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Atrial Fibrillation Detection using Single Lead Portable Electrocardiographic Monitoring: A Systematic Review and Meta-Analysis.

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ABSTRACT

Objectives: Recent advances in technology have allowed for heart rhythm monitoring using portable single-lead electrocardiographic (ECG) monitoring devices, which can be used for early diagnosis of atrial fibrillation (AF). We sought to investigate the AF detection rate using portable ECG devices compared with Holter monitoring.

Setting, participants and outcome measures: We searched the Medline, Embase and Scopus databases (search conducted on 8th May 2017) using search terms related to AF and screening and included studies with adults>18 years using portable ECG devices or Holter monitoring for AF detection. We excluded studies using implantable loop recorders and pacemakers. Using a random-effects model we calculated the overall AF detection rate. Meta-regression analysis was performed to explore potential sources for heterogeneity.

Results: Portable ECG monitoring was used in 18 studies (n=117,436) and Holter monitoring was used in 36 studies (n=8498). The AF detection rate using portable ECG monitoring was 1.7% (95% CI 1.4–2.1), with significant heterogeneity between studies (p<0.001). There was a moderate linear relationship between total monitoring time and AF detection rate (r=0.65, p=0.003), and meta-regression identified total monitoring time (p=0.005) and body mass index (p=0.01) as potential contributors to heterogeneity. The detection rate (4.8%, 95% CI 3.6–6.0%) in 8 studies (n=10,199) which performed multiple ECG recordings was comparable to that with 24 hour Holter (4.6%, 95% CI 3.5–5.7%). Intermittent recordings for 19 minutes total produced similar AF detection to 24 hr. Holter monitoring.

Conclusion: Portable ECG devices may offer an efficient screening option for AF compared to 24 hour Holter monitoring.

Study Registration: Prospero database - April 22nd, 2017(CRD42017061021)

Key words; atrial fibrillation, screening, electrocardiographic monitoring.

Strengths and limitations of this study:

- First systematic review comparing single lead ECG monitoring to 24 hour holter monitoring for AF detection.
- Comprehensive literature search and specific inclusion criteria allowing for large patient numbers.
- Heterogeneity amongst individual studies with regards to patient population, AF definitions and monitoring time.
- Poor reporting of CHA_2DS_2-VASC scores amongst individual studies
- Patient compliance unable to be accounted for in this meta-analysis

Atrial fibrillation (AF) is a leading cause of stroke and heart failure worldwide, is associated with increased all-cause mortality [1 2] as well as substantial financial cost.[3 4] The prevalence of AF increases with age, exceeding more than 15% for those aged 85 and older.[5] The epidemics of obesity, diabetes mellitus and metabolic syndrome have also been associated with the increasing prevalence of AF.[6-8] Up to 20% of patients with stroke have underlying AF, and detection allows the initiation of anticoagulation which is associated with a significant reduction in stroke recurrence.[9]

Early diagnosis of AF may have several benefits, including individualized lifestyle intervention [10] and anticoagulation, and may be associated with a reduction in complications and healthcare costs. The importance of early diagnosis has been recognized in recent guidelines from the European Society of Cardiology (ESC) which recommended opportunistic screening using pulse palpation and 12 lead electrocardiogram (ECG).[11] However, screening for AF is challenging for several reasons; many patients are asymptomatic or may have atypical symptoms. There are a variety of monitoring techniques available, all which vary in diagnostic accuracy and sensitivity, and there is no accepted reference standard. Subclinical AF is associated with an increased risk of stroke, cardiovascular disease and all-cause mortality,[12] although there is controversy surrounding the significance of brief paroxysms of AF and the potential benefit of anticoagulant therapy. Implantable devices are expensive, and not cost effective for mass screening, and the use of external devices for long periods of monitoring require electrodes, which may be poorly tolerated by patients.

Recent advances in technology have allowed for the development of single lead portable electrocardiographic monitoring devices. Multiple devices are available, all using multiple points of finger contact to create a single lead ECG trace. The in-built memory of these devices allows for single or multiple time-point screening. Interpretation from a cardiologist or by automated algorithms has achieved high sensitivity and specificity for AF detection.[13-15] Although they have not been incorporated into the latest AF guidelines, the accuracy, ease of use and potential cost-effectiveness of these devices may lead to them having an important role in AF screening. This paper describes a

systematic review of the published literature to investigate the overall AF detection rate using portable ECG devices compared with traditional Holter monitoring.

Methods.

Search strategy. We conducted our systematic review and meta-analysis using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline (PRISMA).[16] We searched the Medline, Scopus and Embase databases using key terms including "atrial fibrillation/AF and screening/monitoring and electrocardiographic/Holter monitoring" which were mapped to subject headings. We also searched the reference lists to identify other potential articles. The search was limited to adult human subjects >18 years and limited to the English language (Supplementary Table 1). The study was prospectively registered on the Prospero database on April 22nd, 2017(CRD42017061021), and the search was conducted on 8th May 2017.

Study selection. Titles and abstracts of studies identified from the search were reviewed by two independent reviewers (S.R and D.D). Studies which had a primary aim of AF detection in adult participants were included. We included all cohorts including community screening, those with risk factors and recent stroke. The screening methods included portable single lead ECG devices or continuous (Holter) monitoring (up to one week). We included studies which used single lead ECG devices for single episode screening or multiple intermittent screening periods. We included conference abstracts if demographic and outcome data were available. We excluded studies if participants were <18 years or if other forms of monitoring were used (pacemaker, implantable loop recorders, event recorders, monitoring patches and inpatient telemetry). We also excluded studies where AF detection was not the primary aim.

The primary outcome of interest was the detection rate of new AF using either single lead intermittent or continuous monitoring. Our secondary objective was to determine the optimal time of intermittent monitoring which produced equivalent AF detection to continuous monitoring.

Data Collection. Full text manuscripts of studies fitting the inclusion criteria were obtained. Quality of reporting and risk of bias was assessed using the tool developed by Downs and Black.[17] A standardized data-extraction form was used by the reviewers which included information about the

patient demographics, comorbidities, screening strategy, patients with known AF and overall new AF detection rate. Where data were not reported, we attempted to contact the primary authors of the study. Any disagreements between the two reviewers were resolved by consensus or by consulting a third reviewer (TM).

Patient and public involvement. As this is a systematic review, no patient or public involvement was undertaken.

Statistical Analysis. The cumulative AF detection rate for continuous and intermittent monitoring and the 95% confidence interval was calculated using a random effects model. The results were displayed as a forest plot and heterogeneity amongst the studies was assessed using the I^2 statistic. A subgroup analysis was performed by comparing the cumulative detection rate of single lead ECG studies which performed multiple timepoint recordings with 24 hour Holter monitoring studies. Linear regression analysis was used to determine the association between the total monitoring time and AF detection using single lead ECG devices. This formula was used to determine the monitoring time using single lead ECG devices to approximate the overall AF detection rate using 24-hour continuous monitoring. Univariate meta-regression analysis was performed to assess the influence of various clinical and screening factors with AF detection. Publication bias was assessed using a funnel plot and the Egger test. Statistical analysis was performed using Stata v.13 (StataCorp, College Station, TX) with two-tailed p-values <0.05 used to denote statistical significance.

Results

Study Characteristics. The PRISMA flowchart of our included studies is shown in Figure 1. Our initial search strategy identified 5427 studies, with another 26 identified through other sources. After removing duplicate records, 4122 studies were left. After screening those using the inclusion/exclusion criteria, we identified 111 full text studies for detailed review, which excluded 59 studies, leaving 52 full text studies for inclusion in the meta-analysis (see Supplementary table 2 for excluded studies). Of the 52 studies included, 34 used continuous (Holter) monitoring (n=8154),[18-51] 16 (n=117,092) used single lead portable ECG monitoring,[14 15 52-65] and 2 studies (n=344) used both continuous and intermittent single lead monitoring for AF detection in a head to head comparison.[66 67]

The baseline characteristics of the individual studies is presented in Table 1. There was a considerable range in age (54-76 years), and gender (male 29-77%) between studies. As many studies chose healthy volunteers and other studies focused on patients post stroke or those with AF risk factors, there was significant variation in comorbidities such as diabetes, hypertension and obesity. Stroke risk determined by the CHADS or CHA_2DS_2-VASC score was reported in only 14/52 studies (27%). Of the 52 studies, 36 (69%) were conducted in Europe, 8 (15%) were in Asia, 5 (10%) were in North America and 3 (6%) in Australia. Nine studies (17%) were retrospective, the remainder all being prospective cohort or randomized controlled trials.

Of the 18 studies using single lead ECG devices, 10 studies (56%) used a single 10-60 sec recording for AF detection whilst 8 studies (44%) used multiple readings over a 1-52 week period. There were five portable ECG devices used (Table 1). Sixteen studies (89%) used healthy participants with risk factors.[14 15 52-61 63-65 67]. Two studies assessed patients following stroke or transient ischemic attack (TIA).[62 66]

Of the 36 studies using continuous (Holter) monitoring, 27 studies (75%) used 24-hour continuous monitoring,[18-23 25-28 33-36 38 39 41-45 47-50 66 67] 4 studies (11%) used 1 week monitoring,[30-32 51] 2 studies (6%) used 48-hour monitoring,[37 46] 2 studies (6%) used 72-hour monitoring,[24 29] and 1 study (3%) used 96-hour monitoring.[40]

Study	n	Country	Type of patients used	Device Used	Duration of recording (sec)	Frequency of recording /day	Total monitoring (days)	Mean/median age (yrs)	Male (%)	BMI (kg/m2)	HTN (%)	DM (%)	IHD (%)	Previous diagnosis of AF (%)	HF (%)	Previous stroke (%)	Mean/median CHADS2/ CHADS-VASC	Definition of AF	New AF (n)	New AF rate (%)
Bowres et. al. (2014) 52	1000	Australia	Community pharmacy screening	Alive Cor	60	1	0	76	44	NR	62	23	16	10.4	3	7	3.3	Cardiologist Interpretation	15	1.5
Svennberg et. al. (2015) 53	7173	Sweden	Community screening (75-76 yr olds)	Zenicor	30	2	14	75	46	25.9	50	11	9.2	9.2	3.4	9	3.4	30 sec irregular rhythm without p waves or 2x episodes between 10-29 sec	218	3
Proietti et. al. (2016) 54	65747	Belgium	Belgian Heart Week screening	Omron Heartscan HCG-801	30	1	0	58	41	NR	36	21	23	0.5	20	20	2	irregular R-R interval, no distinct p waves, variable atrial cycle length	603	1.1
Kansenbrood et. al. (2016) 55	3269	Holland	Influenza vaccination - opportunistic screening	MyDiagnostik	60	1	0	64.1	49	NR	NR	NR	NR	2.6	NR	NR	NR	Cardiologist Interpretation x 2	37	1.1
Engdahl et. al. (2013) 56	848	Sweden	Community screening (75-76 yr olds) in Halmstad, Sweden	Zenicor	30	2	14	75	43	NR	53	11	NR	9.6	4	10	1.9	30 sec duration of irregular rhythm or >= 2 episodes of 10 or more sec	40	4.7
Hendrikx et. al. (2013) 57	928	Sweden	GP practices	Zenicor	10	2	28	69.8	50	NR	90.3	31.6	19.8	0	3.7	8.6	2	10 sec irregular rhythm without p waves	35	3.8
Hendrikx et. al. (2014) 67	95	Sweden	Referred for presyncope/palpitations	Zenicor	30	2	28	54.1	44	NR	28.4	1.1	8.4	0	0	6.3	1	30 sec irregular rhythm without p waves	9	9.5
Chan et al. (2016) 15	1013	Hong Kong	Patients ≥ 65 yrs with hypertension or diabetes	Alive Cor	60	1	0	68.4	47	NR	90.4	36.6	16.2	2.2	4.4	10.5	3	Cardiologist Interpretation	5	0.5
Sobocinski et. al. (2012) 66	249	Sweden	Patients post TIA/stroke	Zenicor	10	2	30	72	57	NR	65	16	20	0	4	25	3	irregular rhythm of minimum 10 sec without visible p waves	15	6
Deliwa et. al. (2009) 14	606	Sweden	Community event	Zenicor	10	1	0	NR	64	NR	NR	NR	NR	NR	NR	NR	NR	irregular rhythm without visible p waves	6	1
Ramkumar et. al. (2017) 60	204	Australia	Community - ≥ 65 yrs with 1 or more risk factor for heart failure	Remon RM-100	60	5	7	70.1	51	29.1	72.1	56.4	5.9	0	0	NR	3	30 sec duration of irregular rhythm with absent p waves	20	9.8
Hendrikx et. al. (2017) 58	201	Sweden	Patients referred to respiratory clinics with suspicion of obstructive sleep apnoea	Zenicor	30	2	14	56	69	30	51	10	9.2	0	4.6	3.1	NR	Irregular supraventricular extra systoles in series for 30 sec	13	6.5
Claes et. al. (2011) 61	10758	Belgium	Community heart rhythm screening program through medical centres	Omron Heartscan 'HCG-801	30	1	0	59	38	NR	30.6	8.6	12.2	7.2	7.2	5.4	1	Irregular RR intervals, absence of p waves and variable atrial cycle length (when visible)	167	1.6
Samol et. al. (2012) 62	132	Germany	Large proportion post stroke/TIA. Also recruited from diabetes, hypertension and dyslipidemia clinics	Omron Heartscan HCG-801	30	1	0	64	58	NR	67	27	NR	0	3	49	NR	Cardiologist Interpretation x 2	7	5.3
Badilini et. al. (2016) 63	855	UK	Community shopping centre screening	MyDiagnostik	15	1	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	7	0.8
Chan et al. (2016) 59	13122	Hong Kong	Nationwide community screening program	Alive Cor	30	1	0	64.7	29	23.7	38.2	14.8	2.2	0	0.7	2.8	NR	Software algorithm definition with minimum of 30 sec	101	0.8
Chan et al. (2017) 65	10735	Hong Kong	Nationwide community screening program	Alive Cor	30	1	0	NR	NR	NR	NR	NR	NR	1.2	NR	NR	NR	Cardiologist interpretation (≥ 30 sec)	74	0.7
Lowcox et. al. (2017) 64	501	UK	Community based with individuals > 65 yrs with CHADS-VASC score ≥ 2	Alive Cor	30	2x per week	365	72.6	48	NR	54	26	14	0	1.0	7.0	3.0	30 second duration of an irregular rhythm without P waves	19	3.8
Gladstone et. al. (2014) 18	277	Canada	Patients admitted with cryptogenic stroke	Holter	continuous	continuous	1	73.2	56	NR	67	19.3	14.7	0	7	12.6	NR	30 second or longer duration of irregular rhythm	9	3.2
Barthelemy et. al. (2003) 19	60	France	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	64.4	55	NR	50	17	NR	0	NR	27	NR	fibrillatory waves associated with irregular ventricular response ratio at leats 30 sec duration	8	13.3

