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REVIEW ARTICLE

Evaluation and management of residual cardiovascular risk in patients with diabetes☆

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Abstract Presence of diabetes (types 1 and 2) increases the risk of atherosclerotic cardiovascular disease. Despite adequate metabolic control and treatment of vascular risk factors until the goals recommended by the clinical practice guidelines are achieved, residual cardiovascular risk may be very high in some patients with diabetes.

Stratifying the vascular risk for each patient as precisely as possible is therefore necessary.

Consolidated strategies to improve patient prognosis include aggressive reduction of LDL cholesterol, blood pressure control, achievement of the best HbA1c control possible without inducing hypoglycemia, use of hypoglycemic drugs shown to have cardiovascular benefits, and use of platelet aggregation inhibitors in patients with greater initial risk.

Emerging strategies for patients with very high or extreme risk would include use of drugs intended to decrease triglyceride-rich lipoproteins and inflammation.

PALABRAS CLAVE
Diabetes;
Riesgo cardiovascular;
Riesgo residual

Evaluación y manejo del riesgo cardiovascular residual en el paciente con diabetes

Resumen La presencia de diabetes (tipos 1 y 2) incrementa el riesgo de enfermedad cardiovascular aterosclerótica. A pesar de un control metabólico adecuado y un tratamiento de los factores de riesgo vascular hasta alcanzar los objetivos recomendados por las guías clínicas, el riesgo cardiovascular residual de algunos pacientes con diabetes puede ser muy elevado. Es necesario por ello estratificar de la forma más precisa posible el riesgo vascular del paciente individual.

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Estrategias consolidadas para mejorar el pronóstico de los pacientes son la reducción agresiva del colesterol LDL, el control de la presión arterial, la consecución del mejor control posible de la HbA1c, sin inducir hipoglucemias, la utilización de fármacos hipoglucemiantes con beneficio cardiovascular y el empleo de antiagregantes en los pacientes de mayor riesgo inicial.

Estrategias emergentes para pacientes con riesgo muy alto o extremo serían la utilización de fármacos destinados a reducir las lipoproteínas ricas en triglicéridos y la inflamación.

Introduction: the concept of residual cardiovascular risk

The presence of both type 1 and type 2 diabetes mellitus (DM) increases the risk of developing atherosclerotic cardiovascular disease (CVD).[1,2] The risk triples at the peripheral arterial level, and approximately doubles at the coronary or cerebrovascular level.[3]

The intensity of the management of vascular risk factors (RFs) should be adapted to the initial risk (R) to the patient, defined as the probability of the occurrence of atherosclerotic CVD in a given time period (usually 10 years). In epidemiology, the incidence rate (IR), expressed as the number of events per 1000 patient-years, is used to measure the CVD appearance rate. Both parameters (R and IR) can be related either approximately ($R \approx IR \times$ duration of follow-up) or precisely ($R = 1 - e^{-IR \times duration}$). Thus, an average R of 20% over the next 10 years would approximately correspond to that of a population with an IR of 20/1000 patient-years.

It is important to unify the nomenclature in order to stratify the patient risk of atherosclerotic CVD. Both the type of vascular event to be considered and the cut-off points defining the different risk categories should be established. The European cardiovascular (CV) prevention guidelines[4] use CV mortality, while American guides (AHA/ACC)[5] rely on ''hard'' events (major adverse cardiac event [fatal or non-fatal stroke or myocardial infarction] [MACE]), defined as the sum of fatal and non-fatal stroke and acute myocardial infarction (AMI). The R of MACE is approximately three-fold that of CV mortality, though in the elderly it is two-fold, since atherosclerotic CVD is more often fatal with advancing age.[4] Table 1 stratifies the risk categories according to the recommendations of these guides.

Measures of association (relative risk [RR]) and impact (absolute risk difference) are used to compare the magnitude of CVD risk difference between patients with DM (R1) and without DM (R0). Relative risk (RR) measures the strength of the association (RR = R1/R0), while the risk difference (RD) expresses the vascular risk of subjects with DM attributable to the presence of DM itself (RD = R1 − R0). A high RR can be associated with a low RD and vice versa; the measures can therefore be considered complementary.

In the present review, residual CV risk (RCVR)[6] is defined as the R of atherosclerotic CVD that persists in patients with DM after the standard of care recommended by the clinical practice guides has been applied.[7] Due to limitations in extent, the problem of heart failure will not be addressed herein, and the only evaluated CVD will be that of atherosclerotic origin.

