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Prolonged cardiac monitoring for stroke prevention: A systematic review and meta-analysis of randomized-controlled clinical trials

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Abstract

Introduction: Prolonged cardiac monitoring (PCM) substantially improves the detection of subclinical atrial fibrillation (AF) among patients with history of ischemic stroke (IS), leading to prompt initiation of anticoagulants. However, whether PCM may lead to IS prevention remains equivocal.

Patients and methods: In this systematic review and meta-analysis, randomized-controlled clinical trials (RCTs) reporting IS rates among patients with known cardiovascular risk factors, including but not limited to history of IS, who received PCM for more than 7 days versus more conservative cardiac rhythm monitoring methods were pooled.

Results: Seven RCTs were included comprising a total of 9048 patients with at least one known cardiovascular risk factor that underwent cardiac rhythm monitoring. PCM was associated with reduction of IS occurrence compared

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to conventional monitoring (Risk Ratio: 0.76; 95% CI: 0.59–0.96; $I^2 = 0\%$). This association was also significant in the subgroup of RCTs investigating implantable cardiac monitoring (Risk Ratio: 0.75; 95% CI: 0.58–0.97; $I^2 = 0\%$). However, when RCTs assessing PCM in both primary and secondary prevention settings were excluded or when RCTs investigating PCM with a duration of 7 days or less were included, the association between PCM and reduction of IS did not retain its statistical significance. Regarding the secondary outcomes, PCM was related to higher likelihood for AF detection and anticoagulant initiation. No association was documented between PCM and IS/transient ischemic attack occurrence, all-cause mortality, intracranial hemorrhage, or major bleeding.

Conclusion: PCM may represent an effective stroke prevention strategy in selected patients. Additional RCTs are warranted to validate the robustness of the reported associations.

Keywords

Stroke, prevention, prolonged cardiac monitoring, implantable cardiac monitor, atrial fibrillation, anticoagulation

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Introduction

Atrial fibrillation (AF) is associated with an increased risk of first-ever ischemic stroke (IS),[1] as well as early IS recurrence.[2] Moreover, AF-related IS tends to be more severe and is also related to poorer functional outcomes at 3 months compared to IS of other etiologies.[3] Therefore, appropriate anticoagulant treatment for IS prevention is indicated, either as primary prevention in AF patients with at least one non-sex stroke risk factor[1,4] or secondary prevention in the cases of previous IS history.[5]

Yet, the detection of AF is not always an easily accomplished task, with occult AF being diagnosed in 30% of cryptogenic strokes during long-term follow-up.[6] Interestingly, randomized controlled trial data[6,7] and clinical experience[8–10] have provided compelling evidence that the detection of AF among cryptogenic stroke patients increases with prolonged cardiac monitoring (PCM) compared to conventional monitoring with single 24-h Holter rhythm recording. Moreover, several factors have been associated with an increased risk of AF detection in IS patients. Increasing age,[8,9] left atrial enlargement,[9] cortical location of infarction,[11] an increased number of atrial premature beats per 24 h,[11] risk stratification scores (such as CHA_2DS_2-VASc,[4] Brown ESUS-AF,[12] HAVOC,[13] and C_2HEST[14] scores), have been used in clinical practice for the selection of patients that may require additional investigation or more prolonged monitoring.[15,16] Indeed, the duration of implantable cardiac monitoring (ICM) has been independently associated with the likelihood of AF detection among patients with CS, with ICM duration of <6 and >24 months yielding AF detection rates of 5% and 34% respectively.[8]

Nevertheless, whether the detection of subclinical AF through PCM and the subsequent initiation of anticoagulants may lead to stroke prevention remains equivocal.[17] In a previous systematic review and meta-analysis conducted by our international collaborative group including both randomized-controlled clinical trials (RCTs) and observational studies, PCM was associated with a higher rate of AF detection and initiation of anticoagulants and a lower risk of IS recurrence in patients that had a previous history of IS.[18] However, the IS recurrence reduction was driven mostly from the included observational data which may be confounded by inherent limitations (such as potential selection bias or reporting bias), while RCT data did not confirm the effect of PCM on reducing IS recurrence.[18]

In the present updated systematic review and meta-analysis, we sought to assess the association of PCM compared to conventional cardiac monitoring with first-ever and recurrent stroke in patients with known cardiovascular risk factors of stroke, including but not limited to the history of previous IS using exclusively RCT data.

Methods

Standard protocol approvals, registrations, and patient consents

The pre-specified protocol of the present systematic review and meta-analysis has been registered in the International Prospective Register of Ongoing Systematic Reviews PROSPERO (registration ID: CRD42022351471). The meta-analysis is reported according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] This study did not require an ethical board approval or written informed consent by the patients according to the study design (systematic review and meta-analysis).

Data sources, searches, and study selection

A systematic literature search was conducted to identify RCTs evaluating the impact of PCM on stroke prevention (primary, secondary or both) compared to patients receiving conventional cardiac monitoring (controls) for the detection of AF. PCM was defined as the use of any continuous cardiac rhythm monitoring strategy, either

inpatient or outpatient, with a total monitoring duration that exceeded 7 days.[18,20] The literature search was performed independently by three reviewers (LP, ST, and AHK). We searched MEDLINE, and Scopus, using search strings that included the following terms: "stroke," "atrial fibrillation," and "prolonged cardiac monitoring"; the complete search algorithms used in MEDLINE and Scopus are presented in the eMethods provided in the Supplement. No language or other restrictions were applied. Our search spanned from inception of each database to August 14th, 2022. We additionally searched reference lists of published articles manually, to ensure the comprehensiveness of bibliography.

