1. Background information

CG 66 Guideline issue date: May 2008
CG87 Guideline issue date: May 2009
Review date for CG66 & CG87: 2011
National Collaborating Centre: NCGC

2. Consideration of the evidence

Literature search

From initial intelligence gathering including a high-level randomised control trial (RCT) search (run from the cut off point of the original guideline in 2007, to 28th January 2011), 4324 papers were identified. 590 of these were directly relevant to the guideline scope and remit and these references are predominately related to the following ten clinical areas within the guideline:

- Patient education
- Lifestyle/ non-pharmacological management
- Glucose control levels
- Self-monitoring of plasma glucose

NICE consultation document (CG66 & CG87): Type 2 diabetes: the management of type 2 diabetes

1-14 June 2011
- Oral glucose control therapies (1): metformin, insulin secretagogues and acarbose
- Oral glucose control therapies (2): other oral agents and exenatide (DPP-4 inhibitors (sitagliptin, vildagliptin), Thiazolidinediones (pioglitazone, rosiglitazone\(^1\)), GLP-1 mimetic (exenatide))
- Glucose control: insulin therapy (Oral agent combination therapy with insulin and insulin therapy)
- Cardiovascular risk estimation
- Management of blood lipid levels (Statins and ezetimibe, Fibrates, Nicotinic acid)
- Anti-thrombotic therapy

37 questions were developed in the original guideline and relate to the clinical areas above. Qualitative feedback from other NICE departments and the views expressed by the Guideline Development Group (GDG) are also reported. The results of the above are summarised in Table 1. All references identified through the initial intelligence gathering, a high-level RCT search and those derived from the GDG can be viewed in Appendix A.

\(^1\) NICE has temporarily withdrawn its recommendations on the use of rosiglitazone in this guideline due to the European Medicines Agency (EMA) concluding that the benefits of rosiglitazone no longer outweigh its risks and the marketing authorisation has been suspended across the European Union (EU).
### Table 1: Summary of evidence

<table>
<thead>
<tr>
<th>Specific clinical area</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical area 1: Patient Education</td>
<td>Through the intelligence gathering (including a high level RCT literature search) 43 papers 10,12-14,19,23,34,72,92,106,113,121,130,145,166,166,188,222,223,238,255,297,305,312,340,372,375,377,379,397,420,430,439,487,488,498,508,521,524,549,550,567,570,592 relevant to the clinical area / recommendations were identified.</td>
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</tbody>
</table>

**CG66 Clinical question:** Are patient education models effective for people with Type 2 Diabetes?

**Recommendation 1.1.4**

Offer group education programmes as the preferred option. Provide an alternative of

The high level RCT search found 16 14,23,113,130,222,223,238,255,312,375,488,498,508,521,549,550,570 papers relevant to the question and current recommendation. There were 13 RCTs and the rest were systematic reviews looking at different educational interventions.

Of note:

- In the 2005 Cochrane review 130, group based training programmes were found to improve diabetes control and knowledge in the short and long term, with a reduced need for medication
- Peer telephone support may only be of value to some patients 113

No new evidence was identified which would change the direction of current guideline recommendations.
The Diabetes 1:1 structured education programme, showed diabetes-related distress and confidence to self-care to slightly improve with the use of structured education and a manual. However, there was no change in glycaemic control.  

The identified evidence does not change the direction of current guideline recommendations.

### Clinical area 2: Lifestyle management/ non pharmacological management

<table>
<thead>
<tr>
<th>Specific clinical area</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
</tr>
</thead>
</table>
**CG66 Clinical question:** Which forms of dietary advice are effective treatments for people with Type 2 diabetes?

| Recommendations | The high level RCT search found 32,35,36,40,74,76,122,160,180,224,260,263,307,328,334,365,404,411,424,440,509,511,531,548,552,557,559,582,583,586,599,21,50,128,129,155,161,205,219,259,348,349,395,417,418,427,437,500,510,525,584,590,601 papers looking at dietary interventions covering low glycaemic, low fat and high mono unsaturated fat diets, to the use of supplements such as cinnamon and omega 3 oils for weight loss and better glucose control. The evidence identified consisted of 10 systematic reviews and 21 RCTs. No studies were identified that did not support the recommendations in the type 2 diabetes guideline.

The identified evidence does not change the direction of current guideline recommendations. |
| No new evidence was identified which would change the direction of current guideline recommendations. |

**Clinical area 3: Glucose control levels**

<table>
<thead>
<tr>
<th>Specific clinical area</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Through the intelligence gathering (including a high level RCT literature search) 6,8,67,84,105,110,150,183,233,249,258,276,294,325,352,354,356,366,372,414,449,458,585,594,597 relevant to the clinical</td>
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</table>

NICE consultation document (CG66 & CG87): Type 2 diabetes: the management of type 2 diabetes

1-14 June 2011
area / recommendations were identified.

**CG66 Clinical question:** In people with Type 2 diabetes, what should be the target value for HbA$_{1c}$?

| Recommendations | The high level RCT search found 25 papers relevant to the question and current recommendation. The target of HbA$_{1c}$ needs to be reviewed in light of recently published conflicting evidence highlighting concerns about intensive glycaemic control in some groups and its association with an increased mortality with treatment to lower HbA$_{1c}$.

Of note:

- Two meta-analyses and a systematic review have been published looking at glucose control. A 2009 meta-analysis$^{449}$ found that intensive glucose control significantly reduced coronary events without an increased risk of mortality when compared to standard glycaemic control. The CONTROL writing group$^{105}$ found that intensive glucose therapy resulted in a reduction in major macrovascular events but increased major hypoglycaemic episodes. A systematic review$^{294}$ on cardiovascular outcomes and type 2 diabetes found intensive glucose control to only reduce the risk for some cardiovascular disease outcomes (for example, nonfatal myocardial infarction). It was not found to decrease the risk of cardiovascular death or all-cause mortality, and increased the risk for severe hypoglycaemia.

