Management of chronic heart failure

Comments received from external referees and others

All reviewers submitted declarations of interests which were viewed by the guideline development group prior to the addressing comments.

Section	Comments received	Development group response
General		
	I think GP readership would welcome clearer advice on what is expected of them, and what they can expect of specialists.	*This should be improved by addressing the specific peer review comments.*
	Very full document showing update in thinking and organisation of patient centred care.	*No action required.*
	The guideline gives the perception that ivabradine is not in the major drug classes for heart failure. The major classes appear in sections 5.1 to 5.9. Ivabradine appears at the very end after all other treatments (including hydralazine and nitrates). Ivabradine has both SMC and NICE approval and is included in the ESC algorithm for the management of patients with chronic symptomatic systolic heart failure (NYHA functional class II–IV), pg 19. On balance we believe for appropriate patients, Ivabradine is an important part of their treatment regimen and therefore worthy of being added to the major classes section. Would the guideline development group consider adding ivabradine into the 'major drug classes' section?	*Section 5 reordered and ivabradine added to key recommendations.*
	The Royal College of Physicians and Surgeons of Glasgow asked Dr Mark Petrie, Consultant Cardiologist at the Golden Jubilee Hospital, to prepare a response to this guideline. I have read his response which is direct and I believe makes some important points. I have a few additional points to make in relation to the Guideline. Overall I feel it is an excellent guideline and the authors are to be commended.	*Thank you. No action required.*
	Recommendations - Strong and conditional recommendations appear to be given the same weight. Should it be more clear in the text the distinction between the two; ie Rs or Rc. Use HF as abbreviation throughout for heart failure. Summary treatment algorithm pathway as in ESC (their figure 2) would be useful; highlights stepwise and incremental approach to management of HF.	*Strong and conditional recommendations are differentiated by the wording of the recommendation. SIGN addressing a different format to differentiate recommendations.* *Agree* *Added*
	I think this draft needs significant work. I think ideally all the original SIGN 95 statements also need reworked. The consistency of the wording of recommendations needs significantly improved: a. The ACEI recommendation (page 20) starts 'To reduce mortality and hospitalisation' but none of the other recommendations on pharmacological therapies (eg betablockers, MRAs etc) starts like this. This will confuse people and it implies that on ACEIs do this and the others do not. This is obviously not the case.	*Recs reworded to be more consistent, but within the confines of the supporting evidence.*

	b. Contraindications- why are these listed for some drugs (e.g. beta-blockers- page 20) but not others (e.g.ACEIs- page 20). Again this is confusing. c. Some recommendations say 'heart failure due to left ventricular systolic dysfunction' (e.g. ACEIs- page 20) and others say 'chronic heart failure due to left ventricular systolic dysfunction'. Again this is confusing. I cannot also see any logic for the ordering and flow of medications recommendations (e.g. why do things like PHOSPHODIESTERASE INHIBITORS come before medications like Ivabradine?). Surely it makes more sense to order the flow of recommendations in the order in which that you would generally clinically consider them.	*b) Contraindications for ACE inhibitors are widely known. Including them for beta-blockers is aimed at improving confidence in using BBs in a multimorbid population.* *c) changed.* *Section 5 reordered.*
	This set of guidelines appears clunky, and would benefit greatly from more diagrams/figures. Other than being more contemporary, it will not displace the ESC HF guidelines for ease of use. SIGN should offer more of a recommendation for LCZ - the most exciting thing to happen in heart failure since the last guidance in 2007.	*Algorithm added.* *Will be added once SMC advice is published.*
	A well laid out easy to read document. The recommendation at the end of each section gives the reader clarity of evidence. The classification of evidence also gives clarity to the reader. Excellent update with new evidence.	*Thank you. No action required.*
	Perhaps part of the Guidelines could have been abridged to focus more on the thoughts and comments of lay people. This could have been styled in statement form, with direct questions, as to the contents.	*A separate patient version will be produced once this draft is finalised.*
	I'm sorry to be negative/critical but this guideline is a bit of a mess - inconsistently written with lengthy inappropriate emphasis of some areas and very little on others. Seems to be written by someone who thinks meta-analysis is more important than clinical interpretation of evidence form large RCTs (e.g. stuff written on MRAs and ejection fraction. Hugely out of date in certain sections. Scotland will not look good if this gets published as presently written!	*Specific comments from this reviewer will be addressed throughout the report.*
	Throughout the draft reference is made to the patient however I wonder if it is now time to consider using persons living with the impact of CHF. This integrates the patient and their significant other who will be crucial in the overall management of the person on a day to day basis and would be at the heart of person centredness.	*This has been discussed at length. The GDG is aware of the wider issues of people with HF and person-centre care, but it was agreed to use 'patient' as it is a more concise term and is consistent with other SIGN guidelines.*
	Just for the record (as you know), I think the mixing of 'R' and 'A B C and D' recommendations is confusing and unhelpful. They should all be R and conditional if B-D. The wording may need so attention to keep in step with the new way of stating recommendations.	*Old grading system removed.*
	The guideline requires a great deal of revision to be of additive value to recent guidelines such as the 2012 European Society of Cardiology Guidelines. A lot of it is very out of date. The CRT and ICD	*Specific comments addressed in relevant sections.*

	sections require particular attention. LCZ696 must be considered. Any rule that does not allow this to be considered should be over-turned. There are a lot of sections that add very little and should be deleted to allow the key messages to be conveyed.	
	On behalf of the British Society for Heart Failure, I would like to thank you for allowing us to comment on draft 1.8 of the SIGN guideline on the management of chronic heart failure. This guideline should represent the most up-to-date evidence for the management of this syndrome, although - as stated in Section 1.2.4 - only some of the sections have been updated. We have several comments to make: Layout - This guideline does not read particularly well, and for that reason it is unlikely to replace the 2012 ESC heart failure guideline as a resource for Scottish healthcare professionals, unless it represents up-to-date recommendations (which does not appear to be the case (e.g. LCZ). In particular, the device section is poorly written. The order of Section 5: pharmacological therapy is also surprising (e.g. Ivabradine is mentioned in 5.13 - after phosphodiesterase inhibitors, hydralazine, antithrombotics, etc - when the ESC mention in 4th. This should be reconsidered). There are a number of typographical errors, as well as significant inconsistency in the way certain terms are used (e.g. NT-proBNP). We would be delighted to be able to review the final draft of the SIGN heart failure Guideline prior to it being published.	*Specific comments addressed in relevant sections.*
	I was asked to provide external peer review for the updated SIGN guideline on the management of chronic heart failure, focusing on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the sections of the guideline that have been revised. As a health economist I have focussed particularly on those updated sections where economic evidence has been reviewed and used to inform recommendations. Overall, I feel the guideline is well structured and clearly written and that both the clinical and cost-effectiveness evidence informing recommendations has been summarised appropriately and succinctly. Links to SMC guidance on relevant pharmacological therapies have been made, as have references to UK based modelling exercises to inform the cost-effectiveness findings for diagnostics and therapeutic procedures.	*Thank you. No action required.*
	We welcome this updated guideline as a substantial piece of work and hope our comments will help to finalise this guidance.	*Thank you. No action required.*
	Good to see this update. Could I suggest a treatment algorithm? Also an exec summary.	*Algorithm added.* *Quick reference guide will be produced.*

	The current format is misleading. Major drug classes ACEI/ARB/ARA without question. Thereafter reader who is inexperienced may use drugs in order in which they are described eg phosphodiesterase inhibitors and digoxin before ivabradine. Algorhithm would correct this.	*Section 5 reordered.*
Section 1		
1.1	Which are the 'comparable countries'?	*Removed*
	Incidence of CHD. Date of SIGN 95 and of NICE guidelines.	*Dates for all are given. No action required.*
	Should the preamble specifically include those issues, which are of concern for patients with HF in Scotland, ie the use of BNP and the very poor uptake of device therapy? These are issues that have to be addressed to bring us back in line with European practice.	*The GDG considered this to be outwith the remit of the guideline, although this is an issue for discussion at the launch event, which will focus on implementation.*
	A lot has happened in the world of heart failure since 2007. This guidance is timely.	*No action required.*
	I found this section comprehensive and clear to a lay person.	*Thank you. No action required.*
	Clear and concise no comments to add.	*Thank you. No action required.*
	Clearly defined and justified.	*Thank you. No action required.*
	We welcome this updated guideline as a substantial piece of work and agree with the need. We would like to comment on points in sections 2.1, 3.1.4, 3.1.5 and 5.1 and hope this will help to improve the current draft guideline text.	*No action required.*
	Ok.	*No action required.*
1.1.1	New pharma therapies and device therapies merit it.	*No action required.*
	Some of the original SIGN 95 statements that are retained are very clunky and really need reworked. Others (which I will detail in the sections) are just incorrect and/or outdated. In general in relation to some of the SIGN 95 stuff, the consistency of the wording of recommendations needs significantly improved: a. The ACEI recommendation (page 20) starts 'To reduce mortality and hospitalisation' but none of the other recommendations on pharmacological therapies (eg betablockers, MRAs etc) starts like this. This will confuse people and it implies that on ACEIs do this and the others do not. This is obviously not the case. b. Contraindications- why are these listed for some drugs (e.g. beta-blockers- page 20) but not others (e.g. ACEIs- page 20). Again this is confusing. c. Some recommendations say 'heart failure due to left ventricular systolic dysfunction' (e.g. ACEIs- page 20) and others say 'chronic heart failure due to left ventricular systolic dysfunction'. Again this is confusing.	*Repetition of previous comment, which has been addressed*
	Clear and concise.	*Thank you. No action required.*
	Ok.	*No action required.*
1.2.1	Remit to share best practice on current evidence and involving lifestyle changes essential.	*No action required.*
	Clear and concise.	*No action required.*

	Clearly defined.	*No action required.*
	Disappointing that the guideline does not recommend specialist care for patients with HF at the time of diagnosis, not just on discharge from hospital.	*Objectives have been clarified but it is outside the remit of the guideline to recommend at what point in the patient journey patients should see a specialist.*
1.2.2	Makes clear complexities and defines symptoms.	*No action required.*
	Should the definition be changed? ESC definition is clearer. No discussion on stages: distinction between function and stage (can have severe impairment of LV function but be asymptomatic; stage C v NYHA I). Terminology is very important. The diagnosis of HF has to be refined to distinguish those with reduced ejection fraction versus those with preserved ejection fraction. This information defines much of the treatment options. We are now encouraging the distinction should be made in coding of discharges. Encourage terms: HEF-REF, HEF-PEF.	*Definitions have been rewritten. LVSD replaced with HF-REF and HF-PEF throughout the document.*
	It may be worth clarifying in the introduction that the guidelines focus on HF with LVSD and that HF with preserved LV systolic function/ejection fraction is covered in section 5.15.	*Agreed. Definitions section has been revised.*
	Ok.	*No action required.*
1.2.3	Why GPs so far down the list?	*Changed to alphabetical order.*
	Wide range of health professionals and welcomed inclusion of patients and carers.	*No action required.*
	It is interesting that "pathologists" are seen to be more important than cardiac nurses in this section! Where did that come from?	*Changed to alphabetical order.*
	Perhaps the lay out and language could be less technical for patients and carers having access to the guidelines.	*A separate patient version will be produced once this draft is finalised.*
	Appropriate inclusion of users.	*No action required.*
	Clearly stated.	*No action required.*
	Current format difficult for patients and carers to use.	*A separate patient version will be produced once this draft is finalised.*
Section 2		
	LCZ-696 (sacubitril-valsartan): although this new drug has not passed through SMC or NICE yet, this guideline should not be out of date the second it is published. It therefore seems very short-sighted not to mention LCZ here.	*To be added once SMC advice is published.*
2.1	BNP should be recorded: 'by whom?' Currently not available as a test in primary care, neither is echocardiography, so both of these perhaps assume sec care referral. Or is the idea that we should move to make these tests available for GPs?	*This is an implementation decision.* *The key point is to encourage the use of BNP testing.*
	BNP clearly explained.	*No action required.*
	The comments on echocardiography repeat those made in 3.1.5. The statement in bold should be sufficient.	*They are repeated because section 2.1 highlights key recommendations.*

