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Research Paper

A cost comparison of atrial fibrillation monitoring strategies after embolic stroke of undetermined source

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ABSTRACT

Background: Detection of atrial fibrillation (AF) in patients with embolic stroke of undetermined source (ESUS) is challenging due to its paroxysmal nature. We sought to assess AF detection with an insertable cardiac monitor (ICM) and to perform cost analysis for various AF monitoring strategies post-ESUS We applied this cost analysis modeling to recently published Stroke AF and Per Diem trials.

Methods: Retrospective chart review was performed in consecutive hospitalized patients with ESUS who had ICM placed prior to discharge. Utilizing rate of ICM-detected AF and Medicare average payments, we modeled 30-day per-patient diagnostic costs of Immediate ICM insertion prior to discharge versus using a wearable monitor followed by ICM in patients with ESUS, from Medicare and patient out-of-pocket perspectives. Similar modeling strategy and cost analysis was applied to the Stroke AF and Per Diem trials.

Results: In 192 ESUS patients, AF detection increased with length of monitoring: 7.3 % at 14 days, 9.4 % at 30 days, and 17.2 % after a median ~ 6 months (189 days). Cost modeling predicted that immediate ICM leads to $3683–$4070 lower Medicare payments per-patient and $1425–$1503 lower patient out-of-pocket costs compared to Wearable-to-ICM strategies. Using similar modeling in the PER DIEM and STROKE AF trials, the additive costs of the 30-day ELR to ICM strategy ranged from $3786–$3946 from a payer perspective and $1472–$1503 from a patient out-of-pocket perspective.

Conclusions: Use of ICM immediately after ESUS is cost-saving compared to Wearable-to-ICM strategies, due to the cost and low diagnostic yield of short-term wearable cardiac monitoring.

1. Introduction

Stroke is a major public health concern with approximately 795,000 people diagnosed each year, and is among the leading causes of serious long-term disability [1]. Projections estimate that by 2030 there will be a 20.5 % increase in stroke prevalence compared to 2012 [1]. In approximately 30 % of ischemic stroke cases a cause is not identified, leading to the classification of cryptogenic stroke (CS) [2]. Within one year, 9.1 % of CS patients have a recurrent event resulting in additional hospitalizations and increased mortality; rates in embolic stroke of

Abbreviations: AF, Atrial fibrillation; APC, Ambulatory payment classification; CAD, Coronary artery disease; CHF, Congestive heart failure; CPT, Current procedural terminology; CS, Cryptogenic stroke; DM, Diabetes mellitus; DRG, Diagnosis-related group; ECG, Electrocardiography; EF, Ejection fraction; ELR, External loop recorder; ESUS, Embolic stroke of undetermined source; HCPCS, Healthcare common procedure coding system; HTN, Hypertension; ICM, Insertable cardiac monitor; LDS, Limited Data Set; MCOT, Mobile cardiac outpatient telemetry; PPV, Positive predictive value; PVD, Peripheral vascular disease; SD, Standard deviation; TIA, Transient ischemic attack.

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unknown source (ESUS) patients are also high and similar to CS [3,4]. Recent MRI surveillance data demonstrating asymptomatic strokes in CS patients suggest this may be an underestimate [5].

AF is an independent risk factor for stroke, increasing the risk five-fold [1]. Oral anticoagulation in patients with diagnosed AF has been shown to reduce the risk of recurrence substantially [6]. However, detection of AF is a challenging undertaking because AF is often paroxysmal and can occur without symptoms [7]. The Cryptogenic Stroke and underlying Atrial Fibrillation (CRYSTAL-AF) study demonstrated a significantly higher rate of AF detection using prolonged insertable cardiac monitoring (ICM) vs. conventional follow-up after CS (30 % versus 3.0 % at 36 months of follow-up, $p < 0.001$), with higher rates of oral anticoagulant initiation [8]. AF detection had increased eight-fold at 36 months (30 %) in ICM patients compared with at one month of follow-up (3.7 %), indicating that over 80 % of AF detection occurred after 30 days (median time to detection patients = 252 days). Indeed, detection of AF has been shown to increase with longer duration of monitoring [8,9,10,11,12], leading to a recent Level 2a recommendation for long-term rhythm monitoring to detect AF in patients with cryptogenic stroke in the *2021 American Heart Association/American Stroke Association Guideline for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack* [6].

This retrospective study was conducted to 1) assess the incidence of AF detection post-stroke using an ICM (Reveal LINQ, Medtronic, Dublin, Ireland) inserted in patients with ESUS before hospital discharge, and 2) perform a cost analysis for various AF monitoring strategies post-ESUS: ICM monitoring immediately after stroke versus the use of a 14- or 30-day wearable monitor at discharge followed by ICM if the wearable monitor is negative for AF. Additionally, we utilized recently published and publicly available data from two randomized controlled trials to extrapolate our model to a broader population of patients with ischemic stroke beyond those with ESUS alone. These include the PER DIEM (*Post-Embolic Rhythm Detection with Implantable* vs. *External Monitoring*) trial [18] in patients with any arterial ischemic stroke, and the STROKE AF (*Stroke of Known Cause and Underlying Atrial Fibrillation*) trial [19] in patients with ischemic stroke due to large- or small-vessel disease.

