

Oral PCSK9 Inhibitors: Between Promise and Pending Evidence

Inhibidores orales de PCSK9: entre la promesa y la evidencia pendiente

FERNANDO VICHI¹ 

Lowering low-density lipoprotein cholesterol (LDL-C) remains a cornerstone of both the prevention and treatment of atherosclerotic cardiovascular disease (ASCVD), supported by decades of genetic and clinical evidence confirming its causal role. (1) However, a considerable proportion of high-risk patients fail to achieve the recommended targets despite treatment with maximally tolerated statin doses.

Subcutaneous PCSK9 inhibitors (monoclonal antibodies) have represented a substantial advance in this setting, with sustained reductions in LDL-C and demonstrated clinical benefit in terms of cardiovascular events. (2) Nevertheless, their parenteral route of administration and high cost continue to limit their wider adoption.

The systematic review and meta-analysis by Masson et al. (3) updates the available evidence on five oral PCSK9 inhibitors. The authors report LDL-C reductions of nearly 58% compared with placebo, comparable in magnitude to those achieved with injectable drugs, and with no significant difference in adverse events. This meta-analysis incorporates phase 3 data on enlicotide, representing a significant advance over the largely descriptive evidence available until recently. Notably, one of the included studies demonstrated the superiority of an oral inhibitor over ezetimibe and bempedoic acid, two widely used oral alternatives. (4)

That said, several considerations temper this enthusiasm. The number of studies remains small, follow-up does not exceed 12 weeks in most studies, and the results for lipoprotein(a) showed marked statistical heterogeneity ($I^2 = 99.2\%$), which calls for a more cautious interpretation of that point estimate. Furthermore, development of one of the five drugs has already been discontinued for strategic reasons, a reminder that this therapeutic class is still at an early stage. Nor should it be assumed that oral administration alone will resolve the problem of access. Indeed, while this editorial was prepared, the FDA approved enlicotide (Lipfendra) as the first commercially avail-

able oral PCSK9 inhibitor, based on the LDL-C reduction demonstrated in the CORALreef program, at a monthly list price of USD 315 —approximately half that of injectable drugs, but far from a trivial expense. The drug has not yet been approved in Argentina or elsewhere in Latin America, although it is worth noting that several centers in Argentina actively participated in the CORALreef program.

Importantly, no oral PCSK9 inhibitor has yet generated data on hard cardiovascular outcomes. The ongoing CORALreef Outcomes study will be decisive in determining whether these lipid reductions translate into concrete clinical benefits (5).

In conclusion, the study by Masson et al. provides a timely and methodologically sound synthesis of a rapidly evolving therapeutic class. Oral PCSK9 inhibitors represent one of the most promising strategies for optimizing intensive lipid-lowering therapy, but their definitive inclusion in treatment algorithms will have to await larger studies, longer follow-up, and, most importantly, results on hard cardiovascular events.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

REFERENCES

1. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;38:2459-72. <https://doi.org/10.1093/eurheartj/ehx144>
2. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713-22. <https://doi.org/10.1056/NEJMoa1615664>
3. Masson W, Lobo M, Giunta G, Barbagelata L, Nogueira JP. Evi-

REV ARGENT CARDIOL 2026;94:429-430. <https://doi.org/10.7775/rac.v94.i5.21046>

Correspondence: Fernando Vichi, Clínica San Nicolás, Chilecito, La Rioja, Argentina. Email: fernandovichi.vf@gmail.com



<https://creativecommons.org/licenses/by-nc-sa/4.0/>

©Revista Argentina de Cardiología

¹ Specialist in Cardiology (UCC), Cardiovascular Ultrasound (UCC), and Cardiometabolism (UCA). Clínica San Nicolás, Chilecito, La Rioja, Argentina.

dencia actual sobre la eficacia hipolipemiente y seguridad de los inhibidores orales de PCSK9: revisión sistemática y metaanálisis. *Rev Argent Cardiol* 2026;94:302-313. <https://doi.org/10.7775/rac.es.v94.i4.21026>

4. Catapano AL, Mikhailova E, Navar AM, Banka P, Corral P, Saxena M, et al. Oral PCSK9 Inhibitor Enlicitide Versus Oral Nonstatin Therapies: A Phase 3 Randomized Clinical Trial. *J Am Coll Cardiol* 2026;S0735-109705832-8. <https://doi.org/10.1016/j.jacc.2026.03.036>

5. CORALreef Outcomes (Enlicitide Decanoate, MK-0616) Cardiovascular Outcomes Study (MK-0616-015) [Internet]. ClinicalTrials.gov. Available from: <https://clinicaltrials.gov/study/NCT06008756> (NCT06008756)

AUTHORS' REPLY

We thank the author of the letter for his comments and for his assessment of our work. We agree that, at present, the achievement of lipid targets remains sub-optimal due to various patient-related (adherence), physician-related (therapeutic inertia), and health-care system-related (access to treatments) factors. In this context, we believe that oral PCSK9 inhibitors could represent a very promising therapeutic strategy, particularly given the magnitude of LDL-C reduction achieved and the possibility of having an oral alternative to monoclonal antibodies and inclisiran.

