

# Dyslipidemia Induced by Drugs Used for the Prevention and Treatment of Vascular Diseases

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**Abstract:** Dyslipidemia is a major vascular risk factor. Interestingly, several agents used for the prevention and treatment of vascular diseases have an adverse effect on the lipid profile. In addition, agents belonging to the same class (e.g. beta blockers) can have significantly different actions on lipid levels. We summarize the effects of drugs used for the prevention and treatment of vascular diseases on the lipid profile. These effects should be considered when selecting a specific agent, particularly in high-risk patients.

**Keywords:** Dyslipidemia, antihypertensive agents, antidiabetic agents, lipid-modifying agents, antiobesity agents.

## INTRODUCTION

Elevated levels of low density lipoprotein cholesterol (LDL-C) are a major vascular risk factor [1]. Low levels of high density lipoprotein cholesterol (HDL-C) are also associated with higher vascular morbidity and mortality [1-3]. The relationship between triglyceride (TG) levels and vascular events is more controversial but elevated TG levels also appear to be associated with increased vascular risk [4]. Interestingly, several agents that are used for the prevention and treatment of vascular diseases have an adverse effect on the lipid profile (Table 1). The aim of the present review is to summarize the effects of these drugs on lipids.

## SEARCH METHODS

A literature search (using PubMed) was performed using the following key words: “diuretics”, “beta blockers”, “calcium channel blockers”, “angiotensin converting enzyme inhibitors”, “angiotensin receptor blockers”, “alpha blockers”, “moxonidine”, “minoxidil”, “rosiglitazone”, “pioglitazone”, “metformin”, “sulphonylureas”, “insulin”, “acarbose”, “repaglinide”, “nateglinide”, “sitagliptin”, “vildagliptin”, “exenatide”, “pramlintide”, “orlistat”, “sibutramine”, “rimonabant”, “bile acid sequestrants”, “fibrates”, “omega 3 fatty acids”, “LDL-C”, “HDL-C” and “triglycerides” up to 15 June 2009. The authors also manually reviewed the references of retrieved articles for any pertinent material.

## ANTIHYPERTENSIVE AGENTS

Non-selective beta blockers (e.g. propranolol) increase TG levels and lower HDL-C levels without affecting LDL-C

levels [5, 6]. In contrast, beta1-selective blockers (e.g. atenolol and metoprolol) do not appear to have an adverse effect on the lipid profile [5, 7-10] and in some studies increased HDL-C levels and lowered total cholesterol (TC) and TG levels [11]. However, atenolol increased TG levels in other studies [12, 13]. Both non-selective and beta1-selective blockers may exacerbate preexisting hypertriglyceridemia and cases of pancreatitis have been reported in patients treated with these agents [14, 15]. Beta1-selective blockers with intrinsic sympathomimetic activity (celiprolol, acebutolol and nebivolol) lowered LDL-C and TG levels and also increased HDL-C levels [5, 6]. Atenolol lowered HDL-C levels and increased LDL-C and TG levels compared with celiprolol [16]. Nebivolol, a beta1-selective blocker which also stimulates nitric oxide release, does not appear to change lipid parameters significantly [8, 13]. However, a fall in HDL-C levels during nebivolol treatment was reported in another study [17]. Carvedilol, a non-selective beta blocker with alpha1 selective blocking activity, appears to have more beneficial effects on the lipid profile than beta1-selective blockers [11, 18, 19]. Carvedilol did not change TC levels but lowered TG levels and increased HDL-C levels more than atenolol [11]. In another study, atenolol decreased HDL-C levels more than carvedilol [18]. Carvedilol also lowered TC levels more than metoprolol [19]. In addition, metoprolol increased TG levels whereas carvedilol had no significant effect [19]. Interestingly, several polymorphisms of the beta2 and beta3 adrenoreceptor genes appear to be associated with increased risk for experiencing an increase in LDL-C and TG levels during treatment with beta blockers [20, 21].

