Addressing Residual Risk in Type 2 Diabetes

Abordaje del riesgo residual en Diabetes tipo 2

RODRIGO ESPARZA IRAOLA[1]

Type 2 diabetes mellitus (T2DM) represents a global public health challenge. In 2022, it affected 830 million people, with a higher prevalence in low-income countries (1). This disease is linked to an elevated risk of cardiovascular complications such as coronary heart disease, heart failure, stroke, atrial fibrillation, peripheral vascular disease, and chronic kidney disease. In 2021, it was directly responsible for 1.6 million deaths, almost half of which occurred before the age of 70. (1)

Intensive control of classic risk factors -blood glucose, blood pressure, and LDL-C- has been shown to reduce mortality and cardiovascular events. However, a residual risk remains, with hypertriglyceridemia as an independent risk marker. Elevated triglyceride levels are associated with increased mortality in patients with coronary artery disease, reinforcing the need for complementary strategies. (2)

In this context, the REDUCE-IT trial showed that icosapent ethyl (IPE) reduces cardiovascular events by 25% in patients with atherosclerotic disease or T2DM with risk factors, leading to its inclusion in international guidelines. (3, 4)

The study published in the Argentine Journal of Cardiology, "*Eligibility for icosapent ethyl in a real-world population of patients with type 2 diabetes in the Argentine Republic,*" provides relevant local evidence. (5) Analyzing data from the registry of the Cardiometabolic Council of the Argentine Society of Cardiology, the authors observed that one in five patients with T2DM would meet the criteria for receiving IPE, with a higher proportion in secondary prevention (22.8%) than in primary prevention (15.5%). This finding underscores the importance of identifying residual risk in clinical practice and considering specific interventions to reduce it.

A striking finding is that only 25.9% of patients were receiving hypoglycemic drugs with proven cardiovascular benefits, which shows marked therapeutic inertia. This widely documented phenomenon delays the implementation of effective treatments and contributes to a worse prognosis in patients. The causes are multiple and complex: from professional factors (lack of time, lack of knowledge, fear of adverse effects) and patient factors (low adherence, low perception of risk) to healthcare system barriers (access and coverage). There is need to investigate the causes of undertreatment in T2DM and other cardiovascular diseases, as therapeutic inertia compromises the effectiveness of preventive strategies and results in unfavorable clinical outcomes.

In conclusion, this study not only estimates how many patients with T2DM in an Argentine population would be candidates for IPE, but also alerts us to the need to actively address therapeutic inertia and optimize the use of therapies with proven benefits. Recognizing and treating residual risk is essential for advances in scientific evidence to translate into actual benefits for patients.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

REFERENCES

1. World Health Organization. Diabetes [Internet]. Geneva: World Health Organization; November 14, 2024. https://www.who.int/news-room/fact-sheets/detail/diabetes.

2. Klempfner R, Erez A, Sagit BZ, Goldenberg I, Fisman EZ, Kopel E, et al. Elevated triglyceride level is independently associated with increased all-cause mortality in patients with established coronary heart disease: twenty-two-year follow-up of the Bezafibrate Infarction Prevention Study and Registry. Circ Cardiovasc Qual Outcomes 2016;9:100-8. https://doi.org/10.1161/CIRCOUTCOMES.115.002104.

3. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11-22. https://doi.org/10.1056/NEJMoa1812792.

Rev Argent Cardiol 2025;93:391-392. https://doi.org/10.7775/rac.v93.i5.20921

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4. Marx N, Federici M, Schütt K, Ajjan RA, Antunes MJ, et al. ESC Scientific Document Group. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J 2023;44:4043-40. https://doi.org/10.1093/eurheartj/ehad192.
5. Lavalle Cobo AM, Destaville J, Salmeri E, Forte E, Harwicz P, Corral P. Eligibility for icosapent ethyl in a real-world population of patients with type 2 diabetes in Argentina. Rev Argent Cardiol 2025;93:213-6. https://doi.org/10.7775/rac.v93.i3.20898.

