

The International Task Force for Prevention of Coronary Heart Disease

Treatment guidelines for dyslipidemia

The last three years have seen publication of the results of a large number of important trials of lipid lowering therapy. Further, new forms of lipid-lowering medication have become available, either as mono- or combination therapy.

This has led the International Task Force for Prevention of Coronary Heart Disease to formulate this position document in order to guide practitioners in their efforts to reduce the risk of morbidity and mortality from cardiovascular disease in their patients. The main points to take into account in treating dyslipidemia are as follows:

1. Need for data from trials using hard endpoints

Wherever possible, decisions in clinical practice should be based on evidence from controlled clinical trials using hard endpoints such as death or myocardial infarction.

2. Comparisons between different treatment regimens

Ideally, comparisons between different lipid lowering regimens in terms of efficacy and safety require formal head-to-head comparisons. Such an approach was taken in the PROVE IT trial, where the highest approved dose of 40 mg per day of pravastatin was compared to the highest approved dose of 80 mg per day of atorvastatin in patients with acute coronary syndrome. This study showed that the median LDL cholesterol level achieved in the atorvastatin group was 62 mg/dL compared to 95 mg/dL in the pravastatin group. The hazard ratio for the combined primary endpoint (death, myocardial infarction, unstable angina pectoris, revascularization, and stroke) was reduced by 16% in favour of atorvastatin. While this study demonstrated that intense lowering of LDL cholesterol is more efficient in reducing the incidence of the combined endpoint, it cannot answer the question of whether equal degrees of LDL cholesterol lowering produced by different statins produce the same clinical effect. This is not a trivial issue, since *in vitro* studies suggest that different statins exhibit different, potentially important, so-called “pleiotropic” (i.e. non LDL-related) effects.

3. Evidence from trials using surrogate endpoints

A second category of evidence relates to trials using surrogate endpoints such as arterial changes measured using intravascular ultrasound (IVUS), measurement of the intima/media thickness ratio, or the coronary calcium score. In the absence of data from trials using hard end-points, the results of surrogate endpoint trials may be used as a basis for treatment decisions. Nevertheless, interpretation of surrogate endpoint studies is problematic as there is no one-to-one correlation between surrogate endpoints and hard endpoints such as death from myocardial infarction.

4. Comparison of drugs based upon changes in intermediate phenotypes

Comparison of drugs based upon changes in intermediate phenotypes such as the levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, C-reactive protein (CRP) etc. is not always easy. While it is safe to assume that a drop in LDL cholesterol will be associated with clinical benefit, a rise in HDL cholesterol levels, for example, does not necessarily mean that the risk of coronary heart disease is reduced.

In the case of CRP, a recent Task Force panel came to the conclusion that while CRP is a marker of inflammation (including atherosclerotic burden), it is premature to conclude that lowering of CRP by statins necessarily reflects an anti-inflammatory effect of these drugs. It is possible, for example, that statins lower CRP by specifically altering sterol homeostasis in the liver. Evidence for this hypothesis derives from the fact that none of the other well-established acute-phase markers of inflammation such as fibrinogen, interleukin 6 and white blood cell count has consistently been shown to be lowered by statin administration.

A further lesson in this regard can be learned from recent studies of hormone replacement therapy (HRT), which yielded an unfavorable outcome despite a large number of favorable effects of HRT on several intermediate phenotypes such as circulating lipid levels.

5. Intervention strategies to raise HDL cholesterol

As a rule, patients with low HDL cholesterol levels at high global risk benefit from treatment to a disproportionate degree. It is important however to realize that the

clear effects of baseline HDL cholesterol levels on outcome do not necessarily mean that raising HDL cholesterol by treatment directly produces benefit in the same way as lowering LDL cholesterol does.

Many patients with low HDL cholesterol have high triglyceride levels and impaired fasting glucose levels in the context of the metabolic syndrome or type 2 diabetes mellitus. Several studies have shown that these patients benefit from lipid-lowering treatment. The majority of trials have employed statins, but trial evidence also exists for the benefit of fibrates and nicotinic acid. Careful use of combination therapy may also be indicated in such patients.

