Key Therapeutic Topics

Medicines management options for local implementation

Draft for consultation: September 2014
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Laxatives

**Options for local implementation**

- Review and, if appropriate, revise prescribing of laxatives for adults to ensure that they are prescribed routinely only for the short-term treatment of constipation when dietary and lifestyle measures have proven unsuccessful or if there is an immediate clinical need.
- For children and young people, laxatives should be prescribed in line with the NICE clinical guideline on **constipation in children and young people**.
- The NICE clinical guideline on **the use of strong opioids in palliative care in adults** advises that laxatives should be prescribed for everyone starting strong opioids.

**Evidence context**

As discussed in the MeReC Bulletin on **the management of constipation**, most cases of mild or acute functional (idiopathic) constipation in adults can be managed by dietary and lifestyle changes. In adults, laxatives should be reserved for constipation that has not responded adequately to simple interventions, or for when rapid relief of symptoms is needed.

The evidence for the safety and efficacy of all laxatives is limited. This is mainly because many laxatives have been in use for a long time and were licensed when clinical trials were less robust. Few comparative clinical trials have been carried out, although a **Cochrane review** of studies in adults and children concluded that polyethylene glycol was superior to lactulose for outcomes such as stool frequency per week, form of stool, relief of abdominal pain and the need for additional laxatives. Another **Cochrane review** also found evidence that polyethylene glycol preparations may be superior to placebo, lactulose and milk of magnesia (magnesium hydroxide) for childhood constipation.

Prescribing choice mainly depends on the presenting symptoms, the person’s preference, and cost. Prolonged treatment is seldom necessary, except occasionally in the elderly, in palliative care, or to prevent constipation recurring in children.

When managing constipation in children and young people, healthcare professionals should follow the NICE clinical guideline on **constipation in children and young people**. This advises that dietary interventions should not be used alone as first-line
treatment for constipation (as they would be for adults). The guideline recommends polyethylene glycol as first-line laxative treatment for disimpaction and maintenance treatment.

The NICE clinical guideline on the use of strong opioids in palliative care in adults advises that laxatives should be prescribed for everyone starting strong opioids. It recommends that laxatives should be taken regularly at an effective dose and that people should be informed of the importance of medicines adherence.

The NICE clinical guideline on irritable bowel syndrome (IBS) recommends that laxatives should be considered for treating constipation in people with IBS, but that people should be discouraged from taking lactulose.

The NICE technology appraisal on prucalopride recommends this as a possible treatment for chronic constipation only in women for whom treatment with at least 2 laxatives from different classes, taken at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and invasive treatment for constipation is being considered.

The NICE technology appraisal on lubiprostone recommends this as a possible treatment for chronic idiopathic constipation in adults for whom treatment with at least 2 laxatives from different classes, taken at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and invasive treatment for constipation is being considered.

See the NICE Clinical Knowledge Summaries on constipation, constipation in children and palliative cancer care constipation for general overviews of the condition. The NICE pathway on constipation brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams. There is also a NICE quality standard defining clinical best practice for constipation in children and young people.

Prescribing data
A prescribing comparator is available to support this key therapeutic topic – Laxatives ADQ/STAR-PU: the total number of average daily quantities (ADQs) for
laxatives per COST based Specific Therapeutic Group Age-sex weightings Related Prescribing Unit (STAR-PU)\(^1\).

- Data\(^2\) for the quarter April to June 2014 show a 3.2 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 1.15 to 3.75 ADQ/STAR-PU.
- Between Q4 2012/13 (January 2013 to March 2013) and Q1 2014/15 (April to June 2014) there was a 4.4% increase in the comparator value for England (total prescribing) from 1.73 to 1.81 ADQ/STAR-PU.
- Over the same period there was a 7.3% increase in the variation between CCGs, as measured by the inter-decile range\(^3\), an absolute increase of 0.08 ADQ/STAR-PU.

\(^1\) The comparator and associated data are based on the current Key therapeutic topics publication. The comparators will be reviewed in conjunction with the update to this publication. See Feedback on proposals for retaining, amending or retiring 2013/14 comparators.

\(^2\) Data provided by the Health and Social Care Information Centre, September 2014. Source: Information Services Portal, Business Services Authority

\(^3\) The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.
Renin-angiotensin system drugs

Options for local implementation

- Review and, if appropriate, revise prescribing to ensure it is in line with NICE guidance.
- Dual therapy with an angiotensin-converting enzyme (ACE) inhibitor plus an angiotensin receptor blocker (ARB) has only a limited place in treatment – for example, in a small minority of people with heart failure.

Evidence context

The renin-angiotensin system is a major regulatory system of cardiovascular and renal function. The renin-angiotensin system drugs, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blocker (ARBs), are used in a wide range of indications including hypertension, heart failure, treatment after a myocardial infarction, chronic kidney disease and type 1 and type 2 diabetes.

Treatment of these conditions is complex, and there are multiple indications for each drug. The decision to prescribe an ACE inhibitor or an ARB, and whether an ACE inhibitor plus an ARB would be beneficial, should be made with each person individually. Before considering any change in medicine use within this class, a careful medication review is needed, applying the relevant, complex, evidence-based therapeutics to the care of each individual person.

In the NICE clinical guidelines on chronic heart failure, myocardial infarction (MI) – secondary prevention, type 1 diabetes (which is being updated; publication expected August 2015) and type 2 diabetes (which is being updated; publication expected August 2015), ACE inhibitors are the first-line choice when a renin-angiotensin system drug is indicated. ARBs are an alternative to ACE inhibitors if a renin-angiotensin system drug is indicated but an ACE inhibitor cannot be tolerated because of an ACE inhibitor-induced cough. See the table below for details.

In the NICE clinical guideline on hypertension, ACE inhibitors and ARBs are considered to be equivalent with regard to their effect on clinical outcomes. The guideline recommends that either an ACE inhibitor or a low-cost ARB should be offered to non-black people younger than 55 years. MeReC Rapid Review No. 4470 explains the rationale behind this guideline. A Cochrane review of ACE inhibitors
compared with ARBs for primary hypertension concluded that while no evidence of a
difference exists between these 2 classes of drugs for total mortality and
cardiovascular outcomes, the small increase in tolerability for ARBs should be
weighed against its less established degree of evidence of efficacy when choosing
an ARB over an ACE inhibitor for hypertension.

The NICE clinical guideline on chronic kidney disease recommends that a low-cost
renin-angiotensin system antagonist should be offered to people with chronic kidney
disease meeting certain criteria (see table below for details). A renin-angiotensin
system antagonist is defined in the NICE clinical guideline as a drug that blocks or
inhibits the renin angiotensin system including ACE inhibitors, ARBs and direct renin
inhibitors.

For further information on renin-angiotensin system drugs see NICE guidance or
NICE pathways, and the following publications: Eyes on Evidence commentary: Do
renin angiotensin system drugs reduce mortality in hypertension?, Eyes on Evidence
commentary: Angiotensin receptor blockers for chronic heart failure, Medicines
Evidence Commentary: Differences between candesartan and losartan for heart
failure? and Medicines Evidence Commentary: Diabetes mellitus: effect of
angiotensin converting enzyme inhibitors and angiotensin receptor blockers on
cardiovascular events and mortality.

**Dual blockade of the renin-angiotensin system**

In the June 2014 edition of Drug Safety Update, dual therapy with an ACE inhibitor
plus an ARB was not recommended by the Medicines and Healthcare products
Regulatory Agency (MHRA). A European safety review concluded that no significant
benefits of combination use were seen in people who did not have heart failure and
there was an increased risk of hyperkalaemia, hypotension, and impaired renal
function. See the Medicines Evidence Commentary: Efficacy and safety of dual
blockade of the renin angiotensin system for more information.

Dual therapy has only a limited place in treatment – for example, in a small minority
of people with heart failure. The NICE clinical guideline on chronic heart failure
recommends that, following specialist advice, the addition of an ARB licensed for
heart failure is an option that could be considered for people who remain
symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker (see the table below for details). Candesartan and valsartan are the only 2 ARBs licensed as add-on therapy to ACE inhibitors in this situation. The MHRA state that the triple combination of an ACE inhibitor, an ARB, and a mineralocorticoid receptor antagonist or other potassium-sparing diuretic in people with heart failure is not recommended.

In the June 2014 edition of Drug Safety Update, the MHRA advised that people with diabetic nephropathy should not be given an ARB with an ACE inhibitor as they are already prone to developing hyperkalaemia. Combining the direct renin inhibitor, aliskiren, with an ACE inhibitor or an ARB is also strictly contraindicated in people with kidney impairment (estimated glomerular filtration rate <60 mL/minute/1.73 m²) or diabetes.

Table: summary of NICE recommendations on the use of renin-angiotensin system drugs in various indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Relevant NICE clinical guideline</th>
<th>Recommendation in relation to renin-angiotensin system drugs</th>
<th>Recommendation in relation to dual blockade with renin-angiotensin system drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Hypertension: Clinical management of primary hypertension in adults, NICE clinical guideline 127 (August 2011)</td>
<td>Offer people aged under 55 years step 1 antihypertensive treatment with an ACE inhibitor or a low-cost ARB. If an ACE inhibitor is prescribed and is not tolerated (for example, because of cough), offer a low-cost ARB.</td>
<td>Do not combine an ACE inhibitor with an ARB to treat hypertension.</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care, NICE clinical guideline 108 (August 2010)</td>
<td>Offer both ACE inhibitors and beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction. Consider an ARB licensed for heart failure as an alternative to an ACE inhibitor for patients with heart failure due to left ventricular systolic dysfunction who have intolerable side effects with</td>
<td>Seek specialist advice and consider adding an ARB licensed for heart failure (especially if the patient has mild to moderate heart failure) if a patient remains symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker. Other options are adding an aldosterone antagonist licensed for heart failure or hydralazine in</td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
<td>Recommendation</td>
<td>Notes</td>
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<td>------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Myocardial infarction (MI) – secondary prevention</strong></td>
<td>MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 172 (November 2013)</td>
<td>Offer people who present acutely with an MI an ACE inhibitor as soon as they are haemodynamically stable. Continue the ACE inhibitor indefinitely. Offer people after an MI who are intolerant to ACE inhibitors an ARB instead of an ACE inhibitor.</td>
<td>Do not offer combined treatment with an ACE inhibitor and an ARB to people after an MI, unless there are other reasons to use this combination.</td>
</tr>
</tbody>
</table>
| **Chronic kidney disease (CKD)**            | Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care. NICE clinical guideline 182 (July 2014) | Offer a low-cost renin-angiotensin system antagonist\(^a\) to people with CKD and:  
- diabetes and an albumin:creatinine ratio of 3 mg/mmol or more  
- hypertension and an albumin:creatinine ratio of 30 mg/mmol or more  
- an albumin:creatinine ratio of 70 mg/mmol or more (irrespective of hypertension or cardiovascular disease). | Do not offer a combination of renin-angiotensin system antagonists\(^a\) to people with CKD. |
| **Type 1 diabetes**                         | Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults; NICE clinical guideline 15 (July 2004)  
Currently being updated; publication expected August 2015 | ACE inhibitors should be started and, with the usual precautions, titrated to full dose in all adults with confirmed nephropathy (including those with microalbuminuria alone) and type 1 diabetes. If ACE inhibitors are not tolerated, ARBs should be substituted. | Combination therapy with an ACE inhibitor and an ARB is not recommended at present. |
| **Type 2 diabetes**                         | Type 2 diabetes: The management of type 2 diabetes, NICE clinical guideline 87 (May 2009)  
Currently being updated; publication expected August 2015 | First-line blood-pressure-lowering therapy should be a once-daily, generic ACE inhibitor. Exceptions to this are people of African-Caribbean descent or women for whom there is a possibility of becoming pregnant. If continuing intolerance to ACE inhibitor (other than No recommendation on dual blockade. |
A renin-angiotensin system antagonist is defined in the NICE clinical guideline on CKD as a drug that blocks or inhibits the renin-angiotensin system including ACE inhibitors, ARBs and direct renin inhibitors.

