UK National Screening Committee

18 June 2014

Screening for Atrial Fibrillation in the over 65s

Purpose

1. The purpose of this paper is to provide background on the item addressing screening for atrial fibrillation (AF) in the over 65s.

Current policy

2. The current policy is that screening for atrial fibrillation should not be offered.

Review

3. A review of the literature was produced by Solutions for Public Health. This makes several key points:

- Clinical management of the condition is not optimised.
- The treatment for AF includes offering the patient long-term anticoagulants to reduce the risk of stroke, if that risk is above a certain level. It is known that many patients who would benefit from anticoagulants are not taking them. The treatment can last for many years. Screening is likely to detect an increased number of over 65 year olds with AF but it would be ethically unjustifiable to begin this in the context of concern about the management pathway
- There is little evidence as to whether the risk of progression from AF to stroke is equivalent in the screened and clinically detected populations
- The review highlights concerns about operator dependency in the testing process

Consultation

4. Prior to consultation the review has been shared with the National Clinical Director for cardiovascular disease and the Departments of Health in the four countries.

5. A three month public consultation was hosted on the UK National Screening Committee (UK NSC) website. The following stakeholders were contacted directly: AF Association, AntiCoagulation Europe, Arrhythmia Alliance, British Cardiovascular Society, British Heart Foundation (BHF), Central & East London Comprehensive Local Research Network, Education for Health, Heart Rhythm UK, HEART UK, NHS Improvement, Royal College of General Practitioners, Royal College of Physicians, Royal College of Physicians of Edinburgh, Royal College of Surgeons.

6. Responses were received from: AF Association, All Party Parliamentary Group for Atrial Fibrillation, Arrhythmia Alliance, British Heart Foundation, Royal College of Physicians of Edinburgh.

Comments

7. The following themes can be seen across the responses

- all respondents favoured screening
- the need to improve clinical management was a significant concern to all. The BHF agreed that it was ethically unjustifiable to refer patients into a suboptimal clinical service. Other responses pointed to the recently revised NICE guideline (2014), particularly its incorporation of a risk stratification tool (CHA2DS2VAS) to assist with decision making on anticoagulant treatment, as evidence of an increasing consensus on the management of AF. Similarly QOF data from 2013 was used to highlight that improvements were already being achieved
- the review's handling of the risk associated with screen detected AF was questioned but this was to reiterate the findings of the AFFIRM study which suggested an equivalent risk in screen detected and clinically detected AF. However the issues highlighted by the review, relating to study population and confidence intervals, were not addressed in the responses
- the review's concerns about the test values and operator dependency were acknowledged but the responses pointed to new technologies which may remove the problems associated with operator dependency

8. A number of papers were submitted to accompany the responses. These have been discussed with the reviewer but none of the papers altered the conclusions of the review.

Recommendation

9. It is recommended that the current policy is retained but that the statement is expanded to:

   Screening for atrial fibrillation in the over 65 year old population is not recommended as it is uncertain that screening will do more good than harm to people identified during screening for AF.

10. This is because:

- The treatment and care for people with AF is not optimal
- Better evidence is needed about whether AF detected at screening carries the same long term risk of stroke as AF found in the context of other conditions
- The test needs to be improved and standardised.

Consultation Comments

March 2014

1.

UK National Screening Committee
Atrial Fibrillation
Consultation comments

Organisation:	British Heart Foundation		
Name:	Amy Smullen	**Email address:**	XXXXXXXXX
Please tick whether you are making this submission as an individual or on behalf of an organisation. **Individual** ☐ **Organisation** ☒			

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
X	General comment	The British Heart Foundation (BHF) is the nation's leading heart charity. We are working to achieve our vision of a world in which people do not die prematurely or suffer from cardiovascular disease. In the fight for every heartbeat we fund ground breaking medical research, provide support and care to people living with cardiovascular disease and advocate for change. Atrial Fibrillation (AF) is the most common type of significant abnormal heart rhythm. Over 1 million patients are registered on the Quality Outcome Framework Register as AF patients.[1] This therefore represents a large group of patients that the BHF are dedicated to improving detection