6. Definition of primary, secondary and tertiary prevention and implications for therapy

Primary prevention of coronary heart disease refers to measures taken to avoid risk factors and to prevent coronary heart disease before it arises.

Secondary prevention of coronary heart disease refers to the identification of asymptomatic high-risk individuals in the population and aims to avoid worsening of clinically asymptomatic atherosclerosis.

Tertiary prevention of coronary heart disease refers primarily to measures taken to prevent the recurrence of a myocardial infarction.

Risk treatment decisions depend in the first instance on whether established vascular disease is present or not. It is therefore necessary to distinguish between the three forms of prevention defined above.

One of the greatest needs in cardiovascular medicine today is to improve preventive measures directed at the asymptomatic high-risk patient. In such patients, risk can equal or even exceed that of other patients with manifest coronary heart disease. Despite medical advances, nearly half of all persons suffering a first myocardial infarction will be dead within a month, so that significant improvements in mortality can only be achieved by improving primary and secondary prevention. Many persons

with diabetes mellitus and metabolic syndrome fall into this category of asymptomatic high-risk patients.

The case of tertiary prevention is the easiest to make recommendations for. International consensus exists that all such patients should have their LDL cholesterol level lowered to below 100 mg/dL (2.6 mmol/L). This level should not be regarded as absolute, however. Future trials may well show that even more ambitious LDL goals may save lives.

7. Calculating absolute risk of myocardial infarction

Treatment decisions in asymptomatic individuals should be based on the prior determination of the absolute risk of fatal and nonfatal myocardial infarction. In Europe, a scoring scheme for calculating this risk has been derived from the Prospective Cardiovascular Münster (PROCAM) study. This scheme allows the practitioner to easily quantify the absolute risk of his or her patient developing coronary heart disease based on the eight risk factors of age, smoking, family history of coronary heart disease, triglyceride level, LDL cholesterol level, HDL cholesterol level, systolic blood pressure and presence or absence of diabetes mellitus. Geographical adjustment factors are also available to allow the PROCAM risk score to be utilized in populations and regions other than that in which it was derived.

Patients at high risk as calculated using the PROCAM score (absolute event risk \geq 20% in 10 years) need treatment of an intensity equal to that required by patients with symptomatic coronary heart disease. Similar to tertiary prevention, LDL cholesterol levels in such patients should be lowered to at least 100 mg/dL (2.6 mmol/L). In addition, such patients often require additional treatment such as antihypertensive medication and/or aspirin. What matters in these individuals is the degree to which absolute risk is reduced. The higher the gradient in absolute risk before and after treatment, the better the clinical outcome. As a general rule, the benefits of treatment are disproportionately greater in high-risk individuals. This is reflected in cost-benefit analysis in terms of reduced cost (or a lower number needed to treat) in order to prevent a single coronary event.

8. Dosage issues

The starting dose of a statin should result in a lowering of LDL cholesterol of at least 30%. It has been debated in the past if the relationship between LDL cholesterol lowering and reduction in coronary heart disease in high-risk patients is linear or log-linear (curvilinear) in nature, or whether it exhibits a threshold effect. The implications of this discussion are not trivial. A linear relationship implies that equal increments of benefit will accrue for equal degrees of LDL cholesterol lowering at all levels of LDL cholesterol (“the lower the better”). A curvilinear relationship is also “the lower the better”, but with diminishing additional benefit for each additional step of LDL cholesterol lowering. The threshold model, finally, assumes that a certain degree of LDL cholesterol lowering (or a certain on-treatment LDL cholesterol) is required to achieve benefit, but that lowering beyond this threshold does not further improve benefit.

In practice, there is no single rule to decide on which dose of statin is required, although most intervention trials indicate that the curvilinear treatment-benefit relationship most closely describes reality. Different statins may differ in their degree of non-cholesterol lowering or “pleiotropic” effects as these affect outcome. Further, differences in outcome can be expected if LDL cholesterol lowering is carried out in high or low risk individuals, with most benefit being expected in those at high risk.

