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Blood pressure reduction in type 2 diabetic patients: When to start? How far to go? A meta-analysis

Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. **JAMA 2015; 313: 603-15.**

Diabetes mellitus (DM) as well as hypertension (HTN) are risk factors for the incidence of macrovascular and microvascular events. The prevalence of hypertension is higher in patients with DM. Several randomized studies have explored the impact of treating HTN in patients with DM. The latest treatment guidelines recommend slightly higher BP target values in patients with DM than in those without DM, derived from recent studies showing lack of benefit, and even more adverse effects, with more aggressive antihypertensive strategy in the context of DM. However, doubts persist about the certainty of applying this recommendation in all patients.

The authors of the present meta-analysis explored the effect of reducing BP in patients with DM. They selected randomized studies with more than 1000 patients/year of follow-up, in which all were diabetic, or in which results in the subgroup of diabetics were communicated. They were not limited to specific studies of antihypertensive treatment, but also incorporated studies in which BP lowering drugs had been used in another context, such as myocardial infarction (AMI) or heart failure (HF).

The primary end point was all-cause mortality. Furthermore, the effect of reducing BP was explored on the incidence of macrovascular events: AMI, revascularization, stroke or HF; or microvascular events: retinopathy, renal failure or albuminuria.

Finally, for the primary analysis 40 studies (n = 100,354 patients) were included and five additional lower quality studies (n = 4,232) were added to the list for subsidiary analyses. A decrease of 10 mmHg in systolic BP was associated with risk reductions of 13% for overall mortality, 11% for macrovascular events, 12% for coronary events, 27% for stroke, 13% for retinopathy and 17% for albuminuria. All these reductions were statistically significant. The number of patients needed to treat during 10 years to prevent one episode ranged from 11 for albuminuria to 55 for the incidence of coronary events.

There was interaction between the effect of reducing systolic BP by 10 mmHg and mean systolic BP at baseline for some end points: total mortality, cardiovascular events in general, coronary events and HF risk reduction was only evident when the average baseline systolic BP was ≥140 mmHg, and not when it was lower. In the case of stroke there was risk reduction irrespective of the initial BP; in the case of albuminuria, although always evident, risk reduction was significantly greater in studies with average systolic BP ≥140 mmHg.

The same observations can be made considering the mean systolic BP achieved in the active group and taking 130 mmHg as cutoff value: the effects on overall mortality, cardiovascular events in general, coronary events and HF were evident only when systolic BP reached in the active group was ≥130 mm Hg, and not when it was lower. In the case of stroke there was risk reduction irrespective of the BP attained; in the case of albuminuria, although always obvious, risk reduction was significantly greater in studies with mean systolic BP ≥130 mmHg.

Regardless the study initial or final BP, there was a strong tendency for antihypertensive treatment to reduce retinopathy risk, although it did not reach statistical significance.

This meta-analysis has the distinct strength of having considered a huge number of diabetic patients, and not only from studies focusing on HTN, but also from those in which antihypertensive drugs were used in another context. It seems to confirm on a large-scale the results of the ACCORD study regarding the lack of effect on major cardiovascular events in diabetic patients when BP reduction is more pronounced. But another of its merits is having explored the effect of treatment on other end points, demonstrating that with ambitious targets of BP reduction there may be benefits when considering albuminuria or stroke. It is clear that by working with summary or aggregate results and not with individual data we cannot know the exact value of systolic BP in which the risks outweigh the benefits: 130 mmHg is a cutoff value that roughly divides the waters. Moreover, it is a meta-analysis focused on treatment efficacy and not on security, so the price to pay is unclear. In conclusion, it suggests that the most marked benefit is obtained in patients with higher BP values and that the aim of achieving systolic BP values <130 mmHg could be reserved for clearly individualized patients at high risk of neurologic or renal event.

Endarterectomy vs stenting for symptomatic carotid disease. Equally valid options? The ICSS trial

Bonati LH, Dobson J, Featherstone RL, Ederle J, van der Worp HB, de Borst GJ, et al. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. **Lancet 2015;385:529-38. http://doi.org/f25qft**

Atherosclerotic disease of the internal carotid (ADIC) is responsible for 10% to 15% of all strokes. Carotid endarterectomy (CE) reduces stroke risk in symptomatic carotid disease. In several randomized studies carotid stenting (CS) has been shown to be an alternative to surgery but with increased risk of periprocedural stroke (albeit not disabling), and lower incidence of hematoma at the access site, cranial nerve paralysis or acute myocardial infarction (AMI). ICSS, with its recently published 10-year follow-up, has been the largest of these studies.

