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More ambitious antihypertensive treatment targets ensure better results: the SPRINT trial

SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A randomized trial of intensive versus standard blood-pressure control. **N Engl J Med 2015;373:2103-16. http://doi.org/bbxd**

Antihypertensive treatment reduces the incidence of acute myocardial infarction (AMI), stroke and heart failure (HF). There is no clear demonstration of what the systolic blood pressure (SBP) goal should be, but usually a value <140 mm Hg is recommended. Studies conducted in diabetic patients or patients with a history of stroke have shown that to pursue lower SBP values is not associated with better outcomes, except for lower incidence of stroke. Still, the uncertainty remains, and this has been the basis for the design of the recently published SPRINT trial.

The SPRINT study was designed and sponsored by the National Heart Lung and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke and the National Institute on Aging of the United States. It was a randomized, open, controlled study, comparing two strategies in hypertensive patients: SBP <140 mm Hg (standard treatment, ST) or SBP <120 mm Hg (intensive treatment, IT). Patients with a SBP between 130 and 180 mm Hg, >50 years and with at least one of the following cardiovascular risk criteria: clinical or previous subclinical cardiovascular disease, excluding stroke; at least 15% 10-year-risk of events according to the Framingham score; kidney failure (except due to polycystic kidney disease) ranging between 20 and 59 ml/min/1.73 m2; and age ≥75 were included in the study. Patients with diabetes and with a history of stroke were excluded. The primary endpoint (PEP) was a composite of AMI, other acute coronary syndromes, stroke, acute decompensated HF and cardiovascular death. An endpoint referred to kidney failure was also defined: in patients with glomerular filtration rate (GFR) <60 ml/min/1.73 m2, a combination of decline in GFR >50%, dialysis or transplantation; in patients with higher filtration rate, a decrease of 30%, to a value <60 ml/min/1.73 m2. The incidence of albuminuria was also explored. The physicians participating in each branch of the study were free to choose the treatment drug, but were recommended to use evidence-based drugs. In the ST branch a target SBP between 135 and 139 mm-Hg was established, and presence of lower follow-up values led to lowering treatment doses. For an annual PEP incidence of 2.2% in the ST branch and 20% reduction in the IT branch a total of 9,250 patients were considered to be necessary for a maximum follow-up of 6 years.

The study was initiated in 2010 and the enrolment of 9,361 patients was completed in 2013. In August 2015, on the recommendation of the Safety Committee, it was discontinued with an average follow-up of 3.26 years. The average age of participants was 68 years (28% were ≥75), a little over 64% were male and 28% had chronic kidney disease. Mean baseline BP at study initiation was 139.7/78.1 mmHg. Mean SBP in the ST branch throughout the course of the study was 134.6 mmHg and in the IT branch 121.5 mmHg, with an average number of antihypertensive drugs used of 1.8 and 2.8, respectively.

The annual incidence of PEP was 1.65% in the IT branch and 2.19% in the ST branch (HR 0.75, 95% CI .64-89); the difference after the first year became significant. There was no significant difference in the incidence of AMI or stroke; however, the difference was significant in acute HF (HR 0.62, 95% CI 0.45-0.84), in cardiovascular death (0.25% vs. 0.43% per year, HR 0.57, 95% CI 0.38- 0.85) and all-cause death (1.03% vs. 1.40% per year, HR 0.73, 95% CI 0.60-0.90). Among patients with baseline kidney failure (just over 28%), there was no difference in the outcome. Among those with preserved renal function on admission, the incidence of GFR decline, as previously defined, was higher with IT: 1.2% vs. 0.35% per year (HR 3.49, 95% CI 2.44-5.10). The incidence of serious adverse events (mortal, life threatening or motivating hospitalization or justifying additional pharmacological or non-pharmacological measures) was not significantly different, (38.3% vs. 37.1%, p=0.25); however, there was significant difference in the incidence of hypotension, syncope and kidney failure, in all cases between 2% and 4% with IT, and between 1.5% and 2.5% with ST.