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Jabaudon et al. (2004) 20	149	Switzerland	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	66.9	68	NR	58	16.7	16.8	4.7	NR	16.8	NR	NR	7	4.7
Koudstaal et. al. (1986) 21	100	Holland	Retrospective study of 100 patients admitted with stroke/TIA	Holter	continuous	continuous	1	60.9	74	NR	NR	NR	41	NR	NR	NR	NR	NR	5	5
Hornig et. al. (1996) 22	268	Germany	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	59.1	61	NR	43.7	34	NR	NR	14.9	45	NR	NR	10	3.3
Rizos et. al. (2012) 23	496	Germany	Patients admitted with stroke/TIA	Holter	continuous	continuous	1	69	62	NR	78.8	24.6	NR	NR	NR	22.2	3	Cardiologist interpretation (≥ 30 sec)	14	2.8
Kouchert et. al. (1999) 24	82	Germany	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	3	59.7	57	NR	36.5	NR	17.1	NR	NR	NR	NR	Small irregular baseline undulations of variable amplitudes and morphology at a rate >350/min with an irregular ventiruclar response for at leats 1 min.	5	6
Schaer et. al. (2009) 25	241	Switzerland	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	68.7	59	NR	76	25	41	7	NR	4.6	NR	NR	0	0
Sauer et. al. (2004) 26	425	Switzerland	Retrospective review of patients post stroke/TIA with Holter monitoring	Holter	continuous	continuous	1	67.4	61	NR	NR	NR	NR	NR	NR	1.2	NR	Self-terminating sequence of >30 seconds of irregular RR intervals and the presence of fibrillatory P waves.	9	2.1
Shafqat et. al. (2004) 27	465	Pakistan	Retrospective review of consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	66.8	56	NR	NR	NR	NR	NR	NR	NR	NR	NR	5	2.4
Lazzaro et. al. (2012) 28	133	USA	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	63.1	50	NR	70	29.3	18.8	0	NR	2.3	NR	Supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with fibrillatory waves varying in amplitude, shape, and timing, replacing consistent P waves and with a duration >30 sec	8	6
Grond et. al. (2013) 29	1135	Germany	Patients admitted in 7 German centres with stroke/TIA	Holter	continuous	continuous	3	67	55	27.4		20.4	7.3	0	5.8	17.4	NR	≥ 1 period of >30 sec duration of an absolute arrhythmia without detectable P waves and without a pttern more consistent with an alternate diagnosis	49	4.3
Stahrenberg et. al. (2010) 30	224	Germany	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	7	68	58	27.6	72.9	22.3	14.8	0	5.2	16.2	NR	2 x Cardiologist interpretation of software algorithm detection of events	28	12.5
Ritter et. al. (2013) 31	60	Germany	Patients admitted with cryptogenic stroke	Holter	continuous	continuous	7	61.8	57	NR	70	11.7	13.3	NR	0	NR	4	Cardiologist interpretation (> 30 sec)	1	1.7
Higgins et. al. (2013) 32	50	Scotland	Patients admitted with stroke/TIA	Holter	continuous	continuous	7	67.1	48	NR	56	8	16	0	NR	NR	NR	Cardiologist interpretation (> 30 sec)	4	8
Hendrikx et. al. (2014) 67	95	Sweden	Patients investigated for palpitations and presyncope	Holter	continuous	continuous	1	54.1	42	NR	28.4	1.1	8.4	0	0	6.3	1	30 sec irregular rhythm without p waves	2	2.1
Sirkkar et. al. (2014) 33	52	India	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	59.5	77	NR	51.9	23.1	15.4	0	1.7	7.7	NR	30 sec irregular rhythm without p waves	3	5.8
Wachter et. al. (2017) 34	198	Germany	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	73.2	62	NR	80.7	26.4	9.1	0	4.6	21.7	4.8	>30 seconds rhyhtm with irregular RR intervals and the presence of fibrillatory P waves.	9	5
Gumbinger et. al. (2012) 35	192	Germany	Patients admitted with stroke/TIA	Holter	continuous	continuous	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2	1
Alhadramy et. al. (2010) 36	426	Canada	Retrospective review of patients post stroke/TIA with Holter monitoring	Holter	continuous	continuous	1	64.9	48	NR	58.2	14.1	14.1	0	1.6	6.3	NR	Irregular ventricular response in the absence of p-waves or with fibrillatory waves	11	2.5
Mochocinski et. al. (2012) 66	249	Sweden	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	72	57	NR	65	16	20	0	4	25	3	irregular rhythm of minimum 10 sec without visible p waves	5	2
Dangayach et. al. (2011) 37	51	USA	Retrospective audit of patients admitted with cryptogenic stroke	Holter	continuous	continuous	2	58.2	43	NR	35.3	16	15.7	7.4	NR	NR	NR	NR	15	29.4

Gunalp et. al. (2006) 38	26	Turkey	Patients admitted with ischaemic stroke	Holter	continuous	continuous	1	66	69	NR	61	26	31	NR	NR	NR	NR	NR	11	42.3
Fonseca et. al. (2013) 39	80	Portugal	Patients admitted with cryptogenic stroke	Holter	continuous	continuous	1	69.3	53	NR	71.3	28.8	11.3	NR	NR	22.5	NR	NR	17	21
Manina et. al. (2014) 40	114	Italy	Patients admitted with cryptogenic stroke	Holter	continuous	continuous	4	63.1	NR	NR	52.6	9.6	NR	NR	NR	NR	NR	Irregular ventricular response in the absence of p waves or with fibrillatory waves	29	25.4
Tayawa et. al. (2007) 41	308	Japan	Consecutive patients admitted with ischaemic stroke	Holter	continuous	continuous	1	72.6	60	NR	70.1	25.3	NR	20.4	NR	NR	NR	small irregular baseline undulations of variable amplitude and morphology at a rate of 300-350/min associated with irregular ventricular response	26	8.4
Shibazaki et. al. (2012) 42	536	Japan	Consecutive patients admitted with ischaemic stroke	Holter	continuous	continuous	1	72.4	64	NR	65.9	25.7	9.8	NR	0.3	NR	NR	NR	12	2.2
Vandebroucke et. al. (2004) 43	136	Belgium	Retrospective audit of patients admitted with ischaemic stroke	Holter	continuous	continuous	1	68	52	NR	NR	NR	NR	NR	NR	NR	NR	NR	7	5.1
Yokogawa et. al. (2013) 44	68	Japan	Consecutive patients admitted with ischaemic stroke	Holter	continuous	continuous	1	69.9	54	NR	66.2	14.7	NR	NR	NR	NR	NR	irregular and uncoordinated atrial electrical activity on surface ECG lasting > 30 sec	17	25
Atmuri et. al. (2012) 45	140	Australia	Retrospective audit of patients admitted with ischaemic stroke/TIA	Holter	continuous	continuous	1	NR	NR	NR	65	20	37.1	18.6	NR	NR	NR	NR	12	8.6
Salvatori et. al. (2015) 46	274	Italy	Cohort study of patients ≥ 65 yrs with hypertension in multiple GP clinics	Holter	continuous	continuous	2	70	54	NR	100	15	9	7	4	2.2	NR	Cardiologist interpretation	4	1.5
Beaulieu-Boire et. al. (2013) 47	284	Canada	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	70.6	52	NR	68.7	26.7	27.4	NR	2.2	22.3	NR	Cardiologist interpretation	18	6.3
Dogan et. al. (2011) 48	400	Turkey	Retrospective review of patients admitted post stroke	Holter	continuous	continuous	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	40	10
Jauen et. al. (2008) 49	126	Canada	Retrospective review of patients admitted post stroke	Holter	continuous	continuous	1	NR	NR	NR	NR	NR	NR	7	NR	NR	NR	NR	9	7.1
Suissa et. al. (2012) 50	354	France	Consecutive patients admitted with ischaemic stroke	Holter	continuous	continuous	1	62.4	57	NR	51.1	18.6	NR	0	NR	NR	NR	Cardiologist interpretation	2	0.6
Wachtlhahrt et. al. (2013) 51	224	Germany	Patients admitted with ischaemic stroke	Holter	continuous	continuous	7	68.5	59	NR	73.2	22.3	15.2	NR	5.4	24.1	NR	>30 second irregular rhythm	29	12.9

AF – Atrial Fibrillation BMI – Body Mass Index (kg/m^2) DM – Diabetes Mellitus HF – Heart Failure HTN - Hypertension IHD – Ischaemic Heart Disease

Table 1 – Summary of included trials investigating AF detection using single lead ECG devices or Holter Monitoring

Overall AF detection. The combined AF detection rate using single lead ECG monitoring (n=117,436 from 18 studies) was 1.7% (95% CI 1.4% – 2.1%). The cumulative AF detection rate using continuous (Holter) monitoring (n=8498 from 36 studies) was 5.5% (95% CI 4.4% – 6.6%). There was significant heterogeneity between studies (I^2 = 94% for single lead ECG monitoring, 87% for Holter monitoring). The overall new AF detection rate is presented in Figure 2.

Comparison of multiple intermittent monitoring to 24 hour Holter. There was significant variation in the monitoring time using both single lead and Holter monitoring which contributed to the difference in the cumulative detection rate seen in Figure 2. Figure 3 compares the detection rate of multiple intermittent single lead recordings to 24-hour continuous monitoring, which is used routinely in clinical practice. There were 8 studies (n=10,199, mean weighted age 68.8±8.4 years from 6 studies, 47% male from 8 studies) that performed multiple intermittent single lead ECG recordings and 27 studies (n=6284, mean weighted age 67.8±5.1 years from 23 studies, 58% male from 23 studies) that used 24-hour Holter monitoring. From the data available, the multiple intermittent ECG group had a lower AF risk to the 24-hour Holter group (hypertension – 55% (n=8 studies) vs 65% (n=20 studies), diabetes mellitus – 15% (n=8 studies) vs 22% (n=20 studies), heart failure – 3.3% (n=8 studies) vs 3.9% (n=11 studies), ischemic heart disease – 11% (n=6 studies) vs 19% (n=15 studies) and previous stroke/TIA – 9% (n=7 studies) vs 16% (n=15 studies)) respectively. The combined AF detection rate was 4.8% (95% CI 3.6–6.0%) using multiple intermittent ECG recordings. The cumulative AF detection rate using 24-hour Holter monitoring was 4.6% (95% CI 3.5–5.7%).

Association between monitoring time and AF detection. Using single lead ECG devices, we found a moderate linear relationship between the total monitoring time and AF detection rate (β=0.13, R^2 = 0.42). Using this formula, we noted that approximately 19 minutes of total intermittent monitoring produced similar AF detection to 24-hour continuous monitoring (Figure 4). The study by Halcox et. al. was an outlier, with a much lower AF detection rate than other studies (3.8% from 52 minutes of total monitoring) and this reduced the linear correlation between total monitoring time and AF detection rate [64]. Exclusion of these data led to a stronger linear relationship (β=0.26, R^2 =

0.80) and a much lower total intermittent monitoring time required (12 min) to produce a similar AF detection rate to 24 hour Holter monitoring.

Meta-regression. Sources of heterogeneity in the 18 studies using single lead ECG monitoring were investigated using meta-regression (Table 2). Monitoring time per participant (β=0.11, 95% CI 0.04-0.18, p=0.005) and body mass index (β=1.1, 95% CI 0.58-1.5, p=0.01) were associated with AF detection.

Variable	Number of studies	β (95% C.I)	P value
Age (years)	15	0.00 (-0.22 – 0.24)	0.95
Monitoring time per participant (min)	18	0.11 (0.04 – 0.18)	0.005
Body Mass Index (kg/m^2)	4	1.1 (0.58 – 1.5)	0.01
CHADS Score (%)	11	-0.13 (-2.6 – 2.4)	0.91
Hypertension (%)	14	0.01 (-0.08 – 0.10)	0.75
Previous diagnosis of AF (%)	16	-0.13 (-0.50 – 0.24)	0.46
Ischaemic Heart Disease (%)	12	-0.10 (-0.42 – 0.21)	0.48
Previous stroke (%)	13	0.06 (-0.09 – 0.19)	0.45
Male gender	16	0.10 (-0.04 – 0.24)	0.16

Table 2 – Meta Regression Analysis for AF detection (Single lead ECG studies)

Sensitivity Analysis. A number of outlier studies were observed in the meta-analysis that could influence the cumulative AF detection rate.[37-40 44] Removal of these outlier studies resulted in a reduction in the overall AF detection rate in all Holter studies (table 3) and for 24 hour Holter studies (table 4). When these outlier studies were removed the overall AF detection rate for 24 hour Holter was 3.86% (95% C.I 2.88% – 4.83%), much lower than the detection rate by multiple intermittent ECG recordings using portable single lead devices (4.78%, 95% C.I 3.58% – 5.97%). A cumulative meta-analysis (figure 5) did not show any significant variation in the AF detection rate

Study Omitted	AF detection rate (%) in remainder	95% C.I (%)
Dangayach et. al. (2011)	5.27	4.17 – 6.38
Fonseca et. al. (2013)	5.26	4.15 – 6.36
Gunalp et. al. (2006)	5.32	4.21 – 6.42
Manina et. al. (2014)	5.11	4.03 – 6.20
Yadogawa et. al. (2013)	5.25	4.14 – 6.35
All studies excluded	4.31	3.36 – 5.26

over time using either Holter or single lead ECG monitoring.

Table 3 – Outlier studies omitted (all Holter studies) to assess the change to the overall AF detection rate

Study Omitted	AF detection rate (%) in remainder	95% C.I (%)
Fonseca et. al. (2013)	4.30	3.21 – 5.39
Gunalp et. al. (2006)	4.39	3.30 – 5.47
Yadogawa et. al. (2013)	4.30	3.22 – 5.38
All studies excluded	3.86	2.88 – 4.83

Table 4 – Outlier studies omitted (24 hour Holter) to assess the change to the overall AF detection rate

Publication bias. Publication bias was explored using a funnel plot of all included studies (Supplemental Figure 1). There was significant publication bias in both single lead ECG device and Holter monitoring studies (Egger test, $p=0.003$ and $p<0.001$ respectively).

Quality of studies. A summary of the quality analysis (Supplemental Table 3) showed that overall quality of reporting was moderate. All studies described the primary objective of the trial and included a summary of the main findings. Detailed comorbidities of the study participants were only adequately reported in 28/52 (54%), and limitations were discussed in 35/52 (67%) of studies. Most had a very selective patient population, 31/52 (60%) were post stroke/TIA cohorts.

Discussion

Our study is the only systematic review that we are aware of that has studied the overall AF detection rate of single lead portable ECG devices. The results of our systematic review suggest a linear relationship between monitoring time per patient and AF detection rate. Single timepoint screening has an approximate 1% AF detection rate which can be increased to around 5% when

multiple recordings are performed. We noted that approximately 19 minutes of intermittent monitoring produced similar detection rates to conventional 24 hours continuous Holter monitoring.

