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# ANTILIPEMIC AGENTS

## BASIC SUMMARY

| Drug Class | Example | Mechanism of Action | Target Lipid Effect | Other Lipid Effects |
|---|---|---|---|---|
| **LDL Target – Statin** | | | | |
| HMG-CoA Reductase Inhibitors | ▪ Atorvastatin<br>▪ Rosuvastatin | ▪ Inhibits the enzyme HMG-CoA reductase, which reduces hepatic cholesterol production<br>▪ Upregulates LDL receptors to extract LDL | ↓LDL ≥ 50% (High-Intensity)<br>↓LDL 30-50% (Mod-Intensity) | ↓TG ~ 20%<br>↑HDL ~ 10% |
| **LDL Target – Nonstatin** | | | | |
| ACL Inhibitors | ▪ Bempedoic acid | ▪ Inhibits ATP-citrate lyase (ACL), which reduces hepatic cholesterol production<br>▪ Upregulates LDL receptors to extract LDL | ↓LDL ~ 15% to 30%<br>(> effects when used alone) | TG: Neutral<br>↓HDL ~ 5% |
| ANGPTL3 Inhibitors | ▪ Evinacumab | ▪ Inhibits angiopoietin-like 3 peptide (ANGPTL3), which then increases lipoprotein lipase (LPL) & endothelial lipase (EL) activity, resulting in a reduction in TG, LDL, and HDL | ↓LDL ~ 50%<br>(added to existing max therapy) | ↓TG ~ 50%<br>↓HDL ~ 30% |
| Bile Acid Sequestrants | ▪ Colesevelam | ▪ Binds to bile salts to prevent their enterohepatic reabsorption/recycling | ↓LDL ~ 15 to 30% | ↑TG ~10% |
| Cholesterol Absorption Inhibitors | ▪ Ezetimibe | ▪ Inhibits intestinal cholesterol absorption at Niemann-Pick C1-Like 1 (NPC1L1) peptide | ↓LDL ~20% | ↓TG ~10%, ↑HDL~5% |
| PCSK9 Inhibitors | ▪ Alirocumab<br>▪ Evolocumab | ▪ Inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9) binding on hepatic LDL receptors, allowing for the increased hepatic clearance of circulating LDL | ↓LDL ~ 55% | ↓ApoB100 ~50% |
| Small Interfering RNA | ▪ Inclisiran | ▪ Decreases PCSK9-mediated degradation of LDL receptors while also increasing LDL-r gene expression to increase removal of circulating LDL | ↓LDL ~50%<br>(added to existing max therapy) | ↓TG ~ 15%<br>↑HDL ~ 8% |
| **Triglyceride (TG) Target** | | | | |
| Fibrates | ▪ Fenofibrate<br>▪ Gemfibrozil | ▪ Stimulates PPAR-α transcription, which reduces the production of VLDL while also increasing the catabolism of VLDL in circulation (the result is a decrease in TG concentrations) | ↓TG ~20% to 50% | ↓LDL ~5% to 20%<br>↑HDL ~ 20% |
| MTP Inhibitors | ▪ Lomitapide | ▪ Inhibits microsomal triglyceride transfer protein (MTP) in hepatocytes and enterocytes to reduce the formation of TG and ApoB-containing particles to reduce VLDL & LDL | ↓ LDL ~50%<br>↓TG 35-65% | ↓ApoB100 ~50% |
| Omega-3 Fatty Acids | ▪ Icosapent ethyl | ▪ Reduces the synthesis of TG-rich VLDL by inhibiting diacyl-glycerol acetyl-transferase (DGAT)<br>▪ Increases degradation of ApoB100 and fatty acid oxidation by the liver | ↓TG ~ 40% | LDL ~ +/-<br>↓ApoB100 ~10% |
| **Miscellaneous Target** | | | | |
| Niacin | ▪ Niacin | ▪ Reduces the peripheral mobilization of free fatty acids for the liver to use and also reduces the hepatic synthesis of TG-rich VLDL (exact mechanisms unknown) | ↓TG ~ 40%<br>↑HDL up to ~ 30% | ↓LDL ~5% to 20%<br>↓Lp(a) ~ 25% |

Note: The reported changes in lipids represent the editor's best effort to summarize the main clinical effect based on data from various reputable sources of information and reported clinical trial data. The numbers are not meant to be exact for all patients. Small variations in or use of exact numbers are not the intended goal for providing general context related to the use of these treatments in a diverse population of people with many confounders likely present.

