

# COMPASS Therapeutic Notes on Aspects of Cardiovascular Medicine

**Note: this guidance does NOT cover cardiovascular aspects of diabetes. A separate edition will cover this at a later date.**

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Section 1 Hypertension

Section 2 Dyslipidaemia

Section 3 Antiplatelet Agents

## Abbreviations:

<b>HTN</b>	Hypertension	<b>RCT</b>	Randomised Controlled Trial
<b>BP</b>	Blood Pressure	<b>ACEI</b>	Angiotensin-converting enzyme inhibitor
<b>SBP</b>	Systolic Blood Pressure	<b>Ang-II-RA</b>	Angiotensin II receptor antagonist
<b>DBP</b>	Diastolic Blood Pressure	<b>CCB</b>	Calcium channel blocker
<b>BHS</b>	British Hypertension Society	<b>TC</b>	Total cholesterol
<b>NICE</b>	National Institute of Clinical Excellence	<b>LDL</b>	Low-density lipoprotein
<b>CVD</b>	Cardiovascular Disease	<b>TG</b>	Triglycerides
<b>CHD</b>	Coronary Heart Disease	<b>HDL</b>	High-density lipoprotein

## Section 1: Medical Management of Hypertension

### What is hypertension?

Hypertension (HTN) (in people without diabetes) is defined as a sustained SBP of 140 mmHg or more, and/or a sustained DBP of 90 mmHg or more.<sup>1,2</sup>

In 95% of patients with HTN there is no identifiable cause;<sup>3</sup> this is termed "essential" or "primary" hypertension. "Secondary HTN" is the result of an underlying cause.

### What can cause secondary HTN?

**Renal disorders** are the most common causes of secondary HTN. **Vascular disorders** such as coarctation of the aorta or renal artery stenosis can also cause HTN. Other causes of secondary HTN can include **endocrine disorders** such as primary hyperaldosteronism (Conn's syndrome).

### Which drugs can cause HTN?

- Non-steroidal anti-inflammatory drugs
- Ciclosporin
- Cocaine and other substances of abuse
- Combined oral contraceptive pill
- Corticosteroids
- Leflunomide
- Sympathomimetics (may be found in over-the-counter cough and cold remedies) e.g. ephedrine and phenylpropanolamine etc.
- Liquorice (in some herbal medicines).

### What is the global burden of HTN?

HTN is one of the most important preventable causes of premature morbidity and mortality worldwide.<sup>4</sup> More than a quarter of the world's adult

population were shown to have HTN in 2000. Men and women have a similar overall prevalence and HTN increases with age consistently all over the world.<sup>5</sup>

### Why is good control of BP important?

Good BP control is of paramount importance in ensuring optimal prevention of adverse cardiovascular events, such as strokes and myocardial infarctions.

### How well is HTN currently being managed in the UK?

HTN responds well to treatment, but only 10-30% of diagnosed hypertensive patients in the UK have their BP controlled.<sup>6</sup>

### Why is HTN being badly managed?

One of the key reasons for poor control of HTN is the use of monotherapy.<sup>6</sup> This contrasts with the evidence from trials that have consistently shown that the majority of patients require two or more drugs to achieve BP targets.

### What is the target for blood pressure?

Guidelines for the management of HTN

have been issued recently by both NICE and BHS.<sup>1,7</sup> Though broadly similar in scope, they differ in detail. One of the areas in which they differ is target BP:

- **NICE** recommends a target of **140/90 mmHg or less** for non-diabetic people with HTN.<sup>7</sup>

- **The British Hypertension Society (BHS)** recommends a target of **140/85 mmHg or less** for non-diabetic people with HTN.<sup>1</sup>

### What are the different grades of HTN?

Table ONE gives the various grades of HTN as classified by BHS.

### When should antihypertensives be started?

See Table TWO.

### When should someone's risk of CVD be assessed?

If HTN is sustained and the person does not have established cardiovascular disease (CVD), or other major atherosclerotic disease, a formal assessment of CVD risk may help to

**Table ONE: BHS classification of blood pressure levels<sup>1</sup>**

	Systolic BP (mmHg)	Diastolic BP (mmHg)
Optimal BP	<120	<80
Normal BP	<130	<85
High-normal BP	130-139	85-89
Grade 1 HTN (mild)	140-159	90-99
Grade 2 HTN (moderate)	160-179	100-109
Grade 3 HTN (severe)	≥180	≥110
Isolated systolic HTN (grade 1)	140-159	<90
Isolated systolic HTN (grade 2)	≥160	<90

**Table TWO: BHS treatment thresholds for intervention<sup>1</sup>**

BP	Absence or presence of complications	When to treat
≥ 220/120mmHg		Treat immediately
180-219/110-119mmHg		Confirm over 1-2 weeks and then treat
160-179/100-109mmHg	Cardiovascular complications, target organ damage, or diabetes <b>present</b>	Confirm over 3-4 weeks and then treat
160-179/100-109mmHg	Cardiovascular complications, target organ damage, or diabetes <b>absent</b>	Institute lifestyle measures and measure BP weekly. Treat if BP persists at these levels over 4-12 weeks.
140-159/90-99mmHg	Cardiovascular complications, target organ damage, or diabetes <b>present</b>	Confirm within 12 weeks and then treat
140-159/90-99mmHg	Cardiovascular complications, target organ damage, or diabetes <b>absent</b>	Recommend lifestyle measures, re-measure BP at monthly intervals. If mild HTN persists, estimate 10-year CVD risk and treat if risk ≥ 20%

guide the treatment choice.

The following individuals can be assumed to have >20% CVD risk:

- a sustained BP of  $\geq 160/100$  mmHg, or
- a previous myocardial infarction, angina, non-haemorrhagic cerebrovascular disease, peripheral vascular disease, or
- diabetes, or
- atherosclerotic renovascular disease

**How should cardiovascular risk be assessed?**

New risk charts have been produced by the Joint British Societies to help determine CVD risk and support treatment decisions for people with mild HTN. These charts can be found at: [www.bhsoc.org/Cardiovascular\\_Risk\\_Charts\\_and\\_Calculators.htm](http://www.bhsoc.org/Cardiovascular_Risk_Charts_and_Calculators.htm) or at the back of the BNF. It should be noted that these charts now include **cardiovascular** risk prediction for primary prevention rather than **coronary** risk prediction, as was the case previously. Cardiovascular disease risk includes non-fatal MI and stroke, coronary and stroke death and new angina. A CVD risk of 20% over 10 years is considered to be similar to a CHD risk (non-fatal MI, coronary death and new angina) of about 15%. For each person choose the table matching their gender, age and smoking status (smoker = current smoker or a person who has stopped smoking within the past 5 years). If no high-density lipoprotein (HDL) cholesterol result is available for the total cholesterol (TC) to HDL ratio, use the total serum cholesterol value as this assumes HDL is 1.00 mmol/l.

**Lifestyle Modifications**

**What lifestyle modifications are recommended to prevent HTN?**

The following lifestyle modifications have been proposed:<sup>1</sup>

- maintain normal body weight (e.g. BMI 20-25kg/m<sup>2</sup>).
- dietary salt intake should be less than 6 grams per day.
- engage in regular aerobic physical activity such as brisk walking (more than 30 minutes per day, most days of the week).
- limit alcohol consumption to no more than 3 units/day in men and no more than

2 units/day in women.

- consume a diet rich in fruit and vegetables (at least 5 portions per day).
- consume a diet with reduced content of saturated fat and total fat.

**Will changes in lifestyle benefit people who already have HTN?**

Taking regular aerobic exercise can reduce SBP and DBP by about 2-3mmHg.<sup>9-11</sup>

Salt reduction from an average of 10 to 5 grams daily lowers BP by about 5/2mmHg.<sup>12</sup>

Alcohol intake above 21 units per week is associated with BP elevation that is reversible by reducing the intake.<sup>13-15</sup>

Consumption of 2 to 7 portions of fruit and vegetables daily lowers BP by around 7/3mmHg in hypertensive patients.<sup>16</sup>

**Pharmacotherapy of HTN**

In unselected hypertensive populations, no one class of agent is any more effective at lowering BP than another. Overall, single drug therapy will reduce BP by, on average about 7-8%; however there is substantial interpatient variation in response.<sup>17</sup> The level of BP control rather than the class of drug used to achieve it primarily determines the benefits of BP-lowering therapy.

**What should treatment be started with?**

NICE and BHS differ in their recommended first line antihypertensive:

Each class of antihypertensive has compelling indications for use in specific patient groups, and also compelling contraindications (see Table THREE). When none of these special considerations apply, **BHS** recommends that initial drug selection should follow their AB/CD algorithm (see later).

**NICE** currently recommends that drug treatment should normally begin with a low dose thiazide diuretic. (In people less than 55 years old, with moderately raised BP, consider beginning with a beta-blocker).

**Why do NICE and BHS differ in their choice of initial antihypertensive?**

**NICE** bases its recommendations on the

following:

- **ALLHAT**<sup>18</sup>, which showed that a regimen based on a thiazide or thiazide/like agent was unsurpassed as a first-line antihypertensive drug and was at least as effective as an ACEI or a CCB.

- **Meta-analysis** of data from 42 long term randomised controlled trials (n=192,478) confirmed that none of the other antihypertensive drug classes were significantly better than low-dose thiazide diuretics for preventing any major cardiovascular disease outcome.<sup>19</sup>

**BHS** recommendations are based on an assumption that HTN can be classed as 'high or low renin'.<sup>20</sup> Treatment should begin with a category of drug that either inhibits the renin-angiotensin system or not:

- ACE inhibitors, A-II RAs, or beta-blocker drugs being more effective in Caucasian people less than 55 years old who have high renin concentrations.

