



GUIDELINES

ON THE USE OF

LIPID LOWERING DRUGS

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Remit of Group

The working Group on the use of Lipid Lowering Drugs was established to:-

Provide regional guidance on the use of lipid lowering drugs in the prevention and treatment of atherosclerotic disease taking account of:-

- existing evidence and guidelines; and
- cost and benefit of implications for the population of Northern Ireland.

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CREST GUIDELINES ON THE USE OF LIPID LOWERING DRUGS

Summary

- The major approaches to lowering population levels of risk factors for vascular disease remain:
 - control of tobacco;
 - reducing fats, calories, and salt in the diet, and
 - encouraging physical activity.
- If more people at increased risk of coronary heart disease (CHD) were appropriately treated with aspirin and antihypertensive drugs, helped to stop smoking and changed their diet, then a large number would have their CHD risk sufficiently reduced to make statin treatment less cost effective.
- The level of total cholesterol by itself is a poor predictor of disease.
- Primary and secondary prevention of vascular disease must be clearly separated.
- A full lipid profile, including HDL-cholesterol and total: HDL ratio, should form the basis of any treatment decision.
- Such treatment should always be part of a holistic approach to the patient, with attention to lifestyle interventions.
- Treatment decisions should not be made on the basis of a single sample.

INTERVENTION LEVELS

Dietary intervention should precede and accompany any drug intervention.

SECONDARY PREVENTION

1. A total cholesterol of $>5\text{mmol/l}$ or LDL-cholesterol $>3\text{ mmol/l}$ despite dietary advice²; or
2. A total: HDL cholesterol ratio of $>5:1$ despite dietary advice; or
3. A TG of $2\text{-}4\text{ mmol/l}$ with an HDL-cholesterol of $<0.8\text{mmol/l}$; or
4. An isolated TG of $>4\text{ mmol/l}$ if secondary causes have been excluded.

The target for treatment is to keep levels below these.

PRIMARY PREVENTION

- Only measure lipids in those patients who would fulfil the criteria for treatment on the basis of their risk of developing vascular disease, as assessed from the tables.
- Intervene in those at significant risk.
- Those patients in the high risk category (red area) should be treated as per secondary prevention.

The target for treatment is then the same as above.

Note that very high triglyceride levels ($>10\text{ mmol/l}$) justify treatment in their own right because of the risk of pancreatitis.

1.0 INTRODUCTION

- 1.1 At first sight it would appear that there is already a plethora of guidelines available in the field of hyperlipidaemia, and so another would be superfluous, but we make no apologies for joining in the queue to offer advice. Some of the current guidelines are very cumbersome, which limits their applicability (eg the joint guidelines of the European Society of Cardiology, European Atherosclerosis Society and the European Society of Hypertension¹, or the joint guidelines of their UK counterparts²). Others have been criticised as too restrictive (eg the Sheffield Risk Table³). What most busy doctors want is a simple distillation of the best advice which they can apply to patients they see on an everyday basis, and this document is an attempt to provide just that.

Both the Northern and Southern Health and Social Services Boards have spent a considerable time on this topic, and so representatives of these Boards formed part of a multidisciplinary team to prepare the present document.

2.0 PRINCIPLES OF INTERVENTION IN THE MANAGEMENT OF HYPERLIPIDAEMIA

- 2.1 Four important points were to serve as the basis for our guidelines:
- a. *Primary* and *secondary* prevention must be clearly separated. The logic behind cholesterol reduction in the secondary prevention of vascular disease is irrefutable, and so the debate is who to treat as primary prevention;
 - b. A formal lipid profile, preferably with calculation of the total: HDL cholesterol ratio, was felt to be a more secure basis for treatment than simple total cholesterol alone, although many of the published guidelines use the latter;
 - c. Treatment of hyperlipidaemia should always be part of a holistic approach to risk factor intervention, particularly with regard to hypertension and smoking;
 - d. Simply quoting figures without explaining the logic behind them would be unlikely to encourage rational prescribing, or patient compliance.

3.0 SECONDARY PREVENTION

- 3.1 This refers to treatment of patients with known vascular disease. This includes patients with strokes or transient ischaemic attacks, and those with peripheral vascular disease, as well as those with ischaemic heart disease such as a history of myocardial infarction or bypass surgery.

Why 5.2 mmol/l?

- 3.2 This is because the epidemiological studies showing an exponential relationship of risk with increasing levels of cholesterol mainly came from the USA⁴, which still uses mass units, so that 5.2 mmol/l is 200 mg/dl. There is nothing special about this figure, and indeed the recent report of the Standing Medical Advisory Committee recommends intervention in such patients at a level of 4.8 mmol/l.

