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Reduction of major events with evolocumab in the FOURIER study

Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al; FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. **N Engl J Med. 2017;376:1713-22. http://doi.org/b4j9**

We have already referred, in previous publications, to the use of proprotein convertase subtilin-kexin type 9 (PCSK9) inhibitors, monoclonal antibodies that generate about 60% reduction in LDL cholesterol values. Previous phase 2 and 3 studies had shown reduced incidence of cardiovascular events, but due to the number of patients included and the follow-up time, the total number of events considered did not exceed 100. The FOURIER study was designed to confirm the safety and efficacy of a PCSK9 inhibitior, evolocumab (E) in a large study. This is a randomized, multicenter study comparing E to placebo in patients between 40 and 85 years of age with proven atherosclerotic disease: coronary artery disease, non-hemorrhagic stroke or peripheral vascular disease under high-dose statin therapy (atorvastatin 40 to 80 mg/day, rosuvastatin 20 to 40 mg/day or equivalent), although a dose of atorvastatin of at least 20 mg daily was admitted. Patients could receive ezetimibe, and their LDL cholesterol should be at least 70 mg/dl. The primary endpoint (EP) was a composite of cardiovascular death, acute myocardial infarction (AMI), stroke, hospitalization for unstable angina or need for revascularization surgery. The secondary EP was the combination of the first three components mentioned. The efficacy analysis was done by intention to treat and the safety study only in those patients who received at least one dose of the study drug or placebo. Between 2013 and 2015, 27,564 patients were included, randomized on a 1:1 ratio to receive E (one 140 mg subcutaneous injection every 2 weeks, or a monthly injection of 420 mg, at the patient's choice) or placebo. Average age was 62.5 years and 75% of patients were men. Among them, 81% had a history of AMI, 19% of stroke and 13% of peripheral vascular disease. In 80% of cases patients were hypertensive and slightly more than 36% diabetic. Between 75% and 80% of patients were on beta-blockers and a renin-angiotensin-aldosterone system inhibitor; 92% received aspirin. Regarding statin therapy, 69.3% received high intensity and 30.4% moderate intensity treatment. Only 5% were treated with ezetimibe. Median LDL cholesterol was 92 mg/dl, with an interquartile range (IQR) of 80-109 mg/dl.

Median follow-up was 26 months. At 48 weeks, LDL cholesterol reduction with E was 59% (mean absolute reduction of 56 mg/dl, which allowed a median LDL cholesterol value of 30 mg/dL). Low density lipoprotein cholesterol reduction allowed attaining ≤70 mg/dl in 87% of patients, ≤40 mg/dl in 67%, and of ≤ 25 mg/dl in 42% of patients, compared to 18%. 0.5% and 0.1%, respectively, in the placebo group. This marked reduction in LDL cholesterol was accompanied by a decreased rate of events: the primary EP occurred in 9.8% in the E group vs. 11.3% in the placebo group (HR 0.85, 95% CI 0.79-0.92). The secondary EP occurred in 5.9% in the E group versus 7.4% in the placebo group (HR 0.80, 95% CI 0.73-0.88). The reduction was specifically verified in the incidence of AMI, stroke and need for revascularization, with no decline in hospitalization for unstable angina, cardiovascular death, or death from all causes. The reduction in the incidence of the primary and secondary EP was more marked after the first year. No difference in the effect was found in the subgroups defined by baseline LDL cholesterol, statin treatment intensity or administration scheme. The incidence of adverse events was similar in both groups: there were no excess muscle disorders, neurocognitive impairment, new diabetes or cataracts. Only a greater predominance of reaction at the site of injection was observed: 2.1% vs. 1.6%. Only in 0.3% of cases the development of antibodies against the medication was verified.

This study confirms the lowering power of iPCSK9 on LDL cholesterol. What should be noted is that the decline achieved was well beyond the objectives set in the usual practice. And that the marked decrease was accompanied by a reduction of cardiovascular events in accordance with the decrease of LDL cholesterol levels, albeit to a lesser degree than that predicted by the meta-analysis of Silverman et al., which we discussed in an earlier issue (Rev Argent Cardiol 2016; 84:524-30). It will be recalled that this meta-analysis presented an observed RR of 0.61 and an expected one of 0.49 for each LDL cholesterol decrease of 38.7 mg/dl. In the FOURIER study, a greater reduction in LDL cholesterol (average 56 mg/dl) resulted in RR of 0.85. However, in these patients, who started from a low median LDL cholesterol value (92 mg/dl) and were also treated with the rest of the medication useful in secondary prevention, a reduction in mortality could not be achieved. It was also impossible in the IMPROVE IT study, where a final LDL-cholesterol of 54 mg/dl was attained starting from a value of 70 mg/dl. Perhaps because of this, the relative reductions in AMI, stroke and revascularization, between 21% and 27%, are more striking than the absolute reductions (a reduction of approximately 0.7 AMI, 0.2 stroke and 0.7 revascularization procedures per 100 patients/year). It is clear that in a population so well treated in general, and with a median follow-up of barely over 2 years, it was illusory to expect something else. Neverthe-

