JORGE THIERER MTSAC

Hypertension as a cause of cardiovascular disease: a population registry in over a million patients

Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. **Lancet 2014;383:1899-911.http://doi.org/f2r45b**

There is a well-known association between arterial hypertension (AHT) and death from coronary artery disease and stroke (S). There is no similar information regarding the relationship with other cardiovascular diseases and their prognostic implications. Using a program that allows the acquisition of longitudinal data from electronic medical records in England, this work accessed to information of primary care patients treated between 1997 and 2010, who were 30 years of age or older and free from cardiovascular disease. They were considered to have AHT if their blood pressure (BP) was ≥ 140/90 mm Hg and if they had a previous diagnosis or were treated with antihypertensive drugs. Isolated systolic AHT was defined as systolic blood pressure (SBP) ≥ 140 mm Hg, with diastolic blood pressure (DBP) < 90 mm Hg, and isolated diastolic AHT was described as DBP ≥ 90 mm Hg, with SBP <140 mm Hg. The end point was the occurrence of cardiovascular disease, considering 12 presentation forms: stable or unstable angina, acute myocardial infarction, coronary death, heart failure, sudden cardiac death, transient ischemic attack (TIA), ischemic S, subarachnoid and intracerebral hemorrhage, abdominal aortic aneurysm (AAA), and peripheral vascular disease.

The study included 1,258,006 subjects (58% women). Forty-three percent had AHT, and median follow-up was 5.2 years. The lifetime risk of cardiovascular disease at 30 years of age was 63% in people with AHT and 46% in those with normal BP. At age 30, having AHT resulted in 5 cardiovascular disease-free years of life lost, and at age 80, in 1.6 disease-free years of life lost.

Each increase of 20 mm Hg in SBP and 10 mm Hg in DBP (taking as reference 115/75 mm Hg) was associated with a significantly increased risk of general cardiovascular disease (HR adjusted for age and sex of 1.41 and 1.28, respectively). However, the degree of AHT association with several diseases was heterogeneous. The strongest SBP associations were with stable angina and subarachnoid and intracerebral hemorrhage, (HR between 1.41 and 1.44) and the weakest were with AAA (HR 1.08) and TIA (HR 1.15). The strongest DBP associations were with subarachnoid and intracerebral hemorrhage and AAA (HR between 1.42 and 1.50), and the weakest were with peripheral vascular disease (HR 1.07) and TIA (HR 1.15).

Adjusting for other vascular risk factors did not change substantially the described HR. Adjusting for treatment reduced the HR between 20% and 30%, except for S. The association of AHT with the disease decreased with increasing age (higher HR between 30-59 years than for 80 years or more). Isolated systolic AHT was more prevalent than isolated diastolic AHT (prevalence of 35% vs. 10% between 30 and 59 years, and 64% vs. 0.6% at 80 years or more), and its association with the occurrence of cardiovascular disease was much stronger.

The importance of this publication lies in the high number of studied patients and the wide spectrum of pathologies considered. Presence of AHT still indicates high risk of cardiovascular disease occurrence, even under treatment. It shows that not all diseases are equally associated to AHT, highlighting the existence of endpoints hitherto scarcely taken into account that should be considered in future clinical trials of antihypertensive drugs or strategies, and encouraging the search of pathophysiological hypotheses to explain the reason for these differences. The prognostic weight lies in the systo-diastolic and isolated systolic AHT, while slight relevance can be assigned, in prevalence and risk, to isolated diastolic AHT.

Are natriuretic peptides useful in the prognostic assessment of aortic stenosis?

Clavel MA, Malouf J, Michelena HI, Suri RM, Jaffe AS, Mahoney DW, et al. B-type natriuretic peptide in aortic stenosis clinical activation: impact on long-term survival. **J Am CollCardiol 2014; 63:2016-25. http://doi.org/f2rstx**

In patients with aortic stenosis (AS), treatment decision making is based on clinical and echocardiographic criteria. Natriuretic peptides express increased wall stress of both ventricles, and there is abundant information of its use in heart failure. It is reasonable to ask whether they will be useful in the context of AS. We present a cohort study that attempts to give an answer.

