National Institute for Health and Clinical Excellence

Hyperglycaemia
Guideline Consultation Comments Table
7 June – 8 July 2011

Type	Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Association for Clinical Biochemistry	12.00	Full	General	General	Contents noted	Thank you.
SH	Association of British Clinical Diabetologists (ABCD) / Royal College of Physcians	9.00	Full	1.1.1	5	'Intensive insulin therapy' is not defined whereas 'acute hyperglycaemia' is. Please rectify this.	Thank you, this has been added to the recommendation.
SH	Association of British Clinical Diabetologists (ABCD) / Royal College of Physcians	9.01	Full	1.1.1 and 1.1.2	5	Having chosen this topic NICE, have understandably documented a lack of robust outcome evidence from randomised controlled trials. Given that 3 of the 4 studies reviewed did not achieve normoglycaemia and separation of the groups receiving active insulin infusions and standard therapy, this is unsurprising. However as these NICE recommendations stand, with the option for adopting local guidelines, there is real potential for confusion and variation. Current best practice guidance from SIGN (Scotland) and the American Diabetes Association and the European Society for Cardiology all promote control of hyperglycaemia with ACS for at least 24 hours after admission. Current national and international recommendations for in patient care seek to avoid persistent hyperglycaemia (> 11	Thank you for your comment. The SIGN guidance is based on evidence from DIGAMI 1 and 2 and we have highlighted the drawbacks of these papers in chapter 3. The ADA/ACCE recommendations are aimed at patients who are critically ill and have no specific recommendations for patients with ACS and hyperglycaemia. Overall, the GDG agreed that there is a lack of evidence showing that intensive insulin therapy is beneficial in patients with ACS and hyperglycaemia. As a result, a 'do not do' recommendation was made. However, the group did understand the importance of treating hyperglycaemia and made a separate recommendation (see 1.1.2) to ensure that it was not left untreated.

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						mmol/l) in general. The lack of any target glycaemia range in the current NICE document also raises challenges. The current national (England) TITAN observational evaluation of the feasibility of achieving glycaemic control with insulin infusion during ACS (4-8 mmol/l) should inform this .	Recommendation 1.1.2 has been amended to provide an example of what a local protocol may recommend. The target blood glucose level of <10mmol/L was agreed as this was the upper limit of the target blood glucose level used in the included studies. A minimum threshold was avoided as this varied across the studies and the group wanted to avoid an arbitrary figure.
SH	Association of British Clinical Diabetologists (ABCD) / Royal College of Physcians	9.02	Full	1.1.1	5	NICE recognise that ACS and hyperglycaemia is a high risk situation with poor prognosis . The proposed recommendations are at odds with earlier published guidance from within the UK, Europe and the USA. These proposals also conflict with current national recommendations for in patient diabetes care bundles where current best practice aims to correct hyperglycaemia (> 11 mmol/l). ABCD feel strongly that as they stand the guidance may lead to confusion and inertia which may further prejudice in patient diabetes care. In principle ABCD support the recommendation (Appendix B) for a large randomised controlled trial of ACS and hyperglycaemia correction but given the logistical and cost issues involved feel this may not be feasible	Thank you for your comment. The SIGN guidance is based on evidence from DIGAMI 1 and 2 and we have highlighted the drawbacks of these papers in chapter 3. The ADA/ACCE recommendations are aimed at patients who are critically ill and have no specific recommendations for patients with ACS and hyperglycaemia. Overall, the GDG agreed that there is a lack of evidence showing that intensive insulin therapy is beneficial in patients with ACS and hyperglycaemia. As a result, a 'do not do' recommendation was made. However, the group did understand the importance of treating hyperglycaemia and made a separate recommendation (see 1.1.2) to ensure that it was not left untreated.
SH	Association of British Clinical Diabetologists (ABCD) / Royal College of Physcians	9.03	Full	1.1.1	5	There is no comment on the practical issues of managing hyperglycaemia during initial primary angioplasty during STEMI care.	Thank you for your comment. Although we acknowledge that this is an important issue, this is outside the scope of this guideline.
SH	Association of British Clinical Diabetologists	9.04	Full	1.1.3	5	HbA1c limitations in diagnosis of diabetes- need to be elucidated	Thank you for your comment. Review question 3 focuses on identifying patients

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	(ABCD) / Royal College of Physcians					(haemoglobinopathies , anaemia , renal failure especially amongst ethnic groups at high risk of these conditions)	who are at high risk of progression to diabetes. The diagnosis of diabetes is outside the scope of this document and is covered by diabetes guidance (see NICE CG15 and CG66). Formal testing and diagnosis of diabetes will normally take place following referral to primary care after the acute episode as some distortion of blood glucose levels may be expected during the inpatient admission.
SH	Association of British Clinical Diabetologists (ABCD) / Royal College of Physcians	9.05	Full	1.1.4	5	ABCD dispute the recommendation about the lack of role of Glucose Tolerance Testing for subsequent diagnosis of diabetes after ACS and are aware that both fasting glucose and HbA1c lacked sensitivity compared to glucose tolerance testing in diagnosis of diabetes in the study by Ishihara et al (Eur Heart J 2006 ; 27: 2413-2419)(see later comments)	Thank you for your comment. Review question 3 focuses on identifying patients who are at high risk of progression to diabetes. The diagnosis of diabetes is outside the scope of this document and is covered by diabetes guidance (see NICE CG15 AND CG66). Formal testing and diagnosis of diabetes will normally take place following referral to primary care after the acute episode as some distortion of blood glucose levels may be expected during the inpatient admission. The GDG specifically discussed that patients with low fasting glucose and/or Hba1c would be less likely to develop diabetes so OGTT testing would not be as important in this group of patients.
SH	Association of British Clinical Diabetologists (ABCD) / Royal College of Physcians	9.06	Full	3.2.5	28	The statement that the GDG 'recognised that the risk of adverse events associated with uncontrolled hyperglycaemia were high and it was felt a separate recommendation should be made to ensure that hyperglycaemia is managed' is supported by ABCD but does not appear in the final	Thank you for your comment. Uncontrolled hyperglycaemia refers to hyperglycaemia that is not managed appropriately and this has been amended in the guideline.

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						recommendations. This would seem to contradict the summary recommendation. There is no definition of what constitutes 'uncontrolled hyperglycaemia' – ABCD would suggest it is > 11 mmol/l.	
SH	Association of British Clinical Diabetologists (ABCD) / Royal College of Physcians	9.07	Full	3.1.2	8	Evidence review of HI-5 study. The authors state in a more recent paper documenting the benefit of insulin infusion on abnormal ECG findings (Gan et al , Diabetic Med 2009 : 26: 174-176), that beyond the intention to treat analysis , a fivefold reduction in mortality was achieved when a treatment target of mean blood glucose of < 8 mmol/l was achieved within the first 24h after admission. The quality assessment of this finding was judged to be low although the other studies evaluated singularly failed in their study design to improve glycaemia to enable the impact of this on outcome to be evaluated.	Thank you for your comment. This finding was discussed by the GDG and it is documented in section 3.1.3.8 of the guideline. The outcome was downgraded based on variation in current practice and the risk of imprecision.
SH	Association of British Clinical Diabetologists (ABCD) / Royal College of Physcians	9.08	Full	3.1.2	8	More recent RCTs of the beneficial impact of intensive glucose control on surrogate measures of cardiovascular function after ACS (e.g Heart 2011 : 97 : 803-809) have not been included in the evidence review.	Thank you. The evidence reviewed focused on the main outcomes as specified in the scope. Surrogate measures such as platelet reactivity were not considered important outcomes by the GDG.
SH	Association of British Clinical Diabetologists (ABCD) / Royal College of Physcians	9.09	Full	3.2.2	19.	A similar but larger observational study to MINAP was not included in the evidence review . (Kosiborod et al Arch Intern Med 2009 ; 169:438-446) . This evaluated 7820 ACS with admission hyperglycaemia (> 7.8 mmol/l) and concluded that glucose normalisation after admission with AMI is associated with better survival, in line with MINAP.	Thank you for your comment. The MINAP study was included as it was a UK based paper including patients with ACS and hyperglycaemia without a previous diagnosis of diabetes. Kosiborod et al (2009) is a US based paper where current practice may differ. The administration of insulin varied in this study and only 17% of insulin treated patients received IV insulin.

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							Therefore this paper was not considered for inclusion for the review questions.
SH	Association of British Clinical Diabetologists (ABCD) / Royal College of Physcians	9.10	Full	3.3.2	30	The evidence review has not included a large report from the Euro Heart survey on Diabetes and the Heart which demonstrated that oral glucose tolerance testing (rather than fasting glucose alone) is required for appropriate classification of diabetes after presentation with ACS. (Bartnik et al.Heart 2007 ; 93:72-77)	Thank you for your comment. Review question 3 focuses on identifying patients who are at high risk of progression to diabetes. The diagnosis of diabetes is outside the scope of this document and is covered by diabetes guidance (see NICE CG15 and CG66). Formal testing and diagnosis of diabetes will normally take place following referral to primary care after the acute episode as some distortion of blood glucose levels may be expected during the inpatient admission.
SH	British Dietetic Association	16.00	General			The BDA would like to express their thanks at being given the opportunity to respond to your consultation document. We do not have any comments at this stage	Thank you for your comment.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	11.00	Full	General	5	While acknowledging that the evidence does not support treating with a given IV insulin protocol, we were disappointed that NICE did not provide any guidance on the main subject of the guidelines (i.e. when to use IV insulin in patents with hyperglycaemia and ACS). We think NICE should try and arrange a national consensus viewpoint on this subject rather than suggesting local guidelines are used, as local guidelines may not exist, and would lead to widely variable management ("postcode" management). A group such as the Association of British Clinical Diabetologists (ABCD) could be	Thank you for your comment. The management of hyperglycaemia using methods other than intensive insulin was not the focus of this guideline. However, the GDG did agree that it was important to manage hyperglycaemia appropriately and this is reflected in recommendation 1.1.2. This recommendation has been amended to provide an example of what a local protocol may recommend. The target blood glucose level of <10mmol/L was agreed as this was the upper limit of the target blood glucose level used in the included studies. A minimum glycaemic level was avoided as this varied across the studies and the

