HOSPITAL CHRONICLES 2006, SUPPLEMENT: 215–220

Individualized Tailoring of Hypolipidemic Pharmacological Treatment

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ABSTRACT

The validation of the lipid hypothesis, which pertains to the relationship between dyslipidemia and atherogenesis, has established the central role of hypolipidemic treatment in the frontline of primary and secondary prevention of coronary artery disease. However, the complexity of the lipoprotein disorders, which are usually associated with more than one biochemical abnormalities, and the availability of several hypolipidemic agents in the existing therapeutic armamentarium with combined beneficial effects of variable intensity on several lipoproteins, have stressed the need for the development and implementation of easily applicable therapeutic algorithms which will enable the individualized tailoring of hypolipidemic management with maximal efficiency and safety. One such algorithm of individualized tailoring of hypolipidemic therapy is being proposed in this brief overview.

Abbreviations and Acronyms
apoCII: apolipoprotein CII
apoB: apolipoprotein B
CAD: coronary artery disease
CETP: cholesterol ester transfer protein
FFA: free fatty acids
HDL-C: high-density lipoprotein cholesterol
IDL: intermediate density lipoprotein
LDL-C: low-density lipoprotein cholesterol
LPL: lipoprotein lipase
TLC: therapeutic lifestyle changes
VLDL: very low density lipoprotein

KEY WORDS: *dyslipidemia; hypercholesterolemia; lipid-lowering treatment; statins; ezetimibe; fibrates; lipoproteins; coronary artery disease*

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The ultimate target of lipid-lowering therapy is to decrease the risk of coronary heart disease. Thus, the priorities in hypolipidemic treatment should be ranked according to the existing state of evidence concerning the relationship between cholesterol or triglyceride levels and the risk of coronary artery disease (CAD). A plethora of data have demonstrated the log-linear relationship between low-density lipoprotein cholesterol (LDL-C) levels and coronary heart disease risk in a wide scale of LDL-C concentrations [1-4] High-density lipoprotein cholesterol (HDL-C) levels are also inversely associated with the presence of CAD, while a randomized trial has demonstrated that pharmacological interventions targeting low HDL-C levels have a role in the secondary prevention of cardiovascular events among patients with low baseline HDL cholesterol levels [5] The role of hypertriglyceridemia as a coronary risk factor has not been fully elucidated. The correlation between elevated triglyceride levels and the risk of CAD is not established in multivariate analyses due to the association of hypertriglyceridemia with diabetes, obesity, alcohol consumption and chronic renal failure. However, hypertriglyceridemia has been demonstrated to be an independent risk factor for CAD in several subgroups of patients including women, diabetics and middle-aged and elderly men [6].

THERAPEUTIC LIFE STYLE CHANGES

It is imperative to emphasize the primary role of physical activity, weight control

and dietary changes in the management of all subjects with an impaired lipid profile. Regular exercise training has been shown to increase HDL-C in a dose-dependent manner and reduce plasma triglyceride concentrations [7-9]. The adoption of a diet low in cholesterol and saturated fat is estimated to decrease LDL-C levels by 11 to 15% and probably by even 20% [10]. Furthermore, weight loss has a beneficial effect on HDL and triglyceride levels [11-13]. Thus, therapeutic lifestyle changes (TLC) should always be integrated in the lipid-lowering therapeutic strategy and in cases of mild or even moderate lipid disorders the abovementioned interventions may suffice to reach the target lipid levels.

LOWERING LDL-CHOLESTEROL

The clinical scenarios where lipid lowering treatment is needed could be briefly summarized in the following cases (1) elevated LDL-C; (2) elevated non-HDL-C in patients with high levels of triglycerides (200 to 500 mg/dL); (3) low HDL-C; (4) diabetic dyslipidemia; and (5) very high triglycerides. In all these clinical situations, the primary goal is to reduce the LDL-C plasma concentration to the corresponding target level which is determined by the individual's risk of CAD according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) recommendations (Table 1) [14,15]. The available drugs which primarily lower LDL-C are hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins), bile acid binding resins, and ezetimibe, a recently developed selective inhibitor of intestinal cholesterol absorption (Table 2) [16]. Among these LDL-C lowering agents the drugs of first choice for achievement of LDL-C goal should be a member of the statin group largely due to their favourable safety profile combined with their demonstrated potency in reducing LDL-C and adverse cardiovascular events in primary [17,18] and secondary [1-4,19-21] prevention trials. When statins can not be used because of patient intolerance or contraindications, ezetimibe or bile acid resins should be suggested in combination with therapeutic lifestyle changes in order to achieve the treatment goal. Bile acid resins and ezetimibe are not systemically absorbed and thus can be administered in subgroups of patients in whom systemic exposure should be rather avoided, such as children, young patients and women of childbearing age.

