
Pharmacotherapy of Dyslipidemia

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Definition

- **Dyslipidemia** is defined as:
 - elevated total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, or triglycerides (TG)
 - a low high-density lipoprotein (HDL) cholesterol or
 - a combination of these abnormalities.
- **Hyperlipoproteinemia**
 - an increased concentration of the lipoprotein macromolecules that transport lipids in the plasma.

Pathophysiology

- **Cholesterol:** essential for cell membrane formation & hormone synthesis
- Lipids not present in free form in plasma; circulate as lipoproteins
- 3 major plasma lipoproteins:
 - **VLDL** carries ~10 to 15 % of total serum cholesterol; carried in circulation as TG; $VLDL = TG/5$
 - **LDL** carries 60 to 70% of total serum cholesterol; IDL is also included in this group
 - **HDL** carries 20 to 30% of total serum cholesterol; reverse transportation of cholesterol

Cont...

- Elevated TC & LDL and reduced HDL cholesterol are associated with the development of **coronary heart disease (CHD)**.

Cont...

- The **response-to-injury hypothesis** states that the following risk factors lead to endothelial dysfunction and a series of cellular interactions that culminate in **atherosclerosis**.
 - oxidized LDL
 - mechanical injury to the endothelium
 - excessive homocysteine
 - immunologic attack or
 - infection-induced changes in endothelial and intimal function

Cont...

- **The eventual clinical outcomes may include:**
 - Angina
 - myocardial infarction
 - Arrhythmias
 - Stroke
 - peripheral arterial disease
 - abdominal aortic aneurysm and sudden death.

Cont...

- **Once in the artery wall,**
 - LDL is chemically modified through oxidation and non enzymatic glycation.
 - Mildly oxidized LDL then recruits monocytes into the artery wall.
 - These monocytes then become transformed into macrophages that accelerate LDL oxidation.

Cont...

- Fredrickson-Levy-Lees classification of primary/genetic hyperlipoproteinemia

Type	Lipoprotein Elevation
I	Chylomicrons
IIa	LDL
IIb	LDL + VLDL
III	IDL (LDL ₁)
IV	VLDL
V	VLDL + Chylomicrons

IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

Lipoprotein Abnormalities: 2° Causes

Hypercholesterolemia

- hypothyroidism
- obstructive liver disease
- nephrotic syndrome
- anorexia nervosa
- acute intermittent porphyria

Medications

- progestins
- thiazide diuretics
- glucocorticoids
- β -blockers
- isotretinoin
- protease inhibitors
- cyclosporine
- mirtazipine
- sirolimus

Cont...

Hypertriglyceridemia

- obesity
- DM
- lipodystrophy
- glycogen storage disease
- ileal bypass surgery
- sepsis
- pregnancy
- monoclonal gammopathy: multiple myeloma, lymphoma
- acute hepatitis
- systemic lupus erythematosus

Cont...

- **medications**

- alcohol
- estrogens
- isotretinoin
- β -blockers
- glucocorticoids
- bile acid resins
- thiazides
- asparaginase
- interferons
- azole antifungals
- mirtazipine
- anabolic steroids
- sirolimus

Cont...

Low high-density lipoprotein

- malnutrition
- obesity
- medications
 - non-ISA β -blockers
 - anabolic steroids
 - isotretinoin
 - progestins

Clinical Presentations

- Many patients are asymptomatic for many years before the disease is clinically evident
- Patients may manifest the following
 - repeated attacks of pancreatitis and abdominal pain
 - eruptive cutaneous xanthomatosis
 - Hepatosplenomegaly
 - peripheral polyneuropathy

CLINICAL PRESENTATION

General

Most patients are asymptomatic for many years before disease is clinically evident

Patients with the metabolic syndrome may have three or more of the following: abdominal obesity, atherogenic dyslipidemia, increased blood pressure, insulin resistance with or without glucose intolerance, prothrombotic state, or proinflammatory state

Symptoms

None to severe chest pain, palpitations, sweating, anxiety, shortness of breath, loss of consciousness or difficulty with speech or movement, abdominal pain, sudden death

Signs

None to severe abdominal pain, pancreatitis, eruptive xanthomas, peripheral polyneuropathy, high blood pressure, body mass index $>30 \text{ kg/m}^2$ or waist size >40 inches in men (35 inches in women)

Diagnosis

- A **fasting lipoprotein profile** including total cholesterol, LDL, HDL, and triglycerides should be measured in all adults 20 years of age or older at least once every 5 years.
- Two determinations, 1 to 8 weeks apart, are recommended to **minimize variability** and to obtain a reliable baseline.