New evidence was identified which may change the direction of current guideline recommendations. |
Some of the RCTs which underpin the systematic reviews:

- In the ACCORD study, intensive therapy (targeting a glycated haemoglobin level below 6.0%) for 3.5 years compared to standard therapy (targeting a level from 7.0 to 7.9%) was associated with a higher mortality and did not significantly reduce major cardiovascular events.
- The ADVANCE study demonstrated a reduction in HbA1c to 6.5% decreased cardiovascular events (relative reduction of 10%, major and microvascular events).
- In the VADT study on veterans with poorly controlled type 2 diabetes, there was no significant effect on major cardiovascular events, death or microvascular complications (apart from progression of albuminuria p=0.01).
- UKPDS trial on intensive glucose control found that after 10 years there continued to be a reduction in microvascular risk, risk of an myocardial infarction and all cause mortality.

Secondary analyses of note:

- Three secondary analyses on the ACCORD trial found the following key issues: that the results cannot exclude the role of chance, the need to identify low versus high risk groups who may have different glucose level targets, the connection between hypoglycaemia and cardiovascular risk.
- The Currie study\textsuperscript{110} which examined two cohorts of patients looked at the association between HbA\textsubscript{1c} and survival. A U-shaped relationship was demonstrated with an HbA\textsubscript{1c} level of 7.5% having the lowest hazard ratio. Low and high mean HbA\textsubscript{1c} levels were associated with a higher all-cause mortality and cardiac events.

A NICE guideline for hyperglycaemia in patients with acute coronary syndrome\textsuperscript{383} is currently out for consultation. The recommendation for diabetic patients presenting with acute coronary syndrome and hyperglycaemia is:

- Do not routinely offer intensive insulin therapy to manage hyperglycaemia in patients admitted to hospital for an acute coronary syndrome (ACS).

Although the evidence has been reviewed in the context of ACS, this would not necessarily cover the primary prevention of micro and macrovascular events in patients with type 2 diabetes.

There is conflicting evidence surrounding the HbA\textsubscript{1c} recommended level and it is felt that the new evidence identified would warrant an update of these recommendations.

The identified evidence may change the direction of current guideline recommendations.
### Clinical area 4: Self-monitoring of plasma glucose

<table>
<thead>
<tr>
<th>Specific clinical area</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
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<tbody>
<tr>
<td></td>
<td>Through the intelligence gathering (including a high level RCT literature search) 40 papers relevant to the clinical area / recommendations were identified.</td>
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</table>

**CG66 Clinical question:** Is self-monitoring effective for blood glucose control in patients with Type 2 diabetes?

**Recommendations**

1.4.1 - 1.4.3  

The high level RCT search found 40 papers relevant to the question and current recommendation. Eleven systematic reviews were identified, most of which demonstrated a limited effect on glycaemic control with the self-monitoring of blood glucose (SMBG) for non-insulin using individuals with diabetes.

**Of note:**

- In the DiGEM trial [168], there was no significant improvement in glycaemic control when SMBG compared to usual care, for non-insulin-treated patients. This included with or without education on how to incorporate the readings into self-care. It also concluded that it was not cost-effective.

New evidence was identified which may change the direction of current guideline recommendations.
In a 2010 Health Technology Assessment, SMBG was also shown to have limited clinical effectiveness in non-insulin managed patients with type 2 diabetes and is therefore thought not to be cost-effective. SMBG may be more effective with appropriate education and if patients can self adjust their medication in response to the glucose readings.

NHS Diabetes 2010, provide full summaries of the evidence, that for many people with non-insulin treated diabetes, whether or not integrated with self-management education, the impact of SMBG may not be clinically important.

HbA1c targets need to be reviewed (see recommendations 1.3.1, 1.3.3-1.3.6).

Due to the new evidence demonstrating SMBG to have limited effectiveness and additional associated costs, for patients with non-insulin type 2 diabetes; an update of the guideline’s recommendation is suggested.

The identified evidence may change the direction of current guideline recommendations.
## Clinical area 5: Oral glucose control therapies (1): metformin, insulin secretagogues and acarbose

<table>
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<tr>
<th>Specific clinical area</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
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<tbody>
<tr>
<td></td>
<td>Through the intelligence gathering (including a high level RCT literature search) 62 studies relevant to the clinical area / recommendations were identified.</td>
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</table>

### 1.5.1 Metformin

**CG66 Clinical question:** Is metformin as monotherapy or in combination with oral antidiabetic drugs effective in the control of blood glucose in people with Type 2 diabetes compared to other oral antidiabetic drugs regimens or placebo?

**Recommendations 1.5.1.1- 1.5.1.6**

The high level RCT search found 28 papers relevant to the question and current recommendation of which there were 5 systematic reviews. The studies identified support the current recommendations. A recent systematic review looked at whether the use of metformin reduces a patient’s risk of cancer. From the meta-analysis of the data there was no significant reduction in the risk of cancer demonstrated. In comparison, another systematic review demonstrated a reduced risk of cancer incidence compared with other treatments in patients with diabetes.

No new evidence was identified which would change the direction of current guideline recommendations.
No new evidence was identified which would warrant an update of the guideline recommendations at this time.

The identified evidence does not change the direction of current guideline.

### Clinical area 6: Oral glucose control therapies (2): other oral agents and exenatide

<table>
<thead>
<tr>
<th>Specific clinical area</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
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</thead>
</table>
1.6.1 DPP-4 inhibitors (sitagliptin, vidagliptin)

CG87 Clinical question: What is the additional effect of adding a DPP-4 inhibitor to dual therapy compared with placebo?

CG87 Clinical question: What is the effect of using a DPP-4 inhibitor in combination with metformin when compared with a sulfonylurea added to metformin?