Classically, practice guidelines of the most important scientific societies have set targets of antihypertensive treatment of less than 140/90 mm Hg values. So far, there had been no clear evidence of the advantage of lowering these values. In this sense, the SPRINT trial is a real innovation, particularly by demonstrating cardiovascular and overall mortality reduction. Among PEP components, it is interesting to note that, excluding cardiovascular death, a significant decrease occurred in HF, with no evidence of significant reduction in AMI, stroke or renal function worsening in those with prior involvement. This leads to consider the possible link between mortality and the incidence of HF. A more detailed publication would help to clarify

this point. Intensive treatment involves at least 1 death less in nearly 3 follow-up years, and 1 cardiovascular death less in almost 6 years. Some points however should be observed: a) the study excluded diabetics and patients with prior stroke, in whom previous studies had not demonstrated advantage of such an intensive treatment; b) patients included were over 50 years and with increased cardiovascular risk (more than 60% with increased risk of events at 10 years ≥15% according to the Framingham score); and c) there was a higher incidence of some adverse events with IT. It would be desirable to have more information on the drugs more associated with the incidence of serious events, and of the patients' profile more likely to present them.

Meanwhile, it is clear that the SPRINT trial is a warning to our usual behavior: we should not be content with a SBP of 140 mm Hg in a high proportion of patients; at the same time, we should pay attention to the patients' baseline characteristics and their outcome with the treatment instituted, to avoid the incidence of serious adverse events. A meta-analysis of 123 studies and over 613,000 participants in the forthcoming issue of The Lancet (Ettehad et al.), with a wide range of baseline SBP levels and presence of comorbidities, confirms 13% reduction in overall mortality for every SBP decrease of 10 mm Hg and suggests SBP values below 130 mm Hg, reinforcing the findings of the SPRINT study.

Meta-analysis of devices in patients with heart failure

Woods B, Hawkins N, Mealing S, Sutton A, Abraham WT, Beshai JF, et al. Individual patient data meta-analysisof mortality network effects of implantable cardiac devices. **Heart 2015;101: 1800-6.http://doi.org/bbwp**

Since the beginning of this century, treating subgroups of patients with heart failure and reduced ejection fraction (HFDEF) with implantable devices has gained increasing acceptance. Implantable cardioverter defibrillators (ICD), resynchronizers (RSC) and devices with both capabilities (RSC-D) have confirmed improved patient outcome and have specific indications in clinical practice guidelines. However, in many cases, patients have baseline characteristics which make them suitable for either device. Clinical and economic criteria are then put forward in dispute relating to specific cases, where the evidence arising from one or other randomized clinical trial (RCT) is not conclusive. We present a meta-analysis that has two great qualities: a) it is a meta-analysis of individual data, and therefore the characteristics of each patient are taken into account, b) it is a network meta-analysis, where comparison between two strategies does not only arise from the study performed, but from indirect information stemming from other trials. Thus, the HR which results from comparing strategies A and C, not only arises from the RCT comparing A and C, but from the HR emerging from the product of comparing strategies A and B by the HR arising from comparing strategies B and C.

The meta-analysis included 13 large RCTs comparing any of the devices with medical treatment (MT) or two devices mutually. Among the RCTs considered we can mention the COMPANION, SCD HeFT, CARE HF, MADIT, MADIT II, RAFT and REVERSE trials. A total 12,638 patients, with mean follow-up of 2.5 years, and 99% of patients with EF ≤35% were analyzed. As expected, in the RCTs where RSC or RSC-D were tested, the QRS width was slightly larger, and left bundle branch block (LBBB) and FC III were more frequent than in those where ICD was compared to MT. Based on baseline characteristics in which RCTs or meta-analysis multivariate analyses have been shown to influence treatment outcome, subgroups were built considering the following four variables: gender (male or female), age (<60 years, ≥60 years), QRS width (<120 ms, 120-149 ms, ≥150 ms) and presence or absence of LBBB. The primary endpoint was overall mortality.

Compared with MT: a) RSC-D significantly reduced mortality in all subgroups analyzed, except in women under 60 years, with QRS between 120-149 ms and without LBBB (which can be attributed to chance); b) RSC only significantly reduced mortality in men or women over 60 years with QRS ≥150 ms and LBBB morphology, although there was a clear tendency to reduced mortality in women under 60 years with wide QRS and LBBB, and in women over 60 years with QRS between 120-149 ms without LBBB, or QRS ≥150 ms without LBBB; c) ICD reduced mortality in all men subgroups, while among women reduction only occurred in the subgroup under 60 years, with QRS between 120-149 ms and without LBBB (which can be attributed to chance).

