Archivos de Cardiología de México

PERMANYER

Check for updates

SPECIAL ARTICLE

Latin American Consensus on management of residual cardiometabolic risk. A consensus paper prepared by the Latin American Academy for the Study of Lipids and Cardiometabolic Risk (ALALIP) endorsed by the Inter-American Society of Cardiology (IASC), the International Atherosclerosis Society (IAS), and the Pan-American College of Endothelium (PACE)

Consenso latinoamericano para el manejo del riesgo residual cardiometabólico. Consenso realizado por la Academia Latinoamericana de Lipidología y Riesgo Cardiometabólico (ALALIP), con el aval de la Sociedad Interamericana de Cardiología (SIAC), la Sociedad Interamericana de Aterosclerosis (IAS) y el Colegio Panamericano de Endotelio (PACE)

Carlos I. Ponte-Negretti[1], Fernando S. Wyss[2], Daniel Piskorz[3], Raul D Santos[4], Raul Villar[5], Alberto Lorenzatti[6], Patricio López-Jaramillo[7], Peter Toth[8], A. Juan J. Amaro[9], Alfonso K. Rodrigo[10], Fernando Lanas[11], Miguel Urina-Triana[12], Jofre Lara[13], T. Osiris Valdés[14], José R. Gomez-Mancebo[15], Alfonso Bryce[16], Leonardo Cobos S.[17], Adriana Puente-Barragan[18], Vladimir E. Ullauri-Solórzano[19], Felix A. Medina-Palomino[20], Alfredo F. Lozada[21], Maritza Duran[22], Percy Berrospi[23], David Miranda[24], Juan J Badimon[25], J. José R. González[26], and Peter Libby[27]*

[1]*Unit of Cardiometabolic Medicine, La Floresta Medical Institute, Caracas, Venezuela;* [2]*Services and Cardiovascular Technology of Guatemala CARDIOSOLUTIONS, Guatemala, Guatemala;* [3]*Institute of Cardiology Sanatorio Británico SRL Rosario, Argentina;* [4]*Lipid Clinic Heart Institute (InCor) University of Sao Paulo Medical School Hospital, Sao Paulo, Brazil;* [5]*Integra Médica, La Serena, Chile;* [6]*Department of Cardiology, Hospital Instituto Médico DAMIC/Rusculleda Foundation for Research in Medicine, Cordoba Argentina;* [7]*Integral Center for the Prevention of Cardiometabolic Diseases (CIPCA) and Instituto Masira, UDES, Bucaramanga, Colombia;* [8]*University of Illinois College of Medicine, Peoria, Illinois, Michigan State, USA;* [9]*Clinica Santa Sofía, Caracas, Venezuela;* [10]*Advanced Center for Metabolic Medicine and Nutrition, Santiago de Chile, Chile;* [11]*University of La Frontera, Temuco, Chile;* [12]*Faculty of Health Sciences, Simón Bolívar University, Barranquilla Colombia;* [13]*Department of Cardiology, Hospital Solca Guayaquil, Ecuador;* [14]*Central Medical Center La Romana, Dominican Republic;* [15]*Department of Cardiology, Hospital Universitario de Caracas, Universidad Central de Venezuela, Caracas, Venezuela;* [16]*CARDIOGOLF Research Unit, El Golf Clinic, Lima, Peru;* [17]*Cardiology Service, Hospital El Pino, Cardiocob Research Unit, Santiago de Chile, Chile;* [18]*Centro Médico Nacional 20 de Noviembre (ISSSTE), Mexico City, Mexico;* [19]*Hospital Metropolitano, Quito, Ecuador;* [20]*Univeridad Peruana Cayetano, Hospital Nacional Cayetano Heredia, Peru;* [21]*Austral University Hospital, Buenos Aires, Argentina;* [22]*FISPEVEN (Foundation for Clinical Research in Public and Epidemiological Health in Venezuela), Clínica El Ávila, Caracas, Venezuela;* [23]*Cardiology Service, SANNA Clinica El Golf, Lima, Peru;* [24]*Clínica San Felipe, Lima, Peru;* [25]*Atherothrombosis Research Unit, Cardiovascular Institute, The Mount Sinai School of Medicine, New York, USA;* [26]*University Hospital Complex of Santiago de Compostela, Santiago de Compostela, Galicia, Spain;* [27]*Division of Cardiovascular Medicine, Department of Medicine, Brigham and Womens' Hospital, Harvard Medical School, Boston, MA, USA*

Abstract

Background: *Hypertension, hyperglycemia, dyslipidemia, overweight, obesity, and tobacco (smoking, chewing, and vaping), together with a pro-inflammatory and procoagulant state, are the main risk factors related to atherosclerotic cardiovascular*

Correspondence:
*Carlos I. Ponte-Negretti
E-mail: ciponten@gmail.com

Date of reception: 08-01-2021
Date of acceptance: 14-05-2021
DOI: 10.24875/ACM.21000005

Available online: 28-06-2021
Arch Cardiol Mex (Eng). (ahead of print)
www.archivoscardiologia.com

disease. **Objective and methods:** *A group of experts from the Americas, based on their clinical expertise in cardiology, cardiovascular prevention, and cardiometabolic (CM) diseases, joined together to develop these practical recommendations for the optimal evaluation and treatment of residual CM risk factors in Latin America, using a modified Delphi methodology (details in electronic TSI) to generate a comprehensive CM risk reduction guideline, and through personalized medicine and patient-centered decision, considering the cost-benefit ratio The process was well defined to avoid conflicts of interest that could bias the discussion and recommendations.* **Results:** *Residual risk reduction should consider therapeutic options adapted to specific patient needs, based on five treatment objectives: triglyceride-rich lipoproteins, inflammation, impaired glucose metabolism, high blood pressure, and prothrombotic status. Comprehensive control of all CM risk factors should be a priority to deal with this important public health problem and prevent premature deaths. The recommendations in this paper address the evidence-based treatment of CM risk and are intended for clinical application in Latin American countries.*

Key words: *Residual risk. Cardiovascular risk. Cardiometabolic risk factors. Atherosclerotic cardiovascular disease. Inflammation. Thrombosis.*

Resumen

Antecedentes: *Un grupo de factores de riesgo cardiometabólicos (hipertensión, hiperglucemia, dislipidemia, sobrepeso, obesidad y tabaco (fumado, masticado, vaporizado), junto con un estado proinflamatorio y procoagulante, son los principales factores de riesgo relacionados con la enfermedad cardiovascular aterosclerótica.* **Objetivo y métodos:** *Basándose en su experiencia en cardiología, prevención cardiovascular y enfermedades cardiometabólicas, un grupo de expertos de las Américas se unió para desarrollar estas recomendaciones prácticas para la evaluación y tratamiento óptimos de los factores de riesgo cardiometabólicos residuales en América Latina, utilizando una metodología Delphi modificada con el objetivo de generar una guía integral de pautas para la reducción del riesgo cardiometabólico, mediante la medicina personalizada y la decisión centrada en el paciente teniendo en cuenta la relación costo-beneficio. El proceso fue bien definido para evitar conflictos de intereses que podrían sesgar la discusión y las recomendaciones.* **Resultados:** *La reducción del riesgo residual debe considerar opciones terapéuticas adaptadas a las necesidades específicas del paciente, basadas en 5 objetivos de tratamiento: lipoproteínas ricas en triglicéridos inflamación, metabolismo de la glucosa, presión arterial alta y estado protrombótico. El Control integral de todos los factores de riesgo cardiometabólicos debe ser una prioridad para hacer frente a este importante problema de salud pública y prevenir las muertes prematuras. Las recomendaciones de este documento abordan el tratamiento basado en evidencia del riesgo cardiometabólico y están destinadas a la aplicación clínica en los países de América Latina.*

Palabras claves: *Riesgo residual. Riesgo cardiovascular. Riesgo cardiometabólico. Enfermedad cardiovascular aterosclerótica. Inflamación. Trombosis.*

Introduction

Cardiovascular diseases (CVD) are the primary cause of death and disability in adults around the world[1]. The most frequent form of CVD is atherosclerotic CVD (ASCVD), which is a manifestation of multiple toxic cardiometabolic (CM) risk factors: elevated blood pressure, dysglycemia, dyslipidemia, overweight, obesity, and tobacco usage (smoking, chewing, and vaping). These risk factors induce progressive arterial wall injury by numerous maladaptive responses (endothelial dysfunction, inflammation, prothrombotic, and pro-oxidant state), that begins decades before the occurrence of the first clinical event. Comprehensive CM risk control strategies should optimally treat all CM risk factors.

Based on the foregoing, the ALALIP (Latin American Academy of Lipidology and CM Prevention), together with IASC, IAS, and PCE, convened a group of experts from the Americas, based on their clinical expertise in: cardiology, cardiovascular prevention, and CM diseases, to develop practical recommendations for the optimal evaluation and treatment of CM risk factors in Latin America. The process was well defined to avoid conflicts of interest that could bias the discussion and recommendations.

We use a modified Delphi methodology aims to generate a comprehensive CM risk reduction guideline, using personalized medicine and patient-centered decision considering the cost-benefit ratio, based on three premises[2,3]:

1) Global vision derived from a multidisciplinary expert discussion to incorporate the best scientific evidence.