Cont...

- If the total cholesterol is >200 mg/dL, a second determination is recommended, and if the values are more than 30 mg/dL apart, **the average of three values** should be used.
- Patient evaluation
 - Age
 - Gender (if female, menstrual and estrogen replacement status)
 - physical examination and
 - laboratory investigations

Cont...

- A complete history and physical examination should assess
 - cardiovascular risk factors
 - family history of premature cardiovascular disease or lipid disorders
 - secondary causes of hyperlipidemia
 - presence or absence of symptoms/complications

Desired Outcome

- The goals of treatment are **to lower total and LDL cholesterol** in order to reduce the risk of first or recurrent events such as:
 - Myocardial infarction
 - Angina
 - Heart failure
 - Ischemic stroke or
 - peripheral arterial disease

Treatment:

General Approach

- The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) recommends that a **fasting lipoprotein profile** and **risk factor assessment** be used in the initial classification of adults

TABLE 1

Classification of Total, LDL, and HDL Cholesterol and Triglycerides

Total cholesterol	
<200 mg/dL	Desirable
200–239 mg/dL	Borderline high
≥240 mg/dL	High
LDL cholesterol	
<100 mg/dL	Optimal
100–129 mg/dL	Near or above optimal
130–159 mg/dL	Borderline high
160–189 mg/dL	High
≥190 mg/dL	Very high
HDL cholesterol	
<40 mg/dL	Low
≥60 mg/dL	High
Triglycerides	
<150 mg/dL	Normal
150–199 mg/dL	Borderline high
200–499 mg/dL	High
≥500 mg/dL	Very high

Cont...

- If the total cholesterol is <200 mg/dL, then the patient has a desirable blood cholesterol level
- In patients with borderline-high blood cholesterol (200 to 239 mg/dL), assessment of risk factors is needed to more clearly define disease risk.
- If the HDL is also >40 mg/dL, no further follow-up is recommended for patients without known CHD and who have fewer than two risk factors
- Decisions regarding classification and management are based on the LDL cholesterol levels

TABLE 2 Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals^a

Age

Men: ≥ 45 years

Women: ≥ 55 years or premature menopause without estrogen-replacement therapy

Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative or before 65 years of age in mother or other female first-degree relative)

Cigarette smoking

Hypertension ($\geq 140/90$ mm Hg or on antihypertensive medication)

Low HDL cholesterol (< 40 mg/dL)^b

CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^aDiabetes is regarded as a CHD risk equivalent.

^bHDL cholesterol (≥ 60 mg/dL) counts as a “negative” risk factor; its presence removes one risk factor from the total count.

TABLE 3**LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLCs) and Drug Therapy in Different Risk Categories**

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate TLCs (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 (optional goal: <70)	≥100	≥100 (<100: consider drug options) ^a
Moderately high risk: 2+ risk factors (10-year risk 10–20%)	<130	≥130	≥130 (100–129: consider drug options)
Moderate risk: 2+ risk factors (10-year risk <10%)	<130	≥130	≥160
Lower risk: 0–1 risk factor ^b	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

CHD, coronary heart disease; LDL, low-density lipoprotein.

^aSome authorities recommend use of LDL-lowering drugs in this category if LDL cholesterol <100 mg/dL cannot be achieved by TLCs. Others prefer to use drugs that primarily modify triglycerides and HDL (e.g., nicotinic acid or fibrates). Clinical judgment also may call for deferring drug therapy in this subcategory.

