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Physical Activity and Prognosis in Coronary Patients. It's never too late!

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Different observational studies have pointed out the lower risk of cardiovascular and all-cause mortality in patients with coronary heart disease who engage in regular physical activity (PA) compared with those who are sedentary. For this reason, clinical practice guidelines recommend PA as an essential part of the life regimen in coronary patients. However, the evidence cited generally comes from studies in which PA has been defined at a single point in time, or is expressed as the average of more than one assessment. When we refer to the behavior of patients regarding PA over time, the information is more scattered and sometimes contradictory. Is the favorable prognosis maintained in those who leave PA? Can prognosis be improved in those who start PA late? To answer these questions, a meta-analysis of prospective observational studies was carried out, whose results are reported here.

Nine follow-up studies of patients with coronary heart disease, with at least two assessments about whether or not the patient was performing regular PA were included. The association of the variable with all-cause mortality, and in 6 of them also with cardiovascular mortality, was defined in these studies. Based on the data, the PA trajectory of the patients was classified into 4 categories: those who always remained inactive (reference category), those who were always active, those who increased PA over time, and those who decreased it. Going from inactive to active was defined as an increase, and the opposite situation as a decrease. The association of each category with total or cardiovascular mortality had been expressed in each study as HR (95% CI), generally with adjustment for age, gender, and traditional risk factors, and in some studies also with comorbidities, alcohol consumption or socioeconomic level. A total of 33 576 patients were considered (one of the studies included 22 227), with a mean age of 62.5 years. One study included only women, another 2 only men, and the rest patients of both genders, with a female prevalence between 18% and 56%. None of the studies included patients with heart failure or peripheral vascular disease. Mean follow-up ranged from 4.2 to 15.7 years.

Compared with those who remained inactive, the HR (95% CI) for all-cause mortality was 0.50 (0.39-0.63) for those who remained active; 0.55 (0.44-0.70) for those who increased their PA, and 0.80 (0.64-0.99) for those who decreased it. Heterogeneity was moderate to high (I2 between 65.9% and 73.8%). In four cohorts with acute coronary heart disease (n=25 010), and compared with those who remained inactive, the HR (95% CI) was 0.38 (0.25-0.56) for those who remained active, 0. 44 (0.32-0.60) for those who increased their PA, and 0.65 (0.48-0.88) for those who decreased it. Five cohorts included 8566 patients with chronic disease; compared with those who remained permanently inactive, the HR (95% CI) for the other three categories was 0.60 (0.50-0.73), 0.69 (0.59-0.82), and 0.92 (0.71-1.19), respectively.

Five cohorts (n=25 900) included patients selected from exclusive coronary heart disease registries. Taking the always inactive category as reference, the HR (95% CI) for total mortality was 0.34 (0.25-0.47) in the permanently active patients, 0.39 (0.25-0.61) in those with increased PA, and 0.56 (0.47-0.68) in those who decreased it. In 4 cohorts with 7676 coronary patients selected from general population cohorts, compared with those who remained inactive, the HR (95% CI) for the other 3 categories was 0.63 (0.55-0.71), 0.67 (0.60-0.79), and 0.93 (0.75-1.15), respectively.

In 6 studies (n=9422) the relationship of PA with cardiovascular mortality was investigated; compared with those who remained inactive, the HR (95% CI) for cardiovascular mortality was 0.49 (0.39-0.62) in those who were permanently active, 0.63 (0.51-0.78) in those in whom PA increased and 0.91 (0.67-1.24) in those with decreased PA.

There are several reasons to associate PA with a better cardiovascular prognosis: improved cardiorespiratory fitness, decreased insulin resistance and incidence of diabetes, reduced inflammatory and neurohormonal activation, and decreased weight and high blood pressure levels. Specifically, in relation with coronary circulation, attenuation of endothelial dysfunction with increased generation of nitric oxide and reduced free radical formation, promotion of collateral circulation, angiogenesis and decreased platelet activation have been reported, also adding to these systemic effects the reduction in the incidence of cancer and cognitive disorders.

The issue to consider in this relationship between PA and better prognosis is the presence of confounders. People who practice PA are generally younger, and age is a strong evolutionary determinant. They are also people with better health and functional capacity;

therefore, the prevalence of cardiovascular risk factors is lower. A better socioeconomic condition is another factor associated with greater availability of time to perform PA on a regular basis, and we know that it is also closely related to the vital prognosis.

This meta-analysis has the merit of not considering a single point in determining the PA performed, but contemplating the trajectory. It is part of the line of studies that focus on the evolution of a parameter (renal function, weight, glycosylated hemoglobin) or behavior (smoking, for example), and hence honors the concept that the prognosis does not depend exclusively on how well or bad they are at a given moment, but also, and to a large extent, how they change favorably or unfavorably over time.

Therefore, it is already interesting to point out that beyond the obvious (being always active is associated with a better cardiovascular and global prognosis than being always inactive), going from inactive to active also improves the prognosis (a good reason to start), and even, in general, the fact of having performed PA regularly, even if it has then been abandoned, still seems to entail a certain advantage (much lower, it must be said, than for persistent or increasing PA) compared to never having practiced it. Although, in this last circumstance, the reduction of PA, the data are not so conclusive, and some of the analyses cited (total mortality in chronic coronary heart disease, stroke mortality), as we can see, indicate that the protective effect of PA is lost if it is abandoned.

As limitations we can mention that it is not a meta-analysis of individual data, but of the summary estimates of each of the studies. The follow-up times are varied (between 4 and almost 16 years), and we do not have information about the time elapsed between the first and the second assessment. The mere passing of the years naturally leads to a decrease in PA. Physical activity categorization is based on self-report, and there is no quantification of it. Is going from sustained and regular PA to maintaining reduced and infrequent PA enough to be considered always active? In the evaluation of the PA trajectory, the parallel trajectory of its determinants (age, comorbidities, frailty) is not considered. We do not know the incidence of cardiac or extracardiac diseases during follow-up that may have reduced PA and be responsible for the worse prognosis. And, very importantly, patients with heart failure or peripheral vascular disease, vital determinants of exercise capacity, were not included, nor do we know their incidence in those free of these conditions in the initial assessment, but taking into account that they could be patients with early coronary heart disease, they may have appeared during the course of follow-up and be responsible for many cases of PA abandonment.

