Revista Colombiana de Cardiología
Órgano oficial de la Asociación Sociedad Colombiana de Cardiología & Cirugía Cardiovascular
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SPECIAL ARTICLE

From residual risk concept to practice: History, development, evolution of the concept and current status

Del concepto del riesgo residual a la práctica: Historia, desarrollo, evolución del concepto y estado actual

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Abstract

Residual cardiovascular risk is defined as the risk of cardiovascular events that persists in patients despite reaching low-density lipoprotein cholesterol, blood pressure and blood sugar treatment goals, according to the current treatment standards. In light of today's evidence, residual risk changes the perspective beyond the current definition toward several aspects like residual thrombotic risk; residual metabolic risk and the role of lipoprotein a, triglycerides, remnant cholesterol and HDL; the residual risk of diabetics aside from A1C control; and residual inflammatory risk. All of these are treatment goals which affect the outcomes, producing a greater reduction of residual cardiovascular risk.

Keywords: *Residual cardiovascular risk, residual metabolic risk, residual diabetic risk, residual inflammatory risk.*

Resumen

El riesgo cardiovascular residual se define como el riesgo de eventos cardiovasculares que persiste en los pacientes a pesar de alcanzar los objetivos del tratamiento para el colesterol de lipoproteínas de baja densidad, la presión arterial y la glucemia de acuerdo con los estándares actuales de manejo. A la luz de la evidencia actual, el riesgo residual cambia su mirada más allá de su actual definición, hacia varios aspectos, como el riesgo trombótico residual, el riesgo metabólico residual y el papel de la lipoprotína a, los triglicéridos, los remanentes de colesterol y HDL, el riesgo residual del diabético aparte del control de la A1C, y el riesgo inflamatorio residual. Todos estos son objetivos terapéuticos con impacto en los resultados de una mayor disminución del riesgo cardiovascular residual.

Palabras clave: *Riesgo cardiovascular residual, riesgo metabólico residual, riesgo diabético residual, riesgo inflamatorio residual.*

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Date of reception: 27-04-2023
Date of acceptance: 26-07-2023
DOI: 10.24875/RCCAR.M23000214

Available online: 06-10-2023
Rev Colomb Cardiol. 2023;30(Supl2):4-16
www.rccardiologia.com

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Background

The current treatment of patients for cardiovascular disease prevention indicates the importance of treating several risk factors, seeking to achieve the recommended goals for LDL cholesterol (LDL-c), blood pressure, and glycemic control. In this regard, type 2 diabetes mellitus itself is a major risk factor for cardiovascular disease.

As shown in the STENO-2 study, multifactorial intervention was insufficient to prevent the onset or progression of microvascular disease in up to 50% of patients with type 2 diabetes mellitus.

There is sufficient scientific evidence to show that statins are the cornerstone of dyslipidemia treatment, but even so, a significant risk of cardiovascular disease persists despite effective treatment for lowering LDL-c. The information from a recent meta-analysis which included 90,056 participants (18,686 with diabetes) in 14 randomized trials showed that one out of seven patients treated with statins experienced cardiovascular events over the course of five years, and that an additional reduction in LDL-c, with maximum statin doses, did not eliminate the residual risk[1].

All of this led to the need to review and renew the focus of effective interventions which could reduce the residual risk of cardiovascular events and microvascular complications in patients with dyslipidemias receiving optimal medical treatment in line with the current standard care guidelines. The treatment of atherogenic dyslipidemia, which is typically found in patients with metabolic abnormalities, was far from optimal, which led to an initial focus on residual lipid risk.

Thus, the Residual Risk Reduction Initiative (R3I) was established to deal with this problem. The first proposal was to highlight the evidence of atherogenic dyslipidemia's contribution to residual macrovascular risk and microvascular complications despite the standards of care for dyslipidemia and diabetes at that time, and to recommend therapeutic intervention to reduce it, supported by the evidence and expert consensus.

Lifestyle modification was the first important step, often followed by reinforcing pharmacological treatment, adding other drugs like niacin, fibrates and omega-3 to statin treatment, with which some improvement was achieved in all the remaining lipid risk factors.

In short, the R3I underscored the need to employ healthy lifestyle changes and pharmacotherapeutic interventions to deal with the elevated residual cardiovascular risk in patients with dyslipidemia who were being treated according to the standard recommendations at that time[2].

Definition of residual risk according to the Residual Risk Reduction Initiative

Residual cardiovascular risk is defined as the risk of cardiovascular events which persists in patients despite reaching the treatment goals for low-density lipoprotein cholesterol (LDL-c), blood pressure and blood sugar, according to the current treatment standards.

Development and evolution of the concept

Inflammation

Statins have been known to have pleiotropic effects which go beyond LDL-c reduction. Many studies have shown the resulting anti-inflammatory effects. In the JUPITER study, the administration of 20 mg of rosuvastatin per day lowered CRP (ultra-sensitive C-reactive protein) (us-CRP) by 37% compared with the placebo[3]. Interestingly, the magnitude of hsCRP reduction achieved with rosuvastatin was proportional to the reduction in cardiovascular risk. Individuals who achieved hsCRP levels <2 mg/L demonstrated a 55% reduction in the primary endpoint compared to those with hsCRP levels ≥ 2 mg/L (p = 0.007); however, this benefit was not separate from the reduction in LDL-c. Likewise, in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) study, patients who reached levels of us-CRP < 2 mg/l had fewer recurrent cardiovascular events. Nevertheless, whether the benefits of statins are related to LDL-c reduction, decreased inflammation, or a combination of these factors is still a matter of debate[4].

The direct causal role of inflammation in cardiovascular disease was not formally proven until the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) which recruited 10,061 participants with a history of myocardial infarction (MI), optimized LDL-c and us-CRP > 2 mg/l and randomized them to optimal medical therapy (OMT) plus placebo vs. OMT plus canakinumab, a fully human monoclonal antibody targeting interleukin-1b (IL-1b)[5]. It is important to highlight that previous studies showed that canakinumab has no effect on LDL-c. For the primary endpoint of efficacy for non-fatal MI, non-fatal stroke or cardiovascular death, a benefit was found with a 150 mg dose (HR = 0.85; 95% CI = 0.74-0.98; p = 0.021) and a 300 mg dose (0.86; 95% CI = 0.75-0.99; p = 0.031) of canakinumab compared with placebo.

