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Comparison between different strategies to prevent contrast-induced nephropathy: the PRESERVE Study

Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin SS, et al. Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine. **N Engl J Med 2018;378:603-14. http://doi.org/cnw3**

Contrast-induced nephropathy (CIN) is defined as renal function impairment following administration of intravenous iodine contrast in different imaging studies. An increase in creatinine >25% or >0.5 mg/dL, which may reach its peak between the third and fifth day, is usually considered as cutoff value. It has been pointed out that CIN is associated with worse prognosis and different measures are taken to prevent it. Administration of isotonic saline solution (SS) before and after the diagnostic procedure is the most frequent step. Its mechanism of action points to the dilution of the contrast medium to attenuate its direct toxic effect, and to reduce activation of the renin angiotensin system, that due to renal vasoconstriction can generate spinal hypoxia and increase the risk of nephrotoxicity. But different protocols recommend the infusion of sodium bicarbonate (SB), under the assumption that urine alkalinization can decrease epithelial damage in the renal tubules induced by contrast, or oral administration of N-acetylcysteine (NAC), considering its ability to prevent the effect of reactive oxygen species formed by the effect of iodinated substances. Each of these measures has been shown in some studies to decrease the incidence of CIN, but the results have not been uniform. On the other hand, in general, the endpoint has been the change in creatinine level, without evidencing a clear clinical effect in terms of serious adverse event reduction (sustained renal function impairment, need for dialysis or death).

To clarify this point, the randomized PRESERVE study was carried out with a 2×2 factorial design, comparing SS 0.9% (154 mmol/L) vs. SB 1.26% (150 mmol/L) and in parallel NAC vs. placebo. Four groups were thus defined: SS-NAC, SS-placebo, SB-NAC and SB-placebo. It was carried out in 53 centers in the USA, Australia, Malaysia and New Zealand, including patients undergoing a coronary or non-coronary angiography, and who had glomerular filtration rate between 15 and 44.9 ml/min/1.73 m2 according to the MDRD formula, or between 45 and 59.9 ml/min/1.73 m2 if they were also diabetic. Emergency patients and those presenting instability in creatinine values, defined as a variation ≥25% in the last 3 days, were excluded.

In the comparison between SS and SB, an infusion rate of 1-3 ml/kg/h was established in 1 to 12 hours prior to angiography, at the discretion of the treating physicians, to total 3-12 ml/kg; 1-1.5 ml/kg/h during the procedure and 1-3 ml/kg/h in 2 to 12 hours after the procedure, to total 6 to 12 ml/kg. In the comparison between NAC and placebo, 1200 mg was indicated one hour before, 1200 mg in the following hour and then 1200 mg every 12 hours in the following 4 days. The final endpoint was the combination of death, need for dialysis (90 days after the procedure) or sustained renal function impairment (increase in creatinine ≥50% compared to baseline, confirmed in a second measurement at 14 days) evaluated at 90-104 days after the procedure. The secondary endpoints consisted of the individual components of the primary endpoint, and the incidence of CIN defined as indicated above. A total of 7,680 patients were considered to be necessary to demonstrate with 90% power, reduction of the primary endpoint from 8.7% to 6.5% with any of the interventions explored.

The study began in February 2013 and in March 2017, after an interim analysis, when 4,993 patients had been included, it was discontinued due to futility, as no evidence of significant reduction of events was found so far with any of the strategies. Patient mean age was 69.8 years, 93.6% were men and 81% were diabetic. Median creatinine was 1.5 mg/dL and glomerular filtration rate was 50.2 ml/min/1.73 m2. Coronary angiography was performed in slightly over 90% of patients and angioplasty in 28.5%. The contrast media used had low osmolarity or were isoosmolar, as they are the ones that ensure less CIN incidence, and median contrast medium volume was 85 ml. Median volume infused to compare SS vs. SB was 344 ml before, 114 ml during and 570 ml after angiography, similar in both groups. In 81% of cases patients adhered to NAC or placebo treatment. The primary endpoint occurred in 4.4% of patients with SB vs. 4.7% with SS (p NS), and in 4.6% with NAC vs. 4.5% with placebo (p NS). Contrast-induced nephropathy was present in 9.5% of the patients with SB vs. 8.3% with SS (p NS), and in 9.1% with NAC vs. 8.7% with placebo (p NS). There was no interaction between SB and NAC.

