Acute coronary syndrome

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.

Invited reviewers:		
GA	Mr Gordon Adamson	Specialist Clinical Pharmacist, Cardiac Services, Golden Jubilee National Hospital, Clydebank
AB	Dr Alan Begg	General Practitioner, Townhead Practice Montrose and Honorary Senior Lecturer, University of Dundee
CB	Professor Colin Berry	Consultant Cardiologist, Golden Jubilee National Hospital, Glasgow
NB	Dr Nicholas Boon	Retired Consultant Cardiologist, Edinburgh
RD	Dr Russell Duncan	Consultant, Emergency Department, Ninewells Hospital, Dundee
DH	Dr David Hogg	GP Principal, Arran Medical Group, Isle of Arran
EMac	Eleanor MacDonald	Lay Reviewer, Orkney
JR	Dr Julie Ronald	Consultant in Emergency Medicine, Emergency Department, Ninewells Hospital, Dundee
DS	Mr Dennis Sandeman	Cardiology Nurse Consultant, Victoria Hospital, Kirkcaldy
AT	Professor Adam Timmis	Professor of Clinical Cardiology, Bart's Heart Centre, London
OW	Professor Olivia Wu	Professor in Health Technology Assessment, University of Glasgow
Open consultation:		
GA	Miss Gillian Armstrong	Cardiac Rehabilitation Team Lead, NHS Greater Glasgow & Clyde
LB	Mrs Laura Burgess	Clinical Specialist Physiotherapist – Cardiac Rehabilitation, Wythenshawe Hospital (part of UHSM), Manchester
CPG		CVD Psychology Group (members from all other SIGN CVD groups)
SD	Dr Susannah K Dawson	GP, Clinical Lead Community Hospitals NHSWI, Benbecula Medical Practice & Ospadal Uibhist's Bharraigh
AF	Dr Andrew Flapan	Consultant Cardiologist, Royal Infirmary of Edinburgh
PH	Dr Peter Henriksen	Consultant Cardiologist, Edinburgh Heart Centre
JJ	Jan Jones	Principal Pharmacist, Scottish Medicines Consortium
KL	Dr Kevin Lock	Market Access Manager, Cardiovascular, AstraZeneca, Luton
MSD		Merck Sharp & Dohme, Hertfordshire
JP	Mr James Parnham	Head of HOHTA, Eli Lilly and Company Ltd, Basingstoke
LR	Dr Luke Roberts	Senior Medical Advisor, Bayer Healthcare PLC, Newbury
RCPSG		Royal College of Physicians & Surgeons, Glasgow
NU	Professor Neal Uren	Clinical Director for Cardiac Services, Royal Infirmary of Edinburgh
BW	Mrs Barbara Wilkinson	Lay Representative, Dundee
LT	Mrs Louise Taylor	Head of Service, Heart Manual Department, Astley Ainslie Hospital, Edinburgh
IT	Dr Iain Todd	Consultant in Cardiovascular Rehabilitation, Astley Ainslie Hospital, Edinburgh

Section		Comments received	Development group response
General			
	EMac	This is a comprehensive guideline. The layout of each section is easy to read although very technical. The evidence has been interpreted accurately and the recommendations are clear and easy to understand. The use of bold print is eye catching and make it a useful tool for doctors. The section on some of the drugs used is very medical but when you read the recommendations it is very clear. Each section is clearly titled.	*Thank you.*
	GA	Overall a good guideline, and overall I agree with most of the drug related updates.	*Thank you.*
	BW	I have only looked at Section 10.2 and my comments are of the proof reading/stylistic kind, rather than on the content.	*Thank you.*
	RD	Clear, comprehensive and well presented. Literature interpretation and the rationale behind advice decisions appear well presented.	*Thank you.*
	CB	Thank you for asking me to review this document. re Key recommendations – the external reviewers should be given the opportunity to reconsider the committee's key final recommendations (Section 2) as the current recommendations may change in light of this review process, factoring in the comments from all of the reviewers.	*The key recommendations are agreed by the guideline development group and reflect their view on which recommendations should be prioritised for implementation.*
	NB	The overall balance of the document reflects issues that were prominent when it was first written but are no longer controversial or topical. Unfortunately this gives it a rather outdated feel. I am not sure how this can be overcome without embarking on a complete rewrite but feel that some rebalancing is possible; for example it would be appropriate to reduce the material on thrombolysis and expand the sections on intervention. There are also some important omissions 1. The value of using tools to identify the risk of complications such as bleeding such as CRUSADE, ACUITY and ACTION should be highlighted . Circulation 2009; 119 : 1873-82 2. There is genuine doubt on how to manage certain subsets of ACS patients and a section devoted to these "special situations" would be very helpful. This might include: • ACS in Pregnancy • ACS in patients with advanced Renal Failure • Implications and management of Bleeding • Management of ACS who are taking or have an indication for oral anticoagulant therapy Finally, I would like to congratulate the review group on a job well done.	*GDG agreed that thrombolysis section should be reduced to reflect current practice. The volume of section has been reduced without changing the conclusions.* *This was not identified by the GDG as a priority when setting key questions.* *Outwith remit of the update* *Outwith remit of the update* *Outwith remit of the update* *The GDG agrees that this is an important clinical issue, however is complicated by a wide range of patient-specific factors and it was felt that the decisions should be made on an individual basis and tailored to the unique circumstances of each patient.* *Thank you.*

	DS	Excellent update	*Thank you.*
	AB	I look forward to seeing this guideline published and its implementation effect on current practice.	*Thank you.*
	MSD	MSD welcomes the opportunity to comment on the draft SIGN guideline titled “Acute coronary syndrome (ACS)”. MSD supports the development of evidence-based guidelines acknowledging the benefit of providing further direction to health care professionals.	*Thank you.*
	KL	In the absence of any details of the systematic literature reviews performed for this guideline, it is not possible to provide comments on the evidence base used to develop these draft guidelines.	*The search strategy will be available at the time of publication of the guideline. All recommendations are supported by evidence as detailed in the list of references.*
	AF	A lot of hard work has gone into this and this is to be applauded but the patient safety and pragmatism is also important.	*Thank you. Agree.*
	DH	Highlights of 'best practice' including model ACS pathways would be handy. When we developed ours 10 years ago (and I refreshed this 4 years ago) there really weren't many available. I think there is still an appetite for this - particularly for smaller community hospitals where we don't have the capacity to produce/clinically govern lots of different clinical pathways. Could there be any thought to a Scottish ACS Pathway that could subsequently be modified where necessary for local requirements? Air transfer is fraught with considerations regarding prioritisation, resource limitations and competency of the retrieval team involved (paramedic/ EMRS etc.). It is difficult, but with 1/3 Scottish population living in rural areas, and with a high number of island-based populations, I think it's important for a Scottish guideline to give due consideration to this. We have developed trigger points (based on observations etc.) with EMRS and GJNH and would be happy to share.	*While certain interventions and tests can be recommended universally, the exact implementation and service delivery is affected by specific factors which are unique to each setting, for example the types of admissions accepted by different hospitals, the complexity of case mix managed at each site, the volume of cath labs and the interaction with the regional ambulance service capacity. While we agree that local pathways are helpful, these should be developed <u>within the local setting</u> to incorporate important local circumstances and factors while remaining consistent with the national guideline. To this end, we have included an algorithm of a possible pathway for assessment and treatment of patients with ACS.* *Agree that local protocols are needed. EMRS already have a national protocol.*
Section 1			
1.1	NB	I think this section would benefit from a brief review of the evidence that patients treated in accordance with evidence based guidelines have better outcomes than those who are not treated in this way (I acknowledge that this can be found in 4,1). I also think there should be some justification for producing a Scottish Guideline alongside NICE, ESC and ACC/AHA guidelines. The other relevant evidence based guidelines should be listed and important differences highlighted.	*Covered in 4.1.* *SIGN guidelines are tailored to the Scottish context. Evidence gathered by NICE is considered where it is relevant and appropriate for the key questions asked by GDGs. Comparison with other guidelines is not the purpose of this guideline.*
	AB	Thank you for asking me to peer review this important clinical guideline which reflects recent changes to the evidence base.	

		Grading of recommendations The hybrid system of 'strong' recommendations contrasting with original grading in SIGN 93 may lead to confusion. Grading of the recommendations in a progressive way based on the level of evidence resulted in a level of consistency which can be potentially be lost with this new approach.	*Agree that dual approach may be confusing. Decision taken by SIGN to use only the new ungraded recommendation format.*
1.1.1	AF	This is well done by a knowledgeable group	*Thank you.*
1.2.1	NB	The reader should be told if the SIGN guideline will confine its recommendations to this supported by conclusive clinical trials (grade A evidence) or venture to address important clinical dilemmas where the best course of action is debatable. I suspect that most clinicians would find the latter more helpful.	*Recommendations are based on a wide range of evidence types of which the clinical trial is only one. Recommendations reflect the type, quality and relevance of published findings; where evidence is equivocal or lacking, this is stated.*
	SD	Badly worded, a bit confused as to what it was trying to tell me so I didn't try to reword this myself.	*Agree. Text reworded.*
	AB	The duration of dual antiplatelet therapy with aspirin and a P2Y12-receptor will be controversial and potentially deviate from current clinical practice. It is the one area where primary care require clear guidance to be issued and communicated at the time of discharge. Reference to pre-hospital management is also referred to within the guideline.	*Agree.*
	AF	This is fine but there are few warnings regarding the applicability of the guideline.	*Paragraph re-worded.*
1.2.2	SD	Doesn't make clear whether the guideline includes primary care (especially in view of 1.2.1 talking about treatment after discharge).	*Agree. Sentence added.*
	Un-known	As the statement refers to the diagnosis and management of ACS I would suggest including laboratory professionals in the list of target users.	*Agree. Text amended.*
1.4	GA	Good comment.	*Thank you.*
	NB	The advent of hs troponin testing has resulted in an big increase in the number of patients diagnosed as non ST elevation MI and a corresponding fall in the number of patients given a diagnosis of "unstable angina". This should be acknowledged and quantified.	*Agree. Now covered in revised section 3.2.*
	LO	In this section and generally, some consistency is required as to whether it is acute coronary "syndrome" or "syndromes".	*The correct term is 'acute coronary syndrome' and this has been corrected.*
	SD	I have not come across MI type 1 and type 2 - this should be clear, especially where rural hospitals and non-specialists may be providing some initial treatment prior to transfer to a specialist unit.	*This is already covered by existing reference to Table 1 and by text on classification of MI in section 3.2. Further explanation in this section is not appropriate.*
	AB	There may be a case to reference Table 1 (section 3) at the end of this paragraph.	*Table 1 has been moved into this section.*
	JR	"An ACS may occasionally occur in the absence of ECG changes or elevation in biochemical markers..." - what is meant by occasionally? What is the incidence of this?	*Word 'occasionally' deleted.*
	AF	This section is well written and helpful however it neglects to discuss that the changing definitions mean that many more patients are included under the diagnostic umbrella of ACS, patients that previously will have been excluded from many of	*Thank you. The reviewer is mistaken on two points. First, whilst the change in criteria for the diagnosis of myocardial infarction has increased the diagnosis of myocardial infarction in Scotland from*

		the trials referenced in the guideline and so changing the broad nature of the definition means that many patients will subjected to treatments where we do not know if there are benefits. This applies to treatments for prognosis because symptoms can always be treated on their merits.	*16,649 per annum in 2000 to 23,000 per annum in 2011, this has been offset by a reduction in the rates of diagnosis of unstable angina from 9,896 in 2000/1 to 1,823 in 2014/5. Indeed, the overall rates of diagnosis of acute coronary syndrome have fallen from 26,370 in 2000 to 24,821 in 2011 [ISD Scotland]. Second, the majority of clinical trials have enrolled patients with acute coronary syndrome encompassing both patients with myocardial infarction and unstable angina (with or without elevated cardiac troponin concentrations). Therefore, patients previously diagnosed with unstable angina and now identified as having myocardial infarction were enrolled in these trials, and the evidence base referred to in the guideline remains relevant to current practice. Finally, implementation of the universal definition of myocardial infarction in 2007 was associated with a halving in the rates of recurrent myocardial infarction and death in patients identified by the use of a more sensitive troponin assay (Mills NL et al JAMA 2011). This was associated with better targeting of evidence based therapies to this group of patients.*
1.5	CB	Recent epidemiology statistics from the British Heart Foundation indicate that CVD and premature CV death (most likely secondary to IHD/MI) is persistently high in women. Timmis A. Cardiovascular mortality in the UK: good news if you live in the South. Heart. 2015 Aug;101(15):1180-1. doi: 10.1136/heartjnl-2015-307887. Epub 2015 Jun 3. Bhatnagar P, Wickramasinghe K, Williams J, Rayner M, Townsend N. The epidemiology of cardiovascular disease in the UK 2014. Heart. 2015 Aug;101(15):1182-9. doi: 10.1136/heartjnl-2015-307516. Epub 2015 Jun 3.	*Agreed. The Bhatnagar paper states that 29% of all deaths in men and 28% in women were due to CVD. However, CVD was the leading cause of death in women, but not in men, despite the lower proportional rate.* *The point may be that CVD death rates have been falling more rapidly in men than in women.* *A sentence has been added to describe this observation.*
	AT	Prognosis based on in-hospital and subsequent outcomes hugely under-estimate risk by failing to consider pre-hospital mortality which represents the largest pool of adverse outcomes.	*Prehospital mortality is not within the remit of this guideline.*
Section 2			
Section 3			
3.1.1	DS	Advice to call 999 after 3rd dose of GTN spray is contradictory to BHF guidelines regarding GTN spray use which advises patients to call 999 after second use of GTN spray. BHF guidelines (BHF website under conditions then angina https://www.bhf.org.uk/heart-health/conditions/angina) are: You can take these steps: 1.Stop what you are doing and sit down and rest.	*Agreed. This section was not updated and evidence to support changing it has not been reviewed. A sentence has been added highlighting the BHF advice and this has been summarised in the GPP.*

