Hypertension clinic drug choices: tips for pharmacist prescribers

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In the second of our two-part series on helping pharmacist independent prescribers set up and run a hypertension clinic in primary care, Briegeen Girvin discusses the factors to consider when prescribing and monitoring antihypertensive drugs and statins.

This series aims to help prepare pharmacist independent prescribers to run a hypertension clinic for the first time. The first article (featured in the June 2019 issue of Prescriber) covered the importance of drawing up a treatment plan and other practical aspects of running a hypertension clinic. This second article explores some of the main factors to consider when prescribing antihypertensives and statins, including their adverse effects and monitoring requirements. For full details on these medicines, consult the latest edition of the BNF or Summaries of Product Characteristics within the electronic Medicines Compendium (eMC) at https://www.medicines.org.uk/emc/.

Initiating antihypertensive drugs and statins

For more information on evidence-based prescribing of antihypertensive drugs, see the review by Mark Pucci in the April 2019 issue of Prescriber and NICE guidance. Only about a quarter of all patients with hypertension will be well controlled on monotherapy. Three-quarters are likely to require two or more antihypertensive drugs to reach target.

In practice, combining two or more drugs allows lower doses to be used, which is likely to be better tolerated than titrating one antihypertensive drug up to maximum dose.

Since most patients will require more than one antihypertensive, recent European guidelines recommend starting two antihypertensive drugs at once for most patients. However, I initiate one drug at a time as this allows identification of those who only require monotherapy. Similarly, if patients experience adverse effects, having prescribed one drug at a time makes it easier to determine which one the patient is not tolerating. If a patient is eligible for both
antihypertensive and statin treatment, I try to control blood pressure first before introducing the statin.

**Which antihypertensive drug to try first**

NICE currently recommends an ACE inhibitor or angiotensin II-receptor blocker (ARB) first line in younger patients (under 55 years old) and a calcium-channel blocker (CCB) first line in older patients (over 55 years old). However, a CCB should be first line for people of African or Caribbean family origin of any age.² (Note that the NICE guideline on hypertension is currently being updated, and the new recommendations are expected to be published in August.) If blood pressure is not controlled on monotherapy, NICE recommends combining an ACE inhibitor or an ARB with a CCB. If blood pressure is still not controlled, NICE recommends adding a thiazide-like diuretic.² NICE also states that an ACE inhibitor and an ARB should not be combined together.

Of these three drug groups, you may find that in practice, choice will depend upon both tolerability and paying close attention to individual compelling indications or contraindications for each group. For example, ACE inhibitors and ARBs are contraindicated in pregnancy and could be considered a questionable first choice in women of childbearing age. In patients with peripheral oedema or heart failure or at risk of developing heart failure, a thiazide-like diuretic should be prescribed in preference to a CCB.

Fourth-line options include further diuretic treatment, such as addition of low-dose spironolactone (unlicensed indication). Doxazosin and beta-blockers are also potential fourth-line antihypertensive drugs. Doxazosin is further down the list of options because in the ALLHAT study, the doxazosin arm was withdrawn due to a 25% increase in risk of cardiovascular events (mostly heart failure and stroke) compared with clortalidone.⁶ Beta-blockers are also further down the list of options because they have shown poorer outcomes than other antihypertensive drugs, particularly in terms of reduction in risk of stroke.⁷ However, if a patient has ischaemic heart disease, heart failure, palpitations or other compelling indication for a beta-blocker, then it should be considered first line.

Listening to heart sounds before starting antihypertensive drugs can help to detect heart murmurs. If these are heard, the patient should be referred to a GP in the practice. Some antihypertensive drugs, particularly vasodilating antihypertensives, can cause hypotension and collapse when given to patients with significant cardiac valvular obstruction. For example, the **BNF** advises that ACE inhibitors should be used with care in patients with severe or symptomatic aortic stenosis and to use ARBs with caution in patients with aortic or mitral valve stenosis. Aortic stenosis is listed as a contraindication to felodipine and lercanidipine and significant aortic stenosis is listed as a contraindication to amiodipine.⁸

Some general points to consider when prescribing antihypertensive agents and statins are shown in Table 1.

