Key therapeutic topics

Medicines management options for local implementation

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Foreword

I am delighted to welcome the latest update of the Key therapeutic topics – Medicines management options for local implementation document, produced by the Medicines and Prescribing Centre at NICE. This document supports Medicines Optimisation, but is not formal NICE guidance.

After consultation and feedback from the NHS and partner organisations on the therapeutic topics included in this document, the 14 topics from January 2013 have been retained and updated in the light of new guidance and important new evidence.

The prescribing comparators developed to support previous versions of the Key therapeutics topics document will be reviewed to ensure they support this latest update. Further details can be found on the Health and Social Care Information Centre (HSCIC) and NHS Business Services Authority (NHSBSA) websites.

Included in this update is prescribing comparator data provided by HSCIC that highlights the excellent progress made on the original key therapeutic topics. The data demonstrate improvements (in terms of reduced variation in prescribing and movement of the mean in the desired direction) in a number of areas.

Thank you once again for your continuing hard work in the pursuit of high quality prescribing and medicines optimisation.

Yours sincerely

Dr Bruce Warner
Deputy Chief Pharmaceutical Officer NHS England
KTT1: 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 guideline on constipation in children and young people.
- The NICE 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 managing 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 (CD007570) 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 (CD009118) 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 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 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 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 guidance 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 guidance 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 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, an absolute increase of 0.08 ADQ/STAR-PU. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

\(^1\) The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2013). Data provided by the Health and Social Care Information Centre (September 2014; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the Health and Social Care Information Centre website and the Information Services Portal, Business Services Authority.
KTT2: 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 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 table 1 for details.

In the NICE 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
people younger than 55 years (except for black people of African or Caribbean family origin, who should be offered a calcium-channel blocker). MeReC Rapid Review No. 4470 explains the rationale behind this guideline. A Cochrane review (CD009096) 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 the weaker evidence for the efficacy of ARBs when choosing an ARB over an ACE inhibitor for hypertension.

The NICE 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 1 for details). A renin-angiotensin system antagonist is defined in the NICE 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 commentaries Do renin-angiotensin system drugs reduce mortality in hypertension? and Angiotensin receptor blockers for chronic heart failure
- Medicines Evidence Commentaries Differences between candesartan and losartan for heart failure? and 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 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 guideline on chronic heart failure recommends that, after seeking 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 table 1 for details). Candesartan and valsartan are the only 2 ARBs licensed as add-on therapy to ACE inhibitors in this situation. The MHRA states 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 because 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.
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<th>Relevant NICE guideline</th>
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<th>Recommendation in relation to dual blockade with renin-angiotensin system drugs</th>
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<tr>
<td>Hypertension</td>
<td>Hypertension: Clinical management of primary hypertension in adults, NICE guideline CG127 (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>
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<td>Heart failure</td>
<td>Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care, NICE guideline CG108 (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 ACE inhibitors.</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 combination with nitrate.</td>
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<td>Myocardial infarction (MI) – secondary prevention</td>
<td>MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction, NICE guideline CG172 (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>
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<td>Indication</td>
<td>Relevant NICE guideline</td>
<td>Recommendation in relation to renin-angiotensin system drugs</td>
<td>Recommendation in relation to dual blockade with renin-angiotensin system drugs</td>
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| Chronic kidney disease (CKD) | Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care. NICE guideline CG182 (July 2014) | Offer a low-cost renin-angiotensin system antagonist 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 to people with CKD. |
| Type 1 diabetes | Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults. NICE guideline CG15 (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 guideline CG87 (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 renal deterioration or hyperkalaemia), change to an ARB. | No recommendation on dual blockade. |

*A renin-angiotensin system antagonist is defined in the NICE guideline on chronic kidney disease 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%. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

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2 The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2013). Data provided by the Health and Social Care Information Centre (September 2014; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the Health and Social Care Information Centre website and the Information Services Portal, Business Services Authority.
KTT3: 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 guideline on lipid modification (published July 2014) updates and replaces NICE guideline 67 (published May 2008) and NICE technology appraisal guidance 94 (published January 2006). It also updates recommendations relating to lipid modification therapy in the NICE 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 guideline on chronic kidney disease [published July 2014]).

Statins

The NICE 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, rosvastatin 5 mg daily, simvastatin 20–40 mg daily.
- High intensity: more than 40% LDL-C reduction; atorvastatin 20–80 mg daily, rosvastatin 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 has produced a patient decision aid [Taking a statin to reduce the risk of coronary heart disease and stroke](#) to help a person making this decision weigh up the possible advantages and disadvantages of the different options.

