

JORGE THIERER ^{MTSAC}

Cardiovascular risk and events in different-income countries: the PURE study

Yusuf S, Rangarajan S, Teo K, Islam S, Li W, Liu L, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med* 2014; **371**: 818-27. <http://doi.org/xcq>.

Between 1930 and 1950, cardiovascular disease (CV) rate increased in high-income countries, remaining low in those with middle and low incomes. Since the mid-seventies, CV mortality has been decreasing in high-income countries (HIC), possibly due to the decrease in the prevalence of coronary risk factors and in medical care improvement. Correspondingly, an increase in the incidence of CV disease in the middle-income (MIC) and low-income (LIC) countries has been observed and today it is estimated that 80% of CV disease burden lies in these countries. What are the causes and underlying mechanisms? What is the associated incidence and mortality of CV disease? To answer this question the PURE prospective cohort study was designed, including 628 adult urban and rural communities in 17 countries: 4 LIC (Bangladesh, India, Pakistan and Zimbabwe), 10 MIC (Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, Poland, South Africa and Turkey) and 3 HIC (Canada, Sweden and United Arab Emirates).

In each community dwellings with at least one adult between 35 and 70 years, who planned to stay in the same house for at least 4 years more, were selected. Using standardized questionnaires, national, community, housing and individual data, were collected; the latter with the same questionnaire used in the INTERSTROKE and INTERHEART studies. For each participant the INTERHEART risk score (IS) was estimated in a version that included data on age, gender, smoking, diabetes, hypertension, family history, waist-hip ratio, psychosocial factors, diet and physical activity, but that excluded cholesterol. The score ranges from 0 to 48 points and a higher score implies greater risk factor burden.

The study comprised 156,424 adults, most of which were included between 2005 and 2009. Average IS was higher when the country's income was greater: 12.49 in HIC, 10.47 in MIC and 8.48 in LIC ($p < 0.001$). In HIC, IS was higher in rural areas, while in MIC and LIC, IS was higher in urban areas. In subjects with and without prevalent CV disease, use of aspirin, statins, beta-blockers and renin-angiotensin system blockers was greater when the country's income level was higher. A similar pattern was obtained for revascularization procedures. Mean follow-up was 4.1 years (completed in 97.5% in HIC, in 94.4% in MIC and only

85.9% in LIC). Cardiovascular mortality was 2.6%; among non-fatal events, the incidence of myocardial infarction was 1.1%, of stroke 0.8%, of heart failure 0.3% and of non-major CV events leading to hospitalization 0.8%. Despite the greater average IS, mortality was lower in HIC: 2.4 ‰/year compared to 5.59 ‰/year in MIC and 9.23 ‰/year in LIC ($p < 0.001$). The tendency did not change after adjusting for IS. The same method was repeated for major CV events, but was reversed for non-major CV events (higher rate of events in HIC). The percentage of participants who died after a CV event was greater when the country's income was lower. The rate of major CV events and associated mortality was higher in MIC and LIC rural areas than in urban areas.

The PURE registry highlights the complex relationship between risk factors, CV disease and its evolution: it is in low-income countries where, despite lower burden factors, the incidence of major cardiovascular events and associated mortality is greater. To partially explain these findings, it could be postulated that it is very probable that the dissimilar access to health care and different diagnosis and treatment modalities (incompletely studied in the registry) modulates the relationship between CV disease and severe events. That same inequity also helps us understand the difference between urban and rural areas only detectable in HIC. This is another reason to exercise extreme imagination and develop health policies according to each and every situation in order to reduce the gap.

SIGNIFY study: when more is not better

Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med* 2014;**371**:1091-9. <http://doi.org/xcr>

Elevated heart rate (HR) is an adverse prognostic factor in the general population and in the context of chronic heart failure and coronary artery disease. Ivabradine (I) is a drug which acting on the If current, reduces HR without causing hypotension or conduction disorders. The SHIFT study performed in patients with heart failure and left ventricle ejection fraction (LVEF) < 35% demonstrated that HR reduction with I was associated with decreased combined end point of death or hospitalization. Will I also be beneficial in stable, chronic coronary patients with LVEF > 40%? The SIGNIFY trial, a randomized, multicenter, double-blind, placebo (P)-controlled study tried to answer this question.