Observational studies, cohort studies, non-controlled studies, case series and case reports reporting on PCM methods for AF detection with the aim of stroke prevention were excluded. Commentaries, editorials, and narrative reviews were also excluded. All retrieved studies were independently assessed by the three reviewers (LP, ST, and AHK) and any disagreements were resolved after discussion with a fourth tie-breaking evaluator (GT).

Quality control, bias assessment, and data extraction

Eligible studies were subjected to quality control and bias assessment employing the Cochrane Collaboration tool (RoB 2) for RCTs.[21] Quality control and bias assessment was conducted independently by three reviewers (LP, ST, and AHK), and disagreements were settled by consensus after discussion with the corresponding author (GT).

Data extraction was performed in structured reports, including author names, date of publication, study design, country, PCM method used, non-PCM method involved, and patients' characteristics.

Outcomes

The primary outcome of interest was the association of PCM with first-ever or recurrent IS occurrence compared to conventional cardiac rhythm monitoring in patients without AF and at least one cardiovascular risk factor (e.g. hypertension, diabetes mellitus, heart failure) or previous history of IS. This outcome was also assessed in subgroup analysis after stratification according to the active strategy of PCM (either ICM or other non-ICM strategies).

Secondary outcomes of interest comprised the association of PCM with: (1) occurrence of IS or transient ischemic attack (TIA); (2) AF detection; (3) anticoagulant initiation; (4) all-cause mortality; (5) intracranial hemorrhage; (6) major bleeding; and (7) device-related adverse events. The previous secondary outcomes of interest were also assessed in subgroup analyses after stratification according to the PCM strategy [ICM vs. other strategies (non-ICM)].

Statistical analysis

For the pairwise meta-analysis, we calculated for each dichotomous outcome of interest the corresponding risk ratios (RR) with 95% confidence interval (95% CI) for the comparison of outcome events among patients receiving PCM versus controls. The random-effects model of meta-analysis (DerSimonian and Laird)[22] was used to calculate the pooled estimates. To test the robustness of our results, all analyses were repeated by calculating the corresponding odds ratios (OR) with 95% CI.[23] Subgroup differences between different PCM strategies were assessed by the Q test for subgroups.[24] For the outcome of device-related adverse events, we calculated the corresponding pooled proportion with 95% CI, after the implementation of the variance-stabilizing double arcsine transformation as previously described.[25] Sensitivity analyses were also performed, by restricting the analysis to studies that assessed the primary outcome of this meta-analysis (occurrence of IS) at a follow-up duration of at least 12 months.

Heterogeneity was assessed with the I^2 and Cochran Q statistics. For the qualitative interpretation of heterogeneity, I^2 values $>50\%$ and values $>75\%$ were considered to represent substantial and considerable heterogeneity, respectively. The significance level for the Q statistic was set at 0.1. Publication bias across individual studies was assessed when more than four studies were included in the analysis of the outcomes of interest, using both funnel plot inspection and the Egger et al.'s linear regression test,[26] and the equivalent z test for each pooled estimate with a two-tailed p value <0.05 was considered statistically significant. Furthermore, analysis of dichotomous outcomes allowed the calculation of the fragility index (FI),[27,28] which was assessed based on the classification by Mun et al.[29] suggesting that a $FI \leqslant 4$ was indicative of a non-robust result; a $4 < FI \leqslant 12$ corresponded to a somewhat robust result; a $12 < FI \leqslant 34$ indicated a robust result; and, finally, a $FI > 34$ was suggestive of a highly robust result. It should be noted, though, that FI has been recently criticized and should be interpreted as an additional measure of robustness and in conjunction with the other available statistical summaries that have been also used in the current meta-analysis.[30]

All statistical analyses were performed using the Cochrane Collaboration's Review Manager (RevMan 5.3) Software Package (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014),[31] and R software version 3.5.0 (package: metafor).[32]

Data availability statement

All data generated or analyzed during this study are included in this article and its supplementary information files.

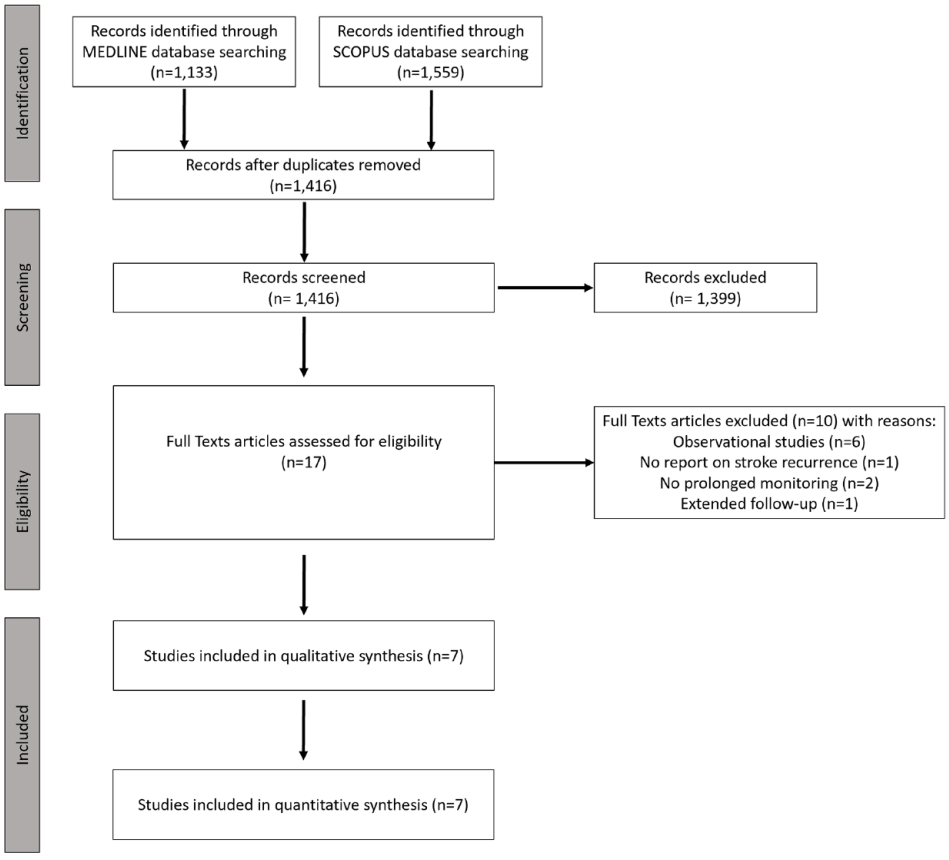

Figure 1. Flowchart of systematic review.

