In his name

- Presented by M.M. Khastar
- 2020

- Source:

UptoDate

Herink M, Ito MK. Medication Induced Changes in Lipid and Lipoproteins. In: Endotext. MDText.com, Inc., South Dartmouth (MA); 2000.

Drug-Induced lipid changes

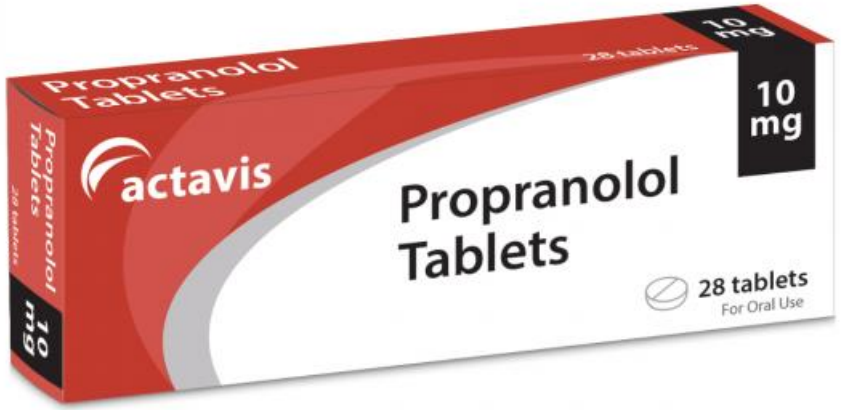
- Several medications and medication classes have been reported to affect the lipid profile. Risk factors include elevated lipid levels at baseline and high cardiovascular (CV) risk patients. This should be considered when evaluating patients with elevated levels of total cholesterol (TC), low-density lipoproteins cholesterol (LDL-C), non-high-density lipoprotein cholesterol (Non-HDL-C), triglycerides (TG) and reductions in high-density lipoprotein cholesterol (HDL-C). Cardiovascular medications, antipsychotics, anticonvulsants, hormones and certain immunosuppressives are just some of the more commonly known medications to have a negative impact on lipid levels.
- Today, We'll discuss about Cardiovascular drugs.

Cardiovascular Drugs That May Cause Dyslipidemias

	LDL Cholesterol	Triglycerides	HDL Cholesterol
Cardiovascular /Endocrine			
Amiodarone	↑Variable	↔	↔
ß-Blockers	↔	↑10-40%	↓5-20%
Loop diuretics	↑5-10%	↑5-10%	↔
Thiazide diuretics (high dose)	↑5-10%	↑5-15%	↔
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	↑3-8%	↔↓	↑Variable

ANTIHYPERTENSIVE DRUGS

- There is an abundance of literature and comprehensive reviews discussing the potential harmful effects of antihypertensive drugs on lipoprotein metabolism and there remains much debate about the actual long term implications, if any, of these changes. The diuretics and ß-adrenergic blockers have the most data to support their adverse effects on lipid levels.



Diuretics

- Thiazide and loop diuretics have been associated with increases in plasma cholesterol in studies of patients with hypertension.
- Use of high-dose thiazide diuretics (≥50 mg/day) may negatively affect lipoprotein levels, as seen in small studies, and some investigators have suggested that as a result, diuretics could worsen coronary artery disease (CAD).Total cholesterol levels can be increased by approximately 4% and LDL-C levels by approximately 10%. High density lipoprotein levels are not affected, while TG concentrations can also be elevated by 5-15%. Low dose hydrochlorothiazide (12.5 – 25 mg/day) has been shown not to effect plasma lipids in otherwise healthy men and women. The dose appears to be a factor in resulting cholesterol levels; however, there are conflicting data regarding whether the effects on lipid levels is primarily caused by higher doses. Long term effects beyond one year remain undetermined as more recent studies showed that effects are short term and serum lipid levels return to initial levels. Additionally, thiazide diuretics have been shown to decrease the risk of cardiovascular (CV) events despite this effect on lipid levels.

