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Association between implantable loop recorder use and secondary stroke prevention: a meta-analysis

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ABSTRACT

Objective To conduct a meta-analysis of randomised controlled trials (RCTs) to evaluate the impact of ILR use on occurrence of recurrent stroke.

Methods PubMed, EMBASE, CENTRAL and ClinicalTrials.gov were searched from 1966 to November 2021 to identify RCTs comparing ILR versus non-ILR in patients with ischaemic stroke. Relative risk (RR) with 95% CI was used as a measure of the effect of ILR versus non-ILR on recurrent stroke, recurrent ischaemic stroke, AF detection and oral anticoagulant (OAC) initiation. A fixed-effect estimate based on the Mantel-Haenszel method was computed.

Results We identified three RCTs with 1233 patients with ischaemic stroke. Among three included RCTs, 54 recurrent stroke events were reported in two RCTs and 84 recurrent ischaemic stroke events were reported in three RCTs. Pooled results showed that patients who received ILR versus no ILR was not associated with a significantly reduced risk of recurrent stroke (5.6% vs 8.0%; RR 0.70; 95% CI 0.42 to 1.19) or recurrent ischaemic stroke (5.7% vs 7.9%; RR 0.72; 95% CI 0.48 to 1.10). Compared to non-ILR patients, ILR patients had higher rates of AF detection (12.9% vs 2.4%; RR 5.31; 95% CI, 3.10 to 9.11) and OAC initiation (15.2% vs 5.5%; RR 2.77; 95% CI 1.90 to 4.03).

Conclusions Patients assigned to ILR vs non-ILR did not have a significantly reduced risk of recurrent stroke or recurrent ischaemic stroke despite higher rates of AF detection and OAC initiation. Sufficiently powered RCTs of ILR to assess the risk of recurrent stroke are warranted.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Implantable loop recorders (ILR) was superior to conventional follow-up for detecting atrial fibrillation after ischaemic stroke.

WHAT THIS STUDY ADDS

⇒ Evidence from randomised trials suggests that patients assigned to ILR compared with non-ILR did not have a significantly reduced risk of recurrent stroke or recurrent ischaemic stroke despite higher rates of atrial fibrillation detection and oral anticoagulants initiation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ ILR could not be universally recommended as a standard strategy for patients with ischaemic stroke to prevent recurrent stroke. Sufficiently powered randomised controlled trials of ILR to assess the risk of recurrent stroke and cost-effectiveness of such a strategy are warranted.

INTRODUCTION

Clinically diagnosed AF after a stroke or a transient ischaemic attack is associated with significantly increased risk of recurrent ischaemic stroke.[1] As oral anticoagulant (OAC) therapies are superior to antiplatelet therapies in preventing recurrent stroke in patients with ischaemic stroke and AF,[2] and two completed large randomised controlled trials of embolic stroke with undetermined source (ESUS) suggest that empiric anticoagulation following ESUS is not proven to be a good strategy,[1 3 4] the need to perform additional cardiac monitoring for AF including subclinical AF may help guide the choice of optimal antithrombotic therapy.

A prior randomised controlled trial suggested implantable loop recorders (ILR) was superior to conventional follow-up for detecting AF after cryptogenic stroke, but the trial was not powered to detect differences in recurrent stroke.[5] Since use of an ILR is relatively expensive and invasive, it is crucial to confirm that such a strategy is beneficial for secondary stroke prevention before it can be universally applied to patients with ischaemic stroke. Encouragingly, several relevant randomised controlled trials on this topic have been published recently.[6 7]

The objective of this study was to conduct a systematic review and meta-analysis of published randomised controlled trials to properly clarify whether a strategy of patients receiving ILR, compared with a strategy of patients not receiving ILR, was associated with a reduced risk of recurrent stroke in patients with ischaemic stroke.

METHODS

This meta-analysis was executed following the instructions of the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement.[8] This study was a meta-analysis of randomised controlled trials and did not need institutional review board or ethics committee approval. The protocol was registered with PROSPERO (CRD42021281152).

Patient and public involvement

This study was a meta-analysis of publisehd randomised controlled trials and therefore patients and public were not involved.