AUTHORS' REPLY

We would like to thank Dr. Rodrigo Esparza Iraola for his observations and comments regarding our recently published article.

We agree with his reflection on the importance of identifying residual risk in daily practice in order to implement interventions aimed at reducing it, ethyl icosapentenoate being one possible strategy for this purpose.

When discussing residual risk in diabetes, Lawler et al. propose the use of drugs with proven cardiovascular benefits (GLP-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors) as a strategy to reduce it. 1. In this regard, we agree with Dr. Esparza Iraola that 3 out of 4 patients did not receive these groups of drugs and that inertia might be its cause. However, it is important to note that we used data from a cohort of patients evaluated between May and July 2019 to carry out this work. 2. We consider this factor to be important since this date coincides with the publication of cardiovascular safety studies of different molecules in populations with lower cardiovascular risk than those included in the first studies Moreover, it precedes the publication of international and national guidelines with the participation of scientific cardiology societies in which these drugs are included as part of the recommendations for reducing cardiovascular risk. On the other hand, as Dr. Esparza Iraola rightly points out, there are related issues that we must consider as barriers in the healthcare system. In this regard, Resolution 2820/2002 updated Annex I on the "Rules for the Provision of Medicines and Supplies for People with Diabetes," included the first of the two groups of drugs with proven cardiovascular benefits (SGLT2 inhibitors) as medications covered by the healhtcasre system for certain patients with type 2 diabetes. 3. We would like to thank you once again for the contributions highlighted in your letter, as they enrich the debate on such an important issue as the underuse of strategies with evidence of reducing cardiovascular risk.

Augusto Lavalle Cobo MTSAC

REFERENCES

1. Lawler PR, Bhatt DL, Godoy LC, Lüscher TF, Bonow RO, Verma S, et al. Targeting cardiovascular inflammation: next steps in clinical translation. Eur Heart J 2021;42:113-31. https://doi.org/10.1093/eurheartj/ehaa099
2. Forte E, Buso C, Duczynski P, Lavalle Cobo A, Harwicz P, Giorgi M, y cols. Clinical Characteristics and Cardiometabolic Control of Persons with Diabetes in the Cardiology Office in Argentina. Rev Argent Cardiol 2020;99:517-24. https://doi.org/10.7775/rac.es.v88.i6.18201
3. https://www.argentina.gob.ar/normativa/nacional/resoluci%C3%B3n-2820-2022-375042/texto

Genetic Testing in Hypertrophic Cardiomyopathy, Beyond the Initial Result

Estudio genético en miocardiopatía hipertrófica, más allá del resultado inicial

GUIDO ANTONIUTTI[1]

Understanding the clinical characteristics of our population enables the optimal allocation of healthcare resources, ensuring that the greatest number of patients benefit from the available means according to their clinical impact. Hypertrophic cardiomyopathy (HCM) is a clear example of a disease that must be analyzed from the workup process to the therapeutic approach, both of which are expensive. This analysis should be conducted with the aim of predicting and preventing the most serious outcomes, such as sudden

Rev Argent Cardiol 2025;93:392-393. https://doi.org/10.7775/rac.v93.i5.20930

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cardiac death and progression to heart failure, with the greatest possible specificity, while maintaining sensitivity.

The study by Parodi JB et al. (1) is a highly relevant population-based analysis that aligns with previous studies that have attempted to predict which patients with HCM will have a pathogenic (P) or likely pathogenic (LP) variant in genetic testing, such as that of Bos JM et al. (2), which led to the development of the Mayo Clinic score in 2014. Both studies agree, even though they involve different populations, that the reverse septal curvature pattern is associated with a higher probability of a positive genetic test with P or LP variants.