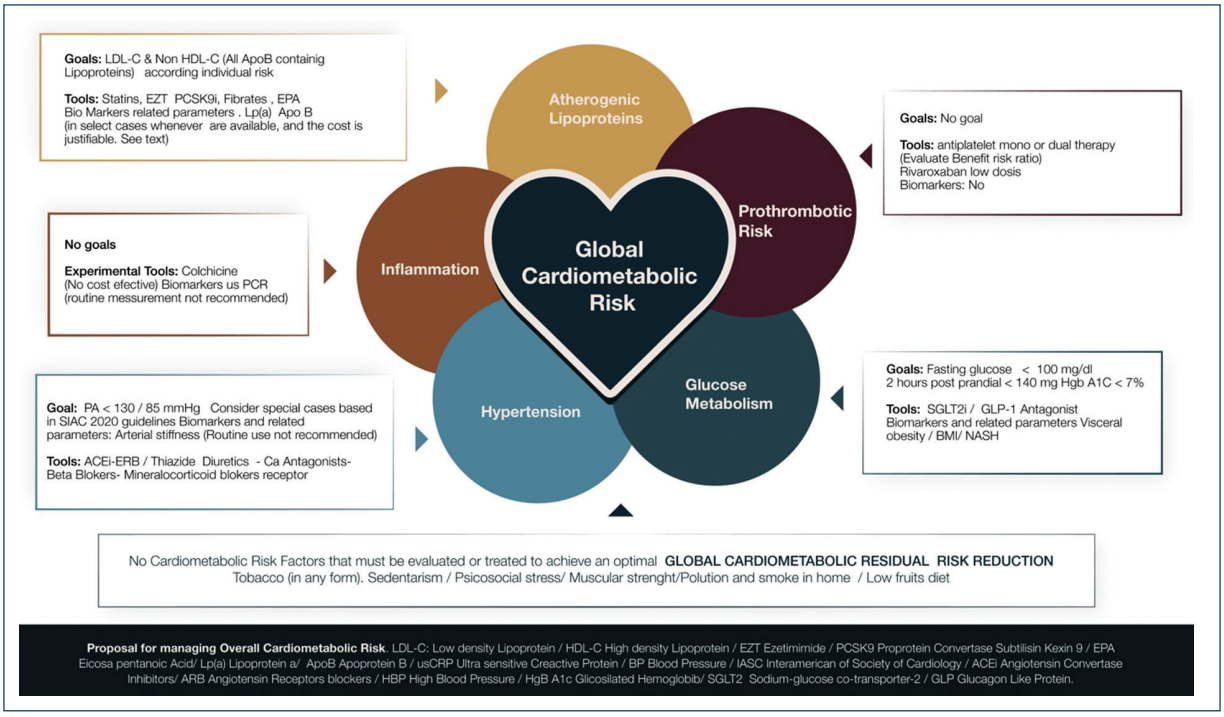

Figure 1. Proposal for managing overall cardiometabolic risk.

2) Developing criteria to identify relevant clinical issues.
3) Define practical pathways to improve daily clinical care.

In suppl. table 1, we made a detailed description of the document preparation process, the guidelines used for the construction of recommendations and the qualification of evidence.

Residual risk (RR) represents the risk which persists despite reaching the proposed treatment goals for the classic CM risk factors according to the current guidelines[4]. RR applies in primary and secondary prevention scenarios and rises as the individual baseline global risk rises[5]. The concept emerged from the statin trials. Low-density lipoprotein cholesterol (LDL-C) levels are the primary target in patients with dyslipidemia[6]. However, despite reaching LDL-C levels as low as < 70 mg/dl, RR often persists, particularly in higher risk individuals. Originally, RR aimed at identifying and treating atherogenic dyslipidemia (AD): elevated triglyceride (TG), low high-density lipoprotein cholesterol (HDL-C) levels, and a higher proportion of small and dense LDL-C (LDL pattern B)[7,8]. However, the RR concept should extend beyond AD and apply to all other uncontrolled ASCVD risk factors.

The recommendations by this consensus panel are summarized in figure 1 and table 1. RR reduction should consider therapeutic options adapted to specific patient needs, based on five treatment objectives: TG-rich lipoproteins (TgRL), inflammation, impaired glucose metabolism, high blood pressure (HBP), and prothrombotic status. This approach acknowledges various pathophysiological pathways and identifies therapies to consider, with no hierarchical classification, to accomplish an optimal RR reduction, aimed at delivering precise, and personalized medicine[9]. The pharmacotherapy assessed includes: statins, ezetimibe (EZT)[10], proprotein convertase subtilisin/kexin 9 inhibitors (PCSK9i)[11,12], eicosapentaenoic acid (EPA)[13], canakinumab[14], colchicine[15-18], metformin, sodium-glucose cotransporter 2 inhibitors (SGLT2i)[19,20], glucagon-like peptide-1 (GLP-1) receptor agonists[19,20], dual antiplatelet therapy[21,22], and rivaroxaban[23].

CM risk enhancing factors should be assessed routinely, including smoking, physical inactivity, psychosocial stress, inadequate diet, muscle strength, and environmental pollution, which contribute to the risk of CV disease and CV death, in particular, in middle- and low-income countries[24]. CM risk goes beyond the traditional risk

Table 1. Summary of recommendations with level of evidence

RECOMMENDATIONS		Class	Level	Ref
CMR assessment and management				
Comprehensive assessment of CMR, including the objectives and their corresponding therapies, benefit-risk ratio, and cost-effectiveness must be discussed with the patient and his/her relatives		I	A	
Optimum treatment should be implemented to achieve the optimal CMR reduction		I	A	
LDL-C goals according to risk category				
Low risk: LDL-C < 115 mg/dL/Non-HDL-C < 145 mg/dL High risk: LDL-C < 70 mg/dL (or at least 50% reduction)/Non-HDL-C < 100 mg/dL Very high risk: LDL-C < 55 mg/dL (or at least 50% reduction)/Non-HDL-C < 85 mg/dL		I	A	5-9
Atherogenic Dyslipidemia: Non-HDL-C (second therapeutic objective after achieving the primary goal: LDL-C based on risk category)		I	A	4,5,7,8,13,36,37
In patients that, despite receiving statins at adequate doses and being at the right goal according to their risk profile, experience a recurrent atherosclerotic cardiovascular event, their LDL-C goal may be < 40 mg/dl.		IIb	C	11-13
Diagnostic strategies				
- Routine calculation of Non-HDL-C (surrogate for ApoB): - Lp(a) measurement to assess risk. Indications: - Premature or progressive ASCVD with maximum lipid-lowering therapy - Familial hypercholesterolemia - Premature or progressive ASCVD with maximum lipid-lowering therapy - Premature ASCVD in family members - Direct relatives with elevated Lp(a) - Failure to achieve expected LDL-C reduction with statin therapy		I	B	32 52,53 52,53
- Whenever the means are available and the cost is justifiable, Lp(a) should be measured		IIa	B	
- Measuring Lp(a) in patients not included in the above-mentioned cases is not recommended		III	C	
HDL-C goals or pharmacological therapy not recommended		III	A	32-34,36
Therapeutic strategies				
	Risk/Clinical Condition/Goal			
Non-pharmacological: - Nutrition, exercise, weight loss and smoking cessation	For every patient, regardless of the risk	I	A	17,21,37,64,69-73
	As a strategy to help elevate HDL-C	IIa	C	17,21,37,64,69-73
Monotherapy with statins	Initial therapy to the lower LDL-C and achieve the goal based on the risk. Select the molecule and dose according to the percentage reduction required to achieve the goal. Use the maximum tolerable dose with no time limit.	I	A	26-30
Monotherapy with Ezetimibe	Only in case of proven statin intolerance and requiring less than 20% LDL-C reduction	IIb	C	
Statins with Fenofibrate	Primary prevention	IIa	B	40,41
	Secondary prevention	IIb	C	
Statins and gemfibrozil	Contraindicated	III	A	5,37

(Continues)

Table 1. Summary of recommendations with level of evidence (*Continued*)