Diuretics

- Loop diuretics have similarly shown to increase LDL-C and TG with some studies showing changes of comparable magnitude and some showing effects that are less than thiazide diuretics. However, the effects appear to be acute and not expected at time intervals longer than the duration of action of furosemide (6 to 8 hours). One possibility is that hormones stimulated in response to decreased intravascular volume are responsible for some changes in lipid and lipoprotein levels. The effects of monotherapy with potassium-sparing diuretics on lipid levels is largely unknown, but the combination of a potassium-sparing diuretic and a thiazide show similar changes as monotherapy with a thiazide diuretic, suggesting no impact from potassium-sparing diuretics.
- The mechanism of increased lipid levels caused by diuretics remains unclear.

ß-Blockers

- The metabolic adverse effects of ß-blockers depend on dose and specific drug. While ß-blocking agents have negligible effect on serum TC or LDL-C, they can increase TG levels from 10 to 40% and decrease HDL-C levels by approximately 5 to 20%.
- The alterations in lipoprotein levels from ß-blockers does not appear to be a class effect, and agents with intrinsic sympathomimetic activity (ISA), ß1-selectivity, or vasodilatory effects (Table 2) are associated with a less pronounced effect.[9]Non-selective ß-blockers which cause peripheral vasoconstriction through peripheral ß-adrenergic receptors seem to increase insulin resistance, leading to lowering of HDL-C, and increased TG.[25]Whereas, agents that are cardioselective and/or have alpha-1-adrenoreceptor blocking activity do not appear to increase insulin resistance.

Pharmacological Properties of ß-Blockers

Table 2. Pharmacological Properties of ß-Blockers			
	Beta Selectivity	Intrinsic sympathomimetic (ISA) or α-blocking	Vasodilating Properties
More pronounced effect on lipid levels			
Atenolol	ß1 selective	-	-
Betaxolol	ß1 selective	-	-
Bisoprolol	ß1 selective	-	-
Metoprolol	ß1 selective	-	-
Nadolol	Nonselective	-	Vasoconstricting
Propanolol	Nonselective	-	Vasoconstricting
Timolol	Nonselective	-	Vasoconstricting
Less pronounced effect on lipid levels			
Acebutolol	Nonselective	ISA	Vasoconstricting
Penbutolol	Nonselective	ISA	Vasoconstricting
Pindolol	Nonselective	ISA	Vasoconstricting
No effect on Lipid levels			
Carvedilol	Nonselective	α-blocking	Vasodilating
Labetolol	Nonselective	α-blocking	Vasodilating
Nebivolol	ß1 Selective	-	Vasodilating

Potential Mechanism of ß-blocker Induced Dyslipidemia

Inhibition of insulin release

Insulin resistance

Weight gain

Inhibition of lipolysis

Reduced activity of lipoprotein lipase enzyme

Endothelial dysfunction

OTHER CARDIOVASCULAR MEDICATIONS

- **Amiodarone:**

Amiodarone, a potent antiarrhythmic drug, increases plasma cholesterol levels, reported in case reports. Amiodarone increases LDL-C levels as a result of a decreased expression of the LDL-receptor gene. In addition, amiodarone induced hypothyroidism can cause alterations in lipid metabolism as hypothyroidism is one of the most common causes of secondary hyperlipidemia. Amiodarone contains 39.4% iodine on weight basis which may cause hyperthyroidism or hypothyroidism. Research demonstrates that long-term amiodarone treatment induces a dose-dependent increase in plasma cholesterol, in part due to thyroid hormone deficiency and a decrease in the number of LDL receptors.