In conclusion, this meta-analysis indicates a strong association between sustained PA, or its onset, and a favorable prognosis, but does not allow to infer causality.

Socioeconomic deprivation: the forgotten predictor of cardiovascular risk

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Numerous registries have shown that low socioeconomic status is a strong predictor of higher risk of cardiovascular events, beyond traditional risk factors. Nevertheless, many randomized or observational studies, when defining baseline patient risk, do not take it into account, and it neither appears among the variables considered in different scores or prediction rules. However, some recent scores (ASSIGN, QRISK3) have incorporated socioeconomic deprivation or poverty as a constitutive variable. We are going to comment on an observational study aiming to define whether scores that include this deprivation have greater predictive capacity than other traditional ones that do not consider it. A cohort of 15 506 subjects between 35 and 65 years of age drawn from the GS: SFHS Scottish registry, with 60% women, and mean age of 51 years, was analyzed. Based on the SIMD score (it derives from the participants' postal code, and considers 7 deprivation domains: income, housing, education, employment, health, access to housing services, crime), participants were grouped into 5 quintiles, which were later condensed into three categories: group 1, maximum deprivation (the lowest quintile, 12% of participants), group 2 (quintiles 2 to 4, 52% of participants) and group 3, least deprivation (quintile 5, 30% of the total study population). Six percent of participants could not be analyzed because there was no score value. Group 1 participants were younger (median age of 48 years vs. 51 years in group 2 and 53 years in group 3), and were more frequently women, current smokers and diabetic. In a 10-years follow-up, the incidence of a composite of non-fatal acute myocardial infarction (AMI), non-fatal stroke and cardiovascular death was higher in group 1: 6.7% vs. 4.7% in group 2 and 4.2% in group 3. In a model adjusted by age, sex, body mass index and traditional risk factors, belonging to group 1 was associated with a significantly higher risk than belonging to group 3 (OR 1.50, 95% CI 1.12-1.99). This difference was mainly due to the higher risk of AMI (adjusted OR 1.96, 95% CI 1.28-2.98). But, although group 1 had greater incidence of stroke and cardiovascular death than the other 2 groups, in these cases the differences were not significant).

The ASSIGN, SCORE 2 and PCE scores was calculated in each participant at follow-up initiation. The ASSIGN score considers age, total cholesterol, HDL cholesterol, systolic blood pressure, diabetes, family history of cardiovascular death, daily cigarette consumption (10 cigarettes per day are added in patients with rheumatoid arthritis), and the SIMD score (socioeconomic deprivation)/10. The SCORE 2 (European)

considers age, and total cholesterol, HDL cholesterol, systolic blood pressure, diabetes and smoking, alone, and their interaction with age. The PCE score (mixed AHA and ACC cohort equation) considers age, the age squared in women, total cholesterol, HDL cholesterol, systolic blood pressure, diabetes, and smoking, as well as the interaction of total cholesterol, HDL cholesterol and smoking with age.

Score calibration was evaluated in the three scores (coincidence between the predicted and the observed incidence of cardiovascular events). In group 1 (patients with greatest deprivation) the ASSIGN score evidenced good calibration: there was no significant difference between predicted (8.39%) and observed (9.13%) incidence; conversely, both SCORE 2 (predicted and observed incidences: 4.63% and 6.43%, respectively) and the PCE score (predicted and observed incidences; 4.66% and 6.69%, respectively) underestimated the risk of events. In group 2, the three scores showed good calibration, without difference between predicted and observed incidence. In group 3, the ASSIGN score again demonstrated adequate calibration (predicted and observed incidences: 6,45% and 6.21%, respectively), while the other two scores evidenced a significant tendency to overestimate the risk of cardiovascular events, with predicted and observed incidences of 4.72% and 3.97% for SCORE 2 and 4.85% and 4.22% for the PCE score, respectively..

Higher cardiovascular risk associated with a worse socioeconomic condition has been considerably demonstrated in a vast number of observational studies. The reasons that explain this association have not been completely explained. But as we go lower in the social scale the prevalence of risk factors is greater, the food quality worse, with more working hours and greater restriction of access to the healthcare system. A large part of the socioeconomic level prognostic weight lies precisely in the inequity of resources and the time dedicated to health care in its different levels, beyond the traditional risk factors. The present work elegantly shows this issue. By comparing a score that takes into account the socioeconomic level with another two that do not do so, we can see that among people with less resources, only considering the usual risk factors underestimates the risk of events (this specifically expresses the role of deprivation, which adds risk not taken into account by the traditional approach) while among those better positioned in the social scale, even though the burden of risk factors is high, the better socioeconomic condition makes them weigh less in the prognosis than expected..

As limitations we can refer two usually mentioned biases. The first is the ecological bias: it is interesting to recall that the SIMD score starts considering the postal code, that is, the place of residence of participants, assuming that different dwelling location is clearly associated with a dissimilar economic situation. And although it is true that some neighborhoods can be identified with people of higher or lower resources, not all the inhabitants of each conglomerate share univocally the same condition. This means that in some cases the analysis may have fallen into an ecological fallacy. The second is the bias of response or participation: even though all the registry participants were randomly invited to take part in this study, there was a more frequent affirmative response in those of better socioeconomic status, so that the relationship of deprivation with the prognosis could have been underestimated.

And finally, a reflection. In general, even when cardiovascular risk is pointed out as associated with deprivation, the postulated solution is usually a more intensive treatment of the more important risk factors. As if the socioeconomic condition were an unmodifiable risk, as age or sex. This could be right if all the prognostic burden of deprivation rested on these factors. But it is clear, deprivation also entails educational and working disadvantages and adverse life conditions (less access to basic services, greater exposure to hostile environment) which, we believe, are not solved with statins or beta-blockers. To assume the prognostic role independently of the social condition, and work to decrease inequity seems unavoidable. The worse cardiovascular prognosis is not an exclusive problem of Medicine.

