NICE National Institute for Health and Care Excellence

Key therapeutic topics

Medicines optimisation: key therapeutic topics

Published: February 2016

Contents

Foreword

I am delighted to welcome the latest update of *Medicines optimisation: key therapeutic topics* produced by the Medicines and prescribing programme at NICE. Key therapeutic topics continue to be developed in collaboration with the PPRS/Medicines optimisation programme and inform the medicines optimisation dashboard but are **not formal NICE guidance**.

After consultation and feedback from the NHS and partner organisations on the therapeutic topics included in this document:

- 11 topics from January 2015 have been retained
    - renin-angiotensin system drugs: dual therapy
    - lipid-modifying drugs (now includes omega-3 fatty acid supplements)
    - high-dose inhaled corticosteroids in asthma
    - hypnotics
    - low-dose antipsychotics in people with dementia
    - first-choice antidepressant use in adults with depression or generalised anxiety disorder
    - antibiotic prescribing – especially broad spectrum antibiotics
    - three-day courses of antibiotics for uncomplicated urinary tract infection
    - type 2 diabetes mellitus
    - non-steroidal anti-inflammatory drugs
    - wound care products

- 2 topics have been retired
    - laxatives
    - minocycline

- 3 topics have been added
    - biosimilar medicines
    - non-vitamin K antagonist oral anticoagulants (NOACs)

- acute kidney injury (AKI): use of medicines in people with or at increased risk of AKI

All the current 14 topics have been updated in the light of new guidance and important new evidence.

The prescribing comparators developed to support previous versions of *Medicines optimisation: key therapeutic topics* 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 are 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.

The appropriate use of medicines has never been so high profile, as highlighted in the recently published Carter Review, Operational productivity and performance in English NHS acute hospitals: unwarranted variations. 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

Biosimilar medicines

Options for local implementation

- Develop and agree local policies to support the managed introduction of biosimilar medicines into care pathways safely and effectively as they become available, taking into account regulatory advice, relevant national guidance, patient factors and cost.
- Review and, if appropriate, revise prescribing of medicines for which biosimilar medicines exist to ensure it is in line with these policies.
- Ensure all biological medicines, including biosimilar medicines, are prescribed by brand name so that products cannot be automatically substituted at the point of dispensing. The choice of whether a patient receives a biosimilar or originator biological medicine rests with the responsible clinician in consultation with the patient.

Evidence context

The NHS England publication, What is a biosimilar medicine? states that a biosimilar medicine is a biological medicine which is highly similar to another biological medicine already licensed for use. It is a biological medicine which has been shown not to have any clinically meaningful differences from the originator biological medicine in terms of quality, safety and efficacy. The continuing development of biological medicines, including biosimilar medicines, creates increased choice for patients and clinicians, increased commercial competition and enhanced value propositions for individual medicines. Biosimilar medicines have the potential to offer the NHS considerable cost savings and widen the access to innovative medicines.

NICE position statement on evaluating biosimilars

NICE's position statement on evaluating biosimilar medicines was published in January 2015. This states that biosimilars notified to the NICE topic selection process for referral to the Technology Appraisal programme will usually be considered in the context of a Multiple Technology Appraisal, in

parallel with their reference products in the indication under consideration. The Department of Health has confirmed that a technology appraisal remit referred to NICE enables NICE to decide to apply the same remit, and the resulting guidance, to relevant licensed biosimilar products which subsequently appear on the market. In other circumstances, where it is considered a review of the evidence for a biosimilar medicine is necessary, NICE will consider producing an evidence summary: new medicine.

Licensing and comparability

Biosimilar medicines introduced into the UK market are authorised by the European Medicines Agency (EMA). The EMA has produced a document covering a series of questions and answers on biosimilar medicines. Biological medicines such as monoclonal antibodies, growth hormone and insulin are produced in or derived from living systems. The size and complexity of biological medicines, as well as the way they are produced, may result in a degree of natural variability in molecules of the same active substance, particularly in different batches of the medicine. The active substance of a biosimilar and its reference medicine is essentially the same biological substance but, just like the reference medicine, the biosimilar has a degree of natural variability. When approved, this variability and any differences between the biosimilar and its reference medicine will have been shown not to affect safety or effectiveness.

In the development of a biosimilar, there is no requirement to demonstrate clinical benefit to patients *per se* as this has been shown for the reference medicine. Instead, biosimilars undergo a comprehensive regulatory process which demands extensive comparability studies that demonstrate similarity to the reference medicine. The benefits and risks are then inferred from the similarity of the biosimilar medicine to the reference medicine in terms of quality, efficacy and safety. Biosimilar medicines are usually licensed for all the indications in the licence of the originator biological medicine, but this requires appropriate scientific justification on the basis of demonstrated or extrapolated equivalence. They are generally used at the same dose and route of administration as the biological reference medicine and have the

same contraindications and warnings in their summaries of product characteristics. However, the ongoing safety of any biosimilar or originator biological medicine is monitored separately (see below).

Any biological drug is likely to be modified several times during its production history and development, for example when there is a change in manufacturing process. After each such change, a similar comparability exercise that is carried out for a biosimilar is carried out to ensure that the new biological drug is similar to the old one. Therefore from a scientific and regulatory point of view, the active substance of the biosimilar could be viewed as just another version of the active substance of the originator. See the NHS publication Answers to commonly asked questions about biosimilar versions of infliximab and The NHS England publication, What is a biosimilar medicine? for more details.

Brand name prescribing and pharmacovigilance

In the UK, the MHRA recommends that all biological medicines, including biosimilar medicines, are prescribed by brand name (February 2008 edition of Drug Safety Update). Because biosimilar and reference biological medicines that have the same international non-proprietary name (INN) are not presumed to be identical in the same way as generic non-biological medicines, brand name prescribing ensures that the intended product is received by the patient. It ensures that products cannot be automatically substituted at the point of dispensing. The choice of whether a patient receives a biosimilar or originator biological medicine rests with the responsible clinician in consultation with the patient.

Pharmacovigilance is important for biosimilar medicines and every biosimilar authorised by the EMA will have a risk management plan in place (details of which will be in the European Public Assessment Report). Based on similarity being demonstrated with the reference medicine, the biosimilar can also refer to the safety experience gained with the reference medicine. As with all new medicines, biosimilars have a 'black triangle' in the first years after approval and any suspected adverse drug reactions should be reported through the

Yellow Card Scheme (see the June 2009 edition of Drug Safety Update on the black triangle scheme for more information).

Patient registers are used to monitor for emerging safety and efficacy issues with biological medicines, and the MHRA supports the recording of brand names and batch numbers for traceability when reporting suspected adverse drug reactions (November 2012 edition of Drug Safety Update). UK Medicines Information has developed a validated tool to determine potential safety issues associated with new medicines, and these 'in-use product safety assessment reports' will be published for new biosimilar medicines as they become available. The in-use product safety assessment report for infliximab biosimilars states that brand name prescribing is vital if products are to be identified appropriately at the points of dispensing and administration. As with all biological medicines, for each patient, a traceable record of the brand, batch number, and other vital details of the product used should be made. Reporting and monitoring of patients through clinical registries will enable collection of specific data on serious adverse events, and these mechanisms will act in addition to routine pharmacovigilance activities. Safe introduction and ongoing safe use of biosimilars requires practitioner, patient and manufacturer engagement with these processes.

Managing the introduction of biosimilar medicines

The NICE adoption resource Introducing biosimilar versions of infliximab: Inflectra and Remsima, has been produced to help manage the introduction of biosimilar medicines into care pathways safely and effectively. NHS organisations shared their learning and experiences of introducing biosimilar medicines and these are presented as a series of examples of current practice. They are not presented as best practice but as real-life examples of how NHS sites have planned and managed the introduction of biosimilars. Local organisations will need to assess the applicability of the learning from the examples of current practice, taking into consideration the time, resources and costs of an implementation programme.

The NHS staff involved in the production of the NICE adoption resource reported that the use of biosimilars can reduce costs, allowing more treatment

with new medicines, as long as the appropriate follow-up and monitoring systems are in place to manage risk and patient needs and expectations. Particular tips for managing the introduction of biosimilar medicines included:

- Identify clinical and pharmacy champions to take the lead in introducing biosimilars.
- Consult all stakeholders (including patients) to ensure confidence in using biosimilars.
- Provide information about the EMA licensing process for biosimilars, extrapolation and equivalence, and the manufacturing process (including intra-product manufacturing changes for both biological medicines and their biosimilars).
- Identify the potential cost-saving and re-investment opportunities and explore gain-share agreements.
- Seek formal approval at the local formulary committee once there is clinical consensus to include biosimilars on the formulary.
- Collect baseline data and agree metrics to be collected during and after the introduction of biosimilars.
- Submit data to national audits and registries.

Prescribing data

Biosimilar versions of epoetin, filgrastim and somatropin have been available for some time. As for all medicines, the safety of biosimilar medicines is continuously monitored after authorisation, and no particular safety concerns have arisen for these biosimilar medicines that have required regulatory action to be taken. Recently, biosimilar versions of infliximab (Inflectra and Remsima) and insulin glargine (Abasaglar) have been launched in the UK, and further biosimilar versions of adalimumab, bevacizumab, etanercept, pegfilgrastim, rituximab and trastuzumab are expected to be available in the next few years.

Biosimilars have the potential to offer the NHS considerable cost savings, especially as biological medicines are often expensive and are often used to treat long-term conditions. The NHS England publication, What is a biosimilar

medicine? states that biosimilar medicines are more challenging and expensive to develop than generic medicines. Whilst they cannot offer the same percentage price reductions as traditional generic medicines, nevertheless, there are significant savings associated with increased competition between biological medicines, including biosimilar medicines. Recent research has given clear evidence that the additional competition is bringing value and opportunity to widen access for patients in some circumstances. However, this research also demonstrates that biosimilar medicine uptake across Europe to date shows very different patterns, depending on the class of biological medicine and the procurement measures in place. Costs for both biosimilar and originator biological medicines may vary locally depending on local contractual arrangements, and Regional Pharmacy Procurement Specialists will be able to provide more details.

There are currently no prescribing comparators for this topic. The development of new prescribing comparators to support this key therapeutic topic will be explored by the NHS England Medicines Optimisation Intelligence Group[1].

The medicines optimisation dashboard, which brings together a range of medicines-related quality indicators from across sectors, has recently included a prescribing comparator on biosimilars. This is % of infliximab, which is the percentage of the total infliximab used for both the originator biological medicine and biosimilar versions by volume. The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

[1] 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.

Non-vitamin K antagonist oral anticoagulants (NOACs)

Options for local implementation

- NICE has issued technology appraisal guidance on the use of the 4 non-vitamin K antagonist oral anticoagulants (NOACs), apixaban, dabigatran, edoxaban and rivaroxaban, in several clinical settings. All 4 NOACs must be included in local formularies for use in line with this guidance, with no additional funding or formulary restrictions.
- Review and, if appropriate, revise prescribing and local policies relating to antithrombotics, including NOACs, to ensure these are in line with NICE guidance.
- Several factors are likely to affect the choice of antithrombotic for an individual. NICE has produced a patient decision aid to support discussions about anticoagulant options for people with atrial fibrillation.

Evidence context

The 4 non-vitamin K antagonist oral anticoagulants (NOACs) currently licensed in the UK are apixaban, dabigatran, edoxaban and rivaroxaban. NICE has issued technology appraisal guidance on the use of NOACs in several clinical settings. These are summarised in table 1.