Patients who were diagnosed with moderate to severe AS and with aortic valve area (AVA) ≤ 1.5 cm2, were consecutively recruited for the study. Those with rheumatic or congenital etiology, myocardial infarction during the previous 8 weeks, or high ventricular response atrial fibrillation, were excluded from the study. Clinical data, echocardiographic Doppler and a B-type natriuretic peptide (BNP) value, were collected in all patients. The ratio between measured BNP and maximum age and gender-expected BNP was calculated for each patient. A ratio >1 was considered as BNP activation. The primary endpoint was overall mortal-

ity and the secondary endpoint was mortality under medical treatment, censoring patients at the time of valve replacement.

The study included 1953 patients, 60% with symptomatic AS. Mean AVA was 1.03 ± 0.26 cm2 and peak aortic jet velocity was 3.78 ± 0.95 m/sec. Average left ventricular ejection fraction (LVEF) was 57%, with 22% of patients with LVEF < 50%. Seventy-five percent of patients had BNP ratio > 1. Overall survival at 2, 5 and 8 years was 73%, 49% and 34%, respectively. In a multivariate model (adjusted for age, sex, systolic blood pressure, body surface area, symptoms, indexed AVA, comorbidities, creatinine, hemoglobin, and LVEF), a BNP ratio > 1 was an independent predictor of mortality with a HR of 1.91 (95% CI 1.55-2.35, p < 0.0001). Risk was greater at higher ratio: between 1 and 2, HR 1.49; between 2 and 3, HR 2.12; greater than 3, HR 2.43.

The prognostic value of BNP was similar when patients under medical treatment were exclusively considered: mortality at 8 years was 49% in patients with ratio ≤ 1 and 13% with ratio > 1 (p < 0. 0001). Likewise, in a subgroup of 565 patients with asymptomatic AS and LVEF > 50%, BNP was an independent predictor of mortality, with 75% survival at 8 years if the ratio was ≤ 1 and 38% if it was higher (HR 2.35, 95% CI 1.57-3.56, p < 0.0001). In an analysis limited to patients with severe asymptomatic AS (AVA < 1 cm2, or peak velocity > 4 m/s), the prognostic value of BNP was even higher, with HR of 3.02, 4.64 and 7 38 for ratios of 1 to 2, 2 to 3, and > 3, respectively.

A new prognostic marker, which expresses ventricular involvement or increased afterload, appears in the context of AS. While not all significant baseline characteristics may have been taken into account, those considered in the multivariate analysis seem to be enough to provide clinical entity to increased BNP. Certainly, in the individual patient the value of the peptide should be considered in context. It is essential to know the expected value for age, but other variables (renal function, cardiovascular disease, arrhythmia, weight) also influence the determination, complicating the interpretation of its increased level when this is not marked. With this caveat, the major utility seems to be assisting decision making in asymptomatic AS, when establishing surgical time. Prospective studies based on this strategy will eventually confirm if it contributes to improve the prognosis.

Thrombolytic therapy reduces mortality in intermediate risk pulmonary embolism: a meta-analysis of 16 randomized studies.

Chatterjee S, Chakraborty A, Weinberg I, Kadakia M, Wilensky RL, Sardar P, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. **JAMA 2014;311:2414-21.http://doi.org/trc**

The effectiveness of thrombolytic therapy (TT) in pul-

monary thromboembolism (PTE) is an unresolved issue. So far, there has not been a clear demonstration of mortality reduction with respect to anticoagulants, and therefore, the indication is usually reserved for PTE with hemodynamic instability and marked right ventricular (RV) function involvement. The indication is much more diffuse for less severe cases, due to the associated risk of bleeding and lack of patent benefit. Most studies have included a small number of patients (usually less than 100). Since the last Cochrane Collaboration systematic review (2009) new randomized studies, including the PEITHO study (1,005 patients) have been published. This justifies re-evaluating TT effect in PTE, especially when risk is not high.