RECOMMENDATIONS		Class	Level	Ref
Statins and ezetimibe	Initial therapy: If reduction required in LDL-C is > 55%	IIa	C	
	Second line after potent statins at maximum dose and failure to achieve the LDL-C goal	IIa	B	10
Statins and PCSK9i	Second line after potent statins at maximum dose and failure to achieve the LDL-C goal. Assess and inform the patient about cost-benefit ratio and make decision together with the patient.	IIa	A	11,12,27,30,33,34
Therapeutic strategies in case of high or very high risk after maximum tolerable doses of potent statins				
Increase the statin dose or switch to a more potent statin		IIa	B	25,26,30
Add ezetimibe		IIa	B	10,48
Add PCSK9i, if available and there is an acceptable cost-benefit ratio. Inform and decide together with the patient.		IIa	A	11,12,29,30,33,34,37,48
PCSK9i triple therapy (Statins + Ezetimibe + PCSK9i) High risk and failure to achieve the goal with dual therapy. The potential of familial hypercholesterolemia must be assessed.		IIa	C	48
EPA (4 g/d) for patients with established ASCVD or high risk diabetic patients already on a statin and with TG > 135 mg/dl.		IIa	B	13,48
Maintain lipid lowering treatment for an indefinite period of time, at the dose and with the initial regimen, in order to achieve optimum goals based on individual risk estimation, unless unequivocal side effects develop		I	C	49-51
Fenofibrate 160 mg/d/High-risk diabetics with at least one RF TG ≥ 200 mg/dl and HDL-C ≤ 40 mg/dl and LDL-C on target based on risk under statin therapy		IIb	C	40,41
Diabetic patients – glucose lowering medications as an option to reduce cardiometabolic risk				
CV risk reduction should be a primordial goal in patients with T2DM, in addition to achieving a proper HbA1c reduction		I	A	54-56
It is necessary to discuss the cost-benefit ratio of these novel drugs with the patients before prescribing them		I	A	54-67
SGLT2i (empagliflozin, canagliflozin, and dapagliflozin) may be prescribed as a first line drug for the purpose of controlling glycemia and reducing CV risk in patients with CVD, HF, CKD, or high to very high CM risk		I	B	58-67
SGLT2i could be a second line option after stable doses of metformin		IIa	B	58-67
In patients with HF and CKD, with or without T2DM, the use of SGLT2I must be considered		I	A	62-64
GLP-1 (Liraglutide, semaglutide, and dulaglutide) Prior to the use of insulin or together with basal insulin to prevent insulin intensification. As first line therapy in overweight/obese patients with no insulin indication.		IIa	B	20,65-67
GLP-1 (Liraglutide, semaglutide, and dulaglutide) Clinical evidence of ACSVD or high to very high cardiometabolic risk, after metformin		IIa	B	20,65-67
Hypertension				
The use of a fixed-dose combination is recommended in moderate and high-risk patients as a strategy to improve adherence		I	A	68
Inflammation				
Despite being an important component in pathophysiology and residual risk, there is no recommendation to measure or treat pro-inflammatory risk.		III	C	14,15,69
Colchicine could be a useful anti-inflammatory strategy when started early in a post MI scenario and in patients with evidence of stable coronary disease, after treatment with statins, aspirin and ACEI/ARB		IIb	B	15-18

(Continues)

Table 1. Summary of recommendations with level of evidence (*Continued*)

RECOMMENDATIONS	Class	Level	Ref
Hs-CRP as a routine approach to lower RCR is not recommended	III	C	
Prothrombotic risk			
Aspirin (prior bleeding assessment) in high to very high-risk patients	IIa	A	21
Aspirin stable CAD and non-cardioembolic ischemic stroke or TIA	I	A	22,23,71
Following ACS or after a percutaneous arterial intervention, patients should receive dual antiplatelet therapy for as long as necessary, depending on the setting and clinical judgment	I	A	70
For ACS, rivaroxaban 2.5 mg BID may be considered, after discontinuation of parenteral anticoagulation, in addition to aspirin and clopidogrel, for 1 year, in the absence of previous TIA or stroke, and with low risk of bleeding	IIb	B	72
Patients with atherosclerosis in ≥ 2 vascular beds or two additional risk factors (current smoking, diabetes, renal insufficiency, HF, or non-lacunar ischemic stroke ≥ 1 month), rivaroxaban 2.5 mg BID may be considered	IIb	B	72
Clopidogrel/severe PAD of the lower extremities	IIa	B	71,72
Rivaroxaban 2.5 mg BID + aspirin 100 mg OD Severe PAD of the lower extremities (low risk of bleeding)	IIa	B	72
Recently vascularized PAD (low risk of bleeding)	I	B	72
With all antithrombotic and anticoagulant strategies, bleeding is an important risk; therefore, the net clinical benefit must to be carefully considered in every patient before prescribing them.	I	A	19-21,72
Behavioral and Lifestyle-associated Cardiometabolic Risk factors			
Obesity, lack of physical activity, inadequate diet, alcohol abuse, and smoking are all risk factors to consider and assess and to intervene in patients with CMR and in the assessment of RCR	I	A	24,73-77
Compliance assessment as an overall risk component must be evaluated in every patient	IIa	B	73
In patients with low or non-adherence, implement strategies that have proven to be helpful, such as using fixed-dose combinations, and polypill based on availability in each country could be an effective choice	IIa	B	73-77
General considerations			
Social determinants for CVD or social risk in Latin America must be assessed, since these are basically related to the level of education, income, environmental pollution, models of and access to healthcare services	IIa	A	24,39,68
We strongly recommend the formation of global cardiometabolic risk units to accomplish these goals. This strategy will reduce cardiovascular morbidity-mortality, establishing global cardiometabolic risk protocols that will enable the development of healthy habits, as well as an articulated treatment of all risk factors.	IIa	A	24,39,68

CM risk: cardiometabolic risk; RF: risk factor; RCR: residual cardiometabolic risk; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; Non HDL-C: non-high density lipoprotein cholesterol; Lp(a): lipoprotein a; ASCVD: atherosclerotic cardiovascular disease; PCSK9i: proprotein convertase subtilisin/kexin type 9 inhibitors; EPA: eicosapentaenoic acid; TG: triglyceride; SGLT2i: sodium/glucose cotransporter 2 inhibitors; GLP-1: glucagon-like peptide 1; ACEI: angiotensin convertase enzyme inhibitors; ARB: angiotensin receptor blocker; Hs-CRP: high sensitivity C-reactive protein; CAD: coronary artery disease; TIA: transient ischemic attack; ACS: acute coronary syndrome; HF: heart failure; PAD: peripheral arterial disease.

factors and, hence, ASCVD prevention involves the proactive evaluation of all of these risk factors.

Based on the above discussion, this consensus recommends a comprehensive assessment of CM risk (IA). Once the risk factors are identified, treatment should be implemented to achieve the optimal CM risk reduction (IA). The heightened risk persists as long as all of the factors are not systematically screened and treated. All treatment options must be discussed with the patient and, where appropriate, with his/her family (IA).

Dyslipidemia

The final goal of lipid-related CM risk is to decrease concentrations of all circulating pro-atherogenic ApoB containing lipoproteins (IC)[25]. Achieving the LDL-C risk-stratified target is the primary goal in treating patients with dyslipidemia. Evidence with statin and non-statin therapies, including gastroileal bypass, in different populations with different baseline LDL-C levels and varying risks, has shown a robust association between the reduction of LDL-C and the decline in CM risk[26-30].

This consensus recommends reducing LDL-C as the primary objective for RRR (IA).

However, it has been observed that, in patients treated with statins, there is a persistent RR secondary to several causes, including:

1) Use of inadequate, low doses of statins.
2) Failure to achieve an optimal LDL-C target.
3) Persistently elevated TgRL concentrations despite adequate LDL-C goal with statin therapy[31].

Lp(a) definitely could be considered a fourth lipid cause of persistent RR, see below in paragraph 1.4 for specific recommendations and management.

Suppl. Table 2 summarizes the results of recent trials that tested different types of drugs as adjuvant therapies with statins in patients with high and very-high CVR. The LDL-C values achieved in the trials with EZT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), PCSK9i Further Cardiovascular Outcomes Research with PCSK9i in Subjects with Elevated Risk (FOURIER), and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY), are the lowest reported in the history of clinical trials[10,11,12]. LDL-C values as low as ≤ 10 mg/dl were achieved, accompanied by a significant and safe incremental CVR reduction over and above that observed with statin therapy. These findings suggested that "lower is better, but lowest is best"[11-13,32].

There is no known LDL-C threshold below which there is physiological hazard; in fact, many genetic polymorphisms that give rise to the lower LDL-C are protective against the development of atherosclerosis. Meta-analyses show that there is no increased risk for either ischemic or hemorrhagic stroke with the achievement of very low LDL-C. Moreover, the EBBINGHAUS (Evaluating PCSK9i Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects) trial demonstrated no heightened risk for cognitive impairment even when attaining ultra-low LDL-C of < 10 mg/dL[32,33].

In these trials, the ARR was small, which may be due to the fact that most patients were being treated with high statin doses, and their baseline LDL-C was relatively low, as compared to the previous statin monotherapy trials. However, ARR significantly improves as the risk of patients increases[34].

Therefore, to be cost-effective, it is indispensable to select patients based on their risk and use these therapies in those patients most likely to benefit from them. The patient and, when appropriate, the family, should be included in the decision-making process.