- CCBs or thiazide diuretic drugs being more effective in Caucasian people 55 years or over, or people of African descent of any age who have low renin concentrations.<sup>21</sup>

The initial antihypertensive selection in the AB/CD approach was based on the findings of:

- A randomised double blind trial (n=1292) that compared BP lowering by different drugs. It found D to be less effective in young Caucasians and C was more effective (at all ages) than A or B in the Afro-Caribbean population.<sup>22</sup>
- Two drug rotation studies.<sup>21,23</sup>
- Renin profiling studies.

In October 2005, it was confirmed that NICE, BHS & the National Collaborating Centre for Chronic Conditions are to jointly review HTN guidelines with the aim of providing clearer guidance. This guidance is awaited.

**If target BP is not achieved using monotherapy what is recommended?**

Additional drugs should be added to achieve the target BP or until further treatment is inappropriate or declined. Many people require two or more drugs to

**Table THREE: Compelling Indications, Contraindications and Cautions for the Major Classes of Antihypertensive Drugs.<sup>8</sup>**

Class of Drug	Compelling Indication	Caution	Compelling Contraindication
<b>Alpha-blockers</b>	Benign prostatic hypertrophy	Postural Hypotension Heart Failure	Urinary incontinence
<b>ACE Inhibitors</b>	Heart failure Left Ventricular dysfunction Post MI or established CVD Type 1 diabetic nephropathy	Renal impairment Peripheral vascular disease	Pregnancy Renovascular disease
<b>Angiotensin-II receptor antagonists</b>	ACE intolerance Heart failure Left Ventricular dysfunction Diabetic nephropathy	Renal impairment Peripheral vascular disease	Pregnancy Renovascular disease
<b>Beta-blockers</b>	MI Angina	Heart failure Peripheral vascular disease	Asthma / COPD Heart block
<b>Calcium channel blockers - dihydropyridine</b>	Isolated systolic HTN in elderly patients	-	-
<b>Calcium channel blockers – rate limiting</b>	Angina	Combination with beta-blocker	Heart block Heart failure
<b>Thiazides / thiazide-like diuretics</b>	Elderly patients		Gout

achieve BP targets and up to a third of people will require three or more drugs.<sup>1</sup> Antihypertensives from different classes generally have an additive effect when prescribed together. Sub-maximal dosages of two drugs may result in larger falls in BP and fewer adverse effects than maximal dosages of a single drug.

Sometimes a clinical decision may have to be made whether to intensify drug treatment to achieve target or settle for a BP that is less than target. People not achieving their target BP, or for whom further treatment is inappropriate or declined, will still obtain benefit from any reduction in BP.<sup>7</sup>

#### What does NICE recommend for add-on treatment?

**NICE recommends a stepwise approach to adding drugs in an attempt to achieve the target BP.**

- If a drug is **tolerated** but target BP is not achieved - add second line treatment.
- If a drug is **not tolerated** - discontinue and proceed to second line treatment.

**Second line** treatment should be selected according to whether the person has a raised risk of new-onset Type 2 diabetes.

In people **at risk** of Type 2 diabetes:

- Add an ACEI (or A-II RA if ACEI not tolerated).

In people **not at risk** of Type 2 diabetes:

- Add a beta-blocker or,
- Add a thiazide if a beta-blocker was used first line.

[Note: It may be best to explore alternative options to a thiazide combined with a beta-blocker where possible.]

If a **third line** treatment is required:

- Add a calcium-channel blocker.

If further BP lowering is indicated consider:

- An ACEI or beta-blocker (if not yet used),
- Another antihypertensive drug,

- Referral to a specialist.

#### What does BHS recommend for add-on treatment?

BHS recommendation for combining antihypertensives is summarised in their AB/CD treatment algorithm. See BOX ONE.

#### How often should patients with HTN be reviewed?

NICE recommends BP should be monitored annually in patients with HTN. However, the current GMS contract quality indicators (BP4 and BP5) specify a 9-monthly interval.<sup>24</sup>

#### What general principles of drug treatment can be applied to HTN?

Where possible, use agents which are taken only **once a day**. People adhere to once daily BP lowering regimens better than to regimens requiring two or more doses a day.<sup>25</sup> Prescribe **generic drugs** where appropriate in order to minimise cost. An interval of at least **four weeks** is generally recommended after initiating treatment to evaluate response.<sup>1</sup>

#### Thiazide and thiazide-like diuretics

##### Which drugs are in this category?

**Bendroflumethiazide** and **hydrochlorothiazide** are thiazide diuretics. **Chlortalidone** and **indapamide** are thiazide-like diuretics.

##### Which thiazide diuretic should be used first-line?

**Bendroflumethiazide** is effective, safe, well tolerated, and economical.

**Chlortalidone** has good evidence for efficacy at lowering BP and improving cardiovascular outcomes.<sup>18</sup>

#### Prescribing Notes:

**Thiazide and thiazide-like** diuretic use in HTN may be associated with **hypokalaemia** (drug and dose dependent), **impaired glucose tolerance** (worse at higher doses or when combined with a beta-blocker), and small rises in **LDL-cholesterol** and **triglycerides**. Thiazide and thiazide-like diuretic use is associated in some patients with **erectile dysfunction**, although this can be limited by using low diuretic doses. Their efficacy is reduced in those receiving **NSAIDs**, and they should be avoided in patients with a history of **gout** or those receiving **lithium**.

#### What dose of diuretic should be used?

**Use relatively low doses for the treatment of HTN.** Thiazides have a shallow dose response curve. Higher doses are unlikely to have additional clinical benefits and are more likely to cause marked changes in blood glucose and lipid levels. **Bendroflumethiazide** is initiated and maintained at a dose of 2.5 mg/day. **Chlortalidone** is initiated at a dose of 25 mg/day and if inadequate response is obtained, the dose can be increased to 50 mg/day.

#### Is there a place for the use of potassium-sparing diuretics in HTN management?

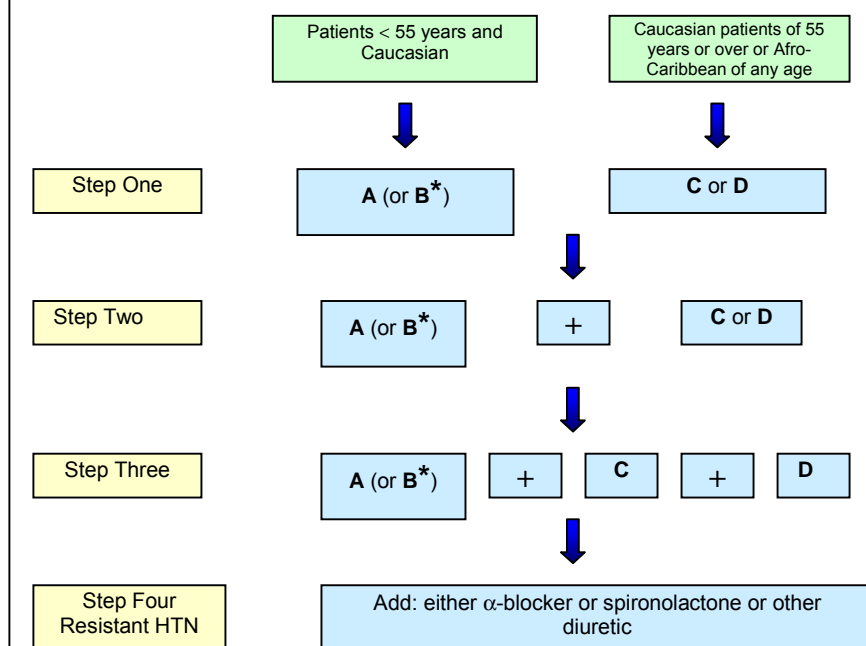
**Spirolactone** may play an important role in BP lowering in those patients with "resistant" HTN in whom BP may be dependent on hyperaldosteronism.

If a potassium-sparing diuretic is combined with an ACEI or A-II RA, the risk of hyperkalaemia may be increased.

#### Do loop diuretics have a place in HTN management?

Loop diuretics have no place in the **routine management** of HTN, except in patients with impaired renal function. Loop diuretics have a role in the management of severe, resistant HTN when large doses of vasodilators, such as minoxidil, are used.

#### BOX ONE: The BHS AB/CD algorithm.



#### Key

**A:** ACE inhibitor or AIIA  
**B:** Beta-blocker  
**C:** Calcium channel blocker  
**D:** Diuretic (thiazide)

\* Combination therapy involving B and D may induce more new onset diabetes compared with other combination therapies

## Beta-blockers



### Prescribing Notes:

**Beta-blockers** differ in their duration of action, their selectivity for beta-1 receptors, lipophilicity and partial agonist activity. Side effects include lethargy, limb aches, impaired concentration / memory, erectile dysfunction, vivid dreams. There is evidence that beta-blockers increase the likelihood of new-onset diabetes, particularly when combined with thiazide or thiazide-like diuretics.

### Which beta-blocker should be used first-line?

**Atenolol** is cardioselective, has a simple once-daily dosing, is inexpensive, and is widely used in the UK.

### What dose of atenolol should be used?

Patients should be started on 25 to 50mg of atenolol daily. For those who do not respond adequately, stepwise increases up to a daily dose 100 mg can be considered. However, because of a shallow dose response for reducing BP, adding another antihypertensive drug may be a better option than increasing the dose of atenolol.