Early diagnosis of AF: AF creates a significant burden on both patients as well as the health care system. AF will continue to rise in incidence and the costs to the health care system will continue to increase, due to aging, sedentariness, and the prevalence of obesity and the metabolic syndrome.[3 68] Early diagnosis offers the possibility for early initiation of treatment which may reduce the occurrence of the complications which may lead to reduced hospital admissions and associated health care costs. Early treatment for AF can be achieved in different ways. Patients with subclinical AF have an increased risk of stroke and cardiovascular events, like those with established AF.[12 69] Anticoagulation may help reduce the incidence of stroke in this cohort.

The close relationship between metabolic syndrome and AF has encouraged research into the benefits of lifestyle intervention. Aggressive lifestyle intervention in patients with AF undergoing catheter ablation has been reported to lead to a reduction in symptom burden, improved quality of life and the need for repeat ablation procedures.[10] It remains to be tested whether initiation of lifestyle intervention and aggressive risk factor modification following the early diagnosis of AF may be associated with positive LA remodeling and reduction of disease progression. Such a process may lead to additional health benefits, including reduction in cardiovascular risk and improvement in exercise capacity.

AF screening and feasibility. AF is a leading cause of stroke and heart failure in the community. As well as an association with increased all-cause mortality, it is associated with reduced quality of life. The availability of preventive therapies, including anticoagulation, has led to increasing recognition of the importance of AF screening for early diagnosis. However, AF screening shares the limitations of screening with other diagnostic tests. The screening tool must have high sensitivity, and needs to be inexpensive and cost effective. We also need to minimize and have a method of addressing false positives. Current guidelines recommend opportunistic screening using pulse palpation and 12 lead ECG.[11] In a previous systematic review this was associated with a new AF detection rate of approximately 1%.[5] Pulse palpation may be non-specific in patients with other irregular rhythms such as ventricular ectopy, and 12 lead ECG is only able to capture a single timepoint for screening.

There are multiple other methods for AF detection. Continuous Holter monitoring is probably the most commonly used in clinical practice, especially in stroke cohorts. It has the potential advantage of assessing heart rhythm throughout the day and may be useful in detecting nocturnal subclinical AF. However, the disadvantages include the cost of Holter monitoring (especially for mass screening), the inconvenience of leads and electrodes (which may affect compliance), and typical limitation to 1-2 days of capture (as extended periods are more cumbersome and less cost-effective. Other event recorders are again expensive and limited to symptomatic patients. Extended period monitoring using implantable devices have shown promise in the cryptogenic stroke population (where many have been diagnosed with paroxysmal AF),[70] but they are invasive and not feasible for mass screening.

Portable single lead ECG devices permit multiple 30-60 second recordings to be captured, and downloaded to a computer. These devices have several potential advantages over Holter monitoring. They are leadless and require finger contact (and are hence easy to use and acceptable to patients). They have a high degree of sensitivity for identifying AF.[71-73] Most interface with a web-based cloud system where ECG rhythms can be wirelessly transferred to clinicians, allowing rapid analysis and diagnosis. The development of automated algorithms to detect AF is helpful for mass screening. In two small studies they have demonstrated superior AF detection compared with 24 hour Holter monitoring.[66 67] Although screening using these portable devices are currently not in the latest AF guidelines, they may offer a feasible option for mass screening. Screening using these devices has been demonstrated to be cost effective.[74 75]

We noted a moderate linear association between monitoring time and AF detection rate. Single timepoint screening for 30-60 sec achieved an overall detection rate of approximately 1%. This is no better than what has been reported using pulse palpation or 12 lead ECG, hence does not add any incremental benefit in screening programs [5]. Multiple intermittent recordings improve AF detection; we found that at least 19 minutes of total monitoring should be performed to achieve detection rates similar to 24 Holter monitoring.

The linear relationship between monitoring time and AF detection rate (R^2=0.80) and the reproduction of AF detection rates of 24 hour Holter monitoring with only 12 minutes of intermittent

monitoring was possible in our study only after exclusion of an outlier.[64] Despite the inclusion of elderly participants with at least one risk factor for AF, the use of a validated single lead ECG device and a prolonged monitoring period, that study had a lower AF detection rate (3.8%) than the remaining studies, even using a shorter monitoring period.[53 56 57] Relatively low rates of adherence (only approximately 25% completed 2 x 30 second ECG recordings every week for the full year of monitoring) may be a potential explanation for the lower AF detection rate noted.[64]

Limitations: There are several challenges inherent in this meta-analysis of studies investigating AF detection. The most important is the target screening population. Most studies did not report the CHADS or CHA_2DS_2-VASC score, a history of previous stroke, or other co-morbidities. Consequently, it was difficult to ascertain if the risk profiles of patients in these studies were equivalent. Most Holter monitoring studies were performed in the stroke population – which is likely a population with higher AF risk than many studies using portable ECG devices, which recruited mainly healthy participants or those with AF risk factors from the community. The significant heterogeneity amongst both Holter and portable ECG device studies make it difficult to perform direct comparisons between both groups. The type/duration of monitoring and type of device used will also influence the overall AF detection rate and varied significantly between studies. There are several possible confounders which may not have been taken into account. The validity of the linear regression analysis comparing detection time and rate may be limited due to the significant differences in study population, study design and AF definitions. However, despite these limitations, the analysis may provide some important inferences into AF screening. Multiple intermittent ECG recordings achieved a similar AF detection rate to 24 hour Holter monitoring. This may suggest that in a similar cohort of patients with the same comorbidities, single lead intermittent monitoring may be superior for AF detection.

Compared to 24-hour continuous monitoring, single lead portable ECG monitoring is more patient dependent. Good patient compliance is essential to obtain multiple readings across different timepoints which improves sensitivity. The analysis performed does not take into account patient compliance as this is difficult to assess and poorly reported across the individual studies. Most single lead device manufacturers have proprietary automated AF detection algorithms which were used for

diagnosis. Not all of these algorithms have had rigorous testing and comparison to a reference standard. It is also difficult to distinguish AF from other supraventricular tachycardias using single lead ECG devices as the P wave is often not readily discernible. The use of different automated algorithms makes AF definitions non-standardized and can potentially create issues with both over and underdiagnoses.

There are other limitations in this analysis. The efficacy of intermittent monitoring is critically dependent on AF burden and density. All studies varied in their monitoring period and strategy. The linear regression model used was able to determine a total intermittent monitoring time which produced similar AF detection rates to 24-hour continuous monitoring. However, it is difficult to translate the total monitoring time into an effective monitoring strategy. For example, we are unable to determine from our analysis if 12 x 60 second recordings over 12 consecutive days is different to 2 x 60 second recordings daily for 6 consecutive days. The definitions of AF also vary between studies. Many are based on individual physician interpretation and criteria for diagnosis were not explicitly specified. The duration of AF varied from 10-30 seconds between studies, although a cut-off of 30 seconds, was the most widely adopted practice.

Conclusion: Single lead portable ECG devices may offer an efficient screening option for AF compared to 24 hr. Holter monitoring. Total monitoring time is related with AF detection and a total of 19 minutes may achieve a similar detection rate to 24 hour Holter monitoring.

Contributors: SR – Performed the literature search and analysis of individual studies. Involved in the statistical analysis, manuscript preparation and editing. TM – Is guarantor. Developed project idea/rationale. Involved in data analysis and manuscript preparation and editing. NN – Involved in data and statistical analysis as well as manuscript preparation and editing. DD – Performed the literature search and analysis of individual studies. Involved in the manuscript preparation and editing. DP – Involved in analysis of individual studies and statistical analysis. Involved in

manuscript preparation and editing. JK – involved in the project outline, data analysis, manuscript preparation and editing.

Data Sharing: Further figures and data available in supplementary material.

BMJ Group declaration of interests statement

I have read and understood the BMJ Group policy on declaration of interests and declare the following interests: *[list them or state "none"]*.

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Figure Legends

Figure 1 – Overview of inclusion and exclusion of studies based on the PRISMA flowchart

Figure 2 – Forest Plot showing the overall AF detection rate between single lead ECG devices and Holter monitoring

Figure 3 – Forest Plot comparing the AF detection rate between 24 hour Holter monitoring and performing multiple intermittent single lead ECG recordings

Figure 4 – Graph showing the linear relationship between total monitoring time and AF detection rate in single lead ECG devices

Figure 5 – Cumulative Meta-analysis showing minimal variation in AF detection over time using Holter and single lead ECG devices.

Supplementary Figure 1 – Funnel Plots for Holter monitoring and single lead ECG device studies

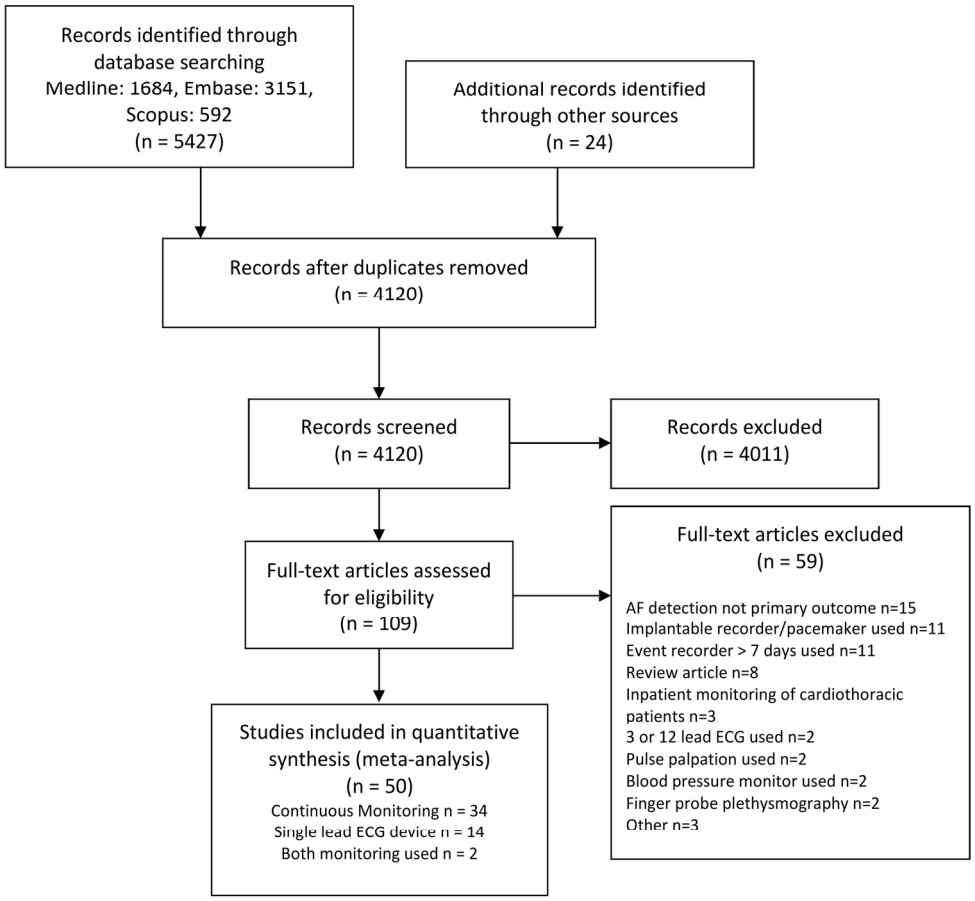


Figure 1

170x163mm (300 x 300 DPI)

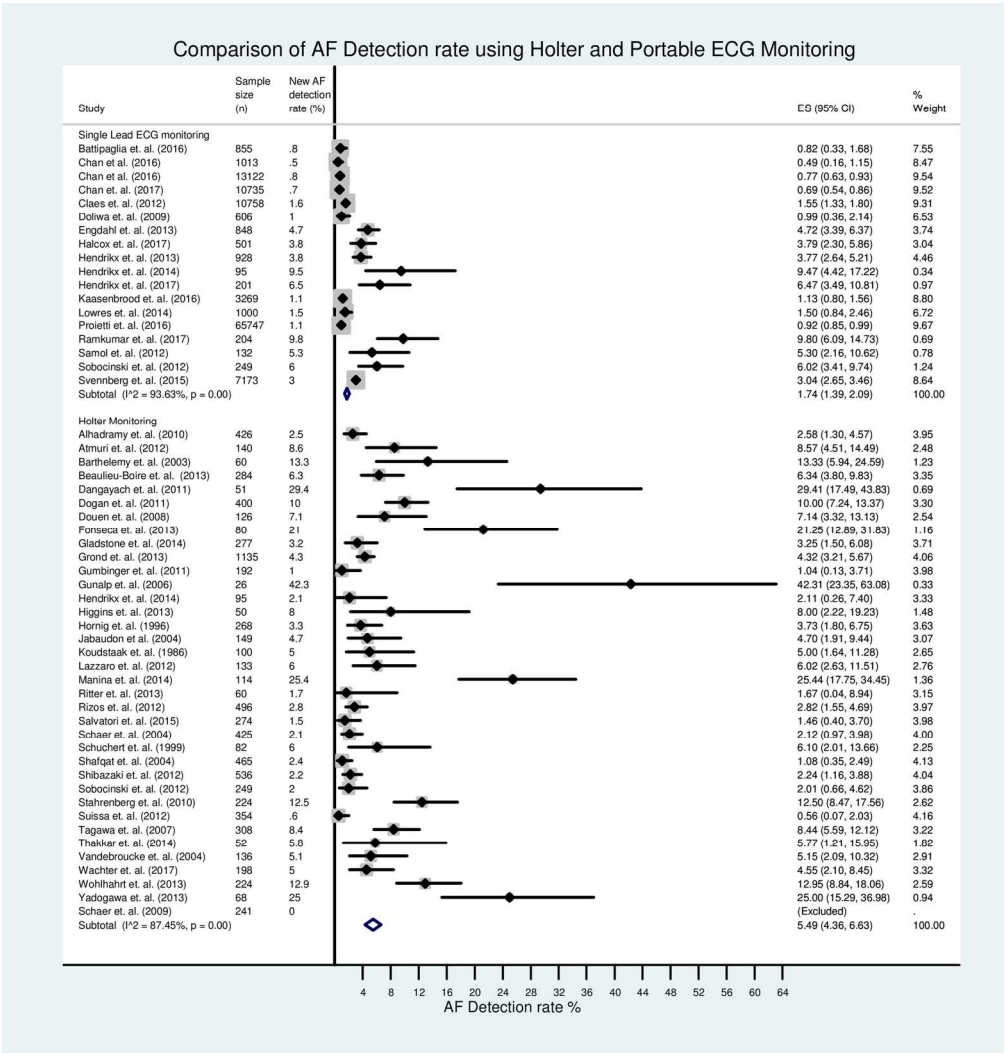


Figure 2

152x159mm (300 x 300 DPI)