A recently published meta-analysis considered all randomized studies where TT was compared with anticoagulant therapy (unfractionated or low weigh the parin, vitamin K antagonists, or fondaparinux) in PTE patients, considering mortality as endpoint. The primary efficacy endpoint was overall mortality, and the secondary endpoint, PTE recurrence, and the primary safety endpoint was major bleeding and the secondary endpoint intracranial hemorrhage. Patients were considered at low risk (hemodynamically stable without RV dysfunction), at intermediate risk (hemodynamically stable, with objective evidence of RV dysfunction), at high risk (hemodynamically unstable and/or with systolic blood pressure<90 mm Hg) or unclassifiable (when the study provided no data).

Sixteen studies published between 1970 and 2014 with 2115 patients (9.9% low risk, 70.9% intermediate risk, 1.5% high risk and the rest unclassifiable) were considered. Mortality with TT was significantly lower at a mean follow-up of 81 days: 2.17% vs. 3.89% with anticoagulants (OR 0.53, 95% CI 0.32-0.88), with a needed to treat (NTT) number of 59 patients to prevent one death. There was also reduction in recurrent PTE: 1.17% vs. 3.04% (OR 0.40, 95% CI 0.22-0.74). The benefit was remarkable in patients at intermediate risk (most of the patients included), with an OR of 0.39 (95% CI 0.19 to 0.82).

But, conversely, TT showed excess of major bleeding: 9.24% vs. 3.42% (OR 2.73, 95% CI 1.91 to 3.91), with an episode of excess bleeding per 18 patients treated; and excess of intracranial hemorrhage: 1.46% vs. 0.19% (OR 4.63, 95% CI 1.78 to 12.04).

There was overall net clinical benefit with the use of TT (difference between excess mortality with anticoagulation and excess intracranial hemorrhage with TT).

An analysis which took into account the age of the patients showed that in those ≤ 65 years there was a significant reduction in mortality with no excess of bleeding; however, in those >65 years the situation was reversed, with a reduction in mortality that did not reach full statistical significance (OR 0.55, 95% CI 0.29-1.05), but with a significant increase in major bleeding: 12.9% vs. 4.1% (OR 3.10, 95% CI 2.10-4.56).

This meta-analysis helps to strengthen TT indication in intermediate-risk PTE, for which the indica-

tion was hitherto unclear. Even the PEITHO study, which included the largest number of patients, had failed to demonstrate reduced mortality. Age seems important when making decisions. Nevertheless, it should be decided case by case, as over 65 years of age there was tendency to a favorable effect. The variability in the definitions, types and thrombolytic doses used in the different studies and the fact that it is not a meta-analysis of individual data may be considered as study limitations. Due to underrepresentation of low risk patients, definite conclusions cannot be drawn on these patients.

Are we accurate in our clinical classification of atrial fibrillation ?

Charitos EI, Purerfellner H, Glotzer TV, Ziegler PD. Clinical classifications of atrial fibrillation poorly reflect its temporal persistence: insights from 1,195 patients continuously monitored with implantable devices. **J Am Coll Cardiol 2014;63:2840-8.http://doi.org/f2skx7**

With slight variations in the definition, treatment guidelines agree in the clinical classification of atrial fibrillation (AF) as paroxysmal (which ends spontaneously in < 7 days), persistent (lasting > 7 days or requiring cardioversion, electric or pharmacological therapy) and permanent (when installed arrhythmia is accepted, rhythm control is abandoned and frequency control is adopted as strategy). The classification is useful as inclusion criteria in clinical trials and influences decision making. The shorter the AF duration, the higher the possibility of choosing a rhythm control strategy, whose success will be evaluated according to the re-emergence or not of the arrhythmia, and whether this is paroxysmal or persistent.

