

AF-SCREEN International Collaboration Steering Committee Response to USPSTF review and recommendations

General Comments

The USPSTF has given an “I” recommendation on whether ECG screening for Atrial Fibrillation (AF) should be recommended, the meaning of which is the following: *“The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined”*

This collective response to the USPSTF draft recommendation statement and the underpinning Evidence Synthesis # 164, is being submitted by Ben Freedman (Sydney, Australia), John Camm (London, UK), Hugh Calkins (Baltimore USA), Jeff Healey (Hamilton, Canada), Mårten Rosenqvist (Stockholm, Sweden), Renate Schnabel (Hamburg, Germany), and Jiguang Wang (Shanghai, China). Together, we constitute the steering committee of AF-SCREEN International Collaboration (<http://www.afscreen.org/steering-committee/>).

AF-SCREEN International Collaboration position

Our organisation was formed in 2015, with the stated aim: “to promote discussion and research about screening for unknown or under-treated atrial fibrillation as a way to reduce stroke and death,” (<http://www.afscreen.org/>). Our group now has 147 members from 33 countries, encompassing a broad range of health professionals and academics including not only cardiologists and cardiac electrophysiologists, but also neurologists, geriatricians, epidemiologists, health economists, general and primary care physicians, nurses, pharmacists, physiotherapists, and patient advocates. There are 21 US members of AF-SCREEN including Hugh Calkins (Johns Hopkins University) who is a member of the steering committee.

In May 2017, our group published a white paper on screening for AF in the journal *Circulation*¹. Key point #6 which received 97% agreement (102/105 online anonymous votes) of the members at the time stated that: “There is a need to perform large randomized controlled studies using hard end points (including stroke, systemic embolism, and death), of strategies for screening, to strengthen the evidence base to inform guidelines and national systematic screening strategies.” The concluding words of the abstract stated that: “Based on current knowledge, this white paper provides a strong case for AF screening now while recognizing that large randomized outcomes studies would be helpful to strengthen the evidence base.”

Thus, AF-SCREEN International Collaboration would be in agreement with the USPSTF that there are significant research needs and gaps required to inform national organisations such as the USPSTF on systematic screening with ECG. **However, the steering committee (and indeed our membership) believe there is sufficient evidence to recommend opportunistic screening/case finding for AF now. This is a point of departure from the conclusions of the draft recommendation statement of the USPSTF.** Sixty of our members collectively drafted the manuscript, examined the totality of the evidence, not just RCTs, and through a Delphi process (white paper online supplement)¹ developed key points/recommendations that were voted on by all the membership at the time, requiring >85% agreement for consensus

in an anonymous online vote. The relevant key points #1 and 2 as published, state the following:

Key Point 1

Screen-detected AF as found on single-timepoint screening or intermittent 30-second (ECG) recordings over 2 weeks is not a benign condition and, with additional stroke risk factors, carries sufficient risk of stroke to justify consideration of screening and therapy to prevent stroke. (103/105, 98% agreed)

Key Point 2

Single-timepoint screening of people ≥ 65 years of age in the clinic or community appears justified based on yield of screening and likely cost-effectiveness. For those >75 years of age or in younger age groups at high risk of AF or stroke, 2 weeks of twice-daily intermittent AF screening may be warranted. (97/104, 93% agreed 1st sentence; 89/104, 86% agreed, 2nd sentence).

1. Data other than RCTs

While we agree that the evidence from RCTs on ‘whether systematic screening for AF with ECG results in more good than harm’ is lacking (KQ1, also encompassing answers to KQs 2-5), this is because such studies have not been done or concluded. Although this is recognised in the review and recommendations, and is well known to researchers working in this area, the review has paid insufficient attention to other relevant data of a lesser nature or quality. We feel this approach to available data is not helpful in placing the recommendation and its implications in context. It will also result in an underestimate of the potential preventable burden, which a screening program would aim to achieve. This reduces the likelihood for strong advocacy from the USPSTF to fill the research needs and gaps, or for recommendation of opportunistic screening/case finding.

It was well known to those who have followed the literature in this field that there were no RCT studies that directly answered KQs 1, 4, and 5, and consequently, the Task Force report and evidence summary could have been very brief. The USPSTF systematic review has confirmed the absence of such studies. The Task Force instead chose to perform another systematic review and meta-analysis on whether anticoagulants are worthwhile in clinical rather than screen-detected AF, i.e. benefits and harms of OACs and antiplatelets, although this has been well examined previously in a number of published reviews and meta-analyses, and in guidelines including AHA/ACC/HRS, ESC, ACCP, NICE, with essentially similar findings. However, as pointed out below (Point #2), the methodology used for a re-analysis of the benefits and harms of treatment has a major conceptual flaw.