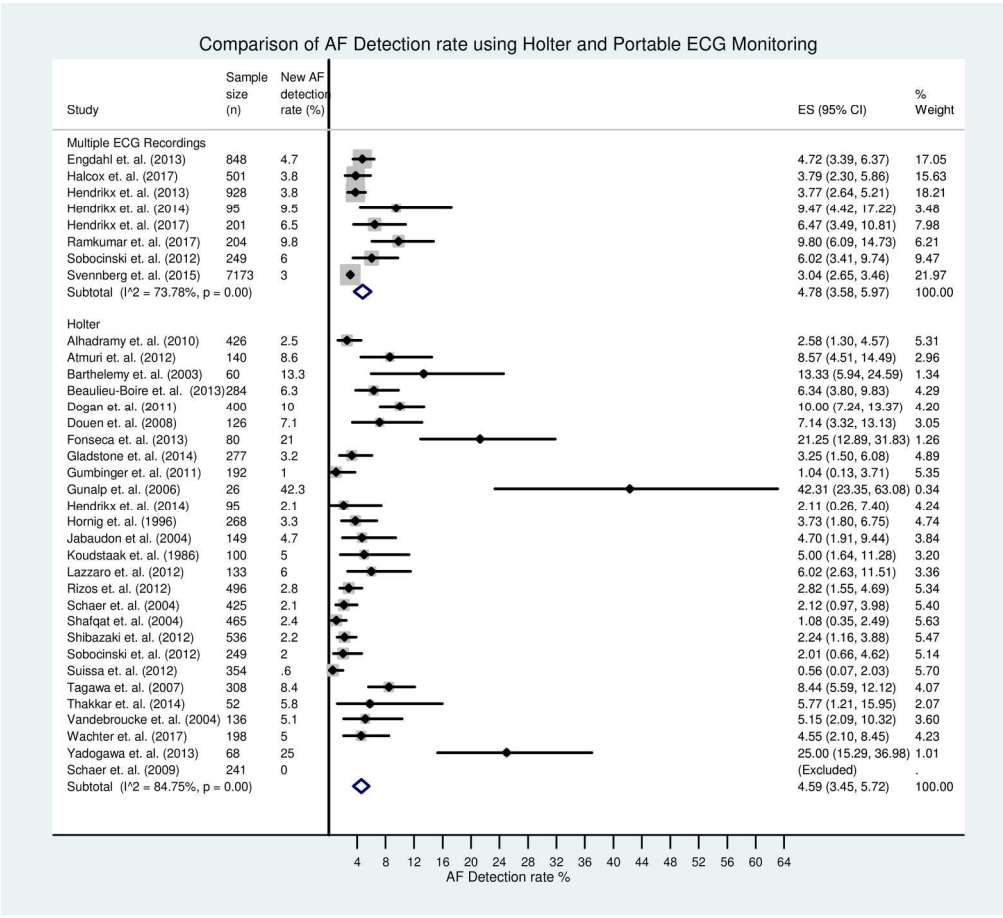


Figure 3

201x183mm (300 x 300 DPI)

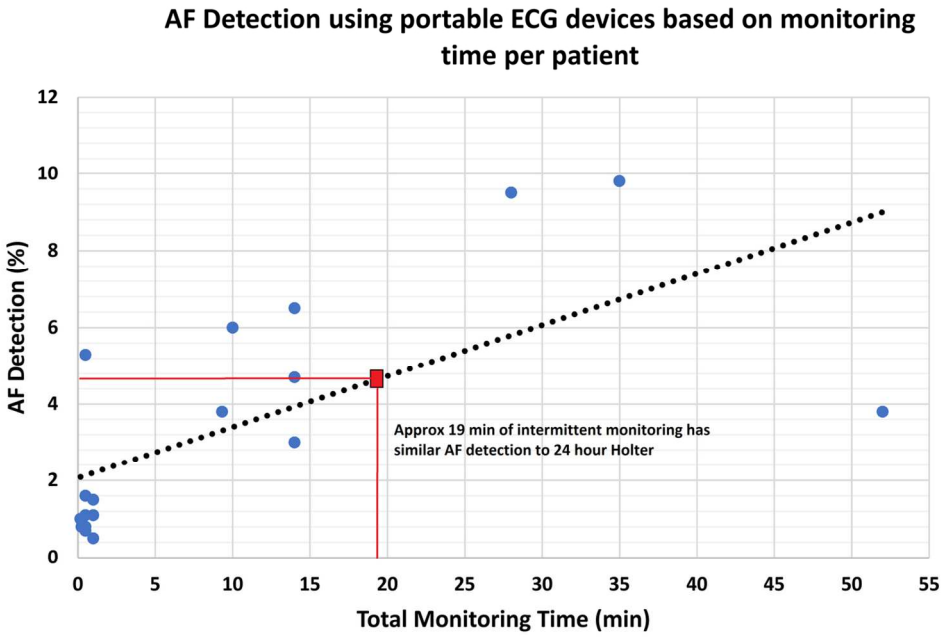


Figure 4

125x84mm (300 x 300 DPI)

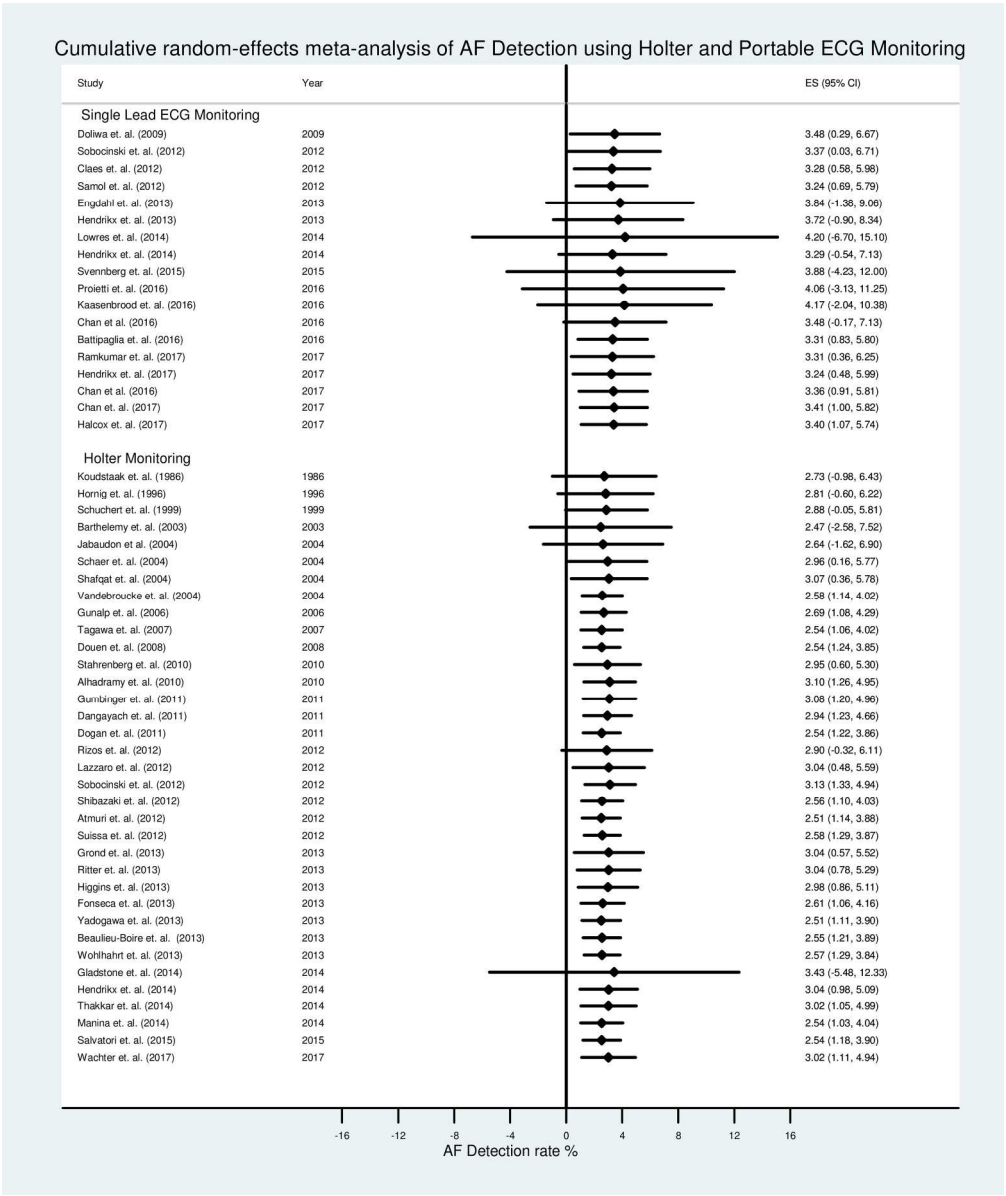
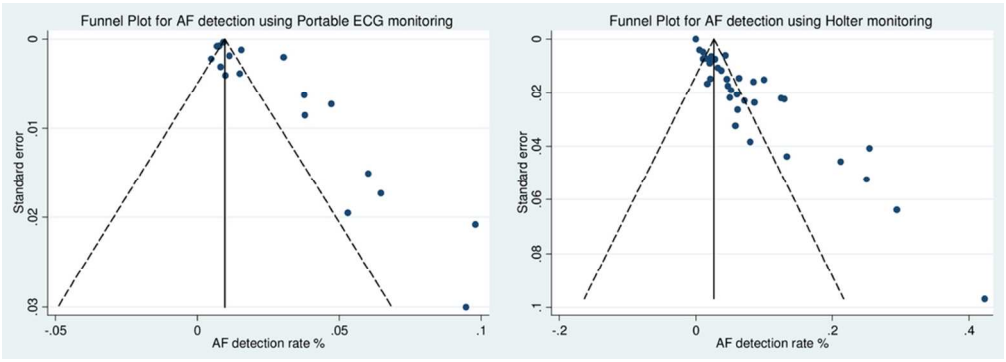


Figure 5

203x241mm (300 x 300 DPI)



88x31mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5/6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6-11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11/12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11/12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11/12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16/17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Atrial Fibrillation Detection using Single Lead Portable Electrocardiographic Monitoring: A Systematic Review and Meta-Analysis.

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Secondary Subject Heading:	Cardiovascular medicine
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Atrial Fibrillation Detection using Single Lead Portable Electrocardiographic Monitoring: A Systematic Review and Meta-Analysis.

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Running title: Atrial fibrillation detection

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ABSTRACT

Objectives: Recent advances technology advnaces have allowed for heart rhythm monitoring using single-lead electrocardiographic (ECG) monitoring devices, which can be used for early diagnosis of atrial fibrillation (AF). We sought to investigate the AF detection rate using portable ECG devices compared with Holter monitoring.

Setting, participants and outcome measures: We searched the Medline, Embase and Scopus databases(conducted on 8th May 2017) using search terms related to AF screening and included studies with adults>18 years using portable ECG devices or Holter monitoring for AF detection. We excluded studies using implantable loop recorders and pacemakers. Using a random-effects model we calculated the overall AF detection rate. Meta-regression analysis was performed to explore potential sources for heterogeneity. Quality of reporting was assessed using the tool developed by Downs and Black.

Results: Portable ECG monitoring was used in 18 studies(n=117,436) and Holter monitoring was used in 36 studies(n=8498). The AF detection rate using portable ECG monitoring was 1.7%(95% CI 1.4–2.1), with significant heterogeneity between studies(p<0.001). There was a moderate linear relationship between total monitoring time and AF detection rate(r=0.65, p=0.003), and meta-regression identified total monitoring time(p=0.005) and body mass index(p=0.01) as potential contributors to heterogeneity. The detection rate(4.8%, 95% CI 3.6–6.0%) in 8 studies(n=10,199) which performed multiple ECG recordings was comparable to that with 24 hour Holter(4.6%, 95% CI 3.5–5.7%). Intermittent recordings for 19 minutes total produced similar AF detection to 24 hr. Holter monitoring.

Conclusion: Portable ECG devices may offer an efficient screening option for AF compared to 24 hour Holter monitoring.

Study Registration: Prospero database - April 22nd, 2017(CRD42017061021)

Key words; atrial fibrillation, screening, electrocardiographic monitoring.

Strengths and limitations of this study:

- First systematic review comparing single lead ECG monitoring to 24 hour holter monitoring for AF detection.
- Comprehensive literature search and specific inclusion criteria allowing for large patient numbers.
- Heterogeneity amongst individual studies with regards to patient population, AF definitions and monitoring time.
- Poor reporting of CHA_2DS_2-VASC scores amongst individual studies
- Patient compliance unable to be accounted for in this meta-analysis

Atrial fibrillation (AF) is a leading cause of stroke and heart failure worldwide, is associated with increased all-cause mortality [1 2] as well as substantial financial cost.[3 4] The prevalence of AF increases with age, exceeding more than 15% for those aged 85 and older.[5] The epidemics of obesity, diabetes mellitus and metabolic syndrome have also been associated with the increasing prevalence of AF.[6-8] Up to 20% of patients with stroke have underlying AF, and detection allows the initiation of anticoagulation which is associated with a significant reduction in stroke recurrence.[9]

Early diagnosis of AF may have several benefits, including individualized lifestyle intervention [10] and anticoagulation, and may be associated with a reduction in complications and healthcare costs. The importance of early diagnosis has been recognized in recent guidelines from the European Society of Cardiology (ESC) which recommended opportunistic screening using pulse palpation and 12 lead electrocardiogram (ECG).[11] However, screening for AF is challenging for several reasons; many patients are asymptomatic or may have atypical symptoms. There are a variety of monitoring techniques available, all which vary in diagnostic accuracy and sensitivity, and there is no accepted reference standard. Subclinical AF is associated with an increased risk of stroke, cardiovascular disease and all-cause mortality,[12] although there is controversy surrounding the significance of brief paroxysms of AF and the potential benefit of anticoagulant therapy. Implantable devices are expensive, and not cost effective for mass screening, and the use of external devices for long periods of monitoring require electrodes, which may be poorly tolerated by patients.

Recent advances in technology have allowed for the development of single lead portable electrocardiographic monitoring devices. Multiple devices are available, all using multiple points of finger contact to create a single lead ECG trace. The in-built memory of these devices allows for single or multiple time-point screening. Interpretation from a cardiologist or by automated algorithms has achieved high sensitivity and specificity for AF detection.[13-15] Although they have not been incorporated into the latest AF guidelines, the accuracy, ease of use and potential cost-effectiveness of these devices may lead to them having an important role in AF screening. This paper describes a

systematic review of the published literature to investigate the overall AF detection rate using portable ECG devices compared with traditional Holter monitoring.

Methods.

Search strategy. We conducted our systematic review and meta-analysis using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline (PRISMA).[16] We searched the Medline, Scopus and Embase databases using key terms including "atrial fibrillation/AF and screening/monitoring and electrocardiographic/Holter monitoring" which were mapped to subject headings. We also searched the reference lists to identify other potential articles. The search was limited to adult human subjects >18 years and limited to the English language (see search strategy for Medline database in supplementary material). The study was prospectively registered on the Prospero database on April 22nd, 2017(CRD42017061021), and the search was conducted on 8th May 2017.