CG87 Clinical question: What is the effect of using a DPP-4 inhibitor in combination with a sulfonylurea when compared with a thiazolidinedione in combo with a sulfonylurea added to metformin? (no relevant studies were found in the CG87 literature search)

CG87 Clinical question: What is the effect of using a DPP-4 inhibitor in combination with a thiazolidinedione when compared with a sulfonylurea in combination with a thiazolidinedione? (no relevant studies were found in the CG87 literature search)

CG87 Clinical question: What is the effect of using a DPP-4 inhibitor in combination with metformin when compared with a thiazolidinedione in combination with metformin?

CG87 Clinical question: What is the effect of adding a DPP-4 inhibitor to dual oral therapy when compared with adding insulin to dual oral therapy?

CG87 Clinical question: What is the effect of adding a DPP-4 inhibitor to dual oral therapy when compared with adding a thiazolidinedione to dual oral therapy?

CG87 Clinical question: What is the effect of adding a DPP-4 inhibitor to triple oral therapy when compared with insulin plus metformin?

Recommendations

1.6.1.1-1.6.1.5

The high level RCT search found 58 papers relevant to the question and current recommendation. All the evidence identified looking at sitagliptin and No new evidence was identified which would change the direction of current guideline.
vitagliptin agreed with the current recommendations.

Of note:

- A new member of the class, saxagliptin is now available. Two RCTs\textsuperscript{133,268} were identified in the literature search which found saxagliptin when combined with metformin compared to sazagliptin or metformin treatments alone, demonstrated a statistically significant improvement across key glycaemic parameters. Another RCT\textsuperscript{245} found that the addition of saxagliptin to thiazolidinedione significantly improved glycaemic parameters compared to thiazolidinedione alone.

- Linagliptin another new member of the Gliptin Class in combination with metformin showed a significant reduction in HbA\textsubscript{1c} in patients taking metformin with uncontrolled type 2 diabetes compared to patients taking metformin and a placebo. There was no increased risk of hypoglycaemia or weight gain\textsuperscript{520}.

- An alogliptin RCT\textsuperscript{132} in patients with type 2 diabetes, demonstrated alogliptin to be safe and significantly improve glucose control compared to placebo. Another RCT\textsuperscript{465} showed alogliptin to improve glucose control when it was added to insulin treated patients with type 2 diabetes with or without background treatment with metformin. There was also no increased risk of hypoglycaemia or weight gain.

- An RCT\textsuperscript{415} looking at the addition of dutogliptin to patients on a background medication of metformin, a thiazolidinedione or metformin plus a thiazolidinedione
found it to improve glycaemic control compared to a placebo. Two doses were tested, with the higher dose (400mg) had a greater improvement in glucose control compared to 200mg. There are several DPP-4 drugs in development but no further details are known.

- A systematic review and economic evaluation[^563] on the newer agents for blood glucose control in type 2 diabetes found sitagliptin and vildagliptin had lower costs and side effects compared to glitazone, with similar effectiveness.

The recommendations would not be likely to change but may include adding in further members of the class.

The identified evidence does not change the direction of current guideline.

### 1.6.2 Thiazolidinediones (pioglitazone, rosiglitazone[^2])

**CG66 Clinical question:** Are the glitazones (pioglitazone and rosiglitazone) effective in the control of blood glucose in people with Type 2 diabetes either alone or in combination compared to other antidiabetic treatment regimens?

**CG87 Clinical question:** How safe are rosiglitazone and pioglitazone and do their safety profiles differ?

[^2]: NICE has temporarily withdrawn its recommendations on the use of rosiglitazone in this guideline due to the European Medicines Agency (EMA) concluding that the benefits of rosiglitazone no longer outweigh its risks and the marketing authorisation has been suspended across the European Union (EU). NICE consultation document (CG66 & CG87): Type 2 diabetes: the management of type 2 diabetes.
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>The high level RCT search found 47 papers relevant to the question and current recommendation. Following the withdrawal of rosiglitazone, papers including this treatment were excluded. All RCTs and systematic reviews supported the use of pioglitazone apart from one meta-analysis which found serious heart failure was increased by its use, although without an associated increase in mortality. Additional evidence to note:</th>
</tr>
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| 1.6.2.1 – 1.6.2.8 | - Changes in the price of pioglitazone, with its patent expiring soon will potentially result in 10-15% price reduction. It may then be the most cost-effective option as third line therapy, displacing the indication for insulin or DPP-4’s at this level. It may also be cost-effective as second line alongside sulfonylureas, and displacing the option of DPP-4’s in those at risk of hypoglycaemia.  
- The economic impact of the introduction of saxagliptin also needs to be considered.  
- The Food and Drug Administration (FDA) and the EMA (European Medicines Agency) has announced a malignancy review of pioglitazone which may impact the recommendations |

The recommendations need to be revised to formally account for the withdrawal of

New evidence was identified which may change the direction of current guideline recommendations.
rosiglitazone. In addition to this, the changes in prices and production of new treatments mean a health economic analysis should be undertaken to ensure the most cost-effective sequencing of oral pharmacological treatments.

The identified evidence may change the direction of current guideline and an update is felt to be warranted at this time.

### 1.6.3 GLP-1 mimetic (exenatide)

| Clinical question: Is exenatide effective in the control of blood glucose in people with Type 2 diabetes either alone or in combination compared to other antidiabetic treatment regimens? |
| CG66 Clinical question: What is the additional effect of adding a GLP-1 mimetic (exenatide) to dual therapy when compared with placebo? |
| CG87 Clinical question: What is the additional effect of adding a GLP-1 mimetic (exenatide) to metformin when compared with placebo? |
| CG87 Clinical question: What is the additional effect of adding a GLP-1 mimetic (exenatide) to a thiazolidinedione and a sulfonylurea compared with placebo? (no relevant studies were found in the CG87 literature search) |
| CG87 Clinical question: What is the effect of adding a GLP-1 mimetic (exenatide) versus insulin to dual therapy (metformin and a sulfonylurea)? |
| CG87 Clinical question: What is the effect of adding a GLP-1 mimetic (exenatide) versus thiazolidinediones to dual therapy (metformin and a sulfonylurea)? |
**CG87 Clinical question:** What is the effect of replacing insulin with a GLP-1 mimetic (exenatide)?