		2.Take your GTN spray and tablets, according to your doctor or nurse's instructions. The pain should ease within a few minutes – if it doesn't, take a second dose. 3.If the pain does not ease within a few minutes after your second dose, call 999 immediately.	
	AB	This refers to patients with known coronary heart disease but it is not clear if it is only those who have ongoing angina symptoms or those who have been effectively symptom free and then develop chest pain –can we assume that the approach the same?	*If patients haven't had angina symptoms presumably they wouldn't have a GTN spray so this section wouldn't apply to them.*
	AT	Why does this section limit itself to GTN? What about aspirin for example?	*Aspirin in covered in section 4.4*
3.2	NB	Some mention of novel biomarkers such as heart fatty acid binding protein (H-FABP) and micro RNA is warranted. This should also include the value of array testing and rule out models.	*There is currently insufficient evidence for use of other biomarkers in clinical practice. Also, the GDG believes this topic is too academic for a general national clinical guideline.*
	DS	Diagnostic thresholds are different for different assays but should you recommend standardising interpretation of results for specific assays? For example Lanarkshire and Fife both use the Roche assay but use different criteria for diagnosing myocardial infarction. Lanarkshire use a relative delta rise in Troponin of >20% Fife use an absolute rise of >10 ng/L. A patient in Lanarkshire with Troponin of 15ng/L then 18ng/L will be diagnosed with MI, in Fife the same patient will not. There is some evidence to suggest an absolute delta rise should be used. Circulation. 2011;124:136-145; originally published online June 27, 2011;doi: 10.1161/CIRCULATIONAHA.111.023937 At the end of paragraph 4 where "early rule out" is mentioned would it be worth including the negative predictive value of HS Troponin both on admission and the increase at 3 hours in line with NICE guideline for the use of HS Troponin? (NICE Myocardial infarction (acute): Early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays) section 3.9) (page 8) -Recommendation patients should have HS Troponin done on "presentation and at 3 hours" could say "3 hours after admission" to prevent any confusion.	*No.* *There is insufficient evidence to specify change criteria and recommendations would need to be provided for all cardiac troponin assays currently used in Scotland. As such, we have used the same approach as the universal definition in recommending the diagnosis of myocardial infarction be made when there is "a rise and/or fall in cardiac troponin concentration where at least one value is above the 99th centile upper reference limit (URL)." The NPV included in the NICE guideline were based on modelling in a hypothetical population of 1,000 patients rather than actual performance of the assays and therefore there is uncertainty in these estimates and we have chosen not to include these in our guideline.* *We have amended the recommendation to make clear that repeat testing should be 3 hours after presentation.*
	KL	We welcome the recommendation of the guideline development group concerning the use of high sensitivity troponin assays in the diagnostic pathway for acute coronary syndrome. We believe this represents an opportunity to standardise the biochemical diagnosis of myocardial infarction and subsequent therapeutic pathways in patients.	*Thank you.*
	AB	My interpretation of this section is that a move to high-sensitivity troponin test is what is being recommended which will improve outcomes.	*Thank you.*
	JR	"Recommendation - measurement of cardiac troponin on presentation and at 3 hours with a high sensitivity assay should be considered as an alternative to serial measurement over 10-12 hours.." – is there a particular area this should	*No. The important thing is that it is done, not where it is done.*

		be done? Should these patients still be admitted to a medical admission unit or is this something that can be done in the Emergency Department?	
	RCPSG	Clear and well-written. Entirely agree.	*Thank you.*
	AF	Again this is well written but by changing the definition of ACS and including many patients who are troponinin positive who would have been troponin negative previously the applicability of the treatments and recommendations collected in a much higher risk group of patients should be questioned. This is especially important where invasive treatments such as PTCA and Surgery carry an increased initial mortality.	*See response to this reviewer in 1.4 above.*
	DH	Guidance about TropI as opposed to TropT would be helpful - most near-patient testing (commonly used is iStat) is based on TropI. We would welcome better guidance on what the 'normal range' is for this - there seems to be some dubiety.	*Laboratory high-sensitivity troponin I and T assays have similar sensitivity and specificity, and either are recommended for clinical use. There are point-of-care assays, used as a triage tool in some community areas, and these are not recommended over laboratory testing for diagnosis. The normal reference range is not well established, due to imprecision of the assays at low concentrations. As such the results of POC tests should be verified by laboratory testing.*
Section 4			
	GA	'in accordance with ambulance service clinical practice guidelines' A very vague statement. Do they have a name or number to include?	*Yes. Reference has been added and text slightly revised*
	CB	Paragraph 2, suggest add the following sentence: "In a patient with ECG features consistent with acute STEMI, if transmission of the ECG from the scene is not possible, ambulance crews should be encouraged not to delay but instead to transfer the patient directly to the primary PCI centre. Other potential causes of delay in transfer, e.g. insertion of an intravenous cannula on scene, should also be avoided."	*Disagree. This is already standard practice in SAS and covered by their existing protocols.*
	DS	? Include prompt, speedy or timely in front of "Pre-hospital treatment of patients with..."	*Disagree. Unnecessary to state this.*
	SD	Pre-hospital treatment may include thrombolysis by ambulance paramedics prior to onward transfer, especially in very remote and rural areas. (supported by telemetry of 12 lead ECG to GJNH).	*Already covered in section 5.2*
	AF	Some consideration needs to be given about data collected from patients where the previous definitions were used to recruit them into trials and whether this is appropriate for the new definition.	*See response to previous comments from this reviewer.*
4.1	DS	Excellent	*Thank you.*
	SD	I live on one of the smaller islands in the outer Hebrides. We must, by default, initiate care for ACS and MI whilst awaiting transfer to a specialist service. This paragraph does not recognise or support this.	*The guideline covers in-hospital management. Local protocols will be in place to cover pre-hospital management in remote and rural areas (see above).*
	AB	There has been a significant change in service delivery in recent years. It should be highlighted that the move to an intervention-driven service	*Agreed. A sentence has been added to acknowledge the change of emphasis in the guideline.*

		which varies depending on available resources, time after symptom onset and presentation, who they present to, as well as available local resources are affected by subsequent recommendations within the guideline.	
4.2	AF	If revascularisation carries little overall mortality benefit these patients are no *(sic)* dying from an arrhythmia in hospital? Do we need any monitoring for NSTEMI ?	*This section was not updated.* *There is a mortality benefit but can't be prescriptive in all cases. Monitoring is required for NSTEMI.*
4.4.2	NU	Prasugrel and ticagrelor It is stated that a post-hoc analysis subgroup analysis of prasugrel in STEMI showed a 1.0% absolute reduction in all-cause mortality. It is not stated which time point was selected but the Triton TIMI-38 trial from which this is quoted had this effect at 30 days but did not transfer out to 12 months. On this basis, this should be modified or removed as it gives the impression of a sustained benefit of prasugrel on mortality. The cost per QALY for ticagrelor of £3,966 is derived from SMC 99/11. This cost-effectiveness calculation is provided to the SMC by Astra Zeneca (who make ticagrelor) and is not independently verified. This should be stated as it gives the impression that it is correct and objective. In the recommendations, it is not clear why a hierarchy of ticagrelor over prasugrel and both over clopidogrel has been described particularly in the light of the recommendations from section 8.1.2 (to use these drugs for three months only in the majority of cases see below).	*Agreed. The guideline has been revised to cite the primary end points of both trials (the longer term outcomes). While the absolute risk reduction in favour of prasugrel is the same across long and short-term follow-up periods (1.0%), it is no longer statistically significant at 15 months.* *Penultimate sentence in final paragraph of 4.4.2 changed to clarify this.* *While the content of the guideline is accurate, the wording of the rationale for the recommendations has been clarified to give a more transparent justification for the choices of antiplatelets* *Recommendations in 8.1.2 amended (see relevant section below).*
	AT	Not sure where the recommendation for aspirin and prasugrel in PPCI comes from??	*See first comment above for NU*
	JP	Daiichi Sankyo and Lilly welcome the update to this guideline and look forward to the publication of the recommendations which will provide guidance and influence best practice in Scotland.	*Thank you.*
	KL	Please note that the appropriate reference for the SMC recommendation of ticagrelor is SMC 699/11 (p12 and elsewhere). To help ensure patient safety and appropriate prescribing, we believe it should be made explicit within the recommendations in this section that the antiplatelet doses refer only to the 12 hour period following an ACS event.	*SMC reference corrected.* *Text has been added clarifying loading and daily doses for each DAPT.*
	SD	Ticagrelor mis-spelt in paragraph	*Corrected.*
	AB	It should be noted that the CURE trial was performed at a time where there was a different approach to subsequent revascularisation. An indication should be given on how to assess the risk of bleeding with ticagrelor or prasugrel in order to decide when to use clopidogrel. On the basis of these recommendations should	*We agree that this is a difficult clinical problem, but are not aware of clear evidence to guide practice. This has been added to the recommendations for future research* *See section 4 – first two paragraphs. The Ambulance Services Clinical Practice guideline specifies dual antiplatelet therapy with aspirin and clopidogrel.*

		there be a change in the approach taken by ambulance crews in the community as to what second agent to aspirin should be used?	
	RCPSG	Agree with presentation of evidence and recommendations, although for recommendation three some more explicit advice may be considered – eg. "Patients with acute coronary syndrome should be considered for aspirin (300 mg) and clopidogrel (300 mg) where the risks (bleeding) outweigh the benefits (reduction in recurrent atherothrombotic events) of prasugrel or ticagrelor *(for example, avoiding prasugrel in those with a history of prior stroke/TIA, those over the age of 75, and those with body weight < 60kg)".*	*Agreed. Contraindications and cautions from the BNF have been added to this section and gathered into contiguous paragraphs.*
	AF	I am afraid that I have great patient safety concerns if we are expected to manage effectively 3 different antiplatelet regimes. The benefits are so small that prescribing errors or misunderstandings may seriously threaten any gains achieved by prescribing powerful anti platelet drugs for different periods of time. Currently there is a broad understanding that clopidogrel for 12 months is appropriate whether or not you receive a stent. To have different regimes for stents and no stents, drug releasing and bare metal stents, and then different anti platelet agents for differing groups of patients creates an environment for confusion. A simple pragmatic approach would be for clopidogrel for 12 months unless the Consultants clearly explains why not and specifies the length of treatment. No discuss is raised around the potential impact of the increased side-effect profile of these newer antiplatelet agents and the effect that this may have on consultation rate and discontinuation against medical advice. These may offset any small health gains.	*Agree that this is complicated and that the small mortality benefit may be lost if patients receive the wrong treatments. These drugs are, however, prescribed by cardiologists, trained to make such decisions. The GDG consider that the evidence supports the existing recommendations.* *Implementation of the recommendations must be done locally with patient safety in mind.*
	JJ	"Studies comparing prasugrel to clopidogrel, and ticagrelor to clopidogrel, have shown that ticagrelor (for the prevention of acute coronary syndrome) and prasugrel (for the prevention of atherothrombotic events in patients with ACS undergoing primary or delayed PCI) are cost-effective treatment options compared to clopidogrel with a manufacturer's base case cost per quality adjusted life year (QALY) for ticagrelor of £3,966 *(see section 11.4, SMC 99/11)* " Suggest clarification that the ICER was estimated by the manufacturer	*Text relating to specific QALY deleted to bring section into line with other sections of the guideline.'*
4.5.1	CB	I recommend adding the following sentence: "The therapeutic effects of unfractionated heparin given intravenously should be monitored with checks of the activated clotting time (ACT)."	*This section was not updated so no new evidence was reviewed that might support this suggested change.*
4.5.3	CB	A new sub-section should be created to discuss the recent evidence on bivalirudin in invasively managed ACS patients undergoing PCI. Specifically, the evidence from HEAT-PCI and recent comprehensive network analysis of RCTs Naverese et al Thromb Haemost 2015; July 16:114(4).	*This section was not updated so no new evidence was reviewed that might support this suggested change.*
	NB	That is a pity because an excellent UK trial that demonstrated that routine use of unfractionated	*As above.*

		heparin was preferable to bivalirudin in patients undergoing primary PCI for ST elevation MI has been published since SIGN 93. Lancet 2014; 384 : 1849-58.	
4.5.4	DH	Transfers often cross health board boundaries. NHS A&A doesn't use fondaparinux, but Glasgow does - but most of our STEMI (or high GRACE scoring NSTEMIs) go directly to GJNH. A pan-Scotland prescribing policy would be helpful, if difficult to achieve! i (see *also comment on 5.2)*	*Agree, but developing such a policy is outwith the scope of the guideline.*
4.5.5	GA	Please consider mentioning the following: • 'More recently one meta-analysis provides evidence that dabigatran etexilate, a direct thombin inhibitor, is associated with a significantly increased risk of MI.' • SMC advice for dabigatran etexilate (672/11) uses a Markov model and predicts that per 10,000 AF patients treated with dabigatran versus warfarin there would be 241 more acute myocardial infarctions (of which 3 would be fatal). * Rivaroxaban/apixaban are factor Xa inhibitors, with a different mechanism from dabigatran and thus may explain increased MI risk with dabigatran' Ref Douxfils J, Buckinx F, Mullier F et al. Dabigatran etexilate and risk of myocardial infarction, other cardiovascular events, major bleeding, and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2014 Jun 6;3(3):e000515. doi: 10.1161/JAHA.113.000515. SMC. dabigatran etexilate 110mg and 150mg hard capsules (Pradaxa®) Furthermore, I may have misunderstood however I find the following statement very confusing: 'Further SMC advice pertaining to the cost effectiveness of apixaban (836/13) and dabigatran etexilate (672/11) is available, though it relates to a subgroup of ACS patients …'. My question is Which Subgroup of ACS patients do you mean? As far as I am aware the SMC advice for Apixaban, rivaroxaban and dabigatran: • applies to AF patients in general. • does not reference previous ACS or MI as a thrombotic risk factor for anticoagulation of AF patients. • do not include the term acute coronary syndromes. • Use the Markov model does take account of potential risk of developing MI when prescribed the NOACs. My advice is please consider rewording!	*The evidence from this review has now been included in the guideline (now section 8.2.1).* *Agree. Sentence deleted.*
	LR	Section 4.5.5 addresses the management of patients within the first 12 hours of an acute coronary syndrome (ACS). Rivaroxaban co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine is indicated for the prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers.	*Agree. Section 4.5.5 moved to become new section 8.2.1.* *The evidence from this review has now been included in the guideline.*