In the majority of cases, a moderate dose of a high efficacy statin (rosuvastatin, atorvastatin, simvastatin, and pravastatin in order of decreasing potency) is expected to achieve the LDL-C goal. However, in patients with highly increased LDL-C baseline levels, including subjects with heterozygous familial hypercholesterolemia and LDL-C levels ranging between 250 and 400 mg/dL, the therapeutic target would be a decrease in mean LDL levels by 50 to 75%, which can not be achieved with

TABLE 1. LDL-C goals and cutoff levels for initiation of TLC and drug treatment in different risk categories (Adult Treatment Panel III guidelines).

Risk Category	LDL-C goal	Cut-off level for TLC initiation	Cut-off level for initiation of pharmacological treatment
High risk: CHD* or CHD risk equivalents†	<100 mg/dL	≥100 mg/dL	≥100 mg/dL
(10-year risk > 20%)	(optional goal: <70 mg/dL)		(<100 mg/dL: consider drug options)
Moderately high risk: 2+ risk factors‡	<130 mg/dL§	≥130 mg/dL	≥130 mg/dL
(10-year risk 10% to 20%)			(100–129 mg/dL; consider drug options)
Moderate risk: 2+ risk factors‡	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
(10-year risk <10%)			
Lower risk: 0–1 risk factor‖	<160 mg/dL	≥160 mg/dL	≥190 mg/dL
			(160–189 mg/dL: LDL-lowering drug optional)

* CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

†CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for CHD >20%.

‡ Risk factors include cigarette smoking, hypertension (BP ≥140/90 mmHg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥ 45 years; women ≥55 years).

§ Optional LDL-C goal <100 mg/dL.

‖ Almost all people with zero or 1 risk factor have a 10-year risk <10%, and 10-year risk assessment in people with zero or 1 risk factor is thus not necessary.

TABLE 2. Mechanism of action, dose range, major lipid effects and adverse effects of lipid-lowering medications

Agents	Mechanism of action	Dose range	Major effects on lipid levels	Major adverse effects
Statins (HydroxyMethylGlutaryl-Coenzyme A reductase inhibitors)				
Rosuvastatin	Inhibition of the rate limiting step of cholesterol synthesis resulting in ↑ expression of LDL receptors, ↓ hepatic production of LDL, VLDL and ↑ LDL-C plasma clearance	10-40 mg	10 mg ↓ LDL 45%*†	Reversible elevation in transaminases and myositis
Atorvastatin		10-80 mg	10 mg ↓ LDL 39%*†	
Simvastatin		10-80 mg	20 mg ↓ LDL 35%*†	
Fluvastatin		20-80 mg	40 mg ↓ LDL 25%*†	
Lovastatin		20-80 mg	40 mg ↓ LDL 31%*†	
Pravastatin		10-40 mg	40 mg ↓ LDL 34%*†	
Cholesterol absorption inhibitor				
Ezetimibe	Interference with the intestinal cholesterol transporter Niemann Pick C1-like1 protein 1	10 mg	10 mg ↓ LDL 18%	Few side effects (similar adverse effect profile with placebo)
Bile acid binding resins				
Cholestyramine	Inhibition of bile acid reabsorption	2-24 gr	↓ LDL 10-30% in a dose dependent manner	Gastrointestinal intolerance
Colestipol		5-30 gr		
Fibrates				
Gemfibrozil	Interaction with transcription factor	600-1200 mg	1200 mg ↑HDL 6%, ↓TG 31% [5]	Dyspepsia, gallstones, ↑ transaminases, interaction with anticoagulants, myopathy
Fenofibrate	PPARα regulating transcription of LPL, apoCII and apoB genes	200 mg	200 mg ↑HDL 5%, ↓ TG 29% [37]	
Bezafibrate		400 mg	400 mg ↑HDL 18%, ↓ TG 21% [30]	
Niacin				
Nicotinic acid	Decreased hepatic secretion of VLDL and decreased FFA mobilization from the periphery	1-3 gr	↓ TG 20-50%, ↑ HDL 15-35%, ↓ LDL 5-25%	Skin flushing, hyperglycemia, hyperuricemia, hepatotoxicity, gastritis
Omega-3 fatty acids				
Omega-3 fatty acids	Decreased VLDL synthesis	3-5 gr	↓ TG 25-30%, ↑ HDL 1-3%, ↓ LDL 5-10%	Gastrointestinal disturbances