	Included in clinical examination are details of initial investigation. Should be separate sections.	*Title changed in 3.1.5*
	There is a terrible inconsistency with the way "NT-proBNP" is written throughout the document. Could this be addressed please?	*Changed*
	This too was fairly understandable, and prior to any tests the reasons for these would be explained to the patient.	*No action required.*
	It is more conventional to refer to B-type natriuretic peptide rather than brain natriuretic peptide and the guideline is inconsistent throughout in this respect. We should encourage measurement of LVEF and not “LV systolic function” as all the trial evidence is based on LVEF. Why recommend measurement of “diastolic function”? What will it achieve? How/what to measure. This is likely to cause more confusion and problems than will solve!	*Changed* *Terminology changed throughout the document.* *Removed*
	Appropriate inclusion.	*No action required.*
	The wording is rather odd “should be recorded to indicate the need for” seems unusual. I think there also needs to be an emphasis its use on where there is diagnostic uncertainty. Where the clinical diagnosis is clear, patients should receive an echocardiogram.	*Changed to measured.* *There is a GPP on receiving echocardiogram.*
	See comments under main section of guideline.	*No action required.*
	ECG and natriuretic peptide provide different information. The evidence presented in the document clearly indicates that ECG is inferior to natriuretic peptide testing in identifying patients who require echocardiography. However, ECG gives additional diagnostic value to detect other conditions, e.g. atrial fibrillation, and we believe the guidelines should recommend natriuretic peptide testing and ECG. The wording of the draft guideline would likely not lead to the recommended change in clinical practice.	*New GPP added to sect 3.1.3 and algorithm amended*
	Role of natriuretic peptides welcomed.	*No action required.*
2.2	Wide range described.	*No action required.*
	We are also asking to see if you and your colleagues thought it would be useful to add an additional recommendation in section 2.2 to clarify the advice for patients contraindicated to beta blockers and what to do if ongoing symptoms of heart failure despite optimal treatment (including beta blockers) and heart rate above 75bpm, in this situation consider adding ivabradine.	*Ivabradine advice is given for these patients.*
	2nd paragraph – I believe this paragraph is difficult to read and could be improved. It is a key point in the guideline and I would suggest the following along the same lines as the previous paragraph “To reduce mortality and hospitalisation, patients with all NYHA functional classes of heart failure who are intolerant of angiotensin converting enzyme inhibitors, should be given an angiotensin receptor blocker unless contraindicated.”	*Changed*

	See relevant comments in other sections. All bar one statement needs reworked.	*Comments addressed in other sections.*
	I do not see why SIGN is not advocating the use of LCZ-696 here. The PARADIGM study was the largest HF treatment study, was stopped early because of overwhelming benefit (from 30 days) over our current gold standard the ACE inhibitor. This guideline will be dated before it is on the shelves. The beta-blocker therapy recommendation "unless contraindicated by a history of .....hypotension" should be SYMPTOMATIC hypotension. Can we specify "CKD 4-5" rather than "CKD>3" which may be confusing	*Recommendation to be added once SMC advice is published.* *Disagree. Asymptomatic syst BP of 80 should not get BB.* *changed*
	This is complex, and many patients would not understand the treatments discussed. Many health professionals struggle to fully comprehend pharmacological issues.	*A separate patient version will be produced.*
	The first two recommendations for an ACE inhibitor and ARB are confusing. Why does the ARB recommendation mention LVSAD/HF after an acute MI but this is not so for an ACE inhibitor? Better to stick to chronic HF and not try and cover LVSD/HF after an acute MI as well. Beta-blocker – doesn't cover LVSD/HF after an acute MI which ARB recommendation does. The use of "A" for ACE I/ARB and beta-blockers but "R" for MRAs is very confusing. Why is old terminology ("aldosterone antagonist") used instead of MRA? Why is the MRA recommendation written differently than a beta-blocker? Again, why acute MI here but not for ACE inhibitors (SAVE, AIRE, TRACE etc.) or a beta-blocker (CAPRICORN)? Why use "post" MI – stick to English! Why is sacubitril-valsartan not mentioned here nor ivabradine?	*Acute MI removed.* *MI removed from ARB recommendation.* *Changed* *Ivabradine added.* Sacubitril-valsartan will be added once advice from SMC is published.
	R1 - Prefer term mineralocorticoid receptor antagonist (MRA) to aldosterone antagonist. R2 - chronic should be >3. How do we define high potassium since it is not uncommon to run potassium high.	*AA changed to MRA.* *Now says K>5.0*
	"Patients with chronic heart failure due to left ventricular systolic dysfunction alone, or heart failure, left ventricular systolic dysfunction or both following myocardial infarction who are intolerant of angiotensin converting enzyme inhibitors should be given an angiotensin receptor blocker." I do not understand this paragraph. Why is the phrase "myocardial infarction" included? What does "to left ventricular systolic dysfunction alone, or heart failure, left ventricular systolic dysfunction or both" mean? This is a heart failure not a post-MI left ventricular dysfunction guideline. Even if SIGN was to include these trials the wording should be improved.	*Reworded* *MI removed*

	"All patients with heart failure due to left ventricular systolic dysfunction of all NYHA functional classes should be started on beta blocker therapy as soon as their condition is stable (unless contraindicated by a history of asthma, heart block or hypotension)." "Hypotension" here should be "symptomatic hypotension".	*See previous comment.*
	"Patients with left ventricular systolic dysfunction who have been admitted to hospital with heart failure, or stable patients who have ongoing symptoms of heart failure (NYHA class II to IV) despite optimal treatment, should be given aldosterone antagonists unless contraindicated by the presence of renal impairment (chronic kidney disease stage >3) and/or elevated serum potassium concentration." This is very confusing. The phrase "Patients with left ventricular systolic dysfunction who have been admitted to hospital with heart failure, or stable patients who have ongoing symptoms of heart failure (NYHA class II to IV)" essentially means all patients with heart failure due to LVSD. The phrase "who have been admitted to hospital" is redundant.	*This is consistent with trials entry criteria.*
	"Should be given aldosterone antagonists unless contraindicated by the presence of renal impairment (chronic kidney disease stage >3) and/or elevated serum potassium concentration." These drugs are now called mineralocorticoid receptor antagonists. "CKD stage >3" is not the term used in trials as inclusion criteria in trials. It would be better to specify the cut offs used in the trials. "Elevated serum potassium" is too vague. I would specify those values used in trials to ensure that patients are not denied prescription based on vague terms.	*Changed to MRA.* *Trials had different cut offs.* *Now says K>5.0*
	The term "aldosterone antagonists" is used, although this has largely been replaced by "mineralocorticoid receptor antagonists." "Unless contra-indicated by the presence of renal failure" – the degree of renal impairment should be quantified. "Unless contra-indicated by…hypotension", should perhaps be "symptomatic hypotension." Ivabradine is not mentioned – whilst this is no more than a 4th line agent its absence is notable.	*Changed to MRA* *Added* *As above* *Added*
	See comments under main section of guideline.	*Comments addressed in main section.*
2.3	Recommendation surrounding use of defibrillators useful.	*No action required.*
	As mentioned by Dr Petrie, I agree that this paragraph should not start with a negative statement. It should start with the key areas where implantable cardioverter defibrillators and cardiac resynchronisation therapy are of undoubted value and then, as a last sentence, mention for clarity the specific situation when implantable cardiac	*Recommendations removed and replaced with NICE table.*

	defibrillators are not indicated.	
	What is the justification for having CRT as a 'should be considered' recommendation. Given the raft of evidence I think this is incorrect.	*Recommendations removed and replaced with NICE table.*
	Recommendations for CRT should be "with or without a defibrillator component".	*Recommendations removed and replaced with NICE table.*
	This was explained in a friendly format.	*Given other feedback, the recommendations have been removed and replaced with NICE table.*
	It seems very odd to start with a negative recommendation for ICDs. Why are the recommendations for an ICD and CRT rolled into one? I don't think many people would agree with CRT in a patient in NYHA class II with a QRS duration of 120 msec and a RBBB configuration which is what the first part of this recommendation seems to say. This recommendation makes no initial mention of LVEF either. I really think that this section needs rewritten. The subsidiary recommendations are largely OK but the initial text is very confusing.	*Recommendations removed and replaced with NICE table.*
	The wording of the first recommendation is confusing. I would just state that CRT-P only is recommended. Top 3 recommendations. Consider reordering and rewording to aid clarity. These are really hard to read and it may be better to just use a table format. There is also the issue regarding RBBB and whether patients with RBB should also get CRT.	*Recommendations removed and replaced with NICE table.*
	1st Recommendation - Suggest make same change suggested in 6.1.1 1st recommendation below, to make statement slightly clearer.	*Recommendations removed and replaced with NICE table.*
	Recommendation - "Implantable cardiac defibrillators should not be given to patients with heart failure, left ventricular ejection fraction < 35% and NHYA class IV. If QRS is 120 ms or more, with or without left bundle branch block, cardiac resynchronisation therapy with pacing should be considered." This statement should not be the first to introduce the ICD/ CRT section. The biggest problem we have in Scotland is dramatic under-utilisation of both therapies (recent data presented at National Advisory Committee for Heart Disease). Implant rates are approximately 50% of those in England. This reflects lack of knowledge of indications and degree of benefit. These guidelines should present the evidence clearly for non-experts to easily interpret so that patients can benefit. Positive statements re both ICD and CRT should come first. The first sentence is valid but few would consider an ICD in patients in NYHA IV. I do not understand the second sentence. It does not seem to refer to ICDs but to CRT? Should it be a separate point. "Cardiac resynchronisation therapy with pacing" is an unusual term. This sentence should be reconsidered and clarified. If it means "cardiac resynchronisation therapy should be considered in patients with QRS duration>120ms-1" that should be the sentence. The word considered is wrong. The strength of evidence	*Recommendations removed and replaced with NICE table.*

	is over-whelming for CRT in terms of reduction in heart failure hospitalisations and mortality. The word "recommended" should be used. The evidence suggests > 130ms-1. In other international guidelines they are "recommended". "Considered" is far too weak. This section must be dramatically revised. It is not currently suitable for publication. Recommendation – "For patients with heart failure with left ventricular ejection fraction < 35% with QRS of 120-149 ms without left bundle branch block and NYHA class I-III implantable cardiac defibrillators should be considered." In other guidelines these have a class 1a recommendation. Recommendation – "For patients with heart failure with left ventricular ejection fraction < 35% with QRS of 120–149 ms with left bundle branch block cardiac resynchronisation therapy with an implantable cardioverter defibrillator should be considered for those with NHYA class II-III. For those with class NYHA class I implantable cardiac converter should be considered." That CRT is indicated in NYHA IV patients is not captured except in the table. Recommendation – "For patients with heart failure with left ventricular ejection fraction < 35% with QRS ≥ 150 ms with or without left bundle branch block, NHYA class I-III, resynchronisation therapy with an implantable cardioverter defibrillator should be considered." Again, CRT should be recommended not considered.	
	The device guidance is very muddled and is almost unintelligible. Perhaps the NICE table would be better here too, as it has been endorsed by Healthcare Improvement Scotland. Scotland already has a CRT implant rate a third of that of the other Home Nations. This guideline should help address this imbalance. It should be LVEF≤35% (i.e. not <35%). What is an "implantable cardiac converter"?? Presumably you mean "implantable cardioverter defibrillator."	*Recommendations removed and replaced with NICE table.*
	See comments under main section of guideline.	*Comments addressed in other sections.*
2.4	Once again assumes a hospital audience. GP readers will probably give up at this point.	*GPP added to stress importance of community and home base care.*
	Range useful.	*No action required.*
	This section could stress a patient led multi-disciplinary approach. The patient and carers being kept informed.	*GPP added to stress multidisciplinary nature of follow-up care.*
	Could this title change to Discharge planning and care in the community? Anticipatory care planning	*GPP added to stress inclusion of ACP and*

