



Prescriber

Case Notes

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**Calcium channel blocker
prescribing: balancing efficacy,
tolerability and cost-effectiveness**

Introduction



Cathal Daly

In 2006, the National Institute for Health and Clinical Excellence (NICE) and the British Hypertension Society (BHS) issued consolidated clinical guidelines for the primary care management of essential hypertension in adults.¹ The guidelines were a partial update to previous guidance CG18² and were designed to identify cost-effective approaches to managing patients with hypertension, including the threshold for initiating drug therapy.

A central element of the BHS/NICE guidelines is the ACD treatment algorithm (Figure 1), which defines the pharmacological treatment pathway for patients newly diagnosed with essential hypertension. Beta-blockers are no longer recommended as a routine initial therapy for hypertension, and other classes of anti-hypertensive medication such as calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACE inhibitors) and thiazide diuretics are preferred as first- and second-line therapies.

Angiotensin receptor blockers (ARBs) are usually used only if the patient is intolerant to ACE inhibitors. CCBs and thiazide diuretics are recommended first-line for patients aged over 55 years or any patient of Afro-Caribbean origin. In patients younger than 55 years ACE inhibitors are recommended first-line, with CCBs and thiazide diuretics as second-line.¹

The BHS/NICE ACD algorithm has defined the standard for hypertension management. It should be noted that the algorithm is for management of uncomplicated hypertension, and would not necessarily be appropriate in situations where additional complicating factors such as diabetes are present.

The target set out in the BHS/NICE guidance is to reduce blood pressure to 140/90mmHg or less, adding more drugs as needed, until further treatment is inappropriate or declined.¹ A number of factors must be considered when selecting anti-hypertensive medication. These include efficacy, tolerability, patient-specific contraindications, cost, ease of use and patient preference. In the treatment of essential hypertension, tolerability is of central importance, since the goal is to establish the patient on a medication which they will remain using in the long term. Adverse side-effects may disrupt adherence, particularly since hypertension is generally asymptomatic.

Importantly, the BHS/NICE guidelines do not specify which particular drugs from within each class should be prescribed. While the major classes of