**ACE inhibitors and angiotensin II-receptor blockers**

The Northern Ireland Formulary first-choice ACE inhibitors for treating hypertension are lisinopril, ramipril and perindopril.⁹ Of these three, my first choice is lisinopril as it appears to be more effective in terms of reducing blood pressure compared with other ACE inhibitors and ARBs. This is based on my clinical experience rather than scientific evidence but is likely to be due to its long duration of action.¹⁰

**Monitoring requirements**

Before starting an ACE inhibitor or ARB, baseline kidney function tests and serum electrolytes are required. These need to be repeated within one to two weeks of starting the drug or increasing the dose.¹¹ ACE inhibitors and ARBs raise serum potassium levels. If kidney function is normal, lisinopril can be started at 10mg and increased to the usual dose of 20mg daily. I rarely increase beyond this dose as the dose-response curve tends to flatten. Lower initial and maintenance doses may be required for certain patients, eg those with chronic kidney disease (CKD). For more details, consult the Summary of Product Characteristics in the eMC.¹²

**What to do if renal function deteriorates**

Guidelines advise that if estimated glomerular filtration rate (eGFR) falls by 25% or more, or if plasma creatinine increases by 30% or more from baseline, stop the ACE inhibitor or ARB or reduce to a previously tolerated dose once potential alternative causes of renal impairment have been ruled out. If the changes in renal function are less than described, do not modify the dose but repeat the test in one to two weeks. Stop the ACE inhibitor or ARB if serum potassium rises above 6.0mmol/L and other drugs known to cause high serum potassium have been discontinued.¹¹ If planning on re-introducing an ACE inhibitor or ARB, agree with the GPs when to retest and reintroduce treatment.

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**Table 1. Points to consider when prescribing antihypertensive agents and statins**

- Before choosing an antihypertensive agent, carefully consider its contraindications, compelling indications and expected adverse effects
- Prescribe medications that have a good evidence base. These will tend to be the ones listed in local formularies
- Where possible, prescribe medications that can be taken once daily
- Ensure that all doses are appropriate for the patient’s level of renal function
- All secondary prevention patients should be offered a statin (atorvastatin 80mg)
- Offer primary prevention patients a statin (atorvastatin 20mg) if their risk of developing CVD is ≥10% over the next 10 years
- Ensure that patients are called for review of their blood pressure and that all required monitoring has been done

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The close monitoring of renal function during initiation of ACE inhibitors and ARBs is necessary in order to detect patients with renal artery stenosis, in whom these drugs can cause a severe deterioration in renal function. The most common cause of renal artery stenosis is atherosclerosis and so the risk factors for renal artery stenosis are similar to those for atherosclerosis, eg advanced age, high blood pressure, high cholesterol, diabetes, obesity, smoking, a family history of early cardiovascular disease (CVD) and lack of exercise. The Renal Drug Handbook is an excellent source of information on what medicines can be prescribed and at what dose according to renal function.

**Calcium-channel blockers**

Dihydropyridine CCBs are commonly used to treat hypertension. The Northern Ireland Formulary first-choice dihydropyridine CCB is amlodipine; the second choice is felodipine. Their main adverse effects are headache, flushing and ankle oedema. These adverse effects are dose dependent, for example they occur at a higher rate with amlodipine 10mg daily than 5mg daily. I advise patients that in many cases, headache or flushing improves over time.

Ankle oedema caused by CCBs is not thought to be harmful but may affect adherence. In practice, I find that females are less tolerant of ankle oedema than males (based on clinical experience rather than scientific evidence). Possible strategies to reduce ankle oedema include dose reduction, or stopping/changing the medication. There are reports that CCB-induced ankle oedema is less common when the drug is given in combination with an ACE inhibitor orARB. It is not improved by addition of a diuretic as CCB-induced ankle oedema is not related to fluid retention but is due to an increase in capillary pressure, leading to leakage of fluid. A meta-analysis found that low doses of the newer lipophilic dihydropyridines, eg lercanidipine 10mg, and the non-dihydropyridine CCBs, eg diltiazem, are associated with a lower incidence of oedema. I personally do not initiate diltiazem (or other non-dihydropyridine CCBs) due to their effects on cardiac conduction. If you are considering commencing diltiazem, I would recommend first discussing this with one of the GPs in your practice.

**Thiazides and related diuretics**

The Northern Ireland formulary first-line choice thiazide or related diuretic is indapamide (either 2.5mg daily or modified-release 1.5mg daily), with bendroflumethiazide 2.5mg daily second line. These agents increase serum uric acid and are therefore contraindicated in gout. They can also cause hypokalaemia, possible changes in lipid profile and impaired glucose tolerance. These adverse effects are dose dependent and are not a significant cause for concern when using currently recommended low doses.