[1] Quality Outcomes Framework (2013) prevalence data

		and treatment for. The BHF is dedicated to helping detect undiagnosed cases of AF. This includes raising public awareness of how a simple pulse check can help to identify an irregular heart rhythm. The BHF therefore warmly welcomes the opportunity to partake in the UK National Screening Committee (UKNSC) consultation on proposed screening for Atrial Fibrillation (AF) in patients aged 65 and over. We strongly believe that there should be a national screening process implemented to detect AF in adults aged 65 and over. We support this recommendation for a number of reasons. First, AF can present both symptomatically- symptoms can vary, and can include palpitation, breathlessness, feeling faint and tiredness- but importantly AF can often present asymptomatically. Screening would provide an effective detection method especially for asymptomatic cases of AF. This is important because screening for AF can detect other underlying heart conditions, that otherwise would have gone undiagnosed offering clinicians an important tool against the fight against heart disease, including metabolic disorders such as hypothyroidism. Secondly, AF is a risk factor of thrombotic stroke. With this in mind there are clear benefits of early

		detection and management of AF to prevent the incidence of stroke. The benefits are two fold, first; as an important cost benefit to the health and social care system, as prevention of stroke is more cost effective than managing incidence in terms of capacity and resources. Secondly; the improvement in patient's quality of life is a huge benefit. The detection of AF through a screening process can lead to effective treatment and management of condition and restoration of quality of life, not to mention the chance of prevention against the devastating effects stroke. (Here we point to the three studies, points 5-7 referenced on page 5 as key evidence to support this) This cost savings argument also applies to those underlying heart conditions that may also be picked up as part of a screening programme. We also believe that the introduction of a screening policy would increase awareness of AF in the wider population in particular those aged 65 and over, encouraging self-screening, using a process such as 'Know Your Pulse'
Page 5 Section 7	*The authors state that, after correction for baseline difference, mortality and major events were similar in the two groups.*	This highlights that the risk of mortality or death following stroke did not differ in cases of symptomatic or asymptomatic AF strengthening the case for a screening programme.
Page 6 Section 8	*The known modifiable risk factors for AF are a history of myocardial infarction, angina, diabetes mellitus, hyperthyroidism, stroke or TIA (Hobbs et al 2005:5).However, robust evidence that managing these risk factors does indeed reduce the incidence of AF is limited.*	If evidence that managing risk factors for AF is limited then the possible benefits of a screening programme are clear. It is more effective to detect incidence and treat than attempting to reduce incidence.

Page 7 Section 11	*The 2005 HTA concluded that active screening for AF detects additional cases over current practice, and that the preferred method of screening in patients aged 65 or over in primary care is opportunistic pulse taking, with follow-up electrocardiography if the pulse is irregular (Hobbs et al 2005:63).*	We feel this pathway appropriate as treatment will not commence until AF is confirmed through ECG.
Page 7 Section 12	*The gold standard for diagnosis of AF is a 12-lead ECG read by at least one cardiologist.*	With this it is important to strike a balance between gold standard and realistic procedures. It is more likely that GP's will review ECG results in this setting. GPs need to be supported though diagnosis and access to cardiological support.
Page 8 Section 16	*Finger probes and modified blood pressure monitors might reduce the number of ECGs that need to be read to confirm or exclude a diagnosis of AF, but a screening programme would still generate substantial additional numbers of ECGs.*	The majority of GP surgeries are now equipped with ECG machines. We think interpretation of the ECG is more of an issue. (please see above)
Page 12 Section 35	*The decision to prescribe warfarin should be driven more by patients" risk of stroke than by the risk of bleeding (Chen et al 2011).*	BHF welcome this comment. It is a concern that currently some clinicians prescribe with bleeding as a primary concern.
Page 13 Section 36	*Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme*	This is imperative to the success of an AF screening programme as optimum treatment must be available for those who present as AF patients through the screening programme.
Page 14 Section 40	*It appears that the potential gains from ensuring that the right patients with clinically–diagnosed AF are anticoagulated exceed the likely gains from introducing opportunistic screening for AF by about an order of magnitude.*	BHF do not see these as mutually exclusive and should be promoted concurrently.
Page 16 Section 46	*There have been no randomised controlled trials of screening for AF that have assessed its impact on mortality or morbidity.*	The BHF would therefore welcome a randomised control trial to fill this evidence gap.
Page 16 Section 50	*It is likely, but not proven, that a national screening programme for atrial fibrillation in people aged 65*	BHF strongly support this statement.

