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**AV junction ablation and cardiac resynchronization therapy: an unbeatable combination in the treatment of atrial fibrillation?**

Brignole M, Pentimalli F, Palmisano P, Landolina M, Quartieri F, Occhetta E et al. AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: the APAF-CRT mortality trial. *Eur Heart J* 2021; 42:4731-9. <https://doi.org/10.1093/eurheartj/ehab569>

In the treatment of patients with concomitant atrial fibrillation (AF) and heart failure (HF), a series of randomized studies conducted before 2010 (RACE-HF, AFFIRM-HF, AF-CHF, CAFÉ II) compared a rhythm control strategy versus rate control strategy. Both strategies were based on the use of antiarrhythmic drugs or negative dromotropic agents. Despite better results were expected in the rhythm control arm, there was no significant difference in mortality or in the incidence of embolic events between the two arms, and, in fact, there were more hospitalizations in the rhythm control arm. The results were explained by the difficulty in maintaining persistent sinus rhythm in addition to the adverse effects of the medication, which are greater in patients with ventricular dysfunction. Over the past decade, the use of AF catheter ablation therapy, especially pulmonary vein isolation, has increased significantly. Several studies have reported improvements in ventricular function, and the CASTLE AF study even reported improved outcomes in patients with HF and reduced left ventricular ejection fraction (LVEF). However, the fact that the population was highly selected (only one patient out of 10 patients evaluated was included) reduced the impact of the conclusions. More recently, the results of the CABANA study, which included 15% of patients with HF, demonstrated no advantage for ablation therapy in the intention-to-treat analysis, whereas a per-protocol analysis showed the opposite finding. In 2020, we commented a meta-analysis (Rev Argent Cardiol 2020; 88:487-496) involving all the studies in patients with AF and HF comparing catheter ablation with medical therapy. Six studies, (including the CASTLE AF trial) and the subgroup of heart failure patients in the CABANA study, were considered. A total of 1112 patients were included; mean age was 64 years, 78% were men, with a mean duration of AF of 14 months, mean left atrial diameter of 48 mm and mean follow-up of 2.7 months. Except for the CABANA study, which did not provide data on LVEF, LVEF was < 35% in the other 6 studies. Compared with medical treatment, catheter ablation was associated with lower all-cause mortality (OR, 0.51: 95% CI. 0.36-0.74), lower readmissions

(OR, 0.44: 95% CI, 0.26-0.76), and similar rate of stroke (2.8% vs. 4.7%; p NS). Mean improvement of LVEF after the procedure was almost 7%.

But AF catheter ablation is a technically difficult procedure, requires highly trained operators, and most patients do not qualify to be included in the trials mentioned above; in fact, in a real-life study in the United States involving almost 290,000 patients, less than 10% met such criteria. For this reason, when pharmacological control of the ventricular response is not effective, AV junction ablation and implantation of a permanent pacemaker seems to be an attractive option. Obviously, this strategy ensures rate regularization, but it frequently leads to complications such as dyssynchrony due to permanent right ventricular pacing, resulting in impairment of left ventricular function. In consequence, implantation of a cardiac resynchronization therapy (CRT) device is the obvious answer to preserve the benefit of AV block and avoid the adverse effects caused by right ventricular pacing.

The APAF-CRT study explored the usefulness of a strategy of AV junction ablation and biventricular resynchronization (CRT) in patients with markedly symptomatic AF and narrow QRS, compared to pharmacological heart rate control. The study consisted of 2 phases, one focused on morbidity and another focused on mortality which has been recently published. The first phase, with a median follow-up of 16 months, demonstrated that the invasive strategy reduced the incidence of a combined end point of mortality, worsening HF, or hospitalization for HF (HR, 0.38; 95% CI 0.18-0.91). With these results, the investigators initiated a second phase, focused on mortality, that overlapped with the end of the previous phase. Patients with the following criteria were included: severely symptomatic permanent AF (> 6 months), narrow QRS ( $\leq$  110 ms) and at least one hospitalization for HF in the previous year; and were randomly assigned to AV junction ablation and CRT or pharmacological rate control therapy. If necessary, an implantable cardioverter defibrillator (ICD) was implanted in both arms. The primary endpoint was all-cause mortality. The secondary endpoint was a composite of all-cause mortality or hospitalization due to HF. Patients were followed up for a maximum period of 4 years; the investigators estimated that 27 events would be necessary for the trial to have 80% power to detect a reduction in mortality. The outcomes were analyzed according to the intention-to-treat principle. The study was conducted from October 2014 until December 2020, when the Data Safety Monitoring Board recommended terminating the trial prematurely on account of the evident superiority of the results in one study arm. A total of 140 patients were random-

ized; 133 of these (63 in the invasive therapy arm) were finally included for analysis. Mean age was 73 years and more than 50% were men. Mean LVEF was 41% and was  $\leq 35\%$  in 41%. There was an imbalance in the treatment with digoxin (60% in the drug arm versus 32% in the ablation-CRT arm); more than 80% of patients in both arms were treated with beta-blockers. An ICD was implanted to 26 patients in the ablation+CRT arm and to 20 patients in the drug arm (p NS). After optimization of drug therapy in both arms, mean heart rate was 70 beats per minute (bpm) in the invasive therapy arm and 82 in the drug arm.

