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Spironolactone emerges as the best option in the treatment of resistant hypertension. The PATHWAY-2 trial

Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. **Lancet 2015; pii: S0140-6736(15)00257-3. http://doi.org/9kq**

Resistant hypertension (RHTN) is defined as the suboptimal control of blood pressure treated with three drug families: a diuretic, a calcium antagonist and a rennin-angiotensin system antagonist/inhibitor. Ten percent of hypertensive patients are affected by RHTN. Sodium retention or heterogeneous states with different etiologies are postulated among the causes that produce it. The PATHWAY 2 trial, conducted in the United Kingdom, explored which could be the best alternative fourth drug for the adequate control of BP in patients with RHTN. The first hypothesis postulated that this drug could be spironolactone (S) and compared it with an alpha-blocker, doxazosin (D) and a beta-blocker, bisoprolol (B). The study included patients with RHTN, with office systolic BP of at least 140 mmHg (135 mmHg in diabetics) and 130 mmHg in home measurements. All BP assessments were performed using automated monitoring. After a 4-week run-in period with placebo, patients were randomly assigned to 12-week treatment with S, 12 weeks with B, 12 with D and 12 with placebo. During the first 6 weeks, each group of patients received either S 25 mg, or B 5 mg, or D 4 mg or placebo, and in the following 6 weeks the corresponding dose was doubled. In the 4 days prior to the 6-week and 12-week visits, BP was measured daily at home (3 morning and 3 evening measurements, totaling 21 of 24 measurements; the average of approximately 6 to 18 measurements taken between days 2 to 4 was considered as final measurement); the day of the visit defined office BP.

Study duration was 1 complete year. A stratified data analysis was performed: first, mean systolic BP was compared between S and placebo. If the difference was significant, then the comparison was made between S and the average between B and D; finally, if the difference in BP was significant, the comparison was made between S and each of the other two drugs separately.

Between 2009 and 2014, 335 patients were included in the study. Average age was 61 years and 69% were men. Average BP was 147.6/84.2 mmHg at home and 157/90 mmHg in the office. Patients had adequate renal function with mean glomerular filtration rate of 90 ml/min and 14% were diabetic. At the end of the study (314 were analyzed because 21 were lost to the study), the 4.1 mmHg BP reduction with respect to baseline in the placebo group was clearly higher with drugs: 12.8 mmHg with S, 8.7 mmHg with D and 8.3 mmHg with B; S was superior to D (4.04 mmHg difference) and B (4.48 mmHg difference).

In a subanalysis considering plasma renin activity (PRA) at study initiation, the BP decrease with S was inversely correlated with PRA, whereas no correlation was found with D and B effects. Spironolactone achieved more marked effects than the other two drugs in almost all the PRA range; only for the highest values, the effects of the three drugs were similar. Taken together, results show that with some of these drugs 68.9% of cases attained home systolic BP <135 mmHg, but only S achieved this result in a significantly larger proportion of patients (58%). The rate of adverse events was very low; only 2% of patients with S had potassium levels >6 mEq/L.

This is the first study randomly comparing different therapeutic options in patients with RHTN. It has a precise methodological design, with close patient follow-up. The good renal function and low diabetes prevalence found in these patients might explain the low incidence of adverse events, which we might assume as higher in the usual clinical practice. Further studies are needed to analyze whether S is superior to the other options for its diuretic effect (in which case an increase in the diuretic dose could be postulated) or if the hyperaldosteronism present in many patients is added to this effect. A mean sodium decrease close to 2 mEq/L with S should be considered when treating elderly patients. A question that may be posed in the future: will S become now the best fourth drug to treat RHTN, or the medical community will start to use it earlier in the therapeutic strategy, or even in patients with conventional HTN? Would this approach be justified and beneficial, indifferent, or even deleterious? New randomized trials will be able to answer these questions. And for the end, the observation that longer follow-up seems essential to verify the incidence of adverse events and the persistence of a favorable effect.

