerstown). 2016;17(12):863-9.
Reason	Single arm
Mittal 2016	Mittal S, Rogers J, Sarkar S, Koehler J, Warman EN, Tomson TT, et al. Real-world performance of an enhanced atrial fibrillation detection algorithm in an insertable cardiac monitor. Heart Rhythm. 2016;13(8):1624-30.
Reason	Single arm
Muller 2017	Muller P, Ivanov V, Kara K, Klein-Wiele O, Forkmann M, Piorkowski C, et al. Total atrial conduction time to predict occult atrial fibrillation after cryptogenic stroke. Clin Res Cardiol. 2017;106(2):113-9.
Reason	Single arm
Nasir 2017	Nasir JM, Pomeroy W, Marler A, Hann M, Baykaner T, Jones R, et al. Predicting Determinants of Atrial Fibrillation or Flutter for Therapy Elucidation in Patients at Risk for Thromboembolic Events (PREDATE AF) Study. Heart rhythm. 2017;14(7):955-61.
Reason	Single arm
Pedersen 2018	Pedersen KB, Madsen C, Sandgaard NCF, Diederichsen ACP, Bak S, Brandes A. Subclinical atrial fibrillation in patients with recent transient ischemic attack. J Cardiovasc Electrophysiol. 2018;29(5):707-14.
Reason	Single arm
Poli 2016	Poli S, Diedler J, Hartig F, Gotz N, Bauer A, Sachse T, et al. Insertable cardiac monitors after cryptogenic stroke--a risk factor based approach to enhance the detection rate for paroxysmal atrial fibrillation. Eur J Neurol. 2016;23(2):375-81.
Reason	Single arm
Reiffel 2017	Reiffel JA, Verma A, Kowey PR, Halperin JL, Gersh BJ, Wachter R, et al. Incidence of Previously Undiagnosed Atrial Fibrillation Using Insertable

	Cardiac Monitors in a High-Risk Population: The REVEAL AF Study. JAMA Cardiol. 2017;2(10):1120-7.
Reason	Single arm
Ritter 2013	Ritter MA, Kochhauser S, Duning T, Reinke F, Pott C, Dechering DG, et al. Occult atrial fibrillation in cryptogenic stroke: detection by 7-day electrocardiogram versus implantable cardiac monitors. Stroke. 2013;44(5):1449-52.
Reason	Single arm
Seow 2018	Seow S-C, How A-K, Chan S-P, Teoh H-L, Lim T-W, Singh D, et al. High Incidence of Occult Atrial Fibrillation in Asian Patients with Cryptogenic Stroke. J Stroke Cerebrovasc Dis. 2018;27(8):2182-6.
Reason	Single arm
Ziegler 2015	Ziegler PD, Rogers JD, Ferreira SW, Nichols AJ, Sarkar S, Koehler JL, et al. Real-World Experience with Insertable Cardiac Monitors to Find Atrial Fibrillation in Cryptogenic Stroke. Cerebrovasc Dis. 2015;40(3-4):175-81.
Reason	Single arm
Ziegler 2017	Ziegler PD, Rogers JD, Ferreira SW, Nichols AJ, Richards M, Koehler JL, et al. Long-term detection of atrial fibrillation with insertable cardiac monitors in a real-world cryptogenic stroke population. Int J Cardiol. 2017;244:175-9.
Reason	Single arm

Appendix I Critical Appraisal of the Included RCTs

Study name	**EMBRACE**	
Risk of bias	Judgement	Comment
Random sequence generation (selection bias)	Low	“Randomization was performed with the use of a Web based system and a variable block size”
Allocation concealment (selection bias)	High	Open label study
Blinding of participant and personnel (performance bias)	High	Open label study
Blinding of outcome assessment (detection bias)	High	Not blinded
Incomplete outcome data (attrition bias)	Low	Low number of drop-outs
Selective reporting (reporting bias)	High	Quality of life was not reported.
Study name	**CRYSTAL-AF**	
Risk of bias	Judgement	Comment
Random sequence generation (selection bias)	Low	Randomization was achieved by interactive voice response telephone system. Patients was stratified according to stroke or TIA, and the presence of PFO. The number of hypertensive patients is higher in the ICM arm. Other than that, we found no evidence that the randomization was compromised
Allocation concealment (selection bias)	High	Study was not blinded
Blinding of participant and personnel (performance bias)	High	Study was not blinded to participants or investigators
Blinding of outcome assessment (detection bias)	High	Study was not blinded to the adjudication committee
Incomplete outcome data (attrition bias)	High	At 6 months, the attrition rate was low (5.0% in ICM arm, 10.5% in control arm). Starting from 12 months, a large portion of patients dropped out from the study. By 36 months, only 10.9% in ICM arm and 10.9% in control arm remained in the study. The high attrition rate was the main reason for the 10% difference between the estimated detection rate and the observed detection rate at 36 months.
Selective reporting (reporting bias)	Low	All relevant and pre-specified outcomes reported.