Cardiogenic shock: refining the classification

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Kapur NK, Kanwar M, Sinha SS, Thayer KL, Garan AR, Hernandez-Montfort J et al. Criteria for Defining Stages of Cardiogenic Shock Severity. **J Am Coll Cardiol 2022;80:185-98. https://doi.org/10.1016/j.jacc.2022.04.049.**

In 2019, the Society for Cardiovascular Angiography and Interventions (SCAI) released a classification of the stages of cardiogenic shock (SCAI SHOCK), to favor its detection and treatment. There are 5 stages of increasing severity, based on clinical criteria, laboratory and hemodynamic data. In a description that is not intended to be exhaustive, we can characterize each of them. Stage A considers patients who do not have any clinical or paraclinical findings suggestive of shock, but are at risk of presenting it, for example, because they are undergoing an extensive acute myocardial infarction (AMI), or because they present heart failure, acute heart failure de novo or decompensated chronic heart failure. Stage B (pre-shock) includes patients with arterial hypotension, with systolic blood pressure (SBP) < 90 mm Hg or mean arterial pressure (MAP) < 60 mm Hg and heart rate (HR) > 100 beats/min, with signs of pulmonary or systemic congestion, but without clinical or hemodynamic manifestations of hypoperfusion; with a cardiac index (CI) ≥ 2.2 L/min/m 2 , and normal lactic acid and renal function values, although with elevated

natriuretic peptides. In stage C (classic shock) clinical and laboratory manifestations (elevated lactic acid, impaired renal function) of hypoperfusion are added to hypotension (present even when vasoactive drugs or temporary mechanical support are used), and this is confirmed by a CI < 2.2 L/min/m 2 , a wedge pressure > 15 mm Hg, decreased cardiac output and pulmonary artery pulsatility index. In stage D (due to deterioration) the picture of hypotension and hypoperfusion worsens despite the instituted treatment, and hemodynamics cannot be improved. In stage E (extreme), the condition is refractory to treatment, with malignant ventricular arrhythmia, hemodynamic collapse, pulseless electrical activity, cardiac arrest, and the need for cardiopulmonary resuscitation.

Since the publication of this classification until now, numerous prospective and retrospective registries have been published, with between 166 and 10,004 patients, confirming the association of increasing severity of shock with higher mortality. The prevalence of each of the stages of the SCAI SHOCK classification varied between the studies, a fact attributable to the inclusion criteria in each case, different baseline profiles, the criteria used to define belonging to one or another stage, and the various diagnostic tools considered. Some of the studies did not include patients in stage A, which logically increased the proportion of patients in the remaining 4 stages. Stage B has often been defined solely on the basis of clinical criteria; in stage C, most studies used a lactic acid value ≥ 2 mmol/L as diagnostic criteria; there were discrepancies about whether a patient with vasopressors should be included in stage B or C; stage D was defined by elevation of lactic acid and/or the need to increase the doses of vasoactive drugs or mechanical support; and the reasons for including a patient in stage E were variable (lactic acid ≥ 5-10 mmol/L, pH ≤ 7.2, need for multiple vasopressors or devices, or cardiopulmonary resuscitation). Each publication used a single set of variables, and therefore did not consider in its population the ability to reclassify patients and vary the diagnostic power by using alternative definitions for each stage. This meant that the mortality associated with the different categories varied according to the baseline profile and the specific definition of each stage. We must remenber that criteria for deciding hemodynamic support with devices, which one (and their availability!) vary between centers, so the same stage may present different mortality depending on the instituted treatment. On the other hand, it became evident that, within each stage, and depending on clinical findings, different degree of biomarkers elevation and new hemodynamic criteria that relate basic parameters (for example, the shock index, HR/SBP ratio), subgroups with different risk can be defined. Thus, a high-risk patient in one stage may have higher mortality than a low-risk patient in a higher stage. And finally, it should be remembered that the presence of resuscitated cardiopulmonary arrest obscures the prognosis at any stage.

All this leads to a constant reassessment of the criteria used, to achieve more granularity in the prognostic capacity of the classification, in order to detect the greatest risk of events early and to be able to institute the necessary therapy in time (or decide the transfer to a higher complexity center). This year, a consensus document of the world's leading cardiology and transplant societies was published, which seeks to refine the 2019 classification. There are no significant changes in stage A. In stage B, the concept of hemodynamic instability is highlighted, and admits a slight deterioration of renal function, beyond the elevation of natriuretic peptides. In stage C, the presence of hypoperfusion is emphasized, and it is accepted that hypotension may not be present. It is an essential criterion that some pharmacological or mechanical intervention be required, beyond the volume contribution. Lactic acid should be ≥ 2 mmol/L, and manifestations of worsening renal function (increase in creatinine to 1.5 mg/dL, or an increase > 0.3 mg/dL) and liver function may be considered. Hemodynamic measurement is strongly recommended, with CI < 2.2 L/min/m 2 and wedge pressure > 15 mm Hg as central criteria. In stage D, clinical, laboratory, and hemodynamic parameters worsen; there is an increased dose or number of drugs needed, and mechanical circulatory support. In stage E, circulatory collapse is present despite maximum treatment, the patient is typically unconscious, lactic acid is > 8 mmol/L and pH is < 7.2.

But the prognosis of patients with cardiogenic shock also recognizes other determinants. Hence, the consensus we are commenting on, proposes a 3-axis predictive model. One of them is the severity of the shock, expressed in the parameters that we have discussed so far: the stage of the SCAI SHOCK classification, the hemodynamic and laboratory parameters, the toxic effects of the drugs. Another, effect modifier factors: age, comorbidities, frailty, inflammation, reversible or non-reversible organ failure, cardiac arrest, coma. And the third, the etiology (AMI, heart failure) and the phenotype of the shock: left, right or biventricular dysfunction; de novo acute heart failure or chronic failure; congestion profile and biomarkers.