Hypertrophic cardiomyopathy has traditionally been considered a monogenic disease caused by variants in sarcomeric genes. While this assessment is not false, it is incomplete. A detailed analysis of sarcomeric genes can identify the genetic cause in 30 to 60% of cases, according to the series reported. If we only consider this pathogenesis, we would be leaving 40-70% of diagnosed patients without a genetic explanation for their disease. The constant analysis of variants found necessitates periodic reviews of genetic tests to assess the potential reclassification of those previously designated as negative as positive. One such example is the p.Arg652Lys variant in MYH7 (3) in a region of Spain, which was previously considered a variant of uncertain significance (VUS) and is currently P. In this context, the recent identification of non-sarcomeric genes associated with HCM, such as FHOD3, (4) has expanded the genetic spectrum of the disease. An analysis of intermediate-effect variants (IEVs) has recently been published. While these variants do not reach the category of P or LP, they influence the development of the disease. According to García Hernández S et al., (5) these IEVs account for 4.8% of HCM cases and modulate both the phenotype and clinical events when found in combination with P or LP variants.

Given the aforementioned reasons, it is imperative to ascertain the population to which patients with HCM belong and, following the results of a genetic test, to carry out a detailed analysis of the variants found. This analysis should consider the possibility of finding VUS or IEVs as the ultimate causes of the disease. A thorough understanding of HCM genetics improves diagnostic accuracy, facilitates optimized risk stratification, and allows for personalized therapeutic decisions)

Ethical considerations
Not applicable.

Conflicts of interest
None declared.

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

REFERENCES

1. Parodi JB, Carosella L, Mando F, Munin M, Salamé M, Guetta J, et al. Correlation Between Genetic Testing and Phenotype in a Cohort of Patients with Hypertrophic Cardiomyopathy. Rev Argent Cardiol 2025;93:295-301. https://doi.org/10.7775/rac.v93.i4.20915

2. Bos JM, Will ML, Gersh BJ, Kruisselbrink TM, Ommen SR, Ackerman MJ. Characterization of a phenotype-based genetic test prediction score for unrelated patients with hypertrophic cardiomyopathy. Mayo Clin Proc. 2014;89:727-37. https://doi.org/10.1016/j.mayocp.2014.01.025.

3. Antoniutti G, Caimi-Martinez FG, Álvarez-Rubio J, Morlanes-Gracia P, Pons-Llinares J, Rodríguez-Picón B, et al. Genotype-Phenotype Correlation in Hypertrophic Cardiomyopathy: New Variant p.Arg652Lys in MYH7. Genes (Basel) 2022;13:320. https://doi.org/10.3390/genes13020320.

4. Ochoa JP, Sabater-Molina M, García-Pinilla JM, Mogensen J, Restrepo-Córdoba A, Palomino-Doza J, et al. Formin Homology 2 Domain Containing 3 (FHOD3) Is a Genetic Basis for Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2018;72:2457-67. https://doi.org/10.1016/j.jacc.2018.10.001.

5. García Hernandez S, de la Higuera Romero L, Fernandez A, Luisa Peña Peña M, Mora-Ayestaran N, Basurte-Elorz MT, et al. Redefining the Genetic Architecture of Hypertrophic Cardiomyopathy: Role of Intermediate-Effect Variants. Circulation 2025;152:1060-75. https://doi.org/10.1161/CIRCULATIONAHA.125.074529

JACC Scientific Statement. J Am Coll Cardiol. 2023;9;81:1810-34. https://doi.org/10.1016/j.jacc.2023.01.049

AUTHORS' REPLY

We thank Dr. Guido Antoniutti for his valuable comments on our study and fully agree with his assessments.

Hypertrophic cardiomyopathy (HCM) is essentially a genetic disease, and advances in molecular research continue to refine our understanding. While a significant proportion of cases can be explained by pathogenic variants in sarcomeric, structural, or regulatory genes, usually with an autosomal dominant pattern of inheritance, we already know that this monogenic model does not encompass the full complexity of the disease. After a thorough analysis of the genetic test results, some patients remain genetically elusive. This can comprise 30 to 60% of cases, depending on the series, and could be explained by the combined contribution of rare intermediate-effect variants (oligogenic model) or the cumulative impact of common low-effect variants (polygenic model). The characterization of these intermediate-effect variants, as Dr. Antoniutti has correctly pointed out, represents a significant advance for a better understanding of the genetic origin of HCM.