2. Methods

This was a single center retrospective chart review in consecutive patients ≥18 years old diagnosed with a stroke meeting ESUS criteria [13] after ≥48 h of telemetry monitoring absent for AF, and who had an ICM placed prior to discharge during the study period of May 2014 through October 2015. Spectrum Health's institutional review board approved the study protocol. A standard multidisciplinary protocol was developed between our electrophysiology and neurology departments to identify patients with ESUS. Once ESUS was confirmed by a board-certified vascular neurologist, an electrophysiology consult was triggered for an ICM.

Patients who met inclusion criteria were ≥18 years old, hospitalized with ESUS, and had no AF detected during the initial 48-hour inpatient telemetry. We specifically included ESUS patients as opposed to CS patients since ESUS patients are presumed to have a cardioembolic source which would be more likely detected by the ICM if AF is the culprit. CS is a broader definition and may include non-cardioembolic etiologies and incomplete workup [14], whereas ESUS can be accounted as a subtype of cryptogenic stroke which has the highest suspicion of occult AF as the source of the stroke. Patients with prior history of AF or who were not candidates for long-term oral anticoagulation were excluded.

Data was collected from multiple electronic medical records and included age at ICM implant, sex, ejection fraction (EF), and history of congestive heart failure (CHF), hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), peripheral vascular disease (PVD), and prior stroke. ICM data was used to identify AF during follow-up. All AF episodes were independently reviewed by a board-certified electrophysiologist for diagnosis of AF. Subjects were grouped into two categories: those with AF detected by ICM and those with no AF detected by the end of follow-up. Nominal ICM settings for AF detection were programmed in all patients [15]. Quantitative data are expressed as n (%) or mean ± SD as noted. Data were analyzed using the chi-square test for nominal variables, and the *t*-test for unequal variances for quantitative variables. Significance was assessed at $p < 0.05$. The Research Electronic Data Capture (REDCap) database system was utilized for data collection; Microsoft Excel and SAS 9.4 (Cary, NC: SAS Institute Inc. 2013) were utilized for analysis.

2.1. Cost modeling analysis

Utilizing the rate of ICM-detected AF in our study population along with national data on Medicare U.S. national average payment rates, we modeled the 30-day total per-patient diagnostic costs of the strategy of ICM insertion prior to hospital discharge versus two alternative cardiac monitoring strategies (each of which utilize a wearable monitor as the first monitoring modality). The three cardiac monitoring strategies modeled were:

- **Immediate ICM Strategy:** ICM placement immediately prior to discharge.
- **MCOT to ICM Strategy:** 30-day external Mobile Cardiac Outpatient Telemetry (MCOT) monitoring upon discharge, followed by ICM placement in the patients without AF detection after MCOT monitoring.
- **Extended Holter to ICM Strategy:** 14-day extended Holter patch (Zio, iRhythm Technologies, San Francisco, CA) followed by ICM placement in the patients without AF detection after extended Holter monitoring.

A cost analysis was performed for all diagnostic-related costs within 30 days of the acute cryptogenic stroke event, from a Medicare perspective as well as a patient out-of-pocket perspective. Costs associated with the Immediate ICM strategy included: the initial cryptogenic stroke hospitalization (including an ICM consultation and ICM insertion procedure), and an in-person ICM device interrogation during the month post-insertion. In the Wearable monitor to ICM strategies, the modeled costs included: the initial stroke hospitalization, the MCOT or Extended Holter monitor (device and recording/interpretation/report), and in the patients remaining undiagnosed after the external monitor, an in-person follow-up consultation for ICM and subsequent ICM insertion in an outpatient setting (weighted average of 20.3 % in-office and 79.7 % outpatient hospital, based on ICM insertion volumes in the Medicare 2019 Physician/Supplier Procedure Summary file). The equations used in calculating average per-patient costs are described in Appendix Table 1.

Costs for outpatient services were derived from the calendar year 2021 CMS national physician fee schedule and final rule files, and represent U.S. national average Medicare payment amounts. Amounts are inclusive of both Medicare payment and patient responsibility. Medicare payments for inpatient hospitalizations are based on analysis of the national Medicare Limited Data Set (LDS) 5 % Fee-for-service file [16] January 1, 2010-December 31, 2019 (N = 5240), and represent the average Medicare payment for an acute unspecified ischemic stroke hospitalization with diagnosis code ICD-9434.91, 435.9, 434.11; or ICD-10 I63.9 in patients without an existing documented stroke etiology (please see Appendix Table 2 for detailed inclusion/exclusion criteria). Both facility and physician fees are included in all outpatient and inpatient amounts. Patient out-of-pocket responsibility was estimated based on Medicare detailed patient cost information provided for 2021 (*Medicare Costs at a Glance*, accessed via https://www.medicare.gov/your-medicare-costs/medicare-costs-at-a-glance on 12/20/2020).