less the theory that "the lower the better" seems not to have reached the LDL cholesterol floor. Such short follow-up also raises uncertainty about the incidence of longer-term adverse events. Current studies are aimed at answering this question. And to conclude, another harsh topic: is this treatment cost effective today? Surely not as an extended strategy in a well monitored and controlled population. Patients at very high risk of events and poor response to standard treatment seem to be better candidates.

High incidence of subclinical thrombosis in prosthetic aortic valves: should treatment be changed after the procedure?

Chakravarty T, Søndergaard L, Friedman J, De Backer O, Berman D, Kofoed KF, et al; RESOLVE; SAVORY Investigators. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. **Lancet 2017;389:2383-92. http://doi.org/cbqg**

In patients with severe aortic valve stenosis, surgical replacement (AVR) has been the procedure of choice. In recent years, a new option has emerged, transcatheter aortic valve implantation (TAVI), at first for patients considered to be at high surgical or inoperable risk, and with the passage of time and evidence of new randomized studies, and according to the center's experience, also for patients of intermediate surgical risk. We have recently observed reports on the incidence of subclinical prosthetic thrombosis in patients undergoing TAVI. Two aortic replacement registries, with TAVI or AVR with biological valve (bAVR) are now confirming these data and raising questions about the routine treatment.

The RESOLVE registry was held at the Cedars Sinai Center in Los Angeles between late 2014 and early 2017. The SAVORY registry was implemented in Copenhagen between mid-2014 and late 2016. Both studies included patients subjected to bAVR or TAVI, with peri or post procedural computed tomography (CT) to define thickening and valve mobility. The times to CT scan were variable, and the patients were not consecutive, so as to reflect the result of different approaches to diagnosis and treatment after the procedure. When present, the reduction in valve mobility was classified as mild (<50%), moderate (50-70%), severe (>70%) or lack of mobility.

The authors present data of 890 patients, 84% undergoing TAVI and the rest bAVR. Logically, the latter were younger (71.92 vs. 80.7 years) and had lower prevalence of comorbidities. Median time from the procedure to the CT scan was 58 days for TAVI and 163 days for bAVR (p <0.001). Decreased valve mobility was detected in 106 patients (12%), 13% of TAVI cases and 4% of b AVR cases (p=0.001). The affected leaflet thickness was higher with TAVI: 5 mm vs. 1.85 mm (p=0.0004), and the degree of mobility reduction was also greater in cases where it was detected: 71% vs. 57% (p=0.004).

Regarding treatment at the time of detecting mobility limitation, 7.5% of the 106 patients were anticoagulated, 59.5% were treated with an antiplatelet agent, 29.2% with double antiplatelet therapy (DAPT), and the rest with no medication. On the other hand, among those without altered valve mobility, 27.5% were anticoagulated, 43.6% treated with an antiplatelet agent, 22.6% with DAPT, and the rest with nothing (p<0.0001). Anticoagulated patients were treated with warfarin or new oral anticoagulants (NOAC) in almost the same proportion. The prevalence of decreased mobility reduction was 4% in anticoagulanted patients, 15% in non-anticoagulated patients, and specifically 16% in those treated with an antiplatelet agent and 15% in those treated with DAPT.

In a multivariate analysis, age, low left ventricular ejection fraction, TAVI treatment and not receiving anticoagulants were predictors of reduced mobility. At a mean follow-up of 540 days, patients with valve dysfunction were more exposed to present a transient ischemic attack (TIA) not related to the procedure: 3.5% vs. 0.6% per year (p=0.002). In all patients in whom the abnormal mobility was followed by the onset of anticoagulation, the disorder disappeared at follow-up, while it persisted or progressed in 91% of those who were not anticoagulated after the finding.