And now, a recent publication allows us to explore more deeply the clinical and prognostic profile of each of the the classification stages. The CSWG (Cardiogenic Shock Working Group) is an academic consortium of 17 community and university hospitals that has been developing a cardiogenic shock registry since 2016, with data related to patients clinical and paraclinical characteristics, and evolution. Between 2016 and 2020, 3455 patients were included. In 1565 baseline parameters were available; in the remaining 1890 data on the changes of these parameters during evolution were added. The SCAI SHOCK stage on admission, and when possible, the maximum stage reached on admission were retrospectively defined. The cut-off value for each of the clinical, laboratory, and hemodynamic parameters was defined based on the literature and researchers consensus. Unlike the original classification, belonging to stage B was defined by the presence of hypotension (SBP 60-90 mm Hg or MAP 50-65 mm Hg),

or hypoperfusion (lactate between 2 and 5 mmol/L or alanine aminotransferase between 200 and 500 U/L), without the need for drug or mechanical support. Let us remember that, for the official classification, stage B was defined by hypotension, without hypoperfusion. Stage C was defined by hypotension and hypoperfusion, using the same criteria as stage B; or patients with shock treated with a drug or circulatory support device. Stage D was defined by hypotension (with the same BP cut-off values as in the previous stages) and hypoperfusion (lactate 5-10 mmol/L or alanine aminotransferase > 500 U/L), or the need for 2-5 drugs or devices. Those treated with 1 drug or device, with persistent hypotension or hypoperfusion, were also included in stage D. Stage E was defined by hypotension (SBP < 60 mm Hg or MAP < 50 mm Hg) or hypoperfusion (lactate > 10 mmol/L or pH ≤ 7.2) or the need for more than 3 drugs or 3 devices. Patients admitted to the hospital after cardiac arrest were also considered stage E.

Mean age of the patients was 61.6 ± 14.6 years; 70.5% were men; 54% hypertensive, 36% diabetic, 26% had atrial fibrillation (AF) and 16% renal failure. Mean SBP at admission was 107 mm Hg; mean HR 91 beats/min; mean left ventricular ejection fraction, LVEF, evaluated in almost 2500 patients, was 22%. The aetiology of shock was AMI in 32% of cases, congestive heart failure (CHF) in 52%, and other causes (postcardiotomy, myocarditis, etc.) in the rest. Patients with AMI, compared to those with CHF, were older, with higher prevalence of hypertension and diabetes, higher LVEF (27% vs 20%) and higher values of MAP and lactate; but HR, and prevalence of AF and renal failure was lower.

Hospital mortality was 35%, significantly higher in patients with AMI (42%) than in those with CHF (25%). Non-survivors were older (mean 65 vs 60 years), had a higher prevalence of comorbidities, higher transaminase and lactate values, lower pH and bicarbonate values, and worse renal function; filling pressures were in them lower. There was no difference between survivors and non-survivors in cardiac index or LVEF. In 3167 patients, data was available for on the number of vasoactive drugs and support devices used, from 0 to 4 or more. This then allowed to analyze the relationship between intensity of treatment and mortality, considering 5 levels of increasing intensity. Mortality ranged from 7.4% at level 1 to 67.3% at level 5. Each increase in intensity was associated with an overall OR of 2.30 for higher mortality (OR 2.43 in patients with CHF and 2.04 in patients with AMI). In a stratified analysis according to the number of drugs used, the need for a greater number of devices translated into a worse prognosis; the results were repeated when stratifying the patients according to the number of devices, and considering the number of drugs.

In 1890 patients, data was available on the SCAI stage at admission and the maximum reached during hospitalization, defined on the aforementioned criteria. The higher the basal stage and the maximum stage reached, the higher mortality; 90% of patients in stage B, 68% in stage C and 18% in stage D passed to a more advanced stage during hospitalization. The time needed to worsen the condition was an average of 52 hours for stage B, 103 for stage C and 178 for stage D. It should be mentioned that mortality for those who reached stage E ranged between 71% and 81% for patients in stage B to D, and was lower, 53% for those who initially presented this stage. Mortality was higher for patients with AMI than for those with CHF when the baseline stage was D or E, and when the maximum reached stage was C, D, or E.

Gone are the days when cardiogenic shock was defined dichotomously by a constellation of clinical signs and a precise hemodynamic pattern: the patient was or was not in shock. The evidence of previous stages with a not so clear presentation, the progress in the understanding of a pathophysiology that is increasingly complex, and more and more patient records allow us to classify with greater granularity pictures of increasing severity. As in the case of chronic heart failure with its stages A (patient at risk) to D (advanced heart failure), the SCAI SHOCK classification represents an attempt to put order in the assessment of cardiogenic shock, from its latent manifestation to desperate condition. Better characterization of patients will allow a more precise definition of prognosis and a more rational choice of therapy. Since a series of continuous variables are considered in the definition of severity (blood pressure, lactate, pH, natriuretic peptides, liver enzymes, hemodynamic parameters, among others), it is logical that different cut-off values for each of them influence the prevalence of each clinical category, of each stage. And we have to sum the appearance of new measurements or determinations, previously not taken into account, that can improve the prognostic yield. More frequently each time, therapeutic progress downplays some variable and instead unmasks the importance of another. For this reason, it is difficult to assume that we will achieve a definitive and immutable classification, and, on the contrary, it is to be expected that this task of refining the categorization of patients will be increasingly intense and disruptive. In this sense, it is worth highlighting the change in the definition of stage B, now defined by the presence of hypotension or hypoperfusion, when previously it was only defined in the presence of hypotension; a pre-shock picture with normotensive hypoperfusion may occur, and it has prognostic value. The idea of prioritizing the manifestations of hypoperfusion even when blood pressure is not compromised expands the number of patients at risk, and forces us to be more exhaustive in our examination. The demonstration of a worse prognosis in the cardiogenic shock due to AMI than in that of CHF, even when the LVEF was 7 points higher and the hemodynamic parameters similar, speaks of the importance of the speed of installation of myocardial damage, and of compensatory mechanisms surely longest established in patients with CHF. The fact that E stage mortality is greater when it is the destination stage than when it is the initial form of presentation, refers to more severe patients, who despite the instituted treatment

have increased hemodynamic compromise.

Of course, we can point out possibilities for improvement in this classification attempt. Considering the number of drugs and devices is an initial way to define the intensity of treatment. Taking into account the doses and duration of each intervention could be more adjusted to reality. Similarly, it is desirable that baseline renal function and its worsening be an integral part of future classification adjustments. The registry has brought to the fore the dynamic nature of cardiogenic shock, and illustrates the worse prognosis that progressing through the stages of severity entails. Like any classification, it generates a simplification of reality. The forecast linked to each stage is the summary measure of what has happened with each patient included in it. At each step we can, based on the aetiology, comorbidities, and various variables, some already considered, others not taken into account, be finer and more precise in estimating individual risk.