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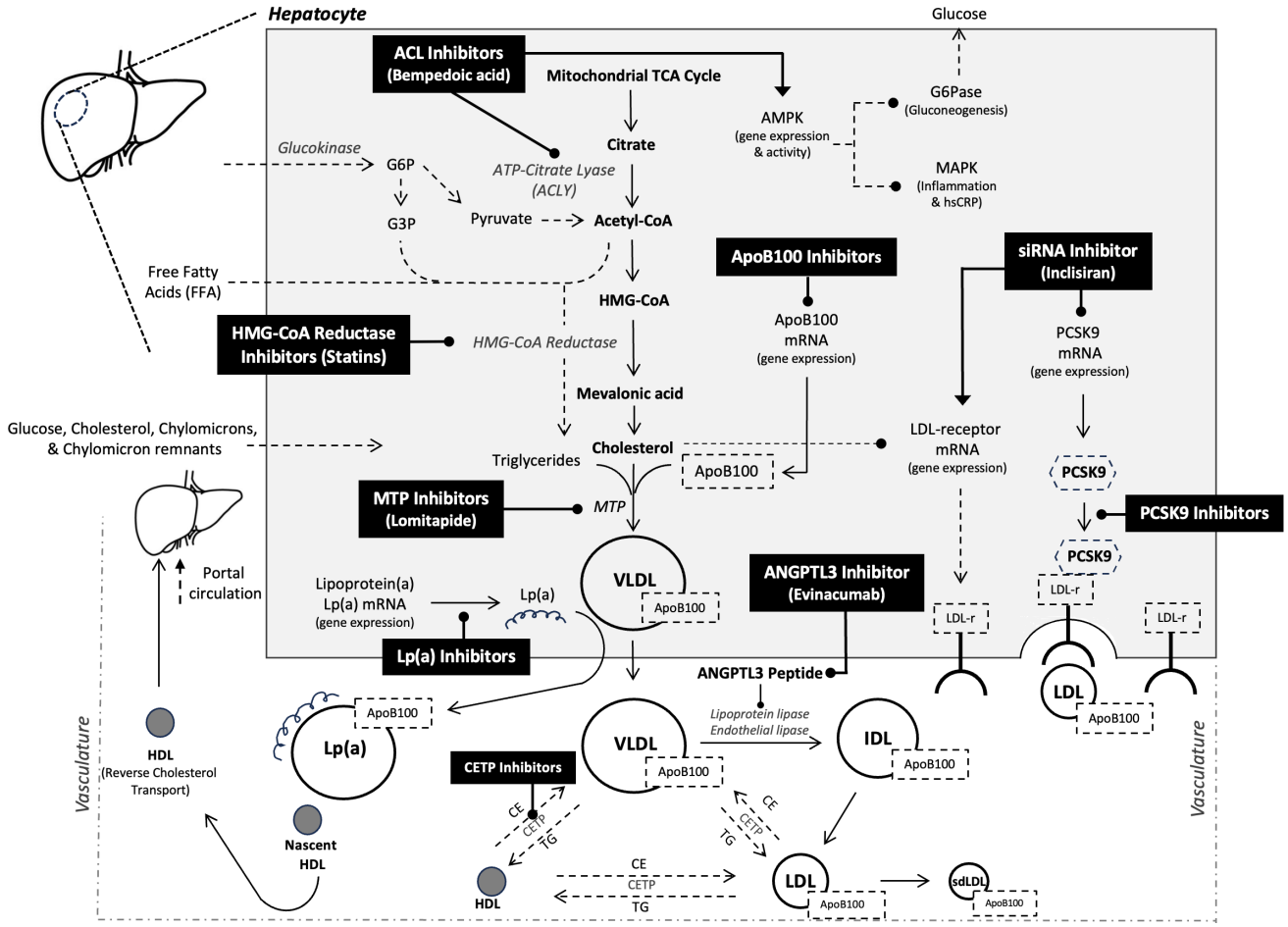
# CHOLESTEROL & LIPOPROTEIN METABOLISM