Table 1: NICE technology appraisal guidance on NOACs

Indication	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Prevention of VTE after elective hip or knee replacement	Recommended as an option: TA245[a]	Recommended as an option: TA157[a]	Not licensed for this indication	Recommended as an option: TA170[a]
Treatment and secondary prevention of DVT and/or PE	Recommended as an option: TA341[a]	Recommended as an option: TA327[a]	Recommended as an option: TA354[a]	Recommended as an option: TA261[a] and TA287[a]
Prevention of stroke and systemic embolism in people with non-valvular AF	Recommended as an option in specified circumstances: TA275[a]	Recommended as an option in specified circumstances: TA249[a]	Recommended as an option in specified circumstances: TA355	Recommended as an option in specified circumstances: TA256[a]
Prevention of adverse outcomes after acute management of ACS with raised biomarkers	Not licensed for this indication	Not licensed for this indication	Not licensed for this indication	Recommended as an option in specified circumstances: TA335[a]

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; DVT, deep vein thrombosis; PE, pulmonary embolism; TA, technology appraisal; VTE, venous thromboembolism.

[a] See the technology appraisal for full details of NICE's recommendations.

The technology appraisal guidance summarised in table 1 should be read in the context of the relevant NICE guidelines, which set out the alternative treatments:

- Venous thromboembolism in adults admitted to hospital: reducing the risk (published January 2010)
- Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing (published June 2012)
- Atrial fibrillation: the management of atrial fibrillation (published June 2014)

- Myocardial infarction (MI): cardiac rehabilitation and prevention of further MI (published November 2013)

The NICE pathways on venous thromboembolism: orthopaedic surgery, treating venous thromboembolism, atrial fibrillation and myocardial infarction: secondary prevention bring together all related NICE guidance and associated products on the conditions in a set of interactive topic-based diagrams. NICE has also published quality standards on venous thromboembolism prevention and atrial fibrillation: treatment and management which are concise sets of prioritised statements designed to drive measurable quality improvements within these areas. It should be noted that, consistent with the NICE guideline, quality statement 2 for atrial fibrillation states: 'Adults with atrial fibrillation are not prescribed aspirin as monotherapy for stroke prevention.'

In some instances, not all the NOACs recommended as options in later technology appraisals are mentioned in the relevant NICE guideline. This is because they were not licensed for the indication at the time the guideline was published. Nevertheless, they should be considered as equal options alongside the NOAC(s) mentioned: see Demonstrating compliance with NICE technology appraisal guidance.

As with all its recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions and the person's values and preferences. (NICE has produced a patient decision aid to support discussions about anticoagulant options for people with atrial fibrillation.) This discussion should aim to help the person to reach a fully informed decision.

The absence of direct comparisons between different NOACs and differences in study populations, analyses and other factors in key studies raise difficulties when choosing among them for different indications. Several factors are likely to affect the choice for an individual. The discussion should therefore consider all the possible alternative antithrombotic options, including the advantages and disadvantages of each as appropriate to the individual person's clinical circumstances, needs, values and preferences. These are likely to include:

- the likely benefits from anticoagulation per se
- the risk of bleeding
- the likelihood that the person will be able to maintain consistent anticoagulation with the different options (that is, the need for a high proportion of time in therapeutic range for warfarin and the need for high adherence for NOACs)
- potentially interacting drugs
- renal and hepatic function
- the person's past experiences, attitudes towards blood testing and their preference for once or twice daily dosing
- the relative size of the capsules/tablets and their suitability for compliance aids (if relevant).

The NICE guideline on MI: cardiac rehabilitation and prevention of further MI advises against using a NOAC in combination with dual antiplatelet therapy in people who have had an MI. It recommends considering using warfarin and discontinuing treatment with a NOAC in such people, unless there is a specific clinical indication to continue it. This relates to people who have an indication for anticoagulation, such as atrial fibrillation which may or may not be related to their MI. The full guideline explains that the recommendation arises from the limited evidence for the use of NOACs in this context, and the likely increased risk of bleeding. This is a different scenario from that considered in the NICE technology appraisal guidance on rivaroxaban after acute coronary syndrome. The licensed dose of rivaroxaban for preventing adverse outcomes after acute coronary syndrome is 2.5 mg twice a day; this is lower than the licensed dose for other indications (10–20 mg once a day). The risk of bleeding is therefore also likely to be lower.

Bleeding is a risk common to all anticoagulants. In the October 2013 edition of Drug Safety Update, the MHRA issued advice on the contraindications and warnings for the 3 NOACs licensed at the time (apixaban, dabigatran and rivaroxaban), and these have also been incorporated into the summary of product characteristics (SPC) for edoxaban. Care should be taken when considering prescribing a NOAC to a person with other conditions, procedures

or concomitant treatments that may increase the risk of major bleeding. The MHRA advises that impaired renal function may be a contraindication for using an anticoagulant medicine, or may require a dose reduction: see manufacturers' SPCs for more information.

The NICE guideline on chronic kidney disease recommends that healthcare professionals should consider apixaban in preference to warfarin in people with a confirmed eGFR of 30–50 ml/min/1.73 m^2 and non-valvular atrial fibrillation who have 1 or more specified risk factors for stroke. The full guideline explains that this recommendation is based on a pre-specified subgroup analysis of the ARISTOTLE study (Granger et al. 2011). This found that, compared with warfarin, apixaban reduced the rate of stroke, death, and major bleeding, and people with impaired kidney function (eGFR 25–50 ml/min/1.73 m^2) had the greatest reduction in major bleeding with apixaban compared with warfarin.

The SPC for edoxaban states that, when edoxaban was used for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation, a trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared with well-managed warfarin. Therefore, edoxaban should be used in people with non-valvular atrial fibrillation and high creatinine clearance only after a careful evaluation of the individual thromboembolic and bleeding risk.

Demonstrating compliance with NICE technology appraisal guidance

Commissioners have a statutory responsibility to make funding available for a medicine recommended by a NICE technology appraisal, usually within 3 months of its publication. Under the NHS Constitution, patients have a right to receive all medicines recommended by NICE if they and their healthcare professional think that the medicine is right for them. In practical terms, this means that all 4 NOACs must be included in local formularies for use in line with the technology appraisal guidance, with no additional funding or formulary restrictions. For example, providers or commissioners cannot

recommend that any individual NOAC (or any other medicine, such as warfarin) is used **routinely** in preference to the others, or say that a particular medicine is available only if the formulary first choice is contraindicated or not tolerated. However, providers or commissioners can advise clinicians on the factors that should be considered when selecting a NOAC, and also that a particular medicine is preferred locally if an individual patient and clinician have agreed that they have no special reason for preferring one of the medicines over another. This is a subtle but important distinction. Further information is available in the document 'Frequently asked questions about NICE compliance', published on the NICE website.

Prescribing data

There are currently no prescribing comparators for this topic. The development of new prescribing comparators to support this key therapeutic topic will be explored by the NHS England Medicines Optimisation Intelligence Group[2].

The medicines optimisation dashboard, which brings together a range of medicines-related quality indicators from across sectors, does however include several cardiovascular and coronary heart disease metrics related to this key therapeutic topic. These include:

- Atrial fibrillation: access to audit tool, which is the number of downloads of the software that supports audit of patients prescribed anticoagulants for atrial fibrillation in relation to the number of practices within the CCG. Note: this can currently only measure practices who are engaged with the GRASP tool.
- Atrial fibrillation (AF004) % achieving upper threshold or above, which is the percentage of practices in a CCG that achieve upper threshold or above (70% or more inclusive of exceptions) for QOF indicator AF004.

[2] 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.

- Atrial fibrillation (AF004) % underlying achievement, which is the number of patients with atrial fibrillation whose latest record of a CHADS2 score is greater than 1 who are currently treated with anticoagulation therapy.
- Oral anticoagulants % items, which is the proportion of prescription items for apixaban, dabigatran and rivaroxaban and the proportion of prescription items for warfarin as a percentage of the total number of prescription items for oral anticoagulants.

The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

Apixaban, dabigatran and rivaroxaban are also included in the Innovation Scorecard, published by the Health and Social Care Information Centre. The Innovation Scorecard aims to improve transparency within the NHS of what treatments recommended by NICE are available within Trusts and CCGs and at National and Area Team level. It is intended to support monitoring of compliance with NICE Technology Appraisal recommendations and to assist the NHS in the identification of variation, which can be explained, challenged or acted upon. It is not intended to be used for performance management.

Acute kidney injury (AKI): use of medicines in people with or at increased risk of AKI

Options for local implementation

- A national programme – Think Kidneys – has been set up with the aim of preventing the avoidable harm caused by acute kidney injury.
- Review and, if appropriate, revise prescribing and local policies that relate to assessing the risk of acute kidney injury to ensure these are in line with the NICE guideline on acute kidney injury.
- Review and, if appropriate, revise prescribing and local policies that relate to preventing, identifying and managing acute kidney injury, to ensure these are in line with the NICE guideline.

Evidence context

A national programme – Think Kidneys – has been set up with the aim of preventing the avoidable harm caused by acute kidney injury. Renal function is vulnerable to quite modest reductions in blood pressure or blood volume, including dehydration arising from diarrhoea or vomiting. The full NICE guideline on acute kidney injury (AKI) notes that it is a common problem among people admitted to hospital (occurring in 13–18% of such people), especially older people. AKI is a feature of many severe illnesses and patients are usually under the care of clinicians practicing in specialties other than nephrology. In addition, AKI is seen increasingly in primary care in the absence of any acute illness. Many drugs can be harmful to the kidneys especially in people with AKI or at risk of it for non-pharmacological reasons. In addition, other drugs – such as those with a narrow therapeutic range and those that are cleared by the kidneys – may cause toxicity in the setting of AKI and acute illness, requiring additional monitoring, dose adjustment and measurement of drug levels (see below for more details).

The NICE guideline on AKI gives guidance on the following areas:

- **Assessing the risk of AKI.** This includes investigating for AKI in people with acute illness who have predisposing risk factors, including recent use of drugs with nephrotoxic potential such as non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, renin-angiotensin system (RAS) drugs or diuretics, especially if the person is hypovolaemic. People with no clear acute component to their illness but certain other factors should also be investigated for AKI. People receiving iodinated contrast agents and people having surgery should have their risk of AKI assessed. The guideline notes that there is an increased risk of AKI if drugs with nephrotoxic potential are used in the perioperative period (in particular, NSAIDs after surgery).
- **Preventing AKI.** This includes following recommendations in the NICE guideline on acutely ill patients in hospital on using track and trigger systems (early warning scores) to identify adults who are at risk of AKI, and using similar systems for children and young people. The guideline recommends measures to reduce the risk of AKI in people receiving iodinated contrast agents who are at increased risk. It advises considering temporarily stopping RAS drugs in certain situations, and specifically advises health professionals to seek advice from a pharmacist about optimising medicines and drug dosing in all people with or at risk of AKI.
- **Detecting AKI and identifying its cause.** This includes monitoring serum creatinine in all people with or at risk of AKI.
- **Managing AKI.** The guideline makes specific recommendations about when loop diuretics may and may not be appropriate, and recommends against using low-dose dopamine to treat AKI.
- **Information and support for patients and carers**. This includes discussing the risk of developing AKI with people at higher risk, particularly the risk associated with conditions leading to dehydration (for example, diarrhoea and vomiting) and drugs with nephrotoxic potential (including over-the-counter NSAIDs).

See the guideline for full details of the recommendations. NICE has also published quality standards on AKI, which are concise sets of prioritised

statements designed to drive measurable quality improvements within this area.

