

HDL Functionality, CETP Inhibitors, and Exercise Training: Where are We?

Raul D. Santos^{1,2} and Pedro Gabriel Senger Braga^{3,4}

Hospital Israelita Albert Einstein,¹ São Paulo, SP – Brazil

Universidade de São Paulo,² São Paulo, SP – Brazil

Clínica Pró-Coração,³ São Paulo, SP – Brazil

Departamento de Cardio-Oncologia – Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,⁴ São Paulo, SP – Brazil

Exercise training is well established as an effective strategy to increase high-density lipoprotein cholesterol (HDL-C) concentrations, especially in people with high triglycerides and excess visceral adiposity, and is consistently associated with a lower risk of cardiovascular disease (CVD).¹ However, the traditional stratification of CVD risk based solely on HDL-C levels has been increasingly challenged by evidence highlighting the importance of assessing HDL particle functionality rather than HDL-C levels alone. This paradigm shift gained particular attention following clinical trials of cholesteryl ester transfer protein (CETP) inhibitors, in which substantial pharmacologically mediated increases in HDL-C failed to translate into improved cardiovascular outcomes. CETP inhibitor trials reported marked elevations in HDL-C, ranging from approximately 31% to 133%, whereas exercise training typically induces a much more modest increase, on the order of 2% to 5%.²⁻⁵ Despite these quantitative differences, both interventions have been shown to enhance aspects of HDL functionality. In exercise-based interventions, increases in HDL-C are accompanied by improvements in HDL-mediated cholesterol uptake, commonly assessed by cholesterol efflux capacity (CEC), a metric that more accurately reflects reverse cholesterol transport and CVD risk than HDL-C concentration alone.⁶⁻¹⁰ Mechanistically, CETP inhibition also enhances HDL cholesterol efflux capacity, indicating that pharmacologically enlarged HDL particles may retain functional properties. Nevertheless, adverse off-target effects and the artificial modulation of lipoprotein metabolism may partly explain the neutral or unfavorable cardiovascular outcomes observed in several CETP inhibitor trials.^{2,4,5} Together, these findings underscore that, although both exercise training and CETP inhibition substantially increase circulating HDL-C, the biological context, qualitative effects on HDL particles, and clinical implications differ fundamentally between these interventions, reinforcing the need to move beyond HDL-C quantity when evaluating cardiovascular risk and therapeutic strategies.

High-density lipoprotein and exercise training

Exercise training is associated with a modest but consistent increase in HDL-C, typically 2 to 5 mg/dL, as demonstrated in randomized trials and meta-analyses.^{11,12} Although quantitatively limited compared with pharmacological approaches, this increase is strongly influenced by exercise dose, intensity, and duration, with higher volumes and vigorous-intensity aerobic exercise yielding more pronounced effects, including reduced body weight and triglyceride levels.⁷ Mechanistically, exercise enhances skeletal muscle lipoprotein lipase activity, increases apolipoprotein A-I production, and improves reverse cholesterol transport flux rather than merely increasing cholesterol content within HDL particles. Several clinical studies have demonstrated that exercise-induced increases in HDL-C are often accompanied by improvements in HDL functionality, particularly CEC. In the STRRIDE-PD and E-MECHANIC trials, only high-dose or vigorous-intensity exercise significantly improved radiolabeled CEC, suggesting a threshold effect for functional benefit.⁷ Other interventions have reported improvements in ATP-binding cassette transporter A1 (ABCA1)-mediated efflux, endothelial anti-inflammatory properties, and HDL antioxidant capacity, although results varied by population characteristics and experimental assays.^{8-10,13}

A prospective cohort study within the Henry Ford Exercise Testing Project (FIT Project) investigated the relationship between isolated low HDL-C, cardiorespiratory fitness, and long-term mortality in adults. In this analysis, individuals with isolated low HDL-C (defined as HDL-C < 40 mg/dL for men and < 50 mg/dL for women) and LDL-C and triglycerides < 100 mg/dL exhibited significantly lower mean fitness and higher mortality over a mean follow-up of 10.3 ± 5 years compared with those with optimal lipid profiles.¹ Mortality was particularly elevated among participants with isolated low HDL-C who achieved less than 6 metabolic equivalents (METs) during exercise testing, with adjusted hazard ratios of 1.73 (95% confidence interval 1.18–2.54) and 1.90 (95% confidence interval 1.19–3.04) for < 6 and 6–10 MET categories, respectively; no significant difference was observed among those attaining ≥ 10 METs.¹⁴ These results underscore that, while isolated low HDL-C is associated with increased mortality risk, higher cardiorespiratory fitness attenuates this risk, highlighting the critical interplay between fitness and lipid phenotypes in cardiovascular risk stratification.¹²

