Ideal study

Population:	People who have not sought medical attention on account of symptoms associated with AF
Presentation:	Asymptomatic/not sought medical attention on account of symptoms associated with AF presenting to primary care or the community (for example community pharmacists). Individuals may be invited to screening regardless of medical history (this may be done on the basis of age, systematic screening); present to the GP for an unrelated issues (for example flu vaccination, opportunistic screening); or based on their medical history/the presence of risk factors that are associated with AF (targeted screening)
Prior tests:	No prior testing for AF
Index test:	Any non-invasive test that could be utilised in a primary care setting or the community
Purpose:	Screening test, to identify people with AF who have not sought medical attention on account of symptoms associated with AF
Target disorder:	AF
Reference standard:	12-lead ECG interpreted by a cardiologist

The 'ideal' study for AF screening tests

Low risk of bias

- A consecutive or random sample of people was enrolled
- A case-control design was avoided
- Inappropriate exclusions were avoided (for example the presence of a different condition that may cause arrhythmia for example atrial flutter, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, heart block, tachy-brady syndrome)
- The index test was objective or was interpreted without knowledge of the reference standard.
- The reference standard was a gold standard diagnostic technique (12-lead ECG interpreted by a cardiologist)

- The reference standard was objective or was interpreted without the knowledge of the index test.
- All index tests and the reference standard were performed concurrently.
- If cut-offs were used these were pre-specified.
- All participants received all tests and the reference standard.
- There were no unclear/uninterpretable test results.
- All participants were included in the analysis

High applicability

- The population is asymptomatic/has not sought medical attention on account of symptoms associated with AF. The population has undergone no prior testing for AF.
- The population was recruited into the screening study based on:
    - No criteria or age ('ideal' for systematic screening)
    - Presentation to the GP/other setting for an issue unrelated to AF ('ideal' for opportunistic screening)
    - Medical history/presence of risk factors associated with AF ('ideal' for targeted screening)
- The test is performed and interpreted in primary care or the community.
- The reference standard is the gold standard diagnostic technique (12-lead ECG interpreted by a cardiologist)

QUADAS-2

Domain 1: Patient selection

Risk of Bias: Could the selection of patients have introduced bias?

Describe the method of patient selection

Signalling question 1: Was a consecutive or random sample of patients enrolled?

Yes/No/Unclear

Yes If a consecutive or random samples of patients was enrolled.

Signalling question 2: Was a case control-design avoided?

Yes/No/Unclear

Yes If the study did not use a two-gate entry procedure (i.e did not include any patients on the basis of having diagnosed AF)

Signalling question 3: Did the study avoid inappropriate exclusions?

Yes/No/Unclear

Yes If inappropriate exclusions were avoided (for example excluding based on the presence of a different condition that may cause arrhythmia for example atrial flutter, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, heart block, tachy-brady syndrome)

Appropriate exclusions: diagnosed AF; patients with paced rhythms/pacemakers/defibrillators/other cardiac devices; severe medical condition preventing participation (e.g. severe dementia or terminal illness); age

Unclear If exclusions are not detailed

Conclusion: Could the selection of patients have introduced bias?

High/Low/Unclear

(If the response to all the signalling questions is 'yes' the study can be considered at a low risk of bias; if the response to question 2 is 'no' (i.e. a case-control design was used) then it will be judged that the study is at high risk of bias)

Applicability: Are there concerns that the included patients and setting do not match the review question?

Describe included patients (prior testing, presentation, intended use of index test and setting)

Signalling question 1: Was the population asymptomatic/had not sought medical attention on account of symptoms associated with AF?

Yes/No/Unclear

Signalling question 2: Was the population recruited from primary care/the community?

Yes/No/Unclear

Signalling question 3: Was inclusion into the study independent of the results of prior testing that could be used to detect AF?

Yes/No/Unclear

Type of screening programme question:

Was the population recruited based on:

- No criteria or age (systematic screening)

- Presentation to the GP/other setting for an issue unrelated to AF (opportunistic screening)
- Medical history/presence of risk factors associated with AF (targeted screening). NB GRASP-AF score includes items for congestive heart failure, hypertension, age≥75, diabetes mellitus, prior stroke/TIA/thromboembolism and vascular disease.
- Other

Signalling question 4: Was the population representative of the population that would be expected to be tested by systematic screening, opportunistic screening or targeted screening?

