Question 7 evidence tables

Question 7: What is the role of prolonged cardiac monitoring in the detection of AF in ischaemic stroke of otherwise undetermined aetiology?

NB Any discrepancies between reviewers in evidence quality and comment were discussed at the corresponding evidence review meeting

AF = atrial fibrillation, ECG = echocadiogram, ILR = implantable loop recorder, ICM = implantable cardiac monitoring, ELR = external loop recorder, MCOT = mobile cardiac outpatient telemetry, NOAC = New/Novel Oral Anticoagulation, SR = systematic review, MA = meta-analysis, RCT = randomised controlled trial, IPDMA = individual patient data meta-analysis, MDT = multidisciplinary team, PICO = patient/population, intervention, comparison and outcomes, OR = odds ratio, CI = confidence interval, QoL = quality of life, ADL = activities of daily living, OR = odds ratio, RR = relative risk, aOR = adjusted odds ratio, cOR = crude odds ratio, CI = confidence interval, RoB = risk of bias, I2 = heterogeneity statistic.

REF ID	Source	Setting, design & subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
902	K. T. Koh et al (2021). Smartphone electrocardiogram for detecting atrial fibrillation after a cerebral ischaemic event: A multicentre randomized controlled trial. Europace. 23: 1016-1023	Multicentre RCT. 203 patients included; randomly assigned to undergo one 24h Holter monitor (control group, n=98) vs. 30 day smartphone ECG monitoring (intervention group, n=105).	30 seconds TDS smartphone ECG using KardiaMobile	Primary: detection of A Fib > 30 seconds at 90 days Secondary: use of oral anticoagulation at 90 days	A Fib lasting >_30 s was detected in 10 of 105 patients in the intervention group and 2 of 98 patients in the control group (9.5% vs. 2.0%; P = 0.024).	++ Prolonged cardiac monitoring improves pick up of A Fib. Smartphone apps are increasingly accessible and minimises the requirement for multiple return hospital appointments.
902	K. T. Koh et al (2021). Smartphone electrocardiogram for detecting atrial fibrillation after a cerebral ischaemic event: A multicentre randomized controlled trial. Europace.	Open Label multicentre RCT, 203 participants to undergo Holter monitoring (control group, n = 98) vs. 30-day smartphone ECG monitoring TDS (intervention group, n = 105)	Patients record ECGs on smartphone KArdia App 3 times a day for 30 days	Atrial Fibrillation > 30 seconds. Initiation of OAC	AF lasting >_30 s was detected in 10 of 105 patients in the intervention group and 2 of 98 patients in the control group (9.5% vs. 2.0 P = 0.024)	++ Greater than 24-hour monitoring improves diagnosis of underlying AF. Though use of smartphone apps may not be practical in all patients following stroke

REF ID	Source	Setting, design & subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	23: 1016-1023					
903	D. Ko et al (2022). Meta-Analysis of Randomized Clinical Trials Comparing the Impact of Implantable Loop Recorder Versus Usual Care After Ischemic Stroke for Detection of Atrial Fibrillation and Stroke Risk. American Journal of Cardiology. 162: 100-104.	MA of 3 trials: CRYSTAL-AF 2014, STROKE-AF 2021, PER DIEM 2021. 1233 participants.	Implantable loop recorded insertion versus usual care.	Primary: Atrial Fibrillation detection and recurrent stroke or TIA Secondary: oral anticoagulation commencement	The 12-month AF occurrence was 13% in ILR groups and 2.4% in control groups. The 12-month incidence of stroke or TIA was 7.8% in the ILR group versus 8.9% in controls. After AF detection with either ILR or usual care, OAC was started in 97% of cryptogenic stroke in CRYSTAL AF, 68% small or large artery strokes in STROKE-AF, and 100% of all ischemic strokes in PER DIEM	++ MA of three trials.
903	D. Ko et al (2022). Meta-Analysis of Randomized Clinical Trials Comparing the Impact of Implantable Loop Recorder Versus Usual Care After Ischemic Stroke for Detection of Atrial Fibrillation and Stroke Risk. American Journal of Cardiology. 162: 100-104.	MA of 3 Trials; Crystal AF, Stroke AF and Per Diem; (1,233 participants)	ILR implant versus usual care 2 trials (crystal and Stroke AF) did not define usual care. In Per Diem it was a 30 day monitor	AF Detection Stroke	The 12-month AF detection was 13% in the ILR group and 2.4% in controls. ILR was more likely to detect AF compared with usual care (OR 5.8, 95% confidence interval 3.2 to 10.2). Stroke or transient ischemic attack occurred in 7% with ILR and 9% with usual care (OR 0.8, 95% confidence interval 0.5 to 1.2).	++ Meta-analysis of 3 RCTs
904	A. Ungar et al (2021).	Prospective study 20 Italian centres	Implantable cardiac monitor	Atrial fibrillation detection	A fib diagnosed in 92 (27.5%) of patients.	- No control groups

