IV. DRUGS THAT LOWER PLASMA LIPIDS [ANTIHYPERLIPIDEMIC DRUGS]

أ- **نظرة عامّة :**

١. إنّ إنقاص كولِسْتيرول C البلازما المرتفع ، تغذويّاً أو دوائيّاً ينقص إختطار التَصَلُّبُ العَصيدِيّ atherosclerosis والمرض القلبي التاجي CHD الناجم عنه .

2. إرتفاع ثُلاَثِيُّات الغليسريد TGs يسبّب إلتهاب بنكرياس مهدّد للحياة ....

٣. فَرْطُ بروتيناتِ الدَّمِ الشَّحْمِيَّة hyperlipoproteinemias :

(أ)- ينقل الـ C في البلازما في جسيمات لبّها كاره للماء من إسترات الكوليسترول و ثُلاَثِيّات الغليسريد TGs ومحاطة بغلاف فسفولبيدي و C حرّ ، وواحد أو أكثر من صميم بروتيني apoproteins . وتفرّق جسيمات البروتين الشحمي هذه بنسبة الـ TG إلى إسترات C وبنمط الصميم البروتيني إلى **LDL و VLDL و IDL و HDL .**

(ب)- يتجلّى مرض شحوم البلازما بارتفاع الـ **TGs** أوالـ **C** . **ويرتفع كلاهما** بحالات معقّدة .

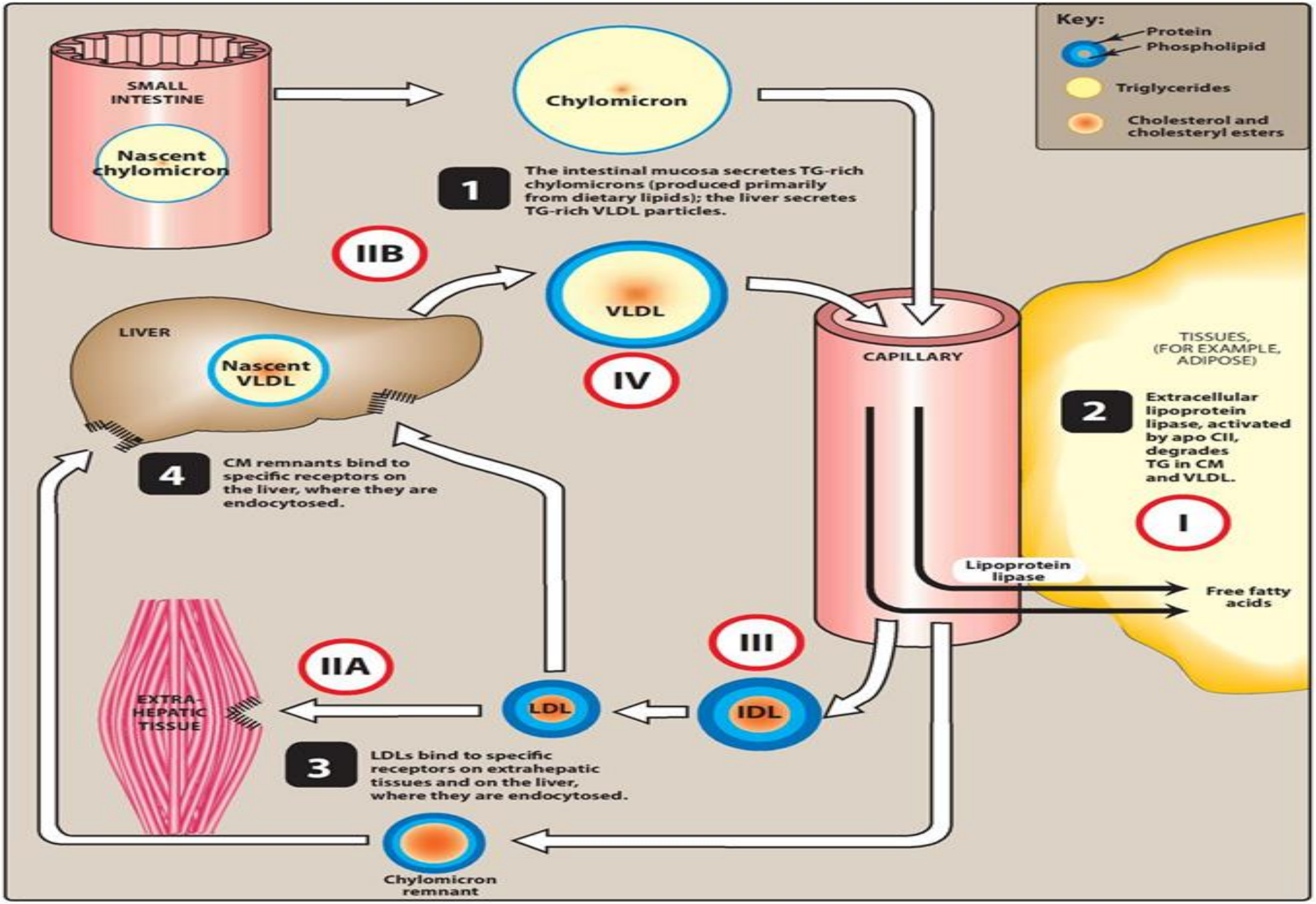
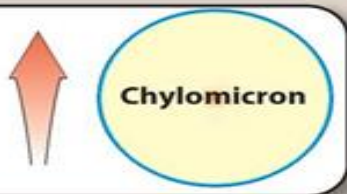


Figure 23.2
Metabolism of plasma lipoproteins and related genetic diseases. Roman numerals in the *white circles* refer to specific genetic types of hyperlipidemias summarized on the facing page. CM = chylomicron; TG = triglyceride; VLDL = very–low-density lipoprotein; LDL = low-density lipoprotein; IDL = intermediate-density lipoprotein; apo CII = apolipoprotein CII found in chylomicrons and VLDL. (Figure continues on next page.)

Type I (FAMILIAL HYPERCHYLOMICRONEMIA)

- Massive fasting hyperchylomicronemia, even following normal dietary fat intake, resulting in greatly elevated serum TG levels.
- Deficiency of lipoprotein lipase or deficiency of normal apolipoprotein CII (rare).
- Type I is not associated with an increase in coronary heart disease.
- Treatment: Low-fat diet. No drug therapy is effective for Type I hyperlipidemia.



Type IIA (FAMILIAL HYPERCHOLESTEROLEMIA)

- Elevated LDL with normal VLDL levels due to a block in LDL degradation. This results in increased serum cholesterol but normal TG levels.
- Caused by defects in the synthesis or processing of LDL receptors.
- Ischemic heart disease is greatly accelerated.
- Treatment: Diet. Heterozygotes: *Cholestyramine* and *niacin*, or a statin.

Type IIB (FAMILIAL COMBINED [MIXED] HYPERLIPIDEMIA)

- Similar to Type IIA except that VLDL is also increased, resulting in elevated serum TG as well as cholesterol levels.
- Caused by overproduction of VLDL by the liver.
- Relatively common.
- Treatment: Diet. Drug therapy is similar to that for Type IIA .

Type III (FAMILIAL DYSBETALIPOPROTEINEMIA)

- Serum concentrations of IDL are increased, resulting in increased TG and cholesterol levels.
- Cause is either overproduction or underutilization of IDL due to mutant apolipoprotein E.
- Xanthomas and accelerated vascular disease develop in patients by middle age.
- Treatment: Diet. Drug therapy includes *niacin* and *fenofibrate*, or a statin.

Type IV (FAMILIAL HYPERTRIGLYCERIDEMIA)

- VLDL levels are increased, whereas LDL levels are normal or decreased, resulting in normal to elevated cholesterol, and greatly elevated circulating TG levels.
- Cause is overproduction and/or decreased removal of VLDL and TG in serum.
- This is a relatively common disease. It has few clinical manifestations other than accelerated ischemic heart disease. Patients with this disorder are frequently obese, diabetic, and hyperuricemic.
- Treatment: Diet. If necessary, drug therapy includes *niacin* and/or *fenofibrate*.

Type V (FAMILIAL MIXED HYPERTRIGLYCERIDEMIA)

- Serum VLDL and chylomicrons are elevated. LDL is normal or decreased. This results in elevated cholesterol and greatly elevated TG levels.
- Cause is either increased production or decreased clearance of VLDL and chylomicrons. Usually, it is a genetic defect.
- Occurs most commonly in adults who are obese and/or diabetic.
- Treatment: Diet. If necessary, drug therapy includes *niacin*, and/or *fenofibrate*, or a statin.

Figure 23.2 (Continued)

Figure 22.1 Summary of antihyperlipidemic drugs. HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; OTC = over-the-counter; PCSK9 = proprotein convertase

ب- الأدوية المفيدة في علاج فرط شحوم الدم :

١. مثبطات الـ 3-hydroxy 3-methyl glutaryl-coenzyme A reductase [HMG-CoA reductase] (statins) :

Lovastatin [mevinolin] [Mevacor] , **simvastatin** [Zocor] , **pravastatin** [Pravachol] , **fluvastatin** [Lescol] , **atorvastatin** [Lipitor] , and **rosuvastatin** [Crestor] lower LDL cholesterol and total cholesterol .