The PRESERVE study has two undeniable merits: it is a large study exploring a clinical endpoint, beyond the usual biochemical determinations used to define CIN. In addition, it is a study that included patients with some of the characteristics that make us fear that the phenomenon will occur: those with baseline renal dysfunction, elderly and diabetic. In that sense, its representativeness is unquestionable. Perhaps we can object that the intervention rate was low, which goes

hand in hand with a relatively low amount of contrast, considering that the increase in risk is generally indicated when the volume exceeds 100 ml. Similarly, we did not know how many had ventricular dysfunction, and what was the prevalence of hemodynamic involvement at the time of the study. Although it may be argued that the evidence is not conclusive due to the early suspension of the study, the number of patients included and the clear lack of difference in favor of any of the strategies seems irrefutable. Although it could be sustained that there are delineated subgroups in which a strategy could offer better results, it is difficult to presume that in the future there will be another study with a clinical endpoint and enough number of patients. Use of SS is generally recommended by practice guidelines. Although the results of this study can be read as validating this point, it is not less true that with the use of SB there was a similar outcome, so we could not appreciate the advantage for either of the two expanders. However, it is clear that the use of NAC in this context seems to have little sense.

The CASTLE-AF trial: Can catheter ablation for atrial fibrillation in patients with heart failure offer prognostic improvement?

Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. **N Engl J Med 2018; 378: 417-27. http://doi.org/cnw2**

Atrial fibrillation (AF) and congestive heart failure (CHF) usually coexist. Each overshadows the forecast of the other. In the context of CHF with AF, some studies, the most important of which was the AF-CHF trial, could not demonstrate that a rhythm control strategy was superior to one based on heart rate control. It has been said that part of the explanation for this phenomenon must lie in the fact that the drugs used to control rhythm (amiodarone, for example) have adverse effects and their effectiveness decreases with the passage of time, allowing reappearance of the arrhythmia. For years, the treatment based on the use of catheters for AF ablation has been added to the rhythm control strategy. There have been a series of small studies, with selected patients, in which AF ablation has generated an increase in left ventricular ejection fraction (LVEF) and symptomatic improvement, but there has been lack of firm evidence on improvement of more significant endpoints.

The CASTLE-AF trial selected patients with CHF, LVEF ≤35%, in functional class II to IV, with paroxysmal or persistent AF, who rejected antiarrhythmic treatment with drugs, or in whom drugs failed or generated significant adverse effects. To ensure adequate monitoring of their outcome during follow-up, they should have implanted cardioverter defibrillator alone or combined with a resynchronizer to allow daily monitoring of rhythm and detection of AF recurrence. Patients were randomly assigned in a 1: 1 ratio to drug treatment (with the aim of controlling rhythm or heart rate at the choice of the attending physician) or to undergo pulmonary vein isolation (with additional lesions according to their understanding) to achieve ablation of the arrhythmia. When heart rate control was chosen in the medical treatment (MT) group, an objective of 60-80 beats/minute at rest and 90-115 in moderate activity was imposed. In the ablation group, the operators should have at least an experience of 50 previous procedures Ablation was not performed in patients with left atrial appendage thrombus until its resolution. In all cases, warfarin was administered for 6 months after the procedure. After enrolling in the study, each patient went through a 5-week run-in phase during which the CHF treatment was adjusted. Recurrence was defined as the appearance during follow-up of AF lasting at least 30 seconds in device monitoring. The primary endpoint was a composite of death or hospitalization for CHF. It was postulated that the study would end when 195 events had occurred, with preliminary interim analyses when the first 65 and 130 events had taken place. It was thus assumed that a significant difference with 80% power would be detected with 33% risk reduction in the ablation group compared with the MT group. A modified intention-to-treat analysis was planned, in which events occurring during the run-in phase were not considered, and in which in the first 12 weeks after the procedure only deaths were considered, but not hospitalizations.

The study began in January 2008, and was carried out in Europe, the USA and Australia. Up to January 2016, 3,013 patients had been considered for inclusion, among which 398 were enrolled and only 363 (12%) were effectively included after 5 weeks of run-in phase (179 in the ablation group, 184 in the MT group). Since the inclusion rate was very low, when only 133 events had occurred, the study was discontinued. Until then, median follow-up in the two groups had been slightly above 3 years. Median age was 64 years and median LVEF 32%. Almost 60 % was in FC II and 28% in FC III. Despite the inclusion criteria, 11% of patients were in FC I, and less than 2% in FC IV. In 46% of cases the treatment with amiodarone had not been effective, in 13% it had generated significant adverse effects and in the rest of the cases patients had refused to receive it.

In the ablation group, this was effectively carried out in 84.4% of patients (average of 1.3 procedures per patient; in 24.5% of cases it was necessary to repeat the procedure at follow-up) and the rest was crossed to MT. In the MT group, the heart rate control strategy was used in 70% of cases and rhythm control in the remaining 30%. At follow-up, 9.8% crossed to the ablation group. The primary endpoint occurred in 28.5% of cases in the ablation group and in 44.6% in the MT group (HR 0.62, 95% CI 0.43-0.87). There was a significant reduction in total mortality (13.4% vs. 25%), cardiovascular mortality (11.2% vs. 22.3%) and

hospitalization due to CHF (20.7% vs. 35.9%). At 5 years, the ablation group evidenced a median 8-point increase in LVEF compared with 0.2 in the MT group, and the proportion of patients in sinus rhythm was 63.1% vs. 21.7% ($p < 0.001$).