We also recognize the importance of regularly reviewing genetic test results, taking into account the potential for reclassifying variants and identifying additional implicated genes.

We would like to thank Dr Antoniutti for his comments again, which enhance the interpretation of genetic research in HCM and promote a comprehensive understanding of this complex disease.

Josefina Parodi
On behalf of the authors

Impact and Significance of the SONQO-CALCHAQUÍ Program on Cardiovascular Health in Indigenous Communities

Impacto y significado del Programa SONQO-CALCHAQUÍ en la salud cardiovascular de las comunidades originarias

MARÍA GABRIELA AGUIRRE MAJUL[1]

The SONQO-CALCHAQUÍ Program (1-4) exemplifies efforts to promote cardiovascular health in indigenous communities in northern Argentina, particularly in the Calchaquí Valleys. In my view, this project not only offers a comprehensive medical approach, but also reflects a deep commitment to cultural preservation and respect for the unique characteristics of high-altitude populations.

First, it is essential to emphasize the significance of this initiative in terms of healthcare accessibility. The populations of Cachi, Coranzulí, and Quilmes live in isolated environments with extremely limited access to specialized medical care. SONQO-CALCHAQUÍ offers a comprehensive evaluation in a few hours encompassing laboratory tests, electrocardiogram, echocardiogram, vascular tests, and physical endurance tests. This enables hundreds of people to receive crucial information for the prevention and monitoring of cardiovascular diseases in a single day, which would otherwise require years of fragmented care.

The program also demonstrates a remarkable balance between science and cultural sensitivity. The evaluation takes into account the population's diet, which combines indigenous elements, such as llama meat and local vegetables, with processed products. Recommendations are contextualized without imposing urban models that may be impractical or foreign. By measuring physical activity, sleep, and lifestyle habits, professionals can take a comprehensive approach that respects local identity.

However, this effort also highlights a critical challenge: the increasing westernization. The presence of overweight, obesity, and waist circumference alterations indicates that changes in eating habits and lifestyle could affect the long-term cardiovascular health of these communities. Therefore, I believe it is crucial for future programs to keep on promoting early detection and educating people about healthy habits, adapted to the local worldview and resources.

Finally, SONQO-CALCHAQUÍ serves as a replicable model for other rural and isolated territories, demonstrating that the combination of technology, professional training, and cultural respect can generate a real and sustained impact.

This program demonstrates how preventive medicine can be effective and become more humane. It provides medical data and raises awareness about the overall health of historically marginalized communities.

In summary, SONQO-CALCHAQUÍ is more than just a cardiovascular study; it is a commitment to life, culture, and health equity. Projects of this magnitude deserve attention, ongoing support and replicability because they demonstrate how science can serve those in need in a direct and respectful manner.

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

REFERENCES

1. Galdeano RS, Mauro SO, Abregú D, Flores L, Zeballos GS, Fiszman L, et al. SONQO-CALCHAQUÍ Program 4th Edition 2024. Evaluation of cardiovascular variables in a native high mountain community. Rev Argent Cardiol 2025;93:287-94. https://doi.org/10.7775/rac.es.v93.i4.20914

2. Galdeano RS, Vogelmann OA, Mauro SO, Scattini G, Alderete R, Pastore FA, et al. 2023 SONQO-CALCHAQUÍ III Program: Evaluation of Cardiovascular Variables in Native Communities of the Calchaqui Valleys (Northwest Argentina). Rev Argent Cardiol 2024;92:429-36. https://doi.org/10.7775/rac.es.v92.i6.20847