It is important to highlight that decreasing CRP to < 2 mg/l led to a 25% reduction in major adverse cardiovascular events (MACE) and a 31% reduction in cardiovascular mortality and all-cause mortality, with no effect on LDL-c. There was no significant reduction in mortality when the CRP levels remained above 2 mg/l[5].

A recent clinical study evaluating low doses of colchicine after an MI, the Colchicine Cardiovascular Outcomes Trial (COLCOT), showed a reduction in the primary endpoint comprised of cardiovascular death, cardiac arrest, non-fatal MI, stroke or angina leading to revascularization (HR = 0.77; 95% CI = 0.61-0.96; p = 0.02). The CRP was only measured in a subgroup of 207 patients, with a mean placebo-adjusted percent change in CRP of -10.1% after six months in those randomized to colchicine[6]. The widespread use of anti-inflammatory drugs to prevent cardiovascular events is still not widely recommended, especially in those without elevated systemic inflammation, although colchicine is ultimately a low-cost option for secondary prevention in selected patients, according to the previous findings.

Based on the previous discussion, as well as multiple observations of higher rates of atherosclerotic cardiovascular disease in patients with chronic inflammatory diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, psoriasis, human immunodeficiency virus, etc.), there is a growing recognition of the importance of the link between inflammation and cardiovascular disease. The study in the town of Tsimane, a pre-industrial community in Bolivia, was a case study on the importance of the role of inflammation in atherosclerotic cardiovascular disease. In this population, despite the fact that many people had elevated inflammatory markers (51% of the participants had an us-CRP > 3.0 mg/l), the study found that having a lower prevalence of traditional risk factors led to fewer cardiovascular events[7]. This example emphasizes the importance of traditional risk factors in risk evaluation. Among the 2019 American College of Cardiology (ACC)/American Heart Association (AHA) recommendations for primary prevention, chronic inflammatory diseases are considered to potentiate risk and may be considered when the quantitative risk assessment using traditional risk factors appears to underestimate the risk of atherosclerotic cardiovascular disease. Thus, the inflammatory pathway becomes an important pathway for future studies on the prevention of cardiovascular diseases.

Inflammation and hyperlipidemia contribute jointly to atherothrombotic disease. However, when patients are treated with intensive statin therapy, the relative contributions of inflammation and hyperlipidemia to the risk of future cardiovascular events can change, a fact which has implications for the choice of adjuvant cardiovascular therapy. A study recently published by Ridker et al.8 evaluated the relative importance of high-sensitivity CRP and LDL-c as determinants of the risk of serious adverse cardiovascular events, cardiovascular death and death from all causes among patients receiving statins. The investigators conducted a collaborative analysis of patients at high risk for atherosclerotic disease who received statins and participated in the PROMINENT, REDUCE-IT or STRENGTH multinational trials. The quartiles of increased baseline us-CRP and increased baseline LDL-c were evaluated as predictors of future major adverse cardiovascular events, cardiovascular mortality and all-cause mortality.

The study included 31,245 patients and found that the residual inflammatory risk was significantly associated with a higher incidence of major adverse cardiovascular events, cardiovascular mortality and all-cause mortality related to higher us-CRP levels. In contrast, the relationship of the residual cholesterol risk was neutral for major adverse cardiovascular events (highest LDL-c quartile vs. lowest LDL-c quartile), and small for cardiovascular mortality and all-cause mortality (Fig. 1, Fig. 2).

The investigators in this analysis of 31,245 patients who received statins concluded that the residual inflammatory risk evaluated through us-CRP was a stronger predictor of the risk of future cardiovascular events and death than the residual cholesterol risk evaluated through LDL-c. Although the current data should not be used to disregard the crucial role of adjuvant lipid reduction beyond the use of statins for patients with persistent or refractory hypercholesterolemia, they do suggest that it is unlikely that only addressing LDL-c will completely reduce atherosclerotic risk and that the inflammatory pathways have not yet been completely exploited to lower the rate of fatal and non-fatal cardiovascular events. They also consider that the combined use of aggressive lipid-lowering and anti-inflammatory therapies could become the standard of care for atherosclerotic disease in the future[8].

These results show the role of inflammation in residual risk scenarios. Now, the residual risk horizons are broadened to consider not only residual lipid risk, but also the role of inflammation within the residual risk components, introducing the concept of residual inflammatory risk.

Thrombosis

Anticoagulation

In patients with established cardiovascular disease, antiplatelet agents are an essential component of optimal medical therapy. Despite the appropriate use of antiplatelets, the risk of atherothrombosis and sub-

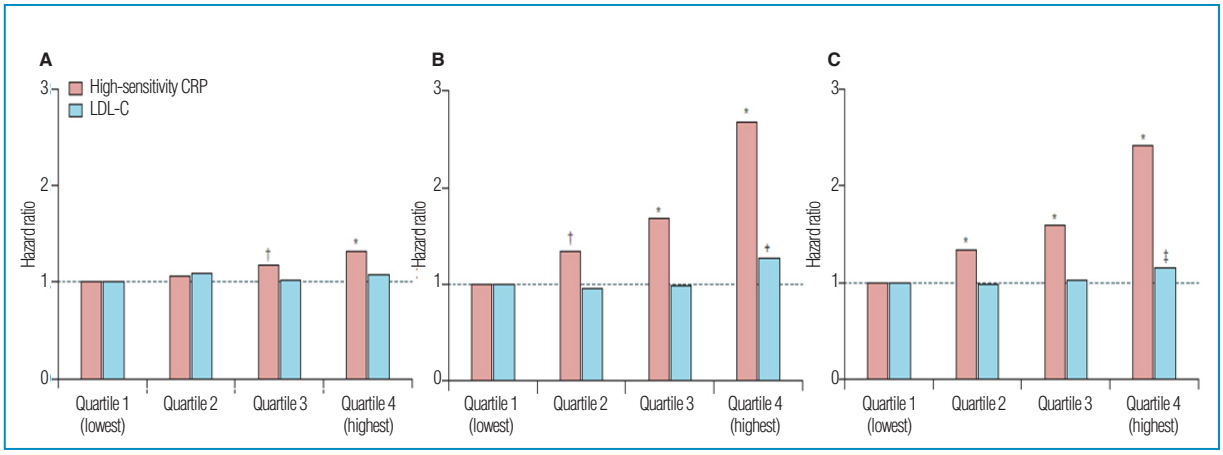

Figure 1. Residual inflammatory risk evaluated through us-CRP and residual lipid risk evaluated through LDL-c, as predictors of future cardiovascular events and death[8].
*p < 0.0001. †p < 0.01. ‡p < 0.05. The information from the combined study cohort shows: **A**: major cardiovascular events. **B**: cardiovascular mortality. **C**: all-cause mortality.
CRP: C-reactive protein. LDL-c: low-density lipoprotein cholesterol.