Based on our analysis, to achieve an optimal RRR level, the members of this consensus recommend the following targets for LDL-C (IA):

– Low risk: LDL-C < 115 mg/dl/Non-HDL-C < 145 mg/dl
– Moderate risk: LDL-C < 100 mg/dl/Non-HDL-C < 130 mg/dl
– High risk: LDL-C < 70 mg/dl (or at least 50% reduction)/Non-HDL-C < 100 mg/dl
– Very high risk: LDL-C < 55 mg/dl (or at least 50% reduction)/Non-HDL-C < 85 mg/dl

In patients failing to attain these values, a RR associated with insufficiently reduced LDL-C levels will persist. In patients that, despite receiving statins at adequate doses and being at the right goal according to their risk profile, experience a recurrent atherosclerotic cardiovascular event, their LDL-C goal is < 40 mg/dl. (IIbC)

1.1. TgRL, Remnants, and HDL – Recently published evidence, which includes prospective longitudinal cohorts, Mendelian randomization studies, and randomized clinical trials, shows that TgRL are a component of residual CM risk. Therefore, this panel considers that non-HDL-C, that represent every apoB atherogenic particles including cholesterol remnants, must be assessing. LDL-C overlooks the atherogenic potential of remaining apoB particles; even lipoprotein (a) also carrying apoB is included in the LDL cholesterol measurement. Indeed, cholesterol remnants as all the TgRL, cause ASCVD just like LDL[35]. This may be especially important in individuals treated with statins, in obese patients, and in patients with DM or Pre DM in whom cholesterol content in C- LDL is lower than other remnants apoB-containing particles and more cholesterol is transported in TgRL. In those situations, apoB and also non-HDL cholesterol identifies patients with an increased number of cholesterol-containing TG-rich apoB-containing particles, these patients continue to be at high risk of ASCVD events even with C-LDL in target.

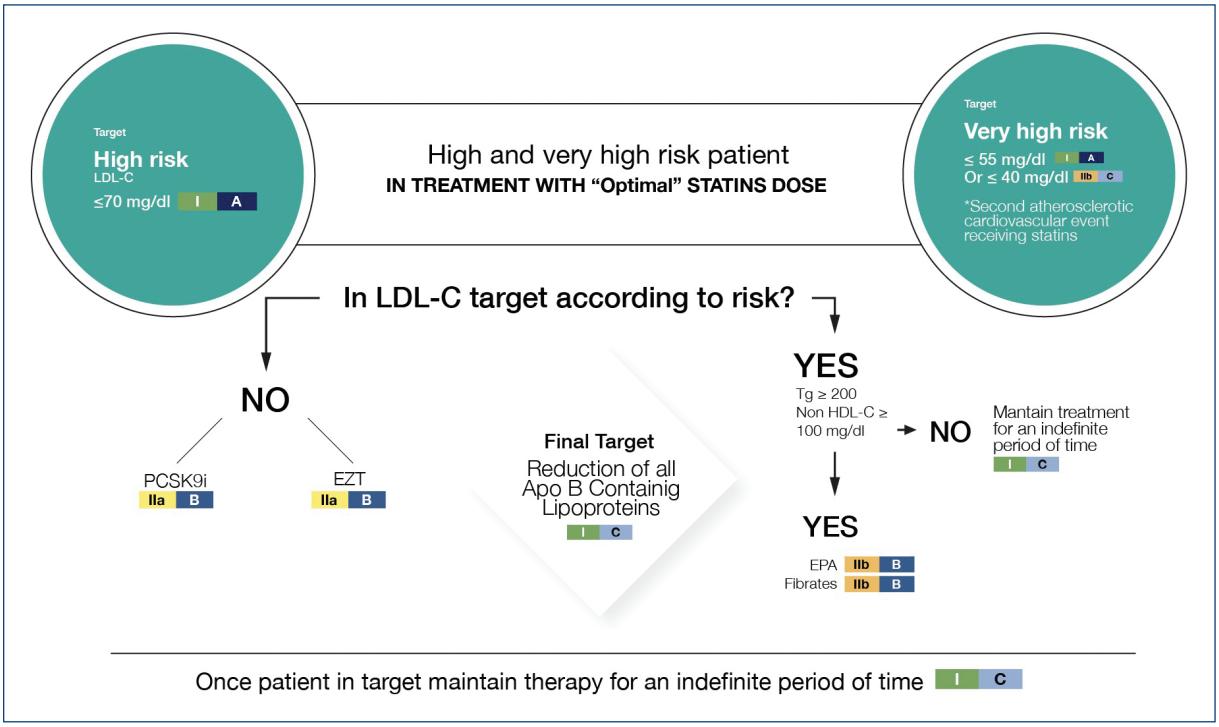

Figure 2. Simplified drug combination algorithm to accomplish therapeutic goals.

That's why we, consider that Non HDL-C should be considered as a secondary goal, once the LDL-C target has been reached[36-40] (IA), and lowering the non-HDL-C to risk-stratified levels as a second therapeutic objective (IA), since it represents all of the Apo-B-carrying proatherogenic lipoproteins[39,40].

Apo-B and remnants measurement is expensive and not widely available all Latin American countries. Non-HDL-C determination is simple, cost-effective, and has an excellent correlation with TgRL levels, ApoB containing particles and remnants; hence, it can be used as a surrogate marker for Apo B[36]. This consensus recommends a routine calculation of non-HDL-C in all patients (IB) as an Apo B surrogate. In the locations where the measurements of ApoB are possible and it is affordable for the patient, it could be measure after a cost benefit discussion with the patients (IIb).

Epidemiological studies have shown an inverse relationship between low levels of HDL-C and CVR, but it should not be treated since the CCTs that have tested pharmacological strategies to raise levels of HDL-C to the lower the risk CV events have failed to demonstrate any efficacy[41,42]. This consensus statement does not recommend pharmacological therapy for low HDL-C and agrees that there should not be any HDL-C goals at the present time (IIIA).

1.2. Adjuvant pharmacological therapies to statins to treat TgRL Achieving the therapeutic goals of all circulating pro-atherogenic ApoB containing lipoproteins[25,36] is necessary to achieve optimal CM risk reduction. In many subjects, particularly in those at high and very-high risk, the goals are not achieved with statin monotherapy and, hence, adjuvant therapies should be used. Combination therapy is a common strategy in other conditions such as HBP and T2DM and results in higher rates of therapeutic goal attainment.

A critical analysis based on the levels of evidence available for the various therapeutic classes was conducted, regarding their ability to reduce RR when combined with statins. This consensus panel focused on omega-3 fatty acids (O3FA) and fibrates as adjunctive therapy to treat residual CM risk related to high Tg levels.

FIBRATES: According to available evidence from secondary endpoint analyses, fenofibrate is the only molecule with enough evidence of reducing CM risk and may be indicated for both primary (IIaB) and secondary prevention (IIbC)[43,44]. The combination of statins with gemfibrozil is contraindicated (IIIC) since gemfibrozil inhibits their glucuronidation and can lead to

myopathy and rhabdomyolysis. Ciprofibrate should not be used due to lack of evidence (IIIC).

O3FA: eicosapentaenoic acid and docosahexaenoic acid (EPA/DHA) have the ability to reduce TG and have been tested in several CCTs with divergent or inconclusive results[45-47]. The REDUCE-IT trial, with a highly purified EPA ethyl ester, demonstrated a significant MACE reduction and reduced CV mortality in patients at high and very high risk, treated with statins, with LDL-C at target but Tg > 150 mg/dl[13].

Simplified drug combination algorithm to accomplish therapeutic goals (Fig. 2), the class of drugs with the most conclusive and robust evidence are the statins; consequently, they are indicated as first line agents, using the maximum tolerated dose (IA) (Suppl. Table 3).

Only in the event of a proven statin intolerance and requiring < 20% LDL-C reduction can we recommend monotherapy with EZT (IIbC).

The drugs recommended for use in combination with statins are: EZT and PCSK9i[48] (IIaA).

In patients with an LDL-C > 55% above the goal, EZT could be in the initial combination (IIbC), or as a second-line adjuvant therapy following high dose potent statins and failing to accomplish the LDL-C goal (IIaB).

In high- or very high-risk patients failing to accomplish the goals after treatment with statin, the following may be recommended:

– Increase doses or switch to a more potent statin (IIaB)
– Add EZT(IIaB)
– Add PCSK9i, if available and cost-effective (IIaA)
– In patients achieving the LDL-C goal, but with a fasting Tg > 150 mg/dl, (after lifestyle changes for 6 weeks), EPA dose of 4 g/d could be prescribed (IIaB)
– In patients who persist with Tg > 200 mg/dl, fenofibrate could be prescribed at a dose of 160 mg (IIbC)
– Among high risk patients (with established ASCVD or diabetic with multiple risk factors) with TG > 150 mg/dl, icosapent ethyl can be prescribed at a dose of 2.0 g twice daily (IIa).

1.3. Lipid-lowering treatment duration atherosclerotic disease is a systemic immune inflammatory process that is progressive secondary to exposure of the arterial wall to various risk factors with damage accruing over time.

The 20 year follow-up of "*West of Scotland Coronary Prevention Study*" showed a 24% reduction in myocardial infarction (MI), 18% in coronary events, and a 35% decrease in HF-related hospital admissions. No reduction was observed in non-CV deaths or stroke[49]. Prospective studies on the impact of discontinuing statins have reported a 33% increase in CVE and a risk of hospital admissions with 42% increase in stroke, after 1 year of treatment discontinuation[50,51].

When combining outcomes data with cost-effectiveness data, we conclude that the use of statins for long-term treatment is efficacious and justified.

This consensus panel recommends the prescription of statins for an indefinite time, at the dose necessary to achieve optimal LDL-C goals based on individual risk (IC), unless unequivocal side effects develop such as myalgia or myopathy, although these are relatively infrequent.