^bAlmost all people with 0–1 risk factor have a 10-year risk <10%; thus 10-year risk assessment in people with 0–1 risk factor is not necessary.

Cont...

- ATP III recognizes the **metabolic syndrome** as a secondary target of risk reduction after LDL-C has been addressed.
- This syndrome is characterized by:
 - abdominal obesity
 - atherogenic dyslipidemia (elevated triglycerides, small LDL particles, low HDL cholesterol)
 - increased blood pressure
 - insulin resistance (with or without glucose intolerance) and
 - prothrombotic and proinflammatory states.
- If the metabolic syndrome is present, the patient is considered to have a **CHD risk equivalent**.

Treatment:

Non-pharmacologic Therapy

- Initial treatment for any lipoprotein disorder is TLC (Therapeutic Lifestyle Changes)
 - restricted total fats, saturated fats, cholesterol intake
 - modest increase in polyunsaturated fat
 - increased soluble fiber intake
 - exercise: moderate intensity 30 min/day most days
 - caution in high risk patients or those with CAD
 - weight reduction (initial goal of 10%) if needed
 - smoking cessation
 - treat HTN

TABLE 4**Macronutrient Recommendations for the Therapeutic Lifestyle Change Diet**

Component^a	Recommended Intake
Total fat	25–35% of total calories
Saturated fat	<7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Carbohydrates ^b	50–60% of total calories
Cholesterol	<200 mg/day
Dietary fiber	20–30 g/day
Plant sterols	2 g/day
Protein	Approximately 15% of total calories
Total calories	To achieve and maintain desirable body weight

^aCalories from alcohol not included.

^bCarbohydrates should derive from foods rich in complex carbohydrates, such as whole grains, fruits, and vegetables.

Cont...

- If all recommended dietary changes from the NCEP were instituted, the estimated average reduction in LDL would range from **20% to 30%**.

Treatment:

Pharmacologic Therapy

Bile Acid Resins (Cholestyramine, Colestipol, Colesevelam)

- The primary action of BARs is to bind intestinal bile acid
 - Increase fecal bile excretion
 - Stimulate bile acid synthesis from cholesterol
 - Up regulate LDL receptors
 - But increases hepatic VLDL production

Cont...

- GI complaints most commonly reported are:
 - Constipation
 - Bloating
 - epigastric fullness
 - Nausea and
 - flatulence
- These adverse effects can be managed by
 - increasing fluid intake
 - using stool softeners

Cont...

- Other potential adverse effects include
 - impaired absorption of fat-soluble vitamins A, D, E & K
 - hyponatremia and hyperchloremia
 - GI obstruction and reduced bioavailability of acidic drugs such as
 - warfarin, nicotinic acid, thyroxine, acetaminophen, hydrocortisone, hydrochlorothiazide, loperamide, and possibly iron.
 - Drug interactions may be avoided by alternating administration times with an interval of 6 hours or greater between the BAR and other drugs.

Niacin (nicotinic acid)

- Reduces the hepatic synthesis of VLDL, which in turn leads to a reduction in the synthesis of LDL.
- Also **increases HDL** by reducing its catabolism.
- The principal use of niacin is
 - for mixed hyperlipidemia or as a second-line agent in combination therapy for hypercholesterolemia.
- It is a first-line agent or alternative for the treatment of hypertriglyceridemia and diabetic dyslipidemia.

Cont...

- Niacin has many **common adverse drug reactions**;
 - most of the symptoms and biochemical abnormalities seen do not require discontinuation of therapy.
- **Cutaneous flushing and itching** appear to be prostaglandin mediated
 - can be reduced by taking aspirin 325 mg shortly before niacin ingestion.
 - Taking the niacin dose with meals and slowly titrating the dose upward may minimize these effects.

Cont...

- Concomitant alcohol and hot drinks may magnify the flushing and pruritus from niacin
 - they should be avoided at the time of ingestion.
- **GI intolerance** is also a common problem.
- Potentially important laboratory abnormalities occurring with niacin therapy include
 - elevated liver function tests
 - hyperuricemia and
 - hyperglycemia

Cont...