Risk of atherosclerotic cardiovascular disease in patients with diabetes

Diabetes mellitus as a potential coronary risk equivalent

There are diseases which in themselves define high vascular risk, and one of them is DM.[4] However, the convenience of attributing DM with a risk equivalent to that of established CVD has been widely criticized. Observational studies in the Finnish population[8–10] suggested the possibility that DM could be considered a coronary risk equivalent, with similar CV mortality in type 1 and type 2 DM. These findings have not been universally reproduced, however, and a meta-analysis specifically comparing the risk of AMI in patients with type 2 DM without prior AMI versus that of patients with prior AMI but no DM[11] reported a lower risk (odds ratio [relative risk estimate in logistic regression models] [OR] = 0.56; 95% confidence interval [95%CI]: 0.53—0.60) in patients with DM.

The RR seen in the studies may depend on patient age, time since DM onset, and the socioeconomic status of the population. To better define the ''mean'' RR conferred by DM, we can consider the results of the large meta-analyses: the Emerging Risk Factors Collaboration (ERFC)[12,13] and the Prospective Studies Collaboration and Asia Pacific Cohort Studies Collaboration (PSC). According to both meta-analyses, CVD risk is approximately double in people with DM, and CV mortality rates in patients with DM fall into the very high risk category. It should also be noted that in both, the increase in RR was greater in women and in younger individuals. The PSC also established that DM increased the risk of CV mortality in patients with established CVD (hazard ratio [relative risk estimate in Cox regression models] [HR] = 1.85; 95%CI: 1.69−2.03).

Risk of cardiovascular disease in patients with diabetes mellitus at the present time

Improvements in healthcare have led to a descending trend in the IR of CVD over time.[15] Data collected in the United States[16] between 1990 and 2010 show reductions in the IR for AMI of 67.8% (14.1 vs. 4.5/1000) and for stroke of 52.7%

Table 1 Classification of atherosclerotic cardiovascular disease risk according to the type of vascular event considered.

R (% in 10 years)	MACE (AHA/ACC guides)	CVM (ESC/EAS guides)
Low	<7.5 (from 5 to 7.5 may be considered at the limit between low and moderate)	<1
Moderate	7.5—19	1—4
High	20—29	5—9
Very high	≥30	≥ 10

MACE: major vascular event (fatal or non-fatal stroke or myocardial infarction); CVM: cardiovascular mortality; R: risk or probability of occurrence of the event considered, expressed as a percentage within 10 years.
Prepared by the authors.

(11.2 vs. 5.3/1000). Since the decreases in rates are greater in patients with DM than in the general population, the trend is towards a decrease in RR conferred by the presence of DM on comparing the years 1990 and 2010 (3.8 vs. 1.8 for AMI and 3.1 vs. 1.5 for stroke). In addition, a reduction in the IR for hospital admission due to CVD has been recorded over the years[17] in Sweden in patients with type 1 and type 2 DM. However, in countries with lower per capita income levels, DM still more than triples the risk of CVD.[18]

In order to better define current R in both types of DM,[19,20] data can be consulted from the Swedish national diabetes registry (NDR), which includes virtually all patients with DM in Sweden. Patients with type 2 DM showed only a slight increase in CV mortality (HR = 1.14; 95%CI: 1.13−1.15). As expected, the IR increased with age (from 2.2 in those under 55 years to 47.2/1000 in those over 75 years of age). It is very important to emphasize that the HRs attenuated with age (from triple in patients under 55 years of age to virtual equality in patients over 75 years of age); thus, it is younger patients that might require a greater intensification of therapeutic care.

In patients with type 1 DM from the same Swedish registry (mean age 35.8 years, disease duration 20.4 years, and mean HbA1c concentration 8.2%), the increase in the risk of CV mortality (HR = 4.60; 95%CI: 3.47−6.10) was very marked, particularly in women and in younger patients. It should be noted that although the HRs were higher, the poorer the metabolic control and the more advanced the renal impairment of the patients, even individuals with HbA1c < 7% and normoalbuminuria had an approximately three-fold increase in risk.

An important message here is that the lower RR produced by DM at the present time, with respect to previous decades, should be interpreted as a favorable consequence of the application of the current treatment recommendations.