REF ID	Source	Setting, design & subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Detection of subclinical atrial fibrillation after cryptogenic stroke using implantable cardiac monitors. European Journal of Internal Medicine. 92: 86-93.	334 patients Follow up 23.6 months (IQR 14.6-31.5 months)			These patients were older with higher CHADS2VASC scores (than those without). First episode was asymptomatic in 81 (88.1%). SCAF daily burden ≥5 minutes was 22.0%, 24.1% and 31.5% at 6, 12, and 24 months post ICM implantation. Median time to first day with AF was 60 (IQR 18-140) days	No uniform protocol ie cryptogenic stroke as defined by each of the 20 centres Device used unable to detect AF shorter than two minutes
904	A. Ungar et al (2021). Detection of subclinical atrial fibrillation after cryptogenic stroke using implantable cardiac monitors. European Journal of Internal Medicine. 92: 86-93.	Prospective study of ICM patients in 20 Italian centres. 336 patients following for 23.6 months (IQR 14.6-31.5)	ICM implant	Atrial fibrillation	Subclinical AF was diagnosed in 92 (27.5%) patients. Subclinical AF daily burden ≥5 minutes was 22.0%, 24.1% and 31.5% at 6, 12, and 24 months after ICM implantation	- Non-randomised data, No comparison arm
905	B. H. Buck et al (2021). Effect of implantable vs prolonged external electrocardiographic monitoring on atrial fibrillation detection in patients with ischemic stroke: The per diem randomized clinical trial. JAMA - Journal of the American Medical Association. 325:	Open label randomised clinical trial at three hospitals. 300 patients enrolled. Follow up over 12 months	Randomly assigned 1:2 to prolonged ECG monitoring with an implantable loop recorder (n=150) or an external loop recorder (n=150)	Primary: the development of definite AF or highly probable AF (adjudicated new AF lasting 2 minutes within 12 months of randomization). Secondary: time to event analysis of new AF, recurrent ischemic stroke, intracerebral haemorrhage, death, and device-related serious	The primary outcome was observed in 15.3% (23/150) of patients in the implantable loop recorder group and 4.7% (7/150) of patients in the external monitoring	**++** 24/150 discontinued in ILR group, 17 discontinued in ELR group

REF ID	Source	Setting, design & subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	2160-2168			adverse events within 12 months		
905	B. H. Buck et al (2021). Effect of implantable vs prolonged external electrocardiographic monitoring on atrial fibrillation detection in patients with ischemic stroke: The per diem randomized clinical trial. JAMA - Journal of the American Medical Association. 325: 2160-2168	Open label RCT in 3 centres, which enrolled 300 patients over	Participants were randomly assigned 1:1 to prolonged electrocardiographic monitoring with either an implantable loop recorder (n = 150) or an external loop recorder (n = 150) with follow-up visits at 30 days, 6 months, and 12 months	Definite AF or highly probable AF prespecified secondary outcomes including time to event analysis of new AF, recurrent ischemic stroke, intracerebral hemorrhage, death, and device-related serious adverse events within 12 months	The primary outcome was observed in 15.3% (23/150) of patients in the ICM recorder group and 4.7% of control	**++** Randomized data, clear follow-up
906	Y. Lu et al (2021). Insertable cardiac monitors for detection of atrial fibrillation after cryptogenic stroke: a meta-analysis. Neurological Sciences. 42: 4139-4148	Meta analysis of 23 studies mostly from USA (n=5) and Germany (n=7). 3472 patients included in total.	Implantable cardiac monitor	Atrial fibrillation detection	The overall proportion of atrial fibrillation detected by ICM in cryptogenic stroke patients was 25% (95% confidence interval [CI], 22–29%)	+ Meta analysis The biggest study included was a prospective US study that included 1247 patients
906	Y. Lu et al (2021). Insertable cardiac monitors for detection of atrial fibrillation after cryptogenic stroke: a meta-analysis. Neurological Sciences. 42: 4139-4148	MA of 23 studies, 3473 patients, Included RCTs, CC, retrospective or prospective.	ILR implant	New Diagnosis of AF	the proportion of atrial fibrillation detected using ICM was positively correlated with monitoring time. 9.6% AF of < 6 months, up to 36.5% AF is > 36 months	+. Meta-analysis, but many of the studies non randomised and /or retropective
907	Y. Miyazaki et al (2021). Atrial fibrillation after ischemic stroke detected	Multicentre (5 stroke centres), prospective	7 day holter monitoring using a chest strap monitor	Primary: detection of AF	The detection rate of AF using the 7-day Holter	- non randomised