### Has the first-line use of atenolol in HTN been called into question?

Some authors have cast doubts on the use of atenolol as a suitable antihypertensive.<sup>26-29</sup> In both MRC studies,<sup>30,31</sup> beta-blockers failed to significantly reduce cardiovascular morbidity and mortality. In fact the incidence of stroke was two to four times higher in patients receiving beta-blockers than in patients on thiazide diuretics and not different from those receiving placebo. The only benefit demonstrated was a small reduction in strokes in non-smokers aged less than 65 years.<sup>31</sup> This reduction was significant in men only.

## Calcium Channel Blockers



### Prescribing Note:

If a prescription is written for "amlodipine besilate" then the pharmacist must dispense Istin<sup>®</sup>, whereas the generic product could be dispensed against a prescription written as "amlodipine" or "amlodipine maleate". The salts are all clinically equivalent.

### How are calcium channel blockers classified?

Calcium channel blockers (CCBs) can be classified as either "dihydropyridine CCBs" or "rate-limiting CCBs". (See Table FOUR).

### Which dihydropyridine CCBs are suitable for the treatment of HTN?

**Amlodipine**, or **once-daily modified-release nifedipine** or **felodipine** are suitable first-choices of dihydropyridine CCB.

There are many other dihydropyridine CCBs licensed for the treatment of HTN but short-acting and immediate-release dihydropyridine formulations are

Table FOUR: Classification of Calcium Channel Blockers

Group	Examples
Dihydropyridine CCBs	Amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nifedipine, nimodipine, nisoldipine.
Rate-limiting CCBs	Diltiazem and verapamil.

associated with large variations in BP and reflex tachycardia, and should be avoided.

### Which rate-limiting CCBs are indicated for the treatment of HTN?

Diltiazem and verapamil are both licensed for the treatment of HTN.

### Is oedema associated with CCBs?

Oedema is the main side effect of CCBs. About 5% of patients on rate-limiting CCBs will experience drug-related oedema compared with 10-25% receiving a dihydropyridine CCB. If oedema occurs with one of these agents and is troublesome, the dosage should be lowered since it is a dose related effect. Switching to a different CCB or antihypertensive agent may help.<sup>32</sup> In addition, using an ACEI along with a CCB may lessen the CCB-related oedema.<sup>33</sup> It is important to realise that because of the physiology, diuretic therapy does not ameliorate CCB oedema because it is not a state of fluid overload.

## Angiotensin-Converting Enzyme Inhibitors



### Prescribing Note:

An acute fall in BP following the introduction of ACEIs can occur in patients with dehydration or heart failure. It is rarely seen, however, when therapy is initiated in uncomplicated hypertensive patients.

### Which ACE inhibitors are indicated for the treatment of hypertension?

**Enalapril**, **lisinopril**, **perindopril**, **ramipril**, or **trandolapril** are suitable as first-choice angiotensin-converting enzyme inhibitors (ACEIs). These are established ACEIs with trial data for improving cardiovascular outcomes in hypertensive populations and can all be taken once a day.

Captopril is no longer recommended as a first-choice ACEI. It has a shorter half-life than other ACEIs and needs to be taken in divided doses.

Cilazapril, fosinopril, imidapril, moexipril, and quinapril are alternative options but there is less trial data relating to their use.

### Which ACEIs are available as generics?

Captopril, enalapril, fosinopril, lisinopril, ramipril and quinapril are available as generics.

### What about ACEI-induced cough?

Its incidence is about 5-20%<sup>34</sup> and it is not dose related.<sup>35</sup> There is a predisposition to ACEI cough in women, Afro-Caribbean's and Asians. Characteristics of the cough include a tickle in the throat, a mild cough, or a severe hacking cough. If a cough occurs, the ACEI should be

stopped. It generally disappears within a period of a few days to weeks. Bradykinin accumulation is probably responsible; there is no pulmonary dysfunction.<sup>32</sup>

## Angiotensin-II Receptor Antagonists

### What is the role of Angiotensin-II Receptor Antagonists in HTN?

Angiotensin-II Receptor Antagonists (A-II RAs) can be used for patients who are truly intolerant of ACEIs.

### When compared to other antihypertensive agents, how effective are A-II RAs?

There have been three RCTs performed to determine how antihypertensive regimens based on A-II RAs compared with other treatments for HTN. They are the LIFE<sup>36</sup>, SCOPE<sup>37</sup> and VALUE<sup>38</sup> studies. From these trials it has been recognized that A-II RAs appear to be at least as effective as other types of antihypertensives in preventing cardiovascular events, provided BP is equally well lowered.

### Are there differences in efficacy amongst the A-II RAs?

There is evidence that, despite similarities, the A-II RAs may vary in their effects. For example, small studies have shown that newer A-II RAs, when titrated to optimal doses, are significantly more effective than losartan at reducing BP in patients with mild to moderate HTN.<sup>39,40</sup> Another study found that olmesartan and irbesartan produced significantly greater mean decreases in BP after 8 weeks than either losartan or valsartan.<sup>41</sup> Another eight week study found that candesartan was more effective than losartan (in terms of the % of responders and the mean decrease in BP).<sup>42</sup>

### How well are A-II RAs tolerated?

A-II RAs are generally very well tolerated. Studies show that losartan is better tolerated than captopril<sup>43,44</sup> or atenolol.<sup>36</sup> Although studies have suggested differences in efficacy between the A-II RAs there do not appear to be significant differences in tolerability among the class.<sup>41</sup>

The ELITE II study<sup>44</sup> showed that patients taking losartan were significantly less likely to discontinue because of troublesome cough than those taking captopril. With an asymptomatic condition such as HTN, long-term compliance can be a problem and side-effects have been shown to lead to non-compliance, or to under-treatment with suboptimal doses.<sup>45</sup>

### **The Anglo-Scandinavian Cardiac Outcomes Trial- Blood Pressure Lowering Arm (ASCOT-BPLA)**

#### **What was the aim of ASCOT-BPLA?**

The aim of this RCT was to evaluate the effect on non-fatal MI and fatal CHD of combinations of one of two antihypertensive regimens.<sup>46</sup>

- Amlodipine (5 to 10mg) with or without perindopril (4 to 8mg), or
- Atenolol (50 to 100mg) with or without bendroflumethiazide (1.25 to 2.5mg).

The secondary endpoints were all-cause mortality, total stroke, primary endpoint minus silent MI, all coronary events and procedures, cardiovascular mortality, and non-fatal and fatal heart failure. Analysis was by intention to treat.

#### **What was the patient population?**

ASCOT-BPLA enrolled over 19,000 patients with HTN, aged 40-79 with at least three other risk factors. 91% of the study population were taking antihypertensive treatment prior to the trial.

#### **Why was the study terminated early?**

ASCOT-BPLA was stopped early, after a mean of 5.5 years follow-up, on the recommendation of its Data Safety Monitoring Board, due to significant differences in cardiovascular events and total mortality favouring the amlodipine-based regimen.

#### **What were the results of ASCOT-BPLA?**

Compared with the atenolol-based regimen, the amlodipine-based regimen was **not significantly** more effective at reducing the risk of the primary endpoint (HR 0.9, 95%CI 0.79-1.02). The authors acknowledge that the study was underpowered for the primary endpoint as the study was terminated early. However, the secondary outcomes were reported to be statistically significant as follows:

- Fatal and non-fatal stroke (HR 0.77 95%CI 0.66-0.89).
- Total cardiovascular events and procedures (HR 0.84 95% CI 0.78-0.90)
- All-cause mortality (HR 0.89 95%CI 0.81-0.99), for the amlodipine and atenolol based regimens respectively.

#### **How can the statistically significant difference in secondary outcomes be explained?**

The benefits in terms of secondary outcomes in favour of the amlodipine-based regimen can be explained by the 2.7/1.9mmHg greater BP reduction in the amlodipine group.<sup>47</sup>

#### **Should the results from ASCOT-BPLA change the recommended management of HTN?**

No. ASCOT-BPLA failed to show any difference in primary outcome between amlodipine-based and atenolol-based regimens. ASCOT-BPLA has **not** undermined the findings of ALLHAT.<sup>18</sup> A regimen based on a thiazide or thiazide-like diuretic is still the most appropriate for the majority of patients with HTN. A beta-blocker can be added if BP is not controlled, unless the patient is at high risk of developing diabetes. If the patient is at high risk of developing diabetes, either an ACEI or a CCB can be used in preference to a beta-blocker.

### **Oral contraceptives and BP**

#### **Does the Combined Oral Contraceptive (COC) pill have an effect on blood pressure?**

In the majority of users of the COC there is a slight, measurable increase in both SBP and DBP within the normotensive range.<sup>48-50</sup> In a small proportion of women (about 1%), severe HTN may be induced.<sup>51</sup> The effect seems to be idiosyncratic and BP may rise rapidly many months or even years after first starting a COC.

#### **Does the progestogen-only pill (POP) affect blood pressure?**

Data suggest that POPs do not increase BP.<sup>49,52</sup> The POP can be used by women with HTN either related to COC-use or other causes provided the HTN is well controlled.

#### **In a woman taking a COC, how frequently should BP be measured, and why is it so important?**

Since current use of COCs is not only associated with an increase in BP but also in risk of stroke and MI,<sup>53</sup> BP should be measured prior to COC use and 6-12 months thereafter.<sup>1,48,49,54</sup>

#### **At what levels of BP should the COC be stopped?**

A BP measurement of 160/100mmHg or above on repeated testing is an absolute contraindication to the COC.