This study presents several important points. First of all, it is the one with the largest number of patients undergoing aortic valve replacement or implantation with CT scan monitoring during follow-up and detection of disorders compatible with prosthetic thrombosis. We say compatible because there is no pathological confirmation of the presence of thrombus, but the strong association of the findings with the presence or absence of anticoagulants, the increased risk of TIA in the case of limited valve mobility and valve thickening, and the disappearance of the findings after the introduction of anticoagulant therapy are very strong signs. The phenomena described present a much higher incidence of subclinical thrombosis with TAVI than with bAVR. Although the times to CT scan were shorter with TAVI, presumably favoring the detection of a phenomenon linked to the procedure, in the multivariate analysis time to CT scan was not a predictor of the finding. It is worth noting that only 16% of patients with suspected thrombosis had a transvalvular gradient >20 mmHg on the echocardiogram, suggesting that we cannot rely in this method to suspect the pathology. The registry data question the current and routine indication of DAPT post TAVI, and raise doubts on whether it will be necessary to anticoagulate the patients for at least a few months. Randomized studies currently attempt to answer this question. It is true that as in any registry, it is possible to assume the presence of confounders not considered in the analysis, and logically presume observation bias due to a different follow-up according to baseline characteristics, type of procedure, etc. In fact, there was no definite scheme for conducting the studies or neurological follow-up (suggesting that the incidence of embolic events could be even greater). Attention is also drawn to the similar outcome with warfarin or NOAC, the latter with few data in the context of bAVR or TAVI. In summary, based on these findings, at least a stricter follow-up of patients and a

more active search for subclinical thrombosis should be considered, and in case this were found, and logically attending the risk of bleeding, which is also greater in fragile patients subjected to TAVI, propose anticoagulant therapy until larger studies give a definitive answer.

Target systolic and diastolic blood pressure in patients at high cardiovascular risk. A subanalysis of the ONTARGET and TRASCEND studies

Böhm M, Schumacher H, Teo KK, Lonn EM, Mahfoud F, Mann JFE, et al. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. **Lancet 2017;389:2226-37. http://doi.org/gbh5gc**

While treatment guidelines of the different scientific societies suggest a blood pressure target <140/90 mmHg, the SPRINT study disrupted the hornet by pointing out that tending to a systolic blood pressure target (SBP) <120 mmHg generated a prognostic improvement, with decreased mortality. Different criticisms were made to the design of the study and to the way of measuring blood pressure (BP). Now, a subanalysis of the randomized ONTARGET and TRASCEND trials questions the idea of an intensive antihypertensive treatment.

As will be recalled, both studies included patients at least 55 years old, with cardiovascular or cerebrovascular disease, peripheral vascular disease or diabetes with target organ damage. In the ONTARGET trial, patients who tolerated angiotensin-converting enzyme inhibitors (ACEIs) were randomly assigned to ramipril 10 mg/day, telmisartan 80 mg/day, or a combination of both. In the TRASCEND trial, patients intolerant to ACE inhibitors were assigned to telmisartan 80 mg/day or placebo. In the ONTARGET study there were no differences in the outcome between the three groups. In the TRASCEND study, telmisartan produced a non-significant reduction of events.

The analysis of both combined databases here presented, including 30,937 patients (25,127 from the ONTARGET study), studied the relationship between baseline BP and BP values attained (the mean of all measurements made at a median follow-up of 56 months) with the incidence of major events in a combined endpoint of cardiovascular death, acute myocardial infarction (AMI), stroke or hospitalization for heart failure (HF), as well as with each of them separately and all-cause mortality. The analysis was performed adjusting for age, gender, risk factors and cardiovascular history, renal function, physical activity, educational level, alcohol consumption and treatment.

Regarding baseline BP: a) *SBP*: taking as reference an initial BP value between 120 and 139 mm Hg, patients with SBP ≥140 mmHg presented a significant higher incidence of the combined endpoint of stroke, HF and all-cause mortality, while the incidence of cardiovascular death and AMI was only significantly higher in those with SBP ≥160 mmHg. Patients with SBP <120 mmHg did not show a higher rate of events than those with SBP between 120 and 139 mmHg. b) *Diastolic BP (DBP)*: taking as reference an initial value between 70 and 79 mmHg, patients with DBP <70 mmHg had a higher incidence of the primary endpoint and AMI, HF and all-cause mortality, and a tendency to an increased risk of cardiovascular death. Only the risk of stroke was not higher in those with very low DBP. The incidence of the primary endpoint, AMI and HF was lower in patients with DBP ≥90 mmHg.

Concerning BP achieved at follow-up: a) *SBP*: taking as reference a value between 120 and 139 mm Hg, those who reached higher SBP were at greater risk of the combined endpoint, of each of its components separately and of overall mortality. But there was also a higher risk of the combined endpoint, cardiovascular death, and total death for those who achieved a SBP <120 mmHg; b) *DBP*: taking as reference an initial value between 70 and 79 mm Hg, patients with DBP ≥80 mmHg presented with a higher incidence of the primary endpoint and stroke; and those with DBP ≥90 mmHg, had a higher incidence of cardiovascular and overall death, AMI and HF. However, in those with DBP <70 mmHg, the incidence of the primary endpoint, AMI, HF and all-cause death was higher. Only the incidence of stroke did not increase with DBP values below reference. Analyses in which patients with significant comorbidity or not treated with antihypertensive drugs were excluded showed similar results.