The open, multicenter, randomized ICSS study enrolled patients of at least 40 years with symptomatic ADIC causing at least 50% reduction of the arterial lumen and in whom CE or CS were considered equally valid options. It excluded patients with a history of major stroke and those previously treated with CE or CS. Patients were randomly assigned in a 1 to 1 ratio to CE or CS, stratified by center, seeking to equalize both groups by age, gender, side of stenosis and presence of contralateral carotid occlusion. Follow-up was at 30 days, 6 months and annually thereafter. The primary end point was the occurrence of fatal stroke (if death occurred within 30 days of the event) or disabling stroke (if the Rankin scale score had increased to ≥ 3 at 30 days). Secondary end points were death, overall stroke and incidence of periprocedural events (those that occurred within 30 days of the procedure).

The study comprised 50 centers with 1,713 patients of whom 1,710 actually participated; 857 in the CE group and 853 in the CS group. Mean age was 70 years, 70% were men, 70% were hypertensive and 22% were diabetic. Symptomatic arterial injury of 70% to 99% was present in 90% of patients and the rest presented with injury of 50% to 69%. Contralateral carotid presented with injury of 70% to 99% in 13% of cases and was occluded in 5% of cases.

Median follow-up was 4.2 years. There were no significant differences at 5 years in the primary endpoint (6.4% with CS and 6.5% with CE) or all-cause mortality (17.4% vs. 17.2%, respectively). In the CS group the incidence of any stroke (15.2% vs. 9.5%, HR 1.71, 95% CI 1.28-2.30) exceeded 5 years, mainly attributable to non-disabling events. Similarly, a combined endpoint of death or periprocedural stroke or ipsilateral stroke at follow up was more frequent. In a per protocol analysis, the difference in the incidence of any stroke was apparently due to events in the contralateral or vertebrobasilar territory rather than in the treated carotid. There was no difference in the incidence of restenosis.

The most recent guidelines for the treatment of symptomatic carotid disease accept CS as a valid alternative to CE. An important part of the evidence considered in meta-analyses and guidelines comes from the study we present here, due to the number of patients and length of follow-up. It is true that the risk of stroke is higher with CS, but not of fatal or disabling stroke. The advantage of CS arises from the lower rate of cardiovascular complications and, as we see, the long-term mortality is similar. As with any medical practice the best decision in the individual case will be taken considering injury, patient characteristics (ICSS could not prove it, but combined data from other studies suggest increased risk with CS in patients over 70 years) and operator experience (ICSS had apparently worse outcomes in those enrolling fewer than 50 patients, suggesting that the volume of treated patients influences the results, something not confirmed by all studies)

Hospitalization for pneumonia predicts long-term cardiovascular events

Corrales-Medina VF, Alvarez KN, Weissfeld LA, Angus DC, Chirinos JA, Chang CC, et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. **JAMA 2015;313:264-74. http://doi.org/26q**

It is well known that there is an association of infectious processes (including those of the respiratory tract) with higher incidence of short term cardiovascular events (CVE). In a previous publication we have already discussed the relationship of flu with the incidence of acute myocardial infarction (AMI) and cardiovascular death. Activation of inflammatory phenomena and the coagulation cascade, endothelial dysfunction, atherosclerotic plaque destabilization and ischemia as a result of myocardial oxygen demand are considered the responsible mechanisms. Pneumonia is one of the most common causes of hospitalization. The authors of this study sought to determine whether, beyond the expected short-term effect, hospitalization for pneumonia involves an increased risk of long-term CVE.