Should we add acetazolamide to loop diuretics in the treatment of congestion in acute heart failure? ADVOR study

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Relief of manifestations of congestion is a primary goal of treatment in hospitalization for heart failure. In the DOSE study, only 15% of the patients were free of congestion 72 hours after admission. In the ADHERE registry, with more than 100 000 hospitalizations for heart failure, 20% of patients were discharged with weight gain compared to admission. We know that insufficient diuretic treatment and congestion still present at patient discharge is a strong predictor of short-term readmission. Different diuretics can be added to loop diuretics to optimize their effects. The ADVOR study, a randomized study of acetazolamide vs. placebo in patients hospitalized for acute decompensated heart failure, has just been presented at the European Congress of Cardiology. As we know, acetazolamide is a carbonic anhydrase inhibitor. These drugs potently inhibit carbonic anhydrase, resulting in decreased reabsorption of sodium bicarbonate in the proximal convoluted tubule. The use of these agents in patients with heart failure is temporary, and they are usually indicated to correct metabolic alkalosis that presents as a "shrink" phenomenon in response to the administration of other diuretics. When used repeatedly, they can cause metabolic acidosis as well as severe hypokalemia.

ADVOR patients had to have some manifestation of congestion (edema, pleural effusion, or ascites) and elevation of natriuretic peptides (NT-proBNP > 1000 pg./mL or BNP > 250 pg./mL). In addition, they had to have been receiving at least 40 mg/day of furosemide or equivalent for at least 1 month before admission The presence of pleural effusion was confirmed by radiography or pleural ultrasound, that of ascites with abdominal ultrasound. Patients with glomerular filtration rate < 20 mL/min/1.73m 2 were excluded, as those who were treated with another diuretic that acts on the proximal convoluted tube, including SGLT2 inhibitors, and those treated with more than 80 mg of intravenous furosemide before randomization. Patients were randomly assigned to receive a 500-mg intravenous bolus of acetazolamide or placebo on the day of randomization and for the next 2 days or until complete decongestion. Loop diuretics were administered intravenously, doubling the dose that the patient had been receiving orally, in a single bolus on the day of randomization and in two doses separated by at least 6 hours on the following 2 days. Congestion was quantified with a score of 0 to 10, with peripheral edema contributing 0 to 4 points, and pleural effusion and ascites 0 to 3 points each. The score was calculated on the morning of each day during hospitalization, and at outpatient follow-up up to 3 months. If on the second morning of the study, after the first 30-48 hours of randomization, the cumulative urinary volume was <3.5 L, treatment with loop diuretics could be escalated. The primary end point was congestion status quantified by score on day 3, with the goal of achieving complete decongestion (defined as the absence of all signs of systemic congestion except trace edema, score no greater than 1) without the need for dose escalation of loop diuretics. Secondary endpoints were a composite of death from any cause or rehospitalization for heart failure at 3 months, and length of stay. It was considered that in the placebo arm 15% of the patients would achieve complete decongestion, and it was suggested that in the acetazolamide arm this would occur in 25% of the cases. With a power of 80%, a 2-tailed p value < 0.05, and an expected rate of loss to follow-up of 5% of patients, this represented a needed number of 519 enrolled patients. The analysis was done by intention to treat among all those who had received at least one dose of acetazolamide or placebo.

Between November 2018 and January 2022, 2915 patients were screened in 27 centers, and 519 were included in the study, 259 in the acetazolamide arm. The mean age was 78 years, just over 66% were men, the median congestion score was 4 (IQR 3-6). 92.1% had edema, 52.6% pleural effusion, 8.9% ascites. The median outpatient dose of furosemide in the previous month was 60 mg (IQR 40-100). The mean left ventricular ejection fraction (LVEF) was 43%, and the median NT-proBNP was 6,173 pg/mL (IQR 3,068-10,896). The median glomerular filtration rate at the time of random assignment was 39 mL/min/1.73 m2 (29-52). Forty-seven percent of the patients had diabetes, 72% had a history of atrial fibrillation. At the time of hospitalization, 52% were treated with inhibitors or antagonists of the renin angiotensin system or sacubitril valsartan, 81% with beta-blockers and almost 42% with antialdosterone drugs.

The primary endpoint was achieved by 30.5% in the placebo arm and 42.2% in the acetazolamide arm (RR 1.46; 95% CI 1.17-1.82; p<0.001). When considering in

each group the patients in whom the dose of diuretics was escalated (7 in each), the estimate of the effect of acetazolamide did not change. On the morning of day 2, the mean urine volume and natriuresis were 4.6 L and 468 mmol in the active arm, compared to 4.1 L and 369 mmol in the placebo arm. The proportion of patients alive at discharge in whom complete decongestion was achieved was 62.5% with placebo and 78.8% with acetazolamide, with RR 1.27; CI 95% 1.13-1.43. The median length of stay was just over 1 day shorter with acetazolamide (8.8 vs 9.9 days), a statistically significant 11% reduction. There was no difference in the incidence of death from any cause or hospitalization for heart failure (29.7% vs 27.8%, p NS); neither in the renal safety endpoint (doubling of creatinine, drop in filtrate of at least 50% or need for dialysis; 2.7% with acetazolamide, 0.8% with placebo, p=0.10) nor in the incidence of hypokalemia (5.5% vs 3.9%). No cases of severe metabolic acidosis were recorded. There were no differences in subgroup analysis when considering age, sex, LVEF, or baseline glomerular filtration rate; on the other hand, a different effect was seen when considering the previous dose of oral furosemide or equivalent, with a RR of complete decongestion of 1.78 (95% CI 1.33-2.36) in those treated with up to 60 mg per day, and 1.08 (95% CI 0.76-2.55) in those treated with higher doses.