After a median follow-up of 29 months, 18 patients in the drug arm crossed over to the invasive therapy arm, all-cause mortality was 11% in the ablation+CRT arm and 29% in the drug arm (HR, 0.26; 95% CI, 0.10-0.65). The estimated death rates at 2 years were 5% and 21%, respectively, and at 4 years, 14% and 41%, respectively. There was a significant reduction on the composite secondary end point: 29% in the invasive therapy arm vs. 51% in the drug arm (HR, 0.40; 95% CI, 0.22-0.63). There was no interaction with the use of digoxin or with LVEF.

*Loss of atrial kick, rapid ventricular rate, and irregular RR intervals leading to dyssynchrony are some of the mechanisms through which AF generates and worsens HF. We have already learned from the RACE II study how a rate control strategy alone does not seem to be sufficient to ensure better outcome. When rate control is achieved with drugs, RR intervals are still irregular. AV junction ablation with permanent pacing ensures reaching the desired HR and regularization of RR intervals. This mechanism may be in part responsible for the better outcome. We know that the use of CRT in HF with reduced LVEF and AF has not demonstrated the same benefit achieved with patients in sinus rhythm. This has been attributed, in particular, to the fact that rapid ventricular response may limit the number of paced beats, and therefore the benefit of resynchronization therapy. However, several meta-analyses indicate that, if AV junction ablation is performed in CRT device recipients with AF, the benefit is similar to that obtained in those with sinus rhythm. However, we should point out a different situation. In patients with reduced LVEF, HF and wide QRS, the primary indication is CRT; AV junction ablation emerges as an adjuvant measure to maximize the effect of resynchronization therapy. In the APAF-CRT study, the patients present severely symptomatic AF, poorly controlled with medication, but with narrow QRS: the primary indication is AV junction ablation and CRT is used to attenuate the adverse effect of RV pacing required after ablation. These are not patients with primary indication for CRT. In fact, resynchronization therapy is contraindicated in patients with QRS < 130 ms because it is associated with a worse outcome. And, on the other hand, CRT is indicated in patients with reduced LVEF. In this study, almost 60% of the patients had LVEF > 35%. The combination of AV junction ablation and CRT seems to have made the*

*most of each intervention and attenuated the deleterious effects. Compared with AF ablation studies, the APAF-CRT study included patients almost 10 years older and the results of AF ablation are expected to be less promising in elderly patients, with a lower success rate due to greater structural damage. But new alternatives arise: will it be necessary to use CRT, or could His bundle pacing be considered to maintain an effective rhythm? A final reflection: the significance of the results with such a small sample size, which implies a number needed to treat, NNT, of only 3.7, is noteworthy. How many interventions can boast of such power? Further information from other trials or registries may confirm the power of the intervention.*

### **Value of ventricular arrhythmia in stress tests: a daily doubt.**

Refaat MM, Gharios C, Moorthy MV, Abdulhai F, Blumenthal RS, Jaffa MA et al. Exercise-Induced Ventricular Ectopy and Cardiovascular Mortality in Asymptomatic Individuals. *J Am Coll Cardiol* 2021; 78:2267-7. <https://doi.org/10.1016/j.jacc.2021.09.1366>

It is known that the presence of high-grade premature ventricular contractions (PVCs) during exercise in patients with coronary artery disease is associated with adverse outcome, especially if they occur during the recovery phase. However, when a patient with no known coronary artery disease or cardiovascular disease visits us with an exercise stress test showing high-grade PVCs, the questions are: ¿should we prioritize them? ; ¿do they entail a worse course?; ¿should we order additional tests? The results of an analysis carried out in a cohort with long-term follow-up are now available to contribute to answering these questions.

A prospective cohort study on the prevalence and prognostic value of dyslipidemia was conducted in the United States between 1972 and 1976. All those patients with elevated lipid values, and an additional random sample of 15% of all those interviewed at the initial visit, underwent a second interview which included interrogation, physical examination, laboratory tests, and an exercise stress test. Stress testing was not performed in patients with systolic blood pressure > 200 mm Hg or < 90 mm Hg, diastolic blood pressure > 120 mm Hg, significant cardiovascular disease, or with R-on-T type PVCs or runs of ventricular tachycardia (VT) on ECG. Finally, 8652 underwent exercise stress test.

This analysis included asymptomatic patients and excluded those with angina, intermittent claudication, left ventricular hypertrophy, myocardial infarction, stroke, cardiac surgery, cardiovascular surgery and treatment with digoxin or other antiarrhythmic agents, except for beta-blockers. High-grade PVCs were defined as either frequent (>10 per minute), multifocal, repetitive (couplets, triplets or VT) or R-on-T type. The presence of these PVCs during the exercise phase, the recovery (up to 6 minutes) phase, or both phases was considered.