2. Exclusion of patients for KQ 4 and 5: *“For KQs on benefits (KQ 4) and harms (KQ 5) of treatment, we excluded studies of adults with known heart disease, heart failure, and/or previous stroke or TIA.”*(page 6 Evidence Synthesis, number 164). This has been done in the belief that such disease is already known to the responsible clinician and is therefore under surveillance, and should not be included in population screening. Regrettably, patients with these disorders are more likely to develop AF², which is often silent and therefore goes undetected despite surveillance. Moreover, such patients are at higher risk of stroke should

they develop AF according to the CHA₂DS₂VASc scoring system. Although it may be a purist approach to exclude patients with known disease from systematic screening, such exclusions do not make sense from the perspective of the main rationale for population screening for AF - i.e. stroke prevention in people with unknown, silent AF. Not only do the patients who have been excluded have a greater likelihood of developing incident AF, their risk of stroke is significantly greater than people without these co-morbidities (all contribute independently to risk of stroke in the CHA₂DS₂VASc score). Pulse taking, auscultation and electrocardiography are not done routinely at follow-up visits for patients with known co-morbidities, so asymptomatic AF will not be detected. If the same flawed logic to exclude patients with co-morbidity was followed further, it should also be applied to patients with diabetes and hypertension. Again, this is clearly incorrect, as patients with both these common co-morbidities also have a higher incidence of AF, and a higher risk of stroke with AF, because of the co-morbidity. Any population systematic screening by invitation from electoral rolls for example, would not seek to exclude patients with any of these conditions or co-morbidities, as they are precisely the people in the population that screening should include. This exclusion from the analysis of KQ 4 and 5 is therefore unnecessary, and would not be sensible for any implementation of population screening.

As further evidence of the conceptual flaw, a study presented at the AHA Nov 2017 scientific sessions (Lowres N et al, Abstract 20082: Guideline-based Screening for Atrial Fibrillation: Analysis of Yield and Stroke Risk. *Circulation*. 2017;136 (Suppl 1):A20082), contained the largest meta-analysis of screening, with 61,212 people aged ≥ 65 years screened in either clinics or community settings in the past 10 years included (poster available on request). The analysis included 1,058 people found with new AF, a detection rate of 1.7%. More than two thirds had a CHA₂DS₂VASc score greater than that from age alone, indicating presence of co-morbidity. In the 899 subjects with new AF and an available CHA₂DS₂VASc score, 617 (69%) had at least 1 co-morbidity, and 34% had 2 or more co-morbidities (manuscript in preparation, unpublished analysis, data can be provided upon request). Applying an exclusion based on co-morbidities for population screening would therefore exclude the majority of patients who would be at highest risk of developing AF, and also at highest risk of stroke. The STROKESTOP study (Svennberg et al³) lists the baseline characteristics including comorbidities in those with new population-based systematic screening-detected AF. There were 2.8% with CHF, 52% hypertension, 13.3% diabetes, 9.6% prior stroke, and 14.3% vascular disease. In the screening study of Sandhu et al⁴, 7% had CHF, 66% hypertension, 24% diabetes, 10% prior stroke, and 14% vascular disease. Thus medical surveillance of such patients with known cardiovascular disease comorbidities is clearly not detecting unknown asymptomatic AF, and it would make no sense to exclude such people with the highest risk of development of AF and the highest risk of stroke, from either systematic or opportunistic screening.

3. Extrapolation of benefits and harms from clinical AF: We agree that extrapolation of benefits and harms of oral anticoagulant (OAC) and antiplatelet therapy for clinical AF, to screen-detected AF, as implied by the USPSTF review, is likely to be valid. Justification for this, however, requires knowledge of the prognosis of screen-detected AF, both in absolute terms, and relative to prognosis of clinical AF. It also requires knowledge of the effect of treatment in such patients. To determine the prognosis of screen-detected AF and its response to treatment would require an observational study of screen-detected AF which

did not permit treatment, and/or an RCT in screen-detected AF comparing OAC therapy with placebo. Such studies would be considered to be unethical by most physicians, and therefore have not been done and will not be done in the future.