OTHER CARDIOVASCULAR MEDICATIONS

- **Sodium-Glucose Co-Transporter 2 (*SGLT2*) Inhibitors**
- The SGLT2 inhibitors lower blood glucose and hemoglobin A1c (HgA1c) through inhibiting SGLT2 in the proximal tubule, thereby blocking reabsorption of glucose and increasing the renal excretion of glucose. There are currently four SGLT2 inhibitors available and approved for the treatment of type 2 diabetes mellitus. In addition to their effects on glucose lowering, SGLT2 inhibitors have been shown to have positive effects on other metabolic parameters, including body weight and blood pressure.
- These agents have shown to increase LDL-C while also increasing HDL-C with variable effects (decreasing or no effect) on TG.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors and their effects on low density lipoprotein cholesterol (LDL-C)

Generic	Brand	Dose-Related Effects on LDL-C
Canagliflozin	Invokana®	4.5% - 8.0%
Dapagliflozin	Farxiga®	2.9%
Empagliflozin	Jardiance®	2.3% - 6.5%
Ertugliflozin	Steglatro®	2.6% - 5.4%

Cardiovascular Drugs That May Cause Dyslipidemias

	LDL Cholesterol	Triglycerides	HDL Cholesterol
Cardiovascular /Endocrine			
Amiodarone	↑Variable	↔	↔
ß-Blockers	↔	↑10-40%	↓5-20%
Loop diuretics	↑5-10%	↑5-10%	↔
Thiazide diuretics (high dose)	↑5-10%	↑5-15%	↔
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	↑3-8%	↔↓	↑Variable

Antihypertensive drugs with neutral or beneficial effects on plasma lipid levels

- **Angiotensin-converting enzyme inhibitors** — The angiotensin-converting enzyme (ACE) inhibitors appear to have no significant effect on plasma lipids and may minimize or prevent the rise in lipids induced by diuretic therapy (via an unknown mechanism).
- **Angiotensin receptor blockers** — In most clinical studies, angiotensin receptor blockers (ARBs) had either a neutral or modest beneficial effect on lipid levels.
- **Calcium channel blockers** — The calcium channel blockers appear to have either a neutral or mildly beneficial effect on the lipid profile.

Antihypertensive drugs with neutral or beneficial effects on plasma lipid levels

- **Alpha blockers** — The selective alpha-1 blockers, specifically prazosin, doxazosin, and terazosin, improve lipoprotein lipase activity and consistently demonstrate favorable effects on plasma lipids. These drugs lower total cholesterol by approximately 3 to 5 percent, reduce triglyceride levels by 3 to 4 percent, and mildly raise HDL cholesterol.
- **Sympathetic blockers** — The effect of the centrally acting sympathetic inhibitors, methyldopa, clonidine, and guanabenz, on the lipid profile has not been well studied. Both favorable and detrimental changes have been reported. On average, there is little, if any, change in lipid levels.

REVIEW ARTICLE

Drug Safety 2001; 24 (6): 443-456
0114-5916/01/0006-0443/$22.00/0

Drug-Induced Lipid Changes

A Review of the Unintended Effects of Some Commonly Used Drugs on Serum Lipid Levels

Aukje K. Mantel-Teeuwisse, Judith M.E. Kloosterman, Anke Hilse Maitland-van der Zee, Olaf H. Klungel, Arijan J. Porsius and *Anthonius de Boer*

Department of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands

Table I. Direction and magnitude of changes in serum lipid levels induced by different drug classes. Changes are percentage increases (↑) or decreases (↓)

Drug class	Total cholesterol	LDL-cholesterol	HDL-cholesterol	Triglycerides
Cardiovascular drugs				
Diuretics				
thiazide diuretics	↑ 5 to 10	↑ 5 to 10	NC	↑ 5 to 15
loop diuretics	↑ 5 to 10	↑ 5 to 10	NC	↑ 5 to 10
potassium-sparing diuretics	NC	NC	NC	NC
indapamide	NC	NC	NC	NC
β-Blockers	NC	NC	↓ 5 to 20	↑ 10 to 40
celiprolol	↓ 0 to 10	↓ 0 to 20	↑ 3 to 40	↓ 5 to 25
ACE inhibitors	NC	NC	NC	↑ (?)
Calcium antagonists	NC	NC	NC	NC
α-Blockers	↓ 5	↓ 5	↑ 2 to 5	↓ 4 to 14

Thanks!