The study included patients of at least 55 years of age with the above-mentioned conditions, in sinus

rhythm, HR > 70 beats per minute (bpm), who had 1 major adverse prognostic factor (angina of class 2 or higher according to the Canadian Cardiovascular Society, evidence of ischemia or hospitalization for coronary event in the previous year) or 2 minor adverse prognostic factors (dyslipidemia, diabetes, current smoking, peripheral vascular disease or age \geq 70 years). After a 2-4 week P run-in period to confirm clinical stability, patients were randomly assigned to I or P. The initial dose was 7.5 mg every 12 hours (5 mg in patients \geq 75 years) which, according to HR and symptoms, was reduced to 5 mg every 12 hours, or increased to 10 mg every 12 hours. The target HR was 55-60 bpm. The primary end point was cardiovascular death or nonfatal myocardial infarction. Secondary end points were each separate primary end point component and death from any cause.

Finally, the study included 19,102 patients. Mean age was 65 years and mean LVEF 56.5%; 43% were diabetic, 73% had previous myocardial infarction and 63% angina of class 2 or higher. Patients were very adequately treated: 91% with aspirin, 92% with statins, 83% with beta-blockers, and a corresponding number were treated with renin-angiotensin system inhibitors and antagonists. Mean HR at study baseline was 77 bpm and at 3 months it was 60 bpm with I and 70 bpm with P.

At a median follow up of 27 months there was no difference in the primary end point: 6.8% with I and 6.4% with P (HR 1.08, 95% CI 0.96-1.20; $p = 0.20$). There was also no significant difference in any of the secondary end points. An unexpected result was the worst outcome with I in patients with angina of class 2 or higher: the primary end point occurred in 7.6% with I and 6.5% with P (HR 1.18; 95% CI 1.03-1.35; $p = 0.02$), with matching data for cardiovascular death (HR 1.16, 95% CI 0.97-1.40; $p = 0.11$) and nonfatal infarction (HR 1.18, 95% CI 0.97-1.42; $p = 0.09$). There was a higher incidence of adverse effects with I, mainly symptomatic and asymptomatic bradycardia (7.9% and 11%, respectively, compared to just over 1% for each with P), phosphenes (5.4% vs. 0.5% with P) and atrial fibrillation (5.3% vs. 3.8% with P).

The study results question, at least partially, the idea that elevated HR must always be a therapeutic target. Possibly, in stable patients with good ventricular function and very adequate medication, the effect of HR reduction is poor. As in other conditions and biological variables there may be, at least in coronary patients, a J-shaped curve and so a marked reduction in HR is detrimental (hypoperfusion, prothrombotic events?), mainly in symptomatic patients. Another question regarding the dose is why a higher dose than in previous studies was sought. Perhaps the I dose used was excessive (in fact, the incidence of bradycardia was higher than in previous studies using the same drug). New analyzes are necessary to decipher the enigma. Elevated HR does not seem to have a unique interpretation.

Altered carbohydrate metabolism: a cause of myocardial damage

Selvin E, Lazo M, Chen Y, Shen L, Rubin J, McEvoy JW, et al. Diabetes mellitus, prediabetes, and incidence of subclinical myocardial damage. *Circulation* 2014;130:1374-82. <http://doi.org/xcs>

Diabetes and prediabetes are independent predictors of coronary events, heart failure and mortality. There are different reasons for this phenomenon: higher prevalence of coronary risk factors, more extensive and severe coronary disease, and inadequate treatment of concomitant factors. However, it is postulated that hyperglycemia per se may exert harmful effects: endothelial dysfunction, inflammation and myocardial damage. A recent subanalysis of the ARIC study seems to confirm this hypothesis.