The best approximation of the prognosis of screen-detected AF is to examine the outcomes in cohort studies of patients with AF detected incidentally in the absence of symptoms. This seems accepted by the USPSTF, and has been partly examined in appendix A contextual question 2. However, just after the cut-off date for the USPSTF review, two very large cohort studies^{5 6} were published in abstract form in EHJ and presented at ESC in August 2016 . These compared patients who were asymptomatic at AF presentation, with those experiencing symptoms, and in one study⁵, those with AF diagnosed in association with a hospital admission with either a primary or secondary AF discharge diagnosis. Copies of the posters of those presentations from the large Garfield registry (Gibbs et al)⁶, and from the same primary care cohort study already reviewed in Appendix A (Martinez et al)^{5 7 8} could be provided to the USPSTF. Both show comparable if not worse prognosis regarding stroke, after adjustment, than those who were symptomatic at presentation. This adverse and similar prognosis of incidentally detected asymptomatic AF needs much greater emphasis in the report, as it could profoundly alter the interpretation of much of the report (see Analogy with screening for hypertension, point #4 and point #7).

4. Analogy with USPSTF recommendation on screening for hypertension: The USPSTF has had a grade A recommendation to screen for hypertension since 1996. The recommendation was reaffirmed in 2003, and again in 2007 and 2015. For the 2003 affirmation, the publication stated *“Hypertension can be effectively detected through office measurement of blood pressure. Treatment of elevated blood pressure in adults can reduce cardiovascular events. The magnitude of risk reduction depends on the degree of hypertension and the presence of other cardiovascular risk factors. Available studies have found no important adverse effects on psychological well-being and mixed effects on the absenteeism rates of adults who are screened and labeled as being hypertensive.”*

The conclusion of the abstract stated:

“Substantial indirect evidence supports the effectiveness of screening adults to detect hypertension and treating them to reduce cardiovascular disease.”

Thus the recommendations were not based on RCTs of screening but substantial indirect evidence.

a). For hypertension, there were no RCTs of screening to show that systematic population screening for hypertension resulted in net benefit over harm compared to a policy of not screening. This was the case in 1996, 2003 and 2007, and yet a grade A recommendation for screening was made because of the “substantial indirect evidence,” which the USPSTF does not use in its recommendation on screening for AF. If the indirect evidence available were taken into full consideration, this would result in the same recommendation as for hypertension – i.e. a class A recommendation for opportunistic screening/case finding. One community screening RCT was found in the 2015 guideline update, however, this guideline update focussed on measurement of blood pressure – office vs home or ambulatory BP.

b). In AF, like hypertension (for which measurement of blood pressure is both the screening test and the diagnostic test), the screening test using either 12-lead ECG or a single lead

rhythm strip from a handheld device, is at the same time, the diagnostic test which confirms the diagnosis of AF. Unlike screening tests for many cancers, no further test other than ECG is required to establish the diagnosis. The use of single lead AF screening, moreover, is less subjective than BP measurement, which requires having the patient relax, sitting in a chair (feet on floor, back supported) for >5min, avoid caffeine, exercise, and smoking for at least 30 min before measurement, ensuring his/her bladder is empty, and neither the patient nor the observer should talk during the rest period or during the measurement (2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline on High Blood Pressure).

c). In hypertension there are few if any specific symptoms (unless there is malignant hypertension), so screen-detected hypertension is assumed to have the same prognosis as hypertension in general. In AF, both specific and non-specific symptoms do occur, but especially in the elderly (those over age 65, with the highest stroke risk), asymptomatic unknown AF is common as shown in the systematic review. There is considerable and increasing evidence, some available only after the review had been undertaken, to show that the prognosis of incidentally detected asymptomatic AF (analogous to hypertension detected by screening/opportunistic case finding or by opportunistic screening/case finding for AF), has at least as bad a prognosis as symptomatic AF with regards to stroke and mortality, and therefore should be regarded similarly (see point #3 above).

d). Treatment of hypertension is significantly less effective than anticoagulant treatment of AF with elevated CHADS₂ or CHA₂DS₂VASc scores. VKA therapy reduces stroke risk by 0.64, and all-cause mortality by 0.26⁹, with NOAC reducing all cause mortality further¹⁰, balanced by an acceptable risk of major bleeding. It is most unusual for any screening test for a condition to result in therapy that could decrease all-cause mortality, as well as having a large effect on prevention of stroke. Thus all major guidelines have a uniform recommendation for OAC treatment for AF.

