Reducing pancreatitis risk in patients with hypertriglyceridemia

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Clinical question

Do triglyceride-lowering medications (fibrates, statins, niacin, omega-3 fatty acids) reduce the risk of pancreatitis in patients with hypertriglyceridemia?

Bottom line

No RCTs have assessed the effect of fibrates or other triglyceride-lowering medications on pancreatitis risk in patients with very high triglyceride levels (≥5.6 mmol/L). In patients with triglyceride levels lower than 5.6 mmol/L, fibrates either have no effect on pancreatitis or increase the absolute risk by about 0.1% over 5 years, while statins lower the risk by 0.1%.

Evidence

No RCT examined effects of triglyceride-lowering medications on patients with very high triglyceride levels.

- A meta-analysis[1] of cardiovascular (CV) RCTs of fibrates (7 RCTs; 40,162 patients; average baseline triglyceride levels of 1.6 to 2.1 mmol/L) and statins (21 RCTs; 153,414 patients; average baseline triglyceride levels of 1.3 to 2.1 mmol/L) evaluated patient pancreatitis risk at about 5 years (differences statistically significant):
  -Fibrates: 0.4% versus 0.3% placebo; statins: 0.2% versus 0.3% placebo.
- The largest RCT[2] of pemafibrate versus placebo (10,497 patients with type 2 diabetes; fasting triglyceride levels of 2.3 to 5.5 mmol/L [median 3.1 mmol/L] and high-density lipoprotein cholesterol levels <1.0 mmol/L) found the risk of pancreatitis after 3.4 years was 0.5% in both groups.
- There was no evidence that niacin or omega-3 fatty acids affected pancreatitis risk in any triglyceride group.

Context

- Alcohol overuse and gallstone disease account for most acute pancreatitis cases, whereas hypertriglyceridemia accounts for less than 5% of cases.[3] Fibrates (except possibly pemafibrate)[2] increase the risk of gallstone development by about 1% over 6 years,[4,5] potentially being the reason for a net increase in pancreatitis.
- Guidelines recommend fibrates for patients with elevated triglyceride levels to reduce triglyceride-related pancreatitis risk, but they differ in threshold triglyceride level needed to begin treatment (5.6 to 11.2 mmol/L).[6,7]
- The 5-year risk of acute pancreatitis based on triglyceride concentration ranges (cohort study of 1.5 million patients) includes the following[8]: 4.5 to 10.0 mmol/L, 0.8%; 10.1 to 20.0 mmol/L, 1.5%; and greater than 20 mmol/L, 3.5%.
- Cardiovascular benefits: Fibrates reduce only nonfatal coronary events (19% relative risk reduction [RRR]) versus placebo, with no benefit when added to statins.[9,10] Statins reduce CV events (25% to 35% RRR) and all-cause mortality (10% RRR) compared with placebo, usual care, or no statin treatment.[10]

Implementation

Hypertriglyceridemia is an independent risk factor for pancreatitis but not for CV events.[8] Patients with triglyceride levels 10 mmol/L or lower have a 5-year risk of pancreatitis less than 1% and are unlikely to derive meaningful reductions in pancreatitis risk from medications. Evidence on how to manage patients at higher risk (eg, triglyceride levels >20 mmol/L) is lacking. Statins should be first-line treatment, as this lipid-lowering medication class is the only one proven to reduce pancreatitis risk and to have additional CV benefits. Lifestyle changes that lower triglyceride levels and pancreatitis risk (eg, losing weight, increasing physical activity, reducing simple carbohydrate intake, restricting alcohol intake) should also be discussed.

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Competing interests
None declared

References

1. Preiss D, Tikkanen MJ, Welsh P, Ford I, Lovato LC, Elam MB, et al. Lipid-modifying therapies and risk of pancreatitis: a meta-analysis. *JAMA* 2012;308(8):804-11.
2. Das Pradhan A, Glynn RJ, Fruchart JC, MacFadyen JG, Zaharris ES, Everett BM, et al. Triglyceride lowering with pemafibrate to reduce cardiovascular risk. *N Engl J Med* 2022;387(21):1923-34. Epub 2022 Nov 5.
3. Hassanloo J, Béland-Bonenfant S, Paquette M, Baass A, Bernard S. Prevalence, severity and management of hypertriglyceridemia-associated pancreatitis; a 7-year retrospective cohort study at Canadian quaternary care hospitals. *J Clin Lipidol* 2022;16(4):455-62. Epub 2022 May 21.
4. Bodmer M, Brauchli YB, Krähenbühl S, Jick SS, Meier CR. Statin use and risk of gallstone disease followed by cholecystectomy. *JAMA* 2009;302(18):2001-7.
5. Coronary Drug Project Research Group. Gallbladder disease as a side effect of drugs influencing lipid metabolism. Experience in the Coronary Drug Project. *N Engl J Med* 1977;296(21):1185-90.
6. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, et al. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97(9):2969-89. Erratum in: *J Clin Endocrinol Metab* 2015;100(12):4685.
7. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;73(24):3168-209. Erratum in: *J Am Coll Cardiol* 2019;73(24):3234-7.
8. Patel RS, Pasea L, Soran H, Downie P, Jones R, Hingorani AD, et al. Elevated plasma triglyceride concentration and risk of adverse clinical outcomes in 1.5 million people: a CALIBER linked electronic health record study. *Cardiovasc Diabetol* 2022;21(1):102.
9. Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* 2010;375(9729):1875-84. Epub 2010 May 10.
10. Dugré N, Lindblad AJ, Perry D, Allan GM, Braschi É, Falk J, et al. Lipid-lowering therapies for cardiovascular disease prevention and management in primary care. PEER umbrella systematic review of systematic reviews. *Can Fam Physician* 2023;69:701-11 (Eng), e189-201 (Fr).

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