An SBP of between 140-159mmHg and DBP of between 90-99mmHg is a relative contraindication; the risks may outweigh the benefits and may indicate changing to a POP.

#### **Can women on antihypertensives be prescribed a COC?**

A COC might be acceptable with good BP control and careful monitoring in a young, non-smoking woman who accepts the extra risk, will use no other method of contraception, and after full consultation with the clinician supervising control of the HTN. This presupposes that the HTN

has not been caused by the COC. It would not be acceptable for any woman with HTN caused by a COC to remain on it and be given antihypertensives.

### **Hypertension – A Summary**

- Hypertension (in people without diabetes) is defined as a sustained SBP of 140 mmHg or more, and/or a sustained DBP of 90 mmHg or more.<sup>1,2</sup>
- The risk assessment charts produced by the Joint British Societies now include **cardiovascular** risk prediction for primary prevention rather than **coronary** risk prediction, as was the case previously. A CVD risk of 20% over 10 years is considered to be similar to a CHD risk of about 15%.
- The following lifestyle modifications have been recommended in primary prevention of HTN: maintain normal body weight, keep dietary salt intake to < 6grams per day, take regular exercise, limit alcohol consumption, eat plenty of fruit and vegetables, reduce consumption of saturated fat.
- In unselected hypertensive populations, no one class of agent is any more effective at lowering BP than another. The level of BP control rather than the class of drug used to achieve it primarily determines the benefits of BP-lowering therapy.
- **Bendroflumethiazide** is widely used in the UK, and is effective, safe, well tolerated, and economical.
- **Atenolol** is cardioselective, has a simple once-daily dosing, is inexpensive, and is widely used in the UK.
- **Amlodipine**, or once-daily modified-release **nifedipine** or **felodipine** are suitable first-choices of dihydropyridine CCB.
- **Enalapril, lisinopril, perindopril, ramipril, or trandolapril** are suitable as first-choice angiotensin-converting enzyme inhibitors.
- A-II RAs can be used for patients who are truly intolerant of ACEIs.
- ASCOT-BPLA failed to show any difference in primary outcome between amlodipine-based and atenolol-based regimens.

## Section 2: Medical Management of Dyslipidaemia

National guidelines for the prevention of CVD identify modification of lipid profiles, and particularly reduction of LDL-cholesterol, as a major target. The British<sup>1</sup> and European<sup>55</sup> guidelines agree that attempts to reduce the incidence of CVD should start with education and lifestyle changes, including stopping smoking, stress reduction, increased physical activity, weight reduction and dietary modification. Comorbid conditions, such as HTN and diabetes, should be controlled appropriately.

### What is dyslipidaemia?

Dyslipidaemia includes conditions such as hypercholesterolaemia (familial and non-familial), elevated LDL-cholesterol levels, depressed HDL-cholesterol levels, hypertriglyceridaemia or mixed hyperlipidaemia (elevated LDL-cholesterol and TG levels).<sup>56</sup>

### Should a trial of dietary management alone be tried before starting drug treatment?

All people with dyslipidaemia should be given diet and lifestyle advice. Dietary management can reduce baseline lipid levels by 1-5%. It can be effective as a sole treatment in a small number of well-motivated people.<sup>57</sup> Someone with established CVD or familial dyslipidaemia should be started on drug treatment as soon as possible. A trial of dietary management is not necessary, because the person is at high risk of further CVD events. However, dietary management should still be used in conjunction with drug treatment to reduce lipid levels.

People with a 10-year risk of over 30% but no CVD may benefit from a three-month trial of dietary management. If cholesterol targets are not met after three months, drug treatment will be required in addition to dietary modification.<sup>58</sup> However, it would be reasonable to start drug treatment sooner if cholesterol levels are particularly high.

### Is there an age limit for offering drug treatment for dyslipidaemia?

There is no upper age limit for offering treatment. Until the Heart Protection Study (HPS), trials of statins selected mostly mature men under the age of 75 years with raised lipid levels. It is now recognised that the protective effect of statins extend to women, older and younger people, and that statins are protective against CVD, even at low baseline cholesterol levels.<sup>59-61</sup>

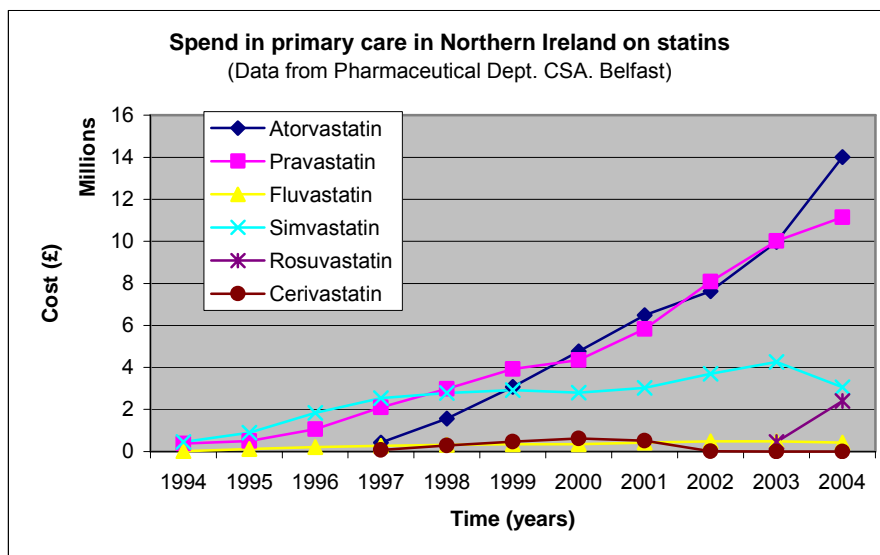
### For how long should people receive drug treatment for dyslipidaemia?

The National Service Framework for Coronary Heart Disease recommends that treatment be continued indefinitely, given the absence of studies on stopping treatment with lipid-lowering drugs.<sup>62</sup>

### What are the targets for patients with dyslipidaemia?

BHS guidelines advise the use of doses of statin to achieve stringent targets:<sup>1</sup>

- **Total Cholesterol** less than **4.0mmol/l**, or reduced by 25%, whichever would result in the lower level.



- **LDL-cholesterol** less than **2.0mmol/l**, or reduced by 30%, whichever would result in the lower level.

In **secondary prevention** (including those patients with type 2 diabetes), patients with a TC of 3.5mmol/l or more qualify for treatment. In **primary prevention**, patients with both a 10-year risk of CVD of 20% or over **and** a TC of 3.5mmol/l or more are considered suitable for treatment. If the BHS guidelines are adopted, it could result in more than 20% of the adult population being considered for both BP lowering treatment and high-dose statins!<sup>63</sup> Note: very high triglycerides levels (more than 10mmol/l) justify treatment in their own right because of the risk of pancreatitis.

### What cholesterol targets are set in the GMS contract?

The targets set in the General Medical Services contract for the Quality and Outcomes Framework reward according to the proportion of patients (with CVD, cerebrovascular disease, or diabetes) with TC of 5mmol/l or less. Maximum points are earned if more than 60% of people reach this target. However, it is important not to neglect people with atherosclerotic peripheral vascular disease, who also benefit from statins, although they are not included in the Framework.

### How low should cholesterol go?

Current USA guidelines recommend an LDL-cholesterol level of less than 2.6mmol/l as the goal for patients with stable CVD and a goal of 1.8mmol/l in patients at particularly high risk.<sup>64</sup> Many American clinicians, however, have suggested a goal of 1.8mmol/l in patients with stable CVD on the basis of the effectiveness of high-dose statins, such as 80mg daily of atorvastatin in patients with acute coronary syndromes.<sup>65</sup> Such low targets are supported by other studies including the Treating to New Targets (TNT) trial in which patients (with stable CVD) received 80mg atorvastatin daily and achieved an average LDL-cholesterol of 2.0mmol/l. This low LDL-cholesterol was

associated with a 22% relative risk reduction for major cardiovascular events and a 25% relative risk reduction in stroke. There was no reduction in overall mortality.<sup>66</sup> However, until the safety of an 80mg atorvastatin daily dose has been established the balance of risk versus benefit should be carefully assessed before adopting such targets.

### What can be performed as an initial screening tool?

Non-fasting TC and HDL-cholesterol is adequate as an initial screening test since neither TC nor HDL-cholesterol is affected by meals.

### What decisions can be made on the basis of this initial screen?

People with a raised TC (greater than 5mmol/l) should have a FASTING lipid profile to confirm the results before a decision about treatment is made.

### Why is a full lipid profile useful?

Measurement of TC alone may not disclose more subtle issues such as a combination of a low HDL-cholesterol and a raised triglycerides level, which is recognised as potentially atherogenic.<sup>67</sup>

### Why is it important to measure "fasting" lipids?

Recent food ingestion does not change levels of TC or HDL-cholesterol, but does increase triglycerides (TG) levels. This then has an effect on the LDL-cholesterol since LDL-cholesterol is calculated using the TG level. Therefore all full lipid profiles should be taken after an overnight fast.

Cholesterol is also subject to biological variability within each individual. Treatment decisions should not be made on the basis of a single sample. Two samples should be taken at least a week apart, particularly if TC is close to a decision level.