Safety and efficacy of digoxin use: an exhaustive meta-analysis

Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GY, et al. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. **BMJ 2015;351:h4451. http://doi.org/9kr**

Although used for more than 200 years, digoxin (D) still generates controversies. Among seven random-

ized trials performed in the context of heart failure treatment, the DIG trial, dated 18 years ago, was the most important, evidencing a neutral D effect on mortality and reduced hospitalization. On the other hand, there is no randomized trial using D for the treatment of atrial fibrillation. Faced with this lack or remote clinical trial performance, different registries have suggested that use of D is associated to greater mortality risk (independently of baseline variables indicating its prescription, as D tends to be used in sicker patients).

A systematic review and meta-analysis on this topic has just been released, covering all the medical literature published to date (randomized and observational studies). It explored the Medline (from 1960 to 2014) and Embase (from 1980 to 2014) databases, with the Cochrane collaboration as well as that from additional sources. It initially considered 1,916 publications, 52 of which met the criteria to be analyzed. These 52 publications included 621,845 patients, with 2,248,775 patients followed-up per year. Among them, 23.3% were treated with D; the rest, according to the type of study, with placebo or control. Patients treated with D were in average 2.4 years older, and had a significantly higher incidence of diabetes, atrial fibrillation, heart failure, and use of diuretics and antiarrhythmic drugs. There was a trend of higher prevalence of women and a significant lower use of beta-blockers.

An adequate analysis of mortality could be performed in 41 studies. In some studies, more than one type of comparison was made between D and placebo or control, so that the total number of comparisons was 75. The association of D treatment with higher mortality varied according to the study design. In unadjusted, observational studies (33 comparisons), D was associated to RR or HR of 1.76 (95% CI 1.57-1.97). In observational, multivariate, adjusted studies, RR (8 comparisons) was 1.61 (95% CI 1.31-1.97), while HR (14 comparisons) was 1.17 (95% CI 1.07-1.29). When observational studies tried to match treated and untreated patients by a series of baseline characteristics based on a propensity score for D use, RR (6 comparisons) was 1.18 (95% CI 1.09-1.26), while HR (7 comparisons) was 1.07 (95% CI 0.96-1.19). Finally, in 7 randomized studies, RR was 0.99 (95% CI 0.93-1.05).

Use of D was associated with a reduced risk of hospitalization (95% CI 6%-11%), and limited information due to the number of observations suggested that serum digoxin levels between 0.5-0.9 ng/mL were associated with lower mortality and higher levels with worse prognosis.

This complete analysis suggests that studies with higher bias risk (unadjusted observational studies) assign higher risk to D; as the bias risk is lower, the association of D with higher mortality decreases, until in randomized studies, excess risk is null. Does this definitely solve the discussion? If randomized studies include highly selected populations, their internal validity is high, but the external validity is threatened. What would be D behavior today, with a standard of heart failure treatment very different from that in the DIG study, and broader inclusion criteria? The greater use of beta-blockers and antialdosterone drugs, would it allow the manifestation of the beneficial effects of the drug by decreasing the risk of arrhythmia and digitalis toxicity, or, on the contrary, it would turn D into an inefficient treatment, unable even of reducing hospitalization? And what would be the results of its use in the treatment of atrial fibrillation, in the context of a clinical trial? New trials, more pragmatic in patient inclusion, seem necessary. And, what is to be done until they are performed, or even worse, if this never happened? We should be careful when using it, considering all the available evidence, including observational data, which although biased, also count: careful with the dosage, the renal function, the patient's weight, the electrolyte measurements and the presence of baseline arrhythmia. Serum digoxin level assessment may be, with all its limitations, in patients at greater risk, a way of decreasing it.