3. Galdeano RS, Holownia D, Palavecino DO, Abregú JD, Benger J, Alderete R, et al. 2022 SONQO-CALCHAQUÍ Program: Evaluation of Cardiovascular Variables in a Mid- and High Mountain Calchaquí Population of Tucumán. Rev Argent Cardiol 2024;92:287-94. https://doi.org/10.7775/rac.es.v93.i4.20914

4. Galdeano RS, Holownia D, Palavecino DO, Abregú JD, Rivas Jordan MS, Frías Silva M, et al. 2022 SONQO-CALCHAQUÍ Program: Evaluation of Cardiovascular Variables in a Mid- and High Mountain Calchaquí Population of Tucumán. Rev Argent Cardiol 2021;89:20-6. https://doi.org/10.7775/rac.es.v89.i1.19095

Rev Argent Cardiol 2025;93:394-395. https://doi.org/10.7775/rac.v93.i5.20929

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AUTHORS' REPLY

We appreciate the summary made by Dr. María Gabriela Aguirre Majul of the different editions of the SONQO Calchaquí Program. As the doctor indicates, the idea behind this program is to conduct cardiovascular assessments of the indigenous populations in the valleys of northwestern Argentina and to study their lifestyle within its sociocultural context. Although the communities studied share similar characteristics in several respects, each community has distinctive features that must be addressed specifically. In this regard, the most recent edition, completed in early October of this year in Susques (Jujuy, at 3,890 meters above sea level), included researchers in the social sciences. We share the reader's concern about the westernization of lifestyles that is being observed. To that end, joint actions by scientific societies, universities, and health systems are necessary to support these communities in maintaining healthy lifestyles and modifying those that are not.

Yours sincerely,

Claudio Joo Turoni MTSAC
on behalf of the authors

A Functional Look at Transthyretin Cardiac Amyloidosis Beyond Deposition

Más allá del depósito, una mirada funcional a la amiloidosis cardíaca por transtiretina

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Cardiac transthyretin amyloidosis (ATTR-CA) is no longer a rare and silent entity but has rather become a diagnostic and therapeutic challenge for modern cardiology. We know that the extracellular deposition of misfolded amyloid protein in cardiac tissue has a significant impact on ventricular function. The article by Carvelli MV et al. invites us to look beyond amyloid deposition and explore its relationship with myocardial flow reserve (MFR) and global longitudinal strain, thereby evaluating the functional dimension that could predict ventricular deterioration. (1)

Previous literature has documented microvascular dysfunction in amyloidosis and other infiltrative cardiomyopathies using various noninvasive techniques, including positron emission tomography, the gold standard, (2,3) cardiac magnetic resonance imaging, transthoracic Doppler echocardiography, and contrast-enhanced echocardiography.

Using cadmium-zinc-tellurium (CZT-SPECT) detectors, the authors achieved simultaneous assessment of perfusion and amyloid distribution with a resolution that redefines the limits of nuclear imaging. The finding of reduced MFR in patients with ATTR-CA, even in the absence of epicardial coronary artery disease, supports the hypothesis that microvascular dysfunction is a key pathophysiological mechanism. (4) However, the most striking aspect of the study is what was not found: no correlation between the magnitude of amyloid deposition, global longitudinal strain and MFR.

This result invites us to rethink the paradigm. Is amyloid deposition the only relevant factor in the functional progression of the disease? Or are we facing a more complex interaction between inflammation, extrinsic compression, and tissue toxicity? The homogeneous distribution of amyloid observed in polar maps challenges the classic "Japan flag plot pattern" and suggests that functional deterioration may precede or even be independent of structural compromise.

The study also introduces a methodological innovation: the measurement of MFR using CZT-SPECT, an accessible, reproducible, and noninvasive technique. In this context, MFR emerges not only as a physiological marker but also as a potential tool to inform prognostic stratification and therapeutic follow-up. A reduction in MFR could anticipate symptoms of angina and functional deterioration or guide the initiation of specific therapies such as tafamidis.