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						commissioned to do this.	group wanted to avoid an arbitrary figure.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	11.01	Full		5	We agreed that we should not 'routinely offer intensive insulin therapy to manage hyperglycaemia in patients admitted to hospital for an acute coronary syndrome' but felt that there should be clearer definition of which patients should receive intravenous insulin using a sliding scale. Our consensus was that all patients with type 1 diabetes and most patients with type 2 diabetes currently on insulin therapy should have IV insulin, with an aim to keep blood glucose between 7-11mmol/l. We had difficulty agreeing which other patients (that is, those not using insulin previously) should receive IV insulin with some individuals thinking this should happen in patients with blood glucose above 15mmol/l and others above 20mmol/l; but, we all agreed that this always should be judged on a patient by patient basis.	Thank you for your comment. The GDG agreed that it was important to manage hyperglycaemia appropriately. Recommendation 1.1.2 has been amended to provide an example of what a local protocol may recommend. The target blood glucose level of <10mmol/L was agreed as this was the upper limit of the target blood glucose level used in the included studies. A minimum glycaemic level was avoided as this varied across the studies and the group wanted to avoid an arbitrary figure.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	11.02	Full		5	We feel that the statement do not 'routinely offer intensive insulin therapy to manage hyperglycaemia in patients admitted to hospital for an acute coronary syndrome' should be prefaced by a statement that this is due to low quality evidence in its favour and not because insulin therapy causes harm.	Thank you for your comment, however the discussion about the quality of evidence is reported in the evidence review and the evidence to recommendation sections. Quality ratings do not form part of the final recommendations. Recommendation 1.1.2 has been amended to provide an example of what a local protocol may recommend. The target blood glucose level of <10mmol/L was agreed as this was the upper limit of the target blood glucose level used in the included studies. A minimum glycaemic level was avoided as this varied

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							across the studies and the group wanted to avoid an arbitrary figure.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	11.03	Full		5	One colleague felt it was very important to also offer a screening OGTT to patients without previously known diabetes post ACS, not just HbA1c and fasting glucose, so that patients with IGT or diabetes with a 2-hour glucose >11.1 but normal HbA1c and FBG can be identified and managed actively e.g. with metformin, eye screening and foot screening. This was also proposed as a future research question.	Thank you for your comment. Review question 3 focuses on identifying patients who are at high risk of progression to diabetes. The diagnosis of diabetes is outside the scope of this document and is covered by diabetes guidance (see NICE CG15 and CG66). Formal testing and diagnosis of diabetes will normally take place following referral to primary care after the acute episode. The GDG discussed that carrying out an OGTT in acute settings may be difficult and it was also agreed that there is a risk of false positive results as patients with ACS are likely to have distorted blood glucose levels.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	11.04	Full		5	We recognise that a fasting plasma glucose earlier than 4 days might reflect the acute event. A cardiologist colleague explained that with an effort to get patients out of hospital, some patients are discharged 48 hours after PCI so will the guidelines please clarify who will check the fasting glucose and HbA1c after 4 days and what should be done about the result (? the GP).	Thank you. The GDG agreed that test results 4 days after the acute event were more likely to reflect stable blood glucose levels. Testing patients outside of secondary care is outside the scope of this guideline.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	11.05	Full	General		The guidance needs a statement that trial data from several trials have shown that lowering glucose post ACS by whatever means had advantages (despite this not being the primary endpoint of the studies). Therefore absence of evidence that intensive insulin infusions are not beneficial does not imply that actively managing	Thank you for your comment. The GDG discussed the importance of managing hyperglycaemia after an episode ACS and this is reflected in recommendation 1.1.2.

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						glycaemia is not beneficial or is harmful.	
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	11.06	Full	General		It is not clear how the trials selected were categorised into diabetes and 'no-diabetes' as there is a lot of overlap in this in the inclusion criteria.	Thank you. The evidence review section for review questions 1 and 2 has been amended to make this clearer.
SH	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	11.07	Full	General		We understood from reading the materials that observational studies show that the patients with ACS and better glycaemic control fare better (live longer) than those with ACS and worse glycaemic control. While we also recognise that this observation might reflect confounding, can this message be included in this guidance?	Thank you for your comment. The introduction section of the guideline now includes a short paragraph on the effect of persistently elevated blood glucose levels on mortality.
SH	Department of Health	13.00	Full	General	General	I am disappointed in this draft guidance and would request that it is substantially reviewed, please. The aim is to assist healthcare professionals managing hyperglycaemic patients with acute coronary syndrome (ACS). This document may, in fact, worsen the care of such patients by giving the impression that little action is needed and leaving decisions to local guidance. The literature reviews take a limited view, focusing solely on ACS and hyperglycaemia yet there is relevant literature about the management of hyperglycaemia in acutely ill people, and patient information, for example. The recommendations are mostly negative and do not fully reflect the diabetes	Thank you for your comments. The scope of this guideline was limited to the management of ACS and hyperglycaemia and so the literature review was also limited to this specific population. The evidence for the use of intensive insulin therapy was reviewed in patients with ACS who did and did not have diabetes. Although DIGAMI 1 showed a significant reduction in mortality, no significant effects of intensive insulin were reported on mortality in studies published after this paper. The drawbacks of the DIGAMI 1 study have been documented in section 3.1.5 and the risk of hypoglycaemia was also discussed. Based on the evidence and the expertise of the GDG, a recommendation to not routinely offer intensive insulin therapy was reached.

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						specialist community's view on this topic. One diabetologist said "overall don't get the feeling that this guidance is dramatically going to change the quality of in-hospital hyperglycaemic care and if anything will be an excuse for worsening given the absence of any positive management plans." I would strongly suggest that the guideline group seeks oral evidence from national experts such as Dr Maggie Sinclair Hammersley and Dr Clive Weston	Although negative phrasing is used, a 'do not do' recommendation is as important as a 'do' recommendation. The group did agree that it was important to ensure that hyperglycaemia was managed using methods other than intensive insulin therapy. This is reflected in recommendation 1.1.2 and has been amended to provide an example of what a local protocol may recommend. The target blood glucose level of <10mmol/L was agreed as this was the upper limit of the target blood glucose level used in the included studies. A minimum threshold was avoided as this varied across the studies and the group wanted to avoid an arbitrary figure.
SH	Department of Health	13.01	Full	1.1.1	5	This is not a good start as it says "Do not…" A positive first message might be better.	Thank you for your comment, the review question focused on the use of intensive insulin therapy to treat patients with ACS and hyperglycaemia and so this recommendation has been placed first. As the GDG did not recommend the use of intensive insulin this has been phrased as a 'do not do' recommendation. Although negative phrasing is used, this type of recommendation is as important as a 'do' recommendation. Recommendation 1.1.2 has also been amended to clarify that patients with hyperglycaemia should be managed.
SH	Department of Health	13.02	Full	1.1.1	3 and 5	Define intensified insulin therapy – and is this subcutaneous (intermittent or insulin	Thank you, the definition for intensive insulin therapy has been amended.

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						pump) or variable rate intravenous insulin infusion?	
SH	Department of Health	13.03	Full		3	Do not focus solely on insulin – what do clinicians do about other anti-diabetic therapy, please?	Thank you for your comment. Although we acknowledge that the use of other non-insulin diabetic treatment is important, this is beyond the scope of this guideline and was not addressed in any of the review questions.
SH	Department of Health	13.04	Full	1.1.1	5	This contradicts ADA / AACE guidance and SIGN guidance: Diabetes Care (2009) June 32(6): 1119-1131 SIGN guideline 93 Acute Coronary Syndromes (2007)	Thank you for your comment. The SIGN guidance is based on evidence from DIGAMI 1 and 2 and we have highlighted the drawbacks of these papers in chapter 3. The ADA/ACCE recommendations are aimed at patients who are critically ill and have no specific recommendations for patients with ACS and hyperglycaemia. Overall, the GDG agreed that there is a lack of evidence showing that intensive insulin therapy is beneficial in patients with ACS and hyperglycaemia. As a result, a 'do not do' recommendation was made. However, the group did understand the importance of treating hyperglycaemia and made a separate recommendation (see 1.1.2) to ensure that it was not left untreated.
SH	Department of Health	13.05	Full	1.1.3	5	Glucose testing should follow WHO guidance – fasting venous plasma glucose HbA1c testing should follow WHO guidance issued in January 2011 http://www.who.int/cardiovascular_diseases/report-hba1c_2011_edited.pdf	Thank you for your comment. Review question 3 focuses on identifying patients who are at high risk of progression to diabetes. The diagnosis of diabetes is outside the scope of this document and is covered by diabetes guidance (see NICE CG15 and CG66). Formal testing and

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							diagnosis of diabetes will normally take place following referral to primary care after the acute episode as some distortion of blood glucose levels may be expected during the inpatient admission. The thresholds published by the WHO refer to diagnostic thresholds for diabetes and this is not part of the review question.
SH	Department of Health	13.06	Full	1.1.2	5	"in accordance with local guidelines" – this is potentially dangerous as some units may not have local guidelines and even if they do, are they safe and up-to-date? This is wholly unsatisfactory and much clearer guidance must be given. NHS Diabetes has published national guidelines about safe use of insulin and hypoglycaemia, for example. For patients having procedures such as primary angioplasty there are perioperative care guidelines. http://www.diabetes.nhs.uk/safe_use_of_insulin/ http://www.diabetes.nhs.uk/publications_and_resources/reports_and_guidance/ :- Management of adults with diabetes undergoing surgery and elective procedures: improving standards: Full Report - Management of adults with diabetes undergoing surgery and elective procedures: improving standards -	Thank you for your comment. Recommendation 1.1.2 has been amended to provide an example of what a local protocol may recommend. The target blood glucose level of <10mmol/L was agreed as this was the upper limit of the target blood glucose level used in the included studies. A minimum threshold was avoided as this varied across the studies and the group wanted to avoid an arbitrary figure. NICE is only able to refer to other NICE guidance and publications by the Department of Health. The methodologies used to form other guidance may differ substantially from NICE methods.

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						Full Report (PDF 993KB) - guidelines aimed to improve standards of care for people with diabetes undergoing operative or investigative procedures requiring a period of starvation. Safe and Effective use of Insulin in Hospitalised Patients - March 2010 Safe and Effective use of Insulin in Hospitalised Patients (PDF 1MB) The Hospital Management of Hypoglycaemia in Adults with Diabetes Mellitus - March 2010 The Hospital Management of Hypoglycaemia in Adults with Diabetes Mellitus (PDF 2.5MB)	
SH	Department of Health	13.07	Full	1.1.4	5	Agree that OGTT is not needed (unless HbA1c cannot be used in a particular patient e.g. because of anaemia).	Thank you for your comment.
SH	Department of Health	13.08	Full	1.1.6	6	It is not enough just to tell patients that they are at risk of diabetes. What type of diabetes? – Type 2. What symptoms do they look out for? What do they do if they have these symptoms?	Thank you for your comment. Recommendations 1.1.6 and 1.1.7 have been amended to include more information
SH	Department of Health	13.09	Full	1.1.7	6	Who is offering the annual monitoring? The hospital coronary care unit? The GP? This is very much part of the GP's role. So there needs to be a recommendation that the GP is told, in writing, with a copy to the patient, about the non-diabetic hyperglycaemia and the need for monitoring, please.	Thank you, this has now been clarified in recommendation 1.1.7.
SH	Department of Health	13.10	Full	General	General	There is no mention of metformin – a very common treatment in overweight patients	Thank you for your comment. Although we acknowledge that the use of other non-