Overall, reduced mortality achieved with RSC-D (42%) was higher than that achieved with RSC (19%) or ICD (18%).

In the comparison between devices: a) there was no significant difference between RSC and RSC-D in subgroup analyses; b) there was significant reduction in mortality with RSC-D compared to ICD in men and women over 60 years with QRS ≥150 ms and LBBB, in women under 60 with QRS ≥150 ms and LBBB, and in women over 60 years with QRS between 120-149 ms without LBBB or QRS ≥150 ms without LBBB; c) RSC was superior to ICD in women over 60 years, with QRS ≥150 ms and LBBB, and conversely, it was clearly lower in men under 60 years, with QRS between 120-149 ms with or without LBBB.

In general, we can conclude that, although in many cases different devices can generate similar effects on mortality, RSC devices focus their benefits in women and patients with wide QRS and LBBB, and ICD in younger men. Given the choice, a wide QRS and LBBB profile turns us to consider RSC, and if so, RSC-D, by the evidence of greater reduction in mortality, even when it is not specifically verified in any subgroup

in particular. Nevertheless, the choice will be further influenced in each case by specific characteristics (comorbidities, availability, etc.)

Natriuretic peptide guided therapy: keys to a better implementation

Brunner-La Rocca HP, Eurlings L, Richards AM, Januzzi JL, Pfisterer ME, Dahlström U, et al. Which heart failure patients profit from natriuretic peptide guided therapy? A meta-analysis from individual patient data of randomized trials. **Eur J Heart Fail 2015;17:1252-61.http://doi.org/bbwq**

Several meta-analyses have shown that, compared with conventional therapy for heart failure, based on the signs of congestion and indications of practice guidelines, treatment guided by natriuretic peptide (BNP or NT-proBNP) values in order to achieve a certain percentage reduction or specific absolute values, can generate a significant reduction in mortality. However, there are so many factors related with the increase of these peptides (age, concomitant cardiovascular and non-cardiovascular disease), that the question is whether guided therapy (GT) should be recommended in all patients. A recent meta-analysis of GT randomized studies vs. conventional treatment contributes to outline a rational GT use. This meta-analysis of individual data included eight studies, with 1,731 patients with heart failure and decreased ejection fraction (≤45%, HFDEF) and 301 patients with heart failure and preserved ejection fraction (>45% HFPEF). Patients with HFPEF were older, more often women, with higher prevalence of hypertension and renal dysfunction, and with more diuretic and less beta blocker treatment.

In HFDEF patients, GT was associated with reduced mortality (HR 0.78, 95% CI 0.62-0.97) and hospitalization for heart failure (HR 0.80, 95% CI 0.67-0.97). A closer analysis showed that reduced mortality was concentrated in patients without pulmonary or peripheral vascular disease, diabetes or cardiovascular or cerebrovascular disease (HR 0.61, p=0.008), whereas in patients with these comorbidities there was no apparent GT effect (HR 0.94, p=0.65). Similarly, GT benefit was observed in patients <75 years (HR 0.68, p=0.03) and not in those >75 years (HR 0.87, p=0.35), though when adjusted by the presence of comorbidities, the influence of age disappeared.

In HFPEF patients, GT was not associated with reduced mortality (HR 1.22, 95% CI 0.76-1.96) or hospitalization for heart failure (HR 1.01, 95% CI 0.67-1.53). None of the discussed comorbidities referred to for HFDEF influenced GT response, but instead this was more effective in patients with hypertension and in those without renal dysfunction. Again, GT seemed to work better in those patients <75 years, but the adjustment for comorbidities eliminated this difference.

This meta-analysis helps define the field in which GT could be effective: in that of HFDEF patients without significant comorbidities. This may help explain why, in different analyses, younger patients have benefited from this strategy. In all registries, patients with HFDEF are all younger than those with HFPEF; the prevalence of comorbidities increases with age. It is possible that the presence of different comorbidities may have such a prognostic value that GT is no longer effective in improving outcome. It is noteworthy that renal dysfunction has only been influential in patients with HFPEF. Despite acknowledging that the prognostic value of elevated peptides could be lower in the presence of renal impairment (per se cause of their increase), the meta-analysis suggests that in HFDEF their values should be taken into account. Finally, we must consider that the number of patients with HFPEF was low. Thus, the fact that new randomized or observational studies may change some of these conclusions cannot be excluded.