The ARIC study was a cohort study conducted at four sites in the United States. It explored the association of baseline clinical and laboratory data with long-term prognosis in 15,792 participants selected by sampling. The first visit took place between 1987 and 1989. There were three follow-up visits approximately every three years, and a fifth visit between 2011 and 2013. On the second visit (1990-1992) a highly sensitive troponin T (hs-cTnT) assay was performed. The present analysis selected 9,051 participants who on the second visit were free of clinical cardiovascular disease, with hs-cTnT < 14 ng/ml. The end point was the occurrence of hs-cTnT above the value at visit 4 (between 1996 and 1998) in participants who had not developed clinically patent cardiovascular disease; i.e., the incidence of subclinical myocardial damage. Diabetic patients were defined by medical diagnosis of the pathology, those treated with hypoglycemic agents or with HbA1C > 6.4%, and prediabetic patients were those with HbA1C between 5.7% and 6.4%. At baseline, 23.1% of participants had prediabetes and 7.8% diabetes. Prediabetes and diabetes were progressively associated with older age and prevalence of obesity, hypertension, ventricular hypertrophy and dyslipidemia compared to normal carbohydrate metabolism. Even within normal values, the presence of borderline hs-cTnT was higher in prediabetic and diabetic patients (values between 9 and 13 ng/ml in 9.6% and 15.3% of patients, respectively, compared with 6.2% in normal patients) During the 1996-1998 visit, 8,165 participants had not developed overt clinical cardiovascular disease since 1990-1992. The incidence of hs-cTnT \geq 14 ng/ml was 3.7% in those without prediabetes or diabetes, 6.4% in prediabetic patients (RR 1.40, 95% CI 1.08-1.80) and 10.8% in diabetic ones (RR 2.47, 95% CI 1.78-3.43). Adjustment for gender, age, risk factors and treatment did not alter the relationships. Patients with elevated hs-cTnT had worse long-term prognosis; in the multivariate analysis, high hs-cTnT was an independent predictor of coronary heart disease, heart failure and death. The combination of diabetes with elevated hs-cTnT was a strong predictor

of poor prognosis, with HR of 3.84 (95% CI 2.52-5.84) for coronary heart disease, 6.37 (95% CI 4.27-9.51) for heart failure and 4.36 (95% CI 3.14-6.07) for mortality compared to those without either condition.

The reasons why the incidence of myocardial damage is greater in those with abnormal carbohydrate metabolism are diverse: microcirculatory damage, direct effect on the heart muscle, systemic inflammatory condition, activation of protein kinase C and promotion of ventricular hypertrophy. This study points out myocardial damage irrespective of clinically evident cardiovascular disease as one of the reasons why diabetes and prediabetes are associated with worse outcome. Alternatively it may be thought that this myocardial damage is the first or one of the first manifestations of the disease which will then be characteristically expressed. It is clear that other mechanisms should be explored beyond the prevention of atherosclerotic disease to improve the prognosis of people with prediabetes and diabetes, and that measurement of hs-cTnT may help to define a higher risk population among them.

Poor usefulness of antialdosterone drugs in ST-segment elevation myocardial infarction without heart failure: the REMINDER study

Montalescot G, Pitt B, Lopez de Sa E, Hamm CW, Flather M, Verheugt F, et al. Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: the Randomized Double-Blind Reminder Study. **Eur Heart J** 2014;35:2295-302.<http://doi.org/xct>

Mineralocorticoid receptor antagonists have been shown to reduce mortality in the context of chronic heart failure (HF) with advanced FC II to FC IV (RALES and EMPHASIS studies) and in acute myocardial infarction (AMI) with low left ventricular ejection fraction (LVEF), accompanied by diabetes or HF symptoms (EPHESUS study). The multicenter, randomized, double-blind, placebo-controlled REMINDER study explored their role in ST-segment-elevation AMI in patients without history or current HF symptoms.

Patients with LVEF < 40%, hypertrophic cardiomyopathy, significant valvular stenosis, glomerular filtration rate < 30 mL/min/1.73 m² or plasma creatinine > 2.5 mg/dL were excluded from the study. Patients were assigned to receive eplerenone (E) or placebo (P), with the first dose within 24 hours, and if possible, within 12 hours of symptom onset. The initial dose was 25 mg, with the intention of increasing it to 50 mg since the second day. The primary end point was the composite of time to cardiovascular death, rehospitalization, prolonged in-hospital stay due to sustained ventricular tachycardia or ventricular fibrillation, LVEF ≤ 40% at 1 month or more from randomization or NT-proBNP after the first month greater than 450 pg/mL, 900 pg/mL or 1,800 pg/mL depending on whether patient age was < 50, 50 to 70 or > 70 years, respectively. The secondary end points

were each of the primary end point components, plus cardiac defibrillator or resynchronizer implantation, or repeat-AMI.