So, the clinical classification is accurate? The analysis of two observational studies (OMNI and TRENDS) of patients with implanted devices for different conditions (pacemakers, defibrillators, resynchronizers) sheds doubt on this assumption. It included 1195 patients with AF, 1091 clinically defined as paroxysmal and in the remaining 104 as persistent, with at least 180 days recordings and maximum follow-up of 365 days. In addition to the clinical classification (CC), a classification derived from the device recordings (DC) considered four categories: no AF (no day with > 5 minutes AF); paroxysmal (at least 1 day with AF > 5 minutes, but < 7 consecutive days with AF > 23 hours); persistent (at least 7 consecutive days with AF > 23 hours) and permanent (every day with AF > 23 hours, or AF > 95% of total monitoring time).

In patients who according to CC had paroxysmal AF, DC revealed the same diagnosis only in 46.6%, absence of AF in 34.5%, persistent AF in 16.8% and permanent AF in the remaining 2.1%. In patients that CC classified as persistent AF, DC showed the same diagnosis only in 32.7%, absence of AF in 21.1%, paroxysmal AF in 32.7% and permanent AF in the remaining 13.5%. The scarce concordance between CC and DC is shown in a kappa coefficient of only 0.12.

Although the time period with AF was significantly different between paroxysmal and persistent AF (medians of 0.1% and 4% of total time, respectively), there was, for any proportion of time in AF, a considerable overlap between both clinical types of AF with limited capacity to discriminate between them, resulting in an area under the ROC curve of only 0.67.

Several factors seem to significantly influence CC; thus, for example, a greater proportion of time in AF, worse left ventricular ejection fraction and no coronary etiology were independently associated with the diagnosis of persistent AF.

This publication does not analyze whether treatment changes during the course of follow-up influenced the discordance between the initial CC and device measurements all along the following year. A successful antiarrhythmic treatment, or correction of concomitant pathology, might explain why a third of paroxysmal manifestations and a fifth of persistent AF according to CC did not present AF during the follow-up year. Beyond this doubt, the data presented in this study brings to light the scant correspondence between what we believe and what really is in the context of AF. Obviously, we cannot advocate the use of devices to clarify the doubt, but perhaps more frequent electrocardiographic consultations and monitoring and a higher suspicion index may help to shorten the breach.

Aortic sclerosis; an entity with clinical significance

Coffey S, Cox B, Williams MJ. The prevalence, incidence, progression, and risks of aortic valve sclerosis: a systematic review and meta-analysis. **J Am Coll Cardiol 2014;63:2852-61.http://doi.org/f2skxp**

Aortic valve thickening and calcification without hemodynamic involvement is called aortic sclerosis (AoScl). By definition, AoScl is asymptomatic. It is diagnosed by an imaging study, which in our country is mainly one of the different types of echocardiogram. The prevalence of AoScl is higher in the aging population. Although it is relatively frequent in this age group, its evolution is not fully clear and neither whether it entails an adverse prognosis.

A systematic review and meta-analysis was performed to answer these questions. It included 22 prospective studies where AoScl prevalence, incidence, associated factors and prognosis were studied.

Prevalence data obtained from 19 studies with over 43,000 participants indicated a clear association with average population age. When mean age was below 60 years, prevalence was generally under 10%, but reached 41% in a study in which average age was 81 years. A meta-regression analysis defined 1.5% increase in AoScl prevalence per year of age.

Data of AoScl incidence was obtained from 5 studies. In studies using tomography, the annual incidence varied between 1.7% and 4.1%, while the ones using

echocardiography showed 7.5% to 8.8% variation. Information about progression to aortic stenosis, assessed either clinically or by imaging studies, was also obtained from 5 studies, with a low annual rate between 1.8% and 1.9%.