آليّة الفعل MOA : مثبّطات تنافسيّة للإنزيم المحدّد لمعدّل تصنيع الكوليستيرول 3-hydroxy 3-methyl glutaryl-coenzyme A reductase [HMG-CoA reductase] . وبنقص تصنيع الـ C تحدث زيادة معاوضة في قبط C البلازما من قبل الكبد عبر زيادة عدد مستقبلات الـ LDL على الكبد . تُنقِصْ الـ C الكلّي ٣٠-٥٠% و LDL-C ٦٠% (rosuvastatin) . تستعمل لخفض C الدم العائلي وغيره . تسبّب إلتهاب العضلات **myositis و إنحلال الربيدات (العضل المخطط)** rhabdomyolysis ، قلق ، هياج ، **سميّة كبديّة وزيادة الـ aminotransferases .**

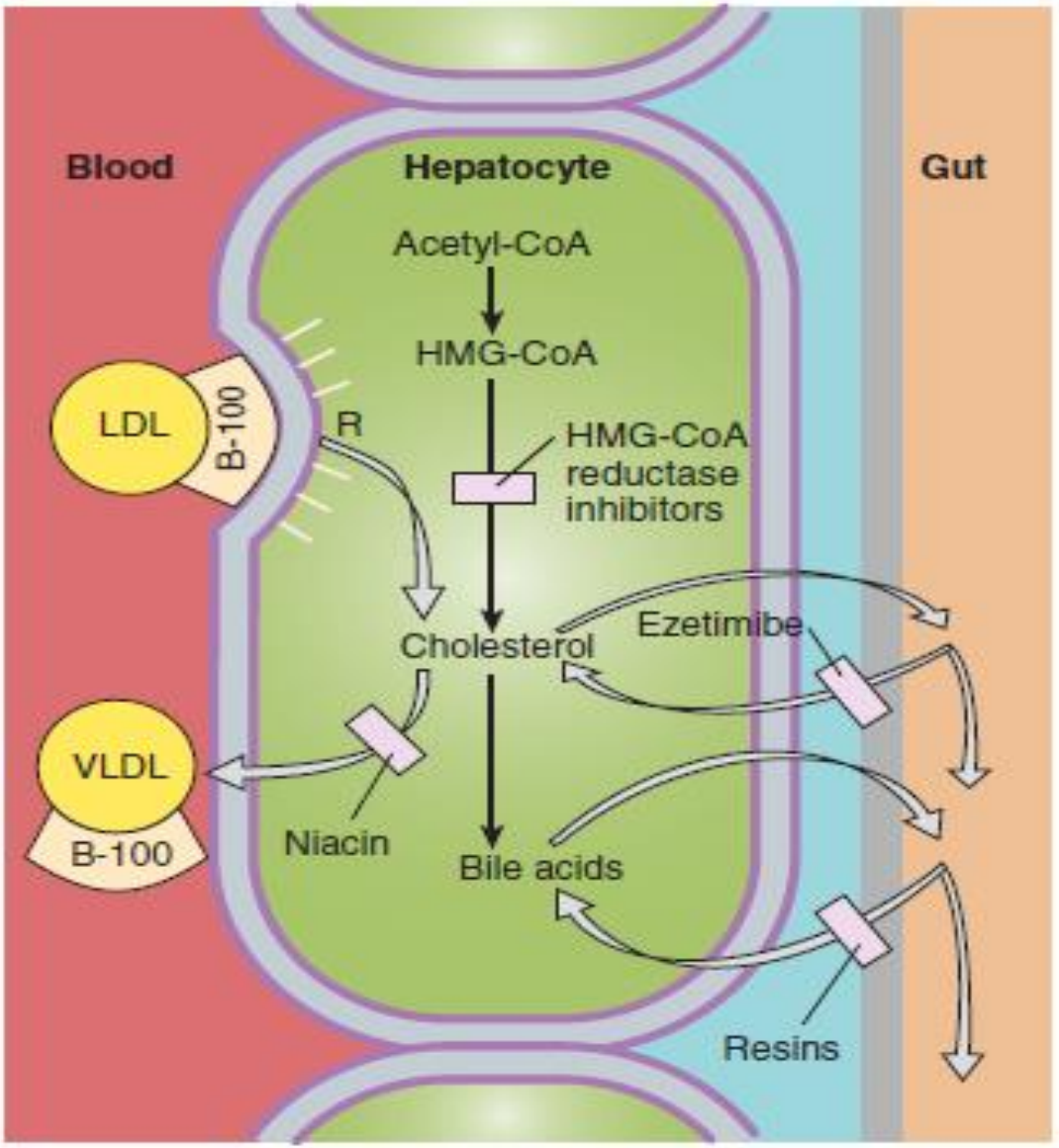


FIGURE 35–2 Sites of action of HMG-CoA reductase inhibitors, niacin, ezetimibe, and resins used in treating hyperlipidemias. Low-density lipoprotein (LDL) receptors are increased by treatment with resins and HMG-CoA reductase inhibitors. VLDL, very-low-density lipoproteins; R, LDL receptor.

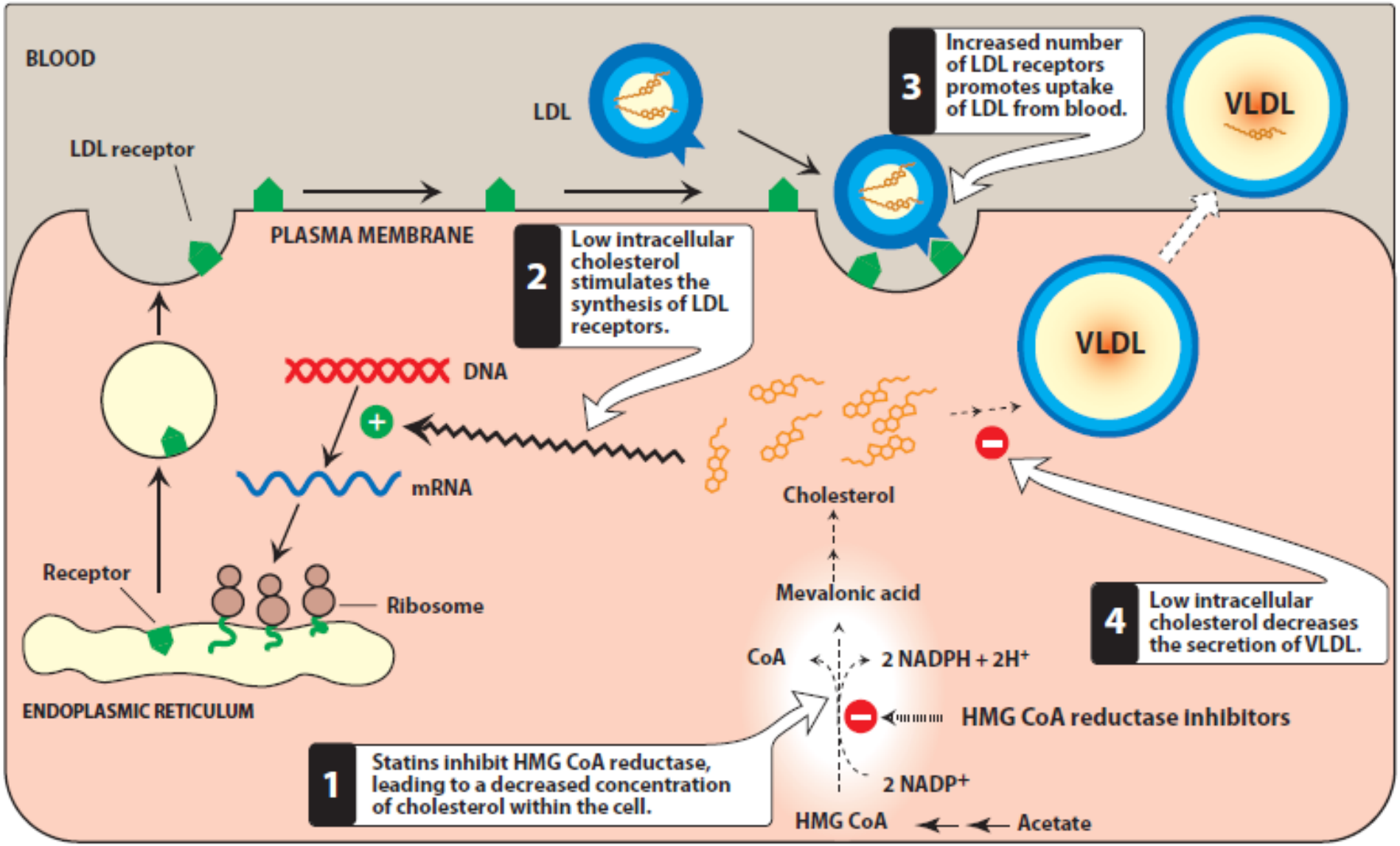


Figure 23.5

Inhibition of HMG CoA reductase by the statin drugs. HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein; VLDL = very–low-density lipoprotein.