Rev Argent Cardiol 2025;93:395-396. https://doi.org/10.7775/rac.v93.i5.20928

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In line with this perspective, it is worth mentioning the AMYTRE protocol, (5) conducted by Bastien Vançon et al., which aims to confirm coronary microvascular dysfunction and evaluate the effect of tafamidis on it. The primary outcome will be the variation of stress and rest myocardial blood flow and MFR between baseline and 24 months after tafamidis treatment.

In conclusion, this study marks a turning point in ATTR-CA research, despite its limited sample size. It reminds us that seeing the deposition is not enough; we must also understand its functional impact. The future of cardiology will combine diagnostic accuracy with physiological sensitivity. This paper is a significant step in that direction, inviting further exploration of the heart beyond its anatomy.

Ethical considerations
Not applicable.

Conflicts of interest
None declared.

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

REFERENCES

1. Carvelli MV, Meretta A, Gobbo M, Corneli M, Spaccavento A, del Rosario Rodríguez M, et al. Analysis of Myocardial Flow Reserve in Patients with Transthyretin Cardiac Amyloidosis. Its Relationship with Cardiac Amyloid Distribution and Global Longitudinal Strain. Rev Argent Cardiol 2025;93:279-86. https://doi.org/10.7775/rac.v93.i4.20906

2. Bravo PE, Di Carli MF, Dorbala S. Role of PET to evaluate coronary microvascular dysfunction in non-ischemic cardiomyopathies. Heart Fail Rev 2017;22:455-64. https://doi.org/10.1007/s10741-017-9628-1.

3. Kourek C, Briasoulis A, Magouliotis DE, Georgoulias P, Giamouzis G, Triposkiadis F, et al. Recent advances in the diagnostic methods and therapeutic strategies of transthyretin cardiac amyloidosis. World J Cardiol 2024;16:370-9. https://doi.org/10.4330/wjc.v16.i7.370.

4. Dorbala S, Vangala D, Bruyere J Jr, Quarta C, Kruger J, Padera R, et al. Coronary microvascular dysfunction is related to abnormalities in myocardial structure and function in cardiac amyloidosis. JACC Heart Fail 2014;2:358-67. https://doi.org/10.1016/j.jchf.2014.03.009.

5. Vançon B, Bisson A, Courtehoux M, Bernard A, Bailly M. A study protocol for an observational cohort investigating cardiac transthyretin amyloidosis flow reserve before and after Tafamidis treatment: The AMYTRE study. Front Med (Lausanne). 2022;9:978293. https://doi.org/10.3389/fmed.2022.978293.

AUTHORS' REPLY

We sincerely thank Dr. Nápolí, Dr. Colaiacovo, Dr. Solá, and Dr. Garcilaso de la Vega for their interest and valuable comments on our paper "Analysis of Myocardial Flow Reserve in Patients with Transthyretin Cardiac Amyloidosis. Its Relationship with Cardiac Amyloid Distribution and Global Longitudinal Strain."

We fully agree that transthyretin cardiac amyloidosis (ATTR-CA) should be approached from a comprehensive perspective that considers not only the burden of amyloid deposition but also its functional impact. In this regard, the assessment of myocardial flow reserve (MFR) provides relevant pathophysiological information, even in the absence of epicardial coronary artery disease, and could play a prognostic and therapeutic role in monitoring these patients.

We particularly appreciate the authors' view of microvascular dysfunction as a key mechanism and their mention of ongoing studies such as the AMYTRE protocol, which will help elucidate the relationship between MFR and response to treatment with tafamidis.

We agree that the future challenge will be to integrate structural, functional, and molecular findings for a better understanding of disease progression and optimization of clinical management.

We would like to express our gratitude once again for this academic exchange, which enriches the discussion and stimulates scientific collaboration in this field.

María Victoria Carvelli [MTSAC]
on behalf of the authors