- Niacin-associated hepatitis is more common with **sustained-release preparations** and their use should be restricted to patients intolerant of regular-release products.
- Niacin is contraindicated in patients with active **liver disease**, and it may exacerbate preexisting gout and diabetes.

HMG-CoA Reductase Inhibitors

**(Atorvastatin, Fluvastatin, Lovastatin, Pravastatin,
Rosuvastatin, Simvastatin)**

- Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase,
 - interrupting the conversion of HMG-CoA to mevalonate, the rate-limiting step in de novo cholesterol biosynthesis.
 - Reduced synthesis of LDL and enhanced catabolism of LDL mediated through LDL-Rs appear to be the principal mechanisms for lipid-lowering effects.

Cont...

- When used as monotherapy, statins are the **most potent** total and LDL cholesterol-lowering agents and among the **best tolerated**.
- Total and LDL cholesterol are reduced in a dose-related fashion by **30% or more** when added to dietary therapy.

Cont...

- Combination therapy with a **statin and BAR** is rational because numbers of LDL-Rs are increased, leading to
 - greater degradation of LDL cholesterol
 - intracellular synthesis of cholesterol is inhibited and
 - enterohepatic recycling of bile acids is interrupted.
- Combination therapy with a **statin and ezetimibe** is also rational because
 - ezetimibe inhibits cholesterol absorption across the gut border and adds 12% to 20% further reduction when combined with a statin or other drugs

Cont...

- **Adverse effects**

- Constipation, in fewer than 10% of patients
- elevated serum aminotransferase levels (primarily alanine aminotransferase (ALT))
- elevated creatine kinase levels
- Myopathy and rarely
- rhabdomyolysis

Statin Choice

Choose medication and dose to achieve the desired LDL-C reduction intensity

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
<i>Lowers LDL-C $\geq 50\%$</i>	<i>Lowers LDL-C 30-50%</i>	<i>Lowers LDL-C $< 30\%$</i>
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 10-40 mg- FDA does not recommend use of simvastatin 80 mg due to increased risk of myopathy Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg* Fluvastatin 40 mg BID Pitavastatin 2-4 mg*	Simvastatin 10 mg* Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg * Pitavastatin 1 mg*

* Never tested in RCT

Fibric Acids

(Gemfibrozil, Fenofibrate, Clofibrate)

- Fibrate monotherapy is effective in **reducing VLDL**,
 - But a reciprocal rise in LDL may occur and total cholesterol values may remain relatively unchanged.
 - Plasma HDL concentrations may rise 10% to 15% or more with fibrates.

Cont...

- **Adverse effects**

- GI complaints occur in 3% to 5% of patients
- rash in 2%, dizziness in 2.4% and
- transient elevations in transaminase levels and alkaline phosphatase in 4.5% and 1.3%, respectively.
- Clofibrate and, less commonly, gemfibrozil may enhance the formation of gallstones.

Cont...

- **A myositis syndrome**
 - myalgia, weakness, stiffness, malaise, and elevations in creatine kinase and aspartate aminotransferase may occur and seems to be more common **in patients with renal insufficiency**
- Fibrates may potentiate the effects of oral anticoagulants
 - the international normalized ratio (INR) should be monitored very closely with this combination.

Ezetimibe

- Ezetimibe interferes with the absorption of cholesterol from the intestine
- It is approved as both monotherapy and for use with a statin.
- The dose is 10 mg once daily, given with or without food.
- When used alone, it results in an approximate 18% reduction in LDL cholesterol.

Cont...

- When added to a statin, ezetimibe lowers LDL by about an additional 12% to 20%.
- A combination product (**Vytorin**) containing ezetimibe 10 mg and simvastatin 10, 20, 40, or 80 mg is available.
- Ezetimibe is well tolerated; approximately 4% of patients experience GI upset

Cont...