Although, as already mentioned, previous studies have shown benefit of catheter ablation for AF in patients with CHF, this is the first to show evident clinical advantage. To the already proven improvement of LVEF (almost 8 points increase), CASTLE-AF adds a significant reduction in mortality by half, and almost as much in the risk of hospitalization due to CHF. What are the data that make us doubt about the possibility of generalizing these findings? The study selected patients in whom medical treatment with the best available drug would have failed, or been rejected by them, added to the fact that surely in those who were included the invasive procedure was deemed feasible, for reasons that are not clearly explained. If, in the intervening electrophysiologists' the opinion it was understood that the ablation had little chance of success, either for anatomical or clinical reasons, surely the patient would not have been randomly assigned. As in any randomized study, only those patients in which a priori the probability of success looks similar between the strategies to be compared are included. Therefore, it should be noted that in 8 years only less than 400 patients were included, barely 12% of those initially considered. It is unfortunate that we do not know the differences between the minority that was incorporated in the study and those who were not. Moreover, we do not know what medical treatment was concomitantly used in both groups, and the role it played in the prognostic determination. As the study was not blinded, we can assume that the co-intervention rate may have differed. Nevertheless, the message of the trial is that in clearly selected patients and in expert hands, catheter ablation of AF in the context of CHF is an option to be considered, and that it can be clearly advantageous with respect to MT.

The importance of optimal medical treatment in low-risk stable coronary heart disease: the ORBITA trial

Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. **Lancet 2018;391:31-40. http://doi.org/gctx2p**

It is firmly believed that percutaneous coronary intervention (PCI) for the treatment of chronic stable angina guarantees full symptomatic relief. Previous studies (especially the COURAGE trial) have suggested that in patients with one-vessel lesion, medical treatment (MT) is associated to a similar outcome as that provided by PCI for acute myocardial infarction (AMI) and death. But the concept persists that ischemic relief will be greater with PCI.

As the studies comparing PCI with MT were not blinded, it cannot be ruled out that PCI, beyond its real influence in treating the coronary lesion and increasing oxygen delivery, does not have a placebo effect. That is, the single fact of having undergone the procedure generates in the patient a sensation of improvement. To demonstrate that PCI entails a placebo effect, a coronary angiography should be done and the PCI effectively performed in some patients and not in others. Logically, the patient and the physicians in charge of the patient should ignore whether the procedure was done or not, and it would be optimal to have evidence of the ischemia during follow-up. A study with these characteristics would seem to be impracticable due to ethical reasons. However, the authors of the ORBITA trial developed it achieving more than interesting results.

The ORBITA trial was a randomized study carried out in 5 centers of the United Kingdom. Patients aged 18 to 85 years, presenting with angina or equivalent symptoms, one-vessel disease with ≥70% lesion and candidates for PCI were included in the study. Patients with ≥50% lesion in other vessels, main left coronary artery lesion or chronic total occlusion, acute coronary syndrome, history of myocardial revascularization surgery, severe heart valve disease, ventricular dysfunction or contraindications to receive drug-eluting stents were excluded from the study.

During the enrollment period, the severity of the angina was assessed, heart rate and blood pressure were measured and quality of life questionnaires were administered. The MT of stable angina was then optimized for 6 weeks, according to the guidelines and the patient's clinical situation, followed by a new measurement of the initial variables, with the addition of a stress echocardiography with dobutamine and a cardiopulmonary test of oxygen consumption. The angiography (radial or femoral access) with fractional flow reserve (FFR) assessment was done with the patient under sedation and with headphones to listen to music; he was then randomly allocated to undergo PCI or not. The operating physicians did not know the results of the FFR study. All the patients were pretreated with double antiplatelet therapy which was continued until the end of the study. The procedure was followed by a second double-blind phase lasting 6 weeks, in which neither the physicians following the patients (different from those performing the angiography) nor the patients knew whether the PCI had been performed or not. All the determinations and studies done before the angiography were repeated in the final visit. It was postulated that PCI would result in a 30-second increase in the time of exercise performance measured in the cardiopulmonary test compared with placebo. Two hundred patients would be necessary to demonstrate this effect with 80% power.