	and over would produce more benefit than harm, provided that the NHS can greatly improve its performance in providing safe anticoagulant therapy to appropriate patients.	
Page 17 Section 53	*However, a formal assessment of the cost-effectiveness of a screening programme is required. It should include the costs of detecting cases and take into account the possibility that patients with screen-detected AF have a lower risk of stroke than patients with clinically-diagnosed AF.*	Alongside a formal cost-effectiveness assessment the costs to the social care system should also be taken into consideration.
Page 20 Section 'Implications for Policy'	*First, it would be unethical to introduce a screening programme without being confident that screen-detected patients would be well managed. Second, the potential gains from ensuring that the right patients with clinically–diagnosed AF are properly anticoagulated exceed the likely gains from introducing a screening programme by an order of magnitude*	We believe that this is fundamental to the success and efficacy of the screening programme and should form the basis of a decision to implement.
Page 20 Section 'Implications for Policy'	*It is uncertain whether screen-detected AF carries the same risk of stroke as AF that is detected through routine clinical practice.*	If it is uncertain then this strengthens the need for a screening programme.
Page 21 Section 'Implications for Policy'	*good quality patient decision aids need to be developed to ensure that patients are equipped to make decisions that reflect individual values as well as evidence of benefits and harm.*	BHF strongly support this point.

2.

UK National Screening Committee

Atrial Fibrillation

Consultation comments

Organisation:	Arrhythmia Alliance		
Name:	Mrs Trudie Lobban MBE FRCP Edin	**Email address:**	[redacted]
Please tick whether you are making this submission as an individual or on behalf of an organisation. **Organisation**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
4	Overall document	The impact of AF-related stroke is significant however it should also be considered that AF has other associated risks and implications, such as heart failure and dementia. In all cases, there is an impact upon an individual's psychological well-being and quality of life. In light of the importance to prevent stroke, heart disease and to reduce the burden on health and social care services, the opportunity to embrace screening routinely and opportunistically can and should be encouraged and supported. The ease and multiple routes for screening are aplenty; chronic disease clinics for e.g. diabetes, pharmacy, routine reviews for the high risk population and at flu clinics. The data included in the report is substantial, and highlights the need for improved medical management of AF patients in terms of their therapy prescription and oversight. We are aware that there are techniques, new treatments and information to support the effective management of AF patients. For instance, better education amongst healthcare professionals of 2014 AF Guidelines and the tools available to

		support the detection and ongoing management of patients with AF, will lead to better patient outcomes. We would urge the NSC to meet with A-A to review the current evidence, need and challenge. Screening will identify high risk patients, save lives, prevent debilitating strokes and reduce costs to NHS. We feel strongly about advocate screening.

3.

UK National Screening Committee

Atrial Fibrillation

Consultation comments

Organisation:	AF Association		
Name:	Jo Jerrome	**Email address:**	[redacted]
Please tick whether you are making this submission as an individual or on behalf of an organisation. **Organisation**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 1		AF Association welcome the review document considering 'Screening for AF for people aged 65 years and over' although dated, April 2nd 2012.
Page 4	Point 2	GRASP-AF (Heart, 2012 Cowan C et al) highlights AF prevalence across England between 1.7%-1.8%. Given the rise in prevalence in each decade, the increase stroke risk that accompanies age, the option to link screening for AF with the annual influenza inoculations offered to the 65 years+, screening for AF in this population would seem the most effective, efficient and beneficial.
Page 4	Point 3	The increased risk of stroke due to AF has been highlighted in many studies. Specific AF population groups have been defined, and these formulated into an assessment schema – $CHADS_2$ and CHA_2DS_2VASc each of which have been validated, endorsed and are now recommended by the European Society of Cardiology (ESC) AF Guidelines (2010 and 2012), and in the