The initial sample calculation (612 patients) considered a rate of events of 42% at 6 months in the placebo group and 33% in the eplerenone group, 22% event reduction with treatment, 80% power and p = 0.05. Interim analysis revealed only 21% rate of events between both groups; thus, to keep the expected event reduction, sample size was increased to 1,012 patients, who were enrolled between 2010 and 2012. Mean age was 58 years, slightly more than 80% were men, and AMI was anterior in 38% of cases. Eighty-three percent of patients received renin-angiotensin inhibitors-antagonists, and 88% beta-blockers. Eighty-six percent underwent percutaneous coronary intervention and 5% thrombolysis. At a mean 10.5-month follow-up period, the primary end point occurred in 18.2% of patients with E and 29.4% with P (covariant-adjusted HR 0.58, 95% CI 0.45-0.76, p < 0.0001). The difference depended exclusively on NT-proBNO increase (16% with E vs. 25.9% with P). None of the other composite end point components showed difference. As in other studies with this type of drugs, there was excess hyperkalemia with E (5.6% vs. 3.2%; p = 0.09) and excess hypokalemia with P (5.6% vs. 1.4%; p < 0.001).

The REMINDER study illustrates how a composite end point may differ significantly between the intervention and its control, the difference being driven by the least important component. In patients with such low clinical risk (prevalence of inferior AMI, high reperfusion rate, absence of heart failure, and approximately 2.5% annual events) it is clear that a larger number of patients should have been included (more than 20,000 according to the authors' calculations) to demonstrate a significant reduction of 10% to 15% in major cardiovascular events. And even in that case we could have asked about the clinical value of that finding. A lower increase in NT-proBNP levels, without clear evidence of better outcome is not sufficient to justify antialdosterone drug recommendation in this type of patients.

Should total arterial revascularization be the standard of care in cardiac surgery?

Buxton BF, Shi WY, Tatoulis J, Fuller JA, Rosalion A, Hayward PA. Total arterial revascularization with internal thoracic and radial artery grafts in triple-vessel coronary artery disease is associated with improved survival. **J Thorac Cardiovasc Surg** 2014;148:1238-43; discussion 43-4.<http://doi.org/xcv>

Different arguments have been used to sustain that exclusive use of arterial bridges in the context of coronary artery bypass grafting (CABG) would provide advantages compared to the traditional practice (mammmary artery bridge, generally to the anterior descending artery and venous bridges to the rest of the coronary vessels). The work here presented goes in that direction.

A retrospective study was performed in 8 Australian

centers, involving 6,059 patients with three-vessel lesion submitted to CABG from 1995 to 2010. Among these patients, 2,988 (49.3%) received total arterial revascularization (TAR), 786 (13%) a mammary artery bridge and venous bridges and the remaining 2,285 a combination of more than one arterial bridge and venous bridges. The latter were excluded from the study.

In the 2,988 patients with TAR, the left mammary artery was used as bridge in 2,978 (99.7%) of cases: to the anterior descending artery in 88% (with sequential bridge to the diagonal artery in 21%) and to the circumflex artery in 12%. The right mammary artery was used in 1,089 patients (36.4%) to revascularize the right coronary artery in 36% of cases, the circumflex artery in 34% and the anterior descending and diagonal arteries in another 34% (the sum > 100% is due to their use in sequential bridges). In half of the cases it was used in situ and in the other half as free grafting. A radial artery was used in 50% of cases and both arteries in 48%. Taking this into account and the high rate of sequential bridges, a total of 4,858 distal anastomoses were performed using the radial artery: 45% with the right coronary artery, 42% with the circumflex artery and the rest with the anterior descending artery.

Compared with patients treated with one mammary artery bridge and venous bridges, TAR patients were younger, more frequently men, had lower prevalence of diabetes, cerebrovascular disease and previous myocardial infarction and better ventricular function. In these patients, the prevalence of left main coronary artery occlusion was lower. Surgical times were slightly reduced and 30-day-adjusted mortality was lower: 1.3% vs. 3.2%, with reduced incidence of perioperative complications. At 15 years, patients in the TAR group experienced significantly higher survival: 62% \pm 1% vs. 35% \pm 2%; $p < 0.0001$.

As the difference in early and long-term mortality could be attributed to the different characteristics of both groups, the authors performed two correction procedures to define whether the different prognosis of both strategies was due to the intervention. First, they did a multivariate analysis adjusting baseline variables; in this analysis, there was no longer difference in mortality at 30 days, but at 15 years, TAR was superior to the other group (HR 0.79, 95% CI 0.70-0.90, $p < 0.001$). In addition, they generated a propensity score for TAR based on variables that predicted its use, and formed 384 pairs of patients with similar propensity score, each pair formed by one patient with TAR and another without TAR. This approach also showed no difference in the early outcome; however, in the long-term outcome, survival at 15 years was 54% \pm 3% with TAR vs. 41% \pm 3% without TAR.

