Non-Statin Lipid-Lowering Agents
M Holler - Last updated: 10/2016

Drug/Class	Generic? Y/N	Lipid Effects (monotherapy)	Lipid Effects (w/ statin)	Outcomes Data	Cost (30-day)	Comments
Cholestyramine *(Questran)* Bile acid sequestrant	Y	LDL ↓: 9% (4 g to 8 g/day); 21% (16 g to 20 g/day); 23% to 28% (>20 g/day) HDL ↑: 4% to 8% (16 to 24 g/day) TG ↑: 11% to 28% (4 g to 24 g/day)	Further LDL ↓: about 10% (8 g) to about 20% (24 g) Further HDL ↑: 0% to 10%	<u>Primary prevention, men:</u> reduces need for bypass, and combined endpoint of coronary heart disease, death, and nonfatal MI (NNT = 59 for 7 years) <u>Secondary prevention, men:</u> with diet, reduces cardiac events vs usual care (not placebo-controlled; events not a primary outcome). Slows progression and increases regression of atherosclerosis.	$404, generic packets (16 g/day)	Can be difficult to tolerate due to gastrointestinal side effects such as constipation and gas Can bind to other drugs and reduce absorption (e.g. levothyroxine, OCs, vitamins, digoxin, warfarin, BBs, thiazides, fat-soluble vitamins, mycophenolate, NSAIDs/APAP) Take 1 hr before or 4 hrs after other meds GI side effects (constipation, diarrhea, flatulence, nausea) Poor compliance (4 packets/ day) Avoid use if: bowel obstruction, TGs > 500
Colesevelam *(WelChol)* Bile acid sequestrant	N	With 3.75 g/day: LDL ↓: 15% to 19.1% HDL ↑: 3% to 8.1% TG ↑: 10% (~20% when used with insulin or SUs)	With 3.75 g/day: Further LDL ↓: 10% to 16% Further HDL ↑: 3% to 7%	None	$678 (3.75 g/day)	Studied in combo w/ atorvastatin, lovastatin, pravastatin, and simvastatin Lower risk of GI side effects compared to cholestyramine and colestipol Can bind to other drugs and reduce absorption (see above) Poor compliance (6 tabs/day) GI side effects (constipation, diarrhea, flatulence, nausea)

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						Avoid use if: bowel obstruction, TGs > 500
Colestipol *(Colestid)* Bile acid sequestrant	Y	LDL ↓: 5% (2 g/day) to 26% (16 g/day) HDL: no effect TG ↑: 10% to 15% (2 to 16 g/day)	Further LDL ↓: 10% (5 g/day) 12% (10 g/day)	Reduces progression of atherosclerosis and events when combined with niacin or lovastatin (not a primary outcome).	$236, generic packs (10 g/day)	Available as granules, packs, tablets Can be difficult to tolerate due to GI side effects such as constipation and gas Can bind to other drugs and reduce absorption (see above) GI side effects (constipation, diarrhea, flatulence, nausea) Avoid use if: bowel obstruction, TGs > 500
Exetimibe *(Zetia)* Cholesterol absorption inhibitor	N (going generic Dec 2016)	LDL ↓: 15-25% HDL ↑: 2-3% TG ↓: 5-10% (with 10 mg/day)	Further LDL ↓: 25% Further HDL ↑: 3% Further TG ↓: 14%	With simvastatin 20 mg, reduces first major atherosclerotic event in chronic renal disease – SHARP trial (2011) Adding ezetimibe to simvastatin 40 mg post-ACS prevents one CV event for every 50 patients treated for 7 yrs (vs simvastatin alone) – IMPROVE-IT trial (2015)	$343 (10 mg/day) *Vytorin*: $339 (10 mg/ simva 20 mg/ day)	Consider ezetimibe as a statin add-on for high-risk patients who: • can't tolerate a high-intensity statin • don't get the expected 50% LDL reduction with a high-intensity statin
Fenofibrate *(Tricor)* Fibrate	Y	LDL ↓: 10-20% HDL ↑: 11% TG ↓: 23.5% to 54.5% (greatest drop in patients with highest	Further LDL ↓: 0% to 6% Further HDL ↑: 13% to 17% Further TG ↓: 20% to 32%	<u>Prevention of CV events in T2DM</u>: • did not reduce primary composite outcome (non-fatal MI or CV death) • improved non-fatal MI (24%↓), coronary revascularization (21%↓), progression to	$172 generic tablets (145 mg/day) $59, generic capsules (135 mg/day)	First-line for TG >1000 mg/dL Option for TG <u>≥</u>500 mg/dL or low HDL Preferred over gemfibrozil for use with statins (fewer AEs) Requires <u>renal dose adjustment</u>