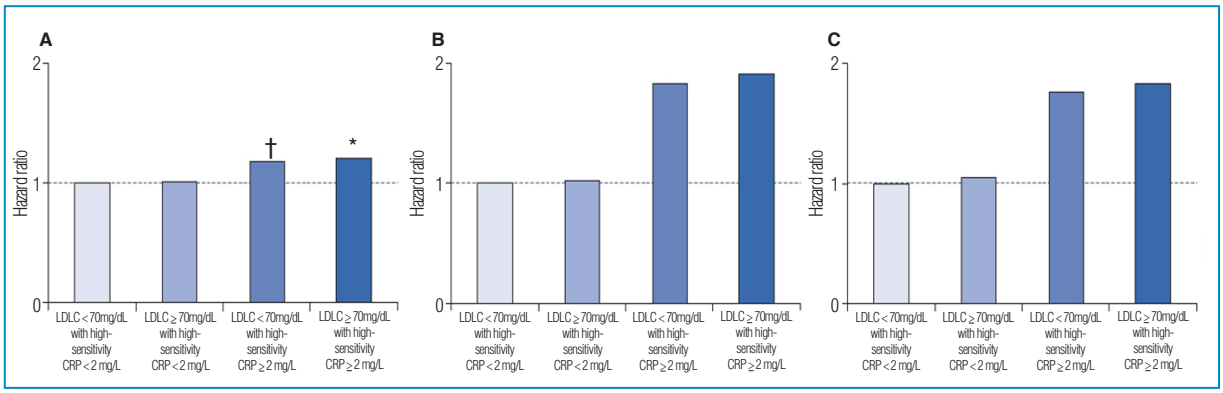

Figure 2. Combined analysis of us-CRP and LDL-c as predictors of future cardiovascular events and death[8].
*p < 0.0001. †p < 0.01.
The information from the combined study cohort shows: **A**: major cardiovascular events. **B**: cardiovascular mortality. **C**: all-cause mortality.
The data are shown in four groups according to baseline LDL-c and us-CRP.
CRP: C-reactive protein. LDL-c: low-density lipoprotein cholesterol

sequent cardiovascular events usually persists with the use of aspirin. For example, in the Antithrombotic Trialists' Collaboration Study which included 16 randomized clinical trials on secondary prevention, with 17,000 patients, while aspirin reduced the risk of serious vascular events, this primary endpoint still occurred in 6.7% of the patients, compared with 8.2% in the placebo group[9]. Therefore, interest was aroused in identifying patients who could benefit from intensification of the antithrombotic or anticoagulant therapy. Two clinical studies have proven the usefulness of adding low-dose anticoagulation to the antiplatelet treatment. In the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome- Thrombolysis in Myocardial Infarction Trial 51 (ATLAS ACS 2-TIMI 51), the addition of low-dose rivaroxaban (2.5 or 5 mg twice a day) to antiplatelet therapy after a recent cardiovascular event (with 93% of the patients on dual antiplatelet therapy) decreased the

relative risk by 16% for major adverse cardiovascular events[10]; however, this benefit was tempered by an increase in major bleeds (2.1 vs. 0.6%; p < 0.001) and intracranial hemorrhage. Another study, Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS), also showed that a low dose of rivaroxaban plus aspirin vs. aspirin alone led to a 24% reduction in the primary endpoint and a 22% reduction in the net clinical benefit evaluation criterion (composed of the primary endpoint, fatal hemorrhage and symptomatic hemorrhage in a critical organ or area)[11]. It is important to note that in a subgroup analysis, the magnitude of the benefit was even more pronounced in those with peripheral artery disease, a population with a higher atherosclerotic burden which usually affects several vascular beds and, therefore, has a higher risk of thrombotic events. Given these findings, low doses of rivaroxaban appear to be a promising pathway toward further reducing the residual thrombotic risk.

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is a pillar of treatment up to one year after percutaneous coronary intervention (PCI). However, the benefit of extending DAPT beyond 12 months has been less clear. The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis In Myocardial Infarction 54 (PEGASUS-TIMI 54) study showed that adding ticagrelor to aspirin led to a 16% reduction in MACE[12]. Meanwhile, a meta-analysis of six trials evaluating the long-term efficacy of DAPT in the setting of stable cardiovascular disease following an acute coronary syndrome (ACS) showed similar results[13]. Despite this, the benefits of prolonged DAPT were tempered by a higher risk of severe (but not fatal) bleeding.

This information, based on these clinical outcomes, introduces another important concept: residual thrombotic cardiovascular risk.

Residual metabolic risk

Lipoprotein (a)

Lipoprotein (a) [Lp(a)] is a particle similar to LDL bound covalently to apoliprotein (a) [apo (a)], a non-functional plasminogen imitator[14]. Lipoprotein (a) plays an active role in vascular atherothrombosis, and its plasma levels are highly hereditary[15]. In the INTERHEART study, an Lp(a) > 50 mg/dl was associated with a higher risk of MI (OR = 1.48; 95% CI = 1.32-1.67; p < 0.001)[16]. A JUPITER sub-analysis showed that Lp(a) was a strong predictor of residual risk in patients who were already on a statin (adjusted HR = 1.27; 95% CI = 1.01-1.59; p = 0.04), regardless of LDL-c and other risk factors[17]. However, whether Lp(a) should be a treatment goal is still under debate. While epidemiology and genetics suggest that Lp(a) is a cause of atherosclerotic cardiovascular disease and calcified aortic stenosis[18], randomized controlled trials have not been performed to answer this question.

In the FOURIER study, evolocumab lowered Lp(a) levels by a median of 26.9%, which was moderately correlated with the change in LDL-c (r = 0.37)[19]. In patients with a baseline Lp(a) above the median, evolocumab was associated with a 23% reduction in the risk of death from coronary heart disease, MI or urgent revascularization (compared with placebo), while there was only a 7% reduction in those with an Lp(a) below the median (p for interaction = 0.07). It is important to note that, in a post-hoc analysis of the Phase III ODYSSEY trials, the reductions in Lp(a) were not significantly associated with reductions in MACE, regardless of the LDL-c, except in the highest baseline Lp(a) values (> 105 nmol/L), where the Lp(a) reductions with alirocumab led to significant risk reductions beyond the reduction in LDL-c[20].