It has recently been suggested that it may not be necessary to titrate the statin dose (“treat to target” approach) and that use of a single fixed dose may be sufficient in all cases (“fire and forget” approach). The latter approach, however, has a serious drawback in that it may lead to under-treatment in persons at high global risk. This strategy also overlooks the need to monitor lipid levels both an indicator of compliance and a guide to deciding on the appropriate treatment.

Definite answers to some of these questions are expected from upcoming studies such as the Treating to New Targets (TNT) study using 10 mg vs. 80 mg of atorvastatin over a prolonged duration.

9. Treatment of dyslipidemia in women

A particular challenge is to decide on the best cardiovascular prevention in women, especially in women after the menopause. Nevertheless, post-hoc analysis of various trials suggests that statins are as effective in women as in men.

It is important to emphasize that hormone replacement therapy (HRT) is not an evidence-based modality to prevent CHD. It is strongly suggested that HRT aimed at the treatment of perimenopausal symptoms and/or the prevention of osteoporosis should not be undertaken without prior ascertainment of absolute risk for myocardial infarction. The selection of the appropriate HRT regimen and strategy (oral vs. patch, choice of estrogen, progestin, selective estrogen-receptor modulator (SERM), or tibolone) may be influenced by the specific risk factor profile in individual cases. The unwanted increase in CHD risk in women undergoing HRT should be counterbalanced by statin treatment.

A component of the unfavorable cardiovascular risk benefit profile of HRT is hypercoagulability which is enhanced by high circulating levels of triglyceride and/or lipoprotein (a) (Lp(a)). A sharp rise in the Lp(a) level may accompany the drop in female sex hormones during the menopause. In consequence, a full lipid profile should be performed in peri- and post-menopausal women, including fasting triglycerides and Lp(a). It is recommended that women with such a clustering of risk factors should be referred to a specialist, e.g. a lipidologist, for initial treatment.

10. Lifestyle

Except in very high-risk patients, drug treatment should always be preceded by a pre-specified period of lifestyle modifications. Not infrequently, diet modification, exercise, smoking cessation and weight reduction may yield appropriate reduction of absolute risk without the need for statin therapy. In addition, it should be emphasized that drug treatment of risk factors does not alleviate that need for lifestyle correction. The combination of a healthy life style and drug intervention will generate the most benefit.

11. Educational issues

Education of physicians and advice to the public concerning the proven benefit of lifestyle adjustment and lipid medication is ongoing. Currently, only a minority of

those patients who need it receive appropriate advice on risk reduction and therefore remain at an inappropriately high risk level. In view of the epidemic of obesity, special attention should be given to efforts to prevent and/or correct overweight and obesity, especially in children and adolescents.

In analogy to the successful public health measures that have been implemented in many countries with regard to smoking, legislators must pay increased attention to this problem in the future.

12. Combination therapies, the “polypill”

Several drugs that are widely used in primary prevention should be more widely used in combination with each other. It has been suggested that a “polypill” might considerably improve compliance. There is, however, a need to formally demonstrate that expected benefit of such a polypill in controlled clinical trials.

13. Treatment in the elderly

Current majority opinion is that the benefits of lipid lowering extend to the elderly. There does not appear to be an age limit above which preventive measures are no longer indicated. However, the dangers of polypharmacy and altered drug metabolism due to impaired renal and/or hepatic function should always be borne in mind when treating elderly patients.

14. Safety considerations

Overall, the statins currently on the market are remarkably safe when used at their recommended dosages. This has led the authorities in the UK to approve self-medication with simvastatin at a low dose (10 mg/day) for men above age 55 with increased coronary heart disease risk (absolute coronary event risk 10-15% in 10 years) and for men aged 45 to 54, or women above 55, with additional risk factors such as positive family history, smoking and overweight.

It should be noted, however, that while the safety of this approach is beyond doubt, there are no hard end-point trials supporting the efficacy of such a low dose of simvastatin. Further, this treatment may lead to a false sense of security among both doctors and patients, with the latent danger of under-treatment.

15. Stroke

Several large meta-analyses have shown that the reduction in cardiovascular risk by statins is not limited to coronary heart disease but also extends to ischemic stroke, albeit to a lesser degree.

