Monitoring for Atrial Fibrillation in Discharged Stroke and Transient Ischemic Attack Patients: Recommendations

Recommendations Report

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# Table of Contents

ABBREVIATIONS .................................................................................................................. II

1. SUMMARY OF RECOMMENDATION.............................................................................. 1  
   1.1 Technology ............................................................................................................... 1

2. METHODS....................................................................................................................... 2

3. DETAILED RECOMMENDATIONS................................................................................. 2  
   3.1 Rationale .................................................................................................................. 2  
   3.2 Considerations ........................................................................................................... 3

4. BACKGROUND ............................................................................................................... 4  
   4.1 Research Questions ................................................................................................. 5

5. SUMMARY OF THE EVIDENCE.................................................................................... 5  
   5.1 Clinical Evidence ...................................................................................................... 5  
   5.2 Economic Evidence .................................................................................................. 6  
   5.3 Patient Preference and Experience Evidence ......................................................... 7

REFERENCES ..................................................................................................................... 8

APPENDIX 1: HEALTH TECHNOLOGY EXPERT REVIEW PANEL .................................. 10
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
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<tr>
<td>ECG</td>
<td>electrocardiography</td>
</tr>
<tr>
<td>ELR</td>
<td>external loop recorder</td>
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<tr>
<td>ESUS</td>
<td>embolic stroke of undetermined source</td>
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<tr>
<td>HTA</td>
<td>health technology assessment</td>
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<tr>
<td>HTERP</td>
<td>Health Technology Expert Review Panel</td>
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<tr>
<td>ICER</td>
<td>incremental cost-effectiveness ratio</td>
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<td>ILR</td>
<td>implantable loop recorder</td>
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<tr>
<td>MCOT</td>
<td>mobile cardiac outpatient telemetry</td>
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<tr>
<td>OAC</td>
<td>oral anticoagulant</td>
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<tr>
<td>QALY</td>
<td>quality-adjusted life-year</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
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1. Summary of Recommendation

An ischemic stroke is caused by thrombosis of the cerebral vessels or by emboli from a proximal arterial source or the heart. This blockage deprives the brain cells of vital oxygen and nutrients leading to cell death. A transient ischemic attack (TIA) is a neurological deficit lasting less than 24 hours, caused by cerebral ischemia.

Atrial fibrillation (AF) is a type of cardiac arrhythmia, which causes pooling of blood that leads to thrombosis formation and may cause a stroke or TIA. Patients with AF but no history of stroke have a stroke risk of 4.5% per year; however, anticoagulation therapy, can reduce this risk to 1.4% per year. Often patients with AF will not have any symptoms, and therefore they are difficult to identify. Roughly 30% to 40% of first-time ischemic strokes are due to an unknown cause, and are referred to as an embolic stroke of undetermined source (ESUS). Patients who have experienced ESUS may have undiagnosed, or occult, AF. Determining whether they do have AF can be important to help prevent future strokes or TIAs.

Long-term electrocardiography (ECG) monitoring using outpatient cardiac monitoring devices can identify occult AF that is undetectable by other means. To this end, outpatient cardiac monitoring devices providing increased mobility for patients and the ability to transmit data wirelessly have been developed, and allow for longer-term surveillance outside the hospital setting. These devices include ambulatory Holter monitors, external loop recorders (ELRs), mobile cardiac outpatient telemetry (MCOT) devices, and implantable loop recorders (ILRs).

CADTH conducted a health technology assessment (HTA) on the clinical effectiveness and cost-effectiveness of cardiac monitoring devices in patients discharged from hospital following a stroke or TIA, to help inform decisions about these devices. Patient perspectives and experiences regarding the value and impact of outpatient AF cardiac monitoring devices were also considered.

For patients who have been discharged from hospital after a stroke or TIA and who did not undergo continuous cardiac monitoring while in hospital, the Health Technology Expert Review Panel recommends seven days of continuous outpatient cardiac monitoring with an ambulatory Holter monitor or external loop recorder.

1.1 Technology

Ambulatory Holter monitors typically have three to eight leads connected to a patient’s chest, and a small monitor that is carried in a pouch around their neck or waist. Data from the monitor’s continuous recording are stored, then transmitted via the Internet. Patients are also able to mark symptomatic events. Holter monitors can record up to 72 hours, depending upon the particular device.