1.4. Lipoprotein (a) Lp(a) a unique apo(a) and an apoB-containing lipoprotein particle is one of the most important genetically determined risk factors for CVD. Mendelian randomization studies provide strong support for causality for Lp(a) as a causal risk factor for ASCVD, aortic stenosis, and heart failure. Roughly 25% of the general white population have Lp(a) > 30 mg/dL, level associated with high risk. In Latin America it is important to realize that it is demonstrated pronounced differences between ethnic groups (is highest in black people), and differences may depend of standardization of assays, characteristics of population and sample[52,53].

Based on the evidence available, the consensus agreed that Lp(a) is a cause of residual CM risk Many epidemiologic studies confirm that elevated serum levels of Lp(a) herald risk for ASCVD (IB).

The object of measuring Lp(a) is not to provide treatment, but its assessment to reclassify patients to a higher risk group. Consequently, this consensus panel recommends that whenever the means are available and the cost is justifiable, Lp(a) should be measured (IIaB).

Clinical conditions in which Lp(a) measurement is recommended (IB):

– Early onset or progressive ASCVD with maximum lipid lowering therapy
– Familial hypercholesterolemia
– Early onset of ACVD in family members
– Direct relatives with elevated Lp(a).

Measuring Lp(a) in patients not included in the above-mentioned cases is not recommended. (IIIC)

2. GLOBAL CM RISK REDUCTION The "*Prospective Urban Rural Epidemiology*" (PURE) trial[24] showed that over 70% of CVD may be attributed to a small number of CM risk factors: HBP, TgRL, diabetes,

pre-diabetes, and abdominal obesity. Hence, this consensus emphasizes the necessity for a comprehensive control of all of these factors for an optimal CM risk reduction.

3. GLUCOSE METABOLISM Individuals with T2DM or prediabetes have a higher CM risk; their primary cause of death is CVD[54]. T2DM medical therapy includes glycemic control to avoid acute metabolic complications and long-term strategies to reduce the risk of micro- and macro-vascular events.

There is a continued need for the development of new antidiabetic drugs and to assess their impact on CM risk and CV safety in adequately designed CCT. Historically, clinical trials taught us that the intensive reduction in HbA_{1c} (< 7%) has a significant impact on microvascular complications, but not on macrovascular events[55,56]. However, the development of newer antiglycemic agents has now provided physicians with the therapeutic means to reduce glycemic indices and reduce risk for macrovascular events, such as MI, ischemic stroke, and CV mortality.

Based on the above discussion, this consensus recommends that CV risk reduction should be a primordial goal in patients with T2DM, in addition to achieving a proper HbA1c reduction (IA).

3.1. SGLT2 inhibitors Sodium-glucose cotransporter 2 inhibitors (SGLT2i): dapagliflozin, empagliflozin, and canagliflozin, induce glucosuria by inhibiting the uptake of glucose along the proximal tubule, reduce serum glucose levels, promote diuresis and sodium elimination, lower BP, and serum uric acid and are associated with weight loss. Other effects include lowering intraglomerular pressure and proteinuria, preventing tubulo-interstitial and glomerular injury, inhibiting the sodium-proton exchanger, and increasing hematocrit, serum beta-hydroxybutyrate, and angiotensin 1-7[57]. These medications have a low risk for hypoglycemia.

These drugs have been tested in several clinical trials (Suppl. Table 4) and have demonstrated consistent cardio-renal-vascular protection, regardless of the diagnosis or not of T2DM[58-67].

Based on the results of these clinical trials, this consensus panel recommends:

1) In patients with T2DM and established CVD, HF, CKD or high to very high CM risk, SGLT2i may be prescribed as a first-line drug for the purpose of controlling glycaemia and reducing CV risk (IB).
2) SGLT2i may be used as a second line option after metformin. (IIaB)

Table 2. Recommendations for managing lifestyle changes

Risk factor	Goal	Type of therapy
Obesity	BMI < 25 WAIST-HIP RATIO Males: < 0.90 Females: < 0.84	Indicate: • Lifestyle changes • Diet 800-1500 Kcal/day • Exercise 200-300 min/week • Metabolic surgery in patients with a BMI > 35 and two comorbidities or a BMI > 40 Potential recommendation: • Orlistat
Smoking	Smoking cessation	Recommended: • Psychotherapy • Chewing gum • Drug therapy • Bupropion, Varenicline Tobacco in any form not allowed (Vaping, inhaling chewing, etc.)
HBP	<140/90	Indicated: • Lifestyle changes • Salt intake 7.5-12 g/day • Physical activity 200-300 min/week with 40% strength
Dysglycemia DM	Hba1c < 5.7 Hba1c < 7	Recommended • Fiber-rich diet and reduced intake of refined carbohydrates • Physical activity at least 150 min/week with 40% strength

3) In patients with HF and/or CKD, with or without T2DM, the use of SGLT2I should be considered (IA).
4) Regard chronic kidney disease emerging evidence derived from RCTs and meta-analyses demonstrate a cardio-protective and nephro-protective effects of SGLT2i. We recommend their use in patients with baseline eGFR up to 30 mL/min/1.73 m^2.

3.2. GLP-1 receptor agonists Glucagon-like peptide-1 receptor agonists are the only injectable non-insulin therapy for controlling T2DM, with high glucose-lowering power (with low risk of hypoglycemia), and significant weight loss[20].

Liraglutide, semaglutide, and dulaglutide have been proven to reduce the risk of MACE (Suppl. Table 4), whereas lixisenatide and extended-release exenatide have a neutral effect[65-67].

This consensus recommends GLP-1 receptor agonists (liraglutide, semaglutide, and dulaglutide) as a treatment option in patients with evidence of ASCVD who are at high risk after metformin, or before the use of insulin, or together with basal insulin to prevent insulin intensification; this could be a parenteral first line therapy in overweight patients with no insulin indication (IIaB). Availability of and accessibility to these medications should be considered and it is necessary to discuss the cost-benefit ratio with the patients before prescribing (IA).

Hypertension

HBP is the risk factor with the highest attributable risk; BP control is critical in reducing CM risk. A detailed discussion about the BP goals and treatment regimens is beyond the scope of this paper (refer to the IASC Statement)[68].

Pharmacological therapy should start at BP ≥ 140/90 mm Hg; the recommended goals should be < 130/85 mm Hg. The recommended drug classes are: ACE inhibitors/angiotensin receptor blockers, thiazide diuretics, calcium antagonists, and beta-blockers. Mineralocorticoid receptor blockers may be prescribed in difficult to manage cases or refractory HBP. The use of fixed dose combination therapy is recommended in moderate- and high-risk patients as a strategy to improve BP control and long-term adherence (IA).

Inflammation

Plays a pivotal role in atherogenesis, acute plaque rupture, and ASCVD-related events[9]. Therefore, inflammation is a significant factor to consider as a cause of RR.

Three pharmacological strategies have been tested in trying to show that, by selectively and independently reducing vascular inflammation, a decline in RR is achieved.

a) Canakinumab: The CANTOS trial reported a significant benefit; it is a drug with an extremely high cost and hence it is not recommended for the treatment of patients with an elevated RCR (IIIC)[14]. It is also not approved for this indication.
b) Colchicine: An affordable anti-inflammatory drug has been tested targeting inflammation to reduce CV risk[15-18]. Colchicine Cardiovascular Outcomes Trial (COLCOT) demonstrated a beneficial impact of low-dose colchicine (0.5 g/d) in the post-MI setting. A recent analysis shows that early initiation of colchicine within the first 3 days after MI is associated with a greater reduction of the primary endpoint[15].

In LODOCO 2 (a trial which used low doses of colchicine), the primary end point was reduced significantly[17]. Low-dose therapy was not associated with any serious adverse effects.

Results of the Colchicine in Patients with Acute Coronary Syndrome (COPS) trial showed that colchicine does not improve CV outcomes in patients with ACS. The differences with the previous results could be in part due to the size of the cohort studied[18].

5.3. Methotrexate: The Cardiovascular Inflammation Reduction Trial (CIRT) observed that, at low doses, it failed to reduce the risk of CV events[69].

The major implications of these findings are that it may be possible to reduce the risk of CV events in patients with stable coronary disease by targeting inflammation. This consensus recommends that:

a) Colchicine could be a useful anti-inflammatory strategy if started early in a post MI scenario and in patients with evidence of stable coronary disease, after treatment with statins, aspirin, and ACEI/ARB (IIbB).
b) This consensus does not recommend assessing inflammation hs-CRP as a routine approach to the lower RCR (IIIA).

Prothrombotic status

Effective and safe anti-thrombotic therapy using antiplatelet[21,22] and anticoagulation drugs[70-72] is essential to reducing RCR. This consensus recommends the use of an antithrombotic therapy, depending on the drug type and patient's clinical scenario:

a) In patients with high or very-high cardiovascular risk, assess the risk of bleeding and consider aspirin therapy (IIaA).
b) All patients with stable coronary disease and non-cardioembolic ischemic stroke or TIA should receive aspirin (75-81 mg) (IA).
c) Following ACS or after a percutaneous arterial intervention, patients should receive dual antiplatelet therapy for as long as necessary, depending on the setting and clinical judgment (IA)[21,22].
d) For ACS, rivaroxaban 2.5 mg BID may be considered, in addition to aspirin and clopidogrel, for 1 year, in patients with an elevated risk of ischemia, in the absence of the previous TIA or stroke, and with low risk of bleeding (IIbB)[23,72].
e) In patients with severe lower extremity PAD, clopidogrel may be considered (IIaB).

f) In patients with severe PAD of the lower extremities and with low risk of bleeding, the combination of rivaroxaban 2.5 mg BID plus aspirin 100 mg/day could be considered (IIaB)[71].

g) In patients with recently vascularized PAD and low risk of bleeding, the combination of rivaroxaban 2.5 mg BID plus aspirin 100 mg/day is recommended (IB)[70].