	should be commenced and shared between secondary care and primary care.	*care in the community.*
	This should be for patients with heart failure due to LVSD as there is no evidence for nurse-led care post-discharge.	*Nurses are part of the MDT follow up discussed in the evidence statement. This is taken from SIGN 95.* *In many parts of the UK nurses are involved in care of patients with HF without LVSD.*
2.5	Good practice point - an important one in the community, where this group are likely to have multiple morbidities and polypharmacy.	*GPP amended to stress importance of multidisciplinary care and communication between primary and secondary care.*
	Important for chronic heart failure and provision of care at home seen as desirable and details of implementation useful.	*GPP reworded.*
	This section covered the sensitivities of this area adequately.	*No action required.*
	Why are we putting a purely opinion based "good practice point" (I don't agree that it is) in the highlights at the start of the guideline (and not even mention ivabradine)?? This is very puzzling.	*Guideline group felt it was important to stress the importance of discharge and anticipatory care planning, despite lack of evidence.* *Ivabradine has now been added to key recommendations.*
	This should be done through the starting of an anticipatory care plan by an electronic key information summary being shared between primary and secondary care.	*This is an implementation issue and outwith the guideline remit.*
	Consider changing narrative from Palliative care approach to Principles of palliative care, with focus on symptom relief and rationalisation of non-essential treatments should be considered by all clinicians managing patients with chronic heart failure.	*Section on palliative care has been amended and reflects this point.*
Section 3		
	Again, NT-proBNP is the abbreviation that should be used.	*Changed*
3.1.1	Basic investigations - this section again skirts the issue of availability of tests, whilst whetting our appetite with the possibility of ECG as an alternative to BNP.	*Outside remit of guideline to discuss availability of tests.*
	Investigation of symptoms recommended.	*No action required.*
	The table might lead to confusion in that the symptoms are on one side and the signs on the other and people may think that the symptoms on the left relate to the signs on the right. It would be better to have a table which had, first of all, symptoms typical on the left and less typical on the right and then signs underneath that, with specific on the left and less specific on the right. I appreciate that this table was reproduced from another manuscript and therefore any change would require discussion with the authors. I believe it would be worth emphasising, when discussing the basic tests being done for heart failure, that from time to time, depending on the symptoms, there may be other causes to consider such as harmochromatosis, pheochromocytoma and other conditions which might give rise to tachycardia induced heart failure such as thyrotoxicosis.	*This is taken directly from ESC guideline. We have added a thicker line down the middle to make it clearer.*
	This gave the information necessary in carrying out a diagnosis.	*No action required.*

	Appropriate.	*No action required.*
	Typo 1st paragraph – the text should say “table 1” instead of “table 2”.	*Text amended.*
3.1.2	What patients should receive outlined.	*No action required.*
	BNP “depending on local circumstances” – has to be stronger than this – it is unacceptable that BNP is not routinely available in Scotland.	*Outwith guideline remit.*
	Can it state BNP or NT-proBNP please?	*Changed*
	Perhaps a little consideration should be given to various expertise given with in other hospitals.	*Service provision is a consideration for local implementation.*
	What does MICE stand for? Why mention only BNP and not NT proBNP?	*Section moved to 3.1.1 and reworded.*
	Appropriate.	*No action required.*
	MICE scoring system – does this mean if answer to all is yes, then refer for echo? Suggest this needs clarified. 3rd paragraph - typo ‘techonology’ should be “technology”.	*Section reworded.*
	One of the key questions in Annex 1 relates to the use of clinical scoring algorithms to help identify people with suspected heart failure for further investigation. This does not appear to have been answerable based on available evidence. However, given it is one of the key update questions, this finding could perhaps be made clearer; i.e. given a bit more prominence in the text of the guideline (3.1.2). Establishing the effectiveness of this approach has been appropriately identified as further research recommendation.	*This section has been reworded.*
	Lacks clarity. Echocardiography does not suggest a diagnosis of heart failure - that is a clinical diagnosis. Echo may indicate the underlying aetiology. Unlikely that many will have access to BNP but not ECG.	*Echo does help make HF diagnosis which is how it is worded.* *There is a bigger section on echo in 3.1.5.*
3.1.3	So ECG only 60% specificity.	*Yes. Additional sentence included to stress that it is useful as a rule out test.*
	NA for patient rep.	*No action required.*
	The ECG should be a basic early investigation in heart failure regardless of whether BNP is available or not. Figure 1 - Pathway should put BNP in separate box: NICE concluded BNP should be used in preference to ECG to determine need for echocardiogram. Needs to be reflected in statement, should be no getting away from what is best, otherwise managers will say ECG is ok and money need not be spent on BNP. What is specialist assessment? No mention of heart failure clinics delivered by multidisciplinary team. Combining info obtained from ECG and BNP refines the algorithm.	*There is a GPP which states ECG should be carried out* *Pathway changed to say ECG and BNP should be carried out.* *These issues are for local implementation to determine.* *No action required.*

	Has ECG been assessed in HEF-PEF, should apply this statement to systolic heart failure.	*The group think this is clear.*
	The ECG section is wrong/out of date. An ECG is easily as evidence-based as BNP – it is used to decide whether or not CRT is indicated (QRS/BBB), whether ivabradine might be used (HR > 70/min) and whether an oral anticoagulant should be considered (AF) as well as whether a pacemaker might help (bradycardia/AV block).	*New GPP added and algorithm changed*
	Appropriate.	*No action required.*
	Please see our comments in section 2.1	*New GPP added and algorithm changed.*
3.1.4	And BNP clearly superior at 91%. Is it possible to recommend that this should be available in primary care to help with prioritisation of referrals?	*Outwith the remit of the guideline to recommend where BNP is available.*
	The recommendation should make it clear that BNP is preferred to ECG ie "B-type natriuretic peptide or NT pro-BNP levels are the best test to indicate the need for echocardiography and should be recorded. An ECG should only be used if BNP testing is not available."	*Recommendation changed.*
	This section should be called 'NATRIURETIC PEPTIDES' and not 'B-TYPE NATRIURETIC PEPTIDE'. This is both confusing, given NT-proBNP is referred to, and BNP is likely going to become rapidly outdated in the wake of LCZ696. 'BNP <100 pg/ml (<29 pmol/l) or NT-proBNP <400 pg/ml (<47 pmol/l), in the absence of heart failure therapy: heart failure is an unlikely cause for the presentation. (Page 4)'. The cut offs recommended for BNP and/or NT-proBNP are also not suitable for primary care use and/or stable cardiology outpatients clinics. They are only applicable to patient presenting at hospital with the acute signs and symptoms of heart failure. The suitable cut-offs for BNP in primary care and/or outpatients is <35pg/ml. It this guideline solely for acute staff? Given the above, the following statement also needs reworked: Patients with suspected heart failure and a BNP level above 400 pg/ml (116 pmol/litre) or an NT-proBNP level above 2000 pg/ml (236 pmol/litre) should be referred for echocardiography and specialist assessment within two weeks.	*Changed* *NICE evidence is based on studies in primary care. Section reworded to reflect that.*
	Again, inconsistency with the abbreviation "NT-proBNP". With the advent of LCZ-696, monitoring with BNP will not be reliable, and emphasis should be made of the potential superiority of NT-proBNP in this role. Figure 1 should also not have NT-proBNP in brackets for this reason. I would have "NT-proBNP or BNP"	*Changed* *Sentence added to the monitoring section.* *Brackets removed.*
	"Brain" NP becomes B-type NP here. Describing BNP as a muscle relaxant is a bit odd! Abbreviate B-type natriuretic peptide to BNP after first use – jumps around. The recommendation should	*Terminology made consistent.* *Muscle relaxant removed.* *Rec amended.* *Pg/ml measures are taken directly from NICE.*

	presumably say a BNP (or NT proBNP) level (singular) should be recorded (measured?) – not levels. NICE does not allow use of pg/ml (only allows ng/l) – does SIGN have a different position? The good practice point about an ECG is misplaced here and in correct. An ECG is easily as evidence based as BNP – it is used to decide whether or not CRT is indicated (QRS/BBB), whether ivabradine might be used (HR > 70/min) and whether an oral anticoagulant should be considered (AF) as well as whether a pacemaker might help (bradycardia/AV block).	*GPP moved and reworded*
	Appropriate.	*No action required*
	To make this recommendation of using BNP as a screening test for the exclusion of the need for echocardiography (which is what this is otherwise we would (? should) echo everyone with suspected CHF) then you need to give the negative predictive value for BNP (and ECG). This is not in the text and needs to be there to justify the recommendation. Also should the term 'guide' rather than 'indicate' be used? Finally the recommendation is for a test to avoid another test (is this what the evidence suggested?). Where there is ready provision of echocardiography this can be performed first line. It is odd that BNP deserves a recommendation and echo (and other imaging) does not given that this is central to the diagnosis and investigation of CHF. Page 10. Two recommendations. What is the evidence for these time lines? They seem reasonable but certainly have to be conditional and sound more like a good practice point than based on fact. What happens if you wait twice as long? Is there any harm (apart from delay)?	*Added a comment in sect 3.1.3 around the rule out purpose of the test. The work that is referenced provides the figures.* *Wording changed* *This would be impractical to implement* *This is based on expert opinion from the NICE guideline.*
	Should it perhaps be a good practice point for health boards to provide and offer BNP testing?	*This is outwith the remit of the guideline.*
	One of the main revisions in this section relates to the role of B-type natriuretic peptide in the diagnosis pathway (3.1.4), and whether there is evidence for improved outcomes associated with earlier referral for echocardiography in those with moderate high BNP. It appears no evidence has been identified here, but the case for early referral has been recommended based on logical reasoning and expert opinion (following the approach recommended by NICE). This seems reasonable.	*No action required*
	The level of diagnostic accuracy study evidence for natriuretic peptide testing was graded as 2++. We would like to comment that the rating scale used is more suitable for interventional studies than for diagnostic accuracy studies and that the presented evidence for natriuretic peptide testing is in fact the highest level of evidence for accuracy studies. Please also see our comments in under section 2.1.	*SIGN methodology rates such papers as 2++.*