In addition to the 30-day costs, the total diagnostic costs were modeled for our full follow-up period, incorporating the costs of long-

term ICM monitoring, including monthly or alert-driven remote monitoring.

An additional analysis was undertaken to model the impact of real-world patient compliance with wearable patch monitors, which was reported to be 54.3 % of prescribed wear-time in the largest study to-date [17] to report compliance with wearable monitors (N = 26,751).

2.2. PER DIEM and STROKE AF patient population adaptations

In addition to our ESUS population, we applied our model of Immediate to ICM compared to 30-day ELR to ICM to a broader patient population of ischemic stroke patients, utilizing the rates of AF detection after 30 days of continuous AF monitoring with ICM reported in two recently published randomized controlled trials with publicly available results: the PER DIEM trial [18] (4.7 % of patients diagnosed) and the STROKE AF trial [19] (2.6 % of patients). Although 30-day AF detection rates were reported for ELR monitoring in the PER DIEM trial (showing a non-statistically significantly lower AF detection rate of 3.3 % compared to ICM), we chose to utilize the 30-day AF detection rate in the ICM arm for consistency with the methodology in our study and the reported data from STROKE AF trial.

3. Results

A total of 215 patients with diagnosis of ESUS after extensive stroke workup were reviewed for the study; 192 patients met inclusion criteria and were included in the analysis. Four (2 %) of the 192 patients included in the study were lost to follow-up. Only one of those lost to follow-up was lost within the first 30 days of study.

Patient demographic and clinical characteristics are displayed in Table 1, stratified by those with and without AF detection at the end of follow-up (median 189 ± 109 days). CHA_2DS_2VASC scores were significantly higher in the patients with AF detected during follow-up, driven by the components of higher age and pre-existing hypertension.

During the median follow-up of 189 days after ESUS, the cumulative incidence of AF detection was 17.2 % (33 patients) (Table 2). A total of 7.3 % (14 patients) had AF detected in the first 14 days after implantation and 2.1 % (4 cases) had AF detected in between days 15–30, while an additional 7.8 % (15 cases) had AF detected between 30 days and the end of follow-up at median 189 days. As the rates of AF detection using an initial 14-day or 30-day monitor would total 7.3 % and 9.4 % respectively (assuming patient compliance to prescribed wearable monitoring), long-term ICM monitoring would be required for approximately 90.6–92.7 % of patients.

Among the patients with AF detected, the percentage of time spent in AF averaged 7.2 % and ranged from a minimum <0.1 % to maximum 49.8 % (note: data available for n = 23 patients). The longest duration of AF detected averaged 12.6 h (n = 24), and ranged from 2 min to 99.0 h.

Table 1
Patient characteristics in patients with and without AF detection after six months cardiac monitoring following ESUS.

Variable	No AF detected n = 159 (82.8 %)	AF detected n = 33 (17.2 %)	p-Value
Sex			0.131
Female	64/159 (40.3 %)	18/33 (54.6 %)	
Male	95/159 (59.7 %)	15/33 (45.5 %)	
Age at index stroke, mean ± SD	65.2 ± 13.5	73.5 ± 9.8	0.0001*
Median	64.5	75.0	
Ejection fraction %, mean ± SD	60 ± 8.4	58.5 ± 8.2	0.357
Median	60	60	
Congestive heart failure	9/159 (5.7 %)	4/33 (12.1 %)	0.179
Hypertension	122/159 (76.7 %)	32/33 (97.0 %)	0.008*
Diabetes mellitus	47/159 (29.6 %)	10/33 (30.3 %)	0.932
Prior stroke	30/159 (18.9 %)	6/33 (18.2 %)	0.927
Coronary artery disease	34/159 (21.4 %)	8/33 (24.2 %)	0.718
Peripheral vascular disease (PVD)	17/159 (10.7 %)	6/33 (18.2 %)	0.228
$CHADS_2VASc$ before stroke, mean ± SD	2.8 ± 1.8	3.9 ± 1.4	0.0009*
Median	3.0	4.0	

Abbreviations: AF, atrial fibrillation; ESUS, embolic stroke of undetermined source; SD, standard deviation.
* Statistically significant difference, $p < 0.05$.

Table 2
Incidence of ICM-detected AF following ESUS event.

Days of follow-up after cryptogenic stroke event	Patients with AF detected, n (%)
0 to 14 days	14 (7.3 %)
15 to 30 days	4 (2.1 %)
30 days to end of follow-up (median 189 +/− 109 days)	15 (7.8 %)
Total patients with AF detected	**33 (17.2 %)**

Abbreviations: AF, atrial fibrillation; ICM, insertable cardiac monitor; ESUS, embolic stroke of undetermined source.