Behavioral And Lifestyle-Associated CM Risk Factors

Obesity, physical inactivity, inadequate diet, alcohol abuse, and smoking are enhancing risk factors to consider for evaluation in patients with CM risk and in the assessment of RCR (IA)[24,73-77].

Poor compliance and lack of long-term adherence are behavioral attitudes that are additional risk factor in patients with CM risk. Depression and anxiety could increase the lack of adherence to drugs and lifestyle modifications. Therefore, it is mandatory to inquire about poor adherence as an overall risk component, usually associated with the number of pills prescribed. This consensus recommends the implementation of strategies to improve compliance and hence reduce risk, such as using fixed-dose combinations in patients prescribed individual components, based on availability in each country (IA).

Table 2 summarizes the recommendations for these risk factors in all patients.

To minimize the incidence of CVD in the population, as well as to reduce RCR, physicians must be aware of the importance of risk factors and lifestyles, so that they may routinely and systematically explain them to the patient, their family, including children and adolescents, at each visit.

What has been described as the social determinants for CVD or social risk in Latin America must be assessed, since these are basically related to the level of education, income, and access to health-care services (IA). Finally, this consensus wants to underscore the need to evaluate and treat CM risk in a comprehensive and integrated way to achieve an optimal control of all risks. In this respect, we strongly recommend that global CM risk units be formed to accomplish this goal. This strategy will reduce cardiovascular morbidity-mortality; establishing global CM risk prevention protocols that will enable the development of healthy habits, as well as an articulated treatment of all risk factors (IA).

Acknowledgments

The authors would like to thank Lic. Ximena Sánchez Aquique for their logistic support during the development of the manuscript, and Andrea Niño for the unevaluable assistance in final spelling and grammar of the manuscript.

Funding

Tecnofarma S.A. de C.V. A private Laboratories contributed with an unrestrictive grant used exclusively for the logistical expenses of the research meeting.

Conflicts of interest

On behalf of all Co-Authors, I Carlos I. Ponte-Negretti the corresponding author do have the responsibility for the submission. All authors were requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within 3 years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2018;392:1736-88.
2. Januzzi JL Jr., Ahmad T, Binder LG, Hucker WJ, Kumbhani DJ, Maddox TM. et al. 2019 Methodology for creating expert consensus decision pathways: a report of the American college of cardiology. J Am Coll Cardiol. 2019;74:1138-50.
3. Crawford M, Wright G. Delphi method. In: Wiley StatsRef: statistics Reference Online. United States: Wiley; 2016. p. 1-6.
4. Fruchart JC, Davignon J, Hermans MP, Al-Rubeaan K, Amarenco P, Assmann G, et al. Residual risk reduction initiative (R3i). Residual macrovascular risk in 2013: what have we learned? Cardiovasc Diabetol. 2014;13:26.
5. Averna M, Stroes E, Alterations Beyond LDL Expert Working Group. How to assess and manage cardiovascular risk associated with lipid alterations beyond LDL. Atheroscler Suppl. 2017;26:16-24.
6. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388:2532-61.
7. Ganda O, Bhatt D, Mason P, Miller M, Boden W. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. JACC. 2018;72:330-43.

8. Ferrari R, Catapano AL. Residual cardiovascular risk. Eur Heart J Suppl. 2016;18:C2-12.
9. Patel KV, Pandey A, de Lemos JA. Conceptual framework for addressing residual atherosclerotic cardiovascular disease risk in the era of precision medicine. Circulation. 2018;137:2551-3.
10. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al, IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387-97.
11. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, el al, FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376:1713-22.
12. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al, ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379:2097-107.
13. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al, CM REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019;380:11-22.
14. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al, CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377:1119-31.
15. Bouabdallaoui N, Tardif JC, Waters DD, Pinto FJ, Maggioni AP, Diaz R, et al. Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the colchicine cardiovascular outcomes trial (COLCOT). Eur Heart J. 2020;41:4092-9.
16. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019;381:2497-505.
17. Nidorf SM, Fiolet AT, Mosterd A, Eikelboom JW, Schut A, Opstal TS, et al, LoDoCo$_2$ Trial Investigators. Colchicine in patients with chronic coronary disease. N Engl J Med. 2020;383:1838-47.
18. Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, et al. Colchicine in patients with acute coronary syndrome: the Australian COPS randomized clinical trial. Circulation. 2020;142:1890-900.
19. Zou CY, Liu XK, Sang YQ, Wang B, Liang J. Effects of SGLT2 inhibitors on cardiovascular outcomes and mortality in Type 2 diabetes: a meta-analysis. Medicine (Baltimore). 2019;98:e18245.
20. Sinha B, Ghosal S. Meta-analyses of the effects of DPP-4 inhibitors, SGLT2 inhibitors and GLP1 receptor analogues on cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure. Diabetes Res Clin Pract. 2019;150:8-16.
21. Bittl JA, Baber U, Bradley SM, Wijeysundera DN. Duration of dual antiplatelet therapy: a systematic review for the 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. J Am Coll Cardiol. 2016;68:1116-39.
22. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al, PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372:1791-800.
23. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al, COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med. 2017;377:1319-30.
24. Yusuf S, Joseph P, Rangarajan S, Islam S, Mente A, Hystad P, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet. 2020;395:795-808.
25. Rana JS, Liu JY, Moffet HH, Boklage SH, Khan I, Karter AJ. Risk of incident atherosclerotic cardiovascular disease events by achieved atherogenic lipid levels among 62,428 statin-treated individuals with diabetes mellitus. Am J Cardiol. 2018;122:762-7.
26. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670-81.
27. Sabatine MS, Wiviott SD, Im K, Murphy SA, Giugliano RP. Efficacy and safety of further lowering of low-density lipoprotein cholesterol in patients starting with very low levels: a meta-analysis. JAMA Cardiol. 2018;3:823-8.
28. 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.
29. Mundi S, Massaro M, Scoditti E, Carluccio MA, van Hinsbergh VW, Iruela-Arispe ML, et al. Endothelial permeability, LDL deposition, and cardiovascular risk factors-a review. Cardiovasc Res. 2018;114:35-52.
30. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA. 2016;316:1289-97.
31. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. Circ Res. 2016;118:547-63.
32. Masana L, Girona J, Ibarretxe D, Rodríguez-Calvo R, Rosales R, Vallvé JC, et al. Clinical and pathophysiological evidence supporting the safety of extremely low LDL levels-The zero-LDL hypothesis. J Clin Lipidol. 2018;12:292-9.e3.
33. Giugliano RP, Mach F, Zavitz K, Kurtz C, Im K, Kanevsky E, EBBINGHAUS Investigators. Cognitive function in a randomized trial of evolocumab. N Engl J Med. 2017;377:633-43.
34. Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, Ceska R, et al, FOURIER Investigators. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. Lancet. 2017;390:1962-71.
35. Ditlev C, Johannesen L, Bødtker Mortensen M, Langsted A, Nordestgaard BG. Apolipoprotein B and non-HDL cholesterol better reflect residual risk than LDL cholesterol in statin-treated patients. J Am Coll Cardiol. 2021;77:1439-50.
36. Ballantyne CM, Bertolami M, Hernandez Garcia HR, Nul D, Stein EA, Theroux P, et al. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: measuring effective reductions in cholesterol using rosuvastatin therapy (MERCURY) II. Am Heart J. 2006;151:975.e1-9.
37. Perrone V, Sangiorgi D, Buda S, Degli Esposti L. Residual cardiovascular risk in patients who received lipid-lowering treatment in a real-life setting: retrospective study. Clinicoecon Outcomes Res. 2016;8:649-55.
38. Johansen CT, Hegele RA. Using mendelian randomization to determine causative factors in cardiovascular disease. J Intern Med. 2013;273:44-7.
39. Ponte-Negretti CI, Isea-Perez JE, Lorenzatti AJ, Lopez-Jaramillo P, Wyss-Q FS, Pintó X, et al. Atherogenic dyslipidemia in Latin America: prevalence, causes and treatment: expert's position paper made by the Latin American academy for the study of lipids (ALALIP) endorsed by the inter-American society of cardiology (IASC), the South American society of cardiology (SSC), the Pan-American college of endothelium (PACE), and the international atherosclerosis society (IAS). Int J Cardiol. 2017;243:516-22.
40. Villines TC, Stanek EJ, Devine PJ, Turco M, Miller M, Weissman NJ, et al. The ARBITER 6-HALTS trial (Arterial biology for the investigation of the treatment effects of reducing cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis): final results and the impact of medication adherence, dose, and treatment duration. J Am Coll Cardiol. 2010;55:2721-6.
41. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365:2255-67.
42. ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC Jr., Grimm RH Jr., Cutler JA, et al. Effects of intensive blood-pressure control in Type 2 diabetes mellitus. N Engl J Med. 2010;362:1575-85.
43. Scott R, O'Brien R, Fulcher G, Pardy C, D'Emden M, Tse D, et al. Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study Investigators. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with Type 2 diabetes and various components of the metabolic syndrome: the fenofibrate intervention and event lowering in diabetes (FIELD) study. Diabetes Care. 2009;32:493-8.
44. ORIGIN Trial Investigators, Bosch J, Gerstein HC, Dagenais GR, Díaz R, Dyal L, Jung H, et al. N-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med. 2012;367:309-18.
45. The ASCEND Study Collaborative Group. Effects of n-3 fatty acid supplements in diabetes mellitus. N Engl J Med 2018;379:1540-50.
46. Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, et al, Omega-3 Treatment Trialists' Collaboration. Associations of Omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77 917 individuals. JAMA Cardiol. 2018;3:225-34.
47. Ponte-N C, Machado HL. Lipidología y prevención cardiovascular La era de las combinaciones llegaron para quedarse. JACC Spanish Ed 2020;1:120-3.
48. Ford I, Murray H, McCowan C, Packard CJ. Long-term safety and efficacy of lowering low-density lipoprotein cholesterol with statin therapy: 20-year follow-up of west of Scotland coronary prevention study. Circulation. 2016;133:1073-80.
49. Thanassoulis G, Sniderman AD, Pencina MJ. A long-term benefit approach vs standard risk-based approaches for statin eligibility in primary prevention. JAMA Cardiol. 2018;3:1090-5.
50. Willeit P, Ridker PM, Nestel PJ, Simes J, Tonkin AM, Pedersen TR, et al. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. Lancet. 2018;392:1311-20.
51. Verbeek R, Hoogeveen RM, Langsted A, Stiekema LC, Verweij SL, Hovingh GK, et al. Cardiovascular disease risk associated with elevated lipoprotein(a) attenuates at low low-density lipoprotein cholesterol levels in a primary prevention setting. Eur Heart J. 2018;39:2589-96.