These findings suggest that exercise improves both the quantity and quality of HDL, even when absolute changes in HDL-C are modest, as shown in Table 1. Importantly,

Keywords

HDL Cholesterol; Cholesterol Ester Transfer Proteins; Exercise

Mailing Address: Pedro Gabriel Senger Braga •

Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – Av. Dr. Enéas Carvalho de Aguiar, 44. Postal Code 05403-900, Cerqueira César, São Paulo, SP – Brazil

E-mail: pedro.senger@gmail.com

Manuscript received February 23, 2026, revised manuscript April 15, 2026, accepted April 15, 2026

DOI: <https://doi.org/10.36660/abc.20260145i>

these HDL-specific adaptations occur alongside broader cardiometabolic improvements, including enhanced insulin sensitivity, reduced triglycerides, lower blood pressure, and decreased systemic inflammation.

High-density lipoprotein and cholesteryl ester transfer protein inhibition

In contrast, CETP inhibitors produce marked elevations in HDL-C far greater than those achieved with lifestyle interventions.^{2,5,15,16} Torcetrapib, dalcetrapib, evacetrapib, and anacetrapib increase HDL-C primarily by inhibiting the transfer of cholesteryl esters from HDL to apolipoprotein B-containing lipoproteins, resulting in cholesterol-enriched, larger HDL particles. Mechanistic studies in humans have demonstrated that CETP inhibition generally improves HDL functional metrics, including total and ABCA1-mediated CEC, and increases concentrations of pre- β 1 HDL, a key initial acceptor of cellular cholesterol.^{17,18} These findings countered early concerns that CETP inhibitor-induced HDL might be dysfunctional. However, despite preserved or enhanced efflux capacity, most CETP inhibitors failed to reduce cardiovascular events in large outcome trials. Torcetrapib increased cardiovascular events and all-cause mortality due to off-target effects, including aldosterone

activation and blood pressure elevation.² Dalcetrapib and evacetrapib were clinically neutral despite substantial increases in HDL-C and favorable functional signals.^{5,16} As shown in Table 2, only anacetrapib demonstrated a modest reduction in major coronary events, an effect largely attributed to reductions in non-HDL cholesterol rather than the magnitude of HDL-C elevation itself. Currently, obicetrapib, a novel CETP inhibitor, is being tested in patients with still-elevated LDL-C despite lipid-lowering therapy, with the aim of preventing CVD events not by raising HDL-C but by reducing apolipoprotein B-containing pro-atherogenic lipoproteins (PREVAIL Study, ClinicalTrials.gov NCT05202509).

Quantity versus quality

Collectively, these data reinforce the concept that changes in HDL-C concentration alone are an inadequate surrogate biomarker for cardiovascular protection. Exercise induces smaller increases in HDL-C but promotes a coordinated improvement in HDL functionality and systemic cardiometabolic health, whereas CETP inhibition produces large increases in HDL-C with inconsistent clinical benefit. Notably, the improvements in HDL function observed with exercise occur within a physiological

Table 1 – Clinical exercise studies assessing HDL functionality in humans

Study (year)	Population and design	Main functional results	Key interpretation
Sarzynski et al., ATVB (2018) ⁷	Randomized exercise trials; prediabetes/overweight adults (STRIDE-PD) and overweight/obese adults (E-MECHANIC); 6 months; varying dose/intensity	STRIDE-PD: global radiolabeled efflux $\uparrow$ ~6.2% only in the high-amount/vigorous-intensity group. E-MECHANIC: non-ABCA1 efflux $\uparrow$ ~5.7% in the highest dose group (20 kcal/kg/week) versus control; no consistent change in ABCA1 efflux.	Suggests a dose/intensity threshold: prolonged vigorous/high-dose endurance training improves efflux measures.
Stanton et al., JAHA (2022) ⁸	Healthy young men; supervised sequential moderate- then high-intensity training (within-subject design)	ABCA1-mediated efflux $\uparrow$ 13.5% after moderate-intensity training and remained $\uparrow$ 17.3% after subsequent high-intensity training.	Exercise can improve ABCA1-specific efflux, with benefits maintained after higher intensity
Boyer et al., Am J Physiol Endocrinol Metab (2018) ¹³	Men with abdominal obesity and dyslipidemia; 1-year lifestyle program (healthy diet + increased physical activity/exercise) versus control	J774-HDL-CEC $\uparrow$ 14.1%; HepG2-HDL-CEC $\uparrow$ 3.4%; no change in controls; improvements tracked with apolipoprotein A-I changes.	Sustained lifestyle change (including exercise) improves HDL efflux capacity in dyslipidemic abdominal obesity.
Woudberg et al., Lipids in Health and Disease (2018) ⁹	Obese women; exercise intervention versus control	Exercise did not change HDL cellular efflux capacity.	Exercise did not affect HDL efflux.
Zhu et al., Frontiers in Physiology (2024) ¹⁰	Lean, obese nondiabetic, and obese T2DM adults; short-term HIIT program (15 days)	Efflux capacity improved only in lean subjects.	HIIT-related changes in HDL function appear metabolically context-dependent.