Electronic loop recorders (ELRs) use chest electrodes or a wristband to continuously monitor cardiac activity. The device can be set to recognize a certain heart rate range and the recorder is activated by changes in the rate. The recorder can also be activated by a hand-held activator when a patient notices symptoms of an arrhythmic event. The devices can be worn for up to 30 days, but most are only capable of storing approximately 10 minutes of activity. The data are transmitted to the physician or data centre via telephone.
Implantable loop recorders (ILRs) operate similarly to ELRs, but are implanted beneath the skin, through a small incision. They automatically record cardiac arrhythmias or can be patient-activated. The devices can remain implanted for about three years and are removed afterward. Storage capacity is up to 50 minutes.

Mobile cardiac outpatient telemetry (MCOT) devices use three or four electrodes to monitor cardiac activity. The data are sent to the patient’s cellphone, then sent in real time to a data centre. The sensor can store from six hours to 30 days of data and the device is worn for up to 30 days.

2. Methods

CADTH conducted an HTA on the clinical effectiveness, cost-effectiveness, and related patient preferences and experiences of outpatient cardiac monitoring devices in patients who have experienced a stroke or TIA. The Health Technology Expert Review Panel (HTERP) developed recommendations on the appropriate use of outpatient cardiac monitoring devices based on the evidence presented in the HTA report. HTERP members reviewed the HTA evidence, discussed all elements of the HTERP deliberative framework, and developed a consensus-based recommendation through discussion and deliberation. Additional information on the HTERP process is found on the HTERP page of the CADTH website: www.cadth.ca/collaboration-and-outreach/advisory-bodies/health-technology-expert-review-panel.

3. Detailed Recommendations

The objective of these recommendations is to provide advice for Canadian health care decision-makers about the use of outpatient cardiac monitoring devices. These recommendations are relevant for patients who have been discharged from hospital following a stroke or TIA, including but not limited to those with ESUS, and who have received no prior in-hospital continuous cardiac monitoring (e.g., in-hospital Holter, continuous in-patient cardiac telemetry, or continuous ECG monitoring).

For patients who are discharged from hospital after a stroke or TIA and who did not undergo continuous cardiac monitoring while in hospital, HTERP recommends seven days of continuous outpatient cardiac monitoring with an ambulatory Holter monitor or ELR.

3.1 Rationale

- When patients are monitored for more than 24 hours, the likelihood of diagnosing AF is substantially increased.
- In patients who are eligible to take oral anticoagulants (OACs) if diagnosed with AF and who did not receive in-hospital continuous monitoring (patients who received ECG only), seven days of monitoring with ambulatory Holter or ELR is likely to identify a substantial number of patients with AF at an acceptable incremental cost compared with standard of care (defined as providing 24-hour monitoring to 60% of patients).
- Continuous outpatient monitoring is likely to diagnose more patients with AF than 24-hour in-hospital cardiac monitoring. However, continuous outpatient monitoring for patients who have already received in-hospital continuous cardiac monitoring (e.g., in-hospital Holter,
continuous in-patient cardiac telemetry, or continuous ECG monitoring) is unlikely to be cost-effective, as the likelihood of diagnosing additional patients with AF (i.e., the incremental diagnostic yield) may not be sufficient to compensate for the substantial increase in testing costs.

- In addition to ischemic stroke or TIA patients, the overall findings suggest that outpatient cardiac monitoring for the detection of AF is warranted in patients with ESUS, as monitoring of this subpopulation also demonstrated high diagnostic yields.
- Most patients perceive ambulatory Holter monitors and ELRs as easy to use and relatively comfortable.

### 3.2 Considerations

As HTERP worked the question of outpatient monitoring for AF through its deliberative framework, the following considerations were put forth as part of its discussion.