Appendix J Economic literature review: Quality of Reporting of Included CEA studies (CHEERS)

Article	Study Type	Target population and subgroups	Setting and location	Study perspective	Comparators	Time horizon	Discount rate	Choice of health outcomes	Measurement of effectiveness	Measurement and valuation of preference-based	Estimating resources and costs	Currency, price date, and conversion	Choice of model	Assumptions	Analytic methods	Study parameters	Incremental costs and outcomes	Characterizing uncertainty	Characterizing heterogeneity	Study Findings and Discussion of limitations	Source of Funding	Conflict of Interest
Diamantopoulos 2016	CEA-model based	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
CADTH report 2016	CEA-model based	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	NA	Y

Appendix K Economic literature review: Summary of finding

Author, year , country	Currency , year	Time horizon (in years)	Outcome	Intervention	Cost of Intervention	QALYs intervention	Comparator	Cost of Comparator	QALYs Comparator	Incremental QALY	Incremental Cost	Main results - ICER (base-case)
Diamantopoulos 2016, UK	£, year unknown	Lifetime	QALY, EQ-5D	ICM	£19,631	7.367	SoC	£17,045	7.216	0.151	£2,587	£17,175/QALY
CADTH report 2016, Canada	CAD, 2016	Lifetime	QALY, HUI	ICM (Warfarin)	$180,789	3.185	SoC (Warfarin)	$176,957	3.176	0.009	$3,832	$414,732/QALY
				ICM (Apixaban)	$181,141	3.193	SoC (Apixaban)	$177,078	3.178	0.015	$4,063	$273,815/QALY
				ICM (Dabigatran)								$420,062/QALY
				ICM (Rivaroxaban)								$390,578/QALY

Appendix L BC background mortality from Stats Canada

Age	Background mortality probability	Age	Background mortality probability
50 years	0.00245	86 years	0.07458
51 years	0.00265	87 years	0.08362
52 years	0.00286	88 years	0.09386
53 years	0.00309	89 years	0.10545
54 years	0.00335	90 years	0.11861
55 years	0.00363	91 years	0.1332
56 years	0.00394	92 years	0.14896
57 years	0.00428	93 years	0.16588
58 years	0.00465	94 years	0.18396
59 years	0.00507	95 years	0.20947
60 years	0.00552	96 years	0.23035
61 years	0.00602	97 years	0.25216
62 years	0.00658	98 years	0.27474
63 years	0.00719	99 years	0.29788
64 years	0.00787	100 years	0.32138
65 years	0.00862	101 years	0.345
66 years	0.00945	102 years	0.3685
67 years	0.01037	103 years	0.39165
68 years	0.0114	104 years	0.41424
69 years	0.01254	105 years	0.43606
70 years	0.01381	106 years	0.45695
71 years	0.01522	107 years	0.47678
72 years	0.0168	108 years	0.49543
73 years	0.01856	109 years	0.51284
74 years	0.02052	110 years and over	1
75 years	0.02272		
76 years	0.02518		
77 years	0.02793		
78 years	0.03102		
79 years	0.03449		
80 years	0.03839		
81 years	0.04277		
82 years	0.0477		
83 years	0.05325		
84 years	0.05952		
85 years	0.06659		

Note: The formula used to adjust the annual probability of mortality for those patients who experienced an adverse event was $p_{AEmortality} = 1 - EXP\left(\left(-LN\ (1 - background\ mortality\ probability\ )\right) * HR\ of\ AE\ \text{(in Table 6.4)}\right)/26$