A nested cohort study was performed in two observational prospective studies carried out in the United States to study risk factors, incidence and progression of cardiovascular disease: the ARIC study (recruiting 17,792 subjects from 45 to 64 years between 1987 and 1989) and the CHS study (including 5,888 subjects of at least 65 years between 1989 and 1994). In both cases, follow-up was extended until the end of 2010. In each of the studies, a "case" cohort (subjects who throughout the first 15 years of follow-up had been discharged from hospital with a diagnosis of pneumonia, the time to this event being called "time-to-pneumonia") and a randomly selected "control" cohort (matched in a 2 to 1 ratio with the cases by age ± 5 years and who had not presented this condition in the "time-to-pneumonia" of the case), were selected. Patients with cardiovascular disease at baseline or those who presented this condition prior to time-to-pneumonia in the cases or its equivalent time in the controls were excluded from both groups. The primary end point was incidence of CVE after index event. The incidence of events was adjusted for demographic variables, cardiovascular risk factors and comorbidities.

The ARIC study defined 680 cases and 1,360 controls. Cases had a higher prevalence of coronary risk

factors and subclinical atherosclerosis. Average age was 55 years. After time-to-index event in cases or its equivalent in controls, cases´ mortality at 1 month and at 1, 5 and 10 years was 12%, 25%, 44% and 76%, respectively; and significantly lower in controls: 0.3%, 2%, 8.5% and 21%, respectively. There was a higher incidence of CVE in cases: 0.9% vs. 0.3% at 1 month, 1.1% vs. 0% between 1 and 3 months, 3.1% vs. 0.9% between 3 months and 1 year, and 2.6% vs. 0.8% between 1 and 2 years, with adjusted HR between 1.9 and 2.4, all significant.

The CHS study defined 591 cases and 1,182 controls. Here cases also had a higher prevalence of risk factors and subclinical vascular disease. The average age was 73 years. After time-to-index event in cases or its equivalent in controls, mortality in cases at 1-month and 1, 5 and 10 years was 19%, 36%, 59% and 71%, respectively; and significantly lower in controls: 0.7%, 8%, 34% and 64%, respectively. There was a higher incidence of CVE in cases, with a high risk ratio during the first month: 10.6% vs. 0.5% (adjusted HR 4.1), which remained significantly higher than 1 at 10 years. The increased risk of CVE remained even when hospitalizations for pneumonia and heart failure were excluded.

This analysis of nested cohorts in two large observational studies demonstrates the association between pneumonia and CVE. It has the merit of being presented in healthy subjects of different ages, with similar findings in both studies. The existence of this short-term association is perhaps not surprising: it may be explained by the different pathophysiological reasons mentioned. But it is not less challenging that the association persists over several years and is maintained despite adjusting for numerous baseline variables, to the extent that the authors postulate it as a true "risk factor". May a pneumonia requiring hospitalization 6 years ago really be responsible for increased risk of AMI today? Can the mechanisms triggered by an infection that has been resolved persist activated for so long? If pneumonia is really a risk factor, we might expect that pneumococcal vaccination in populations at risk of infection would decrease the incidence of AMI at follow-up, beyond the first year. Is it so? The CAPAMIS study, conducted in Spain in more than 27,000 subjects over 60 years of age could not demonstrate that the vaccine reduced the risk of AMI at 1 and 3 years. Or possibly, if this association were real, is there an unclear condition that makes us more susceptible to infection and also to plaque accident? The answer is that, as in any observational study, we cannot rule out the presence of residual confusion and unknown variables, truly responsible for what we observe.

Relationship between type of atrial fibrillation and outcome, a risk factor little considered: a subanalysis of the ROCKET-AF trial

Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, et al. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. **Eur Heart J 2015;36:288-96. http://doi.org/26r**

The most important risk factors to determine the risk of stroke and systemic embolism in the context of non-valvular atrial fibrillation (AF) are considered in the CHADS2 and CHA2DS2-Vasc scores. These scores define the indication for oral anticoagulation. As we know, AF can assume different forms of presentation, and for clinical purposes (including decisions about the most effective antiarrhythmic treatment) it can simply be differentiated in paroxysmal AF (PaAF) and persistent AF (PeAF). Paroxysmal AF ends spontaneously in less than 7 days and PeAF lasts more than 7 days or requires intervention to be resolved. There are symptomatic, anatomic and physiological differences between both, but the type of AF is not considered when anticoagulant therapy is indicated. This subanalysis of the ROCKET-AF trial (which compared the effect of rivaroxaban vs. warfarin on the incidence of stroke or systemic embolism in the context of non-valvular AF) shows the influence of the type of AF on patient outcome.