Hydrochlorothiazide at a dose of 6.25-12.5 mg/day does not appear to adversely affect the lipid profile [22]. Hydrochlorothiazide 25 mg/day did not change TC or HDL-C levels but increased TG levels [12, 23]. A number of meta-analyses showed that hydrochlorothiazide at a dose > 25 mg/day increases TC and TG levels more than lower doses

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**Table 1. Adverse Lipid Effects of Agents Used for the Prevention and Treatment of Vascular Diseases**

Agent	Adverse Effect on The Lipid Profile	Reference
Non-selective beta blockers	↑ TG levels ↓ HDL-C levels	[5, 6, 14, 15]
Beta1-selective blockers	↑ TG levels (no effect or ↓ in other studies)	[5, 7-15]
Nebivolol	↓ HDL-C levels (no effect in other studies)	[8, 13, 15]
Hydrochlorothiazide (≥ 25 mg/day)	↑ TG levels ↑ TC levels	[6, 22]
Chlorthalidone	↑ LDL-C levels	[6]
Indapamide	↑ LDL-C levels (no effect in other studies)	[6, 21, 24]
Pioglitazone	↑ LDL-C levels	[46, 47]
Rosiglitazone	↑ LDL-C levels ↑ TG levels	[46, 47]
Orlistat	↓ HDL-C levels	[56]
Bile-acid sequestrants	↑ TG levels	[1, 64-66]
Fibrates	↑ LDL-C levels (in patients with hypertriglyceridemia)	[1, 67]
Omega-3 fatty acids	↑ LDL-C levels (in patients with severe hypertriglyceridemia)	[68-70]

TG = triglyceride; HDL-C = high density lipoprotein cholesterol; TC = total cholesterol; LDL-C = low density lipoprotein cholesterol.

[6, 24]. In addition, thiazide diuretics lowered HDL-C levels only in diabetic patients [6]. Interestingly, the increase in LDL-C and TG levels with thiazide diuretics appears to be more pronounced in men [6]. In addition, the rise in LDL-C levels appears to be greater in patients with higher baseline LDL-C levels [6]. Chlorthalidone increased LDL-C levels more than other thiazide diuretics [6]. The non-thiazide diuretic indapamide at a dose of 2.5 mg/day or at 1.5 mg/day in a sustained release form reduced blood pressure to an extent similar or greater than hydrochlorothiazide 25 mg/day [23, 25]. Indapamide in these doses did not change TC, TG or HDL-C levels [23, 26]. However, in a meta-analysis indapamide did not change TG levels but increased LDL-C levels [6]. In comparative studies, indapamide 2.5 mg/day and hydrochlorothiazide 12.5 mg/day had a similar effect on lipid profile [27]. However, indapamide 2.5 mg/day increased TG levels more than hydrochlorothiazide 25 mg/day [23].

Calcium channel blockers appear to have neutral effects on the lipid profile [6, 28-31]. An increase in HDL-C levels was also reported in some studies [12, 32].

Angiotensin converting enzyme inhibitors increased HDL-C levels and lowered TC and TG levels in some reports [12, 30, 33]. In others, they did not affect the lipid profile [7, 34] or lowered only LDL-C [35] or TG levels [6]. Angiotensin II receptor blockers increased HDL-C levels and lowered LDL-C and TG levels [28, 36-39]. In other studies they did not affect the lipid profile [35] or lowered only LDL-C levels [40].

Some large randomized controlled trials compared the effects of different classes of antihypertensive agents on the lipid profile. In the Losartan Intervention For Endpoint re-

duction in hypertension (LIFE) study, HDL-C levels decreased less with losartan-based treatment than with atenolol-based treatment [41]. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), TC levels decreased more with amlodipine- and lisinopril-based treatment than with chlorthalidone-based treatment [42]. However, it is difficult to compare the effects of antihypertensive agents on lipids in randomized controlled trials since most patients in these studies are treated with multiple classes of antihypertensive agents.

Doxazosin, an alpha1-blocker, increased HDL-C levels and lowered LDL-C and TG levels [6, 33, 43]. Other alpha blockers have similar beneficial effects on the lipid profile [6]. The less frequently used antihypertensive agents moxonidine and minoxidil appear to lower LDL-C levels without affecting TG or HDL-C levels [44, 45].