Triglycerides and remnant cholesterol

Triglycerides and triglyceride-rich lipoproteins have also been identified as important contributors to residual risk. Triglycerides are derived from the diet (chylomicrons and their remnants) and the liver (VLDL and its remnants) and circulate in the blood. Lipoprotein lipase (LPL) covers the luminal surface of the capillaries and hydrolyzes the core triglycerides to free fatty acids (FFAs) and glycerol. As FFAs are released, the triglyceride particles are physically remodeled (becoming smaller as they lose TG and surface phospholipids) and chemically remodeled (becoming relatively cholesterol-enriched). These partially lipolyzed triglycerides are known as remnant particles[21]. Remnant cholesterol, calculated as total cholesterol minus HDL-c, has a concurrent association with cardiovascular disease and mortality[22].

High-density cholesterol (HDL-c)

One of the most surprisingly concordant relationships in cardiovascular epidemiology is the association between low levels of high-density lipoprotein cholesterol (HDL-c) and atherosclerotic cardiovascular disease. In the Framingham cohort, there was a gradual risk reduction for each 1 mg/dl increase in HDL-c concentration. At this point, it was expected that HDL-c levels would redirect cardiovascular risk; however, although the controlled randomized trials with niacin and cholesteryl ester transfer protein in-

hibitors were effective in raising HDL-c, they did not lead to a reduction in major adverse cardiovascular events. Very high HDL-c levels have been found to be associated with poorer outcomes in large general population studies in Canada and Denmark[23,24]. Evolving understanding has suggested that the functional measurement of HDL may be more clinically useful than its concentration. As a proof of principle, a functional HDL measurement, cholesterol efflux capacity, showed the ability to predict prevalent and incident coronary artery disease[25]. In the Dallas Heart Study, in 2,924 patients with no known atherosclerotic cardiovascular disease, there was a 67% reduction in the cardiovascular risk of those in the highest quartile of cholesterol efflux capacity, compared with the lowest quartile (HR = 0.33; 95% CI = 0.19-0.55). It is important to note that cholesterol efflux capacity was weakly correlated with the HDL-c level (Spearman's correlation coefficient of 0.07; $p < 0.05$). Currently, low HDL-c (and perhaps very high levels) are useful for identifying patients at risk for adverse events, although no pharmacological treatment targeting HDL-c has proven to be effective in reducing cardiovascular risk. There are ongoing studies today with apolipoprotein A-1 infusions to test if increasing or improving HDL function can reduce residual risk, where previous efforts to increase HDL-c concentration have failed[26].

This information, based on these clinical results, adds another important concept: residual metabolic cardiovascular risk.

Diabetes

For years, none of the medications used to treat diabetes proved able to reduce cardiovascular events or mortality. The advent of glucagon-like peptide-1 receptor agonists (GLP-1-RA) and sodium-glucose co-transporter-2 (SGLT2) inhibitors hailed a new era in diabetes care. In 2015, the Empagliflozine, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPAREG OUTCOMES) trial marked the beginning of a paradigm shift in the treatment of diabetes and cardiovascular diseases. Since then, a series of trials have shown improvement in cardiovascular outcomes with these two drug classes. An important consideration is that the benefits found with these medications occurred in a cohort in which most of the patients were on optimal or almost optimal medical therapy, according to the guidelines. For example, in EMPAREG OUTCOMES, 81% of the patients were taking angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), 77% were taking statins, and 82% were taking aspirin. Despite this, the primary composite outcome (cardiovascular death, non-fatal MI or non-fatal stroke) occurred in 12.1% of the placebo group, with 5.9% of the deaths during the three-year follow up due to cardiovascular causes. Although empagliflozine was acclaimed as a big success for relative risk reduction, with 14% for the primary endpoint and a surprising 38% for cardiovascular death, these reductions were associated with a significant proportion (10.5%) of participants who suffered major adverse cardiovascular events, as almost 4% died from cardiovascular causes. Although these trials indicate a significant advance in the care of patients with diabetes, they also serve to highlight the substantial residual risk which exists despite adherence to standard optimal medical therapy. However, we cannot assert that only SGLT2 inhibitors and GLP-1-RAs can modify cardiovascular risk in diabetic patients, as this would disregard metabolic control and cardiovascular risk studies such as UKPDS, one of many in which the "legacy effect"[27] of glycemic control has been recognized. Two concepts support this effect; first, the importance of early diagnosis, and second, optimal early intervention. In patients who initially achieved adequate HbA1c control compared with the control group, despite A1c homogenization after study closure, long-term follow-up showed a lower mortality and incidence of myocardial infarction in those with good initial metabolic control.

Figure 3 shows that the earlier A1c control (red) is achieved, the lower the burden of disease compared with those who achieved control five years later (blue).

Likewise, Figure 4 shows that the earlier the diagnosis, the greater the relative risk reduction in total mortality and myocardial infarction.

Furthermore, in the Kaiser Permanente cohort follow-up28, the length of exposure to an elevated A1c was a potentiating factor for macrovascular risk. Thus, an A1c of more than 9% in the first year increased the risk by 48%, but the same A1c sustained over time increased the risk by more than 100% after seven years (HR = 2.113) (Fig. 5).

It should be clarified that, from a pathophysiological perspective, insulin resistance is a determining factor in the genesis of cardiovascular risk in patients with impaired glucose tolerance, and, since both prediabetic and diabetic patients share the same insulin resistance (differing only in their ability to produce insulin), prediabetic patients have an 89% higher cardiovascular risk, in terms of HbA1c, compared to normal patients[29].