Why measure total: HDL cholesterol ratio?

- 3.3 Whilst it is true that recent major intervention trials such as the Scandinavian Simvastatin Survival Study (4S)⁵, the West of Scotland study (WOSCOPS)⁶ and the Cholesterol and Recurrent Events study (CARE)⁷ tend to focus on changes in total and LDL – cholesterol, epidemiological studies suggest that measurement of HDL-cholesterol and hence total: HDL ratio is more informative⁸ (see later). In addition, simple measurement of total cholesterol alone may not disclose more subtle problems such as the combination of a low HDL-cholesterol and a raised triglyceride, which is now recognised as potentially atherogenic⁹. **We therefore recommend a full lipid profile in all patients with known vascular disease.**

Must the blood sample be taken when fasting?

- 3.4 Recent food ingestion does not change the levels of total or HDL-cholesterol, but does increase triglyceride (TG) levels. If the TG levels are >4 mmol/l, the formula for the derivation of LDL-cholesterol is invalid. Therefore all lipid profiles should be taken after an overnight fast, but if the TG level is <2 mmol/l despite food ingestion, it is definitely normal and the LDL-cholesterol derivation valid.
- 3.5 Total and LDL-cholesterol levels are reduced by trauma such as accidents, myocardial infarction or surgery, so sampling should be avoided at times of stress.

Cholesterol is also subject to biological variability within the individual. **Treatment decisions should not be made on the basis of a single sample.** The two samples should be at least a week apart.

Are triglycerides important?

- 3.6 If the fasting TG level is >10 mmol/l, there is a considerable risk of pancreatitis, and treatment is justified on these grounds alone, usually with a fibrate. The debate continues on whether more moderate elevations of TG are an independent risk factor for the development of vascular disease, but the general opinion is that they probably are^{10,11}. In particular, the combination of a low HDL-cholesterol and a moderately raised TG is atherogenic, as noted above⁹.
- 3.7 Moderate elevations in fasting TG levels are very often secondary to other causes, in particular alcohol abuse, diabetes, hypothyroidism (even when clinically occult), or renal disease (especially nephrotic syndrome), and these conditions should be actively excluded before any intervention is planned. In addition, concurrent drug therapy may have an adverse effect on lipid metabolism (such as diuretics or retinoids), and so alternatives should be considered. Most vasodilator antihypertensive drugs are lipid-neutral or even favourable, whereas beta-blockers may have a slight adverse effect.

Should I treat cholesterol alone?

- 3.8 No – a broader approach is needed, targeted for each individual. The help of a practice nurse is often invaluable here. In addition to the classical risk factors of hypertension, diabetes and cigarette smoking, advice should be given on more general lifestyle factors, such as regular dynamic exercise, keeping to a reasonable body weight, and avoiding alcohol excess. Just as important is to explain that hyperlipidaemia is not an “illness”, and so patients should be encouraged to live a normal and full life. As a part of secondary prevention in general, it is also an opportunity to check that other important treatment measures are in place – aspirin, β -adrenoceptor antagonists if there has been a previous myocardial infarct, or an ACE inhibitor if there is evidence of left ventricular dysfunction.

Is diet alone effective?

- 3.9 In the patient with an isolated moderate elevation in TG levels, simple obesity can be a significant contributing factor, and reduction of body weight to nearer the predicted level may be all that is required. In other patients, an attempt should be made to reduce

the contribution of fat to the daily calorie intake to 30%, of which not more than 10% should be saturated. Ideally, this advice is best given by a Dietician, but this is not always possible. Basically, this corresponds to a “healthy diet” as understood by the general population, and so in many patients there may not be much room for further dietary intervention. In any case, it is rare to reduce cholesterol levels by >15% by dietary means alone, and so **if therapeutic targets are not met after a reasonable period (say three months), drug treatment will be required in addition to such dietary modification.** It is important to note that changing the diet may have benefits other than just lipid lowering, such as antithrombotic or possible antioxidant effects.

Who should I treat with drugs?