## PHARMACOTHERAPEUTIC INTERVENTIONS



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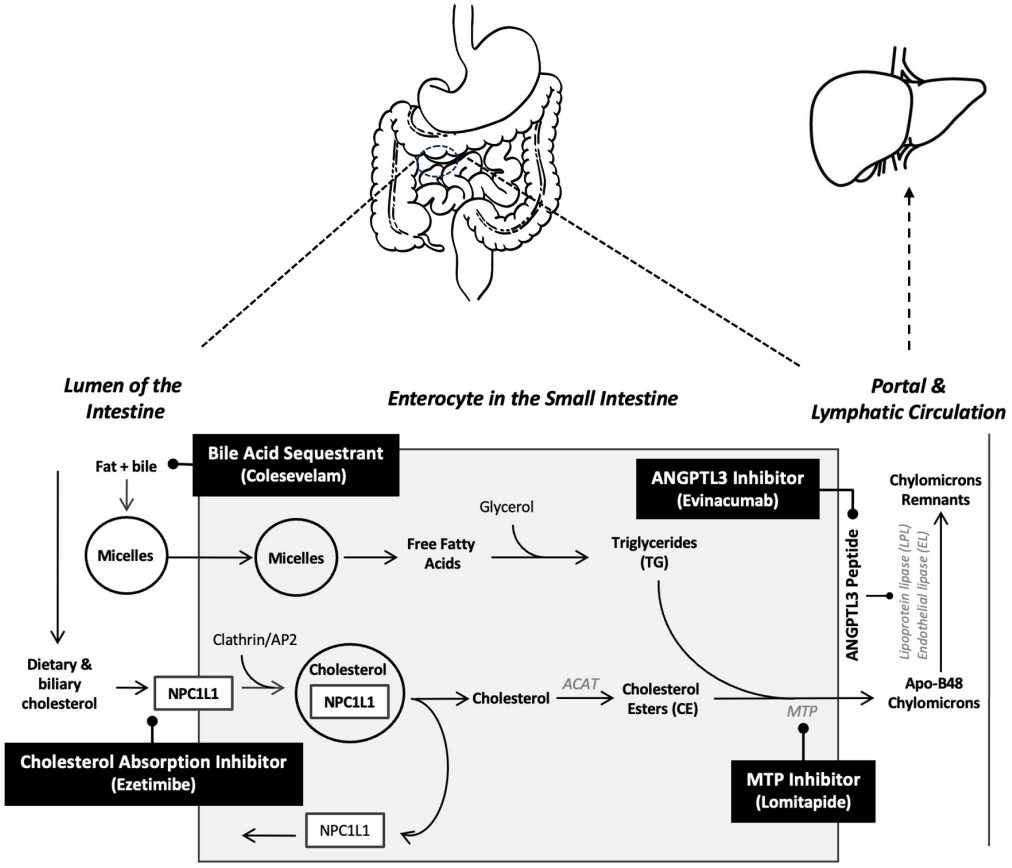
# DIETARY CHOLESTEROL ABSORPTION

## PHARMACOTHERAPEUTIC INTERVENTIONS



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# STATIN DOSE EQUIVALENCE

## BY LDL LOWERING INTENSITY

| Statin | Low-Intensity | | Moderate-Intensity | | High-Intensity | |
|---|---|---|---|---|---|---|
| LDL-C Lowering | < 30% | | 30-50% | | > 50% | |
| Rosuvastatin | | | 5 mg | 10 mg | 20 mg | 40 mg |
| Atorvastatin | | | 10 mg | 20 mg | 40 mg | 80 mg |
| Pitavastatin | | 1 mg | 2 mg | 4 mg | | |
| Simvastatin | 5 mg | 10 mg | 20 mg | 40 mg | | |
| Pravastatin | 10 mg | 20 mg | 40 mg | 80 mg | | |
| Lovastatin | 10 mg | 20 mg | 40 mg | | | |
| Fluvastatin | 20 mg | 40 mg | 80 mg | | | |