Hyponatraemia may occur with thiazide diuretics. The NICE Clinical Knowledge Summary (CKS) on hyponatraemia provides an in-depth review on the risk factors for and management of the condition. It is more commonly seen in patients with heart failure, liver disease or renal disease. Hyponatraemia with thiazide diuretics is more likely to develop when patients are taking other medicines that also cause hyponatraemia. Other medicines commonly associated with hyponatraemia are SSRIs, antipsychotics, NSAIDs and carbamazepine. Other medications that less commonly cause hyponatraemia include sulfonylureas, tricyclic antidepressants, proton-pump inhibitors, ACE inhibitors and ARBs. If a patient develops hyponatraemia on a thiazide diuretic, it is worthwhile considering if other drugs that reduce sodium levels could be stopped and also enquiring about the patient’s fluid intake, as in some cases a high water intake may be a contributory factor.

**Monitoring requirements**

Before starting a thiazide diuretic, baseline kidney function tests and serum electrolytes are required. This should be repeated in four weeks and then annually.

**Antihypertensive drugs and erectile dysfunction**

When starting antihypertensive drugs, some patients express concerns about their potential to cause erectile dysfunction. There are no properly designed randomised controlled trials to definitively say whether or not antihypertensive drugs cause erectile dysfunction. However, a recent review has concluded that there is evidence to suggest that older antihypertensive drugs (ie diuretics, beta-blockers, centrally acting drugs) have a negative impact on erectile function and that newer drugs seem to have either neutral (eg ACE inhibitors, CCBs) or beneficial (eg ARBs, nevirapinol) effects. However, it is worthwhile noting that in early studies on diuretics that reported erectile dysfunction, much higher doses of diuretics were used than are currently recommended.

**Antihypertensive drugs and acute kidney injury**

Be familiar with the potential for certain antihypertensive medications to cause acute kidney injury (AKI). NICE CKS is a useful resource for both managing acute kidney injury and for its prevention. In its advice to give to patients who are taking potentially nephrotoxic drugs on what to do during times of acute illness, CKS states: “Advise the person to seek medical advice in the event of acute illness (for example diarrhea or vomiting) to discuss temporarily stopping medications that may increase the risk of AKI such as ACE inhibitors, ARBs and diuretics.”

**Statins**

In its guidance on CVD risk assessment and reduction, NICE advises to offer atorvastatin 80mg to all secondary prevention patients and atorvastatin 20mg to primary prevention patients who have a risk of developing CVD of ≥ 10% over the next 10 years, and to aim for a >40% reduction in non-HDL cholesterol. NICE recommends the use of QRSK2 but lists some exceptions to the use of this tool, eg offer atorvastatin 20mg to all patients with CKD as these patients are at high risk of developing CVD. The NICE guideline also provides information about lifestyle and dietary advice, for example eating at least five portions of fruit and vegetables per day, reducing saturated fat intake, incorporating aerobic and
muscle strengthening exercises, smoking cessation and maintaining a healthy weight.\textsuperscript{22}

**Monitoring requirements**

Measure liver enzymes (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) at baseline and then at three months and 12 months after starting a statin but not again unless clinically indicated. Statin treatment should be discontinued (or not started) if ALT or AST are more than three times the upper limit of normal (ULN).\textsuperscript{22}

In general, routine measurement of creatine kinase levels are not required at baseline nor throughout treatment with a statin. However, NICE advises to measure creatine kinase at baseline if patients have previously experienced persistent generalised muscle pain. If creatine kinase levels are more than five times the ULN, repeat the measurement after seven days. If creatine kinase levels are still more than five times the ULN, do not start a statin, but if they are raised but less than five times the ULN, NICE suggests starting a statin at a lower dose. Patients should be advised to seek medical advice if they develop muscle pain, tenderness or weakness while being treated with a statin, and creatine kinase levels should be measured.\textsuperscript{22}

NICE advises trying three different statins before concluding that a patient is statin intolerant. It also advises not to routinely offer any of the following other lipid-lowering treatments to prevent CVD: fibrates, nicotinic acid, omega-3 fatty acids, bile-acid sequestrants or any combinations of these drugs with statins. Ezetimibe can be considered for primary hypercholesterolaemia in patients who cannot tolerate a statin or in addition to a statin in those who are not controlled on a statin.\textsuperscript{23}

**Conclusion**

Lowering blood pressure by 20mmHg systolic (or 10mmHg diastolic) halves the risk of dying from stroke, ischaemic heart disease and other vascular causes.\textsuperscript{24} Running a dedicated clinic to control blood pressure and related risk factors is therefore an excellent opportunity for pharmacist independent prescribers to use their medicines knowledge and skills, and to improve patient care.

**References**

9. Health and Social Care Board. Northern Ireland Formulary. 2.0 Cardiovascular system. Available from: http://infoformulary.hscni.net/Formulary/Adult/2.0/Pages/default.aspx

**Declaration of interests**

None to declare

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