### What co-existing conditions could be causing a raised TC?

**Hypothyroidism** (even sub-clinical) is the most important cause of secondary hyperlipidaemia. Other causes of secondary hyperlipidaemia include:

- Type 2 diabetes,

Agent	Daily dose range	Cost for 28 days treatment*
Atorvastatin (Lipitor®)	10mg to 80mg	£18.03 to £28.21
Fluvastatin (Lescol®, Lescol XL®)	20mg to 80mg	£12.72 to £16.00
Pravastatin (generic)	10mg to 40mg	£3.42 to £6.55
Rosuvastatin (Crestor® ▼)	10mg to 40mg	£18.03 to £29.69
Simvastatin (generic)	10mg to 80mg	£2.12 to £26.79
Simvastatin + ezetimibe (Inegy® ▼)	20mg/10mg to 80mg/10mg	£33.42 to £41.21

\* Based on BNF 50.<sup>8</sup>

- Renal disease,
- Liver disease,
- Alcoholism.

These conditions should be addressed before any intervention is planned.

#### **How significant are raised triglycerides levels?**

A raised TG level is an independent risk factor for CVD, but because it is subject to huge biological variation, it makes a poor predictor of CVD outcome. People with both a raised TC and raised TG are at greater risk of CVD than are people who just have raised TC.

As stated previously, a fasting TG level greater than 10mmol/l is a considerable risk for pancreatitis. Treatment is justified on these grounds alone.

#### **How significant are low levels of HDL-cholesterol?**

Decreased levels of HDL-cholesterol are also an independent risk factor for CVD. A 0.026mmol/l increase in HDL-cholesterol is associated with a relative risk reduction of 2% in men and 3% in women.

#### **How often should the lipid-profile be assessed?**

A lipid profile should be assessed at least twice before initiating treatment (see above), three months after starting treatment, and at 6 monthly intervals thereafter.<sup>58</sup>

#### **Have patients been shown to reach their cholesterol targets?**

Despite effective treatment strategies for dyslipidaemia numbers of patients achieving their target cholesterol levels remain low.<sup>69-75</sup> **Suboptimal dosages of**

statins have been identified as the main reason for this failure.<sup>69-73</sup> In addition, **poor patient compliance** plays a part. There may be reluctance on the part of the clinician to increase the dose of lipid-lowering drugs due to safety or tolerability concerns.<sup>76-79</sup> Where a statin is indicated, the results of the 4S study would suggest that over 70% of people should achieve a TC of 5.2mmol/l or less using doses of simvastatin 20mg to 40mg daily.<sup>80</sup>

#### **Which patients should be referred to a lipid clinic?**

Referral is appropriate in cases of:

- Suspected familial hyperlipidaemia (i.e. when the person has TC greater than 7.5mmol/l, or a LDL-cholesterol greater than 4.9mmol/l AND at least one of the following: tendon xanthoma in him/herself or in a first or second degree relative; family history of premature CVD; family history of TC greater than 7.5mmol/l.
- Suspected familial combined hyperlipidaemia, i.e. mixed hyperlipidaemia and a family history of hyperlipidaemia or premature CVD.
- Failure to meet target lipid reduction despite maximally tolerated therapy.
- Severe hypercholesterolaemia: initial TC greater than 10mmol/l
- Very severe hypertriglyceridaemia: TG greater than 10mmol/l.

#### **Do patients stay on their lipid-lowering therapy long-term?**

Adherence rates from hyperlipidaemia trials show considerable variation ranging from 37 to 80%, depending on study design, duration of follow-up, method of measurement etc. Not surprisingly, primary prevention trials appear to have

higher discontinuation rates than secondary prevention trials.<sup>81</sup>

### **Drug therapy of dyslipidaemia**

If Total Cholesterol is raised due to an increase in the LDL-cholesterol, then a **statin is the drug of choice**. If there is a mixed hyperlipidaemia, or an isolated moderate rise in TG, a fibrate is the drug of choice. Other drugs, such as resins, fish oils, ezetimibe and nicotinic acid, are now essentially third line agents, to be added to one of the above.

#### **Which statin?**

For the purpose of initiating therapy there is no data to suggest the superiority of any one statin over the others in reducing cardiovascular events.<sup>68</sup> All statins reduce LDL-cholesterol in a non-linear, dose-dependent manner. Of the statins licensed in the UK, **simvastatin, pravastatin and atorvastatin** have the most solid body of evidence for efficacy and safety. NICE have indicated that when the decision has been made to prescribe a statin, therapy should be initiated with a drug with a low acquisition cost.<sup>68</sup> Simvastatin is currently priced lowest amongst the statins. (see Table FIVE).

#### **Which lipid-lowering agents are available generically?**

Colestyramine powder, bezafibrate, fenofibrate, gemfibrozil, pravastatin, simvastatin and nicotinic acid are all available generically. Prescribing generically available lipid-lowering agents may help to offset the increased costs associated with an increased rate of prescribing.

#### **Which statin starting dose?**

There has been considerable debate about the starting dose for statins:

The "evidence-based dose" strategy uses the doses used in the major trials as the starting dose. The rationale is that the best evidence of efficacy is for these doses.

The "titrate to target" strategy uses lower starting doses to minimize the risk of toxicity. Many people will not need a higher dose to achieve targets of cholesterol; and doubling the dose only reduces cholesterol levels by a further 5-6%. The NSF for CHD currently recommends this approach.<sup>62,82</sup>

#### **Is statin therapy cost-effective?**

In their Final Appraisal Determination on statins, NICE concluded that statin therapy is cost effective for people with clinical evidence of CVD (SECONDARY prevention). In addition, statin therapy for PRIMARY prevention would be cost effective for individuals at 20% or greater 10-year risk of developing CVD.<sup>68</sup> (See Table SIX).

#### **Is there any evidence for the use of aggressive statin therapy in patients with CVD?**

Intensive lipid-lowering therapy with higher dose statins improves clinical outcomes and reduces the progression of atherosclerosis.<sup>83,84</sup> This has been

Scenario	Economic Evaluation - incremental cost per QALY*	
SECONDARY prevention of CVD events	£8,000 to £13,000 in all ages groups	
PRIMARY prevention of CVD events (at a 10-year risk of a CVD event of between 30% to 5%).	age 45 years	£5000 to £12,000
	age 55 years	£6000 to £14,000
	age 65 years	£6000 to £20,000
	age 75 years	£9000 to £32,000
	age 85 years	£15,000 to £50,000

\* QALY = Quality Adjusted Life Years

Note: incremental cost per QALY of £20,000 or less is generally considered to be an effective use of NHS resources. Above £30,000/QALY the case for the supporting technology has to be increasingly strong.

attributed to greater reductions in the levels of LDL-cholesterol in particular.<sup>85</sup>

**PROVE-IT** was a double blind RCT in patients admitted with ACS within the previous 10 days.<sup>83</sup> Patients were randomised to receive "standard therapy" (**pravastatin** 40mg daily) or "intensive therapy" (**atorvastatin** 80mg daily). Results showed a 16% reduction in the risk of death or a major CV event with atorvastatin compared to pravastatin. This study makes the case for aggressive therapy for most people admitted with coronary chest pain, rather than using conventional statin doses and there may be a case to intensify treatment in those with recent MI already on less intensive therapy.<sup>86</sup> However, the authors of the study suggest caution, stating: "*Patients in clinical practice generally have more coexisting conditions than did our patients, and they may not tolerate a high dose statin regimen as well as our patients did*".<sup>83</sup>

The **IDEAL** study<sup>87</sup> addressed the issue of whether **atorvastatin** 80mg daily shows any benefit if compared with **simvastatin** 20 or 40mg daily (a better representation of "standard therapy" for patients in the UK). In this study of patients with previous MI, use of atorvastatin 80mg daily did NOT result in a significant reduction in the primary endpoint of major coronary events, but did reduce risk of other composite endpoints and non-fatal MI. There were no differences in cardiovascular or all-cause mortality.

The **ALLIANCE** study, published in November 2004, was an open RCT of people with CVD and raised cholesterol who were randomised to receive "aggressive therapy" (up to **atorvastatin** 80mg daily) or "usual care".<sup>86</sup> Significantly fewer CV events occurred with "aggressive therapy" compared with usual care (23.7% versus 27.7%).

There is no evidence for the use of aggressive statin therapy for primary prevention.<sup>90</sup>

#### Are statins safe at higher doses?

Concerns have been raised with regard to non-cardiovascular deaths and the use of higher dose statins. For example, in the TNT study,<sup>66</sup> there were increased

numbers of deaths from non-cardiovascular causes in patients assigned to receive atorvastatin 80mg daily as compared to those receiving 10mg daily.

### Newer lipid-lowering agents

#### What is the role of rosuvastatin?

Rosuvastatin (**Crestor**®▼) was launched in 2003. It compares similarly to atorvastatin at half its milligram equivalent (e.g. rosuvastatin 40mg is similar to atorvastatin 80mg in lipid-lowering).<sup>91</sup> Although there is interest in using rosuvastatin as a more potent drug to achieve targets, there is presently insufficient evidence from clinical studies assessing morbidity and mortality outcomes to support its use in such a manner. It seems rational to reserve rosuvastatin for cautious use in the management of difficult-to-treat cases until more information is available.