5. Evidence of harm from screening: There are scant data of psychological harm of screening from the SAFE study, as most of the comparisons (negative) were between the systematic screening and the opportunistic arms. The only data comparing a small number of screen negative and screen positive patients was done at 17 months, when an AF diagnosis had been present in the screen positives for over one and a half years, and many were appropriately on warfarin therapy. A difference in anxiety at that time point would be anticipated, and has never been a reason to withhold therapy or not inform patients of an AF diagnosis requiring therapy. Qualitative studies show excellent patient acceptance of ECG screening.^{11 12 13 14} The psychological effects are minimised by the fact the ECG is both the screening test and the diagnostic test. No tests other than ECG and its interpretation are required, so the result is available almost immediately. For any false positive ECG diagnoses, the worst additional test required for diagnosis is another ECG, so any such cases can very quickly be discovered and the patient reassured. Any other tests form a routine part of the therapeutic work up of the condition, required in all patients with AF, rather than as fall-out from the diagnostic test. The harms of treatment (primarily bleeding from anticoagulation) are those that are well established for AF treatment as being outweighed by the benefits of reduced stroke, death and MI, hence the positive therapeutic recommendations in all published guidelines.

6. Timing of final recommendation and results in relation to STROKESTOP study results

(p4): The USPSTF has mentioned that there are some ongoing RCTs of ECG screening for AF, and included mention of the STROKESTOP study, but with only brief details provided. The results of this study including 5 years of follow-up have been brought forward as compared to the NCT listing and are planned to be available for the ESC Scientific Congress in August 2018, not in 2019 as listed in the USPSTF recommendation and the NCT listing. As this is the largest RCT of screening for AF with hard outcomes (stroke, death, bleeding), positive findings might completely change the USPSTF recommendations within 6 months of their release. Indeed, in the long-term follow-up of the STROKESTOP pilot study (in press in *Europace*, accepted Jan 11th 2018), there was a significant difference in stroke rate between the intervention area and an adjacent non-intervention control area (non-randomised). An important finding from the pilot, was that in those with paroxysmal asymptomatic AF detected in the study, the majority were still paroxysmal and asymptomatic at 5 year follow-up, making it unlikely that usual care would pick up most patients with time.

7. Effectiveness of early detection and treatment (p5): *“The USPSTF did not find any trials of treatment of asymptomatic, screen-detected participants.”* It is correct, that there are no RCTs on this question. Similarly, as noted above, there are no observational data of deliberately untreated screen-detected AF, so the USPSTF did examine 4 cohort studies of incidentally-detected asymptomatic AF. However, the USPSTF failed to note that one cohort study examined the response to treatment of incidentally detected asymptomatic AF. In this UK primary care cohort study (Martinez et al 2014,⁷ and Freedman et al 2016⁸), the adjusted outcomes of patients on OAC treatment were compared with patients who did not receive antithrombotic treatment, and also to age and gender matched patients in the same practices without AF. The outcomes of treatment vs no treatment were similar to the outcomes seen in the RCTs of clinical AF. This part of the study analysis was also not mentioned in the potential benefits and harms section (point #3) nor was it listed in the appendix of the review, but it is the only study germane to KQs 4 and 5 and therefore informs the potential benefits and harms which may be seen if screening was undertaken as in KQ1.

8. Detection: Systematic screening vs opportunistic screening = opportunistic case finding.

There were only 2 RCTs found in the systematic review, and the USPSTF concluded that there was insufficient evidence to assess whether systematic screening with ECG detected more AF than usual care. However, in the SAFE study, the only trial that examined it, “screening” for AF detected more cases than usual care. The results of systematic screening with ECG were essentially identical to “opportunistic screening” (pulse palpation followed by ECG if irregular), and both detected significantly more AF cases than usual care, therefore the USPSTF statement is incorrect.

Because systematic screening detected no more cases than opportunistic case finding, called “opportunistic screening” in the study, and variably the same terminology in the task force report, an erroneous conclusion was reached that opportunistic screening/case finding could be equated with usual care. This may be because the intervention included pulse taking which can be considered part of usual care, and the pulse was taken by health professionals before an ECG was performed in the intervention. We agree that pulse taking (or auscultation) can be performed during a routine clinical visit. However, the SAFE intervention is not the same as usual care, as anecdotally, the pulse is infrequently