Radial vs. femoral access in acute coronary syndrome angioplasty: final evidence.

Andò G, Capodanno D. Radial versus femoral access in invasively managed patients with acute coronary syndrome: A systematic review and meta-analysis. **Ann Intern Med 2015;163:932-40. http://doi.org/bbwr**

In the last 20 years, radial access (RA) in the context of coronary angioplasty in acute coronary syndrome (ACS) has gained a progressively increasing importance compared to the traditional femoral access (FA). Its main advantage is periprocedural bleeding reduction that is acknowledged as determinant of poor outcome. Some meta-analyses have also suggested reduction of ischemic events, and others have been able to demonstrate reduced mortality. However, many of the studies considered have been single-center studies with poor methodological quality. That is why the authors of this work decided to present a systematic review of randomized, methodologically faultless trials, comparing RA vs. FA in ACS with periprocedural, in-hospital and 30-day reported events.

Four studies with a total of 17,133 patients were selected: RIFLE STEACS and STEMI RADIAL (which included only patients with ST-segment elevation), RIVAL and MATRIX (which included patients with and without ST-segment elevation). Mean age ranged between 62 and 65 years, and 72% to 79% of patients were men. Mean procedural duration was only slightly higher with RA: 0.11 minutes, a statistically significant difference due to the number of observations. Radial access to FA crossover was 6.3% and the reverse almost 4 times lower: 1.7%.

The use of RA was clearly superior in almost all endpoints considered: overall death (RR 0.73, 95% CI 0.59-0.90), access site bleeding (RR 0.36, 95% CI 0.28-0.47), and major bleeding (RR 0.57, 95% CI 0.37-0.88). There was, however, no difference in the incidence of acute myocardial infarction or stroke. There was some heterogeneity in the results for major bleeding and ac-

cess crossover, but not for death or heart attack.

This meta-analysis confirms what the MATRIX study had already outlined [discussed in a former issue of this Journal (Rev Argent Cardiol 2015; 83:376-82)]: the use of RA in ACS angioplasty is associated with reduced mortality, and this result goes together with a significant reduction of bleeding at the site of access and of major bleeding. The reasons why bleeding is associated with mortality are manifold, spanning from the creation of a prothrombotic state in parallel with the forced interruption of antithrombotic treatment, with higher incidence of ischemic events, to anemia, and in some cases, the deleterious effect of transfusions. The resistance of some operators to the allegedly greater difficulty of the procedure might be diluted with the clear evidence of improved outcome, the clinically null difference in duration with either access and the low (though significant) impact on the need for conversion from RA to FA.

Physical activity reduces the incidence of heart failure: a meta-analysis of observational data

Pandey A, Garg S, Khunger M, Darden D, Ayers C, Kumbhani DJ, Mayo HG, de Lemos JA, Berry JD. Dose-Response Relationship Between Physical Activity and Risk of Heart Failure: A Meta-Analysis. **Circulation 2015;132:1786-94. http://doi.org/bbws**

It is well known that physical activity (PA) correlates inversely with the incidence of coronary artery disease, and effectively, AHA-ACC guidelines recommend 150 minutes per week of moderate to intense aerobic PA to reduce the risk of coronary artery events. Although in Western countries the most important cause of heart failure (HF) is coronary heart disease, there is no clear information on whether PA is able to decrease the incidence of HF and whether there is a dose-response relationship. A meta-analysis of observational data answers this question.

The authors selected all cohort studies published between 1995 and 2014 exploring the association between PA and the incidence of HF, taking into account all types of PA (occupational, recreational, etc.). Four categories were considered based on collected information: low, mild, moderate and high. When the data was available PA was measured in MET-minutes per week (product of PA intensity expressed in MET by the time taken to perform it, during a week). For example, if a 5 MET activity is carried out during 100 minutes per week it implies 500 MET-minutes per week. Effectively, 500 MET-minutes per week are the minimum PA recommended by guidelines to prevent cardiovascular events.

As it is clear that there are variables which might confound the relationship between PA and the incidence of HF (older people, who have higher prevalence of coronary risk factors and comorbidities, perform the least PA and have greater propensity for presenting with coronary disease), the meta-analysis considered the association measurements emerging from the multivariate analysis in each individual work.