We can then speak of a J-curve for the SBP achieved: values above 140 mmHg and below 120 mmHg were generally associated with worse outcome, and the same happened with the DBP attained: values below 75 mmHg were associated with higher incidence of all endpoints except stroke. The lower the baseline SBP, the greater the risk associated with smaller decreases during follow-up: for example, in those with an initial SBP <120 mmHg, a decrease of only 10 mmHg already implied a significant increase in the primary endpoint; whereas, in those with a SBP between 120 and 140 mmHg a decrease of 20 mmHg was necessary to reach a similar risk. The only risk that never increased, with any baseline SBP and any decrease in SBP, was stroke.

The ONTARGET and TRASCEND studies were not performed to evaluate antihypertensive treatment, since 30% of patients included were not. However, baseline SBP values are similar to those of the SPRINT trial: 139.7 mmHg in the SPRINT trial, almost 142 mmHg in the ONTARGET trial and around 141 mmHg in the TRASCEND trial. Why are the results different? It has been repeatedly stated that the manner of taking BP in the SPRINT study ensures results that may be 10 to 15 mm Hg lower than those conventionally recorded in other studies. Regarding the findings of the present analysis we must emphasize that they arise from observation in the context of two randomized studies, where the treatment was randomly assigned, but not the target BP. It cannot be ruled out that, in fact, the worst outcome in patients who achieved lower SBP is due to the presence of comorbidities, which, independently of the statistical adjustment, are the ones responsible for the higher incidence of events and even of a greater decrease in SBP by a reverse causality phenomenon.

Nevertheless, the results are similar to those of studies that randomly assigned an intensive vs. a conservative treatment in diabetics, such as the ACCORD trial, and to the results of different meta-analyses that in the same population suggest increased risk of events when starting from a SBP <140 mmHg or when a SBP of 130 mmHg is reached. Similarly, we observed in the HOPE study how treatment with candesartan and hydrochlorothiazide was beneficial in patients with SBP >143 mmHg and harmful in those with SBP <131 mmHg.

In conclusion, this analysis is consistent with the recommendation of practice guidelines: to look for a target SBP not below 120 mmHg and a target DBP not below 70 mmHg. But is this recommendation the same for all patients? Surely not; each patient has a risk of events beyond their BP; in each of them BP can play differently; according to the greater risk of one or other event we can pose more or less ambitious goals. A higher decrease in SBP may increase the risk of AMI and reduce the risk of stroke. It is difficult for us to discriminate in each case the relative risk of each event, but, for example, in a patient with a history of stroke and carotid disease, it may be useful to be more aggressive and in an incompletely revascularized coronary artery we may be able to tolerate higher BP levels.

Frailty: two examples of its influence in cardiological practice

Shimura T, Yamamoto M, Kano S, Kagase A, Kodama A, Koyama Y, et al; OCEAN-TAVI Investigators. Impact of the Clinical Frailty Scale on Outcomes After Transcatheter Aortic Valve Replacement. **Circulation 2017;135:2013-24. http://doi.org/f99d2k**

Ravindrarajah R, Hazra NC, Hamada S, Charlton J, Jackson SHD, Dregan A, et al. Systolic blood pressure trajectory, frailty, and all-cause mortality >80 years of age: Cohort study using electronic health records. **Circulation 2017;135:2357-68. http://doi.org/gbjvsg**

In recent years there has been growing interest in the concept of frailty. This is defined as an aging-associated condition, consisting in the decrease of resilience, which is the capacity to overcome different pathological conditions. The impossibility of adequately responding to the presence of stressors is related to an adverse outcome, including greater risk of hospitalization or death and poor results of different medical interventions. We present two publications about frailty and its association with usual aspects of medical practice.

Transcatheter aortic valve implantation (TAVI) is a procedure where frailty is specially considered, as it is a complex and costly intervention generally performed in elderly patients at high or forbidding surgical risk, in whom it is logical to recommend frailty assessment among the baseline conditions to decide whether the procedure can be carried out. In order to refine candidate selection for TAVI, some recent publications evaluated the role of frailty in the result of the procedure and the long-term outcome of these patients. We present a Japanese registry with a large number of enrolled patients.