#### Are there any safety concerns with rosuvastatin?

The highest licensed dose (40mg daily) of rosuvastatin has been associated with a higher rate of adverse effects, including rhabdomyolysis. The manufacturers of **Crestor**®▼ have issued advice to use rosuvastatin 40mg only in patients in most need of treatment and not at risk of muscle side effects (see BOX TWO). Due to racial differences in pharmacokinetic profiles, the dose of rosuvastatin for Asian patients should not exceed 20mg daily.<sup>92</sup>

#### What is ezetimibe?

Ezetimibe (**Ezetrol**®▼) is the first in a new class of lipid-regulating agents that works by inhibiting absorption of dietary and biliary cholesterol across the intestine without affecting the absorption of TGs or fat-soluble vitamins. It is licensed both as monotherapy and in combination with a statin. Unlike bile-acid sequestrants, it does not affect the absorption of other drugs. There is no long-term safety or efficacy data for ezetimibe.<sup>95</sup> At present it is prudent to reserve ezetimibe for cautious use in the management of difficult-to-treat cases.<sup>95</sup>

#### What is Inegy®▼?

**Inegy**®▼ is a combination product where each tablet contains 10 mg ezetimibe and 20, 40 or 80 mg of simvastatin. Co-

### BOX TWO: Advice on using rosuvastatin<sup>93,94</sup>

All patients must start on an initial dose of 5mg or 10mg daily\*. This can be increased if considered necessary after four-weeks.

The 40mg dose is contraindicated in patients with predisposing risk factors for muscle toxicity.

Specialist supervision is recommended when the 40mg dose is given.

The 40mg dose should only be necessary for the minority of patients with severe hypercholesterolaemia at high CV risk.

\* A starting dose of 5 mg is recommended in patients >70 years, in patients with mild to moderate renal impairment, in patients with predisposing factors to myopathy and for patients of Asian ancestry.

administration of ezetimibe with simvastatin has been shown to produce an additive LDL-cholesterol lowering effect of around 15% compared with simvastatin monotherapy.<sup>96</sup> Although ezetimibe co-administered with simvastatin appears well tolerated, there is no evidence that this strategy is any safer than maximising the dose of simvastatin.

### Adverse effects of the statins

#### What are the most commonly reported adverse effects of the statins?

In the major RCTs of statins, rates of treatment withdrawal due to adverse effects were low and it is generally considered that statins have a favourable risk-benefit profile.<sup>97</sup> Gastrointestinal symptoms, headache and rash are the most common adverse events reported during statin treatment, with an incidence of up to 5%. Elevations of liver enzymes, without any associated clinical symptoms, occur in about 1-2% of patients.

#### How can statins adversely affect the liver?

Adverse hepatic effects occur only rarely during statin therapy and manifest primarily as asymptomatic elevations in serum levels of aminotransferases in about 1 to 2% of patients.<sup>98</sup> During long-term statin therapy, six-monthly monitoring of liver enzymes is recommended and may be especially

Table SEVEN: Drug interactions with lipid-lowering agents<sup>88</sup>

Agent	Interacting drug	Consequences of interaction	Importance and Management
Simvastatin	Warfarin	Prolongation of prothrombin time and bleeding.	Only some patients will develop this interaction. Monitor INR in the early stages of concurrent use in all patients or if the statin dose is changed.
Simvastatin	Grapefruit juice	Concomitant simvastatin and grapefruit juice has resulted in 9-fold increases in simvastatin serum levels. <sup>89</sup>	Patients on simvastatin should avoid drinking grapefruit juice.
Atorvastatin		Large quantities of grapefruit juice (over 1.2L daily for 5 days) increased serum levels of atorvastatin significantly.	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.
Fibrates	Warfarin	Fibrates increase the effects of oral anticoagulants. Severe bleeding (fatal in some instances) has been reported.	Warfarin dose may need to be reduced by about a third and further adjustments made according to changes in INR.
Simvastatin	Inhibitors of CYP3A4 (azole antifungals, macrolide antibiotics, and HIV protease inhibitors).	Risk of dose-related adverse effects, including rhabdomyolysis.	This is an established interaction of clinical importance. Avoid concurrent use of itraconazole or ketoconazole. If a short course of azole antifungal is considered essential, temporary withdrawal of the statin has been advised.

important for patients taking high-dosage regimens as a progressive increase in liver enzyme elevations has been noted at **higher dose ranges**.<sup>99</sup> Treatment should be discontinued if aminotransferase levels exceed three times the upper limit of normal. Statins are contraindicated in patients with active liver disease.

#### How common is myopathy or rhabdomyolysis with the statins?

Myopathy is a rare, serious adverse effect occurring in less than 1% of patients on statins. Symptoms include, unexplained muscle soreness or weakness accompanied by increases in serum creatine kinase values exceeding 10 times the upper limit of normal, leading occasionally to myoglobinuria secondary to rhabdomyolysis. The risk is increased in patients with renal impairment and by the concurrent use of fibrates.<sup>89</sup>

The exact mechanism by which statins cause rhabdomyolysis remains unclear, but the risk appears to be dose-related. Risk factors include:

- underlying muscle disorders,
- renal impairment,
- untreated hypothyroidism,
- alcohol abuse,
- age over 70 years,
- concomitant use of other lipid-lowering treatment,
- history of myopathy with any lipid-lowering treatment,
- interactions (e.g. with drugs inhibiting cytochrome p450).<sup>100</sup> Patients receiving any statin should be asked to report muscle pain, weakness or cramps immediately, and stop treatment until this has been investigated. If symptoms are severe or if creatine kinase is greater than 5 times the upper limit of normal, treatment should be withheld.<sup>100</sup>

#### Primary versus secondary prevention

Primary and secondary prevention must be clearly separated. Since the evidence for cholesterol reduction in secondary prevention is significant, the question becomes who to treat as primary prevention.

#### Which patients should receive a statin as primary prevention?

NICE has recommended statin therapy as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD.<sup>68</sup>

#### Interactions with lipid-lowering agents

See Table SEVEN

#### Does food affect the bioavailability of statins?

Concomitant food consumption does not affect the bioavailability of simvastatin. Food appears to reduce the bioavailability of pravastatin and fluvastatin without altering their effects on LDL-cholesterol

levels.<sup>98</sup> Atorvastatin and rosuvastatin can be taken with or without food.

#### Prescribing Point

Simvastatin, pravastatin and fluvastatin should be taken in the evening.<sup>101-105</sup>

Atorvastatin and rosuvastatin can be taken at any time of day.<sup>106,107</sup>

#### “Over the Counter” simvastatin

Simvastatin 10mg tablets can be supplied by a pharmacist without a prescription, in conjunction with appropriate lifestyle advice, to people who are at moderate CVD risk (20%) over the next 10 years. This applies to:

- All men aged 55 years and over
- Men aged 45-55 and women aged over 55 who have a family history of CVD, are smokers, are obese, or are of south Asian descent.

People with CVD or diabetes should not be sold simvastatin over-the-counter and will be referred back to their GP by the pharmacist.

Higher doses of simvastatin cannot be bought from a pharmacy.

The decision to make simvastatin available over-the-counter has attracted some controversy,<sup>108-110</sup> with complaints about the consultation process prior to reclassification, disagreement about potential benefits and concern about safety issues.

The Royal Pharmaceutical Society of Great Britain has produced guidance on the sale of over-the-counter simvastatin (see [www.rpsgb.org.uk](http://www.rpsgb.org.uk)).

#### Phytosterols

Diet therapy is the cornerstone of strategies to lower cholesterol and reduce the risk of CVD. Incorporating foods fortified with plant sterol and stanol esters into the daily diet can substantially enhance the cholesterol-lowering effect of diet, including in patients already taking statins.<sup>111</sup> The recent introduction of stanol- and sterol-enriched foods is an important development.

Plant-derived stanols and sterols, also called phytosterols, are known to lower serum cholesterol levels<sup>112</sup> and have therefore been added to fat-containing foods (margarines, salad dressings, mayonnaise). Phytosterols are structurally related to cholesterol and inhibit the absorption of dietary cholesterol and the reabsorption of biliary cholesterol from the intestine.

#### Are phytosterol-enriched foods effective in lowering cholesterol?

The evidence suggests that consuming 2grams per day of phytosterols lowers LDL-cholesterol levels by 10%. At present there are no studies that have directly assessed if phytosterols lower CVD risk.

#### Are the effects of phytosterols additive to those of statins?

The best evidence for the additive effects of phytosterols in patients receiving statins has come from four double-blind randomised, placebo-controlled trials.<sup>113-116</sup> Each administered phytosterols in doses of 2 to 3 grams per day for 4 to 8 weeks. Reductions in LDL-cholesterol ranged from 7% to 11%, findings similar to those that have been reported in subjects not taking statins. The magnitude of the additional decrease in LDL-cholesterol observed in these RCTs is slightly greater than that which would be expected from doubling the dose of the statin.<sup>115</sup> Whether statin dose can be safely and cost-effectively reduced by the addition of phytosterol products has yet to be documented.

#### Are there any safety concerns with phytosterol-enriched foods?

The evidence suggests that intake of the recommended 2grams per day of phytosterols effectively lowers LDL-cholesterol levels, produces no serious adverse effects and poses no health risks of concern.<sup>111</sup>

#### Dyslipidaemia – A Summary

- BHS guidelines advise targets of:<sup>1</sup>
  - **TC** less than **4.0mmol/l**, or reduced by 25%, whichever would result in the lower level.
  - **LDL-cholesterol** less than **2.0mmol/l**, or reduced by 30%, whichever would result in the lower level.
- Non-fasting TC and HDL-cholesterol is adequate as an initial screening test
- Hypothyroidism, type 2 diabetes, renal disease, liver disease, and alcoholism can cause hyperlipidaemia.
- Of the statins licensed in the UK, **simvastatin**, **pravastatin** and **atorvastatin** have the most solid body of evidence for efficacy and safety. NICE have indicated that when the decision has been made to prescribe a statin, therapy should be initiated with a drug with a low acquisition cost.<sup>68</sup> **Simvastatin** is currently priced lowest amongst the statins.
- Until the safety of aggressive lipid lowering with high dose statins has been established, the balance of risk versus benefit should be carefully assessed.
- Reserve the use of **rosuvastatin** or **ezetimibe** for cautious use in the management of difficult-to-treat cases until more information is available.
- Treatment with a statin should be discontinued if aminotransferase levels exceed three times the upper limit of normal.
- Myopathy is a rare, serious adverse effect occurring in less than 1% of patients on statins.