Canadian Cardiovascular Society Guidelines recommend a minimum 24 hours of ECG in-hospital monitoring for the detection of AF for patients being investigated for an ischemic stroke or TIA,\(^1\) yet standard practice varies across Canada. Findings from the clinical review concluded that a longer duration of monitoring appears to result in a greater likelihood of detecting AF, with substantial increases when monitoring for longer than 24 hours. With few comparative studies, there was uncertainty regarding the relative clinical effectiveness of outpatient cardiac monitoring devices for AF monitoring in discharged stroke or TIA patients compared with each other and with no monitoring. In addition to ischemic stroke or TIA patients, the overall findings suggest that outpatient cardiac monitoring for the detection of AF is warranted in patients with ESUS, as this monitoring of this subpopulation also demonstrated high diagnostic yields. Interpretation of clinical findings was limited by the significant amount of clinical and statistical heterogeneity between studies, which included different patient populations, durations of monitoring, and definitions of AF.

The optimal duration of outpatient cardiac monitoring remains uncertain, but when compared with standard of care (24-hour monitoring for 60% of patients), seven-day cardiac monitoring was found to be cost-effective in relatively healthy patients following a stroke or TIA who have not otherwise been evaluated using continuous monitoring technologies. However, differences in billing codes for these devices may differ between jurisdictions and should be considered. For example, serial testing conducted for seven days using individual one-day billing codes may no longer be cost-effective. Seven-day monitoring can be performed using Holter or ELR depending on local costs and availability. ELRs are not currently available in all Canadian jurisdictions. Outpatient monitoring with ILR for up to three years compared with standard practice (defined as 38% of patients receiving ECG or 24-hour Holter monitoring within six months) was not cost-effective among ESUS patients receiving prior in-hospital ECG or 24-hour Holter monitoring. The economic review also suggested that 30-day ELR is unlikely to be cost-effective compared with 24-hour Holter monitoring. There was not enough evidence to recommend MCOT at this time. Interpretation of the economic models is limited, as many comparisons of interest were not evaluated, there were many structural assumptions, and models considered patients at average risk after stroke or TIA.

The 2015 Canadian Stroke Best Practice recommendations state that prolonged ECG monitoring up to 30 days is recommended for the detection of intermittent (paroxysmal) AF in selected patients where the electrocardiogram or initial cardiac rhythm monitoring does not show atrial fibrillation.\(^12\) The authors recommend a greater monitoring duration than what the overall results of this report suggest (30 days versus seven days). However, their recommendation does not specify what type of cardiac monitoring device should be used, and it
remains uncertain whether costing implications were considered. According to the authors, their recommendation is based on “level B” evidence (i.e., evidence from a single randomized controlled trial [RCT] or consistent findings from two or more well-designed non-randomized and/or non-controlled trials, and large observational studies).\(^{12}\)

There was insufficient evidence in the clinical review to suggest any differences in safety (i.e., stroke recurrence and stroke and/or all-cause mortality) between the outpatient monitoring devices. The review of patient preferences and experiences was likewise limited, with insufficient evidence, but concluded that overall, most patients perceive ambulatory Holters and ELRs as easy to use and relatively comfortable. Interpretation of the patient preference and experience evidence is further limited by the inclusion of a broader patient population than patients who had experienced a stroke or TIA, including all patients who have used outpatient monitoring devices for any indication. No Canadian studies were found, and no studies used validated outcome measures. A systematic assessment of compliance was outside the scope of this review. However, HTERP clinical experts suggested there may be additional compliance issues when monitoring for longer than 30 days compared with a seven-day monitoring device.

No studies were identified on the ethical, legal, and social implications associated with outpatient cardiac devices for AF monitoring. As well, no clinical studies addressed the implementation considerations (technical requirements, staffing, training, and accreditation) for outpatient monitoring devices for AF monitoring. Privacy issues regarding the transmission of personal information should be considered. In comparison with 24-hour monitoring, the recommendation of seven-day monitoring with ELRs or ambulatory Holter monitors may require added resources, including additional cardiac monitoring devices and clinical personnel.

In the future, with further research, emerging technologies such as intermittent hand-held ECG monitors, which were outside the scope of this report, may prove to be a cost-effective option for outpatient cardiac monitoring. Additional research on the optimal duration of monitoring is needed. Shorter or longer duration of monitoring may be clinically appropriate for certain patients based on their personal risks, baseline health and comorbidities, and testing preferences. While HTERP does not recommend the use of outpatient cardiac monitoring beyond seven days with an ambulatory Holter or ELR, or any outpatient monitoring with ILRs and MCOT devices, shared physician-patient decision-making should be considered in this context.