A 10-year follow-up study of the randomized, controlled, multicenter DIAbetes and diffuse coronary NArrowing (DIANA) study, which included 302 patients, compared the efficacy of the lifestyle intervention and pharmacological intervention (voglibose/nateglinide) over one year of follow up to determine its effect in reducing postprandial hyperglycemia in early-stage type 2 diabetics (glucose intolerance or recently diagnosed T2DM). In this study, MACEs (all-cause mortality, non-fatal MI or unplanned coronary revascularization) were compared in the three assigned treatments (lifestyle intervention/voglibose/nateglinide) and in patients with and without improvement in postprandial hyperglycemia (reversal of impaired glucose tolerance, normal glucose tolerance, or reversal of diabetes mellitus to impaired glucose tolerance/normal glucose tolerance on an oral glucose tolerance test with a 75 g glucose load). Over the 10-year follow-up period after the end of this clinical trial, neither voglibose nor nateglinide reduced MACE; likewise, improved postprandial hyperglycemia was not associated with a reduction in MACE. However, in subjects with impaired glucose tolerance (n = 143), this glycemic management significantly re-

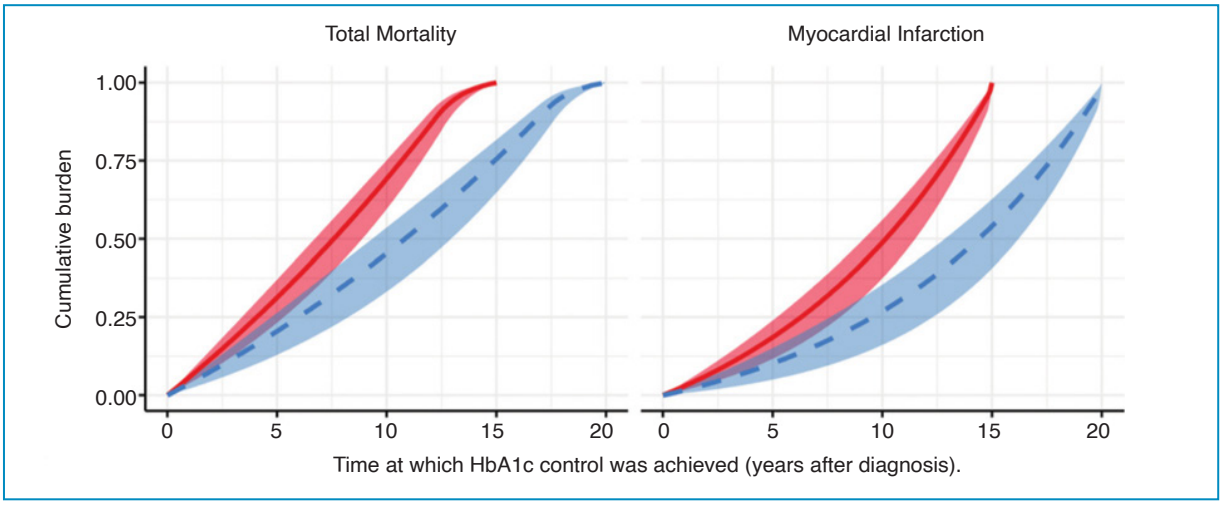

Figure 3. Timing of glycosylated hemoglobin A1c control and death from infarction[27].

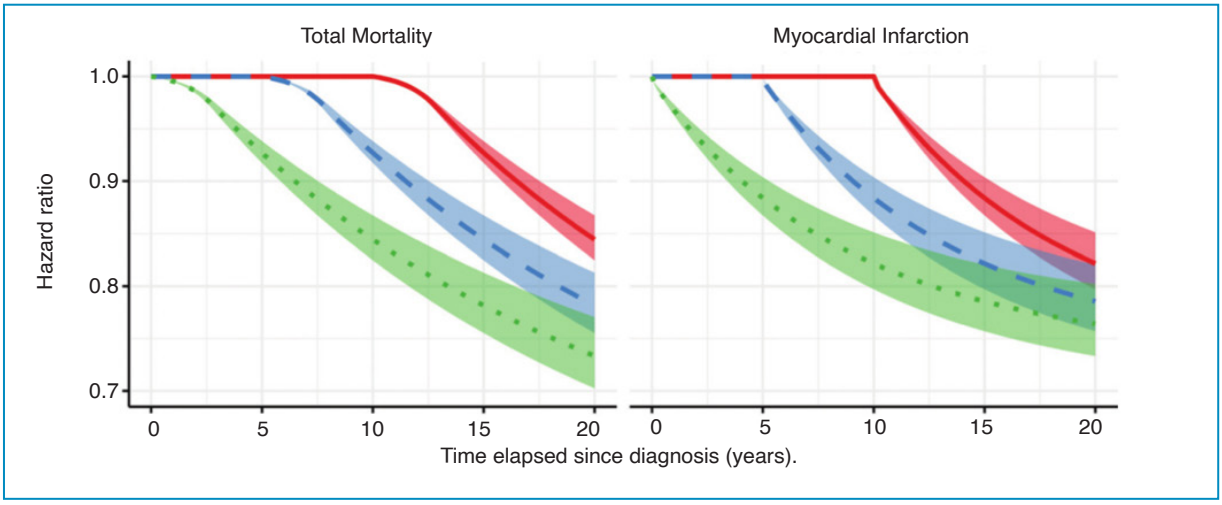

Figure 4. Time elapsed since diagnosis and risk of death and myocardial infarction[27].

duced the onset of MACE (HR = 0.44; 95% CI: 0.23-0.86; p = 0.01); especially unplanned coronary revascularization. In conclusion, in this follow-up study, early improvement in postprandial hyperglycemia significantly reduced MACE and unplanned coronary revascularization in patients with impaired glucose tolerance during the 10-year study follow-up[30].

The importance of this study lies in the fact that improvement in impaired glucose tolerance, prior to the onset of diabetes mellitus, has an important impact on the reduction of future cardiovascular events (Fig. 6).

In a meta-analysis of more than 18,000 patients with diabetes, treated with statins, for every 1 mmol/l (39 mg/dl) reduction in LDL-c produced by statin treatment, there was a proportional 9% reduction in mortality and 13% reduction in vascular mortality, regardless of the prior history of cardiovascular disease[31]. Therefore, at least one moderate-intensity statin would be indicated for all diabetic patients between 40 and 75 years old, while a high-intensity statin would be indicated for those with established atherosclerotic cardiovascular disease or high cardiovascular risk.