NHS England, in partnership with the UK Renal Registry, has launched a 3-year programme – Think Kidneys – with the aim of preventing avoidable harm from AKI. The website includes a number of resources, including a medicines optimisation toolkit for AKI, educational resources aimed at different health and social care professional groups, and information for the public. This toolkit includes a medicines optimisation proforma (points to consider relating to prescribing for a person with AKI), a list of high-risk drugs and appropriate related actions, and links to further useful resources. Wessex Strategic Clinical Networks have produced 3 AKI resources that may be useful locally: a pathway for hospital care and another for primary care, and primary care top ten tips (which may also be useful in secondary care). The Centre for Pharmacy Postgraduate Education (CPPE) has also launched a learning campaign on acute kidney injury.

The Royal Pharmaceutical Society produced a medicines optimisation briefing about AKI, with a related article, in February 2015. This includes advice on 'sick day rules' and states: 'If a person taking an RAS drug, diuretic, metformin or NSAID develops new diarrhoea, sickness, or both, they should suspend taking this medicine (without first speaking to their GP) until they are clearly improving; then they should restart their medicines. If they are not improving within 24 hours then medical advice should be sought urgently.' However, the NHS England Think Kidneys Programme Board issued an interim position statement on sick day rules in July 2015. This notes that although there is strong professional consensus that advice on sick day rules should be given, the evidence that provision of such advice reduces net harm is very weak. It is possible that there are potential harms associated with widespread provision of sick day rules, particularly when people have not been clinically assessed and where it is unclear at what level of ill health the medicine should be discontinued. The Programme Board recommends that health professionals should discuss the possible causes of AKI with patients and carers including the need to maintain fluid balance during episodes of

acute illness. It advises that it is reasonable for clinicians to provide sick day rule guidance on temporary cessation of medicines to patients deemed at high risk of AKI based on an individual risk assessment. However, the Board considers that investment in a systematic approach to increase uptake of sick day rules by patients should only be undertaken in the context of a formal evaluation.

Prescribing data

There are currently no prescribing comparators for this topic. The development of new prescribing comparators to support this key therapeutic topic will be explored by the NHS England Medicines Optimisation Intelligence Group[3].

[3] 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.

Renin-angiotensin system drugs: dual therapy

Options for local implementation

- Dual therapy with an angiotensin-converting enzyme (ACE) inhibitor plus an angiotensin receptor blocker (ARB) has only a limited place in treatment, specifically in a small minority of people with heart failure.
- Review and, if appropriate, revise prescribing of dual therapy to ensure it is in line with NICE guidance on hypertension, chronic heart failure, chronic kidney disease, myocardial infarction - secondary prevention, type 1 diabetes and type 2 diabetes.

Evidence context

The June 2014 edition of Drug Safety Update highlighted a European safety review into dual therapy with an ACE inhibitor plus an ARB. This review concluded that no significant benefits of dual therapy 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 NICE medicines evidence commentary Efficacy and safety of dual blockade of the renin-angiotensin system for more information. UK Medicines Information (UKMi) has also published a medicines question and answers resource on the rationale and evidence for combining ACE inhibitors with ARBs for treating hypertension and for preventing vascular events.

Dual therapy has only a limited place in treatment, specifically 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 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. UKMi has published a medicines question and answers resource on the use of a combination of ACE inhibitors with ARBs in patients with heart failure.

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 m^2) or diabetes.

For further information on renin-angiotensin system drugs see the NICE pathways on hypertension, chronic heart failure, chronic kidney disease, myocardial infarction - secondary prevention and diabetes. A separate key therapeutic topic on acute kidney injury (AKI): use of medicines in people with or at increased risk of AKI is also available.

Table 1: Summary of NICE recommendations on the use of renin-angiotensin system drugs in various indications

Indication	Relevant NICE guideline	Recommendation in relation to renin-angiotensin system drugs	Recommendation in relation to dual blockade with renin-angiotensin system drugs
Hypertension	Hypertension in adults: diagnosis and management. NICE guideline CG127 (August 2011)	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.	Do not combine an ACE inhibitor with an ARB to treat hypertension.

Heart failure	Chronic heart failure in adults: management. NICE guideline CG108 (August 2010)	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.	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.
Myocardial infarction (MI) – secondary prevention	Myocardial infarction: cardiac rehabilitation and prevention of further MI. NICE guideline CG172 (November 2013)	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.	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.

Chronic kidney disease (CKD)	Chronic kidney disease in adults: assessment and management. NICE guideline CG182 (July 2014)	Offer a low-cost renin-angiotensin system antagonist[a] to people with CKD and: • diabetes and an albumin:creatinine ratio of 3 mg/mmol or more • hypertension and an albumin:creatinine ratio of 30 mg/mmol or more • an albumin:creatinine ratio of 70 mg/mmol or more (irrespective of hypertension or cardiovascular disease).	Do not offer a combination of renin-angiotensin system antagonists[a] to people with CKD.
Type 1 diabetes	Type 1 diabetes in adults: diagnosis and management. NICE guideline NG17 (August 2015)	Start a trial of a renin–angiotensin system blocking drug as first-line therapy for hypertension in adults with type 1 diabetes. 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.

Type 2 diabetes	Type 2 diabetes in adults: management. NICE guideline NG28 (December 2015)	First-line antihypertensive drug treatment 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.	Do not combine an ACE inhibitor with an ARB to treat hypertension.
[a] 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 was previously available to support this key therapeutic topic – **ACE inhibitor % items**. This comparator has been retired from Q1 2015/16 data onwards and therefore data are not presented[4].

[4] 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.

Lipid-modifying drugs

Options for local implementation

- When a decision is made to prescribe a statin, the NICE guideline on lipid modification recommends using a statin of high intensity and low acquisition cost.
- People with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with the technology appraisal guidance for that drug in this indication: ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia.
- The NICE guideline on lipid modification recommends that bile acid sequestrants, nicotinic acid, fibrates and omega-3 fatty acid compounds should **not** generally be offered (see the guideline for details).
- Review and, if appropriate, revise prescribing of lipid-modifying drugs including statins, ezetimibe, bile acid sequestrants, fibrates, nicotinic acid, and omega-3 fatty acid compounds to ensure it is in line with NICE guidance.

Evidence context

The NICE guideline on lipid modification (published July 2014) makes recommendations on the care and treatment of people at risk of cardiovascular disease (CVD) and people who have had previous CVD. This includes people with chronic kidney disease, type 1 diabetes and type 2 diabetes.

People with familial hypercholesterolaemia are outside the scope of the NICE lipid modification guideline and this key therapeutic topic. There is a separate NICE guideline on the identification and management of familial hypercholesterolemia (which is being updated; publication expected January 2017). A technology appraisal on evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia is also in progress (publication expected April 2016).

NICE has also published quality standards on cardiovascular risk assessment and lipid modification, which are concise sets of prioritised statements designed to drive measurable quality improvements within these areas.

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
    - rosuvastatin 5 mg daily
    - simvastatin 20–40 mg daily.
- High intensity (more than 40% LDL-C reduction):
    - atorvastatin 20–80 mg daily
    - rosuvastatin 10–40 mg daily
    - simvastatin 80 mg daily.

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

Primary prevention of cardiovascular disease

Before offering statin treatment for primary prevention of 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 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 CKD. 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 CKD 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 CKD 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 m^2 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.

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.

A large observational study, which was discussed in a NICE medicines evidence commentary, Statins: many people who stop treatment due to side effects may be able to restart treatment, suggested that many people who have discontinued statins because of an adverse event, especially muscle pain, may be able to restart the same or a different statin.

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 with people who are stable on a low-intensity statin or medium-intensity statin (such as 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

The only high-intensity 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 CVD (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 recommends that people with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with the technology appraisal guidance for that drug in this indication. This guidance has subsequently been reviewed and was published in February 2016: ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. This technology appraisal guidance makes

explicit reference both to the NICE lipid modification guideline and also to the NICE guideline on familial hypercholesterolaemia: identification and management. The guideline on familial hypercholesterolaemia is being updated; publication expected January 2017.

The technology appraisal guidance recommends ezetimibe monotherapy as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults in 2 broad situations:

- As an alternative to a statin in people in whom statins are contraindicated or not tolerated; intolerance is defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.
- In addition to **initial** statin therapy in people 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 (defined as above) **and** consideration is being given to changing from initial statin therapy to an alternative statin.

Appropriate control of cholesterol concentrations should be based on individual risk assessment according to national guidance on managing cardiovascular disease in the relevant populations. Therefore, in the second of the situations above, in people with non-familial hypercholesterolaemia, adding ezetimibe to **atorvastatin** (the initial statin therapy recommended in the guideline) is an option if (and only if) a greater than 40% reduction in non-HDL cholesterol is not achieved:

- despite optimising adherence and timing of the dose of atorvastatin and optimising adherence to diet and lifestyle measures, **and**
- increasing the dose of atorvastatin (if started at less than 80 mg daily) is not effective or not tolerated or the person has to decrease the dose because of tolerability problems, **and**

- changing to a different statin is being considered.

See the NICE guideline on familial hypercholesterolaemia for guidance on appropriate control of cholesterol concentrations in people with this condition.

The large, multicentre, randomised controlled trial IMPROVE-IT (Cannon et al, 2015) was discussed in a NICE medicines evidence commentary, Acute coronary syndrome: ezetimibe added to simvastatin (IMPROVE-IT study). IMPROVE-IT found that adding ezetimibe to simvastatin 40 mg after acute coronary syndrome produced a greater reduction in risk of cardiovascular events than simvastatin 40–80 mg alone. However, the effect of the combination on this risk is that which would be predicted from the degree of LDL cholesterol-lowering seen with a high-intensity statin such as atorvastatin 20–80 mg daily. The study provides no reason to depart from recommendations in the NICE lipid modification guideline.

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 CKD 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 CKD or type 1 or type 2 diabetes, and should **not** be recommended in combination with a statin in these indications. See the NICE guideline on familial hypercholesterolaemia on the possible use of bile acid sequestrants, fibrates and nicotinic acid in people with this condition, who are outside the scope of this key therapeutic topic.

Omega-3 fatty acid compounds

The NICE guideline on lipid modification recommends that people with or at high risk of CVD 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 primary or secondary prevention of CVD, alone or in combination with a statin, including in people

with CKD 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 CVD. In addition, the NICE guideline on secondary prevention of myocardial infarction (MI) recommends that healthcare professionals should **not** offer or advise people who have had an MI to use omega-3 fatty acid capsules or omega-3 fatty acid supplemented foods to prevent another MI.

Prescribing data

The following prescribing comparators were available to support this key therapeutic topic, but these have been retired from Q1 2015/16 data onwards and therefore data are not presented[5]:

- **Low cost lipid-modifying drugs**
- **Lipid modifying drugs: ezetimibe % items**

A new prescribing comparator is available to support this key therapeutic topic[6].

- **Other lipid modifying drugs: % items**: the number of prescription items for bile acid sequestrants, fibrates, nicotinic acid, omega-3 fatty acid compounds and 'other lipid modifying drugs' (BNF 2.12 sub-set) as a percentage of total prescription items for BNF 2.12.

The development of further new prescribing comparators to support this key therapeutic topic will be explored by the NHS England Medicines Optimisation Intelligence Group[5].

[5] 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.
[6] The comparators and associated data presented here are based on the previous Key therapeutic topics publication (January 2015). Data provided by the Health and Social Care Information Centre (October 2015; 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.