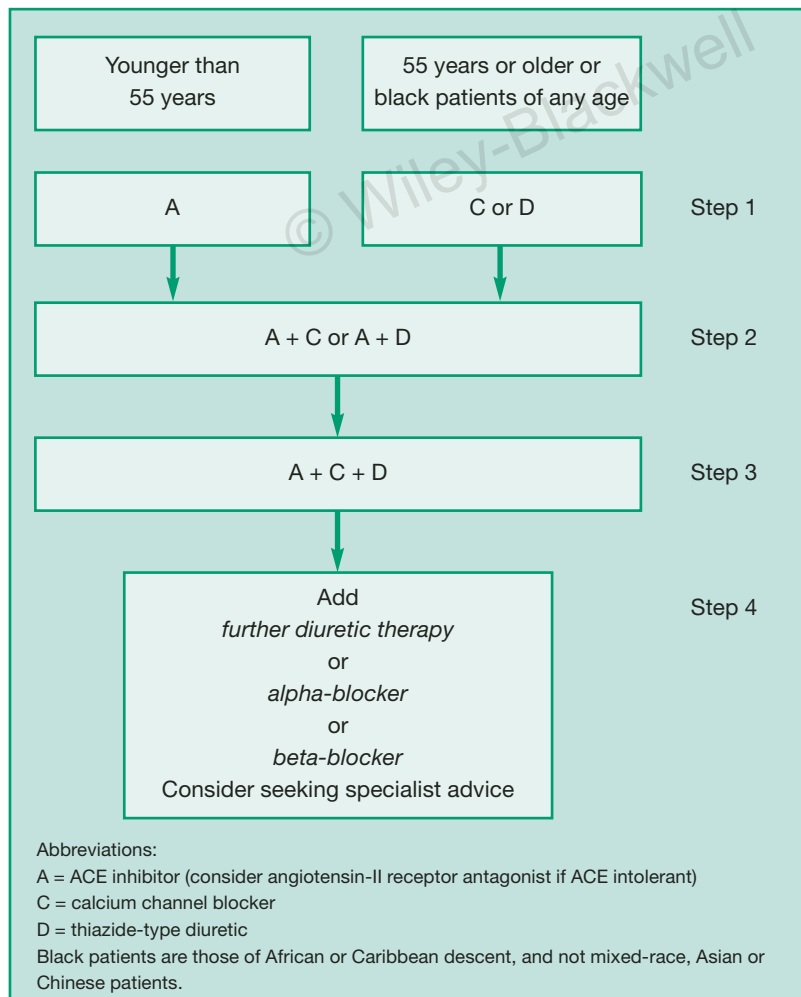


Figure 1. BHS/NICE ACD treatment algorithm for essential hypertension¹

antihypertensive have classical class-associated side-effect profiles (see Box 1), there may be clinically significant distinctions between different drugs within the same class. An example of this variability is provided by the CCB class, with a number of clinical trials^{3–6} and a recent clinical audit⁷ demonstrating systematic distinctions in the incidence and severity of side-effects between specific CCBs. This is of direct importance in primary care, since implementation of BHS/NICE guidance can be made

- Beta-blockers – increased risk of new-onset diabetes,^{8,9} bronchospasm, fatigue, coldness of extremities and sleep disturbances with nightmares¹⁰
- Thiazide diuretics – hypokalaemia, hyponatraemia,^{11,12} impairment of glucose metabolism with resultant onset of type 2 diabetes¹²
- CCBs – swollen ankles, flushing¹³
- ACE inhibitors – cough¹⁴

Box 1. Common class-associated side-effects of antihypertensive drugs

considerably more effective by defining first- and second-line CCBs within each medical practice. This ensures that the second-line drug is clearly defined if the first-line drug is poorly tolerated, so that medications which show the optimal balance of cost-effectiveness, efficacy and tolerability are consistently prescribed, thereby helping to avoid unnecessary class-switching, addition of further drugs or additional expense.

Case 1



Dr Wasim Baqir

Mr JL is a 54-year-old man who was first identified as hypertensive by his GP, with a blood pressure (BP) of 205/115mmHg. At this point he was smoking 10 cigarettes and drinking 6–10 pints of lager per day. His BMI was 32.9 and cardiovascular disease (CVD) risk was calculated at 61% over 10 years. Blood tests suggested a risk of diabetes and hypercholesterolaemia, with glucose level of 12.0mmol/l and overall cholesterol of 8.0mmol/l. No abnormalities were detected in electrolytes or ECG. He was referred to the hypertension clinic at his GP practice for treatment.

In line with current BHS/NICE guidelines, an ACE inhibitor was prescribed (lisinopril 10mg/day). Lifestyle changes were also suggested and implemented, namely a reduction in alcohol intake, smoking cessation and exercise.

After one month, there was an improvement in blood glucose and cholesterol levels, electrolytes and

renal function remained satisfactory, and BP had decreased to 157/94mmHg. Lisinopril dosage was raised to 20mg/day over the next two months. However, no further BP reduction was observed at the monthly check-ups. The dosage of lisinopril was reduced back to 10mg/day, as the higher dosage had not improved BP control, yet had increased the likelihood of side-effects. At the same time, the patient was started on the CCB amlodipine, at 5mg/day. This ensured that BHS/NICE guidelines were followed, since the patient remained on an ACE inhibitor and was started on a CCB, in accordance with the ACD algorithm. A substantial reduction in BP was observed after one month (139/83mmHg). However, the patient complained of ankle swelling, which was sufficiently uncomfortable that he had recently stopped taking the amlodipine. He was switched to another CCB, lercanidipine, at 10mg/day.

At the next consultation one month later, BP remained stable at 139/82mmHg and the ankle oedema had fully resolved. Six months later BP remains stable, controlled by the combination of lisinopril 10mg/day and lercanidipine 10mg/day, with an absence of troubling adverse effects.