Yes/No/Unclear

Conclusion: **Are there concerns that the included patients and setting do not match the review question?**

High/Low/Unclear

(If the response to all the signalling questions is 'yes' then concerns over applicability are low. If the population was not recruited from primary care/the community then applicability concerns are high)

Domain 2: Index test

Risk of Bias: Could the conduct or interpretation of the index test have introduced bias?

Describe the index test and how it was conducted and interpreted:

Signalling question 1: Were the index test results interpreted without knowledge of the results of the reference standard?

Yes/No/Unclear

Yes If the index test was always conducted and interpreted before the reference standard, or
If the index test was objective, or
If the interpreters of the index test were blinded to the results of the reference standard.

Signalling question 2: If a threshold was used, was it pre-specified?

Yes/No/Unclear/NA

Yes If threshold used were pre-specified, and were not defined post-hoc based on study data.

Signalling question 3: Did the person interpreting the index test have access to information or training that would not be available if the test was to be performed in the community/in primary care?

Conclusion: Could the conduct or interpretation of the index test have introduced bias?

Yes/No/Unclear

(If the response to all the signalling questions is 'yes' the study can be considered at a low risk of bias. If the threshold was not pre-specified then the risk of bias is high)

Applicability: Are there concerns that the index test, its conduct, or its interpretation differ from the review question?

Signalling question 1: Was the index test performed in primary care or the community?

Yes/No/Unclear

Signalling question 2: Was the index test interpreted in primary care, in the community, or using an automated method?

Yes/No/Unclear

Signalling question 3: Was the index test performed and interpreted without the person performing and interpreting the test having to undergo special training?

Signalling question 4: Were the same clinical data available when the test was interpreted as would be available when the test was used in practice?

Yes If interpreters had accesses to the same clinical data as when the test would be interpreted in practice. NB studies that blinded interpreters to clinical data are still of high applicability because it may be that GP notes and medical records are not available in a screening setting.

Conclusion: Are there concerns that the index test, its conduct, or its interpretation differ from the review question?

High/Low/Unclear

(If the response to all the signalling questions is 'yes' then concerns over applicability are low. If the index test was interpreted by a cardiologist/someone in secondary care then the concerns about applicability are high.)

Domain 3: Reference standard

Risk of Bias: Could the reference standard, its conduct or its interpretation have introduced bias?

Describe the reference standard and how it was conducted and interpreted

Signalling question 1: Is the reference standard likely to correctly classify AF

Yes If 12-lead ECG interpreted by a cardiologist

Signalling question 2: Were the reference standard results interpreted without knowledge of the results of the index test?

Yes/No/Unclear

Yes If the reference standard was always conducted and interpreted before the reference standard or if the reference standard was objective or if the interpreters of the reference standard were blinded to the results of the index test.

Conclusion: Could the conduct or interpretation of the reference test have introduced bias?

High/Low/Unclear

(If the response to all the signalling questions is 'yes' the study can be considered at a low risk of bias.)

Applicability: Are there concerns that the target condition as defined by the reference standard does not match the condition?

Conclusion: Are there concerns that the target condition as defined by the reference standard does not match the condition?

High/Low/Unclear

(Low if 12-lead ECG interpreted by a cardiologist)

Domain 4: Flow and timing

Risk of Bias: Could the patient flow have introduced bias?

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)

Describe the time interval and any interventions between index test(s) and reference standard

Signalling question 1: Were the index test and reference standard performed within 7 days of each other?

Yes/No/Unclear

Signalling question 2: Did all patients receive the same reference standard?

Yes/No/Unclear

Yes If all patients received the same reference standard

Signalling question 3: Were ≥80% of patients included in the analysis?

Yes/No/Unclear

Yes If <20% of participants were excluded due to missing/un-interpretable tests?

Conclusion: **Could the patient flow have introduced bias?**

High/Low/Unclear

(If the response to all the signalling questions is 'yes' the study can be considered at a low risk of bias)