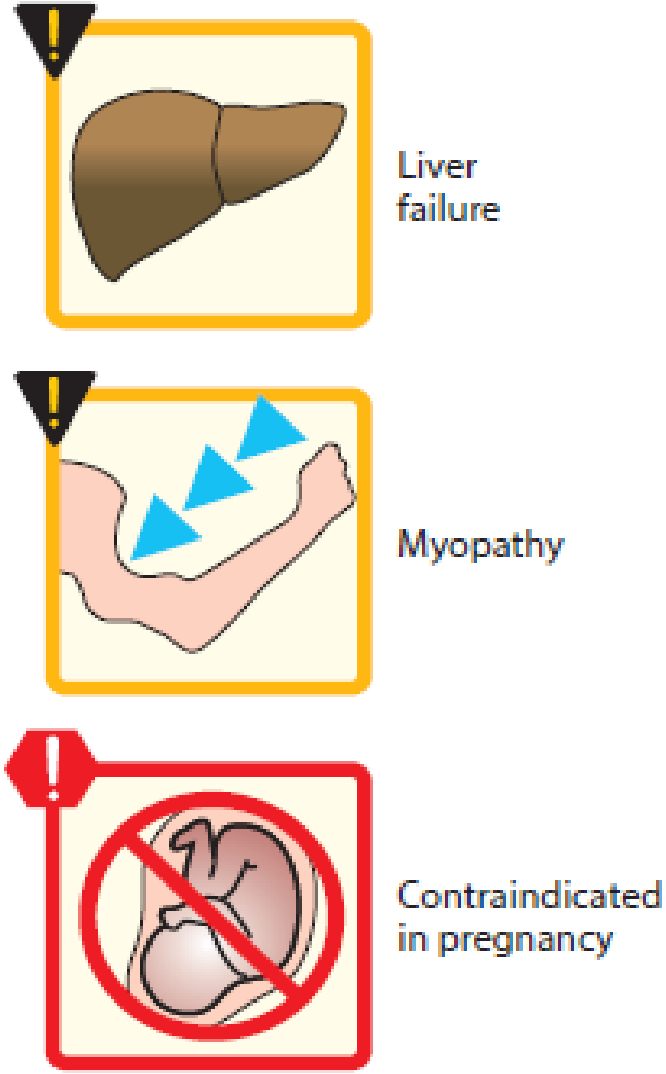


Figure 23.7
Some adverse effects and precautions associated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors.

يتميّز عوز النياسين / الفيتامين B3 (البلاغرا pellagra / داء الذرة/الاعتماد على الذرة "three M's": meat (pork fatback); molasses; and meal (cornmeal).) بالتهاب الجلد dermatitis و الخرف dementia و الإسهال diarrhea (3Ds) . يلاحظ عادةً مع الكحوليّة المزمنة و متلازمة سوء الإمتصاص .. يتواجد في اللحوم الحمراء و السمك و الدجاج والخضار و dairy products

B. *Niacin (nicotinic acid)*

Niacin [NYE-uh-sin] reduces LDL-C by 10% to 20% and is the most effective agent for increasing HDL-C. It also lowers triglycerides by 20% to 35% at typical doses of 1.5 to 3 g/day. *Niacin can be used in combination with* statins, and fixed-dose combinations of long-acting *niacin with lovastatin and simvastatin are available. [Note: the* addition of *niacin to statin therapy has not been shown to reduce the risk of ASCVD events.]*

1. Mechanism of action

At gram doses, *niacin strongly inhibits lipolysis in adipose tissue, thereby reducing production of free fatty acids* (Figure 22.8). The liver normally uses circulating free fatty acids as a major precursor for triglyceride synthesis. Reduced liver triglyceride levels decrease hepatic VLDL production, which in turn reduces LDL-C plasma concentrations.

٢. الـ ***Niacin (nicotinic acid)*** **:** ينقص الـ LDL-C ١٠ — ٢٠% وهو الأقوى في زيادة الـ HDL-C . ينقص الـ TG ٢٠ — ٣٥% بالجرعات ١,٥ — ٣ غ/يوم. يمكن توليفه مع ستاتين. يستعمل بجرعات أصغر كثيراً كفيتامين لمعالجة داء الذرة (بِلاغْرَة) pellagra .

أ. آليّة الفعل : يثبط تحلل الشحم في النسيج الشحمي فينقص إنتاج الأحماض الدهنية الحرة(الشكل ٢٢ .٨) . إذ أنّ الكبد يستخدم الأحماض الدهنية الجائلة طليعةً مهمة لتصنيع الـ TGs. نقص TGs الكبد يُنقِص إنتاج الـ VLDL، مما ينقص تركيز الـ LDL-C في البلازما .

Niacin **inhibits the intracellular lipase** of adipose tissue via receptor-mediated signaling, possibly reducing VLDL production by decreasing the flux of free fatty acids to the liver. Sustained inhibition of lipolysis has not been established, however.

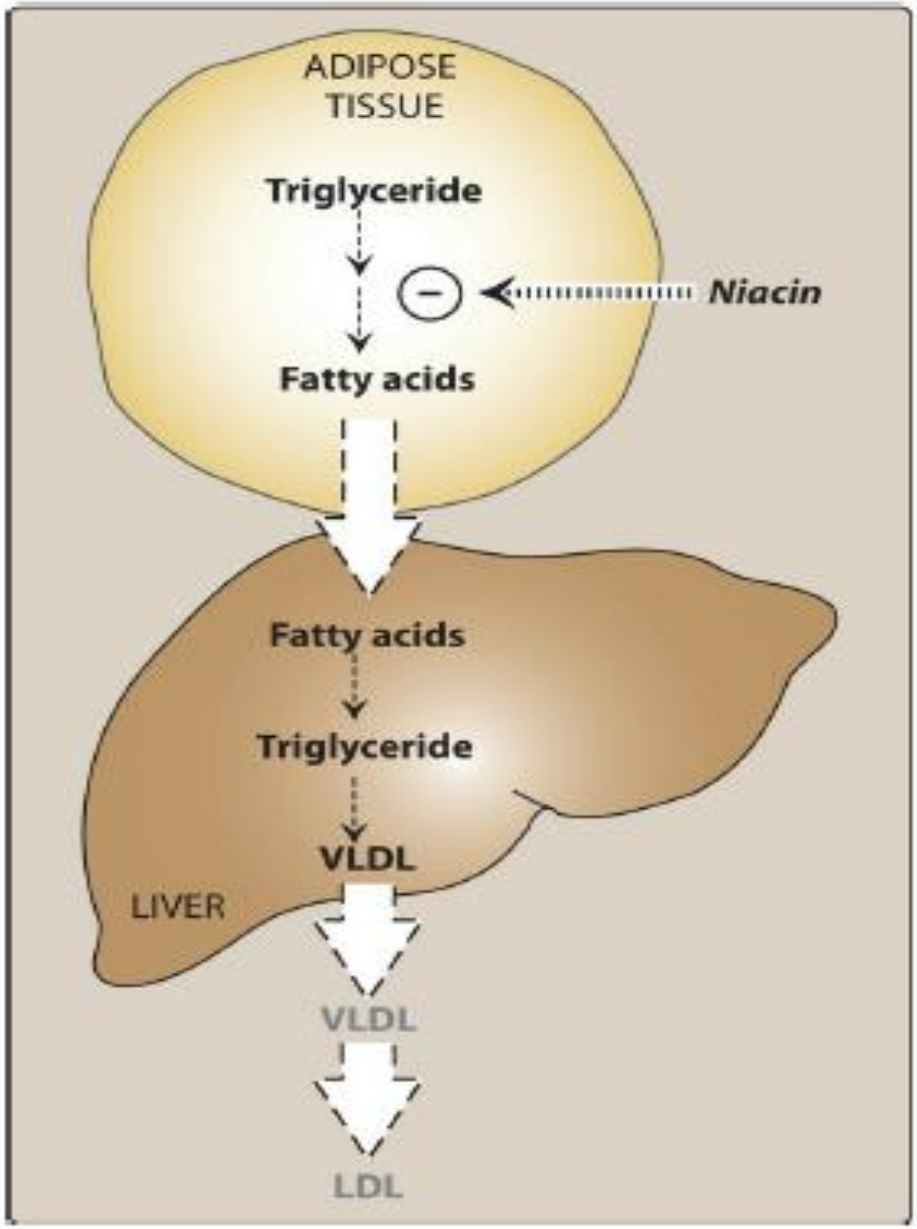


Figure 22.8 *Niacin* inhibits lipolysis in adipose tissue, resulting in decreased hepatic very–low-density lipoprotein (VLDL) synthesis and production of low-density lipoprotein (LDL) in the plasma.

Nicotinic acid : inhibits TG production & **VLDL secretion**. MOA: **affects on lipolysis via a G-protein-coupled orphan receptors called HM74A and present in adipocyte membrane. It also influences hepatic diacylglycerol transferase** .

(ب)- **التأثيرات الضائرة :**

(١)- تورّد ، حكّة أو شعور حرق الجلد (بسبب الـ PG وإطلاق H الذي يمكن تجنبه بأخذ أسبرين قبله بنصف ساعة) . تناوله بعد الوجبات يُنقص أيضاً تأثيراته الجانبيّة .

(٢)- تنشيط الـ transaminase وفرط السكّر و **اضطراب الهضم** وقرحة المعدة وتأثيرات كلويّة ً **إرتفاع حمض اليوريك البلازمي** ووذمة بقعيّة macular edema .

Fibrates : decrease VLDL markedly, and hence TG.

MOA : agonist for a subset of lipid-controlled gene regulatory elements [*PPARs*],*PPARα* (nuclear receptors) increase transcription of gene for lipoprotein lipase,ApoA1 and ApoAs . They increase hepatic LDL-C uptake..

بَيرُوكْسِيّ سابقة في التسميات الكيميائية تدل على وجود أكسجين زائد عن الإشباع

C. Fibrates. *Fenofibrate [fen-oh-FIH-brate] and gemfibrozil [jem-FI-broh-zill] are derivatives of fibric acid that lower serum* triglycerides and increase HDL-C.

1. Mechanism of action

The peroxisome proliferator–activated receptors (PPARs) are members of the nuclear receptor family that regulate lipid metabolism. PPARs function as ligand-activated transcription factors. Upon binding to their natural ligands (fatty acids or eicosanoids) or antihyperlipidemic drugs, PPARs are activated. They then bind to peroxisome proliferator response elements, which ultimately leads to decreased triglyceride concentrations through increased expression of lipoprotein lipase (Figure 22.9) and decreased apolipoprotein (apo) CII concentration. *Fenofibrate is* more effective than *gemfibrozil in lowering triglyceride levels. Fibrates also increase HDL-C by increasing the* expression of apo AI and apo AII.