52. Bertoluci MC, Rocha VZ. Cardiovascular risk assessment in patients with diabetes. Diabetol Metab Syndr. 2017;9:25.
53. Low Wang CC, Everett BM, Burman KD, Wilson PW. Cardiovascular safety trials for all new diabetes mellitus drugs? Circulation. 2019;139:1741-3.
54. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2017;24:44-51.
55. Verma S, McMurray JJ. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018;61:2108-17.
56. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al, The EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in Type 2 diabetes. N Engl J Med. 2015;373: 2117-28.
57. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al, CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in Type 2 diabetes. N Engl J Med. 2017;377: 644-57.
58. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al, MS DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in Type 2 diabetes. N Engl J Med. 2019;380:347-57.
59. Kluger AY, Tecson KM, Barbin CM, Lee AY, Lerma EV, Rosol ZP, et al. Cardiorenal outcomes in the CANVAS, DECLARE-TIMI 58, and EMPA-REG OUTCOME trials: a systematic review. Rev Cardiovasc Med. 2018;19:41-9.
60. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al, EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383:1413-24.
61. McMurray JJ, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, et al, DAPA-HF Committees and Investigators. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). Eur J Heart Fail. 2019;21: 665-75.
62. Heerspink HJ, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al, DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383:1436-46.
63. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al, LEADER Steering Committee, LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in Type 2 diabetes. N Engl J Med. 2016;375:311-22.
64. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al, SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with Type 2 diabetes. N Engl J Med. 2016;375:1834-44.
65. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al, REWIND Investigators. Dulaglutide and cardiovascular outcomes in Type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394:121-30.
66. Wyss F, Coca A, Lopez-Jaramillo P, Ponte-Negretti C. The Task Force for the Management of Arterial Hypertension of the Interamerican Society of Cardiology (IASC), Reviewers from the European Society of Hypertension (ESH), Latin-American Society of Hypertension (LASH), and the Spanish Society of Cardiology (SSC). Position statement of the Interamerican society of cardiology (IASC) on the current guidelines for the prevention, diagnosis and treatment of arterial hypertension 2017-2020. Int J Cardiol Hypertens. 2020;6:100041.
67. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, CIRT Investigators. Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med 2019;380:752-76.
68. Capell WH, Bonaca MP, Nehler MR, Chen E, Kittelson JM, Anand SS, et al. Rationale and design for the vascular outcomes study of ASA along with rivaroxaban in endovascular or surgical limb revascularization for peripheral artery disease (VOYAGER PAD). Am Heart J. 2018;199:83-91.
69. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al, COMPASS Investigators. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391:219-29.
70. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, et al, ATLAS ACS 2-TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366:9-19.
71. Nocon M, Hiemann T, Müller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2008;15:239-46.
72. American Heart Association. Council on Lifestyle and Cardiometabolic Health. Available from: https://www.professional.heart.org/professional/MembershipCouncils/ScientificCouncils/UCM_322856_Council-on-Lifestyle-and-Cardiometabolic-Health.jsp. [Last accessed on 2018 Sep [19].
73. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Arch Intern Med. 2009;169:659-69.
74. Barua RS, Rigotti NA, Benowitz NL, Cummings KM, Jazayeri MA, Morris PB, et al. 2018 ACC expert consensus decision pathway on tobacco cessation treatment: a report of the American college of cardiology task force on clinical expert consensus documents. J Am Coll Cardiol. 2018;72:3332-65.
75. Sosa-Liprandi Á, Sosa Liprandi MI, Alexánderson E, Avezum Á, Lanas F, López-Jaramillo JP, et al. Clinical impact of the polypill for cardiovascular prevention in Latin America: a consensus statement of the inter-American society of cardiology. Glob Heart. 2019;14:3-16.e1.

Archivos de Cardiología de México

PERMANYER

Check for updates

SPECIAL ARTICLE

Latin American Consensus on management of residual cardiometabolic risk. A consensus paper prepared by the Latin American Academy for the Study of Lipids and Cardiometabolic Risk (ALALIP) endorsed by the Inter-American Society of Cardiology (IASC), the International Atherosclerosis Society (IAS), and the Pan-American College of Endothelium (PACE)

Consenso Latinoamericano para el manejo del riesgo residual cardiometabólico. Consenso realizado por la Academia Latinoamericana de Lipidología y Riesgo Cardiometabólico (ALALIP), con el aval de la Sociedad Interamericana de Cardiología (SIAC), la Sociedad Interamericana de Aterosclerosis (IAS) y el Colegio Panamericano de Endotelio (PACE)

Carlos I. Ponte-Negretti[1], Fernando S. Wyss[2], Daniel Piskorz[3], Raul D Santos[4], Raul Villar[5], Alberto Lorenzatti[6], Patricio López-Jaramillo[7], Peter Toth[8], A. Juan J. Amaro[9], Alfonso K. Rodrigo[10], Fernando Lanas[11], Miguel Urina-Triana[12], Jofre Lara[13], T. Osiris Valdés[14], José R. Gomez-Mancebo[15], Alfonso Bryce[16], Leonardo Cobos S.[17], Adriana Puente-Barragan[18], Vladimir E. Ullauri-Solórzano[19], Felix A. Medina-Palomino[20], Alfredo F. Lozada[21], Maritza Duran[22], Percy Berrospi[23], David Miranda[24], Juan J Badimon[25], J. José R. González[26], and Peter Libby[27]*

[1]Unit of Cardiometabolic Medicine, La Floresta Medical Institute, Caracas, Venezuela; [2]Services and Cardiovascular Technology of Guatemala CARDIOSOLUTIONS, Guatemala, Guatemala; [3]Institute of Cardiology Sanatorio Británico SRL Rosario, Argentina; [4]Lipid Clinic Heart Institute (InCor) University of Sao Paulo Medical School Hospital, Sao Paulo, Brazil; [5]Integra Médica, La Serena, Chile; [6]Department of Cardiology, Hospital Instituto Médico DAMIC/Rusculleda Foundation for Research in Medicine, Cordoba Argentina; [7]Integral Center for the Prevention of Cardiometabolic Diseases (CIPCA) and Instituto Masira, UDES, Bucaramanga, Colombia; [8]University of Illinois College of Medicine, Peoria, Illinois, Michigan State, USA; [9]Clinica Santa Sofía, Caracas, Venezuela; [10]Advanced Center for Metabolic Medicine and Nutrition, Santiago de Chile, Chile; [11]University of La Frontera, Temuco, Chile; [12]Faculty of Health Sciences, Simón Bolívar University, Barranquilla Colombia; [13]Department of Cardiology, Hospital Solca Guayaquil, Ecuador; [14]Central Medical Center La Romana, Dominican Republic; [15]Department of Cardiology, Hospital Universitario de Caracas, Universidad Central de Venezuela, Caracas, Venezuela; [16]CARDIOGOLF Research Unit, El Golf Clinic, Lima, Peru; [17]Cardiology Hospital El Pino, Cardiocob Research Unit, Santiago de Chile, Chile; [18]Centro Médico Nacional 20 de Noviembre (ISSSTE), Mexico City, Mexico; [19]Hospital Metropolitano, Quito, Ecuador; [20]Univeridad Peruana Cayetano, Hospital Nacional Cayetano Heredia, Peru; [21]Austral University Hospital, Buenos Aires, Argentina; [22]FISPEVEN (Foundation for Clinical Research in Public and Epidemiological Health in Venezuela), Clínica El Ávila, Caracas, Venezuela; [23]Cardiology Service, SANNA Clinica El Golf, Lima, Peru; [24]Clínica San Felipe, Lima, Peru; [25]Atherothrombosis Research Unit, Cardiovascular Institute, The Mount Sinai School of Medicine, New York, USA; [26]University Hospital Complex of Santiago de Compostela, Santiago de Compostela, Galicia, Spain; [27]Division of Cardiovascular Medicine, Department of Medicine, Brigham and Womens' Hospital, Harvard Medical School, Boston, MA, USA

Correspondence:
*Carlos I. Ponte-Negretti
E-mail: ciponten@gmail.com

Date of reception: 08-01-2021
Date of acceptance: 14-05-2021
DOI: 10.24875/ACM.21000005

Available online: 28-06-2021
Arch Cardiol Mex (Eng). (ahead of print)
www.archivoscardiologia.com

Suppl. Table 1. Using a modified Delphi methodology with emphasis on literature related with ASCVD and CM risk factors, we conducted a comprehensive systematic review and structured communication to achieve consensus.