REF ID	Source	Setting, design & subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	by chest strap-style 7-day holter monitoring and the risk predictors: Educateesus. Journal of Atherosclerosis and Thrombosis. 28: 544-554	observational study. 206 patients included.			monitoring was 6.8% (95% CI 4.1%-11.1%).	Small numbers of patients with AF detection
907	Y. Miyazaki et al (2021). Atrial fibrillation after ischemic stroke detected by chest strap-style 7-day holter monitoring and the risk predictors: Educateesus. Journal of Atherosclerosis and Thrombosis. 28: 544-554	Multicentre (5) prospective observational study of 206 patients	7 day Holter monitoring	New Diagnosis of AF	7 day detecton rate on Holter monitor was 6.8%	- Non-randomized,
908	J. J. Noubiap et al (2021). Rhythm monitoring strategies for atrial fibrillation detection in patients with cryptogenic stroke: A systematic review and meta-analysis. IJC Heart and Vasculature. 34: 100780.	SR and MA. 47 articles included with a pooled sample of 8215 participants.	Implantable cardiac monitor	Detection of AF	Rate of AF was 12.2% (95% CI 9.4–15.0) at 3 months, 16.0% (95% CI 13.2–18.8) at 6 months, 18.7% (95% CI 15.7–21.7) at 12 months, 22.8% (95% CI 19.1–26.5) at 24 months, and 28.5% (95% CI 17.6–39.3) at 36 months. Using mobile cardiac outpatient telemetry (MCOT), the pooled rate of AF was 13.7% (95% CI 10.2–17.2) at 1 month.	++ MA
908	J. J. Noubiap et al (2021).	SR and MA of 47 studies with a pooled population of 8215	ILR implant	Af Detection rates	rate of AF was 12.2% (95% CI 9.4–15.0) at 3	++, MA.

REF ID	Source	Setting, design & subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Rhythm monitoring strategies for atrial fibrillation detection in patients with cryptogenic stroke: A systematic review and meta-analysis. IJC Heart and Vasculature. 34: 100780.				months, 16.0% (95% CI 13.2–18.8) at 6 months, 18.7% (95% CI 15.7–21.7) at 12 months, 22.8% (95% CI 19.1–26.5) at 24 months, and 28.5% (95% CI 17.6–39.3) at 36 month	Significant patient number
909	S. J. Edwards et al (2020). Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke: A systematic review and economic evaluation. Health Technology Assessment. 24: v-184.	Systematic review One RCT – Crystal AF (n=441) allocated. 26 observational studies identified (after widening the eligibility criteria).	Implantable cardiac monitor for AF detection.	AF detection	By 36 months, atrial fibrillation was detected in 19% of patients with an implantable cardiac monitor and in 2.3% of patients receiving conventional follow-up	++ All three monitors reviewed had few side effects
909	S. J. Edwards et al (2020). Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke: A systematic review and economic evaluation. Health Technology Assessment. 24: v-184.	Systematic Review. 1 RCT (441 patients) and 26 Observational studies included.	ILR Also sought to compare 3 different manufacturers	Atrial Fibrillation Stroke recurrence	In Crystal AF at 36 months 19% AF detection vs 2.3%. No significant difference in Stroke recurrence	++ Well conducted SR
910	S. Triantafyllou et al (2020). Implantable Cardiac Monitoring in the	Prospective, single centre observational study. Conventional cardiac monitoring – repeated Holter	Conventional cardiac monitoring vs ILR	AF detection	AF detection was higher in the ICM cohort (21.1%) compared to the conventional cardiac	- Non randomised Conventional cardiac monitoring had a median