Prescription Cost Analysis data of prescriptions dispensed in the community in England shows national statin and ezetimibe prescribing. In terms of costs, rosuvastatin 10–40 mg daily is between £216.32 and £349.70 per patient per year more costly than atorvastatin 20–80 mg daily at equivalent LDL-C-lowering doses. Adding ezetimibe 10 mg daily to a statin would cost an additional £342.03 per year (Drug Tariff January 2016).

Other lipid modifying drugs: % items

- Data for the quarter April to June 2015 show a 5.8 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 1.08% to 6.26%.
- Between Q2 2013/14 (July to September 2013) and Q1 2015/16 (April to June 2015) there was a 16.3% decrease in the comparator value for England (total prescribing) from 2.74% to 2.29%.
- Over the same period there was a 24.6% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 0.57%. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

High-dose inhaled corticosteroids in asthma

Options for local implementation

- Inhaled corticosteroids (ICS) are the first-choice regular preventer therapy for adults and children with asthma, but the dose should be titrated to the lowest dose at which effective control of asthma is maintained to minimise side effects.
- Review the use of ICS routinely in people with asthma, and step down the dose and use of ICS when clinically appropriate.
- The NICE quality standard for asthma states that people with asthma should receive a structured review at least annually and have a written personalised action plan. It is important to ensure that all people with asthma are treated optimally; this includes stepping-up and stepping-down treatment appropriately.

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 propionate. Children prescribed ICS should have their growth monitored annually (although isolated growth failure is not a reliable indicator of adrenal suppression).

The BTS/SIGN guideline on the management of asthma recommends that reductions in ICS dose should be considered every 3 months, decreasing the dose by approximately 25–50% each time. Data suggest that this is realistic and possible without compromising patient care (see Hawkins et al. 2003). For some children with milder asthma and a clear seasonal pattern to their symptoms, a more rapid dose reduction during their 'good' season is feasible. The guideline states that stepping down therapy once asthma is controlled is recommended, but often not implemented, leaving some people over-treated. The BTS/SIGN guideline also advises that regular review of patients as treatment is stepped down is important. When deciding which drug to step down first and at what rate, the severity of asthma, the side effects of the treatment, time on current dose, the beneficial effect achieved, and the patient's preference should all be taken into account.

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.

There are several ICS/LABA combination inhalers available containing different ICS (see the equivalence table in the BTS/SIGN guideline on the management of asthma for details). In addition to combination inhalers containing fluticasone propionate, there is a combination inhaler containing fluticasone furoate (see the NICE evidence summary new medicine publication on fluticasone furoate/vilanterol [Relvar Ellipta] combination inhaler in asthma for details). The summaries of product characteristics for Relvar Ellipta state that people with asthma should be given the strength of Relvar Ellipta containing the appropriate fluticasone furoate dosage for the severity of their disease. In people with asthma, fluticasone furoate 100 micrograms once daily is approximately equivalent to fluticasone propionate 250 micrograms twice daily, while fluticasone furoate 200 micrograms once daily is approximately equivalent to fluticasone propionate 500 micrograms twice daily.

The NICE quality standard for asthma states that people with asthma should receive a structured review at least annually and have a written personalised action plan. They should also receive 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. Asthma UK have since issued a report on the scale of concerns around asthma prescribing (see the medicines evidence commentary Asthma: new review of prescribing data highlights safety concerns). It is important to ensure that all people with asthma are treated optimally; this includes stepping-up and stepping-down treatment appropriately.

NICE guidelines on asthma: diagnosis and monitoring (anticipated publication date to be confirmed) and asthma management (which includes the pharmacological management of chronic asthma; anticipated publication June 2017) are currently underway.

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 NHS England Medicines Optimisation Intelligence Group. However, there are several clinical and technical issues around the development of a meaningful comparator for this topic.

The medicines optimisation dashboard, which brings together a range of medicines-related quality indicators from across sectors, does however include several respiratory metrics related to this key therapeutic topic. These include:

- Asthma (AST003) % achieving upper threshold or above, which is the percentage of practices in a CCG that achieve upper threshold or above (70% or more inclusive of exceptions) for QOF indicator AST003.
- Asthma (AST003) % underlying achievement, which is the percentage underlying achievement at CCG level for QOF indicator AST003 inclusive of exceptions.

- Emergency asthma admissions, which is the number of emergency attendances for asthma per 100 patients on the practice asthma disease register.

Hypnotics

Options for local implementation

- The risks associated with hypnotics, such as falls, cognitive impairment, dependence and withdrawal symptoms, are well recognised. Hypnotics should be used only if insomnia is severe, using the lowest dose that controls symptoms for short periods of time.
- 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 medicines 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. 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.

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.

A new offence of driving with certain controlled drugs above specified limits in the blood came into force in March 2015. Prescription drugs covered by the new offence include amphetamine (e.g. dexamphetamine or selegiline), clonazepam, diazepam, flunitrazepam, lorazepam, methadone, morphine or opioid-based drugs (e.g. codeine, tramadol or fentanyl), oxazepam and temazepam. Although only a few benzodiazepines and opioids are included in the list above, all benzodiazepines and opioids can impair driving ability. See the July 2014 edition of Drug Safety Update and the Drugs and driving: the law government webpage for more details.

A modified-release melatonin product (Circadin) is licensed as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in people aged 55 years or over. The recommended initial duration of treatment is 3 weeks. If there is a response to treatment, it can be continued for a further 10 weeks. See the NICE Clinical Knowledge Summary on insomnia for more information on melatonin and a general overview of the condition.

Concerns have been raised regarding the over-use of psychotropic medicines such as antipsychotics and antidepressants in people with learning disabilities. This is addressed in 3 reports published in 2015 by the Care Quality Commission, Public Health England and NHS Improving Quality.

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)[7].

- Data for the quarter April to June 2015 show a 3.9 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.12 to 0.47 ADQ/STAR-PU.
- Between Q2 2013/14 (July to September 2013) and Q1 2015/16 (April to June 2015) there was a 14.0% decrease in the comparator value for England (total prescribing) from 0.29 to 0.25 ADQ/STAR-PU.
- Over the same period there was a 17.9% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 0.04 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.

The medicines optimisation dashboard, which brings together a range of medicines-related quality indicators from across sectors, includes the prescribing comparator outlined above. The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

[7] The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2015). Data provided by the Health and Social Care Information Centre (October 2015; 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.

Low-dose antipsychotics in people with dementia

Options for local implementation

- The harms and limited benefits of using low-dose antipsychotics for treating dementia in people who exhibit challenging behaviours are well recognised.
- 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.

Evidence context

The NICE/SCIE guideline on dementia (which is being updated, publication expected September 2017) gives recommendations on the care of people with all types of dementia. This includes managing behavioural and psychological symptoms of dementia. The NICE quality standards on dementia and supporting people to live well with dementia describe concise sets of prioritised statements designed to drive measurable quality improvements within these areas. 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 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[8] 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. These resources build on the NICE/SCIE guideline on dementia and include strategies to reduce inappropriate prescribing of antipsychotics. In the May 2012 edition of Drug Safety Update

[8] In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using a medicine outside its authorised indications. Informed consent should be obtained and documented.

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.

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.

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.

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). Older people have a higher exposure to citalopram due to an age-related decline in metabolism and elimination. Therefore, the maximum dose of citalopram has been restricted to 20 mg daily in people older than 65 years. 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.

Concerns have been raised regarding the over-use of psychotropic medicines such as antipsychotics and antidepressants in people with learning disabilities. This is addressed in 3 reports published in 2015 by the Care Quality Commission, Public Health England and NHS Improving Quality.

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 NHS England Medicines Optimisation Intelligence Group[9]. 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. 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

[9] 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.

2006 to 2011 (from 14.25% to 4.46%, a 69% reduction in relative terms). Nevertheless, although reductions in prescribing rates were seen across all geographical areas of England, there was still considerable variation in the percentage of people diagnosed with dementia prescribed an antipsychotic.

First-choice antidepressant use in adults with depression or generalised anxiety disorder

Options for local implementation

- Non-drug interventions are the mainstay of treatment for many people with depression or generalised anxiety disorder, with drugs generally reserved for more severe illness or when symptoms have failed to respond to non-drug interventions.
- Review and, if appropriate, revise prescribing of antidepressants in adults to ensure that it is in line with NICE guidelines on depression in adults, depression in adults with a chronic physical health problem and generalised anxiety disorder and panic disorder in adults.

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 general overviews 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, depression in children and young people (recommendations on psychological therapies and antidepressants were updated in March 2015) and social anxiety

disorder. 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 an adult with depression, the NICE guideline on depression in adults recommends that it should normally be a selective serotonin reuptake inhibitor (SSRI) in generic form. SSRIs are equally effective as other antidepressants and have a favourable risk–benefit ratio. Similarly, if drug treatment is indicated for GAD, and an adult chooses to take medication, the NICE guideline on GAD in adults 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[10]. The NICE guideline on depression in adults recommends that dosulepin should **not** be prescribed for adults with

[10] In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using a medicine outside its authorised indications. Informed consent should be obtained and documented.

depression because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose.

The full guideline on depression in adults concluded that antidepressants have largely equal efficacy and that choice should mainly depend on side-effect profile, people's preference and previous experience of treatments, propensity to cause discontinuation symptoms, safety in overdose, interactions and cost. However, a generic SSRI is recommended as first-choice because SSRIs have a favourable risk–benefit ratio. Neither escitalopram nor any of the available 'dual action' antidepressants, such as venlafaxine and duloxetine, were judged to have any clinically important advantages over other antidepressants. Results from meta-analyses (Gartlehner et al. 2011 and 3 Cochrane reviews: Cipriani et al. 2012, CD006534, Cipriani et al. 2012, CD006533 and Purgato et al. 2014, CD006531) have provided no evidence to depart from NICE guidance when selecting antidepressants for people with depression.

The full guideline on GAD and panic disorder in adults 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. The MHRA has issued guidance on the use and side effects of SSRIs and serotonin and noradrenaline reuptake inhibitors (SNRIs), their safety, use in pregnancy and the risk of suicidal behaviour (published December 2014). 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. In addition, the November 2014 edition of Drug Safety Update issued a reminder to test liver function before and during treatment with agomelatine.

Concerns have been raised regarding the over-use of psychotropic medicines such as antipsychotics and antidepressants in people with learning disabilities. This is addressed in 3 reports published in 2015 by the Care Quality Commission, Public Health England and NHS Improving Quality.

Prescribing data

Three prescribing comparators are available to support this key therapeutic topic[11]:

- **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).
- **Antidepressants: first choice % items:** the number of prescription items for SSRIs (sub-set of BNF 4.3.3) prescribed by approved name as a percentage of the total number of prescription items for 'selected' antidepressants (sub-set of BNF 4.3).

[11] The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2015). Data provided by the Health and Social Care Information Centre (October 2015; 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.

- **Dosulepin % items**: the number of prescription items for dosulepin as a percentage of the total number of prescription items for ‘selected’ antidepressants (sub-set of BNF 4.3).

Antidepressants: ADQ/STAR-PU

- Data for the quarter April to June 2015 show a 3.7 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.14 to 0.50 ADQ/STAR-PU.
- Between Q2 2013/14 (July to September 2013) and Q1 2015/16 (April to June 2015) there was an 11.5% increase in the comparator value for England (total prescribing) from 0.30 to 0.33 ADQ/STAR-PU.
- Over the same period there was a 17.4% increase in the variation between CCGs, as measured by the inter-decile range, an absolute increase 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.