Key questions about epidemiology, pathophysiology, diagnosis, and treatment of CM risk were discussed by the panel organized into balanced work groups. We made two rounds of discussion first web based and second in a presential meeting. As a convention those recommendations that had 100% agreement was consider unanimous; consensus those with at least 80% and disagreement those with less than 80%. All the recommendations were included in the final document, which was submitted for a validation phase by experts external. This endeavor aimed to define practical, comprehensive cardiometabolic risk reduction strategies, using personalized medicine and patient-centered decision making while considering cost-benefit ratio.

Key questions about the topics allocated to each work group were designed. The answers were approached from three different perspectives:

a. Clinical content: defined as the clinical decisions they are trying to influence and the necessary information to impact the decision.

To this end, the following questions were asked:

b. Tool: a check list was developed and e-mailed which helped in decision-making. The answers and comments were reviewed over a period of six weeks and a 2-day in person meeting was held in Lima, Perú. The modified Delphi methodology was used in the analysis of the answers, and the answers submitted by each participant were used to express the level of consensus measured as a percentage. After analyzing the trends, the structure of the question was changed in accordance with the comments received, to optimize the agreement which was considered adequate if 80% agreement was reached.

c. Publication: defined as the final guiding document that justifies the clinical content, in addition to the guidelines for using the tool in practice.

The recommendations and evidences were classified following the European Society of Cardiology Methodology as:

Class I: The treatment or procedural is effective, useful, and beneficial and is recommended.

Class II conflicts or controversy regard the effective, useful, and beneficial.

IIa Weight in favor and should be considered.

Group 1
It there really an overall residual cardiometabolic risk or is it just that the goals to manage the traditional risk factors are insufficient?
Specific, non-traditional causes of residual cardiometabolic risk
Specific causes of cardiometabolic risk
Group 2
Is the increase in triglyceride-rich particles and a low LDL-C a cause of residual risk?
Is it possible to treat these lipid disorders?
Failure to achieve a sufficiently low LDL-C goal may be a cause for residual risk?
Which should be LDL-C goal to achieve an optimum risk reduction?
Would Lp (a) be a cause of residual? Should it be measured? Specific scenarios Should Lp (a) be treated? Which should be the goal?
Group 3
Critical analysis of the results based on the different therapeutic classes in their ability to reduce risk when combined with statins: PCSK9i, ezetimibe, omega 3, fibrates, miscellaneous
Group 4
Which is the primary LDL-C goal?
Which is the Non-HDL or triglycerides secondary goal?
Should triglycerides be treated in patients with increased residual risk?
Which should be the LDL-C goal in high-risk patients?
How to reach the goal?
How should a patient that meets the LDL-C goal but persists with elevated triglycerides be approached?
Group 5
Need for an overall cardiometabolic risk reduction

IIb Evidence is less robust or less well establish and may be recommended.

Class III The treatment or procedural is not effective, useful, or beneficial and even it could be harmful. Is not recommended.

Leveles of Evidences

A: Data derived from multiple clinical randomized trials or meta analyses.

B: Data derived from single clinical trials or large non randomized trial.

C: Experts opinion

Suppl. Table 2. Comparative risk reduction and NNT achieved in the trials adjunctive therapy trials: IMPROVE-IT, FOURIER, ODYSSEY, and REDUCE-IT[10-13]

Study primary endpoints (Total patients)	LDL-C (mg/dl) Mean baseline both groups	LDL-C Final (mg/dl)	ARR	RRR	NNT
IMPROVE-IT CVD, major CVD, Stroke N: 18,144	95	EZT 50 Pbo 65	1.8%	10% HR: 0.90 (95% CI: 0.84-0.96	56
FOURIER CVD, AMI, Stroke, Admission for UA or revascularization N: 27,564	92	Ev 30 Pbo 88	1.5%	20%: HR: 0.80 (95% CI: 0.73-0.88)	67
ODYSSEY CVD, non-fatal AMI, Ischemic stroke, hospital admission due to UA N: 18,924	92	Al 48 Plc 96	1.6%	15% HR: 0.85 (95% CI: 0.78-0.93)	63
REDUCE-IT CVD, MI, Stroke, need to revascularize, unstable angina N:8,179	75 (Tg 216)	EPA LDL-C 77 Tg 177 Pbo LDL-C 82 Tg 220.5	4.8%	24.8% HR:0.75 (95% CI: 0.68-0.83)	21

ARR: absolute risk reduction; RRR: relative risk reduction; NNT: number needed to treat; HR: hazard ratio; EZT: ezetimibe; Ev: evolocumab; Al: alirocumab; Pbo: placebo; CVD: cardiovascular death; IM: myocardial infarction; UA: unstable angina.

Suppl. Table 3. Statins dosage

Statin	Dosage		
	Low-intensity (LDL-C reduction < 30%)	Moderate-intensity (LDL-C reduction 30-< 50%)	High-intensity (LDL-C reduction > 50%)
Atorvastatin	NA	10-20 mg	40-80 mg
Fluvastatin	20-40 mg	80 mg	NA
Lovastatin	20 mg	40 mg	NA
Pitavastatin	1 mg	2-4 mg	NA
Pravastatin	10-20 mg	40-80 mg	NA
Rosuvastatin	NA	5-10 mg	20-40 mg
Simvastatin	10 mg	20-40 mg	NA

LDL-C: low-density lipoprotein-cholesterol; NA: non applicable.

Suppl. Table 4. Beneficial effects on the reduction of cardiovascular events from the use of SGLT 2 inhibitors and GLP-1 analogues (RRR)

Trial and drug	Cardiovascular mortality HR (95% CI)	Hospitalization due to HF HR (95% CI)	Non-fatal acute MI HR (95% CI)	Non-fatal stroke HR (95% CI)	Renal endpoint* HR (95% CI)
EMPAREG-outcome (empagliflozin) T2DM at high risk of CVD	0.62 (0.49-0.77)	0.65 (0.5-0.85)	0.67 (0.7-1.09)	1.24 (0.92-1.67)	0.54 (0.40-0.75)
EMPEROR Reduced (empagliflozin) T2DM and high risk of CVD	0.92 (0.75-1.12)	0.69 (0.59-0.81)	Not reported	Not reported	0.50 (0.32-0.77)
CANVAS-Program (canagliflozin) T2DM and high risk of CVD	0.87 (0.72-1.06)	0.67 (0.52-0.87)	0.85 (0.69-1.05)	0.9 (0.71-1.15)	0.60 (0.47-0.77)
DECLARE TIMI-58 (dapagliflozin) Patients with T2DM	0.98 (0.82-1.17)	0.73 (0.61-0.88)	0.89 (0.77-1.01)	1.01 (0.84-1.21)	0.53 (0.43-0.66)
DAPA-HF (dapagliflozin) HFprEyf NYHA II-III-IV T2DM or not	0.82 0.69-0.98	0.70 0.59-0.83	Not reported	Not reported	0.71 (0.44-1.16)
DAPA-CKD (dapagliflozin) CKD T2DM or not	0.81 (0.58-1.12)	Not reported	Not reported	Not reported	0.56 (0.45-0.68)
LEADER (liraglutide) T2DM and high risk of CVD	0.78 (0.66-0.93)	0.87 (0.73-1.05)	0.88 (0.75-1.03)	0.89 (0.72-1.11)	Not reported
SUSTAIN-6 (semaglutide) T2DM	0.98 (0.65-1.48)	1.11 (0.77-1.61)	0.74 (0.5--1.08)	0.61 (0.3-0.99)	Not reported
REWIND (dulaglutide) T2DM and high risk of CVD	0.91 (0.78-0.06)	Not reported	0.96 (0.79-1.16)	0.76 (0.61-0.95)	0·85 (0.77-0.93)

*Declining kidney function, onset of end-stage kidney disease, or kidney failure death.
T2DM: type 2 diabetes mellitus; CD: cardiovascular disease; HFprEyF: heart Failure with preserved ejection fraction; NYHA: New York Heart Association; MI: myocardial infarction.