Data sources and searches

We searched PubMed (1966 to 20 November 2021), EMBASE (1966 to 20 November 2021), the Cochrane Central Register of Controlled Trials (CENTRAL) and the clinical trial registry maintained at ClinicalTrials.gov, using the keywords as: 'cardiac monitoring' or 'cardiac rhythm monitoring' or 'implantable loop recorder' or 'insertable cardiac monitor' or 'ICM' or 'ILR' or 'prolonged monitoring' and 'stroke' or 'transient ischemic attack' or 'embolic stroke of undetermined source' or 'cerebral ischemia' or 'cryptogenic stroke' and 'atrial fibrillation' or 'atrial flutter'. We restricted our search to human and trials and there was no language restriction. We reviewed the Introduction and Discussion parts of retrieved trials, related review articles, and relevant meta-analysis to identify additional trials.

Study selection

Criteria for trial inclusion were as below: (1) the study design was a randomised controlled trial, (2) patients had a history of ischaemic stroke, (3) patients assigned to the active group received an ILR versus patients assigned to the control group did not receive an ILR, (4) recurrent stroke or recurrent ischaemic stroke was reported as an end point, and (5) number of patients and the number with recurrent stroke or recurrent ischaemic stroke were reported separately in each group. We excluded studies if (1) patients with documented AF before randomisation, (2) patients assigned to the active group did not receive ILR or (3) haemorrhagic stroke could not be completely excluded as an index stroke.

Data abstraction

We extracted data about baseline characteristics, which included: age, sex, methods of ILR and control groups, duration of cardiac monitoring and follow-up, and patient number in each group. Data on primary and secondary outcomes from each trial were also extracted, which included the number with recurrent stroke, recurrent ischaemic stroke, newly detected AF, OAC initiation, all-cause mortality, haemorrhagic stroke, and transient ischaemic attack in both the ILR and non-ILR arms. One investigator (W-YH) abstracted the data, and another investigator (ML) reviewed the abstracted data. Any discrepant judgments were resolved by joint discussion.

Quality assessment

The risk of bias in each trial, which included sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, was evaluated by using the Cochrane risk of bias tool.[9]

Statistical analysis

Data were analysed based on the intention-to-treat principle. The coprimary end points were recurrent stroke and recurrent ischaemic stroke. The secondary end points were newly detected AF, OAC initiation, all-cause mortality, haemorrhagic stroke, and transient ischaemic attack. Relative risk (RR) with 95% CI was used as a measure of ILR versus non-ILR on risk of primary and secondary end points. We assessed heterogeneity by p value of χ^2 statistics and I^2, which describes heterogeneity between studies. We regarded an I^2 statistic <40% as low, 40%–74% as modest, and >74% as considerable heterogeneity.[10] The fixed-effects model based on Mantel-Haenszel method was used to calculate the pooled estimate when two or more trials provided sufficient data for a given outcome if there was low heterogeneity between studies. Two-sided $p<0.05$ was considered statistically significant in all analyses. Publication bias was assessed by funnel plots when there were at least 10 studies were included in the meta-analysis.[9] All statistical analyses for this meta-analysis were conducted with the Cochrane Collaboration's Review Manager Software Package (RevMan 5.4).

RESULTS

We identified seven full articles for detailed assessment, of which one was excluded since it was not a randomised controlled trial,[11] 2 were excluded because patients assigned to the active group did not receive ILR,[12 13] and 1 was excluded because haemorrhagic stroke could not be completely excluded as an index stroke.[14] Our final analysis included three randomised trials comparing ILR and non-ILR with 1233 individuals (figure 1).[5–7] The characteristics of these three trials are shown in table 1. Among three included randomised controlled trials, 54 recurrent stroke events were reported in two trials and 84 recurrent ischaemic stroke events were reported in three trials. The device used in the ILR group of the three trials was Medtronic Reveal LINQ insertable cardiac rhythm monitoring system.[5–7] Index stroke was cryptogenic ischaemic stroke in one trial,[5] all ischaemic subtypes eligible in one trial,[6] and stroke attributed to large- or small-vessel disease in one trial.[7] Patients assigned to the non-ILR group received follow-up visits scheduled at 1, 6 and 12 months and unscheduled visits in the event of symptom occurrence in one trial,[5] usual care specific to each participating site in one trial,[7] and received conventional external loop recorder monitoring for 30 days in one trial.[6] Among patients with AF in the ILR group,