Antidepressants: first choice % items

- Data for the quarter April to June 2015 show a 1.3 fold variation in prescribing rates at CCG level, from 59.7% to 79.3%.
- Between Q2 2013/14 (July to September 2013) and Q1 2015/16 (April to June 2015) there was a 0.53% decrease in the comparator value for England (total prescribing) from 69.6% to 69.2%.
- Over the same period there was a 2.55% increase in the variation between CCGs, as measured by the inter-decile range, an absolute increase of 0.23%. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

Dosulepin % items

- Data for the quarter April to June 2015 show a 10.2 fold variation in prescribing rates at CCG level, from 0.56% to 5.66%.

- Between Q2 2013/14 (July to September 2013) and Q1 2015/16 (April to June 2015) there was a 28.2% decrease in the comparator value for England (total prescribing) from 3.14% to 2.25%.
- Over the same period there was a 26.7% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 0.77%. 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 medicines optimisation dashboard, which brings together a range of medicines-related quality indicators from across sectors, includes several mental health metrics related to this key therapeutic topic. These include 2 of the prescribing comparators outlined above (Antidepressant [selected]: ADQ/STAR PU [ADQ based] and Antidepressants: first choice % items) plus:

- Depression (DEP002) % achieving upper threshold or above, which is the percentage of practices in a CCG that achieve upper threshold or above (80% or more inclusive of exceptions) for QOF indicator DEP002.
- Depression (DEP002) % underlying achievement, which is the percentage underlying achievement at CCG level for QOF indicator DEP002 inclusive of exceptions.

Antibiotic prescribing – especially broad spectrum antibiotics

Options for local implementation

- Antibiotic resistance poses a significant threat to public health, especially because antibiotics underpin routine medical practice.
- Review and, if appropriate, revise prescribing and local policies that relate to antimicrobial stewardship to ensure these are in line with the NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. A guideline on antimicrobial stewardship: changing risk-related behaviours in the general population is expected to be published in March 2016.
- Review and, if appropriate, revise current prescribing practice and use implementation techniques to ensure prescribing is in line with Public Health England (PHE) guidance on managing common infections, the Department of Health's guidance Start smart − then focus, local trust antimicrobial guidelines and the Antimicrobial Stewardship in Primary Care collaboration TARGET antibiotics toolkit.
- Review the total volume of antibiotic prescribing against local and national data.
- Review quinolone, cephalosporin, co-amoxiclav 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.

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. The

Department of Health and Public Health England's report on *Clostridium difficile* infection: how to deal with the problem from 2008 recommends that trusts should develop restrictive antibiotic guidelines that use narrow-spectrum agents alone or in combination as appropriate. The report suggests that these guidelines should avoid recommending clindamycin and second- and third-generation cephalosporins (especially in older people) and should recommend minimising the use of quinolones, carbapenems (for example, imipenem and meropenem) and prolonged courses of aminopenicillins (for example, ampicillin and amoxicillin). Broad-spectrum antibiotics should be used only when indicated by the person's clinical condition, and their use should be reviewed after the results of microbiological testing or based on the sensitivities of causative bacteria.

The Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) recommends the Start smart − then focus approach. This recommends that, if immediate antibiotic treatment is necessary, the clinical diagnosis and continuing need for antibiotics should be reviewed within 48−72 hours. A study of Start smart − then focus, which was discussed in a NICE eyes on evidence article Implementation of antibiotic prescribing guidance, concluded that most hospital antibiotic policies in England 'start smart' by recommending broad-spectrum antibiotics for empirical therapy in severe infections. However fewer 'focus' by reviewing the ongoing need for antibiotics after a couple of days, as recommended.

A NICE evidence summary: medicines and prescribing briefing on Clostridium difficile infection: risk with broad-spectrum antibiotics outlines 3 meta-analyses on this infection. The first of these, Slimings and Riley (2014), concluded that cephalosporins and clindamycin are the antibiotics most strongly associated with hospital-associated *C. difficile* infection. Subgroup analyses showed that, although first-generation cephalosporins appear to carry a lower risk of *C. difficile* infection than second- or third-generation cephalosporins, there is no definitive evidence to prove this. Also, co-amoxiclav and piperacillin-tazobactam were associated with an increase in the risk of infection. The other 2 meta-analyses, Brown et al. (2013) and Deshpande et al. (2013),

found that, for community-associated infection, the strongest association was seen with clindamycin, cephalosporins and quinolones. Trimethoprim and sulfonamides (co-trimoxazole) were associated with an increased risk of infection in all 3 meta-analyses but data were not reported for trimethoprim alone, which is most commonly used in England. The 3 meta-analyses have many limitations and, because of those limitations and the observational nature of the studies, they cannot definitively establish a causal relationship between particular antibiotics and *C. difficile* infection. Changes in antibiotic prescribing practice, the frequent use of multiple antibiotics and other potential confounding factors make it difficult to determine the relative risk for individual antibiotics.

Public Health England's English surveillance programme antimicrobial utilisation and resistance (ESPAUR) report includes national data on antibiotic prescribing, antibiotic resistance and hospital antimicrobial stewardship implementation. This shows that, in general practice, use of cephalosporins and quinolones decreased, but use of co-amoxiclav significantly increased between 2010 and 2013. In hospitals, the use of narrow-spectrum antibiotics (phenoxymethylpenicillin, flucloxacillin and erythromycin) decreased and the use of broad-spectrum antibiotics such as co-amoxiclav, piperacillin-tazobactam and meropenem significantly increased during the same period.

The *C. difficile* ribotyping network (CDRN) report, published by Public Health England, found that the strains of *C. difficile* identified and the antibiotics most frequently reported as being associated with *C. difficile* infections referred to the CDRN have changed markedly. In 2007/08, cephalosporins and quinolones were the most commonly cited antibiotics, but they were superseded by co-amoxiclav and piperacillin-tazobactam in 2011/12 and 2012/13.

These data should be interpreted with caution and should not be considered to indicate conclusively which antibiotics have the highest risks of *C. difficile* infection. Nevertheless, they show that antibiotic prescribing practice and the epidemiology of *C. difficile* infections are changing. The NICE evidence summary concludes that, without clear evidence showing that 1 particular

antibiotic or class of antibiotic is ‘low-risk’, only general recommendations are possible and healthcare professionals should follow antibiotic guidelines that recommend that all broad-spectrum antibiotics are prescribed appropriately and with careful stewardship.

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 also a cause for concern. Resistance to quinolones has increased 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.

Although identifying the cephalosporin and quinolone classes as ‘high-risk’ may have been an important control measure in reducing the risk of *C. difficile* infection, an unintended consequence of this may have been a recent increase in clinically inappropriate prescribing of co-amoxiclav and other broad-spectrum antibiotics, such as piperacillin-tazobactam. These antibiotics have a very limited set of recommended clinical indications. 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. Piperacillin-tazobactam is an intravenous antibiotic and is not generally used in primary care. However,

according to the ESPAUR report, it has become 1 of the top 5 antibiotics recommended in empiric guidelines for 10 common infections in NHS acute trusts.

Co-trimoxazole is not recommended in PHE guidance for primary care for any infections, nor does it appear in the list of antibiotics most commonly recommended in empiric guidelines for 10 common infections in NHS acute trusts. However, anecdotal evidence suggests use is increasing. The British National Formulary advises that co-trimoxazole is associated with rare but serious side effects (for example, Stevens-Johnson syndrome, bone marrow depression and agranulocytosis) and states that it should only be considered for UTI and acute exacerbations of chronic bronchitis when there is bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer this combination to a single antibacterial; similarly it should only be used in acute otitis media in children when there is good reason to prefer it.

The Department of Health website has information on antibiotic resistance, and resources to help reduce inappropriate antibiotic prescribing. See also the TARGET antibiotics toolkit, which was 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. In secondary care, the Department of Health's Start smart − then focus is recommended.

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

A NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use was published in August 2015 and a

guideline on antimicrobial stewardship: changing risk-related behaviours in the general population is expected to be published in March 2016. A NICE pathway on prevention and control of healthcare-associated infection brings information on this subject together.

NICE has also published quality standards on infection prevention and control and surgical site infection, which are concise sets of prioritised statements designed to drive measurable quality improvements within these areas.

Prescribing data

The Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI), which provides advice to the government on minimising the risk of healthcare associated infections, has agreed antimicrobial prescribing quality measures for primary and secondary care. NHS England's Planning guidance for 2015/16 for NHS foundation trusts includes a national quality premium measure on antibiotics for clinical commissioning groups.

Two prescribing comparators are available to support this key therapeutic topic[12]. 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).

[12] The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2015). Data provided by the Health and Social Care Information Centre (October 2015; 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.

- **Co-amoxiclav, cephalosporins & quinolones % items:** the number of prescription items for co-amoxiclav, 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 2014/15 (April 2014 to March 2015) show a 2.26 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.68 to 1.53 items/STAR-PU.
- Between Q4 2013/14 (January 2014 to March 2014) and Q4 2014/15 (January 2015 to March 2015) there was a 0.64% increase in the comparator value for England (total prescribing) from 0.314 to 0.316 items/STAR-PU.
- Over the same period there was a 5.68% increase in the variation between CCGs, as measured by the inter-decile range, an absolute increase of 0.005 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.

Co-amoxiclav, cephalosporins & quinolones % items

- Data for 2014/15 (April 2014 to March 2015) show a 4.1 fold variation in prescribing rates at CCG level, from 4.4% to 18.0%.
- Between Q4 2013/14 (January 2014 to March 2014) and Q4 2014/15 (January 2015 to March 2015) there was a 6.4% decrease in the comparator value for England (total prescribing) from 10.6% to 9.9%.
- Over the same period there was a 6.4% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 0.47%. 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 medicines optimisation dashboard, which brings together a range of medicines-related quality indicators from across sectors, includes the 2 prescribing comparators outlined above. The medicines optimisation

dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

Three-day courses of antibiotics for uncomplicated urinary tract infection

Options for local implementation

- A 3-day course of antibiotics is sufficient for acute symptomatic uncomplicated urinary tract infection in most women who are not pregnant.
- 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 Public Health England (PHE) guidance on managing common infections.
- Review and, if appropriate, revise prescribing and local policies that relate to antimicrobial stewardship to ensure these are in line with the NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. A guideline on antimicrobial stewardship: changing risk-related behaviours in the general population is expected to be published in March 2016.

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 women 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* (*E. 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 3 times daily) are recommended as alternative first-line options. Note that, based on evidence that the higher dose is more effective, the dose of pivmecillinam recommended by PHE differs from the licensed dose of 400 mg immediately followed by 200 mg 3 times daily (see the summary of product characteristics).

PHE guidance on managing common infections notes that resistant *E. coli* bacteraemia is increasing in the community. It recommends that risk factors for resistance should be considered and culture and sensitivity testing should be performed if first-line treatment for UTI fails. See the guidance for more information. PHE has also produced guidance for primary care on diagnosing UTI and understanding culture results. This advises when to send urine for culture in various populations, for example, people aged over 65 years or with catheters and children.

A MeReC bulletin on managing common infections in primary care stated that, although rates of antibiotic resistance might be reported to be high in UTI, 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 in UTI 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. See the NICE evidence summary: medicines and prescribing briefing on Clostridium difficile infection: risk with broad-spectrum antibiotics for more information.

A Cochrane review (CD004682) 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, 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 includes national data on antibiotic prescribing (including data for UTI), 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 guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use was published in August 2015 and a guideline on antimicrobial stewardship: changing risk-related behaviours in the general population is expected to be published in March 2016.