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						with diabetes – and they are at particular risk of coronary disease. Should it be stopped before and after PTCA? When should it be restarted? BNF reminds of the risk of lactic acidosis with metformin in patients with myocardial infarction.. It appears that the question of what to do about non-insulin anti-diabetic therapy was not considered.	insulin diabetic treatment is important, this is beyond the scope of this guideline and was not addressed in any of the review questions.
SH	Department of Health	13.11	Full	General	General	There is no mention of pioglitazone – which should be stopped in patients with cardiac failure and used with caution in patients with cardiac disease	Thank you for your comment. The use of oral hypoglycaemic drugs is beyond the scope of this guideline and was not addressed in any of the review questions.
SH	Department of Health	13.12	Full	General	General	No mention of nateglinide, repaglinide – BNF says substitute insulin during myocardial infarction.	Thank you for your comment. The use of oral hypoglycaemic drugs is beyond the scope of this guideline and was not addressed in any of the review questions.
SH	Department of Health	13.13	Full	General	General	No mention of saxagliptin, sitagliptin and vildagliptin can all cause peripheral oedema	Thank you for your comment. The use of oral hypoglycaemic drugs is beyond the scope of this guideline and was not addressed in any of the review questions.
SH	Department of Health	13.14	Full	General	General	There are also multiple interactions and warnings when cardiac drugs and anti-diabetic drugs are given together	Thank you for your comment. In all our guidance we state clinicians should use up to date BNF information for drug dosing and interactions and it is therefore outside of our remit to discuss this.
SH	Department of Health	13.15	Full	3.2.5	28	The MINAP data are observational, but the strength is that these are UK "real-world" data. I would strongly suggest asking MINAP to provide up-to-date data (the paper was 2007) as my understanding is that this supports the earlier reports. Please invite the MINAP team to provide up-to-date evidence to the NICE guideline	Thank you for your comment. The GDG agreed that the MINAP data were a good indicator of current practice in the UK. However, it was also acknowledged that this was observational data and had limited value in assessing the effectiveness of intensive insulin (for other drawbacks of MINAP data please see section 3.2.5). In

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						committee.	addition, only published research papers relating to the review questions were searched for. Unpublished studies were not included.
SH	Department of Health	13.16	Full	3.4.1	39	Why restrict the literature search for patient information to ACS and hyperglycaemia? General information about risk of diabetes and the tests offered could be used. Or a link to a recognised source of information about diabetes e.g. Diabetes UK.	Thank you for your comment. The scope of this guideline was restricted to patients with hyperglycaemia and ACS, therefore the literature searches were also limited to this specific population. NICE is only able to refer to other related NICE guidance and Department of Health publications. Recommendation 1.1.6 and 1.1.7 have been amended to provide more information to patients before they have been formally diagnosed with diabetes.
SH	Department of Health	13.17	Full	3.4.5	43	The guidance mentions different ethnic groups but to say "routine follow-up would allow these groups to be assessed appropriately" is not sufficient. Equality issues include the greatly increased risk of ACS in women with diabetes vs those without diabetes, the risk that ACS may be not be properly or promptly diagnosed in women, especially South Asian women, the increased risk of both ACS and diabetes in South Asian patients, and in other ethnic groups, the increased risk of ACS and diabetes in people with increased social deprivation etc. This section should be expanded to ensure equality issues are covered or readers should be signposted to relevant information elsewhere.	Thank you for your comment. Although we recognise the importance of this issue, the risk of ACS and the diagnosis of diabetes are outside the scope of this guideline. This review question focused on patient information needs for patients who have ACS and hyperglycaemia without a previous diagnosis of diabetes. The GDG agreed that experiencing an acute event would override any biological predisposition to developing diabetes. The evidence review for this guideline did not find any subgroups based on ethnicity or gender that showed poorer outcomes associated with the use of intensive insulin.
SH	Department of Health	13.18	Appendices	Appendix B	55	I agree with the research questions	Thank you for your comment.

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SH	Diabetes UK	6.00	Full	1.1.1	5	Please can the recommendation give a definition of "intensive insulin therapy" to provide clarity for practitioners. This would help ensure there is no misinterpretation that could lead to no insulin therapy being provided to people with diabetes who have ACS.	Thank you, this has been added to the recommendation.
SH	Diabetes UK	6.01	Full	1.1.1 and 1.1.2	5	Members of the professional diabetes community have expressed concern about the lack of detail regarding recommendations for the management of people with diabetes and ACS, and in particular the recourse to local guidelines. There is concern this could lead to the worsening of care/ status quo, with postcode lottery care. It is questioned whether the draft guideline as it stands will improve care for people with diabetes and people at risk of developing it.	Thank you for your comment. Recommendation 1.1.2 and has been amended to provide an example of what a local protocol may recommend. The target blood glucose level of <10mmol/L was agreed as this was the upper limit of the target blood glucose level used in the included studies. A minimum threshold was avoided as this varied across the studies and the group wanted to avoid an arbitrary figure.
SH	Diabetes UK	6.02	Full	1.1.1 and 1.1.2	5	Are preliminary findings available from the extension of the MINAP ACS study that would usefully inform these recommendations in the guideline, and were these sought out? http://www.diabetes.nhs.uk/our_work_areas/inpatient_care/acute_coronary_syndrome/	Thank you for your comment. Although we recognise the importance of this study, only published research papers relating to the review questions were searched for. Preliminary findings from the MINAP ACS study have not been published and so does not form part of the evidence review.
SH	Diabetes UK	6.03	Full	1.1.1	5	The recommendation contradicts both SIGN guidelines and the joint ADA and AACE consensus statement: SIGN guideline 93 Acute Coronary Syndromes (2007)	Thank you for your comment. The SIGN guidance is based on evidence from DIGAMI 1 and 2 and we have highlighted the drawbacks of these papers in chapter 3 of the guideline. The ADA/ACCE recommendations are aimed at patients who are critically ill and have no specific

Type	Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						Diabetes Care (2009) June 32(6): 1119-1131	recommendations for patients with ACS and hyperglycaemia. Overall, the GDG agreed that there is a lack of evidence showing that intensive insulin therapy is beneficial in patients with ACS and hyperglycaemia. As a result, a 'do not do' recommendation was made. However, the group did understand the importance of treating hyperglycaemia and made a separate recommendation (see 1.1.2) to ensure that it was not left untreated.
SH	Diabetes UK	6.04	Full	1.1.1 and 1.1.2	5	Were experts such as Dr Maggie Sinclair-Hammersley and Dr C Weston and consulted to inform guidance development, and was it possible to access any preliminary findings from the TITAN-ACS study?	Thank you. **The GDG included a range of specialists in the field. Specifically the GDG included two cardiologists, a diabetologist, a physician in acute medicine, a specialist diabetes nurse, a general practitioner with special interest in diabetes and a patient representative.** While we recognise the importance of such studies, only published research papers relating to the review questions were searched for. Preliminary findings from the TITAN-ACS study have not been published and so does not form part of the evidence review.
SH	Diabetes UK	6.05	Full	General comment	5 and 6	The language used is often in the negative, eg "Do not". Clearer phrasing of the recommendation could assist with preventing confusion.	Thank you for your comment. NICE uses active phrasing of recommendations. As the GDG did not recommend the use of intensive insulin this has been phrased as a 'do not do' recommendation. Although

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							negative phrasing is used, this type of recommendation is as important as a 'do' recommendation. Recommendation 1.1.2 has also been amended to clarify that hyperglycaemia should be managed in patients with ACS.
SH	Diabetes UK	6.06	Full	General question	5	Is there evidence that would support recommendations on whether or not metformin should be stopped when people with diabetes are admitted with ACS, and for how long?	Thank you for your comment. Although we acknowledge that the use of other non-insulin diabetic treatment is important, this is beyond the scope of this guideline and was not addressed in any of the review questions. As a result the evidence was not reviewed and recommendations for this topic cannot be made.
SH	Diabetes UK	6.07	Full	General question	5	Is there evidence that would support recommendations about whether or not metformin should be stopped for 48hours post angiogram on all people with diabetes or just those with a history of renal impairment/moderately raised creatinine.	Thank you for your comment. Although we acknowledge that the use of other non-insulin diabetic treatment is important, this is beyond the scope of this guideline and was not addressed in any of the review questions. As a result the evidence was not reviewed and recommendations for this topic cannot be made.
SH	Diabetes UK	6.08	Full	1.1.1 and 1.1.2	5	Although we recognise this is a guideline specifically about the management of ACS and hyperglycaemia, there is a wealth of work that has been undertaken by the inpatient diabetes community on the subject of inpatient diabetes management that could be referred and sign posted to in this part of the recommendations. This includes information for people with diabetes, guidelines for management of DKA, hypoglycaemia, perioperative care, Think Glucose materials and recommendations,	Thank you for your comment. The scope of this guideline was restricted to patients with hyperglycaemia and ACS, therefore the literature searches were also limited to this specific population.

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						NPSA safety alerts and information for people with diabetes: http://www.diabetes.nhs.uk/our_work_areas/inpatient_care/ http://www.diabetes.org.uk/Guide-to-diabetes/Support_for_managing_your_diabetes/In_hospital/ Inclusion of this would help support the holistic care of people with diabetes with ACS in hospital.	
SH	Diabetes UK	6.09	Full	1.1.3	5	The recommendation for intervention on day 4 appears to have come from one very small study.	Thank you for your comment. This recommendation was based on the evidence review and the expertise of the GDG. Specifically the GDG discussed that blood glucose levels would be distorted as a result of the ACS and that test results on day 4 may be more stable.
SH	Diabetes UK	6.10	Full	1.1.3 and 1.1.4	5	Clinicians will need to decide which is the most appropriate option for diagnosing diabetes as HbA1c will not be an appropriate tool for some individuals as indicated by the WHO guidance: http://www.who.int/chp/media/news/releases/2011_1_diabetes/en/index.html	Thank you for your comment. Review question 3 focuses on identifying patients who are at high risk of progression to diabetes. The diagnosis of diabetes is outside the scope of this document and is covered by diabetes guidance (see NICE CG15 AND CG66). Formal testing and diagnosis of diabetes will normally take place following referral to primary care after the acute episode as some distortion of blood glucose levels may be expected during the inpatient admission. The use of Hba1c to diagnose diabetes does not form