		Updated NICE AF Guidelines, 2014 (draft published Jan 2014, Final published June 2014), in which CHA_2DS_2VASc is strongly endorsed as the risk assessment scoring approach of choice. Current data indicates that the risk of an AF-related stroke rests on the factors incorporated in the CHA_2DS_2VASc schema. What is absolutely crucial is that there is no evidence (a priori or otherwise) to indicate that asymptomatic AF carries any lesser risk than symptomatic AF. Clearly it is more straightforward to recruit symptomatic patients to randomised comparisons and hence the relative lack of randomised data in the asymptomatic group.
Page 7 - 11	Point 11 - 32	There are a number of tested methods now available that can readily detect an irregular pulse and diagnose atrial fibrillation (AF). The key may not be 100% sensitivity but moderately high sensitivity combined with widespread applicability. '**Know Your Pulse'** has been shown to be effective in detecting the irregular pulse. It is cost free, takes just a minute, can be administered by a range of trained healthcare workers, and is easily carried out during routine, chronic disease, pharmacy check-ups and inoculation sessions. Discussion and surveys have shown pulse taking to be viewed as reassuring and an important part of health monitoring, by current AF patients, carers and the general public. It also helps share awareness of self-monitoring that can lead to earlier detection and diagnosis.

		While 12 lead ECG can be viewed as the 'gold standard' in diagnosis and clinical trials, as the report correctly states, trained interpretation of the ECG is required and unnecessary for the identification of almost all AF cases. New technology is becoming available which provides easy, fast and accurate point of care access to an ECG which can be saved / emailed and on some devices, interpret the ECG. NICE gave guidance on WatchBP AF and blood pressure monitor following trials (including GP-based trials) in the UK: **WatchBP Home AF for opportunistically detecting atrial fibrillation during diagnosis and monitoring of hypertension** **Issued: January 2013** NICE medical technology guidance 13 Evidence of using this device in Outpatients and in Primary Care is attached to this email **AliveCor** iPhone ECG heart monitor has FDA approval and is now being used in pharmacies, inpatient cardiac wards, outpatients, GP surgeries and by individuals capturing ECG recordings that can be saved and emailed to a healthcare professional for interpretation. The AF Association can provide further details, including an Australian trial by Professor Ben Freeman, which screened 1000 people attending pharmacists and as a direct result diagnosed ten previously

		undetected AF cases. Accordingly, modern technologies are now enabling inexpensive, immediate and effective screening for AF to be offered in a wide variety of settings.
Page 9	Point 20+	A great deal of work is on going to support the improved management of AF. **Warfarin** is an effective oral anticoagulant but has been sub-optimally prescribed. This needs to change through enhanced education programmes as set-up and sponsored by organisations like AFA. Conversely, **Aspirin (anti-platelet therapy)** has been over prescribed, especially to the elderly at increased risk and for who anticoagulation would be far more effective at reducing risk. **New oral anticoagulants** have been approved by NICE (2012, 2013) in STA for: Dabigatran, Rivaroxaban, Apixaban, and in October 2014 consideration for a NICE MTA is expected on these therapies. However uptake has been lower than expected and real life data is only currently available from the UK for the past 12-18 months. **However**, a great deal of education, awareness and review of policy, standards and local guidelines has been undertaken and continues to be reviewed. NICE will be publishing the updated AF Guidelines in June 2014. The updated guidelines are expected to remove the use of aspirin as an option in AF-stroke management; recommend CHA2DS2VASc as the assessment schema, and provide further guidelines and real-practice examples of effective management of AF patients at risk of an

		AF-related stroke. Updated NICE guidelines, the GRASP-AF review tool, on-going educational training and pending NICE Quality Standards which will reflect and support the updated guidelines will all work to support clinicians to effectively, knowledgably and confidently manage AF.
Page 16	Point 46	The AF Association agrees that further trials are required and many are underway and likely to be initiated as therapy options for AF increase. However, pilot models of screening have already indicated that there is considerable undetected AF amongst the over-65-year-old population, and delaying detection too often results in devastating, preventable ischaemic strokes. An AF-related stroke is more likely to be disabling and fatal. 50% of people who suffer an AF-related stroke will die within the following first year. AF-related strokes are costly – to the NHS, the cost of the first year's health and social care is estimated at £44,000. Also to their individual and their family, where their lives are irrevocably changed. Health, outlook, opportunity, income, wellbeing and mobility are suddenly changed. 50% of those who do survive never return home, but need full time care. Those who do frequently rely upon partners as carers and the future is uncertain.
Page 20	Implications for Policy	Across the UK (and internationally), the risk stratification and appropriate management for thromboembolic risk in AF has been highlighted and guidelines have been agreed. .