Likewise, we agree that these results should be interpreted with caution. As we noted in our study, the available evidence remains relatively recent, with

limited follow-up in a substantial proportion of studies and no data on clinical cardiovascular outcomes for this new therapeutic class. However, it should be noted that, currently, the absence of cardiovascular outcomes data also applies to inclisiran, which nevertheless represents an additional therapeutic tool in clinical practice. The results of ongoing cardiovascular outcomes studies will be essential to establish the clinical benefit of both strategies.

Furthermore, when we prepared our manuscript, we had no information on the prices of these drugs, much less on what they might cost in our country if they were marketed. In this regard, the possibility that an oral formulation could help reduce costs and, more importantly, promote greater market competition must, for the time being, be considered a hypothesis, as we presented in our study. Even if the prices of these drugs in their country of origin were known, any extrapolation to other markets would remain imprecise, given that prices and conditions of access may vary substantially among countries.

We thank the author once again for enriching the discussion on the potential and current limitations of this therapeutic strategy.

Walter Masson 

Hospital Italiano, Buenos Aires

The Impact of Ischemic Burden on Current Medical Practice

El impacto del monto isquémico en la práctica médica actual

PAULA ELIZABETH BARBOZA¹, CLAUDIA MARIANA CORTÉS²

Historically, the assessment of myocardial ischemia has been a useful tool in clinical cardiology for risk stratification and decision-making. For this assessment, in the field of nuclear cardiology, Hachamovitch and colleagues, in their large-scale observational study, determined that an ischemic burden (IB) exceeding 10% of ventricular mass, in the absence of extensive myocardial necrosis, identified patients who benefited from an invasive strategy and early revascu-

larization compared with medical therapy in terms of survival. (1)

Over the years, both medical treatment and revascularization techniques have improved significantly. This led to the conduct of randomized trials to identify which subgroups benefited from an initial invasive strategy (2–4). Among these was the ISCHEMIA trial, which demonstrated that, in patients with moderate-to-severe ischemia, both initial medical therapy

REV ARGENT CARDIOL 2026;94:430-431. <https://doi.org/10.7775/rac.v94.i5.21047>

Correspondence: Paula E Barboza, Autonomous City of Buenos Aires. Email: pebarboz@ffavaloro.org



<https://creativecommons.org/licenses/by-nc-sa/4.0/>

©Revista Argentina de Cardiología

¹ Staff member of the Nuclear Medicine Department, Fundación Favaloro University Hospital, Autonomous City of Buenos Aires.

² Chief of the Nuclear Medicine Department, Favaloro Foundation University Hospital, Autonomous City of Buenos Aires.

and invasive therapy reduce major cardiovascular events and mortality without significant differences. (5) However, it is important to note that this study used the performance of a coronary angiography (via CT angiography) as an initial evaluation criterion to rule out severe left main coronary artery disease or non-obstructive coronary artery disease, thereby excluding these patients from the study.

In light of the bibliographic references presented thus far, it is evident that the study titled “*Evaluation of the Clinical Management and Follow-up of Patients with Severe Myocardial Ischemia Detected by Triggered SPECT*” (6) provides an interesting update on these topics within the context of a public hospital in our country. Of primary relevance is the selection of patients with IB greater than or equal to 10% on a myocardial perfusion scan. The study evaluates the therapeutic approach (invasive versus conservative) adopted by treating physicians in this group upon finding these results of severe myocardial ischemia.

This observational, retrospective, single-center study by Herrero et al. provides valuable insights, as it demonstrates that treating physicians were significantly more likely to order an initial invasive study in the cohort of patients with a IB of 16% or higher. Furthermore, this subgroup of patients had the highest percentage of revascularization. This could be the starting point for reconsidering the value of IB in guiding therapeutic management.

This study had limitations, such as the considerable number of follow-up losses and the short median duration of longitudinal evaluation (18 months). However, it demonstrated a higher number of major cardiovascular events in revascularized patients, with a significant number occurring within the first month after the procedure. Given this finding, longer-term follow-up could be valuable to assess the performance of the medical treatment arm, considering that adherence may decline over time.