Incidence of coronary heart disease and stroke: the risk of working too much

Kivimaki M, Jokela M, Nyberg ST, Singh-Manoux A, Fransson EI, Alfredsson L, et al. Long working hours and risk of coronary heart disease and stroke: a systematic review and meta-analysis of published and unpublished data for 603,838 individuals. **Lancet 2015;386:1739-46. http://doi.org/9ks**

Although there are meta-analyses demonstrating an excess risk in the incidence of coronary heart disease in persons working more hours per week, some doubts may be posed: the possibility of publication bias (only positive result studies are published, the possibility of reverse causality (patients with prior undiagnosed disease reduce their working time, and are those who present more frequent events, weakening the possible association), and the lack of consideration that the socioeconomic level may play as confounding variable (in developed countries persons of higher socioeconomic level work more hours, but the poor suffer the greatest incidence of cardio and cerebrovascular disease). To overcome these limitations the authors of the study performed a systematic review and meta-analysis of published and unpublished cohort prospective studies and analyzed the overall data and also after exclusion of those having presented events in the first 3 follow-up years (to rule out the reverse causality risk). Excess of working hours was uniformly considered as ≥55 hours per week. A total of 25 studies were included (6 of them published) from Europe, Israel, United States and Australia.

The association between working hours and the incidence of coronary heart disease (death or infarction was explored in 22 of these studies (5 published and 17 unpublished). A total of 603,838 persons free from

known coronary heart disease were considered at inclusion, with mean follow-up of 8.5 years. Compared with the other categories, the ≥55 hours per week category was associated with a RR adjusted by age, sex and socioeconomic level of 1.13 (95% CI 1.02-1.26, p=0.016). No significant differences were found when considering region, published or unpublished studies, as well as taking or not into account the events of the first 3 follow-up years. In high quality studies, a subanalysis gave a significant result: working many hours was associated with a clear excess of coronary artery events in patients with low socioeconomic level (RR 2.18, 95% CI 1.25-3.81, p=0.006), but not in those of intermediate or high level.

Fourteen studies (only 1 published) explored the relationship of working hours with the incidence of stroke. They considered 528,908 persons, free from stroke at the time of inclusion, and mean follow-up of 7.2 years. The association with working hours was stronger than for coronary heart disease. Compared with the rest of categories, the ≥55 hours per week category was associated with a RR adjusted by age, sex and socioeconomic level of 1.33 (95% CI 1.11-1.61, p=0.002). A clear dose-response relationship was seen when categorizing working hours: compared with those working 36-40 hours per week, a progressively greater incidence of stroke was observed in those working 41-48 hours (RR 1.10, p=0.024), 49-54 hours (RR 1.27, p=0.02) and more than 54 hours (as already seen, with RR 1.33).

This analysis shows a certain risk of coronary heart disease and more marked risk of stroke in patients whose working time exceeds 55 hours. The reasons of the authors are speculative and stem from considering that those working more hours are seated, then linking the time spent working with the known association between physical inactivity and vascular risk (due to higher inflammatory and neurohumoral activity, endothelial dysfunction and risk of thrombosis). It is a pity that risk could not be adjusted by the presence of coronary artery risk factors, as well as not considering the influence of the type of work. Is the risk the same for those who work many hours, in which they develop a physical activity compared with those with intellectual or management work? The coronary artery disease analysis according to the socioeconomic level might suggest that this is not the case: the risk of those who work too much is very high in those at the low socioeconomic level (in people where a more physically active work is assumed) and not in those of intermediate or high levels (who are presumed to spend more hours seated).

Finally, a comment on the discussion: the authors point out that considering the excess of events in this group, more attention should be paid in them to primary prevention, working on traditional risk factors. It is surprising that there is no mention of considering working condition improvement of those who develop a sedentary work for many hours (for example, providing protected time to make some type of physical activity) or make long working hours unnecessary to obtain an adequate retribution in people of the lower socioeconomic level.

Contemporary ways of cardiovascular disease presentation: are there differences between men and women?