Prognostic data were acquired from 6 studies. Aortic sclerosis was associated with coronary adverse events, stroke, overall mortality and cardiac death. Adjustment for traditional risk factors reduced the force of association, but without losing statistical significance. Thus, the presence of AoScl implied a HR of 1.68 (95% CI 1.31-2.15) for coronary events, 1.27 (95% CI 1.01-1.60) for stroke, and an adjusted HR of 1.36 (95% CI 1.17-1.59) for all-cause mortality and of 1.69 (94% CI 1.32-2.15) for cardiovascular death. In one of the computed tomography studies, after adjusting for calcium score, AoScl stopped being an independent predictor of coronary events, but not of mortality.

Aortic sclerosis is a frequent finding in daily practice in aging patients. We usually reduce its importance by explaining it is a common finding of older age and generally we do not adopt any conduct. In this sense, this meta-analysis is revealing, showing that it is a marker of increased risk of events, even after adjusting for age, sex and cardiovascular risk factors. An interesting aspect is that the rate of aortic stenosis progression is low, suggesting that the associated bad prognosis is not due to its change into a severe valve disorder, but probably to the expression of disseminated vascular endothelial disease. More studies about its natural history are deemed necessary.

Atrial fibrillation: lack of concordance between empirical scores and physician assessments of embolism and bleeding risk

Steinberg BA, Kim S, Thomas L, Fonarow GC, Hylek E, Ansell J, et al. Lack of concordance between empirical scores and physician assessments of stroke and bleeding risk in atrial fibrillation: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. **Circulation 2014;129:2005-12.http://doi.org/trd**

The decision to anticoagulate patients with atrial fibrillation (AF) depends on the estimated risk of embolic stroke and other systemic embolisms. The $CHADS_2$ score is preferably used in daily practice to assign a specific risk according to the presence of certain variables: age, diabetes, hypertension, heart failure, and previous stroke. The $CHADS_2$ Vasc score incorporating the evaluation of female gender and history of vascular disease has been recommended in the last years.

The perceived bleeding risk with the adopted treatment also influences the decision to anticoagulate the patient. Again, some scores help in the decision, as the ATRIA and HAS-BLED scores. Ideally, the definite conduct should emerge from the balance between stroke risk and bleeding risk. So, how much

do the aforementioned scores influence the decision? Do physicians define patient management according to them, or based on their own criteria and a subjective evaluation of either risk?

The United States ORBIT-AF registry enrolled ambulatory patients with AF managed by primary care physicians, cardiologists or electrophysiologists. This study included patients with non-reversible AF, in whom the $CHADS_2$ score (considering score 0 = low risk, 1 = intermediate risk and ≥ 2 = high risk) and the ATRIA score (with score ≤ 3 = low risk, 4 = intermediate risk and ≥ 5 = high risk) were calculated. Moreover, physicians were requested to subjectively define stroke and bleeding risk for each patient as low (if they considered that it was < 3% annually), intermediate (3-6%) or high (> 6%). These cut-off values were prospectively chosen for adequate correlation with the score-defined categories.

The study included 10,094 patients. The $CHADS_2$ score indicated low, intermediate and high risk in 6%, 22% and 72% of patients, respectively; however, the physicians-estimated corresponding values were 41%, 43% and 16%. Physician-estimated risk matched the score in 78% of low $CHADS_2$ score patients, in 33% of those with intermediate $CHADS_2$ score (62% of which were considered low risk by physicians) and in only 21% of high $CHADS_2$ score patients (very low agreement between both classifications according to weighted-kappa coefficient: 0.10). The multivariate analysis showed that medical judgment was less influenced by age, diabetes, hypertension and heart failure (4 of the 5 score components) and very influenced by history of stroke, marked AF symptoms and non-independent patient lifestyle. Physicians used oral anticoagulants in 52% of low risk $CHADS_2$ score patients and in 70 % of those at clinically defined low risk, compared with 80% and 81%, respectively, in high risk patients.