		triglycerides) (with 145 mg/day)	(with 200 mg/day – Canadian dosing)	albuminuria, and reduced laser treatments for retinopathy • non-significant increase in CV death <u>As statin add-on</u>, did NOT lower risk of non-fatal MI, non-fatal stroke, or CV death more than statin alone Based on AIM-HIGH, ACCORD, HPS2-THRIVE studies…FDA removed labeling approving concomitant use of fibrates (and niacin) with statins – no clear benefit		Associated with reversible increase in Scr Unclear risk of cholelithiasis (avoid in pts with history)
Gemfibrozil *(Lopid)* Fibrate	Y	LDL ↓: 10-15% HDL ↑: 6% TG ↓: 33% to 50% (greatest drop in patients with highest triglycerides) (with 1200 mg/day)	Further TG ↓: 41% Further HDL ↑: 9%	<u>Primary prevention, men:</u> reduced sudden cardiac death plus fatal/nonfatal MI by 22% (VA-HIT study) to 34% (HHS study) NNT = 71 over 5 years Secondary prevention of nonfatal MI plus cardiac death in men with low HDL NNT = 23 over 5 years <u>No mortality benefit</u>	$146, generic (1200 mg/day)	First-line for TG > 1000 mg/dL Option for TG <u>></u> 500 mg/dL or low HDL Requires <u>renal dose adjustment</u> Avoid with statin – concurrent use DOUBLES statin concentration Unclear risk of cholelithiasis (avoid in pts with history)
Niacin (*Niacor* – IR) (*Niaspan* – ER/SR)	Y	LDL ↓: 14% to 17% (*Niaspan* 2 g/day) 12% (niacin immediate-release 1.5 g/day and *Niaspan* 1.5 g/day)	Further LDL ↓: 8% (*Niaspan* 1 g/day) 31% (*Niaspan* 2 g/day)	<u>Secondary MI prevention:</u> one less MI for every 30 patients treated for five years (Coronary Drug Project) <u>As statin add-on</u>, reduces carotid intima-media thickness (surrogate marker)	$5 (*Niacor* 1 g/day) $329 (*Niaspan* 1 g/day)	Option for TG <u>></u> 500 mg/dL Raises HDL more than any other agent Available as *Niaspan*/lovastatin (*Advicor*) and *Niaspan*/simvastatin (*Simcor*)

		HDL ↑: 22% to 35% (2 g/day *Niaspan*) 17% (niacin immediate release 1.5 g/day) 20% to 22% (*Niaspan* 1.5 g/day) TG ↓: 20% to 50%	Further HDL ↑: 23% (*Niaspan* 1 g/day) 27% (*Niaspan* 2 g/day) Further TG ↓: 24% (*Niaspan* 1 g/day) 27% (*Niaspan* 2 g/day)	as compared to ezetimibe in patients with lower HDL <u>No CV event benefit from combo of niacin + statin</u> vs statin alone in patients with well-controlled LDL, low HDL, and high TG. <u>No mortality benefit</u>	$7 (niacin ER generic 1g/day) $267 (*Advicor* 20 mg/1 g daily) $287 (*Simcor* 20 mg/1 g daily)	Dose-dependent risk of hyperglycemia (especially in patients with T2DM) and liver toxicity May increase risk of statin myopathy Most common side effects: flushing, itching, rash, HA ER formulation better tolerated, but more hepatotoxic (though risk is relatively low for doses of 1-2g/day or less)
Icosapent ethyl *(Vascepa)* EPA; ~ 1g omega-3 per capsule (ultra-pure, no DHA)	Y	LDL: No effect HDL: No effect TG ↓: 27%	Further TG ↓: 21.5% (4 g/day), 10.1% (2 g/day) Further LDL ↓: 6.2% (4 g/day)	None available Currently being studied in combo w/ statin; pts w/ high CV risk and high TGs – REDUCE-IT trial	$281 (4 g/day)	Option for TG ≥ 500 mg/dL Safe for use with statins Use caution with fish or shellfish allergy Less likely to raise LDL (compared to *Lovaza*)
Omega-3 ethyl esters *(Lovaza)* EPA/DHA; ~1g omega-3 per capsule	Y	LDL ↑: 44.5% (when TG are elevated) HDL ↑: 9.1% TG ↓: 45% (with 4 g/day)	LDL ↑: 0.7% Further HDL ↑: 3.4% Further TG ↓: 29.5% (with 4 g/day)	<u>Secondary prevention:</u> reduces cardiovascular death, sudden death, and combined endpoint of death, non-fatal MI, and non-fatal stroke <u>Secondary prevention in patients with, or at risk for, T2DM</u>: did NOT reduce CV events (note: ~50% of patients were taking a statin) Study in progress – in combo	$248 (generic, 4 g/day)	Option for TG <u>≥</u> 500 mg/dL Safe for use with statins Associated with an increase in risk for recurrence of symptomatic afib or flutter within first 3 months of therapy Use with caution with fish or shellfish allergy Remind patients using OTC fish