George J, Rapsomaniki E, Pujades-Rodriguez M, Shah AD, Denaxas S, Herrett E, et al. How Does Cardiovascular Disease First Present in Women and Men? Incidence of 12 Cardiovascular Diseases in a Contemporary Cohort of 1 937 360 People. **Circulation 2015;132:1320-8. http://doi.org/9kt**

In the last decades we have assisted to a decrease in the incidence of acute myocardial infarction (AMI) and stroke in developed countries. However, other manifestations of cardiovascular disease (CVD), as angina, do not seem to have had the same evolution. It is understood that once the symptoms of CVD appear, primary prevention ends and secondary preventions begins. Is the form of CVD presentation different in men and women? Is the male sex an equally strong risk factor for all the conditions that express this disease? The aim of this contemporary British cohort study was to answer these questions. It presents as a point of interest that it was based on the analysis of electronic data-associated registries: a primary prevention registry representing 4% of the English population, which is characterized in terms of age, sex and socioeconomic level; one of hospitalization for acute coronary syndrome; one about the diagnosis and elective and urgent procedures at the hospitals of the English national health system, and death statistics.

A total of 1,937,360 patients at least 30 years old, free from known cardio or cerebrovascular disease at inclusion were selected and followed-up for at least 1 year. The primary endpoint was the initial presentation of CVD in any of the following manifestations: stable angina, unstable angina, nonfatal AMI, heart failure (HF), unexpected coronary heart disease, a composite of cardiac arrest, sudden death and ventricular arrhythmia, transient ischemic attack (TIA), ischemic or hemorrhagic stroke, abdominal aorta aneurysm (AAA), peripheral vascular disease (PVD), and unspecified stroke or coronary heart disease cases. Age (by decade), sex adjusted by age as continuous variable, presence of traditional cardiovascular risk factors, treatment with statins and antihypertensive drugs, and use of contraceptive agents in women were considered for the analysis.

As befitting a primary prevention population, the cohort was young (41.5% had between 30 and 39 years, and an additional 20.9% between 40 and 49 years; only 10.4% were 70 years or more) with prevalence of men up to 49 years, and women at more advanced ages. The incidence of hypertension increased with age, with more women receiving treatment; use of statins was

low, and medication was more prevalent in men.

In a median follow-up of 6 years, 6% of cohort participants presented with some manifestation of CVD, with men representing 52% of cases. The presentation condition differed according to age and sex. The most frequent presentation in men was nonfatal AMI (almost 20% of cases versus slightly more than 10% in women, and with higher incidence in all age groups until they became matched at 80 years). Logically, the older the age, the lower the incidence of AMI as initial disease manifestation; therefore, in patients between 30 and 39 years, nonfatal AMI represented 27.9% of events in men and 11.2% in women, whereas it was approximately 10% in men and women ≥80 years. The presentation as stable or unstable angina was similar in men and women, and tended to decrease with age. However, the incidence of HF as first expression of CVD started to increase at 60 years in both sexes, becoming the most frequent initial presentation in patients above 80 years. Similarly, the presentation of TIA or stroke increased with age and was more frequent in women.

Women were older than men. An analysis of the association between age-adjusted sex and initial CVD presentation revealed that male sex is not equally strong as predictor of all conditions: the HR was <1.5 for TIA, hemorrhagic stroke and unstable angina, between 1.5 and 2 for stable angina, ischemic stroke, HF, PVD and sudden death, and between 3.6 and 5 for AAA, nonfatal AMI and sudden coronary heart disease death. Only in the case of subarachnoid hemorrhage, male sex appeared as a protective factor, with an age-adjusted HR of 0.69.

This cohort study reveals the importance of having quality records, and the level of information that can be achieved when you have them. Knowing the different incidence of cardiovascular conditions according to age and sex helps to adopt adequate decisions in public health management as well as in individual practice. One of the strengths of this study was not considering hospitalized patients only. The data presented with questions about whether it is adequate to use the same cardiovascular risk score in all primary prevention patients, regardless the dissimilar incidence of different pathologies according to age and sex, in order to adopt the best decisions in each case; for example, in the case of hypertension, favor the use of renin-angiotensin system antagonists or inhibitors if the risk of HF prevails. New rules for more specific prediction of different CVD may be necessary, although it is true that we must still work in a wider implementation of the ones we have.