### Prescribing data

A prescribing comparator is available to support this key therapeutic topic – **ACE inhibitor % items**: the number of prescription items for ACE inhibitors as a percentage of the total number of prescription items for all drugs affecting the renin-angiotensin system excluding aliskiren.

- Data for the quarter April to June 2014 show a 1.3 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 61.3% to 77.3%.
- Between Q4 2012/13 (January 2013 to March 2013) and Q1 2014/15 (April to June 2014) there was a 1.3% decrease in the comparator value for England (total prescribing) from 71.0% to 70.1%.
- Over the same period there was a 1.6% increase in the variation between CCGs, as measured by the inter-decile range, an absolute increase of 0.13%.

1 The comparator and associated data are based on the current Key therapeutic topics publication. The comparators will be reviewed in conjunction with the update to this publication. See [Feedback on proposals for retaining, amending or retiring 2013/14 comparators](#).

2 Data provided by the [Health and Social Care Information Centre](#), September 2014. Source: [Information Services Portal](#), Business Services Authority

3 The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.
Lipid-modifying drugs

Options for local implementation

- Review and, if appropriate, revise prescribing of lipid-modifying drugs including statins, ezetimibe, fibrates, nicotinic acid and bile acid sequestrants to ensure it is in line with NICE guidance.

Evidence context

The NICE clinical guideline on lipid modification (published July 2014) updates and replaces NICE clinical guideline 67 (published May 2008) and NICE technology appraisal guidance 94 (published January 2006). It also updates recommendations relating to lipid modification therapy in NICE clinical guidelines on type 1 diabetes (published July 2004) and type 2 diabetes (published May 2009) and gives advice on lipid modification in people with chronic kidney disease: the guideline is referred to in the NICE clinical guideline on chronic kidney disease (published July 2014).

Statins

The NICE clinical guideline on lipid modification recommends that the decision whether to start statin therapy should be made after an informed discussion between the clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy. Before starting statin treatment baseline blood tests should be conducted and the person should be clinically assessed: comorbidities and secondary causes of dyslipidaemia should be treated.

For the purpose of the guideline, statins are grouped into 3 different intensity categories according to the percentage reduction in low-density lipoprotein cholesterol (LDL-C; see appendix A of the guideline for more information):

- Low intensity: 20%–30% LDL-C reduction; fluvastatin 20–40 mg daily, pravastatin 10–40 mg daily, simvastatin 10 mg daily.
- Medium intensity: 31%–40% LDL-C reduction; atorvastatin 10 mg daily, fluvastatin 80 mg daily, rosuvastatin 5 mg daily, simvastatin 20–40 mg daily.
• High intensity: more than 40% LDL-C reduction; atorvastatin 20–80 mg daily, rosuvastatin 10–40 mg daily, simvastatin 80 mg daily.

When a decision is made to prescribe a statin, the guideline recommends using a statin of high intensity and low acquisition cost.

**Primary prevention of cardiovascular disease**

Before offering statin treatment for primary prevention of cardiovascular disease (CVD), NICE recommends discussing the benefits of lifestyle modification with the person and, if possible, the management of all other modifiable CVD risk factors should be optimised.

NICE recommends offering atorvastatin 20 mg daily for primary prevention to people who have a 10% or greater 10-year risk of developing CVD (estimated using the **QRISK2** assessment tool), including those with type 2 diabetes and chronic kidney disease. Among people with type 1 diabetes, primary prevention with statins may be considered in all adults and should be offered to adults who are older than 40 years, or have had diabetes for more than 10 years or have established nephropathy or have other CVD risk factors. In adults with type 1 diabetes treatment should be started with atorvastatin 20 mg daily.

**Secondary prevention of cardiovascular disease**

NICE recommends that statin treatment for people with CVD (secondary prevention) should usually start with atorvastatin 80 mg daily. However, in people with chronic kidney disease the initial dose should be 20 mg daily, and in other people a dose lower than 80 mg daily should be used if there are potential drug interactions with existing therapy, a high risk of adverse effects or the patient prefers a lower dose.

**Follow-up of people started on statin treatment**

NICE recommends measuring total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment as above after 3 months of treatment, **aiming** for a greater than 40% reduction in non-HDL cholesterol. If this reduction in non-HDL cholesterol is not achieved, NICE recommends:
• discussing adherence and the timing of the dose
• optimising adherence to diet and lifestyle measures
• **considering** increasing the dose if the person started on less than atorvastatin 80 mg daily and they are judged to be at higher risk because of comorbidities, risk score or using clinical judgement.

In people with chronic kidney disease, any increase in dose should take account of the person’s renal function. NICE also advises healthcare professionals to provide annual medication reviews for people taking statins, using these reviews to discuss medicines adherence and lifestyle modification and address CVD risk factors. An annual non-fasting blood test for non-HDL cholesterol may be considered, so as to inform the discussion.

An [analysis of data from the LIPID study](#), published in 2008, found that a single cholesterol level reading may well under- or over-estimate a person’s true average cholesterol level by up to 14%.

The guidance also provides recommendations about monitoring for adverse effects of statins, and managing intolerance to statins. It advises that, if a person is not able to tolerate a high-intensity statin, the aim should be to treat with the maximum tolerated dose. NICE recommends telling the person that any statin at any dose reduces CVD risk. If someone reports adverse effects when taking high-intensity statins, the following strategies should be discussed with them:

• stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin
• reducing the dose within the same intensity group
• changing the statin to a lower intensity group.

**People currently taking other doses of statins**

NICE recommends that healthcare professionals should discuss the likely benefits and potential risks of changing to a high-intensity statin (such as atorvastatin 20 mg daily or more) with people who are stable on a low-intensity statin (such as pravastatin 40 mg daily) or middle-intensity statin (such as atorvastatin 10 mg or...
simvastatin 40 mg daily) when they have a medication review, and agree with the person whether a change is needed.

**Rosuvastatin and high-dose simvastatin**

When a decision is made to prescribe a statin, the NICE lipid modification guideline recommends using a statin of high intensity and low acquisition cost. The only statin specifically named in the guideline recommendations is atorvastatin 20–80 mg daily. Other possible high-intensity statins are rosuvastatin 10–40 mg daily and simvastatin 80 mg daily. In the May 2010 edition of Drug Safety Update, the Medicines and Healthcare products Regulatory Agency advised that there is an increased risk of myopathy associated with simvastatin 80 mg daily, and that this dose should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risk.

The NICE full guideline on lipid modification notes that the clinical outcomes of the only study that compared atorvastatin with rosuvastatin for prevention of cardiovascular disease (SATURN) were inconclusive. The full guideline states ‘Given the considerably higher cost of using rosuvastatin, it would need to be considerably more effective than atorvastatin for there to be a possibility that its use could be cost effective. In the absence of trial evidence of greater effectiveness the guideline development group are therefore unable to recommend the use of rosuvastatin’.

**Ezetimibe**

The NICE clinical guideline on lipid modification (published July 2014) recommends that people with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with the technology appraisal for that drug in this indication; Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (published November 2007). This states that ezetimibe is an option for people with primary (heterozygous-familial or non-familial) hypercholesterolaemia in 2 broad situations:

- as an alternative to a statin in adults in whom statins are contraindicated or not tolerated.
• in addition to a statin in adults who have started statin treatment but whose serum total or LDL cholesterol concentration is not appropriately controlled (either after appropriate dose titration or because dose titration is limited by intolerance to the initial statin therapy) and consideration is being given to changing from initial statin therapy to an alternative statin.

Thus, in the second of these situations, adding ezetimibe to atorvastatin is an option if a greater than 40% reduction in non-HDL cholesterol is not achieved with atorvastatin after the measures recommended in the NICE lipid modification guideline have been tried (see above) and changing to a different statin is being considered.

The guideline states that health professionals should be aware that when deciding on lipid modification therapy for the prevention of CVD, drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality. There remains no published evidence that ezetimibe, alone or added to a statin, reduces the risk of CVD or mortality compared with an active comparator. The SHARP study compared simvastatin 20 mg plus ezetimibe with placebo in people with chronic kidney disease. Although this found that the combination reduced the risk of CVD events compared with placebo, it provides no information as to how simvastatin 20 mg plus ezetimibe would compare with monotherapy with any statin at any dose on the risk of CVD. The IMPROVE-IT study is a double blind randomised controlled trial of ezetimibe plus simvastatin compared with simvastatin monotherapy in people with stabilised high-risk acute coronary syndrome. It is scheduled to complete in September 2014.

**Bile acid sequestrants, fibrates and nicotinic acid**

The NICE clinical guideline on lipid modification (published July 2014) recommends that bile acid sequestrants (anion exchange resins) and nicotinic acid (niacin) should not be offered for primary or secondary prevention of CVD, alone or in combination with a statin, including in people with chronic kidney disease or type 1 or type 2 diabetes. The guideline recommends that fibrates should not be routinely offered for monotherapy for primary or secondary prevention of CVD including in people with chronic kidney disease or type 1 or type 2 diabetes, and should not be recommended in combination with a statin in these indications.
Omega-3 fatty acid supplements
These are the subject of a separate key therapeutic topic.

Prescribing data
Statin dose and choice
A prescribing comparator is available to support this key therapeutic topic – Low cost lipid-modifying drugs: Number of prescription items for generic statin preparations listed under category M in part VIII of the Drug Tariff as a percentage of the total number of prescription items for all statins, plus the total number of prescription items for combination of simvastatin/ezetimibe, plus total number of prescription items for ezetimibe alone.