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┌─────────────────────────────────────┐
│ Title and abstracts review, n=898    │
│ (Pubmed, n= 398; EMBASE, n=364;      │
│ CENTRAL, n=66; Clinicaltrials.gov,   │
│ n=70)                                 │
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              │        ┌──────────────────────────────────────┐
              │───────▶│ 891  were excluded because articles  │
              │        │      were review, duplication, no    │
              ▼        │      ischemic stroke or transient     │
┌─────────────────────────────────┐   │      ischemic attack population      │
│ 7 articles retrieved for         │   └──────────────────────────────────────┘
│ detailed assessment              │
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              │───────▶│ 4 were excluded due  to              │
              │        │   1  not randomized controlled trial │
              ▼        │   2  intervention arm is not ILR     │
┌─────────────────────────────────┐   │   1  hemorrhagic stroke could not be │
│ 3 trials included in the         │   │      excluded as an index stroke     │
│ meta-analysis                    │   └──────────────────────────────────────┘
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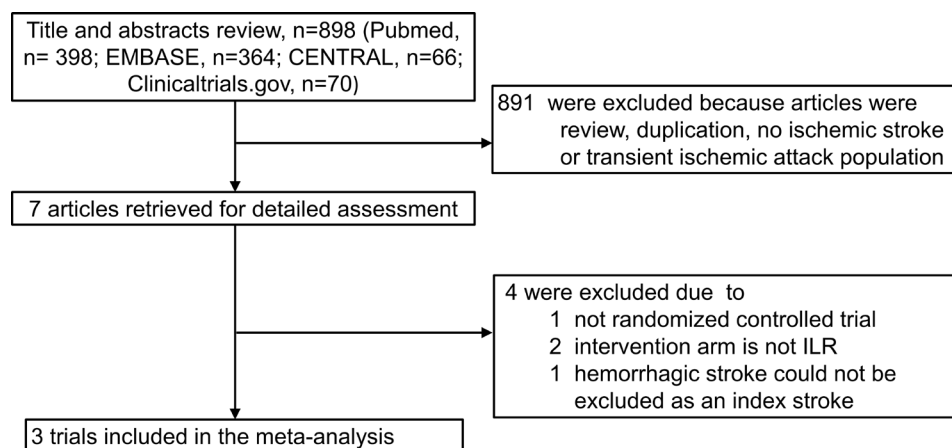
Figure 1 Flow of study selection. ILR, implantable loop recorder.

the median duration for the longest single episode of AF detected was 1.5 hours in one trial[7] and 11.2 hours in another trial.[5] The time from index stroke to enrollment were ≤10 days,[7] ≤3 months,[5] and ≤6 months,[6] respectively. The duration of ILR use was 12 months in the included trials.[5–7] Among patients with AF in the ILR group, the median duration for the longest single episode of AF detected was 1.5 (IQR 0.2–8.8) hours in one trial[7] and 11.2 (IQR 0.7–19.6) hours in another trial.[5] The Cochrane risk of bias assessment for the included trials is summarised in online supplemental figure 1. The performance bias of the all three trials was considered as high because of the non-blinding of these trials.