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>The high level RCT search found 31 papers relevant to the question and current recommendation. Most of the identified RCTs and systematic reviews support the recommendations. One systematic review did suggest the possible link of exenatide with acute pancreatitis. It was recommended that additional clinical trial data and in-depth case report analysis is needed for a complete evaluation. Additional evidence to note:</th>
</tr>
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<tbody>
<tr>
<td>1.6.3.1-1.6.3.3</td>
<td>- Since the NICE publication of (TA203), liraglutide needs to be included in the type 2 diabetes guidance</td>
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<td>- A study looking at once weekly exenatide compared with insulin glargine in patients with type 2 diabetes, found that the change in HbA1c at 26 weeks was greater in patients taking exenatide but at the expense of a higher dropout rate from adverse events. Once weekly exenatide has been licensed in Europe and the launch will be later on this year</td>
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<tr>
<td></td>
<td>- A study comparing liraglutide once a day and exenatide twice a day found liraglutide to have a greater improvement in glycaemic control and was generally better tolerated</td>
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<td></td>
<td>- A systematic review and economic evaluation on the newer agents for blood</td>
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New evidence was identified which may change the direction of current guideline recommendations.
glucose control in type 2 diabetes found exenatide to appear to be clinically and cost-effective when oral therapy has failed, as an alternative to starting insulin

New evidence has been identified which may change the direction of current guideline.

### Clinical area 7: Glucose control: insulin therapy

<table>
<thead>
<tr>
<th>Specific clinical area</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
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</table>
### 1.7.1 Oral agent combination therapy with insulin

**CG66 Clinical question:** Is insulin in combination with oral antidiabetic drugs effective in the control of blood glucose compared to insulin alone in people with Type 2 diabetes?

**CG87 Clinical question:** What is the additional effect of adding a pioglitazone to an insulin?

#### Recommendations

| 1.7.1.1 & 1.7.1.2 | A high level RCT search found 42 papers relevant to the question and current recommendation. Systematic reviews, one meta-analysis and several RCTs were identified which demonstrated the beneficial effects of different oral agents when used in combination with insulin. Additional evidence to note:  
- Sitagliptin has been approved in the EU for combination therapy with insulin  
- The drop in price of pioglitazone will change the cost-effectiveness of its use in combination  
- New drugs combining liraglutide and lixisenatide are heading for insulin combination licenses, which will have profound cost implications and it will need its cost-effectiveness reviewed. In 2014, albiglutide will have a similar impact. Taspoglutide is no longer in development. | New evidence was identified which may change the direction of current guideline recommendations. |

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NICE consultation document (CG66 & CG87): Type 2 diabetes: the management of type 2 diabetes

1-14 June 2011
In an RCT\textsuperscript{81} looking at twice daily exenatide in basal insulin (glargine) treated patients with type 2 diabetes, the addition of the exenatide injections led to an improvement in glycemic control without increased hypoglycemia or weight gain. Another RCT\textsuperscript{386} looking at the same combination of exenatide with insulin but in obese type 2 diabetics found very significant reductions in weight and the insulin doses required.

The evidence identified impacts on the cost-effectiveness of different treatment regimes and may therefore affect the choice of recommended oral agents to be used alongside insulin. Advice is also needed on the use of combined insulin and GLP-1 agonists. It is therefore felt that an update is warranted at this time.

New evidence was identified which may change the direction of current guideline recommendations.

### 1.7.2 Insulin therapy

| Recommendations 1.7.2.1 and 1.7.2.3 | A high level RCT search found 2 papers\textsuperscript{41,319} relevant to the question and current recommendation. Both studies report how patient willingness and empowerment can improve their glycaemic control. | No new evidence was identified which would change the direction |

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NICE consultation document (CG66 & CG87): Type 2 diabetes: the management of type 2 diabetes

1-14 June 2011
No new evidence was identified which may change the direction of current guideline recommendations.

**CG66 Clinical question:** Are long acting insulin analogues (insulin glargine (Lantus®)) effective in the control of blood glucose compared to NPH insulin, biphasic insulin regimes?

**CG66 Clinical question:** Are the biphasic insulin preparations (premixes) effective in the control of blood glucose compared to NPH in people with Type 2 diabetes?

**CG66 Clinical question:** Are the biphasic human insulin preparations effective in the control of blood glucose compared to biphasic analogue preparations in people with Type 2 diabetes?

**CG66 Clinical question:** Are multiple analogue insulin injection regimens effective (meal time and basal insulin) compared to basal insulin or biphasic insulin regimes?

**CG66 Clinical question:** What methods of delivery of insulin therapy are effective at improving clinical outcomes in Type 2 diabetes?

**CG87 Clinical question:** Does the effectiveness differ between NPH insulin and a long-acting insulin analogue (insulin glargine, insulin detemir) when a basal insulin is indicated?