Discussion of Case 1

This case illustrates the importance of considering a within-class switch when prescribing anti-

hypertensives if a drug within a given class is poorly tolerated. Amlodipine caused a marked drop in BP, but was not well tolerated due to ankle oedema, to the

extent that it was discontinued by the patient. Rather than switching the patient to another class, a within-class switch to lercanidipine resulted in stable BP control

and was well tolerated. This illustrates that antihypertensives within the same class may have differing tolerability profiles. These findings correlate with those of a recent clinical audit of 1507 hypertensive patients, which showed improved tolerability of lercanidipine over amlodipine. Twice as many

patients discontinued therapy with amlodipine in comparison to lercanidipine, with almost four times as many patients treated with amlodipine citing ankle oedema as their primary reason for discontinuing treatment.⁷ Since hypertensive patients are often free of obvious troubling symptoms, selecting a drug with

an optimal tolerability profile is an essential consideration in ensuring long-term compliance. Carrying out a within-class switch also leaves the prescriber with a greater range of options in the future, in terms of prescribing from other classes of antihypertensive, should additional BP control become necessary.

Case 2



Dr John B Pittard

This case study describes a 61-year-old male who is a retired language teacher. He had recently moved to the area, and attended an appointment with the practice nurse for a new patient medical and to renew an existing prescription for antihypertensive medication. Following an initial examination and blood pressure reading, he was referred to his new GP for a medication review.

The patient had a seven-year history of treatment for hypertension, and was taking atenolol 50mg/day and bendroflumethiazide 2.5mg/day. He had previously been prescribed nifedipine, but discontinued due to headaches and flushing. BP readings had generally been taken annually. BP from the recent series of readings showed a mean of 157/93mmHg. At the initial consultation with his new GP, the patient presented as a non-smoker, drinking 20 units of alcohol per week, with moderate added salt intake. BMI was 28. There was no family history of cardiovascular disease. BP was 156/92mmHg at this examination. Estimated glomerular filtration rate (eGFR) was over 60ml/min/1.73m². Urea and electrolyte levels were within normal limits. Total cholesterol level was

5.7mmol/l. The patient was given advice on how to follow a moderate walking exercise plan and reduce salt intake. Changes were made to the patient's drug regimen in order to reduce BP and follow updated BHS/NICE guidelines. Atenolol was replaced with lisinopril, started at 10mg/day, increasing to 20mg/day after two weeks.

One month later, urea and electrolytes remained normal, and BP was 153/90mmHg. In accordance with BHS/NICE guidelines, an additional drug from a third class was added with the aim of achieving the target BP of $\leq 140/90$ mmHg; the guidelines specified use of a calcium channel blocker. Given the patient's previous intolerance to nifedipine, lercanidipine was prescribed at 10mg/day.

At the next examination six weeks later, the patient remained healthy and lercanidipine was well tolerated. BP was 148/89mmHg. Lercanidipine dosage was increased to 20mg/day, and the ACE inhibitor and thiazide diuretic medications were combined by prescribing lisinopril 20mg/hydrochlorothiazide 12.5mg in single tablet formulation. Two months later BP remained well controlled at 144/86mmHg and the combination therapy was well tolerated. The patient was happy with the two tablets once-daily dosage regimen, and the sustained BP control confirmed that he remained compliant.

Discussion of Case 2

This patient's hypertension was successfully managed using a combination of antihypertensives from different classes, in accor-

dance with the ACD treatment algorithm, where beta-blockers are no longer recommended as first-line therapy for hypertension. At the initial consultation, atenolol was therefore replaced

with the ACE inhibitor lisinopril. The thiazide diuretic bendroflumethiazide was not changed, as this class is one of the recommended first-line treatments for patients over 55 years. BP

remained considerably above target after one month, requiring further intervention. An antihypertensive from the CCB class was prescribed, in accordance with the ACD algorithm. This patient had previously shown intolerance to nifedipine due to headache and flushing. Lercanidipine was found to provide good tolerability

and effective lowering of BP. Combination therapy using drugs from multiple classes is necessary in hypertension management if adequate BP control cannot be achieved using a single drug. However, each drug included in the regimen must provide both efficacy in terms of consistent BP lowering, and tolerability, to

ensure that the patient continues taking the medication over a sustained period. Careful selection of the drug from within each class is therefore of central importance. Choosing lercanidipine as the optimal CCB was the final step in establishing an effective combination therapy appropriate for long-term use.