3.1.5	If we accept this is secondary care only then the evidence would seem to suggest that BNP testing should be more readily available.	*No action required*
	Diagnostic algorithm – it should be NP/NT proBNP AND ECG. An ECG is always indicated. LVEF should be measured. See earlier comment about diastolic function. The high resolution comment is silly (no one is going to suggest the alternative).	*Changed* *It is not necessary to measure LVEF at the diagnostic stage.* *High resolution comment removed.*
	Fig 1- What about clinical suspicion of CHF and normal ECG, where BNP testing not available – Echo or not?	*BNP testing should be made available across Scotland. The group would therefore prefer not to complicate the algorithm with additional clinical scenarios.*
	Figure 1 – we would argue that NT-proBNP should now be suggested before BNP – particularly as the inevitable use of LCZ-696 will render subsequent measurement of BNP (but not NT-proBNP) unreliable.	*Prefer to leave both as an option. NT pro-BNP should be used for monitoring.*
3.2	Introduction. The section on coronary angiography is out of date. It should be considered if the patient has angina and is a candidate for revascularization. Even if the patient doesn't have angina some would advocate revascularization (and therefore angiography) if there is a substantial area of ischaemic but viable myocardium. CT coronary angiography should be mentioned. Indeed, I think the whole imaging section is outdated.	*GPP updated.*
3.2.1	Role of MRI seems very understated.	*Imaging section updated.*
	Nobody really does MUGA or PET. CMR should have more prevalence in this modern era.	*Imaging section updated.*
	Very out of date - see above.	*Imaging section updated.*
	There should be some recommendation about imaging here especially as the lowly chest x-ray gets a recommendation all of its own. Echo is straight forward and given that there is a recommendation for BNP, there must surely be one for echo. Many would also welcome a recommendation for MRI as this is often used rather indiscriminately. Clear indications such as haemochromatosis/thalassaemia as well as the need for fibrosis imaging for revascularisation decisions (recommendation made later in the guideline).	*Imaging section updated but there is insufficient evidence to support a recommendation.*
	Imaging techniques – CMR should receive more of a recommendation. MUGA and PET are not in common usage.	*Imaging section updated but there is insufficient evidence to support a recommendation.*
Section 4		
4.1	Might there be a useful illustration for units, easier to follow than having this in text.	*This section has been removed.*
4.4.1	The balance of evidence does not favour salt restriction and this section is out of date.	*Section revised.*
4.6	Need to specify which QOF year you are referring to - minor changes from year to year, and big change expected in 2017.	*Date added.*

	Inclusion of depression and its treatment important.	*No action required.*
	Having said that “There is insufficient evidence to guide clinicians as to which screening or assessment measures to use with this population”, it does not follow that “All patients on the CHD register should be screened for depression using the Whooley questionnaire which asks two standard questions…” The reference given here (41) is a link to the measure - Whooley (typo) Screen: Depression and it is not possible to reach it with the link address given. http://www.bcbst.com/providers/Behavioral-Health-Toolkit/PDFs/Whooley%20Depression%20Screening%20Tool.pdf A more relevant reference might be Whooley, Mary A. "To screen or not to screen?: Depression in patients with cardiovascular disease." Journal of the American College of Cardiology 54.10 (2009): 891-893. She concludes that screening can be of benefit, but only when combined with a collaborative care intervention. Although I agree with the intention of this section i.e. that it is clinically important to identify mental health problems such as Depression and Anxiety in this population and to offer Evidence Based Interventions, I think that the guidelines need to be clear about what follows from the evidence and if it is a recommendation for good practice e.g. screen people for depression and anxiety as one would in the general population, that this needs to be made explicit in the text. Also, that the reason for choosing one measure over another (when none are recommended by the literature) needs to be given. A screening tool such as the PHQ 4 would allow brief screening for Depression and Anxiety (see comments on Anxiety below). The section on Mood Disorders 4.6 page 17 focussed solely on Depression. I am aware that the Key Question in this update was specific to “heart failure and depression”. I suspect that this is due to the increased risk of mortality (shown in some studies) and poorer prognosis associated with depressed mood. However the prevalence of anxiety has also been shown to be high in people with heart failure. Yohannes, A. M., et al. "Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles." International journal of geriatric psychiatry 25.12 (2010): 1209-1221. As with depression, evidence related to mortality, morbidity and prognosis is mixed, but might also be worthy of consideration in future guidelines. A recent study (Lossnitzer, Nicole, et al. "A patient-centered perspective of treating depressive symptoms in chronic heart failure: What do patients prefer?." Patient education and counseling 98.6 (2015): 783-787.) considering patient (CHF) perspectives on psychosocial treatment of depression, found that the most favoured treatment option was a low-threshold service with supportive talks. They also suggested that “Future studies investigating the improvement of patient-centred care in CHF patients should include measurements	*There are no high quality randomised controlled trials providing evidence that the screening programme effectively reduces morbidity.* *Paragraph on Whooley removed.* *Whilst there is recognised high prevalence of anxiety within this population, at the time of writing there is insufficient evidence available to answer any questions regarding the treatment of anxiety in people with HF. Added as a research recommendation.*

	of generalized anxiety." I wondered whether this might be worth considering in Recommendations for Research 11.2?	
	"Disease-anagement programmes". Should this read Disease-management?	*Amended*
	Mood and mental health of a patient has to be considered by a clinical psychologist if a member of the team considers it as appropriate. Social work should also be considered in respect of patients coming to terms with life changes.	*The guideline recommends that all people with HF are screened for depression. This recommendation is relevant for all staff within health and social care settings.*
	This is a very confusing section. Why does it mention CHD registers and palliative care? Why?	*Sentences removed.*
	There is a typo in the last paragraph of page 17 - it should state 'Disease Management' - there is a missing 'M'.	*Amended*
	At the end of the introduction to this section please add a sentence it is now recognised that patients with advanced progressive illnesses such as heart failure also often have existential distress at the end of life which may be interpreted as depression as factors such as loss of meaning and purpose may be common in both these issues. Recent qualitative research has shown that patients may consider themselves not depressed but down. [1, 2] 1. Leeming A, Murray SA, Kendall M: The impact of advanced heart failure on social, psychological and existential aspects and personhood. Eur J Cardiovasc Nurs 2014, 13(2):162-167. 2. Murray SA, Kendall M, Grant E, Boyd K, Barclay S, Sheikh A: Patterns of Social, Psychological, and Spiritual Decline Toward the End of Life in Lung Cancer and Heart Failure. J Pain Symptom Manage 2007, 34(4):393-402.	*This is outside the remit of the key question so a systematic search has not been conducted in this area.*
Section 5		
	Para 2 need to emphasise that this is for HEF-REF. Limited discussion about HF and atrial fibrillation, one situation which clearly straddles HEF-REF and HEF-PEF, need to emphasise importance of anticoagulation.	*Changed* *This will be covered in the arrhythmia guideline.*
	Why refer to LVSD? Current terminology prefers HF-REF (and HF-PEF).	*Changed*
	I found the order a little strange since it is not the order drugs are usually considered: ACEI or alternatives BB or alternatives MRAs Diuretics Others.	*Order changed.*
5.1	Do cost effectiveness calculations allow for reduction in hospital input for patients if GPs were to be allowed to measure it?	*The economic analyses are based on studies set in secondary care.*
	Clearly set out but not qualified to comment on clinical content.	*No action required.*
	Should this section come later, ie after treatments have been described?	*Section has been moved.*

	This section should be called 'NATRIURETIC PEPTIDE-GUIDED TREATMENT' rather than specifically 'BTYPE NATRIURETIC PEPTIDE-GUIDED TREATMENT', as this implies that it does not include NTproBNP which is does. It is currently confusing. Ditto, the section stating B-type natriuretic peptide-guided monitoring may be considered in patients with heart failure aged less than 70 years, especially in the presence of higher baseline N terminal pro BNP levels. The consistency is poor and therefore it is confusing.	*Changed* *Changed*
	Again, NT-proBNP monitoring would be preferred to BNP once LCZ is routinely used	*Amended*
	The recommendation in favour of BNP guided (why not NT proBNP) therapy goes against mainstream practice (e.g. the ESC guidelines). BNP/NT proBNP guided therapy has not been widely accepted because of the small total number of patients studied, the inconsistent findings of the trials, the inadequate standard of treatment in the control group in several studies and the fact that the single largest rail of this approach is still ongoing.	*Changed to NT proBNP* *Added caveat that BNP is not suitable for patients using sacubitril-valsartan (LCZ6969).* *Wording of recommendation 'may be considered' reflects strength of evidence.*
	Agreed, but should we consider more than 'considered'.	*Wording based on strength of evidence.*
	Comprehensive and accurate interpretation of the pharmacological evidence base.	*No action required.*
	By the time this guideline is published LCZ 696 will be available. The discussions around cost-effectiveness will be redundant for 2 reasons. Firstly, BNP will no longer be used as its plasma concentrations are increased by LCZ 696. This will result in NT-BNP being used. Secondly, NT-BNP will be the gateway for prescription of LCZ as this was an inclusion criterion in the clinical trial. NT-BNP will be necessary to target this new (and probably expensive drug) towards those who will benefit. Without NT-BNP there will be widespread prescription to those who would not have got into the clinical trial. It could be argued that this is in the future but to have a 2016 guideline not addressing LCZ and NT-BNP would be silly. I understand that there are rules as to why LCZ cannot currently be discussed. Whatever these rules are they are not patient-centred and lack common sense.	*Publishing advice which may conflict with SMC causes confusion and may lead to inequities in access to the drug across Scotland.* *A sentence has been added to the BNP testing section.*
	BNP guided treatment. In the recommendation, monitoring with BNP will be affected with the use of LCZ-696. NT-proBNP will not be adversely affected.	*Have added caveat that BNP is not suitable for patients using sacubitril-valsartan (LCZ6969) and changed to NT-proBNP.*
	Regarding the recommendation for the consideration of B-type natriuretic peptide-guided treatment, it is unclear what the rational for the <70 years age restriction is, when the reviewed evidence seems to suggest significant benefit and cost-effectiveness for those 75 years and under. Given the apparent conflicting findings of the two referenced meta-analyses, should the recommendations make clearer distinction between BNP-guided therapy and NT-proBNP-guided therapy? To which monitoring/treatment regimens do the cost-effectiveness findings relate?	*Changed to 75 years as only cost effective <75.* *In the studies both BNP and NT-proBNP were found to be cost effective – this has been added to the draft.*

	The evidence cited shows effectiveness of serum natriuretic peptide guided therapy for patients under 75 years of age. The age threshold in the recommendations should reflect this rather than 70 year of age. Given the level of evidence, the recommendation should be worded clearer: "Serum natriuretic peptide-guided monitoring should be considered in patients with heart failure aged less than 75 years, especially in the presence of higher serum natriuretic peptide levels." Regarding the availability of B-type natriuretic peptide testing in Scotland we would like to comment that testing has been widely implemented across the UK, with Roche Diagnostics playing a leading role in the education of primary care health care professionals. Roche is committed to play a similar role in Scotland.	*Changed to 75.*
	Why <70 years rather than <75 years which is what evidence supports? Inconsistent message.	*Changed*
5.2	Include; See Annex 3 for practical guidance on use of ACE inhibitors.	*Added*
	The consistency of the wording of recommendations needs significantly improved: a. The ACEI recommendation (page 20) starts 'To reduce mortality and hospitalisation' but none of the other recommendations on pharmacological therapies (eg betablockers, MRAs etc) starts like this. This will confuse people and it implies that on ACEIs do this and the others do not. This is obviously not the case. b. Contraindications- why are these listed for some drugs (e.g. beta-blockers- page 20) but not others (e.g. ACEIs- page 20). Again this is confusing. c. Some recommendations say 'heart failure due to left ventricular systolic dysfunction' (e.g. ACEIs- page 20) and others say 'chronic heart failure due to left ventricular systolic dysfunction'. Again this is confusing.	*Contraindications have been removed from the recommendations and reference made to the annexes* *Changed*
	Inconsistent approach to describing effects of key disease-modifying drugs.	*The format and content of the recommendations have been made more consistent.*
	Comprehensive and accurate interpretation of the pharmacological evidence base.	*No action required.*
5.3	The consistency of the wording of recommendations needs significantly improved: a. The ACEI recommendation (page 20) starts 'To reduce mortality and hospitalisation' but none of the other recommendations on pharmacological therapies (eg betablockers, MRAs etc) starts like this. This will confuse people and it implies that on ACEIs do this and the others do not. This is obviously not the case. b. Contraindications- why are these listed for some drugs (e.g. beta-blockers- page 20) but not others (e.g. ACEIs- page 20). Again this is confusing.	*Duplicate of previous comments, see 5.2.*