Results

Literature search and included studies

The systematic database search yielded a total of 1133 and 1559 records from the MEDLINE and SCOPUS databases, respectively (Figure 1). After excluding duplicates and initial screening, we retrieved the full text of 17 records that were considered potentially eligible for inclusion. After reading the full-text articles, 10 were further excluded (Supplemental Table 1). Finally, we identified seven eligible studies[6,7,33–37] for inclusion in the systematic review and meta-analysis. Five studies[6,7,33,35–37] exclusively included patients that had a history of prior IS, while two studies[34,36] evaluated patients with at least one known cardiovascular risk factor including but not limited to prior history of stroke. More specifically, the LOOP trial[34] investigated on patients aged 70–90 years that presented an additional cardiovascular risk factor, including prior IS or TIA or systemic embolism, hypertension, diabetes mellitus and heart failure and the SCREEN-AF trial[36] included patients aged 75 years or older with hypertension and $CHADS_2$ (congestive heart failure, hypertension, age $\geqslant$75 years, diabetes, stroke) score $\geqslant$2. The total population of this meta-analysis comprised 9048 patients with at least one known stroke risk factor, including but not limited to history of prior IS/TIA (n=3795; 42% of included patients), that underwent cardiac rhythm monitoring and were evaluated for first-ever or recurrent IS occurrence (Table 1).

Quality control of included studies

The risk of bias in included studies was assessed by the Cochrane risk-of-bias (RoB 2) tool[21] and is presented in Supplemental Figures 1–2. All studies but one[33] presented minor concerns due to deviations from intended interventions. Moreover, two studies[35,36] suffered from bias due to missing outcome data and another one[6] did not meticulously report the blinding process during outcome assessment. Overall, the included RCTs were considered of good quality, presenting only some minor concerns.

Quantitative analyses

An overview of analyses for all primary and secondary outcomes is summarized in Table 2.

Primary outcome. Patients receiving PCM had a reduced risk of IS compared to controls (RR: 0.76; 95% CI: 0.59–0.96; 7 studies; I^2=0%; p for Cochran Q=0.85; Figure 2). However, FI was calculated at 4 indicating that the result is

Table 1. Characteristics of studies included in the systematic review and meta-analysis.

Study name	Centers	Period of enrollment	Target population	N of included patients	PCM method	Control method	AF definition	Follow-up time	Outcomes of interest	
									Primary	Secondary
CRYSTAL AF[6]	55 sites (International: Europe, Canada, US)	June 2009–April 2012	within 90 days of CS, ⩾40 y.o.	441	ICM	ECG monitoring at scheduled and unscheduled visits	>30 s	6 months*	AF	IS, IS/TIA, AC, Mortality, DAE
EMBRACE[7]	16 sites (Canada)	June 2009–March 2012	within 6 months of CS/TIA, ⩾55 y.o.	572	Noninvasive ambulatory ECG 30-day recorder	Conventional 24-h monitor	>30 s	3 months	AF	IS, AC
FIND AF[33]	4 sites (Germany)	May 2013–August 2014	Within 7 days of IS (excl. ipsilateral carotid or intracranial artery stenosis), ⩾60 y.o.	398	10-day Holter-ECG-monitoring at baseline, and at 3 and 6 months	At least 24 h of rhythm monitoring	>30 s	12 months **	AF	IS, IS/TIA, AC, Mortality, MB
LOOP[34]	4 sites (Denmark)	January 2014–May 2016	70–90 y.o., with at least one stroke risk factor (hypertension, diabetes, previous stroke, or heart failure)	6205	ICM	Annual interview with a study nurse and standard contact with the participant's general practitioner	⩾6 min	64.5 months (median)	IS	IS/TIA, AF, AC, Mortality, ICH, MB, DAE
PER DIEM[35]	3 sites (Canada)	May 2015–November 2017	Within 6 months of IS	300	ICM	External loop recorder for 4 weeks.	>2 min (Initially planned >30 s)	12 months	AF	IS, IS/TIA, AC, Mortality, ICH, MB, DAE
SCREEN AF[36]	48 sites (Germany & Canada)	April 2015–March 2019	⩾75 y.o. and history of hypertension	856	2-week ambulatory continuous ECG patch monitor at baseline and at 3 months	Standard clinical care	>5 min (or diagnosed clinically)	6 months	AF	IS, IS/TIA, AC, Mortality, ICH
STROKE AF[37]	33 sites (US)	April 2016–July 2019	Within 10 days of IS attributed to large- or small-vessel disease, ⩾60 y.o. (or ⩾50 y.o. with least 1 additional stroke risk factor)	492	ICM	Usual care consisting of external cardiac monitoring, such as 12-lead ECG, Holter monitoring, telemetry, or event recorders.	>30 s	12 months	AF	IS, IS/TIA, AC, Mortality, ICH, DAE

CS: cryptogenic stroke; ICM: implantable cardiac monitoring; ECG: electrocardiogram; IS: ischemic stroke; AF: atrial fibrillation; AC: anticoagulants; TIA: transient ischemic attack; ICH: intracranial hemorrhage; MB: major bleeding; DAE: device-related adverse events.