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 who have had diabetes for more than 10 years, or who have established nephropathy, or who 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 person 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.

NICE recommends increasing the dose of atorvastatin from 20 mg in people with chronic kidney disease receiving it for primary or secondary prevention of CVD if a greater than 40% reduction in non-HDL cholesterol is not achieved and the person’s eGFR is 30 ml/min/1.73 m² or more. If their eGFR is less than this, any increase in dose should be discussed with a renal specialist. 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 to inform the discussion.

An analysis of data from the LIPID study (Monitoring Cholesterol Levels: Measurement Error or True Change?, by Glasziou et al. 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 NICE guideline on lipid modification 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 MHRA advised that
there is an increased risk of myopathy associated with simvastatin 80 mg daily, and
that this dose should be considered only in people 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](#), Nicholls et al. 2011) 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 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 [which is being updated; publication expected May 2016]). 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.

Therefore, 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 *Follow-up of people started on statin treatment*) and changing to a different statin is being considered.

The guideline states that healthcare 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 (Baigent et al. 2011) 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 (*ClinicalTrials.gov Identifier: NCT00202878*) 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 has been completed but the results have not been published in full in a peer reviewed journal at the time of preparation of this key therapeutic topic.

*Bile acid sequestrants, fibrates and nicotinic acid*

The NICE guideline on lipid modification 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: [Omega-3 fatty acid supplements](#).
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\(^3\).

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

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 MHRA advice; *Drug Safety Update May 2010*). 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)

\(^3\) The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2013). Data provided by the Health and Social Care Information Centre (September 2014; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the Health and Social Care Information Centre website and the Information Services Portal, Business Services Authority.
• atorvastatin 80 mg and rosuvastatin 40 mg daily (55% and 53% respectively).

Rosuvastatin 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).

**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.\(^4\)

• 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 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.

\(^4\) The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2013). Data provided by the Health and Social Care Information Centre (September 2014; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the Health and Social Care Information Centre website and the Information Services Portal, Business Services Authority.
KTT4: 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 to people who are being treated 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 guideline recommends that healthcare professionals should tell people that there is no evidence that omega-3 fatty acid compounds help to prevent cardiovascular disease. This guideline updated and replaced recommendations about omega-3 fatty acid compounds in the guideline on type 2 diabetes (which is being updated, publication expected August 2015).

The NICE 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 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)\(^5\).

- Data 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, an absolute decrease of 0.23 ADQ/STAR-PU. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

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.

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\(^5\) The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2013). Data provided by the Health and Social Care Information Centre (September 2014; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the Health and Social Care Information Centre website and the Information Services Portal, Business Services Authority.
KTT5: 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 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.

In the May 2006 edition of Current Problems in Pharmacovigilance, the MHRA advised 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 the Medicines Evidence Commentary Risk of adrenal insufficiency with inhaled corticosteroids], growth retardation in children and young people [see also the Medicines Evidence Commentary Asthma in children and young people: effects of inhaled corticosteroids on growth], 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 need prolonged treatment with high doses.
of ICS (see the May 2006 edition of Current Problems in Pharmacovigilance for more information). 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 Stepping down inhaled corticosteroids in asthma: randomised controlled trial, 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 guidance 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 the Medicines Evidence Commentary Asthma: study finds many people have a substantial increase in dose of inhaled corticosteroid when started on combination inhaler therapy, found that 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 on fluticasone furoate/vilanterol [Relvar Ellipta] combination inhaler in asthma). In addition, a Drug and Therapeutics Bulletin on Relvar Ellipta for asthma has highlighted concerns that the name and colour of the Relvar Ellipta inhaler could lead to inappropriate use by people believing it to be a reliever.

The NICE quality standard for asthma states 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 Royal College of Physicians’ 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 by the Health and Social Care Information Centre. However, there are several clinical and technical issues around the development of a meaningful comparator for this topic.
KTT6: 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. A case-control study discussed in a Medicines Evidence Commentary Benzodiazepine use and risk of Alzheimer’s disease found that past benzodiazepine use was associated with an increased risk of Alzheimer’s disease. The study suggests that taking benzodiazepines for more than 3 months and the use of agents with longer half-lives strengthen the association, but potential biases in the study limit the conclusions that can be drawn. 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. In the May 2014 edition of Drug Safety Update, the MHRA 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, in the January issue of Current Problems in Pharmacovigilance, 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 guidance 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 guidance 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 about 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 people who may have an addiction to prescribed or over-the-counter medicines and how to approach and help them.