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							part of the review question.
SH	Diabetes UK	6.11	Full	1.1.3 and 1.1.4	5	Please change references to Fasting Blood Glucose to Fasting Plasma Glucose, as this is the recognised term.	Thank you, this was discussed at the GDG meeting and it was agreed this may not be appropriate in an acute setting where capillary blood glucose may be used.
SH	Diabetes UK	6.12	Full	1.1.5	5	This proposal should include recommendations surrounding the need for onward referral for follow up to confirm diagnosis/ monitor people identified with IGR/high risk, and to ensure individuals receive the information, education and interventions to reduce their risk; or if diagnosed to ensure they access the diabetes care they need.	Thank you for your comment. Recommendations 1.1.6 and 1.1.7 have been amended to include more information. Formal testing and diagnosis of diabetes will normally take place following referral to primary care after the acute episode as some distortion of blood glucose levels may be expected during the inpatient admission.
SH	Diabetes UK	6.13	Full	1.1.5 and general	5	The forthcoming NICE guidance on preventing progression from pre diabetes to Type 2 diabetes could have provided this guideline with further recommendations about how to ensure people with IGR /at risk of developing Type 2 diabetes receive the support they need to reduce their risk /prevent the person from developing it.	Thank you. The public health guidance on preventing progression to type 2 diabetes is not yet published and so reference to it cannot be made. This guidance has been added to section 7 on related NICE guidance.
SH	Diabetes UK	6.14	Full	1.1.6	6	Please include the phrase "Type 2" in front of the phrase "diabetes", where it says "at increased risk of".	Thank you, this has been added to the guideline.
SH	Diabetes UK	6.15	Full	1.1.6	6	Please include a requirement in this recommendation that people are provided with information about how they can specifically reduce their risk of developing Type 2 diabetes, information about the symptoms of diabetes, and an explanation about why they have been referred back to their primary care team for follow up.	Thank you for your comment. Recommendations 1.1.6 and 1.1.7 have been amended to include more information.
SH	Diabetes UK	6.16	Full	1.1.6	6	These recommendations would benefit from	Thank you for your comment. Discharge

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				and 1.1.7		including reference to discharge planning that will include the referral and care mentioned as part of comments about recommendation 1.1.5, and the requirement for primary care to provide follow up monitoring, as per 1.1.7	planning has not been specifically mentioned as this was not the focus of the review question. Recommendations 1.1.6 and 1.1.7 now include more information.
SH	Diabetes UK	6.17	Full	1.1.7	6	This recommendation should include reference to the need for a diagnostic test if a person presents with symptoms of diabetes and this should be made explicit in the discharge plan.	Thank you. The diagnosis of diabetes is outside the scope of this guideline. Information has been added to recommendations 1.1.6 and 1.1.7.
SH	Medicines and Healthcare Products Regulatory Agency (MHRA)	7.00	Full	General	General	Recommendations in the draft guideline do not mention use of any specific drugs: the guideline is more about the overall management rather than use of specific drugs, therefore, we do not have any comment.	Thank you for your comment.
SH	Medtronic Ltd	10.00	Full	General	General	Medtronic thanks NICE for the opportunity to comment on this guideline	Thank you for your comment.
SH	Medtronic Ltd	10.01	Full	General	General	Management of hyperglycaemia in patients with ACS remains a controversial area. There is a lack of definitive evidence that can guide as to specific management strategies, treatment thresholds and target glucose levels. In the absence of a definitive randomized trial in this field, it is reasonable to summarize available evidence and expert consensus. In this regard, the current AACE/ADA guidelines provide balanced and reasonable guidance to clinicians for hyperglycaemia management in all hospitalized patients.	Thank you for your comment. The ADA/AACE guidelines are aimed at all patients who are critically ill and there are no specific recommendations for patients with hyperglycaemia and ACS. The AHA statement is similar to the recommendations made in the draft guidance and the same studies have been reviewed. The AHA document only recommends the use of intensive insulin in patients admitted to the ICU, which is not specific to ACS. They also recommend further evaluation of patients without a prior

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						AHA statement on hyperglycaemia (Deedwania et al) is also a good guidance document specifically for patients with ACS.	diagnosis of diabetes, as does the draft guidance. Future large trials are also recommended in patients with ACS in order to address the gap in the research, which is similar to the research recommendation in the draft guidance.
SH	Medtronic Ltd	10.02	Full	General	General	This guidance document has a potentially significant flaw within its meta-analyses methodology, and therefore, potentially with the conclusions based on the outputs of the meta-analysis. This is discussed in more detail in comments in section 3.1.2	Thank you for your comment.
SH	Medtronic Ltd	10.03	Full	1.1.1	5	Hyperglycaemia is defined as glucose level >11 mmol/L (~200 mg/dL). In this regard, the recommendation to "not routinely offer intensive insulin therapy in patients admitted with ACS" could be interpreted to mean that physicians should routinely practice complete "glucose neglect" – i.e. leaving glucose >200 mg/dL. However, at this degree of hyperglycaemia severity, there is clinical trial evidence (DIGAMI) that glucose lowering (of moderate intensity, achieved levels <180 mg/dL) resulted in lower mortality at 30 days as compared with permissive hyperglycaemia (leaving glucose >200 mg/dL). There is also strong evidence that patients with ACS who need CABG have significantly better outcomes (including lower post-operative infection rates) with glucose control as compared with permissive hyperglycaemia. We would suggest that this recommendation is,	Thank you. Although the GDG did not recommend the routine use of intensive insulin, they did agree that hyperglycaemia should be managed in this population. Recommendation 1.1.2 has now been re-worded for clarity and to place more emphasis on the importance of managing hyperglycaemia.

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						therefore, not balanced and is a significant departure from ADA guidelines.	
SH	Medtronic Ltd	10.04	Full	1.1.2	5	In light of 1.1.1 it is less clear what this actually means in practice as local guidelines may vary substantially. Many centres may have no formal guidelines and practice glucose neglect, or use local protocols that have no track record of effectiveness and safety. Others may practice over-aggressive control when not warranted. This recommendation endorses wide practice variations in glucose management. This recommendation contrasts with the current clinical direction in the USA for example when US based guidelines are attempting to minimize these variations (which may be detrimental to patient care). Perhaps NICE would consider expanding what local guidelines should contain and attempt to define a minimum standard for these guidelines for consistency?	Thank you for your comment. Recommendation 1.1.2 has been amended to provide an example of what a local protocol may recommend. The target blood glucose level of <10mmol/L was agreed as this was the upper limit of the target blood glucose level used in the included studies. A minimum threshold was avoided as this varied across the studies and the group wanted to avoid an arbitrary figure.
SH	Medtronic Ltd	10.05	Full	1.1.3	5	Medtronic agree and commend NICE for recommending checking A1c in patients with hyperglycaemia. Data from American Centres show that it should be done not only in patients without known diabetes, but also in those with diabetes (this is also currently recommended by ADA). In the former group, it facilitates diagnosis of previously unknown diabetes. In the latter, it facilitates intensification of therapy among	Thank you for your comment. Review question 3 was specifically aimed at patients who did not have a previous diagnosis of diabetes. The literature for its use in patients with a previous diagnosis of diabetes was not reviewed; therefore specific recommendations for this group cannot be made. The GDG also discussed that blood

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						those with poor glycaemic control (A1c >=9%). The statement that it "should not delay discharge" could perhaps be misinterpreted as a justification for not testing patients if patient throughput is critical. Perhaps NICE would consider clarifying that A1c can be easily added to routine in-hospital blood work, and does not take any additional time?	glucose levels may be distorted before 4 days due to the acute event. When patients are discharged before 4 days, the GDG agreed that these tests would normally take place within primary care during diagnostic investigations for diabetes.
SH	Medtronic Ltd	10.06	Full	3.1.2	8	Medtronic feel it is important to highlight what may be a misunderstanding of the concepts tested in various clinical trials and thus the inclusion of papers in the meta-analysis and by extension the conclusions drawn. CREATE-ECLA trial was included in the meta-analysis in this section, despite the fact that it was a trial of GIK, not a trial of targeted glucose control (This was the subject of a recent review article "***Glucose-Lowering Targets for Patients With Cardiovascular Disease: Focus on Inpatient Management of Patients With Acute Coronary Syndromes.*** *Mikhail Kosiborod and Darren K. McGuire. Circulation 2010;122;2736-2744"* and is attached in case it may assist) It is a major distortion in the meta-analysis – because CREATE-ECLA was a huge trial,	Thank you for your comment. The CREATE-ECLA paper has now been excluded from the analyses. The GDG agreed that the Van der Horst paper specified a target glycaemic range of 7-11mmol/L and were actively attempting to manage blood glucose levels. However, the CREATE-ECLA paper did not specify a target glycaemic range and was considered inappropriate for inclusion.

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						and actually induced higher glucose levels in patients receiving GIK (by the nature of the trial's design), it will completely erase any mortality benefit from DIGAMI (which is really the only trial of targeted glucose control in this patient population that adds value). It is stated that CREATE-ECLA is the trial of "intensive insulin intervention" – which is incorrect. The combined results from this meta-analysis which includes CREATE-ECLA are, therefore, potentially misleading. We would suggest that the analysis is rerun without the CREATE-ECLA study and the conclusions drawn re-examined.	
SH	Medtronic Ltd	10.07	Full	3.1.5	18	It could be interpreted that there is some equivocation on recommending aggressive glucose control in patients with diabetic ketoacidosis and hyperglycaemic hyperosmolar state (which was probably not the Institutes intent). Does the statement that "the evidence has not yet been reviewed" suggest a randomized clinical trial of insulin infusion in patients with diabetic ketoacidosis is needed to show the benefits of treating this group? Perhaps this section could be made clearer?	The management of hyperglycaemia in patients with DKA should be covered by diabetes guidance. Although the GDG acknowledged that the use of intensive insulin may be beneficial, the evidence reviewed did not include any patients with DKA and hyperosmolar and so specific recommendations for these groups could not be made. This section only documents the discussions of the GDG and are not recommendations.
SH	Medtronic Ltd	10.08	Full	3.2.2	19	Patients without known diabetes. Because CREATE-ECLA trial is, again, included inappropriately (not a trial of	Thank you for your comment. The CREATE-ECLA paper has now been excluded and the analyses were run

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						targeted glucose control), the results of this meta-analysis are similarly distorted. In addition, the trial authored by van der Horst is also included – this is also a trial of GIK, not targeted glucose control. Is it the intention of NICE to make recommendations based on studies that were not designed to be used as references in the areas for which they are being used. Both CREATE-ECLA and the van der Horst trial are not attempting to manage hyperglycaemia.	without outcomes from this paper. The overall effect was unchanged by removing this paper from the analyses. The GDG agreed that the Van der Horst paper specified a target glycaemic range of 7-11mmol/L and were actively attempting to manage blood glucose levels. However, the CREATE-ECLA paper did not specify a target glycaemic range and was considered inappropriate for inclusion.
SH	Medtronic Ltd	10.09	Full	3.2.5	28	The authors seem to recognize that inclusion of GIK trials is troublesome – they state that these trials included patients that did not have hyperglycaemia (which is logical, since the hypothesis tested was GIK, not targeted glucose control). This is one of the clear reasons why it can be argued that these trials should not have been included (it is difficult to extrapolate the impact of hyperglycaemia management from a cohort of patients who do not have hyperglycaemia)? Again we would suggest that the Meta-analysis is rerun with the inappropriate studies removed and the conclusions drawn re-examined.	Thank you for your comment. The CREATE-ECLA paper has now been excluded from the analyses. The GDG agreed that the Van der Horst paper specified a target glycaemic range of 7-11mmol/L and were actively attempting to manage blood glucose levels. However, the CREATE-ECLA paper did not specify a target glycaemic range and was considered inappropriate for inclusion.
SH	Medtronic Ltd	10.10	Full	Table 3 Table 6	16 27	In the table for diabetes patients is reported an insulin dose every 3 hours but it is reported only in the tight glycemic control	Thank you for your comment. Table has been amended in the guideline.