- Data for the quarter April to June 2014 show a 1.5 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 66.3% to 97.8%.
- Between Q2 2013/14 (July 2013 to September 2013) and Q1 2014/15 (April to June 2014) there was a 0.3% increase in the comparator value for England (total prescribing) from 93.1% to 93.4%.
- Over the same period there was a 6.0% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 0.3%.

When a decision is made to prescribe a statin, the NICE lipid modification guideline recommends using a statin of high intensity and low acquisition cost. The only statin specifically named in the guideline recommendations is atorvastatin 20–80 mg daily. Other possible high-intensity statins are rosuvastatin 10–40 mg daily and simvastatin 80 mg daily (which is the subject of Medicines and Healthcare products Regulatory Agency advice). Appendix A of the guideline gives the same or similar percentage reduction in LDL-C for:

- atorvastatin 20 mg daily and rosuvastatin 10 mg daily (43% for both)
- atorvastatin 40 mg daily and rosuvastatin 20 mg daily (49% and 48% respectively)
- atorvastatin 80 mg and rosuvastatin 40 mg daily (55% and 53% respectively).

Rosuavstatin 10–40 mg daily is between £217.36 and £353.47 per patient per year more costly than atorvastatin 20–80 mg daily at equivalent LDL-C-lowering doses (Drug Tariff September 2014).
The comparator and associated data are based on the current Key therapeutic topics publication. The comparators will be reviewed in conjunction with the update to this publication. See Feedback on proposals for retaining, amending or retiring 2013/14 comparators.

Data provided by the Health and Social Care Information Centre, September 2014. Source: Information Services Portal, Business Services Authority

Although data are available prior to this period, the revised comparator was introduced in August 2013 in line with the introduction of atorvastatin as a category M medicine.

The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

Ezetimibe

A prescribing comparator is available to support this key therapeutic topic – Lipid modifying drugs: ezetimibe % items: the number of prescription items for ezetimibe and ezetimibe/simvastatin combinations as a percentage of total prescription items for all statins and ezetimibe, including simvastatin/ezetimibe combination products.

- Data for the quarter April to June 2014 show a 5.9 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.91% to 5.38%.
- Between Q4 2012/13 (January 2013 to March 2013) and Q1 2014/15 (April to June 2014) there was a 10.2% decrease in the comparator value for England (total prescribing) from 3.0% to 2.7%.
- Over the same period there was a 9.5% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 0.21%.

The comparator and associated data are based on the current Key therapeutic topics publication. The comparators will be reviewed in conjunction with the update to this publication. See Feedback on proposals for retaining, amending or retiring 2013/14 comparators.
Data provided by the Health and Social Care Information Centre, September 2014. Source: Information Services Portal, Business Services Authority

The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

Bile acid sequestrants, fibrates and nicotinic acid

There are currently no prescribing comparators for these topics.

Omega-3 fatty acid supplements

These are the subject of a separate key therapeutic topic.
Omega-3 fatty acid supplements

Options for local implementation

- Several NICE guidelines recommend against prescribing omega-3 fatty acid supplements for lipid modification and the primary and secondary prevention of cardiovascular disease.
- Review and, if appropriate, revise prescribing to ensure it is in line with NICE guidance.

Evidence context

This key therapeutic topic relates to the licensed indications for omega-3 fatty acid supplements; that is, adjuvant treatment in secondary prevention after myocardial infarction (MI) and endogenous hypertriglyceridaemia as a supplement to diet. Their use in unlicensed indications is outside the scope of this topic.

Several NICE guidelines recommend against prescribing these supplements for lipid modification and the primary and secondary prevention of cardiovascular disease.

The updated NICE clinical guideline on lipid modification (published July 2014) recommends that people at high risk of or with cardiovascular disease should be advised to consume at least 2 portions of fish per week, including a portion of oily fish. However it advises that omega-3 fatty acid compounds should not be offered for the prevention of cardiovascular disease for primary or secondary prevention of cardiovascular disease, alone or in combination with a statin, including in people with chronic kidney disease or type 1 or type 2 diabetes. Moreover, the guidance recommends that healthcare professionals should tell people that there is no evidence that omega-3 fatty acid compounds help to prevent cardiovascular disease. This guidance updates and replaces recommendations about omega-3 fatty acid compounds in the clinical guideline on type 2 diabetes (which is being updated, publication expected August 2015).

The NICE clinical guideline on familial hypercholesterolaemia (FH) recommends that people with FH should be advised to consume at least 2 portions of fish a week (1 of which should be oily fish), but that they should not routinely be recommended to take omega-3 fatty acid supplements.
The NICE clinical guideline on MI - secondary prevention recommends that healthcare professionals should advise people who have had an MI to eat a Mediterranean-style diet (more bread, fruit, vegetables and fish; less meat; and replace butter and cheese with products based on plant oils), but they should not routinely recommend eating oily fish for the sole purpose of preventing another MI. Moreover, the guideline recommends that healthcare professionals should not offer or advise people to use omega-3 fatty acid capsules or omega-3 fatty acid supplemented foods to prevent another MI.

The full guideline on lipid modification notes that high doses of omega-3 fatty acid compounds have been found to reduce plasma triglycerides in a dose-dependent manner. They have no effect on HDL cholesterol and may raise LDL cholesterol. The guideline development group (GDG) concluded that there was no evidence of clinical benefits from omega-3 fatty acid compounds for primary or secondary prevention, including in people with type 2 diabetes, and no outcome trials of omega-3 fatty acid compounds were found in people with type 1 diabetes or chronic kidney disease. The search for evidence in secondary prevention included looking for evidence in people with prior myocardial infarction or stroke, acute coronary syndromes, stable angina or peripheral arterial disease.

Adverse effects were not reported in the studies of omega-3 fatty acid compounds in primary prevention populations or in type 2 diabetes; however, there was evidence of increased gastrointestinal adverse effects for the secondary prevention population, and the GDG considered this as indirect evidence for adverse events in these 2 clinical situations. Overall, the majority of the evidence was of low quality for all outcomes. In addition, because omega-3 fatty acid compounds are common supplements that can be bought over the counter in most pharmacies, supermarkets and food supplements stores, the GDG felt it was important to advise people at risk of cardiovascular disease that the use of such supplements is not supported by clinical evidence.

**Prescribing data**

A prescribing comparator is available to support this key therapeutic topic – Omega-3 ADQ/STAR PU: Number of ADQs for omega-3 fatty acid compounds per Omega-3
fatty acid compounds (BNF 2.12 sub-set) ADQ based Specific Therapeutic Group
Age-sex weightings Related Prescribing Unit (STAR-PU)\(^1\).

- Data\(^2\) for the quarter April to June 2014 show a 62.5 fold variation in prescribing
  rates at Clinical Commissioning Group (CCG) level, from 0.02 to 1.50 ADQ/STAR-
  PU.
- Between Q4 2012/13 (January 2013 to March 2013) and Q1 2014/15 (April to
  June 2014) there was a 26.4% decrease in the comparator value for England
  (total prescribing) from 0.40 to 0.29 ADQ/STAR-PU.
- Over the same period there was a 31.7% decrease in the variation between
  CCGs, as measured by the inter-decile range\(^3\), an absolute decrease of
  0.23 ADQ/STAR-PU.

Annually, approximately 477,000 items of omega-3 fatty acid compounds are
prescribed in primary care in England, at a cost of about £12 million.

\(^1\) The comparator and associated data are based on the current Key therapeutic
topics publication. The comparators will be reviewed in conjunction with the update
to this publication. See Feedback on proposals for retaining, amending or retiring
2013/14 comparators.

\(^2\) Data provided by the Health and Social Care Information Centre, September 2014.
Source: Information Services Portal, Business Services Authority

\(^3\) The inter-decile range is the difference between the highest and lowest values after
the highest and lowest 10% of values have been removed.
High-dose inhaled corticosteroids in asthma

Options for local implementation

- Review the use of inhaled corticosteroids (ICS) routinely in people with asthma.
- Step down the dose and use of ICS when clinically appropriate in people with asthma.

Evidence context

Inhaled corticosteroids (ICS) are the first-choice regular preventer therapy for adults and children with asthma for achieving overall treatment goals. To minimise side effects from ICS in people with asthma, the BTS/SIGN guideline on the management of asthma (which is being updated; expected publication October/November 2014) recommends that the dose of ICS should be titrated to the lowest dose at which effective control of asthma is maintained. Doubling the dose of ICS at the time of an exacerbation is of unproven value and is no longer recommended.

The Medicines and Healthcare products Regulatory Agency (MHRA) advises that the prolonged use of high doses of ICS (as with the use of oral corticosteroids) carries a risk of systemic side effects (for example, adrenal suppression or crisis [see also Medicines Evidence Commentary: Risk of adrenal insufficiency with inhaled corticosteroids], growth retardation in children and young people, decrease in bone mineral density, cataracts and glaucoma). In the September 2010 edition of Drug Safety Update, the MHRA warned that inhaled (and intranasal) corticosteroids can be associated with a range of psychological or behavioural effects (for example, psychomotor hyperactivity, sleep disorders, anxiety, depression and aggression). ICS have also been associated with a dose-related increased risk of both diabetes onset and progression, although this evidence is from an observational study with inherent limitations (see MeReC Rapid Review No. 2485 for details).

The MHRA advises that corticosteroid treatment cards should be routinely provided for people (or their parents or carers) who require prolonged treatment with high doses of ICS. The London Respiratory Network has produced a corticosteroid card that is specifically tailored for people who are using high doses of ICS. The Committee on Safety of Medicines has issued warnings about the use of high-dose ICS, particularly in children and in relation to fluticasone. Children prescribed ICS...
should have their growth monitored annually (although isolated growth failure is not a reliable indicator of adrenal suppression).

The BTS/SIGN guideline on the management of asthma recommends that reductions in ICS dose should be considered every 3 months, decreasing the dose by approximately 25–50% each time. Data suggest that this is realistic and possible without compromising patient care (see Hawkins et al. 2003). For some children with milder asthma and a clear seasonal pattern to their symptoms, a more rapid dose reduction during their ‘good’ season is feasible. The guideline states that stepping down therapy once asthma is controlled is recommended, but often not implemented, leaving some people over-treated.

The NICE technology appraisal on ICS for the treatment of chronic asthma in adults and children aged 12 years and over recommends a combination inhaler, within its marketing authorisation, as an option if treatment with an ICS and a LABA is considered appropriate. A Scottish retrospective database analysis, reported in a Medicines Evidence Commentary: Asthma: study finds many people have a substantial increase in dose of inhaled corticosteroid when started on combination inhaler therapy, found initiating combination ICS plus LABA therapy resulted in widespread increases in ICS dose. The average increase was about 50%, and was substantially greater among people previously on lower ICS doses. This raises questions around the awareness of ICS doses in different preparations, and suggests that an evaluation of the appropriateness of high-dose combination inhaler therapy in primary care is needed.