OCEAN TAVI is a Japanese prospective registry of nine institutions, including 1,215 patients undergoing TAVI between October 2013 and April 2016. Clinical, echocardiographic, procedural and outcome data were recorded. The frailty status of each patient was acquired at baseline based on the Canadian clinical frailty scale (CFS) developed by Rockwood. This scale considers 9 stages, from robust, active and motivated patients (CFS 1) to those with extreme frailty, in whom survival is not estimated above 6 months (CFS 9). It is a semiquantitative scale considering patient symptoms, mobility, inactivity, weariness and disability to perform daily life basic and instrumental activities. To facilitate analysis, patients were divided into five groups according to their position in the scale: non-frail (CFS 1-3), vulnerable (CFS 4), and with mild (CFS 5), moderate (CFS 6) or severe (CFS 7-9) frailty.

Mean age was 84±5 years. Thirty eight percent of patients were non-frail, 32.9% vulnerable, 15.1% mildly frail, 10% moderately frail and 4% severely frail. Increasing degrees of frailty were significantly associated with older age, greater prevalence of females, lower body mass index, higher STS score (median of 7.4 in non-frail patients to 11.7 in severely frail ones), greater prevalence of FC III-IV and peripheral vascular disease. Gait speed and grip strength could be assessed in 930 patients; both significantly decreased with increased frailty. Brain natriuretic peptide values were higher and albumin and hemogoblin levels were lower at progressively higher scale stages. The transfemoral approach was less used the higher the functional involvement, the procedure was longer and the incidence of adverse events (renal failure, major bleeding) was more elevated. There was a great tendency to higher in-hospital mortality as the frailty stage was higher, from 1.7% in non-frail patients to 8.5% in the frailer ones ($p=0.06$) and a significant difference in 1-year mortality in the five groups: 7.2%, 8.6%. 15.7%, 16.9% and 44.1% ($p <0.001$). In the multivariate analysis, FC III-IV, lower hemoglobin and albumin values, increasing creatinine values, lung and liver disease and the presence of frailty were independent predictors of 1-year mortality (HR 1.28 95% CI 1.10-1.49 per each group increase in the classification).

The other study selected explores the relationship between blood pressure (BP) and the frailty concept. It is well known that in elderly patients, a target systolic blood pressure (SBP) not below 140 mmHg is suggested. Different observational studies indicate that in subjects above 75 to 80 years of age, SBP <120 mmHg is associated with greater rate of events and mortality, and that elevated BP values do not seem to constitute a risk factor. The authors of this work used CPRD data, an electronic database of primary care in Great Britain, which approximately covers 7% of the population, around 5 million persons, and is representative of the overall population. This database has demographic, physical exam and laboratory data, and information on diagnosis, treatment prescriptions and complementary studies. A total of 144,403 patients below 80 years of age, registered between 2001 and 2014, who had more

than one SBP record in that period and of whom there were data from the 5 years prior to death or end of study, were selected. Average SBP of all the measurements performed was defined for each patient, and they were classified according to an electronic frailty index (eFI), which considers 36 items (each is a possible deficit, so the proportion of deficits present is established over a total of 36).

Three percent of patients presented average SBP <100 mmHg, 6.4% between 100 and 119 mmHg, 37.3% between 120 and 139 mmHg, 40.8% between 140 and 159 mmHg and 12.5% ≥160 mmHg. Patients with lower SBP were older, with greater prevalence of men, higher rate of comorbidities and greater frailty. In patients with average SBP <110 mmHg, 22% presented no frailty, 38% mild, 28% moderate and 12% severe frailty. Prevalence of frailty was progressively lower in each SBP category, reaching in subjects with SBP ≥16 mmHg 42% non-frail cases, 38% mild, 16% moderate and only 4% severe cases. The lowest cumulative mortality was registered in the SBP category between 140 and 159 mmHg and it was slightly higher in the SBP ≥160 mmHg group. The greatest mortality was found in the group with mean SBP between 110 and 119 mmHg (almost 2 times higher) and especially in the SBP <110 mmHg group (3 times higher). After adjusting for age, diastolic BP, gender, cholesterol, smoking and comorbidities for each SBP category, mortality was markedly increased with each frailty category. This finding occurred both in patients receiving or not antihypertensive treatment. A study of SBP trajectory over the 5 years prior to death or end of study for each patient showed that SBP tended to decrease with the passage of time, specially, in those who die, in whom a drop of approximately 15 mmHg is produced in the 2 years prior to death.