REF ID	Source	Setting, design & subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Secondary Prevention of Cryptogenic Stroke. Annals of Neurology. 88: 946-955.	monitoring - (n=373) vs ILR (n=123)			monitoring cohort (7.5%) p < 0.001	of one holter repeated post initial holter
910	S. Triantafyllou et al (2020). Implantable Cardiac Monitoring in the Secondary Prevention of Cryptogenic Stroke. Annals of Neurology. 88: 946-955.	Prospective, single centre observational study. 373 patients with cardiac monitoring vs 123 with ILRs	Conventional monitoring vs ILR	Atrial Fibrillation detection Stroke recurrence	Af detection was 21.1% vs 7.5%,in favour of ILR. lower cumulative rate (4.1% vs 11.8%, p = 0.013;) of stroke recurrence in the ICM group	- Non-randomised, but reasonably large number
911	N. S. Milstein et al (2020). Detection of atrial fibrillation using an implantable loop recorder following cryptogenic stroke: implications for post-stroke electrocardiographic monitoring. Journal of Interventional Cardiac. 57: 141-147	Prospective study of two centres 343 patients recruited	ILR insertion	AF detection	One year of ILR follow-up was available in 328 (96%) patients. At least 1 episode of AF was observed in 67 (21%) patients	- Non-randomised study ILR inserted within 3.7 +/- 1.5 days of stroke. During the first 30 days of ILR follow-up, only 18 (5%) patients had an episode of AF.
911	N. S. Milstein et al (2020). Detection of atrial fibrillation using an implantable loop recorder following cryptogenic stroke: implications for post-stroke	Prospective Observational study from 2 US centres. 343 patients	ILR implant in all patients, no comparison arm	Atrial Fibrillation	During 1 year of follow-up, 67 (21%) patients had AF.	- Non-randomised, observational study

REF ID	Source	Setting, design & subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	electrocardiographic monitoring. Journal of Interventional Cardiac. 57: 141-147					
912	E. Cuadrado-Godia et al (2020). Ultra-early continuous cardiac monitoring improves atrial fibrillation detection and prognosis of patients with cryptogenic stroke. European Journal of Neurology. 27: 244-250.	Observational study comparing a historical cohort (n=101) with a prospective cohort (n=90) who received an ICM implant prior to discharge.	Both groups received daily ECGs. The conventional strategy included post discharge: serial ECGs, 24 Holter (+/- further ECGs and 7 day Holter as per clinicians best judgement) vs ultra-early ICM group who received an implant pre discharge.	AF detection OAC initiation Stroke recurrence	During hospital admission, AF episodes (65% paroxysmal) were detected in 24% of both cohorts AF detection was higher in the ICM cohort compared to the conventional cohort (70.0% vs. 37.6%, P < 0.001)	**+** Non randomised study
912	E. Cuadrado-Godia et al (2020). Ultra-early continuous cardiac monitoring improves atrial fibrillation detection and prognosis of patients with cryptogenic stroke. European Journal of Neurology. 27: 244-250.	Observation study comparing a historical cohort with a prospectively followed ILR group. Single centre. 191 patients	historical cohort, (n = 101) with serial electrocardiograms and 24-h Holter monitoring vs an ultra-early ILR implanted before discharge (prospective cohort, n = 90).	AF Detection OAC use Stroke detection	At 30 +/- 10 months AF detection was significantly higher in ILR group 70.0% vs. 37.6%, Significantly greater OAC use and lower rate of stroke in ILR arm 3.3% vs 10.9%	**+** Non-randomised, observational study
913	G. Tsivgoulis et al (2019). Duration of implantable cardiac monitoring and detection of atrial fibrillation in ischemic stroke patients: A systematic review and meta-analysis. Journal of Stroke.	SR and MA 28 studies included 4531 patients	ILR implantation	Time to AF detection	Cumulative AF detection rate in patients with ICM was 26% (95% CI) The proportion of AF detection by ICM was positively associated with the duration of	**++** MA with larger patient numbers than previous MAs