- 3.10 In each individual it is important to assess the contribution of lipids to their overall risk. In some cases, lifestyle advice alone may be sufficient (see above). Some patients may have a satisfactory lipid profile without further intervention, but **patients with proven vascular disease will require active drug treatment if the total cholesterol is >5mmol/l, the LDL-cholesterol >3mmol/l, or the total: HDL ratio remains >5:1².** Indeed, some recent studies have suggested that such patients may benefit from drug intervention even if their cholesterol level is apparently normal⁷.
- 3.11 It may be considered that older patients (say over 75) would not need such treatment, but against that, vascular diseases are more common in this age group, and there is increasing interest in treating the elderly. Certainly, there is no rationale for their exclusion on age grounds alone, provided they are otherwise fit and well.
- 3.12 Despite the strong evidence of benefit in patients with ischaemic heart disease (IHD), a survey of secondary prevention carried out 3-4 years ago showed that 78% of men and 86% of women still had a cholesterol of >5.0 mmol/l six months or more after their vascular event, even though some were on drug treatment¹². Clearly there is much work still to be done in this area, before even considering primary prevention. **We would recommend that every effort be made to identify those patients with vascular disease and to ensure that they are receiving adequate preventative measures.**

What about women?

- 3.13 Whilst it remains true that atherosclerotic disease is rare before the menopause, the incidence thereafter rises steeply, and eventually overtakes men. Undoubtedly this is in part related to the rise in cholesterol levels that also occurs at this time. In some patients, this can be reversed by HRT, and this may be a potential second line of treatment in older

women with vascular problems. If hyperlipidaemia persists, then the available evidence suggests that women benefit as much as men from cholesterol reduction⁵.

What are suitable levels for intervention?

3.14 Suitable levels for intervention are:-

1. A total cholesterol of >5 mmol/l or LDL-cholesterol >3 mmol/l despite dietary advice²; or
2. A total: HDL cholesterol ratio of >5:1 despite dietary advice; or
3. A TG of 2-4 mmol/l with an HDL-cholesterol of <0.8 mmol/l; or
4. An isolated TG of >4mmol/l if secondary causes have been excluded.

The therapeutic target is to keep the lipid levels below these.

What drugs should I use?

- 3.15 If the total cholesterol is raised due to an increase in the LDL-cholesterol, then a *statin* is the drug of choice (see Table 1). Simvastatin and pravastatin have been marketed the longest, and have the best trials evidence⁵⁻⁷, but it is probable that the benefits seen could be reproduced by other statins, or even be a result of adequate cholesterol reduction itself.
- 3.16 If there is mixed hyperlipidaemia, or an isolated moderate rise in TG, a *fibrate* is the drug of choice (see Table 2). Again, there is a choice of several drugs available. Fenofibrate and ciprofibrate are effective when taken once daily; and so is bezafibrate, which is less expensive but probably less effective. Gemfibrozil was used in the Helsinki Heart Study¹³, one of the most impressive lipid trials before the current statin studies.
- 3.17 Other drugs, such as resins, are now essentially third line agents, to be added in to one of the above.

Is the treatment safe?

- 3.18 Fibrates have been available for over 30 years, and statins for the past 10 years or so. At no time has their safety been questioned, although long-term studies are not yet available with statins. In the major clinical trials of statins⁵⁻⁷ the side effect rate was indistinguishable from placebo. Both groups of drugs may cause a small rise in liver enzymes, particularly ALT. Both may also rarely cause myositis, characterised by muscle pains and a rise in CK to >10 x normal. This is more likely to occur with combined statin/fibrate treatment, or when they are used with other drugs such as cyclosporin. **We would suggest that liver function tests and CK be checked annually or if symptoms occur.** Treatment should be discontinued if the ALT is >3 x normal, or the CK >10 x normal. Note that elevated gamma-GT is not usually drug-related, but is more likely to be due to alcohol or intrinsic liver disease.
- 3.19 A lipid profile should be measured at least twice before initiating treatment (see above), three months after starting, and at 6 monthly intervals thereafter.

Is treatment cost effective?

- 3.20 No-one disputes that statin treatment reduces mortality as well as vascular event rate in patients with ischaemic heart disease (IHD)⁵, and the cost in this group has been estimated to be about £4,250 per life-year saved for life-long treatment. This compares very favourably with other cardiovascular preventative measures. However, such statistics do not reflect the impact of IHD on the community in Northern Ireland, where the incidence of the disease is so high. Reduction of cholesterol levels together with lifestyle intervention are some positive interventions we can make.

4.0 Primary Prevention

- 4.1 Primary prevention means treating subjects with no known vascular disease. Even so, there is good evidence that drug intervention in this majority population group can reduce coronary events and vascular mortality, and probably all cause mortality as well⁶. There is every reason to suppose that these results, from a population in the West of Scotland, would be directly relevant to Northern Ireland. Nevertheless, on economic grounds it would be hard to justify such large-scale intervention. An overall population intervention strategy involving smoking, diet and physical activity is the preferred option, but to date this has met with limited success.