Orthostatic hypotension, a neglected factor or marker of worse prognosis

Ricci F, Fedorowski A, Radico F, Shah AD, Denaxas S, Herrett E, S et al. Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. **Eur Heart J 2015;36:1609-17. http://doi.org/9kt**

Orthostatic hypotension (OH) is defined as the drop of systolic blood pressure ≥20 mmHg or diastolic blood pressure ≥10 mmHg when standing up, or in a tilt test at 60°. Its prevalence is variable, and usually associated with cardiovascular, renal, neurodegenerative or metabolic disease. It expresses structural (in less than 10% of cases) or functional autonomous nervous system involvement. In the latter case, it can be ascribed to drug action (alpha and beta-blockers, antiarrhythmic, antidepressant, vasodilator and other agents) or to hypovolemic conditions. In a third of cases, no demonstrable cause is found. Although it may generate symptoms associated with cerebral hypoperfusion, even resulting in syncope, in many occasions it is unnoticed by patients, leading to subdiagnosis. Its diagnostic repercussion was so far unclear. A meta-analysis of observational studies comes to fill this void.

Studies published in English between 1966 and 2003, with a minimum 6-month follow-up, at least 100 cases of OH, and with reference of patient outcome regarding death, incidence of cardiovascular disease, heart failure and/or cerebrovascular accident were selected for the analysis. Thirteen studies of 12 United States and European cohorts were included, with a total population of 121,913 patients and an overall median follow-up of 6 years. Prevalence of OH ranged between 4.6% and 42.5%.

Ten studies (n=65,174) explored the relationship between OH and total mortality, resulting in RR of 1.50, 95% CI 1.24-1.81. The association was higher in patients <65 years, with RR 1.78 (95% CI 1.25-2.52) than in the older subgroup, where borderline statistical significance was attained (RR 1.26, 95% CI 0.99-1.62). A high heterogeneity was found in the results.

Four studies (n=49,512) assessed the association of OH with the incidence of coronary heart disease. Although the overall association was positive (RR 1.41, 95% CI1.22-1.63), results were only evidenced in 2 of the 4 studies.

In 3 studies (n=50,096) a strong association was demonstrated between OH and the incidence of heart failure (RR 2.25, 95% CI 1.52-3.33). Finally, 5 studies (n=58,300) examined the association of OH with the incidence of cerebrovascular disease. A positive association was found (RR 1.64, 95% CI 1.13-2.37), though it should be noticed that only 3 of the 5 studies revealed this finding.

Multivariate analysis could not demonstrate the influence of age, sex, traditional risk factors, study quality or follow-up time in the associations.

Several reasons explain why OH is associated with worse prognosis. There is an association with old age, diabetes, Parkinson disease, carotid atherosclerosis and use of different drugs that cannot be ruled out and was not completely explored in the meta-analysis. The greater risk of OH in younger patients seems to indicate that it has a primary role in this age group or suggests a more severe underlying disease, whereas in elderly patients it is another expression of old age. The

mechanisms that might explain its effect in the outcome could be sympathetic and endothelin activation accompanying autonomic dysfunction, many times in the form of "bursts" implying enhanced platelet activation and risk of thrombotic event, as well as repeated episodes of cerebral or myocardial ischemia. It is still not clear whether OH is a true risk factor, an intermediary of other mechanisms or simply a more severe disease marker. What is evident is that it is an aspect we should explore in daily practice, especially when deciding antihypertensive, diuretic or vasodilator treatment.

Hypertension is a predictor of new onset diabetes: results of a cohort study of more than 4 million persons and a meta-analysis of observational studies.