	c. Some recommendations say 'heart failure due to left ventricular systolic dysfunction' (e.g. ACEIs-page 20) and others say 'chronic heart failure due to left ventricular systolic dysfunction'. Again this is confusing.	
	There is greater evidence for the use of carvedilol than the other beta-blockers, and this should be stated first.	*Prefer to recommend beta-blockers as a class rather than looking at head-to-head trials.*
	Inconsistent approach to describing effects of key disease-modifying drugs. Should address issue of role of beta-blockers in patients with atrial fibrillation.	*This has been addressed.* *Meta-analysis and registry data for BB and AF are inconclusive and further trials are need before a recommendation could be made.*
	Comprehensive and accurate interpretation of the pharmacological evidence base.	*No action required.*
	Page 20. Bottom recommendation. Not sure why only three contraindications are mentioned. The recommendation suggests you can start it if other contraindications are present. Suggest the text in parentheses is deleted.	*Contraindications removed from recommendation.*
	Beta-blockers – there is more evidence for the use of carvedilol than bisoprolol and metoprolol (the preparation used in MERIT-HF is not available in the UK).	*Prefer to recommend beta-blockers as a class rather than looking at head-to-head trials.*
5.4	Clearly laid out.	*No action required.*
	Include: see annex 4 for practical advice on use of ARBs.	*Added*
	'Patients with chronic heart failure due to left ventricular systolic dysfunction alone, or heart failure, left ventricular systolic dysfunction or both following myocardial infarction who are intolerant of angiotensin converting enzyme inhibitors should be given an angiotensin receptor blocker.' (Page 21) This is confusing and strays into asymptomatic LVSD, post-MI LVSD, and post-MI HF when other recommendations for ACEIs etc do not. I am unsure of the logic for this? It is very confusing for the reader.	*Changed*
	I don't think it is at all correct to say ARBs mimic the effect of ACE inhibitors. Discussion of CHARM Alternative uses ARR in a different way to earlier sections on ACE inhibitors and beta-blocker why not be consistent? The recommendation for acute MI patients comes out of nowhere! If you are going to mention acute MI you need to mention VALIANT (and also the ACE inhibitor and beta-blocker trials).	*Removed* *Removed*
	R1 - See MRA comment.	*Changed*
	Comprehensive and accurate interpretation of the pharmacological evidence base.	*No action required.*
	Page 21. New recommendation. Pages 22 and 23. Sorry about raising semantics. For this and subsequent recommendations, I would suggest the term "mineralocorticoid receptor antagonist (MRA)" not "aldosterone antagonist" as this is more accurate and correct. Spironolactone and eplenerone block the mineralocorticoid receptor. The latter can be	*Changed to MRA.*

	activated by glucocorticoids as well and indeed there is a lot of evidence that glucocorticoids are the main agonists of the mineralocorticoid receptor.	
	Recommendation – "Patients with chronic heart failure due to left ventricular systolic dysfunction alone, or heart failure, left ventricular systolic dysfunction or both following myocardial infarction who are intolerant of angiotensin-converting enzyme inhibitors should be given an angiotensin receptor blocker." This is confusing. I would remove the repetition of "left ventricular systolic dysfunction or both following myocardial" or simplify it. This is a heart failure not post MI LVSD guideline.	*Changed*
5.5	Clearly explored.	*No action required.*
	Proposed Wording (see below for original wording - Removed) "A large multicentre RCT of a new drug LCZ696 (a sodium salt complex comprised of the neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan) has demonstrated significant benefits compared to enalapril. Patients (n=8,442) were NYHA class II, III, or IV with a LVEF ≤40% (later changed to ≤35% by an amendment to the protocol), and were required to have a plasma NT-proBNP level of at least 600 pg/ml (or a BNP level ≥150 pg/ml), or if they had been hospitalised for heart failure within the previous 12 months, an NT-proBNP level of at least 400 pg/ml (or a BNP ≥100 pg/ml). "The study stopped early due to overwhelming evidence of benefit. LCZ696 reduced the primary endpoint (cardiovascular death or HF hospitalisation) by 20% compared to enalapril (HR 0.80, CI 0.73 to 0.87, P<0.001). Cardiovascular deaths were reduced by 20%, (HR 0.80, CI 0.71 to 0.89, P<0.001) and the risk of hospitalisation for heart failure was reduced by 21% (HR 0.79, CI 0.71 to 0.89, P<0.001). In addition, all-cause mortality was reduced by 16% (HR 0.84, CI 0.76 to 0.93, P<0.001). "The trial included a run-in phase to minimize early drop out after randomization and to ensure that the comparator dose (mean dose of enalapril 16.6 mg daily) with established mortality benefit was achieved during the long term follow up. A total of 12% of patients withdrew during the run-in phase due to an adverse event. "After randomisation, patients in the LCZ696 group were more likely than those in the enalapril group to have symptomatic hypotension (14.0% vs. 9.2%; p<0.001), but these events rarely required the discontinuation of treatment (0.9% in the LCZ696 group vs. 0.7% in the enalapril group; p=0.38). Angioedema was non-significantly more common in the patients taking LCZ696 (0.45% vs 0.24%). Overall, after randomisation, fewer patients in the LCZ696 group stopped their study medication because of any adverse event (10.7% vs. 12.3%, P=0.03).	*Reworded in line with SIGN style.*

	"The drug has not yet been granted a licence in the UK but SMC guidance is anticipated by the end of the year."	
	Is SIGN really not going to recommend this drug in any way? The PARADIGM-HF study should give this a level A recommendation under previous assessment. This represents a major advance in the medical management of HEF-REF. The drug is likely to become available quickly, already being fast tracked by FDA.	*To avoid confusion, we cannot make a recommendation until SMC advice is issued. The guideline will be updated once the SMC decision is known.*
	This guideline is in danger of being outdated before it even goes to print in relation to LCZ696. Discussions at national level are already underway in relation to LCZ696. Given its weight of evidence then I cannot see why SIGN would not wait for these to finish before publishing as essentially LCZ696 will radically alter our treatment algorhythm for patients with Moderate-Severe LVSD and HF, as soon as it is licensed and goes through SMC. This will probably only be 6 months away.	*The guideline will be updated once the SMC decision is known.*
	This section is too brief, and appears dismissive of the true benefit of this new class of drug. Indeed the section on Co-enzyme Q10 is greater!!! SIGN should offer a recommendation.	*Section rewritten.* *To avoid confusion, we cannot make a recommendation until SMC advice is issued. The guideline will be updated once the SMC decision is known.*
	The generic name for LCZ696 is sacubitril-valsartan. The LVEF was ≤40% not <35% and NYHA class was II-IV. Why are no p values cited (as in the other sections). Why no ARR and NNT, as for other sections? The drug is available in the USA and is being fast-tracked in Europe, including the UK.	*Changed.* *LVEF levels included.* *NNTs have been added. SIGN policy is to cite statistics provided in the paper, rather than working out ARRs if they are not given.*
	I assume this can be updated prior to publication. EMA approval likely towards end of year (although SMC will be later). This is a significant development and guideline could be out of date almost immediately if a recommendation is not made.	*The guideline will be updated once the SMC decision is known.*
	Comprehensive and accurate interpretation of the pharmacological evidence base.	*No action required*
	This is the first heart failure guideline to be published since this trial was completed. It was led by a Scot. There will be no more trials in heart failure as it was resoundingly positive. The New England Journal insisted on the word "over-whelming" when describing the benefit. LCZ 696 will definitely be prescribed for those who meet the inclusion criteria. Its approval is being prioritised by the Scottish Medicines Consortium as well as European and US regulatory authorities. To have such a bland section is remarkable. It should be recommended to those who meet the inclusion criteria. It will be subsequently recommended by NICE, the European Society of Cardiology. Heath Boards, clinicians and patients all want to know if it should be used. To "dodge" the issue does not benefit anyone. This also an opportunity to recommend the drug for people who are likely to benefit ie not everyone who is prescribed an ACE inhibitor but those with high BNPs and other inclusion criteria. The comment re angio-oedema is wrong. How can it be "more common" if it was not	*To avoid confusion, we cannot make a recommendation until SMC advice is issued. The guideline will be updated once the SMC decision is known.*

	significant.	
	Angiotensin Receptor Neprilysin inhibitors is a very short section (shorter than the section on nutritional supplements and half the size of iron deficiency!!) and offers no recommendation. This should be reconsidered as the data to support its use is substantial. The run-in period described was a FDA requirement for the trial, and not a way of ensuring that LCZ was seen to be well tolerated. In fact, more patients withdrew in the ACE inhibitor part of the run in, than the LCZ run in. Symptomatic hypotension was more common but treatment withdrawal was the same.	*Section rewritten with more detail.* *To avoid confusion, we cannot make a recommendation until SMC advice is issued. The guideline will be updated once the SMC decision is known.*
	Not available, not licensed. Would need specialist assessment.	*A note has been added that it is available under the EAMS scheme with ADTC conditions.*
5.6	Fully described.	*No action required.*
	The statement that eplerenone being substituted for spironolactone in patients who develop gynaecomastia is in a slightly confusing position because it immediately follows a recommendation regarding the use of eplerenone itself. I believe this would be better located in the area where spironolactone is specifically discussed, ie, after the first recommendation point in this regard.	*Second recommendation removed.*
	In R statement - what is elevated serum potassium that contraindicates prescription? Caution should be should stop prescription caution should be applied at K >5, likewise degree of renal impairment, caution if Cr > 221. CKD 3 not used as a guide in the how to use annexes.	*K>5 added* *Added*
	ALDOSTERONE ANTAGONISTS (page 22)- this is out-dated term and should now be Mineralocorticoid Receptor Antagonists. All references to this should be changed. 'Patients with left ventricular systolic dysfunction who have been admitted to hospital with heart failure, or stable patients who have ongoing symptoms of heart failure (NYHA class II to IV) despite optimal treatment, should be given aldosterone antagonists unless contraindicated by the presence of renal impairment (chronic kidney disease stage >3) and/or elevated serum potassium concentration.' (Page 22). This is totally incorrect. MRAs are only evidenced based in patients with LVEF <35% (i.e. RALES, EPHESUS and EMPHASIS). The above statement implies that we should give these medications to patients with mild LVSD (e.g. LVEF 45-55%) who have been admitted to hospital and/or are chronic stable with NYHA 2-4. There would be no evidence what-so-ever to back this up. The event rate and event type of patients with LVEF>35% vs. those with LVEF<35% is radically different and thus so will the likely benefit/harm ratios of MRAs. This section needs a radical rewrite. The consistency of the wording of	*Changed* *Changed*

	the statement is also poor when compared to other medicines. Patients, post myocardial infarction and with left ventricular ejection fraction ≤ 40% and either diabetes or clinical signs of heart failure, should be considered for eplerenone unless contraindicated by the presence of renal impairment (chronic kidney disease stage >3) and/or elevated serum (page 22). Why is this only down as 'should be considered'? Again I am unsure why contraindications have been listed here when not listed in other medication recommendations and why values have been given to renal impairment but not elevated potassium.	*Removed*
	I think this section should appear before ARBs, as the evidence for MRAs pre-dates that for ARBs, and the recommendation for MRAs is higher than for ARBs. Also, other guidelines use "MRA" rather than "aldosterone antagonists". EMPHASIS-HF was less symptomatic but still severe LVSD.	*Section restructured.* *Changed*
	Why aldosterone antagonist and not MRA? RALES – no entry LVEF given. EMPHASIS-HF-the LVEF was ≤35% not <35%. The inclusion criteria are not complete (QRS duration). Why are different endpoints reported for the different drug classes? EPHESUS – this is very odd. Why one acute MI trial for MRAs but not for other drugs (e.g. SAVE, AIRE, TRACE, and CAPRICORN?) Why pick out sudden death? The section on LVEF is ridiculous! Small numbers, surrogate outcome, selective (much better data for beta-blockers!). It is even more ridiculous to suggest the cost-effectiveness of spironolactone is in doubt if eplerenone is cost-effective! Why do you mean by "elevated" potassium concentration? Be precise. This is another example of a different approach to describing the effects of the key drugs in heart failure.	*Changed to MRA.* *Added* *Added* *Sudden death removed.* *Removed* *Health Economists have reconsidered the HTA on which this is based and felt that while the study showed eplerenone to be cost-effective there were weaknesses in concluding that spironolactone is not cost-effective. The paper has therefore been removed from the evidence statement.*
	The wording..."Spironolactone has not been addressed by SMC..." is the wrong choice of wording as it is misleading. One of SMC's outwith remit criteria is medicines that have been initially licensed and made available to market prior to 2002. Spironolactone is outwith remit so cannot have been assessed by SMC. Aldosterone antagonist bullet point recommendations: There are 2 current pieces of SMC advice relating to eplerenone: May '05 - Eplerenone is accepted in addition to	*This statement has been removed.*