The ATRIA score resulted low, intermediate and high risk in 74%, 9% and 17% of patients, respectively, but physician-estimated risk was 59%, 34% and 7%. Physician risk assessment matched the score in 63% of patients considered at low risk by the ATRIA score, in 33% of those with intermediate ATRIA score (58% of the patients were considered at low risk by physicians) and only in 13% of patients with high ATRIA score. Again, the kappa coefficient was very low: 0.11. Physicians considered anemia as less significant than heart failure, history of gastrointestinal bleeding and vascular fragility. Physicians used oral anticoagulants in 77% of low risk ATRIA score patients and in 73% of clinically-estimated low risk cases, compared with 73% and 68%, respectively, in high risk patients.

This registry of daily practice in the United States reveals procedures which are far different from randomized studies. Medical judgment relies more in subjective criteria than in evidence-based results. Physicians underestimate the risk of stroke, consider for their decision factors which differ from those of scores and take into account the risk of stroke more than the

risk of bleeding. According to these data, and based on the CHADS$_2$ score, we may estimate for every 100 patients, 4 anticoagulated low-risk patients and 15 high-risk who are not. That the final decision is guided more by the risk of stroke than that of bleeding (there is marked difference in the use of anticoagulants in high vs. low stroke risk, but not in high vs. low bleeding risk) could be adequate, due to the clear clinical benefit achieved with anticoagulation in most situations.

Cryptogenic stroke: in search of atrial fibrillation

Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, et al. Atrial fibrillation in patients with cryptogenic stroke.EMBRACE Investigators. **N Engl J Med 2014;370:2467-77.http://doi.org/trf**

Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. CRYSTAL AF Investigators. **N Engl J Med 2014;370:2478-86.http://doi.org/trg**

According to different series, between 20% and 40% of ischemic strokes and up to 50% of transient ischemic attacks (TIA) remain without a clear demonstration of their etiology despite the initial evaluation, and are labeled cryptogenic strokes. In these cases, one of the probable causes is undiagnosed paroxysmal atrial fibrillation (AF) at the moment of stroke occurrence. The demonstration of AF as the cause of stroke has therapeutic implications, since it is indication of oral anticoagulation (OAC),which reduces the incidence of a new stroke more effectively than antiplatelet therapy in the presence of AF. Two recent studies suggest that AF can be demonstrated in many patients with cryptogenic stroke. The EMBRACE study enrolled 572 patients, 55 years of age or older (mean age 72.5 years), presenting with ischemic stroke or TIA in the last 6 months, with no evidence of known AF, and without etiological diagnosis after clinical examination, ECG, at least 24-hour Holter ECG, echocardiogram and brain and neurovascular imaging. They were randomly assigned (with a mean of 75 ± 38 days from the index event) to a new 24-hour Holter ECG or monitoring with an electrocardiographic rhythm recorder attached to a belt around the thorax for 30 days. The primary endpoint was the detection of clinical or monitored AF or atrial flutter of at least 30 seconds duration, within 90 days from randomization. An AF episode was detected in 3.2% of patients with conventional Holter ECG compared with 16.1% with prolonged monitoring (p < 0.001). Only 0.5% of cases were clinically detected; the rest were detected by the aforementioned methods. The longer the monitoring, the better the diagnostic benefit: AF was diagnosed in 7.4% of patients in the first week, reaching 14.8% in the fourth week. The detection of AF was greater when monitoring was performed within 3 months of the index event: 18.5% vs. 9% with later monitoring (p < 0.05).

The CRYSTAL AF study included 441 patients 40 years of age or older (mean age 61.5 years), with diagnosis of cryptogenic ischemic stroke or TIA (after undergoing the usual studies) within the last 90 days, with no evidence of known AF. They were randomized (with a mean of 38 ± 27 days from the index event) to clinical follow-up, with Holter ECG at the discretion of the treating physician, or insertion of a cardiac monitoring device. The primary end point was the detection of AF within 6 months of randomization. An episode of AF was detected in 8.9% of patients with prolonged monitoring vs. 1.4% in the control group (HR 6.4 95% CI 1.9-21.7; p < 0.001). More than 70% of AF cases identified with the device were asymptomatic.