This study provides an explanation for observational findings linking lower SBP with higher mortality in elderly subjects: the inverse causality. It is not that lowering SBP is responsible of the higher incidence of death (the association is independent of antihypertensive treatment), but that subjects presenting greater frailty have lower SBP values, and this falls more in patients at greater risk. The concept of frailty is clearly associated to aging, but aging in which multiple deficits develop with the passage of time turns a subject more vulnerable even to minimal disorders. Falls, acute confusional states, growing disability are some of its manifestations. Different scales have been developed to measure frailty: quantitative or semiquantitative, with objective (albumin, hemoglobin or walking time values) and subjective (exhaustion, depression, etc.) components, or with few or many items (from 5 to 90-item scales). In all cases, the frailest patients have worse outcome, regardless of other baseline conditions. The concept of frailty seems to displace that of age: in different analyses, age is no longer an independent predictor of events when frailty is considered, though it is not less true that the frailest patients are older than those who are not. The difference in age is not great, but as shown in the observational British study, just two years before death, there is a fall in BP associated with greater frailty. This means, as we approach the end of our life, we become frailer. The concept of frailty goes hand in hand with that of therapeutic futility: in very frail patients interventions present a high rate of complications and poor benefit, as shown by different TAVI registries, where 40% to 50% of frailer patients died at one year and surviving ones presented a high incidence of disability. Taking into account this factor may help more rational decisions by physicians and of course, by the patients and their families. As can be seen, this goes from use of antihypertensive drugs to more complex procedures. And the million dollar question is: faced with the initial manifestations of increasing vulnerability, can there be therapeutic conducts capable of changing its course to allow patients a longer life but also less exposed to complications, suffering and limitation? This last challenge is without any doubt as important, or even more important, than the first.

The usefulness of beta-blockers is discussed in different clinical settings. Should we reevaluate their indication?

Dondo TB, Hall M, West RM, Jernberg T, Lindahl B, Bueno H, et al. β-Blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. **J Am Coll Cardiol 2017;69:2710-20. http://doi.org/gbgj7p**

Kotecha D, Flather MD, Altman DG, Holmes J, Rosano G,Wikstrand J, et al. Heart rate and rhythm and the benefit of beta-blockers in patients with heart failure. **J Am Coll Cardiol 2017;69:2885-96. http://doi.org/gbhxjg**

Beta blocker (BB) treatment has been for years the standard care in different cardiac conditions. In recent times, we have been questioning many of these indications based on data from randomized registries or studies. We now present two publications following this line.

Use of BB in patients after an acute myocardial infarction (AMI) is a routine practice for the vast majority of cardiologists. It is based on physiopathological reasons and in a series of randomized studies that more than 30 years ago demonstrated a reduction in mortality and reinfarction. Further analysis showed that the benefit was much more marked in patients with left ventricular dysfunction (LVD) or heart failure (HF) secondary to AMI. On the other hand, the follow-up of these studies did not go beyond 3 to 4 years, turning uncertain the need to extend BB therapy beyond that period. In the last decades, the expansion of reperfusion therapy and the practice of primary angioplasty and drug-invasive treatment, as well as the use of statins, contributed to reduce the ncidence of HF after AMI and reinfarction, and also added doubts about the current usefulness of BB therapy in patients with uncomplicated AMI. Treatment guidelines, however, still strongly recommend the use of BB after AMI, with a recommendation strength varying between I and IIa according to the type of AMI, the presence or not of HF and the scientific society.

Based on data from a prospective British registry

of acute coronary syndrome, the MINAP study, the authors of the proposed analysis question the use of BB in patients with uncomplicated AMI with LVD [left ventricular ejection fraction (LVEF) <30%] or HF. Among the 531,282 patients with AMI admitted to one of 247 centers between January 2007 and June 2013, and followed-up until death or December 2013, those discharged without LVD, HF or treated with loop diuretics, and without use, clear indication or contraindication for BB, were selected. Thus, 179,810 patients were defined (51.1% with ST-segment elevation), of which 94.8% were discharged with BB and the remaining 5.2% without BB. Those treated with BB were on average 5 years younger, more frequently men, with a higher prevalence of ST-segment elevation AMI and lower prevalence of various comorbidities: diabetes, asthma, renal failure, cerebrovascular disease, etc. The use of revascularization procedures during hospitalization and treatment with antiplatelet agents and statins was also greater. Logically, mortality at one year was much lower in patients treated with BB: 4.9% vs. 11.2% ($p < 0.001$). This can be attributed to the different baseline conditions or the treatment itself.