Risk in type 2 versus type 1 diabetes mellitus

The referenced studies[10,19,20] have demonstrated a direct relationship between HbA1c and CVD, though the slope is more marked in type 1 DM. This may be due to the fact that hyperglycemia is the predominant RF in type 1 DM,[21] while in the case of type 2 DM other vascular RFs associated with insulin resistance also play a role.[22] In fact, for equal age, time since disease onset and glycemic control, type 2 DM is associated with an increased risk of CV mortality[23] and with the occurrence of chronic complications[24] compared with type 1 DM. Coronary lesion morphology may also differ, with a greater proportion of non-calcified plaques tending to rupture in type 2 DM as compared to type 1 DM (assuming equal coronary calcium).[25]

The PSC meta-analysis[14] identified a positive association between CVD risk and cholesterol levels, blood pressure (BP) and the body mass index (BMI). Although the RR conferred by these RFs was quite similar independently of the presence of DM, the RD was greater in patients with DM due to their higher initial R. In both type 2 and type 1 DM, it has been seen that the better the control of the vascular RFs (HbA1c, BP, smoking, urinary albumin excretion and low density lipoprotein cholesterol [LDLc]), the lower the risk of CVD.[26,27]

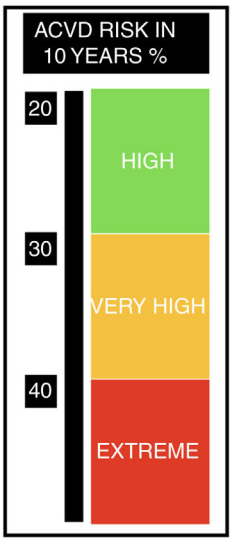
Improved control of the RFs has resulted in a decrease in the IR of CVD in patients with DM.[28] However, because of the high R, the RCVR in patients with DM may still be significant.

Stratification of atherosclerotic cardiovascular disease risk in patients with diabetes

Criteria for stratifying vascular risk

Large meta-analyses and population studies serve to establish the mean R associated with the presence of DM, but not the R of each individual patient, which may be highly variable. Stratification of the initial R of the patients is required to better define the intensity of the therapeutic interventions.[4,7] A number of important aspects must be taken into account.

1 There may be patients with an R that far exceeds the very high risk threshold. In the 1998 study by Haffner et al.,[8] patients with DM and prior AMI had an IR for MACE of 112/1000 (exact R in 10 years of 67%) and for CV mortality of 73/1000 (exact R in 10 years of 52%). Despite the application of the standard of care recommended by the current guides, the placebo groups of the recently published CV safety trials of hypoglycemic drugs show a very high RCVR; the IRs for MACE range from 24.2 to 78.6/1000, depending on the patient inclusion criteria (Fig. 1). This justifies the definition of an extreme risk category, with a consensus-lacking threshold, but which could be applied to an R for MACE in 10 years of ≥40% or CV mortality ≥15%. Recommendations are available[29] regarding groups that could be considered to be at extreme risk: patients with CVD or advanced chronic kidney disease, who have been shown to have the highest R in the clinical trials.[30] Concreting stratification as far as possible, the peak of this extreme risk category corresponds to those patients with DM that have suffered recent acute coronary



CLINICAL TRIAL	n	Duration	Age	100 (recent ACS)	RATE/1000 MACE placebo group	RCVR at 10 years, exact (%)	MACE HR (95%CI)
PROACTIVE (pioglitazone)	5,238	3	62	100	47.3	37.7	0.84 (0.72-0.98)
SAVOR (saxagliptin)	16,492	2.1	65	78	37	30.9	1.00 (0.89-1.12)
EXAMINE (alogliptin)	5,380	1.5	61	100 (recent ACS)	78.6	54.4	0.96 (?-1.16)
TECOS (sitagliptin)	14,671	3	65	100	36	30.2	0.99 (0.89-1.10)
CARMELINE (linagliptin)	6,979	2.2	66	57 (74% chronic kidney disease)	56.3	43	1.02 (0.89-1.17)
EMPA-REG (empagliflozin)	7,020	3.1	63	100	43.9	35.5	0.86 (0.74-0.99)
CANVAS + CANVAS-R (canagliflozin)	10,142	3.6	63	66	31.5	27	0.86 (0.75-0.97)
OECLARE (dapagliflozin)	17,160	4.2	64	41	24.2	21.5	0.93 (0.84-1.03)
ELIXA (lixisenatide)	6,068	2.1	60	100 (recent ACS)	63	46.7	1.02 (0.89-1.17)
LEADER (liraglutide)	9,340	3.8	64	81	39	32.3	0.87 (0.78-0.97)
SUSTAIN-6 (semaglutide)	3,297	2.1	65	83	44.4	35.8	0.74 (0.58-0.95)
EXSCEL (Exenatide LAR)	14,752	3.2	63	73	40	33	0.91 (0.83-1.00)
HARMONY OUTCOMES (albiglutide)	9,463	1.6	64	100	58.7	44.4	0.78 (0.68-0.90)
ORIGIN (glargine)	12,537	6.2	64	59	28.5	24.8	1.02 (0.94-1.11)
DEVOTE (degludec)	7,637	2	65	85	47.1	37.6	0.91 (0.78-1.06)