examined in usual care. The USPSTF does state on p2 that *“few data are available on the current prevalence of screening for atrial fibrillation with ECG or simpler methods, such as pulse palpation or heart auscultation, in the United States”* (presumably referring to opportunistic screening or case-finding). While heart rate is often entered in the eMR, in primary care, this is most frequently taken from the automated reading on a sphygmomanometer, rather than by pulse palpation, and does not detect AF *per se*. Opportunistic screening as in the SAFE study was an active process within the trial requiring an intervention - flagging those patients requiring pulse taking followed by ECG if irregular. The general practices in the active study knew they were part of an intervention to perform opportunistic screening. Regrettably, this is not the same as usual care, nor was the outcome of finding new AF cases in the usual care practices the same as in the “opportunistic screening” practices. This erroneous conflation of the **active** pulse palpation process followed in the SAFE intervention, with usual care, is also demonstrated in the preamble (page 3, evidence synthesis #164): *“Health care professionals, including medical assistants, nurses, and physicians, routinely perform pulse measurement and/or palpation using automated or manual approaches during routine or acute care encounters, which is sometimes referred to as “opportunistic screening” (and this approach could be considered usual medical care). When an irregular pulse is detected during usual medical care, a diagnostic evaluation that includes a standard 12-lead ECG typically is performed and may result in AF case-finding.”* In summary, both systematic ECG screening and opportunistic screening by flagged pulse palpation followed by ECG if irregular, detect more AF than usual care.

9. Detection – prolonged ECG screening vs usual care - REHEARSE-AF study results:

Another important study on this subject published just after the review deadline and presented as a late breaking trial at ESC August 2017, was the REHEARSE-AF study.¹⁵ This RCT examined whether twice weekly patient-activated ECG recordings with a handheld device would detect more new AF than usual care in just over 1000 participants. The findings were that the intervention was significantly more effective than usual care in detection of AF (hazard ratio, 3.9; 95% confidence interval=1.4–10.4; $P=0.007$). This superiority did not include the relatively large numbers with new AF (24 because an AF diagnosis was missed in the medical records, and 18 that were discovered because a screening ECG was performed at entry), leading to exclusion from the prolonged patient-activated monitoring during the study.

10. Potential preventable burden: This is discussed on p2 of the draft recommendation. There is mention that for about 20% of the patients with stroke associated with AF, the stroke is the first manifestation of AF (the reference listed is the current USPSTF evidence review #164, although these data do not seem to be present in that review, and other reviews¹⁶ find a higher proportion of between 1 in 3 to 4). This does not even include an important number of additional cases where AF is detected by monitoring only post-stroke.¹⁶ It would be more helpful to describe the proportion of all ischemic strokes that are associated with AF first, and the proportion of all ischemic strokes where AF is detected for the first time at the time of stroke. This latter figure, the proportion of all ischemic strokes where AF is detected first at the time of stroke is approximately 10% (see Freedman et al, Lancet 2016 and its online appendix¹⁶). Provision of these data in the document would provide a better guide to the potentially preventable burden.

11. Single lead ECG devices: The committee has commented little on screening for AF with ECG devices other than 12-lead ECG. On p 3 the recommendations state that *“the effectiveness of pulse palpation and newer technologies capable of assessing pulse and rhythm as potential screening strategies should be evaluated.”* Unfortunately, the review and recommendations have largely ignored the published non-randomised and randomised studies of screening which evaluated these devices for AF screening. The devices are quicker and cheaper than 12-lead ECG and easier to use. This has economic implications for screening which has not been considered. This is a major deficiency of the report. A summary of such studies may be found in the AF-SCREEN white paper (Circulation 2017)¹, and the EHRA Consensus document (Europace 2017)¹⁷.

12. Screening for AF with ECG is different from many other screening tests. Unlike many other screening tests, the diagnosis of AF is confirmed directly from the ECG screening test. This is also true of single lead rhythm strips from a hand-held device. It has some analogy to the diagnosis of hypertension by screening through use of a sphygmomanometer (see points #4 and 5).

13. Potential cost-effectiveness of ECG screening, mostly handheld: This has been estimated from 8 studies and reviewed in AF-SCREEN white paper (Circulation 2017)¹⁸. All simulations show likely cost-effectiveness. This has not been considered by the USPSTF in its report.

14. Inclusion of untreated known AF as collateral benefit: In population screening of unselected people (except by age) those with known AF will be included in those invited to attend. A significant proportion of those with known AF who would be eligible for anticoagulation, are found to be untreated with anticoagulant. In the USA, such patients may account for over 50% of those with known AF eligible for anticoagulation based on the large PINNACLE registry.¹⁹ In the STROKESTOP study, half of such patients commenced appropriate anticoagulation as a result of the screening procedure followed by a consultation. Because patients with known but inappropriately untreated AF account for up to 20% of all ischemic strokes,¹⁸ this represents a significant collateral benefit, which deserves mention.