The ROCKET study included 14,264 patients. The present analysis excluded 202 patients with recent AF onset. Of the remaining 14,062 patients, 2,514 (18%) had baseline PaAF, and 11,548 (82%) baseline PeAF. Paroxysmal AF patients were slightly younger (median 72 vs. 73 years), with higher prevalence of females (45% vs. 39%), slightly lower heart rate (median 72 vs. 76 bpm) and lower prevalence of diabetes and heart failure. A history of transient ischemic attack but not of stroke was more frequent among these patients. Baseline aspirin treatment was more often (41% vs. 35%) and vitamin K antagonist treatment was less often (56% vs. 64%). Of paramount importance is that there was no significant difference in the CHADS2 (3.5 ± 0.9 in both groups) or CHA2DS2-Vasc (4.9 ± 1.3 in both groups) scores.

At follow-up, and adjusting for age, gender, the remaining components of both scores, renal function, lung disease, heart rate and alcohol consumption, PaAF patients had better outcome. Their HR adjusted for stroke or systemic embolism was 0.79, 95% CI 0.63-1, p=0.048; for stroke the HR was 0.78, 95% CI 0.61-0.99, p=0.045 and for total mortality it was 0.79, 95% CI 0.67-0.94, p=0.006. There was no difference in the incidence of bleeding, or interaction with anticoagulant treatment received in the study.

The sub-analysis presented indicates something that we would endorse "a priori": the "dose" of AF influences outcome. Long-term presence of AF involves greater risk of brain or systemic embolic event and death. Data of anticoagulated patients in this publication complete recently published information on the risk gradient for embolism and stroke presented by paroxysmal, persistent and permanent AF (when there is no interposition of sinus rhythm in the context of

AF) in patients with AF treated with aspirin in the ACTIVE A and AVERROES studies. It is essential to note that this occurs even when CHADS2 and CHA2DS2-Vasc risk scores are similar or differ slightly between the different presentations. The analyses cited suggest we should have a closer follow-up of patients with more advanced forms of AF and prevent them from reaching that situation. However, rhythm and frequency control do not differ in patient outcome; perhaps AF persistence and permanence involve more marked mechanical and electrical atrial remodeling, and greater impact on ventricular function. In this sense, one cannot but regret that none of the cited studies reports whether there are differences in left ventricular ejection fraction among the different forms of AF.

Percutaneous closure of patent formanen ovale: a network meta-analysis

Stortecky S, da Costa BR, Mattle HP, Carroll J, Hornung M, Sievert H,, et al. Percutaneous closure of patent foramen ovale in patients with cryptogenic embolism: a network meta-analysis. **Eur Heart J 2015;36:120-8.http://doi.org/26s**

Up to 40% of ischemic strokes are cryptogenic, that is, they do not have a clear origin. Paroxysmal atrial fibrillation (AF) and patent foramen ovale (PFO) are among the potential causes of these conditions. Several strategies have been postulated for PFO treatment: medical therapy with antiplatelet/anticoagulation agents, surgical treatment and percutaneous closure. This last strategy has been tested in randomized studies but has failed to be superior to medical therapy. Reduced number of patients and lower than expected event rate (both conditions that result in insufficient power to demonstrate a difference) together with the individual characteristics of each device used, are among the reasons postulated to explain lack of positive results.

Therefore, to obtain a clearer perspective a network meta-analysis was performed considering different trials and establishing comparisons among their groups even when they had not been directly implemented. Four randomized trials comparing either a percutaneous device with medical therapy (2 with Amplatzer, 1 with StarFlex), or different devices (Amplatzer, StarFlex and Helex) were considered. A total of 2,963 patients, with mean age ranging between 44.5 and 49.4 years, and a proportion of women varying between 45% and 50% were included in these studies. Stroke was the index event in 58% to 100% of patients and transient ischemic attack (TIA) in 15% to 51%, depending on the study. Presence of atrial septal aneurysm was detected in 23.7% to 36.6% of patients and of shunt through the PFO in 20.8% to 48.8% in the different trials. Mean follow-up varied between 2 and 4.9 years.