In conclusion, this is a valuable observational study that provides evidence to inform decision-making in real-world medical practice.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

REFERENCES

1. Hachamovitch R, Rozanski A, Shaw LJ, Stone GW, Thomson LE, Friedman JD, et al. Impact of ischemia and scar on the therapeutic benefit derived from myocardial revascularization versus medical therapy. *Eur Heart J* 2011;32:1012-24. <https://doi.org/10.1093/eurheartj/ehq500>.
2. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease (COURAGE Trial). *N Engl J Med* 2007;356:1503-1516. <https://doi.org/10.1056/NEJMoa070829>
3. BARI 2D Study Group; Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease (BARI 2D Trial). *N Engl J Med*. 2009;360:2503-2515. <https://doi.org/10.1056/NEJMoa0805796>
4. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction (STICH Trial). *N Engl J Med* 2016;374:1511-20. <https://doi.org/10.1056/NEJMoa1602001>
5. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. *N Engl J Med* 2020;382:1395-407. <https://doi.org/10.1056/NEJMoa1915922>
6. Herrero JA, Brodsky LD, Casuscelli JF, Maciel NR, Rojas Valera RB, Gagliardi J, et al. Evaluation of the clinical management and follow-up of patients with severe myocardial ischemia detected by triggered SPECT. *Rev Argent Cardiol* 2026;94:273-9. <https://doi.org/rac.es.v94.i4.21025>

AUTHORS' REPLY

First, we would like to thank Dr. Barboza and Dr. Cortes for taking the time to read and thoroughly analyze our article; this will encourage those who read this letter to the editor to read the original article.

We agree with the limitations that the authors mention in their letter.

We believe this can serve as a starting point for initiating a multicenter study with longer follow-up to obtain external validation of our results; we consider our publication to be useful as a hypothesis for advancing our understanding of the pathophysiology and decision-making in chronic ischemic heart disease.

Best regards,

The authors

A Gap That Directly Challenges Cardiology

Una brecha que interpela directamente a la cardiología

ANALÍA L. GUAZZONE¹ 

The study by Forte et al. on the treatment gap in patients with type 2 diabetes and cardiorenal disease deserves careful consideration, not only because of its findings but also because of what it implies for our daily practice. (1)

The key finding is a treatment gap exceeding 90%, in class IIa combinations such as gliflozins (SGLT2i) + GLP-1 receptor agonists (GLP-1 RA), or finerenone + SGLT2i, compared with gaps of less than 10% for renin-angiotensin-aldosterone system inhibitors (RAASi)—a finding that should not surprise us, but should certainly concern us. This aligns with the findings reported by Nelson et al. in the United States, where only 2.7% of eligible patients received the full recommended regimen, (2) and confirms that the problem lies not in the available evidence, but in its translation into daily practice.

What makes this study interesting is that it does not report usage rates therapy by therapy, but rather constructs a weighted index that ranks interventions according to their clinical importance. This reveals that the gap is not uniform: it is concentrated in the most recently introduced cardiorenal therapies, such as SGLT2 inhibitors, GLP-1 RA, and finerenone. Meanwhile, “classic” tools (statins, antiplatelet agents, RAASi) maintain acceptable penetration rates. This distinction is clinically relevant because it suggests that the obstacle is not a general reluctance to prescribe, but something more specific: inertia toward new treatments, uncertainty about who should initiate the medication, or a lack of awareness of updated guidelines.

This is where the article particularly challenges cardiologists. Dixon et al. had already documented that the prescribing of SGLT2i and GLP-1 RA varies significantly depending on the prescribing specialty, with lower utilization specifically in cardiology practices (3). If the cardiologist is, in many healthcare systems, the first or only specialized point of contact for patients with cardiorenal disease, delegating the initiation of these therapies to other specialties per-

petuates the gap rather than reducing it.

Two secondary findings from the study deserve special attention in clinical practice: the wider gap observed in women and in older patients. Both patterns have been described previously—the first by Regensteiner et al. in their scientific statement for the *American Heart Association*, (4) and the second in McCoy et al.’s analysis of *Medicare Advantage* beneficiaries (5)—and their replication in an Argentine cohort suggests that these are not local artifacts but rather systematic biases in the prescribing process, possibly linked to misperceptions of risk or tolerability rather than actual contraindications.

As a limitation, I agree with the authors themselves that the observational design precludes establishing causality, and that unmeasured variables—such as coverage, costs, and adherence—likely account for part of the gap. However, this does not detract from the practical message: having a reproducible index to audit one’s own practice and systematically incorporating an eligibility review for GLP-1 RA and finerenone into every consultation with a cardiorenal patient appears to be a concrete, low-cost step toward narrowing this gap between the guidelines and actual prescribing practices.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

(See authors’ conflict of interests forms on the web).