Twelve studies were included (8 from de United States and 4 European) with a total of 370,460 participants and median follow-up of 13 years. Compared with low PA, mild PA was associated with a HR for the incidence of HF of 0.85 (95% CI 0.79-0.92), moderate PA with a HR of 0.78 (95% CI 0.75-0.82) and more intense PA with a HR of 0.70 (95% CI 0.67-0.73). This means that there was a real inverse gradient in the incidence of HF, according to the degree of PA. No differences were found in relation to age and sex. A weekly PA of 500, 1,000 or 2,000 MET-minutes was associated with 10%, 19% and 35% reduction in the risk of HF, respectively, compared with no PA.

This meta-analysis shows a dose-response association in the relationship between PA and the incidence of HF, which is different from the relationship between PA and coronary heart disease, where a plateau is reached for more than 1,000 MET-minutes per week. The involved mechanisms may differ. Regarding the incidence of heart disease, it may be assumed that PA has a beneficial effect by modifying the risk factor profile: decrease of blood pressure and improvement of the glycemic and lipid profile. Concerning the incidence of HF, a reduced sympathetic tone, increased vagal tone, and improved diastolic function and peripheral vasodilator capacity should be added to the decrease of coronary heart disease. As limitations we may consider the observational nature of the studies, in which residual confounding phenomena due to variables not taken into account might be at least partly responsible for the association. Nevertheless, a new beneficial effect of PA is found in this publication, and a new reason to recommend it. And here it would seem (although only a randomized study may have the final answer) that the more, the better.

Is it useful to anticoagulate patients with group I pulmonary hypertension?

Preston IR, Roberts KE, Miller DP, Sen GP, Selej M, Benton WW, et al. Effect of Warfarin Treatment on Survival of Patients With Pulmonary Arterial Hypertension (PAH) in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL). **Circulation 2015;132:2403-11. http://doi.org/bbwt**

Anticoagulant treatment is indicated in patients with group 1 pulmonary arterial hypertension, especially in its idiopathic form (IPAH). The indication is based on observational evidence of non-randomized studies, suggesting better outcome with this treatment. An analysis of the COMPERA European registry, commented in this section of the Journal (Rev Argent Cardiol 2014;82:177-82), confirmed the usefulness of this treatment in IPAH patients, but not in group 1 patients with PAH secondary to scleroderma. Results of the retrospective analysis of another large registry,

the REVEAL study, come to question previous assumptions.

The REVEAL registry included 3,515 patients with group 1 PAH in 55 university or community hospitals in the United States. In the present analysis, patients were divided into four groups according to the etiology of the disease (idiopathic or scleroderma), who had been treated or not with warfarin (W) during follow-up. Patients who were receiving W at the moment of inclusion were excluded from the registry. One hundred and forty-four patients with IPAH and 43 with PAH due to scleroderma who had initiated W at follow-up were selected and matched according to baseline characteristics with the same number of patients by etiology who had not been treated with W. In general, patients treated with W received more frequently treatment with prostanoids and combined treatment with specific therapy. Approximately two-thirds of patients treated with W abandoned treatment during the course of follow-up. In fact, among treated patients, with mean follow-up of 3 years, W treatment was received only during 1 year.

Among patients with IPAH, W did not modify the prognosis (HR 1.42, 95% CI 0.86-2.32. In patients with scleroderma, W was associated with worse outcome (HR 2.03, 95% CI 1.09-3.79), but the difference disappeared after adjusting for baseline clinical and paraclinical characteristics. However, taking into account the effective time with W treatment, and after adjusting by this variable, anticoagulated patients with scleroderma again evidenced poorer prognosis than those without treatment.

Data of the REVEAL registry contradict results from the COMPERA study. Use of W in the idiopathic form but not in scleroderma is useful for the European registry, but worse for the American registry: ineffective in IPAH, and directly harmful in connective tissue disease. The reason for these differences should be sought perhaps in the population: older and with greater prevalence of men in the REVEAL registry, or in the fact that anticoagulated patients had worse clinical and hemodynamic profile. The authors claim that it is possible that in the COMPERA study (that considered patients already treated with W at the beginning of the registry) there could have been bias of immortal time: to consider a patient as anticoagulated it is necessary that he has survived until the moment of anticoagulation onset. This implies that if there is delay in initiating treatment, a cohort with potentially higher survival time since disease onset, than in the case non-treated patients, is selected. Nonetheless, it cannot be ascertained that this has really occurred. However, it can be said that both are observational studies, subject to biases and the presence of confounding variables. It seems clear that oral anticoagulation has no room in PAH secondary to scleroderma: it extends from useless to clearly harmful. Regarding IPAH, a clinical trial that clarifies doubts is still pending.