Figure 1 Cardiovascular safety trials of blood glucose-lowering drugs with the percentage of patients with prevalent cardiovascular disease (CVD). Statistically significant results are highlighted in bold. The residual cardiovascular risk (RCVR) in 10 years of major vascular events (MACE) is extrapolated from the incidence rate (IR) using the formula $R = 1 - e^{-IR \times duration}$.
Prepared by the authors.

syndrome (ACS) and have multiple affected vascular territories (malignant vascular phenotype), and who in the IMPROVE-IT trial[31] presented an IR for MACE of 72/1000 despite reaching LDLc levels of <70 mg/dl.

2 In patients with DM, there are other conditions that directly cause them to be considered as being at very high vascular risk (and in some cases even extreme risk): microvascular disease or long-evolving DM (>10 years in type 2 DM or >20 years in type 1 DM).[5] Both the severity of the microvascular damage[32–34] and the number of affected microvascular territories are associated with a progressive increase in the risk of MACE and CV mortality. It has been found that adding information about the extent of the microvascular alteration in predictive models improves the R classification of the patient.[35]

3 In the case of subjects who do not meet the above criteria, one strategy is to consider that they are at least at high vascular risk. In order to better define whether R is really moderate, high or very high, it is useful to use risk stratification formulas[7] that contemplate the other RFs. The equations specific for DM are not perfect. It has recently been shown that the RECODe risk equation[36] (https://sanjaybasu.shinyapps.io/recode/), based on the ACCORD study and externally validated with data from the Look AHEAD trial, improves the discrimination of MACE and CV mortality risk versus the equations derived from the UKPDS and those recommended by the AHA/ACC,[5] particularly in that it better identifies patients at lesser risk. The new QRISK3 equation (https://qrisk.org/three/)[37] includes the presence of type 1 DM among its parameters.

4 If we seek to precisely identify the small group of individuals at low or moderate risk, more complex tests must be used. In general, the measurement of coronary artery calcium (CAC) is considered more valid than the determination of C-reactive protein (CRP) in reclassifying the risk of individuals in primary prevention.[38] In a meta-analysis of 8 studies[39] with 5 years of follow-up in patients with DM, a CAC score of <10 (28.5% of patients) reduced the estimated probability of MACE from 19% to 2.5%. The AHA/ACC[5] guidelines consider the possibility of avoiding statin therapy in subjects with a CAC score of 0, given its good negative predictive value, though they recognize that it may be less reliable in the context of DM. It should also be taken into account that the risk increases with the duration of DM; the determination of CAC therefore has to be repeated periodically. The Pittsburgh type 1 DM cohort[40] showed an increased risk of CVD with growing CAC volume, which improved risk prediction. Furthermore, those patients who increased their CAC volume between two explorations spaced 4–8 years apart tripled their risk of CVD.

Graphic representation of vascular risk

It can thus be deduced from the above that the classification of vascular risk into two categories (primary and secondary prevention) is too simple. Vascular risk can be represented as a continuous line (Fig. 2), and there are variables which, depending on their number and intensity, place the patient at a specific point on that line. The greater the initial RR, and despite the RR reduction achieved with CV prevention mea-