Different scores and prediction rules have been developed to quantify the degree of congestion at discharge from hospitalization for heart failure, and the risk of events in the short term and up to one year. The presence of peripheral edema, orthopnea, and jugular distention are among the most common manifestations in these scores. Dyspnea, fatigue, rales, appear less frequently. Let's look at some examples. In the EVEREST study, which tested inpatient-initiated tolvaptan vs. placebo, a score based on the first three of the aforementioned signs (each graded between 0 and 3) decreased from a median of 4 at the start of the study to 1 at discharge. At discharge, nearly three-quarters of participants had a score of 0 or 1, and less than 10% of patients had a score of 3. Each point increase in score implied a 30-day risk increase of 34 % for all-cause mortality and 13% for a composite of heart failure hospitalization and mortality. At total follow-up (median nearly 10 months), each point increase implied a 16% increased risk for all-cause death and 11% for death and hospitalization combined. In a combined analysis of the DOSE-AHF studies (which compared 2 strategies of magnitude of diuretic treatment and route of administration) and CARRESS-HF (which evaluated ultrafiltration vs. diuretics in patients with cardiorenal syndrome and hospitalization for heart failure), a very simple score was generated, which took into account orthopnea (≥2 pillows=2 points, <2 pillows=0 points) and peripheral edema (trace = 0 points, moderate = 1 point, severe = 2 points) at baseline, at discharge, and at 60 days. The combination of orthopnea and peripheral edema, 'orthoedema', was defined as absent (0 points), low-grade (score 1 or 2), and high-grade (3 or 4 points). At discharge, 52% of patients had no congestion, 32% low, and 16% high grade. But at 60 days, of all the patients without congestion at discharge, only 35% persisted in that condition; 27% had low-grade congestion, and 38% high-grade. This illustrates how transitory the achieved success can be, and the marked influence of congestion on the evolution of patients.

The ADVOR study shows that, in patients hospitalized for heart failure and with signs of congestion, on a background of treatment with intravenous loop diuretics, the addition of a second diuretic, acetazolamide, with another site and mechanism of action, compared with a placebo generates a greater diuretic and natriuretic response, a more effective and rapid decongestion, and, therefore, a somewhat shorter hospital stay. These effects do not translate into a higher incidence of adverse effects at the renal level and the much-feared metabolic acidosis is conspicuous by its absence. With these results we could feel tempted to recommend the systematic use of this drug in the aforementioned condition; but some objections can be formulated.

In principle, we witness the comparison of a diuretic with a placebo. Were very different efficacy results expected from those presented? ¿Were not presumable more diuresis and natriuresis, and greater decongestion with a diuretic than with its placebo? Are ADVOR's results truly surprising?

¿Is the management of loop diuretics proposed by the protocol the treatment that we establish on a regular basis? Faced with a patient who had been receiving furosemide at a dose of 40 mg, and whom we decided to hospitalize due to clear signs of congestion, would we limit ourselves to using 80 mg intravenously as initial treatment? Would we wait 30 to 48 hours to increase the dose? In fact, the 2019 position paper of the Heart Failure Association of the European Society of Cardiology proposes in a hospitalized patient with congestive heart failure, start intravenous diuretic treatment with loop diuretics and evaluate the response after 6 hours; a diuretic rhythm of less than 100 mL/hour is a reason to double the dose; and continue with this strategy the next day. If there is something that makes the diuretic regimen stand out, it is its flexibility. The ADVOR criteria serve to homogenize therapy, but they seem too rigid to be understood as standard practice. We believe that the instituted protocol deprived furosemide of the possibility of obtaining an earlier and maximum response.

And, referring specifically to the tested agent, we know that it is useful for short-term treatment. But is this the only possible strategy in patients like those studied? Is this drug better than a short course of thiazides, or, even more contentious, than the addition of gliflozins? Compared to acetazolamide, which, beyond its diuretic efficacy, did not manage to modify the vital prognosis in this study, it is difficult not to remember the EMPULSE study, in which empagliflozin, which, like all SGLT2 inhibitors, also acts in the proximal convoluted tubule, achieves, in a similar situation, improvement in the clinical evolution of patients. It should also be remembered that gliflozins have become constituent

drugs for the treatment of chronic heart failure. For all of the above, it is difficult to accept that this study will modify the usual practice of treating acute heart failure, a treatment that, if modified, we believe will lead the canyons in another direction.

Does coronary angioplasty improve prognosis in ischemic heart disease with low ejection fraction? REVIVED-BCIS2 study

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In patients with heart failure and reduced left ventricular ejection fraction (LVEF), the most common etiology in the West is coronary artery disease. In the STICH study, in patients with LVEF ≤ 35% and coronary anatomy suitable for revascularization, CABG did not offer, relative to optimal medical treatment, better results in a primary endpoint of all-cause death at mean follow-up 56 months. An extension of the follow-up beyond 10 years did demonstrate the advantage of surgical revascularization over medical treatment. A STICH substudy questioned the value of the presence of myocardial viability as a condition that would give surgery an advantage when defining prognosis. With a concept similar to that of STICH, we now know the results of the REVIVED-BCIS2 study, which tested revascularization by percutaneous coronary intervention (PCI) vs. medical treatment in patients with HFrEF and demonstrated myocardial viability.

REVIVED-BCIS2 was a British, prospective, multicenter, randomized, open-label study. It included patients with HF and LVEF ≤ 35%, and extensive coronary disease, defined by a value ≥ 6 of a jeopardy score (BCIS) on a scale of 0 to 12, in which higher values express greater extension of coronary disease. Patients had to have demonstrated myocardial viability in at least 4 dysfunctional myocardial segments, in which it was possible to proceed to revascularization with coronary angioplasty. Patients with acute myocardial infarction, AMI, in the last 30 days, sustained ventricular arrhythmia in the last 3, or decompensated HF were excluded. All patients had to receive optimal medical treatment and were randomly assigned to receive or not PCI. In the intervention arm, revascularization should be attempted in all arteries with proximal lesions that perfused viable territories. The degree of revascularization achieved was defined based on a revascularization index: [(pre-intervention risk score – post-intervention score) / pre-intervention score] * 100, so that this index expresses the proportion of territories at risk effectively revascularized. The primary end point was a composite of death from any cause or hospitalization for heart failure at 24 months. Secondary end points were LVEF at 6 and 12 months, and changes in the NYHA classification of CF and in different quality of life scores, KCCQ and EQ-5D-5L. For the calculation of the sample size, it was estimated that 300 events in 700 patients would ensure a power of 85% and a value of $p<0.05$ to confirm a HR of 0.70 for the primary endpoint of invasive treatment compared to conventional treatment, taking into account an estimated 5% loss of patients to follow-up. For the LVEF endpoint, those 700 patients would ensure 90% power to detect a 4% absolute difference with the intervention. The analysis was done by intention to treat.

