UNIT NO. 5

PHARMACOLOGICAL TREATMENT OF HYPERLIPIDEMIA

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PREVIEW

This unit covers the definition, diagnosis, assessment and treatment strategies of hyperlipidemia.

OBJECTIVES

- Identification of Hyperlipidemia
- Treatment Goals
- Initiation of Therapy
- Choice of pharmacological agents
- Monitoring patients during follow-up

IDENTIFICATION OF HYPERLIPIDEMIA

What Is Hyperlipidemia?

Hyperlipidemia is an elevation of lipids (fats) in the bloodstream. These lipids include cholesterol, cholesterol esters (compounds), phospholipids and triglycerides (TG). They're transported in the blood as part of large molecules called lipoproteins.

There are the five major groups of plasma lipoproteins:

- chylomicrons
- very low-density lipoproteins (VLDL)
- intermediate-density lipoproteins (IDL)
- low-density lipoproteins (LDL)
- high-density lipoproteins (HDL)

When hyperlipidemia is defined in terms of a class or classes of elevated lipoproteins in the blood, the term hyperlipoproteinemia is used. Hypercholesterolemia is the term for high cholesterol levels in the blood. Hypertriglyceridemia refers to high TG levels in the blood.

Diagnosis of Hyperlipidemia

In diagnosing hyperlipoproteinemia, a normal plasma total cholesterol (TC) level is difficult to define. A consensus of the National Cholesterol Education Program (NCEP) defines TC levels ≤ 200 mg/dL (≤ 5.18 mmol/L) as desirable, levels between 200 and 240 mg/dL (5.18 and 6.22 mmol/L) as borderline high, and levels ≥ 240 mg/dL (≥ 6.22 mmol/L) as high.

The recently published Ministry of Health Clinical Practice Guidelines on Health Screening recommends that the optimal test for screening for dyslipidemia is a full lipid profile, not just the TC and HDL suggested in older texts.

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The summary of screening guidelines:

- Screening should be carried out in all adults above the age of 40 years on an opportunistic basis. Earlier screening should be considered from the age of 30 years for those with risk factors like hypertension, cigarette smoking and family history of premature coronary heart disease (CHD)
- Screening should be done in all with pre-existing CHD, stroke, peripheral vascular disease, diabetes mellitus, impaired glucose tolerance, impaired fasting glucose, and family history of familial hyperlipidemia.

Serum TC and HDL-C levels can be measured at any time of the day in the non- fasting state. However, TG levels must be obtained after 10–12 hours of fasting. TC, HDL-C and TG are measured directly. LDL cholesterol is usually calculated using the Friedwald formula which is as follows:

$$\text{LDL-C (mmol/L)} = \text{TC} - (\text{HDL-C} + \text{TG}/2.2)$$

This formula cannot be used if the TG is ≥ 4.5mmol/L (400mg/ dL).

Tests should be deferred for at least 2 weeks after a febrile illness. For patients suffering from acute myocardial infarction, the cholesterol level may be depressed between 24 hours to about 3 months after the infarction. Since cholesterol and TG levels show biological variability, it is advisable to obtain at least 2 consecutive estimations (1–8 weeks apart) before deciding on any therapeutic intervention.

TREATMENT GOALS

The goal of treating hyerlipidemia is essentially to prevent atherosclerotic cardiovascular disease (ASCVD). The curvilinear relationship between cholesterol and ASCVD has been clearly borne out by epidemiological data, and clinical interventional studies have proven that lowering cholesterol levels does indeed lower this risk. Both primary and secondary prevention data are available to us now. Despite convincing data and potent therapy available, studies in U.S. have shown that only 38% of the patients attained LDL-C target levels or had values lower than these goals. The greater the number of risk factors, the lower the proportion of patients actually achieving required target levels.

LDL-C goal is the primary target to achieve in the treatment of hyperlipidemia.

The LDL-C target depends on:

- the presence or absence of CHD and other clinical forms of atherosclerotic disease
- the presence or absence of major risk factors (other than LDL- C and diabetes)

The major risk factors of LDL-C are:

- Cigarette smoking
- Hypertension – BP >140/90 mmHg or on antihypertensive medication
- Low HDL cholesterol < 1.0mM
- Family history of premature CHD
  - CHD in male first degree relative < 55 years
  - CHD in female first degree relative < 65 years
- Age – Men > 45 years,
  - Women > 55 years

Based on the risk factor assessment, the LDL-C goals are determined and the targets are as follows:

- CHD or CHD risk equivalents, LDL-C ı 2.6 mmol/l
- Two or more risk factors LDL-C ı 3.3 mmol/l
- Less than 2 risk factors LDL-C ı 4.1 mmol/l

The above targets are derived based on consensus guidelines and have a wealth of clinical data supporting these levels. These levels, especially for those in the high-risk category, are difficult to achieve and require dose titration and combination therapy in some cases.