15. Implanted cardiac ECG monitors and pacemaker/ICD/CRT implanted electronic devices: While implanted electronic devices such as pacemakers, cardioverter-defibrillators, or cardiac resynchronization devices are not placed for the purposes of screening, they do permit continuous ECG surveillance of individuals at risk of developing AF. Implanted cardiac ECG monitors are usually placed for another reason, but after stroke, have been placed specifically to detect AF. There are a number of studies concerning such patients, and it would be worthwhile mentioning these devices,²⁰ and the reasons for excluding them from the review. It would be helpful to state that the risk of stroke appears lower in AF detected by such devices than for clinical AF. It is important to mention because of the large numbers of electronic devices which can provide continuous surveillance of cardiac arrhythmia for months to years, and thereby afford an easily accessible method to opportunistically screen for AF with ECG in routine follow up.

16. Wearable ECG, pulse devices and smartphone ECGs marketed direct to the public:

There is an increasing availability of such devices that are already marketed directly to the public, often to those with low likelihood of developing asymptomatic AF, and if detected, are also less likely to require anticoagulant therapy because of young age and limited comorbidity. Mention of such devices needs greater prominence, with some recommendations made to assist health practitioners deal with the output.²¹ Such devices in the hands of consumers are likely to have a much higher false positive rate than for screening supervised by health professionals, especially for pulse based wearables with no ECG confirmation. It is very likely this will become a significant problem for health professionals in the near future, and is worthy of comment.

17. Recommendations of others (p6): It is stated that *“In 2014, the American Heart Association and the American Stroke Association stated that active screening for atrial fibrillation in the primary care setting among patients older than age 65 years using pulse assessment followed by ECG, as indicated, can be useful (26).”* This review has failed to consider the 2016 AF guidelines of the European Society of Cardiology (endorsed by the European Stroke Organisation). The European Society of Cardiology (ESC) states that opportunistic screening is recommended by pulse palpation or ECG rhythm strip in patients ≥ 65 years.²² The European Heart Rhythm Society (EHRA) recommends opportunistic screening for AF in the community by pulse or ECG rhythm strip for people ≥ 65 and consideration of systematic ECG screening for people ≥ 75 or at high stroke risk.^{23,24} The Royal College of Physicians of Edinburgh (RCPE) 2012 consensus statement says that screening for AF in people ≥ 65 “satisfies the UK National Screening criteria for a screening programme” and should be undertaken in the UK,²⁵ most cost effectively by opportunistic pulse palpation in primary care. The European Primary Care Cardiovascular Society (EPCCS) recommends “active screening for AF” in patients over 65,²⁶ while the Irish Health Information and Quality Authority (HIQA) found that a national screening program for people over 65 in primary care would likely be cost-effective and has recommended implementation of an AF screening program.²⁷ The World Heart Federation recommends opportunistic screening for AF in people aged 65 or older by pulse palpation followed by ECG in its Roadmap for non-valvular AF.²⁸ These recommendations of other significant groups which have considered the question of screening for AF should not be ignored.

We would appreciate that note of the above from the various organizations including the recommendations of AF-SCREEN International Collaboration be made under “Recommendations of Others.”

TABLE of Comments

Number	Issue	Comment
General	<p>Position of AF-SCREEN International Collaboration, and response from its steering committee</p> <p>No large RCT on screening with hard endpoints, but conclusions would differ if more data were considered</p>	<p>We agree that there are no RCT studies yet concluded for systematic population screening, and that these are needed to strengthen the evidence base. This was a strong recommendation of AF-SCREEN. However, there is sufficient evidence for adoption/recommendation of opportunistic screening or case finding for AF</p>
1	Data other than RCTs	<p>Insufficient attention, therefore, underestimates possible preventable burden, reduces advocacy to fill gaps. Also, could change recommendation.</p>
2	<p>Exclusion of patients for with known heart disease, heart failure, or prior stroke from analysis of benefits and harms of AF treatment (KQ 4 & 5). Using same logic would also remove people with diabetes and hypertension</p>	<p>Removes those at highest risk of development of incident AF, and highest risk of stroke. Logic is flawed and would not be used for implementation of population screening. People with additional co-morbidities predominate in those discovered by screening.</p> <p>Removes those at highest risk of development of incident AF, and highest risk of stroke. Logic is flawed and would not be used for implementation of population screening. People with additional co-morbidities predominate in those discovered by screening. Exclusion of cardiovascular co-morbidities would result in missing over two thirds of people with unknown AF at screening who are at the highest risk of stroke.</p>
3	Extrapolation of benefits and harms of treatment from clinical AF to screen-detected AF	<p>Agree with principle, but need to state ethical inability to determine the precise stroke risk and benefit of treatment of screen-detected AF. There are 2 new large cohort studies published in abstract form Aug 2017 showing at least as bad adverse prognosis as symptomatic AF. One cohort study has examined the effects of screening</p>