A total of 368 patients were selected between 2013 and 2017, among which 230 were enrolled and 200

were finally randomly assigned to PCI (n=105) and placebo (n=95). The average number of antianginal drugs at study initiation was close to 1; after the optimization phase it rose to almost 3 and was preserved for the duration of the study. More than 95% of patients received double antiplatelet and statin therapy, 91% calcium channel blockers and 78% betablockers. The anterior descending artery was the culprit vessel in 69% of cases, the right coronary artery in 16% and the circumflex artery or lesser branches in the remaining cases. Mean stenosis area was 84% and mean FFR 0.69. In the PCI group, FFR rose to 0.90 after the procedure. In all cases, drug-eluting stents were implanted.

In the final visit, no significant differences were found in the studies when compared with those before the procedure. The exercise time increased in average 28.4 seconds in the PCI group and 11.6 in the placebo group (NS), so the difference did not reach the expected 30 seconds. Neither were there differences in peak O2 consumption, the time to the first mm of ST-segment depression and even less in the frequency or stability of angina.

The ORBITA trial is the first randomized PCI study compared with placebo. Its design draws attention, something that pleases the authors, although we should recall that there have been similar approaches in other fields: pacemaker studies in the context of hypertrophic cardiomyopathy (in which the device was activated in one group but not in the other), and the SIMPLICITY 3 study, where renal denervation was tested for the treatment of refractory hypertension, and in which the control group underwent renal arteriography without the patients knowing whether they had effectively undergone the procedure or not (this type of control is called sham, a term meaning false, fake, feigned). In our view, a key moment in the ORBITA trial is the 6 weeks prior to randomization, when MT was optimized. The number of drugs used was tripled, and in the light of results, this had a remarkable effect. So much so, that PCI could no significantly improve the results. This enriches our understanding of the physiopathology of angina and reinforces the role of myocardial oxygen demand. Follow-up was short, leaving us wondering how both treatment groups progressed after the end of the study, and whether the differences continued to be so small. Does PCI lose its status for the treatment of stable coronary disease? Certainly not. In the first place, practice guidelines have reserved a place for PCI when MT fails. And decidedly the study was performed in patients where PCI may not have had much to offer, as they were low risk patients. These results do not apply to patients with lesions in more than one vessel with severe symptoms or extensive ischemia despite the best MT, those with ventricular dysfunction and, of course, with acute conditions. But, they are a warning sign to reinforce the attention that must be given to full MT before embarking in invasive procedures.

A very large meta-analysis confirms that it is false that light smoking implies low cardiovascular risk

Hackshaw A, Morris JK, Boniface S, Tang JL, Milenkovic D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. **Br Med J 2018;360:j5855. http://doi.org/cjvg**

It is usually believed among smokers that light cigarette consumption is tolerable, and even more, that it practically entails no risk. Thus, the phrases "I barely smoke, less than 5 cigarettes a day", or "I only smoke one cigarette after lunch or dinner" commonly appear in the medical consultation, as a kind of safe-conduct that allows them to continue with the habit, several times under the tolerant gaze of the treating physician. A British meta-analysis neatly rejects this belief.

A systematic review was performed of articles published in English between 1946 and 2015 in prospective cohort studies, reporting the association between cigarette consumption and the incidence of coronary heart disease (CHD) and stroke. The studies had to report at least 50 events in a relatively healthy population. The subjects under observation were to be divided into a category of never smokers and at least 3 smoker categories according to cigarette consumption. The articles should be able to discriminate the information for men and women, or at least allow adjusting for age and sex. The measurement of interest was the risk associated to smoking 1, 5 or 20 cigarettes a day compared to no smoking, and the percent risk associated to smoking 1 or 5 with respect to 20 cigarettes a day. For example, if smoking one cigarette per day increases risk by 30% and smoking 20 does it by 80%, the risk involved in smoking one cigarette with respect to 20 will be 30%/80%=37.5%.

The meta-analysis was based on 55 publications referring a total of 141 different cohorts. In the studies reporting the risk for CHD in men, the RR for those smoking one cigarette a day was 1.48 (95% CI 1.30-1.69), for those smoking 5 cigarettes this was 1.58 (95% CI 1.39-1.80) and for the ones who smoked 20 cigarettes a day it was 2.04 (95% CI 1.86-2.24). Smoking one cigarette per day implied a median 46% risk of that involved smoking 20; and smoking 5 cigarettes a median 57% risk of that resulting from smoking 20. In the studies reporting risk in women, smoking 1, 5 or 20 cigarettes per day represented a RR for CHD of 1.57, 1.76 and 2.84, respectively. The risk of smoking 1 or 5 cigarettes was 31% and that corresponding to smoking 20 cigarettes was 46%. We can see that the risk involved in smoking any number of cigarettes was higher in women than in men. In the studies not discriminating risk between men and women, consumption of 1 or 5 cigarettes a day represented 53% and 61% of the risk involved in smoking 20 cigarettes, respectively. While in men the relationship decreased with age (the risk implied in smoking 1 cigarette a day compared to smoking 20 was 35% at 45 years of age

and 20% at 65 years), the reverse was seen in women, with values of 11% and 36%, respectively.