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# HMG-COA REDUCTASE INHIBITORS (STATINS)

## PHARMACOKINETIC & PHARMACODYNAMIC DIFFERENCES

| Characteristic | MODERATE-INTENSITY (30% to 50%) | | | | | HIGH-INTENSITY (≥ 50%) | |
|---|---|---|---|---|---|---|---|
| | Fluvastatin | Lovastatin | Pitavastatin | Pravastatin | Simvastatin | Atorvastatin | Rosuvastatin |
| Max Dose (mg)/d | 80 mg | 80 mg | 4 mg | 80 mg | 40 mg | 80 mg | 40 mg |
| Max % LDL Reduction | ~ 35% | ~ 40% | ~ 45% | ~ 35% | ~ 40% | ~ 60% | ~ 60% + |
| Reduction in TG's | ~ 20% | ~ 20% | ~ 20% | ~ 20% | ~ 20% | ~ 35% | ~ 25% |
| Increase in HDL | ~ 10% | ~ 10% | ~ 10% | ~ 10% | ~ 10% | ~ 10% | ~ 10% |
| Plasma Half-life | 3 hrs | 2 hrs | 12 hrs | 1-2 hrs | 1-2 hrs | 14 hrs | 19 hrs |
| Penetration of CNS | No | Yes | Yes | No | Yes | No | No |
| Renal Excretion | 5% | 10% | 15% | 20% | 13% | 2% | 10% |
| Pathway of Elimination | Phase I Influx/Efflux Transporters | Phase I & II Influx/Efflux Transporters | Phase I & II Influx/Efflux Transporters | Phase II Influx/Efflux Transporters | Phase I & II Influx/Efflux Transporters | Phase I & II Influx/Efflux Transporters | Phase I & II Influx/Efflux Transporters |

Note: The reported changes in lipids represent the editor's best effort to summarize the clinical effect based on data from various reputable sources of information and reported clinical trial data. The goal of this table is to provide general context related to the use of these treatments in a diverse population with likely confounders, not to document small variations or exact numbers.

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# HMG-COA REDUCTASE INHIBITORS (STATINS)

## PATHWAYS OF ELIMINATION

| | MODERATE-INTENSITY STATINS (30% to 50%) | | | | | HIGH-INTENSITY STATINS (≥ 50%) | |
|---|---|---|---|---|---|---|---|
| Pathway | Fluvastatin | Lovastatin | Pitavastatin | Pravastatin | Simvastatin | Atorvastatin | Rosuvastatin |
| Phase I Metabolism (Oxidation/Reduction) | CYP2C9 (75%)<br>CYP3A4 (20%)<br>CYP2C8 (5%) | CYP3A4 | CYP2C8/9 (minor) | - | CYP3A4 | CYP3A4 | CYP2C9 (10%) |
| Phase II Metabolism (Conjugation) | | UGT1A1<br>UGT1A3 | UGT1A3<br>UGT2B7 | UGT1A1<br>UGT1A3 | UGT1A1<br>UGT1A3 | UGT1A1<br>UGT1A3<br>UGT2B7 | UGT1A1<br>UGT1A3 |
| Influx Cell Membrane Transporters | OATP1B1<br>OATP2B1 | OTAP1B1 | OATP1B1<br>OATP1B3 | OTAP1B1<br>OATP1B3<br>OATP2B1 | OATP1B1 | OATP1B1<br>OTAP1B3 | OAT1B1/3<br>NTCP<br>OAT2B1 |
| Efflux Cell Membrane Transporters | BCRP<br>P-gp | BCRP<br>P-gp | BCRP | BCRP<br>P-gp | BCRP<br>P-gp | BCRP<br>P-gp | BCRP<br>P-gp |