Between 2013 and 2020, 700 patients were included in 40 centers in Great Britain, 347 in the invasive arm. Their average age was 69 years, 88% were men. Just over half had a previous AMI, and just over 20% had a history of coronary angioplasty. Two thirds of the patients were free of angina, 31% had CF II angina. The mean LVEF was 27%; median threat score 10 (IQR 8-12). 14% of the patients had a left main coronary artery injury, 40% had a 3-vessel injury, and the rest had a 2-vessel injury. The median of NT-proBNP was around 1400 pg./mL.

In the invasive arm, 96.3% of the patients underwent PCI at a median of 35 days from randomization. The BCIS score changed from a mean of 9.3 before the intervention to a mean of 2.7 after it, which implies a revascularization rate of 71% of the involved territories. In a median follow-up of 41 months, the primary endpoint occurred in 37.2% in the PCI arm and 38% in its counterpart (HR 0.99; 95% CI 0.78-1.27; p=0. 96). There was no difference in mortality (31.7% vs 32.6%) or hospitalization for heart failure (14.7% vs 15.3%). LVEF increased on average in absolute terms by 1.8% at 6 months and 2% at 12 months in the invasive arm; and 3.4% and 1.1%, respectively, in the exclusive medical treatment arm, with no significant difference between the two strategies. The KCCQ score initially improved more in the PCI arm (differences of 6.5 points at 6 months and 4.5 at 12 months between both arms, with $p < 0.05$), at 24 months the difference had narrowed to 2, 6 points and statistical significance was lost. The incidence of AMI was similar in both groups (10.7% vs 10.8%); the need for unplanned revascularization was logically lower in the invasive branch: 2.9% vs 10.5%, HR 0.27; 95% CI 0.13-0.53. There was no difference in subgroup analysis taking into account age, LVEF, FC, BCIS score, left main artery disease, or NT-proBNP values.

Being ischemic aetiology the predominant one in the context of HFrEF, and the practice of coronary angioplasty becoming more frequent in this context, it is striking that we have only recently learned of a randomized study on the practice in this context. The design, the concept, the circumstances, remind us of the STICH trial. In both cases in a population of patients with low LVEF (mean 28% in STICH, 27% in REVIVED), with very good medical treatment (86% beta-blockers and 88% renin angiotensin system inhibitors/antagonists in STICH;91 % beta-blockers and 89% drugs that act on the renin angiotensin system and sacubitril valsartan in REVIVED), an invasive treatment (surgery in STICH,

angioplasty in REVIVED) and its long-term effects were tested. In both studies, the inclusion rate was very low (in STICH, an average of 2.5 patients per year per center; in REVIVED 2.6). And in both studies the expected result was not obtained. If in a mean follow-up of 56 months there was no evidence of an advantage for surgery over medical treatment in STICH, what could make us expect something better in REVIVED-BCIS2, with a procedure that does not ensure a more complete revascularization, a shorter follow-up and a more complete medical treatment? In all the observational studies we know in HFrEF field, with their inherent biases, (because there is no randomized study), angioplasty has shown in the best of cases not to differ in its effect from surgery, and in some cases, as in the SCAAR registry that we recently discussed, PCI was outperformed by surgical revascularization. In conclusion, it seemed a priori too optimistic to suppose an advantage for angioplasty in a relatively short follow-up for the explored end points, in patients with optimized medical treatment, a quarter of them also with a cardioverter defibrillator or cardiac resynchronization therapy. At STICH, it took 10 years for the benefit of invasive treatment to become apparent. Will the same thing happen with an extended follow up on REVIVED? And, to conclude, keep in mind that the low inclusion rate surely reflects a common practice in which patients in whom benefit is expected are not admitted to the study; as corresponds to a clinical trial, only patients in whom the treating physician is a priori uncertain about which is the best option, and assumes equivalence between the expected results with one or another behavior should be included. How many are these patients out of the total that we follow with HFrEF, extensive coronary disease and studies with demonstrated viability? At the same time, ¿what role should viability studies play today in our usual practice? Questions that only registries and solid clinical trials with an extended follow-up time will be able to answer.

The beneficial effect of gliflozins in heart failure with left ventricular ejection fraction greater than 40% is confirmed. DELIVER study and meta-analysis with EMPEROR Preserved

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Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomized controlled trials. **Lancet 2022;400:757-67. https://doi.org/10.1016/S0140-6736(22)01429-5**

In mid-2021 we knew the results of the EMPEROR Preserved study. In patients with heart failure (HF) and mildly reduced left ventricular ejection fraction (LVEF) (HFrEF, LVEF 41-49%) or preserved LVEF (HFpEF, LVEF ≥ 50%), empagliflozin, a sodium glucose cotransport inhibitor 2 (SGLT2) demonstrated a significant reduction in a composite end point of cardiovascular death or hospitalization for heart failure, reduced total hospitalizations for heart failure, and attenuated the fall in glomerular filtration rate. For the first time, in a study in the context of HF with LVEF > 40%, the proposed trial end points were reached. This result was transferred to the clinical practice guidelines, and the 2022 AHA/ACC/HSFA guideline included SGLT2i in a prominent place in the treatment of HFpEF and HFpEF, with a 2a B indication (due to evidence from a single randomized study). Cardiovascular death and all-cause death were not reduced. We now know the results of the DELIVER study, with dapagliflozin vs. placebo in similar patients.

DELIVER was a randomized, multicenter, double-blind, placebo-controlled study. It included patients with HF, in FC II-IV, at least 40 years old, with LVEF > 40% and evidence of structural heart disease (left ventricular hypertrophy or left atrial dilatation) in an imaging study in the last 12 months. They had to have an NT-proBNP value ≥ 300 pg./mL if they were in sinus rhythm, or ≥ 600 pg./mL if they had atrial fibrillation or flutter; and a glomerular filtration rate > 25 mL/min/1.73 m 2. There were 2 differences in the inclusion criteria compared to EMPEROR Preserved: inclusion was admitted of patients who previously presented LVEF ≤ 40%, if at the time of admission, it was > 40%; and the inclusion of patients hospitalized for HF was allowed, as long as they no longer required intravenous medication. Patients were randomly assigned to receive dapagliflozin 10 mg daily or placebo. The primary end point was a composite of cardiovascular death or worsening of HF (hospitalization or emergency visit to the ward). Secondary endpoints were total episodes of worsening HF and cardiovascular death, changes in quality of life, cardiovascular death, and all-cause death. Initially, it was considered that 844 events of the primary endpoint in 4700 patients would be enough to demonstrate a significant reduction of cardiovascular death or worsening heart failure. It was decided at the end of 2020 to evaluate all patients and specifically those with LVEF < 60% in parallel; this led to requiring 1117 events in 6100 patients, to have 93% power to detect a 20% reduction in the primary endpoint in the entire population, with a p value of 0.024.