Similarly, ACE inhibitors/ARBs have shown a consequent reduction in cardiovascular events in hypertensive patients with diabetes, especially those with diabetic nephropathy, and, as such, would be indicated in this population. In addition, there is an updated recommendation from the American Diabetes Association for using EPA in patients with diabetes and cardiovascular disease or with risk factors who are on statins and have controlled LDL-c but elevated triglycerides (135-499 mg/dl), based on evidence from

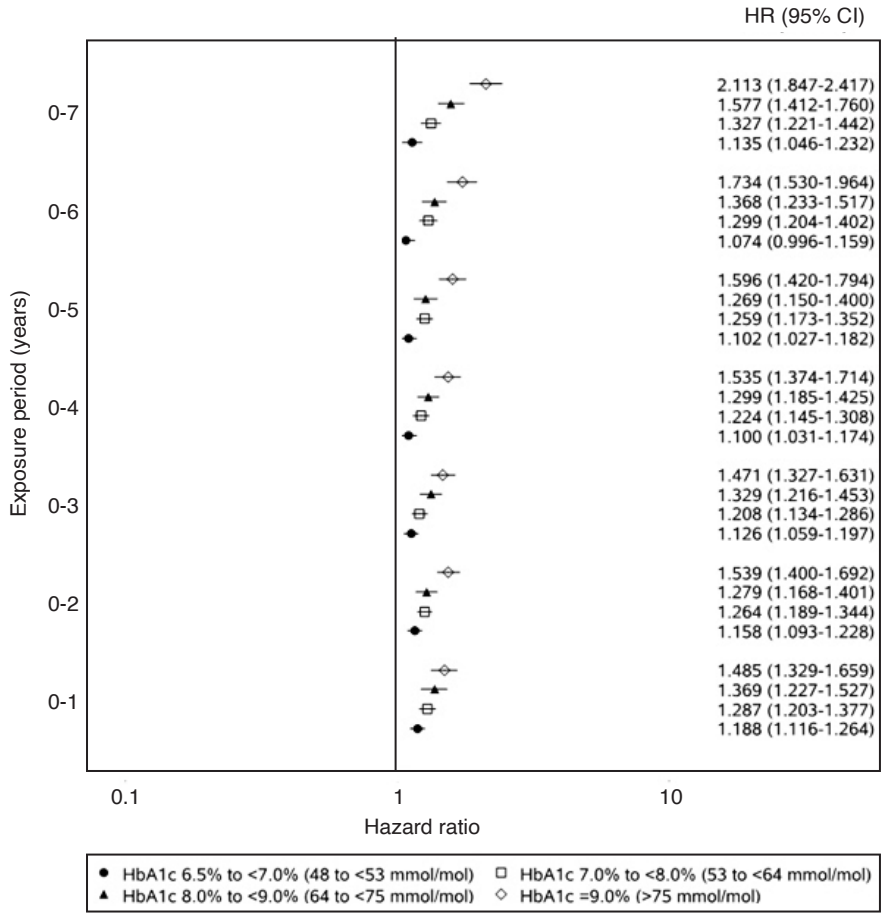

Figure 5. Period of exposure to elevated HbA1c and hazard ratio[28].

the REDUCE-IT study[32]. As new therapies emerge to gradually minimize the risk in this population, it is essential to ensure adherence to proven preventive therapies.

Despite advances in further improving major cardiovascular events apart from glucose, patients with diabetes continue to have a significant residual risk, making diabetes a higher-risk condition (residual diabetic risk), despite standard optimal medical therapy.

The large ongoing clinical study COLCOT-T2D (NCT05633810) will attempt to extend the concept of residual inflammatory risk in primary prevention and test whether inflammation reduction with low doses of colchicine is associated with improved cardiovascular outcomes in 10,000 patients with T2DM who are already on intensive therapy to reduce LDL-c according to the guidelines.

Identifying and treating residual cardiovascular risk is essential for optimizing patient outcomes, especially in those with a risk of recurrent events despite optimal treatment of the traditional risk factors. All of the pathways mentioned for the so-called residual risk should be considered in personalizing the risk prediction and treatment to be instated for each patient. In this regard, then, it is important to recognize the emergent risk and adopt new treatments aimed at these factors (for example, EPA, SGLT2 inhibitors/GLP-1-RA, low-dose rivaroxaban, etc.).

Current state of the concept of residual risk

The current concept of residual risk adds other factors which have been associated with the risk of major cardiovascular events despite optimal therapy, initially in the LDL-c lipid target. Therefore, a contemporary perspective of these residual risk pathways would involve residual inflammatory risk, residual thrombotic risk, and residual metabolic risk including Lp(a), triglycerides and diabetes mellitus. Most of these have critical biomarkers and clinical trial evidence showing a benefit from their treatment as part of secondary prevention, in addition to the use of beneficial drugs for reducing cardiovascular risk beyond glycemic control, like SGLT2 inhibitors and GLP-1-RAs[33] (Fig. 7) .

Additional considerations to the standard therapies based on the evidence of cardiovascular risk factors

This contemporary overview of residual risk factors will help keep them in mind when evaluating patients' risk in secondary prevention, whose current intervention or in future studies will contribute to reducing major cardiovascular events.

Based on the above, the current European guidelines for cardiovascular prevention in clinical practice[34] mention that patients with established atherosclerotic

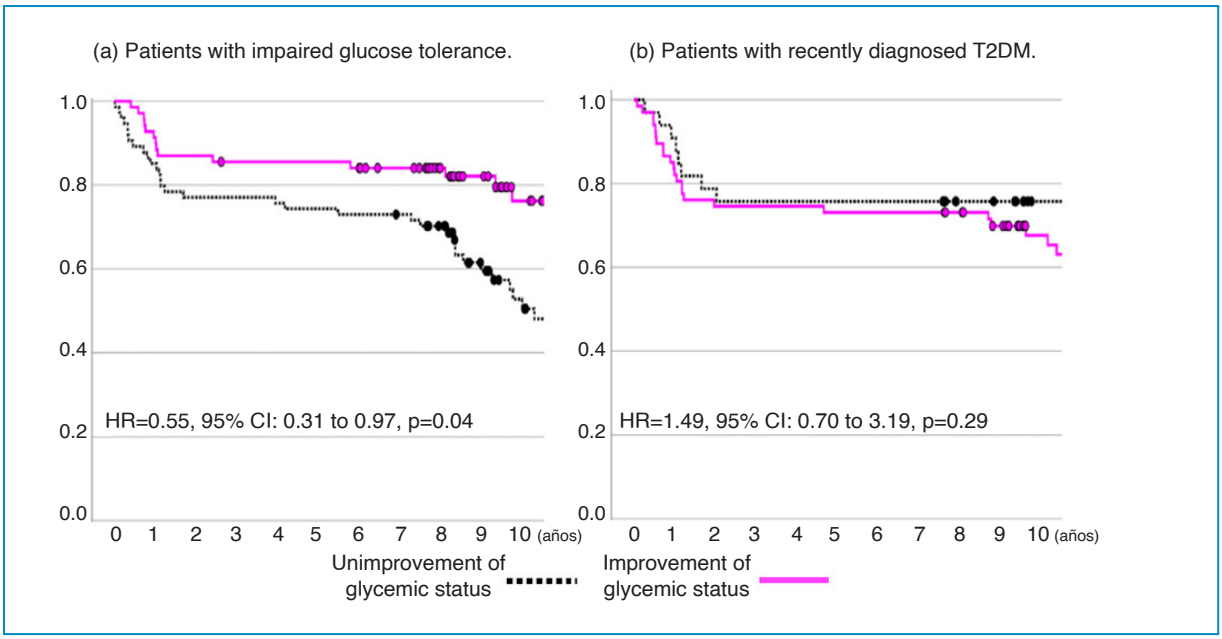

Figure 6. Improved glycemic status and MACE in patients with impaired glucose tolerance and recently diagnosed diabetes mellitus[30].