Prescribing data

A prescribing comparator is available to support this key therapeutic topic – **3 day courses of antibiotics: ADQ/item:** the number of average daily quantities (ADQs) per item for trimethoprim 200 mg tablets, nitrofurantoin 50 mg tablets and capsules, nitrofurantoin 100 mg m/r capsules and pivmeciillinam 200 mg tablets[13].

- Data for the quarter April to June 2015 show a 1.6 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 5.02 to 7.88 ADQ/item.
- Between Q2 2013/14 (July to September 2013) and Q1 2015/16 (April to June 2015) there was a 2.1% decrease in the comparator value for England (total prescribing) from 6.16 to 6.03 ADQ/item.
- Over the same period there was a 1.0% increase in the variation between CCGs, as measured by the inter-decile range, an absolute increase of 0.01 ADQ/item. The inter-decile range is the difference between the highest and

[13] The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2015). Data provided by the Health and Social Care Information Centre (October 2015; 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.

lowest values after the highest and lowest 10% of values have been removed.

Type 2 diabetes mellitus

Options for local implementation

- The NICE guideline on type 2 diabetes in adults: management, which has recently been updated (published December 2015) recommends adopting an individualised approach to diabetes care. Involve people with type 2 diabetes in decisions about their individual glycated haemoglobin (HbA1c) target, and reassess their individual needs and circumstances at each review. Consider stopping any medicines that are not effective.
- Consider carefully, with an individualised approach, the benefits and risks of controlling blood glucose and the use of blood glucose lowering medicines. Review and, if appropriate, revise prescribing to ensure that it is in line with NICE guidance taking into account the person's preferences, comorbidities, risks from polypharmacy, and their life expectancy and consequent chances of benefiting from long-term interventions.
- When choosing and reviewing medicines, take into account the person's individual clinical circumstances, preferences and needs; the medicines' efficacy (based on metabolic response), safety and tolerability; and the licensed indications or combinations available. Consider also the cost of medicines: the NICE guideline recommends choosing medicines with the lowest acquisition cost if 2 in the same class are appropriate.
- The NICE guideline recommends that self-monitoring of blood glucose levels for adults with type 2 diabetes should not routinely be offered. See the guideline for details on when self-monitoring is appropriate.

Evidence context

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance and insufficient pancreatic insulin production, resulting in high blood glucose levels. Type 2 diabetes is commonly associated with obesity, physical inactivity, raised blood pressure and disturbed blood lipid levels, and therefore is recognised to have an increased cardiovascular risk. It is associated with long-term microvascular and macrovascular complications,

together with reduced quality of life and life expectancy. The updated NICE guideline on type 2 diabetes in adults: management (published December 2015) recommends adopting an individualised approach to diabetes care, which takes into account personal preferences, comorbidities, risks from polypharmacy, and the ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. The guideline recommends that the person's needs and circumstances should be reassessed at each review and consideration given to stopping any medicines that are not effective. Controlling blood glucose levels requires a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia. This key therapeutic topic focusses on blood glucose management; however, the NICE guideline also has recommendations on patient education, dietary advice, blood pressure management, antiplatelet therapy and management of complications. Recommendations on the management of blood lipids in people with type 2 diabetes are given in the NICE lipid modification guideline (published July 2014). All these components should be given due consideration in the care of people with type 2 diabetes.

The NICE pathway on diabetes brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams. The NICE quality standards on diabetes in adults describe concise sets of prioritised statements designed to drive measurable quality improvements within this area.

Target blood glucose levels

The NICE guideline on type 2 diabetes in adults: management recommends that people with type 2 diabetes should be involved in decisions about their individual glycated haemoglobin (HbA1c) target and be supported to achieve and maintain this. For adults with type 2 diabetes that is managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia, the guideline recommends supporting the person to aim for an HbA1c level of 48 mmol/mol (6.5%). For adults on a drug associated with hypoglycaemia, the recommended aim is an HbA1c level of

53 mmol/mol (7.0%). If HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher, advice about diet, lifestyle and adherence to drug treatment should be reinforced, the person should be supported to aim for an HbA1c level of 53 mmol/mol (7.0%) and drug treatment should be intensified (taking into account principles of individualised care). When intensification of drug treatment is required the guideline recommends that additional treatments should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.

The target HbA1c level can be relaxed on a case-by-case basis, with particular consideration for people who are older or frail, those with a reduced life expectancy, those for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia, and those for whom intensive management would not be appropriate, such as people with significant comorbidities. The NICE patient decision aid for adults with type 2 diabetes can support the implementation of the guideline recommendations on the individualised agreement of HbA1c targets.

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.

What are the benefits and risks of controlling blood glucose?

The NICE guideline included a review question comparing intensive glycaemic control with conventional glycaemic control in people with type 2 diabetes (see the full NICE guideline for details). This used a Cochrane review (Hemmingsen et al. 2013 [CD008143]) as the primary source of evidence because it included all relevant randomised controlled trials (RCTs). The Cochrane review included 28 RCTs in 34,912 people with type 2 diabetes; the NICE guideline excluded 8 RCTs in which intensive and conventional glycaemic control groups had significant baseline differences in adjunctive treatment for cardiovascular risk factors.

Compared with conventional control, the NICE guideline found that intensive glycaemic control did not statistically significantly reduce death from any cause (relative risk [RR] 0.98, 95% confidence interval [CI] 0.88 to 1.09; 16 RCTs, n=6504) or death from cardiovascular causes (RR 1.15, 95% CI 0.98 to 1.35; 14 RCTs, n=6356). No statistically significant effect of targeting intensive glycaemic control was found on the composite of macrovascular complications (RR 0.98, 95% CI 0.74 to 1.30; 8 RCTs, n=5334), non-fatal myocardial infarction (RR 0.92, 95% CI 0.78 to 1.09; 9 RCTs, n=5902), congestive heart failure (RR 0.82, 95% CI 0.62 to 1.08; 8 RCTs, n=5460), non-fatal stroke (RR 1.06, 95% CI 0.80 to 1.41; 8 RCTs, n=5488) or amputation of lower extremity (RR 0.73, 95% CI 0.42 to 1.25; 7 RCTs, n=5079).

Intensive glycaemic control did reduce the risk of the composite of microvascular complications (RR 0.75, 95% CI 0.61 to 0.92; 3 RCTs, n=4376), but no statistically significant reductions in risk were seen for the individual end points of nephropathy (RR 0.64, 95% CI 0.32 to 1.29; 7 RCTs, n=4754), progression to end-stage renal disease (RR 0.94, 95% CI 0.47 to 1.89; 4 RCTs, n=4803) or retinopathy (RR 0.79, 95% CI 0.56 to 1.11; 5 RCTs, n=4614).

Intensive glycaemic control increased the risk of severe hypoglycaemia (RR 2.23, 95% CI 1.22 to 4.08; 13 RCTs, n=5452) and mild hypoglycaemia (RR 1.85, 95% CI 1.53 to 2.25; 12 RCTs, n=6320). The guideline development group agreed overall that there was evidence to support the setting of target values, but considered it important to ensure that a person's risk of hypoglycaemia is evaluated when setting appropriate target levels.

Self-monitoring of blood glucose

The NICE guideline on type 2 diabetes in adults: management recommends that self-monitoring of blood glucose levels for adults with type 2 diabetes should not routinely be offered unless:

- the person is on insulin treatment or
- there is evidence of hypoglycaemic episodes or

- the person is on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery or
- the person is pregnant, or is planning to become pregnant (see the NICE guideline on diabetes in pregnancy for more information).

Healthcare professionals should also take the Driver and Vehicle Licensing Agency (DVLA) At a glance guide to the current medical standards of fitness to drive into account when offering self-monitoring of blood glucose levels to best advise people with type 2 diabetes about their own particular requirements.

The guideline development group discussed the evidence for self-monitoring of blood glucose and concluded that overall, while a statistically significant difference was observed in HbA1c levels in favour of self-monitoring, this was not clinically meaningful and was unlikely to be cost effective. The reduction in HbA1c levels with self-monitoring was 2 mmol/mol (0.22%), which was less than 5 mmol/mol (0.5%), the agreed threshold for minimal important difference.

The guideline recommends considering short-term self-monitoring of blood glucose levels in adults with type 2 diabetes (and reviewing treatment as necessary) when starting treatment with oral or intravenous corticosteroids or to confirm suspected hypoglycaemia. It is also recommended for health professionals to be aware that adults with type 2 diabetes who have acute intercurrent illness are at risk of worsening hyperglycaemia, and reviewing treatment as necessary.

The guideline recommends that if adults with type 2 diabetes are self-monitoring their blood glucose levels this should be assessed in a structured way at least annually, assessing various issues including the impact on the person's quality of life and the continued benefit of self-monitoring.

Blood glucose lowering therapy

The NICE guideline on type 2 diabetes in adults: management recommends that the choice of medicine for managing blood glucose levels should be

made following a discussion with the individual person about the benefits and risks of drug treatment, and the options available. The guideline recommends an individualised approach to treatment choice taking into account the person's individual preferences and needs, and their individual clinical circumstances, for example, comorbidities and risks from polypharmacy. Choice should also take into account the medicine's efficacy (based on metabolic response), safety and tolerability; and the licensed indications or combinations available. Cost should be taken into account and the guideline recommends choosing medicines with the lowest acquisition cost if 2 in the same class are appropriate. The NICE patient decision aid for adults with type 2 diabetes can support the implementation of the guideline recommendations on the pharmacological management of blood glucose.

Efficacy

Although all blood glucose lowering medicines are effective (at a population level) in reducing HbA1c levels, clinical outcome data, particularly around cardiovascular outcomes, are limited. Improvements in surrogate markers (including HbA1c levels) do not automatically confer benefits on mortality or morbidity, and risks may only become apparent over time when medicines are used widely in a diverse population.

Metformin, sulfonylureas and insulin have outcome data from the UK Prospective Diabetes Study (UKPDS). In UKPDS 33 (UKPDS Group 1998), intensive glycaemic control with sulfonylureas or insulin compared with conventional control (median HbA1c after 10 years follow up: 53 mmol/mol [7.0%] compared with 63 mmol/mol [7.9%]) reduced the risk of microvascular complications, but not macrovascular disease. In UKPDS 34 (UKPDS Group 1998) in people who were overweight or obese, intensive glycaemic control with metformin compared with conventional control (median HbA1c after 10.7 years follow up: 57 mmol/mol [7.4%] compared with 64 mmol/mol [8.0%]) reduced the risk of MI and death from any cause. Long-term follow-up of UKPDS (Holman et al. 2008) found a continued reduction in microvascular risk and emergent risk reductions for MI and death in the sulfonylurea-insulin group and a continued benefit for risk of MI and death in the metformin group.