## Section 3: Antiplatelet Agents

This section of COMPASS Therapeutic Notes will cover the use of antiplatelet drugs (**aspirin**, **clopidogrel** and **modified-release dipyridamole**) in the prevention of cardiovascular events in primary care. Use of antiplatelet drugs in the treatment of AF, heart failure, stable angina, acute management of cardiovascular events or use before or after surgical procedures will not be covered. Nor will the use of antiplatelet drugs in people with diabetes.

As with other measures for reducing the risk of cardiovascular events (lifestyle modification, control of HTN, management of dyslipidaemia) antiplatelet drugs should be prescribed in the context of the individual patient's cardiovascular risk, the likely absolute benefits and harms of treatment, cost and patient preference.

Antiplatelet drugs decrease platelet aggregation and can inhibit thrombus formation in the arterial circulation, where anticoagulants have little effect.

### What is the antiplatelet agent of choice?

**Aspirin** is the antiplatelet agent of choice. It is of comparable efficacy to other currently available antiplatelet agents, it is widely available and inexpensive. The standard dose preparations available in the UK are 75mg and 300mg. Standard, dispersible and enteric-coated preparations are available.

Aspirin is an effective antithrombotic agent at doses between 50mg and 1500mg daily.<sup>117</sup> Aspirin 75mg daily is sufficient to suppress platelet aggregation in most people after several days.<sup>118</sup>

There is no evidence that higher doses are more effective than lower doses, although the risk of bleeding increases with dose. There is an approximate three-fold-lower rate of bleeding complications for patients taking aspirin doses of less than 100mg daily compared with those taking 100-200 mg or more.<sup>119</sup>

### What is clopidogrel?

Clopidogrel (Plavix<sup>®</sup>) is a thienopyridine antiplatelet drug. After activation in the

liver, it inhibits platelet aggregation by irreversibly modifying the platelet adenosine diphosphate (ADP) receptor and thus blocking the pro-aggregatory effects of ADP.

Clopidogrel is licensed for the prevention of atherothrombotic events in people who have had an MI, an ischaemic stroke or have established peripheral arterial disease. Contraindications include severe liver impairment and active pathological bleeding.

### In what situation are clopidogrel and aspirin licensed to be used together?

Currently, the only licensed use of a combination of clopidogrel and aspirin is in non-ST-segment-elevation Acute Coronary Syndrome (ACS).

### What is Acute Coronary Syndrome?

The term "acute coronary syndrome" is used to refer to any group of clinical symptoms associated with acute myocardial ischaemia. It encompasses a spectrum of disorders including acute MI and unstable angina. ACS is usually the result of an acute or subacute primary reduction of myocardial oxygen supply provoked by disruption of an atherosclerotic plaque associated with inflammation, thrombosis, vasoconstriction and microembolisation. The presence of persistent ST-elevation on an ECG usually indicates total occlusion of the affected artery, resulting in necrosis of the tissue supplied by that artery (acute MI). ACS without ST-segment-elevation is classified as either unstable angina or non-ST-segment-elevation MI (NSTEMI). Unstable angina and NSTEMI differ primarily in the severity of myocardial ischaemia. In NSTEMI, the ischaemia is severe enough to result in the release of biochemical markers of myocardial injury, such as troponin, into the blood.

### What is the evidence for the use of aspirin & clopidogrel together in ACS?

The evidence for the use of aspirin and clopidogrel concomitantly in ACS comes mainly from the CURE study.<sup>120</sup> In this RCT, in over 12,000 patients, aspirin 75mg daily was given along with

clopidogrel 75mg daily or placebo. The group of patients taking both aspirin and clopidogrel had significantly fewer cardiovascular events compared with the aspirin-only group.

### Does the concomitant use of aspirin and clopidogrel increase the risk of adverse effects?

When considering addition of clopidogrel to aspirin, the increased benefit obtained by reducing the risk of cardiovascular events must be balanced against the increased risk of harm resulting from major side effects, notably bleeding. In absolute terms, the CURE study<sup>120</sup> demonstrated that for every 100 patients treated for nine months, two additional patients were saved from having a major cardiovascular event by adding clopidogrel to aspirin. However, this was at the expense of one further patient suffering a major bleed.

### For how long should aspirin and clopidogrel be given together?

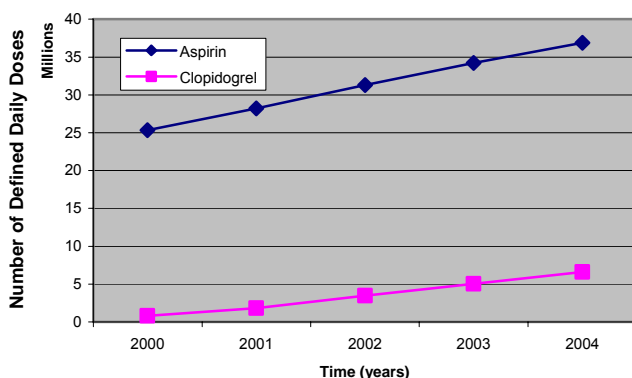
Benefits of clopidogrel in CURE appeared within 30 days and were maintained up to 12 months (the duration of the study).

NICE considered the benefit to harm ratio sufficient to recommend the use of the combination in moderate to high-risk patients with non-ST-segment-elevation ACS for **up to 12 months** following the most recent acute event.<sup>121</sup> Thereafter, treatment should revert to the use of low-dose aspirin alone.

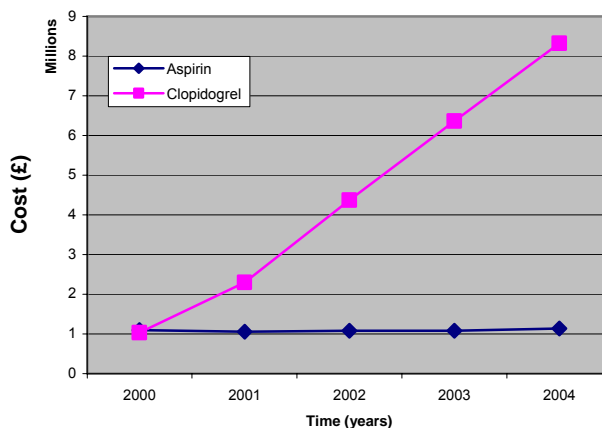
### What is dipyridamole?

Dipyridamole has both antiplatelet and vasodilating properties and is thought to inhibit the uptake of adenosine (a potent inhibitor of platelet aggregation) into blood and vascular cells. Because of the activity of dipyridamole as a vasodilator, it should be used with caution in people with severe coronary artery disease, including unstable angina and/or recent MI, left ventricular outflow obstruction or haemodynamic instability.

**Total volume for aspirin and clopidogrel prescribing in primary care in Northern Ireland**  
(Data from Pharmaceutical Dept., CSA)



**Total cost for aspirin and clopidogrel prescribing in primary care in Northern Ireland**  
(Data from Pharmaceutical Dept., CSA)



### Use of antiplatelet drugs in secondary prevention

#### Are antiplatelet agents effective in secondary prevention?

There is conclusive evidence for the benefits of antiplatelet drugs, particularly aspirin, in preventing cardiovascular events in high-risk patients. Meta-analysis shows that overall, serious cardiovascular events occurred in 10.7% of patients on antiplatelet therapy compared with 13.2% of patients in the control groups (P less than 0.0001).<sup>122</sup>

#### What is the first-line antiplatelet agent in secondary prevention?

Unless contraindicated, **low dose aspirin** should be used indefinitely in anyone who has suffered an MI, stroke or TIA, or who has symptomatic peripheral arterial disease.<sup>123</sup> In most circumstances, aspirin 75mg daily is appropriate.<sup>119</sup>

#### Why is clopidogrel second line?

Although clopidogrel appeared slightly more effective than aspirin in the CAPRIE study,<sup>124</sup> the small absolute increase in efficacy (NNT 196) does not justify its use ahead of aspirin in view of its higher cost (28-day treatment: clopidogrel £35.31, generic low-dose aspirin £0.27) (BNF50 prices).

Clopidogrel 75mg daily can be considered as an alternative to aspirin if aspirin is contraindicated or not tolerated.

#### What is the role of dipyridamole?

Recent NICE guidance recommends that MR-dipyridamole (200mg twice daily) should be considered in addition to low dose aspirin for a period of two years for secondary prevention of ischaemic stroke or TIA. Thereafter, or if dipyridamole is not tolerated, treatment should revert to the use of low-dose aspirin alone.<sup>123</sup> Current evidence does not support the use of MR-dipyridamole alone, standard-release dipyridamole alone or in combination with aspirin, or a combination of aspirin and clopidogrel, for secondary prevention of stroke or TIA.

#### What should be done if a patient suffers a cardiovascular event whilst on an antiplatelet agent?

Although antiplatelet agents reduce the risk of cardiovascular events they do not abolish it. Specialist referral is warranted for any patient who suffers a CV event while on aspirin or clopidogrel.