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						arm. It is strange that the standard treatment does not include any cost related to insulin. Is there an agreed definition of "standard care" available for which to examine the data in the table against? The table itself seems not to consistently report the additional cost related to the tight control treatment. Under the section "glucose meter test strip" are listed the additional tests that they have to do with intensive insulin treatment. This gives rise to several questions: • Where did this information come from, is there the opportunity to examine its source? • Is it based on a protocol and if so which protocol? It is not clear why there are 12 more for diabetes patients and 20 more for non diabetic patients? Some of the times given for test seem high – for example a type 1 diabetic does not spend 5 minutes each time they use a test strip, could we ask where these figures for resource usage were sourced from? Why were Canadian figures used for Glucose meter strip test costs instead of UK BNF and biochemistry costs?	Thanks for your comment. The definition of standard care as agreed by the GDG has been included in the guideline. Thank you for your comments. The information was provided by members of the guide line development group (GDG). The group is made up of experts in this field. Thank you. The GDG provided information on current clinical practise, and based on their expertise agreed that the sub group of people without pre-existing diabetes would usually not be given insulin and as result would require fewer glucose tests than those who were known to have diabetes. The GDG also agreed that whereas the diabetes subgroup would require inputs from a Diabetes Nurse Specialist, those without diabetes would not require this input during the acute phase. Thus the cost related to tight control will differ for the two sub-groups. The guideline has been

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							updated to include this information. Cost of glucose meter strips have been amended in the guideline to those in BNF 61.
SH	National Diabetes Inpatient Specialist Nurse (DISN) UK Group	20.00	Full	General	General	Document very wordy, but easy to follow, Only thought is the 11mmols/ - Dr's and nurses could get confused with the 11mmol/s as cut off for hyperglycaemia, don't think there would be any urgency on the nursing staff side of things, but clearly on CCU it would be actioned – although locally the only currently do over 11mmol/s. the whole document also almost seems like a review of all current research which is valid, but is it relevant in this format. Should it be left with an appendix only? It also does not actually give guidance as we would expect. However we do feel that there is some guidance on action to hyperglycaemia but is easier to find in appendix C.	The definition for hyperglycaemia was reached following GDG consensus and was discussed in detail at a GDG meeting during guideline development. The format of the guideline is consistent across all short clinical guidelines and includes a section that provides an overview of the evidence reviewed. Please see section 1.1 for a list of all recommendations that were formed on the basis of the evidence reviewed.
SH	National Diabetes Inpatient Specialist Nurse (DISN) UK Group	20.01	Appendices	General	General	Appendix C easier to use, clearer in guidance.	Thank you for your comment.
SH	National Diabetes Inpatient Specialist Nurse (DISN) UK Group	20.02	Full	General	General	We like the breakdown of the costs and evidence review within the document.	Thank you
PR	NETSCC, HTA (Ref 1)	18.00	Full	Introduction	3	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** Paragraph 4: states that the first 48 hours	Thank you. The scope outlines the population and setting of the guideline as patients with Acute Coronary Syndrome in secondary care. Long-term management of hyperglycaemia and support beyond the acute phase has been excluded from the

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						after admission with ACS will be covered. This does not appear to have been specified in the scope	guideline (see section 4.3.2). This definition of the acute phase was agreed during the development of the guideline by the GDG.
PR	NETSCC, HTA (Ref 1)	18.01	Full	Introduction	3	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** Paragraph 4: hyperclycaemia is defined as blood glucose above 11 mmol/l. The scope (4.3.1) states that threshold values of blood glucose for intervention will be covered, but this appears to have been preempted by this statement. Many studies reported on use alternative thresholds	Thank you. During the development of the guideline, the GDG agreed that studies would be considered for inclusion if they had provided a definition of hyperglycaemia. This definition may have differed from >11mmol/L that the GDG agreed was a clinically significant and internationally accepted threshold for hyperglycaemia. This has now been added to the evidence review sections of the guideline.
PR	NETSCC, HTA (Ref 1)	18.02	Full	3.4.1	39	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** It is not clear how this research question fits with the scope	Thank you. NICE guidance generally includes on review question focusing on patient experience/information and for this guideline this is for patients who do not have a previous diagnosis of diabetes.
PR	NETSCC, HTA (Ref 1)	18.03	Appendix	Scope 4.3.1	5	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** "Timing and frequency of blood glucose level measures…" is not addressed in the guideline	Thank you, as intensive insulin was not recommended, the timing and frequency of blood glucose measures have not been fully addressed. Recommendation 1.1.2 has been amended to provide more information including an example target glycaemic range.
PR	NETSCC, HTA (Ref 1)	18.04	Full	3.1.2	11	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.**	Thank you for your comment. This section has been footnoted and it reflects observational data.

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						Bottom row of table presents odds ratios for alternative outcomes, comparing groups with blood glucose >8 mmol/l and <8 mmol/l – these do not appear to be intervention effects	
PR	NETSCC, HTA (Ref 1)	18.05	Full	3.1.2	12	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** Both rows of table report intervention effects in subgroups of population. No indication is given as to whether the differences in effect estimates between subgroups (i.e. interactions) are statistically significant	Thank you. P-values have been added to this table; however these refer to the significance between the treatment and control group within the sub-groups. No information on any interactions was provided within the paper.
PR	NETSCC, HTA (Ref 1)	18.06	Full	3.1.4	15	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** Last paragraph: "…intensive insulin therapy is clearly more expensive and less effective…" No definite conclusion has been drawn to say that intensive insulin therapy is less effective than standard care	Thanks for your comment. The paragraph has been reworded.
PR	NETSCC, HTA (Ref 1)	18.07	Full	3.2.2	22-23	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** Last 3 rows of table report effect estimates within subgroups without indicating whether interactions are significant	Thank you. P-values have been added to this table; however these refer to the significance between the treatment and control group within the sub-groups. No information on any interactions was provided within the paper.
PR	NETSCC, HTA (Ref 1)	18.08	Full	3.2.3.2	24	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** To say "Low quality evidence … that	Thank you for your comment. This has been re-worded.

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						intensive insulin non-significantly increased 30-day mortality" makes no sense. The RR is close to one, and the 95% CI is wide enough to indicate that the statistical significance is not close to p=0.05. It could be said that there is no evidence of an effect, but the studies were of low quality. 3.2.3.4 has a similar problem. 3.2.3.5 and 3.2.3.6 are worded better ("…did not significantly reduce…")	
PR	NETSCC, HTA (Ref 1)	18.09	Full	3.2.3.7	25	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** If the study did not report rates of hypoglycaemia, how can this be described as "evidence", whatever the quality?	Thank you. This row has been removed from the GRADE table.
PR	NETSCC, HTA (Ref 1)	18.10	Full	3.2.3.9 3.2.3.11	25	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** Effects are reported to be statistically significant in some subgroups but not others, but not whether these differences constitute statistically significant interactions. It is not appropriate to comment on subgroups effect estimates without reporting whether the differences could be attributable to chance	Thank you. P-values have been added to; however these refer to the significance between the treatment and control group within the sub-groups. No information on any interactions was provided within the paper.
PR	NETSCC, HTA (Ref 1)	18.11	Full	3.2.3.1	25	**2.2 Please comment on the health**	Thank you. This has been amended in the

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				0		**economics and/or statistical issues depending on your area of expertise.** A "non-significant effect" is reported. If it is not significant, it should not be described as an effect	guideline.
PR	NETSCC, HTA (Ref 1)	18.12	Full	3.2.4	26	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** In comparison with usual care, intensive insulin therapy is described as "at best equally effective". Yet 3.2.3.9 and 3.2.3.11 report significant benefits in subgroups (though not whether the interactions are significant), so intensive insulin therapy is "at best" effective in subgroups of the population?	Thank you for your comment. A majority of the studies however did not show that intensive insulin therapy was more effective. The sub-groups which appeared to have some benefits were too under-powered to draw any reasonable conclusions or conduct further analysis on.
PR	NETSCC, HTA (Ref 1)	18.13	Full	3.2.5	28	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** Paragraph 2 notes that some studies included patients that would not be considered to be suffering from hyerglycaemia. Given that the evidence from these trials was downgraded as a result, should they have been included in the first place?	Thank you for your comment, however the GDG agreed that although some patients may have had blood glucose levels above 11mmol/L, the Van der Horst paper specified a target glycaemic range of 7-11mmol/L and were actively attempting to manage blood glucose levels. The CREATE-ECLA paper did not specify a target glycaemic range and has been excluded.
PR	NETSCC, HTA (Ref 1)	18.14	Full	3.2.5	28	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** The threshold of 11 mmol/l to define hyperglycaemia is stated as being	Thank you for your comment. The threshold for hyperglycaemia (blood glucose level above 11mmol/L) was reached using the clinical expertise of the GDG.

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						internationally accepted, but no evidence is presented in a way as to assess this viewpoint	
PR	NETSCC, HTA (Ref 1)	18.15	Full	3.3.2	31	**1.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** The second row of the table reports no serious imprecision, yet some of the CIs are quite wide.	Thank you for your comment, these GRADE rows have now been downgraded for imprecision.
PR	NETSCC, HTA (Ref 1)	18.16	Full	3.3.2	31-32	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** It is not stated whether the effect estimates relate to continuous or binary predictors variables	Thank you for your comment. Table 7 has been amended to include definitions of the outcome and the GRADE table has been footnoted where predictors are continuous variables.
PR	NETSCC, HTA (Ref 1)	18.17	Full	3.3.2	32-33	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** The diagnostic studies are reported as having no serous imprecision, yet no CIs are given for the estimates of diagnostic performance. Given that the number of events for many of these studies was 38, it seems likely that there is considerable uncertainty in some of these estimates	Thank you for your comment, CIs have been added where they are available and these GRADE rows have now been downgraded for imprecision
PR	NETSCC, HTA (Ref 1)	18.18	Full	3.3.2	34	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** Top row: are these continuous or binary	Thank you for your comment. Table 7 has been amended to include definitions of the outcome and the GRADE table has been footnoted where predictors are continuous variables

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						predictors?	
PR	NETSCC, HTA (Ref 1)	18.19	Full	3.3.2	34	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** Bottom 2 rows – "No serious imprecision" but no CIs, and only 36 and 9 cases of diabetes at follow-up	Thank you, this has been amended.
PR	NETSCC, HTA (Ref 1)	18.20	Full	3.3.2	34	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** Bottom row, entries under "Imprecision" and "Other considerations" are transposed	Thank you, this has been amended.
PR	NETSCC, HTA (Ref 1)	18.21	Full	3.3.2	35	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** Footnote e is missing	Thank you, this footnote has been amended.
PR	NETSCC, HTA (Ref 1)	18.22	Full	3.3.3.2	36	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** "Time to angiography" is reported as predictive of the development of diabetes; it is not clear how this is association might plausibly come about	Thank you for your comment. This was reported in the paper as a significant predictor of abnormal glucose tolerance and so has been included in the GRADE table.
PR	NETSCC, HTA (Ref 1)	18.23	Full	3.3.3.4-3.3.3.8, 3.3.3.11	36-38	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** Several diagnostic studies described as moderate quality, yet without CIs for any reported diagnostic measures. The number of patients in total is reported, though	Thank you for your comment. Confidence intervals have been added to the GRADE table (table 8). However, some papers did not report confidence intervals and did not report enough information for the appropriate calculations-these have been footnoted in the table where appropriate.