Emdin CA, Anderson SG, Woodward M, Rahimi K. Usual blood pressure and risk of new-onset diabetes: evidence from 4.1 million adults and a meta-analysis of prospective studies. **J Am Coll Cardiol 2015;66:1552-62. http://doi.org/f3jg8j**

The association between hypertension (HTN) and type 2 diabetes mellitus (DM2) is well known. It is not clear, however, if HTN is a predictor of new onset DM2. Cohort study results are not conclusive; in some the association does not exist, in others it does, but with different strength. We present a cohort study performed in the United Kingdom using a database of electronic records of subjects seen in primary care, free from vascular disease or DM at the time of the first visit. The study included subjects seen between 1990 and 2013, aged between 30 and 90 years and who had had at least one blood pressure (BP) measurement. It explored the association between the initial BP measurement and the incidence of DM2 at follow-up. To avoid regression dilution bias to the mean (a single BP measurement may have excess or defect estimation error from the usual BP), both the initial as subsequent BP measurements during follow-up were used to estimate, by means of a complex statistical procedure, the "usual BP" at the time of inclusion.

Overall, 4,132,138 subjects were included in the study. Median age was 46 years, 55.9% were women and median follow-up was 6.8 years. Baseline BP was an independent predictor of DM2 incidence. After adjusting for age, sex, body mass index (BMI), smoking, antihypertensive treatment and use of statins, every 20 mmHg increase in systolic BP was associated to DM2 incidence with a HR of 1.58 (95% CI 1.57-1.60) and every 10 mmHg increase in diastolic BP, with a HR of 1.52 (95% CI 1.51-1.54). In the case of systolic BP, the association was maximal for values between 120 mmHg and 150 mmHg. The relationship reached a plateau with values below 120 mmHg and above 150 mmHg. A continuous relationship was found for diastolic BP between 70 and 100 mmHg.

Systolic BP as predictor of DM2 incidence was influenced by baseline variables. Thus, for example, for every 20 mmHg the HR was 1.89 if BMI was ≤25 and only 1.19 if BMI was >35. Nevertheless, the absolute number of cases was greater in this subgroup due to the greater risk of DM2 when BMI is elevated. Similarly, in patients from 30 to 50 years of age, the HR was 2 for every 20 mmHg compared with 1.14 among those from 70 to 90 years. However, in absolute values, the increase in BP translated to more DM2 cases in elderly patients.

When compared with the same model, systolic and diastolic BP values preserved their association with DM2, with a HR of 1.42 and 1.51 for every 20 mmHg and 10 mmHg, respectively, increase in BP.

To afford greater reliability, the authors also performed a meta-analysis of 30 prospective observational studies with 285,664 patients; the association of HTN with DM2 had a HR of 1.77 (95% CI 1.53-2.05) for every 20 mmHg increase in systolic BP. This HR was not statistically different from the one found in the cohort study of more than 4 million patients.

The first comment emphasizes, once again, the great importance of having large population registries encompassing different aspects of public health, from primary care to death. These registries, an expression of national resolve, allow, due to the enormous number of patients included, a true epidemiological vision that impacts on significant decision-making. Specifically returning to the results of this study, different reasons might explain why HTN increased the risk of developing DM2. The first is considering that high BP, per se, by generating endothelial dysfunction, has a diabetogenic effect increasing insulin resistance. The frequent association of HTN with obesity could also be posed as a risk factor for DM2 incidence. If this were so, every antihypertensive treatment should reduce this prevalence, and we all know this is not the case. In fact, among antihypertensive drugs, renin-angiotensin system antagonists/inhibitors (RASA) have been shown to decrease the prevalence of DM2, while other drugs, as diuretics, calcium antagonists and most beta-blockers do not reduce and even increase it. That is why it has been postulated that in the pathophysiology of HTN, RAS activation causes the greatest incidence of DM2 and not high BP. Carvedilol, however, has also been shown to reduce DM2. Are then the rest of the drugs ineffective, or other adverse effects on hydrocarbon metabolism oppose the beneficial influence of BP lowering? Finally, it is worth remembering that this work is in line with that of Izo et al., mentioned in this same section in the first issue of the 82nd volume of the Journal, in which preclinical damage expressed as ventricular hypertrophy or carotid atherosclerosis was precursor of DM2 in hypertensive patients.