- Because cardiovascular outcomes with ezetimibe have not been evaluated,
 - it should be reserved for patients unable to tolerate statin therapy or
 - those who do not achieve satisfactory lipid lowering with a statin alone.

TABLE 5**Effects of Drug Therapy on Lipids and Lipoproteins**

Drug	Mechanism of Action	Effects on Lipids	Effects on Lipoproteins
Cholestyramine, colestipol, colesevelam	↑ LDL catabolism ↓ Cholesterol absorption	↓ Cholesterol	↓ LDL ↑ VLDL
Niacin	↓ LDL and VLDL synthesis	↓ Triglyceride ↓ Cholesterol	↓ VLDL, ↓ LDL, ↑ HDL
Gemfibrozil, fenofibrate, clofibrate	↑ VLDL clearance ↓ VLDL synthesis	↓ Triglyceride ↓ Cholesterol	↓ VLDL, ↓ LDL, ↑ HDL
Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin	↑ LDL catabolism ↓ LDL synthesis	↓ Cholesterol	↓ LDL
Ezetimibe	Blocks cholesterol absorption across the intestinal border	↓ Cholesterol	↓ LDL

Fish Oil Supplementation

- Diets high in omega-3 polyunsaturated fatty acids (from fish oil), most commonly eicosapentaenoic acid (EPA),
 - reduce cholesterol, triglycerides, LDL, and VLDL and
 - may elevate HDL cholesterol.
- Fish oil supplementation may be most useful in patients with hypertriglyceridemia

Cont...

- **Lovaza** (omega-3-acid ethyl esters)
 - a prescription form of concentrated fish oil EPA 465 mg and docosahexaenoic acid 375 mg.
 - The daily dose is 4 g/day, which can be taken as four 1-g capsules once daily or two 1-g capsules twice daily.
 - This product lowers triglycerides by 14% to 30% and raises HDL by about 10%.
- Complications of fish oil supplementation such as **thrombocytopenia** and **bleeding disorders** have been noted, especially with high doses

Combination Drug Therapy

- Combination therapy may be considered
 - after adequate trials of monotherapy and for patients documented to be adherent to the prescribed regimen.
- **Two or three** lipoprotein profiles at **6-week intervals** should confirm lack of response prior to initiation of combination therapy.

Cont...

- **Contraindications to and drug interactions** with combined therapy should be screened carefully, and the extra cost of drug product and monitoring should be considered.
- In general, a **statin plus a BAR** or **niacin plus a BAR** provide the **greatest** reduction in total and LDL cholesterol.

Cont...

- Regimens intended to increase HDL levels should include either **gemfibrozil** or **niacin**,
 - statins combined with either of these drugs may result in a greater incidence of hepatotoxicity or myositis.

TABLE 6 Lipoprotein Phenotype and Recommended Drug Treatment		
Lipoprotein Type	Drug of Choice	Combination Therapy
I	Not indicated	—
IIa	Statins	Niacin or BARs
	Cholestyramine or colestipol	Statins or niacin
	Niacin	Statins or BARs
		Ezetimibe
IIb	Statins	BARs, fibrates, or niacin
	Fibrates	Statins or niacin or BARs ^a
	Niacin	Statins or fibrates
		Ezetimibe
III	Fibrates	Statins or niacin
	Niacin	Statins or fibrates
		Ezetimibe
IV	Fibrates	Niacin
	Niacin	Fibrates
V	Fibrates	Niacin
	Niacin	Fish oils

BARs, bile acid resins; fibrates include gemfibrozil or fenofibrate.

^aBARs are not used as first-line therapy if triglycerides are elevated at baseline because hypertriglyceridemia may worsen with a BAR alone.