**CG87 Clinical question:** What is the effect of using insulin glargine compared with insulin detemir?

**CG87 Clinical question:** What is the additional effect of adding a pioglitazone to an insulin?

**Recommendations**

<table>
<thead>
<tr>
<th>1.7.2.4 &amp; 1.7.2.5</th>
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<tbody>
<tr>
<td>The high level RCT search found 72</td>
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<tr>
<td>45,56,86,112,117,156,164,208,251,256,264,271,273,310,350,364,369,438,446,448,455,492,493,533,538,560,563</td>
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</table>

New evidence was identified which may change the direction of current guideline recommendations.
papers relevant to the questions and current recommendations. There were many RCTs and systematic reviews found which tended to favor glargine for reducing nocturnal hypoglycaemia, with one meta-analysis\textsuperscript{251} finding a 50% risk reduction compared to NPH. Of note:

- The European Medicines Agency\textsuperscript{163} released an update on the safety of glargine on the 29\textsuperscript{th} June 2009 in response to its potential association with cancer. They concluded that “the available data does not provide a cause for concern and that changes to the prescribing advice are therefore not necessary”\textsuperscript{163} Since then a nested case control study (published in 2010) has found a possible association between cancer and higher glargine doses\textsuperscript{350}

- A recent review of long-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness\textsuperscript{533} has been published which will have a health economic impact. HbA\textsubscript{1c} was not found to be significantly different between insulin glargine or detemir compared with neutral protamine Hagedorn. Glargine resulted in lower nocturnal hypoglycaemia but no difference in severe hypoglycaemia compared with neutral protamine Hagedorn. Possible equality considerations include individual patient choice versus maximizing health
benefit across a population through efficiency

- A systematic review and economic evaluation\(^5\) on the newer agents for blood glucose control in type 2 diabetes found that NPH should be first line therapy of insulin in type 2 diabetes as per the current NICE guidance. This is based on higher costs and limited clinical benefit of glargine and detemir

- New insulin degludec and a new premix degludec plus are not licensed yet but are due to be launched in approximately 2 years. It is unclear whether it will affect the recommendations as the data is too immature at present. A judgment will have to be made on the health economic impact when further data becomes available

New cost-effectiveness evidence is emerging which could alter the recommendations for the first line insulin therapy and therefore an update is deemed to be warranted.

The identified evidence may change the direction of current guideline recommendations.

**Clinical area 8: Cardiovascular risk estimation**

NICE consultation document (CG66 & CG87): Type 2 diabetes: the management of type 2 diabetes

1-14 June 2011 24
<table>
<thead>
<tr>
<th>Specific clinical area</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
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<tbody>
<tr>
<td></td>
<td>Through the intelligence gathering (including a high level RCT literature search) 16 studies relevant to the clinical area / recommendations were identified.</td>
<td></td>
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<tr>
<td>CG66 Clinical question</td>
<td>Which arterial risk tables, equations or engines for calculation of arterial risk are most predictive of arterial disease in people with Type 2 diabetes?</td>
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</tbody>
</table>
| Recommendation 1.9.1 & 1.9.2 | The high level RCT search found 7 papers relevant to the current recommendation. One RCT focusing on a multifactorial intervention for screening detected Type 2 diabetes, decreased cardiovascular risk factor levels significantly without reducing quality of life. Another RCT found that intensive monitoring of cardiovascular risk factors versus usual care had no significant difference in cardiovascular risk after one year. Of note:  
  - In light of the publication of a study on the use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies; a review of the evidence should be carried out, although this is unlikely to change the current guideline recommendations. | New evidence was identified which may change the direction of current guideline recommendations.          |

NICE consultation document (CG66 & CG87): Type 2 diabetes: the management of type 2 diabetes
recommendation. Some of the key findings from the paper are that, antihypertensives have a similar effect in reducing CHD and stroke events (apart from an increased effect of beta blockers immediately after a myocardial infarction and calcium channel blockers for stroke) and that it should potentially be offered to people over a certain age rather than measuring everyone and treating only a few.

- The UKDPS risk engine\(^\text{102}\) has recently been updated to estimate the cardiovascular disease risk in patients with type 2 diabetes.

New evidence has emerged which may impact on the current recommendations therefore, an update of these recommendations is suggested.

### Clinical area 9: Management of blood lipid levels

<table>
<thead>
<tr>
<th>Specific clinical area</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
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<tbody>
<tr>
<td></td>
<td>Through the intelligence gathering (including a high level RCT literature search) 32 studies relevant to the clinical area / recommendations were identified.</td>
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</table>

#### 1.10.1 Statins and ezetimibe

NICE consultation document (CG66 & CG87): Type 2 diabetes: the management of type 2 diabetes

1-14 June 2011
### CG66 Clinical question: Are statins effective in improving lipid profiles and other outcomes compared to other treatments or placebo in people with Type 2 diabetes?

**Recommendations 1.10.1.2-7**

<table>
<thead>
<tr>
<th>The high level RCT search found 24 papers relevant to the question and current recommendation. One RCT found that in CHD or type 2 diabetic patients previously on simvastatin or atorvastatin who continued to have high LDL-C levels, changing treatment to the combination of simvastatin and ezetimibe was more effective in achieving a LDL-C target of &lt; 2.5 mmol/L than doubling the simvastatin dose. In contrast to recommendation 1.10.2.4 an RCT found that compared to simvastatin alone, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke. Other evidence to note:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- The Medicines and Healthcare products Regulatory Agency (MHRA) issued an alert in May 2010; there is an increased risk of myopathy at a high dose of simvastatin (80mg)</td>
</tr>
<tr>
<td>- The findings from the SEARCH trial (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) suggest that lowering cholesterol may be achieved more safely using lower doses of more potent statins rather increasing the dose of simvastatin</td>
</tr>
</tbody>
</table>

New evidence was identified which may change the current guideline recommendations.
The role of colesevelam (a blinding resin) will need to be considered alongside statins and ezetemibe. A pooled analysis of RCTs\textsuperscript{272} demonstrated colesevelam to reduce HbA1c and LDL-C-compared to placebo which occurred irrespective of its combination with metformin, insulin, or sulfonylurea-based therapy.

Atorvastatin comes off patent later on this year. Depending on the price, it may displace simvastatin in terms of cost-effectiveness and lower toxicity which will impact on the guidelines quite significantly.

New evidence has been identified which may affect the first line choice of statin and the dose at which it is administered. In light of this, it is felt that an update of the guideline recommendations is warranted.

The identified evidence may change the direction of current guideline recommendations.