		Treatment with rivaroxaban should be started as soon as possible after stabilisation of the ACS event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued. Rivaroxaban therefore lies outside of the scope of this section. However, we would like to make several points regarding the accuracy and relevance of statements made in this section. "A systematic review and meta-analysis of seven RCTs (n=30,866) showed that the addition of rivaroxaban, apixaban or dabigatran to dual antiplatelet therapy led to a small reduction in major adverse cardio-vascular events (0.87% in relative terms, 95% CI 0.80 to 0.95; 1% in absolute terms, 95% CI 1% to 2%) compared to dual antiplatelet therapy (aspirin and clopidogrel) alone but more than doubled the risk of clinically significant bleeding (HR 2.34, 95% CI 2.06 to 2.66). This review included patients with non-ST and ST elevation ACS. Trial results were homogeneous and excluded patients with increased risk of bleeding (for example thrombocytopenia) and those with ongoing anticoagulant therapy or patients in whom anticoagulant therapy was planned." The meta-analysis by Oldgren et al, 2013 is cited as evidence to support the statement that rivaroxaban, apixaban or dabigatran, in addition to dual antiplatelet therapy led to a small reduction in major adverse cardiovascular event alongside a doubling of clinically significant bleeding. The use of this reference is misleading in this context because the studies included in this analysis primarily address investigation into secondary prevention following ACS and not the acute management of ACS. Additionally the meta-analysis includes medicines that are not licensed for secondary prevention following ACS, it includes doses of medicines that are not licensed for secondary prevention following ACS and it also includes in the analysis a medicine, Ximelagatran, that has been withdrawn from the market due to safety concerns. It would therefore be difficult for a clinician to draw any conclusion regarding the use of novel oral anticoagulants in acute ACS management from this reference. The only medicine of rivaroxaban, dabigatran or apixaban that is licensed for the prevention of atherothrombotic events after ACS is rivaroxaban in a 2.5mg twice daily dose. None have an indication in the acute management of ACS. In the ATLAS ACS 2 TIMI 51 trial rivaroxaban significantly reduced the primary composite endpoint of CV death, MI or stroke relative to placebo (HR 0.84, 95% CI 0.72-0.97; p = 0.020). The benefit was driven by a reduction in CV death (HR 0.66, 95% CI 0.51-0.86: p =	*Text has been added to clarify that the Oldgren paper addressed the addition of a novel anticoagulant to antiplatelet therapy after an ACS.* *Nonetheless, the hazard ratios for increased bleeding and increased major bleeding were similarly high across agents, particularly when used in addition to dual antiplatelet therapy.* *We note that ATLAS ACS-TIM 46 and ATLAS ACS-TIM 51 obtained similar estimates for the efficacy of rivaroxaban in terms of reduction of MACE when added to DAPT (albeit with only the latter being statistically significant at the conventional cut-off, HR 0.82 and 0.84 respectively). However, in common with all of the agents reported in the meta-analysis, there was a markedly increased risk of*

		0.002) and appeared early with a constant treatment effect over the entire treatment period. Also the first secondary endpoint (all cause death, MI or stroke) was reduced significantly (HR 0.83, 95% CI 0.72-0.97; p = 0.016) (Mega et al N Engl J Med 2012;366:9-19). The incidence rates for the principal safety outcome (non-CABG TIMI major bleeding events) were higher in patients treated with rivaroxaban than in patients who received placebo. However the incidence rates were balanced between rivaroxaban and placebo for the components of fatal bleeding events, hypotension requiring treatment with intravenous inotropic agents and surgical intervention for ongoing bleeding. (Mega et al N Engl J Med 2012;366:9-19) It would therefore be appropriate to cite the individual phase III studies for each of rivaroxaban, apixaban and dabigatran in this context. "Information on outcomes for patients with specific comorbidities is not available and it is not, therefore, possible to know whether the net benefits or harms would be greater or smaller for specific patterns of comorbidity. There are currently no identified factors which could be used to stratify patients into those likely or unlikely to benefit from novel anticoagulant therapy." The second paragraph of section 4.5.5 claims that there are no identified factors which could be used to stratify patients into those likely or unlikely to benefit from novel anticoagulant therapy." This statement is not accurate with respect to secondary prevention following ACS but we accept that it is accurate with respect to the acute management of ACS and this distinction should be made clear. The license for rivaroxaban specifies the subgroup of patients to be those with elevated cardiac biomarkers and without prior stroke or TIA (Xarelto SmPC, May 2015). This subgroup of patients has been identified as receiving the most benefit from rivaroxaban 2.5mg twice daily and represents approximately 80% of the total study population. In this subgroup rivaroxaban significantly reduced the primary composite endpoint of CV death, MI or stroke relative to placebo (HR 0.80, 95% CI 0.68-0.94; P=0.007). This benefit was driven by a reduction in cardiovascular death (HR 0.55, 95% CI 0.41-0.74; P<0.001) and also All-Cause death (HR 0.58, 95% CI 0.44-0.77; P<0.001). This was accompanied by a significant increase in Non-CABG TIMI major bleeding (0.7% vs 1.9%; P<0.001) but no significant increase in Fatal bleeding, Intracranial haemorrhage or fatal intracranial haemorrhage (Mega et al. European Heart Journal (2014) 35 (Abstract Supplement), 992)	*bleeding for both of these trials (HR 3.03 and 2.07 respectively) and for ATLAS ACS-TIM 51 major bleeding (HR 3.34).* *For context, the hazard ratio for major bleeding for novel antiplatelet agents were generally less than 1.5. In summary, we consider that the increased risk of bleeding outweighs the potential benefits of reduction in cardiovascular events for NOACs, particularly when compared with novel antiplatelet agents.* *As such, we agree with the conclusions set out in the Oldgren paper that bleeding risks exceed any possible benefit from the use of NOACs following ACS.* *This guideline does not consider secondary prevention.*

		"No published cost effectiveness studies comparing the addition of rivaroxaban, apixaban or dabigatran to dual antiplatelet therapy alone were found. Rivaroxaban (Xarelto®) for the prevention of atherothrombotic events after an ACS is not recommended by SMC for use within NHS Scotland (see section 11.4, SMC: 1062/15)." An analysis of the cost effectiveness of rivaroxaban in the secondary prevention of ACS in Sweden has been published (Begum, N et al, Cardiol Ther (2015) DOI 10.1007/s40119-015-004103). The analysis concluded that compared with standard antiplatelet therapy alone the use of rivaroxaban in combination with standard antiplatelet therapy was a cost effective treatment option for ACS patients with elevated cardiac biomarkers without a prior history of stroke or TIA in Sweden. Furthermore, NICE technology appraisal guidance (TA335) has reviewed the cost effectiveness of rivaroxaban 2.5mg for secondary prevention following ACS, "rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome". The guidance considered the case for the 2.5 mg dose of rivaroxaban in combination with aspirin plus clopidogrel or with aspirin alone, compared with aspirin plus clopidogrel or aspirin alone in patients with acute coronary syndrome with elevated cardiac biomarkers (STEMI or NSTEMI) and no history of stroke or TIA. The conclusion was that rivaroxaban could be considered a cost effective us of NHS resources in this context. "Further SMC advice pertaining to the cost effectiveness of apixaban (836/13) and dabigatran etexilate (672/11) is available, though it should be noted that the advice relates to a subgroup of ACS patients (see section 11.4)." The third paragraph of section 4.5.5, above, is misleading because SMC advice relating to the cost effectiveness of apixaban and dabigatran in the Non-valvular atrial fibrillation indication is cited. This is not relevant to either the acute or long term management of acute coronary syndrome and should be removed.	*Rivaroxaban is not recommended by SMC for use in NHSScotland for prevention of atherothrombotic events after an ACS.* *Yes, SMC ID number is correct. The Swedish study reference here was published after the literature search was conducted and at the last meeting it was decided reviewing this paper would not add much (I suspect comparator in the Swedish study was clopidogrel but SMC advice was based on comparison with ticagrelor) as SMC advice is the more relevant point. NICE single technology assessments do not have any status in Scotland. SMC has not recommended rivaroxaban for use.* *Agree. This sentence has been deleted.*
	AB	Does this recommendation indicate that there should be no clinical situation where a novel oral anticoagulant should be considered in addition to dual antiplatelet therapy after stenting.	*Yes.*
	RCPSG	Clear and correct	*Thank you*
	OW	"0.87% in relative terms" should read "0.87". Suggest rephrasing "Trial results were homogeneous…". I think you mean there were no evidence of heterogeneity amongst the trials. Typically, heterogeneity relates to the trial population, design and findings; not only the results. Also, there were only 7 studies in the systematic review, test of heterogeneity would be under-powered, so suggest more cautious	*Corrected.* *Agree. Sentence re-phrased as "Overall trial results were similar across study designs and excluded..."*

		wording.	
	JJ	"No published cost effectiveness studies comparing the addition of rivaroxaban, apixaban or dabigatran to dual antiplatelet therapy alone were found. Rivaroxaban (Xarelto®) for the prevention of atherothrombotic events after an ACS is not recommended by SMC for use within NHS Scotland *(see section 11.4, SMC: 1062/15).* Further SMC advice pertaining to the cost effectiveness of apixaban (836/13) and dabigatran etexilate (672/11) is available, though it should be noted that the advice relates to a subgroup of ACS patients *(see section 11.4)."* Suggest remove highlighted text as cost effectiveness based on use in wider AF population. Cost effectiveness in subgroup of ACS patients may be different particularly if use of ticagrelor (and increased bleeding risk) is taken into account. Suggest corresponding SMC advice removed from 11.4 plus rivaroxaban in AF.	*Agree. Final sentence deleted and corresponding SMC advice deleted from section 11.4.*
4.5.6	AT	You first state that specific recommendations for fondaparinux cannot be made in STEMI, and then go on to recommend it in STEMI if repercussion therapy is not given - based on what evidence??	*This section was not updated.* *Evidence derived from OASIS-6 trial.*
4.6.1	AF	The benefits of revascularisation may not apply to patients where ACS has been diagnosed using the new troponin assay. Since there are upfront risks associated with Surgery and PTCA then we may dimly be subjecting a large number of patients to a procedure (as well as keeping them in hospital at great expense) to a risk without a benefit and so may well not be offering them the best advice. It is important to recognise that there is no overall mortality benefit and the main benefits are determined by symptoms and recurrent admissions with MI. Considerable thought is required about the advice to patients with regard to procedures since the risk and benefits are no longer clear. For patients with continuing symptoms and high risk ECG changes then the benefits are more obvious but most of the patients are symptom free within 48 hours. Simply looking at the mortality rate in the control groups of these trials they are very different from those may be defined using the new troponin assays.	*See response to AF in section 1.4.*
4.6.2	NU	The COMMIT/CCS-2 trial is quoted as evidence that intravenous and oral beta-blockers should be given to patients immediately presenting with an acute coronary syndrome in Killip class I acute heart failure. This recommendation occurs despite the fact that of above evidence, none in the case of NSTEMI, or ancient (ISIS-1) or more recent (COMMIT/CCS-2) in the case of STEMI, actually indicates this. COMMIT/CCCS-2 failed to meet either of its co-primary endpoints and even the subgroup analysis suggests that beta-blockers should not be given to patients until stable. Reference 93, which is the COMMIT/CCS-2 trial, is then quoted again as turning into a meta-analysis with 52,645	*This section was not updated.* *In the discussion of the COMMIT/CCS-2 trial, there is a meta-analysis of 28 previous trials. This was incorporated to put the COMMIT/CCS-2 findings in context. Prior studies (unlike COMMIT/CCS-2) included patients without bradycardia, hypotension or acute heart failure. The meta-analysis contained in the Lancet paper included a sub-population of the COMMIT/CCS-2 trial: the "low risk" group of patients who had systolic blood pressure >105 mmHg, heart rate >65 and no overt heart failure (Killip class 1). This low risk group is*