Fluticasone furoate/vilanterol (Relvar Ellipta 92 micrograms/22 micrograms or 184 micrograms/22 micrograms) was launched in January 2014 for the treatment of asthma. According to the summaries of product characteristics, fluticasone furoate 92 micrograms once a day is approximately equivalent to fluticasone propionate 250 micrograms twice a day. Healthcare professionals should be aware of the high potency of fluticasone furoate compared with other ICS. Because a lower strength is not available, the ability to step down treatment is limited (see the NICE evidence summary new medicine: Asthma: fluticasone furoate/vilanterol [Relvar Ellipta] combination inhaler). In addition, a Drug and Therapeutics Bulletin has highlighted
concerns that the name and colour of the Relvar Ellipta inhaler could lead to inappropriate use by patients believing it to be a reliever.

The NICE quality standard for asthma recommends that people with asthma receive a structured review at least annually as well as receiving specific training and assessment in inhaler technique before starting any new inhaler treatment. This is supported by the National review of asthma deaths, which also makes recommendations for improving the care of people with asthma.

See the Clinical Knowledge Summary on asthma for a general overview of this condition. The NICE pathway on asthma brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams

**Prescribing data**

There are currently no prescribing comparators for this topic. The development of a suitable comparator will be explored. However, there are several clinical and technical issues regarding the development of a meaningful comparator for this topic.
Hypnotics

Options for local implementation

- Review and, if appropriate, revise prescribing of hypnotics to ensure that it is in line with national guidance.

Evidence context

Risks associated with the long-term use of hypnotic drugs have been well recognised for many years. These include falls, accidents, cognitive impairment, dependence and withdrawal symptoms. An observational study discussed in an Eyes on Evidence commentary: Benzodiazepines and the risk of dementia suggested that benzodiazepines and ‘Z drugs’ (zaleplon, zolpidem and zopiclone) are also associated with an increased risk of dementia. Another observational study discussed in a Medicine Evidence Commentary: Psychotropic drugs and risk of motor vehicle accidents examined the relationship between exposure to psychotropic drugs and motor vehicle accidents and found that benzodiazepines and ‘Z drugs’ (and antidepressants) were associated with a significantly increased risk of motor vehicle accidents. The Medicines and Healthcare products Regulatory Agency (MHRA) May 2014 edition of Drug Safety Update warned about the risk of drowsiness and reduced driving ability the next day with zolpidem. Another study discussed in an Eyes on Evidence commentary: Prescriptions for anxiolytics and hypnotics and risk of death found that people who were prescribed anxiolytic and hypnotic drugs had a significantly increased risk of death from any cause over a 7-year period.

As long ago as 1988, the Committee on Safety of Medicines advised that benzodiazepine hypnotics should be used only if insomnia is severe, disabling or causing the person extreme distress. The lowest dose that controls symptoms should be used, for a maximum of 4 weeks and intermittently if possible.

The NICE technology appraisal on zaleplon, zolpidem and zopiclone recommends that when, after due consideration of the use of non-pharmacological measures, hypnotic drug therapy is considered appropriate for the management of severe insomnia interfering with normal daily life, hypnotics should be prescribed for short periods of time only, in strict accordance with their licensed indications. A meta-analysis discussed in an Eyes on Evidence commentary: Small benefits of Z drugs
over placebo for insomnia found that ‘Z drugs’ reduce the time taken to fall asleep by 22 minutes compared with placebo but this may not be clinically significant. The NICE technology appraisal states that there is no compelling evidence of a clinically useful difference between the ‘Z drugs’ and shorter-acting benzodiazepine hypnotics from the point of view of their effectiveness, adverse effects, or potential for dependence or abuse. There is no evidence to suggest that if people do not respond to one of these hypnotic drugs, they are likely to respond to another.

The MHRA reinforced the issues regarding addiction to benzodiazepines in the July 2011 edition of Drug Safety Update. Various approaches to reducing hypnotic prescribing can achieve significant success.

An e-learning programme, addiction, misuse and dependency: a focus on over-the-counter (OTC) and prescribed medicines has been developed jointly by the Centre for Pharmacy Postgraduate Education (CPPE) and the Royal College of General Practitioners (RCGP). The programme aims to provide healthcare professionals with a better understanding of how to recognise patients who may have an addiction to prescribed or OTC medicines and how to approach and help patients.

See the NICE Clinical Knowledge Summary on insomnia for a general overview of the condition.

See the NICE Clinical Knowledge Summary on benzodiazepine and z-drug withdrawal for advice on the assessment of a person who is being prescribed long-term benzodiazepines or z-drugs, and on managing withdrawal of treatment.

Prescribing data
A prescribing comparator is available to support this key therapeutic topic – Hypnotics ADQ/STAR PU (ADQ based): Number of average daily quantities (ADQs) for benzodiazepines (indicated for use as hypnotics) and ‘Z drugs’ per Hypnotics (BNF 4.1.1 sub-set) ADQ based Specific Therapeutic Group Age-sex weightings Related Prescribing Unit (STAR-PU)¹.

- Data² for the quarter April to June 2014 show a 4.1 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.12 to 0.51 ADQ/STAR-PU.
- Between Q4 2012/13 (January 2013 to March 2013) and Q1 2014/15 (April to June 2014) there was a 7.7% decrease in the comparator value for England (total prescribing) from 0.30 to 0.28 ADQ/STAR-PU.
- Over the same period there was a 12.1% decrease in the variation between CCGs, as measured by the inter-decile range\(^3\), an absolute decrease of 0.03 ADQ/STAR-PU.

1 The comparator and associated data are based on the current Key therapeutic topics publication. The comparators will be reviewed in conjunction with the update to this publication. See Feedback on proposals for retaining, amending or retiring 2013/14 comparators.

2 Data provided by the Health and Social Care Information Centre, September 2014. Source: Information Services Portal, Business Services Authority

3 The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.
Low-dose antipsychotics in people with dementia

Options for local implementation

- Review and, if appropriate, revise prescribing of low-dose antipsychotics in people with dementia, in accordance with the NICE/Social Care Institute for Excellence (SCIE) clinical guideline on dementia and the NICE quality standard on dementia, and the Alzheimer’s Society best practice guide.

Evidence context

The NICE/SCIE clinical guideline on dementia gives recommendations on the care of people with all types of dementia. This includes managing behavioural and psychological symptoms of dementia. Non-cognitive symptoms and behaviour that challenges are included in the NICE quality standard on dementia. A NICE quality standard for supporting people to live well with dementia discusses care and support of people with dementia and applies to all social care settings and services working with and caring for people with dementia. A NICE pathway on dementia brings together all related NICE guidance and associated products on dementia in a set of interactive topic-based diagrams. See the NICE Clinical Knowledge Summary on dementia for a general overview of the condition.

The harms and limited benefits of using first (typical) and second (atypical) generation antipsychotic drugs for treating dementia in people who exhibit challenging behaviours are well recognised. They have been the subject of several previous reviews and Medicines and Healthcare products Regulatory Agency (MHRA) warnings, collated in MeReC Rapid Review No. 847 and the May 2012 edition of Drug Safety Update.

The NICE/SCIE guideline on dementia recommends that people with dementia who develop non-cognitive symptoms that cause them significant distress or who develop behaviour that challenges should be offered an assessment at an early opportunity to establish likely factors that may generate, aggravate or improve such behaviour. The assessment should be comprehensive and include for example, the person’s physical health, depression, undetected pain or discomfort, side effects of medication, psychosocial factors, physical environment factors, and the person’s religious beliefs and spiritual and cultural identity. Individually tailored care plans that
help carers and staff address the behaviour that challenges should be developed, recorded in the notes and reviewed regularly.

For people with all types and severities of dementia who have comorbid agitation, the NICE/SCIE guideline on dementia recommends that non-pharmacological approaches may be considered including aromatherapy, multisensory stimulation, therapeutic use of music or dancing, animal-assisted therapy, and massage.

The NICE/SCIE guideline on dementia advises against the use of any antipsychotics for non-cognitive symptoms or challenging behaviour of dementia unless the person is severely distressed or there is an immediate risk of harm to them or others. Any use of antipsychotics should include a full discussion with the person and carers about the possible benefits and risks of treatment. In the May 2012 edition of Drug Safety Update, the MHRA advised that no antipsychotic (with the exception of risperidone in some circumstances) is licensed in the UK for treating behavioural and psychological symptoms of dementia. However, antipsychotics are often prescribed off-label* for this purpose.

In September 2010, the Department of Health published an implementation plan for Living well with dementia: a national dementia strategy. In July 2011, a best practice guide, Optimising treatment and care for people with behavioural and psychological symptoms of dementia, was produced by the Alzheimer’s Society and endorsed by the Department of Health. These resources build on the NICE/SCIE guideline on dementia and include strategies to reduce inappropriate prescribing of antipsychotics. In the May 2012 edition of Drug Safety Update the MHRA provides the following advice for healthcare and social care professionals:

**For prescribers considering using antipsychotics in people without a current prescription:**

- Carefully consider, after a thorough clinical examination including an assessment for possible psychotic features (such as delusions and hallucinations), whether a prescription for an antipsychotic drug is appropriate – see the appropriate pathway in the Alzheimer’s Society best practice guide.
For prescribers considering continuing antipsychotics in people with a current prescription:

- Identify and review people who have dementia and are on antipsychotics, with the purpose of understanding why antipsychotics have been prescribed.
- In consultation with the person, their family and carers, and clinical specialist colleagues such as those in psychiatry, establish: whether the continued use of antipsychotics is appropriate; whether it is safe to begin the process of discontinuing their use; and what access to alternative interventions is available.
- Consult the Alzheimer's Society best practice guide.

A Cochrane review which was discussed in a Medicines Evidence Commentary: Dementia: withdrawal of antipsychotic drugs in people with behavioural and neuropsychiatric symptoms evaluated the effect of withdrawing treatment with antipsychotic drugs prescribed for behavioural and neuropsychiatric symptoms in people with dementia. It concluded that these can be withdrawn without detrimental effects on behaviour in many people. This review is consistent with the NICE/SCIE clinical guideline on dementia and the Alzheimer's Society best practice guide.

A randomised controlled trial which was outlined in a Medicines Evidence Commentary: Alzheimer's disease: effect of citalopram on agitation evaluated the efficacy and safety of citalopram for the treatment of agitation in people with Alzheimer’s disease. It found that citalopram 30 mg daily reduced agitation in people with Alzheimer’s disease who were receiving a psychosocial intervention. However, citalopram 30 mg daily worsened cognition and was associated with adverse cardiac effects (an increase in QT-interval). The study provides no reason to depart from the recommendations for managing behavioural and psychological symptoms of dementia in the NICE/SCIE guideline on dementia and the Alzheimer's Society's best practice guide.