REFERENCES

1. Forte EH, Adkiman C, Araya C, Castaño YMN, Conforti MJ, De’Marzian G, et al. Treatment gap in very high-risk patients with cardiorenal disease: analysis of the implementation of evidence-based therapies. *Rev Argent Cardiol* 2026;94:314-22. <https://doi.org/10.7775/rac.es.v94.i4.21027>
2. Nelson AJ, Ardissino M, Haynes K, Shambhu S, Eapen ZJ, McGuire DK, et al. Gaps in Evidence-Based Therapy Use in Insured Patients in the United States With Type 2 Diabetes Mellitus

REV ARGENT CARDIOL 2026;94:432-433. <https://doi.org/10.7775/rac.v94.i5.21050>

Correspondence: Analía L. Guazzone, Email: analiaguazzone@hotmail.com



<https://creativecommons.org/licenses/by-nc-sa/4.0/>

©Revista Argentina de Cardiología

¹ Chief of the Cardiology Department at Sanatorio de la Trinidad Palermo, Autonomous City of Buenos Aires

and Atherosclerotic Cardiovascular Disease. *J Am Heart Assoc.* 2021;10(2):e016835. doi:10.1161/JAHA.120.016835

3. Dixon DL, Salgado TM, Robinson A, Carbone S, Wagner TD, Hyder H, et al. Prescribing patterns of SGLT2 inhibitors and GLP-1 receptor agonists in patients with type 2 diabetes during cardiology, endocrinology, and primary care visits. *Mayo Clin Proc.* 2025;100(4):647-656. doi:10.1016/j.mayocp.2024.08.026

4. Regensteiner JG, Golden S, Huebschmann AG, Barrett-Connor E, Chang AY, Chyun D, et al. Sex Differences in the Cardiovascular Consequences of Diabetes Mellitus: A Scientific Statement From the American Heart Association. *Circulation.* 2015;132(25):2424-2447. doi:10.1161/CIR.0000000000000343

5. McCoy RG, Van Houten HK, Deng Y, Mandic PK, Ross JS, Montori VM, et al. Comparison of Diabetes Medications Used by Adults With Commercial Insurance vs. Medicare Advantage, 2016 to 2019. *JAMA Netw Open.* Feb 1, 2021;4(2):e2035792. doi: 10.1001/jamanetworkopen.2020.35792

AUTHORS' REPLY

Dear Editor:

We thank Dr. Analía L. Guazzone for reviewing our work and for her comments on the implications for cardiology practice. We agree on the need to take an active role in implementing therapies with cardiorenal benefits and to prevent fragmentation across specialties from delaying relevant therapeutic decisions.

The proportional treatment gap index aims to integrate treatment opportunities based on each patient's eligibility. (1) Its potential to guide clinical audits warrants further analysis; its use as a healthcare quality indicator requires an evaluation of its external validity and sensitivity to change. Furthermore, the weighting of its components should not be interpreted as a direct estimate of lost clinical benefit.

We agree with the author that barriers to access deserve special attention. The lack of detailed information on contraindications, tolerability, adherence, coverage, and costs prevents us from attributing the absence of treatment exclusively to therapeutic inertia. (1) Therefore, the identified gap should be understood as a potential opportunity for improvement, which requires reviewing each patient's clinical circumstances and access possibilities.

Regarding differences by age and sex, it should be

noted that the associations with older age and female sex observed in the linear model lost statistical significance in the beta regression. (1) These results are exploratory and warrant further research, but they do not allow us to conclude that systematic prescribing biases exist in our cohort.

As Dr. Guazzone proposes, a structured review of eligibility during the consultation is a reasonable strategy. We suggest complementing this with the documentation of reasons for non-prescription and with agreements among cardiology, diabetes care, and nephrology that define responsibilities for initiating and monitoring treatment. This proposal is consistent with the recommendations of the Argentine Society of Cardiology for implementing cardiorenal units, published in this journal, which promote multidisciplinary teams involving diabetes care, shared protocols, and structured follow-up with quality indicators. (2) In particular, therapeutic combinations should be evaluated based on individual indications and the corresponding recommendation class. Subsequently assessing actual prescribing practices and treatment continuity would help determine whether these actions reduce the observed gap. The purpose of this letter is precisely to encourage the transformation of these findings into concrete interventions whose effectiveness can be measured.

Ezequiel H. Forte

On behalf of the authors

REFERENCES

1. Forte EH, Adjiman C, Araya C, Castaño YM, Conforti MJ, De'Marziani G, et al. Treatment gap in very high-risk patients with cardiorenal disease: analysis of the implementation of evidence-based therapies. *Rev Argent Cardiol* 2026;94:314-22. <https://doi.org/10.7775/rac.es.v94.i4.21027>
2. Thierier J, Scatularo E, Renedo MF, Caruso N, Castellaro C, Lavania G, et al. Recommendations for the implementation of cardiorenal units in the Argentine Republic. *Rev Argent Cardiol* 2025;93(Suppl 7):1-39. <https://doi.org/10.7775/rac.es.v93.s7>