٣- **Fibric acid analogues :** الفيبرات Fibrates : الـ ***Fenofibrate*** والـ ***gemfibrozil*** مشتقات حامض الفبريك تنقص الـ TGs وتزيد الـ HDL-C .

آليّة الفعل : المستقبلات المُنَشِّطة ـــ لِلمُكاثِرْ البَيرُوكْسِيزومي(PPARs) أعضاء من فصيلة مستقبلات نوويّة تُنَظِّم استقلاب الشحم. تعمل الـ PPARs كعوامل انتساخ مُنَشَّطَة ـــ باللجين/الرابط. إذ أنّ ارتباط اللجائن/الربائط الطبيعية(الأحماض الدهنية أو الآيكوزانويدات) أو الأدوية المضادة لفرط الشحوم يُنَشِّط الـ PPARs. ثم ترتبط بعناصر استجابة مُكاثِر البيروكسية، التي تؤدي في النهاية إلى نقص الـ TGs عبرَ زيادة تعبير الـ plasma lipoprotein lipase(الشكل ٢٢ .٩) ونقص الـ apolipoprotein (apo) CII . الفينوفيبرات فعّال أكثر من الجيمفيبروزيل في خفض الـ TGs. تزيد الفيبرات أيضاً الـ HDL-C بزيادتها التعبير عن الصميمين البروتينيين apo AI and apo AII. .

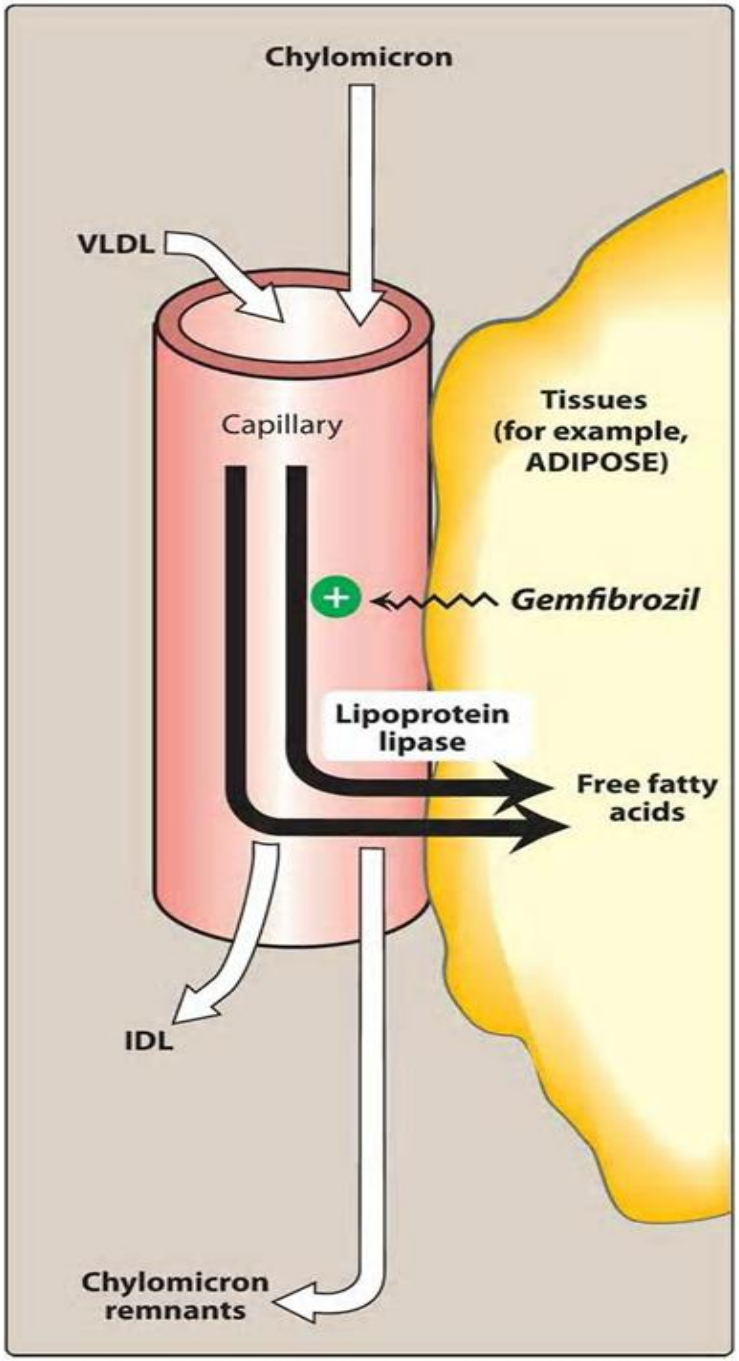


Figure 22.9 Activation of lipoprotein lipase by *gemfibrozil*. VLDL = very-low-density lipoprotein; IDL = intermediate-density lipoprotein.

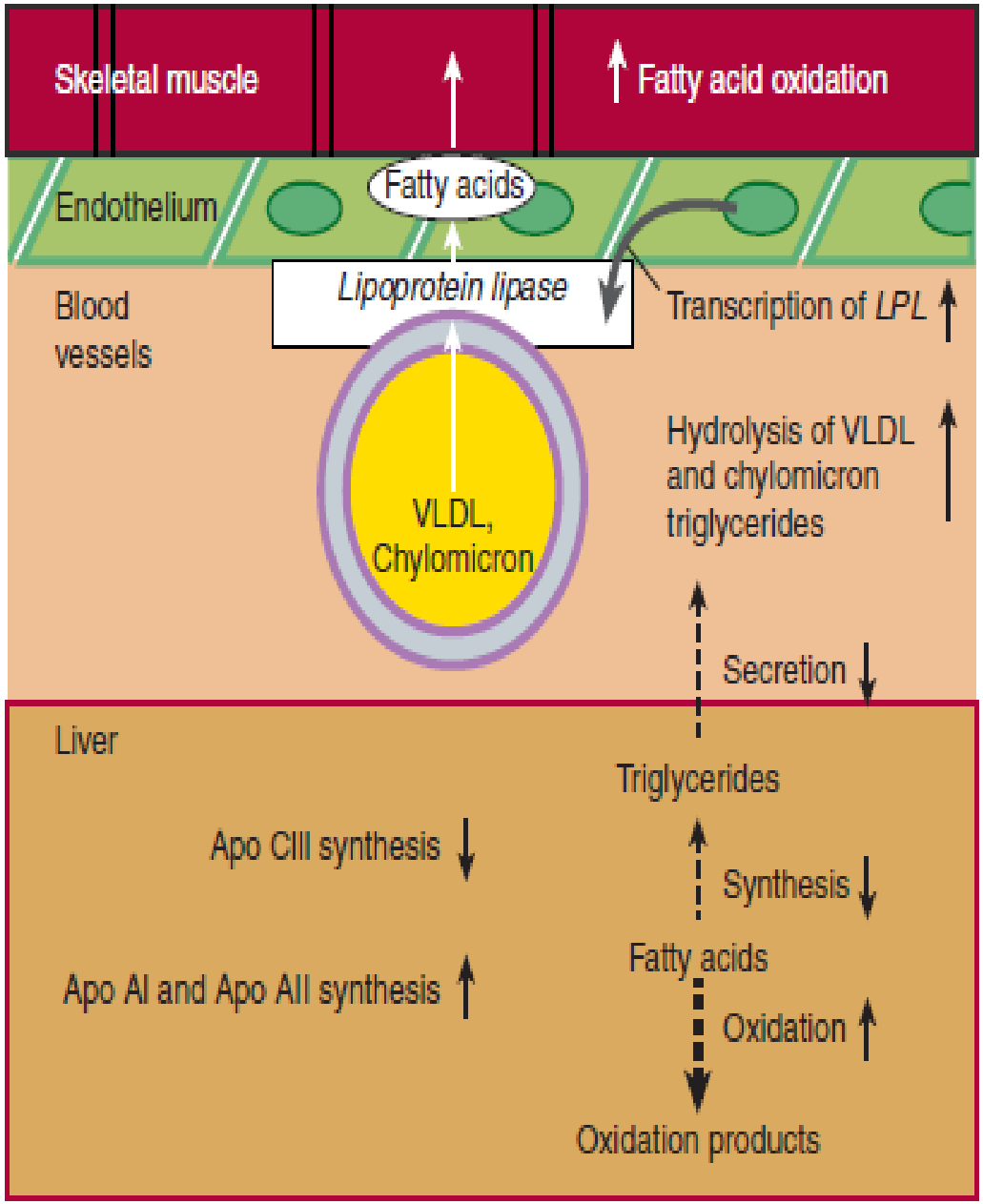


FIGURE 35–4 Hepatic and peripheral effects of fibrates. These effects are mediated by activation of peroxisome proliferator-activated receptor-α, which modulates the expression of several proteins. LPL, lipoprotein lipase; VLDL, very-low-density lipoproteins.

يتميّز عوز النياسين / الفيتامين B3 (البلاغرا pellagra / داء الذرة/الاعتماد على الذرة "three M's": meat (pork fatback); molasses; and meal (cornmeal).) بالتهاب الجلد dermatitis و الخرف dementia و الإسهال diarrhea (3Ds) . يلاحظ عادةً مع الكحوليّة المزمنة و متلازمة سوء الإمتصاص .. يتواجد في اللحوم الحمراء و السمك و الدجاج والخضار و dairy products .