		patients. Is this another paper? Furthermore, how relevant is a study in 46,000+ Chinese people who can be enrolled up to 24 hours after a STEMI where only 50% receive a thrombolytic and none undergo primary PCI. This is at complete variance to modern UK practice and should be discarded as it is completely non-applicable.	*consistent with the MIAMI trial. The meta-analysis confirmed the benefits of beta-blockade in this group of patients and is the basis of the recommendation in the guideline.* *The referencing is therefore correct, as the same study provides both an RCT of beta blockade and a meta-analysis of this and further data.*
	AT	The recommendation for IV BB in ACS seems VERY eccentric following the COMMIT.	*This section was not updated, but evidence has not changed since the last update.*
4.7	GA	Good advice.	*Thank you.*
	AT	Making a statement about tight glycemic control with insulin/glucose seems to ignore the lack of evidence for this in DIGAMI and BIOMARCS-2.	*Covered in existing text.*
	AB	The good practice point on not delaying intervention seems appropriate. Similarly should consideration not be given to a practice point to review the need for insulin prior to Discharge.	*Agree it is important.* *As this is more linked to the management of diabetes than to CV interventions it is felt to be outwith the remit of this guideline.*
	JR	"Patients with clinical ACS and DM or marked hyperglycaemia should have immediate blood glucose control...." - are these patients with confirmed ACS or just suspected ACS?	*Confirmed ACS. Recommendation reworded to clarify.*
	RCPSG	Helpful summary with clear recommendations	*Thank you.*
Section 5			
5.1	AT	The balance between fibrinolytic therapy (several pages) and PPC (a couple of paragraphs) seems wholly inappropriate in 2015. Nowhere is there any guidance about the desirable timing of *(text missing)*	*This section on thrombolytic therapy was not updated and the recommendations remain relevant.* *New text relating to PCI (access routes, see section 7.2 ,has also been added)*
	AB	5 Cross reference to Section 7 and revascularistion in non ST elevation acute coronary syndrome would be helpful in the introduction.	*Agreed. Cross reference has been added.*
5.1.1	AB	Should an idea of timings not be given in the first practice point?	*This is covered in section 5.2.1*
5.1.2	RCPSG	New evidence entirely supports the view presented which should alter practice *We note included in the list of suggestions for further research with respect to use of manual aspiration when there is a heavy thrombus burden, as opposed to routine use.	*Thank you.*
5.2	DH	Rural transfers require a critical decision regarding whether to thrombolyse STEMIs then transfer, or transfer directly with PPCI. We've been working closely with GJNH about developing our protocols here and have come round to the thought that in general STEMIs should be thrombolysed unless clear and confident route to PPCI within 90mins - but some consideration of this decision-making process (taking into account air transport) would be helpful.	*This is a matter for consideration in local protocols.*
5.2.1	AB	Should reference be given to service design in this section if the timings cannot be met (although covered in 5.2.3)?	*As above.*

5.2.2	NB	The section on very early (within 2 hours) thrombolysis reflects a controversy that was active many years ago and is no longer relevant. I would therefore delete this.	*This section on thrombolytic therapy was not updated and the recommendations remain relevant.*
5.2.3	CB	Page 19, Section 5.2.3, final paragraph. Please revise "antiplatelet therapy" to specifically state clopidogrel since there is no evidence for ticagrelor or prasugrel which both increase the risk of major bleeding vs. clopigorel. So "and antiplatelet therapy with clopidogrel".	*This recommendation has been reworded and no longer refers to antiplatelet therapy.*
5.2.5	AB	I accept that a bolus fibrin specific agent is preferred but 5.3.3 may be used to justify non-bolus agents.	*This section on thrombolytic therapy was not updated and the recommendations remain relevant.*
5.5	CB	1st paragraph, 2nd sentence does not make sense. Suggest delete or change 'feasible' to 'plausible'. Paragraph 2 Clinical circumstances: In order to reflect the fact that preventive PCI may only be possible if the catheter laboratory time is available ie no other patients waiting, and the timing is conducive to additional nonemergency PCI ie preferably office hours than 0000 – 0800, I suggest rephrasing is needed to reflect practical considerations, eg "The decision to perform preventive PCI depends on patient factors and clinical circumstances." Overall comment This section lacks a recommendation and the review of the recent randomised trials is unduly critical of the two recent randomised trials in the UK, PRAMI and CULPRIT. The review does not mention the meta-analysis by Kowalewski et al published in Heart (Heart. 2015 Aug 15;101(16):1309-17. doi: 10.1136/heartjnl-2014-307293. Epub 2015 Jun 2) in which ~50% reductions in the risk of recurrent MI and repeat revascularisation are described. The meta-analysis by El-Hayek GE et al (Am J Cardiol. 2015 Jun 1;115(11):1481-6) provides broadly consistent results with the meta-analysis by Kowalewski et al. Other earlier meta-analyses in which non-randomised studies are included have questionable value. The PRAMI trial enrolled participants after successful culprit-artery PCI and when the non-culprit disease was amenable to PCI. PRAMI included a CONSORT flow diagram for enrolment and follow-up (465 of 2428 STEMI patients screened for eligibility were enrolled). Similarly, the CULPRIT trial enrolled 296 of 850 STEMI patients. The guideline committee might consider the fact that both trials had similar designs and had consistent results for a treatment effect based on revascularisation immediately (PRAMI) or within the index admission (CULPRIT), implying the observations in these trials are valid. Clearly, data from larger randomised trials are warranted. Nevertheless, this reviewer suggests that the SIGN guideline should contain a recommendation for immediate or staged revascularisation of non-culprit disease, with a	*Disagree. However "feasible" has been changed to "possible".* *Agreed. Text revised to clarify operational factors involved in choice of PCI* *Agree. New meta-analyses have been reviewed and the text revised to incorporate these. In the considered judgment of the group, no recommendation was warranted.* *Agreed. Reference to these earlier meta-analyses has been removed.* *Disagree. The evidence from the newer meta-analyses does not support a recommendation*

		level of evidence of 1+ based on the two most recent meta-analyses of randomised trial participants (only) and the two recent UK trials. Staged invasive management after discharge following the index hospitalisation exposes patients with non-culprit lesions to early risk of recurrent MI. This early risk is greatest within the first 30 days. Staged management intended during or after the first 30 days exposes post-STEMI patients with multivessel disease to an avoidable risk of recurrent cardiac events. This risk is very clearly outlined in the important JAMA publication by Manish Patel and colleagues involving 28,282 STEMI survivors: Park DW, Clare RM, Schulte PJ, Pieper KS, Shaw LK, Califf RM, Ohman EM, Van de Werf F, Hirji S, Harrington RA, Armstrong PW, Granger CB, Jeong MH, Patel MR. Extent, location, and clinical significance of non-infarct-related coronary artery disease among patients with ST-elevation myocardial infarction. JAMA. 2014 Nov 19;312(19):2019-27. doi: 10.1001/jama.2014.15095. PubMed PMID: 25399277. The following recommendation is suggested: "Angiographically-guided preventive PCI should be considered for non-culprit lesions that are amenable to treatment with the timing of the procedure either immediately in the catheter laboratory after successful culprit-artery PCI or staged subsequently in a second procedure, wherever possible, during the index admission."	*This is a retrospective pooled analysis of 8 RCTs which have been selected by non-systematic means. Results may or may not be representative of the wider STEMI population. No further action was taken.*
	NB	The optimum management of ACS patients with multivessel disease is a very important and very complex issue that deserves a more detailed discussion. I acknowledge that the evidence is not conclusive because the published trials have produced conflicting results, and have been designed in ways that do not address real world issues. Nevertheless, it should be possible to comment on each of the recognized options for assessing and planning treatment of non-Infarct Related Artery (non-IRA) lesions during STEMI include: 1. PCI of IRA and all significant non-IRA lesions at same setting, 2. PCI of significant non-IRA lesions prior to discharge 3. PCI of lesions based on further invasive evaluation (eg, fractional flow reserve or intravascular ultrasound) 4. PCI of significant non-IRA within a few weeks 5. optimum medical therapy for several weeks, with PCI of significant non-IRA if the patient has ongoing angina or a positive stress test.	*Agree. The text has been revised to summarise the revascularisation options, although in a simpler manner than suggested here.*
	AB	Would this section not benefit from a good practice point on what approach should be taken on the basis that there can be a significant variation in clinical practice.	*No – this is not an appropriate use of good practice points. It is not matter of universally applied good practice. It remains to be answered by robust evidence. In the meantime, the shortfalls in the existing evidence base are described.*

	RCPSG	More recent RCTs (PRAMI, CuLPRIT, DANAMI-3 PRIMULTI) support multi-vessel PCI, although the reduction in endpoints is driven by repeat revascularisation. We would support the conclusion, however, that more robust data from further trials are required before a recommendation for multi-vessel PCI can be made.	*Thank you.*
	AF	It is important that units need to present audit data of their outcomes before recommending procedures based on trial outcomes. The audit data should show that unit results are as good or better than trial outcomes.	*The GDG agree that audit of clinical practice is important.*
Section 6			
6.1.1	AF	I am afraid that I find the risk scores misleading and unhelpful since they are heavily weighted by age. The older you are the closer you are to death. Also the risk scores did not use high sensitivity troponin and a lot of causation is required if these are suggested to be used in anyway clinically.	*Section not updated, but agreed that age is important.*
	DH	Thinking about NSTEMIs and unstable angina - clarification about GRACE scoring and its use in determining transfer times/methods would be helpful.	*Section not updated, but information on how to access GRACE 2.0 online has been added* *The GRACE score has been used to triage patients for urgent or soon in-patient or out-patient coronary angiography, but the decisions around patient transfers are more complex and need to consider the patient's symptoms, social circumstance, occupation, and co-morbid conditions. Therefore we have not recommended explicitly that the GRACE score be used to guide transfers.*
	CB	Risk scores such as GRACE are incompletely adopted in emergency care in NHS Scotland, as reflected by local audits. This point needs further consideration.	*There are no ideal risk scores for the triage of patients with suspected acute coronary syndrome in the Emergency Department. Whilst GRACE scores are used in this setting, the score was developed in patients with confirmed myocardial infarction rather than the wider population of patients with chest pain assessed in the Emergency Department. Local practice will vary.*
	AF	Unhelpful of no clinical value	*As above.*
6.2	AF	It should be stressed that this does not mean every patient should have an echocardiogram. For example for those with a near normal 12 lead ECG clinical assessment alone should suffice. There are a huge number of unnecessary echocardiograms performed that consume a huge resource.	*This section was not updated.* *The recommendation is for an assessment of cardiac function, not specifically an echocardiogram. It allows for flexibility of approach.*
Section 7			
7.1.1	AT	RITA-3 reports that benefits of early invasive strategy in NSTEMI no longer apparent after 10 years (Henderson et al. JACC 2015) Surprised you make no recommendations for timing of intervention.	*Timing of intervention was not covered by the update.*
	AF	All the evidence particularly that which refers to invasive treatment was collected prior to the introduction of the new troponin assays. So	*This section was not updated.*

		depending on when the evidence was collected it may not apply to many of the patients with the new assay.	
7.1.2	AT	Surprised you make no recommendations for timing of PPCI, nor any recommendations for decisions concerning fibrinolysis vs PPCI.	*This is covered in section 5.*
7.2	RCPSG	Data well-presented to justify clear recommendation.	*Thank you.*
7.3	GA	Good, I agree, however we need to define 'not adequately treated with P2Y12'. e.g. Does this mean people that presented for PCI within 30 minutes, or patients that vomited/NBM patients etc?	*Disagree. This is too specific.*
	RCPSG	Accepting there is no place for routine therapy, does the evidence not support commencing these in unstable NSTEMI patients already on effective DAPT and LMWH when there is a delay to undertaking angiography but where PCI is planned if anatomy appropriate? *We note included in the list of suggestions for further research*	*The evidence presented does not support this specific conclusion.*
7.4	NU	The literature quoted in this section is not in patients with ACS but in patients with stable angina. On this basis, it is not cogent to the guideline and should be removed.	*While the systematic review by Deb et al "limited our search to published RCTs …to reflect contemporary practices comparing PCI with CABG surgery in patients with stable ischemic CAD..." some of the trials did in fact include those with unstable angina. We have added a sentence to clarify this.*
	AB	My reading of this is that there is still a significant possible role for coronary artery bypass grafting yet the good practice point may not be adhered to resulting in the option not being considered.	*The GPP is there to reinforce the need for action.*
	RCPSG	"A systematic review of 13 RCTs and 4 meta-analyses reported reduced rates of cardiac adverse events following CABG surgery compared to PCI in patients with unprotected left main-stem disease (ULMD), or multi-vessel coronary artery disease (CAD), or left ventricular dysfunction, and complex coronary disease (SYNTAX score greater than 22). In patients with diabetes and multi-vessel CAD (5 of the 13 RCTs) long-term survival and the number of cardiac adverse events were reduced in patients receiving CABG compared with PCI.185 Most of the benefits were seen in reductions in repeated coronary revascularisation procedures." The data does we think reflect all patients undergoing intervention rather than specifically ACS patients. Is there data comparing strategies in ACS separately, eg culprit vessel PCI then randomised to CABG or staged PCI for multivessel disease? *We note included in the list of suggestions for further research*.	*Response as for NU above.*
	AF	Serious consideration needs to be given to this section since again there are different anatomical patterns as well as well as different outcomes that relate to the patient and the nature of the disease and not just the anatomical description of the disease.	*Agree and already covered by the existing GPP.*