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 assessing 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)\(^6\).

- Data 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, an absolute decrease of 0.03 ADQ/STAR-PU. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

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\(^6\) The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2013). Data provided by the Health and Social Care Information Centre (September 2014; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the Health and Social Care Information Centre website and the Information Services Portal, Business Services Authority.
KTT7: 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) guideline on dementia and the NICE quality standard on dementia, and the Alzheimer’s Society best practice guide.

Evidence context

The NICE/SCIE 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 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 Quality outcomes for people with dementia: Building on the work of the national dementia strategy, which is an implementation plan for their guidance 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

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7 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 Prescribing guidance: Prescribing unlicensed medicines for further information.
Update the MHRA provides the following advice for health 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 the 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 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 treating 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.

**Prescribing data**

There is currently no prescribing comparator for this key therapeutic topic, but the
development of a suitable comparator continues to be explored by the Health and
Social Care Information Centre. However, the National dementia and antipsychotic
prescribing audit from 2012 suggests that there has been an encouraging overall
reduction in the proportion of people with dementia being prescribed antipsychotics
in recent years. A re-run of the national data collection for the audit is planned for
2014; see the National Dementia and Antipsychotic Prescribing Audit website for
more details.

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.
KTT8: 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 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 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 guidelines on antenatal and postnatal mental health and on 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. It recommends offering, or referring people for, the least intrusive and 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 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, the NICE guideline on depression 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, the NICE guideline on GAD 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. The NICE guideline on depression 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 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 (Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder, Gartlehner et al. 2011 and 2 Cochrane reviews: Cipriani et al.

8 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 Prescribing guidance: Prescribing unlicensed medicines for further information.
2012, CD006534 and Cipriani et al. 2012, CD006533) 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 MHRA 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.

**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).

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9 The comparators and associated data presented here are based on the previous Key therapeutic topics publication (January 2013). Data provided by the Health and Social Care Information Centre (September 2014; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the Health and Social Care Information Centre website and the Information Services Portal, Business Services Authority.
• **Antidepressants: First choice % items**: the number of prescription items for ‘1\textsuperscript{st} choice’ generic SSRIs as a percentage of the total number of prescription items for selected ‘other antidepressants’.

**Antidepressants: ADQ/STAR-PU**

• Data 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, an absolute decrease of 0.006 ADQ/STAR-PU. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

**Antidepressants: First choice % items**

• Data 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, an absolute increase of 0.42%. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.
KTT9: 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 the updated Public Health England (PHE) guidance on managing common infections.
- 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 Antibiotic prescribing: study suggests there is scope for improvements, 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, recommendations in the Public Health England (PHE) guidance on managing common infections about choice of antibiotic were not followed for 31% of sore throats.
The updated PHE guidance on managing common infections recommends that consideration should be given to a no, or back-up or delayed, antibiotic strategy for acute self-limiting upper respiratory tract infections, and mild urinary tract infections (UTIs). It also advises that people are given supporting information about antibiotic strategies, infection severity and usual duration.

The PHE guidance also 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. This guidance includes restriction of broad-spectrum antibiotics, in particular second- and third-generation cephalosporins and clindamycin (see PHE and the Department of Health’s guidance *Clostridium difficile infection: how to deal with the problem*). The English surveillance programme antimicrobial utilisation and resistance (ESPAUR) report includes national data on antibiotic prescribing, antibiotic resistance and hospital antimicrobial stewardship implementation.

According to PHE guidance on managing common infections, cefalexin and other cephalosporins (cefixime, cefotaxime and ceftriaxone) should be used only in limited situations (for example, second-line in upper and lower UTI in children, and third-line in UTI in women who are pregnant). 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). **PHE guidance on managing common infections** recommends that quinolones are used as first-line treatment only for acute pyelonephritis, acute prostatitis, epididymitis and pelvic inflammatory disease. It states that they should be used in lower respiratory tract infections only when there is proven resistance to other antibiotics.