cardiovascular disease (ACVD) have, on average, a very high risk of recurrent cardiovascular disease events if their risk factors are not treated. Consequently, the European guidelines' flowchart for Stage 1* cardiovascular prevention in clinical practice[34] recommend smoking cessation, adopting a healthy lifestyle and treating risk factors in all patients. Further intensification of risk factor treatment to lower treatment goals (Stage 2) is beneficial for most patients and should be considered, taking into account the 10-year risk of cardiovascular diseases, comorbidities, lifetime risk and the benefit of treatment, fragility and patient preference, in a shared decision-making process. After initial treatment of the risk factors and achieving the treatment goals for those risk factors, the individual residual risk of cardiovascular disease recurrence varies widely and should be considered[35] (Fig. 8). In this article, there is a very substantial variation in the estimated 10-year risk of recurrent vascular events in patients with vascular disease. If all the modifiable risk factors were at the targets recommended by the guidelines, half of the patients would have a 10-year risk of less than 10%. These data suggest that even with optimal treatment, many patients with vascular disease will continue to have a > 20% and even a > 30% 10-year risk, clearly showing an area of unmet medical needs. It is evident that patients with recent acute coronary syndrome or pro-

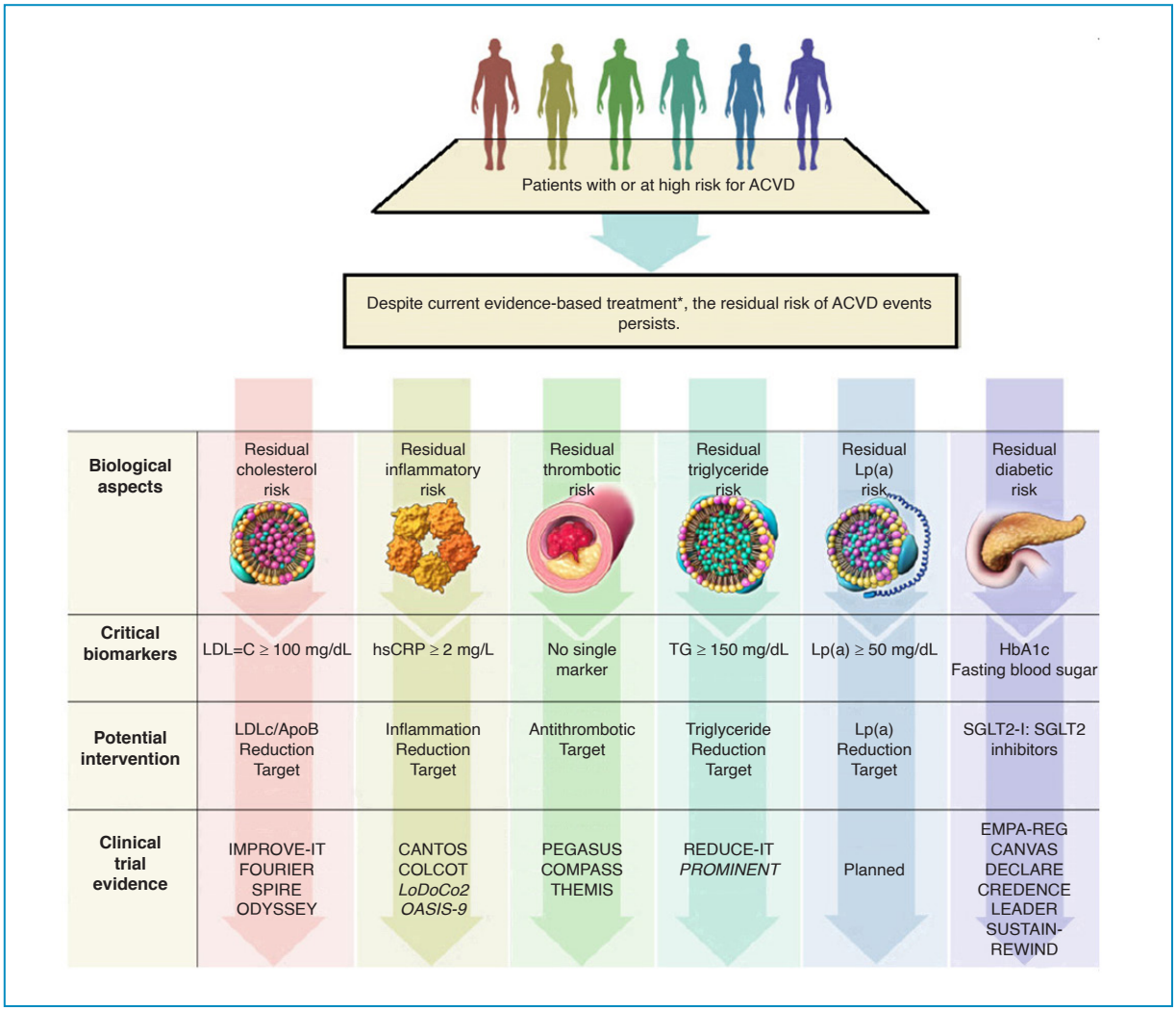

Figure 7. Contemporary residual risk pathways in secondary prevention.
Modified from: Lawler PR, Bhatt DL, Godoy LC, Lüscher TF, Bonow RO, Verma S, et al. Targeting cardiovascular inflammation: next steps in clinical translation. Eur Heart J. 2021;42:113-31.

gressive vascular disease, and patients with diabetes mellitus and vascular disease have an exceptionally high risk of recurrent cardiovascular disease events. For other patients with established cardiovascular disease, the residual risk could be less evident and estimated based on clinical criteria like age, changes in risk factor levels and risk modifiers, or by calculating the residual risk for cardiovascular disease using a calculator.