*In CRYSTAL-AF,[6] data regarding IS occurrence and mortality were available at a follow-up duration of 6 months, while data regarding IS/TIA occurrence, AF detection and AC initiation were reported at a 12-month follow-up duration.

**An extended follow-up of 36-month duration was available for 80% of the patients included in FIND AF.[38]

Table 2. Overview of analyses for primary and secondary outcomes.

Variable	Effect			Fragility Index	Interpretation
	No. of studies	Risk ratio (95% CI)	I^2, p for Cochran Q		
Primary outcome					
IS occurrence	7	0.76 (0.59–0.96)	0%; 0.85	4	Not robust
Secondary efficacy outcomes					
IS/TIA occurrence	6	0.90 (0.74–1.08)	0%; 0.64	11	Somewhat robust
AF detection	7	3.85 (2.59–5.73)	58%; 0.03	73	Highly robust
AC initiation	7	2.16 (1.75–2.66)	35%; 0.16	52	Highly robust
Secondary safety outcomes					
All-cause mortality	6	0.97 (0.83–1.14)	0%; 0.67	24	Robust
Intracranial Hemorrhage	3	0.98 (0.51–1.85)	0%; 1.00	12	Somewhat robust
Major bleeding	3	1.28 (0.96–1.69)	0%; 0.66	3	Not robust
Device-related adverse events	4	1.6% (0.4–3.6%)*	81%; 0.001	NA	NA

IS: ischemic stroke; TIA: transient ischemic attack; AF: atrial fibrillation; AC: anticoagulant; CI: confidence interval; NA: not applicable.
*Pooled rate.

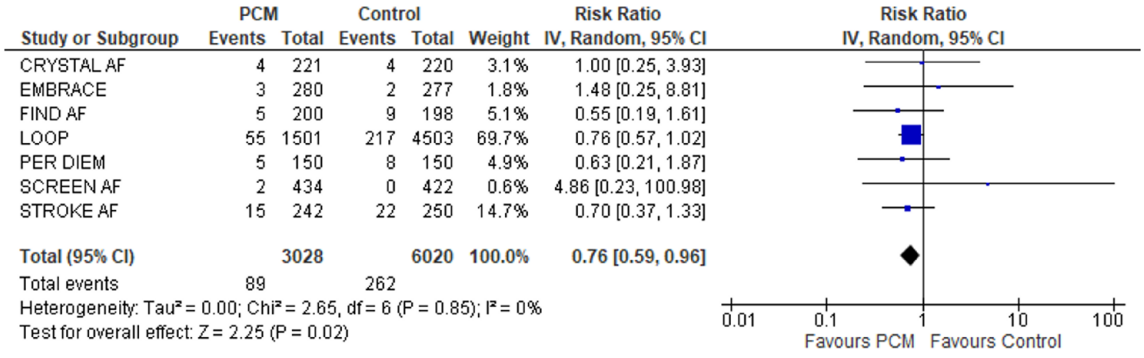

Figure 2. Forest plot presenting the association of prolonged cardiac monitoring (PCM) with occurrence of ischemic stroke compared to controls.

not robust.[29] This association was also significant in the subgroup of RCTs investigating ICM versus conventional monitoring (RR: 0.75; 95% CI: 0.58–0.97; 4 studies $I^2=0\%$; p for Cochran $Q=0.96$, Supplemental Figure 3).

A sensitivity analysis was performed by excluding CRYSTAL-AF,[6] EMBRACE,[7] and SCREEN-AF[36] for which data on IS occurrence were available at 6, 3, and 6 months, respectively. When the remaining four studies[33–35,37] were pooled, the association of PCM with reduced risk of IS was practically identical to the primary analysis (RR: 0.73; 95% CI: 0.57–0.94; 4 studies; $I^2=0\%$; p for Cochran $Q=0.93$; Supplemental Figure 4).

Secondary outcomes. When the occurrence of the composite outcome of IS/TIA was assessed, no significant difference was disclosed between the two groups (RR: 0.90; 95% CI: 0.74–1.08; 6 studies; $I^2=0\%$; p for Cochran $Q=0.64$; Supplemental Figure 5). FI was calculated at 11 which is indicative of a "somewhat robust" result.[29] No differences were also noted in the subgroup analysis stratified by PCM methodology (Supplemental Figure 6). The sensitivity analysis including four studies with a follow-up duration of $\geqslant$12 months confirmed the overall effect of the primary analysis (Supplemental Figure 7).

AF detection was significantly more common in the PCM group compared to controls (RR: 3.85; 95% CI: 2.59–5.73; 7 studies; $I^2=58\%$; p for Cochran $Q=0.03$; Figure 3) and the overall effect was considered highly robust (FI = 73).[29] This association was also significant in the subgroup of RCTs investigating ICM versus conventional monitoring (RR: 3.86; 95% CI: 2.24–6.64; 4 studies; $I^2=59\%$; p for Cochran $Q=0.06$; Supplemental Figure 8). The sensitivity analysis including four studies with a follow-up duration of $\geqslant$12 months confirmed the overall effect of the primary analysis (Supplemental Figure 9).