In both studies the detection of more AF cases translated into greater OAC use in the prolonged monitoring groups.

Probably the AF rate associated with stroke is underrepresented in both studies due to the time elapsed from stroke occurrence until prolonged monitoring. It is not possible to clearly establish that the discovery of AF can explain the cause of stroke in all cases. It is only an indication. Yet, it implies a reasonable doubt, and points to the use of OAC. The difference in the incidence of AF between both studies can be explained by the 11-year disparity in mean age. The question is whether a population at greater risk could be characterized in which prolonged monitoring is more justified. A cost-effectiveness analysis is needed to better define this approach.

Benefit of long-term resynchronization therapy in FC I-II patients and the importance of left bundle-branch block. Seven-year follow-up of the MADIT-CRT study

Goldenberg I, Kutyifa V, Klein HU, Cannom DS, Brown MW, Dan A, et al. Survival with cardiac-resynchronization therapy in mild heart failure. **N Engl J Med 2014;370:1694-701. http://doi.org/trh**

The MADIT-CRT study was carried out in 1820 patients in sinus rhythm, in FC I-II if they had ischemic cardiomyopathy or FC II if they had nonischemic cardiomyopathy, and with indication of implantable cardioverter-defibrillator (ICD). Their left ventricular ejection fraction (LVEF) was ≤ 30 and QRS duration ≥ 130 ms. Patients were randomized in a 3:2 ratio to receive either ICD with resynchronization therapy or ICD alone. Mean LVEF was 24%, 71% had left bundle-branch block (LBBB) and over 65% had QRS ≥ 150 ms. The primary end point was death or heart failure worsening (need for hospitalization or use of intravenous diuretic at the emergency department). At mean follow-up of 2.4 years, the primary end point occurred in 25% of patients with ICD alone, compared to 17% of patients with ICD and resynchronization therapy. Risk reduction was mainly due to new heart failure events: almost 23% in the ICD-only group and 14% in the ICD-resynchronization group. On the other

hand, mortality was the same: approximately 7% in each group. The study ended in June 2009; it was decided to extend it for all 1691 surviving participants until September 2010 (phase 1) and then to prolong it even more, until September 2013, in 854 patients from the centers that agreed to participate. (phase 2). The primary end point was all-cause mortality, and the secondary end point a nonfatal event associated with heart failure, or the composite of death and nonfatal event. Median post-trial follow-up was 5.6 years.

When considering follow-up since the initial enrollment (in the 1818 patients with available admission ECG) to the end of phase 2 in the 854 ongoing patients, there was a clear difference in the outcome according to the presence or not of LBBB during the 7-year follow-up. Among the 1281 patients with LBBB, all-cause mortality was 18% in the ICD-resynchronization group and 29% in the ICD-only group at 7 years (adjusted HR 0.59, 95% CI 0.43-0.80; p< 0.001). A similar reduction in the incidence of nonfatal events was found between both groups, with adjusted HR of 0.38 (95% CI 0.30-0.48; p < 0.001). These results were independent of etiology, gender and QRS duration.

Conversely, in the 537 patients without LBBB there were no differences in mortality or in nonfatal events during the 7-year follow-up. Furthermore, after adjusting for basal characteristics, there was possibly excess mortality in the ICD-resynchronization group, with HR 1.57 (95% CI 1.03-2.39; p = 0.04).

This study reveals that in patients with mild heart failure, the passage of time was necessary to evidence benefit in the hard end points. These results may contribute to strengthen the indication in FC I-II patients. The difference in favor of patients with LBBB, evident in other studies, could be explained by increased mechanical dyssynchrony, or the location of an area of maximum delay just in the ventricular zone accessed with the electrode. The assumed increase in mortality in patients without LBBB should be interpreted with caution: it was obtained from a multivariate analysis, questionable when we are in the presence of a randomized study.