Type	Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						diagnostic measures are based on subgroups (e.g. the denominator for estimating sensitivity is the number of cases)	
PR	NETSCC, HTA (Ref 1)	18.24	Full	3.4.6	44	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected** No evidence was identified to answer the research question, yet the recommendations for this section are lengthier than any other	Thank you. Recommendations for this review question were made on the basis of GDG expertise. There is reference to specific related NICE guidance in recommendation 1.1.5 and this may contribute to the longer length of these recommendations.
PR	NETSCC, HTA (Ref 1)	18.25	Full	General	General	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? B) Complete? i.e. are all the important aspects of the evidence reflected** Given the general lack of evidence and low quality, the research recommendations appear few in number and lacking in focus. E.g. recommendation B1 is very broad and vague. Could more detail be given as to what would be required to be classified as high quality? Are there particular subgroups that merit particular attention?	Thank you. The GDG felt that research recommendations should be prioritised and that the most important research recommendation would be a large RCT investigating the use of intensive insulin in patients with ACS and hyperglycaemia. Subgroup analyses for patients with STEMI vs. NSTEMI and for patients with previously diagnosed diabetes vs. previously unknown diabetes have also been recommended.
PR	NETSCC, HTA (Ref 1)	18.26	Full	General	General	**3.2 Are any important limitations of the evidence clearly described and discussed?** Statements about quality are made with	Thank you. The quality of each study included in the evidence review underwent a critical appraisal. The quality of the evidence is presented in the GRADE tables

Type	Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						little explanation	for each review question. For more details on GRADE please see chapter 6 of the guideline development manual (http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp
PR	NETSCC, HTA (Ref 1)	18.27	Full	10.1	50	**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.** Killip class is described as a measure of severity, but not the direction of the scale	Thank you, this has been amended in the glossary.
PR	NETSCC, HTA (Ref 1)	18.28	Full	3.3.6	39	**1.2 Please comment on whether the research recommendations, if included, are clear and justified.** No research recommendations are made, but the reader is referred to an appendix for details	Thank you. This reference is for research recommendations for the guideline, not for the specific review question.
PR	NETSCC, HTA (Ref 1)	18.29	Full	3.4.6	44	**4.2 Please comment on whether the research recommendations, if included, are clear and justified.** No evidence was identified to answer the research question, yet no research recommendations were made	Thank you. The GDG agreed that the most important research recommendation would be an RCT of intensive insulin therapy vs. standard care and did not feel that a research recommendation was necessary for this review question.
PR	NETSCC, HTA (Ref 2)	18.30	Full	Introduction	3	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)**	Thank you. Long-term management of hyperglycaemia and support beyond the acute phase has been excluded from the guideline (see section 4.3.2 of the scope).

Type	Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						Why focus on the first 48 hours? And why focus on intensive insulin therapy when the objective of this guideline is to review optimal management beyond a particular specific option.	This definition of the acute phase was agreed during the development of the guideline by the GDG. The scope also limits the key clinical issues to inpatient glucometabolic management (glucose, potassium and insulin) of hyperglycaemia in patients with acute coronary syndrome (see section 4.3.1). Therefore the review questions focused on the use of intensive insulin vs. standard therapy.
PR	NETSCC, HTA (Ref 2)	18.31	Full	Introduction	3	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** Why the definition used for hyperglycemia? What is the source of the cut-off point selected?	During the development of the guideline, the GDG agreed that studies would be included if they had provided a definition of hyperglycaemia (please see evidence review sections of the guideline for review question 1 and 2). This definition may have differed from >11mmol/L that the GDG agreed was a clinically significant and internationally accepted threshold for hyperglycaemia. This threshold was reached based on the expertise of the GDG.
PR	NETSCC, HTA (Ref 2)	18.32	Full	1	5	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** Recommendation 1.1.5: when should this advice be offered? Only once before discharge? Should this information be reminded in posterior visits? (perhaps at least annually together with a HBA1c measurement?)	Thank you. This advice should be offered before the patient is discharged (before diagnostic investigations for diabetes) and a heading has been added to section 1.1 for clarity. Patient advice following discharge from secondary care is outside the scope of this guideline.
PR	NETSCC, HTA (Ref 2)	18.33	Full	1	6	**1.1 Are there any important ways in**	Thank you for your comment. There are

Type	Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached) Recommendation 1.1.6: how should this risk be communicated?	some general details of how information should be presented to patients in the 'Patient-centred care' section of the guideline (pg 5). This includes being culturally appropriate and accessible.
PR	NETSCC, HTA (Ref 2)	18.34	Full	3	8	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** The authors mention in the last lines of this page "the evidence was considered to be very low quality". How did the authors evaluate the quality of the evidence? Who evaluated the quality?	Thank you. The quality of each study included in the evidence review underwent a critical appraisal. The quality of the evidence is presented in the GRADE tables for each review question. For more details on GRADE please see chapter 6 of the guideline development manual. Please also see chapter 3 of the guideline development manual for more information on the members of the technical team and their role in the development of the guideline (http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp).
PR	NETSCC, HTA (Ref 2)	18.35	Full	3.1.5	17	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** The authors mention that following up patients beyond the acute phase (first 48 hours) would have a bigger influence on outcomes than intensive insulin therapy. Nevertheless this was not reviewed during the preparation of these guidelines and how and when and by whom this should be done remains unclear. Should not this be considered within the scope of these	Thank you for your comment. This section discusses how the GDG formed their recommendations based on the evidence and their discussions. Although guidance will only be produced for management of hyperglycaemia during the acute phase, the GDG felt that it may have been helpful if the papers followed up patients to assess the longer-term effects of intensive insulin therapy. Guidance on the management of hyperglycaemia beyond 48 hours is beyond the scope of this guideline. Aspects of

Type	Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						guidelines?	longer-term monitoring are addressed in recommendation 1.1.7.
PR	NETSCC, HTA (Ref 2)	18.36	Appendices	Appendix D	General	**2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual).** The search strategy used seems appropriate. Nevertheless, it seems unclear the subsequent process of selection of studies to be included or excluded. How was the selection criteria applied to the references identified with the search strategy? By whom? And how was biased avoided?	Thank you for your comment. The inclusion criteria are set out in the evidence review section for each review question (i.e. 3.1.2 for optimal metabolic management in patients with diabetes). For more details please see the review protocol and full excluded list (Appendices C and D). Please also see chapter 6 of the guideline development manual for more detailed information on the reviewing process. (http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp).
PR	NETSCC, HTA (Ref 2)	18.37	Appendices	Appendix D	General	**2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual).** From the studies selected, how was the relevant information retrieved? Did the authors use a data collection form? How and when was this form designed? And who of the authors extracted this information?	Thank you. Please see chapter 6 of the guideline development manual for more detailed information on the evidence review process. (http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp).
PR	NETSCC, HTA (Ref 2)	18.38	Appendices	Appendix D	general	**2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at**	Thank you. Flow diagrams were presented to the Guideline Development Group (GDG) during the development phase of the guideline and these have been included in Appendix D

Type	Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						http://www.nice.org.uk/page.aspx?o=guidelinesmanual). Perhaps to improve the presentation of the methods used could the authors provide flow diagrams on how the studies for each question were identified and selected/excluded?	
PR	NETSCC, HTA (Ref 2)	18.39	Appendices	Appendix D	General	**2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual).** Why did the authors exclude studies published not in English? And why were reviews rejected when evidence already summarized in previous reviews could have been important to consider as part of the preparation of this guideline?	Systematic reviews were used to ensure that all appropriate studies had been identified by the literature searches but were not included as part of the evidence review. The results of relevant guidelines and systematic reviews were also presented to the GDG during the development of the guideline for discussion. Narrative reviews were excluded. Non-English papers were also excluded as the resources required to translate these papers are not available and would not fit into the short clinical guideline process.
PR	NETSCC, HTA (Ref 2)	18.40	Appendices	Appendix D	General	**2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual).** In general more clarity on the role played by each person that participated in the development of this guideline would be welcome	Thank you for your comment. Please see chapter 3 of the guideline development manual for more information on the members of both the technical team and the GDG and their role in the development of the guideline (http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp).

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PR	NETSCC, HTA (Ref 2)	18.41	Appendices	Appendix D	general	**2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual).** Did the authors evaluate the level of quality of the studies? And how? Who did it? And was the level of quality taken into account?	Thank you. The quality of each study included in the evidence review underwent a critical appraisal. The quality of the evidence is presented in the GRADE tables for each review question. For more details on GRADE please see chapter 6 of the guideline development manual (http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp).
PR	NETSCC, HTA (Ref 2)	18.42	Full	General	General	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** The health economics sections are well presented and justified. As the key interventions under evaluation in this case is not effective, a thorough cost-effectiveness or cost-utility analysis is not required.	Thank you for your comment.
PR	NETSCC, HTA (Ref 2)	18.43	Full	1	5	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** Recommendation 1.1.5: when should this advice be offered? Only once before discharge? Should this information be reminded in posterior visits? (perhaps at least annually together with a HBA1c measurement?)	Thank you. This advice should be offered before the patient is discharged (before diagnostic investigations for diabetes) and a heading has been added for clarity. Patient advice following discharge from secondary care is outside the scope of this guideline.

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PR	NETSCC, HTA (Ref 2)	18.44	Full	1	6	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** Recommendation 1.1.6: how should this risk be communicated?	Thank you for your comment. There are some general details of how information should be presented to patients in the 'Patient-centred care' section of the guideline (pg 5). This includes being culturally appropriate and accessible.
PR	NETSCC, HTA (Ref 2)	18.45	Full	3	8	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** The authors mention in the last lines of this page "the evidence was considered to be very low quality". How did the authors evaluate the quality of the evidence? Who evaluated the quality?	Thank you. The quality of each study included in the evidence review underwent a critical appraisal. The quality of the evidence is presented in the GRADE tables for each review question. For more details on GRADE please see chapter 6 of the guideline development manual. Please also see chapter 3 of the guideline development manual for more information on the members of the technical team and their role in the development of the guideline (http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp).
PR	NETSCC, HTA (Ref 2)	18.46	Full	3.2.6	29	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? B) Complete? i.e. are all the important aspects of the evidence reflected?** Recommendation 1.1.2: why do the authors include the specific cut-off point? What is the evidence for this specific level?	Thank you for your comment. The threshold for hyperglycaemia varied across the studies reviewed for this guideline and this issue was discussed in depth at the GDG meeting. This threshold level was reached using the expertise of the GDG and was felt to be representative of an internationally accepted standard.