4. Background

In-patient cardiac monitoring alone following a stroke or TIA captures only a fraction of occult AF cases, and substantial evidence suggests that the detection rate increases with prolonged surveillance time.\(^2,13,14\) An analysis of the clinical effectiveness, cost-effectiveness, and a review of patient preference and experiences was conducted to inform decisions about discharging stroke patients with outpatient cardiac monitoring devices.

The clinical, economic, and patient preference and experience evidence used for developing this guidance was derived from the CADTH HTA report, Monitoring for Atrial Fibrillation in Discharged Stroke and Transient Ischemic Attack Patients.\(^6\)
4.1 Research Questions
1. What is the clinical effectiveness of outpatient cardiac monitoring devices for AF monitoring in discharged stroke and/or TIA patients:
   • compared with each other
   • compared with no monitoring?

2. What is the cost-effectiveness of outpatient cardiac monitoring devices for AF monitoring in discharged stroke and/or TIA patients:
   • compared with each other
   • compared with no monitoring?

3. What are the perspectives and experiences of adults and their caregivers who have made a decision regarding the use of outpatient cardiac monitoring devices regarding the value and impact of these devices for atrial fibrillation monitoring on their health, health care, and quality of life?

5. Summary of the Evidence

5.1 Clinical Evidence
The systematic review of the clinical effectiveness literature assessed the proportion of post-stroke and/or TIA patients diagnosed with AF by four different outpatient cardiac monitoring devices in 36 studies. Individual study results were presented and synthesized narratively. Pooling estimates of the proportion of patients diagnosed with AF post-stroke or TIA for each device through meta-analysis was not appropriate, given the considerable amount of statistical and clinical heterogeneity.

Evidence has shown that prolonged surveillance using outpatient monitoring devices following patient discharge is able to capture more AF cases than shorter-duration in-hospital cardiac monitoring.\(^2,13,14\) This was generally reflected in our findings, as there was a substantial increase in diagnostic yield when monitoring for longer than 24 hours. Specifically, patients were monitored for the greatest duration with ILRs (ranging between 105 days and 569 days) and demonstrated greater numerical diagnostic yields than patients who were monitored for shorter durations with other devices (i.e., ambulatory Holter monitors, MCOT devices, and ELRs). However, while monitoring patients beyond 30 days demonstrated greater diagnostic yield compared with less than 30 days, improvements were modest.

One RCT comparing MCOT devices to no monitoring did not detect AF in either group and therefore demonstrated no differences between interventions. However, this was a pilot study reporting only the first 20 patients in each group.

Studies comparing ELRs to ambulatory Holter monitors contradicted the trends observed in non-comparative cohort studies. In the cohort studies, patients were monitored mostly for greater duration with ELRs (ranging between three days and 30 days), but there was no clear improvement in diagnostic yield compared with ambulatory Holter monitors (ranging from 1 day to 28 days). When compared directly in two RCTs,\(^15,16\) ELRs demonstrated a statistically superior diagnostic yield compared with ambulatory Holter monitors, although the duration of monitoring was longer with ELR than ambulatory Holter monitor (seven to 30 days versus one day).
In the ambulatory Holter monitor and ELR studies, no pattern was observed between diagnostic yield and type of stroke (ESUS exclusively versus all stroke populations). The majority of MCOT and ILR studies (all but one for each) consisted of ESUS patients exclusively. There was no pattern observed between diagnostic yield and duration of monitoring for MCOT, ELR, and ILR studies. When comparing studies that used ambulatory Holter monitors, the diagnostic yield generally increased with a longer duration of monitoring (greater than one day). With regard to prognostic factors, no pattern was observed between diagnostic yield and mean age for ambulatory Holter monitor, MCOT, and ILR studies. For ELR studies, diagnostic yield generally increased in studies with a greater mean age. For all devices, no pattern was observed between diagnostic yield and sex.