Section 8			
	MSD	In section 8 'Early pharmacological intervention', it would seem that only evidence relating to the effectiveness and safety of statin therapy has been considered. However, in the interest of individualised patient care and clinician prescribing choice, MSD would like to understand if the evidence relating to treatment of patients with ACS in combination with statin therapy, namely ezetimibe has been considered given the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study has reported final results in the last 12 months. The IMPROVE-IT study was designed to assess if additional clinical benefit would be seen with further reductions of LDL cholesterol (LDL-C) to levels below 1.8 mmol/L in patients who had been hospitalised for ACS within the preceding 10 days. A background statin therapy of simvastatin 40mg (+/- uptitration to simvastatin 80mg) with an upper limit for LDL-C level at study entry would be likely to produce an average reduction of LDL-C levels to <1.8 mmol/L. The study found that the addition of ezetimibe to this background statin regimen further reduced LDL-C by a mean of 24%. This additional 24% reduction in LDL-C to a mean of 1.4 mmol/L translated into significant reduction in CV events in this patient population.[1] MSD believes that these data are relevant to the patient population considered within this guideline, and offer a valid treatment option for patients who are intolerant or contra-indicated to statin therapy alone, or in combination with a statin when adequate efficacy has not been achieved. <u>Summary of IMPROVE-IT study, Jones et al. 2015</u> IMPROVE-IT was a multicentre, randomised, double-blind, active-control study in high-risk individuals (n=18,144) presenting with stabilised acute coronary syndrome (ACS) within 10 days[1]. The primary composite efficacy endpoint outcome measure was the time from randomisation to the first occurrence of one of the following events: CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, coronary revascularisation with either PCI or CABG occurring at least 30 days after randomisation, or non-fatal stroke. Treatment with ezetimibe/simvastatin resulted in an absolute risk reduction of 2% (equivalent to a 6.4% relative risk reduction) in the primary efficacy endpoint compared to treatment with simvastatin alone (HR 0.936, 95% CI; 0.89-0.99 *p*=0.016). The primary endpoint occurred in 2,572 of 9,067 subjects (7-year Kaplan-Meier [KM] rate 32.72%) in the ezetimibe/simvastatin group and 2,742 of 9,077 subjects (7-year KM rate 34.67%) in the simvastatin only group in the protocol-defined ITT population. The overall safety and tolerability of ezetimibe/simvastatin in	*Evidence for statin therapy or other alternatives did not form part of this update.*

		IMPROVE-IT, as assessed by evaluation of adverse experiences, revealed no new safety findings related to study therapy, and was consistent with current ezetimibe/simvastatin product labeling. Based on the evidence presented within the IMPROVE-IT trial and the recommendations of NICE TA132, endorsed by the Scottish Medicines Consortium (SMC), MSD requests the inclusion of ezetimibe into the proposed SIGN guideline as a treatment option for the lipid management of patients, for whom: • Statin therapy is contraindicated or not tolerated • Serum total or LDL cholesterol concentration is not appropriately controlled by statin therapy alone.	
8.1.1	CB	This recommendation should be revised to focus the dose of aspirin to be 75 mg daily. Higher doses are associated with increased risk of bleeding and without evidence of benefit	*Agree. Dose in GPP changed to 75 mg.*
	AB	While accepting that the clinical trials used doses greater that 75mgs aspirin (100mgs) is there any pharmacological reason for not simplifying the point by giving only the 75mgs dose – which is what happens in practice.	*As above.*
8.1.2	GA	I find it strange that there is no recommendation on antiplatelet duration for ACUS patients undergoing pPCI i.e. how long for POBA, BMS, DES? Please reconsider clear advice on this.	*We have added text about patients not receiving early PCI. It should now be clear that the main recommendations refer to the current standard of care – early PCI.*
	CB	The new paragraph beginning "Consistent with these trial data on clopidogrel …" provides a timely update on the new data on long term therapy post-MI (1- 3 years) [PEGASUS-TIMI 54, NEJM March 2015]. However, the guideline text does not summarise the evidence for the duration of dual anti-platelet therapy for the newer agents, ticagrelor and prasugrel within the first 12 months, when, importantly, the risk of recurrent cardiac events is highest. The SIGN guideline committee will be familiar with the results of the PLATO and TRITON-TIMI38 trials. Overall, the PLATO trial (ticagrelor, treatment duration 12 months, median treatment duration 277 days; ACS) and TRITON-TIMI38 (prasugrel, treatment duration 6 – 15 months trials demonstrated superiority on efficacy over clopidogrel; ACS undergoing PCI) favoured DAPT therapy for at least 6 months, and 12 months, as is recommended by the NICE technology appraisal guidance (TA236) for ticagrelor. The current ESC guidelines (Hamm et al Eur Heart J 2011) give a recommendation for the duration of dual antiplatelet therapy with a second drug for 12 months (Class 1 recommendation, Level of Evidence A) and for ticagrelor and prasugrel there are Level Class I recommendations, level of evidence B: Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g.	*Thank you.* *We agree that the duration of therapy in these trials should be included in this section of the guidelines and have added a statement to this effect. Nevertheless, for both of these trials the control group was clopidogrel therapy, and neither included a placebo or 'no treatment' control group for any period of the treatment regime. As such, while 12 months ticagrelor was superior to 12 months clopidogrel, 3-6 months of ticagrelor/clopidogrel may have been superior to either – this comparison was not made.* *The 10 trials reported in the Palmineri and Navarese reviews did, however, randomly allocate patients to different durations of dual-antiplatelet therapy and hence were used as the main basis for our recommendations.* *The most recent 2015 ESC guidelines also recommend 12 months duration of therapy. However, these same guidelines also acknowledge that "while a 1-year duration of DAPT in NSTE-ACS patients is recommended, based on individual*

		elevated troponins) , regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced). Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for P2Y12-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life threatening bleeding or other contraindications. The accrual of adverse cardiac events is most recently evidenced by the experience in the FAMOUSNSTEMI clinical trial that involved 350 NSTEMI patients enrolled in 6 UK centres (Layland J et al Eur Heart J, 2014; FASTTRACK publication). The clinical characteristics of the participants in this trial were similar to typical ACS populations in the published literature, and the possibility of selection bias should not detract from the fact that spontaneous MACE events continued to accrue over time up to 12 months when follow-up ended, regardless of the randomised group. Two thirds of the participants in this trial were enrolled in the West of Scotland. These data unequivocally illustrate that spontaneous adverse cardiac events continue to occur, regardless of revascularisation status, and this is to be expected since multivessel coronary disease is typical in the majority of NSTEMI patients. The occurrence of these events was not associated with the type of anti-platelet. Figure. Kaplan Meier plots for major adverse cardiac events in 350 NSTEMI patients during 12 months follow-up in the FFR-guided group and angiography guided group. Layland J et al, Figure 4. Eur Heart J 2014, FASTTRACK publication. Reference 1: Layland J, Oldroyd KG, Curzen N, Sood A, Balachandran K, Das R, Junejo S, Ahmed N, Lee MM, Shaukat A, O'Donnell A, Nam J, Briggs A, Henderson R, McConnachie A, Berry C; FAMOUS–NSTEMI investigators. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. Eur Heart J. 2015 Jan 7;36(2):100-11. doi: 10.1093/eurheartj/ehu338. Epub 2014 Sep 1. PubMed PMID: 25179764; PubMed Central PMCID: PMC4291317. The contemporary data on the progressive accrual of adverse events in the FAMOUS-NSTEMI trial is consistent with registry data, such as from the Scottish patients in the GRACE registry (Eur Heart J 2010; 31: 2755–2764). This reviewer recommends a single unifying recommendation for DAPT in ACS patients: DAPT for 12 months in ACS patients where benefits (reduction in atherothrombotic events) outweigh the risks (bleeding).	*patient ischaemic and bleeding risk profiles, DAPT duration may be shortened (i.e. 3–6 months) or extended (i.e. up to 30 months) in selected patients if required." As such, we believe that our revised guideline which recommends 6-months, but allows that a longer duration may be required for some patients, differs only in degree from the ESC guidelines.* *Presenting the secondary analyses of the CURE and CHARISMA trials in section 8.1.2 may have led to the impression that our recommendations are based primarily on extrapolating from analyses of event rates over time. In fact the recommendations are based on the consistent findings of the 10 trials synthesised in each of the two published meta-analyses (Palmineri and Navarese). We note, as did the ESC reviewers, that these trials included patients with stable coronary artery disease. Nonetheless, for the primary endpoints, estimates were similar in patients with and without ACS (stratified or sub-group analyses were reported in 8 of the 10 trials included in the meta-analyses). A second consideration is that the majority of these trials of DAPT duration did not include any patients taking ticagrelor or prasurgrel, and of the 4 which did include newer antiplatelets, the majority of patients received only clopidogrel (ITALIC 98%, SECURITY 97%, ARCTIC 81% and DAPT 65% clopidogrel). Nonetheless, we believe that even with the under-representation of newer antiplatelet agents, the results from these randomised comparisons outweigh the cited observational findings, particularly as the adverse event of greatest concern – bleeding – is an expected pharmacologic effect of platelet inhibition (Type A adverse effects) and hence is therefore also likely to be related to duration of therapy for newer agents. Indeed major bleeding was increased consistently with longer durations across all 10 trials, while in no trial did a longer duration of therapy confer a mortality benefit.*
	NB	A few years ago there was great interest in the	*As this genetic testing is not part of*

		evidence that about 30% of people have a genetic mutation that means they do respond to clopidogrel as well as the rest of the population. The presence of this mutation was associated with worse outcomes and a series of important trial examining the value of using genetic testing and / or platelet aggregation testing to direct antiplatelet therapy were undertaken. These have shown that such measures are not justified but should be discussed. The optimum use of dual antiplatelet therapy remains unclear and rather confusing. Many clinicians adopt different approaches for some subsets of patients (eg non-invasive therapy, bare metal stent, drug eluting stent, concomitant anticoagulant therapy) and this should be discussed. A table of the recommendations for each subset would be helpful.	*routine clinical care the GDG believe it lies outwith the scope of this guideline.* *We agree that this is confusing and have simplified the recommendations, removing the discussion of patients not receiving early PCI to the text.*
	NU	Acute Coronary Syndrome Reference 66 is not complete in the reference section. Dual anti-platelet therapy after PCI Reference 192 is not complete in the reference section. If an argument is being constructed to argue that patients with an ACS should only receive three months of DAPT, how does this fit it to the recommended use of ticagrelor (or prasugrel) neither of which have any clinical evidence benefit over clppidogrel at three months in the published literature? Furthermore, given that the FDA website confirms an excess of atherothrombotic events with ticagrelor over clopidogrel on discontinuation of the drug at 12 months, then stopping at three months may lead to a similar excess of adverse events. These recommendations need to be revised to reflect the evidence available rather than on extrapolation from mixed meta-analysis.	*References corrected.* *See response to CB above.* *Despite differences in study populations, the results from the 10 included trials were very similar both for cardiovascular end points and bleeding. Moreover, the conclusions do not rest on the use of network meta-analysis methods, as the results of the simple pairwise comparisons yielded similar findings.*
	AT	Your recommendation for 3 months DAPT after stenting is surely wrong? The evidence supports 9-12 Months.	*See response to CB above.*
	JP	The three month duration of treatment in the recommendation of dual antiplatelet therapy for patients with ACS relates to the evidence base for clopidogrel specifically. Treatment with prasugrel up to 12 months is recommended (section 4.2 of prasugrel SPC) unless the discontinuation of prasugrel is clinically indicated.	*See response to CB above.*
	KL	In section 8.1.2, a post-hoc analysis of the CURE study at 3 months is highlighted as a reason for recommending that acute coronary syndrome (ACS) patients receive 3 months of dual antiplatelet (DAPT) therapy. This, despite acknowledging in the same paragraph that the study was not powered to assess temporal effects. There are some limitations to using the CURE study in this context. Firstly, patients were	*See response to CB above.*

		recruited and treated for their ACS event between 1998 and 2000 and this means that the management and treatment of these ACS patients may not reflect current practice. For example, about 80% of patients did not receive a PCI procedure and more potent antiplatelet agents such as ticagrelor were not available at the time. In addition, the centres chosen to recruit patients were those without a routine use of invasive procedures. Secondly, the ACS population in CURE excluded STEMI patients. Therefore it is difficult to understand how a broad all-ACS recommendation for 3 months duration of DAPT can be derived from a NSTE-ACS clinical trial. An evidence base almost 15 years old has been cited in this important section of the draft guideline and it is our opinion that more recent study data should be considered. We also note that 8.1.2 discusses three meta-analyses. Similarly, these studies have some significant limitations that we believe must be acknowledged in the draft guidance if they are to be used in the context of a universal ACS recommendation for 3 months duration of DAPT therapy, or removed completely. • Since the majority of patients received clopidogrel in the meta-analyses, the results cannot be extrapolated to other non-thienopyridine antiplatelet agents such as ticagrelor • Differing study designs and DAPT strategies meant that in some instances 1-year DAPT was classified as 'short treatment' and in other cases as 'longer treatment'. Additionally, these studies do not specifically examine 3 months duration of DAPT therapy and were often underpowered. • It should be acknowledged the cited meta-analyses included mixed patient populations including stable coronary artery disease (CAD) as well as ACS. Therefore the results might not be generalised to higher risk patients such as an ACS population. However, should CURE be assessed for temporal effects, we would like to highlight some UK registry data (1) which we believe casts doubt on the conclusion that the majority of the benefit seen in the CURE study is at 3 months. This is taken from a retrospective observational cohort study using linked data from the MINAP, GPRD, Hospital Episode Statistics (HES), and the Office of National Statistics Mortality Data. 7,543 patients included in this registry were hospitalized for ACS between 2003 and 2009 with a discharge diagnosis of STEMI and NSTEMI whilst patients without troponin elevation were excluded. This descriptive analysis found that clopidogrel discontinuation within 12 months was independently associated	*See response to CB above.* *As only 2 of the 10 trials included a 3-month arm (OPTIMIZE and RESET) we have modified the recommendation to 6 months therapy (7 of the 10 trials had a 3 or 6 month arm).* *The results were similar in patients with and without ACS (see response to CB). Nonetheless, we do specifically state than shorter or longer durations of therapy may be reasonable according to individual patient's risk of bleeding and cardiovascular events.* *See response to CB above.*