Study selection. Titles and abstracts of studies identified from the search were reviewed by two independent reviewers (S.R and D.D). Studies which had a primary aim of AF detection in adult participants were included. We included all cohorts including community screening, those with risk factors and recent stroke. The screening methods included portable single lead ECG devices or continuous (Holter) monitoring (up to one week). We included studies which used single lead ECG devices for single episode screening or multiple intermittent screening periods. We included conference abstracts if demographic and outcome data were available. We excluded studies if participants were <18 years or if other forms of monitoring were used (pacemaker, implantable loop recorders, event recorders, monitoring patches and inpatient telemetry). We also excluded studies where AF detection was not the primary aim.

The primary outcome of interest was the detection rate of new AF using either single lead intermittent or continuous monitoring. Our secondary objective was to determine the optimal time of intermittent monitoring which produced equivalent AF detection to continuous monitoring.

Data Collection. Full text manuscripts of studies fitting the inclusion criteria were obtained. Quality of reporting and risk of bias was assessed using the tool developed by Downs and Black.[17] A standardized data-extraction form was used by the reviewers which included information about the

patient demographics, comorbidities, screening strategy, patients with known AF and overall new AF detection rate. Where data were not reported, we attempted to contact the primary authors of the study. Any disagreements between the two reviewers were resolved by consensus or by consulting a third reviewer (TM).

Statistical Analysis. The cumulative AF detection rate for continuous and intermittent monitoring and the 95% confidence interval was calculated using a random effects model. The results were displayed as a forest plot and heterogeneity amongst the studies was assessed using the I^2 statistic. A subgroup analysis was performed by comparing the cumulative detection rate of single lead ECG studies which performed multiple timepoint recordings with 24 hour Holter monitoring studies. Linear regression analysis was used to determine the association between the total monitoring time and AF detection using single lead ECG devices. This formula was used to determine the monitoring time using single lead ECG devices to approximate the overall AF detection rate using 24-hour continuous monitoring. Univariate meta-regression analysis was performed to assess the influence of various clinical and screening factors with AF detection. Publication bias was assessed using a funnel plot and the Egger test. Statistical analysis was performed using Stata v.13 (StataCorp, College Station, TX) with two-tailed p-values <0.05 used to denote statistical significance.

Patient and Public Involvement. If patients were not involved in this review.

Results

Study Characteristics. The PRISMA flowchart of our included studies is shown in Figure 1 and the search strategy in Supplementary Table 1. Our initial search strategy identified 5427 studies, with another 26 identified through other sources. After removing duplicate records, 4122 studies were left. After screening those using the inclusion/exclusion criteria, we identified 111 full text studies for detailed review, which excluded 59 studies, leaving 52 full text studies for inclusion in the meta-analysis (see Supplementary Table 2 for excluded studies). Of the 52 studies included, 34 used continuous (Holter) monitoring (n=8154),[18-51] 16 (n=117,092) used single lead portable ECG monitoring,[14 15 52-65] and 2 studies (n=344) used both continuous and intermittent single lead monitoring for AF detection in a head to head comparison.[66 67]

The baseline characteristics of the individual studies is presented in Table 1. There was a considerable range in age (54-76 years), and gender (male 29-77%) between studies. As many studies chose healthy volunteers and other studies focused on patients post stroke or those with AF risk factors, there was significant variation in comorbidities such as diabetes, hypertension and obesity. Stroke risk determined by the CHADS or CHA_2DS_2-VASC score was reported in only 14/52 studies (27%). Of the 52 studies, 36 (69%) were conducted in Europe, 8 (15%) were in Asia, 5 (10%) were in North America and 3 (6%) in Australia. Nine studies (17%) were retrospective, the remainder all being prospective cohort or randomized controlled trials.

Of the 18 studies using single lead ECG devices, 10 studies (56%) used a single 10-60 sec recording for AF detection whilst 8 studies (44%) used multiple readings over a 1-52 week period. There were five portable ECG devices used (Table 1). Sixteen studies (89%) used healthy participants with risk factors.[14 15 52-61 63-65 67]. Two studies assessed patients following stroke or transient ischemic attack (TIA).[62 66]

Of the 36 studies using continuous (Holter) monitoring, 27 studies (75%) used 24-hour continuous monitoring,[18-23 25-28 33-36 38 39 41-45 47-50 66 67] 4 studies (11%) used 1 week monitoring,[30-32 51] 2 studies (6%) used 48-hour monitoring,[37 46] 2 studies (6%) used 72-hour monitoring,[24 29] and 1 study (3%) used 96-hour monitoring.[40]

Study	n	Country	Type of patients used	Device Used	Duration of recording (sec)	Frequency of recording /day	Total monitoring (days)	Mean/median age (yrs)	Male (%)	BMI (kg/m2)	HTN (%)	DM (%)	IHD (%)	Previous diagnosis of AF (%)	HF (%)	Previous stroke (%)	Mean/median CHADS2/ CHADS-VASC	Definition of AF	New AF (n)	New AF rate (%)
Bowres et. al. (2014) 52	1000	Australia	Community pharmacy screening	Alive Cor	60	1	0	76	44	NR	62	23	16	10.4	3	7	3.3	Cardiologist Interpretation	15	1.5
Svennberg et. al. (2015) 53	7173	Sweden	Community screening (75-76 yr olds)	Zenicor	30	2	14	75	46	25.9	50	11	9.2	9.2	3.4	9	3.4	30 sec irregular rhythm without p waves or 2x episodes between 10-29 sec	218	3
Proietti et. al. (2016) 54	65747	Belgium	Belgian Heart Week screening	Omron Heartscan HCG-801	30	1	0	58	41	NR	36	21	23	0.5	20	20	2	irregular R-R interval, no distinct p waves, variable atrial cycle length	603	1.1
Kansenbrood et. al. (2016) 55	3269	Holland	Influenza vaccination - opportunistic screening	MyDiagnostik	60	1	0	64.1	49	NR	NR	NR	NR	2.6	NR	NR	NR	Cardiologist Interpretation x 2	37	1.1
Engdahl et. al. (2013) 56	848	Sweden	Community screening (75-76 yr olds) in Halmstad, Sweden	Zenicor	30	2	14	75	43	NR	53	11	NR	9.6	4	10	1.9	30 sec duration of irregular rhythm or >= 2 episodes of 10 or more sec	40	4.7
Hendrikx et. al. (2013) 57	928	Sweden	GP practices	Zenicor	10	2	28	69.8	50	NR	90.3	31.6	19.8	0	3.7	8.6	2	10 sec irregular rhythm without p waves	35	3.8
Hendrikx et. al. (2014) 67	95	Sweden	Referred for presyncope/palpitations	Zenicor	30	2	28	54.1	44	NR	28.4	1.1	8.4	0	0	6.3	1	30 sec irregular rhythm without p waves	9	9.5
Chan et al. (2016) 15	1013	Hong Kong	Patients ≥ 65 yrs with hypertension or diabetes	Alive Cor	60	1	0	68.4	47	NR	90.4	36.6	16.2	2.2	4.4	10.5	3	Cardiologist Interpretation	5	0.5
Sobocinski et. al. (2012) 66	249	Sweden	Patients post TIA/stroke	Zenicor	10	2	30	72	57	NR	65	16	20	0	4	25	3	irregular rhythm of minimum 10 sec without visible p waves	15	6
Deliwa et. al. (2009) 14	606	Sweden	Community event	Zenicor	10	1	0	NR	64	NR	NR	NR	NR	NR	NR	NR	NR	irregular rhythm without visible p waves	6	1
Ramkumar et. al. (2017) 60	204	Australia	Community - ≥ 65 yrs with 1 or more risk factor for heart failure	Remon RM-100	60	5	7	70.1	51	29.1	72.1	56.4	5.9	0	0	NR	3	30 sec duration of irregular rhythm with absent p waves	20	9.8
Hendrikx et. al. (2017) 58	201	Sweden	Patients referred to respiratory clinics with suspicion of obstructive sleep apnoea	Zenicor	30	2	14	56	69	30	51	10	9.2	0	4.6	3.1	NR	Irregular supraventricular extra systoles in series for 30 sec	13	6.5
Claes et. al. (2011) 61	10758	Belgium	Community heart rhythm screening program through medical centres	Omron Heartscan 'HCG-801	30	1	0	59	38	NR	30.6	8.6	12.2	7.2	7.2	5.4	1	Irregular RR intervals, absence of p waves and variable atrial cycle length (when visible)	167	1.6
Samol et. al. (2012) 62	132	Germany	Large proportion post stroke/TIA. Also recruited from diabetes, hypertension and dyslipidemia clinics	Omron Heartscan HCG-801	30	1	0	64	58	NR	67	27	NR	0	3	49	NR	Cardiologist Interpretation x 2	7	5.3
Badilpaglia et. al. (2016) 63	855	UK	Community shopping centre screening	MyDiagnostik	15	1	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	7	0.8
Chan et al. (2016) 59	13122	Hong Kong	Nationwide community screening program	Alive Cor	30	1	0	64.7	29	23.7	38.2	14.8	2.2	0	0.7	2.8	NR	Software algorithm definition with minimum of 30 sec	101	0.8
Chan et al. (2017) 65	10735	Hong Kong	Nationwide community screening program	Alive Cor	30	1	0	NR	NR	NR	NR	NR	NR	1.2	NR	NR	NR	Cardiologist interpretation (≥ 30 sec)	74	0.7
Lowcox et. al. (2017) 64	501	UK	Community based with individuals > 65 yrs with CHADS-VASC score ≥ 2	Alive Cor	30	2x per week	365	72.6	48	NR	54	26	14	0	1.0	7.0	3.0	30 second duration of an irregular rhythm without P waves	19	3.8
Gladstone et. al. (2014) 18	277	Canada	Patients admitted with cryptogenic stroke	Holter	continuous	continuous	1	73.2	56	NR	67	19.3	14.7	0	7	12.6	NR	30 second or longer duration of irregular rhythm	9	3.2
Barthelemy et. al. (2003) 19	60	France	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	64.4	55	NR	50	17	NR	0	NR	27	NR	fibrillatory waves associated with irregular ventricular response ratio at leats 30 sec duration	8	13.3

Jabaudon et al. (2004) 20	149	Switzerland	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	66.9	68	NR	58	16.7	16.8	4.7	NR	16.8	NR	NR	7	4.7
Koudstaal et. al. (1986) 21	100	Holland	Retrospective study of 100 patients admitted with stroke/TIA	Holter	continuous	continuous	1	60.9	74	NR	NR	NR	41	NR	NR	NR	NR	NR	5	5
Hornig et. al. (1996) 22	268	Germany	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	59.1	61	NR	43.7	34	NR	NR	14.9	45	NR	NR	10	3.3
Rizos et. al. (2012) 23	496	Germany	Patients admitted with stroke/TIA	Holter	continuous	continuous	1	69	62	NR	78.8	24.6	NR	NR	NR	22.2	3	Cardiologist interpretation (≥ 30 sec)	14	2.8
Kouchert et. al. (1999) 24	82	Germany	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	3	59.7	57	NR	36.5	NR	17.1	NR	NR	NR	NR	Small irregular baseline undulations of variable amplitudes and morphology at a rate >350/min with an irregular ventiruclar response for at leats 1 min.	5	6
Schaer et. al. (2009) 25	241	Switzerland	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	68.7	59	NR	76	25	41	7	NR	4.6	NR	NR	0	0
Sauer et. al. (2004) 26	425	Switzerland	Retrospective review of patients post stroke/TIA with Holter monitoring	Holter	continuous	continuous	1	67.4	61	NR	NR	NR	NR	NR	NR	1.2	NR	Self-terminating sequence of >30 seconds of irregular RR intervals and the presence of fibrillatory P waves.	9	2.1
Shafqat et. al. (2004) 27	465	Pakistan	Retrospective review of consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	66.8	56	NR	NR	NR	NR	NR	NR	NR	NR	NR	5	2.4
Lazzaro et. al. (2012) 28	133	USA	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	63.1	50	NR	70	29.3	18.8	0	NR	2.3	NR	Supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with fibrillatory waves varying in amplitude, shape, and timing, replacing consistent P waves and with a duration >30 sec	8	6
Grond et. al. (2013) 29	1135	Germany	Patients admitted in 7 German centres with stroke/TIA	Holter	continuous	continuous	3	67	55	27.4		20.4	7.3	0	5.8	17.4	NR	≥ 1 period of >30 sec duration of an absolute arrhythmia without detectable P waves and without a pttern more consistent with an alternate diagnosis	49	4.3
Stahrenberg et. al. (2010) 30	224	Germany	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	7	68	58	27.6	72.9	22.3	14.8	0	5.2	16.2	NR	2 x Cardiologist interpretation of software algorithm detection of events	28	12.5
Ritter et. al. (2013) 31	60	Germany	Patients admitted with cryptogenic stroke	Holter	continuous	continuous	7	61.8	57	NR	70	11.7	13.3	NR	0	NR	4	Cardiologist interpretation (> 30 sec)	1	1.7
Higgins et. al. (2013) 32	50	Scotland	Patients admitted with stroke/TIA	Holter	continuous	continuous	7	67.1	48	NR	56	8	16	0	NR	NR	NR	Cardiologist interpretation (> 30 sec)	4	8
Hendrikx et. al. (2014) 67	95	Sweden	Patients investigated for palpitations and presyncope	Holter	continuous	continuous	1	54.1	42	NR	28.4	1.1	8.4	0	0	6.3	1	30 sec irregular rhythm without p waves	2	2.1
Sirkkar et. al. (2014) 33	52	India	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	59.5	77	NR	51.9	23.1	15.4	0	1.7	7.7	NR	30 sec irregular rhythm without p waves	3	5.8
Wachter et. al. (2017) 34	198	Germany	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	73.2	62	NR	80.7	26.4	9.1	0	4.6	21.7	4.8	>30 seconds rhyhtm with irregular RR intervals and the presence of fibrillatory P waves.	9	5
Gumbinger et. al. (2012) 35	192	Germany	Patients admitted with stroke/TIA	Holter	continuous	continuous	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2	1
Alhadramy et. al. (2010) 36	426	Canada	Retrospective review of patients post stroke/TIA with Holter monitoring	Holter	continuous	continuous	1	64.9	48	NR	58.2	14.1	14.1	0	1.6	6.3	NR	Irregular ventricular response in the absence of p-waves or with fibrillatory waves	11	2.5
Stavocinski et. al. (2012) 66	249	Sweden	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	72	57	NR	65	16	20	0	4	25	3	irregular rhythm of minimum 10 sec without visible p waves	5	2
Dangayach et. al. (2011) 37	51	USA	Retrospective audit of patients admitted with cryptogenic stroke	Holter	continuous	continuous	2	58.2	43	NR	35.3	16	15.7	7.4	NR	NR	NR	NR	15	29.4