	standard therapy to reduce the risk of CV mortality & morbidity between 3-14 days post MI in stable patients with LVD (LVEF 40%) and clinical evidence of HF. July '12 - Eplerenone is accepted in addition to standard optimal therapy to reduce the risk of CV mortality & morbidity in adults with NYHA II CHF and LVEF less than/equal to 30%. The first bullet point in this section potentially suggests use of aldosterone antagonists in a broader group of HF patients than those that SMC has approved in either pieces of advice (for eplerenone). In the second bullet point, SIGN has stated that "Patients, post MI and with LVEF less than/equal to 40% and either diabetes or clinical signs of HF should be considered for eplerenone..... The patient groups are also possibly broader than SMC advice although this might not be significant in practice.	*SMC advice is for eplerenone. Recommendation covers MRAs as a class.* *Removed*
	See 2.2 (R1 - Prefer term mineralocorticoid receptor antagonist (MRA) to aldosterone antagonist. R2 - chronic should be >3. How do we define high potassium since it is not uncommon to run potassium high.)	*Changed* *Changed*
	Comprehensive and accurate interpretation of the pharmacological evidence base.	*No action required.*
	Page 22. Not sure I agree with the contraindications. Someone with heart failure and an eGFR of 59 should be tried on a MRA. Also many patients tolerate an MRA with a borderline elevated potassium. Again I would drop this from the recommendation and there are other contraindications. Discussion of these points can be retained in the text. Page 22. Final recommendation. We should ensure that this is consistent with the ACS Guideline recommendation. Page 23. The first recommendation should be a good practice point or just included in the text. This is not a recommendation.	*The group think this is a valid cut off point.* *Has been removed.* *Changed to GPP.*
	Mineralocorticoid receptor antagonists (a.k.a aldosterone antagonists) should appear before angiotensin receptor antagonists, as ARBs should only be used in those truly intolerant of ACE inhibitors or MRAs. Another point is that the EMPHASIS-HF study was not a study of “less severe symptomatic HF”, but rather a study of less symptomatic but still severe LVSD.	*ARBs considered along with ACE and hence it appears before BB and MRA.* *Changed*
	There is a stated priority to consider cost-effectiveness evidence relating to the use of aldosterone antagonists, which has been done (5.6). This appropriately makes reference to SMC guidance for Eplerenone, and states that SMC have not looked at spironolactone. Given the wording of the two recommendations that follow, it is not	*Change to MRA rather than specific drugs.*

	absolutely clear to me if together these are stating that spironolactone should be considered the first line treatment, and that Eplerenone should only be considered if SMC criteria are met. The first recommendation suggests that any patient with left ventricular systolic dysfunction who has been admitted to hospital with heart failure, or stable patients who have ongoing symptoms of heart failure (NYHA class II to IV) despite optimal treatment, should be given "aldoseterone antagonists" (i.e. suggesting either spironolactone or Eplerenone could be given).	
5.7	Would be helpful to have comment about management of refractory oedema and the role thiazides, including metolazone. Role of temporary withdrawal or reduction in dose of beta blocker.	*The update did not include a review of evidence in this area.*
	This is an over-simplification and borderline dangerous. What about patients with a raised JVP, or ascites? It should read Diuretic therapy should be considered for heart failure patients to relieve clinical signs or symptoms of fluid overload/congestion.	*Changed*
	Comprehensive and accurate interpretation of the pharmacological evidence base.	*No action required.*
5.8	Positioning of ivabradine for heart failure patients in sinus rhythm. Section 5.8 on Digoxin reads as though digoxin is recommended before Ivabradine as an add on therapy for heart failure patients in sinus rhythm who are still symptomatic after optimum therapy. This is inconsistent with the ESC algorithm and also the positioning of Ivabradine as approved by the SMC. We are concerned this will lead to confusion within the clinical community. Digoxin, has demonstrated no mortality benefit for heart failure patients. A recent paper stated "The present systematic review and meta-analysis of all available data sources suggest that digoxin use is associated with an increased mortality risk, particularly among patients suffering from AF." (Please see Vamos M et al 2015 attached). Ivabradine however has demonstrated a reduction in death due to worsening heart failure for patients in sinus rhythm. "Deaths due to heart failure did fall significantly (HR 0•74, 95% CI0•58–0•94, p=0•014)" in the ivabradine group. SHIFT (pg 5, paper attached.) Furthermore we believe that more clarity needs to be provided when proposing alternative strategies for reducing heart rate in patients unable to take a beta blocker. Given the superior heart rate reduction achieved with Ivabradine compared with Digoxin and the additional morbidity and mortality gains as demonstrated in SHIfT we believe Ivabradine should be advocated first for patients in sinus rhythm. We would like to ask if the guideline development group would include ivabradine ahead of digoxin on the basis that we have proved mortality benefit in heart failure patients with sinus rhythm when added to optimal therapy with ACEi, beta blocker and	*Changed* *Section restructured.* *The evidence here is not of sufficient quality to include.*

	MRAs, which is recognised by SMC,NICE, and ESC in their treatment algorithms We are also asking to see if you and your colleagues thought it would be useful to add an additional recommendation in section 2.2 to clarify the advice for patients contraindicated to beta blockers and what to do if ongoing symptoms of heart failure despite optimal treatment (including beta blockers) and heart rate above 75bpm, in this situation consider adding ivabradine.	*This has now been included.*
	I agree that ACE inhibitors, ARBs, Beta blockers and ARNIs are the main drug classes. I would not include digoxin here. If digoxin is going to be included here, ivabradine should also be included. Ivabradine has been shown to reduce heart failure hospitalisation on a background of modern medical therapy.	*Section restructured.*
	Digoxin – the order of drugs in paragraph 3 should be ACE, BB, MRA (not ARB).	*Section restructured.*
5.9	Greater emphasis on statement about using 3 drugs which block RAAS. Could be an R. No patient should receive…	*There is no evidence to support this recommendation.*
	Factually incorrect and Table four is terribly outdated. As above, MRAs are not indicated in patients solely based on NYHA and Table 4 suggests that they are. This needs to be changed.	*The table has been removed and replaced with an algorithm.*
	Should also include LCZ-696.	*Awaiting SMC advice.*
	5.9. (Table) The title is incorrect. This table is for HF-REF. What is the evidence of using a beta-blocker in NYHA Class I? The table doesn't reflect the recommendation to use an ARB in addition to an ACE inhibitor/beta-blocker if a MRA cannot be used.	*Table removed and replaced with an algorithm.*
	Helpful.	*No action required.*
	Some of the drug therapies are introduced by phrases like "To reduce mortality and hospitalisation…" while others are not. The wording and presentation of drugs should be consistent.	*Changed*
	Summary of major drug classes should include ARNI (LCZ) and possibly ivabradine (although we recognise that this drug is no more than 4th line).	*Awaiting SMC advice.*
5.10	I don't see the point in this section. I can think of loads of medications with neutral results from HF RCTs. Why are we focusing on this?	*It was a point of interest when the key questions were set. Section has been restructured so this has been moved further down.*
	Out of date e.g. RELAX-HF (sildenafil in HF-PEF)	*The key question was when used in patients with HF-REF, not PEF.*
	Should there be a recommendation not to use?	*There was insufficient evidence of harms or lack of benefit on which to base a recommendation not to use.*
	This is unduly prominent. A brief word about lack of data would suffice if any comment is warranted. It is difficult to understand why this comes before ivabradine and hydralazine and nitrates.	*Detail included because it was a point of interest when the key questions were set. Section has been restructured so this has been moved further down.*
5.11	I don't see the point in this section. I can think of loads of medications with neutral results from HF RCTs. Why are we focusing on this?	*Disagree, it is a commonly used therapy.*

	Hugely out of date. No mention of WARCEF (quashed aspirin concern). No mention of NOACs! Needs revision.	*A new search has been conducted and the section updated.*
	Should there be a recommendation not to use unless there is another compelling indication?	*The evidence is not strong enough for this.*
5.13	The guideline gives the perception that ivabradine is not in the major drug classes for heart failure. The major classes appear in sections 5.1 to 5.9. Ivabradine appears at the very end after all other treatments (including hydralazine and nitrates). Ivabradine has both SMC and NICE approval and is included in the ESC algorithm for the management of patients with chronic symptomatic systolic heart failure (NYHA functional class II–IV), pg 19. On balance we believe for appropriate patients, Ivabradine is an important part of their treatment regimen and therefore worthy of being added to the major classes section. Would the guideline development group consider adding ivabradine into the 'major drug classes' section? (ESC guidelines (pg 19), SMC advice (pg1) and NICE TA267 (pg 3) are attached.) Wording of ivabradine recommended in patients with a previous admission for heart failure in the last 12 months, this is inconsistent with our license, ESC Acute And Chronic HF guidelines, NICE TA267 and SMC advice (all attached).	*Section restructured.* *The recommendation reflects the evidence.*
	Implications of SMC decision important in update.	*No action required.*
	I believe Ivabradine should be mentioned under Section 5.10 rather than 5.13 with subsequent readjustments of the current points 5.10, 5.11 and 5.12.	*Section restructured.*
	No advice in this section about using ivabradine in patients intolerant of beta blockers.	*The recommendation states patients who are intolerant to beta blocker.*
	This is incorrect on two fronts. Firstly, Ivabradine is only evidenced based in patients with LVEF <35% (i.e. SHIFT study). The above statement implies that we should give this medication to patients with any grade of LVSD (e.g. LVEF 45-55%) who have been admitted to hospital and have heart rate >75bpm. There would be no evidence what-so-ever to back this up. The event rate and event type of patients with LVEF>35% vs. those with LVEF<35% is radically different and thus so will the likely benefit/harm ratios of Ivabradine. Secondly, I think it is not ideal to base the entire recommendation on the SMC's post-hoc cost effectiveness analysis. This section needs a radical rewrite. There is evidence that Ivabradine is cost effective both at >70bpm and >75bpm http://heart.bmj.com/content/100/13/1031.full	*<35% added.* *SMC use data directly supplied by the pharmaceutical company. It is not a post-hoc analysis.* *The paper from Heart has already been considered and included in the evidence statement.*
	This is not very good. Why is it not written as for the other drugs? Why are CV death, HF hospitalisation and all-cause mortality not mentioned separately? Where does the 75 beats/min recommendation come from (trial entry was ≥70 beats/min).	*The primary endpoint of the study was CD deaths and hospitalisation. Have added sentence on all cause mortality, CV deaths and HF deaths.* *Recommendation is in line with SMC approval for patients with ≥75 beats/min.*