1.10.2 Fibrates

NICE consultation document (CG66 & CG87): Type 2 diabetes: the management of type 2 diabetes

1-14 June 2011
**CG66 Clinical question:** Are fibrates effective in improving lipid profiles and other outcomes compared to other treatments or placebo in people with Type 2 diabetes?

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>The high level RCT search found 77,169,235,242,279,292,322 papers relevant to the question and current recommendation. The evidence was conflicting:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.10.2.1 - 1.10.2.4</td>
<td>- A systematic review(^{169}) on the management of mixed dyslipidemia in patients with or at risk for cardiovascular disease: a role for combination fibrate therapy, found that fenofibrates may be useful</td>
</tr>
<tr>
<td></td>
<td>- In the FIELD study(^{292}), the use of fenofibrate resulted in reduced total cardiovascular events and reduced some microvascular complications</td>
</tr>
<tr>
<td></td>
<td>- As per 1.10.1 Statins and ezetimibe evidence; the combination of fenofibrate and simvastatin was not found to reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared to simvastatin alone(^{7})</td>
</tr>
<tr>
<td></td>
<td>- No advantage was demonstrated in an RCT(^{242}) looking at the effect of fenofibrate on carotid intima-media thickness (IMT) for IMT, augmentation index, or biomarkers of inflammation and endothelial function</td>
</tr>
<tr>
<td></td>
<td>As there are studies demonstrating a benefit and others no additive effect of fibrates, it is suggested that the evidence is reviewed to come to a firm conclusion and to update the</td>
</tr>
</tbody>
</table>

New evidence was identified which may change the direction of current guideline recommendations.
<table>
<thead>
<tr>
<th>1.10.3 Nicotinic acid</th>
<th>The high level RCT search found no papers relevant to the question and current recommendation. A focused search was carried out on a new agent Tredaptive which is a combination of nicotinic acid and laropiprant. 50 papers were identified. There were no trials specifically on diabetic populations. One study had a mixed population of diabetic patients and healthy participants which looked at platelet reactivity. It is suggested that further research on tredaptive is needed using a diabetic population. No conclusive evidence has been found to support its use in patients with Type 2 diabetes; therefore it will not change the recommendations at this point in time.</th>
</tr>
</thead>
</table>

Clinical question: Are nicotinic acid derivatives effective in improving lipid profiles and other outcomes compared to other treatments or placebos in people with Type 2 diabetes?

Recommendation 1.10.3.1

Do not use nicotinic acid preparations and derivatives routinely for people with type 2 diabetes. They may have a role in a few people who...
are intolerant of other therapies and have more extreme disorders of blood lipid metabolism, when managed by those with specialist expertise in this area.

Clinical area 10: Anti-thrombotic therapy

<table>
<thead>
<tr>
<th>Specific clinical area</th>
<th>Summary of evidence</th>
<th>Relevance to guideline recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Through the intelligence gathering (including a high level RCT literature search) 9 studies relevant to the clinical area / recommendations were identified.</td>
<td></td>
</tr>
</tbody>
</table>

CG66 Clinical question: Does aspirin prevent vascular disease in people with Type 2 diabetes?

Recommendations 1.11.1-1.11.3

The high level RCT search found 6 papers relevant to the question and current recommendations:

New evidence was identified which may
| New evidence from recent trials impact on the recommendation for the use of aspirin by demonstrating that it is not effective in reducing cardiovascular events.\(^{47,126,403}\) | change the direction of current guideline |
| In a systematic review and meta-analysis, the effect of aspirin on myocardial infarction, stroke and mortality was the same for those with and without diabetes.\(^{85}\) |
| The MHRA (Medicines and Healthcare products Regulatory Authority) issued a drug safety update in October 2009\(^{523}\) for the use of aspirin in primary prevention which it is not currently licensed for: “the balance of benefits and risks should be considered for each individual, particularly the presence of risk factors for vascular disease (including conditions such as diabetes) and the risk of gastrointestinal bleeding”. The risk: benefit ratio is different for patients with type 2 diabetes. This could be incorporated into the type 2 diabetes guideline if it was to be updated |
| One study\(^{24}\) looked patients with Type 2 diabetes who had a sub-optimal response to clopidogrel and it was found that they had enhanced platelet procoagulant activity compared to those with an optimal response suggesting some patients may require higher doses for it to be beneficial. There is currently TA guidance on the use of clopidogrel but this is for the secondary prevention of cardiovascular events (see TA210 in the NICE related guidance section below |

New evidence has been identified which may change the recommendations in type 2
<table>
<thead>
<tr>
<th>diabetes guideline.</th>
</tr>
</thead>
</table>

NICE consultation document (CG66 & CG87): Type 2 diabetes: the management of type 2 diabetes

1-14 June 2011
GDG identification of research currently in progress

Several ongoing clinical trials and research (some publication dates unknown and references not provided) were identified by the GDG members:

- In 2009, NHS Diabetes commissioned an evaluation for the self-monitoring of blood glucose. It is unclear when this work will be completed. 394
- Individual patient data meta-analysis of the six major self monitoring of blood glucose trials will be reported in Summer 2011
- For some patient groups, annual testing intervals for HbA1c are reasonable (papers are submitted for publication, no references were given)
- Systematic reviews of metformin therapy focusing on efficacy in reducing HbA1c over time has been submitted for publication. This will provide additional evidence to underpin recommendations
- The type 2 diabetes pharmacological agents is fast moving field and there are always publications of studies on new agents. Examples include; GLP-1 mimetics, SGLT2 inhibitors (Dapagliflozin TA is currently being scoped, insulin degludec, new DPP-4s
- The 2012 ORIGIN (insulin glargine reports)195 are due for publication soon
- A new member of class (Linagliptin) may be licensed later this year. Minor changes to the recommendations may be needed as it can probably be used if renal impairment is present. Alogliptin is also due to be licensed soon. There is emerging evidence of infection risk
- A major trial, ASCEND (A Study of Cardiovascular Events in Diabetes)2 looking at whether aspirin +/- omega-3 fatty acids compared to placebo +/- olive oil reduce the risk of cardiovascular events in patients with type 1 or type 2 diabetes (without a previous history/clinical signs of arterial disease) should have been completed
in March 2011. The results are awaited. To establish further evidence however, in the interim the recommendations may need to be revised and require a review of all the evidence.