Abdominal obesity and poor prognosis despite normal weight

Sahakyan KR, Somers VK, Rodriguez-Escudero JP, Hodge DO, Carter RE, Sochor O, et al. Normal-Weight Central Obesity: Implications for Total and Cardiovascular Mortality. **Ann Intern Med 2015;163:827-35. http://doi.org/bbwv**

Based on the body mass index (BMI), normal weight is considered for BMI between 18.5 and 24.9 kg/m2, overweight for BMI between 25 and 29.9 kg/m2 and obesity for BMI >30 kg/m2. Presence of obesity is associated to increased risk of coronary events, heart failure and death. However, it has been pointed out that the prognostic information of BMI could be refined if waist circumference (WC) or the waist-hip ratio (WHR) is also taken into account. According to the World Health Organization, abdominal obesity in women is defined as WC >88 cm or WHR ≥0.85, and in men as WC >102 cm or WHR ≥0.90. One cm increase in WC or 0.01 units in WHR is associated with 2% and 5% increased risk of future coronary events, respectively.

In the NHANES III survey carried out in the United States between 1988 and 1994, many respondents provided BMI and WHR data. The authors of this work explored in these persons the value of both determinations to define prognosis. They selected those with BMI >18.5 kg/m2, and free from history of cancer. The representative patterns to calculate the risk of event relationship were absence of abdominal obesity defined as WHR not greater than 0.89 in men and 0.80 in women, and presence of abdominal obesity described as WHR exceeding 1 for both sexes. Similarly, a mean BMI of 22 kg/m2 was established for normal weight, 27.5 kg/m2 for overweight and 33 kg/m2 for obesity. Thus, 6 anthropometric profiles were defined based on both measurements: presence or absence of abdominal obesity in persons with normal weight, overweight or obesity.

The study included 15,184 persons. Mean age was 45 years and 52.3% were women. According to BMI, 39.9% had normal weight, 34.6% overweight and 25.5% obesity. Abdominal obesity was present in 70.2% of cases considering WHR, but only 28.9% according to WC.

Mean follow-up was 14.3 years, during which 3,222 deaths occurred, slightly less than half due to cardiovascular disease.

Among men, the HR for the risk of death in those with normal weight but central obesity was 1.87 (95% CI 1.53-2.29) compared with men with normal weight and without central obesity (profile1). Overweight or obese men according to BMI, but without central obesity did not have worse prognosis than those belonging to profile 1. Conversely, presence of central obesity defined worse prognosis in overweight (HR 1.53, 95% CI 1.27-1.86) and in obese (HR 1.38, 95% CI 1.07-1.78) persons.

Similar results were observed in women. Compared with profile 1 women, those with normal weight but central obesity presented higher risk for mortality (HR 1.48, 95% CI 1.35-1.62). Overweight or obese women according to BMI, but without central obesity had higher tendency to worse prognosis than those of profile 1, but without statistical significance. On the other hand, presence of central obesity defined worse prognosis in overweight (HR 1.56, 95% CI 1.38-1.77) and obese (HR 1.65, 95% CI 1.39-1.97) women.

Body mass index is the expression of lean and fat mass. Therefore, the increase in fat mass and its bodily location cannot be defined solely on BMI. Increased WHR indicates abdominal obesity and hence increase of visceral fat. It is known that abdominal obesity is associated with increased insulin resistance, hypertriglyceridemia, dyslipidemia, atherogenesis and inflammation. Abdominal obesity is usually accompanied by decreased muscle mass in the lower extremities and is associated with increased cardiovascular risk. Conversely, subcutaneous fat accumulation is metabolically less deleterious.

In this study, the correlation between BMI and WHR was poor (r=0.34), reflecting the different information they provide. The novelty of the information presented here is the demonstration that in persons considered with "adequate weight", the visceral accumulation of adipose tissue is associated with poor outcome; in fact, a person with overweight but adequate fat distribution presents half the risk than a person with normal weight and central obesity. Therefore, we should not aim at keeping our patients at an adequate weight, but to prevent the emergence of abdominal obesity regardless the BMI.