Other blood glucose lowering medicines have not shown such cardiovascular benefits in people with type 2 diabetes. For example, in PROACTIVE (Dormandy et al. 2005), pioglitazone did not reduce the composite primary end point of death from any cause, non-fatal MI, stroke, acute coronary syndrome, major leg amputation, coronary revascularisation and leg revascularisation in people with type 2 diabetes and pre-existing major macrovascular disease, but did increase the incidence of oedema, weight gain and heart failure. In SAVOR–TIMI 53 (Scirica et al. 2013), saxagliptin did not reduce the composite primary end point of cardiovascular death, MI, or ischemic stroke, but did increase the risk of admission to hospital because of heart failure in people with type 2 diabetes who had established cardiovascular disease, or were current smokers, or had dyslipidaemia or hypertension. (See the medicines evidence commentary Type 2 diabetes: study finds no benefit from saxagliptin on cardiovascular outcomes). In EXAMINE (White et al. 2013) alogliptin did not reduce the composite primary end point of death from cardiovascular causes, non-fatal MI or non-fatal stroke in people with type 2 diabetes who had had a recent acute coronary syndrome. (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). Similarly, in TECOS (Green et al. 2013) sitagliptin did not reduce the composite primary end point of death from cardiovascular causes, non-fatal MI, non-fatal stroke, or hospital admission for unstable angina in people with type 2 diabetes who had established cardiovascular disease.

A cardiovascular outcome study (EMPA-REG OUTCOME [Zinman et al. 2015)] of the sodium glucose cotransporter 2 (SGLT-2) inhibitor empagliflozin has recently been published. This large RCT found that adding empagliflozin to standard care in people with type 2 diabetes and established cardiovascular disease reduced the risk of cardiovascular outcomes. The composite end point of death from cardiovascular causes, non-fatal MI or non-fatal stroke was reduced with a number needed to treat of 63 over 3 years (hazard ratio 0.86; 95% CI 0.74 to 0.99). However, this was driven by a reduction in the risk of cardiovascular death, not MI or stroke. See the

medicines evidence commentary Type 2 diabetes: study finds empagliflozin reduces adverse cardiovascular outcomes, which discusses this study in more detail.

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).

Because patient orientated outcomes are not reported in many studies of blood glucose lowering drugs, the guideline development group for the recently updated NICE guideline on type 2 diabetes agreed that change in HbA1c would be the main outcome measure to reflect glycaemic control and that a difference of 5 mmol/mol (0.5%) was clinically important.

Safety

The MHRA has highlighted several safety concerns with blood glucose lowering medicines and these are cross referenced in the recently updated NICE guideline on type 2 diabetes. For example, warnings about pioglitazone and risks of heart failure, bladder cancer and use in older people have been incorporated into the summaries of product characteristics, and the guideline recommends that pioglitazone should not be offered or continued in adults with heart failure, hepatic impairment, diabetic ketoacidosis, bladder cancer or uninvestigated macroscopic haematuria. The MHRA reported in the January 2011 edition of Drug Safety Update that cases of heart failure have been reported when pioglitazone was used in combination with insulin (especially in people with pre-existing risk factors for developing heart failure). If the combination is used, people should be observed for signs and symptoms of

heart failure, weight gain, and oedema; and pioglitazone discontinued if any deterioration in cardiac status occurs.

All the glucagon-like-peptide-1 (GLP-1)-based therapies, GLP-1 agonists and dipeptidylpeptidase-4 (DPP-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 (Byetta), and in the September 2012 edition of Drug Safety Update, reports of acute pancreatitis associated with gliptins.

In the June 2015 edition of Drug Safety Update, the MHRA warned about the risk of diabetic ketoacidosis (DKA) with the SGLT-2 inhibitors canagliflozin, dapagliflozin and empagliflozin. Serious and life-threatening cases of DKA have been reported in people taking SGLT-2 inhibitors and, in several cases, blood glucose levels were only moderately elevated, which is atypical for DKA. When treating people who are taking an SGLT-2 inhibitor the MHRA recommends testing for raised ketones in those people with acidosis symptoms, even if plasma glucose levels are near-normal.

Blood glucose lowering therapy

This section outlines recommendations on blood glucose lowering therapy from the NICE guideline on type 2 diabetes in adults: management. See also the algorithm for blood glucose lowering therapy in adults with type 2 diabetes at the end of this section.

Rescue therapy at any phase of treatment

If an adult with type 2 diabetes is symptomatically hyperglycaemic, the NICE guideline recommends considering insulin or a sulfonylurea, and reviewing treatment when blood glucose control has been achieved.

Initial drug treatment

The NICE guideline recommends offering standard-release metformin as the initial drug treatment for adults with type 2 diabetes (or considering a trial of modified-release metformin in people who have had gastrointestinal side

effects with the standard-release preparation). If metformin is contraindicated (for example, in people with renal impairment) or not tolerated, the guideline recommends considering initial drug treatment with a DPP-4 inhibitor (gliptin) or pioglitazone or a sulfonylurea. The guideline also advises that repaglinide is both clinically effective and cost effective if metformin is contraindicated or not tolerated in adults with type 2 diabetes. However there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification. This subsequent constraint on intensification requires discussion with the individual.

First intensification of drug treatment

In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA1c to below the person's individually agreed threshold for intensification, the guideline recommends considering dual therapy with:

- metformin and a DPP-4 inhibitor (gliptin) or
- metformin and pioglitazone or
- metformin and a sulfonylurea or
- metformin and an SGLT-2 inhibitor in certain circumstances.

NICE guidance on treatment with metformin and an SGLT-2 inhibitor is given in NICE technology appraisal guidance on canagliflozin in combination therapy for treating type 2 diabetes, dapagliflozin in combination therapy for treating type 2 diabetes and empagliflozin in combination therapy for treating type 2 diabetes. The SGLT-2 inhibitors in dual therapy with metformin are recommended as options for treating type 2 diabetes, only if:

- a sulfonylurea is contraindicated or not tolerated or
- the person is at significant risk of hypoglycaemia or its consequences.

If metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA1c to below the person's individually agreed threshold for intensification, the guideline recommends considering dual therapy with:

- a DPP-4 inhibitor (gliptin) and pioglitazone or
- a DPP-4 inhibitor (gliptin) and a sulfonylurea or
- pioglitazone and a sulfonylurea.

The guideline development group considered that the overall quality of the evidence for first intensification was moderate to low, and the evidence was weighted towards metformin-based combinations. There was strong evidence from the health economic model showing that GLP-1 mimetics were not cost effective at first intensification and they were not recommended.

Second intensification of drug treatment

If dual therapy with oral drugs has not continued to control HbA1c to below the person's individually agreed threshold for intensification, the guideline recommends considering either triple therapy with oral drugs or starting insulin-based treatment. For triple therapy the following are recommended:

- metformin, a DPP-4 inhibitor (gliptin) and a sulfonylurea or
- metformin, pioglitazone and a sulfonylurea or
- metformin, pioglitazone or a sulfonylurea, and an SGLT-2 inhibitor in certain circumstances.

NICE technology appraisal guidance on canagliflozin and empagliflozin recommend these drugs as options in triple therapy as above. The NICE technology appraisal guidance on dapagliflozin states that dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended, except as part of a clinical trial. The guideline algorithm states that the role of dapagliflozin in triple therapy will be reassessed by NICE in a partial update of that technology appraisal guidance.

If this triple therapy is not effective, not tolerated or contraindicated, the guideline recommends considering combination therapy with metformin, a sulfonylurea and a GLP-1 mimetic for adults with type 2 diabetes who:

- have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or

- have a BMI lower than 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

GLP-1 mimetic therapy should be continued only when people have a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c **and** a weight loss of at least 3% of initial body weight in 6 months). The guideline recommends that a GLP-1 mimetic in combination with insulin should be offered only with specialist care advice and ongoing support from a consultant-led multidisciplinary team.

The guideline development group considered that the overall quality of the evidence for second intensification was low.

Insulin-based treatments

The NICE guideline recommends that a structured programme employing active insulin dose titration should be used when insulin therapy is started in adults with type 2 diabetes. Metformin should be continued in people without contraindications or intolerance. The continued need for other blood glucose lowering therapies should be reviewed: use of an SGLT-2 inhibitor in combination with insulin with or without other blood glucose lowering drugs is recommended as an option in NICE technology appraisal guidance.

When insulin therapy is necessary, the guideline recommends that it should be started from a choice of a number of insulin types and regimens. NPH insulin injected once or twice daily according to need is the preferred option. The long-acting insulin analogues, insulin detemir or insulin glargine can be considered as an alternative in certain circumstances (see the guideline for full details), such as if:

- the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or
- the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or

- the person would otherwise need twice daily NPH insulin injections in combination with oral glucose lowering drugs.

The recommendations for insulin glargine also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate marketing authorisation that allows the use of the biosimilar(s) in the same indication. The guideline development group considered that there was strong evidence that insulin degludec was not cost-effective, and this long-acting insulin analogue was not recommended. Short-acting insulins and pre-mixed (biphasic) insulin preparations are also options in particular circumstances (see the guideline for details).

Several new insulin products have been launched recently and the European Medicines Agency has issued draft guidance to minimise the risk of medication error. In the April 2015 edition of Drug Safety Update the MHRA issued advice to health professionals to minimise the risk of medication errors with recently launched high strength, fixed combination and biosimilar insulin products.

Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

This is outlined below and also available as a pdf.

NICE National Institute for Health and Care Excellence

Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

- Reinforce advice on diet, lifestyle and adherence to drug treatment.
- Agree an individualised HbA1c target based on: the person's needs and circumstances including preferences, comorbidities, risks from polypharmacy and tight blood glucose control and ability to achieve longer-term risk-reduction benefits. Where appropriate, support the person to aim for the HbA1c levels in the algorithm. Measure HbA1c levels at 3/6 monthly intervals, as appropriate. If the person achieves an HbA1c target lower than target with no hypoglycaemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA1c level.
- Base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, the person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
- Do not routinely offer self-monitoring of blood glucose levels unless the person is on insulin, on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery, is pregnant or planning to become pregnant or if there is evidence of hypoglycaemic episodes.

If the person is symptomatically hyperglycaemic, consider insulin or an SU. Review treatment when blood glucose control has been achieved.

ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Offer standard–release metformin
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%)

If standard-release metformin is not tolerated, consider a trial of modified–release metformin

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy with:
  - metformin and a DPP-4i
  - metformin and pioglitazone[a]
  - metformin and an SU
  - *metformin and an SGLT-2i*[b]
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider:
  - triple therapy with:
    - metformin, a DPP-4i and an SU
    - metformin, pioglitazone[a] and an SU
    - *metformin, pioglitazone[a] or an SU, and an SGLT-2i*[b]
  - insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, an SU and a GLP-1 mimetic[c] for adults with type 2 diabetes who:
- have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) **and** specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2, **and** for whom insulin therapy would have significant occupational implications, **or** weight loss would benefit other significant obesity-related comorbidities

METFORMIN CONTRAINDICATED OR NOT TOLERATED

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Consider one of the following[d]:
  - a DPP-4i, pioglitazone[a] or an SU
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%) for people on a DPP-4i or pioglitazone **or** 53 mmol/mol (7.0%) for people on an SU

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy[e] with:
  - a DPP-4i and pioglitazone[a]
  - a DPP-4i and an SU
  - pioglitazone[a] and an SU
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

Insulin-based treatment

- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies[f].
- Offer NPH insulin once or twice daily according to need.
- Consider starting both NPH and short-acting insulin either separately or as pre-mixed (biphasic) human insulin (particularly if HbA1c is 75 mmol/mol (9.0%) or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargine[g] if the person: needs assistance to inject insulin, lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes **or** would otherwise need twice-daily NPH insulin in combination with oral blood glucose lowering drugs.
- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: the person prefers injecting insulin immediately before a meal, hypoglycaemia is a problem **or** blood glucose levels rise markedly after meals.
- Only offer a GLP-1 mimetic[c] in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team[h].
- Monitor people on insulin for the need to change the regimen.
- *An SGLT-2i in combination with insulin with or without other antidiabetic drugs is an option*[b].