* If prescribing off-label, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.
**Prescribing data**

There is currently no prescribing comparator for this key therapeutic topic, but the development of a suitable comparator continues to be explored. However, the National dementia and antipsychotic prescribing audit suggests that there has been an encouraging overall reduction in the proportion of people with dementia being prescribed antipsychotics in recent years.

Based on data from 46% of GP practices across England, the audit found that the number of people newly diagnosed each year with dementia increased by 68% in relative terms from 2006 to 2011. However, there was a decrease of 10.25 percentage points in the number of people with dementia receiving prescriptions for antipsychotic medication over that time (from 17.05% in 2006 to 6.80% of people in 2011, a 60% reduction in relative terms). The proportion of people receiving a prescription for an antipsychotic within a year of being diagnosed with dementia also decreased by 9.79 percentage points from 2006 to 2011 (from 14.25% to 4.46%, a 69% reduction in relative terms). Nevertheless, although reductions in prescribing rates were seen in all English Strategic Health Authorities (SHAs), there was still considerable variation in the percentage of people diagnosed with dementia prescribed an antipsychotic.
First-choice antidepressant use in adults with depression or generalised anxiety disorder

Options for local implementation

- Review and, if appropriate, revise prescribing of antidepressants in adults to ensure that it is in line with NICE guidance.

Evidence context

The use of antidepressants in adults with depression or generalised anxiety disorder (GAD) has been addressed by the NICE clinical guidelines on depression in adults (which is being updated; publication expected May 2017), depression in adults with a chronic physical health problem and GAD and panic disorder in adults. The NICE clinical guideline on common mental health disorders brings these recommendations together and can be used to help clinicians, commissioners and managers develop effective local care pathways for such people.

See the NICE Clinical Knowledge Summaries on depression and GAD for a general overview of these conditions. The NICE pathways on depression and GAD bring together all related NICE guidance and associated products on antidepressants in a set of interactive topic-based diagrams. See also specific NICE clinical guidelines on antenatal and postnatal mental health (which is being updated, publication expected December 2014) and in depression in children and young people (which is being updated, publication expected March 2015). The NICE quality standards on depression in adults, depression in children and young people, and anxiety disorders describe concise sets of prioritised statements designed to drive measurable quality improvements within these areas.

NICE advocates a stepwise approach to managing common mental health disorders, offering or referring for the least intrusive, most effective intervention first. Therefore, non-drug interventions (such as cognitive behavioural therapy [CBT]) should be the mainstay of treatment for many people with depression or GAD, with drugs generally reserved for more severe illness or when symptoms have failed to respond to non-drug interventions.

Prescribing data suggest that there is variation in antidepressant prescribing across localities. In view of the NICE clinical guideline on common mental health disorders,
a review of local antidepressant prescribing is advised. This should be considered alongside the local availability of non-drug treatments, such as CBT.

If an antidepressant is indicated for a person with depression, NICE recommends that it should normally be a selective serotonin reuptake inhibitor (SSRI) in generic form. SSRIs are equally as effective as other antidepressants and have a favourable risk–benefit ratio. Similarly, if drug treatment is indicated for GAD, and a person chooses to take medication, NICE recommends offering an SSRI with sertraline as the first-line option because it is the most cost-effective drug for this condition. However, prescribers should note that sertraline does not currently have a UK marketing authorisation for GAD, so prescribing would be off-label*. NICE recommends that dosulepin should not be prescribed for adults with depression because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose.

The full guideline on depression in adults concluded that antidepressants have largely equal efficacy and that choice should mainly depend on side-effect profile, people’s preference and previous experience of treatments, propensity to cause discontinuation symptoms, safety in overdose, interactions and cost. However, a generic SSRI is recommended as first-choice because of its favourable risk–benefit ratio. Neither escitalopram nor any of the available ‘dual action’ antidepressants, such as venlafaxine and duloxetine, were judged to have any clinically important advantages over other antidepressants. Results from meta-analyses (Gartlehner et al. 2011 and 2 Cochrane reviews: Cipriani et al. July 2012 and Cipriani et al. Oct 2012) have provided no evidence to depart from NICE guidance when selecting antidepressants for people with depression.

The full guideline on GAD and panic disorder found that of the antidepressants available, there were sufficient clinical effectiveness data and an acceptable harm-to-benefit ratio for escitalopram, duloxetine, paroxetine, sertraline and venlafaxine XL. However, the economic analysis concluded that sertraline was the most cost-effective drug for people with GAD because it was associated with the highest number of quality-adjusted life years (QALYs) gained and the lowest total costs among all treatments assessed, including no treatment. As with depression, drug choice in GAD should also be influenced by several other factors relating to the
individual person, including their previous experience of treatments, likely drug interactions, safety and tolerability.

Drug safety warnings on antidepressants that have been issued by the Medicines and Healthcare products Regulatory Agency should be considered. See the December 2007 edition of Drug Safety Update for information on measures to reduce risk of fatal overdose with dosulepin and the December 2011 edition of Drug Safety Update for details about the association of dose-dependent QT interval prolongation with citalopram and escitalopram.

* If prescribing off-label, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

**Prescribing data**

Two prescribing comparators are available to support this key therapeutic topic:

- **Antidepressant (selected): ADQ/STAR PU (ADQ based):** the total number of average daily quantities (ADQs) for selected antidepressant prescribing per Antidepressants (BNF 4.3 sub-set) ADQ based Specific Therapeutic Group Age-sex weightings Related Prescribing Unit (STAR-PU)\(^1\).

- **Antidepressants: First choice % items:** the number of prescription items for ‘1\(^{st}\) choice’ generic SSRIs as a percentage of the total number of prescription items for selected ‘other antidepressants’\(^1\).

**Antidepressants: ADQ/STAR-PU**

- Data\(^2\) for the quarter April to June 2014 show a 3.6 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.13 to 0.46 ADQ/STAR-PU.

- Between Q4 2012/13 (January 2013 to March 2013) and Q1 2014/15 (April to June 2014) there was a 1.6% decrease in the comparator value for England (total prescribing) from 0.312 to 0.307 ADQ/STAR-PU.
• Over the same period there was a 2.9% decrease in the variation between CCGs, as measured by the inter-decile range\(^3\), an absolute decrease of 0.006 ADQ/STAR-PU.

**Antidepressants: First choice % items**

• Data\(^2\) for the quarter April to June 2014 show a 1.4 fold variation in prescribing rates at CCG level, from 53.8% to 75.1%.

• Between Q4 2012/13 (January 2013 to March 2013) and Q1 2014/15 (April to June 2014) there was a 0.2% increase in the comparator value for England (total prescribing) from 63.5% to 63.6%.

• Over the same period there was a 4.3% increase in the variation between CCGs, as measured by the inter-decile range\(^3\), an absolute increase of 0.42%.

\(^1\) The comparator and associated data are based on the current Key therapeutic topics publication. The comparators will be reviewed in conjunction with the update to this publication. See [Feedback on proposals for retaining, amending or retiring 2013/14 comparators.](#)

\(^2\) Data provided by the [Health and Social Care Information Centre](#), September 2014. Source: [Information Services Portal](#), Business Services Authority

\(^3\) The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.
Antibiotic prescribing – especially broad spectrum antibiotics

Options for local implementation

- Review and, if appropriate, revise current prescribing practice and use implementation techniques to ensure prescribing is in line with Public Health England (PHE) guidance.
- Review the total volume of antibiotic prescribing against local and national data.
- Review quinolone, cephalosporin and other broad spectrum antibiotic prescribing against local and national data.

Evidence context

Antibiotic resistance poses a significant threat to public health, especially because antibiotics underpin routine medical practice. The Chief Medical Officer’s report on the threat of antimicrobial resistance and infectious diseases (March 2013) highlights that, while a new infectious disease has been discovered nearly every year for the past 30 years, there have been very few new antibiotics developed. This is leaving the armoury nearly empty as diseases evolve and become resistant to existing drugs. The report highlights that looking after the current supply of antibiotics is equally as important as encouraging development of new drugs.

To help prevent the development of resistance it is important to only prescribe antibiotics when they are necessary, and not for self-limiting mild infections such as colds and most coughs, sinusitis, earache and sore throats. A study, which was outlined in a NICE Medicines evidence commentary [in progress], measured trends in antibiotic prescribing in UK primary care in relation to nationally recommended best practice. It found that antibiotic prescribing for coughs and colds increased from 36% in 1999 to 51% in 2011, with marked variation between practices (range 32% to 65%), despite government recommendations to reduce prescribing for self-limiting mild infections. In addition, in 2011, PHE guideline recommendations regarding choice of antibiotic were not followed for 31% of sore throats.

PHE guideline recommends that simple generic antibiotics should be used if possible when antibiotics are necessary. Broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) need to be reserved to treat resistant disease. They should generally be used only when narrow-spectrum antibiotics are
ineffective because they increase the risk of methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile* and resistant urinary tract infections.

Although MRSA bacteraemias have decreased, this organism remains a serious threat, especially to hospital inpatients. Addressing healthcare-associated *Clostridium difficile* infection also remains a key issue on which NHS organisations have been mandated to implement national guidance that includes restriction of broad-spectrum antibiotics, in particular second- and third-generation cephalosporins and clindamycin (see *Clostridium difficile infection: how to deal with the problem*).

According to PHE guidance (accessed September 2014), cefalexin and other cephalosporins (cefixime, cefotaxime and ceftriaxone) should be used only in limited situations (for example, second-line in upper and lower urinary tract infection [UTI] in children, and third-line in UTI in pregnant women). Clindamycin is recommended only for bacterial vaginosis (as a vaginal cream) and is an option for cellulitis and dental abscess in people with penicillin allergy.

The prescribing of quinolones (for example, ciprofloxacin and ofloxacin) in general practice is a particular cause for concern. Resistance to quinolones is increasing at a considerable rate (for example, quinolone-resistant *Neisseria gonorrhoeae*) and is usually high-level, affecting all the quinolones (see Susceptibility testing of *N. gonorrhoeae* for details). Quinolones are recommended first-line by PHE (accessed September 2014) only for acute pyelonephritis, acute prostatitis, epididymitis and pelvic inflammatory disease. They should be used in lower respiratory tract infections only when there is proven resistance to other antibiotics.

**According to PHE guidance** (accessed September 2014), co-amoxiclav is recommended only for persistent acute rhinosinusitis, upper UTI in children, acute pyelonephritis, facial cellulitis, and the prophylaxis and treatment of infection following bites. It may be used second-line in acute exacerbations of chronic obstructive pulmonary disease if infection is resistant to first-line options.

The [Department of Health website](http://www.dh.gov.uk) has more information on antibiotic resistance, and resources to help reduce inappropriate antibiotic prescribing. See also the [TARGET antibiotics toolkit](http://www.targetantibiotics.com), which has been developed by the Antimicrobial Stewardship in Primary Care collaboration (from several organisations including the Royal College...
of General Practitioners and PHE) to help clinicians and commissioners use antibiotics responsibly.