	Why the need for specialist advice?	*It is consistent with NICE guidance.*
	I found the wording of the ivabradine recommendation is rather clumsy. Suggest rewording it.	*Changed*
	It is wrong to put ivabradine after phosphodiesterase inhibitors and anti-thrombotic therapy, for which there are few data. Ivabradine has a mega-trial showing reduction in heart failure hospitalisation. Ivabradine should come after ACE inhibitors, beta blockers and mineralocorticoid receptor antagonists. This section could be missed by the less thorough reader.	*Section restructured.*
	Ivabradine should not be in position 13. Rather it should be before digoxin.	*Section restructured.*
	The cost-effectiveness evidence and SMC recommendations appear to have been appropriately considered to inform the recommendation on the use of ivabradine.	*No action required.*
	Some concern that ordering of pharmacological therapy suggests drug only of use after all other classes of drugs have been prescribed. Hospital admission not required-inconsistent with license. Agree needs specialist input.	*Section restructured.*
5.14	I have never heard of IV iron being given in the GP setting?	*It occurs in rural areas and is also given in community hospitals.*
	Clear and useful for clinicians.	*Thank you. No action required.*
	Should this section come later along with other problems? Needs statement that oral iron has not been shown to be effective in this context. Is there a place for oral iron?	*It comes ahead of other problems.* *There is no evidence for oral iron.*
	This section is a good illustration of how this guideline is completely skewed. There is a tiny section about sacubitril-valsartan and a huge section about iron deficiency. There are meta-analyses mentioned that are worthless in relation to hard clinical events (and the text is misleading in suggesting that we know this therapy reduces events). Do we know anything about the long-term safety of iron therapy? Even worse ESAs should not be mentioned here at all! They do not treat iron deficiency (actually usually cause iron deficiency). What is “symptomatology”?	*Sacubitril-valsartan section has been redrafted. The iron deficiency section is long because it is a new recommendation.* *The term ‘symptomatology has been removed.*
	I may be wrong here (!), but are the agents not erythropoietin or an analogue rather than substances that release endogenous erythropoietin?	*Changed*
	Useful addition.	*Thank you. No action required.*
5.15	As 5.14.	*No action required.*
	"Normal LV systolic function" described as HF-PEF - actually this is usually LVEF>40% which could just be describing mild LVSD.	*This is now discussed in the Introduction.*
	I think it is incorrect to say that HF-PEF often occurs along with myocardial ischaemia, hypertension…pericardial constriction. These are really the alternative diagnoses that must be	*Changed to ‘might occur’.*

	excluded.	
	Comprehensive and accurate interpretation of preserved ejection fraction or Non-LVSD heart failure.	*Thank you. No action required.*
	Should there perhaps be a recommendation at the end of this section to state that e.g. “Management of heart failure with preserved LV ejection fraction needs to focus on identifying and treating any causes/contributory factors.”	*The evidence is not strong enough to support a recommendation.*
	There is a distinct difference between “heart failure with preserved ejection fraction” (which usually includes patients with a LVEF>40% [which could represent mild systolic dysfunction]) and “normal LV systolic function” (which infers an LVEF>55%. Please stick to HF-PEF.	*This is too detailed to be included in a concise guideline.*
	These patients are complicated and need specialist assessment.	*This was not covered in the guideline’s remit.*
5.16	Typo colchicines. Is using prednisolone in heart failure wise with propensity for increased fluid retention? Prophylactic antagonist therapy?	*Typo corrected.* *Sentence had been replaced with a reference to the British Society of Rheumatology which is in the process of producing a guideline on the management of gout.*
	Typo. Remove 's' from colchicine.	*Typo corrected.*
5.17	With Ivabradine no dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15ml/min. A sub-analysis from SHIFT shows that ivabradine has a neutral effect on renal function and Cardiovascular and safety were similar in patients with and without renal dysfunction. Please see ‘SHIFT Renal’ paper attached.	*This was not an outcome that was included in the guideline’s remit, and the study is a subgroup analysis.*
	Possible cause should include bladder outflow obstruction. Role of renal ultrasound.	*These are outside the remit of the guideline.*
	Renal dysfunction. It is wrong to say that the occurrence of renal dysfunction with an ACE I, ARB or MRA requires dose-reduction or treatment discontinuation. This may be required if substantial renal impairment occurs. Mild-moderate renal dysfunction may not require any change (and loss of treatment benefit). I don’t think there is evidence to suggest renal artery angioplasty.	*Changed to ‘may require’.*
	Heart failure and renal impairment – is “renal angioplasty to enable ACE treatment” really a SIGN recommendation?? Spironolactone is mentioned specifically but also applies to eplerenone (should be “mineralocorticoid receptor antagonists”)	*Agree. This statement has been removed.*
	What is the evidence base for renal angioplasty?	*This statement has been removed.*
5.18	Ivabradine has had a license since 2005 for the treatment of angina patients. Ivabradine has demonstrated a consistent reduction of CV death and hospitalisation for heart failure patients with angina. Please see the abstract attached ‘ACC Procoralan Heart Failure and Angina March 2015’ This is supported in the ESC Heart failure guidelines attached. Please see section 11.3 (pg 35) of the HF ESC guidelines “Beta-blockers are effective agents for angina as well as an essential treatment for	*Ivabradine for treatment of patients with angina is covered in the update to the SIGN guideline on stable angina. This guideline refers readers to that guideline.*

	systolic HF. Certain other effective antianginal drugs have been studied in large numbers of patients with systolic HF and shown to be safe (e.g. ivabradine)."	
	Out of date.	*The SIGN angina guideline is in the process of being updated. A sentence has been added to refer to that guideline for advice.*
5.19	Most trials do suggest the elderly benefit – the non-evidence-based statement to the contrary is dangerous.	*It is suggested that they are still used in elderly people.*
5.19.1	Wow, three lines :)	*There is little evidence and it is not possible to cover everything and keep the guideline concise.*
	As today's major issue this is a vital inclusion with the need to treat the range but primarily to treat the patient.	*Agree*
5.19.2	Important also for patients and carers.	*Agree*
5.19.3	Again comorbidity issues of paramount importance.	*Agree but there is little evidence.*
Section 6		
6.1.1	Obviously new and making update necessary.	*No action required.*
	Clear statement of benefit but should include data demonstrating poor uptake of device therapy, particularly in Scotland. In the table should factors indicating high risk of sudden cardiac death be described in the text? Comment required about those patients in AF.	*This is outside the SIGN remit.* *Section reworded so this is clearer.* *This will be included in the arrhythmias guideline. A reference to it will be added once it has been published.*
	In the recommendation section, the first point should be split after "NYHA class IV". The point about CRT plus or minus a defibrillator should be stated.	*Recommendations removed and replaced with NICE table.*
	I know other experts will comment on section 6 which needs a lot of revision.	*Comments from others addressed.*
	Consider representing these recommendations as a table to aid clarity. At the moment they are rather difficult to follow.	*Recommendations removed and replaced with NICE table.*
	The 1st recommendation might be made clearer and lead better into the following recommendations if changed to: "For patients with heart failure, left ventricular ejection fraction < 35% and NHYA class IV, implantable cardioverter defibrillators are not indicated. For this group of patients, if the QRS is 120 ms or more, with or without left bundle branch block, cardiac resynchronisation therapy with pacing should be considered." 3rd recommendation last line – typo – "cardiac converter" should be "cardioverter." Good practice point - should this be "Patients receiving cardiac resynchronisation therapy and/or an implantable cardioverter defibrillator should be offered pre- and post placement counselling, including discussion of potential shocks from the device, and device deactivation"	*Recommendations removed and replaced with NICE table.* *GPP amended*

	The NICE recommendations are reasonable and should be retained. The comments below must be revised to be informative and accurate (see major comments re Section 2.3).	*Recommendations removed and replaced with NICE table.*
	This section is badly written, and in particular, the recommendations are very muddled. This section should be revised. The use of the NICE table is welcome, but it should state LVEF ≤35% (not "<35%"). It seems strange in a guideline that the first recommendation is not to do something! (i.e. no ICDs in NYHA IV, which is correct but better placed after identifying the patients that do benefit from device therapy. In recommendation 1, the second section starting "If QRS is 120ms or more…" should be a separate point and start "in NYHA class IV with a QRS>120ms, CRT-P should be considered. For patients with QRS 120-149ms with LBBB CRT with an ICD should state "CRT with or without an ICD". Echo CRT data should be mentioned (highlighting the hazard with CRT in narrow QRS.	*Recommendations removed and replaced with NICE table ≤35% amended.* *The caution has been included in paragraph 3.*
	The recommendations on the key update question - on the benefits and harms of ICD/CRT - have made appropriate reference to a recent NICE MTA covering this topic. It seems reasonable that the recommendations based on this MTA should also be applicable to the Scottish population.	*No action required.*
6.1.2	As above.	*No action required.*
	Destination therapy has now been approved by NICE and endorsed by NHS Scotland/HIS.	*This has been added.*
6.1.3	The SERVE-HF study was stopped because of a third increase in cardiovascular mortality with assisted servoventilation. This should be stated.	*A new search was conducted and this section has now been revised.*
	Needs updated in light of SERVE-HF.	*A new search was conducted and this section has now been revised.*
	The SERVE HF trial comes out at the ESC (you will obviously have to wait until then for the evidence!). There has already been a warning from the company suggesting servo-assisted ventilation should not be used in central sleep apnoea. This will cause a lot of confusion and think a recommendation not to use non-invasive ventilation should be made (increases cardiovascular mortality). I also think the term "non-invasive ventilation" is better than "CPAP" as the latter is just one of several forms of non-invasive ventilation.	*A new search was conducted and this section has now been revised.* *CPAP is the term used in obstructive sleep apnoea.*
	This section is not necessary. I would delete it.	*Disagree. Sleep problems are common.*
	Assisted ventilation – SERVE-HF has been stopped early because of a 33% increase in cardiovascular mortality. This is not mentioned here, and this section should be revised accordingly.	*A new search was conducted and this section has now been revised.*

6.1.6	This section misses out STICH hypothesis 2.	*The results of the study were negative and would not change what is already stated.* *Section has been removed.*
6.2.2	Important for clinicians and for patients to be aware.	*No action required.*
	Guidelines seen by patients may find this part frightening, and a balance is required to balance hope and failure with individuals based on their needs.	*There will be a separate version of the guideline produced for patients.*
	Need to mention TAVR and Mitraclip.	*This is not directly relevant to HF.*
	GPP - This is incorrect. Patients with heart failure have been excluded from all other trials of cardiac surgery.	*GPP removed.*
Section 7		
	No mention of use of care bundles.	*This is outwith the SIGN remit.*
7.1.2	Needs to be updated to reflect findings of HOOPS – a Scottish trial and largest in this area!	*This was considered during the scoping of the remit for the update. The results do not change the advice already given so it was decided not to include this paper in the review.*
	There is now a systematic review of the role of pharmacists: Koshman et al. Arch Intern Med. 2008 Apr 14;168(7):687-94.	*This was considered during the scoping of the remit for the update. The results do not change the advice already given so it was decided not to include this paper in the review.*
Section 8		
	Important as importance of home care has increased in its potential benefit to patients.	*No action required*
	Should the new R recommendations be included in section 2?	*The group did not feel these were of top priority compared to the other recommendations highlighted for implementation.*
	Palliative care – what evidence is there to stop treatment? As pointed out earlier most treatments also relieve symptoms. Please read the GPP – it seems to apply to all patients with heart failure!	*At the moment RCT evidence is lacking but advice given is considered to be good practise. The section on stopping treatment has been amended.* *Text amended to explain why it should be considered in all patients.*
	A Palliative care approach should be started for patients with chronic heart failure. A position statement by Jaarsma et al 2008 European Society of Cardiology suggests a model of care whereby care planning is started at a certain stage. In Scotland the Supportive and Palliative Care Indicator Tool can be used by general practitioners and hospital doctors to identify people who are likely to benefit from a palliative care approach.[3] 3. Highet G, Crawford D, Murray SA, Boyd K: Development and evaluation of the Supportive and Palliative Care Indicators Tool (SPICT): a mixed-methods study. BMJ Support & Pall Care 2014, 4(3):285-290.	*GPP and section reworded to cover aspects suggested.*
	2nd paragraph narrative should read: There is inequity of access to palliative care provision compared to patients with cancer. Extrapolating from cancer care, the principles of generalist palliative care should be provided to	*Section has been amended to take these and other peer review comments on board.*