- التأثيرات الضائرة وموانع الإستعمال :

فينوفيبرات يسبّب تحصّي صفراوي cholelithiasis وإلتهاب المرارة cholecystitis و **إضطرابات هضميّة** وغثيان وإسهال خفيف وألم عضلات . وأحياناً تفاعلات جلديّة ونعاس ونادراً نقص الشبق libido عند الذكور .

يزيح الـ sulfonylureas & warfarin من الألبومين .

ينبغي استعماله بحذر في الخلل الكلوي أو الكبدي .

٤- **Ezetimibe (Zetia)®**: يحصر نواقل الـ C في المعي الدقيق ، منقصاً امتصاص الـ C . ينقص لوحده C البلازما ١٨% و TG ١٠% ، وبتوليفه مع ستاتين ينقص C البلازما ٧٢% .

متحمّل جداً ، يسبّب التعب وألم البطن والإسهال .

Cholestyramine [koe-LES-tir-a-meen], colestipol [koe-LES-tih-pole], and colesevelam [koh-le-SEV-e-lam] are anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine (Figure 22.10). The resin/bile acid complex is excreted in the feces, thus lowering the bile acid concentration. This causes hepatocytes to increase conversion of cholesterol to bile acids, which are essential components of the bile. Consequently, intracellular cholesterol concentrations decrease, which activates an increased hepatic uptake of cholesterolcontaining LDL-C particles, leading to a decrease in plasma LDL-C. [Note: This increased uptake is mediated by an up-regulation of cell surface LDL receptors.]

٥- محتجزات الحموض الصفراويّة

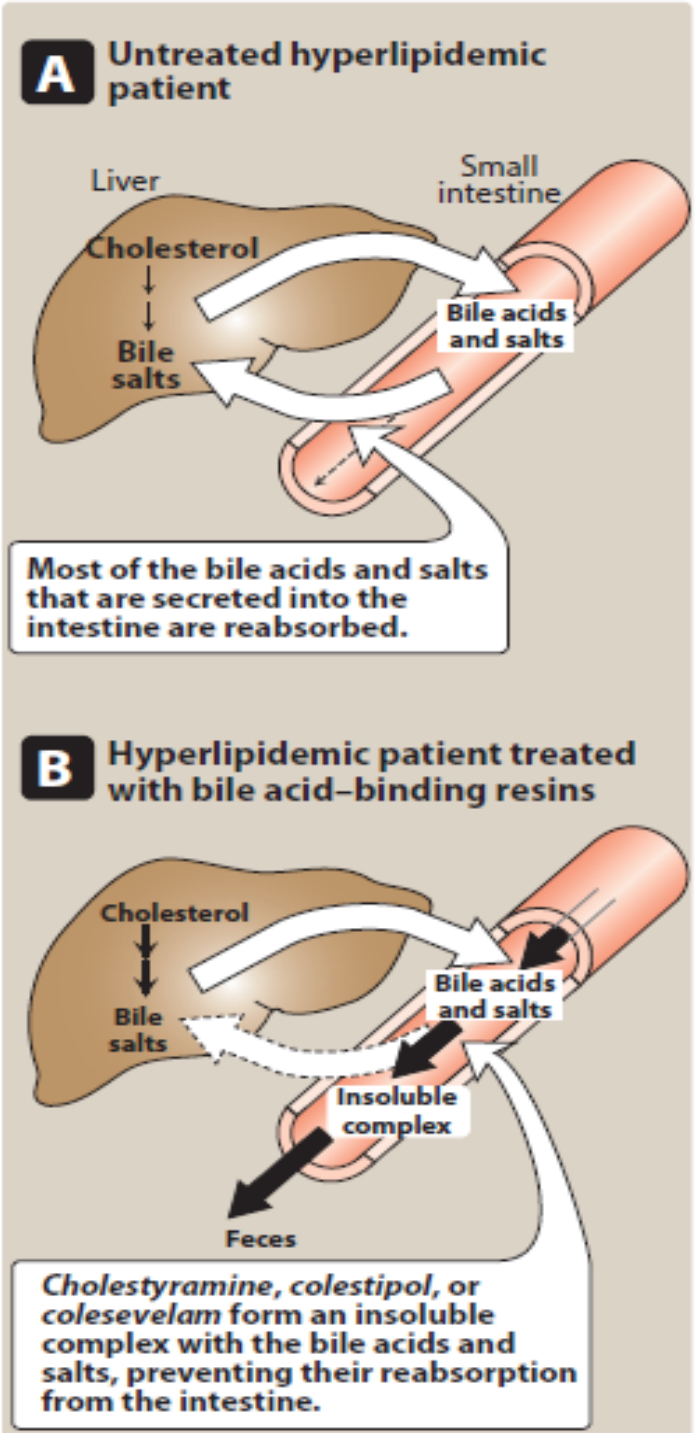
5. *Bile acid sequestrants :* Cholestyramine (Questran)® , **colestipol** (Colestid)® and **colesevelam** (Wel Chol)®

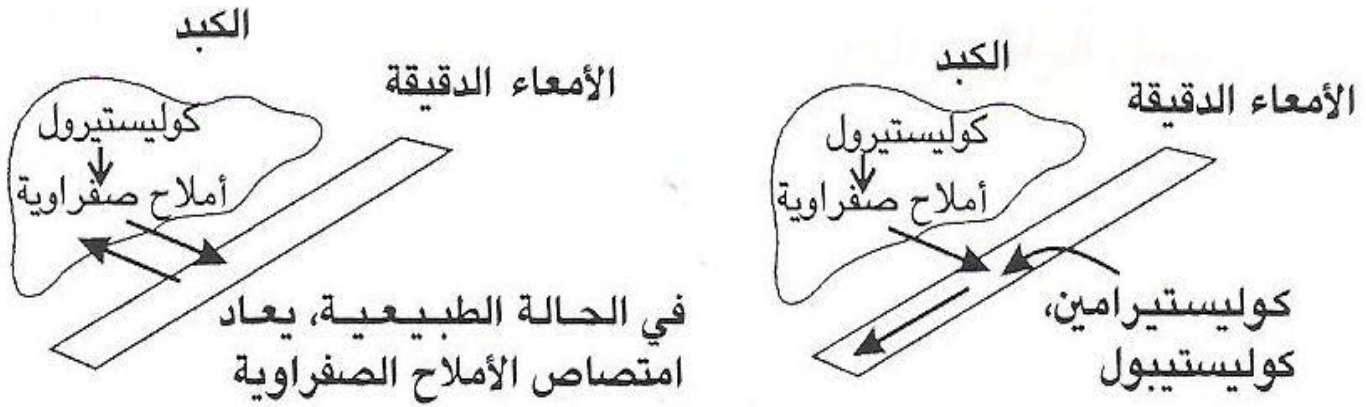
راتينات تربط الأملاح الصفراويّة في الأمعاء وتمنع عودتها إلى الكبد .... . تبادل الكلوريد Cl- مع الحمض الصفراوي . لاتمتصّ عبر المعي .

تستعمل لإنقاص C البلازما (١٠-٢٠%) عند المرضى ذوي بعض مستقبلات LDL الطبيعيّة .

مأمونة ، نادراً ماتسبّب **الإمساك** والغثيان . للـ colesevelam التأثيرات الهضميّة الأقلّ.

تنقص إمتصاص الأدوية اللامتأيّنة ، كالديجيتال والوارفارين ....


A
Untreated hyperlipidemic patient
Liver
Small intestine
Cholesterol
Bile salts
Bile acids and salts
Most of the bile acids and salts that are secreted into the intestine are reabsorbed.
B
Hyperlipidemic patient treated with bile acid–binding resins
Cholesterol
Bile salts
Bile acids and salts
Insoluble complex
Feces
Cholestyramine, *colestipol*, or *colesevelam* form an insoluble complex with the bile acids and salts, preventing their reabsorption from the intestine.



(الشكل 16-1): في الحالة الطبيعية، تُفرَز الأحماض الصفراوية في الأمعاء الدقيقة (Small intestine) ومن ثم يُعاد امتصاصها بشكل كامل تقريباً. يربط الكوليستيرامين (Cholestyramine) والكوليستيبول (Colestipol) الأحماض الصفراوية في الأمعاء الدقيقة ويمنع إعادة امتصاصها. وهذا يُؤدي لأن يستعمل الكبد (Liver) الكوليستيرول في تخليق الأحماض الصفراوية.

F. Proprotein convertase subtilisin kexin type 9 inhibitors

Proprotein convertase subtilisin kexin type 9 (PCSK9) is an enzyme predominately produced in the liver. PCSK9 binds to the LDL receptor on the surface of hepatocytes, leading to the degradation of LDL receptors (Figure 22.11). By inhibiting the PCSK9 enzyme, more LDL receptors are available to clear LDL-C from the serum. ***Alirocumab*** [al-i-ROK-ue-mab] and ***evolocumab*** *[e-voe-LOK-ue-mab] are PCSK9 inhibitors, which are fully humanized* monoclonal antibodies. These agents are used in addition to maximally tolerated statin therapy in patients with heterozygous or homozygous familial hypercholesterolemia, or in patients with clinical ASCVD who require additional LDL-C lowering.