To overcome this difficulty, the authors carried out an analysis using a propensity score, which consisted in defining for each patient the propensity to use BB based on independent predictors of its use, thus generating a score. It was then matched to patients with the same score (and therefore equally likely to be treated with BB), effectively treated with BB or not. This analysis seeks to simulate what occurs in a randomized study, in which patients with equal baseline characteristics are assigned or not to a certain treatment. In this analysis, which included 12,420 untreated patients and 4,263 BB-treated patients, there was no difference in survival at 1 month, 6 months or 1 year according to the use of BB. The results were similar between patients with and without ST-segment elevation. A second analysis, called the instrumental variable, which considers in all patients the effect of BB treatment versus the rest of the therapies recommended by the guidelines, neither showed the influence of BB on survival.

The second study we present is a meta-analysis of individual data from the large BB studies in patients with ambulatory HF and low LVEF, or LVD post AMI, including those treated with carvedilol (the COPERNICUS American carvedilol study, ANZ, CHRISTMAS and CAPRICORN), bisoprolol (CIBIS I and II), metoprolol (MDC and MERIT HF), nebivolol (SENIORS) and bucindolol (BEST). Patients with sinus rhythm (SR) or atrial fibrillation/flutter (AFF) were considered for the analyisis. The relationship between baseline heart rate (HR) and HR achieved with total mortality primary endpoint was analyzed for patients with SR and AF.

The analysis included 18,637 patients, 14,313 in SR and 3,065 with AFF. Compared with patients with SR, those with AF were 5 years older, more frequently in FC III-IV and receiving more treatment with diuretics, digoxin, amiodarone, anti-aldosterone drugs and oral anticoagulation. The LVEF was the same (median of 27%), and the HR was similar, with medians of 80 beats/minute in SR and 81 beats/minute in AFF.

In SR patients, baseline HR was an independent predictor of total mortality in the multivariate analysis, with an excess risk of 11% (95% CI 7-15) for each increase of 10 beats/min. Beta blockers were associated with a reduction of overall mortality (HR 0.73, 95% CI 0.67-0.79) with no significant difference according to baseline HR strata (<70, 70-90, >90 beats/min). Beta blockers decreased HR between 11 and 12 beats/min. The HR achieved at a mean follow-up of just over 6 months had a somewhat stronger relationship with mortality than the change in HR since inclusion.

In patients with AF, baseline HR did not predict overall mortality, despite being similar to that of patients with SR. Neither was the use of BB associated with a reduction in mortality, either globally nor in any of the baseline HR strata, even though the HR reduction was the same as in SR.

Regarding the analysis on post-AMI use of BB, it is worth noting that the current therapy is responsible for patients with less damaged left ventricles, less likely to present with heart failure or arrhythmia. For example, the Swedish Registry of hospitalization for AMI shows that between 1998 and 2010 the hospital incidence of HF with low LVEF fell from 47% to 28%, while the incidence of cases without HF or LVD increased from 25% to 50%. In this type of patients it is feasible that the usefulness of BB is lower. The REACH registry published in 2012 analyzed the utility of BB in different clinical scenarios. In patients with previous AMI matched, as in this case by a propensity score for the use of BB, those treated with BB did not progress differently from those who received the medication. The analysis that we present goes further: it raises the uselessness of BB administered since the time of hospitalization in the case of AMI without HF and LVD. However, we should not take the conclusions as definitive: as we have said several times, pairing by a propensity score allows equalizing the known baseline characteristics, but not the unknown ones. There may then be variables not considered different to explain the similar evolution of both groups. Only randomization allows (at least theoretically) distributing the known and the unknown alike, so that what we observe can be unequivocally attributed to the intervention. To this we must add that to use the propensity score it was necessary to go from almost 180,000 patients to just over 16,000, which implies a significant loss of information, and a selection of patients that makes the findings less applicable to the general population. In summary, the conclusions are feasible, but certainly a randomized study would provide greater strength to the evidence. It is worth remembering that for decades there has been no randomized study of BB in patients with preserved LVEF. A more recent study, CAPRICORN, with carvedilol, demonstrated the beneficial effect of BB only in AMI with depressed LVEF.

Regarding the study of BB in HF with low LVEF and its different effect according to the baseline rhythm, it is an extension of the meta-analysis published by the same group in 2014, and commented in Rev Argent

Cardiol 2015; Vol. 83 (1). It was already evident that although the randomized studies show a reduction in mortality with BB in the context of HF with decreased LVEF, the effect was verified in patients with SR but not in those with AFF. There were different explanations for the finding: from a false positive subgroup analysis, going through the possible interaction of BB with digoxin, of a much more frequent use in patients with AFF, which could lead to negative effects, to the hypothesis that the use of BB would exacerbate the appearance of mostly nocturnal pauses in patients with AF, which in turn favor the onset of malignant ventricular arrhythmia. The current analysis does not clarify these doubts, but allows us to envisage that HR plays a different role according to the baseline rhythm: clearly linked to the prognosis in patients with SR, dissociated from it in AFF patients. And it also suggests that where HR is determinant (in patients with SR) BB can lower mortality, and that there is a relationship with the HR attained. In contrast, in patients where baseline HR does not seem to impact the prognosis (those with AFF), BB do not change patients' fate, even though the decrease achieved in HR is the same. If so, are all the other postulated effects (anti-ischemic, antiarrhythmic, anti-remodeling, etc.) unimportant?