Similar results were obtained when exploring the endpoint of stroke. In men the RR was 1.25 for 1 cigarette a day and 1.64 for 20; in women 1.31 and 2.16, respectively. This means that for both groups, the risk of smoking one cigarette was more than 30% of the risk involved in smoking 20.

The number of observations in each case deserves to be mentioned: in the group of men, a little over 3 million participants in the CHD studies and 3.5 million in the stroke studies; in the group of women, 2.5 and 3.8 million, respectively.

If a linear relationship existed between cigarette consumption and cardiovascular risk, smoking one cigarette per day should represent 5% of the risk entailed by smoking 20. As can be seen from this meta-analysis, we are far away from this assumption. The "innocent" consumption of 1 or 5 cigarettes a day conveys a great share of the risk associated to the consumption of the magical number of 20 cigarettes (daily package). This is because the cigarette components produce such a great effect on the endothelium, with injury, dysfunction, vasoconstriction and platelet aggregation, that minimal exposure is enough to sensibly increase the incidence of events. Some data to be noticed: the proportional risk was greater in women. Since there is lower prevalence of the other risk factors, it is understandable that the difference is greater between women that do and do not smoke, even though consumption is low. The authors also remark that the risk associated to smoking has been growing with respect to non-smokers in the last years. This could be explained by the former inclusion of passive smokers in the non-smoker category, so that the risk relationship between smokers and non-smokers (because the latter were passively exposed to tobacco) was lower. With measures limiting tobacco exposure in public spaces, the difference between smokers and non-smokers becomes more evident. We may regret that this is not a meta-analysis of individual data, and that hence we do not know the real number of daily cigarettes smoked by each individual to categorize the data, but the results are conclusive and different statistical analyses performed by the authors reach similar association measurements. For the same reason, we neither have the time of exposure in each observation, though this information is strongly correlated with age. In conclusion, the patients and we should maximize the measures to ensure smoking cessation if we really wish to diminish risk. No cigarette is trivial.

Three publications on the role of troponin in different clinical scenarios

Troponins I (TnI) and T (TnT) are proteins of the cardiomyocyte contractile apparatus. The increase in their plasma concentration is an essential part of acute coronary syndrome diagnosis and treatment algorithm. But, beyond this context, numerous publications have shown the usefulness of this biomarker in the general population, elderly individuals, patients with chronic cardiovascular disease, and even in extracardiac disorders in hospitalized or ambulatory patients. And the results show that even small troponin elevations are generally associated with worse outcome. We present three studies that contribute to understand the usefulness of their measurement and, as usual, generate new interrogations.

a) Chronic heart failure

Aimo A, Januzzi JL, Jr., Vergaro G, Ripoli A, Latini R, Masson S, et al. Prognostic Value of High-Sensitivity Troponin T in Chronic Heart Failure: An Individual Patient Data Meta-Analysis. **Circulation 2018;137:286-97. http://doi.org/cnwz**

As we know, in the context of chronic heart failure (CHF) troponin levels may be elevated, but different from coronary syndromes, they are lower but persist longer. This increase is attributed to membrane damage, necrosis, apoptosis or cellular autophagy, neurohumoral activation, inflammation or ischemia. A recently published meta-analysis helps to quantify the prognostic value of troponin elevation in CHF patients.

The analysis involved publications in English including patients with CHF having TnI or TnT assessment and long-term prognostic data. The authors of each publication were requested to submit their databases to perform the meta-analysis of individual data. Ten studies with 9,289 patients were included in the analysis, all with TnT assessment (limit for detection: 3 ng/L and normal value up to 14 ng/L) and only 2% with additional TnI measurement. The analysis focused on the predictive value of TnT for 3 endpoints: all-cause death, cardiovascular death and hospitalization for heart failure. Due to the non-normal distribution of troponin and NT-proBNP values, both biomarkers were analyzed using a log2 transformation, since this allows Gaussian distribution and hence a linear relationship with the outcome. Two predictive models were defined: one with sex, age, disease etiology, left ventricular ejection fraction (LVEF), glomerular filtration rate and the logarithm of NT-proBNP, and a second model adding the logarithm of TnT to the previous model variables.