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# HMG-COA REDUCTASE INHIBITORS (STATINS)
## RISK OF LIVER INJURY

| Common Clinical Questions | Answer |
|---|---|
| Are elevations in liver enzymes associated with statins? | Yes |
| Are statin-associated elevations in liver enzymes indicative of damage or dysfunction? | No |
| Do statins increase the incidence of liver failure, liver transplants, or death in general population? | Yes |
| Should liver enzymes be monitored in patients getting long-term statins? | No |
| Are statins “contraindicated” in chronic liver disease or compensated cirrhosis or MSALD (previously referred to as NAFLD) or liver transplantation or autoimmune hepatitis? | No |
| Any safety concerns since FDA changed recommendations to say no liver tests needed after starting statin? | No |
| Do statins need dose adjustments in HIV or HBV or HCV treatment? | Yes |

Take Home Point: The risk of serious hepatotoxicity is ~0.001%. However, the risk is dose- or concentration-dependent.

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# HMG-COA REDUCTASE INHIBITORS (STATINS)

## DEFINITIONS FOR MUSCLE RELATED PROBLEMS

| Muscle ADE | Definition |
|---|---|
| SAMS | Statin-Associated Muscle Symptoms<br>Muscle symptoms reported during statin therapy but not necessarily caused by the statin |
| Myalgia | Unexplained muscle discomfort described often as “flu-like” + normal CK: soreness, aches, stiffness, cramps |
| Myopathy | Muscle pain or weakness with elevations in CK > 10 times the ULN |
| Rhabdomyolysis | Severe form of myopathy but associated with myonecrosis (CK > 40 x ULN)+ myoglobinuria or ARF/AKI |

Take Home Point: The risk of serious statin-induced muscle injury (including rhabdomyolysis is < 0.1%) and appears to be dose- or concentration-dependent.

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# HMG-COA REDUCTASE INHIBITORS (STATINS)

## RISK OF MUSCLE INJURY

| Risk for Muscle Injury | Answer |
|---|---|
| Can statin-associated myalgia be reliably differentiated from placebo? | Yes |
| Is there a reliable index score for statin-associated myalgia? | Yes |
| Are statin-associated muscle complaints altered by acute or chronic activity? | Yes |
| Can patient's intolerant to one statin switch to another? | Yes |
| Is the risk of muscle injury/pain related to the dose or concentration of statins? | Yes |

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# HMG-COA REDUCTASE INHIBITORS (STATINS)
## RISK OF DIABETES

| Risk for Diabetes Mellitus | Answer |
|---|---|
| What is magnitude of risk for Type 2 DM? | ▪ A meta-analysis suggested the risk is ~10% - 20% with OR of 1.09 (95% CI, 1.02 – 1.17) and $I^2$ = 11.2%.<br>  ▪ NNT over 4 years to cause 1 excess case was 255<br>▪ Overall, the risk is modest and is estimated to be ~0.2% per year (depending on the risk of DM in the population assessed), but the risk does not override the CV benefit. |
| What is the impact of statins on glycemic control in diabetics? | ▪ Available data suggests a mean increase of ~0.3% or less.<br>▪ QOE: Low to draw a conclusion |
| Are there any patients who should not be started on statins due to risk of DM? | ▪ Due to unknown clinical importance of this risk, no changes to current recommended practice.<br>▪ SOR: expert opinion; QOE: Moderate |
| What is the mechanism for statin associated DM? | ▪ Unknown<br>▪ SOR: Expert opinion;  QOE: Low |
| Should providers measure glycemic parameters before and during statin use? | ▪ The NLA endorses the ADA recommendations but advises not to delay statin therapy over it.<br>▪ SOR: Expert opinion; QOE: Moderate |
| Are they any recommendations when starting statins in patients without DM? | ▪ Assess for CV risk factors.<br>▪ Consider the measurement of A1C.<br>▪ Emphasize the importance of diet, weight, and physical activity.<br>▪ If DM develops while on a statin, emphasize weight loss, use of hypoglycemic medications (if indicated) , and provide behavioral counseling. |