16. Are there too many guidelines?

Various guidelines have been put out in recent years that differ somewhat in their messages. All, however, show wide areas of agreement and overlap. The differences that do occur have various reasons. Societies, individuals and the pharmaceutical industries all have their own, sometimes competing, interests. The different guidelines must also be seen against the different cultural, demographic, economic and historical backgrounds in which they were developed. Many efforts are underway at present to harmonize guidelines on an international level.

17. New results

Several trials have suggested that patients with type 2 diabetes mellitus show a special benefit from statin treatment. Until very recently, however, it was unclear if all persons with type 2 diabetes mellitus, including those without symptoms of atherosclerosis, would benefit from statins. The Collaborative Atorvastatin Diabetes Study (CARDS) was designed to answer this question. In this study, nearly 3,000 patients with diabetes mellitus were randomized to receive either placebo or 10 mg atorvastatin per day. The study was prematurely stopped after less than four years because of the clear benefit of statin treatment. Compared to patients on placebo, patients on statins showed a 37% reduction in major CVD events (fatal or nonfatal MI, acute CHD death, unstable angina, CABG, fatal and nonfatal stroke) with a 48% reduction in stroke. All-cause mortality was reduced by 27%, although this finding achieved only borderline statistical significance ($p=0.059$). In order to prevent one major CVD event, 27 type 2 diabetics would need to be treated for four years. The results were consistent irrespective of LDL, HDL or triglyceride levels at entry. There was also no evidence of heterogeneity by age, gender, baseline systolic blood pressure, retinopathy, albuminuria or smoking.

It should be pointed out that the effects of statins in diabetics in other trials were analysed on an exploratory post-hoc basis. CARDS is the first study to investigate this question in a hypothesis-based prospective fashion. The greater scientific value of prospective compared to retrospective analyses has direct implications for deciding on treatment.

CARDS suggests that there is no justification for having a threshold LDL cholesterol level as the sole arbiter of which patients with type 2 diabetes should receive statin treatment. Rather, treatment decisions should be based on the overall cardiovascular risk. The authors of CARDS concluded that the debate about whether all patients with type 2 diabetes warrant statin therapy should now focus on whether there are any patients at sufficiently low risk for this safe and efficacious treatment to be withheld.

Summary of recommendations

1. Recently, the Task Force released a statement (see www.chd-taskforce.com) summarizing the evidence that statins differ in their efficacy/safety profiles. Readers of the present document should refer to this statement.
2. All patients with symptomatic atherosclerotic disease require low LDL cholesterol target values, i.e. below 100 mg/dL (2.6 mmol/L). It is not clear at present if even more radical lowering of LDL cholesterol is associated with additional clinical benefit.
3. All asymptomatic patients should have formal risk assessment, e.g. by means of the PROCAM risk score.
4. LDL cholesterol targets in asymptomatic individuals depend upon absolute risk for myocardial infarction. In low-risk patients (i.e. risk of a coronary event less than 10% in 10 years), LDL cholesterol should be lowered to at least 160 mg/dL (4.1 mmol/L); in intermediate-risk patients (i.e. risk 10% -20% in 10 years), LDL cholesterol should be lowered to at least 130 mg/dL (3.4 mmol/L). This approach implies active drug titration ("treat to target" approach).
5. Patients at high absolute risk of major coronary events (20% or greater risk of myocardial infarction or sudden coronary death in 10 years) should receive the same treatment as patients with symptomatic CHD. LDL cholesterol in such patients should be lowered to at least 100 mg/dL (2.6 mmol/L).

6. The evidence at present is that benefits of treatment extend to all sections of the population irrespective of age, gender, race etc.
7. Present evidence suggests that patients with type 2 diabetes mellitus benefit from statin treatment even if they exhibit no symptoms of atherosclerotic disease. This was demonstrated in the recently released data of the CARDS study.

Document of the International Task Force for Prevention of Coronary Heart Disease
prepared by:

Gerd Assmann, Münster, Germany

Paul Cullen, Münster, Germany

Jean-Charles Fruchart, Lille, France

Heiner Greten, Hamburg, Germany

Walter Riesen, St. Gallen, Switzerland

Arnold von Eckardstein, Zürich, Switzerland

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