The LDL-C remains the primary goal, and secondary targets are that of TG ı 2.2 mmol/l and HDL-C ļ 1.0 mmol/l. Individuals with levels of TG ļ 4.5mmol/L (400mg/dL) also have an increased risk of acute pancreatitis and should be treated for this additional reason.

INITIATION OF PHARMACOTHERAPY

Pharmacotherapy should only be started in those who have failed to reach goal lipid levels after lifestyle changes. However, in CHD patients drug therapy can be started simultaneously with lifestyle changes if the LDL-C is ļ 3.3mmol/L (130mg/dL).

The common problems faced in hyperlipidemia are those of hypercholesterolemia with/without hypertriglyceridemia and hypertriglyceridemia alone. Isolated low HDL-C is also another common phenotype but currently there is no guideline on its treatment for primary prevention.

Monotherapy is usually initiated for patients who were unable to reach therapeutic goal with lifestyle measures alone and combination therapy is used if refractory to monotherapy or synergistic combined effects are needed.

The most potent lipid lowering drugs available currently are the hydroxy methyl glutaryl coenzyme A reductase inhibitors (statins). Currently 6 statins are available for use. The cardioprotective property of these drugs is primarily due to reduction of LDL-C. It is also clear that these drugs have other effects, referred to as pleiotropic properties that may also be important. These pleiotropic properties importantly influence the biology of atherosclerosis by modulating immunoregulation, inflammation, coagulation, and vasomotor responsiveness and appear to do so independently of changes in LDL-C.

Selection of a statin should be based on the extent of LDL-C reduction that is desired, cost and other relevant patient factors. The concept that lower is better, although likely to a certain extent, has not been proven and we await results of studies aimed specifically at answering this question. Based on their potency, safety profile and pleiotropic actions, statins are often the drug of choice in the treatment of hypercholesterolemia.

Bile acid sequestrants or resins are agents that bind bile acids in the intestine, preventing their reabsorption in the terminal ileum, and reduce the hepatic pool of bile acids that leads to increased intracellular conversion of cholesterol to bile acids in hepatocytes. This transient decrease in intracellular cholesterol leads to a compensatory increase in HMG CoA reductase activity, increased synthesis and expression of the LDL receptor, and a subsequent increase in the catabolism of LDL particles. The efficacy of this class of drugs is offset by the increase that occurs in HMG CoA reductase activity and in cholesterol synthesis. However, use of a statin in combination with a sequestrant prevents the increase in cholesterol synthesis, thereby further augmenting the decrease in LDL-C. The cholesterol reduction that occurs with this combination is the sum of their individual effects. Resins may increase VLDL synthesis and the serum triglyceride levels to a variable degree and may exacerbate or cause hypertriglyceridemia, particularly those with borderline high TG. Resins are inconvenient to use because they have to be mixed with liquids or foods; Palatability and adverse gastrointestinal effects of sequestrants limit use of large doses. The reduction in LDL-C with maximum doses is approximately 30%. Resins are clearly safe and effective cholesterol lowering agents but may interfere with the absorption of various medications. Their primary role at this time is as an adjunct to statin therapy or as monotherapy for children with hypercholesterolemia.

Fibrates are most effective for treating patients with hypertriglyceridemia and reduced HDL-C. The efficacy of these drugs for reducing triglyceride and increasing HDL-C is related to the magnitude of the hypertriglyceridemia. However, the higher the pretreatment triglyceride level, the less likely that it will be normalized by fibrate treatment alone. Despite mild to modest effects on LDL-C, fibrates cause a desirable shift in LDL particle size from small dense (pattern B) to large/buoyant (pattern A). Gemfibrozil reduced CHD events by 35% in the Helsinki Heart Study and by 22% in the Veterans Administration Low High Density Intervention Trial. Drugs of this class reduce triglyceride and increase HDL-C by stimulating peroxisome proliferator activator receptor. The reduction in triglyceride is mediated by enhanced clearance of triglyceride-rich lipoprotein and decreased VLDL synthesis. Changes in HDL-C and the size of the LDL particle may be secondary to reduced triglyceride levels and/or to increased synthesis of apo A-I and apo A-II.