Gunalp et. al. (2006) 38	26	Turkey	Patients admitted with ischaemic stroke	Holter	continuous	continuous	1	66	69	NR	61	26	31	NR	NR	NR	NR	NR	11	42.3
Fonseca et. al. (2013) 39	80	Portugal	Patients admitted with cryptogenic stroke	Holter	continuous	continuous	1	69.3	53	NR	71.3	28.8	11.3	NR	NR	22.5	NR	NR	17	21
Manina et. al. (2014) 40	114	Italy	Patients admitted with cryptogenic stroke	Holter	continuous	continuous	4	63.1	NR	NR	52.6	9.6	NR	NR	NR	NR	NR	Irregular ventricular response in the absence of p waves or with fibrillatory waves	29	25.4
Tagawa et. al. (2007) 41	308	Japan	Consecutive patients admitted with ischaemic stroke	Holter	continuous	continuous	1	72.6	60	NR	70.1	25.3	NR	20.4	NR	NR	NR	small irregular baseline undulations of variable amplitude and morphology at a rate of 300-350/min associated with irregular ventricular response	26	8.4
Shibazaki et. al. (2012) 42	536	Japan	Consecutive patients admitted with ischaemic stroke	Holter	continuous	continuous	1	72.4	64	NR	65.9	25.7	9.8	NR	0.3	NR	NR	NR	12	2.2
Vandebroucke et. al. (2004) 43	136	Belgium	Retrospective audit of patients admitted with ischaemic stroke	Holter	continuous	continuous	1	68	52	NR	NR	NR	NR	NR	NR	NR	NR	NR	7	5.1
Yokogawa et. al. (2013) 44	68	Japan	Consecutive patients admitted with ischaemic stroke	Holter	continuous	continuous	1	69.9	54	NR	66.2	14.7	NR	NR	NR	NR	NR	irregular and uncoordinated atrial electrical activity on surface ECG lasting > 30 sec	17	25
Atmuri et. al. (2012) 45	140	Australia	Retrospective audit of patients admitted with ischaemic stroke/TIA	Holter	continuous	continuous	1	NR	NR	NR	65	20	37.1	18.6	NR	NR	NR	NR	12	8.6
Salvatori et. al. (2015) 46	274	Italy	Cohort study of patients ≥ 65 yrs with hypertension in multiple GP clinics	Holter	continuous	continuous	2	70	54	NR	100	15	9	7	4	2.2	NR	Cardiologist interpretation	4	1.5
Beaulieu-Boire et. al. (2013) 47	284	Canada	Consecutive patients admitted with stroke/TIA	Holter	continuous	continuous	1	70.6	52	NR	68.7	26.7	27.4	NR	2.2	22.3	NR	Cardiologist interpretation	18	6.3
Dogan et. al. (2011) 48	400	Turkey	Retrospective review of patients admitted post stroke	Holter	continuous	continuous	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	40	10
Gruen et. al. (2008) 49	126	Canada	Retrospective review of patients admitted post stroke	Holter	continuous	continuous	1	NR	NR	NR	NR	NR	NR	7	NR	NR	NR	NR	9	7.1
Suissa et. al. (2012) 50	354	France	Consecutive patients admitted with ischaemic stroke	Holter	continuous	continuous	1	62.4	57	NR	51.1	18.6	NR	0	NR	NR	NR	Cardiologist interpretation	2	0.6
Wachtlhahrt et. al. (2013) 51	224	Germany	Patients admitted with ischaemic stroke	Holter	continuous	continuous	7	68.5	59	NR	73.2	22.3	15.2	NR	5.4	24.1	NR	>30 second irregular rhythm	29	12.9

AF – Atrial Fibrillation BMI – Body Mass Index (kg/m^2) DM – Diabetes Mellitus HF – Heart Failure HTN - Hypertension IHD – Ischaemic Heart Disease

Table 1 – Summary of included trials investigating AF detection using single lead ECG devices or Holter Monitoring

Overall AF detection. The combined AF detection rate using single lead ECG monitoring (n=117,436 from 18 studies) was 1.7% (95% CI 1.4% – 2.1%). The cumulative AF detection rate using continuous (Holter) monitoring (n=8498 from 36 studies) was 5.5% (95% CI 4.4% – 6.6%). There was significant heterogeneity between studies (I^2 = 94% for single lead ECG monitoring, 87% for Holter monitoring). The overall new AF detection rate is presented in Figure 2.

Comparison of multiple intermittent monitoring to 24 hour Holter. There was significant variation in the monitoring time using both single lead and Holter monitoring which contributed to the difference in the cumulative detection rate seen in Figure 2. Figure 3 compares the detection rate of multiple intermittent single lead recordings to 24-hour continuous monitoring, which is used routinely in clinical practice. There were 8 studies (n=10,199, mean weighted age 68.8±8.4 years from 6 studies, 47% male from 8 studies) that performed multiple intermittent single lead ECG recordings and 27 studies (n=6284, mean weighted age 67.8±5.1 years from 23 studies, 58% male from 23 studies) that used 24-hour Holter monitoring. From the data available, the multiple intermittent ECG group had a lower AF risk to the 24-hour Holter group (hypertension – 55% (n=8 studies) vs 65% (n=20 studies), diabetes mellitus – 15% (n=8 studies) vs 22% (n=20 studies), heart failure – 3.3% (n=8 studies) vs 3.9% (n=11 studies), ischemic heart disease – 11% (n=6 studies) vs 19% (n=15 studies) and previous stroke/TIA – 9% (n=7 studies) vs 16% (n=15 studies)) respectively. The combined AF detection rate was 4.8% (95% CI 3.6–6.0%) using multiple intermittent ECG recordings. The cumulative AF detection rate using 24-hour Holter monitoring was 4.6% (95% CI 3.5–5.7%).

Association between monitoring time and AF detection. Using single lead ECG devices, we found a moderate linear relationship between the total monitoring time and AF detection rate (β=0.13, R^2 = 0.42). Using this formula, we noted that approximately 19 minutes of total intermittent monitoring produced similar AF detection to 24-hour continuous monitoring (Figure 4). The study by Halcox et. al. was an outlier, with a much lower AF detection rate than other studies (3.8% from 52 minutes of total monitoring) and this reduced the linear correlation between total monitoring time and AF detection rate [64]. Exclusion of these data led to a stronger linear relationship (β=0.26, R^2 =

0.80) and a much lower total intermittent monitoring time required (12 min) to produce a similar AF detection rate to 24 hour Holter monitoring.

Meta-regression. Sources of heterogeneity in the 18 studies using single lead ECG monitoring were investigated using meta-regression (Table 2). Monitoring time per participant (β=0.11, 95% CI 0.04-0.18, p=0.005) and body mass index (β=1.1, 95% CI 0.58-1.5, p=0.01) were associated with AF detection.

Variable	Number of studies	β (95% C.I)	P value
Age (years)	15	0.00 (-0.22 – 0.24)	0.95
Monitoring time per participant (min)	18	0.11 (0.04 – 0.18)	0.005
Body Mass Index (kg/m^2)	4	1.1 (0.58 – 1.5)	0.01
CHADS Score (%)	11	-0.13 (-2.6 – 2.4)	0.91
Hypertension (%)	14	0.01 (-0.08 – 0.10)	0.75
Previous diagnosis of AF (%)	16	-0.13 (-0.50 – 0.24)	0.46
Ischaemic Heart Disease (%)	12	-0.10 (-0.42 – 0.21)	0.48
Previous stroke (%)	13	0.06 (-0.09 – 0.19)	0.45
Male gender	16	0.10 (-0.04 – 0.24)	0.16

Table 2 – Meta Regression Analysis for AF detection (Single lead ECG studies)

Sensitivity Analysis. A number of outlier studies were observed in the meta-analysis that could influence the cumulative AF detection rate.[37-40 44] Removal of these outlier studies resulted in a reduction in the overall AF detection rate in all Holter studies (table 3) and for 24 hour holter studies (table 4). When these outlier studies were removed the overall AF detection rate for 24 hour Holter was 3.86% (95% C.I 2.88% – 4.83%), much lower than the detection rate by multiple intermittent ECG recordings using portable single lead devices (4.78%, 95% C.I 3.58% – 5.97%). A cumulative meta-analysis (figure 5) did not show any significant variation in the AF detection rate over time using either

Study Omitted	Overall AF detection rate (%)	95% C.I (%)
Dangayach et. al. (2011)	5.27	4.17 – 6.38
Fonseca et. al. (2013)	5.26	4.15 – 6.36
Gunalp et. al. (2006)	5.32	4.21 – 6.42
Manina et. al. (2014)	5.11	4.03 – 6.20
Yadogawa et. al. (2013)	5.25	4.14 – 6.35
All studies excluded	4.31	3.36 – 5.26

Holter or single lead ECG monitoring.

Table 3 – Outlier studies omitted (all Holter studies) to assess the change to the overall AF detection rate

Study Omitted	Overall AF detection rate (%)	95% C.I (%)
Fonseca et. al. (2013)	4.30	3.21 – 5.39
Gunalp et. al. (2006)	4.39	3.30 – 5.47
Yadogawa et. al. (2013)	4.30	3.22 – 5.38
All studies excluded	3.86	2.88 – 4.83

Table 4 – Outlier studies omitted (24 hour Holter) to assess the change to the overall AF detection rate

Publication bias. Publication bias was explored using a funnel plot of all included studies (Supplemental Figure 1). There was significant publication bias in both single lead ECG device and Holter monitoring studies (Egger test, $p=0.003$ and $p<0.001$ respectively).

Quality of studies. A summary of the quality analysis (Supplemental Table 3) showed that overall quality of reporting was moderate. All studies described the primary objective of the trial and included a summary of the main findings. Detailed comorbidities of the study participants were only adequately reported in 28/52 (54%), and limitations were discussed in 35/52 (67%) of studies. Most had a very selective patient population, 31/52 (60%) were post stroke/TIA cohorts.

Discussion

Our study is the only systematic review that we are aware of that has studied the overall AF detection rate of single lead portable ECG devices. The results of our systematic review suggest a

linear relationship between monitoring time per patient and AF detection rate. Single timepoint screening has an approximate 1% AF detection rate which can be increased to around 5% when multiple recordings are performed. We noted that approximately 19 minutes of intermittent monitoring produced similar detection rates to conventional 24 hours continuous Holter monitoring.

Early diagnosis of AF: AF creates a significant burden on both patients as well as the health care system. AF will continue to rise in incidence and the costs to the health care system will continue to increase, due to aging, sedentariness, and the prevalence of obesity and the metabolic syndrome.[3 68] Early diagnosis offers the possibility for early initiation of treatment which may reduce the occurrence of the complications which may lead to reduced hospital admissions and associated health care costs. Early treatment for AF can be achieved in different ways. Patients with subclinical AF have an increased risk of stroke and cardiovascular events, like those with established AF.[12 69] Anticoagulation may help reduce the incidence of stroke in this cohort.

The close relationship between metabolic syndrome and AF has encouraged research into the benefits of lifestyle intervention. Aggressive lifestyle intervention in patients with AF undergoing catheter ablation has been reported to lead to a reduction in symptom burden, improved quality of life and the need for repeat ablation procedures.[10] It remains to be tested whether initiation of lifestyle intervention and aggressive risk factor modification following the early diagnosis of AF may be associated with positive LA remodeling and reduction of disease progression. Such a process may lead to additional health benefits, including reduction in cardiovascular risk and improvement in exercise capacity.

AF screening and feasibility. AF is a leading cause of stroke and heart failure in the community. As well as an association with increased all-cause mortality, it is associated with reduced quality of life. The availability of preventive therapies, including anticoagulation, has led to increasing recognition of the importance of AF screening for early diagnosis. However, AF screening shares the limitations of screening with other diagnostic tests. The screening tool must have high sensitivity, and needs to be inexpensive and cost effective. We also need to minimize and have a method of addressing false positives. Current guidelines recommend opportunistic screening using pulse palpation and 12 lead ECG.[11] In a previous systematic review this was associated with a new AF detection rate of

approximately 1%.[5] Pulse palpation may be non-specific in patients with other irregular rhythms such as ventricular ectopy, and 12 lead ECG is only able to capture a single timepoint for screening. There are multiple other methods for AF detection. Continuous Holter monitoring is probably the most commonly used in clinical practice, especially in stroke cohorts. It has the potential advantage of assessing heart rhythm throughout the day and may be useful in detecting nocturnal subclinical AF. However, the disadvantages include the cost of Holter monitoring (especially for mass screening), the inconvenience of leads and electrodes (which may affect compliance), and typical limitation to 1-2 days of capture (as extended periods are more cumbersome and less cost-effective. Other event recorders are again expensive and limited to symptomatic patients. Extended period monitoring using implantable devices have shown promise in the cryptogenic stroke population (where many have been diagnosed with paroxysmal AF),[70] but they are invasive and not feasible for mass screening.

Portable single lead ECG devices permit multiple 30-60 second recordings to be captured, and downloaded to a computer. These devices have several potential advantages over Holter monitoring. They are leadless and require finger contact (and are hence easy to use and acceptable to patients). They have a high degree of sensitivity for identifying AF.[71-73] Most interface with a web-based cloud system where ECG rhythms can be wirelessly transferred to clinicians, allowing rapid analysis and diagnosis. The development of automated algorithms to detect AF is helpful for mass screening. In two small studies they have demonstrated superior AF detection compared with 24 hour Holter monitoring.[66 67] Although screening using these portable devices are currently not in the latest AF guidelines, they may offer a feasible option for mass screening. Screening using these devices has been demonstrated to be cost effective.[74 75]

We noted a moderate linear association between monitoring time and AF detection rate. Single timepoint screening for 30-60 sec achieved an overall detection rate of approximately 1%. This is no better than what has been reported using pulse palpation or 12 lead ECG, hence does not add any incremental benefit in screening programs [5]. Multiple intermittent recordings improve AF detection; we found that at least 19 minutes of total monitoring should be performed to achieve detection rates similar to 24 Holter monitoring.

The linear relationship between monitoring time and AF detection rate (R^2=0.80) and the reproduction of AF detection rates of 24 hour Holter monitoring with only 12 minutes of intermittent monitoring was possible in our study only after exclusion of an outlier.[64] Despite the inclusion of elderly participants with at least one risk factor for AF, the use of a validated single lead ECG device and a prolonged monitoring period, that study had a lower AF detection rate (3.8%) than the remaining studies, even using a shorter monitoring period.[53 56 57] Relatively low rates of adherence (only approximately 25% completed 2 x 30 second ECG recordings every week for the full year of monitoring) may be a potential explanation for the lower AF detection rate noted.[64]

Limitations: There are several challenges inherent in this meta-analysis of studies investigating AF detection. The most important is the target screening population. Most studies did not report the CHADS or CHA_2DS_2-VASC score, a history of previous stroke, or other co-morbidities. Consequently, it was difficult to ascertain if the risk profiles of patients in these studies were equivalent. Most Holter monitoring studies were performed in the stroke population – which is likely a population with higher AF risk than many studies using portable ECG devices, which recruited mainly healthy participants or those with AF risk factors from the community. The significant heterogeneity amongst both Holter and portable ECG device studies make it difficult to perform direct comparisons between both groups. The type/duration of monitoring and type of device used will also influence the overall AF detection rate and varied significantly between studies. There are several possible confounders which may not have been taken into account. The validity of the linear regression analysis comparing detection time and rate may be limited due to the significant differences in study population, study design and AF definitions. However, despite these limitations, the analysis may provide some important inferences into AF screening. Multiple intermittent ECG recordings achieved a similar AF detection rate to 24 hour Holter monitoring. This may suggest that in a similar cohort of patients with the same comorbidities, single lead intermittent monitoring may be superior for AF detection.