More information on managing common infections can be found in the NICE clinical guideline on respiratory tract infections, the NICE pathway on self-limiting respiratory tract infections – antibiotic prescribing and the MeReC Bulletin on managing common infections in primary care.

NICE is developing guidelines on Antimicrobial stewardship (publication expected May 2015) and Antimicrobial resistance - changing risk-related behaviours (publication expected March 2016).

**Prescribing data**

Two prescribing comparators are available to support this key therapeutic topic. These are:

- **Antibacterial items/STAR-PU**: the number of prescription items for antibacterial drugs (BNF 5.1) per Oral antibacterials (BNF 5.1 sub-set) ITEM based Specific Therapeutic Group Age-sex weightings Related Prescribing Unit (STAR-PU).¹

- **Cephalosporins & quinolones % items**: the number of prescription items for cephalosporins and quinolones as a percentage of the total number of prescription items for selected antibacterial drugs (BNF 5.1).¹

**Antibacterial items/STAR-PU**

- Data² for 2013/14 (April 2013 to March 2014) show a 2.2 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.67 to 1.51 items/STAR-PU.

- Between Q4 2012/13 (January 2013 to March 2013) and Q4 2013/14 (January 2014 to March 2014) there was a 2.8% decrease in the comparator value for England (total prescribing) from 0.32 to 0.31 items/STAR-PU.

- Over the same period there was a 2.3% increase in the variation between CCGs, as measured by the inter-decile range, an absolute increase of 0.002 items/STAR-PU.
Cephalosporins & quinolones % items

- Data\(^2\) for 2013/14 (April 2013 to March 2014) show a 6.1 fold variation in prescribing rates at CCG level, from 2.02% to 12.27%.
- Between Q4 2012/13 (January 2013 to March 2013) and Q4 2013/14 (January 2014 to March 2014) there was a 3.4% decrease in the comparator value for England (total prescribing) from 5.27% to 5.09%.
- Over the same period there was a 3.4% increase in the variation between CCGs, as measured by the inter-decile range\(^3\), an absolute increase of 0.13%.

\(^1\) The comparator and associated data are based on the current Key therapeutic topics publication. The comparators will be reviewed in conjunction with the update to this publication. See Feedback on proposals for retaining, amending or retiring 2013/14 comparators.

\(^2\) Data provided by the Health and Social Care Information Centre, September 2014. Source: Information Services Portal, Business Services Authority.

\(^3\) The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.
Three-day courses of trimethoprim for uncomplicated urinary tract infection

Options for local implementation

- Review and, if appropriate, revise current prescribing practice and use implementation techniques to ensure prescribing of 3-day courses of trimethoprim is in line with Public Health England (PHE) guidance.

Evidence context

According to PHE guidance, a 3-day course of antibiotic is sufficient for acute symptomatic uncomplicated urinary tract infection (UTI) in most women who are not pregnant. Uncomplicated UTI has been defined as infection in a woman with a normal urinary tract and normal renal function. The guidance advises that 7-day courses should be used for men with UTI.

Trimethoprim (200 mg twice daily) is an effective first-line treatment. Nitrofurantoin (100 mg modified-release twice daily) is also suitable, but is currently more expensive (Drug Tariff September 2014).

PHE guidance recommends that culture and sensitivity testing should be performed if first-line treatment fails. A MeReC Bulletin on the management of common infections in primary care stated that, although rates of resistance to trimethoprim have been reported to be high (20–40%), it should be remembered that resistance rates are based on urine samples from hospitals and from primary care. These samples are likely to disproportionately represent more complicated cases and treatment failures, with fewer samples collected from women with uncomplicated UTI. Amoxicillin resistance is common and this drug should be used only if culture and sensitivity testing proves the organism is susceptible. Broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) should be avoided if possible because they increase the risk of Clostridium difficile, methicillin-resistant Staphylococcus aureus (MRSA) and resistant UTIs.

A Cochrane review supports the use of 3-day courses of antibiotic therapy for uncomplicated UTI. Symptomatic failure rate was assessed and, at both short- and long-term follow-up, no significant difference was found in the number of people who still had symptoms following 3-day, or 5- to 10-day, courses of antibiotic treatment.
However, shorter courses of antibiotic treatment were associated with a 17% reduction in side effects. The review concluded that 3 days of antibiotic therapy is similar in effectiveness to 5 to 10 days for achieving symptomatic cure in women aged 18–65 years old who are not pregnant. Longer courses of treatment were more effective than 3 days of treatment in achieving bacteriological cure. Therefore, longer courses may be considered in complicated UTI (for example, pyelonephritis, pregnancy and recurrent UTI) if eradication of bacteriuria is important.

A study, which was outlined in a NICE Medicines Evidence Commentary [in progress], measured trends in antibiotic prescribing in UK primary care in relation to nationally recommended best practice. In uncomplicated UTI in women aged 16–74 years, it found that use of 3-day courses of trimethoprim increased from 8.4% in 1995 to 49.5% in 2011. However, between practice variation was marked. In 2011, the quarter of GP practices with the lowest prescribing rates prescribed short courses in only 16% or fewer episodes of uncomplicated urinary tract infection, compared with 71% in the quarter of practices with the highest rates.

More information on managing uncomplicated UTIs can be found in the MeReC Bulletin on the management of common infections in primary care. See the NICE Clinical Knowledge Summary on lower UTI in women for a general overview of the condition.

A NICE quality standard on urinary tract infections in adults is expected to be published in May 2015.

**Prescribing data**

A prescribing comparator is available to support this key therapeutic topic – 3 days trimethoprim ADQ/item: the total number of average daily quantities (ADQs) per item for trimethoprim 200 mg tablets.

- Data for the quarter April to June 2014 show a 1.8 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 4.73 to 8.45 ADQ/item.
- Between Q4 2012/13 (January 2013 to March 2013) and Q1 2014/15 (April to June 2014) there was a 2.6% decrease in the comparator value for England (total prescribing) from 6.08 to 5.92 ADQ/item.
· Over the same period there was a 0.7% increase in the variation between CCGs, as measured by the inter-decile range\(^3\), an absolute increase of 0.009 ADQ/item.

\(^1\) The comparator and associated data are based on the current Key therapeutic topics publication. The comparators will be reviewed in conjunction with the update to this publication. See Feedback on proposals for retaining, amending or retiring 2013/14 comparators.

\(^2\) Data provided by the Health and Social Care Information Centre, September 2014. Source: Information Services Portal, Business Services Authority

\(^3\) The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.
Minocycline

Options for local implementation

- Review and, if appropriate, revise prescribing of minocycline in light of its potential harms.

Evidence context

Although minocycline has various indications, it is used primarily as one of a number of oral antibiotics available for the treatment of acne. See the NICE Clinical Knowledge Summary on acne vulgaris (which does not recommend minocycline for the treatment of acne) for a general overview of this condition.

Unlike some other drugs in its class (for example, tetracycline and oxytetracycline) minocycline is available as a once-daily treatment and does not need to be taken on an empty stomach. However, there are concerns regarding its place in therapy:

- there are safety concerns specific to minocycline (see below)
- there is no clear evidence that minocycline is more effective or better tolerated than other tetracyclines
- alternative once-daily treatments such as doxycycline and lymecycline are available
- minocycline has a relatively high acquisition cost.

Minocycline has been associated with the following patterns of serious reactions (Cochrane review, 2012):

- early-onset dose-related toxicity reactions resulting in single organ dysfunction (including potentially fatal liver failure)
- autoimmune disorders (such as systemic lupus erythematosus-like syndrome which has a strong relationship with duration of exposure, and autoimmune hepatitis)
- hypersensitivity reactions (including eosinophilia, pneumonitis and nephritis).

In addition, minocycline can cause slate-grey hyperpigmentation of the skin, which may be irreversible (Drug and Therapeutics Bulletin, 2006).
The Cochrane review updated in 2012 found no evidence to justify the use of minocycline for first-line treatment of acne. There was no evidence that minocycline was more effective than other commonly used acne treatments, including other tetracyclines. It was not possible to reliably estimate the likelihood of having an adverse effect while taking minocycline, but it was associated with more severe adverse effects than doxycycline. Also, unlike other tetracyclines, minocycline was associated with lupus erythematosus. In addition, there is no evidence to suggest that the extended-release preparation is safer than standard minocycline preparations.

As well as important quality issues, minocycline remains 1 of the more costly oral options for the treatment of acne. In 2011, the UK Cochrane Centre and NICE estimated that substituting minocycline with an alternative tetracycline could save the NHS approximately £2.2 million.

**Prescribing data**

A prescribing comparator is available to support this key therapeutic topic – Minocycline ADQ/1000 patients: the total number of average daily quantities (ADQs) for minocycline per 1000 patients\(^1\).

- Data\(^2\) for the quarter April to June 2014 show a 41.4 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 1.0 to 41.1 ADQ/1000 patients.
- Between Q4 2012/13 (January 2013 to March 2013) and Q1 2014/15 (April to June 2014) there was a 31.7% decrease in the comparator value for England (total prescribing) from 19.93 to 13.61 ADQ/1000 patients.
- Over the same period there was a 34.7% decrease in the variation between CCGs, as measured by the inter-decile range\(^3\), an absolute decrease of 7.94 ADQ/1000 patients.

\(^1\) The comparator and associated data are based on the current Key therapeutic topics publication. The comparators will be reviewed in conjunction with the update to this publication. See Feedback on proposals for retaining, amending or retiring 2013/14 comparators.
Data provided by the Health and Social Care Information Centre, September 2014. Source: Information Services Portal, Business Services Authority

The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.
Type 2 diabetes mellitus

Options for local implementation

- Consider carefully the risks and benefits of both intensive glycaemic control and use of blood glucose-lowering therapies for type 2 diabetes mellitus. Review and, if appropriate, revise prescribing to ensure that it is in line with NICE guidance.
- Review and, if appropriate, revise prescribing of long-acting insulin analogues for type 2 diabetes mellitus to ensure that it is in line with NICE guidance.
- Review and, if appropriate, revise local use of self-monitoring of blood glucose for type 2 diabetes mellitus to ensure that it is in line with NICE guidance.

Evidence context

The management of people with type 2 diabetes mellitus is complex. It needs an individualised multifactorial approach addressing blood glucose, blood pressure, blood lipids and lifestyle issues (for example, smoking cessation, exercise, losing weight and a healthy diet). Controlling blood glucose needs a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia.

The NICE clinical guideline on type 2 diabetes (which is being updated; publication expected August 2015) recommends that people should be involved in setting their individualised HbA$_{1c}$ target level, which may be above the general target of 48 mmol/mol (6.5%). Any reduction in HbA$_{1c}$ towards the agreed target level is advantageous to future health, but highly intensive management with the aim of reducing HbA$_{1c}$ levels to below 48 mmol/mol (6.5%) should be avoided.