Between August 2018 and December 2020, 10 418 patients were evaluated in 353 centers in 20 countries, including Argentina, and 6,263 were included in the study. The mean age was 71.7 years, 44% were women. 89% had a history of arterial hypertension and 45% of diabetes; 50% of the patients had coronary disease. Seventy-five percent of the patients were in FC II, and more than 24% in FC III. Median baseline NT-proBNP was 1011 pg./mL; the mean glomerular filtration rate was 61 mL/min/1.73m 2 . Mean LVEF was 54%; 34% of patients had LVEF 41-49%, 36% LVEF 50-59%, and the remaining 30% LVEF ≥ 60%. Sixty-seven percent

of patients received inhibitors/antagonists of the renin angiotensin system, and 4% sacubitril valsartan; 76% were treated with beta-blockers and almost 39% with aldosterone antagonists.

In a median follow-up of 2.3 years (IQR 1.7-2.8), just over 14% of both arms abandoned the prescribed drug or placebo. The primary end point occurred in 16.4% of patients in the dapagliflozin arm (7.8% per year) and 18.5% in the placebo arm (9.6% per year) with HR 0.82; CI 95% 0.73-0.92; p < 0.001. There was a significant reduction in worsening HF (5.6% vs. 7.2% per year; HR 0.79, 95% CI 0.69-0.91), but not in cardiovascular death (annual incidence of 3.3 % vs 3.8%; HR 0.88, 95% CI 0.74-1.05) or death from all causes (7.2% vs 7.6% per year; HR 0.94, 95% CI % 0.83-1.07). In the subgroup analysis, there was no difference in the effect of the drug according to age, gender, glomerular filtration rate, diabetes, systolic blood pressure, presence of atrial fibrillation, or NT-proBNP values. The effect of the intervention did not differ either in the patients included in hospitalization or within 30 days of discharge (10.4% of the total) or among those with previous LVEF ≤ 40% (18.4% of those included). The effect was also similar across the LVEF range, with no difference between patients with LVEF 41-49%, 50-59%, or ≥60%. There was an improvement in quality of life with the medication. The incidence of adverse events leading to drug or placebo discontinuation was similar (5.8% in both arms): there were no differences in the incidence of major hypoglycemia (0.2%), significant hypovolemia (1.1%), or serious renal events (2.4%).

Considering data from this study and those from EMPEROR Preserved, a meta-analysis was performed, to define the summary effect on the endpoints of interest in the context of HF with EF > 40%. It was presented in the same session as DELIVER. Considering the 12 251 patients of both studies, a HR of 0.80 (95% CI 0.73-0.87) was obtained as a summary measure of effect on the combined end point of cardiovascular death or hospitalization for HF; and a HR of 0.74 (95% CI 0.67-0.83) as a measure of effect on hospitalization for HF. But what was truly striking was the effect on death of cardiovascular origin: HR 0.88 (95% CI 0.77-1, p=0.052). There was no significant reduction in death from all causes: HR 0.97 (95% CI 0.88-1.06)

The DELIVER study population was, in most of the variables considered, very similar or identical to that of EMPEROR Preserved: patients did not differ in age, proportion of women, LVEF, renal function, use of neurohormonal antagonists. It is worth noting as a distinctive feature the presence of patients hospitalized or recently released from hospitalization for HF, as well as that of patients who had improved their LVEF, going from <40% to >40%. These subgroups contribute to expanding the indication in patients with LVEF >40%. With such similar populations in the two studies, it was also expected that the results would be similar, and in fact there is no heterogeneity in the effect on the endpoints of interest in the meta-analysis.

In this regard, we would like to make a reflection. For many years, the publication of a major study was in itself an event of such magnitude that, for days, weeks and months, the interested parties devoted themselves to its analysis. There were previous studies or there would be later studies with the tested agent, or others from the same or another family on the point of interest, sometimes with non-homogeneous results, or of variable magnitude, even contradictory; and finally we knew of a meta-analysis that came to generate summary information and to shed (or not) a little more light on the matter. Over the years the time distance between the individual studies and their meta-analysis became shorter and shorter; in 2019 we knew DAPA-HF, in 2020 EMPEROR Reduced, and the day after this trial presentation, we already read the published meta-analysis of both. Now, in the same session in which DELIVER was presented, we knew its meta-analysis with EMPEROR Preserved, and as its distinctive finding, the reduction in cardiovascular death, at the limit of statistical significance, without a doubt a true novelty in the field of HF with EF > 40%. It is difficult, then, not to read the results of DELIVER already impregnated by the meta-analysis that contains it.

Until now, we used to recognize the effect of various neurohormonal antagonists on hospitalization for HF, more evident in the lowest range of preserved EF. For the first time, a therapeutic agent appears that fully impacts cardiovascular mortality. The mechanisms possibly involved are many; the reduction of general and systemic inflammatory phenomena, the reduction of epicardial fat, the attenuation of myocardial fibrosis, favorable effects on endothelial function, metabolic phenomena, with greater production and consumption of ketone bodies, the promotion of autophagy with the recycling of damaged organelles and removal of waste products are all plausible reasons. We personally understand that the nephroprotective action (already evidenced in studies with gliflozins in HF with EF ≤40%, and also in EMPEROR Preserved, still pending publication among the DELIVER analyses) must play a significant role.

The EMPEROR Preserved study had suggested (when considering the effect on the total hospitalizations for HF) the possibility that the treatment beneficial effect was lost in patients with LVEF > 60%. This, added to the evidence from studies with neurohormonal antagonists and sacubitril valsartan, led to numerous speculations about the nature of HF with such a high LVEF that justified a different response: amyloidosis or another infiltrative pathology? ¿different mechanisms? In DELIVER, this heterogeneity did not manifest itself: the favorable effect of the drug on different endpoints did not differ above or below 60%. So, ¿is HF with higher LVEF values really another entity? Surely the point is not fully settled.

Nonetheless, however, the reduction in mortality from all causes is still far away, an expression of the importance of non-cardiovascular phenomena in determining death in this population