Compared to 24-hour continuous monitoring, single lead portable ECG monitoring is more patient dependent. Good patient compliance is essential to obtain multiple readings across different timepoints which improves sensitivity. The analysis performed does not take into account patient

compliance as this is difficult to assess and poorly reported across the individual studies. Most single lead device manufacturers have proprietary automated AF detection algorithms which were used for diagnosis. Not all of these algorithms have had rigorous testing and comparison to a reference standard. It is also difficult to distinguish AF from other supraventricular tachycardias using single lead ECG devices as the P wave is often not readily discernible. The use of different automated algorithms makes AF definitions non-standardized and can potentially create issues with both over and underdiagnoses.

There are other limitations in this analysis. The efficacy of intermittent monitoring is critically dependent on AF burden and density. All studies varied in their monitoring period and strategy. The linear regression model used was able to determine a total intermittent monitoring time which produced similar AF detection rates to 24-hour continuous monitoring. However, it is difficult to translate the total monitoring time into an effective monitoring strategy. For example, we are unable to determine from our analysis if 12 x 60 second recordings over 12 consecutive days is different to 2 x 60 second recordings daily for 6 consecutive days. The definitions of AF also vary between studies. Many are based on individual physician interpretation and criteria for diagnosis were not explicitly specified. The duration of AF varied from 10-30 seconds between studies, although a cut-off of 30 seconds, was the most widely adopted practice.

Conclusion: Single lead portable ECG devices may offer an efficient screening option for AF compared to 24 hr. Holter monitoring. Total monitoring time is related with AF detection and a total of 19 minutes may achieve a similar detection rate to 24 hour Holter monitoring.

Contributors: SR – Performed the literature search and analysis of individual studies. Involved in the statistical analysis, manuscript preparation and editing. TM – Is guarantor. Developed project idea/rationale. Involved in data analysis and manuscript preparation and editing. NN – Involved in data and statistical analysis as well as manuscript preparation and editing. DD – Performed the literature search and analysis of individual studies. Involved in the manuscript preparation and

editing. DP – Involved in analysis of individual studies and statistical analysis. Involved in manuscript preparation and editing. JK – involved in the project outline, data analysis, manuscript preparation and editing.

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BMJ Group declaration of interests statement

I have read and understood the BMJ Group policy on declaration of interests and declare the following interests: *[list them or state "none"]*.

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Figure Legends

Figure 1 – Overview of inclusion and exclusion of studies based on the PRISMA flowchart

Figure 2 – Forest Plot showing the overall AF detection rate between single lead ECG devices and Holter monitoring

Figure 3 – Forest Plot comparing the AF detection rate between 24 hour Holter monitoring and performing multiple intermittent single lead ECG recordings

Figure 4 – Graph showing the linear relationship between total monitoring time and AF detection rate in single lead ECG devices

Figure 5 – Cumulative Meta-analysis showing minimal variation in AF detection over time using Holter and single lead ECG devices.

Supplementary Figure 1 – Funnel Plots for Holter monitoring and single lead ECG device studies

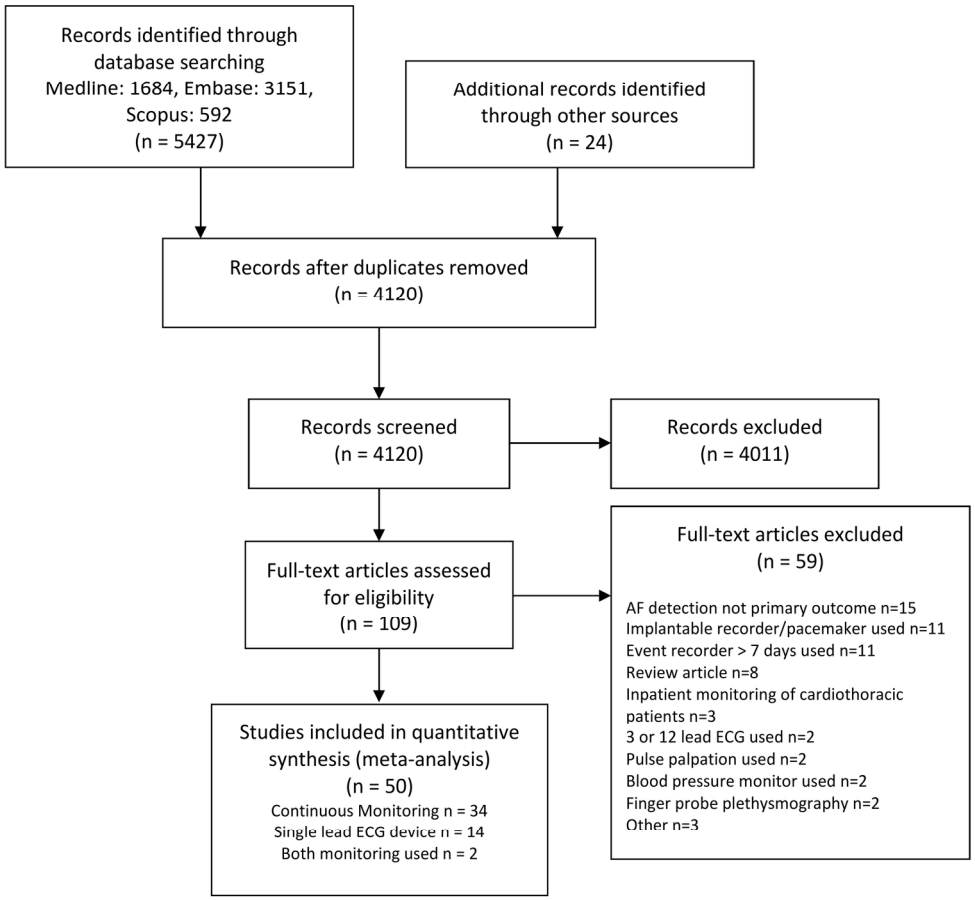

Figure 1

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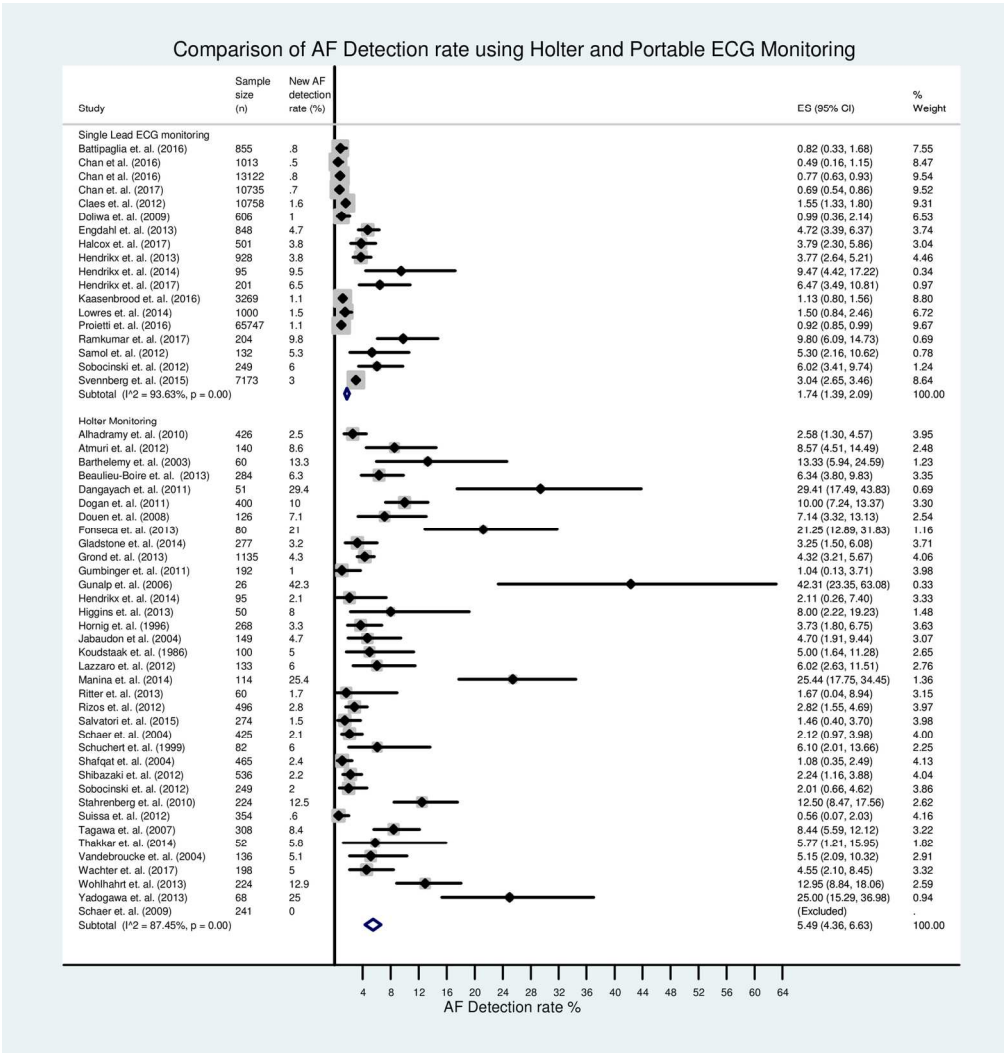

Figure 2

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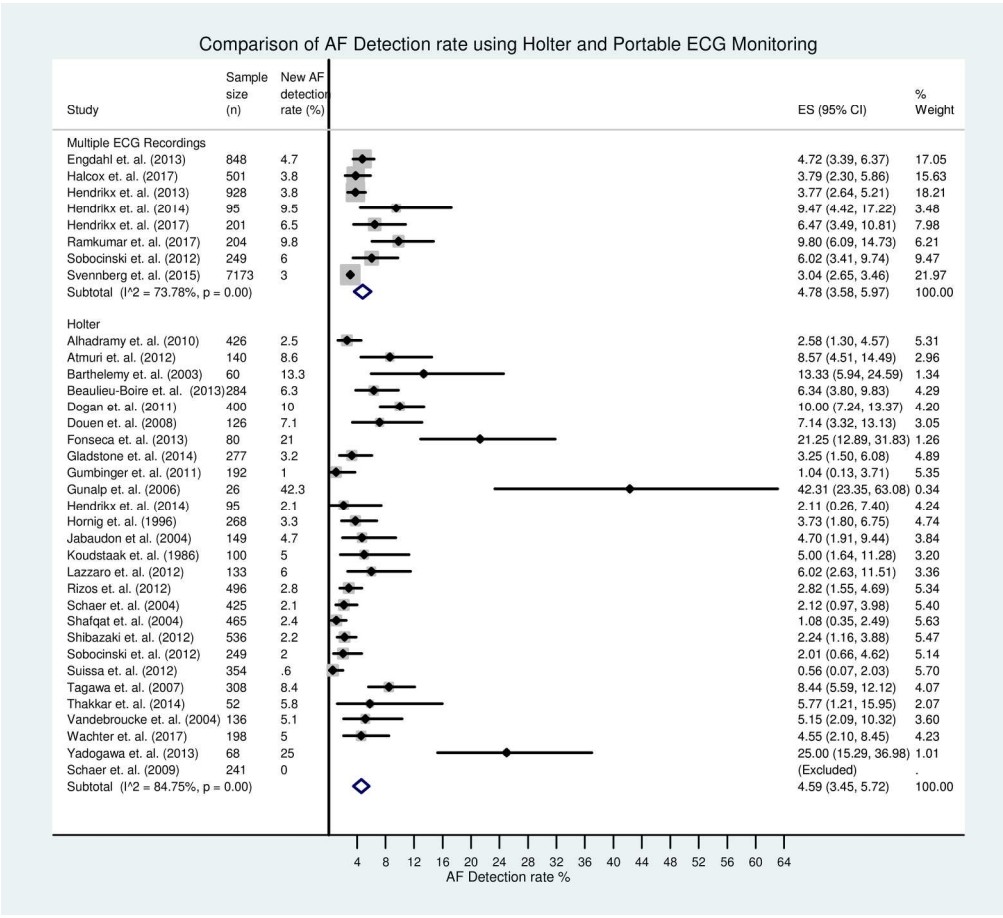

Figure 3

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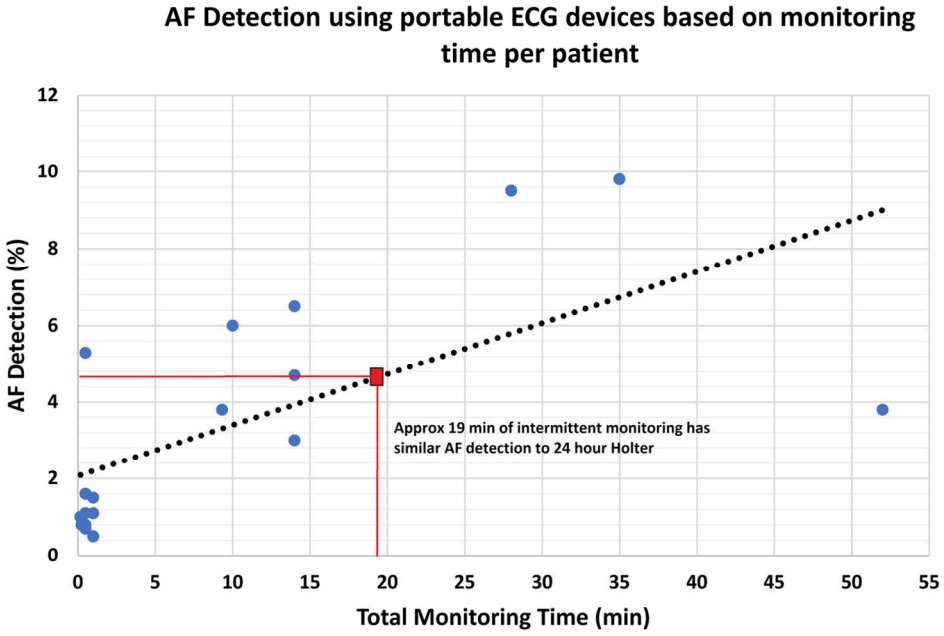