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PR	NETSCC, HTA (Ref 2)	18.47	Full	3.3.6	39	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** Shouldn't the recommendations also include a recommendation on informing patients' risk and lifestyle advice? (Although this is covered by recommendation 1.1.5 in page 44). Beyond the nature of the advice perhaps further information on how and when to provide this advice would be helpful. Why no research recommendations are presented for this question?	Thank you for your comments. The GDG felt that lifestyle advice was an important factor in reducing the risk of progression to diabetes and made a specific recommendation for this (rec 1.1.5). Further information on how often and when to provide this advice (beyond the pre-diagnostic stage) is outside the scope of this guideline as this would normally take place within primary care. The GDG agreed that the most important research recommendation would be an RCT of intensive insulin therapy vs. standard care and did not feel that a research recommendation was necessary for this review question.
PR	NETSCC, HTA (Ref 2)	18.48	Full	3.4.6	44	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** Recommendation 1.1.5, 1.1.6 and 1.1.7: see comments in the box above.	Thank you for your comments.
PR	NETSCC, HTA (Ref 2)	18.49	Full	General	General	**3.2 Are any important limitations of the evidence clearly described and discussed?** In general the authors adequately discuss the limitations encountered in the current evidence. I wonder if it would be useful for the authors to discuss the advice provided on current guidelines elsewhere and	Thank you for your comment. Related guidelines on hyperglycaemia and ACS were presented to the GDG for their discussion however, as they did not form part of the evidence review, they were not included as part of the guideline. NICE are only able to refer to other related NICE guidance and guidance from the

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						compare to the current recommendations.	Department of Health.
PR	NETSCC, HTA (Ref 2)	18.50	Full	General	General	**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.** Overall is succinct, well written and clearly presented.	Thank you for your comment.
PR	NETSCC, HTA (Ref 2)	18.51	Full	General	General	**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.** The guidelines are easy to understand	Thank you for your comment.
PR	NETSCC, HTA (Ref 2)	18.52	Full	General	General	**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.** The recommendations seem adequately reached from the evidence collected	Thank you for your comment.
PR	NETSCC, HTA (Ref 2)	18.53	Full	General	General	**4.2 Please comment on whether the research recommendations, if included, are clear and justified.** They are clear and justified. The overall level of evidence is rather limited therefore the specific recommendations in this guideline are limited by the inherent lack of	Thank you for your comment.

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						evidence. The authors reflect this issue in an adequate manner.	
PR	NETSCC, HTA (Ref 2)	18.54	Appendices	Appendix A	54	**Section five – additional comments** **Please make any additional comments you want the NICE Guideline Development Group to see, feel free to use as much or as little space as you wish.** Competing interests are only presented for the members of the GDG. Shouldn't these be presented also for the members of the short clinical guidelines technical team and for the members of the guideline review panel?	Thank you for your comment. We will include all non declared interests in the published guidance from all NICE staff and GRP members.
PR	NETSCC, HTA (Ref 2)	18.55	Full	9	48	**Section five – additional comments** **Please make any additional comments you want the NICE Guideline Development Group to see, feel free to use as much or as little space as you wish.** In general (main text of guidelines) the authors present a rather limited number of references. Perhaps further references can be added to support specific statements within the text (e.g. the cut-off level suggested)	Thank you for your comment. References are only cited for studies that have been included in the evidence review. Further excluded studies can be found in Appendix D. The cut-off level for hyperglycaemia was reached following GDG consensus and is not based on an evidence review.
SH	NHS Direct	19.00	Full	General		Welcome the guideline and have not comments on the content.	Thank you for your comment.
SH	NHS Sheffield	8.00	Full	General	General	Somewhat secondary care focus on this so little comment to make. It will be critical that	Thank you. Recommendation 1.1.7 has also been amended to clarify that GP's

Type	Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						the discharge communication clearly identifies the hyperglycaemia and future responsibilities of the GP to monitor annually	should offer annual monitoring of high risk patients in primary care. The 'who is this guideline for' section has been amended to include healthcare professionals from primary care.
SH	Roche Products Ltd	17.00	Full	1.1.3	5	We welcome this recommendation and would also recommend that the HbA1c test is performed at the earliest opportunity with the confirmatory FBG test at an appropriate point prior to discharge to ensure structured communication, safe transition and appropriate follow up, including repeat testing independent of the ACS setting, consistent with recent position statements on standards of medical care in diabetes[1,2].	Thank you for your comment. This recommendation was based on the evidence review and the expertise of the GDG. Specifically the GDG discussed that blood glucose levels would be distorted as a result of the ACS and that test results on day 4 may be more stable. Testing independent of the ACS setting is outside the scope of this guideline.
SH	Roche Products Ltd	17.01	Full	2	7	Testing for diabetes. We agree with the statement that oral glucose tolerance tests should not be routinely offered if HbA1c and FBG are within normal range. However, we would request that consideration is given to issuing guidance for individuals with impaired glucose tolerance. In accordance with a WHO Consultation report we would support a statement that individuals with IFG should be given an OGTT to exclude the presence of diabetes in a large patient group that would otherwise be missed[3, 4].	Thank you for your comment. Review question 3 focuses on identifying patients who are at high risk of progression to diabetes. The diagnosis of diabetes is outside the scope of this document and is covered by diabetes guidance (see NICE CG15 and CG66). Formal testing and diagnosis of diabetes will normally take place following referral to primary care following the acute episode. The GDG discussed that carrying out an OGTT in acute settings may be difficult and it was also agreed that there is a risk of false positive results as patients with ACS are likely to have distorted blood glucose levels.
SH	Roche Products Ltd	17.02	Full	General		References:	Thank you for the information.

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						2. American Diabetes Association: Position Statement – Standards of Medical Care in Diabetes. Diabetes Care 2011;34 (Suppl. 1) 3. The International Expert Committee. International Expert Committee Report on the Role of the A1c Assay in the Diagnosis of Diabetes. Diabetes Care 2009; 32(7): 1327-1334 4. World Health Organisation. Definition, Diagnosis and Classification of Diabetes Mellitus and it's Complications: Report of a WHO Consultation.Part 1. Diagnosis and Classification of Diabetes Mellitus. Geneva, World Health Org.,1999 5. World Health Organisation. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia: Report of a WHO/IDF Consultation. Geneva, World Health Org., 2006	
SH	Royal College of Nursing	15.00	General	General		The Royal College of Nursing welcomes this document. The draft guidelines seem comprehensive.	Thank you for your comment.
SH	Royal College of Nursing	15.01	Full	1.1.4	5	Oral glucose tolerance testing (OGTT) - it states that OGTT should not be offered to individuals who have a normal HBA1c or fasting blood glucose.	Thank you for your comment. Review question 3 focuses on identifying patients who are at high risk of progression to diabetes. The diagnosis of diabetes is outside the scope of this document and is

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						We would question the rationale for this recommendation, based on evidence presented in a study by Wallander et al (2008) *Diabetes care 31:36* which shows that OGTT was reliable for early detection of dysglycaemia in post MI patients and that the early detection related to impaired prognosis at one year. This can be masked in post MI patients as things stabilise post MI, the assumption is that the impairment is temporary when Wallander's study would suggest that the MI can be viewed as a 'stress test'. In addition a study by Bartnik et Heart 2007 reported in the *Euro Heart Survey (DM & the heart)*; 93:72 showed that dependent on the guidelines used, misdiagnosis of approximately 40% occurred when using impaired fasting glucose compared with OGTT. Finally, the ESC and EASD guidelines (2007) DOI:140.1093/eurheartj/ehl261 states the following: "(OGTT) is the only way to detect IGT (impaired glucose tolerance). Many subjects with IGT will develop CVD before progressing to diabetes." Page 7 Recommendation: Early stages of hyperglycaemia and	covered by diabetes guidance (see NICE CG15 AND CG66). Formal testing and diagnosis of diabetes will normally take place following referral to primary care after the acute episode as some distortion of blood glucose levels may be expected during the inpatient admission. The GDG specifically discussed that patients with low fasting glucose and/or Hba1c would be less likely to develop diabetes so OGTT testing would not be as important in this group of patients. The studies mentioned are focusing on the diagnosis of diabetes and these studies are not appropriate to answer review question 3.

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						asymptomatic type 2 diabetes are best diagnosed by OGTT	
SH	Welsh Endocrinology and Diabetes Society	14.00	Full	1.14	5	**WEDS overall response** Considerable comment has been received on the recommendation that an OGTT is not offered to patients with HbA1c and Fasting Glucose in the "normal range". The recommendations do not specify this normal range but we interpret the guidance as it stands as indicating a Fasting Glucose below 6.1 WEDS argues against this recommendation. The background for this position is set out in detail in the three lines below which are the individual comments made by three consultants. In summary however; • There is abundant evidence that an OGTT will identify an additional large cohort of patients with diabetes or IGT in patients presenting with ACS and a fasting glucose between 6.1 and 7 • There are further significant data suggesting that additional patients with diabetes or IGT have fasting glucose between 5.5 and 6 • These patients are at particular risk for further cardiovascular disease and should have their risk factors treated aggressively	Thank you for your comment. Review question 3 focuses on identifying patients who are at high risk of progression to diabetes. The diagnosis of diabetes is outside the scope of this document and is covered by diabetes guidance (see NICE CG15 AND CG66). Formal testing and diagnosis of diabetes will normally take place following referral to primary care following the acute episode. The thresholds published by the WHO refer to diagnostic thresholds for diabetes and this is not part of the review question. The GDG aimed to prioritise the research recommendations for this guideline and felt that an RCT comparing intensive insulin therapy vs. standard therapy would be most important for this guideline.