The Quality and Outcomes Framework (QOF) allocates points for achieving 3 levels of glucose control in people with type 2 diabetes: HbA$_{1c}$ of 75 mmol/mol (9%) or less, 64 mmol/mol (8%) or less and 59 mmol/mol (7.5%) or less.

See the NICE Clinical Knowledge Summary on type 2 diabetes for a general overview of the condition. The NICE pathway on diabetes brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams. There is also a NICE quality standard defining clinical best practice for diabetes in adults.
Intensive versus conventional blood glucose control

A Cochrane review identified 28 randomised controlled trials which compared intensive glycaemic control with conventional glycaemic control in people with type 2 diabetes. A total of 18,717 people were randomised to intensive glycaemic control and 16,195 to conventional glycaemic control for between 3 days and 12.5 years. Compared with conventional control, intensive glycaemic control did not reduce death from any cause, cardiovascular death, non-fatal stroke, or cardiac or peripheral revascularisation. Intensive glycaemic control statistically significantly reduced the risk of non-fatal myocardial infarction, amputation of a lower extremity, and microvascular complications (including nephropathy and retinopathy), but increased the risk of severe adverse events and hypoglycaemia. Only 2 trials had a low risk of bias; and the authors of the review suggested that better quality trials are needed in this area.

A randomised controlled trial found no significant benefits for early detection and intensive multifactorial management of type 2 diabetes in improving any patient-oriented cardiovascular outcomes over 5 years, compared with usual care – see MeReC Rapid Review No. 4233.

Newer blood glucose-lowering drugs

Treatment to control blood glucose should be tailored to each person’s clinical needs, with safety paramount. The NICE clinical guideline on type 2 diabetes (which is being updated; publication expected August 2015) currently recommends that metformin should be used as first-line treatment and a sulfonylurea should usually be used as second-line treatment. The evidence base for blood glucose-lowering drugs is particularly complex, with the availability of multiple newer drugs that can be used in varying combinations with older drugs. No randomised controlled trial has included all possible combinations for a long enough period, in a large enough number of people at different stages of type 2 diabetes to show which treatment is optimal.

Although newer blood glucose-lowering drugs are effective at reducing HbA\textsubscript{1c} levels, there are limited clinical outcome data, particularly around cardiovascular effects and long-term safety in people with type 2 diabetes. Improvements in surrogate markers (including HbA\textsubscript{1c} levels) do not automatically confer benefits on mortality or
morbidity, and risks may only become apparent over time when these agents have more widespread use in a diverse population. A large randomised controlled trial of saxagliptin found that adding this drug to other blood-glucose-lowering drugs did not reduce the risk of cardiovascular events or some renal outcomes at around 2 years. However, adding saxagliptin increased the risk of hypoglycaemia and may also have increased the risk of admission to hospital because of heart failure (see the Medicines Evidence Commentary: Type 2 diabetes: study finds no benefit from saxagliptin on cardiovascular outcomes for details). A similar large randomised controlled trial with alogliptin found that adding this drug to other blood-glucose-lowering drugs did not reduce the risk of cardiovascular events in people with type 2 diabetes who had had a recent acute coronary syndrome, over a median of 18 months (see the Medicines Evidence Commentary: Type 2 diabetes: study finds no benefit from alogliptin on cardiovascular outcomes in people with a recent acute coronary syndrome for details).

The Medicines and Healthcare products Regulatory Agency (MHRA) has highlighted several safety concerns with newer blood glucose-lowering drugs. Warnings about pioglitazone and risks of heart failure, bladder cancer and use in older people have been incorporated into the summaries of product characteristics.

All the glucagon-like-peptide-1 (GLP-1)-based therapies, GLP-1 agonists and dipeptidylpeptidase-4 inhibitors (gliptins) have warnings in their summaries of product characteristics about a risk of developing acute pancreatitis. In the March 2009 edition of Drug Safety Update, the MHRA drew attention to reports of severe pancreatitis and renal failure associated with exenatide, and in the September 2012 edition of Drug Safety Update, reports of acute pancreatitis associated with gliptins.

There are several pieces of NICE guidance relating to the use of newer blood glucose-lowering drugs for the treatment of type 2 diabetes that can be accessed from the NICE condition page on diabetes. These include the NICE clinical guideline on type 2 diabetes (which is being updated; publication expected August 2015) and various technology appraisals.
Long-acting insulin analogues

The NICE clinical guideline on type 2 diabetes (which is being updated; publication expected August 2015) recommends that, when insulin therapy is necessary, human NPH (isophane) insulin (for example, Insulatard, Humulin I or Insuman Basal) is the preferred option. Long-acting insulin analogues can be considered in some people, including people who need assistance from a carer or healthcare professional to administer their insulin, people whose lifestyle is restricted by recurrent symptomatic hypoglycaemia, people who would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs, or people who cannot use the device to inject NPH insulin.

The evidence review conducted for the NICE guideline found that there was no difference in HbA$_{1c}$ lowering between long-acting insulin analogues and NPH (isophane) insulin. Compared with NPH (isophane) insulin, insulin glargine and insulin detemir were both associated with statistically significant reductions in the rates of any hypoglycaemia and of nocturnal hypoglycaemia, but not severe hypoglycaemia. The cost-effectiveness analysis found that long-acting insulin analogues did not appear to be cost-effective options when compared with NPH (isophane) insulin. All the incremental cost-effectiveness ratios (ICERs) were outside the conventional limits of cost effectiveness, with ICERs ranging from about £100,000 to £400,000 per quality-adjusted life year (QALY) gained depending on the scenario in which they are used. These are substantially greater than the £20,000 to £30,000 per QALY gained threshold usually considered in NICE’s cost-effectiveness evaluations. The update of the NICE clinical guideline will include the long-acting insulin analogue, insulin degludec.

The ORIGIN study found that, compared with standard care (non-insulin therapy), the early use of basal insulin glargine for a median of 6 years had no effect on cardiovascular outcomes in people with impaired fasting glucose, impaired glucose tolerance or early type 2 diabetes who also had cardiovascular risk factors. As perhaps expected, episodes of severe hypoglycaemia were more common in people receiving insulin glargine. The incidence of a first episode of severe hypoglycaemia was 1.00 per 100 patient-years with insulin glargine and 0.31 per 100 patient-years
with standard care (p<0.001) (see the Medicines Evidence Commentary: Insulin glargine: no effect on cardiovascular outcomes in early type 2 diabetes for details).

Self-monitoring of blood glucose

The NICE clinical guideline on type 2 diabetes (which is being updated; publication expected August 2015) gives recommendations on the place of self-monitoring of blood glucose in people with type 2 diabetes. The guideline recommends that it should be used only if it is going to be an integral part of the person’s self-management education, and the continued benefit of self-monitoring should be assessed in a structured way each year. NICE recommends that self-monitoring of blood glucose is appropriate in some people with type 2 diabetes, and should be available:

- to people on insulin treatment
- to people on oral glucose-lowering medications to provide information on hypoglycaemia
- to assess changes in glucose control resulting from medication and lifestyle changes
- to monitor changes during intercurrent illness
- to ensure safety during activities, including driving.

Healthcare professionals should also be aware of DVLA recommendations on the monitoring of blood glucose, in order to best advise people about their own particular requirements.

A Cochrane review found the overall effect of self-monitoring of blood glucose on glycaemic control in people with type 2 diabetes who were not using insulin was small up to 6 months after initiation, and disappeared after 12 months. There was no evidence that self-monitoring of blood glucose affects patient satisfaction, general wellbeing or general health-related quality of life.

Prescribing data

Newer blood glucose-lowering drugs

The Health and Social Care Information Centre report Prescribing for diabetes in England: 2005/6 to 2013/14 found that the prescribing of ‘other antidiabetic drugs’
(which includes the newer blood glucose-lowering drugs) has increased considerably in recent years. The number of items prescribed increased by 66.5% (18.0 million) from 2005/6 to 2013/14 with a growth in net ingredient cost of 56.3% (£289.2 million).

A prescribing comparator is available to support this QIPP topic: Hypoglycaemic drugs\(^1\): the number of prescription items for metformin and sulfonylureas as a percentage of the total number of prescription items for all antidiabetic drugs\(^2\).

- Data\(^3\) for the quarter April to June 2014 show a 1.3 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 73.3% to 93.8%.
- Between Q4 2012/13 (January 2013 to March 2013) and Q1 2014/15 (April to June 2014) there was a 1.2% decrease in the comparator value for England (total prescribing) from 84.2% to 83.2%.
- Over the same period there was an 8.0% increase in the variation between CCGs, as measured by the inter-decile range\(^4\), an absolute increase of 0.69%.

\(^1\) The name of this prescribing comparator will be changed to ‘Blood glucose-lowering drugs’ when the comparators are reviewed in conjunction with the update to this publication.

\(^2\) The comparator and associated data are based on the current Key therapeutic topics publication. The comparators will be reviewed in conjunction with the update to this publication. See Feedback on proposals for retaining, amending or retiring 2013/14 comparators.

\(^3\) Data provided by the Health and Social Care Information Centre, September 2014.

Source: Information Services Portal, Business Services Authority

\(^4\) The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

Long-acting insulin analogues

The Health and Social Care Information Centre report Prescribing for diabetes in England: 2005/6 to 2013/14 found the net ingredient cost of all insulin therapy in primary care in 2013/14 was £328.3 million; a growth of 48.7% from 2005/6. In the
financial year 2013/4, 1.36 million items of insulin glargine were prescribed at a cost of over £78 million, 690,000 items of insulin detemir were prescribed at a cost of £43 million and 6000 items of insulin degludec at a cost of £675,000. This compared with 460,000 items of NPH (isophane) insulin at a cost of £15 million.

A prescribing comparator is available to support this key therapeutic topic: Long-acting insulin analogues: Number of prescription items for long-acting human analogue insulins as a percentage of the total number of prescription items for all long-acting and intermediate acting insulins excluding biphasic insulins¹.

- Data² for the quarter April to June 2014 show a 2.7 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 36.0% to 97.0%.
- Between Q4 2012/13 (January 2013 to March 2013) and Q1 2014/15 (April to June 2014) there was a 2.4% decrease in the comparator value for England (total prescribing) from 82.6% to 80.6%.
- Over the same period there was a 4.0% decrease in the variation between CCGs, as measured by the inter-decile range³, an absolute decrease of 1.06%.