		with an increased risk of death or MI both compared with those patients persisting with clopidogrel treatment [HR 2.62 (2.17–3.17)] (1). In section 4.4.2, it is highlighted that ticagrelor plus aspirin 'improves clinical outcomes (cardiovascular disease death, recurrent MI and stroke) compared to dual therapy with aspirin and clopidogrel.' It is also highlighted that ticagrelor plus aspirin reduces all-cause mortality across all patients with ACS and reduces stent thrombosis, with an increase in major bleeding. These conclusions are taken from the PLATO study (2), a multi-centre randomised controlled trial of 18,624 all ACS patients where clopidogrel plus aspirin was compared to ticagrelor plus aspirin. Importantly, this study was powered to investigate the primary outcomes at 12 months of treatment. It is AstraZeneca's view that any recommendation for DAPT duration of treatment in section 8.1.2 should refer to the data for the therapy deemed to be providing 'more effective' therapy, as quoted in section 4.4.2. We therefore do not feel it is scientifically rigorous, in this context, to extrapolate a post-hoc analysis of data from the clopidogrel CURE study in 8.1.2. The results of the PLATO are summarised in section 4.4.2 of the draft guideline, however we believe it is a key highlighting that the primary efficacy endpoint curves of ticagrelor plus aspirin compared to clopidogrel plus aspirin continue to diverge over the course of 12 months. In effect, this benefit was seen both early and late with a consistent hazard ratio and benefit of ticagrelor over clopidogrel throughout the year (Table 1). We would also stress that consistent with the overall PLATO population, the benefits accrue for those patients undergoing an invasive or non-invasive treatment strategy (3,4). From randomisation to: Day 30 HR=0.88 ARR (%)=0.6 Day 60 HR=0.84 ARR (%)=1.0 Day 90 HR=0.86 ARR (%)=1.0 Day 120 HR=0.86 ARR (%)=1.1 Day 180 HR=0.85 ARR (%)=1.3 Day 360 HR=0.84 ARR (%)=1.9 Table 1. Hazard Ratio (HR) and Absolute Risk Reduction (ARR) at different time periods in the PLATO study for the primary efficacy endpoint. (2, 5) Subsequent atherothrombotic events can occur at sites distinct from the index event location. In the PROSPECT (6) study which recruited patients who underwent PCI for an ACS event, a similar number of recurrent events were related to new, 'non-culprit' lesions as the original stented 'culprit' lesions. In the DAPT study (7), MI that was not related to stent thrombosis accounted for 55% of the treatment benefit showing that the reduction of MI was approximately as frequent in lesions within the stented artery as in non-stented arteries, thus	*See response to CB above.* *See response to CB above.*

		suggesting a secondary prevention effect of the strategy of prolonged DAPT. Regarding the cost-effectiveness of 12 vs. 3 months DAPT in ACS patients, it should be noted that there are limitations associated to the use of Rogowski et al 2009 (8) in this context. These include the fact that the model captured only NST-EACs patients (i.e. no STEMI patients) and baseline event probabilities were informed by PRAIS-UK - a registry study which followed patients between the years of 1998 and 1999, a period which cannot be considered to reflect modern-day ACS management. Furthermore, the ICERs reported in the draft guideline actually relate to the evaluation of 12 vs. 6 months DAPT, not 12 vs. 3 months. Within their technology appraisal of ticagrelor, the SMC concluded ticagrelor to be a cost-effective use of NHS Scotland resources based on 12 months use. Following extensive sensitivity analysis, the highest ICER for 12 months ticagrelor-based DAPT vs. 12 months clopidogrel-based DAPT was found to be £7,346 per QALY. An additional sensitivity analysis was conducted to evaluate 12 months ticagrelor based DAPT vs. 3 months clopidogrel-based DAPT, resulting in an ICER of £8,905 (9). Since half of the absolute CV risk reduction for ticagrelor observed in PLATO was accrued in months 4 to 12, it would also be reasonable to expect that 12 months ticagrelor-based DAPT would be cost-effective vs. 3 months ticagrelor-based DAPT. Finally, we feel it is important to emphasise that the recommendation for 3 months DAPT duration is at odds with other major European and North American guidelines that consistently recommend up to 12 months of DAPT regardless of stent type in patients in ACS. Here is a brief summary of other well respected guidelines and their recommendation for DAPT therapy: • ESC myocardial revascularization 2014 (10) – 12 months for all ACS PCI managed patients • ESC NSTE-ACS 2011 (11) – 12 months • ESC STEMI 2012 (12) – up to 12 months for Primary PCI patients • AHA/ACC STEMI 2013 (13) – 12 months for Primary PCI patients• AHA/ACC UA/NSTEMI 2012 update (14) – up to 12 months for medically managed and 12 months for PCI managed patients. Based upon the evidence cited and existing guideline positions we would recommend the following; Recommendation 1 Patients with acute coronary syndrome should receive up to 12 months dual antiplatelet therapy where the benefits (reduction in recurrent atherothrombotic events) outweigh the risks (bleeding). Recommendation 2 Patients with acute coronary syndrome who are	*The points raised here are acknowledged. However, on reflection the HTA was deemed appropriate to include as evidence in the guideline.* *The recommendations made in this guideline are based on a thorough review of the published evidence. It is not the role of this guideline to make comparisons with recommendations made in other guidelines as this may mislead readers as to what SIGN itself recommends.* *The first recommendation has been reworded to read:* "Patients with acute coronary syndrome should receive dual antiplatelet therapy for six months. Longer durations may be used where the risks of atherothrombotic events outweigh the risk of bleeding. Shorter durations may be used where the

		not undergoing early percutaneous coronary intervention should be considered for 12 months dual antiplatelet therapy where the benefits (reduction in recurrent atherothrombotic events) outweigh the risks (bleeding). References 1. Boggon R et al. Eur Heart J 2011;32:19 2376-2386. 2. Wallentin et al. New Eng J Med 2009; 361(11): 1045-1057 3. Cannon et al. Lancet 2010; 375: 283-293 4. James et al. 2011; BMJ 2011;342:d3527 5. Data on File AstraZeneca BRIL/008/NOV2010 6. Stone GW et al. N Engl J Med 2011;364:226–235. 7. Mauri L, et al. N Engl J Med. Nov 16, 2014 8. Rogowski W, et al. Health Technology Assessment 2009;13(31):iii-iv, ix-xi, 1-77. 9. Scottish Medicines Consortium. Ticagrelor for the prevention of atherothrombotic events in adult patients with acute coronary syndromes. Detailed Advice Document. Available at: https://www.scottishmedicines.org.uk/files/advice/ticagrelor_Brilique_FINAL_APRIL_2011_amended_030 511_for_website.pdf 10. Wijns W, et al. Eur Heart J 2010;31:2501–2555; 11. Hamm CW, et al. Eur Heart J 2011;32:2999–3054 12. Steg G, et al. Eur Heart J 2012;33:2569–2619 13. O'Gara PT, et al. Circulation 2013;127:e362–425; 14. Jneid H, et al. Circulation 2012;126:875–910;	risks of bleeding outweigh the risk of atherothrombotic events." *For the primary endpoints of the trials included in the meta-analyses results were similar for patients with and without ACS (see table). Nonetheless, we have modified the recommendation to 6 months therapy in view of the fact that most of the short-duration trial arms were for 6 rather than 3 months of therapy.* *We agree that allocating patients with ACS to high and low risk of bleeding and high and low risk of atherothrombotic events is difficult due to a lack of validated tools.* *The first recommendation has been modified to 6 months.*
	PH	Duration of anti-platelet therapy: The new guideline cites the growing body of evidence that short duration DAT is sufficient and provides net benefit in terms of less bleeding. The meta-analyses contain elective and ACS cases. Prescribing only 3 months DAT seems an extreme interpretation of this data for ACS patients. The guideline qualifies this recommendation noting 'a limited role' for extended therapy in some patients but this is too vague to be helpful given that 1) multivessel PCI is common place in ACS patients with diffuse plaque disease and 2) RCT level data is lacking on whether using atherothrombotic/bleeding risk prediction algorithms to tailor DAT following PCI in ACS is beneficial. The PLATO trial noted a delayed benefit from ticagrelor which grew steadily over the duration of the trial. This would support the use of prolonged DAT in ACS patients. Does the 3 month data from PLATO support transition from clopidogrel? Given some uncertainty, 6 months would be a less severe deviation from current guidelines for ACS patients receiving PCI.	

		The second recommendation is for 12 months DAT in patients not receiving early PCI. Does this refer mainly to NSTEMI patients who do not receive a stent? It is hard to see where this fits in clinical practice. There are 2 groups- younger patients who have near normal arteries on angiography and elderly frail patients with severe co-morbidity/renal failure who are not referred for invasive angiography. Neither group seem like a good target for intensive prolonged DAT.	We agree and have removed this recommendation instead providing a discussion of patients not receiving early PCI in the text.
	LR	Section 8 of the guideline provides recommendations on early pharmacological management of ACS beyond the first 12 hours and up to hospital discharge. Rivaroxaban co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. Treatment with rivaroxaban should be started as soon as possible after stabilisation of the ACS event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued. Rivaroxaban may therefore be considered within the remit of the guideline and in particular within the recommendations for early pharmacological management. As noted previously, in the ATLAS ACS 2 TIMI 51 trial rivaroxaban significantly reduced the primary composite endpoint of CV death, MI or stroke relative to placebo (HR 0.84, 95% CI 0.72-0.97; p = 0.020). The benefit was driven by a reduction in CV death (HR 0.66, 95% CI 0.51-0.86: p = 0.002) and appeared early with a constant treatment effect over the entire treatment period. Also the first secondary endpoint (all cause death, MI or stroke) was reduced significantly (HR 0.83, 95% CI 0.72-0.97; p = 0.016). The incidence rates for the principal safety outcome (non-CABG TIMI major bleeding events) were higher in patients treated with rivaroxaban than in patients who received placebo. However the incidence rates were balanced between ivaroxaban and placebo for the components of fatal bleeding events, hypotension requiring treatment with intravenous inotropic agents and surgical intervention for ongoing bleeding. (Mega et al N Engl J Med 2012;366:9-19). In a subgroup of patients with raised biomarkers and no prior stroke or TIA rivaroxaban 2.5mg twice daily significantly reduced the primary composite endpoint of CV death, MI or stroke relative to placebo (HR 0.80, 95% CI 0.68-0.94; P=0.007). This benefit was driven by a reduction in cardiovascular death (HR 0.55, 95% CI 0.41-0.74; P<0.001) and also All-Cause death (HR 0.58, 95% CI 0.44-0.77; P<0.001). This was accompanied by a significant increase in Non-CABG TIMI major bleeding (0.7% vs 1.9%; P<0.001) but no significant increase in Fatal	*Response as for LR comment in 4.5.5.* *Rivaroxaban is not recommended by SMC for use in NHS Scotland for prevention of atherothrombotic events after an ACS.*

		bleeding, Intracranial haemorrhage or fatal intracranial haemorrhage (Mega et al. European Heart Journal (2014) 35 (Abstract Supplement), 992). An analysis of the cost effectiveness of rivaroxaban 2.5mg twice daily in the secondary prevention of ACS in Sweden has been published (Begum, N et al, Cardiol Ther (2015) DOI 10.1007/s40119-015- 004103). The analysis concluded that compared with standard antiplatelet therapy alone the use of rivaroxaban in combination with standard antiplatelet therapy was a cost effective treatment option for ACS patients with elevated cardiac biomarkers without a prior history of stroke or TIA in Sweden. Furthermore, NICE technology appraisal guidance (TA335) "rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome" has been published. The guidance considered the case for the 2.5 mg dose of rivaroxaban in combination with aspirin plus clopidogrel or with aspirin alone, compared with aspirin plus clopidogrel or aspirin alone in patients with acute coronary syndrome with elevated cardiac biomarkers (STEMI or NSTEMI) and no history of stroke or TIA. The conclusion was that rivaroxaban could be considered a cost effective us of NHS resources in this context.	
	AB	The significant change to this section is driven by the introduction of newer agents and the ongoing variation in practice on the length of time dual anti-platelet agents are used for. It needs to be accepted that the CURE and CHARISMA trials took place against a background of a very different landscape in terms of intervention, revascularisation and preventative therapy. In the CURE trial the statistical benefit was lost at 3 months and also the risk of bleeding increases with length of usage especially with the more potent PSY12-receptor agents. However the latter needs to be balanced against less events and any mortality benefits, cardiac or otherwise with the use of more potent agents. I note the influence of two meta-analysis (ref 192 and 193) which may detract from the difference in individual agents of varying potency and well conducted individual comparator trails such as PLATO. My understanding of the PLATO trial with ticagrelor (unlike the CURE trail) is that there was continuing benefit throughout the length of the trial which would, despite the higher bleeding risk, make the case for 12 months beneficial use especially as this approach has been shown to be cost effective. The higher bleeding risk only becomes more relevant in the low risk patient. Discontinuation of anti-platelet therapy It is important to consider the effect of discontinuation of anti-platelet therapy out with clinical trials but in contemporary UK practice. Work that I was involved in (Boggon et al Eur	*Response as for CB above.* *This has not been specifically included in the literature searches, however, we believe that the recommended duration of therapy (six months for most patients) confers the best balance of benefit while*