4	Analogy with USPSTF Grade A recommendation for screening for hypertension	Grade A recommendation for screening for hypertension since 1996, despite no RCT of policy of systematic screening vs no screening. Examination of the data on AF screening should result in an identical positive recommendation about screening for AF
5	Harms of screening	These are overemphasized, and are mostly related to the harms of treatment, which in nearly all cases are outweighed by the benefits, Anxiety reduced by the accuracy of the test, and the fact that the screening test is also the test required to confirm the diagnosis
6	Imminent release of STROKESTOP results and timing of recommendation	This study is a large RCT of systematic screening will likely be presented and published in August 2018. If positive, the recommendation may need to be revised less than 6 months after its final release. STROKESTOP pilot long term follow-up (in press Europace Jan 2018) shows reduced stroke rate in the intervention area compared to a control area. This is important to include now as well.
7	Effectiveness of early detection and treatment	Missed results of one large cohort study (the only study available) examining effect of treatment in incidentally detected asymptomatic AF. This is very important for making the recommendation.
8	Detection: efficacy of systematic ECG screening vs opportunistic screening/case finding vs usual care	Incorrect interpretation of SAFE study. Both systematic ECG screening and opportunistic screening (case finding) by pulse and then ECG if irregular, were more effective than usual care. Incorrect assumption that the intervention used in opportunistic screening in SAFE could be equated with usual care
9	Detection efficacy vs usual care. Missed REHEARSE-AF results	REHEARSE-AF study published Sept 2017 is an RCT showing that intermittent patient activated ECG screening detected more AF than usual care

10	Potential Preventable Burden underestimated	Should state the proportion of all ischemic strokes (approximately 10%) which are related to AF first detected at the time of stroke. Proportion of ischemic strokes related to AF is underestimated.
11	Single lead ECG devices	The review and evaluation largely ignored the observational and randomised studies using single lead ECG devices, which could become the standard for ECG screening for AF
12	Screening vs diagnosis for ECG in AF	It should be acknowledged that ECG screening for AF, unlike most other screening tests, actually diagnoses the condition. This is also true of single-lead rhythm strips which are provided by a handheld device. The implications of this on potential cost-effectiveness have not been mentioned
13	Potential cost-effectiveness of screening	There have been 8 studies of cost-effectiveness of ECG screening for AF using various assumptions and simulations. None has been mentioned.
14	Inclusion of untreated known AF in population screening provides a potential collateral benefit	No mention made of potential collateral benefits if those with known AF included in population screening. If not on appropriate anticoagulation, 50% were commenced on OAC following the screening procedure in the STROKESTOP study.
15	Implanted cardiac monitors, Cardiac implanted devices, and extended continuous ECG recording by wearable monitors	There has been no mention of these devices, which some advocate for targeted ECG screening, and in the case of implanted electronic devices, offer the ability to have continuous opportunistic ECG screening for AF over months to years. Need to review the data on relationship of duration and burden of arrhythmia and stroke risk, and state that brief episodes have a lower stroke risk than clinical AF
16	Wearable devices both ECG and pulse marketed directly to the public for AF screening	Need to mention these, with some direction to health professionals about what detected arrhythmia may mean. Likely to have a higher false positive rate

17	Recommendations of others limited to AHA/ASA	Misses recommendations of many respected international bodies which advocate for screening for AF including with pulse palpation or ECG rhythm strip
----	--	--

References:

1. Freedman B, Camm J, Calkins H, et al. Screening for Atrial Fibrillation: A Report of the AF-SCREEN International Collaboration. *Circulation* 2017; **135**(19): 1851-67.
2. Alonso A, Krijthe BP, Aspelund T, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc* 2013; **2**(2): e000102.
3. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass Screening for Untreated Atrial Fibrillation: The STROKESTOP Study. *Circulation* 2015; **131**(25): 2176-84.
4. Sandhu RK, Dolovich L, Deif B, et al. High prevalence of modifiable stroke risk factors identified in a pharmacy-based screening programme. *Open Heart* 2016; **3**(2): e000515.
5. Martinez C, Katholing A, Freedman B. P3594 Stroke risk in patients with asymptomatic atrial fibrillation (AF) detected incidentally in general practice is comparable to symptomatic AF presentation, and AF presenting first to hospital. *Eur Heart J* 2017; **38**(suppl_1): ehx504.P3594-ehx504.P.
6. Gibbs H, Freedman B, Rosenqvist M, et al. P4602 Similar clinical outcomes of asymptomatic and symptomatic patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. *Eur Heart J* 2017; **38**(suppl_1): ehx504.P4602-ehx504.P.
7. Martinez C, Katholing A, Freedman SB. Adverse prognosis of incidentally detected ambulatory atrial fibrillation. A cohort study. *Thromb Haemost* 2014; **112**(2): 276-86.
8. Freedman B, Martinez C, Katholing A, Rietbrock S. Residual Risk of Stroke and Death in Anticoagulant-Treated Patients With Atrial Fibrillation. *JAMA Cardiol* 2016; **1**(3): 366-8.
9. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; **146**(12): 857-67.
10. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014; **383**(9921): 955-62.
11. Orchard J, Freedman SB, Lowres N, Peiris D, Neubeck L. iPhone ECG screening by practice nurses and receptionists for atrial fibrillation in general practice: the GP-SEARCH qualitative pilot study. *Aust Fam Physician* 2014; **43**(5): 315-9.
12. Lowres N, Mulcahy G, Gallagher R, et al. Self-monitoring for atrial fibrillation recurrence in the discharge period post-cardiac surgery using an iPhone electrocardiogram. *Eur J Cardiothorac Surg* 2016; **50**(1): 44-51.
13. Chan AA, Chan SC, Yan BP. Feasibility and acceptability of atrial fibrillation screening using a hand-held device in general practice setting in Hong Kong. *Value Health* 2017; **20**(9): A599.

14. Lowres N, Neubeck L, Salkeld G, et al. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. *Thromb Haemost* 2014; **111**(6): 1167-76.
15. Halcox J, Wareham K, Cardew A, et al. Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study. *Circulation* 2017; **136**(19): 1784-94.
16. Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. *Lancet* 2016; **388**(10046): 806-17.
17. Mairesse GH, Moran P, Van Gelder IC, et al. Screening for atrial fibrillation: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE). *Europace* 2017; **19**(10): 1589-623.
18. Freedman B, Camm J, Calkins H, et al. Screening for Atrial Fibrillation: A Report of the AF-SCREEN International Collaboration. *Circulation* 2017; **135**(19): 1851-67.
19. Hsu JC, Maddox TM, Kennedy KF, et al. Oral Anticoagulant Therapy Prescription in Patients With Atrial Fibrillation Across the Spectrum of Stroke Risk: Insights From the NCDR PINNACLE Registry. *JAMA Cardiol* 2016; **1**(1): 55-62.
20. Freedman B, Boriani G, Glotzer TV, Healey JS, Kirchhof P, Potpara TS. Management of atrial high-rate episodes detected by cardiac implanted electronic devices. *Nat Rev Cardiol* 2017; **14**(12): 701-14.
21. Kotecha D, Breithardt G, Camm AJ, et al. Integrating new approaches to atrial fibrillation management: the 6th AFNET/EHRA Consensus Conference. *Europace* 2018.
22. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; **37**(38): 2893-962.
23. Mairesse GH, Moran PS, Van Gelder IC, et al. Screening for atrial fibrillation: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE). *Europace* 2017; **0**: 1-35.
24. Kirchhof P, Breithardt G, Bax J, et al. A roadmap to improve the quality of atrial fibrillation management: proceedings from the fifth Atrial Fibrillation Network/European Heart Rhythm Association consensus conference. *Europace* 2016; **18**(1): 37-50.
25. Stott DJ, Dewar RI, Garratt CJ, et al. RCPE UK Consensus Conference on 'approaching the comprehensive management of atrial fibrillation: evolution or revolution?'. *J R Coll Physicians Edinb* 2012; **42**(1): 34-5.
26. Hobbs FR, Taylor CJ, Jan Geersing G, Rutten FH, Brouwer JR, European Primary Care Cardiovascular Society Swg. European Primary Care Cardiovascular Society (EPCCS) consensus guidance on stroke prevention in atrial fibrillation (SPAF) in primary care. *Eur J Prev Cardiol* 2016; **23**(5): 460-73.
27. Health Information and Quality Authority. Health technology assessment (HTA) of a national screening programme for atrial fibrillation in primary care. 2015. <https://www.hiqa.ie/publications/health-technology-assessment-hta-national-screening-programme-atrial-fibrillation-prima> (accessed 24 May 2016).
28. Murphy A, Banerjee A, Breithardt G, et al. The World Heart Federation Roadmap for Nonvalvular Atrial Fibrillation. *Glob Heart* 2017; **12**(4): 273-84.