مثبطات الـ Proprotein convertase subtilisin kexin type 9 (PCSK9) (إنزيم يُنتَج على نحو سائد في الكبد) : يرتبط هذا الإنزيم مع مستقبلات الـ LDL receptor على سطح الخلايا الكبدية، مؤدياً إلى تدركها(الشكل ٢٢ .١١). تثبيط هذا الإنزيم يزيد توافر مستقبلات الـ LDL وتصفية الـ LDL-C بالتالي من المصل. الـ ***Alirocumab*** والـ ***evolocumab*** مثبطان للـ PCSK9 وهما مضادان وحيدا النسيلة مُؤَنسنان على نحو تام. يستعملان بالإضافة إلى المعالجة بالستاتين المُتَحَمَّلَة أعظميّاً(لا تحتمل زيادة الستاتين) عند مرضى فرط كوليستيرول الدم العائلي المُتَغايِري الزَّيجوت و ذوي الزَيْجُوتٍ المُتَمَاثِلَةِ الأَلائِل أو عند المصابين بالداء القلبي الوعائي بالتصلب العصيدي atherosclerotic cardiovascular disease (ASCVD) الذين يتطلبون إنقاصاً إضافيّاً للـ LDL-C .

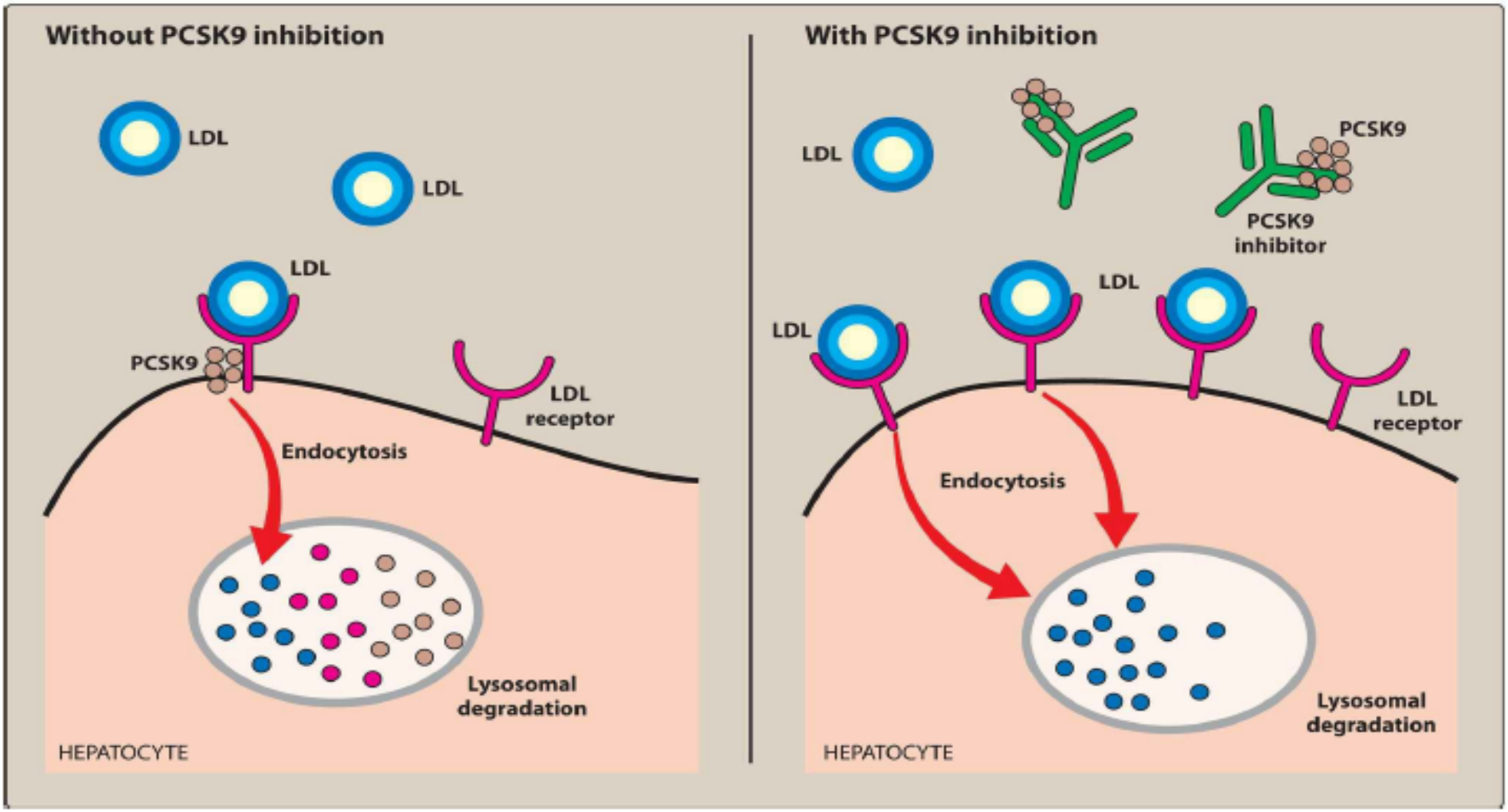


Figure 22.11 Mechanism of action of PCSK9 inhibitors. PCSK9 binds to the LDL receptor on the surface of hepatocytes, leading to degradation of LDL receptors. Inhibition of PCSK9 prevents degradation of LDL receptors and promotes greater clearance of LDL-C from the serum. LDL = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin kexin type 9.

When combined with statin therapy, PCSK9 inhibitors provide potent LDL-C lowering (50% to 70%). They may also be considered for patients with high ASCVD risk and statin intolerance. PCSK9 inhibitors are only available as subcutaneous injections and are administered every two to four weeks. Monoclonal antibodies are not eliminated by the kidneys and have been used in dialysis patients or those with severe renal impairment. PCSK9 inhibitors are generally well tolerated. The most common adverse drug reactions are injection site reactions, immunologic or allergic reactions, nasopharyngitis, and upper respiratory tract infections.

توفر مثبطات الـ PCSK9 خفض للـ LDL-C ٥٠—٧٠% عند توليفها مع ستاتين. قد تعطى أيضاً للمرضى ذوي الإختطار الكبير للداء القلبي الوعائي بالتصلب العصيدي وحالات عدم تحمل الستاتين. تتوافر مثبطات الـ PCSK9 حقنات تحت الجلد فقط وتعطى كل أسبوعين—إلى أربع أسابيع. لا تُطرَح الأضداد وحيدة النسيلة بالكلية وتستعمل لمرضى الدِيال أو المصابين بخلل كلوي وخيم. هذه الأدوية متحملة عموماً . التأثيرات الضائرة الأكثر حدوثاً تفاعلات مقر الحقن وتفاعلات أَرَجِيّة مناعيّة والْتِهابُ البُلْعومِ الأَنْفِيّ وعداوى المسلك التنفسي العلوي .

G. Omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that are predominately used for triglyceride lowering. Essential fatty acids inhibit VLDL and triglyceride synthesis in the liver. The omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in marine sources such as tuna, halibut, and salmon. Approximately 4 g of marine-derived omega-3 PUFAs daily decreases serum triglyceride concentrations by 25% to 30%, with small increases in LDL-C and HDL-C. Over-the-counter or prescription fish oil capsules (EPA/DHA) can be used for supplementation, as it is difficult to consume enough omega-3 PUFAs from dietary sources alone. *Icosapent [eye-KOE-sa-pent] ethyl is a prescription product that contains only EPA and,* unlike other fish oil supplements, does not significantly raise LDL-C.

الأحماض الدهنية العديدة اللاتَشَبُّعْ الأوميغا—٣(PUFAs) : أحماض دهنية ضرورية تستعمل لخفض ثُلاَثِيُّ الغليسريد. تثبط تصنيع الـ VLDL والـ TG في الكبد. يوجد حامض الإيكوزابنتانوئيك (EPA) و الدوكوزاهيكزاينوئيك (DHA)في مصادر بحرية مثل التونا والهلبوت والسلمون. حوالي ٤ ميلي غرام من المشتق—البحري الـ الأوميغا—٣(PUFAs) يومياً ينقص الـ TGs المصلي ٢٠—٢٥% مع زيادة صغيرة في الـ LDL-C والـ LDL-C . يمكن استعمال كبسولات زيت السمك (EPA/DHA) بالوصفة وغير الوصفة متممات ، حيث يصعب استهلاك المقدار الكافي من الأوميغا—٣(PUFAs) في النظام الغذائي فقط . **الإيكوزابنت إيثيل** المُنتَج الوصفي الذي يحتوي فقط على الـ EPA لا يزيد الـ LDL-C على نحو معتد مثل متممات زيت السمك الأُخرى .

Omega-3 PUFAs can be considered as an adjunct to other lipid-lowering therapies for individuals with elevated triglycerides (≥500 mg/dL). Although effective for triglyceride lowering, omega-3 PUFA supplementation has not been shown to reduce cardiovascular morbidity and mortality. The most common side effects of omega-3 PUFAs include GI effects (abdominal pain, nausea, diarrhea) and a fishy aftertaste. Bleeding risk can be increased in those who are concomitantly taking anticoagulants or antiplatelet agents. L7

يمكن اعتبار **الأوميغا—٣(PUFAs)** مساعدة للأدوية الخافضة—للشحوم للأفراد المصابين بزيادة الـ TGs (≥500 mg/dL). المتممات **الأوميغا—٣(PUFAs)** لم تنقص المراضة القلبية الوعائية ونسبة الوفيات رغم فعاليتها في خفض الـ TGs . تتضمن التأثيرات الجانبية الشائعة أكثر للـ **الأوميغا—٣(PUFAs)** تأثيرات معدية معوية(ألم بطن وغثيان وإسهال) و مَذاقٌ تِلْوِيّ سمكي. يزداد اختطار النزف عند المتناولين مضادّات التخثر ومضادّات الصفيحات .