Abbreviations: [DPP-4i]Dipeptidyl peptidase-4 inhibitor, [GLP-1]Glucagon-like peptide-1, [SGLT-2i]Sodium–glucose cotransporter 2 inhibitors, [SU]Sulfonylurea. Recommendations that cover DPP-4 inhibitors, GLP 1 mimetics and sulfonylureas refer to these groups of drugs at a class level.

a. When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'.

b. Treatment with combinations of drugs including sodium–glucose cotransporter 2 inhibitors may be appropriate for some people at first and second intensification; see NICE technology appraisal guidance 288, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions. All three are also recommended as options in combination with insulin. At the time of publication, only canaglifozin and empagliflozin are recommended as options in triple therapy regimens. The role of dapagliflozin in triple therapy will be reassessed by NICE in a partial update of TA288. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal.

c. Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol [1.0%] **and** a weight loss of at least 3% of initial body weight in 6 months).

d. Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification.

e. Be aware that the drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.

f. MHRA guidance (2011) notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

g. The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication.

h. A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care.

Prescribing data

The Health and Social Care Information Centre report Prescribing for diabetes in England: 2005/6 to 2014/15 found that in the financial year 2014/15 there were 47.2 million items prescribed for diabetes at a net ingredient cost of £868.6 million. This was a 4.6% (2.1 million) rise in the number of items and an 8.2% (£65.5 million) rise in the net ingredient cost from 2013/14. 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 199% (3.9 million) from 2005/6 to 2014/15 with a growth in net ingredient cost of 166% (£131.8 million).

The net ingredient cost of all insulin therapy in primary care in 2014/15 was £334.7 million; a growth of 51.6% from 2005/6. In the financial year 2014/15, 1.38 million items of insulin glargine were prescribed at a cost of £79 million, 700,000 items of insulin detemir were prescribed at a cost of £43.5 million and 22,000 items of insulin degludec at a cost of £2.5 million. This compared with 520,000 items of NPH (isophane) insulin at a cost of £16 million.

Two prescribing comparators are currently available to support this key therapeutic topic (based on the NICE guideline on type 2 diabetes which was published in 2009 and has now been updated)[14]. These are:

- **Blood glucose lowering drugs:** the number of prescription items for metformin and sulfonylureas as a percentage of the total number of prescription items for all antidiabetic drugs.

[14] The comparators and associated data presented here are based on the previous Key therapeutic topics publication (January 2015). Data provided by the Health and Social Care Information Centre (October 2015; 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.

- **Long-acting insulin analogues:** the 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.

The development of new prescribing comparators to support this updated key therapeutic topic (which has been updated following the NICE type 2 diabetes guideline update) will be explored by the NHS England Medicines Optimisation Intelligence Group[15]. Data for the **blood glucose lowering drugs** comparator are not presented here because NICE guidance for first intensification has changed. Dual therapy with metformin and a DPP-4 inhibitor (gliptin), or metformin and pioglitazone, or metformin and a sulfonylurea are now all options following initial drug treatment with metformin.

Data for the **long-acting insulin analogues** comparator is presented because NICE guidance has not significantly changed for the choice of insulin treatment in people with type 2 diabetes. NPH insulin injected once or twice daily according to need is still the preferred option, with insulin glargine or insulin detemir (but not insulin degludec) alternatives in certain situations.

- Data for the quarter April to June 2015 show a 2.3 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 41.9% to 96.9%.
- Between Q2 2013/14 (July to September 2013) and Q1 2015/16 (April to June 2015) there was a 3.3% decrease in the comparator value for England (total prescribing) from 81.9% to 79.2%.
- Over the same period there was an 8.1% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 2.1%. 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 medicines optimisation dashboard, which brings together a range of medicines-related quality indicators from across sectors, includes 4 diabetes metrics related to this key therapeutic topic. These are:

[15] 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.

- Antidiabetic drugs (BNF section 6.1.2), which is the proportion of prescription items for sulfonylureas (BNF 6.1.2.1), biguanides (BNF 6.1.2.2) and other antidiabetes drugs (BNF 6.1.2.3): DPP-4 inhibitors, GLP-1 mimetics, insulin release stimulators, intestinal alpha glucosidases inhibitors, SGLT-2 inhibitors and pioglitazone.
- Diabetes Mellitus (DM009) % achieving upper threshold or above, which is the percentage of practices in a CCG that achieve upper threshold or above (92% or more inclusive of exceptions) for QOF indicator DM009.
- Diabetes Mellitus (DM009) % underlying achievement, which is the percentage underlying achievement at CCG level for QOF indicator DM009 inclusive of exceptions.
- Emergency diabetes admissions, which is the number of emergency attendances for diabetes per 100 patients on the practice diabetes disease register.

The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

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 gastrointestinal, renal 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.
- 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 guidance.

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 and high-dose ibuprofen. In the June 2015 edition of Drug Safety Update, the MHRA gave prescribing advice on the use of all NSAIDs. More information is also available in the NICE Clinical Knowledge Summary on NSAIDs: prescribing issues:

- The decision to prescribe an NSAID should be based on an assessment of a person's individual risk factors, including any history of cardiovascular and gastrointestinal illness.
- Naproxen (1000 mg a day or less) and low-dose ibuprofen (1200 mg a day or less) are considered to have the most favourable thrombotic cardiovascular safety profiles of all NSAIDs.

- The lowest effective dose should be used for the shortest duration necessary to control symptoms. A person's need for symptomatic relief and response to treatment should be re-evaluated periodically.

In the May 2009 edition of Drug Safety Update, the MHRA reminded prescribers that NSAIDs may rarely precipitate renal failure and that people at risk of renal impairment or renal failure (particularly older people) should avoid NSAIDs if possible. The MHRA further advised that it is important to consider other concomitant disease states, conditions, or medicines that may precipitate reduced renal function when prescribing NSAIDs. For example, co-prescribing NSAIDs with renin-angiotensin system drugs may pose particular risks to renal function. This combination should be especially carefully considered and regularly monitored if continued. See the NICE medicines evidence commentary Risk of acute kidney injury with concurrent use of antihypertensives and NSAIDs for further information and the separate key therapeutic topic Acute kidney injury (AKI): use of medicines in people with or at increased risk of AKI.

There have been several European Medicines Agency (EMA) reviews and MHRA Drug Safety Updates concerning the cardiovascular safety of NSAIDs:

- In 2005, an 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.
- The July 2008 edition of Drug Safety Update advised that etoricoxib should not be prescribed to people whose blood pressure is persistently above 140/90 mmHg and inadequately controlled, following advice from an EMA review. 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.

- Updated contraindications and prescribing advice for diclofenac were highlighted in the June 2013 edition of Drug Safety Update following publication of an EMA review. See the NICE medicines evidence commentary EMA review of cardiovascular risks of NSAIDs: higher risk with diclofenac compared with ibuprofen/naproxen confirmed and the NICE eyes on evidence article Non-steroidal anti-inflammatory drugs: new information and warnings about cardiovascular risk for more information on this issue. Further to these, the January 2015 edition of Drug Safety Update reported that oral diclofenac was no longer available without prescription.
- The January 2015 edition of Drug Safety Update highlighted updated prescribing advice for aceclofenac, which is now contraindicated in people with certain cardiovascular diseases, in-line with diclofenac and COX-2 inhibitors.
- Following an EMA review, which confirmed that the cardiovascular risk of ibuprofen 2400 mg a day or more is similar to COX-2 inhibitors and diclofenac, the June 2015 edition of Drug Safety Update issued advice on prescribing and dispensing high-dose ibuprofen. The Drug Safety Update commented that it is uncertain whether ibuprofen doses between 1200 mg and 2400 mg per day are associated with an increased cardiovascular risk compared with not taking ibuprofen, because there are only limited data available.
- The June 2015 edition of Drug Safety Update also discussed the possible interaction between ibuprofen and low dose aspirin, noting that occasional ibuprofen use is unlikely to have a clinically meaningful effect on the benefits of low-dose aspirin. However, the possibility that long-term, daily use of ibuprofen might reduce the cardioprotective effects of low-dose aspirin cannot be excluded.

More information is available in the MHRA guidance on COX-2 selective inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs): Cardiovascular safety.

Further to this, a systematic review and meta-analysis of observational studies, which was outlined in a NICE medicines evidence commentary NSAIDs and risk of venous thromboembolism, found that there was a statistically significant increased risk of venous thromboembolism among users of NSAIDs compared to non-users of NSAIDs. However, the meta-analysis had a number of limitations and the results should be interpreted with caution.

More information on the use of NSAIDs can be found in the NICE guidelines on osteoarthritis, rheumatoid arthritis and low back pain (which is being updated; publication expected November 2016). These guidelines include recommendations to 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.

NICE has also published quality standards on osteoarthritis and rheumatoid arthritis, which are concise sets of prioritised statements designed to drive measurable quality improvements within these areas.

A separate key therapeutic topic on acute kidney injury (AKI): use of medicines in people with or at increased risk of AKI is also available.

Prescribing data

Two prescribing comparators are available to support this key therapeutic topic[16]. These are:

- **NSAIDs: ADQ/STAR-PU:** the total number of average daily quantities (ADQs) per oral NSAIDs (BNF 10.1.1 sub-set) COST based Specific Therapeutic Group Age-sex weightings Related Prescribing Unit (STAR-PU).
- **NSAIDs: Ibuprofen & naproxen % items:** the total number of prescription items for ibuprofen and naproxen as a percentage of the total number of prescription items for all NSAIDs.

NSAIDs: ADQ/STAR-PU

- Data for the quarter April to June 2015 show a 4.0 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 0.65 to 2.60 ADQ/STAR-PU.

[16] The comparator and associated data presented here are based on the previous Key therapeutic topics publication (January 2015). Data provided by the Health and Social Care Information Centre (October 2015; 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 Q2 2013/14 (July to September 2013) and Q1 2015/16 (April to June 2015) there was a 9.6% decrease in the comparator value for England (total prescribing) from 1.58 to 1.43 ADQ/STAR-PU.
- Over the same period there was a 12.9% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 0.12 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 2015 show a 1.3 fold variation in prescribing rates at CCG level, from 67.5% to 87.8%.
- Between Q2 2013/14 (July to September 2013) and Q1 2015/16 (April to June 2015) there was a 10.0% increase in the comparator value for England (total prescribing) from 70.9% to 78.0%.
- Over the same period there was an 11.8% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 1.4%. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

The prescribing of diclofenac has reduced in recent years. However, diclofenac still accounts for approximately 1.4 million prescription items (10% of all NSAID items) per year in primary care in England, and there is variation in prescribing across localities.

The medicines optimisation dashboard, which brings together a range of medicines-related quality indicators from across sectors, includes the NSAIDs: ibuprofen & naproxen % items prescribing comparator outlined above. The medicines optimisation dashboard helps NHS organisations to understand how well their local populations are being supported to optimise medicines use and inform local planning. The dashboard allows NHS organisations to highlight variation in local practice and provoke discussion on the appropriateness of local care. It is not intended as a performance measurement tool and there are no targets.

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 people with type 2 diabetes and pressure ulcers , and the prevention and treatment of surgical site infections. 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). The NICE Medicines and Prescribing Programme is currently producing an Evidence summary: medicines and prescribing briefing on wound dressings. This will be used to update the evidence in this key therapeutic topic when it is published.

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 was available for this key therapeutic topic – **Wound care products: NIC/item**. This comparator has been retired from Q1 2015/16 data onwards and therefore data are not presented[17].

[17] 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.

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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