		Heart J 2011 Oct 32(19):2376-86) would suggest a possible increased association between mortality and events depending on the length of clopidogrel therapy within the first year post ACS (ST or non ST elevation). Considering the likely impact of this discontinuation it is important that the guideline development group do not recommend too short a duration of therapy which may encourage inevitable poor concordance and resulting poorer outcomes.	*protecting from risks.*
	RCPSG	"Consistent with these trial data on clopidogrel, a recent large RCT comparing ticagrelor (60 or 90 mg daily) with placebo in 21,162 patients 1-3 years after MI maintained on aspirin, demonstrated a reduction in atherothrombotic events (absolute RR, 1.2%), an increase in major bleeding (absolute risk increase, 1.2-1.5%) but no effect on overall mortality.66 " The PEGASUS trial not directly relevant to ACS as average interval post-MI to starting therapy was 1.7 years, but ?worth including in the secondary prevention guideline. We find the duration of dual therapy a contentious issue, and that SIGN is out of step with other major guidelines (including ESC and AHA/ACC 2014). The meta-analyses show no reduction in ischaemic events from continuing DAPT for 12 months compared to 6 months in a population undergoing PCI; this includes patients with ACS as the indication for intervention, but they do not present the outcomes of this subgroup separately. It is entirely plausible that the risk of further thrombotic events in the nonstented coronary segments is greater in those with ACS than those with chronic stable angina. The available evidence which we have in ACS treated with clopidogrel or ticagrelor is that there is significant benefit from 12months of treatment whether patients are treated medically or with PCI. Ticagrelor has been accepted by SMC as being cost-effective for 12 months of therapy. The case for three months of treatment is not justified from available evidence and cutting the data in this way has previously been rejected (Yusuf, Circ 2007).	*This paper is referenced as it provides additional evidence as to the effect of dual-antiplatelet therapy on cardiovascular and non-cardiovascular outcomes in the period after recovery from myocardial infarction. It is made clear that this is at one-year follow-up.* *See response to CB above.*
	AF	There is a huge potential for errors and a threat to patient safety here that will mitigate the small benefit from use of the more potent drugs. Deviation from the data is also unhelpful and brings a degree of pick and choose and inconsistency to guideline. Again there could be issues for paramedics. We have one of the best systems in the world currently for treating ACS and STEMI and we should think before we change it.	*As above.*
	OW	P.30, para 3, final sentence - "The increasing use of early PCI…"; I don't fully understand this sentence.	*This has been revised for clarity. The sentence now reads "However, the increasing use of early PCI in patients at increased risk of atherothrombotic events may reduce the applicability of these findings."*
	JJ	p. 30 "Patients with acute coronary syndrome should	*See response to CB above.*

		receive **three months** dual antiplatelet therapy " The 3-month recommendation is consistent with SMC clopidogrel advice but economic cases supporting SMC advice for prasugrel and ticagrelor were based on 12-month duration. While text above does state '*No formal health economic analysis has been conducted to determine the cost-effectiveness of three months treatment duration based on the assumption of comparable efficacy, thus no assessment on the cost-effectiveness of this can be made*', I wonder if the recommendation should state '*at least*' three months or '*up to 12 months"*?	*This comment is correct re SMC advice. However, the recommendation has now been changed to six months therapy.*
8.2	JJ	p. 30 Under anticoagulant therapy may wish to note DOACs not recommended – overlaps with 4.5.5	*The material previously situated in section 4 concerning the novel OACs has been moved to section 8.2.1 for clarity and to reduce overlap.*
8.3	DS	Simvastatin is established for prevention. Should those patients with established disease have more aggressive lipid lowering therapies? NICE guidelines (CG181) http://www.nice.org.uk/guidance/cg181/chapter/1-recommendations section 1.3.20.	*This section was not updated and is outwith the remit of this guideline as it relates to prevention.*
	AT	Evidence favours HIGH DOSE statins in ACS	*As above.*
	AB	There is a variation in practice on the use of high dose statin therapy in the short term (80mgs atorvastatin) based. Would a good practice point not help to clarify what to use? 40mgs simvastatin is mentioned whereas current practice would favour atorvastatin.	*This section was not updated.* *The example in the text for simvastatin 40 mg has been deleted.*
8.4.1	DS	A - Does this include those who have revascularisation for single vessel disease post MI?	*Yes.*
	AF	May not apply to the elderly.	*Agree, but this section was not updated.*
8.5	AF	May not apply to the elderly.	*Agree, but this section was not updated.*
8.6	AF	May not apply to the elderly.	*Agree, but this section was not updated.*
8.7	GA	Good	*Thank you.*
	CB	Evidence-based medicines are under-used post-MI. The recommendation for eplerenone should reflect all of the eligibility criteria for heart failure: ie One of the 1) presence of pulmonary rales, 2) chest radiography showing pulmonary venous congestion, 3) or the presence of a third heart sound. Thus it is suggested to include "radiological features or clinical signs of heart failure", since a proportion of patients will have signs of heart failure on the CXR post –MI but not necessarily clinical signs.	*This section was not updated. Points already adequately covered in section 8.7.* *'Clinical signs' changed to 'clinical features' in recommendation.*
	JJ	p. 33 "Patients with myocardial infarction complicated by left ventricular dysfunction (ejection fraction <0.40) in the presence of either clinical signs of heart failure <u>*or diabetes mellitus*</u> should be commenced on long term eplerenone therapy". Patients with diabetes who met the criteria for LVD after acute MI did not have to demonstrate symptoms of HF in the study but the licence only	*Section not updated.* *Noted, however while 90% of the patients in the original EPHESUS trial had signs of HF, a third were eligible because of diabetes without HF, so the clinical implication is that eplerenone may be suitable for those with acute MI plus LVD and either signs of HF or diabetes, in line*

		states '*patients with clinical signs of HF*' therefore may wish to align the recommendation with the licence. (Note this is not new text but was included in the original guideline).	*with the recommendation.*
Section 9			
9.3	RCPSG	Clear and well-presented.	*Thank you.*
Section 10			
	EMac	This section is very good with much less technical terms. The wording is sensitive, the tone of the section is positive, with all the information useful for patients and carers. I feel it addresses all the concerns patients and carers will have. The section on further information and additional websites will also be very helpful for the patient. In conclusion I really have nothing negative to say about this guideline. I feel it is a true reflection of the patients pathway.	*Thank you.*
10.1	LB	Term Phase 1 is outdated, the term early cardiac rehabilitation or the use of Department of Health commissioning stages have replaced it. Check with working group updating cardiac rehabilitation Sign guideline for clarification.	*Agreed. Text replaced.*
	RD	This section was of interest to me and I felt the guidelines offered sound and compassionate advice to medical and other healthcare staff.	*Thank you.*
	AB	The importance of ensuring that misconceptions do not arise is important especially in the era of increased interventions where the indication is often given to the patient that the 'problem has been fixed' acting as a disincentive to continue with long term rehabilitation and secondary prevention.	*Agree.*
	AF	Disappointing that the only randomised controlled trial (West published in Heart) raising the issue regarding the appropriateness of our current approach to rehabilitation is not even discussed.	*Rehabilitation will be covered in the update to SIGN 57 which is currently in development.*
	CPG	'those most at risk' – most at risk for what? Depression/anxiety? Ref 252 – more up-to-date evidence? This is 2001 paper. 'are not as accurate as measurements of anxiety on validated scales' – reword, e.g., may not be or are not always because in some instances, an experienced clinician will accurately pick up on anxiety even if anxiety screen does not. Ref. 13 - The URL listed for this reference on the reference list is an out-of-date link. http://circ.ahajournals.org/content/110/5/588.full This links to the executive summary. From what I can see, this does NOT evidence that subjective judgements are less accurate…..? Hospital anxiety and depression scale - Include more information or references about alternative screening tools e.g. PHQ-9/GAD-7 due to copyright issues nationally?	*Yes, the text has been revised – "those most at risk of psychological distress"…* *This text was not updated.* *This is a quotation from the ACC guideline and reflects the evidence reviewed in that document.* *Agreed. The reference has been corrected.* *This guideline does include a section on the psychosocial impact of STEMI.* *Text not updated. HADS was given as an example of a screening tool.*

10.2	LT	Diagnosis Information is readily accessible via the web and leaflets, however patients need to be properly signposted and the amount of leaflets given out to each patient should be considered so as not to overwhelm individuals',. Studies have shown that leaflets alone are not sufficient compared to tailored, supported cardiac rehabilitation therefore this should be initiated at the earliest opportunity e.g., at diagnosis. This is particularly important to counter misconceptions and reduce anxiety. The Heart Manual programme 1 can be started on diagnosis if the prognosis is appropriate. Discharge/Follow up/Cardiac Rehabilitation "Discuss the benefits of attending cardiac rehabilitation programme emphasising the controlled environment which may give the patient confidence" The above statement overlooks the importance of giving the patient confidence in their own daily lives and also places an unfair emphasis on centre/hospital based rehabilitation. As highlighted by a number of systematic reviews within the past five years 2 3 4 5, there is up to date evidence that home-based rehabilitation such as the Heart Manual programme is as effective as hospital based rehabilitation. Therefore choice of delivery of cardiac rehabilitation should be emphasised to increase adherence and overcome barriers such as poor accessibility, lack of time due to return to work and transport issues. References 1. Lothian Health Board: The Heart Manual Post MI edition 2015. 2. Dalal HM, Zawada A, Jolly K, Moxham T, Taylor RS. Home based versus centre based cardiac rehabilitation: Cochrane systematic review and meta-analysis. BMJ 2010;340:b5631. 3. Clark M, Kelly T, Deighan C. A systematic review of the Heart Manual literature. Eur J Cardiovasc Nurs 2011; 10: 3-13. 4. Blair J, Corrigall H, Angus NJ, Thompson DR, Leslie S. Home versus hospital-based cardiac rehabilitation: A systematic review. Rural and Remote Health 2011;11: 1532. www.rrh.org.au (accessed 27 August 2012) 5. Clark RA, Conway A, Poulsen V, Keech W, Tirimacco R, Tideman P. Alternative models of cardiac rehabilitation: a systematic review. European Journal of Preventive Cardiology, 2013; DOI:2047487313501093	*This has been addressed by the additional text added re Cardiac Rehab in the follow-up/rehab section* *Cardiac rehabilitation is covered by SIGN 57, which is currently being updated.*
	AF	See comment (10.1) - huge resource maintained for small if any long term benefit.	*Rehabilitation will be covered in the update to SIGN 57 which is currently in development.*
	CPG	Provide additional evidence to support the questionnaire survey results? 'Involve partners/relatives/carers' - ?…when appropriate and with consent of patient.	*Not applicable.* *Agreed – text in the assessment section changed to incorporate this.*
	IT	I like the information section in general, but not so sure about the references to Cardiac Rehabilitation. It feels very "old school" i.e.	*Term "controlled environment" changed to "supportive environment"*

		based around encouraging patients to attend CR groups because they are "controlled environments which may give the patient confidence". We know that patients don't get referred as often as they should and, when they are, don't always turn up. Recent research from Dundee shows that many patients have no idea why they were asked to go to CR and what they would get from going. As a rule cardiologists don't have a lot of involvement with the CR programme and so asking them to discuss the benefits is like asking me to discuss the relative merits of different approaches to angioplasty. We need cardiologists to help us sell CR to their patients as part of routine cardiac care. I don't think these statements will do that. The CR guideline will focus on the value of assessment and tailored interventions where required. We need the other guidelines to support the concept of a CR assessment. I would suggest amending the 2 CR statements as follows: • Explain that an assessment by the Cardiac Rehabilitation team will be arranged as part of routine follow-up • Ensure all patients are referred to the Cardiac Rehabilitation team for assessment.	*Cardiac rehabilitation will be covered by the update to SIGN 57.* *This is now covered by the additions made re cardiac rehab and also by explaining that the detail of cardiac rehab provision will be covered in the guideline devoted to CR.* *Agreed. Suggested text added to 'Discharge/Follow up/Cardiac rehabilitation' section of checklist. These points have been amalgamated to avoid repetition.*
10.2.1	BW	Should each bullet point end with a full stop? 'Assessment and Investigation□ Ensure patients are kept informed which and when tests will be performed and what the results of tests are and what they mean' reword to read...'which tests will be performed and when; what the results ...' Bullet point 4 'recognize' Should this be 'recognise' for consistency of spelling? 'Emphasise' appears in bullet point 6 of Discharge/Follow up/Cardiac Rehabilitation 'Listen carefully to the patient's and carers needs' Apostrophe missing in 'carer's'. 'Discharge/Follow up/Cardiac Rehabilitation Emphasise this is a normal and common reaction for the many patients' Omit 'the'.	*Yes, this has been revised.* *Thank you. The text has been more significantly reworded.* *Spelling corrected.* *Corrected.* *Corrected.*
	DS	Very useful.	*Thank you.*
	GA	Discharge/Follow up/Cardiac Rehabilitation Bullet point 2 - suggest " specialist assessment and supervision " rather than "controlled environment". I feel there is a need for additional bullet points to emphasise the multiprofessional input provided by cardiac rehabilitation teams and the flexibility for the patient to access only those components of the service that they are assessed as needing and are ready to change. Ensure patient is aware that if they are not ready to make changes at this point in time, that they can opt in to CR at some point in the future.	*This has been more significantly reworded.* *Agreed. Further points have been added indicating that the patient will be assessed by the cardiac rehab team for tailored support*