Patient average age was 66 years, 60% had ischemic etiology and 85% LVEF <40%. Median TnT was greater the higher the LVEF: 15 ng/L in patients with LVEF <40%, 18 ng/L in those with LVEF between 40 and 49% and 22 ng/L in cases with LVEF ≥50%. Median follow-up was 2.4 years. Each increase of one unit in the log2 TnT was associated to an adjusted HR of 1.48 (95% CI 1.41-1.55) for total mortality, 1.40 (95% CI 1.33-1.48) for cardiovascular death and 1.43 (95% CI 1.36-1.49) for hospitalization due to heart failure. Nine predictive variables of TnT values were found, and the 3 most important were

age, the logarithm of NT-proBNP and glomerular filtration rate. Nevertheless, the changes in these 9 variables explained only 44% of TnT variation. The predictive model with TnT compared with the one without TnT had better discrimination power, with greater area under the ROC curve: 0.744 vs. 0.715 for total mortality, 0.735 vs. 0.711 for cardiovascular mortality and 0.697 vs. 0.664 for hospitalization due to heart failure. The best cutoff value to discriminate prognosis was 18 ng/L for total mortality, 16 ng/L for cardiovascular mortality and 15 ng/L for hospitalization due to heart failure.

This meta-analysis, valuable because it studies individual data, confirms the predictive role of troponin in the context of CHF, associating its increase with disease progression. In fact, its increase not only predicts mortality, but also hospitalization. It is unfortunate that when referring to mortality, it cannot define the form of death: some publications have pointed out that the increase in troponin also implies increased risk of sudden death, beyond the easily understandable death due to disease progression. However, the similarity of cutoff points to discriminate risk of death and hospitalization also stand out, emphasizing the link between both endpoints and contributing to sustain the idea that fundamentally, death due to disease progression is predicted. A value of 18 ng/L is for the authors the best uniform cutoff point and easily remembered for all the events. It is also interesting to remark that despite all the statistical effort not even half of the source of troponin variation can be defined, which indicates how much is still needed to unravel the physiopathology of the increase. The prognosis of patients with CHF obeys to numerous causes. We do not think that troponin assessment is indispensable to arrive to a prognostic conclusion. However, it is a tool that, whenever available, clearly adds information.

b) Patients with acute coronary syndrome and renal impairment

Miller-Hodges E, Anand A, Shah ASV, Chapman AR, Gallacher P, Lee KK, et al. High-Sensitivity Cardiac Troponin and the Risk Stratification of Patients With Renal Impairment Presenting With Suspected Acute Coronary Syndrome. **Circulation 2018;137:425-35. http://doi.org/cnwz**

Diverse publications have pointed out that in different clinical conditions, patients with renal impairment (RI) usually have more elevated troponin values than their counterparts with normal renal function. This phenomenon might conspire against the specificity of the assessment to diagnose or predict an acute coronary syndrome. A new study has considered patients who presented with suspected acute coronary syndrome at the emergency department of two hospitals in Edinburgh between 2013 and 2016, and had at least one TnI assessment. Patients with ST-segment elevation acute coronary syndrome were excluded from the analysis. The reagent detection limit was 1.2 ng/L, and a 99 percentile value of 16 ng/L was assumed in women and 34 ng/L in men. Values above these limits were considered pathological. Glomerular filtration rate (GFR) was based on creatinine values using the MDRD equation. Values below 60 ml/min/1.73m2 were considered RI. Based on the clinical condition of patients with elevated TnI, type 1 acute myocardial infarction (AMI) was defined as that due to plaque rupture, type 2 AMI to increased oxygen demand or decreased oxygen supply, and injury when elevated TnI was not accompanied by an ischemic clinical condition. Diagnostic and predictive TnI behavior was considered in values of 5 ng/L (ensuring a negative predictive value (NPV) of 99.6%) and in values above the 99 percentile, to explore a positive predictive value (PPV).

Among 4,276 patients with at least one available creatinine value, 904 (19%) presented RI, in 85% of cases with GFR between 30 and 59 ml/min/1.72 m2. Patients with RI were older, with greater proportion of women and greater prevalence of coronary risk factors, except smoking. These patients were more frequently receiving antiplatelet agents, betablockers and statins. The incidence of AMI and TnI values were significantly different from patients with normal renal function-

Among patients with RI, type 1 AMI was present in 23% of patients and type 2 AMI in 7%. Only 17% of patients had TnI <5ng/L. Among these patients, slightly more than 1% presented type 1 or type 2 AMI, or death at 30 days (sensitivity 98.3%, NPV 99.3%). Forty percent of patients with RI had values above the 99 percentile, but the assessment was not very specific, only 70.9%, with only 50% PPV for type 1 AMI.

Conversely, among patients without RI, type 1 AMI was present in 12% of patients and type 2 AMI in 3%. Fifty six percent of patients had TnI <5ng/L and in this subgroup AMI was diagnosed in only 0.3% of cases (sensitivity 98.8%, NPV 99.8%). Fifteen percent of patients had values above the 99 percentile, and the assessment was more specific than in the previous case, 92.1%, with 62.4% PPV for type 1 AMI.