Niacin is a drug that reduces Lp(a), LDL-C, and triglyceride and increases HDL-C and LDL particle size, all desirable antiatherosclerotic changes. It is available in

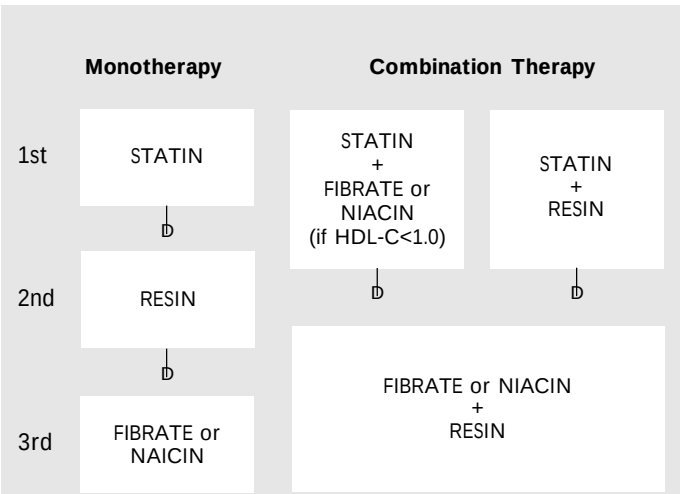
immediate-release and delayed-release preparations. Its major adverse effects have in the past limited its use. These adverse effects are hot flushes, pruritus, gastric irritation, hepatotoxicity and worsening of glucose homeostasis. Niacin also increases serum homocysteine and uric acid levels. Some patients tolerate the immediate-release preparations (approximately 50%), and a greater percent (85%) tolerate the delayed-release preparations. Niacin has been used very effectively alone and in combination with statins as well as with bile acids sequestrants.

Cholesterol absorption inhibitor, ezetimibe is the first drug of this class, was approved for cholesterol lowering. It interferes with the absorption of cholesterol, and when used as monotherapy, reduces LDL-C by 15–20%. It is also effective in patients on a low saturated fat and low cholesterol diet because it blocks reabsorption of cholesterol secreted into bile and the enterohepatic circulation of endogenously produced cholesterol. The reduction in LDL-C is due to increased endogenous catabolism of LDL. Its effects on triglyceride and HDL-C levels are minimal. It can be used very effectively in combination with statins.

The following are 3 suggested algorithms for the common forms of hyperlipidemia.

ALGORITHM 1

Algorithm for Lipoprotein Phenotype IIa (LDL-CkTGk2.8)

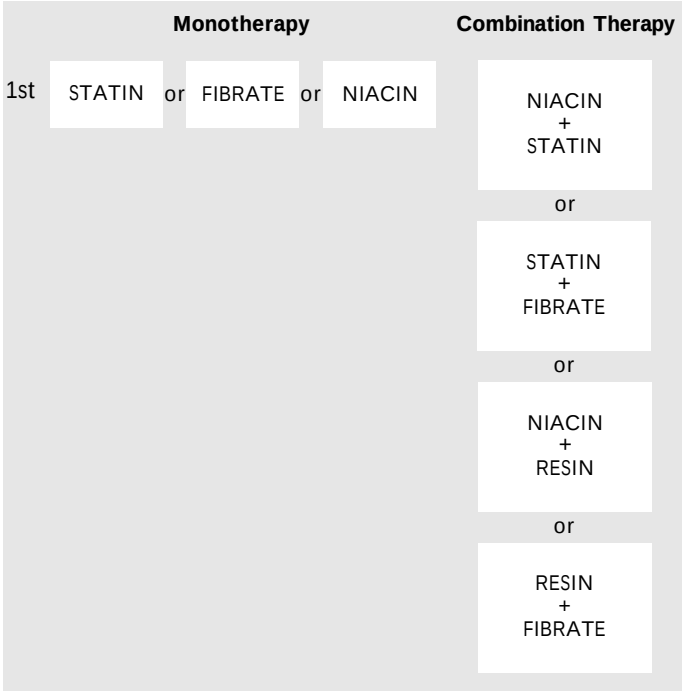


Choice of first line therapy will depend on:
(1) Precaution or contraindiction against use of certain lipid lowering drugs
(2) Ability of patient to tolerate certain lipid lowering drugs
(3) Adverse effects due to certain lipid lowering drugs.