4.2 29% of the adult population in Northern Ireland smokes. Smoking remains the most important cause of premature death in the developed world. Every effort should be made to assist patients to stop smoking. Evidence for smoking cessation strategies in both primary and secondary care is contained in Smoking Cessation Guidelines and their Cost Effectiveness. *Thorax* 53, Supplement 5.

Who should be tested?

4.3 It is clearly impractical to test everyone, and so some choices have to be made. We would suggest that the following approach be adopted:

1. **Measure a lipid profile in those who would be a candidate for treatment, should the levels prove to be abnormal.** To help solve the problem of who should be treated as primary prevention, a widely adopted approach has been to quantify the absolute risk of that individual developing IHD¹⁻³ and to focus on those with a relatively high risk of a related event, say >3% per annum* (30% over a 10-year period). The enclosed tables from the joint British guidelines² emphasise this approach. Depending on gender, the presence of diabetes or cigarette smoking, and the initial visit blood pressure, it is possible to quantify risk. **Those identified as being at low risk (<15% over 10 years; green area) need not be tested for cholesterol.** Their risk status should be repeated at regular intervals, say every 3-5 years.
2. *If the lipid profile is abnormal, offer lifestyle advice.* Dietary advice should be part of a general message including other areas, such as smoking and regular moderate exercise. At this stage the presence of diabetes should have been excluded, and hypertension treated if present.
3. *If profile still abnormal, treat high-risk patients.* Whilst it is reasonable to wait to see if initial measures have been effective, there seems little point in postponing treatment decisions indefinitely – a period of about three months seems reasonable. If at that stage the lipid profile is still abnormal, then **those patients in the high risk category (red area) should be treated with the same means and the same targets as in secondary prevention** (see above). Those with moderate risk (orange area) may be considered for treatment, especially if there are other circumstances (see below). Those with low risk (green area) should be kept under regular observation, say every 1-2 years, and their risk reassessed.

* A 3% risk is equivalent to 4% cardiovascular risk.

4. Whilst such tables undoubtedly help in deciding who to treat on a rational basis, they should not supplant clinical judgement entirely. Those patients with a strong family history of vascular events (occurred in a first-degree relative at age <55 [males] or <65 [females]) should be promoted one level of risk, so that those in the low risk band (green area) could become candidates for treatment, and those in the orange area would be. To date, there is no trial evidence of benefit in patients over the age of 70 years. In contrast, patients with genetically determined dyslipidaemias such as familial hypercholesterolaemia (FH) nearly always require drug treatment, even from childhood, because of their uniquely high risk for the development of IHD – males aged 30-40 with FH are 100 times more likely to develop IHD than controls¹⁴.
5. **Very high triglyceride levels may cause pancreatitis.** A raised cholesterol level is not the only potentially hazardous lipid profile. Lipaemic plasma when fasting should raise the possibility of other abnormalities which can be harmful.

5.0 WHICH PATIENTS SHOULD I REFER TO A LIPID CLINIC?

5.1 Those who:

1. Require combination or multiple treatment;
2. Are intolerant of treatment;
3. Have inherited diseases such as FH;
4. Have active extensive vascular disease; or
5. Have very high triglyceride levels (eg >10 mmol/l)

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TABLE 1

STATIN THERAPY

DRUG	TRADE NAME	DOSE	%↓LDL-C	COSTS FOR 28 DAYS (MIMS JANUARY 2000)
Statins				
Atorvastatin	Lipitor	10 mg	33-41	18.88
		20 mg	33-50	30.60
		40 mg	50	47.04
		80 mg	41-61	94.08
Cerivastatin	Lipobay	100 micrograms	19-21	12.95
		200 micrograms	25-30	17.35
		300 micrograms	28-31	18.20
		400 micrograms	33-38	17.35
Fluvastatin	Lescol	20 mg	16-25	12.72
		40 mg	23-31	12.72
		80 mg	30-34	25.44
Pravastatin	Lipostat	10 mg	17-25	16.18
		20 mg	21-29	29.69
		40 mg	26-34	29.69
Simvastatin	Zocor	10 mg	24-32	18.03
		20 mg	28-40	29.69
		40 mg	36-44	29.69