Access to medicines and cardiovascular health: a substudy of the PURE trial

Khatib R, McKee M, Shannon H, Chow C, Rangarajan S, Teo K, et al; PURE study investigators. Availability and affordability of cardiovascular disease medicines and their effect on use in high-income, middle-income, and low-income countries: an analysis of the PURE study data. **Lancet 2016;387:61-9. http://doi.org/bbwz**

The World Health Organization has posed the objective that at least 50% of people worldwide in need of pharmacological treatment for secondary prevention of cardiovascular diseases should have access to medicines by 2025. However, the PURE epidemiological study revealed that the corresponding percentages were much lower: 25% for aspirin, 15% for statins and in-between percentages for betablockers (BB), angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors (ACEI). The following substudy sheds light on this issue.

Overall, 94,919 households were selected in 596 urban (U) and rural (R) communities from 18 countries (3 high-income countries: Canada, United Arab Emirates and Sweden; 7 upper middle-income countries: Argentina, Chile, Brazil, Poland, Turkey, Malaysia and South Africa; 4 lower middle-income countries: Colombia, Iran, China and occupied Palestine; 3 low-income countries: Bangladesh, Zimbabwe and Pakistan; and India as a separate entity) for which there were monthly income data. Cardiovascular disease requiring secondary prevention was defined in 7,013 persons. Aspirin, statins, (simvastatin, atorvastatin), BB (atenolol and metoprolol) and ACEI (enalapril, ramipril and captopril) costs and availability were considered in each community, taking as reference a pharmacy defined by its proximity (ideally <1 km, but could reach as far as 20 km) to a central or very busy point.

Medicine availability was defined as at least one drug of each family present in the pharmacy at the same time. Medicine affordability by the members of each household was defined as a monthly expenditure for the specific medicine not greater than 20% of the monthly income, after deducing the necessary food expenditure. Data were adjusted by age, sex, smoking habit, educational attainment, history of cancer, U or R location, and need of other medicines. The family income data were collected between 2003 and 2013 and the costs of medicines between 2009 and 2013, but all were adjusted to 2010, according to the World Bank inflation rate.

Availability of the four drug families (U-R location data are presented for each group of countries) evidenced a gradient according to income: it was higher in high-income countries (95%-90%) and in India (89%-81%); intermediate in upper middle-income (80%-73%) and lower middle-income countries (62%-37%) and low in poorer countries (25%-3%).

A patient requiring the four drugs should invest a median of 1% of the household income to purchase it in rich countries, independently of living in an U or R location; 5-6% in a U location and 11% in a R area in upper or lower middle-income countries; 17% and 49% in U and R locations, respectively, in poor countries and 13% and 68% in U and R areas, respectively, in India.

Considering affordability with the above definition, treatment would be unaffordable for 0.1% of households in high-income countries, for 25% in upper middle-income countries, for 33% in lower middle-income countries and for 59% to 60% in India and low-income countries. Even in the higher-income social sectors, medicines would be unaffordable in 5% of households in upper middle-income countries, 21% in lower middle-income countries and 45% in those with low-income.

Among the 7,013 patients with cardiovascular disease, a gradient was also observed in the proportion of those who received 1, 2, 3, or the 4 types of drugs. Effectively, 0% of patients received the 4 drugs in low-income countries and 18% in the richest countries, and one drug in 17% of poorer countries and up to

90% in the richest ones.

This study offers interesting information, though based on assumptions: it acknowledges that availability depends on the presence of drugs in a specific pharmacy, not considering that in certain healthcare systems, drugs may be provided in other centers. Similarly, it establishes affordability as an arbitrary value not greater than 20% or less of the household income; perhaps higher values would give higher estimates. Nonetheless, the material presented is very rich, and the gradient obtained (lower availability and affordability the poorer the country, and worse values in rural than in urban locations) is plausible and draws us near a reality distant from the World Health Organization objectives in vast sectors of the planet. But beyond economic conditionings, there must be other reasons associated with the values found. Even in the richest countries 10% of cardiovascular patients do not receive even one of the 4 types of recommended drugs and more than 80% that do not take the 4 types. Adequate physician knowledge of the disease and evidence when prescribing drugs, and patient attitude beyond the socioeconomic reality, undoubtedly play a significant role. Regarding availability and affordability, improved social conditions and more active and better oriented policies are essential to expand cardiovascular health.