				w/ statin; pts w/ high CV risk and high TGs – STRENGTH trial		oil: dose of 4g/day is needed for max TG lowering (patients often under-dose) For "TG lowering": recommend 4g/day EPA/DHA For "Cardio-protection": recommend 1-2 g/day EPA/DHA
Alirocumab *(Praluent)* Evolocumab *(Repatha)* PCSK9 inhibitors	N	LDL ↓: 38-72% (usually 50-60%) HDL ↑: 4-9% TG ↓: 2-23%	Further LDL ↓: 48% (ODYSSEY, alirocumab) 50-60% (DESCARTES, evolocumab)	Not available 4 CV outcomes studies currently in progress – results expected 2017 (March?) Preliminary data suggests ~50% decrease in CV events	$7000-$14000/year	Injectable biologics (monoclonal antibodies) Approved for treatment of <u>heterozygous</u> familial hypercholesterolemia (in combination with statin) OR in patients w/ CVD who need further lowering of LDL (on max statin, or can't tolerate statin) *Repatha* also indicated for <u>homozygous</u> familial hypercholesterolemia Has NOT yet been proven to improve CV outcomes Lacks long-term safety data Possible side effects: injection site reactions (7%), nasopharyngitis, URI, muscle pain, neurocognitive events (confusion/memory)

Table adapted from: *PL Detail-Document, Non-Statin Lipid-Lowering Agents. Pharmacist's Letter/Prescriber's Letter. July 2015.*

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Average effects of different classes of lipid lowering drugs on serum lipids

Drug class	Serum LDL cholesterol (% change)	Serum HDL cholesterol (% change)	Serum triglycerides (% change)
Bile acid sequestrants	↓ 15 to 30	0 to slight increase	No change*
Cholesterol absorption inhibitors	↓ 17	↑ 1	↓ 7 to 8
Fenofibrate (micronized form)	↓ 6 to 20	↑ 5 to 20¶	↓ 41 to 53
Gemfibrozil	↓ 10 to 15	↑ 5 to 20¶	↓ 35 to 50
Neomycin	↓ 20 to 25	No change	No change
Nicotinic acid (niacin)	↓ 10 to 25	↑ 15 to 35	↓ 25 to 30
Omega 3 fatty acidsΔ	↑ 4 to 49	↑ 5 to 9	↓ 23 to 45
PCSK9 inhibitors	↓ 38 to 72	↑ 4 to 9	↓ 2 to 23
Statins	↓ 20 to 60	↑ 5 to 10	↓ 10 to 33

↑: increase; ↓: decrease; PCSK9 inhibitors: proprotein convertase subtilisin kexin type 9 inhibitors.
* Serum triglyceride levels may increase in patients with pre-existing hypertriglyceridemia.
¶ Increases of 20% are seen in patients with very high triglycerides; increases of 5% are more typical with fibrate monotherapy in patients wi
Δ Lovaza (US trade name) 4 g daily or 12 to 15 g of less purified form of omega-3 fatty acids.