PCM was also associated with higher odds of initiation of anticoagulants for all indications including AF (RR: 2.16; 95% CI: 1.75–2.66; 7 studies; $I^2=35\%$; p for Cochran $Q=0.16$; Figure 4). FI was calculated at 52 that corresponds to highly robust result.[29] This association was also significant

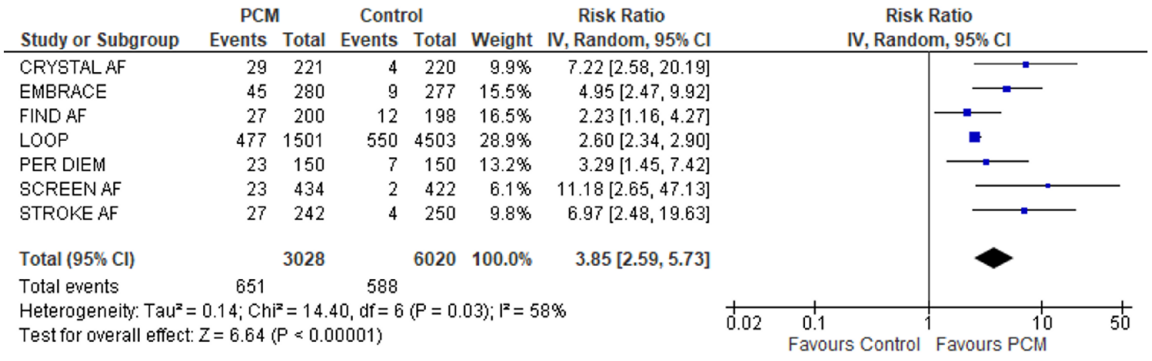

Figure 3. Forest plot presenting the association of prolonged cardiac monitoring (PCM) with atrial fibrillation detection compared to controls.

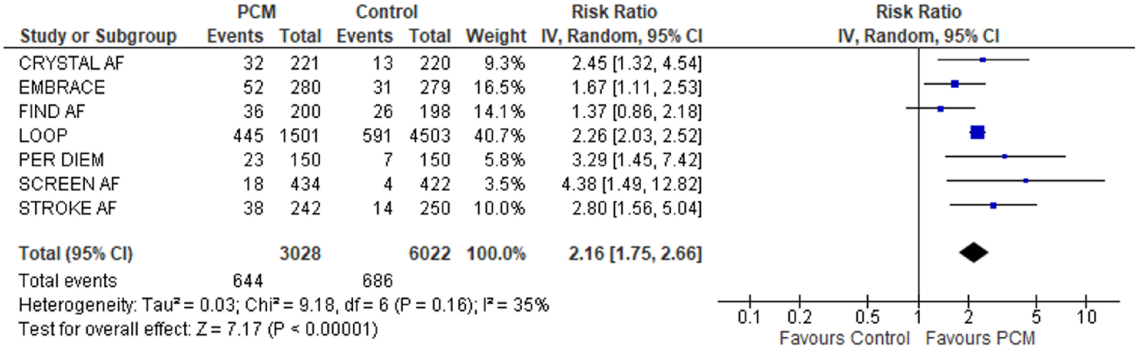

Figure 4. Forest plot presenting the association of prolonged cardiac monitoring (PCM) with initiation of anticoagulants for all indications, including atrial fibrillation, compared to controls.

in the subgroup of RCTs investigating ICM versus conventional monitoring (RR: 2.29; 95% CI: 2.07–2.55; 4 studies; $I^2=0\%$; p for Cochran $Q=0.72$; Supplemental Figure 10). The sensitivity analysis including four studies with a follow-up duration of ⩾12 months confirmed the overall effect of the primary analysis (Supplemental Figure 11).

There was no association of PCM with all-cause mortality (RR: 0.97; 95% CI: 0.83–1.14; 6 studies; $I^2=0\%$; p for Cochran $Q=0.67$; Supplemental Figure 12). FI was calculated at 24 that corresponds to a robust result.[29] No subgroup differences were disclosed when different PCM strategies were assessed (Supplemental Figure 13). The sensitivity analysis including four studies with a follow-up duration of ⩾12 months confirmed the overall effect of the primary analysis (Supplemental Figure 14).

There was no association of PCM with intracranial hemorrhage (RR: 0.98; 95% CI: 0.51–1.85; 3 studies; $I^2=0\%$; p for Cochran $Q=1.00$; Supplemental Figure 15). FI was calculated at 12 that corresponds to a "somewhat robust" result probably owing to the limited number of studies included.[29]

There was no association of PCM with major bleeding (RR: 1.28; 95% CI: 0.96–1.69; 3 studies; $I^2=0\%$; p for Cochran $Q=0.66$; Supplemental Figure 16), but this result was highly fragile (FI = 3).[29] After stratification for different PCM methods, there was no subgroup differences among ICM versus non-ICM strategies (Supplemental Figure 17).

The pooled proportion of device-related adverse events among patients receiving ICM was 1.6% 95% CI: 0.4%–3.6%; 4 studies; $I^2=81\%$; p for Cochran $Q=0.001$; Supplemental Figure 18).

Similar results were obtained for all outcomes, when analysis was repeated by calculating ORs with the corresponding 95% CI (Supplemental Table 2).

Publication bias was evaluated using funnel plots and the Egger's linear regression test for every investigated outcome, when more than four studies were included in the respective analyses. Asymmetry or evidence of small study effects (i.e. publication bias) were not uncovered in any of the outcomes assessed (Supplemental Figures 19–23).

An extended follow-up of 3-year duration was available for 80% of the patients included in FIND AF.[38] Therefore, sensitivity analyses were conducted after including the events for all outcomes assessed in the long-term follow-up intention-to-treat analysis of FIND AF. No changes in both the direction or statistical significance for IS occurrence, IS/TIA occurrence, AF detection, all-cause mortality, and intracranial hemorrhage were noted compared to the primary analyses (Supplemental Figures 24–28).

It should be noted that the MonDAFIS trial[39] was excluded from our primary analysis, based on our prespecified inclusion criteria mandating for continuous cardiac rhythm monitoring strategies with a total monitoring duration that exceeded 7 days. However, we have conducted an additional sensitivity analysis after inclusion of MonDAFIS trial[39] for all the available outcomes. In this sensitivity analysis, the association between PCM and IS occurrence did not remain statistically significant (RR: 0.87; 95% CI: 0.73–1.04; 8 studies; $I^2 = 0\%$; p for Cochran $Q = 0.59$; Supplemental Figure 29), whereas no changes were noted for any of the secondary outcomes (Supplemental Figures 30–35).