When sending text messages is a medical act: results of a randomized study

Chow CK, Redfern J, Hillis GS, Thakkar J, Santo K, Hackett ML, et al. Effect of lifestyle-focused text messaging on risk factor modification in patients with

coronary heart disease: a randomized clinical trial. **JAMA 2015;314:1255-63. http://doi.org/9mn**

We all know the measures we must adopt in cardiovascular disease primary or secondary prevention, acting on blood pressure (BP), carbohydrate and lipid metabolism, body weight and physical activity. Nevertheless, achieving the goals recommended by the different practice guidelines is still difficult, and patient compliance to medical prescription is poor. In the last years, and thanks to the development of cell phones, text messaging (SMS) to patients reminding them of the different measures they must follow, from hygiene and dietary ones to adherence to the pharmacological treatment, has been suggested as a strategy that could greatly strengthen the traditional advice at consultation. Different randomized studies have explored the effect these messages have on the fulfillment of specific goals.

The randomized, single-center, single blind TEXT ME study was performed at a university hospital in a district of Sidney, Australia. The district has a large proportion of foreigners and represents a wide socioeconomic range. Patients >18 years, with history of cardiovascular disease, who owned a cell phone and had an acceptable knowledge of English were selected for the study. They were randomly assigned to receive or not, in addition to the usual prescriptions and recommendations, semi-personal SMS from an interphase in the web, at a rate of 4 weekly SMS during 24 weeks. Messages were randomly sent in different moments of the day, focusing on behaviors and medications that the patient had to take, asking about his compliance or inducing him to follow it. Only smokers received advice on how to quit smoking and only those who normally ate meat received messages concerning the convenience of limiting its consumption. Some SMS were specifically addressed to the name of the recipient. At study initiation, patients who were assigned to be SMS recipients received one message asking them not to mention this to the treating team in order to preserve the blind condition. The primary endpoint was the 6-month change in LDL cholesterol; other endpoints were BP reduction, change in body mass index (BMI) and the percentage of patients in each group that attained the five goals proposed: LDL <77 mg/dL, BP <140/90 mmHg, BMI<25, non-smoking status and 30 minutes of moderate regular exercise, at least 5 days a week.

A total of 710 patients were included in the study, with mean age of 57.6 years. Mean LDL cholesterol was 101 mg/dL, BP 129/83 mmHg and BMI, 29.7. Fifty-three percent of patients were current smokers. Regarding medical treatment, 93.2% were receiving aspirin, 88.5% statins, 71% beta-blockers and 66.2% renin-angiotensin system antagonists/inhibitors. At 6 months, all the variables in the group that received SMS improved, though the magnitude of the change was different. The mean LDL difference between the group that received SMS and that which did not, was only 5 mg/dL (p=0.04); 8 mmHg for systolic BP and 3 mmHg for diastolic BP (p<0.001); 1.3 for BMI (p <0.001), and 293 MET for weekly physical activity (p=0.003). The prevalence of smokers was 26% in the SMS group and 42% in the other group (p <0.001). Three goals were achieved by 62.7% of the SMS group compared with 33.6% in the other group; four or more goals by 28.9% vs.10.3% and the five goals by 4.7% vs. 1.8%. The differences were significant in all cases.

This study has the merit of being randomized and having explored a group of goals in secondary prevention and not just one objective. Considering the expected results, the descent achieved with LDL cholesterol was poor, but not the decrease in BP and weight, and the increase of physical activity and smoking abandonment. The importance of reinforcing recommendations and prescriptions with almost daily reminders during weekdays is undeniable. Some points deserve to be taken into account: the study postulated laboratory or physical exam endpoints, not clinical endpoints. It could not have done so, due to the small amount of patients and short follow-up time. Although the cost seems initially low, there was no formal cost-effectiveness analysis that considers avoided events. The wide use of cell phones undoubtedly implies an opportunity to improve patient adherence, and what was presented in this article is one of the options to achieve it.

Do renin-angiotensin system antagonists decrease mortality in patients with heart failure, low ejection fraction and renal insufficiency? Results from a registry.