In conclusion, new future emerging evidence was identified that may impact current guideline recommendations.

**Guideline Development Group and National Collaborating Centre perspective**

A questionnaire was distributed to the Guideline Development Group (GDG) members to consult them on the need for an update of the guideline based on the original scope. Eight responses were received with respondents highlighting the following in addition to points raised in the summary in Table 1:

**Patient Education (recommendations 1.1.1-1.1.6)**

- The importance of a relaxed and friendly environment for the delivery of patient education needs to be emphasized in the guidance
- Patients need to be made aware that in the long term diet and oral medications may not be sufficient to control blood sugar levels and there may be a progression to the use insulin
- Although it is not specific to the diabetic population, reinforcing the role of education and the prevention of economic losses from unused or wasted medication could be highlighted
- More guidance should be given to patients on the possible side effects of medication prior to commencing it

**Glucose control levels (recommendations 1.3.1-1.4.4)**

- HbA\(_1c\) target levels and its relation to adverse effects such as hypoglycaemia

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• The extensive number of systems for self-monitoring could be reviewed to make suggestions to localities to restrict options to a few recommended devices as there are so many to choose from

• HbA$_{1c}$ values are given in % units, which are currently recommended for replacement by mmol/litre over the next year or so. Changes to the guideline will need to be made however, this would not require a GDG for implementation

Oral glucose control therapies (1): metformin, insulin secretagogues and acarbose (recommendations 1.5.1.1 - 1.5.4.1)

• Metformin sections need to be brought together and reorganized

Oral glucose control therapies (2): other oral agents and exenatide (recommendations 1.6.1.1 - 1.6.3.3)

• A cost-effectiveness review for the once weekly exenatide (TA Diabetes (type 2) – exenatide (prolonged release) is in progress) will need to be carried out as it will have different costs and efficacy compared to twice weekly exenatide. It has not been marketed yet as it is awaiting an SPC agreement

• New GLP-1 agonists are in the pipeline. When is it assumed a class effect or do all of the drugs need to go through a technology appraisal? (see Table 1)

• More data is due to be coming out on fracture risk with pioglitazone. This will be covered in its class review (see Table 1)

Glucose control: Insulin therapy (recommendations 1.7.1.1 – 1.7.3.3)

• Implementation issue: many of the recommendations, care planning and use of Neutral Protamine Hagedorn (NPH) insulin in particular, are poorly executed

• Combined use of long-acting GLP1 agonists and basal insulin is awaiting licensing (see Table 1)

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Blood pressure therapy (recommendations 1.8.1-1.8.13)

- Aliskirin has been launched as a new class for blood pressure therapy but thought not to have an impact on the current recommendations (see the update of the hypertension guideline CG34, due to be published August 2011)
- Angiotensin 2 receptor blockers Losartan and Valsartan which are used for hypertension and diabetic kidney disease are due to come off patent in 2010/11 (see Table 1). This will affect their cost-effectiveness compared to ACE inhibitors

Cardiovascular risk estimation (recommendations 1.9.1-1.9.4)

- There are more competing risk score regimes becoming available which suggests that the methods of risk assessment may need to be reappraised

Management of blood lipid levels (recommendations 1.10.1.1-1.10.4.2)

- Tredaptive (a combination of nicotinic acid and laropiprant) needs to be considered since its approval by the European Medicine Agency (EMA) in 2008 (see Table 1)

Kidney and Eye damage (recommendations 1.12.1-1.13.9)

- There have been many publications on diabetic kidney disease as well as retinopathy. See the blood pressure therapy section above on the use of angiotensin 2 receptor blockers

Nerve damage (recommendations 1.14.1-1.14.5.5)

- The guideline needs to be updated to ensure consistency with the NICE guidance on neuropathic pain (CG96)

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Other

- Guidance for pregnant women (see CG63: Diabetes in pregnancy – management of diabetes and its complications from pre-conception to the post natal period which is due-gone to be updated) and footcare (currently under review for update, CG10: Type 2 diabetes: the prevention and management of foot problems) should be incorporated into the one guideline for type 2 diabetes.

- New guidelines are due to be published in 2011 from the Joint British Societies and should be considered. No further information is available.

- The NHS ‘Year of Care’ programme\(^3\) which focuses on the commissioning of the right services and care planning for patients with long term conditions to enable self management and personalised care should be incorporated into the type 2 diabetes guideline. This will have a health economic impact. The results of the 3 pilots which finished in August 2010 should be reviewed before an economic appraisal and model is built. An external evaluation of the programme should be published in June 2011.

- There is the potential to incorporate annual insulin pen inspections into the Quality Standard (Diabetes in adults quality standard).

- The following audits were identified:
  - National Diabetes Audit \(^1\)
  - National Inpatient audit \(^392\)
  - A safe use of Insulin resource \(^393\)
  - Sixth Diabetes E report \(^392\)
  - Improving the diagnosis, classification and coding of diabetes \(^391\)
  - ABCD nationwide exenatide audit

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Of note; Inpatient care was excluded from the previous CG66 however, inpatient insulin prescribing has been highlighted as a safety issue and potential risk area by a GDG member.

Additional areas identified which were outside the scope

- The role of screening
- The diagnosis of diabetes; cost effectiveness of fasting blood glucose (FBG) versus HbA$_{1c}$
- Bariatric surgery referrals (see CG43: Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children)
- Management of type 2 diabetes in children where is it different to adults

All of the GDG members including the Chair and Clinical Advisor found at least one area of the type 2 diabetes guideline that they felt has sufficient evidence to warrant an update of the guideline.