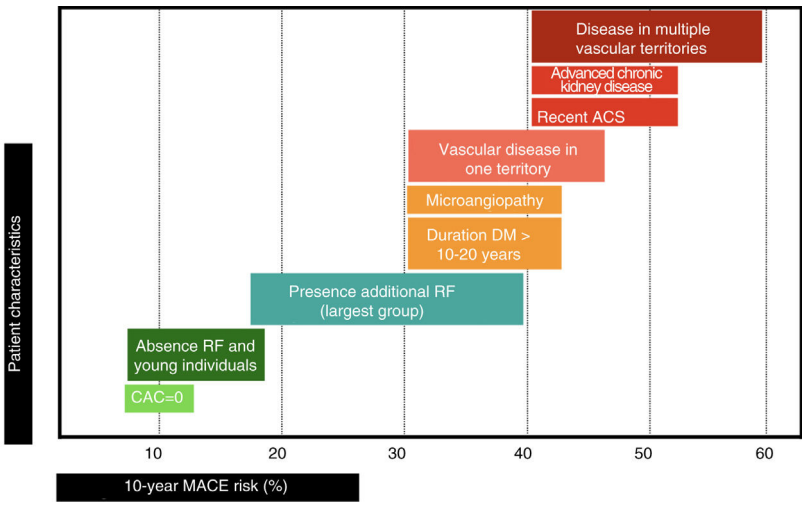


Figure 2 Risk stratification of major vascular events (MACE) in 10 years according to the initial patient characteristics. Prepared by the authors.

sures, the greater the RCVR and, therefore, the greater the need to implement more aggressive preventive strategies, which will be analyzed below.

Therapeutic strategies to reduce residual cardiovascular risk in diabetic patients

Consolidated strategies

Table 2 summarizes the recommended strategies in CV prevention.

Control of vascular risk factors adapted to initial patient risk

The meta-analysis of the ERFC[13] estimated that at the age of 50 years, DM shortened life expectancy by 6 years, secondary in 58% of the cases to an excess of CV deaths. More striking is the situation in type 1 DM, which often manifests at an early age. Data from the Swedish NDR indicate that the earlier the onset of the disease, the greater the number of years lost attributable to DM (up to 16 years in patients diagnosed before 10 years of age).[41]

There is consensus in the guides[4,5,7,29,42] regarding the need for the multifactorial and aggressive management of vascular RFs in patients with type 2 DM adapted to the R of CVD. In addition, there is growing recognition of the need for the early treatment of vascular RFs in patients with type 1 DM in order to delay the threshold of the appearance of CVD.[43]

The LDLc targets are increasingly strict.[29] Data collected from Mendelian randomization studies, epidemiological studies and clinical trials have made it possible to extrapolate that a decrease in LDLc of 40 mg/dl results in a 10% decrease in the RR of CVD during the first year of treatment, 20%–25% after 5 years of treatment, and more than 50% after 40 years of treatment.[44] The higher the initial R, and for equal RR reduction, the higher the RD reached, and thus the lower the number needed-to-treat (NNT) to obtain benefit (NNT = 1/RD).

The goals of blood pressure (BP) control have been subject to controversy in the past decade. A recent meta-analysis[45] suggested that the benefit of aggressive BP reduction is greater in patients without DM than in individuals with DM. However, in patients with DM, an additional decrease in systolic BP (SBP) of 10 mmHg, even below 130 mmHg, resulted in a significant decrease in the RR of MACE (HR = 0.81; 95%CI: 0.70—0.94) and stroke (HR = 0.74; 95%CI: 0.59—0.92), but not of coronary artery disease or CV mortality. The new American[46] and European guides[47] advocate a strategy adapted to the R for CVD, with a target BP of <130/80 mmHg in DM. The ADA[7] suggests BP < 130/80 mmHg in patients with R > 15%, if tolerated without side effects. An important aspect is an insistence upon the need to use ambulatory monitoring or home self-measurement of BP for the diagnosis of arterial hypertension and for adjusting therapy.

Antiplatelet therapy

Patients with diabetes mellitus and atherosclerotic cardiovascular disease

There is a formal indication for antiplatelet therapy with aspirin 75—162 mg/day in patients with DM and established CVD.[7] Dual treatment (aspirin + P2Y12 inhibitor) is required in the first year after ACS, and may be reasonable beyond this period in subjects with very high RCVR and no characteristics associated with an increased risk of bleeding.[48] In the Pegasus-TIMI 54 trial[49] (subjects with AMI 1–3 years previously and in >50% of the cases with multivessel disease), patients with DM randomized to ticagrelor + aspirin experienced a lower risk of MACE (HR = 0.84; 95%CI: 0.72—0.99; RD —5/1000 patient-years), but at the expense of a higher risk of bleeding (HR = 2.56; 95%CI: 1.52–4.33; RD +5/1000 patient-years).

Patients with diabetes mellitus without atherosclerotic cardiovascular disease

In patients with DM but without established CVD, the meta-analysis carried out by Zhang et al.[50] found that treatment with aspirin could decrease the risk of AMI preferentially in

Table 2 Vascular risk factor control objectives adapted to atherosclerotic CVD risk.