Edner M, Benson L, Dahlstrom U, Lund LH. Association between renin-angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study. **Eur Heart J 2015;36:2318-26. http://doi.org/9qs**

Numerous randomized studies have shown that renin-angiotensin system antagonists (RASA) in patients with heart failure and ejection fraction <40% (HFLEF) decrease mortality. Therefore, use of angiotensin-converting enzyme inhibitors (ACEI), and in intolerant patients, angiotensin II receptor blockers (ARB) is a Class I indication in all clinical practice guidelines on this topic. Prevalence of renal insufficiency is high among HFLEF patients. However, the clinical trials we mention consider creatinine levels above 2, 2.2, 2.5 or 3 mg/dL as exclusion criteria , and creatinine clearance <30 ml/min is usually assumed as a contraindication for the use of RASA in this type of patients. Thus, it is unknown whether in patients with severe renal insufficiency (RI) and HFLEF there is a positive prognostic influence of RASA. At the lack of data from randomized trials, the Swedish HF Register decided to study the evolution of these patients in daily practice, according to their treatment or not

with RASA. The study included patients incorporated to the registry (at discharge in those who had been hospitalized, or in the first visit of ambulatory ones) between 2000 and 2013, with HFLEF and severe RI (creatinine >2.5 mg/dL o creatinine clearance <30 ml/min as defined by the Cockcroft-Gault eqaution).

In this period, 24,283 patients were incorporated to the registry, 2,410 of whom (9.9%) complied with inclusion criteria for this study. Among them, 1,602 (66%) were treated with RASA and the rest did not receive this treatment. Patients treated were slightly younger (mean age 82 vs.83 years) and mean creatinine clearance was marginally higher (24 vs. 22 ml/min). Survival was significantly higher in all the treated patients, at 1 year (61% vs.42%) and 5 years (17% vs. 7%), with an overall HR of 0.61, 95% CI 0.56-0.67.

As, logically, treated and untreated patients had different baseline characteristics that might explain the indication or not of RASA as well as dissimilar diagnosis, we attempted to match them by these variables. Multivariate analysis was performed to define the independent predictors of RASA use, and a propensity score was built for each patient (based on 36 variables) expressing the probability that he had been prescribed the medication. Regardless the propensity score, the patient was really or not treated with RASA. A cohort of patients treated or not treated with RASA, matched in a 1:1 ratio according to their propensity score, was then generated. Thus, two cohorts of 602 patients were defined (one with and the other without RASA), with mean age of 83 years, two thirds in FC III-IV, more than half with EF 30-39% and the rest with EF <30%. Average creatinine clearance was 23 ml/min. Among treated patients, RASA drugs were ACEI in 67% of cases, ARB in 31% and both drugs in the remaining 2%. Despite propensity score matching, use of beta-blockers was higher in those treated with RASA (91% vs. 85%); p=0.005). Again, the prognosis was better in treated patients, with 55% vs. 45% survival at 1 year and 15% vs. 8% at 5 years, with an overall HR of 0.76, 95% CI 0.67-0.86. Another analysis was performed of RASA treated and untreated patients to explore the consistency of results, also matched by propensity score, with HFLEF but without severe RI. In this analysis, the HR for mortality was 0.79, similar to that of RI patients.

This analysis of a large population registry attempts to respond a question that cannot be answered with hereto known randomized clinical trials: what is the effectiveness of RASA treatment in patients with HFLEF and severe RI. As every observational study, usual queries can be posed, i.e. despite the effort of trying to balance treated and untreated patients by baseline characteristics (in this case matched by propensity score, in others by multivariate analysis), the truth is that there can be residual confounders: presence of unknown variables associated to RASA indication and which are the real effectors of better outcome. Although this is true, we may also ask what we should do if the randomized study we are waiting for is never done. In this sense, the impression is that in patients with RI and HFLEF there may be room for RASA and that, with closer surveillance, this could lead to a better prognosis. In this sense, and with the same caution, we may comment the work of Molnar et al. (commented in this section, Rev Argent Cardiol 2014;82:177-82) pointing out a better prognosis with the use of RASA in patients with RI.