* Estimated LDL reductions were obtained from US FDA package inserts for each drug.
† For every doubling of the mentioned dose, an approximate 6% additional decrease in LDL-C level can be achieved.

the administration of moderate doses of statins. Thus, the next step would be the administration of either a high efficacy statin in the maximal dose or the addition of ezetimibe or a resin on top of the already administered moderate dose of statin. Among the abovementioned therapeutic alternatives, the first-choice regimen seems to be the combination of moderate statin dose with ezetimibe. The complementary mechanisms of action of these different classes of lipid-lowering drugs ensure an additive LDL-C lowering of about 18% when ezetimibe is added on top of statin [22-24], compared to an average 6% incremental LDL-C reduction achieved by every doubling of statin dose. It is also of primary importance that the enhanced lipid lowering potency offered by the combination of statin with ezetimibe is associated with a safety profile similar to the moderate-dose statin monotherapy. Furthermore, the augmented beneficial effect offered by up-titration of statins should be outweighed against a dose-dependent increase in the incidence of reversible transaminase elevation and myositis. On the other hand though, despite the robust existing data regarding the efficacy of the statin-ezetimibe combination in reducing LDL-C levels, there are no clinical outcome data which may ensure us that the achievement of the LDL-C goal, avoiding incremental dosing of statins, will be translated to morbidity and mortality benefit.

In highly demanding patients with CAD and refractory hypercholesterolemia or with difficult to treat heterozygous or even homozygous familial hypercholesterolemia [25], the combination of moderate statin dose with ezetimibe may prove inadequate to attain the indicated LDL goal. In these cases the next step should be the administration of maximal dose of a high-efficacy statin with ezetimibe or even a triple therapy consisting of maximal statin dose, ezetimibe and resin.

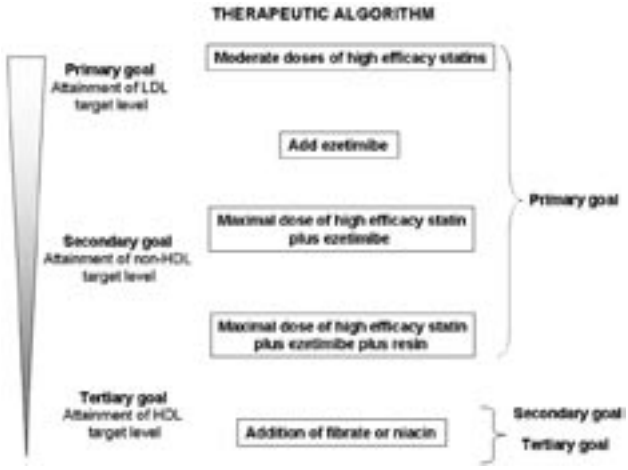

FIGURE 1. Basic principles of lipid lowering management based on NCEP-ATP III defined treatment goals.

INCREASED TRIGLYCERIDE LEVELS

The management of patients with increased triglyceride levels should be addressed under the scope of the general rule that LDL-C levels represent the primary therapeutic target. Once the respective LDL-C goal has been achieved, non-HDL levels (non-HDL-C = TC – HDL-C = VLDL-C + LDL-C, the latter including IDL), which include all cholesterol carrying particles except HDL-C, should represent the secondary goal and the target value should be 30 mg/dL higher than the respective LDL-C goal. The two classes of hypolipidemic agents which have an established role in the treatment of patients with increased triglyceride and/or non-HDL levels are nicotinic acid derivatives and fibrates (Table 2). The major limitation of these agents is their adverse effect profile which necessitates the maintenance of a heightened vigilance, especially in cases of statin and fibrate co-administration in patients with combined dyslipidemias where both LDL-C and non-HDL-C goals should be achieved. Whenever this combination is indicated, fenofibrate should be preferred instead of gemfibrozil or bezafibrate, since fenofibrate does not interfere with statin glucorinidation and thus does not substantially increase the risk of myopathy [26]. Fish oil derived omega-3 fatty acids (eicosapentaenoic acid, C20:5n-3 [EPA] and docosa-hexaenoic acid, C22:6n-3 [DHA]) have also a therapeutic role in the management of patients with hypertriglyceridemia. Doses of omega-3 fatty acids exceeding 3 grams daily, which can only be obtained by consistent supplementation and not by diet, exhibit a triglyceride lowering effect by about 25 to 30%, but also exert an LDL increasing effect by 5-10% [27].