3.1. Cost modeling analysis

U.S. national average Medicare payments and patient out-of-pocket cost estimates used in the cost analysis are listed in Table 3. The diagnostic cost comparison for our models showed the total diagnostic-related costs within 30 days of an acute cryptogenic stroke were on average substantially higher in the Wearable-to-ICM strategies compared to Immediate ICM (Table 4). The incremental costs of the MCOT to ICM strategy compared to Immediate ICM was projected to be $4070 in additional Medicare payments per-patient, with $1503 of additional patient out-of-pocket responsibility on average. The additive cost of the MCOT to ICM strategy was driven by the relatively high cost of the MCOT monitor ($743.22 including facility and professional fees, Table 3) combined with a low diagnostic yield (9.4 %), such that the majority of patients progressed to an outpatient ICM insertion after non-diagnostic wearable monitoring. The Extended Holter to ICM strategy was projected to average $3683 in higher Medicare payments compared to Immediate ICM, with $1425 higher patient out-of-pocket cost. This slight difference in result was due to the lower cost of a 14-day Holter monitor ($194.83) compared to MCOT, with only marginally lower diagnostic yield of 7.3 %.

Also contributing to the additive costs of the Wearable-to-ICM strategies was the difference in national average Medicare perspective costs for an outpatient ICM insertion ($7641.28 national average weighted between outpatient hospital and office-based settings, Table 3), compared to a strategy of inserting ICM *during* the ESUS hospitalization which had an incremental cost of $3645.77 compared to a ESUS hospitalization without ICM procedure ($22,750.11 vs. $19,104.34, Table 2) based on national Medicare real-world claims data [16]. The difference in the national average unit hospitalization cost with and without ICM placement may be expected to be higher than the observed $3645.77; however, this is likely driven by the amount of patients without ICM placement who received other procedures that would result in a surgical DRG. Based on national Medicare data, this would be expected to be 16.1 % of hospitalized ESUS patients. Examples of surgical procedures in this national Medicare population include 1) mechanical thrombectomy or other extirpation procedures (6.7 %), 2) bypass procedures (1.6 %), 3) spinal/cranial drainage and release procedures (3.7 %), 4) angioplasty and stenting/balloon procedures (2.1 %), and 5) other cardiac procedures such as LAA closure, intra-aortic balloon pump, or external heart assist device/pump (2.0 %).

Table 3
Input parameters for Medicare payment and patient out-of-pocket cost analysis.

Parameter	Medicare 2021 national average payment[a]		Estimated traditional Medicare patient out-of-pocket responsibility[b]	
	Facility fee (APC)	Professional fee	Facility fee (APC)	Professional fee
Costs associated with MCOT to ICM strategy				
Acute ESUS inpatient hospitalization **without** ICM insertion[c]	$19,104.34		$1484.00	N/A
Mobile Cardiac Outpatient Telemetry (MCOT) (CPT 93228 and CPT 93229)	$717.05	$26.17	20 %	20 %
Office visit, with established patient (CPT 99214) (represents ICM consultation)	N/A	$100.49	20 %	20 %
ICM insertion in outpatient setting[d] (CPT 33285)	$7551.26	$90.02	$1484.00	N/A
Costs associated with 14-day Extended Holter to ICM strategy				
Acute ESUS inpatient hospitalization **without** ICM insertion[c]	$19,104.34		$1484.00	N/A
14-day Extended Holter monitor (CPT 93246 + 93,247 and CPT 93248):	$167.61	$27.22	20 %	20 %
Office visit, with established patient (CPT 99214) (represents ICM consultation)	N/A	$100.49	20 %	20 %
ICM insertion in outpatient setting[d] (CPT 33285)	$7551.26	$90.02	$1484.00	N/A
Costs associated with Immediate ICM strategy				
Acute ESUS inpatient hospitalization **with** ICM consultation and insertion[c]	$22,750.11		$1484.00	N/A
In-person follow-up ICM device interrogation (CPT 93291)	$24.67	$18.49	20 %	20 %

Abbreviations: APC, ambulatory payment classifications; CPT, current procedural terminology; ESUS, embolic stroke of undetermined source; ICM, insertable cardiac monitor; MCOT, mobile cardiac outpatient telemetry.

[a] Payment rates are inclusive of both Medicare payment and patient responsibility for both facility and professional fees. Note: all non-inpatient payments assume services are performed by provider-based clinic, except for MCOT facility fee (CPT 93229) which assumes service delivered by Independent Diagnostic Testing Facility.

[b] Source: Medicare costs at a glance. Accessed via https://www.medicare.gov/your-medicare-costs/medicare-costs-at-a-glance on 12/20/2020. Model assumes annual Part B deductible has been met & acute stroke hospitalization is first hospitalization of Part A benefit period which begins the day the insured party is admitted as an inpatient in a hospital and ends when the insured party hasn't had any Part A services for 60 days in a row.

[c] Medicare payments for inpatient hospitalizations are based on analysis of Medicare 5 % Fee-for-service database 2010–2019, and represent the median Medicare payment for an acute cryptogenic stroke hospitalization inclusive of payments for all facility and professional fees. Patient responsibility is based on the Part A 2021 patient deductible for each Part A benefit period.