Recurrent stroke and recurrent ischaemic stroke

Recurrent stroke was reported in two trials and there was low heterogeneity among these trials ($I^2=0\%$). Pooled results with the fixed-effects model showed that patients assigned to the ILR group compared with the non-ILR group were not associated with a significantly decreased risk of recurrent stroke (5.6% vs 8.0%; RR 0.70, 95% CI 0.42 to 1.19, p=0.19) (figure 2A).[6 7]
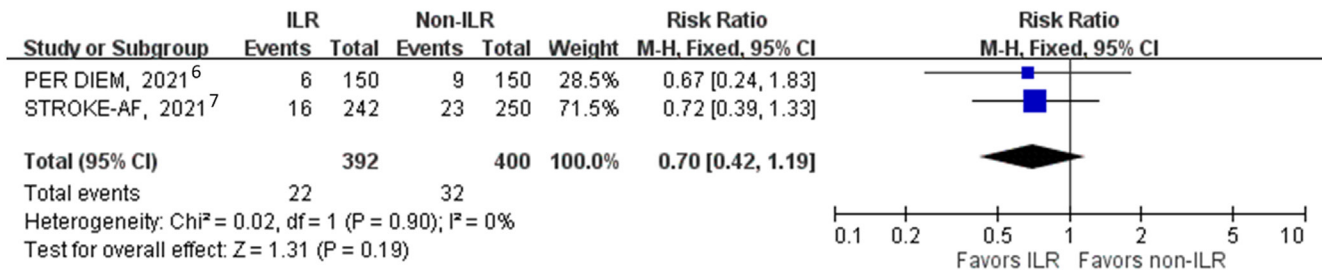
Recurrent ischaemic stroke was reported in all three included trials and there was low heterogeneity among these trials ($I^2=0\%$). Pooled results with the fixed-effects model showed that patients assigned to the ILR group compared with the non-ILR group were not associated

Table 1 Characteristics of included studies

Trial name, published year	CRYSTAL AF, 2014[5]	PRE DIEM, 2021[6]	STROKE-AF, 2021[7]
Population characteristics	Patients aged 40 years of age or older with cryptogenic stroke or TIA	Patients aged 18 years or older with an arterial ischaemic stroke	Patients aged ≥60 years or aged 50 to 59 years with a stroke risk factor and stroke attributed to large- or small-vessel disease
Time from index stroke to enrollment	≤90 days	≤6 months	≤10 days
Sample size (women, %)	441 (37)	300 (40)	492 (38)
Mena age, years	62	64	67
CHA_2DS_2-VAS_c score, median (IQR)	NA ($CHADS_2$ score median: 3)	4 (3–5)	5 (4–6)
% of 24 hours Holter prior to enrolment	71	79	NA
Duration of ILR	12 months	12 months	12 months
Duration needed for qualified new-detected AF	AF ≥2 min	AF ≥2 min	AF ≥2 min
Median (IQR) duration for the longest single episode of AF in the ILR, hours	11.2 (0.7–19.6)	NA	1.5 (0.2–8.8)
Cardiac rhythm monitoring method in the control group	Follow-up visits scheduled at 1, 6 and 12 months and unscheduled visits in the event of symptom occurrence	Conventional external loop recorder monitoring for 30 days	Usual care specific to each participating site.

AF, atrial fibrillation; CRYSTAL AF, the Cryptogenic Stroke and Underlying AF; ILR, implantable loop recorder; NA, not available; OAC, oral anticoagulant; PRE DIEM, the Post-Embolic Rhythm Detection with Implantable versus External Monitoring; STROKE-AF, the Stroke of Known Cause and Underlying Atrial Fibrillation; TIA, transient ischaemic attack.

A

B

Figure 2 Risk ratio with 95% CI of (A) recurrent stroke and (B) recurrent ischaemic stroke in ILR versus non-ILR in patients with ischaemic stroke. M-H, Mantel-Haenszel methods; ILR, implantable loop recorder.

with a significantly decreased risk of recurrent ischaemic stroke (5.7% vs 7.9%; RR 0.72, 95% CI 0.48 to 1.10, p=0.13)[5–7] (figure 2B).

Pooled results with random-effects model obtained similar results.

Newly detected AF and initiation of OACs
Newly detected AF was reported in all three included trials and there was low heterogeneity among these trials (I^2=0%). Pooled results showed that patients assigned to the ILR group compared with the non-ILR group were associated with an increased rate for AF detection (12.9% vs 2.4%; RR 5.31, 95% CI 3.10 to 9.11, p<0.00001)[5–7] (figure 3A).

Initiation of OACs was reported in all three included trials and there was low heterogeneity among these trials (I^2=0%). Pooled results showed that patients assigned to the ILR group compared with the non-ILR group were associated with a significantly increased rate of OAC initiation (15.2% vs 5.5%; RR 2.77, 95% CI 1.90 to 4.03, p<0.00001)[5–7] (figure 3B).