Atherosclerotic CVD risk (% in next 10 years)	Moderate (generally young patients)	High	Very high	Extreme
[0,1–5] HbA1c (%)				
Type 2 DM	< 6.5 if can be reached without hypoglycemia	<7	[0.4—5] < 8	
		Generic goal for most	More lenient as comorbidity and the risk of hypoglycemia increase	
Type 1 DM	<7.5 in <18 years	[0,3–5] Individualize objective according to comorbidity and the risk of hypoglycemia		
	<7 in adults			
[0.1—5]				
Blood pressure (mmHg)	<140/90 (consider < 130/80)	[0,3–5] < 130/80 if it can be reached without side effects		
LDL-cholesterol (mg/dl)	<100	<100	<70	<55
Non-HDL-cholesterol (mg/dl)	<130	<130	<100	<80
Intensity of statin treatment	Moderate[a]	[0,3–5] High[b]		
Antiplatelet therapy[c]	Generally not recommended due to the unfavorable risk/benefit ratio	[0,3–5] ASA at doses of 75—162 mg/day (level of evidence A for established atherosclerotic CVD and level of evidence C without established atherosclerotic CVD) Consider the risk of bleeding		

ASA: acetylsalicylic acid (aspirin); LDLc: low-density lipoprotein cholesterol; DM: diabetes mellitus; Atherosclerotic CVD: atherosclerotic cardiovascular disease; HDL: high-density lipoprotein; PCSK9i: PCSK9i inhibitors; LDL: low-density lipoprotein.
[a]The threshold for the start of systematic statin therapy is 40 years of age. Consider starting from 10 years of age in patients with type 1 DM and LDLc > 160 mg/dl or LDLc > 130 mg/dl with other vascular risk factors, and in patients with type 2 DM and LDLc > 130 mg/dl.
[b]In patients with established CVD and LDL > 70 mg/dl, the addition of PCSK9i is indicated.
[c]When considering antiplatelet therapy, the residual cardiovascular risk in the patient after aggressive control of the other risk factors and the risk of bleeding must be taken into account.
Prepared by the authors.

males (HR = 0.71; 95%CI: 0.50–1.00), and of stroke in women (HR = 0.67; 95%CI: 0.48—0.92). In the recently published ASCEND trial[51] (patients with type 2 DM starting 7 years previously, without CVD, and treated with statins in 75% of the cases), the administration of aspirin versus placebo during a period of 7.4 years reduced the risk of MACE (HR = 0.88; 95%CI: 0.79—0.97; RD —1.5/1000 patient-years), but only at the expense of an increased risk of bleeding (HR = 1.29; 95%CI: 1.09–1.52; RD +1.2/1000 patient-years).

It can be concluded that in patients without established CVD and with a RCVR (estimated after optimum treatment of the other vascular RFs) of over 10% in 10 years, the number of vascular events avoided by antiplatelet therapy will be greater than that of the induced bleeding events. Patients with DM without CVD thus may be amenable to treatment with aspirin if they are classified as being at very high vascular risk. If they belong to the high risk category, careful selection will be needed, the possibility of bleeding being assessed in order to optimize the risk/benefit ratio.

Importance of weight loss

In patients with type 2 DM, a decrease in body weight of >5% should be attempted based on a low-calorie diet and physical exercise.[52] Although the Look AHEAD trial was discontinued due to a lack of efficacy in reducing CVD, the

patients in the intervention group had a lesser need for statins, blood pressure-lowering drugs and insulin. In a secondary analysis,[53] the subjects who achieved ≥10% weight loss showed a significant decrease in CVD risk (HR = 0.79; 95%CI: 0.64—0.98). Although a weight loss of as little as 5% is already significant for health, a decrease of >10% may be even more beneficial.

The possibility of metabolic surgery in patients with type 2 DM associated with a BMI 35—40 kg/m^2 should always be considered (and in future such surgery could even be considered in patients with a BMI 30—35 kg/m^2 conditioned to the availability of healthcare resources), in the event of inadequate RF control despite optimized medical management.[52] In a recent observational study involving 4.7 years of follow-up, CVD risk was found to be lowered (HR = 0.60; 95%CI: 0.42—0.86) in patients with type 2 DM and a BMI > 35 kg/m^2 subjected to surgery (76% with gastric bypass operations).[54]

In patients with type 1 DM, it is important to minimize the impact of intensive treatment upon body weight. The participants in the intensive management group of the Diabetes Control and Complications Trial (DCCT) who exhibited a greater weight increase during the study (entering the obesity range) experienced more vascular events from 14 years of follow-up than those who maintained a virtually stable weight, their rates equalling those of the conventional group.[55] In other words, the benefits of good blood glucose control may be lost if it is associated with progressive weight gain.