[d] Medicare payment for ICM insertion in an outpatient setting represents a weighted average of payments for office ($5200.12) and outpatient hospital ($8152.58) setting based on ICM insertion volumes in the Medicare 2019 Physician/Supplier Procedure Summary file: 20.3 % office, 79.7 % outpatient hospital. Patient responsibility for Part B services is typically 20 % of Medicare payment, unless the service is performed in the outpatient setting and 20 % exceeds the Part A deductible amount for, as is the case for facility payment of ICM insertion in outpatient setting (CPT 33285). In these instances, the patient responsibility for the facility fee is capped at the Part A deductible amount.

Table 4
Total diagnostic-related payer payments within 30 days of ESUS, by monitoring strategy.

Average per-patient Medicare payments	Immediate ICM during stroke hospitalization	MCOT to ICM strategy[a]	14-day extended Holter to ICM strategy[b]
Average acute ESUS hospitalization	**$22,750**	**$19,104**	**$19,104**
Average external monitor-related costs			
External monitor device (recording, interpretation, report)	$0	$743	$195
Office visit for ICM consultation (incurred only in the patients progressing to ICM)[a,b]	N/A; included in hospitalization cost above	$91	$93
Total external monitor-related costs	**$0**	**$834**	**$288**
Average ICM-related costs			
ICM device insertion in outpatient setting[a-c]	N/A; included in hospitalization cost above	$6925	$7084
In-person ICM device check/interrogation post-insertion[d]	$43	$0	$0
Total ICM-related costs	**$43**	**$6925**	**$7084**
Total diagnostic-related Medicare payments per patient (sum of bolded rows above)	**$22,793**	**$26,864**	**$26,476**
Relative cost of strategy compared to immediate ICM strategy	**–**	**$4070**	**$3683**

Abbreviations: ESUS, embolic stroke of undetermined source; ICM, insertable cardiac monitor; MCOT, mobile cardiac outpatient telemetry.

[a] Strategy consists of 30-day MCOT monitoring, followed by ICM in undiagnosed patients. ICM consultation and other ICM-related costs listed in table are only incurred by the 90.6 % of patients who remain undiagnosed after MCOT monitoring (please see Appendix Table 1 for more detail).

[b] Strategy consists of 14-day Extended Holter monitoring, followed by ICM in undiagnosed patients. ICM consultation and other ICM-related costs listed in table are only incurred by the 92.7 % of patients who remain undiagnosed after Extended Holter monitoring.

[c] Based on real-world distribution of ICM insertions in Medicare patients being performed in the office versus outpatient hospital setting - please see Table 3 for details.

[d] It was assumed that all Immediate ICM patients return for an in-person device check within 30 days post-insertion. In the strategies starting with a short-term monitor, the device check would occur post the 30-day window.

Alternatively, if a more simplified approach to hospitalization cost is taken utilizing 2021 Medicare national average payments [20] for stroke hospitalization with Surgical DRGs 040–042 and those with Medical DRGs 064–066 (i.e., estimated cost per stroke hospitalization with and without ICM placement of $16,051 and $9513 respectively), the immediate ICM approach compared to Wearable-to-ICM strategies remains slightly cost-saving by $791–$1178 per patient from a payer perspective, with $1425–$1503 savings from the patient out-of-pocket perspective.

Based on the observed AF detection rates in this study, as the initial short-term monitoring would diagnose only 7.3–9.4 % of the population, the wearable monitors will ultimately be non-diagnostic in the majority of patients (90.6 %–92.7 %). Out of the total costs related to short-term monitors in the Wearable-to-ICM strategies (per-patient external monitor costs of $834 for MCOT and $288 for 14-day Extended Holter, Table 4), the bulk of these costs were attributable to non-diagnostic monitors: averaging $756 and $267 per-patient, respectively. Extrapolated to our study population of 192 patients, this represents approximately $145,000 and $51,000 of non-diagnostic wearable monitor costs respectively. The estimated cost-per-diagnosis with the MCOT and 14-day Extended Holter, calculated as the total cost of the external monitors in the population divided by the number of patients diagnosed, were $8899 and $3950.

In a scenario in which patients receive ICM after hospital discharge rather than immediately during the inpatient stay, the Immediate ICM strategy was also cost-saving: from a payer perspective the resulting amount of cost savings ($3996) was similar as when comparing to a Wearable-to-ICM strategy, as the cost of avoided ELR monitors was counterbalanced by the additional ICM insertions. However, from a patient perspective the cost savings of the Immediate ICM strategy increased further ($2997 average out-of-pocket savings compared to ICM after discharge), as all patients would incur the copay for the outpatient ICM insertion in addition to their initial hospitalization copay.

Per-patient average diagnostic costs were also modeled for the full study follow-up period (median of approximately 6 months) as shown in Appendix Tables 3–4, by incorporating the additional cost of alert-driven or monthly ICM remote monitoring in patients who progress to ICM. The cost of all monitoring strategies increased slightly, since the vast majority of patients in the Wearable-to-ICM strategies progress to ICM monitoring for longer-term follow-up and thus also incur the costs of long-term ICM monitoring post 30 days. Results showed that the incremental additive cost of Wearable-to-ICM strategies compared to Immediate ICM remained similar at 6 months compared to the base case analysis at 30 days.