According to the **PHE guidance**, *co-amoxiclav* is recommended only for persistent acute rhinosinusitis, upper UTI in children, acute pyelonephritis, facial cellulitis, and the prophylaxis and treatment of infection after 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** has more information on antibiotic resistance, and resources to help reduce inappropriate antibiotic prescribing. See also the **TARGET antibiotics toolkit**, which has been developed by the Antimicrobial Stewardship in Primary Care collaboration (from several organisations including the Royal College of General Practitioners and PHE). The website provides several tools to help clinicians and commissioners use antibiotics responsibly, including patient information leaflets and posters, clinician training resources (including e-learning modules on managing acute respiratory tract infections and UTIs) and audit templates.

More information on managing common infections can be found in the NICE 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\(^{10}\). 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).
- **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).

**Antibacterial items/STAR-PU**

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

**Cephalosporins & quinolones % items**

- Data 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%.

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\(^{10}\) The comparators and associated data presented here are based on the previous Key therapeutic topics publication (January 2013). Data provided by the Health and Social Care Information Centre (September 2014; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the Health and Social Care Information Centre website and the Information Services Portal, Business Services Authority.
• Over the same period there was a 3.4% increase in the variation between CCGs, as measured by the inter-decile range, an absolute increase of 0.13%. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.
KTT10: Three-day courses of antibiotics 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 antibiotics is in line with the updated Public Health England (PHE) guidance on managing common infections. A prescribing comparator is available for 3-day trimethoprim.

Evidence context

According to Public Health England (PHE) guidance on managing common infections, a 3-day course of antibiotics 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. In addition, a back-up or delayed antibiotic strategy should be considered for people with mild UTI symptoms and supporting information about antibiotic strategies, infection severity and usual duration should be given.

Nitrofurantoin (100 mg modified-release twice daily) is recommended first-line for people with a glomerular filtration rate (GFR) of over 45 ml/min because general resistance and community multi-resistant Escherichia coli are increasing. If GFR is between 30 and 45 ml/min, nitrofurantoin should be used only if drug resistance is a problem and there is no alternative (see the September 2014 edition of Drug Safety Update for more information). Depending on local resistance patterns, or if GFR is less than 45 ml/min, trimethoprim (200 mg twice daily) or pivmecillinam (400 mg immediately, followed by 200 mg taken 3 times daily) are recommended as alternative first-line options.

PHE guidance on managing common infections recommends that culture and sensitivity testing should be performed if first-line treatment fails. A MeReC Bulletin on managing 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. When narrow-spectrum antibiotics remain effective, broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) should be avoided because they increase the risk of *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA) and resistant UTIs.

A [Cochrane review (CD004682)](https://www.cochrane.org/reviews/en/doi/10.1002/14651858.CD004682.pub4) 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 after 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 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 [Antibiotic prescribing: study suggests there is scope for improvements](https://www.nice.org.uk/guidance/CG161), 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.

The [English surveillance programme antimicrobial utilisation and resistance (ESPAUR) report](https://www.espaur.com/) includes national data on antibiotic prescribing, antibiotic resistance and hospital antimicrobial stewardship implementation. The **TARGET**
antibiotics toolkit, which has been developed by the Antimicrobial Stewardship in Primary Care collaboration (from several organisations including the Royal College of General Practitioners and PHE), provides several tools to help clinicians and commissioners use antibiotics responsibly, including patient information leaflets and posters, clinician training resources (including an e-learning module on managing UTIs) and audit templates.

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 tablets¹¹.

- 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.

¹¹ The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2013). Data provided by the Health and Social Care Information Centre (September 2014; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the Health and Social Care Information Centre website and the Information Services Portal, Business Services Authority.
Over the same period there was a 0.7% increase in the variation between CCGs, as measured by the inter-decile range, an absolute increase of 0.009 ADQ/item. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.
KTT11: 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 1 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 about 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, CD002086, 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 (CD002086) 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 produced a QIPP case study on minocycline for acne vulgaris which 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.\(^{12}\)

- Data 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.

\(^{12}\) The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2013). Data provided by the Health and Social Care Information Centre (September 2014; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the Health and Social Care Information Centre website and the Information Services Portal, Business Services Authority.
• 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, an absolute decrease of 7.94 ADQ/1000 patients. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.
KTT12: 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.
- The NICE guideline on type 2 diabetes is being updated (publication expected August 2015).

Evidence context

The management of 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 guideline on type 2 diabetes (which is being updated; publication expected August 2015) recommends that people should be involved in setting their individualised HbA1c target level, which may be above the general target of 48 mmol/mol (6.5%). Any reduction in HbA1c towards the agreed target level is advantageous to future health, but highly intensive management with the aim of reducing HbA1c 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: HbA1c 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 (CD008143)](#) identified 28 randomised controlled trials that 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 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$_{1c}$ 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$_{1c}$ 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 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 available from NICE’s diabetes web page. These include the NICE guideline on type 2 diabetes (which is
being updated; publication expected August 2015) and various technology appraisal guidance.