للاطلاع

Peroxisome proliferator receptor α (PPAR-α) is yet another nuclear receptor highly expressed in liver and kidneys, which uses lipid-lowering drugs (eg, fenofibrate and gemfibrozil) as ligands. Consistent with its major role in the regulation of fatty acid metabolism, PPAR-α mediates the induction of CYP4A enzymes, responsible for the metabolism of fatty acids such as arachidonic acid and its physiologically relevant derivatives. It is noteworthy that on binding of its particular ligand, PXR, CAR, and PPAR-α each form heterodimers with another nuclear receptor, the retinoid X-receptor (RXR). This heterodimer in turn binds to response elements within the promoter regions of specific *P450 genes to induce gene expression.*

23.1 Which one of the following is the most common side effect of antihyperlipidemic drug therapy?

A. Elevated blood pressure.
B. Gastrointestinal disturbance.
C. Neurologic problems.
D. Heart palpitations.
E. Migraine headaches.

Correct answer = B. Gastrointestinal disturbances frequently occur as a side effect of antihyperlipidemic drug therapy. The other choices are not seen as commonly.

23.2 Which one of the following hyperlipidemias is characterized by elevated plasma levels of chylomicrons and has no drug therapy available to lower the plasma lipoprotein levels?

A. Type I.
B. Type II.
C. Type III.
D. Type IV.
E. Type V.

Correct answer = A. Type I hyperlipidemia (hyperchylomicronemia) is treated with a low-fat diet. No drug therapy is effective for this disorder.

23.3 Which one of the following drugs decreases cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase?

A. Fenofibrate.
B. Niacin.
C. Cholestyramine.
D. Lovastatin.
E. Gemfibrozil.

Correct answer = D. Lovastatin decreases cholesterol synthesis by inhibiting HMG CoA reductase. Fenofibrate and gemfibrozil increase the activity of lipoprotein lipase, thereby increasing the removal of VLDL from plasma. Niacin inhibits lipolysis in adipose tissue, thus eliminating the building blocks needed by the liver to produce triglycerides and, therefore, VLDL. Cholestyramine lowers the amount of bile acids returning to the liver via the enterohepatic circulation.

23.4 Which one of the following drugs causes a decrease in liver triglyceride synthesis by limiting available free fatty acids needed as building blocks for this pathway?

A. Niacin.
B. Fenofibrate.
C. Cholestyramine.
D. Gemfibrozil.
E. Lovastatin.

Correct answer = A. At gram doses, niacin strongly inhibits lipolysis in adipose tissue—the primary producer of circulating free fatty acids. The liver normally utilizes these circulating fatty acids as a major precursor for triglyceride synthesis. Thus, niacin causes a decrease in liver triglyceride synthesis, which is required for VLDL production. The other choices do not inhibit lipolysis in adipose tissue.

23.5 Which one of the following drugs binds bile acids in the intestine, thus preventing their return to the liver via the enterohepatic circulation?

A. Niacin.
B. Fenofibrate.
C. Cholestyramine.
D. Fluvastatin.
E. Lovastatin.

Correct answer = C. Cholestyramine is an anion-exchange resin that binds negatively charged bile acids and bile salts in the small intestine. The resin/bile acid complex is excreted in the feces, thus preventing the bile acids from returning to the liver by the enterohepatic circulation. The other choices do not bind intestinal bile acids.

- Difficulty level: Hard
- **28.** Each of the following patients (1 to 5) was found to have an abnormal lipid profile and was placed on a lipid-lowering diet for 4 months. None had any history of ischemic heart disease. The results of the patients' fasting lipid profile after 4 months of diet are given in the following table.

	Triglycerides (mg/dL)	LDL (mg/dL)	HDL (mg/dL)
1	300	120	20
2	190	130	25
3	300	210	20
4	230	180	65
5	180	120	45
Normal values	< 200	< 130	> 35

- *Abbreviations:* HDL, high-density lipoprotein; LDL, low-density lipoprotein.
- For which one of the following patients would it be <u>most</u> important to recommend an antihyperlipidemic drug at this time?
- **A.** Patient 1 **B.** Patient 2 **C.** Patient 3 **D.** Patient 4 **E.** Patient 5
- Learning objective: Outline the therapeutic uses of antihyperlipidemic drugs.
- 28. **C** All of the patients except patient 5 should start a lipid-lowering drug therapy, as they still have an abnormal lipid profile after 4 months of diet. Patient 3, however, is the one who needs the drug therapy **the most**, because he has three risk factors: high triglycerides, high low-density lipoprotein (LDL), and low high-density lipoprotein (HDL) levels.
- A Patient 1 has high triglycerides, normal LDL cholesterol levels, and low HDL cholesterol levels (two risk factors).
- B Patient 2 has normal triglycerides and normal LDL cholesterol levels but low HDL cholesterol levels (one risk factor).
- D Patient 4 has marginally high triglycerides and high LDL cholesterol levels but very high HDL cholesterol levels (an HDL > 60 mg/dL represents a negative risk factor).

12. A 46-year-old man suffering from familial hypercholesterolemia was found to have total cholesterol of 430 mg/dL despite many months of treatment with lovastatin. Triglyceride levels were normal. His physician decided to add niacin to the therapeutic regimen. Which of the following molecular actions most likely mediated the therapeutic efficacy of niacin in the patient's disease?

- **A.** Inhibition of very-low-density lipoprotein (VLDL) production by the hepatocyte
- **B.** Inhibition of high-density lipoprotein (HDL) synthesis by the liver
- **C.** Increase of circulating fibrinogen
- **D.** Stimulation of lipolysis in adipose tissue
- **E.** Decreased absorption of exogenous cholesterol
- **Learning objective: Explain the mechanism of action of niacin.**
- 12. **A Niacin inhibits very-low-density lipoprotein (VLDL) production by hepatocytes, which in turn decreases production of low-density lipoprotein (LDL). The mechanism of this action is still uncertain but seems to involve**
  - ***A decreased synthesis of triglycerides by the liver***
  - ***An inhibition of lipolysis in adipose tissue, which in turn causes a decreased delivery of free fatty acids to the liver***
  - **A stimulation of lipoprotein lipase activity, which enhances hydrolysis of VLDL and delivery of triglycerides to adipose tissue**

B Niacin actually increases the synthesis of high-density lipoprotein (HDL) by the liver. It also can cause hyperuricemia in about 20% of patients by an unknown mechanism.

C Niacin causes a substantial reduction of fibrinogen levels, which can be of value in case of atherosclerosis or thrombosis.

D Niacin actually inhibits lipolysis of triglycerides by hormone- sensitive lipase in adipose tissue.

E Niacin has negligible effects on exogenous cholesterol absorption.

Difficulty level: Medium

14. A 52-year-old obese man suffering from **gout** and **hypertension** was found to have low-density lipoprotein (LDL) **cholesterol** of 360 mg/dL (normal < 130 mg/dL) and a serum uric acid of 15.5 mg/dL (normal 4.0–8.5 mg/dL). Other laboratory values were within normal limits. A lipid-lowering therapy was prescribed. Which of the following antihyperlipidemic drugs would be relatively contraindicated in this patient?

A. Cholestyramine **B.** Niacin **C.** Ezetimibe **D.** Lovastatin **E.** Gemfibrozil

Learning objective: Describe the main contraindications of niacin.

14. **B** Niacin is relatively contraindicated in patients suffering from gout and hyperuricemia because it tends to increase uric acid levels.

A Cholestyramine could be appropriate in this patient because he has an isolated increase of low-density lipoprotein (LDL).

C, D Statins are effective in all disorders involving elevated levels of LDL.

E Fibrates are useless (reduction of LDL is usually negligible) but not contraindicated in this patient.

- **15.** A 56-year-old woman suffering from **familial hypercholesterolemia** was found to have total cholesterol of 470 mg/dL (normal < 200 mg/dL) despite many months of treatment with lovastatin. Triglyceride levels were normal. The physician decided to **add niacin** to the therapeutic regimen. Which of the following drugs should be given during the first days of therapy to avoid niacin-induced flushes?
- **A.** Warfarin **B.** Atropine **C.** Aspirin **D.** Prazosin **E.** Gemfibrozil
- **Learning objective: Describe the clinically relevant drug interactions with niacin.**
- 15. **C** The cutaneous vasodilation and uncomfortable flushes are adverse effects that most people experience after each dose of niacin. They seem to be primarily prostaglandin-mediated, and therefore an aspirin (or another nonsteroidal anti-inflammatory drug) can alleviate the flushing in many patients. Because these effects undergo rapid tolerance, aspirin is needed only during the first days of therapy.
- A There is no rationale for the use of warfarin. In fact, niacin can cause a substantial reduction of circulating fibrinogen
- levels, which actually reduces the risk of thrombosis.
- B There is no rationale for the use of atropine. Moreover, the drug would worsen the cholestyramine-induced constipation.
- D Prazosin would increase the niacin-induced vasodilation.
- E **Gemfibrozil is used only in case of hypertriglyceridemia**. In this patient, triglyceride levels are normal.

- Pellagra was especially a problem for the poor in the South whose meals usually consisted of the "three M's": meat (pork fatback); molasses; and meal (cornmeal). Today pellagra continues to be a problem in developing countries where there is significant malnutrition or where niacin-deficient foods such as corn and rice are the primary sources of nutrition
  - كانت البلاغرا مشكلة للفقراء في الشمال الذين تتكون وجباتهم عادةً من اللحوم والدبس و الذرة . اليوم تستمر مشكلة البلاغرا في الدول النامية في وجود سوء التغذية أو الأطعمة المعوزة—النياسين مثل اعتماد التغذية على الذرة والأرز .

F. Omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that are predominately used for triglyceride lowering. Essential fatty acids inhibit VLDL and triglyceride synthesis in the liver. The omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in marine sources such as tuna, halibut, and salmon. Approximately 4 g of marine-derived omega-3 PUFAs daily decreases serum triglyceride concentrations by 25% to 30%, with small increases in LDL-C and HDL-C. Over-the-counter or prescription fish oil capsules (EPA/DHA) can be used for supplementation, as it is difficult to consume enough omega-3 PUFAs from dietary sources alone. *Icosapent* [eye-KOE-sa-pent] *ethyl is a prescription product that contains only* EPA and, unlike other fish oil supplements, does not significantly raise LDL-C. Omega-3 PUFAs can be considered as an adjunct to other lipid-lowering therapies for individuals with significantly elevated triglycerides (≥500 mg/dL). Although effective for triglyceride lowering, omega-3 PUFA supplementation has not been shown to reduce cardiovascular morbidity and mortality. The most common side effects of omega-3 PUFAs include GI effects (abdominal pain, nausea, diarrhea) and a fishy aftertaste. Bleeding risk can be increased in those who are concomitantly taking anticoagulants or antiplatelets.

تستعمل الأحماض الدُهْنِيَّة العَديدة اللاتَشَبُّع لخفض ثُلاَثِيُّ الغليسريد . إذ تثبط تصنيع الـ VLDL والـ TG في الكبد . توجد الـ omega-3 PUFAs **eicosapentaenoic acid** (**EPA**) والـ **docosahexaenoic acid** (**DHA**) في مصادر بحرية مثل التونا والـهلبوت halibut (أضخم الأسماك المفلطحة) والسلمون . إنّ ٤ غرام من هذه المشتقات يومياً تنقص الـ TG ٢٥%--٣٠% مع زيادة قليلة للـ LDL-C والـ HDL-C . يمكن استعمال كبسولات زيت السمك (EPA/DHA) مكملات .. يمتاز الـ ***Icosapent ethyl*** *المحتوي على* **EPA** فقط بعدم زيادة الـ LDL-C كثيراً . تعد الـ omega-3 PUFAs مساعدة لخافضات الشحوم عند مرضى ارتفاع الـ TG (≥500 mg/dL). لم تنقص هذه المكملات نسبة المرض القلبي الوعائي والوفيات . تسبب اضطرابات هضمية (ألم بطن وغثيان وإسهال) و مَذاقٌ تِلْوِيّ سمكي . قد يزداد اختطار النزف مع تناول مضادات التخثر أو مضادات تكدس الصفيحات .

Allele [ˈaliːl] NOUN . Genetics **alleles** (plural noun)

each of two or more alternative forms of a gene that arise by mutation and are found at the same place on a chromosome.Also called allelomorph.

=

An allele is a variant form of a given gene. Sometimes, the presence of different alleles of the same gene can result in different observable phenotypic traits, such as different pigmentation. A notable example of this trait of color variation is Gregor Mendel's discovery that the white and purple flower colors in pea plants were the result of "pure line" traits which could be used as a control for future experiments. However, most genetic variations result in little or no observable variation.

=

An allele is an alternative form of a gene. Organisms typically have two alleles for a single trait, one being inherited from each parent.

=

Any of the possible forms in which a gene for a specific trait can occur. In almost all animal cells, two alleles for each gene are inherited, one from each parent.

=

Allele definition, any of several forms of a gene, usually arising through mutation, that are responsible for hereditary variation.

Heterozygous vs Homozygous FH

May 19, 2014 / By Marie Louise Brumit /

6 Comments

Familial hypercholesterolemia, or FH, is an inherited genetic disorder that affects the body's ability to manage cholesterol. The result is very high levels of LDL, or "bad" cholesterol, from birth. This protracted exposure to high levels of LDL leads to a twenty fold increase in the risk of premature cardiovascular disease. Only about 10% of people with FH have been diagnosed. Diagnosis is important because there are many available treatments and early aggressive treatment can lower your risk for heart disease or stroke.

Inheriting FH: Understanding Autosomal Dominance

The gene mutation that causes FH is autosomal dominant. This means that a parent with the disorder has a 50% chance of passing that gene to each of his or her children. If a child inherits the gene, because it is dominant, he or she will have the disorder. The term autosomal vs x-linked refers to the fact that the gene is not related to the sex chromosomes. It does not matter if it is the mother or the father who has the gene, or if the child is a girl or a boy.

Autosomal dominant disorders, like FH, tend to appear in each generation in a family. Because of this, people with FH have a family history of heart disease or stroke. However, if the child does not inherit the FH gene from his or her affected parent, he or she will not have the disorder and cannot pass it on to the next generation.

Heterozygous vs Homozygous FH

If you inherit the FH gene from one parent you will have heterozygous FH, meaning you have one FH gene and one normal gene. About 1 in 250 people around the world have heterozygous FH. Heterozygous FH is characterized by very high LDL cholesterol (above 190 for adults or above 160 for children) and a family history of high cholesterol, heart disease or stroke.

If both of your parents have FH and you inherit the FH gene from each of them, you will have homozygous FH, meaning you have two FH genes. Having two FH genes makes the disorder much more severe. Homozygous FH is very rare. Approximately 1 in one million people worldwide has homozygous FH. Homozygous FH is characterized by extremely high levels of LDL cholesterol and symptoms can be seen in childhood. Homozygous FH is much more difficult to treat adequately and people with homozygous FH can suffer from cardiac events even before the teen years.

Mechanism of Action. In adipose tissue, niacin inhibits the lipolysis of triglycerides by hormone-sensitive lipase, which reduces transport of free fatty acids to the liver and decreases hepatic triglyceride synthesis. Niacin and related compounds (e.g., 5-methylpyrazine-2-carboxylic-4-oxide, *acipimox*) may exert their effects on lipolysis by inhibiting adipocyte adenylyl cyclase. A GPCR for niacin has been identified and designated as GPR109A; it couples to G_i (Wise et al., 2003); its mRNA is highly expressed in the adipose tissue and spleen, sites of high-affinity nicotinic acid binding (Lorenzen et al., 2001). Acting on this receptor, niacin stimulates the G_i–adenylyl cyclase pathway in adipocytes, inhibiting cyclic AMP production and decreasing hormone-sensitive lipase activity, triglyceride lipolysis, and release of free fatty acids. Niacin also may inhibit a rate-limiting enzyme of triglyceride synthesis, diacylglycerol acyltransferase-2 (Ganji et al., 2004).

In the liver, niacin reduces triglyceride synthesis by inhibiting both the synthesis and esterification of fatty acids, effects that increase apoB degradation. Reduction of triglyceride synthesis reduces hepatic VLDL production, which accounts for the reduced LDL levels. Niacin also enhances LPL activity, which promotes the clearance of chylomicrons and VLDL triglycerides. Niacin raises HDL-C levels by decreasing the fractional clearance of apoA-I in HDL rather than by enhancing HDL synthesis. This effect is due to a reduction in the hepatic clearance of HDL-apoA-I, but not of cholesteryl esters, thereby increasing the apoA-I content of plasma and augmenting reverse cholesterol transport. In macrophages, niacin stimulates expression of the scavenger receptor CD36 and the cholesterol exporter ABCA1. The net effect of niacin on monocytic cells

The β receptors mediate activation of hormone-sensitive lipase in fat cells, leading to release of free fatty acids into the circulation (Chapter 8). This increased flux of fatty acids is an important source of energy for exercising muscle. β Receptor antagonists can attenuate the release of free fatty acids from adipose tissue. Non-selective β receptor antagonists consistently reduce HDL cholesterol, increase LDL cholesterol, and increase triglycerides. In contrast, β_1-selective antagonists, including celiprolol, carteolol, nebivolol, carvedilol, and bevantolol, reportedly improve the serum lipid profile of dyslipidemic patients. While drugs such as propranolol and atenolol increase triglycerides, plasma triglycerides are reduced with chronic celiprolol, carvedilol, and carteolol (Toda, 2003).

In contrast to classical β blockers, which decrease insulin sensitivity, the vasodilating β receptor antagonists (e.g., celiprolol, nipradilol, carteolol, carvedilol, and dilevalol) increase insulin sensitivity in patients with insulin resistance. Together with their cardioprotective effects, improvement in insulin sensitivity from vasodilating β receptor antagonists may partially counterbalance the hazard from worsened lipid abnormalities associated with diabetes. If β blockers are to be used, β_1-selective or vasodilating β receptor antagonists are preferred. In addition, it may be necessary to use β receptor antagonists in conjunction with other drugs, (e.g., HMGCoA reductase inhibitors) to ameliorate adverse metabolic effects (Dunne et al., 2001).

β Receptor agonists decrease the plasma concentration of K^+ by promoting the uptake of the ion, predominantly into skeletal muscle. At rest, an infusion of epinephrine causes a decrease in the plasma concentration of K^+. The marked increase in the concentration of epinephrine that occurs with stress (such as myocardial infarction) may cause hypokalemia, which could predispose to cardiac arrhythmias. The hypokalemic effect of epinephrine is blocked by an experimental antagonist, ICI 118551, which has a high affinity for β_2 and β_3 receptors. Exercise causes an increase in the efflux of K^+ from skeletal muscle. Catecholamines tend to buffer the rise in K^+ by increasing its influx into muscle. β Blockers negate this buffering effect.

to its receptors on muscle and adipose cells. Insulin has potent effects to reduce lipolysis from adipocytes, primarily through the inhibition of hormone-sensitive lipase, and increases lipid storage by promoting lipoprotein lipase synthesis and adipocyte glucose uptake. Finally, insulin stimulates amino acid uptake and protein synthesis and inhibits protein degradation in muscle and other tissues; it thus causes a decrease in the circulating concentrations of most amino acids.