In an additional scenario incorporating real-world patient compliance with wearable patch monitors of 54.3 % of prescribed wear-time [17], the estimated yield with the initial monitor decreases from 9.4 % to 5.1 % for MCOT and from 7.3 % to 4.0 % for Extended Holter, with the cost-per-diagnosis for each wearable approach increasing substantially to $16,473 (MCOT) and $7358 (Extended Holter), Appendix Tables 5–6. In this scenario, the additive cost of the MCOT to ICM strategy compared to Immediate ICM was modeled to increase from $4070 to $4402 from a Medicare perspective; similarly, the additive costs of the Extended Holter to ICM approach increased from $3683 to $3941.

3.2. PER DIEM and STROKE AF patient population adaptations

When modeling a broader patient population of ischemic stroke patients based on the PER DIEM and STROKE AF trials, the additive costs of the 30-day ELR to ICM strategy ranged from $3786–$3946 from a payer perspective and $1472–$1503 from a patient out-of-pocket perspective, at 30 days post-stroke (Appendix Tables 7–8). Additive costs were slightly lower compared to an ESUS population due to the lower cost of an ELR compared to an MCOT monitor, although this was tempered by the lower diagnostic yield observed after 30 days in these trials (2.6 %–4.7 %) compared to our ESUS cohort (9.4 %).

4. Discussion

The first objective of our study was to assess the incidence of AF post ESUS with an ICM inserted prior to hospital discharge in a real-world cohort. In our study of 192 subjects with ESUS, the AF detection rate was 17.2 % after a median 189 days of monitoring, with a detection rate of 9.4 % during the first 30 days. In the CRYSTAL-AF study, 12.4 % of patients with cryptogenic stroke were found to have AF detected by an ICM at 12 months, with mean detection in these patients at 84 days [8]. Our detection rate of 17.2 % is higher than described in CRYSTAL-AF (potentially due to the older age of our study population, as well as the slightly higher AF sensitivity of the newer LINQ ICM device, or timing of ICM insertion), however it is in alignment with other studies that have reported higher AF detection rates after CS/ESUS [12,21,22,23]. Additionally, detection rates in studies of cryptogenic stroke patients may differ slightly from our population of ESUS patients identified only after extensive stroke workup to determine non-lacunar, nonatherosclerotic strokes of presumable embolic origin (i.e., not including patients in whom stroke work-up is incomplete) [13]. In previous studies, various methods of monitoring have conferred different AF detection rates in CS and ESUS patients, from 2.7 % on admission EKG, to a wide range of 0–24 % at 21–30 days with external loop recorders (ELRs)/MCOTs, to 30.0–50.4 % at 36 months with ICMs; our study aligns with others in the sense that the likelihood of AF detection increases with the duration of monitoring [8,9,10,11,12,12,21,22,23].

Among patients diagnosed with AF, the time spent AF and duration of longest AF episode averaged 7.2 % and 12.6 min, respectively. The minimum duration of AF detectable by Reveal LINQ ICM is 2 min – thus it is possible that additional patients may have had undetected AF <2 min; however we expect this would have minimal impact on the analysis as it is rare for patients with AF to experience episodes <2 min only [15]. Although the duration of longest AF episode ranged widely from only 2 min to 99 h, the vast majority (87.5 %) of patients experienced an AF episode of 6 min or greater, which has been shown to be associated with a significant increase in the risk of stroke or systemic embolism [24,25].

The second objective of our study was to perform a cost comparison of Immediate ICM as the first monitoring modality after the ESUS event, versus an approach of first using a wearable monitor (30-day MCOT or 14-day Extended Holter monitor) as the initial monitoring modality followed by an ICM in patients with ESUS. Cost analysis demonstrated that the estimated total diagnostic-related Medicare payments associated with the Immediate ICM strategy were $3683–$4070 lower per-patient compared to either of the Wearable-to-ICM strategies (Table 4). Immediate ICM also led to patient out-of-pocket savings, in the range of $1503–$1425 per patient (Table 5). In our scenario analysis, when real-world patient compliance with wearable monitors was taken into account, the estimated cost-savings of Immediate ICM increased further. Results were robust in the broader patient population of ischemic stroke patients from the PER DIEM and STROKE AF trials (Appendix Tables 7–8), as the diagnostic yields during the initial external monitoring period were similarly low in these populations.

While it may be intuitive to assume that a strategy of initial wearable monitoring followed by ICM would save overall costs in the ESUS population due to avoided ICM monitoring costs, our data indicates that the likelihood of detection with a wearable monitor is low in the first 14–30 days post-ESUS; for the vast majority of patients (90.6 %–92.7 %) additional monitoring with ICM is necessitated and additional costs are accrued on an average per-patient basis.