Using complex mathematical models, the network meta-analysis as able to calculate the probability that each treatment (medical therapy and every device used) had of being the best, the second, the third or the last in its ability to prevent stroke, TIA, AF and overall mortality in a "all against all" comparison. The annual event rate was similar in the 4 studies: stroke between 0.5% and 1.4%, TIA between 0.5% and 1.8%, AF between 0.2% and 0.6% and overall mortality between 0 and 0.5%.

Median procedural success was 99.1% for Amplatzer, 94.7% for StarFlex and 100% for Helex. At 6 months, PFO closure was effective with Amplatzer in 95.9% of cases, with StarFlex in 90.3% and with Helex in 85.9%.

Compared with medical treatment, only the Amplatzer device significantly reduced stroke risk (RR 0.30, 95% CI 0.17-0.84) with NNT (number needed to treat to reduce one event) of 29 patients (95% CI 21-109). In the overall comparison, the Amplatzer device had the highest probability of being the best treatment to prevent stroke (77.1), and the lowest probability for medical therapy (0.4%). Regarding the other end points, no device was superior to medical therapy.

Compared with results of individual studies which were unable to clearly demonstrate PFO closure superiority over medical therapy, this meta-analysis suggests that the invasive treatment is preferable, and this is its greatest merit. It is interesting to point out that beyond the ability to adequately close PFO, the device risk of AF and device thrombosis strongly influence patient outcome: the tool used to reduce the incidence of embolic stroke may in turn trigger a stroke by favoring thrombi or initiate AF. Therefore, some proviso should be considered: not all devices are equal, and the success and complication rates vary among them. Only Amplatzer proved to be effective, StarFlex increased 8-fold the risk of AF compared to medical therapy while Amplatzer only 2. So, beyond the adequate selection of patients and the operator experience, the material used has a great weight on the outcome. It is expected that with better device design and materials, future results will improve even more.

Usefulness of a coronary sinus device to relieve refractory angina. The COSIRA trial.

Verheye S, Jolicoeur EM, Behan MW, Pettersson T, Sainsbury P, Hill J, et al. Efficacy of a device to narrow the coronary sinus in refractory angina. **N Engl J Med 2015;372:519-27.http://doi.org/26t**

Different options have been postulated throughout time to treat refractory angina in patients who are not candidates for revascularization due to their coronary anatomy. In the last years, an endoluminal, balloon-expandable, stainless steel, hourglass-shaped device has been designed for percutaneous implantation in the coronary sinus to increase its pressure. In stud-

ies with a reduced number of patients, this device has proved its efficacy to treat refractory angina. The COSIRA trial was conducted with a more ambitious design and larger number of patients to confirm these findings.

It included patients with Canadian Cardiovascular Society functional class (FC) III-IV angina who had not improved symptoms after at least one month of intensive medical therapy. All participants were required to have left ventricular ejection fraction (LVEF) > 25%, evidence of ischemia in evocative testing and coronary anatomy unable to undergo coronary bypass graft surgery or percutaneous coronary intervention. Patients underwent right heart catheterization with coronary sinus angiography and only those with suitable coronary anatomy were randomly assigned to undergo either device implantation or a sham procedure, in which device implantation was simulated with medical management and procedural time similar to those of the real intervention. The primary end point was the proportion of patients that improved two FC at 6 months. Secondary end points included the improvement of at least one FC in the same period, exercise tolerance in stress testing and changes of wall motion in dobutamine stress testing. One hundred and twenty-four patients were estimated to be necessary to obtain with 80% power a statistically significant difference ($p<0.05$) in the primary end point of 40% in the treatment group and 15% in the control group. Owing to the long recruitment time and the difficulty to include patients, enrolment was suspended after including 104 participants (52 in each group).

Mean age was 67.8 years and 81% of patients were men. Eighty-four percent of patients were in FC III and the rest in FC IV. An average of 6.7% of patients did not receive any medication, 19.2% one, 39.3% two and the rest, three or more. The device was successfully implanted in 96% of cases. At 6 months, 35% of participants in the treatment group and 15% in the control group improved at least two FC ($p=0.02$), and at least one FC in 71% vs. 42%, respectively ($p=0.003$). Although quality of life improvement was higher in the treatment group, there was no difference in angina stability and frequency. Mean baseline exercise duration was 441 and improved 59 seconds (13%) at 6 months in the treatment group and was 464 seconds and improved 4 seconds (1%) in the control group, with a trend to show difference between the two groups ($p=0.07$). Mean time to ST-segment depression of 1 mm during stress testing was prolonged from 384 to 433 s (13%) in the treatment group and from 437 to 455 s (4%) in the control group (p=ns). Three infarctions and one death occurred in the control group, and only one preprocedural infarction in the treatment group.