Figure 4

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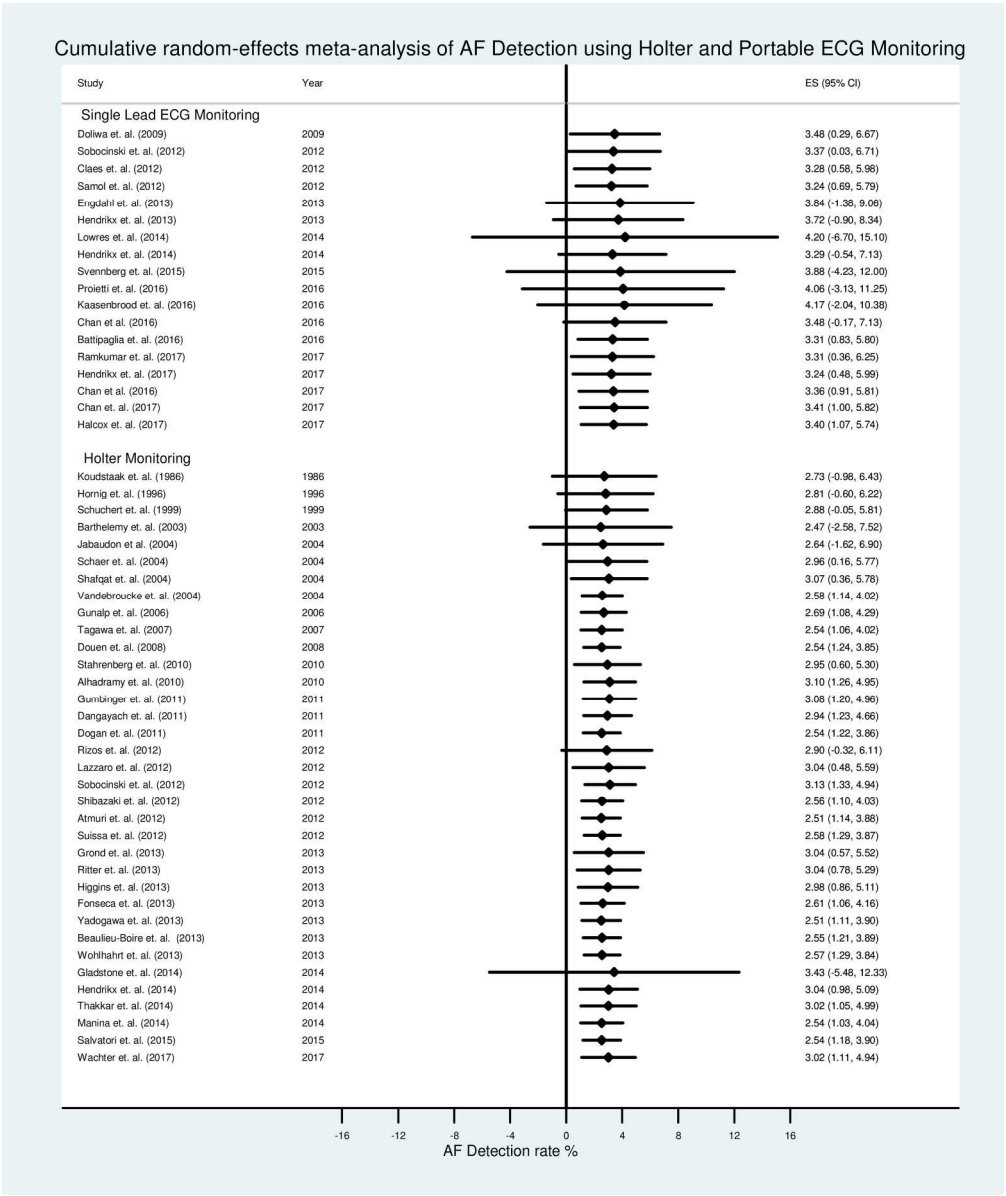

Figure 5

203x241mm (300 x 300 DPI)

Supplementary Table 1.

Database: Ovid MEDLINE

Search Strategy:

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1 exp Atrial Fibrillation/ (46578)

2 atrial fibrillation.tw. (48670)

3 AF.tw. (26772)

4 Mass Screening/ (94291)

5 1 or 2 or 3 (69465)

6 screening.tw. (382365)

7 Monitoring, Ambulatory/ (7308)

8 Electrocardiography/ (185379)

9 Electrocardiography, Ambulatory/ or Arrhythmias, Cardiac/ or Electrocardiography/ (232205)

10 monitoring.tw. (353950)

11 Diagnosis/ (17394)

12 electrocardiography.tw. (11752)

13 ECG.tw. (52917)

14 7 or 8 or 9 or 12 or 13 (258115)

15 4 or 6 or 10 or 11 (769528)

16 5 and 14 and 15 (1684)

Supplementary Table 2.

Author	Year	Reason for exclusion
Barrett et. al.	2014	Primary outcome not AF detection
Bhatt et. al.	2011	28 day event recorder used for AF detection
Kamel et. al.	2013	21 day mobile cardiac outpatient telemetry unit used for AF detection
Miller et. al.	2013	30 day mobile cardiac outpatient telemetry unit used for AF detection
Rabenstein et. al.	2013	21 day mobile cardiac outpatient telemetry unit used for AF detection
Tayal et. al.	2008	21 day mobile cardiac outpatient telemetry unit used for AF detection
Flint et. al.	2012	30 day event recorder used for AF detection
Christensen et. al.	2014	Implantable loop recorder used for AF detection
Cotter et. al.	2013	Implantable loop recorder used for AF detection
Dion et. al.	2010	Implantable loop recorder used for AF detection
Sanna et. al.	2014	Implantable cardiac monitor used for AF detection
Merce et. al.	2013	Implantable loop recorder used for AF detection
Elijovich et. al.	2009	30 day event recorder used for AF detection
Wallmann et. al.	2007	Serial 7 day event recorders used for AF detection
Kral et. al.	2015	Substudy (poster) only investigating patients <40 yrs
Lip et. al.	2016	AF detection not primary objective
Anczykowski et. al.	2016	Trans-telephonic event recorder used for arrhythmia detection
Baturova et. al.	2016	AF detection not primary objective
Yu et. al.	2009	Retrospective review with missing demographic data and AF detection not primary objective
Destaghe et. al.	2016	Primary purpose was assessing test performance of 2 different ECG devices
Lowres et. al.	2016	Post cardiothoracic surgery patients with known episode of AF post-op
Benito et. al.	2015	12 lead ECG used for screening
Bury et. al.	2012	3 lead ECG used for screening
Turakhia et. al.	2015	Wearable patch used for ambulatory monitoring
Tieleman et. al.	2014	AF screening not primary objective
Rabenstein et. al.	2015	Review article
Sposato et. al.	2015	Review article
Schnabel et. al.	2009	Main aim was to develop an AF risk score
Chamberlain et. al.	2011	Main aim was to develop an AF risk score
Lowres et. al.	2013	Review article
de Vito et. al.	2014	AF in post orthopaedic surgery patients with inpatient monitoring
Magee et. al.	2007	Post cardiothoracic surgery patients with inpatient monitoring
Her et. al.	2013	Post cardiothoracic surgery patients with inpatient monitoring
Freedman et. al.	2016	Editorial article
Turakhia et. al.	2016	Review article
Levin et. al.	2015	Cost analysis primary objective
Fitzmaurice et. al.	2007	Pulse palpation used for AF detection
Rhys et. al.	2013	Pulse palpation used for AF detection
Ziegler et. al.	2010	Used implantable devices for AF detection
Akiyama et. al.	2017	Wearable patch used for AF detection
Thom et. al.	2016	Review article
Engdahl et. al.	2017	Trial design paper
Rojo-Martinez et. al.	2013	Implantable cardiac monitor used for AF detection

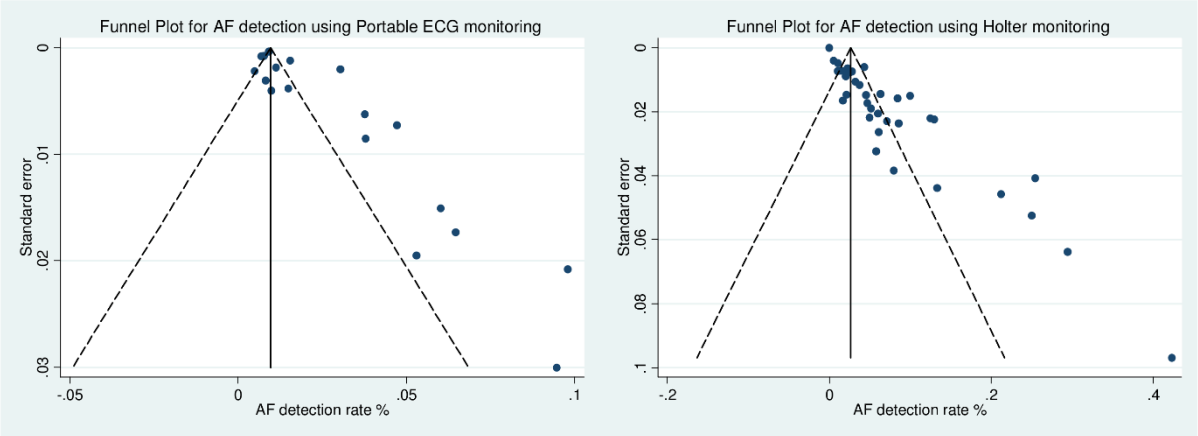
Poisson et. al.	2011	Review article
Etgen et. al.	2013	Implantable cardiac monitor used for AF detection
Marazzi et. al.	2012	Blood Pressure monitor used for AF detection
Wiesel et. al.	2014	Blood Pressure monitor used for AF detection
Lewis et. al.	2011	Finger probe plethysmography used for AF detection
McManus et. al.	2016	Iphone based plethymography used for AF detection
Shanmugam et. al.	2012	Heart failure patients with cardiac resynchronization therapy
Keach et. al.	2015	Review article
Borian et, al.	2014	Implantable devices used for AF detection
Alonso et. al.	2013	Primary aim was to determine clinical score to assess AF risk
Steven et. al.	2016	Trial design paper - wearable sensors for AF detection
Lau et. al.	2013	Primary aim was to determine accuracy of AF algorithm
Gaillard et al.	2010	Transtelephonic monitoring used for AF detection
Orlov et. al.	2007	AF detection based on patients with permanent pacemakers
Martinez et. al.	2014	Primary aim was to determine prognosis of patients with subclinical AF
Wang et al.	2017	Trial design paper

Supplementary Table 3.

Study	Objective and outcome described	Appropriate reporting of comorbidities	Inclusion criteria specified	Incomplete Outcome Data	Efforts to reduce bias	Limitations discussed	External validity of study discussed
Lowres et. al. (2014)	Yes	Yes	Yes	No	No	No	Yes
Svennberg et. al. (2015)	Yes	Yes	Yes	No	No	Yes	Yes
Proietti et. al. (2016)	Yes	Yes	Yes	No	No	Yes	Yes
Kaasenbrood et. al. (2016)	Yes	No	Yes	Yes	No	Yes	No
Engdahl et. al. (2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hendrikx et. al. (2013)	Yes	Yes	Yes	No	No	Yes	Yes
Hendrikx et. al. (2014)	Yes	Yes	Yes	No	No	Yes	Yes
Chan et al. (2016)	Yes	Yes	Yes	Yes	No	No	Yes
Sobocinski et. al. (2012)	Yes	Yes	Yes	No	No	Yes	Yes
Doliwa et. al. (2009)	Yes	No	Yes	No	No	Yes	Yes
Ramkumar et. al. (2017)	Yes	Yes	Yes	No	No	Yes	Yes
Hendrikx et. al. (2017)	Yes	Yes	Yes	No	No	Yes	Yes
Claes et. al. (2011)	Yes	Yes	Yes	Yes	No	Yes	Yes
Samol et. al. (2012)	Yes	Yes	Yes	No	No	Yes	Yes
Battipaglia et. al. (2016)	Yes	No	No	No	Yes	Yes	Yes
Chan et al. (2016)	Yes	Yes	Yes	No	Yes	Yes	Yes
Chan et al. (2017)	Yes	No	Yes	No	No	Yes	Yes
Halcox et. al. (2017)	Yes	Yes	Yes	No	No	Yes	Yes
Gladstone et. al. (2014)	Yes	Yes	Yes	No	Yes	Yes	Yes
Barthelemy et. al. (2003)	Yes	Yes	Yes	No	Yes	No	No
Jabaudon et al. (2004)	Yes	Yes	Yes	No	No	No	Yes
Koudstaal et. al. (1986)	Yes	No	Yes	No	No	No	No
Hornig et. al. (1996)	Yes	No	Yes	No	Yes	No	Yes
Rizos et. al. (2012)	Yes	Yes	Yes	No	Yes	Yes	Yes
Schuchert et. al. (1999)	Yes	No	Yes	No	No	No	No
Schaer et. al. (2009)	Yes	Yes	Yes	No	No	Yes	Yes
Schaer et. al. (2004)	Yes	No	Yes	No	No	Yes	Yes
Shafqat et. al. (2004)	Yes	No	Yes	No	No	No	Yes
Lazzaro et. al. (2012)	Yes	Yes	Yes	No	No	Yes	Yes
Grond et. al. (2013)	Yes	Yes	Yes	Yes	Yes	No	Yes
Stahrenberg et. al. (2010)	Yes	Yes	Yes	Yes	Yes	No	Yes
Ritter et. al. (2013)	Yes	Yes	Yes	No	No	No	Yes
Higgins et. al. (2013)	Yes	No	Yes	No	Yes	Yes	Yes

Thakkar et. al. (2014)	Yes	Yes	Yes	No	Yes	Yes	Yes
Wachter et. al. (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gumbinger et. al. (2012)	Yes	No	Yes	No	Yes	No	Yes
Alhadramy et. al. (2010)	Yes	Yes	Yes	No	Yes	Yes	Yes
Dangayach et. al. (2011)	Yes	Yes	Yes	No	Yes	No	Yes
Gunalp et. al. (2006)	Yes	No	Yes	No	Yes	No	No
Fonseca et. al. (2013)	Yes	Yes	Yes	No	Yes	Yes	Yes
Manina et. al. (2014)	Yes	No	Yes	No	Yes	No	Yes
Tagawa et. al. (2007)	Yes	No	Yes	No	Yes	Yes	Yes
Shibazaki et. al. (2012)	Yes	Yes	Yes	No	Yes	Yes	Yes
Vandebroucke et. al. (2004)	Yes	No	Yes	No	No	Yes	Yes
Yodogawa et. al. (2013)	Yes	No	Yes	No	Yes	Yes	Yes
Atmuri et. al. (2012)	Yes	No	Yes	No	No	Yes	Yes
Salvatori et. al. (2015)	Yes	Yes	Yes	No	Yes	No	Yes
Beaulieu-Boire et. al. (2013)	Yes	Yes	Yes	No	Yes	Yes	Yes
Dogan et. al. (2011)	Yes	No	Yes	No	No	Yes	No
Douen et. al. (2008)	Yes	No	Yes	No	Yes	No	No
Suissa et. al. (2012)	Yes	No	Yes	No	Yes	Yes	Yes
Wohlhahrt et. al. (2013)	Yes	Yes	Yes	No	Yes	Yes	Yes

Supplementary Figure 1.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5/6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6-11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11/12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11/12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11/12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16/17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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