All-cause mortality, haemorrhagic stroke and transient ischaemic attack
All-cause mortality was reported in all three included trials and there was low heterogeneity among these trials (I^2=0%). Pooled results showed that all-cause mortality was not significantly different between active and control groups (1.8% vs 2.7%; RR 0.66, 95% CI 0.31 to 1.40, p=0.28)[5–7] (online supplemental figure 2).

Haemorrhagic stroke was reported in two trials and there was low heterogeneity among these trials (I^2=0%). Pooled results from two trials showed that the risk of haemorrhagic stroke was not different between active and control groups (0.5% vs 0.5%; RR 1.02, 95% CI 0.14 to 7.18, p=0.99)[6 7] (I^2=0%) (online supplemental figure 3).

Transient ischaemic attack was reported in two trials and there was low heterogeneity among these trials (I^2=0%). Pooled results from two trials showed that the risk of transient ischaemic attack was not significantly different between active and control groups (2.6% vs 0.8%; RR 3.37, 95% CI 0.94 to 12.13; p=0.06)[6 7] (online supplemental figure 4).

Effects of adopting ILR versus non-ILR on primary and secondary outcomes among patients with ischaemic stroke are presented in the table 2.

Publication bias
Since only three trials were included in the current meta-analysis, publication bias was not assessed by the funnel plots.

DISCUSSION
In this meta-analysis, comprising three randomised controlled trials that enrolled 1233 patients with ischaemic stroke, we found that patients assigned to ILR compared with non-ILR did not have a significantly reduced risk of recurrent stroke or recurrent ischaemic stroke, although
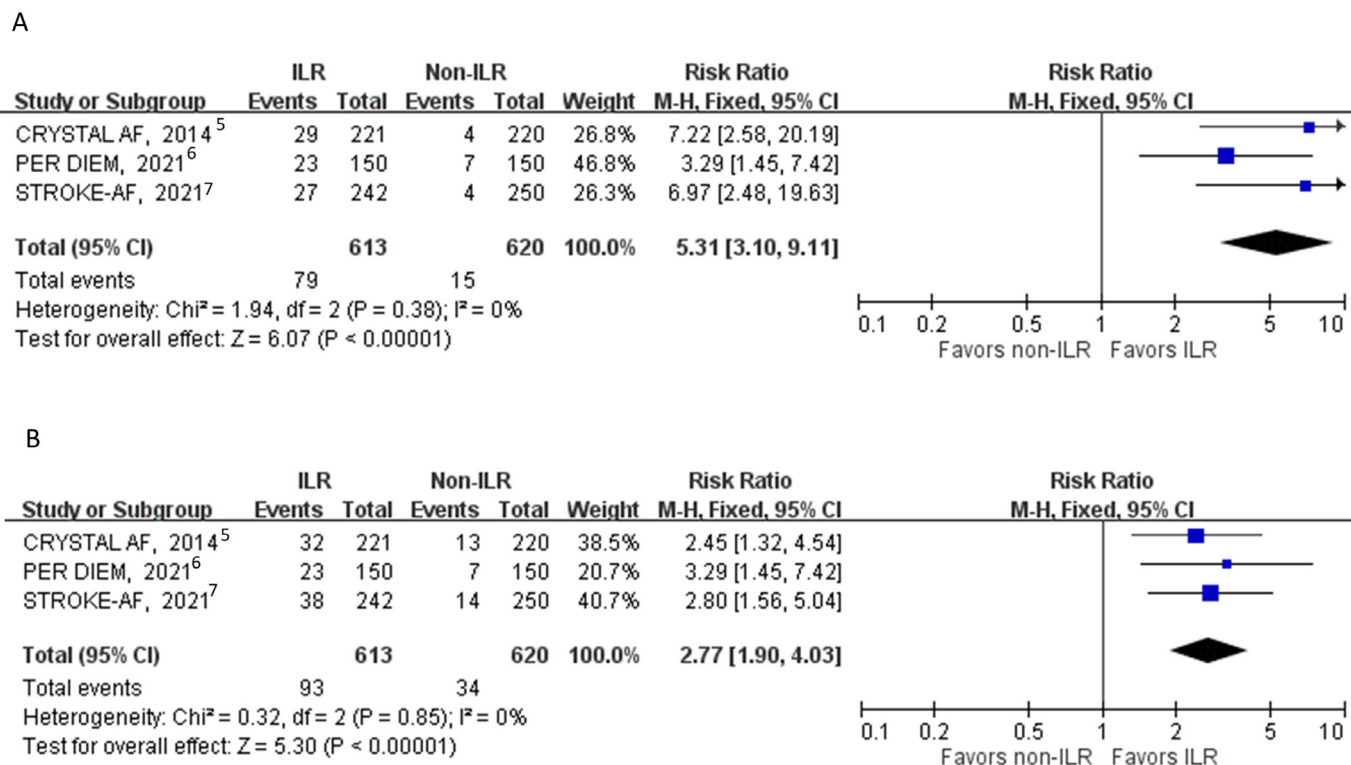
A