The risk of recurrent cardiovascular disease will be mainly influenced by the classical risk factors, the site of vascular disease and kidney function. Risk stratification tools for secondary prevention include the Secondary Manifestations of Arterial Disease (SMART) risk score (available on the ESC CVD Risk application) for estimating the residual 10-year cardiovascular disease risk in patients with stable established atherosclerotic cardiovascular disease defined as coronary disease, peripheral vascular disease or cerebrovascular disease[36], and the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) risk model,

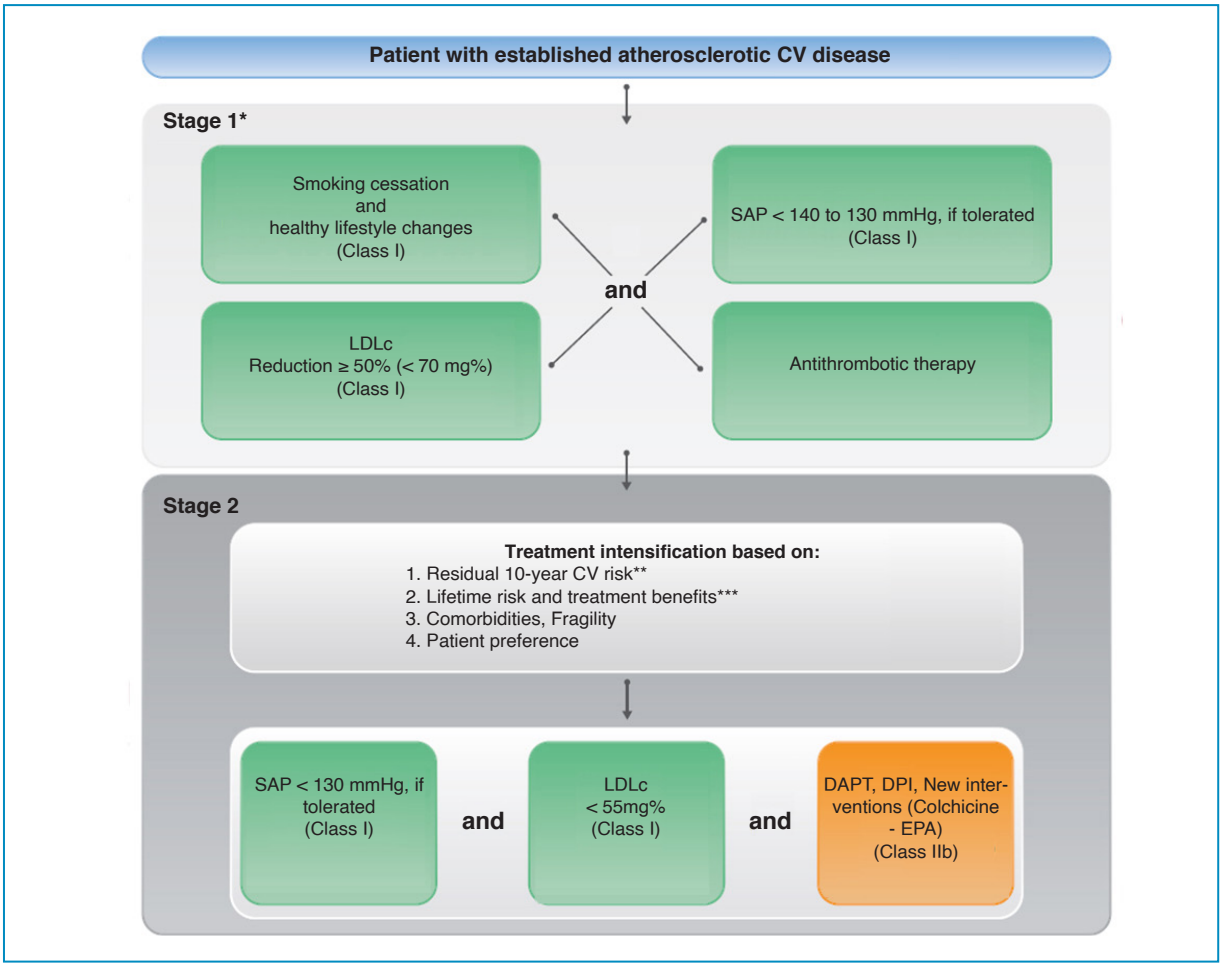

Figure 8. Flowchart of cardiovascular risk and the treatment of risk factors in patients with established atherosclerotic cardiovascular disease.

Modified from: Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227-337.

**For patients with recent ACS, these prevention goals are part of CR (Class I/A).*

***In patients 70 years old or older, a high 10-year risk may be associated with a lower absolute lifetime benefit of the treatment, due to their limited life expectancy.*

****The lifetime benefit of the treatment is expressed as additional CVD-free life years due to a given intervention or treatment. intensification.*

which estimates the two-year risk of recurrent cardiovascular disease in patients with stable coronary disease[37]. Occasionally, the risk of recurrent cardiovascular disease is very high despite maximum (tolerated) conventional treatment. In these cases, novel but less established preventive treatments like dual antithrombotic therapy, icosapent ethyl or anti-inflammatory treatment with colchicine could be considered.

Conclusions

Based on the definition of residual cardiovascular risk as the persistent risk of cardiovascular events in patients despite reaching the LDL-c, blood pressure and glycemic treatment goals according to the current management guidelines endorsed by the guidelines, new risk factors involved in what is known as residual risk have been detected which have been changing and developing the concept over time as well as the research into factors related to residual risk of cardiovascular disease. This evolution of the concept to a definition involving residual lipid risk and its current status together with residual inflammatory risk, residual metabolic risk (triglycerides and cholesterol remnants, Lp(a), and diabetes), has led to changes in the recommendations currently suggested by the cardiovascular prevention guidelines in clinical practice[34].

Funding

None.

Conflicts of interest

None.

Declaration of originality

The authors declare that the content of this article is original and has not been previously published, nor has it been sent or submitted for consideration to any other journal, as a whole or in part.

Ethical responsibilities

Human and animal protection. The authors declare that no experiments were conducted on animals or humans for this study.

Data confidentiality. The authors declare that no patient data are included in this article.

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

Use of artificial intelligence to generate text. The authors delcare that they have not used any type of artificial intelligence generator to draft this manuscript or create the figures, graphs, tables or their respective captions or titles.

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