Implementation and post publication feedback

In total, 223 enquiries were received from post-publication feedback, most of which were routine. 21 queries were received mainly relating to corrections to the wording of the guideline and concerns over the cholesterol recommendations. Other complex queries included:

- Concerns over BMI and the use of exanatide
- Units of HbA$_{1c}$ (not an evidence issue)
- Definition of markedly hyperglycaemic
- Optometry referrals
- Cost implications of implementing CG66, type 2 diabetes guideline.

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Implementation feedback reported different issues amongst organisations:

- It is suggested that guidance relevant to children’s services should be clearly indicated. A concern was highlighted around the use of structured education
- Guidance need to take account of linked community and social services in the future
- Preventative and non surgical interventions are underdeveloped
- Original type 2 diabetes guideline was challenging to implement because it had an unusually high financial impact on the trust
- Difficulty in implementing some of the guidance because when it was written it didn’t have a mental health trust in mind
- Increased admissions seen with hypoglycaemia and concern that it is linked to the lower HbA1c targets and anomaly between the QOF indicator and NICE guideline
- Suggested that NICE look at betaketones via near patient testing devices
- Links to Osteoarthritis guideline (CG59) asking for clarification on why certain treatments are only offered to those over 45 years of age
- A pathway around podiatry would be helpful
- Incorporation of more standards related to children’s care
- Routine activity data has demonstrated an increase in pharmacological treatments for type 2 diabetes, which was greater than anticipated in 2009. The reasons for this may include an increase in the prevalence of diabetes, changes in prescriptions or that lifestyle changes and education programmes need to be strengthened. The increase in the use of metformin and sulphonylureas are in line with the NICE guidance. The NHS atlas of variation in healthcare showed considerable variations in health spending across England.
The evidence identified through post publication enquiries suggest that the guideline should be updated.

**Relationship to other NICE guidance**

The following NICE guidance is related to CG87:

<table>
<thead>
<tr>
<th>Guidance</th>
<th>Review/ publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG15: Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults, 2010</td>
<td>Review: July 2011</td>
</tr>
<tr>
<td>CG34: Hypertension: management of hypertension in adults in primary care, 2006</td>
<td>Update due to be published August 2011</td>
</tr>
<tr>
<td>CG Hyperglycaemia in acute coronary syndromes: management of hyperglycaemia in people with acute coronary syndromes (in development)</td>
<td>Publication: October 2011</td>
</tr>
<tr>
<td>CGE: Management of type 2 diabetes: retinopathy</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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| CGF: Management of type 2 diabetes: renal disease, prevention and early management (replaced by CG66), 2002 | N/A |
| CGG: Management of type 2 diabetes: management of blood glucose (replaced by CG66), 2002 | N/A |
| CGH: Management of type 2 diabetes: management of blood pressure and blood lipids (replaced by CG66), 2002 | N/A |
| TA53: Diabetes (types 1 and 2) – long acting insulin analogues, 2002 | Review: TBC |
| TA60: Diabetes (types 1 and 2) – patient education models, 2003 (reviewed 2006, partially updated by CG66 and CG87) | Review: TBC |
| TA63: Glitazones for the treatment of type 2 diabetes (replaced by CG66), 2003 | N/A |
| TA203: Diabetes (type 2) – Liraglutide, 2010 | Review: May 2012 |
| TA in progress: Diabetes (type II) exenatide (prolonged release) | Publication: February 2012 |
| TA in progress: Diabetes – buccal insulin | Publication: TBC |
| TA in progress: Diabetic macular oedema | Publication: TBC |
| TA in progress: Macular oedema (diabetic) – fluocinolone acetonide intravitreal implant | Publication: TBC |
| TA in progress: Macular oedema (diabetic) – pegaptanib sodium | Publication: TBC |
| TA in progress: Macular oedema (diabetic) – ranibizumab | Publication: TBC |
| TA in progress: Dapagliflozin for the treatment of type 2 diabetes | Publication: TBC |
| Public health guidance: preventing the progression from pre-diabetes, in progress | Publication: May 2012 |
| QOF indicator NM13: The percentage of patients with diabetes with a record of a foot examination and risk classification: 1) low risk (normal sensation, palpable pulses), 2) increased risk (neuropathy or absent pulses), 3) high risk (neuropathy or absent pulses plus deformity or skin changes or previous ulcer) or 4) ulcerated foot within the preceding 15 months, August 2010 | Review: TBC |
| QOF indicator NM12: The percentage of patients with diabetes with a record of testing of foot sensation using a 10g monofilament or vibration (using biothesiometer or calibrated tuning fork), within the preceding 15 months, August 2010 | Review: TBC |

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Anti-discrimination and equalities considerations

No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation.

The original guideline provided advice for the management of type 2 diabetes in adults, but did not cover the prevention and management of foot problems (there is separate guidance CG10 and CG119 for inpatient management of people with diabetic foot ulcers and infection), primary prevention of type 2 diabetes and screening or problems which do not arise primarily from diabetes in particular patient groups who may also have diabetes.

Conclusion

From the evidence and intelligence identified through the process, it suggests that some areas of the guideline may need updating at this stage, particularly in relation to:

- Target HbA$_{1c}$ levels and units
- Self monitoring of blood glucose
- Pharmacological intervention evidence updates including the effect of drugs coming off patency and newly licensed medication and their health economic impact:
  - The use of aspirin for the primary prevention of cardiovascular events
  - New members of the Gliptin Class (linagliptin, saxagliptin, alogliptin)
  - Simvastatin maximum dose and concurrent use of other lipid lowering medications
  - Pioglitazone and atorvastatin are both due to come off patency later this year
3. Review recommendation

The guideline should be considered for an update at this time.

National Clinical Guidelines Centre
June 2011
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