This retrospective analysis suggests that TAR offers improved long-term survival compared to the usual practice. The reasons to explain this finding are manifold: greater long-term permeability of arterial bridges because their endothelium is less permeable, greater antithrombotic capacity, nitric oxide production, and

resistance to adhesion molecules. In addition, due to their low caliber, arterial bridges would generate lower turbulent flow at the anastomosis and the native vessel, and hence lower atherosclerosis progression. Doubts, if any, remains on TAR advantage in a combination of more than one arterial bridge (e.g. bilateral mammary artery) and venous bridges. A limitation for TAR use is the procedural difficulty perceived by surgeons, risk of complications and longer operative time. In this analysis, the incidence of adverse events was similar with both strategies. Evidently, the value of a learning curve should be considered. Neither the multivariate analysis nor the use of propensity score could eliminate in a retrospective study the presence of residual confusion, i.e. variables not considered in the analysis that might explain the difference. Randomized studies will finally provide more conclusive evidence.

Fractional reserve flow meta-analysis

Johnson NP, Toth GG, Lai D, Zhu H, Açar G, Agostoni P, et al. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. **J Am Coll Cardiol** 2014;64:1641-54.<http://doi.org/f2vk3p>

Fractional reserve flow (FRF) evaluation is a tool that helps decision making in case lesions are found in the coronary angiography. Its value theoretically ranges between 0 (absolute absence) and 1 (normal FRF). There is a strong association between FRF < 0.75-0.80 and ischemic evidence in a functional test. Hence, in randomized studies of FRF use or not use compared to the traditional practice of lesion severity visual estimation, a FRF cut-off point among these values has been chosen as threshold for decision making. However, as in the case of all continuous measurements, it can be postulated that in all the variable FRF range there will be, for each value, a certain relationship between the short and long-term rate of events if medical therapy (MT) or coronary revascularization (CR), with percutaneous intervention or surgery, is chosen. It is possible that with near normal FRF values, MT is preferable to CR, because the procedure risk is higher than that with MT, whereas as FRF decreases the advantage of CR increases. Are the afore-mentioned values, then, the ones that best discriminate the outcome between MT and CR? Is there a FRF value where the choice of one or the other treatment is indifferent? These are the questions the authors of this meta-analysis try to answer.

They performed two analyses: one centered on observational randomized studies, and the other on patients. In the first case, the studies included those reporting mean or median FRF for a homogeneous group of treatment (discriminated for each one in case of comparison between MT and CR), excluding studies of non-atherosclerotic disease or acute myocardial infarction (AMI), with at least 180-day follow-up and major event (ME) incidence reporting: death,

AMI or culprit vessel or lesion revascularization. Using meta-regression, a linear relationship was established between FRF and ME for each treatment, with the intercept of both lines indicating the indifference point. This analysis included 51 studies with 90 different cohorts (43 from patients undergoing CR and the rest MT), analyzing 8,418 patients and 9,173 lesions. Median FRF in the CR cohorts was 0.69 (interquartile range 0.61-0.77). In more than 75% of cases CR was by percutaneous coronary intervention. Median FRF in MT cohorts was 0.87 (interquartile range 0.82-0.91). The intercept of the linear regression between ME and FRF for both types of treatment was at FRF of 0.75, but after adjusting for the follow-up period it increased to 0.90: below that value, and increasingly as we get farther away from it, CR provided better outcome than MT.

Patient-centered analysis, with similar inclusion criteria, was based on studies providing individual patient data to perform a meta-analysis associating FRF with ME. This analysis included 37 studies (22 of them used in the preceding analysis), with 6,061 patients (49% with CR, 9/10 by percutaneous coronary intervention) and 6,961 lesions. Median FRF for lesions treated with CR was 0.70 (interquartile range 0.59-0.76). Median FRF for lesions with MT was 0.87 (interquartile range 0.83-0.92). The intercept of the linear regression between FRF and ME for both types of treatment was at FRF of 0.67, but after adjusting by percent stenotic diameter (only variable statistically and clinically significantly associated with FRF) it increased to 0.76. Below this value, CR offered better outcome than MT.