		As already stated, the updated AF NICE guideline is about to be released. Therefore the AF Association believes that any suggestion that treatment of AF is not agreed, is now outdated and not appropriate. There is no doubt from our perspective that thousands of strokes could be prevented and many lives saved if screening for AF were instituted in a systematic programme of education with comprehensive implementation. Furthermore, while screening aims to reduce the risk of AF-related strokes, AF Guidelines also largely agree on appropriate rate and rhythm management strategies for atrial fibrillation. AF increases the risk of stroke by five fold. It is also associated with a three-fold increase in Heart Failure, trebles the risk of dementia, doubles the risk of mortality and morbidity and doubles the risk of depression. Management of rate and rhythm has considerable health, outcome and cost benefits. In 2008, OHE found that patients with primary or secondary diagnosis of AF occupied 5.7 million bed days at a cost to the NHS of £1,873 million. Outpatient costs accounted for £205 million, and inpatient costs other than bed days cost £124 million ['Keeping Our Fingers on The Pulse', AF Association,

		Office of Health Economics]. AF screening will result in earlier diagnosis access to effective stroke, rate and rhythm management for AF. This will save lives, improve outcomes and reduce costs to NHS and the individual. While further research is needed, the AF Association firmly believes that there is enough evidence supporting effective management to urge the national Screening Committee to recommend screening for AF in the over 65 years population. We would welcome meeting with the Committee to discuss this further.

UK National Screening Committee

Atrial Fibrillation

Consultation comments

Organisation:	All Party Parliamentary Group for Atrial Fibrillation (APGAF) – APGAF is supported by AF Association		
Name:	Jo Jerrome	**Email address:**	[redacted]

Please tick whether you are making this submission as an individual or on behalf of an organisation.

Organisation

NB: The All Party Parliamentary Group for AF is chaired by Glyn Davies MP in partnership with the AF Association.

The response was prepared with support from, Professor A John Camm, Consultant Cardiologist and Electrophysiologist, and Trustee of AF Association, Dr Matthew Fay, GPwSI in Cardiology, Dr Andreas Wolff, GPwSI.

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
	Point 3	Many known AF patients were found by opportunistic pulse taking /ECGs and that the current cohort of AF patients, treated or not, does not consist of purely symptomatic patients. In fact up to 40% of patients in Framingham were only found by routine examination (JAMA 1994;271:840-844). Furthermore none of the randomised controlled trials using antithrombotic therapies to prevent thromboembolic complications in AF exclude asymptomatic AF patients. It is not surprising that around 20% of acute AF related strokes occur in patients who did not know they had AF, not dissimilar to the 25% of AF patients suspected to have undiagnosed AF (Stroke 1995; 26:1527-1530).
	Point 6	ASSERT investigated atrial high rate events detected by devices. Interesting as it is, this data has limited relevance to an AF

		screening programme.
	Point 7	AFFIRM data supports the notion that asymptomatic AF carries the same stroke risk and there is no evidence to suggest this is would be incorrect, nor reason APGAF can think of that would suggest differently (adjusted HR 1.07, 95%CI 0.79-1.46).
	Point 12	Step 1 pulse palpation. Morgan's paper (BJGP 2002; 52: 373-380) and Sudlow's (BMJ 1998; 317: 327-28), both show a higher sensitivity. While sensitivity of 92% and a specificity of 91% for computer assisted ECG interpretation by GPs is not ideal, it is a good deal better than various other screening programmes (for example, breast screening).
	Point 25	We would like to reiterate our comment made in Point 3
	Point 38	Stroke risk stratification has now a greater influence on the choice of antithrombotic agent as in the older evidence quoted. See Cowan et al (Heart 2013), Kakkar et al (GARFIELD registry) and Holt et al. (BJGP 2012; 62: 710-7). There are now far fewer low risk patients anticoagulated and increasing risk scores correspond with higher rates of anticoagulation. It is also important to note that not all CHADS2 = 0 patients on warfarin are inappropriately anticoagulated. Around 25% are considered to be high risk according to CHADSVASc, some patients take anticoagulation for other indications and some are in the peri-cardioversion phase.