Case 3



Beverley Cox

Mrs K is a 78-year-old female who is widowed and lives alone. Her daughter visits regularly and helps a little with the shopping and housework, but generally speaking Mrs K is quite independent. She was diagnosed with hypertension eight years ago and was initially treated with atenolol, which was titrated upwards to 50mg daily. However, she developed a wheeze which was thought to be due to bronchospasm, a known side-effect of beta-blockers, so atenolol was stopped and substituted with the CCB amlodipine at a dose of 5mg daily.

At a review of her hypertension management, her BP was found to be raised at 158/84mmHg. Her blood tests showed nothing of concern regarding renal or hepatic function. Glucose and lipid levels were all within normal limits. On questioning, it was apparent that Mrs K was 'forgetting' to take her tablet almost every other day – in fact she was intentionally omitting her medication because she had developed swollen ankles, which reduced her mobility.

Her prescription was changed to 10mg of lercanidipine, a CCB which is less likely to cause ankle oedema but which may continue to confer the benefits of blood pressure lowering using the class of drug recommended by the BHS/NICE guidelines. At her last visit, Mrs K's blood pressure was within normal limits and she was not suffering from any troubling side-effects.

Discussion of Case 3

The original decision to switch Mrs K to the CCB amlodipine was made in line with the BHS/NICE guidelines on the primary care management of hypertension, which suggest using either a thiazide diuretic or a CCB as first-line therapy in people over the age of 55 years. At the time, Mrs K was reluctant to consider a thiazide diuretic as she was concerned that a 'water tablet' would restrict her ability to get out and about. Understanding the importance of

involving patients in decision making, I therefore suggested that we opt for a CCB and chose amlodipine. However, it was now clear that the amlodipine was not going to suit Mrs K, as she was avoiding taking her tablets because she had developed ankle oedema which had reduced her mobility and impacted on her ability to care for herself and her home. This decision not to take her treatment was clearly affecting her blood pressure control, putting her at risk of cardiovascular events, such as stroke and heart attack.

I therefore decided to stop amlodipine treatment. However, I was keen, as was Mrs K, to keep her treatment within the CCB therapy group – she did not want diuretics and ACE inhibitors would not be first-line choice for her age group. Bearing all of this in mind I decided to move to lercanidipine, a CCB which is less likely to cause ankle oedema but which can continue to confer the benefits of blood pressure lowering using the class of drug recommended by the BHS/NICE guidelines.

Commentary



Cathal Daly

Selecting the optimal drug from within a class is of central importance in the management of essential hypertension, in order to

ensure that the patient remains concordant and thus achieves long-term stable BP control. The three case studies presented here illustrate that not all antihypertensives from within a given class are the same with regard to tolerability. Failure to correctly identify that a patient is experiencing troubling side-effects and is no longer adhering to their drug regimen has serious implications for the control of their hypertension. A balance must be sought between efficacy, tolerability and cost-effective prescribing.

The three case studies discussed in this supplement refer to prescribing choices of antihypertensive medication within the framework of the ACD treatment algorithm specified in the consolidated BHS/NICE guidelines (Figure 1). Although this provides clear guidance for usage of the main classes of antihypertensive, it does not specify which drug within each class should be prescribed.

With regard to prescribing choices, it is important to consider the differences in tolerability profiles among CCBs. If the first CCB tried by the patient proves to be poorly tolerated or there are issues with patient adherence, it is worthwhile making a within-class switch so that a second drug within the same class can be trialled before moving to another class of antihypertensive. To this end, it would seem sensible that

first- and second-line CCBs are clearly defined within each practice, to ensure that within-class switches are implemented with optimal efficiency.