	patients, carers and family by their regular professionals, where the level of need is of low to moderate complexity, and should be given equal priority alongside diagnosis and treatment. Consider changing: A palliative care approach to Palliative care principles which focus on symptom relief and rationalisation of non-essential treatments should be considered by all clinicians managing persons living with and dying from advancing heart failure.	
	This section should be shortened. SIGN is an evidence-based process. A good practice point would suffice with acknowledgement that more research should be conducted.	*While this area has little evidence the group considered it an important part of the patient journey which needs to be considered.*
8.2	Unlike many heart failure medications, ivabradine has demonstrated a small but significant improvement in quality of life, this is not mentioned at all in section 8.2. Please find attached the data from SHIFT QOL paper.	*Ivabradine is covered in a separate section. We would prefer not to cover individual drugs in this section.*
	Appropriate narrative.	*No action required.*
8.3	Appropriate narrative.	*No action required.*
8.3.1	Again of importance to patients and carers as well as those delivering care.	*No action required.*
	Should consider changing the narrative to "Dyspnoea is a common debilitating symptom in chronic heart failure. Opioids may ameliorate…"	*Changed*
8.3.2	The HOT trial appears to be negative and is awaiting publication.	*Publication will be outwith the timescales for inclusion in the guideline.*
8.4	Important especially in the context of Advance Care Planning.	*No action required.*
	The 4th recommended point requires further explanation specifically to delineate situations where deactivation would not necessarily be linked to a DNACPR decision. Apart from that, I feel that the palliative care section is strong and shouldn't be altered.	*This is taken directly from the UK Resuscitation guideline. We could add an example, but it would make it more lengthy and be inconsistent with the other recommendations.*
	What about statins? Aspirin?	*Covering individual drugs in every clinical scenario in this section would be too lengthy. It is covered in section 8.4, and individual decisions should be based on clinical judgement.*
	Consider using rationalisation of treatments rather than discontinuation...	*Changed*
	There are five recommendations here. None of which should be recommendations as there is no specific 'evidence'. They are very worthy and sensible statements and should probably be good practice points.	*Changed to bullet points.*
	Discontinuing treatments – statins are not mentioned, and yet there are two large studies stating a neutral effect. Furthermore, aspirin may increase hospitalisation.	*Covering individual drugs in this section would be too lengthy. It is covered by statement in section 8.4. The WARCEF trial refutes the risk of aspirin.*

Section 9		
	Line 2, typo heart failure.	*Amended*
	Typing error in the first paragraph second sentence ("hear failure").	*Amended*
9.1.1	Important increase in awareness of effects disease may have in providing a barrier to effective involvement of patients in their treatment.	*No action required.*
	There are many more than 2 studies reporting cognitive impairment in heart failure.	*Sections have not been updated if new evidence is unlikely to change the advice already given.*
	Useful to include involvement of carers at an early stage if cognitive deficits identified.	*Agreed, but feel this is going into too much detail.*
9.1.2	Admirable.	*No action required.*
	The sentence ends …",such as responding to patient's cues and asking fewer leading questions." I wondered whether it would be helpful to be specific about preferred behaviour i.e. asking more open questions (if this is what is suggested in the review). Should Reference 180 be 2004 not 2005? Fellowes D, et al. Cochrane Database Syst Rev. 2004.	*Amended*
9.2	Who does what, in terms of discussing treatment options, for instance?	*Who does what is a decision for implementation and too detailed for the guideline.*
	A specific technique is mentioned, "Teach-back". I am not sure how many people would take the time to look up this method if they weren't familiar with it? I would recommend, either including a brief description or just saying "Following discussions with patients it is useful to check their understanding by asking them to explain or demonstrate in their own words what you have discussed with them. Treatment - Clinicians are asked to discuss with patients how they are coping and managing distress (including depression and anxiety) & then at Follow up to do the same. It might be helpful to have a source of support specific to Anxiety in section 9.3. (e.g. Anxiety UK www.anxietyuk.org.uk/get-help-now/anxietyinformation/) and or to emphasise the sections on mood on the BHF or CHSS websites. Or perhaps include additional NHS self-help sites e.g. www.moodjuice.scot.nhs.uk, (provides information and self-help for patients and professionals). www.nhs24.com/usefulresources/livinglife/ CBT telephone service.	*Changed* *Suggested websites added.*
	This is a really important section however should the check list be an appendix?	*All SIGN guidelines include patient information checklist as an integral part of the guideline.*
	Particularly useful as will contribute to meaningful contribution by patients in areas of treatment choices and outcomes.	*No action required.*
	Palliative Care Section at the bottom of the page. Narrative should perhaps read: • offer appropriate and timely discussion regarding supportive palliative care issues with the patient and family.	

	• aim of supportive palliative care • key professionals/organisations likely to be involved in their care • comprehensive assessment of physical, psychological, emotional, social & occupational domains • priorities of care including preferred place of care and death as appropriate • advance care planning.	*This section is pointers or prompts on information patients may need rather than a protocol for treatment.*
	Checklist states need for specialist assessment - correctly so, but this is not included anywhere else in the guideline that I can find. It should be!	*This has been reworded. It is outwith the guideline's scope to determine when a specialist should be seen.*
9.3	Very useful as information from team not available 24/7 and good range provided to assist in self management.	*No action required.*
	The best website of all – Heartfailurematters.org is not listed!	*Added*
	Sources of further information – I have updated the paragraph about BHF for the ACS guideline and Beatrice has amended it - recommend changing the current content in the HF guideline so that it is the same.	*Amended*
Section 10		
10.1	Excellent. Essential to think beyond actual guideline to implementing it.	*No action required.*
10.2	Again will inform those who have to deliver in this area.	*No action required.*
10.3	Doing this sort of audit in primary care would likely require a careful look at READ coding issues.	*Outside the SIGN remit. READ codes are being addressed by the Heart Failure Hub.*
	Essential as providing evidence and should include patient feedback.	*Outcomes for these trials may include QoL.*
	• The number of patients with a diagnosis of heart failure which has been confirmed by BNP or NT pro-BNP levels and/or an echocardiogram • the number of patients with heart failure due to LVSD treated with an ACE inhibitor • the number of patients with heart failure due to LVSD treated with a beta blocker • the number of patients with heart failure due to LVSD treated with an AA • the number of patients fitted with a CRT • the number of patients with symptomatic heart failure who receive a home visit from a specialist nurse. I do not see why looking at the 'number' of any of these things is useful. Surely it needs to be a percentage?	*Changed to percentage.*
	Audit is required but is currently not supported by NHS Scotland.	*Audit is being addressed by the HF Hub.*
10.4	Closer working enabled and health technology information a useful feature of the guideline update.	*No action required.*

Section 11		
11.1	As indicated contribution of health technology enhances.	*No action required.*
11.1.1	Very useful.	*No action required.*
	Recent qualitative research has revealed multi-dimensional physical, psychological, social and existential issues in people with advanced heart failure. Leeming A, Murray SA, Kendall M: The impact of advanced heart failure on social, psychological and existential aspects and personhood. Eur J Cardiovasc Nurs 2014, 13(2):162-167. 2. Murray SA, Kendall M, Grant E, Boyd K, Barclay S, Sheikh A: Patterns of Social, Psychological, and Spiritual Decline Toward the End of Life in Lung Cancer and Heart Failure. J Pain Symptom Manage 2007, 34(4):393-402.	*The results of the patient search, which included qualitative research, were used to inform the outcomes when agreeing the remit and key questions.*
11.1.2	Again health economics for choices to be made essential.	*No action required.*
11.2	This is very arbitrary list! For all that I can see how that some of the topics influenced the writing of the guideline others seem biased. There would be a host of equally valid questions (e.g. RCT of beta-blockers in SR vs AF, MRAs in NYHA 2-4 & LVEF 35-55% etc). I am unsure how this list was determined.	*The list reflects the gaps in the evidence identified from the literature review of the key questions used to produce the update to the guideline.*
11.2	Intervention study to identify how best anticipatory care planning can be carried out comprehensively in people with advanced heart failure and comorbidities.	*There is a recommendation on anticipatory care, phrased differently.*
Annexes		
	All useful and good range.	*No action required.*
	The Annexes are outdated and require major revision.	*Practical aspects of the main drugs have not changed.*
Annex 1	I was not clear why the Key Question considered (pg. 54) Section 4.6 just 3 Psychological Therapies i.e. CBT, Mindfulness & IPT? SIGN guidelines (Non-pharmaceutical management of depression in adults) also include Behavioural Activation, Problem Solving Therapy, and Short term psychodynamic psychotherapy. I doubt that this will have influenced the findings but it may not fully represent the Evidence Based Interventions available. I hope that these comments are helpful.	*For the sake of time and resources available the key question focused on interventions which may have had sufficient quality evidence to support a recommendation.*
	It is CRT-pacemaker not "CRT pacers".	*Amended*
Annex 2	The target dose of Lisinopril is 20-35mg NOT 20mg. The whole premise of target dosing comes from the ATLAS study which confirms this (http://circ.ahajournals.org/content/100/23/2312.full)	*Dose changed and referenced to BNF.*
Annex 3	First-line treatment (along with beta blockers) in patients with NYHA Class II –IV HF intolerant of an ACE inhibitor. Why not I-IV? Second-line treatment (after optimisation of ACE inhibitor and beta blocker) in patients with NYHA Class II– III HF who cannot take an aldosterone antagonist (The safety and efficacy of spironolactone used with an ACE inhibitor and an	*No ARB study includes Class I.* *It is based on trials of spironolactone.* *The annexes are also cited directly from the original publication.*

	ARB (as well as beta blocker) is uncertain and the use of all three inhibitors of the renin–angiotensin–aldosterone system together is not recommended). Why is spironlactone singled out and not also eplerenone?	
Annex 4	Under contraindications 'persisting signs of congestion' is listed. Does this mean that all patients with persistent ankle oedema should not be beta-blocked? Obviously not. This should be a caution and not a contra-indication.	*BB trials included stable patients only (with no persistent signs of congestion etc).*
	A heart rate<60/min is not a "contraindication to beta-blockers! Nebivolol was not shown to reduce mortality.	*This is debatable. The statement is taken from another guideline and we have permission to reprint on the basis that it is cited verbatim.* *Guideline states mortality **or** morbidity.*
Annex 5	Second line treatment (after optimisation of ACE inhibitor and beta blocker) in patients with NYHA class IIIV HF. (The safety and efficacy of spironolactone used with an ACE inhibitor and an ARB (as well as beta blocker) is uncertain and the use of all three inhibitors of the renin–angiotensin–aldosterone system together is not recommended). As per my earlier comments, this is factually incorrect and needs a radical rewrite. MRAs have no evidence in LVEF>35%. Why also is the EPHESUS criteria not in this section, when it is recommended earlier in the guideline?	*The annex is intended to be practical guidance rather than a full explanation of exactly which patients to treat. This is covered in the section on MRAs.* *EPHESUS applies mainly to post MI, not to all HF.*
Annex 6	Drugs to avoid in HF - Beta blockers, potentially confusing without explanation.	*BBs have been removed.*
	This sections needs radically updated. Firstly, the inclusion of beta-blockers is just confusing. There are also many medications that are best avoided but are not mentioned (to name a few, Adalimumab, infliximab, Anthracyclines (doxorubicin, daunorubicin), Clozapine, Moxonidine, Pseudoephidrine/ Ephedrine etc). I am not sure how the section was put together originally and now rechecked?	*BBs have been removed.* *Moxonidone added. The others are very specialist and the annex focuses on those which are prescribed routinely.*