Forty-six percent of patients had more than one TnI assessment. Among patients with RI, the combination of a first value >99 percentile plus 20% difference of the second value with respect to the first, increased specificity to almost 80%, but at the expense of decreased sensitivity. Among patients without RI, this procedure did not increase specificity but reduced sensitivity. In both groups of patients, the presence of elevated TnI levels implied increased risk of events at one year, but the impact was greater in patients with RI (24% vs. 10%, adjusted HR 2.19, 95% CI 1.54-3.11). Increased troponin below the 99 percentile also implied greater risk in patients with RI: for each double increase in values, the adjusted HR was 2.62 vs. 1.42 in those with normal renal function.

The first point that deserves to be considered is

the bad prognosis RI entails: it doubles the incidence of type 1 and type 2 AMI compared with those with normal renal function. Different reasons explain this phenomenon; patients with RI have greater prevalence of risk factors with the addition of neurohumoral activation, inflammation, endothelial dysfunction and malnutrition. These patients have greater prevalence of anemia, which contributes to explain especially the higher incidence of type 2 AMI when confronted with increased myocardial O2 demand. As we see, their troponin values are higher, and few patients have low values: in this study, only 1 out of every 5 patients had TnI <5 ng/L, compared with more than half of the patients with normal renal function. And although, this result is associated with greater incidence of AMI among patients with RI, we must not forget that 70% of them did not have AMI. That is why specificity for the diagnosis of AMI was only 70% and the PPV value was similar to flipping a coin: 50%. In this context, two assessments may somehow improve specificity, but at the expense of decreasing sensitivity. We should emphasize that this troponin elevation attributed to RI and which is not AMI is not innocuous: it implicates more extensive vascular and metabolic disease and has also prognostic value, even though it does not require urgent coronary angiography. Can the specificity of its assessment in patients with RI be improved to diagnose AMI? Some publications report that in stable patients TnI circulates in very small fragments, whereas in an acute coronary syndrome intact larger fragments are released to the circulation. It remains to be seen whether progress in TnI assessment helps to differentiate these conditions, but in the meantime let us know that elevated troponin is not a phenomenon we should rule out in the patient with RI.

c) Troponin and healthy lifestyle

Fretz A, McEvoy JW, Rebholz CM, Ndumele CE, Florido R, Hoogeveen RC, et al. Relation of Lifestyle Factors and Life's Simple 7 Score to Temporal Reduction in Troponin Levels Measured by a High-Sensitivity Assay (from the Atherosclerosis Risk in Communities Study). **Am J Cardiol 2018;121:430-6. http://doi.org/gc56wc**

Slightly elevated troponin values are no enough to diagnose acute coronary syndrome, but may imply subtle and persistent myocardial damage. In fact, as we have mentioned, in elderly patients with apparently no cardiovascular disease, small troponin elevations predict poorer prognosis. A recent publication of the ARIC study suggests that lifestyle changes may help to reduce troponin.

ARIC was a prospective cohort study carried out in four United States communities, recruiting individuals between 45 and 64 years of age. The study started in 1987 and follow-up concluded between 2011 and 2013. In visits 2 (1990 to 1992) and 4 (1996 to 1998), high-sensitivity TnT (hsTnT) was measured together with routine tests. For this publication and based on available information, the LS7 score was also retrospectively calculated. This score, released in 2011 by the American Heart Association, defines favorable metabolic and lifestyle conditions based upon diet, body mass index, physical activity, blood glucose level, blood pressure, cholesterol and smoking. Each of these components assumes a score between 0 (poor) and 2 (ideal), so that the global score ranges between 0 and 14. The final endpoint was the passage from hsTnT ≥5 ng/L in visit 2 to <5 ng/L in visit 4, defined as undetectable hsTnT incidence. A value of 5 ng/L was chosen as cutoff point, as it was the lowest value with reliable assessment.

Among a total of 9,256 patients who in visit 2 were free from cardiovascular or cerebrovascular disease, 33% had hsTnT ≥5 ng/L. Women, normotensive and non-diabetic persons had more frequently undetectable values. At follow-up, 20% of patients with elevated troponin presented values <5 ng/L in visit 4. Patients with higher baseline LS7 score, as well as those that maintained or improved the score in successive visits had significantly more probability of hsTnT reduction (average 7.9 vs. 7.3 in those that did not). Not being obese in visits 2, 3 and 4 and keeping an ideal physical activity (150 minutes per week of moderate activity or 75 minutes of intense activity) was a robust predictor of decreased hsTnT levels. Conversely, diet and smoking were not associated with the endpoint.