Step progression from 1st to 2nd to 3rd choice is considered when therapeutic goals are not achieved, in which case combination therapy will be considered.

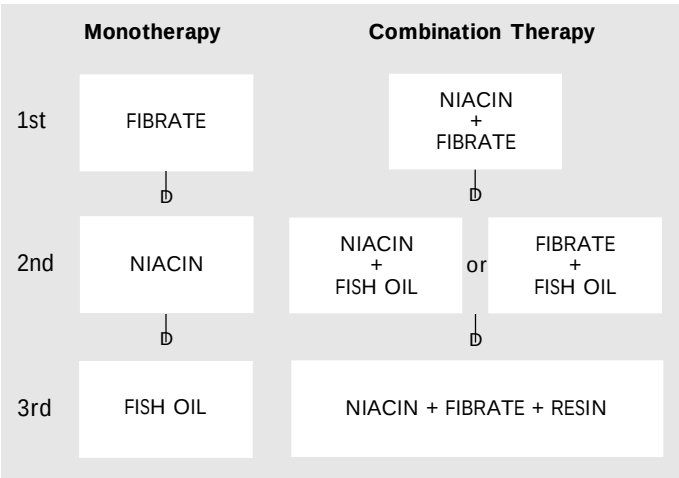
ALGORITHM 2

Algorithm for Lipoprotein Phenotype IIb (LDL-C 3.4 TG O 2.8–4.8)



ALGORITHM 3

Algorithm for Lipoprotein Phenotype IV [(LDL-C < 3.4 and TG 2.8–4.5) or (TG 4.5–11.2 regardless of LDL-C)] and Phenotype V with TG > 11.2



The efficacy of each group of lipid lowering therapy is outlined in Table 1.

Table 1. Efficacy Lipid Lowering Agents

Drug	LDL-C (↓)	HDL-C (↑)	TG (↓)
Statins	18–70%	5–15%	7–30%
Resins	15–30%	3–5%	–/↑
[redacted]	5–25%	10–20%	20–50%
	5–25%	15–35%	20–50%
	15–20%	1–5%	5–10%

MONITORING PATIENTS ON LIPID LOWERING THERAPY

Table 2 shows one protocol used for monitoring patients on lipid lowering therapy.

Table 2. Protocol for Monitoring Patients on Lipid Lowering Therapy

Drug	If titrating or dose not met		If goal met	
	Lipids	LFTS	Lipids	LFT
HMG CoA Reductase Inhibitors	At 6-12 week intervals until goal met		3mthly x 2, then 6mthly x 2, then yearly	At 6-12w (if recent dose change) then 6-12mthly
Fibrates	At 6-12week intervals until goal met		3mthly x 2, then 6mthly x 2, then yearly	At 6-12w (if recent dose change) then 6-12mthly
Niacin	At 6-12w intervals until goal met	6-12w, then 6-12mthly, then yearly	3mthly x 2, then 6mthly x 2, then yearly	At 6-12w (if recent dose change) then 6-12mthly
Combination therapy (any 2 of : statins/niacin/fibrate)	At 6-8w intervals until goal met		3mthly x 2, then 6mthly x 2, then yearly	At 6-12w (if recent dose change) then 6-12mthly

LEARNING POINTS

- Dyslipidemia is one of the most important modifiable risk factors for CHD. Despite the availability of highly effective lipid-modifying agents, many patients still do not reach lipid targets established by National guidelines
- Reduction of LDL-C by 50–70% is possible with statin monotherapy or the use of statins in combination with other lipid lowering agents. Combination of statins with fibrates or niacin should be considered for patients with persisting dyslipidemia and undesirable non-HDL-C levels who are at high risk for CHD events
- Physicians should always keep in mind that treatment is aimed at reducing ASCVD as a whole and not just reducing hyperlipidemia
- Thus vigilance for screening and treating all the major risk factors will yield maximum benefit to the patient.

RECOMMENDED READINGS

1. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA.* 2001; 285:2486-97.

2. Wong ND, Ridker PM. Preventive Cardiology: Wong ND and Kashyap ML. Cholesterol and Lipids. New York, NY: McGraw-Hill; 2000.

3. V Fuster, R. Ross, and EJ Topol. Atherosclerosis and Coronary Artery Disease. Lippincott-Raven Publsihers. Philadelphia; 1996.