TABLE 7**Comparison of Drugs Used in the Treatment of Hyperlipidemia**

Drug	Dosage Forms	Usual Daily Dose	Maximum Daily Dose
Cholestyramine (Questran)	Bulk powder/4-g packets	8 g three times daily	32 g
Cholestyramine (Cholybar)	4 g resin per bar	8 g three times daily	32 g
Colestipol hydrochloride (Colestid)	Bulk powder/5-g packets	10 g twice daily	30 g
Colesevelam (Welchol)	625-mg tablets	1,875 mg twice daily	4,375 mg
Niacin	50-, 100-, 250-, and 500-mg tablets; 125-, 250-, and 500-mg capsules	2 g twice daily	9 g
Extended-release niacin (Niaspan)	500-, 750-, and 1,000-mg tablets	500 mg	2,000 mg
Extended-release niacin + lovastatin (Advicor)	Niacin/lovastatin 500-mg/20-mg tablets	500 mg/20 mg	1,000 mg/20 mg
	Niacin/lovastatin 750-mg/20-mg tablets	—	—
	Niacin/lovastatin 1,000-mg/20-mg tablets	—	—

Fenofibrate (Tricor)	67-, 134-, and 200-mg capsules (micronized); 54- and 160-mg tablets	54 mg or 67 mg	201 mg
Gemfibrozil (Lopid)	300-mg capsules	600 mg twice daily	1.5 g
Lovastatin (Mevacor)	20- and 40-mg tablets	20–40 mg	80 mg
Pravastatin (Pravachol)	10-, 20-, 40-, and 80-mg tablets	10–20 mg	40 mg
Simvastatin (Zocor)	5-, 10-, 20-, 40-, and 80-mg tablets	10–20 mg	80 mg
Atorvastatin (Lipitor)	10-, 20-, 40-, and 80-mg tablets	10 mg	80 mg
Rosuvastatin (Crestor)	5-, 10-, 20-, and 40-mg tablets	5 mg	40 mg
Ezetimibe (Zetia)	10-mg tablet	10 mg	10 mg
Simvastatin/ezetimibe (Vytorin)	Simvastatin/ezetimibe 10 mg/10 mg, 20 mg/10 mg, 40 mg/10 mg, and 80 mg/10 mg	Simvastatin/ezetimibe 20 mg/10 mg —	Simvastatin/ ezetimibe 80 mg/10 mg —

Gemfibrozil, fenofibrate, and lovastatin are available as generic products. This table does not include all drugs used for treating dyslipidemia.

Treatment of Diabetic Dyslipidemia

- Diabetic dyslipidemia is characterized by
 - Hypertriglyceridemia
 - low HDL and
 - minimally elevated LDL
- ATP III considers diabetes to be a CHD risk equivalent, and the primary target is to lower the LDL to <100 mg/dL.
- **Statins are considered by** many to be the drugs of choice because the primary target is LDL.

Evaluation of Therapeutic Outcomes

- Short-term evaluation of therapy for hyperlipidemia is
 - based on response to diet and drug treatment as measured in the clinical laboratory by **TC, LDL-C, HDL-C, and TG**.
- Many patients treated for primary hyperlipidemia have no symptoms or clinical manifestations of a genetic lipid disorder, so monitoring is **solely laboratory based**.

Cont...

- In patients treated for secondary intervention, symptoms of atherosclerotic cardiovascular disease, such as angina or intermittent claudication, may improve **over months to years.**
- Xanthomas or other external manifestations of hyperlipidemia should regress with therapy.

Cont...

- Monitoring is needed every few months during dosage titration.
- Once the patient is stable, monitoring at intervals of 6 months to 1 year is sufficient.
- Adverse effects of drugs monitored

Cont...

- **For statins**
 - Patients receiving statins should have a fasting panel **4 to 8 weeks** after the initial dose or dose changes.
 - Liver function tests should be obtained at baseline and periodically thereafter based on package insert information.
 - Some experts believe that monitoring for hepatotoxicity and myopathy should be triggered by symptoms.

Cont...

- Patients with multiple risk factors and established CHD should also be monitored and evaluated for progress in managing their other risk factors such as
 - blood pressure control
 - smoking cessation
 - exercise and weight control and
 - glycemic control (if diabetic).

Cont...

- Evaluation of dietary therapy with diet diaries and recall survey instruments allows information about diet to be collected in a systematic fashion and may improve patient adherence to dietary recommendations.