Longer duration of monitoring appears to result in a greater likelihood of detecting AF, for any definition of AF (paroxysms of any duration versus at least one paroxysm longer than 30 seconds). The clinical and prognostic significance of short-duration paroxysms is unknown and may become important to patients and clinicians as more patients are identified in this group through expanded monitoring. With few comparative studies, there was insufficient evidence to distinguish the clinical effectiveness between devices or the optimal duration of long-term monitoring.

5.2 Economic Evidence
The economic findings were based on three separate analyses. The incremental cost-effectiveness ratio (ICER) of seven-day cardiac monitoring compared with standard practice (in which 60% of patients received 24 hours of Holter monitoring) in patients with a very recent history of stroke or TIA who did not receive in-hospital continuous monitoring (patients who received ECG only) was between $50,000 and $80,000 per quality-adjusted life-year (QALY) gained depending on the rate of OAC uptake and the OAC prescribed. Targeted monitoring to relatively healthy post-stroke patients and those with a higher suspected likelihood of AF further improves the cost-effectiveness of seven-day cardiac monitoring compared with standard practice.

Longer-term monitoring, such as 30-day ELR or ILR, in patient cohorts similar to those studied by Gladstone et al.\textsuperscript{15} or Sanna et al.,\textsuperscript{3} had ICERS greater than $85,000 per QALY gained and are therefore unlikely to be cost-effective based on commonly accepted thresholds in Canada. Both of these cohorts were selected as higher-risk cohorts based on their stroke type, but both cohorts had already undergone at least 24 hours of continuous monitoring. As a result, the incremental diagnostic yields were not sufficient to compensate for the substantial increase in testing costs incurred for all patients. As technologies such as ELRs decrease in cost, they may become cost-effective in target populations. ILRs are unlikely to be cost-effective for the purpose of investigating AF in a post-stroke population.

Cardiac monitoring after stroke or TIA for the investigation of AF can be cost-effective. To ensure cost-effective use of monitoring, the incremental cost compared with standard practice must be relatively small, the diagnostic yield must be substantial, the patient cohort must be relatively healthy, and the initiation of OACs in newly diagnosed patients must be high. To achieve a high diagnostic yield, the patient cohort must be one with a high expected prevalence of AF based on their medical history, type of stroke and stroke symptoms, their recent discharge after their stroke, and few investigations for AF in hospital.
5.3 Patient Preference and Experience Evidence

A review of nine studies that included data regarding patient perspectives and experiences suggests that most patients perceive outpatient cardiac monitoring devices to be comfortable and easy to use, and satisfaction with outpatient cardiac monitoring is high. Patient preferences for one device type over another appear to be based on participant perceptions of overall comfort and ease of use related to such attributes as material, comfort, and fit. Side effects experienced include skin irritation (e.g., itching, bleeding, inflammation), pressure, and difficulty bathing. It is unclear whether outpatient monitoring has any impact on quality of life or anxiety.

If outpatient monitoring is to be effective, monitoring devices need to be comfortable and easy to use and have few painful side effects, so that people are more likely to comply with monitoring recommendations. While a systematic assessment of compliance was outside the scope of this review, the results suggest that negative side effects might result in reduced compliance. This suggestion is supported by results of studies included in the accompanying clinical review, which report adverse skin reactions, discomfort, irritation, and inflammation as reasons for non-compliance with ELRs and ambulatory Holters and refusal to provide consent for implantation of an ILR.\textsuperscript{3,17-20}
References


Appendix 1: Health Technology Expert Review Panel

The Health Technology Expert Review Panel (HTERP) consists of up to seven core members appointed to serve for all topics under consideration during their term of office, and up to five expert members appointed to provide their expertise for a specific topic. For this project, four expert members were appointed; their expertise included internal medicine, clinical chemistry, pathology, and family medicine. The core members include health care practitioners and other individuals with expertise and experience in evidence-based medicine, critical appraisal, health technology assessment, bioethics, and health economics. One public member is also appointed to the core panel to represent the broad public interest.

HTERP is an advisory body to CADTH and is convened to develop guidance or recommendations on non-drug health technologies to inform a range of stakeholders within the Canadian health care system. Further information regarding HTERP is available at www.cadth.ca/en/advisory-bodies/health-technology-expert-review-panel.

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