Discussion

The present study has shown that PCM is associated with a reduced risk of IS occurrence and a higher likelihood of AF detection and initiation of anticoagulants among patients with at least one known risk factor for stroke, including the history of previous stroke. Moreover, safety outcomes, including all-cause mortality, intracranial hemorrhage or major bleeding, were not increased in patients who underwent PCM compared to patients who underwent conventional cardiac rhythm monitoring strategies. Device-related adverse events were recorded in 1.6% of patients receiving ICM.

In a previous systematic review and meta-analysis conducted by our group, analysis of RCT data failed to reach statistical significance with regard to the association of PCM and risk of recurrent stroke (RR: 0.72; 95% CI: 0.49–1.07; 5 studies; $I^2 = 0\%$; p for Cochran $Q = 0.91$).[18] However, this meta-analysis did not include the results of LOOP trial[34] and SCREEN-AF trial[36] assessing PCM in both primary and secondary prevention settings and did not address potential safety issues in relation to PCM.

Another systematic review and meta-analysis that included RCTs evaluating patients in the primary prevention setting showed the screening for AF was significantly associated with stroke reduction.[40] However, in this study the cardiac monitoring strategies applied (prolonged or intermittent) and the definition for stroke used (IS or composite of stroke and systemic embolism) varied among the included studies. In our study, we restricted the inclusion criteria to studies evaluating PCM methods for AF detection and extracted data for our prespecified outcomes only.

In the LOOP trial,[34] patients between the age of 70 and 90 years, with at least one additional cardiovascular risk factor (history of hypertension, diabetes mellitus, heart failure, or previous stroke or TIA or systemic embolism), were randomized to either receive ICM or to conventional monitoring with study interviews and/or communication with general practitioner if necessary. Although this RCT could have been considered as a primary prevention trial, approximately 25% of the enrolled patients had a history of previous stroke, TIA or systemic embolism and received ICM in the setting of secondary stroke prevention. Likewise, in SCREEN-AF trial,[36] older individuals with at least a history of hypertension were included; yet almost 10% of them had also a history of previous stroke, TIA or systemic embolism. However, with regard to the subgroup of patients with prior IS, the time from index event to randomization is not reported in any of the two studies.[34,36] In a post-hoc subgroup analysis of IS occurrence that was performed stratified by the different settings in which the studies were conducted (secondary stroke prevention versus combination of primary and secondary stroke prevention), no significant differences were revealed between the two subgroups (p for subgroup difference = 0.63; Supplemental Figure 36).

Importantly, LOOP trial[34] is the only RCT that was designed with IS occurrence as a primary outcome of interest, while the rest of the included studies investigated primarily the endpoint of AF detection (Table 1). The addition of LOOP trial[34] that represents by far the largest RCT in terms of sample size increased the power of the current meta-analysis and shifted the overall effect size that crossed the boundary of statistical significance (RR: 0.76; 95% CI: 0.59–0.96) without any evidence of heterogeneity ($I^2 = 0\%$). However, it should be noted that this association was not robust based on the calculated FI of 4. Additionally, statistical significance was not preserved when LOOP trial[34] was excluded from analysis (Supplemental Figure 37). In view of these considerations, further RCTs are required to increase the robustness of the effect of PCM on reducing the risk of first-ever or recurrent stroke.

When studies with PCM duration of 7 days or less were included in our analysis, PCM was no longer associated with IS reduction. This is in accordance with our previous work,[18] in which we showed that the association of PCM with secondary stroke prevention did not reach statistical significance in the subgroup of RCTs, when the MonDAFIS trial[39] evaluating PCM with a limited monitoring duration (up to 7 days) was included in the analysis. Although the duration of cardiac monitoring has been associated with AF detection,[25] the optimal duration of PCM for stroke prevention remains currently unknown.

ICM has been shown to be superior compared to other PCM strategies in detecting AF and initiating anticoagulation in a meta-analysis of randomized and observational data.[18] Furthermore, in the current meta-analysis, a subgroup analysis of RCTs comparing ICM with conventional cardiac monitoring documented that ICM was also associated with a lower risk of IS occurrence and higher odds of AF detection and anticoagulant initiation. This observation lends support to recent European Stroke Organisation (ESO) recommendations on AF screening that advocate the use of ICM instead of non-ICM monitoring strategies for AF detection in patients with cryptogenic IS or TIA.[41] Nevertheless, it should be acknowledged that there is ambiguity and clinical equipoise regarding the most effective

monitoring strategies for AF detection in patients with IS due to large artery atherosclerosis, small vessel disease or other determined etiopathogenic mechanisms.[42] Notably, three RCTs included in the present systematic review recruited patients with several subtypes of stroke, including but not limited to cryptogenic stroke (i.e. FIND AF,[33] PER DIEM,[35] and STROKE-AF[37]); the rate of AF detection in the "enhanced" monitoring group was significantly higher compared to the standard monitoring group in all IS subtypes. PCM has a high yield of AF detection in unselected stroke patients according to the available observational data that indicate an AF detection rate of 12%.[43] These findings underscore the potential co-existence of AF in IS patients with well-established non-cardioembolic etiologies and potentially justify the wider application of ICM in all IS subtypes. Potential biomarkers and risk stratification scores may guide a more individualized approach for selecting patients at stroke risk for PCM as part of primary or secondary stroke prevention management.[16,44,45]