Importance of the choice of blood glucose-lowering therapy

The choice of hypoglycemic treatment should seek to avoid weight gain and the possibility of hypoglycemia.[52] Although there is no definitive evidence as to whether hypoglycemia is truly a causal factor of CV mortality or simply a marker of frail patients at increased risk of death, a meta-analysis evaluating the possibility of bias concluded that severe hypoglycemia doubled the risk of CVD (HR = 2.05; 95%CI: 1.74–2.42; population attributable fraction 1.56%) and that the observed association was unlikely to be fully justified by the confusion generated by the associated comorbidities.[56] In addition, a meta-analysis of studies with continuous blood glucose monitoring of patients with type 1 and type 2 DM has shown that hypoglycemia, particularly at night, leads to QT interval prolongation and to a decrease in heart rate variability, both being sudden death markers.[57]

In recent years, many CV safety trials have been published, leading to modifications in clinical practice by demonstrating the additional benefits of certain drugs beyond their effect upon glycemic control (Fig. 1). The therapeutic groups that have most consistently shown CV benefit are the GLP-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2i). These are therefore the drugs of choice in patients with established CVD.[52] As can be seen in Fig. 1, not all members of these therapeutic groups have achieved significant results, the strength of evidence being greater for liraglutide and empagliflozin.[52]

A meta-analysis[58] of GLP-1 RAs (including liraglutide, semaglutide, exenatide and lixisenatide, but not albiglutide) has shown that, on average, the reduction of risk of MACE (HR = 0.90; 95%CI: 0.82—0.99) and CV mortality (HR = 0.87; 95%CI: 0.79—0.96) is significant. Most of the patients had established CVD. The significant effect of some class members (liraglutide, semaglutide, albiglutide) but not others (exenatide, lixisenatide) may be attributable to their different potency, duration of action, molecular structure and formulation (the latter being related to adherence).

A meta-analysis[59] of SGLT2i (including empagliflozin, canagliflozin and dapagliflozin) also showed a statistically significant reduction in the risk of MACE (HR = 0.89; 95%CI: 0.83—0.96) and CV mortality (HR = 0.84; 95%CI: 0.75—0.94), in addition to a markedly favorable effect on the risk of heart failure and the progression of kidney disease. An interesting finding is that in a stratified analysis, the benefit upon MACE and CV mortality occurred only in patients with established CVD. Also relevant is the fact that in patients with initial CVD, the decrease in the risk of CV mortality was more intense and only significant with empagliflozin, in the group in which patients with higher initial R were included (CV mortality IR of the placebo group in the EMPA-REG trial: 20.2/1000; IR placebo in CANVAS: 16.8/1000; IR placebo DECLARE: 11.6/1000). With SGLT2i, the heterogeneity of results may possibly be due more to patient baseline characteristics than to differences between molecules: the greater the initial R, the greater the benefit in terms of CVD reduction.

Lastly, it should be noted that although not highlighted in the recent guides, pioglitazone has also shown positive effects in terms of CVD progression. The careful selection of patients (the preferred indication in the event of high insulin resistance or non-alcoholic fatty liver disease), maximizing the benefits of pioglitazone and minimizing its side effects (osteoporosis, heart failure), may help to expand the use of this drug in the future.[60]

Emerging strategies to reduce residual cardiovascular risk in very high or extreme risk scenarios

We will probably see new therapeutic possibilities in the future to gradually reduce the RCVR of DM.

Detection of patients in whom intensive glycemic treatment can optimize the risk-benefit balance

In this regard, two genetic variants were identified in the ACCORD trial[61] that increase the risk of CV mortality in the event of intensive treatment. In fact, the intensive treatment of 1000 high genetic risk subjects causes 38 vascular deaths and prevents 8 acute myocardial infarctions, while the same treatment in low genetic risk subjects prevents 14 vascular deaths and 30 infarctions.