Self-monitoring of blood glucose

There is currently no prescribing comparator for this topic.
Non-steroidal anti-inflammatory drugs

Options for local implementation

- Review the appropriateness of non-steroidal anti-inflammatory drug (NSAID) prescribing widely and on a routine basis, especially in people who are at higher risk of both gastrointestinal and cardiovascular morbidity and mortality (for example, older people).
- If an NSAID is needed, use ibuprofen (1200 mg per day or less) or naproxen (1000 mg per day or less). Use the lowest effective dose and the shortest duration of treatment necessary to control symptoms.
- Review and, if appropriate, revise prescribing of etoricoxib to ensure it is in line with Medicines and Healthcare products Regulatory Agency (MHRA) advice and the NICE clinical guideline on osteoarthritis.
- Co-prescribe a proton pump inhibitor with NSAIDs for people with osteoarthritis, rheumatoid arthritis or low back pain (which is being updated; publication expected November 2016) [for people over 45 years], in accordance with NICE clinical guidelines.

Evidence context

There are long-standing and well-recognised gastrointestinal and renal safety concerns with all NSAIDs. There is also substantial evidence confirming an increased risk of cardiovascular events with many NSAIDs, including COX-2 inhibitors and some traditional NSAIDs such as diclofenac.

In the February 2009 edition of Drug Safety Update, the MHRA recommended that the lowest effective dose of an NSAID should be prescribed for the shortest duration of treatment necessary for control of symptoms.

In 2005, a review by the European Medicines Agency (EMA) identified an increased risk of thrombotic events, such as heart attack and stroke, with COX-2 inhibitors. In 2006, they also concluded that a small increased risk of thrombotic events could not be excluded with non-selective NSAIDs, including diclofenac, particularly when they are used at high doses for long-term treatment. This risk does not appear to be shared by ibuprofen at 1200 mg per day or less, or naproxen at 1000 mg per day.
In 2012, a new EMA review on the cardiovascular safety of NSAIDs highlighted further evidence that diclofenac is associated with higher cardiovascular risks than the other non-selective NSAIDs, and similar cardiovascular risks to the COX-2 inhibitors. Naproxen and low-dose ibuprofen (1200 mg per day or less) are still considered to have the most favourable thrombotic cardiovascular safety profiles of all non-selective NSAIDs. See the Medicines Evidence Commentary: EMA review of cardiovascular risks of NSAIDs: higher risk with diclofenac compared with ibuprofen/naproxen confirmed and Eyes on Evidence commentary: Non-steroidal anti-inflammatory drugs: new information and warnings about cardiovascular risk.

In the June 2013 edition of Drug Safety Update the MHRA highlighted updated contraindications and prescribing advice for diclofenac following the publication of the EMA review. In August 2013 a public consultation was also launched on the continued availability of oral diclofenac as a Pharmacy (P) medicine and in particular on risk-minimisation measures as advised by the Commission of Human Medicines.

In June 2014 an EMA Review was started to evaluate the cardiovascular risks of high-dose ibuprofen (2400 mg per day) taken regularly for long periods. The review will also evaluate evidence on the interaction of ibuprofen with low-dose aspirin to decide whether current advice to healthcare professionals is sufficient.

Other safety concerns have been highlighted with etoricoxib specifically. The MHRA has advised that etoricoxib may be associated with more frequent and severe effects on blood pressure than some other COX-2 inhibitors and NSAIDs, particularly at high doses. The summary of product characteristics states that hypertension should be controlled before treatment with etoricoxib and special attention should be paid to blood pressure monitoring during treatment. Blood pressure should be monitored within 2 weeks of starting etoricoxib treatment, and periodically thereafter. If blood pressure rises significantly, alternative treatment should be considered.

The NICE clinical guideline on osteoarthritis recommends against using etoricoxib 60 mg as a first-line treatment on the basis of cost effectiveness. For the treatment of osteoarthritis, the maximum licensed dose of etoricoxib recommended in the summary of product characteristics is 60mg daily. The EMA assessed the long-term benefits and risks of etoricoxib in people with rheumatoid arthritis or ankylosing
spondylitis and concluded that the benefits outweighed the risks in these conditions when used at a dosage of 90 mg daily.

The 2014 updated NICE clinical guideline on osteoarthritis does not make new recommendations on pharmacological management. NICE intends to commission a full review of evidence on the pharmacological management of osteoarthritis to inform a further guideline update. This will start once the MHRA’s review of the safety of over-the-counter analgesics is completed. Until that update is published, the original recommendations (from 2008) on the pharmacological management of osteoarthritis remain current advice.

It is important to take account of drug interactions when co-prescribing NSAIDs with other medicines (see summaries of product characteristics). For example, co-prescribing NSAIDs with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may pose particular risks to renal function. This combination should be especially carefully considered and regularly monitored if continued. See the Medicines Evidence Commentary: Risk of acute kidney injury with concurrent use of antihypertensives and NSAIDs for further information on this issue.

See the NICE Clinical Knowledge Summary on NSAIDs—prescribing issues for a general overview of this topic.

**Prescribing data**

Two prescribing comparators are available to support this key therapeutic topic. These are:

- **NSAIDs: ADQ/STAR-PU**: the total number of average daily quantities (ADQs) of all NSAIDs prescribed per COST based Specific Therapeutic Group Age-sex weightings Related Prescribing Unit (STAR-PU)\(^1\).
- **NSAIDs: Ibuprofen & naproxen % items**: the total number of ibuprofen and naproxen items prescribed as a percentage of the total number of all NSAID prescription items\(^1\).
**NSAIDs: ADQ/STAR-PU**

- Data\(^2\) for the quarter April to June 2014 show a 3.8 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.72 to 2.74 ADQ/STAR-PU.
- Between Q4 2012/13 (January 2013 to March 2013) and Q1 2014/15 (April to June 2014) there was a 4.1% decrease in the comparator value for England (total prescribing) from 1.57 to 1.50 ADQ/STAR-PU.
- Over the same period there was a 10.5% decrease in the variation between CCGs, as measured by the inter-decile range\(^3\), an absolute decrease of 0.1 ADQ/STAR-PU.

**NSAIDs: Ibuprofen & naproxen % items**

- Data\(^2\) for the quarter April to June 2014 show a 1.5 fold variation in prescribing rates at CCG level, from 56.3% to 85.9%.
- Between Q4 2012/13 (January 2013 to March 2013) and Q1 2014/15 (April to June 2014) there was an 11.7% increase in the comparator value for England (total prescribing) from 66.9% to 74.7%.
- Over the same period there was a 22.4% decrease in the variation between CCGs, as measured by the inter-decile range\(^3\), an absolute decrease of 3.49%.

The prescribing of diclofenac has reduced in recent years. However, diclofenac still accounts for approximately 2 million prescription items (13% of all NSAID items) per year in primary care in England, and there is variation in prescribing across localities.

\(^1\) The comparator and associated data are based on the current Key therapeutic topics publication. The comparators will be reviewed in conjunction with the update to this publication. See Feedback on proposals for retaining, amending or retiring 2013/14 comparators.

\(^2\) Data provided by the Health and Social Care Information Centre, September 2014. Source: Information Services Portal, Business Services Authority

\(^3\) The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.
Wound care products

Options for local implementation

- Review and, if appropriate, revise prescribing of wound dressings to ensure that the least costly dressings that meet the required clinical performance characteristics are routinely chosen.

- Prescribe the minimum quantity of dressings sufficient to meet people’s needs.

- Do not routinely choose antimicrobial (for example, silver, iodine or honey) dressings ahead of non-medicated dressings.

Evidence context

NICE has published guidelines on the prevention and management of foot problems in type 2 diabetes (which is being updated; publication expected July 2015), pressure ulcers: prevention and management of pressure ulcers, surgical site infection, and inpatient management of diabetic foot problems (which is being updated; publication expected July 2015). Although these clinical guidelines give important recommendations about wound care, they do not make recommendations on specific products.

Prescribers’ ability to choose wound dressings on the basis of clinical evidence is hindered by the relative lack of robust clinical or cost-effectiveness evidence, as highlighted in numerous systematic reviews (see the MeReC Bulletin on evidence-based prescribing of advanced wound dressings and the Cochrane reviews on wounds). Although there is some evidence that modern or advanced dressings (for example, hydrocolloids, alginates and hydrofibre dressings) are more clinically effective than conventional dressings (such as paraffin gauze) for treating wounds, there is insufficient evidence to distinguish between them.

A large number of wound dressings are available with a wide range of physical performance characteristics (such as size, adhesion, conformability and fluid handling properties). Although laboratory characterisation tests provide a means of comparing their performance, they cannot always predict how the dressings will perform in the clinical situation.

Dressing selection should be made following careful clinical assessment of the person’s wound, their clinical condition, and their personal experience and
preferences. In the absence of any robust clinical evidence to guide choice, prescribers should routinely choose the **dressing with the lowest acquisition cost** and the performance characteristics appropriate for the wound and its stage of healing.

There is at present no robust clinical or cost-effectiveness evidence to support the use of antimicrobial dressings (for example, silver, iodine or honey) over non-medicated dressings for preventing or treating chronic wounds. Indiscriminate use should be discouraged because of concerns over bacterial resistance and toxicity. Antimicrobial dressings may be considered to help reduce bacterial numbers in wounds, but should be avoided unless the wound is infected or there is a clinical risk of the wound becoming infected.

The [British National Formulary (BNF)](https://www.medicines_complete.com/bnf) advises that dressings containing silver should be used **only** when infection is suspected as a result of clinical signs and symptoms. They should not be used on acute wounds (because there is some evidence that they delay healing) or used routinely for managing uncomplicated ulcers. Antimicrobial dressings should be prescribed for defined short periods of time and their use reviewed regularly.

Wound care products are sometimes prescribed in large quantities to people for use on an as-needed basis. The minimum quantity of dressings necessary to meet people’s needs should be prescribed to reduce avoidable wastage. The frequency of dressing change should be appropriate for the wound and dressing type. Healthcare professionals making visits to people with chronic wounds should monitor supplies to prevent stockpiling.

Further information on the prescribing of dressings for chronic wounds in primary care can be found in the MeReC Bulletin on [evidence-based prescribing of advanced wound dressings](https://www.medicinescomplete.com/me-rec-bulletin-2013-03-5-evidence-based-prescribing-for-adults-nocare-wounds).

**Prescribing data**

A [prescribing comparator](https://www.medicinescomplete.com/me-rec-bulletin-2013-03-5-evidence-based-prescribing-for-adults-nocare-wounds) is available for this topic – **Wound care products**:

**NIC/item:** the net ingredient cost (NIC) per item for wound care products\(^1\). The comparator is to be retired\(^2\) (date to be agreed) and therefore data is not presented.
1 The comparator is based on the current Key therapeutic topics publication.

2 See Feedback on proposals for retaining, amending or retiring 2013/14 comparators.

About these key therapeutic topics
This document summarises the evidence-base on these key therapeutic topics which have been identified to support the QIPP medicines use and procurement work stream. It is not formal NICE guidance.

For information about the process used to develop the Key therapeutic topics – medicines management options for local implementation document, see the integrated process statement.

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