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# HMG-COA REDUCTASE INHIBITORS (STATINS)
## COGNITIVE CHANGES

| Cognitive Effects | Answer | SOR | QOE |
|---|---|---|---|
| Should a baseline cognitive assessment be done prior to starting? | NO | Expert opinion | Low |
| Are statins associated with negative effects on cognition? | NO | Strong | Low to Moderate |
| What should a provider do if a patient reports cognitive symptoms? | Cognitive testing & rule out other factors | Expert opinion | Low |
| Consider other drugs: Anticholinergic medications, 1st generation antihistamines, benzodiazepines, opioids | | | |

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# LANDMARK PRIMARY PREVENTION TRIALS

## CORONARY HEART DISEASE

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| Study | Year | n | Drug | Results |
|---|---|---|---|---|
| LRC-CPPT | 1984 | 1,906 | Cholestyramine | CHD incidence ↓ 18.9% |
| HHS | 1987 | 2,051 | Gemfibrozil | CHD incidence ↓ 34% |
| WOSCOPS | 1995 | 3,302 | Pravastatin | Death from all CVD ↓ 32%; non-fatal MI ↓ 31% |
| AFCAPS/TexCAPS | 1998 | 3,304 | Lovastatin | First acute event ↓ 37% |
| PROSPER | 2002 | 3,239 / 5804 | Pravastatin | HR, 0.94 (0.77-1.15; p=0.19). Combined CVD no different |
| ASCOT-LLA | 2003 | 10,305 | Atorvastatin | Stopped early. Nonfatal MI & fatal CHD ↓ 36% and stroke ↓ 27%. |
| Juniper | 2008 | 17,802 | Rosuvastatin | hsCRP > 2 mg/dL; 20% risk reduction in overall mortality |

LRC-CPPT = Lipid Research Clinics Coronary Primary Prevention Trial; HHS = Helsinki Heart Study; WOSCOPS = West of Scotland Coronary Prevention Study; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; PROPSER = PROspective Study of Pravastatin in the Elderly at Risk; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm



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# LANDMARK SECONDARY PREVENTION TRIALS

## CORONARY HEART DISEASE

| Study | Year | n | Drug | Results |
|---|---|---|---|---|
| 4S | 1994 | 2,221 | Simvastatin | CHD mortality ↓ 42% |
| CARE | 1996 | 2,081 | Pravastatin | CHD death or nonfatal MI ↓ 24% |
| LIPID | 1998 | 4,512 | Pravastatin | CHD death ↓ 24% |
| MIRACL | 2001 | 1,538 | Atorvastatin | Recurrent events ↓ 16%; stroke ↓ 50% |
| PROSPER | 2002 | 2,565 | Pravastatin | Elderly pts* (70-82 yrs); Combined CVD ↓ by 22% |
| HPS | 2002 | 20,536 | Simvastatin | All cause mortality ↓ by 13%; Coronary death rate ↓ 18% |
| PROVE IT | 2004 | 4,162 | Atorvastatin vs Pravastatin | Composite CVD ↓ 16% |

4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol and Recurrent Events Trial; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease Study; MIRACL = Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study; PROSPER = PROspective Study of Pravastatin in Elderly at Risk; HPS = Health Protection Study; PROVE IT TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in MI 22 Study.



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# STATIN & PROTEASE INHIBITOR
## DRUG INTERACTIONS

| Characteristic | Lovastatin | Pravastatin | Simvastatin | Atorvastatin | Fluvastatin | Rosuvastatin |
|---|---|---|---|---|---|---|
| Protease Inhibitors | | | | | | |
| Atazanavir/RTV | avoid | - | avoid | low dose | - | AUC ↑213%<br>Cmax ↑600% |
| Fosamprenavir | avoid | - | avoid | AUC ↑150% | - | AUC ↑8% |
| Indinavir | avoid | - | avoid | low dose | - | - |
| Lopinavir / RTV | avoid | AUC ↑33% | avoid | AUC ↑ 5.8x | - | AUC ↑ 2-5 x |
| Nelfinavir | avoid | - | AUC ↑505% | AUC ↑ 74% | - | - |
| Saquinavir /RTV | avoid | level ↓50% | AUC↑ 3059% | Level ↑450% | - | - |
| Tipranavir / RTV | avoid | - | avoid | AUC ↑ 9x | - | - |
| Darunavir / RTV | avoid | AUC ↑ 5-fold | avoid | Low dose | - | - |