Our present meta-analysis includes all RCTs that have been completed to date investigating PCM efficacy in reducing the risk of first-ever or recurrent stroke. In addition, we have included previously unpublished data on stroke occurrence from 3 RCTs.[6,7,33] Despite these strengths, several limitations of our study should also be acknowledged. First, the duration of follow-up for the assessment of first-ever or recurrent stroke occurrence varied across studies. More specifically, CRYSTAL-AF[6] and SCREEN-AF[36] had a primary follow-up period of 6 months, while EMBRACE[7] assessed the outcomes of interest at 3 months. On the other hand, the remaining trials had a follow-up period of at least 12 months. To address this shortcoming, we conducted sensitivity analyses by excluding trials with a follow-up duration of <12 months for the assessment of stroke occurrence. Interestingly, the sensitivity analysis yielded identical results to the primary analysis. In addition, as evident from the overview of included trials presented in Table 1, there were also differences in the threshold for AF detection, while all RCTs except for LOOP trial[34] were not powered to uncover differences in stroke risk reduction. Another potential limitation is the fact that LOOP trial and SCREEN-AF trial included patients with and without previous IS history; thus, evaluating PCM effectiveness in the setting of both primary and secondary stroke prevention.[34,36] However, individual patient data were not available regarding our primary outcome of interest (i.e. IS occurrence) and a relevant subgroup analysis (primary versus secondary prevention) could not be performed. Specifically for LOOP trial, separate data stratified by history of stroke were available only for the composite outcome of stroke (including IS and intracranial hemorrhage) and systemic arterial embolism,[34] but not for IS occurrence which was our primary outcome. Importantly, though, there was no significant modifying effect of previous history of stroke with regards to the primary outcome of LOOP trial ($p=0.28$).[34] Additionally, no significant heterogeneity among included studies was unraveled in our meta-analysis, despite the inclusion of LOOP study. Furthermore, some concerns were documented during quality assessment regarding minor deviations from intended interventions (prolonged vs conventional cardiac monitoring) in the included RCTs. Last and most important, the lack of robustness with regard to the association of PCM with reduction of first-ever and recurrent stroke indicates caution in the interpretation of this meta-analysis results. The results of the Find-AF2 (Intensive Rhythm Monitoring to Decrease Ischemic Stroke and Systemic Embolism; https://www.clinicaltrials.gov; Unique identifier: NCT04371055), the ARTESiA (Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-Detected Sub-Clinical Atrial Fibrillation; https://www.clinicaltrials.gov; Unique identifier: NCT01938248) and NOAH (Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes; https://www.clinicaltrials.gov; Unique identifier: NCT02618577) trials will provide additional randomized evidence to increase the robustness of an updated meta-analysis.

Conclusion

In conclusion, the current meta-analysis showed that PCM was associated with a lower risk of first-ever or recurrent IS and a higher likelihood of AF detection and initiation of anticoagulants, without presenting any safety issues, compared to usual strategies of cardiac rhythm monitoring in patients with cardiovascular risk factors, including previous history of IS. These findings highlight that PCM may represent an effective stroke prevention strategy in selected patients, but additional RCTs are warranted to validate the robustness of the reported associations.

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Trial registration

The pre-specified protocol of the present systematic review and meta-analysis has been registered in the International Prospective Register of Ongoing Systematic Reviews PROSPERO (registration ID: CRD42022351471).

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Supplemental material

Supplemental material for this article is available online.

References

1. Hindricks G, Potpara T, Dagres N, et al. Corrigendum to: 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; 42: 373–498.
2. Arboix A and Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev* 2010; 6: 150–161.
3. Henninger N, Goddeau RP Jr, Karmarkar A, et al. Atrial fibrillation is associated with a worse 90-Day outcome than other cardioembolic stroke subtypes. *Stroke* 2016; 47: 1486–1492.
4. Lip GY and Nielsen PB. Should patients with atrial fibrillation and 1 stroke risk factor (CHA2DS2-VASc score 1 in men, 2 in women) Be anticoagulated? Yes: even 1 stroke risk factor confers a real risk of stroke. *Circulation* 2016; 133: 1498–1503.
5. Klijn CJ, Paciaroni M, Berge E, et al. Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke Organisation guideline. *Eur Stroke J* 2019; 4: 198–223.
6. Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014; 370: 2478–2486.
7. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014; 370: 2467–2477.
8. Tsivgoulis G, Katsanos AH, Grory BM, et al. Prolonged cardiac rhythm monitoring and secondary stroke prevention in patients with cryptogenic cerebral ischemia. *Stroke* 2019; 50: 2175–2180.
9. Liantinioti C, Palaiodimou L, Tympas K, et al. Potential utility of neurosonology in paroxysmal atrial fibrillation detection in patients with cryptogenic stroke. *J Clin Med* 2019; 8: 8.
10. Triantafyllou S, Katsanos AH, Dilaveris P, et al. Implantable cardiac monitoring in the secondary prevention of cryptogenic stroke. *Ann Neurol* 2020; 88: 946–955.
11. Favilla CG, Ingala E, Jara J, et al. Predictors of finding occult atrial fibrillation after cryptogenic stroke. *Stroke* 2015; 46: 1210–1215.
12. Ricci B, Chang AD, Hemendinger M, et al. A simple score that predicts paroxysmal atrial fibrillation on outpatient cardiac monitoring after embolic stroke of unknown source. *J Stroke Cerebrovasc Dis* 2018; 27: 1692–1696.
13. Kwong C, Ling AY, Crawford MH, et al. A clinical score for predicting atrial fibrillation in patients with cryptogenic stroke or transient ischemic attack. *Cardiology* 2017; 138: 133–140.
14. Li YG, Bisson A, Bodin A, et al. C(2) HEST score and prediction of incident atrial fibrillation in poststroke patients: a French nationwide study. *J Am Heart Assoc* 2019; 8: e012546.
15. Haeusler KG, Gröschel K, Köhrmann M, et al. Expert opinion paper on atrial fibrillation detection after ischemic stroke. *Clin Res Cardiol* 2018; 107: 871–880.
16. Dilaveris PE, Antoniou C-K, Caiani EG, et al. ESC Working Group on e-Cardiology Position Paper: accuracy and reliability of electrocardiogram monitoring in the detection of atrial fibrillation in cryptogenic stroke patients. *Eur Heart J* 2022; 3: 341–358.
17. Kim AS, Kamel H, Bernstein RA, et al. Controversies in stroke: should patients with embolic stroke of undetermined source undergo intensive heart rhythm monitoring with an implantable loop recorder? *Stroke* 2022; 53: 3243–3247.
18. Tsivgoulis G, Triantafyllou S, Palaiodimou L, et al. Prolonged cardiac monitoring and stroke recurrence: A meta-analysis. *Neurology* 2022; 98: e1942–e52.
19. Page MJ, McKenzie JE, Bossuyt PM, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. *J Clin Epidemiol* 2021; 134: 103–112.
20. Tayal AH, Tian M, Kelly KM, et al. Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. *Neurology* 2008; 71: 1696–1701.
21. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898.
22. DerSimonian R and Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 2015; 45: 139–145.
23. Bakbergenuly I, Hoaglin DC and Kulinskaya E. Pitfalls of using the risk ratio in meta-analysis. *Res Synth Methods* 2019; 10: 398–419.
24. Borenstein M and Higgins JP. Meta-analysis and subgroups. *Prev Sci* 2013; 14: 134–143.