Another important consideration in the selection of a cardiac monitoring strategy is the potential for patient loss to follow-up during or between monitoring modalities in a ‘short-to-long-term monitoring’ strategy. In our cohort of 192 patients who received an ICM during the acute stroke hospitalization, only 2 % (n = 4) patients were lost to follow-up, suggesting excellent retention of patients at high risk of developing AF. Conversely, the proportion of patients who do not move on to long-term ICM monitoring after an initial trial of wearable short-term monitoring has been shown to be surprisingly high, with a recent U.S. electronic health records study of 28,374 stroke patients [26] finding that in patients given wearable monitors as the first monitoring modality, only 3.4 % progressed to long-term monitoring. While it is unclear what proportion of this low pull-through is due to loss to follow-

Table 5
Total diagnostic-related patient out-of-pocket costs within 30 days of ESUS, by monitoring strategy.

Average patient out-of-pocket costs	Immediate ICM during stroke hospitalization	MCOT to ICM strategy[a]	14-day extended Holter to ICM strategy[b]
Average acute ESUS hospitalization	**$1484**	**$1484**	**$1484**
Average external monitor-related costs			
External monitor device (recording, interpretation, report)	$0	$149	$39
Office visit for ICM consultation (incurred only in the patients progressing to ICM)[a,b]	N/A; included in hospitalization cost above	$18	$19
Total external monitor-related costs	**$0**	**$167**	**$58**
Average ICM-related costs (incurred only in the patients progressing to ICM)[a-c]			
ICM device insertion in outpatient setting[c]	N/A; included in hospitalization cost above	$1345	$1376
In-person ICM device check/interrogation post-insertion[d]	$9	$0	$0
Total ICM-related costs	**$9**	**$1345**	**$1376**
Total diagnostic-related out-of-pocket costs per patient (sum of bolded rows above)	**$1493**	**$2996**	**$2917**
Relative cost of strategy compared to immediate ICM strategy	–	**$1503**	**$1425**

Abbreviations: ESUS, embolic stroke of undetermined source; ICM, insertable cardiac monitor; MCOT, mobile cardiac outpatient telemetry.

[a] Strategy consists of 30-day MCOT monitoring, followed by ICM in undiagnosed patients. ICM consultation and other ICM-related costs listed in table are only incurred by the 90.6 % of patients who remain undiagnosed after MCOT monitoring (please see Appendix Table 1 for more detail).

[b] Strategy consists of 14-day Extended Holter monitoring, followed by ICM in undiagnosed patients. ICM consultation and other ICM-related costs listed in table are only incurred by the 92.7 % of patients who remain undiagnosed after Extended Holter monitoring.

[c] Based on real-world distribution of ICM insertions in Medicare patients being performed in the office versus outpatient hospital setting - please see Table 3 for details.

[d] It was assumed that all Immediate ICM patients return for an in-person device check within 30 days post-insertion. In the strategies starting with a short-term monitor, the device check would occur post the 30-day window.

up versus a difference in clinical care, this presents a stark contrast to the >90 % of patients that our data suggest would remain undiagnosed after an initial 14–30 day monitor and in whom longer-term monitoring may be warranted.

As ICMs can remain in place up to 3–5 years, it is likely that additional patients in our population will be diagnosed with AF after longer-term monitoring. While our study was limited to shorter-term follow-up as our intent was to compare efficacy and costs of the *initial* strategy within the immediate post-stroke period, a recent cost-effectiveness analysis [27] utilizing a patient lifetime horizon to compare a strategy of immediate ICM versus Wearable-to-ICM monitoring in CS patients found that the immediate ICM approach was cost-saving over the lifetime of the patient, driven by the avoided costs of non-diagnostic wearable monitors. Patient outcomes were slightly improved due to earlier detection and stroke prophylaxis, particularly in scenarios taking into account the potential for patient fall-out after short-term monitoring.

When we compared the demographics and clinical attributes of our patients with and without AF detection during the study follow-up, CHA_2DS_2VASC scores were significantly higher in the group with AF detected: 3.9 ± 1.4 vs. $2.8 + 1.8$ at baseline pre-stroke in AF and Non-AF patients, respectively ($p = 0.0009$). This was driven by higher age (median 73 versus 65 years) and underlying hypertension (97.0 % vs. 76.7 %, $p = 0.008$), Table 1. Previous studies have shown that larger left atrial size and non-sustained episodes of AF were independently associated with a higher incidence of AF after CS [10]. Another study found those diagnosed with AF were older, and had higher CHA_2DS_2VASC scores [28]. These data along with our findings may point towards early predictors of AF in patients with ESUS. Further study is warranted on the predictors of early versus late AF recurrence to aid in the stratification of patients to an AF monitoring strategy post-ESUS. Our analysis demonstrated that the costs of wearable monitors that were ultimately non-diagnostic are not trivial, suggesting at a population level that significant cost savings may be accrued if immediate ICM placement is done for the lower-risk patients (i.e. potentially those who are younger and without hypertension) who are more likely to require prolonged monitoring. Since patients in our study who were older and who had hypertension were more likely to have AF detected, a more cost-effective strategy may be to place a 30 day monitor in that population and only if negative then place an ICM.