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# MONOCLONAL ANTIBODY (mAB)

## SUBSTEM B NAMING & TYPE - WORLD HEALTH ORGANIZATION

| Name Ending | Type of Antibody |
|---|---|
| -umab | 100% human antibody |
| -zumab | Humanized (only 5-10% mouse make up the complementarity-determining-regions (CDR) |
| -ximab | Chimeric (67% human Fc or constant regions + 33% mouse make up the variable regions) |
| -omab | Murine (100% mouse) |
| -xizumab | Combined humanized & chimeric chains |
| -axomab | Rat/Mouse Chimer |
| -emab | Hamster |
| -amab | Rat |
| -imab | Primate |

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# MONOCLONAL ANTIBODY (mAB)

## SUBSTEM A NAMING & TARGET - WORLD HEALTH ORGANIZATION

| Name Ending | Target Class | Example |
|---|---|---|
| -b(a)--mab | Bacterial | -bixumab; -bumab |
| -c(i)--mab | Cardiovascular | -cixumab; -cumab |
| -f(u)--mab | Fungal | -fuzumab; -fumab |
| -k(i)--mab | Interleukin | -kiximab; -kumab |
| -l(i)--mab | Immunomodulating | -liximab; -lumab; -lixizumab |
| -n(e)--mab | Neural | -nezumab; -numab |
| -s(o)--mab | Bone | -somab; -sumab |
| -tox(a)--mab | Toxin | -toxazumab; -toxumab |
| -t(u)--mab | Tumor | -tuzumab; -tumab; -tomab |
| -v(i)--mab | Viral | -vizumab; -vumab |

Note: If Substem B starts with an “x” or “z”, a 2nd vowel (noted in parenthesis) is added to avoid problems with pronunciation.

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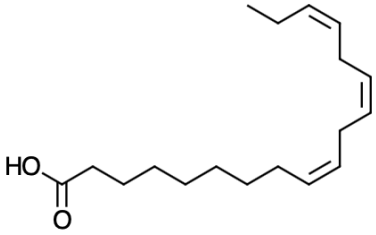
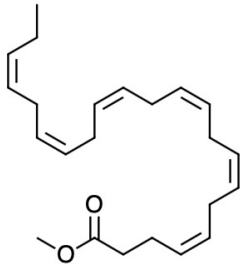
# OMEGA FATTY ACIDS

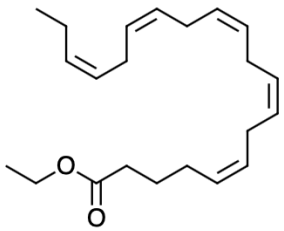
## OMEGA-3 FATTY ACIDS




ALA
(alpha-linolenic acid)
20:3(ω-3)

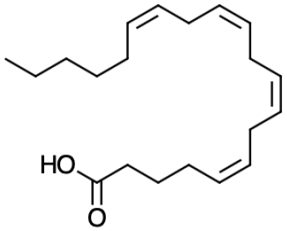



DHA
(docosahexaenoic acid)
20:6(ω-3)




EPHA
(eicosapentaenoic acid)
20:5(ω-3)

## OMEGA-6 FATTY ACID




AA
(arachidonic acid)
20:4(ω-6)

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# COMPARISON OF OMEGA-3 FATTY ACIDS

| PUFA | Brand Name | Indications | Fatty Acid Content | Notes |
|---|---|---|---|---|
| Omega-3 Ethyl Esters | Lovaza | Hypertriglyceridemia | ▪ EPA = 465 mg<br>▪ DHA = 375 mg | ▪ Take without regard to meals.<br>▪ Causes more GI effects (dysgeusia, dyspepsia, “fishy burps”)<br>▪ Refrigerate the capsules to reduce “fishy” burps. |
| Icosapent Ethyl | Vascepa | Hypertriglyceridemia<br>CVD risk reduction with elevated TG | ▪ EPA 960 mg | ▪ Take with food (given this way during clinical trials).<br>▪ LDL elevations may be reduced since DHA is absent. |

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