REF ID	Source	Setting, design & subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	21: 302-311.				monitoring (<6 months: 5% [95% CI] ≥6 months: 21% [95% CI], >12 months: 26% [95% CI] and >24 months: 34% [95% CI]).	
913	G. Tsivgoulis et al (2019). Duration of implantable cardiac monitoring and detection of atrial fibrillation in ischemic stroke patients: A systematic review and meta-analysis. Journal of Stroke. 21: 302-311.	MA including 28 studies (RCTs, CC studies and cohort studies) 4,531 patients	ILR. No comparator arm	Time to Atrial Fibrillation detection.	Cumulative AF detection rate in patients with ICM was 26% Af detection was 5% < 6months and increase sequentially to 34% at > 24 months	++ MA with large patient numbers
914	G. Tsivgoulis et al (2019). Prolonged Cardiac Rhythm Monitoring and Secondary Stroke Prevention in Patients with Cryptogenic Cerebral Ischemia. Stroke. 50: 2175-2180	MA of four studies (2 RCTs and 2 observational studies). 1102 patients.	Prolonged cardiac rhythm monitoring (3 used ICM and one used non-invasive 10 day ambulatory ECG monitoring) versus short term monitoring	AF detection	Increased incidence of: atrial fibrillation detection (RR 2.46; 95% CI, 1.61–3.76) and anticoagulant initiation (RR 2.07; 95% CI, 1.36–3.17) and decreased risk of: recurrent stroke (RR 0.45; 95% CI, 0.21–0.97) and recurrent stroke/TIA (RR 0.49; 95% CI, 0.30–0.81) for prolonged cardiac monitoring patients	FIND AF uses a shorter prolonged cardiac monitoring method than Brown ESUS AF
914	G. Tsivgoulis et al (2019). Prolonged Cardiac Rhythm Monitoring and Secondary Stroke Prevention in Patients	MA of 4 studies (2 RCTs and2 observational) 1102 patients	ILR versus conventional therapy	Atrial fibrillation detection	incidence of AF detection (RR=2.46; 95% CI, 1.61–3.76), increased incidence of NOAC use (RR=2.07; 95% CI, 1.36–3.17) and decreased risk	++ MA of RCT and large OS Reasonably large number of patients

REF ID	Source	Setting, design & subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	with Cryptogenic Cerebral Ischemia. Stroke. 50: 2175-2180				of both recurrent stroke (RR=0.45; 95% CI, 0.21–0.97) and recurrent stroke/TIA (RR=0.49; 95% CI, 0.30–0.81) for ILR patients	
915	C. Israel et al (2017). Detection of atrial fibrillation in patients with embolic stroke of undetermined source by prolonged monitoring with implantable loop recorders. Thrombosis and Haemostasis. 117: 1962-1969	Prospective single centre study 123 patients	ILR implantation	AF detection	Mean follow-up of 12.7±5.5 months, AF was documented and manually confirmed in 29 of 123 patients (23.6 %).	- Non-randomised
915	C. Israel et al (2017). Detection of atrial fibrillation in patients with embolic stroke of undetermined source by prolonged monitoring with implantable loop recorders. Thrombosis and Haemostasis. 117: 1962-1969	Prospective single centre observational study. 123 patients with ESUS enrolled over 18-month period	ILR	Atrial Fibrillation detection	AF detected in n 29 of 123 patients (23.6 %) at 12.7 +/- 5.5 months	- Non-randomised.
916	G. Tsivgoulis et al (2022). Prolonged Cardiac Monitoring and Stroke Recurrence: A Meta-analysis. Neurology. 98: 1942-e1952.	MA of 8 studies (5 RCT, 3 observational) 2994 patients	Prolonged cardiac monitoring (ILR vs non ILR) compared to reference method (30-day ILR vs ECG monitoring at various intervals versus Holter/telemetry)	Primary: stroke recurrence Secondary: AF detection, anticoagulation use and ICH occurrence post same	PCM was associated with a lower risk of recurrent stroke during follow-up in observational studies (RR 0.29, 95% CI 0.15–0.59), but not in RCTs (RR 0.72, 95% CI 0.49–1.07)	++ MA of RCT and robust observational study data

REF ID	Source	Setting, design & subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					PCM after IS/TIA had a higher rate of AF detection and anticoagulant initiation in RCTs (RR 3.91, 95% CI 2.54–6.03; RR 2.16, 95% CI 1.66–2.80, respectively) and observational studies (RR 2.06, 95% CI 1.57–2.70; RR 2.01, 95% CI 1.43–2.83, respectively	
916	G. Tsivgoulis et al (2022). Prolonged Cardiac Monitoring and Stroke Recurrence: A Meta-analysis. Neurology. 98: 1942-e1952.	MA including 3 RCTs and 5 Oss 2994 patients	ILR versus conventional rhythm monitoring	Primary outcome was rate of stroke. Secondary outcome of AF detection, OAC use, ICH	Reduction in stroke noted in OS not RCT AF &coagulation initiation was higher for ILR compared to nonILR devices (RR 2.78, 95% CI 1.18–6.67; RR 2.00, 95% CI 1.02–4.00;	**++** MA of RCT and robust observational data