A meta-analysis of the 10 studies comparing strategy based on FRF ($n = 4,893$) versus one based on anatomy ($n = 10,688$) evidenced a clear decrease in the number of procedures using the FRF strategy (42% vs. 95%), together with ME reduction (HR 0.82, 95% CI 0.78-0.87) and increased freedom from angina (HR 1.10, 95% CI 1.03-1.17). The intercept varied according to the clinical and angiographic condition (diabetes, main coronary vessel lesion or bridge lesion).

This systematic review and meta-analysis seems to confirm that a FRF value close to 0.80 is, in the case of individual patients, not only the one that best discriminates the presence of ischemia, but also the one that best differentiates outcome according to the established treatment. Nonetheless, if in most cases only one conduct is adopted for a certain condition (only 2% of lesions with FRF < 0.75 received MT and only 10% of lesions with FRF > 80 were submitted to CR: the rate of ME in both contexts was poor), this implies that the confusion by indication is feasible. The recently published FAME 2 study completes the picture, by randomly demonstrating that in lesions with FRF < 0.80 a percutaneous coronary intervention strategy improves the outcome with respect to MT. Two additional comments: it cannot be firmly ascertained that every ME in the outcome is due to the lesion considered at

the moment of FRF assessment; as with any biological finding, the value of 0.80 should be considered within the context and not rigidly, (MT with FRF of 0.81, CR with FRF of 0.79?).

End points

Stolker JM, Spertus JA, Cohen DJ, Jones PG, Jain KK, Bamberger E, et al. Rethinking composite end points in clinical trials: insights from patients and trialists. *Circulation* 2014;130:1254-61. <http://doi.org/xcw>

Clinical trials are using more frequently a composite end point (CEP) as primary EP in randomized studies. The intention of showing effect on an individual EP is belonging to the past. Progress in medical treatment, among other reasons, has decreased the incidence of each isolated EP; a CEP allows increasing statistical power to find a significant effect, hence decreasing costs. Ideally, the importance of the different CEP components should be similar, but many times hard events as death appear combined with those not so definitive (hospitalization) and clearly others of less hierarchy (echocardiographic or biochemical alterations). A proposal has been made to weigh the different CEP components according to the contribution each might have on effect assessment. But, how is the relative weight of each component accurately defined? Do patients and researchers agree on the importance of each EP? A survey was designed by the authors of this study on the relative value of five components usually forming part of a cardiovascular clinical trial CEP: death, myocardial infarction (AMI), stroke, coronary revascularization and hospitalization for angina. The CEP had a final value of 25 points, that each participant should distribute among the five components according to his/her perception of their relative importance (e.g. 9, 5, 6, 3 and 2, for the five isolated EP in the cited order). Next, each score was transformed to a 100-point scale (in the same example: 36, 20, 24, 12 and 8). The ratio of each nonfatal EP relative to death was then calculated (e.g. if death was assigned 36 points and AMI 20, the ratio AMI/death was $20/36 = 0.55$). Thus, each survey provided information on the weight assigned to each CEP component and their relative weight with respect to death. The survey was applied: a) in person to randomly selected patients in the ambulatory clinic or any diagnostic study waiting room in a healthcare and academic center in Kansas dedicated to cardiovascular medicine and b) by e-mail to responsible researchers of clinical trials on statins or coronary revascularization between 2000 and 2009. The survey was answered by 785 patients (more than 95% of invited participants) and 164 researchers (approximately 60% of those invited). Among patients, 54% were men, 54% had at least 65 years, 25% had previous AMI, 33% had undergone prior percutaneous coronary intervention and 15% prior coronary revascularization surgery. Median weight for each CEP component in a 100 scale was: 25 points for death, 28

for AMI, 27 for stroke, 12 for revascularization and 7 for hospitalization due to angina. It should be noted that in patients AMI and stroke weighed slightly more than death, with 1.12 and 1.08 ratios, respectively. The ratios for revascularization and hospitalization were 0.48 and 0.28. Multivariate analysis showed significant discrepancy according to age (patients < 45 years considered death 2 times more severe than AMI or stroke, those between 45 and 64 years were equally concerned about the three EP, and among those of at least 65 years, AMI and stroke were considered more severe than death, even 2 times or higher more severe in patients > 85 years), annual income (more concern about death in patients with high income, and for AMI and stroke in those with low income) and race (AMI was considered to be more severe by black patients).