**Long-acting insulin analogues**

The NICE 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 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 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 to best advise people about their own particular requirements.

A Cochrane review (CD005060) 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 key therapeutic topic:

**Hypoglycaemic drugs:** the number of prescription items for metformin and sulfonylureas as a percentage of the total number of prescription items for all antidiabetic drugs\(^\text{13}\).

- Data 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, an absolute increase of 0.69%. 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.

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\(^{13}\) The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2013). Data provided by the Health and Social Care Information Centre (September 2014; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the Health and Social Care Information Centre website and the Information Services Portal, Business Services Authority.
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 insulins\(^\text{14}\).

- Data 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 range, an absolute decrease of 1.06%. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

**Self-monitoring of blood glucose**

There is currently no prescribing comparator for this topic.

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\(^{14}\) The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2013). Data provided by the Health and Social Care Information Centre (September 2014; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the Health and Social Care Information Centre website and the Information Services Portal, Business Services Authority.
KTT13: 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 a day or less) or naproxen (1000 mg a 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 MHRA advice on the safety of selective COX-2 inhibitors and the NICE guideline on osteoarthritis.
- Co-prescribe a proton pump inhibitor with NSAIDs for people who have osteoarthritis, rheumatoid arthritis or for people over 45 years who have low back pain in accordance with NICE guidelines (see the NICE guidelines on osteoarthritis, rheumatoid arthritis and low back pain [which is being updated; publication expected November 2016]).

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 European Medicines Agency (EMA) review on COX-2 inhibitors identified an increased risk of thrombotic events, such as heart attack and stroke, with these types of NSAIDs. In 2006, the EMA 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 a day or less, or naproxen at 1000 mg a day.

In 2012, a further EMA review on the cardiovascular safety of NSAIDs highlighted more 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 a 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 after the publication of the EMA review. In August 2013, an MHRA public consultation was 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 a 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. In its updated advice on the safety of selective COX-2 inhibitors, the MHRA 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 guideline on osteoarthritis does not recommend using etoricoxib 60 mg as a first-line treatment on the basis of cost effectiveness. In the summary of product characteristics, the maximum licensed dose of etoricoxib that is recommended for treating osteoarthritis is 60 mg daily. The EMA’s assessment of the long-term benefits and risks of etoricoxib in people with rheumatoid arthritis or ankylosing spondylitis concluded that the benefits outweighed the risks in these conditions when used at a dosage of 90 mg daily.

The 2014 updated NICE 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 the guideline 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.

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\textsuperscript{15}. 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).

- **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.

**NSAIDs: ADQ/STAR-PU**

- Data 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, an absolute decrease of 0.1 ADQ/STAR-PU. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

**NSAIDs: Ibuprofen & naproxen % items**

- Data 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%.

\textsuperscript{15} The comparators and associated data presented here are based on the previous Key therapeutic topics publication (January 2013). Data provided by the Health and Social Care Information Centre (September 2014; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the Health and Social Care Information Centre website and the Information Services Portal, Business Services Authority.
• Over the same period there was a 22.4% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 3.49%.

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

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.
KTT14: 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 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 after 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) 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.
**Prescribing data**

A prescribing comparator is available for this key therapeutic topic – **Wound care products**: NIC/item: the net ingredient cost (NIC) per item for wound care products. The comparator is to be retired (date to be agreed) and therefore data are not presented\(^\text{16}\).

**About these key therapeutic topics**

This document summarises the evidence base on key therapeutic topics which have been identified to support Medicines Optimisation. **It is not formal NICE guidance.**

For information about the process used to develop the Key therapeutic topics, see the [integrated process statement](#).

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**Contact NICE**

National Institute for Health and Care Excellence  
Level 1A, City Tower, Piccadilly Plaza, Manchester M1 4BT

[www.nice.org.uk](http://www.nice.org.uk); [nice@nice.org.uk](mailto:nice@nice.org.uk); 0300 323 0140

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\(^\text{16}\) The comparator is based on the previous Key therapeutic topics publication (January 2013). For details of any update to the comparators refer to the [Health and Social Care Information Centre](#) website and the [Information Services Portal](#), Business Services Authority.