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						• Many will also have diabetic microvascular complications There is therefore consensus within WEDS that OGTTs should be mandatory in all patients with Fasting Glucose between 6.1 and 7 whose HbA1c is <6.5% In contrast there is no consensus about the timing of the OGTT. With opposing views based on practicality/diagnostic yield/completeness achieved by screening an inpatient population and the concern that diagnostic accuracy is less certain until the patient is recovered, 6 weeks after ACS **WEDS recommends** that the guideline recommendations formally specify the diagnostic cut off levels of Fasting Glucose (Diabetic at >7, Normal at <6.1) and HbA1c (Diabetic at >6.5%), which a wide body of world opinion now agrees now specify diabetes and normality **WEDS recommends** that the guideline specifically demands that OGTTs should be carried out on all patients with fasting glucose between 6.1 and 7 whose HbA1c is <6.5% **WEDS recommends** the addition of a research question to the guidance which specifies;	

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						• Additional work on the group of patients whose fasting Glucose is 5.5 – 6, and • The diagnostic accuracy, practicality and diagnostic yield of carrying out those OGTTs on Day 4 or later during the admission for ACS, or 6 weeks after discharge	
SH	Welsh Endocrinology and Diabetes Society	14.01	Full	1.14	5	**Comments of consultant reviewer 1** Individuals with macrovascular disease are more likely to have an abnormal 2 hour (impaired glucose tolerance (IGT) or Diabetes) than FPG value (impaired fasting glucose (IFG) or Diabetes) (1, 2). The risk of macrovascular disease in patients with IGT is greater than in IFG and is of the same order as those with Diabetes. Up to 2/3rds of individuals screened by OGTT with stable and unstable coronary artery disease will have IGT or Diabetes (3). However increasingly the OGTT is no longer being used to routinely screen for Diabetes and international opinion favours the use of HbA1c and fasting plasma glucose. A FPG ≥7.0mmol/L is an accurate predictor of the presence of Diabetes but a FPG value ≤7mmol/L is inaccurate at excluding a diagnosis of Diabetes. HbA1c and FPG should be the minimum tests used to detect Diabetes in a group that has already demonstrated its risk (ACS). The addition of a 2 hour post OGTT value, in a group that is often a captive audience, is likely to diagnose additional individuals with IGT and	Thank you for your comment. Review question 3 focuses on identifying patients who are at high risk of progression to diabetes. The diagnosis of diabetes is outside the scope of this document and is covered by diabetes guidance (see NICE CG15 AND CG66). Formal testing and diagnosis of diabetes will normally take place following referral to primary care following the acute episode.

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						Diabetes who would benefit from appropriate referral to screening and management pathways. 1 DECODE Study Group, the European Diabetes Epidemiology Group: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 161:397–405, 2001 2 M Bartnik, L Ryden, K Malmerg, j Orvig, K Pyorala, E Standl. R Ferrari, M Simoons, J Soler-Soler. Oral glucose tolerance test is needed for appropriate classification of glucose regulation in patients with coronary artery disease: a report from the Euro Heart Survey on Diabetes and the Heart. Heart 2007; 93:72-77. 3 LG Mellbina, M Anselminob, R Larsa: Diabetes, pre-diabetes and cardiovascular risk: European Journal of Cardiovascular Prevention & Rehabilitation 17 (1): s9-14, 2010 An HbA1c ≥7% or ≤5.5% has been shown to predict with 97.5% confidence the presence or absence of Type 2 Diabetes (4). However there is a significant chance that individuals between these 2 values may still have IGT or Diabetes. Screening by	

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						HbA1c and FPG is undoubtedly more convenient but whilst they will already be treated for their lipid and blood pressure parameters, excluding routine OGTT in this at risk group may well lead to delayed diagnosis of Diabetes and their subsequent entry onto beneficial management and screening pathways for Diabetes such as retinal screening. 4 ZX Lu, KZ Walker, K O`Dea, KA Sekaris, JE Shaw. A1C for screening and diagnosis of Type 2 Diabetes in Routine clinical practice. Diabetes Care 2010 April; 33(4): 817–819.	
SH	Welsh Endocrinology and Diabetes Society	14.02	Full	1.14	5	**Comments of consultant reviewer 2** • ***Recommendation 1.1.4*** 1. This recommendation could be made clearer by specifying a threshold value for fasting glucose and HBA1c for which OGTTs should be undertaken such that : (a) Patients with fasting > 7.0 mmol/L have diabetes, should be managed as such and do not need OGTT (b) Fasting < 6.1 mmol/L is normal and no further tests required (c) Fasting 6.1-6.9 mmol/L should have an OGTT as these will include patients with IFG, IFG+IGT, or diabetes	Thank you for your comment. Review question 3 focuses on identifying patients who are at high risk of progression to diabetes. The diagnosis of diabetes is outside the scope of this document and is covered by diabetes guidance (see NICE CG15 AND CG66). Formal testing and diagnosis of diabetes will normally take place following referral to primary care after the acute episode. There was not enough evidence to support specific threshold values. Published thresholds refer to diagnostic thresholds for diabetes and this is not part of the review question.

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						It therefore appears that the guidelines are recommending the same thresholds for OGTTs in ACS as in the general population. 2. The ACS group is a high risk group so one would have expected that the thresholds for doing OGTTs would not be set at the same level as in the general population. This is the point of the studies of OGTT in the ACS setting. Patients will be missed even with a cut-off of 6.1 mmol/L. Using 5.5 mmol/L improves sensitivity but will lead to more OGTTs (54% of all ACS patients). A fasting glucose of 5.8 mmol/L was the optimal cut-off for detecting diabetes in Okosieme's study 3. It is not clear whether "normal" was recommended in order to reduce the number of OGTTs performed or because more evidence is needed on optimal cut-off values. 4. OGTTs should not be encouraged in hospital and should preferably be arranged as outpatient 4-6 weeks after the event.	
SH	Welsh Endocrinology and Diabetes Society	14.03	Full	1.14	5	**Comments of consultant reviewer 3**	Thank you for your comment. Review question 3 focuses on identifying patients

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						Recommendation 1.1.4 In those patients admitted with ACS there is an opportunity to screen those with a macrovascular risk factor in an environment that will allow ready testing. **<u>No recommended "threshold level"</u>** Although noted that evidence has shown fasting blood glucose and HbA1c could be used to predict diabetes there is not enough evidence to support a recommended threshold level. This needs clarification. Levels therefore vary between different studies for both HbA1c (>7% greatest prediction of diabetes mellitus) and FBG (>7mmol/l greatest predictor) and will affect numbers potentially diagnosed. Those missed will be those with FBG 6.1-6.9 mmol/l and with HbA1c measured between 5.6 and 6.9%. Other problems - in some hospitals HbA1C is not readily available taking a few days to be processed. Are we delaying the inevitable diagnosis, with an opportunity to screen with a test with high sensitivity in those at risk? **<u>Role of OGTT</u>** OGTT not as important if HbA1c and fasting blood glucose are "normal," but what is normal? Patients will be missed with	who are at high risk of progression to diabetes. The diagnosis of diabetes is outside the scope of this document and is covered by diabetes guidance (see NICE CG15 and CG66). Formal testing and diagnosis of diabetes will normally take place following referral to primary care following the acute episode.

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						impaired glucose tolerance and diabetes with normal HbA1c and/or fasting blood glucose, who by definition have already experienced one ACS event and have high risk for the future. Post discharge OGTT will mean that patients will be missed as there will be undoubtedly a percentage who will not attend for this test and not all will be under care of diabetologist for follow up	
SH	Welsh Endocrinology and Diabetes Society	14.04	Full	General		**WEDS overall response** All patients admitted with ACS with established or newly diagnosed Diabetes should be screened for other Diabetes complications during their inpatient stay e.g. retinopathy particularly if commenced on insulin.	Thank you for your comment. Follow-up care and screening for patients who have been diagnosed with diabetes should be covered by the diabetes guidance (CG66 and CG15).
SH	Welsh Endocrinology and Diabetes Society	14.05	Full	General		**WEDS overall response** Diabetic (new and established) patients admitted with ACS should be referred for review by a Diabetes inpatient team	Thank you for your comment. Follow-up care for patients who have been diagnosed with diabetes should be covered by the diabetes guidance (CG66 and CG15).

These stakeholder organisations were approached but did not respond:

Abbott Diabetes Care
Abertawe Bro Morgannwg (ABM) University NHS Trust
Aintree University Hospitals NHS Foundation Trust
Airedale NHS Foundation Trust
Allergan Pharmacueticals

Anglian Community Enterprise
Association of British Insurers (ABI)
Association of Clinical Pathologists
AstraZeneca UK Ltd
BMJ
Bristol-Myers Squibb Pharmaceuticals Ltd
British Heart Foundation
British Medical Association (BMA)
British National Formulary (BNF)
British Psychological Society
British Society for Paediatric Endocrinology and Diabetes (BSPED)
Care Quality Commission (CQC)
Connecting for Health
Countess of Chester Hospital NHS Foundation Trust
Department for Communities and Local Government
Department for Education
Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)
Department of Health, Social Services & Public Safety, Northern Ireland (DHSSPSNI)
Dudley Group of Hospitals NHS Trust
East and North Herts NHS Trust
Education for Health
Edwards Lifesciences
Federation of Ophthalmic & Dispensing Opticians (FODO)
Gloucestershire Hospitals NHS Trust
Gloucestershire LINk
Great Western Hospitals NHS Foundation Trust
Healthcare Improvement Scotland
Healthcare Quality Improvement Partnership
Humber NHS Foundation Trust
Institute of Biomedical Science
Institute Metabolic Science
Interhealth Canada
Johnson & Johnson Medical
Juvenile Diabetes Research Foundation
Kidney Research UK
Lambeth Community Health
Leeds PCT
LifeScan & Animas

Liverpool Community Health
Luton & Dunstable Hospital NHS Foundation Trust
Merck Sharp & Dohme Ltd
Ministry of Defence (MoD)
Mother and Child Foundation
National Patient Safety Agency (NPSA)
National Treatment Agency for Substance Misuse
NETSCC, Health Technology Assessment
NHS Clinical Knowledge Summaries Service (SCHIN)
NHS Pathways
NHS Plus
NHS Western Cheshire
Northumberland Hills Hospital, Ontario
Novartis Pharmaceuticals UK Ltd
Novo Nordisk Limited
Oxford Radcliffe Hospitals NHS Trust
PERIGON Healthcare Ltd
Pfizer Limited
Plymouth Hospitals NHS Trust
Poole and Bournemouth PCT
Primary Care Cardiovascular Society
Public Health Wales
RioMed Ltd.
Rotherham NHS Foundation Trust
Royal Brompton & Harefield NHS Foundation Trust
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of General Practitioners Wales
Royal College of Midwives
Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health
Royal College of Pathologists
Royal College of Physicians London
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons of England
Royal Pharmaceutical Society of Great Britain
Royal Society of Medicine

Royal United Hospital
Sacyl
Sanofi-Aventis
Scottish Clinical Biochemistry Managed Diagnostic Network
Scottish Intercollegiate Guidelines Network (SIGN)
Scottish Nutrition & Diet Resources Initiative
Sheffield Children's NHS Foundation Trust
Sheffield Teaching Hospitals NHS Foundation Trust
Social Care Institute for Excellence (SCIE)
Society for Acute Medicine
Society of Chiropodists & Podiatrists
Solent Healthcare
South Asian Health Foundation
South Staffordshire PCT
South Tees Hospitals NHS Trust
Trafford NHS Provider Services
UCLH NHS Foundation Trust
UK Clinical Pharmacy Association (UKCPA)
UK National Screening Committee
UK Ophthalmic Pharmacy Group
United Kingdom Clinical Pharmacy Association (UKCPA)
Verity - The PCOS Self Help Group
Welsh Assembly Government
Welsh Scientific Advisory Committee (WSAC)
Western Health and Social Care Trust
Wirral University Teaching Hospital NHS Foundation Trust
Worcestershire PCT
York Teaching Hospital NHS Foundation Trust