Among researchers, 70% was at least 20 years past their medical formation stage. The multivariate analysis showed no differences among them regarding their cardiology specialty or the time dedicated to medical practice. In their surveys, median weights for EP on a 100 point scale were 40 points for death, 25 for AMI, 21 for stroke, 8 for revascularization and 5 for hospitalization due to angina. The ratios of non-fatal EP relative to death were half of those assigned by patients ($p < 0.001$).

This survey has revealing data: for patients, age, income and race are important in cardiovascular event grading, and death is not always the worst outcome; for researchers, death is clearly the worst outcome and their evaluation of the other EP is not as bad as that of patients. We could argue whether that difference occurs because researchers are closer to being similar to younger patients with higher income or if, independently of this, they have a different evaluation due to their condition and inclinations. Unfortunately, the study lacks this analysis. But what clearly emerges is that if, as it seems, CEP continue to be commonly used, and within the framework of a patient-centered medicine, their preferences and beliefs should be considered when risks are evaluated to decide the value of an intervention.

Obesity in children is not a sign of good health: the Bogalusa study

Lai CC, Sun D, Cen R, Wang J, Li S, Fernandez-Alonso C, et al. Impact of long-term burden of excessive adiposity and elevated blood pressure from childhood on adulthood left ventricular remodeling patterns: the Bogalusa Heart Study. *J Am Coll Cardiol* 2014;64:1580-7. <http://doi.org/f2vzhk>

Obesity and hypertension are strong predictors of left ventricular hypertrophy (LVH), which, in turn, is associated to greater cardiovascular morbidity and mortality. Four cohort studies in children followed-up until adulthood have shown that the risk starts in childhood. The Bogalusa study, in Louisiana, adds new data about the burden of risk factors for LVH and how these factors weigh in the transition from childhood to adulthood. Between 1973 and 2010, the Bogalusa

Heart Study carried out 9 cross-sectional studies in children between 4 and 18 years of age and 10 cross-sectional studies in adults between 19 and 52 years who had already been examined during childhood. This modality of periodic cross-sectional studies applied to the same participants allows having a longitudinal vision of their evolution. The analysis presented here considers 1,061 participants that in the mentioned period underwent four clinical exams including blood pressure (BP) and body mass index (BMI) assessments, with at least two of these exams during childhood (on average, the first evaluation around 10 years of age) and two in adulthood (on average, the last assessment around 38 years), and who, between 2004 and 2010, already adults, were submitted to an echocardiogram. This was used to calculate the formula of left ventricular mass, which was indexed by height^{2.7}, resulting in left ventricular mass index (LVMI). Left ventricular hypertrophy was defined as LVMI > 46.7 g/m^{2.7} in women and > 49.2 g/m^{2.7} in men. Also, relative wall thickness (RWT) was calculated as the sum of septal and posterior wall thicknesses divided by LV end-diastolic diameter. A concentric LV geometry was considered for RWT > 0.42.

Based on the above, four patterns were defined: a) normal, without LVH and with RWT ≤ 0.42, b) concentric remodelling, without LVH and with RWT > 0.42, c) eccentric LVH, with LVH and RWT ≤ 0.42 and d) concentric LVH, with LVH and RWT > 0.42. In addition, an area under the curve (AUC) was defined considering the repeated BP and BMI measurements since childhood to adulthood, adjusted by follow-up years. Prevalence of concentric remodelling and eccentric and concentric LVH was 9.1%, 10.2% and 4.2%, respectively. There was greater prevalence of both types of LVH in black than white adults. Adjusting by age, sex and race, the first childhood value, the last adult value, total AUC and incremental AUC, both of systolic BP and BMI, were predictors of LVMI, and by logistic regression of LVH, especially eccentric. Body mass index was consistently a stronger predictor of LVH than systolic BP.

This study confirms the role of overweight and obesity in the genesis of LVH and provides novel information on the role of disease burden. There are various reasons why obesity can originate LVH: sympathetic and inflammatory activation, insulin resistance, sodium retention, endothelial dysfunction and, evidently, hypertension. However, in different analyses, BMI did not have a significant interaction with BP in its effect on LVMI, clearly suggesting an independent role. Patients with antihypertensive therapy, in whom BP would be expected to have greater impact on LV geometry alteration, were excluded from the analysis. This might have biased the results towards an overestimation of the influence of obesity, but nonetheless, does not rule out findings. Overweight and obesity in childhood cannot be regarded as a cute phenomenon or expression of good health: they are the first expression of a disease we must learn to stop.