### Use of antiplatelet drugs in primary prevention

#### Is there any evidence for the use of antiplatelet agents in primary prevention?

Aspirin has been shown to reduce the risk of non-fatal MI and fatal CHD in patients without previous cardiovascular disease.<sup>125</sup> However, aspirin significantly increases the risk of major gastrointestinal bleeds.

People at risk of CVD gain most benefit from the use of aspirin.<sup>125</sup> Currently, low dose aspirin is recommended for primary prevention in people aged 50 years and over with a 10 year CVD risk greater than or equal to 20% provided HTN is controlled.

For primary prevention, use of aspirin and other antiplatelet drugs needs to be placed in the context of other less harmful and potentially more effective primary prevention measures (lifestyle modification, control of HTN, management of dyslipidaemia).<sup>126</sup> For people at low risk of an event, risks of an adverse effect of aspirin may outweigh the benefits.

There is no evidence to support the use of antiplatelet drugs other than aspirin for the primary prevention of cardiovascular events.<sup>126</sup>

### Adverse effects of antiplatelet agents

#### What are the common adverse effects of aspirin?

Adverse effects of aspirin include allergy (e.g. bronchospasm), gastric irritation, ulceration and bleeding, constipation, renal failure and bleeding at other sites (bruising, subconjunctival and intracranial). The risk of haemorrhagic stroke is about 1 in 2500 patient-years.<sup>127</sup> The risk of GI symptoms and bleeding is dose-dependent, but is still increased even at low doses.<sup>128</sup>

#### Which aspirin preparation is safer?

There is no evidence that using enteric coated formulations of aspirin provide less of a risk of gastrointestinal adverse effects than the use of dispersible aspirin 75mg.<sup>129</sup> Aspirin dispersible 75mg tablets can be swallowed whole with a glass of water or dispersed in water prior to administration.

#### What are the common adverse effects of clopidogrel?

Bleeding is the most common reaction reported in post-marketing experience, usually during the first month of treatment with clopidogrel.

#### Are there any less gastrointestinal effects with clopidogrel than aspirin?

There is no robust evidence that clopidogrel is a safer alternative to low-dose aspirin or that its use is associated with a lower risk of gastrointestinal side effects. Although, in CAPRIE,<sup>124</sup> clopidogrel was associated with an approximate one-third reduction in the incidence of GI bleeding compared with aspirin, this study used a 325mg dose of aspirin. This higher aspirin dose is known to significantly increase the risk of bleeding (possibly three-fold) relative to aspirin 75mg.<sup>119</sup>

#### What is genuine aspirin intolerance?

True aspirin intolerance is defined by either:<sup>123</sup>

- proven hypersensitivity to aspirin-containing medicines, or
- a history of severe dyspepsia induced by low-dose aspirin.

#### What can be recommended for patients with genuine aspirin intolerance?

Where aspirin is contraindicated, or there is genuine aspirin intolerance, clopidogrel can be considered as an alternative for secondary prevention of cardiovascular events. However, the number of people who are genuinely intolerant of aspirin is believed to be small.<sup>123</sup> People who

experience dyspepsia while taking aspirin should have no more than 75mg daily and co-prescription of a proton pump inhibitor (PPI),<sup>126</sup> such as omeprazole, should be considered before switching to clopidogrel.

#### What are the common adverse effects of dipyridamole?

Adverse reactions at therapeutic doses are usually mild. Vomiting, diarrhoea and symptoms such as dizziness, nausea, dyspepsia, headache and myalgia have been observed. These tend to occur early after initiating treatment and may disappear with continued treatment. As a result of its vasodilating properties, dipyridamole may cause hypotension, hot flushes and tachycardia. Worsening of the symptoms of coronary heart disease such as angina and arrhythmias. Hypersensitivity reactions such as rash, urticaria, severe bronchospasm and angioedema have been reported.

### Antiplatelet Agents – A Summary

- **Aspirin** is the antiplatelet agent of choice.
- Aspirin 75mg daily is sufficient to suppress platelet aggregation in most people after several days.<sup>118</sup>
- Clopidogrel (Plavix®) is an antiplatelet drug licensed for the prevention of atherothrombotic events in people who have had an MI, an ischaemic stroke or have established peripheral arterial disease.
- The only licensed use of a combination of clopidogrel and aspirin is in non-ST-segment-elevation Acute Coronary Syndrome (ACS).
- Clopidogrel and aspirin can be used together in moderate to high-risk patients with non-ST-segment-elevation ACS for **up to 12 months** following the most recent acute event.<sup>121</sup> Thereafter, treatment should revert to the use of low-dose aspirin alone.
- Unless contraindicated, low dose aspirin should be used indefinitely in anyone who has suffered an MI, stroke or TIA, or who has symptomatic peripheral arterial disease.<sup>123</sup>
- Where aspirin is contraindicated, or there is genuine aspirin intolerance, clopidogrel can be considered as an alternative for secondary prevention of cardiovascular events. However, co-prescription of a proton pump inhibitor (PPI),<sup>126</sup> such as omeprazole, should be considered before switching to clopidogrel.

### Useful Websites:

- European Cardiology Society ([www.escardio.org](http://www.escardio.org))
- British Cardiac Society ([www.bcs.com](http://www.bcs.com))
- Primary Care Cardiovascular Society ([www.pccs.org.uk](http://www.pccs.org.uk))
- British Hypertension Society ([www.bhsoc.org](http://www.bhsoc.org))
- Heart UK ([www.heartuk.org.uk](http://www.heartuk.org.uk))

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COMPASS Therapeutic Notes are circulated in Northern Ireland to the following:

- General Practitioners
- Pharmacists
- Extended/Supplementary Prescribers
- Others interested in prescribing issues

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## COMPASS THERAPEUTIC NOTES ASSESSMENT

Aspects of Cardiovascular Medicine

COMPASS Therapeutic Notes are circulated to GPs, nurses, pharmacists and others in Northern Ireland. Each issue is compiled following the review of approximately 250 papers, journal articles, guidelines and standards documents. They are written in question and answer format, with summary points and recommendations on each topic. They reflect local, national and international guidelines and standards on current best clinical practice. Each issue is reviewed and updated every three years.

Each issue of the Therapeutic Notes is accompanied by a set of assessment questions. These can contribute 2-3 hours towards your CPD requirements. Submit your completed MCQs to the appropriate address (shown below). Assessment forms for each topic can be submitted in **any order** and at **any time**.

If you want copies of Therapeutic Notes and MCQ forms for this and any other topic then you can either:

Visit the COMPASS Web site: [www.centralservicesagency.n-i.nhs.uk/display/compass](http://www.centralservicesagency.n-i.nhs.uk/display/compass)

or

Email your requests to: [keenanl@csa.n-i.nhs.uk](mailto:keenanl@csa.n-i.nhs.uk)

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# COMPASS THERAPEUTIC NOTES ASSESSMENT

## Aspects of Cardiovascular Medicine

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Successful completion of this MCQ form equates with 2 hours Continued Professional Development time. Circle your answer TRUE (T) or FALSE (F) for each question. When completed please post this form to the relevant address shown overleaf.

### 1 Hypertension

a	Evidence from trials shows that the majority of patients require two or more drugs to achieve BP targets.	T	F
b	Risk prediction charts produced by the Joint British Societies include <b>cardiovascular</b> risk prediction rather than <b>coronary</b> risk prediction, as was the case previously.	T	F
c	Salt reduction from an average of 10 to 5 grams daily lowers BP by about 10/4mmHg.	T	F
d	The level of BP control rather than the class of drug used to achieve it primarily determines the benefits of BP-lowering therapy.	T	F

### 2 Hypertension

a	British Hypertension Society recommends that initial antihypertensive selection be based on their AB/CD algorithm.	T	F
b	ASCOT-BPLA showed marked differences in primary outcome between amlodipine-based and atenolol-based regimens.	T	F
c	The progestogen-only pill can be used by women with HTN either related to COC-use or other causes provided the HTN is well controlled.	T	F
d	A BP measurement of 160/100mmHg or above on repeated testing is an absolute contraindication to the combined oral contraceptive.	T	F

### 3 Dyslipidaemia

a	Even individuals with established CVD or familial dyslipidaemia should have a trial of dietary management alone.	T	F
b	Treatment decisions should not be made on the basis of a single sample. Two samples should be taken at least a week apart, particularly if TC is close to a decision level.	T	F
c	Alcoholism is the most important cause of secondary hyperlipidaemia.	T	F
d	For the purpose of initiating therapy there is no data to suggest the superiority of any one statin over the others in reducing cardiovascular events.	T	F

### 4 Dyslipidaemia

a	At present it is prudent to reserve ezetimibe and rosuvastatin for cautious use in primary care for the management of difficult-to-treat cases.	T	F
b	Patients receiving any statin should be asked to report muscle pain, weakness or cramps immediately, and stop treatment until this has been investigated.	T	F
c	Statins should always be taken at night	T	F
d	Evidence suggests that consuming 2grams per day of phytosterols lowers LDL-cholesterol levels by 30%.	T	F

### 5 Antiplatelet agents

a	Aspirin is the antiplatelet agent of choice.	T	F
b	Clopidogrel 75mg daily can be considered as an alternative to aspirin if aspirin is contraindicated or not tolerated.	T	F
c	There is no evidence to support the use of antiplatelet drugs other than aspirin for the primary prevention of cardiovascular events.	T	F
d	Patients experiencing dyspepsia whilst on aspirin are said to be aspirin intolerant	T	F