Multiple factors should be considered when determining appropriate monitor selection for individual patients, including risk level, potential loss to follow-up, and patient preference, in addition to clinician judgement. Additionally, the economic implications of cardiac monitoring should be discussed with the patient to ensure shared decision-making, as out-of-patient costs for cardiac monitoring modalities vary widely based on the payer, plan, clinical setting/site of service, and the particular clinical situation. In our institution we have an entire ICM team that meets with patients and provides information about the potential costs they will incur based on their health plan.

4.1. Limitations

This was a retrospective chart study and was limited to the data available in the medical records and the available follow-up time of patients in our health system. Patient follow-up consisted of a median of 189 days, and as such the longer-term AF detection rates with ICM monitoring up to three years is not represented. Likewise, long-term clinical events such as recurrent strokes were not within the timeframe or scope of this study, as the aim was to compare initial cardiac monitoring strategies during the immediate post-stroke period.

As a control group was not available, we simulated scenarios utilizing ICM data to model alternative patient care pathways; however, this unique methodology allowed us to analyze the potential impact of alternative interventions in a patient population without the impact of confounding variables which could exist in separate patient cohorts.

This analysis does not include a comparison to a wearable-monitor-only strategy, as our goal was to compare the strategies during the immediate post-stroke period specifically directed at long-term monitoring strategies. A recently published cost analysis studied this issue and found long-term ICM monitoring to be more economically attractive compared to a short-term 30-day monitor alone [29]. Additionally, a strategy of empiric anticoagulation of ESUS patients without AF monitoring was not tested, as the RE-SPECT ESUS trial was not able to show a patient benefit [30] and recent cost analysis based on the trial projected empiric anticoagulation of ESUS patients to be a cost-additive strategy due to increased bleeding costs [31].

We did not collect information on adverse events related to ICM insertion, as this is rarely encountered with recent ICM technology. Utilizing rates from the recent ICM RCTs (0.7 % and 1.8 % for PER DIEM and STROKE AF, respectively) and the average costs related to ICM removal procedures from a recent economic analysis ($738.10 Medicare

national average) [27], the additional cost related to adverse events would be estimated to average between $5.17–$13.29 per patient. Thus, this would be unlikely to change our study conclusions. Finally, while our cost analysis focuses on national average payer perspective and patient costs, future work could focus on hospital perspective economics of stroke pathways, which is likely to vary significantly by healthcare system and geographic region of the U.S.

5. Conclusions

AF detection increased steadily along with the duration of cardiac monitoring in a population of ESUS patients after ICM monitoring for a median follow-up of approximately 6 months. Our cost analysis demonstrates ICM insertion prior to hospital discharge is a cost-saving approach compared to a strategy of short-term wearable monitoring followed by ICM in undiagnosed patients, from both Medicare cost and patient out-of-pocket perspectives. This is driven by the cost of the wearable device and low likelihood of AF detection during the first 2–4 weeks following an acute ESUS event, such that an ICM is needed in >90 % of patients. Our cost analysis projected that this strategy resulted in similar benefits in the broader populations of ischemic stroke patients from two large randomized trials, PER DIEM and STROKE AF. Given the potential economic benefit of the Immediate ICM approach compared to a sequential Wearable-to-ICM strategy, the use of ICM prior to hospital discharge should be considered. Further studies should be done comparing these diagnostic strategies.

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NC trial design, analysis, interpretation and article drafting; PB data collection, analysis, and article drafting; SCR data analysis, interpretation and article drafting.; JF data analysis, interpretation and article drafting; AA data interpretation and article drafting; MB data interpretation and article drafting; KC data collection, analysis, and article drafting; MD data interpretation and article drafting; SD data interpretation and article drafting; ATD data interpretation and analysis, and article drafting; DE data interpretation/analysis and article drafting; WJ data interpretation and article drafting; JM data interpretation and article drafting; MK data interpretation and article drafting; SR data collection, analysis, and article drafting; RS data collection, analysis, and article drafting; AW data interpretation and article drafting; VR data interpretation/analysis and article drafting; AG trial design, interpretation and article drafting.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nagib Chalfoun reports statistical analysis and writing assistance were provided by Medtronic Inc. Sarah Rosemas (employee of medtronic) reports financial support was provided by Medtronic Inc. Sarah Rosemas reports a relationship with Medtronic Inc. that includes: employment and equity or stocks. Nagib Chalfoun reports a relationship with Medtronic Inc. that includes: consulting or advisory, non-financial support, and speaking and lecture fees. Andre Gauri reports a relationship with Medtronic Inc. that includes: consulting or advisory, non-financial support, and speaking and lecture fees. Muhib Khan reports a relationship with Medtronic Inc. that includes: funding grants and travel reimbursement. Shelly Rosema reports a relationship with Medtronic Inc. that includes: speaking and lecture fees. John Fox reports a relationship with Medtronic Inc. that includes: consulting or advisory.

NC and AG are consultants to Medtronic. SCR is an employee and stockholder of Medtronic. MK has received grant to attend conference from Medtronic. SR has been adjunct speaker for Medtronic. JF has served on advisory Board for Medtronic.

Appendices. Supplementary data

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