The mechanism whereby this device (whose origin stems from the idea of coronary sinus ligation in the middle of the last century) can relieve ischemia is not completely clear. It is assumed to generate recruitment of collateral circulation, favoring blood flow distribution from the epicardium to the more ischemic endocardium. The study deserves some criticisms: Is it possible to speak of refractory angina when 26% of patients receive at most one medication, and 65% two or less? Can patients with an exercise stress test lasting more than 7 seven minutes and who take more than 6 minutes to present with 1 mm of ST-segment depression be considered to have refractory angina? Was the number of patients sufficient to unravel the causal mechanisms? For example, the mean time to 1 mm of ST-segment depression was measured in only 11 patients of each group. If according to the authors, the prevalence of refractory angina is growing so much worldwide, why was it so difficult to recruit patients? This small-dimension study, with some weak aspects, should in any case be regarded as the source for larger trials to work out the true usefulness of this procedure.

A meta-analysis confirms the favorable effect of blood pressure lowering in mild hypertensive patients

Sundstrom J, Arima H, Jackson R, Turnbull F, Rahimi K, Chalmers J, et al. Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis. **Ann Intern Med 2015;162:184-91. http://doi.org/26v**

When we refer to the beneficial effects of antihypertensive treatment, we usually employ data from studies including patients with moderate or severe hypertension (HTN). Many of these patients also have cardiovascular disease. However, most hypertensive patients have grade 1 or mild HTN (with values of 140-159/90-99 mmHg for systolic and diastolic BP, respectively), without history of cardiovascular or cerebrovascular disease. In this context data are not clear, as no individual clinical trial alone was able to demonstrate the benefit of BP lowering in these patients. The aim of the present meta-analysis was to evaluate the effect of antihypertensive treatment on overall mortality, death of cardiovascular origin and major cardiovascular events (stroke, heart failure and coronary events) in grade 1 hypertensive patients. It considered two data sources: individual data from 10 randomized clinical trials in mild hypertensive patients evaluating drugs vs. placebo or more intensive vs. less intensive drug regimen mainly in diabetic patients (n=6,361), and summary data from three studies specifically in mild non-diabetic hypertensive patients (n=8,905) from a total of 15,266 patients.

Median follow-up was 4.4 years. Mean BP reduction in studies with available individual data was 3.6/2.4 mmHg for systolic and diastolic BP, respectively. Overall mortality was 4.4%. There was a low incidence of cardiovascular events: 2.8% for coronary events, 1.8% for stroke, and 2.5% for heart failure. Antihypertensive treatment was systematically as-

sociated with event risk reduction, but only reached statistical significance for overall death (OR 0.78, 95% CI 0.67-0.92), cardiovascular death (OR 0.75, 95% CI 0.57-0.98) and stroke (OR 0.72, 95% CI 0.55-0.94). Absolute risk reduction at 5 years was low: 0.4% to 1.4% for overall death, 0.8% for cardiovascular death and 0.8% for stroke.

The merit of this meta-analysis lies in demonstrating something usually claimed but usually without definite evidence in individual trials: the importance of lowering BP in mild hypertensive patients without previous cardiovascular disease. Small BP reductions improve life prognosis. The relative risk reduction is similar to that obtained in populations with more severe HTN, or with previous cardiovascular disease. As baseline risk is lower, it is logical to assume that absolute risk is also low. Some methodological doubts can, however, be postulated, though they do not reduce the credit of the conclusions. An elevated proportion of patients were diabetic; especially in them (but we can extend the comment to the rest) it is difficult to deny with certainty presence of subclinical cardiovascular disease, as it is responsible for part of the initial risk. Also, some patients were already taking antihypertensive agents at inclusion; if they had not taken them their BP values would have been higher, and we know very well that the risk associated with a certain BP value is not the same if the patient is treated. Aside from these small criticisms, the importance of acting when BP is "slightly" elevated is corroborated by this analysis.