THE ROLE OF HDL-CHOLESTEROL

Accumulating data further validating the role of HDL-C as a CAD risk factor have provided a sufficient state of evidence for the NCEP-ATPIII to define HDL-C levels as the tertiary goal of hypolipidemic treatment. The American Heart Association has recently redefined low HDL-C levels as <40 mg/dL for men and <50 mg/dL for women [28] and the American Diabetes Association has adopted these cut-off levels as the HDL-C goal for diabetic patients [29]. When dietary changes, weight loss and exercise training have proven inadequate to achieve the abovementioned HDL goals, pharmacologic treatment should be instituted. Despite the fact that statins have a modest efficacy in increasing HDL levels, their administration for treatment of patients with increased LDL-C levels, in terms of targeting the primary LDL goal, might prove adequate in combination with TLC to reach the target HDL levels. Among statins, rosuvastatin has been shown to exert a slightly more potent effect on HDL-C in comparison to atorvastatin, simvastatin and pravastatin [30]. In patients with combined dyslipidemia, who maintain decreased HDL levels despite the achievement of LDL and non-HDL target levels with statin monotherapy or statin plus ezetimibe, the addition of niacin or fenofibrate is indicated. It should be highlighted that despite the initial concerns regarding the administration of niacin in diabetics due to the exerted hyperglycemia, recent trials have demonstrated the safe feasibility of this regimen with the prerequisite of glucose monitoring and proper adjustment of antidiabetic agents [31,32]. The addition of fenofibrate in the hypolipidemic regimen of patients with mixed hyperlipidemias might result to an increase of LDL-C, which albeit paradoxical, is attributed to the augmenting effect of fibrates on lipoprotein lipase activity. In patients with isolated low HDL cholesterol, niacin is the agent of choice. The common and limiting side effect of flushing is considered to be prostaglandin mediated and thus can be mitigated by concurrent use of low aspirin dose.

Recently, a new class of hypolipidemic drugs, cholesterol ester transfer protein (CETP) inhibitors, which raise HDL cholesterol and lower LDL cholesterol, has been developed, but are still used in trial settings only. HDL mimetic agents are another group of agents that offer much promise. CETP is a plasma glycoprotein that facilitates the transfer of cholesteryl esters from HDL-C to Apo-B containing lipoproteins. Torcetrapib, a CETP inhibitor, has been shown to be effective, safe and well tolerated when used in combination with atorvastatin therapy [33]. Torcetrapib has been shown to increase HDL cholesterol levels by 46% when given alone and by 61% when given in combination with atorvastatin, as well as to decrease LDL cholesterol levels by more than that achieved by atorvastatin alone. Future trials evaluating the efficacy and safety of such drugs remain to establish whether these new therapeutic

agents will reduce the risk for atherosclerosis.

LIPID LOWERING IN DIABETICS

Diabetics represent a subgroup of patients with high prevalence of combined dyslipidemia usually consisting of slightly increased LDL-C levels, small LDL particles, increased triglycerides and decreased HDL-C levels. The lipid-lowering management of diabetic patients with an adverse lipid profile should not divert from the general rule that "LDL-C comes first", using statins as a first-line agent since their administration has been associated with significant reduction in cardiovascular events among diabetics [19,20,34,35]. However, a significant proportion of diabetics who have succeeded their primary LDL-C goal, still have low HDL-C, raised triglycerides, and small LDL particles. In order to achieve the secondary and tertiary goals of lipid-lowering treatment, either niacin or fenofibrate, the only member of the fibrate class that can be co-administered with statins with relative safety, can be selected. However, the rather disappointing results of the FIELD study, whereby fenofibrate failed to demonstrate a significant reduction of the primary endpoint versus placebo in diabetic patients, combined with a nonsignificant increase in cardiac mortality and a modest increase in HDL by 5%, further established the role of statins as first choice agents in diabetic dyslipidemia, while raised concern regarding the additive benefit of fenofibrate administration on top of statins in diabetics [36]. It would thus be prudent to suggest the use of niacin on top of statins in diabetic patients with decreased HDL levels, limiting the use of fenofibrate in diabetics with increased triglycerides or those who can not tolerate niacin.

CONCLUSION

In conclusion, lowering of LDL cholesterol levels to the NCEP-ATPIII treatment goals should be set as top priority in the management of dyslipidemic patients, while the attainment of non-HDL and HDL target levels respectively represent the secondary and tertiary goal. The implementation of treatment algorithms defined on the basis of achieving the abovementioned goals is expected to enhance our efficiency in tackling dyslipidemia, thus paving the way towards cardiovascular disease prevention.

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