Nevertheless, (and this is true for AMI with good ventricular function and without HF as well as for HF with AF) none of the analyses presented suggests that BB are harmful, but rather point to their presumed lack of effectiveness. With this in mind, there will be those who feel less driven to use them in these conditions; there will also be some who (and here we sign up) until things become clearer, think that it is neither a bad option to maintain their use based on the overall outcome of HF studies, and the findings of old randomized studies in patients with AMI. In either case, randomized studies dedicated to answering these questions are welcome.

Usefulness of cardiac defibrillators in nonischemic heart failure with reduced ejection fraction: a meta-analysis refutes de DANISH trial

Al-Khatib SM, Fonarow GC, Joglar JA, Inoue LYT, Mark DB, Lee KL, et al. Primary prevention implantable cardioverter defibrillators in patients with nonischemic cardiomyopathy: A meta-analysis. **JAMA Cardiol 2017;2:685-8. http://doi.org/cchb**

Demonstration of reduced mortality with implantable cardioverter defibrillators (ICD) in nonischemic heart failure (HF) with left ventricular ejection fraction (LVEF) <35% has followed a tortuous pathway. At that time, the DEFINITE trial was unable to determine a statistically significant effect, and the same happened with the nonischemic subgroup of patients of the SCD HeFT study. A meta-analysis performed by Desai et al. in 2004, taking into account these studies and other smaller ones (CAT and AMIOVIRT) was able to demonstrate a significant reduction of overall mortality in this group of patients. We recently reported the results of the DANISH trial in Rev Argent Cardiol 2016;84:524-30. In this study, patients with nonischemic HF and LVEF<35%, without significant coronary artery disease, or with up to two-vessel disease not considered to be responsible for ventricular dysfunction, in FC II-III (and IV if resynchronization therapy pacemaker implantation was planned) and under optimal treatment, were randomly assigned in a 1:1 ratio to receive ICD. It included 1,116 patients, with median age of 63 years, 53% in FC II, 45% in FC III and the rest in FC IV. Median LVEF was 25% and median QRS duration 146 ms. In 58% of cases resynchronization therapy was also indicated. In a median follow-up slightly above 5 years and a half, there was no difference in the incidence of overall or cardiovascular mortality, but the rate of sudden cardiac death was significantly lower. The subgroup analysis revealed interaction with age: use of ICD in patients younger than 68 years of age generated a significant decrease of 36% in overall mortality. A trend for interaction with NT-proBNP levels (p=0.06) was also found, with significant reduction in patients with levels below 1.177 pg/ml. Their global results indicated that universal use of ICD for primary prevention in nonischemic patients under optimal medical treatment does not improve prognosis. But, we add, at the same time they pointed out that in younger patients and with lower cardiac involvement (in whom the risk of sudden death is proportionately higher) the indication should at least be taken into account.

We now know the results of a meta-analysis that considers four studies: CAT, DEFINITE, SCD HeFT and also the DANISH trial. It included 1,874 patients, 937 with conventional treatment and 937 with ICD. The HR ratio for overall mortality (0.75, 95% CI 0.61-0.93; p=0.008) was favorable for ICD, with no heterogeneity among studies.

This meta-analysis seems to put thing in the right place: it suggests that the results of the DANSIH study are not enough to decide the futility of ICD for primary prevention of overall mortality in nonischemic patients. It has the limitation of not being a meta-analysis of individual data, thus not allowing a clearer definition of subgroups with greater strength of evidence. Other meta-analyses on the subject have been published this year (Romero et al, J. Interv.Card Electrophysiol; Kolodziejczak et al. Ann Intern Med), all arriving to the same conclusion: the reduction of mortality in patients with nonischemic etiology. All these analyses imply a message: we must not a priori forget or reject the use of ICD in these patients. The results of the DANISH study are not enough to declare the futility of ICD therapy; however, they may modulate our conduct, reminding us that in elderly patients with nonischemic HF and reduced LVEF, with low risk of overall death and excellent medical treatment, the efficacy of ICD may be lower than expected.