25. Tsivgoulis G, Katsanos AH, Köhrmann M, et al. Duration of implantable cardiac monitoring and detection of atrial fibrillation in ischemic stroke patients: a systematic review and meta-analysis. *J Stroke* 2019; 21: 302–311.
26. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
27. Atal I, Porcher R, Boutron I, et al. Fragilty index of meta-analyses, https://clinicalepidemio.fr/fragility_ma/ (2019, accessed 14 August 2022).
28. Desnoyers A, Nadler MB, Wilson BE, et al. A critique of the fragility index. *Lancet Oncol* 2019; 20: e552.
29. Mun KT, Bonomo JB, Liebeskind DS, et al. Fragility Index meta-analysis of randomized controlled trials shows highly robust evidential strength for benefit of <3 hour intravenous alteplase. *Stroke* 2022; 53: 2069–2074.
30. Carter RE, McKie PM and Storlie CB. The Fragility Index: a P-value in sheep's clothing? *Eur Heart J* 2017; 38: 346–348.
31. Deeks J, Higgins J and Altman D. Chapter 10: analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, et al. (eds.) *Cochrane handbook for systematic reviews of interventions version 6.3*. Cochrane, 2022, https://training.cochrane.org/handbook/current/chapter-10 (accessed 14 August 2022).
32. Viechtbauer W. Conducting meta-analyses in *R* with the metaforpackage. *J Stat Softw* 2010; 36: 1–48.
33. Wachter R, Gröschel K, Gelbrich G, et al. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AF(RANDOMISED)): an open-label randomised controlled trial. *Lancet Neurol* 2017; 16: 282–290.
34. Svendsen JH, Diederichsen SZ, Højberg S, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP study): a randomised controlled trial. *Lancet* 2021; 398: 1507–1516.
35. Buck BH, Hill MD, Quinn FR, et al. Effect of implantable vs prolonged external electrocardiographic monitoring on atrial fibrillation detection in patients with ischemic stroke: the PER DIEM randomized clinical trial. *JAMA* 2021; 325: 2160–2168.
36. Gladstone DJ, Wachter R, Schmalstieg-Bahr K, et al. Screening for atrial fibrillation in the older population: a randomized clinical trial. *JAMA Cardiol* 2021; 6: 558–567.
37. Bernstein RA, Kamel H, Granger CB, et al. Effect of long-term continuous cardiac monitoring vs usual care on detection of atrial fibrillation in patients with stroke attributed to large- or small-vessel disease: the STROKE-AF randomized clinical trial. *JAMA* 2021; 325: 2169–2177.
38. Wachter R, Weber-Krüger M, Hamann GF, et al. Long-term follow-up of enhanced Holter-electrocardiography monitoring in acute ischemic stroke. *J Stroke* 2022; 24: 98–107.
39. Haeusler KG, Kirchhof P, Kunze C, et al. Systematic monitoring for detection of atrial fibrillation in patients with acute ischaemic stroke (MonDAFIS): a randomised, open-label, multicentre study. *Lancet Neurol* 2021; 20: 426–436.
40. McIntyre WF, Diederichsen SZ, Freedman B, et al. Screening for atrial fibrillation to prevent stroke: a meta-analysis. *Eur Heart J* 2022; 2: oeac044.
41. Rubiera M, Aires A, Antonenko K, et al. European Stroke Organisation (ESO) guideline on screening for subclinical atrial fibrillation after stroke or transient ischaemic attack of undetermined origin. *Eur Stroke J* 2022; 7: VI.
42. Demeestere J, Fieuws S, Lansberg MG, et al. Detection of atrial fibrillation among patients with stroke due to large or small vessel disease: a meta-analysis. *J Am Heart Assoc* 2016; 5: e004151.
43. Katz JM, Eng MS, Carrazco C, et al. Occult paroxysmal atrial fibrillation in non-cryptogenic ischemic stroke. *J Neurol* 2018; 265: 2237–2242.
44. Schweizer J, Arnold M, König IR, et al. Measurement of midregional Pro-Atrial natriuretic peptide to discover atrial fibrillation in patients with ischemic stroke. *J Am Coll Cardiol* 2022; 79: 1369–1381.
45. Wasser K, Weber-Krüger M, Gröschel S, et al. Brain natriuretic peptide and discovery of atrial fibrillation after stroke: a subanalysis of the Find-AF(RANDOMISED) Trial. *Stroke* 2020; 51: 395–401.

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