	Point 40	Without doubt, there is a need to improve the current management of already known AF

		patients however we do not believe this should preclude an AF screening programme. In the first year of the AF QOF changes (April 2013) anticoagulation rates rose to nearly 66% excluding exception reporting. We understand this is the most up to date set of UK data and encouraging.

	Point 43-45	There is good evidence that good INR control and higher TTRs correspond with better outcomes. The largest UK data set showed an average TTR of 63% which compares very favourable to almost all RCTs (Gallagher Thrombosis and Haemostasis 2011; 106 (5):9 (5):968-977).

	Point 51	The cost effectiveness of AF screening was thoroughly assessed as part of the SAFE programme and considered cost effective. Warfarin has been shown to be highly cost effective in SPAF and NOACs are considered cost-effective when compared with warfarin.

		The All Party Parliamentary Group would welcome meeting with the Committee to discuss screening in AF.

4.

COMMENTS ON

UK NATIONAL SCREENING COMMITTEE

SCREENING FOR ATRIAL FIBRILLATION IN PEOPLE AGED 65 AND OVER - A DRAFT REPORT

The Royal College of Physicians of Edinburgh is pleased to respond to the UK National Screening Committee on its draft report on *Screening for Atrial Fibrillation in People aged 65 and over*.

The College is very supportive of such a screening programme and notes that the draft report refers in several places to our recent Consensus Statement on AF. Our advice is that screening should continue, and we draw your attention to a recent Australian review which may also be helpful.

Screening to identify unknown atrial fibrillation: A systematic review, Nicole Lowres; Lis Neubeck; Julie Redfern; S. Ben Freedman. University of Sydney, ANZAC Research Institute and Department of Cardiology, Concord Hospital, Sydney, New South Wales, Australia; The George Institute for Global Health, Sydney, New South Wales, Australia. (Thrombosis and Haemostasis" 110.2/2013).

Also, the field has changed with the availability of new technologies to support opportunistic screening and we draw your attention to an earlier Australian Study, again from the Concord Hospital team and published by the BMJ.

Screening Education and Recognition in Community Pharmacies of Atrial Fibrillation to prevent stroke in an ambulant population aged >=65 years (SEARCH-AF stroke prevention study): a cross-sectional study protocol. Lowres N, Freedman SB, Redfern J, McLachlan A, Krass I, Bennett A, Briffa T, Bauman A, Neubeck L. (BMJ Open. 2012 Jun 25;2(3). pii: e001355. doi: 10.1136/bmjopen-2012-001355. Print 2012).

All College responses are published on the College website www.rcpe.ac.uk.

Further copies of this response are available from Lesley Lockhart (tel: XXXXXXXXX or email XXXXXXXXX)

8 January 2014

5.

Ameet Bakhai, Consultant Cardiologist and Heart Failure Lead Barnet

This is a very well written draft.

The only big ticket items I would like to draw attention to are:

1. Low Bradford uptake rates are not necessarily indicative of the UK

2. Individuals found to have AF when screened during other medical conditions – example – eye problems or dental problems may be more likely to take up anticoagulation then those found in the community

3. Cost effectiveness of a programme that used pulse detection technology to screen and then ECG to diagnose is more likely to be cost effective then an ECG based strategy alone.

4. Asymptomatic AF detection has an increased risk of heart failure and the benefits of reducing tachycardiomyopathy are not directly mentioned or considered and may be a useful addition.

5. Additional non-Vitamin K agents have now been considered by NICE and the document should be updated.

6. Several companies have now solved the issue of large scale uploading of ECGs for specialist diagnosis example - Zenicor in Europe, Cardiocomms in USA

7. Atrial flutter may not be detected if irregular pulse is a screening mechanism.

8. The value of AF screening added to a health checks programmes such as the NHS Health Checks has not been addressed here.

9. Incidental additional benefits of detecting AF via ECG may include detecting ischemia / LBBB / right heart strain and poor LV function all of which would have additional cost effectiveness benefits including finding important valvular heart disease..

NB: Ameet also submitted 3 AF articles (Kirchoff et al. 2013, a european study from Dobreanu et al. 2013 and Saveleiva et al. 200) in addition to this submission