	AB	This is an important and very comprehensive checklist. On the basis of my comment in 10.1 would you consider including under treatment a statement that professionals should guard against giving the impression that the underlying coronary heart disease has been effectively treated.	*No change needed.*
	RCPSG	"Patients feel strongly that it is important to receive early accurate diagnosis and treatment" in consultation with the specialist team. There are real difficulties in establishing credibility when patients have been informed inappropriately that they have had an MI on the basis of serum troponins. The initial picture may be unclear and it is appropriate to inform the patient that ACS is one of the options under consideration and await clarification. This is in keeping with a later statement under 'Treatment': "Ensure consistent information is given by all healthcare professionals involved in the patient‟s care. Conflicting information can be detrimental to the patient"	*Agreed. Uncertainties about diagnosis should be communicated to the patients as early as possible. This has been added*
	CPG	'The checklist is neither exhaustive nor exclusive' – We understand that these points came from the focus group, so these are clearly the issues that those patients identified. I thought perhaps a couple of the points could be amended slightly e.g. they state 'Explain to the patient how to distinguish between indigestion and cardiac pain', could we change that to 'how to distinguish between cardiac pain and non-cardiac pain e.g. indigestion, anxiety'; and 'Advise the patient of all the ways that they can help themselves to improve their chance of a good recovery, in particular by emphasising the changes in lifestyle which can help to prevent further heart problems - essentially by not smoking, eating healthily, keeping weight down, keeping fit through exercise, and limiting alcohol intake', could we add in something about psychological well being, especially since they do cite a study that reducing psychological distress has the potential to improve long-term outcomes.	*Agree. Bullet points reworded.* *Agreed. Psychological well-being is an important facet of cardiac rehabilitation and will be covered by the update to SIGN 57. This has also been added to this section by emphasising the commonness of feeling "low".*
10.2.1	CPG	We had started to go through the checklist 10.2.1 which could be reworded and shortened in places but then wondered, would that be going against the ethos of inviting patient input? In the style of it, it seems a strange bed fellow with the technicalities of the peer-reviewed guidelines elsewhere in the document. But perhaps that's no bad thing?!	*No change required.*
10.3	AB	The BHF is the UK's national heart charity	*Noted, however there are other national charities. The text has been revised to emphasise that the charity has national status and is the largest funder of research in the UK.*
10.3.1	LT	www.theheartmanual.com	*This is relevant only as part of a supported self-management programme.*
	CPG	Just another query rather than comment - on what grounds were those particular additonal websites (10.3.1) selected over and above other potentially equally relevant ones? Not that those listed aren't relevant but is there any issue about	*The list was provided by NHS24. Additional, relevant, websites can be added if a rationale for doing so is provided.*

		being seen to advocate some third sector organisations over others? Or some co-morbidities over others (e.g. action on depression but not anxiety uk for instance).	
Section 11			
11.2	AF	Currently we consume huge resources achieving little and this reflects the so called 'evidence based medicine' movement which seems to dominate guideline writing. Most patients are unique and the drawback from guidelines is that they apply to diseases and not individual patients. The guidelines make suggestions which are then interpreted as standards or 'must do' and lead to accepted practices that do not benefit the majority of patients (the differences in benefits for patients in controlled trials are small and the majority do well) this means that we treat the majority of patients for no benefit. Huge resource is consumed and little is achieved.	*No response needed.*
11.3	DS	We ve had many versions of ACS audit over the past few years, many of which have been time consuming with little in the way of feedback afterwards. A suggestion - In the same way you have suggested a checklist for provision of information this could be a chance to standardise both care and audit criteria. The heart failure bundles have been a great success in ensuring standardisation in care for these patients. An ACS bundle (checklist e.g. reperfusion type and treatment times, Echo, secondary prevention medication, rehab referral etc...) could both ensure standardisation in care and audit criteria. We are in the process of developing one in Fife. Could you include something similar as a good practice point?	*This is outwith the scope of the guideline update.*
	AF	Audits concentrate on process. Audit should concentrate on outcomes not process, process should be audited second to outcomes. This would allow decision making in the patients interest rather than following a process. This is critical to use of risky treatments less so to tablets which can be stopped. Audit should be appropriately funded and designed.	*Audit involves both structured process and outcomes.*
11.4	AF	Guidelines currently are written by experts, but this brings many agendas such as research, etc into play the process should require experts to present the data to guideline writing panel. The links between Pharmaceutical and Medical device Companies research Universities and individual Doctors is too strong to not influence the writing of a pragmatic guideline. A good example is how the evidence base for statins applies to two or three but not those commonly currently prescribed.	*The SIGN methodology is designed to minimise the risk of bias in the guideline development process.*
	JJ	p.43 Suggest remove DOAC AF advice. Noticed that earlier SMC advice re prasugrel, eplerenone, fondaparinix, enoxaparin and clopidogrel is not included.	*Agree, removed.* *Only new drugs which are included in recommendations made after 2007 are included in this section.*
Section 12			
12.1	KL	In the absence of any details of the systematic literature reviews performed for this guideline, it is not possible to provide comments on the	*The search strategy will be published along with the guideline.*

		evidence base used to develop these draft guidelines.	
	AF	This should be presented to a non expert medical panel.	*Unclear what is meant by this comment.*
12.1.1	AF	Very little is written regarding the wishes of the patient and how the benefits and risks of treatment are presented.	*This is standard text replicated in each SIGN guideline reflecting the literature search conducted to inform the setting of key questions.*
12.2	CB	1. Organisation of the section There are multiple research recommendations for research. It is suggested the questions be organized thematically eg 1) Epidemiology post-MI, 2) Invasive management, 3) Drug therapy post-MI, 4) Sociodemographic factors. 2. Critique of the existing questions Some of the questions could be more specifically defined or framed to be realistically addressed by a clinical study • What are the benefits of ticagrelor and prasugrel on long-term survival? • Which ACS patients gain most from complete revascularisation and which are at greatest risk from prolonged procedures? • In patients with ACS, is PCI or CABG the most effective revascularisation strategy? Some questions seem difficult to justify • What is the clinical effectiveness, safety and cost-effectiveness of glycoprotein IIb/IIIa inhibitors in patients with ACS pre-treated with ticagrelor? • (given that in this SIGN guideline update, GpIIbIIIa are not recommended for routine use). Or already addressed in previously published trials • What is the clinical effectiveness and safety of upstream glycoprotein IIb/IIIa inhibitors in patients with high-risk non-ST elevation MI or ST elevation MI being transferred to regional PCI centres? • Does manual thrombectomy compared to usual care improve outcomes in patients with ST elevationMI undergoing primary PCI with a large thrombus burden? (see subgroup data within TASTE and TOTAL) 3. Addressable research questions that are relevant to patients in NHS Scotland, as suggested by this reviewer: The most important research question is: Evidence-based medicine and health outcomes in NHS Scotland: address the knowledge gap in NHS Scotland on implementation of SIGN-ACS guidelines and health outcomes. The case for a MINAP-like-e-registry. 1. Given increased longevity overall in the Scottish population and improved early survival post-MI, is the time-of-onset of heart failure post-MI shifting to one of late-onset? What is the long term incidence of heart failure post-MI in NHS Scotland. 2. Compared to standard invasive management guided by coronary angiography, what is the clinical and health economic value of	*Thank you. Some of these points have been incorporated, although for points referring to layout, it is not possible to apply this consistently to all research recommendations.* *Noted, although this is a subjective view which may not be shared by others.* *This may be a valid and worthy question to assess from a cost-effectiveness point of view. However, in reality this may be a*

		management guided by functional assessment of coronary disease severity by fractional flow reserve measurement in ACS patients (STEMI and NSTEMI)? 3. When should revascularisation be performed in STEMI patients with multivessel disease? 4. In higher risk patients with acute STEMI, after initial reperfusion by angioplasty or thrombectomy, is routine deferral of stent implantation post-reperfusion (e.g. 9 – 72 hours) associated with a reduction in major adverse cardiac events and heart failure post-STEMI? (cf NCT01717573) 5. Does the novel agent LCZ696 reduce adverse cardiac events compare with standard care treatment with an ACE inhibitor or angiotensin receptor blocker post-MI 6. In post-MI patients at very high risk of ventricular tachycardia/fibrillation, what is the health economic value of a wearable cardioverter defibrillator as a bridge to ICD (or not). 7. What are the factors associated with non-adoption of ACS risk scores in emergency care and how might adoption be improved? 8. In survivors of acute myocardial infarction, does eplerenone reduce adverse cardiac events in the longer term in patients without either (1) LV dysfunction and/or (2) heart failure, or (3) both of these problems? 9. What is the optimal anti-thrombotic management of patients with failed thrombolysis undergoing 'rescue' PCI. 10. Social deprivation and outcomes post-MI: Understanding the socio-economic factors that may be associate with adherence with secondary prevention post-MI, including compliance with therapy, cardiac rehabilitation, and cigarette smoking. 11. Cardiovascular disease kills more women than cancer, but this is not the case in men: what are the factors associated with premature cardiovascular death in women and how can these factors be modified? [ref, Timmis Heart 2015;0:1–2. doi:10.1136/heartjnl-2015-307887; Bhatnagar P, et al. Heart 2015;0:1–8. doi:10.1136/heartjnl-2015-307516] Subjects not included in the SIGN guideline that should be considered - Implantable cardiac defibrillator therapy post-MI - timing of early assessment of LV ejection fraction - need for repeated assessment at/after 30 days post-MI - LVEF criterion for referral for primary ICD - Relevant trials: Multicenter Automatic Defibrillator Implantation Trial I, Multicenter UnSustained Tachyardia Trial, Multicenter Automatic Defibrillator Implantation Trial II, and Sudden Cardiac Death in Heart Failure Trial. Relevant publications 1: Hess PL, Laird A, Edwards R, Bardy GH, Bigger JT, Buxton AE, Moss AJ, Lee KL, Hall WJ, Steinman R, Dorian P, Hallstrom A,	*difficult question to find such specific literature on.* *This agent was not approved by SMC at the time of guideline drafting* *Agreed – this has been added*

		Cappato R, Kadish AH, Kudenchuk PJ, Mark DB, Al-Khatib SM, Piccini JP, Inoue LY, Sanders GD. Survival benefit of primary prevention implantable cardioverter-defibrillator therapy after myocardial infarction: does time to implant matter? A meta-analysis using patient-level data from 4 clinical trials. Heart Rhythm. 2013 Jun;10(6):828-35. doi: 10.1016/j.hrthm.2013.02.011. Epub 2013 Feb 13. PubMed PMID: 23416381; PubMed Central PMCID: PMC4037291. 2. Scott PA, Gorman S, Andrews NP, Roberts PR, Kalra PR. Estimation of the requirement for implantable cardioverter defibrillators for the primary prevention of sudden cardiac death post-myocardial infarction based on UK national guidelines (2006). Europace. 2008 Apr;10(4):453-7. doi: 10.1093/europace/eun042. Epub 2008 Mar 3. PubMed PMID: 18319266.	*These topics were not included in this update.*
	NB	The identification and management of patients with type 2 myocardial infarction and myocardial injury should be listed as a major research priority.	*Agree. This has been added*
	KL	Several areas for further research contain a mis-spelling of P2Y12 as PSY12.	*Corrected.*
	AB	The areas that are highlighted for further research where there was insufficient evidence include the cost of prescribing PSY12-receptor antagonists for a year effectiveness of 3 months ticagrelor or prasugrel followed by 9 months clopidogrel compared with 12 months of the newer agents benefits of ticagrelor and prasugrel on long term survival change in risk if PSY12-receptor is stopped after one year. My point would be to emphasise that recommendations need to be made on the basis of existing good quality published outcome data using strategies that are cost effective but bearing in mind that differences between individual agents are specifically highlighted.	*See responses to section 8.1.2.*
	AF	Poor, and we really need to ask what we are achieving.	*Unclear if this comment refers to the quality of the literature searching or to the cost-effectiveness of the recommended treatments.*
12.2	AF	I would concentrate on outcomes related research from studying the real life Scottish Population.	*Comment noted. Thank you.*
12.3	NB	This is a very important area of acute medicine that deserves detailed attention. The limited update that is proposed is not really adequate and I feel that a complete rewrite should be undertaken before 2018. See general comments.	*Comment noted. Thank you.*