B

Figure 3 Risk ratio with 95% CI of (A) newly-detected AF and (B) OAc initiation in ILR vs non-ILR in patients with ischaemic stroke. AF: atrial fibrillation M-H, Mantel-Haenszel methods; ILR, implantable loop recorder; OAC: oral anticoagulants.

higher rates of newly detected AF and initiation of OACs were found in the ILR group. Based on the evidence currently available, ILR could not be universally recommended as a standard strategy for patients with ischaemic stroke to prevent recurrent stroke.

There might be several possible explanations for why use of ILR did not translate to significant reduction of recurrent stroke in patients with ischaemic stroke despite higher rates of newly detected AF and higher OAC initiation in the ILR arms of the trials. First, since recurrent stroke was not the primary outcome of original trials, it is conceivable that individual trials did not have adequate statistical power to show the reduction of recurrent stroke and even with meta-analytic pooling of the trials, there was a statistical power problem in this meta-analysis. In the current meta-analysis, only 54 events of recurrent stroke were identified and it was therefore less likely to obtain statistically significant results. Still, we found the point estimate of the recurrent stroke was 0.70 with the upper bound of the CI of the risk ratio being 19% larger than 1.0, implying that the ILR strategy might be associated with a trend of reduced recurrent stroke. Second, there was a poor temporal correlation between AF and recurrent stroke as one included trial showed that among 16 recurrent strokes in the ILR group, only one occurred in a patient who had AF detected prior to the recurrent stroke.[7] Third, device-detected AF burden is associated with an increased risk of ischaemic stroke in patients with cardiac implanted electronic devices.[15] A recent study suggested that excess stroke risk above baseline was highest within 5 days of an episode of AF of 5.5 hours or more in duration and diminished rapidly thereafter.[16] It

Table 2 Effects of adopting ILR versus non-ILR on primary and secondary outcomes in patients with ischaemic stroke

Outcomes	ILR, n/N (%)	Non-ILR, n/N (%)	Relative risk (95% CI)	Risk difference (95% CI)
Recurrent stroke[6][7]	22/392 (5.6)	32/400 (8.0)	0.70 (0.42 to 1.19)	−2% (−6% to 1%)
Recurrent ischaemic stroke[5–7]	35/613 (5.7)	49/620 (7.9)	0.72 (0.48 to 1.10)	−2% (−5% to 1%)
Newly detected AF[5–7]	79/613 (12.9)	15/620 (2.4)	5.31 (3.10 to 9.11)	10% (8% to 13%)
Initiation of OACs[5–7]	93/613 (15.2)	34/620 (5.5)	2.77 (1.90 to 4.03)	10% (6% to 13%)
All-cause mortality[5–7]	11/613 (1.8)	17/620 (2.7)	0.66 (0.31 to 1.40)	−1% (−3% to 1%)
Haemorrhagic stroke[6][7]	2/392 (0.5)	2/400 (0.5)	1.02 (0.14 to 7.18)	0% (−1% to 1%)
Transient ischaemic attack[6][7]	10/392 (2.6)	3/400 (0.8)	3.37 (0.94 to 12.13)	2% (0% to 4%)

AF, atrial fibrillation; ILR, implantable loop recorder; OAC, oral anticoagulant.

is possible that a substantial portion of ILR-detected AF may be a lower burden, shorter duration and carrying a relatively lower risk of stroke.[14]