LDL-cholesterol: the lower the better

The PCSK9 inhibitors (PCSK9i) achieve LDLc reductions of 50%–70%, and have shown reductions in vascular events of approximately 15% in secondary prevention, with similar efficacy in patients with and without DM.[62] Their clinical efficacy per unit change in LDLc is similar to that of statins.[44] In addition, there appears to be no LDLc threshold below which there is no longer any benefit. In the FOURIER trial, subjects achieving LDLc < 10 mg/dl were those with the low-

est IR of MACE, with no increase in adverse effects.[63] The greater the RCVR, the more cost-effective[5] the use of PCSK9i will be. The ADA recommends adding ezetimibe or PCSK9i to statin therapy in patients with DM and established CVD in the presence of LDLc > 70 mg/dl.[7]

Targeting atherogenic dyslipidemia

Atherogenic dyslipidemia may be defined as an alteration including hypertriglyceridemia, decreased high density lipoprotein cholesterol (HDLc), a predominance of dense LDL particles, and increased triglyceride-rich lipoprotein cholesterol (TRLc). This lipid phenotype contributes to RCVR in patients in whom the LDLc goal has been reached,[64] since the TRL particles and their remnants may be even more atherogenic than the LDL particles. The therapeutic interventions, as reviewed by Sandesara et al.,[65] are as follows:

- The use of fibrates. This is not recommended on a general basis, though it may be indicated in patients with triglycerides $\geq$204 mg/dl and HDLc $\leq$34 mg/dl.[7] The definitive answer regarding their potential usefulness may come from the PROMINENT trial, which will assess the efficacy of pemafibrate combined with statins in patients with DM and mixed dyslipidemia.
- The use of omega-3 fatty acids. Although the results have been controversial to date, in the REDUCE-IT trial, an eicosapentanoic acid formulation (icosapent ethyl) at a dose of 4 g daily was administered to patients with CVD or DM, and with triglyceride levels of 150—500 mg/dl, recording a significant reduction in the risk of MACE in patients with DM (HR = 0.77; 95%CI: 0.68—0.87). The beneficial results may be due to the high dose used and to an antithrombotic effect.[66]
- Therapies aimed at improving TRL metabolism: anti-Apo-C III (volanesorsen) and anti-angiopoietin-3 (evinacumab) drugs.
- Anti-apolipoprotein A drugs, which have achieved reductions of up to 92% in Lp(a).

Targeting inflammation

Although inflammatory markers (CRP, interleukin [IL]-6) have little predictive value in patients without CVD,[38] there is evidence in patients with DM that they can predict events in those individuals with established CVD.[67] In this regard, a very important finding in the Fourier trial was that the risk of CVD increased when the CRP values increased, even if the patients reached LDLc < 20 mg/dl.[68]

The usefulness of targeting inflammation has been confirmed by specific interventional studies. In the CANTOS trial, the administration of canakinumab (a monoclonal antibody targeted to IL-1ß) in patients with prior AMI (40% of them with DM) and CRP > 2 mg/l reduced the risk of MACE by 15%, and similarly in patients with and without DM. Most interestingly, the clinical benefit was related to the CRP levels achieved: only when CRP < 2 mg/l was reached were there significant reductions in the risk of MACE (HR = 0.75; 95%CI: 0.66—0.85) and CV mortality (HR = 0.69; 95%CI: 0.56—0.85).[69] Chronic inflammation favors the progression of atherosclerosis and increases the vulnerability of the plaque to rupture. It is therefore plausible that treatments intended to correct such inflammation will afford CV benefit, as indicated by Kottoor and Arora.[70]

Conclusions: key points in the evaluation and management of residual cardiovascular risk

Based on the review of the epidemiology of atherosclerotic CVD in DM, it can be concluded that:

1 Both type 1 and type 2 DM increase the risk of the occurrence of CVD.
2 There is a clear relationship between the improved control of vascular RFs seen in recent decades and the decrease in RR conferred by the presence of DM.
3 Despite the achievement of the control objectives recommended by the clinical practice guides, the RCVR of patients with DM may remain very high.

As recommendations for reducing RCVR, the following can be mentioned:

1 Careful stratification of the vascular risk of the individual patient, taking into account that the higher the R, the greater the eventual RCVR. It is particularly important to detect patients at very high or even extreme risk (particularly those with established CVD or microvascular disease).
2 The combating of clinical inertia, which could delay the achievement of the goals recommended by the guides.
3 The use of the available therapeutic strategies that have demonstrated efficacy in clinical trials, adapted to the patient characteristics. These include the use of blood glucose-lowering drugs with specific CV benefits (GLP-1 RAs and SGLT2i) and intensive LDLc reduction (with the use of PCSK9i if necessary).
4 Continued research into promising fields to reduce RCVR. Emerging strategies for patients at very high or extreme risk include the use of drugs aimed at reducing triglyceride-rich lipoproteins and inflammation.

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