Cost-effective prescribing

Two of our case studies showed that the CCB amlodipine was efficacious in lowering BP. Although amlodipine is available as an inexpensive generic, and is an appropriate drug to be recommended as a first-line choice within the CCB class, our observations suggest that the risk of side-effects occurring with amlodipine is relatively high, particularly at 10mg dosage. Reported side-effects were related to an unacceptable level of peripheral oedema. The strong association of amlodipine with this effect is supported by published research data.³

Newer CCBs such as lercanidipine offer a similar level of efficacy to amlodipine with a lower incidence of side-effects.³⁻⁵ If the patient experiences side-effects or is non-adherent when prescribed a CCB, a switch to another, newer, CCB such as lercanidipine is recommended before increasing dosage or adding more drugs.

Besides amlodipine, some other CCBs are available as generics. However, those which are modified-release formulations are not recognised as generics by the NHS and will be dispensed as branded drugs at potentially significant cost.

Lercanidipine will not fall into this category once the patent expires (January 2010) because it is not a modified-release preparation. Even at the current branded price, lercanidipine is significantly

cheaper than many CCBs on the market. At the time of going generic it is likely to become an even more cost-effective treatment choice.

Adherence

If an antihypertensive drug proves ineffective, or is effective initially but then ceases to control blood pressure, it is essential to check that the patient is actually taking the medication. Poor tolerability is likely to disrupt adherence, resulting in the patient either not taking the medication correctly or discontinuing it entirely. This may appear to the prescriber as a lack of efficacy.

Troubling side-effects associated with antihypertensive medication have potentially serious implications for the health of the patient. This is illustrated in Case 1 where Mr JL stopped taking amlodipine altogether due to intolerable ankle oedema. Stopping medication in this manner will almost certainly lead to a deterioration in BP control. In addition, unpleasant side-effects can lead to significant psychosocial comorbidities and decreased quality of life. For example, in Case 3, Mrs K developed ankle oedema in response to amlodipine treatment which significantly reduced her mobility. Mrs K lives alone and is an independent person. As a result of her reduced mobility, she became more reliant upon others for support. The psychological impact of such changes should not be underestimated. Furthermore, this disrupted her adherence with the amlodipine, resulting in worsening hypertension.

To avoid such situations arising, when newly prescribing a CCB, it

is important to discover whether the patient has any previous history of swollen ankles or is likely to suffer from this effect. If this is the case, the patient should be prescribed a well-tolerated CCB that is less likely to cause

oedema, rather than be started on amlodipine and subsequently switched.

In conclusion, a cost-effective medication regimen that provides efficacious control of blood pressure along with a good level

of tolerability will promote long-term adherence. This can be achieved through implementation of the BHS/NICE guidelines, together with selection of the optimal drug from within each class for each patient.

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Declaration of interest

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most common side-effects were flushing, peripheral oedema, palpitations, tachycardia, headache, dizziness, and asthenia. **Legal category:** POM. **Package quantities and price:** 10 mg Blister packs of 28 tablets – £5.80. 20 mg Blister packs of 28 tablets – £11.00. **Marketing authorisation number:** 10 mg tablets PL04595/0005, 20 mg tablets PL04595/0010. **Marketing authorisation holder:** Recordati Industria Chimica e Farmaceutica SpA, Via Matteo Civitali 1, 1 – 20148 Milan, Italy. **Distributed by:** Recordati Pharmaceuticals Limited, Knyvett House, The Causeway, Staines, Middlesex, TW18 3BA. Tel: +44 (0)1784 898300. Fax: +44 (0)1784 895103. Further information is available from Recordati Pharmaceuticals Ltd. **Date of preparation:** March 2006. **®** Zanidip is a Registered Trade Mark. © Recordati 2006. **References:** 1. Leonetti G, Magnani B, Pessina AC *et al.* Am J Hypertens 2002;15:932-940. 2. Lund-Johansen P *et al.* J Hypertens 2003;21:1003-10. 3. Pedrinelli R. J Hypertens 2003;21:1969-1973. 4. Borghi C *et al.* Blood Pressure 2003;12:(Suppl.1):14-21.

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