We would first like to draw attention to the fact that a third part of the subjects included in the analysis had troponin values above the limit of detection, despite not having clinical symptoms or history of cardiovascular disease. This indicates the high incidence of asymptomatic progression of myocardial damage in middle-aged persons. Although we may question the study (self-reported physical activity and diet data, and that a score devised in 2011 is applied to data collected 20 years before), the truth is that the possible errors can be randomly attributed equally to patients who did as to those who did not improve their troponin values. Troponin was measured prospectively, and ARIC is a study that has stood out by its meticulous follow-up and the quality of its publications. The association of elevated hsTnT with obesity and sedentarism emphasize the idea that subclinical myocardial damage attributable to the progression of atherosclerotic phenomena, or at least endothelial dysfunction, are at the base of the poor prognosis these two conditions imply. The LS7 score globally captures the behavior regarding diet, physical activity and traditional risk factors. The study results show that favorable lifestyle changes can reverse the initial cardiovascular involvement. We cannot rule out, however, additional residual confounding variables: presence of other conditions that might also have contributed to generate changes in the biomarker measurement.

Revealing data on the incidence of heart failure in a British registry of 4 million individuals

Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. **Lancet 2018;391:572-80. http://doi.org/gc2j5s**

Even though developed countries have administrative databases to obtain information on different diseases, there is lack of specific and reliable data on the incidence of many of these diseases. And despite it is daily repeated that heart failure (CHF) threatens to become a true epidemic in the XXI century, there is no relevant statistics concerning the annual incidence of this disease and how it has evolved during the course of the past years. A primary health care registry in the United Kingdom of Great Britain and Northern Ireland, called CPRD (Clinical Practice Research Datalink) records anonymous electronic data on approximately 7% of the population since 1985.

The present work was planned to study the temporal evolution of CHF incidence in the CPRD, between 2002 and 2014, in men and women ≥16 years of age. Patients with diagnosis of CHF between 1985 and 2002, as well as those hospitalized for this cause between 1998 and 2002 were excluded from the analysis. Neither were individuals developing CHF in the year following inclusion considered in the study, so as not to incorporate persons who already had CHF at the time of entering the study. Heart failure incidence was defined from the moment of diagnosis in primary care or the first hospitalization for this cause in the secondary data. Baseline clinical data were those acquired as nearly as possible to the index registry. The registry also considered 17 accompanying clinical conditions (from anemia to thyroid disorders) and socioeconomic conditions. The incidence of CHF was determined using crude rates and rates standardized by age and sex. Among a total of 4,045,144 patients included between 2002 and 2014, those who already had CHF or presented the disease in the first year following inclusion were excluded from the study, leaving 3,992,417 patients, with mean follow-up slightly above 6 years. During this period, 93,074 patients presented incidence of CHF.

Mean age at the time of diagnosis was 76.7 years, and 49% were women. Mean age rose slightly but significantly from 76.5 years in 2002 to 77 years in 2014. The standardized incidence of CHF by age and sex decreased by 7%, from $358/10^5$ in 2002 to $333/10^5$ in 2014. This decline was homogeneous in the whole age range, except for those >85 years, who evidenced increased CHF. However, the crude incidence increased by 2%, from $288/10^5$ in 2002 to $295/10^5$ in 2014. Heart failure prevalence standardized by age and sex remained stable, between 1.5% and 1.6%, whereas unadjusted prevalence ranged between 1.3% and 1.4%, because due to population growth in Great Britain the number of HF patients increased from 750,000 in 2002 to 920,000 in 2014. Adjusting by age, the incidence was 50% greater in men than in women, but because women reach a more advanced age, the number of cases only differed by 9%. Mean age at the time of diagnosis was 74 years in men and 79 in women.

The mean number of comorbidities at the time of diagnosis grew from 3.4 to 5.4 between the limits of the study period, with 3 or more accompanying diseases present in 68% of patients in 2002 and 87% in 2014. The socioeconomic level was also strongly associated to differences in the incidence. The least favored quintile had slightly more than 60% excess risk of CHF incidence with respect to the most favored quintile; and age at the time of diagnosis was 3.5 years lower in poorer versus more affluent patients.

This large population-based study explains many of the usually reported statements on CHF epidemics. Different from acute myocardial infarction, whose incidence has significantly decreased in many developed countries, the standardized incidence of CHF has practically remained unchanged. This is logical if we acknowledge that CHF is a disease strongly associated with ageing, which cannot be prevented. Older age, natural population growth and the more effective treatment of other cardiac and non-cardiac conditions which previously generated greater mortality, explain that the adjusted incidence has barely shifted, while the absolute number of patients has substantially increased. It draws attention that women, which represent half of the cases, are older at the time of diagnosis. Effectively, the number of comorbidities increases in older patients and effective treatment generates more survivors in a condition more exposed to present others. Finally, neither is it strange that the poorer the socioeconomic level, the greater the incidence, and at a younger age: the combination of more risk factors, worse living conditions and more restricted access to the healthcare system are sufficient, though incomplete, explanation. Huge efforts will be necessary to combine actions focused on the individual with social measures to help ward off the ghost of the growing incidence and prevalence of CHF.