ABCA1: ATP-binding cassette transporter A1; CEC: cholesterol efflux capacity; T2DM: type 2 diabetes mellitus; HIIT: high-intensity interval training; J774: macrophages cell line; J774-HDL-CEC: laboratory assay that measures cholesterol efflux capacity.

milieu characterized by reduced inflammation and improved endothelial function, whereas CETP inhibition targets a single metabolic pathway. This distinction may explain why exercise-associated increases in HDL-C are consistently linked to cardiovascular benefits, whereas pharmacologically induced elevations in HDL-C are not.

Clinical implications

From a clinical and translational perspective, these findings suggest that raising HDL-C per se should not be a primary therapeutic goal unless accompanied by demonstrable improvements in HDL functionality and overall cardiovascular risk. Exercise remains a uniquely effective intervention, as it improves HDL function in a biologically integrated manner, even when HDL-C changes are modest. Conversely, the experience with CETP inhibitors underscores the limitations of targeting HDL-C levels without fully capturing its functional and systemic roles. In summary, exercise produces smaller but more physiologically coherent and clinically meaningful effects, whereas CETP inhibitors highlight a dissociation between HDL-C elevation, HDL functionality, and cardiovascular

outcomes. While the final verdict on CETP inhibitors remains pending, exercise should be prescribed as a cornerstone of CVD prevention, owing to its favorable effects on blood pressure and glucose metabolism, thereby reducing cardiovascular risk.

Acknowledgements

RDS is supported by a grant from the National Council for Scientific and Technological Development, Brazil (CNPq, grant number 303771/2023-2). PGSB receives a postdoctoral fellowship (CNPq, grant number 88887.102383/2025-00).

Conflicts of interest declaration

RDS is a consultant for AstraZeneca, Daiichi Sankyo, Eli Lilly, Esperion, MSD, Novartis, Novo Nordisk, and Ultragenyx. He has received speaker honoraria from Amgen, Adium, Axon Pharma, Novo Nordisk, Novartis, Eli Lilly, Daiichi Sankyo, Torrent, Libbs, and Chiesi. He has participated in trials sponsored by Amgen, Arrowhead, AstraZeneca, Ionis, MSD, Novartis, and Sanofi/Regeneron.

Table 2 – ICETP inhibitors and HDL functionality in humans

Drug (study)	Population	Main functional results	Key interpretation
Torcetrapib – mechanistic human studies (Yvan-Charvet et al.) ¹⁸	Hypercholesterolemic subjects	Modest increase in CEC at 60 mg; greater increase at 120 mg	HDL functionality improved, but did not translate into clinical benefit due to off-target effects
Dalcetrapib – dal-ACUTE	Patients after ACS	Increase in HDL-C and apolipoprotein A-I with improved cholesterol efflux	HDL functional improvement observed in inflammatory setting.
Dalcetrapib – genotype analysis (Tardif et al.) ¹⁷	Post-ACS patients stratified by genotype	Improved efflux capacity in specific genotypes only	HDL functionality response is genetically determined.
Evacetrapib – mechanistic substudy	Patients with dyslipidemia	Significant increase in total and ABCA1-specific efflux	Marked improvement in HDL functionality despite neutral clinical outcomes.
Anacetrapib – DEFINE mechanistic substudy	Patients with coronary artery disease	Consistent increase in CEC	Functional HDL improvement aligned with modest clinical benefit.

ACS: acute coronary syndrome; CEC: cholesterol efflux capacity.

References

- Couillard C, Després JP, Lamarche B, Bergeron J, Gagnon J, Leon AS, et al. Effects of Endurance Exercise Training on Plasma HDL Cholesterol Levels Depend on Levels of Triglycerides: Evidence from Men of the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study. *Arterioscler Thromb Vasc Biol*. 2001;21(7):1226-32. doi: 10.1161/hq0701.092137.
- Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, et al. Effects of Torcetrapib in Patients at High Risk for Coronary Events. *N Engl J Med*. 2007;357(21):2109-22. doi: 10.1056/NEJMoa0706628.
- Bowman L, Hopewell JC, Chen F, Wallendszus K, Stevens W, Collins R, et al. Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease. *N Engl J Med*. 2017;377(13):1217-27. doi: 10.1056/NEJMoa1706444.

4. Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, Brewer HB, Fox KAA, et al. Evacetrapib and Cardiovascular Outcomes in High-Risk Vascular Disease. *N Engl J Med*. 2017;376(20):1933-42. doi: 10.1056/NEJMoa1609581.
5. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, et al. Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome. *N Engl J Med*. 2012;367(22):2089-99. doi: 10.1056/NEJMoa1206797.
6. Ruiz-Ramie JJ, Barber JL, Sarzynski MA. Effects of Exercise on HDL Functionality. *Curr Opin Lipidol*. 2019;30(1):16-23. doi: 10.1097/MOL.0000000000000568.
7. Sarzynski MA, Ruiz-Ramie JJ, Barber JL, Slentz CA, Apolzan JW, McGarrah RW, et al. Effects of Increasing Exercise Intensity and Dose on Multiple Measures of HDL (High-Density Lipoprotein) Function. *Arterioscler Thromb Vasc Biol*. 2018;38(4):943-52. doi: 10.1161/ATVBAHA.117.310307.
8. Stanton KM, Kienzle V, Dinnes DLM, Kotchetkov I, Jessup W, Kritharides L, et al. Moderate- and High-Intensity Exercise Improves Lipoprotein Profile and Cholesterol Efflux Capacity in Healthy Young Men. *J Am Heart Assoc*. 2022;11(12):e023386. doi: 10.1161/JAHA.121.023386.
9. Woudberg NJ, Mendham AE, Katz AA, Goedecke JH, Lecour S. Exercise Intervention Alters HDL Subclass Distribution and Function in Obese Women. *Lipids Health Dis*. 2018;17(1):232. doi: 10.1186/s12944-018-0879-1.
10. Zhu L, An J, Luu T, Reyna SM, Tantiwong P, Sriwijitkamol A, et al. Short-Term HIIT Impacts HDL Function Differently in Lean, Obese, and Diabetic Subjects. *Front Physiol*. 2024;15:1423989. doi: 10.3389/fphys.2024.1423989.
11. Pourmontaseri H, Farjam M, Dehghan A, Karimi A, Akbari M, Shahabi S, et al. The Effects of Aerobic and Resistant Exercises on the Lipid Profile in Healthy Women: A Systematic Review and Meta-Analysis. *J Physiol Biochem*. 2024;80(4):713-25. doi: 10.1007/s13105-024-01030-1.
12. Smart NA, Downes D, van der Touw T, Hada S, Dieberg G, Pearson MJ, et al. The Effect of Exercise Training on Blood Lipids: A Systematic Review and Meta-Analysis. *Sports Med*. 2025;55(1):67-78. doi: 10.1007/s40279-024-02115-z.
13. Boyer M, Mitchell PL, Poirier P, Alm  ras N, Tremblay A, Bergeron J, et al. Impact of a One-Year Lifestyle Modification Program on Cholesterol Efflux Capacities in Men with Abdominal Obesity and Dyslipidemia. *Am J Physiol Endocrinol Metab*. 2018;315(4):E460-8. doi: 10.1152/ajpendo.00127.2018.
14. Whelton SP, Dardari Z, Marshall CH, Ahmed H, Brawner CA, Ehrman JK, et al. Relation of Isolated Low High-Density Lipoprotein Cholesterol to Mortality and Cardiorespiratory Fitness (from the Henry Ford Exercise Testing Project [FIT Project]). *Am J Cardiol*. 2019;123(9):1429-34. doi: 10.1016/j.amjcard.2019.02.009.
15. Brousseau ME, Schaefer EJ, Wolfe ML, Bloedon LT, Digenio AG, Clark RW, et al. Effects of an Inhibitor of Cholesteryl Ester Transfer Protein on HDL Cholesterol. *N Engl J Med*. 2004;350(15):1505-15. doi: 10.1056/NEJMoa031766.
16. Nicholls SJ, Nelson AJ, Ditmarsch M, Kastelein JJP, Ballantyne CM, Ray KK, et al. Safety and Efficacy of Obicetrapib in Patients at High Cardiovascular Risk. *N Engl J Med*. 2025;393(1):51-61. doi: 10.1056/NEJMoa2415820.
17. Tardif JC, Rh  aume E, Perreault LPL, Gr  goire JC, Zada YF, Asselin G, et al. Pharmacogenomic Determinants of the Cardiovascular Effects of Dalcetrapib. *Circ Cardiovasc Genet*. 2015;8(2):372-82. doi: 10.1161/CIRCGENETICS.114.000663.
18. Yvan-Charvet L, Matsuura F, Wang N, Bamberger MJ, Nguyen T, Rinninger F, et al. Inhibition of Cholesteryl Ester Transfer Protein by Torcetrapib Modestly Increases Macrophage Cholesterol Efflux to HDL. *Arterioscler Thromb Vasc Biol*. 2007;27(5):1132-8. doi: 10.1161/ATVBAHA.106.138347.