#### ANTIDIABETIC AGENTS

Both rosiglitazone and pioglitazone increased LDL-C levels [46, 47]. However, it appears that pioglitazone lowers small dense LDL particles (which are potentially more atherogenic) whereas rosiglitazone has a smaller or no effect on LDL size [48-50]. In addition, rosiglitazone increased TG levels whereas pioglitazone decreased TG levels [46]. Both these thiazolidinediones increased HDL-C levels [46, 51]. In comparative studies, pioglitazone induced a greater reduction in TG levels, a larger increase in HDL-C levels, a smaller increase in TC and LDL-C levels as well as a greater shift towards larger, more buoyant LDL particles [48-50]. Other antidiabetic agents appear to have neutral or beneficial effects on the lipid profile. Metformin decreased TG and LDL-C levels and did not affect HDL-C levels [46]. Sulphonylureas, acarbose and glinides (repaglinide and nateg-

linide) decreased TG levels and did not affect LDL-C or HDL-C levels [46]. The “newer” oral antidiabetic drugs sitagliptin and vildagliptin (which inhibit dipeptidyl peptidase IV) appear to have a neutral effect on the lipid profile [52]. Preliminary data suggest that vildagliptin improves postprandial lipemia [53]. Insulin appears to reduce TG and increase HDL-C levels, particularly in patients with poor glycemic control [54]. “Newer” antidiabetic agents administered by subcutaneous injection include exenatide (a glucagon-like peptide 1 agonist) and pramlintide (an amylin analogue) [54]. Neither exenatide nor pramlintide appear to alter the lipid profile significantly [52, 55].

### ANTIOBESITY AGENTS

Orlistat not only reduces body weight but also lowers LDL-C levels [56]. However, a small but significant decrease in HDL-C levels was reported during orlistat treatment [56]. Orlistat does not appear to alter TG levels significantly [56]. Sibutramine, another agent approved for the management of obesity, decreases TG levels and increases HDL-C concentration [56]. Sibutramine does not significantly affect LDL-C levels [56]. Rimonabant, an antiobesity agent that was withdrawn for safety reasons, increased HDL-C levels and reduced TG levels [57-63].

### LIPID PROFILE-MODIFYING AGENTS

Bile-acid sequestrants (resins) decrease LDL-C levels but also increase TG levels [1]. Colesevelam, a newer resin which appears to be better tolerated than older members of this class, also increased TG levels [64-66]. Accordingly, resin monotherapy is contraindicated in patients with TG levels > 400 mg/dl (4.5 mmol/l) and should be avoided when TG levels are > 200 mg/dl (2.2 mmol/l) [1].

In patients with hypercholesterolemia, fibrates lower LDL-C levels by 10-20% [1, 67]. However, an increase in LDL-C levels might be observed when fibrates are given to patients with hypertriglyceridaemia [1, 67]. This appears to be due to an increase in very low density lipoprotein (VLDL) lipolysis by lipoprotein lipase [67].

Omega-3 fatty acids lower TG levels but increase LDL-C levels, particularly in patients with severe hypertriglyceridemia [68-70]. This increase in LDL-C levels appears to be due to a shift to larger, more buoyant and (potentially) less atherogenic LDL particles [68, 71, 72]. Interestingly, in patients with hypertriglyceridemia who were treated with statins, adding omega-3 fatty acids did not affect LDL-C levels [73]. In addition, omega-3 fatty acids lowered LDL-C levels in patients with normal TG levels [68, 70].

### CONCLUSIONS

Several drugs used for the prevention and treatment of vascular diseases appear to have an adverse effect on the lipid profile. Moreover, agents belonging to the same class (e.g. beta-blockers) can have significantly different actions on lipid levels. These effects might have to be considered when selecting a specific agent, particularly in high-risk patients. However, it is unclear whether the adverse lipid effects of these agents reduce their protective effect against vascular events. In addition, the effect on lipids is a surrogate endpoint. Therefore, only large randomized clinical trials

with vascular endpoints should guide our therapeutic decisions.

### LIST OF ABBREVIATIONS

HDL-C	=	High density lipoprotein cholesterol
LDL-C	=	Low density lipoprotein cholesterol
LIFE	=	Losartan Intervention For Endpoint reduction in hypertension
TC	=	Total cholesterol
TG	=	Triglyceride
VLDL	=	Very low density lipoprotein

### DECLARATION OF INTEREST

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