Intravenous iron for patients with heart failure: an option to consider? The CONFIRM-HF trial

Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. **Eur Heart J 2015;36:657-68.**

In recent years we have learnt that iron deficiency has prognostic value in several diseases, aside from anemia. Actually, some observational studies seem to indicate that iron deficiency, and not anemia, is associated with adverse outcome in heart failure (HF). Iron is essential for erythropoiesis, but its deficiency is also substrate for dyspnea and effort intolerance. Blood iron level is not a good expression of total body iron, and ferritin may be increased as marker of greater inflammatory activity. There is nearly 40% prevalence of iron deficiency in HF patients (approximately 60% in anemic patients and 30% in non-anemic ones), and has predictive value. In patients with end-stage HF, regardless the decrease of transferrin saturation, there is myocardial iron deficiency with decreased number of transferrin receptors partly due to catecholamine and aldosterone effect.

Intravenous iron tested in small studies with different administration schemes has suggested improvement in ejection fraction and the 6-minute-walk test. A recent meta-analysis of four studies, with 370 patients treated with intravenous iron and 224 controls shows improved quality of life and effort capacity and lower hospitalization for HF, and no effect on mortality or greater incidence of adverse events as infections and neurologic or gastrointestinal disorders.

The CONFIRM-HF trial selected patients with HF in FC II-III, LVEF≤45%, BNP>100 pg/mL or NT-proBNP>400 pg/mL and with absolute (ferritin>100 ng/mL) or relative (ferritin between 100 and 300 ng/mL, with transferrin saturation<20%) iron deficiency. They were randomly assigned to receive intravenous iron (ferric carboxymaltose) or placebo. The initial iron dose was 500-1,000 mg, with reinforcement at 6 weeks, if necessary, totalling 500-2,000 mg. In weeks 12, 24 and 36, additional doses of 500 mg were administered if indicated by iron deficiency markers. The primary end point was the change in the 6-minute-walk test at week 24. Changes in functional class, quality of life and incidence of hospitalization and all-cause mortality or death specifically due to HF were also evaluated.

Three hundred and one patients were effectively included (150 in the active group), with mean age of 69 years, mean LVEF 37%, 57% of patients in FC II and the rest in FC III. Average hemoglobin was 12.4 g/dL and ferritin 57 ng/mL; only 10.6% had ferritin values≥100 ng/mL.

At week 24 the 6 minute.walk test was significantly longer in the treated group, with a mean difference of 33 meters, due almost equally to an increase in the distance walked in the group who received iron as to a decrease in the placebo group. At weeks 36 and 52, the results were preserved. There was also improvement in quality of life. During follow-up, there was no difference in annual mortality (8.9% with iron, 9.9% with placebo), but there was a trend to reduction in the incidence of general (26.3% vs. 37%, p=0.14) and cardiovascular (16.6% vs.26.3%; p=0.097) annual hospitalizations, and a significant reduction of hospitalizations for HF (7.6% vs. 19.4%, HR 0.39, 95% CI 0.19-0.82; p<0.01).

The CONFIRM-HF trial is, up to the present, the only study that individually shows reduction in hospitalization for HF with intravenous iron therapy. Its results, however, go in the direction of the referred meta-analysis. It is important to highlight that there was no interaction with hemoglobin levels.-with an expected mean value-, considering that almost half of the patients were women. This reinforces the concept of iron deficiency as therapeutic target per se. Nevertheless, it should be emphasized that almost 90% of patients had low ferritin levels <100 ng/mL, so no conclusions can be drawn on the benefit of this therapy in patients with higher values. It is regrettable that no evaluations were made on the follow-up of systolic and

diastolic ventricular function, natriuretic peptides, etc, which would have helped to understand effort capacity improvement and reduction in the rate of hospitalization. Whether oral iron is or not a treatment option (of course, less expensive and simpler to administer, although it appears associated a priori with greater intolerance and without evidence until now that it improves paraclinic HF end points) and whether other intravenous iron preparations can be used, is something to analyze in future studies. On the other hand, cost-effectiveness studies showing the advantage of using ferric carboxymaltose in different contexts and clinical situations are imperative. In the meantime, we would advice to be on the alert about the existence of iron deficiency in our patients with HF, and consider it as an objective especially when it is marked and in patients with frequent hospitalizations or worse functional class.