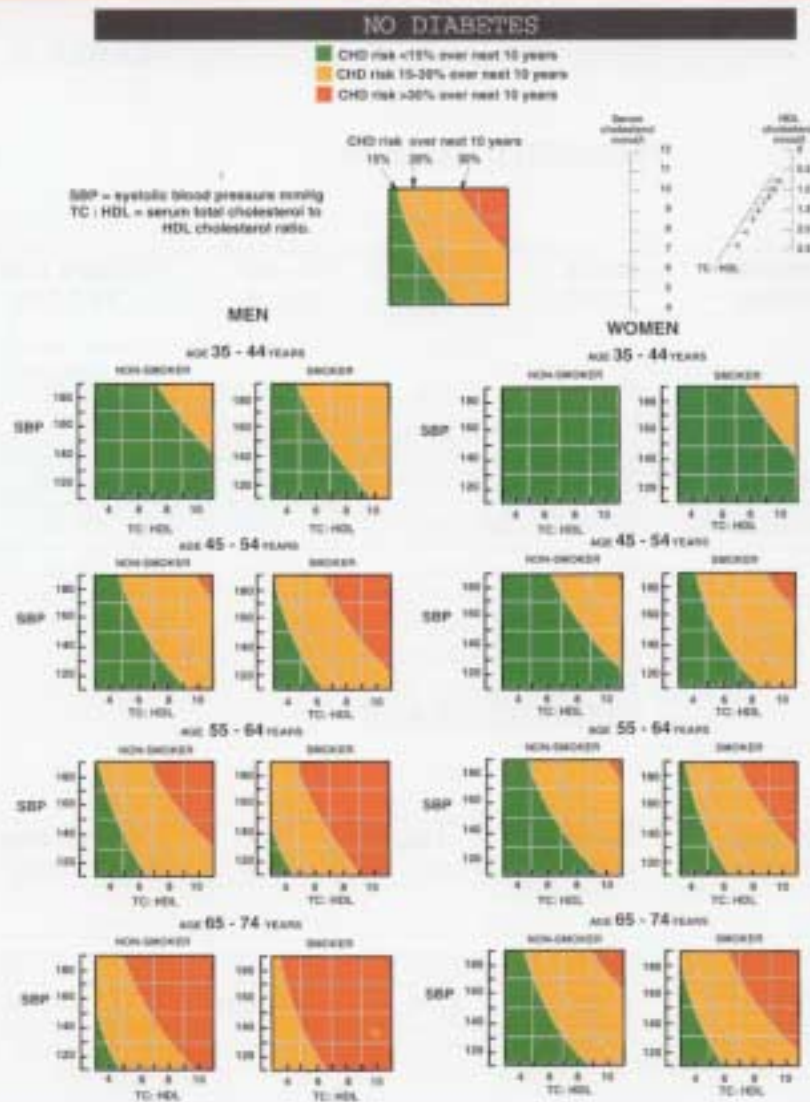
TABLE 2**FIBRATE THERAPY**

DRUG	TRADE NAME	DAILY DOSE	↓ LDL-C %	↓ TG %	COSTS FOR 28 DAYS
Fibrates					
Bezafibrate	Bezalip Mono	400 mg	10 (Type II)	40-50 20-30	8.12
Ciprofibrate	Modalim	100 mg	23	33	13.38
Fenofibrate	Lipantil Micro	200 mg	19	40	21.75
Gemfibrozil	Lopid	1200 mg	11	35	29.64

RESIN THERAPY

DRUG	TRADE NAME	DAILY DOSE	↓ LDL-C %	↓ TG %	COSTS FOR 28 DAYS
Resins					
Cholestyramine	Questran	12-24 g	Up to 20	0-mild↑	29.48-58.96
Cholestipol	Colestid	5-30 g	5-35	0-mild↑	11.18-67.08

TABLE 3



How to use the Coronary Risk Prediction Chart for Primary Prevention

These charts are for estimating coronary heart disease (CHD) risk (non fatal MI and coronary death) for individuals who have not developed symptomatic CHD or other major atherosclerotic disease.

The use of these charts is not appropriate for patients who have existing disease which already puts them at high risk. Such diseases are:

- CHD or other major atherosclerotic disease
- Familial hypercholesterolaemia or other inherited dyslipidaemia
- Established hypertension (systolic BP > 160 mmHg and/or diastolic BP > 100 mmHg) or associated target organ damage
- Diabetes mellitus with associated target organ damage
- Renal dysfunction

- To estimate an individual's absolute 10 year risk of developing CHD find the table for their gender, diabetes (yes/no), smoking status (smoker/non smoker) and age. Within this square define the level of risk according to systolic blood pressure and the ratio of total cholesterol to HDL cholesterol. If there is no HDL cholesterol result then assume this is 1.0mmol/l and then the lipid scale can be used for total cholesterol alone.
- High risk individuals are defined as those whose 10 year CHD risk exceeds 15% (equivalent to a cardiovascular risk of 20% over the same period). As a minimum those at highest risk (> 30% red) should be targeted and treated now, and as resources allow others with a risk of > 15% (orange) should be progressively targeted.