Structural or functional abnormalities of the heart, readily evaluated by non-invasive transthoracic echocardiogram, were not incorporated into the OAC decision making in these included trials. Subgroup analyses of a ESUS trial suggested that rivaroxaban compared with aspirin may be associated with a reduced risk of recurrent ischaemic stroke among ESUS patients with moderate or severe left atrial enlargement or with left ventricular dysfunction.[17 18] For patients with ischaemic stroke having extremely low burden of AF, initiation of OACs could be reserved for patients having such structural or functional abnormalities of the heart to achieve maximal benefits for secondary stroke prevention.[19 20]

In addition to expensive cost, another concern is that ILR is an invasive procedure and patients may be worried about if there are some complications related to the procedure. The procedure-related adverse effects reported in the trials include infection at the insertion site (0.5%–2.4%),[5 7] skin erosion overlying the device (0.7%),[6] incision site haemorrhage (0.9%),[7] and implant site pain (0.5%),[7] which were generally regarded as minor side effects. Such potential adverse effects might be considered as negligible if future evidence could suggest that adopting ILR is a useful strategy for secondary stroke prevention.

Recently, Ko *et al* published a meta-analysis of randomised controlled trials and suggested that stroke or transient ischaemic attack were not different between ILR and usual care (OR 0.8, 95% CI 0.5 to 1.2).[21] Our meta-analysis was distinct from their meta-analysis[21] in several aspects. First, we used recurrent stroke and recurrent ischaemic stroke as the coprimary endpoints whereas recurrent stroke or transient ischaemic attack was used as the main endpoint in a recent paper.[21] Recurrent stroke or recurrent ischaemic stroke is regarded as a 'hard endpoint' and has been used in two included trials[6 7] and therefore might be a more appropriate endpoint for the main analysis. Second, we conducted analyses based on risk ratio, not OR, because risk ratios are more directly clinically meaningful than ORs in randomised controlled trials and cohort studies.[22] Third, we found pooled risk ratio of the recurrent stroke was 0.70 in ILR versus control, implying that the ILR strategy might be associated with a trend of reduced recurrent stroke and therefore sufficiently powered randomised controlled trials of ILR among patients with ischaemic stroke might be warranted.

Limitations

There are several limitations in this meta-analysis. First, there were some variations in the characteristics and designs of the included randomised controlled trials. Although the populations of the included trials were patients with ischaemic stroke, the characteristics of the ischaemic stroke and the monitoring methods of control arm varied among included trials. The non-ILR group in the Post-Embolic Rhythm Detection with Implantable vs External Monitoring (PRE DIEM) trial used external loop recorder monitoring for 30 days,[6] whereas other trials used usual care for cardiac monitoring, which was much shorter than PRE DIEM trial. Second, we excluded Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals (LOOP) trial because we did not know whether subgroup of history of stroke were restricted to history of ischaemic stroke and only combined end point of stroke or systemic arterial embolism was reported.[14] Third, not all patients had 24-hour Holter monitoring before they were enrolled in the included trials. Patients without 24-hour Holter monitoring may have had AF that would have been detected if such monitoring had been completed before study enrollment. Fourth, the lack of respective information of the quality and persistence of OAC among included trials may affect the outcome of recurrent stroke. Since this is a meta-analysis of published trials, rather than a pooled analysis of individual patient data, further analysis could not be conducted. Fifth, the role of remote home monitoring in the early diagnosis of AF is not considered in all studies. Since an early diagnosis[16] of prolonged AF (greater than 5.5 hours) can have a decisive impact on the outcome, home monitoring could be a strong means to immediately diagnose AF episodes.

CONCLUSIONS

In conclusion, despite higher rates of newly detected AF and subsequent OAC initiation, patients with ischaemic stroke who were randomly assigned to an ILR follow-up strategy, was not associated with a significantly reduced risk of recurrent stroke or recurrent ischaemic stroke, when compared with patients who did not receive an ILR follow-up strategy. Larger and sufficiently powered RCTs of ILR among patients with ischaemic stroke to assess the risk of recurrent stroke and cost-effectiveness of such a strategy are warranted.

reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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