The cohort was made up of 5486 asymptomatic individuals; mean age was 45 years, 58% were men and 50% had dyslipidemia. High-grade PVCs occurred during exercise in 1.8% of the patients, during recovery in 2.4% and during both periods in 0.8%. Participants with high-grade PVCs (during any phase of exercise testing) were about 15 years older, had higher prevalence of hypertension and diabetes, achieved target heart rate (HR) less frequently, presented ST-segment depression  $\geq 1$  mm more commonly, and exercise duration was shorter; after exercise, heart rate recovery to baseline values was lower. Over an average follow-up period of 20 years, those with high-grade PVCs during both exercise phase and recovery phase had significantly higher rates cardiovascular mortality (19.8% vs. 5.4%) and all-cause mortality (48.5% vs. 14.7%) vs. those without. Something similar occurred with those who presented high-grade PVCs during the recovery phase: they presented higher cardiovascular mortality (27.1% vs. 5.1%) and all-cause mortality (52.6% vs. 14.4%) compared with those without PVCs. After adjusting for age, sex, coronary risk factors, family history and indicators of exercise performance, high-grade PVCs occurring during the exercise phase were not associated with adverse outcome (HR for cardiovascular mortality, 1.34; 95% CI, 0.79-2.26, and HR for all-cause mortality, 1.18; 95% CI, 0.83-1.69). On the contrary, high-grade PVCs during the recovery phase remained significantly associated with higher risk of cardiovascular mortality (HR 1.68; 95% CI, 1.09-2.60), but there was no significant association between PVCs with all-cause mortality (HR, 1.15; 95% CI, 0.85-1.56). There was no interaction with sex or risk factors. Despite the independent prognostic value of high-grade PVCs for cardiovascular mortality, they did not contribute to improve the discriminatory capacity or reclassification of a model that included the aforementioned clinical variables.

*Different meta-analyses have indicated the prognostic value of exercise-induced PVCs in the general population, mostly involving people with known cardiovascular disease, or in those undergoing a stress test due to the presence of symptoms or high clinical suspicion. So far, specifically speaking of asymptomatic patients without cardiovascular disease, the information available comes from 4 studies involving 1239 patients. In the case of patients with coronary artery disease, it was already clear that the adverse prognosis is due to the PVCs in the recovery phase. The information for asymptomatic patients was not so clear. In this regard, the present study stands out for the number of patients included (more than 4 times the sum of the previous studies) and because it clearly establishes the differential prognostic value of PVCs during the exercise phase and the recovery phase in a population free of overt cardiovascular disease. It is worth emphasizing that previous meta-analyses considered overall PVCs, and this study ups the ante: even high-grade PVCs in asymptomatic patients lose prognostic value when they occur during*

*the exercise phase, after adjusting for clinical and stress test-related conditions. Which is the reason for the prognostic value of high-grade PVCs in the recovery phase? Exercise-induced ventricular arrhythmias are explained by an increase in the sympathetic tone; they are the result of a physiological response which, in the absence of structural heart disease, of a substrate predisposing to perpetuation of the arrhythmia and of complex forms, do not negatively affect the prognosis. In contrast, ventricular arrhythmias in the recovery phase are due to insufficient vagal tone, with failure to restore the autonomic balance. In this sense, HR recovery (the restoration of baseline HR at the end of exercise, which also depends on the parasympathetic nervous system) is another prognostic marker: those patients who take longer to recover have a worse outcome. Ventricular arrhythmias in the recovery phase and delayed HR recovery are two markers of deficient autonomic modulation. The interesting finding in this study is that the prognostic value of high-grade PVCs for cardiovascular mortality persisted even after adjusting for HR recovery, raising the possibility that other mechanisms, besides insufficient parasympathetic tone, may be involved. Poor HR recovery has been reported to be associated with endothelial dysfunction and inflammation; these factors may contribute to explain the findings. And another matter to consider: are PVCs occurring in asymptomatic patients during the recovery phase following exercise a predictor of worse outcome, or do they evidence underlying structural and functional abnormalities that condition the adverse prognosis?*

*So, which is the practical consequence of this presentation? As we have seen, the addition of ventricular arrhythmias after exercise does not improve the discriminative ability of a clinical model. Thus, there does not seem to be a powerful reason to generate new strategies. In any case, the fact that they involve worse cardiovascular outcome may be a reason to monitor these patients more closely, at least for the early identification of other disorders that require treatment.*

#### **Additional evidence supporting early surgery for severe aortic stenosis. The AVATAR trial**

Banovic M, Putnik S, Penicka M, Doros G, Deja MA, Kockova R et al. Aortic Valve ReplAcemenT versus Conservative Treatment in Asymptomatic SeveRe Aortic Stenosis: The AVATAR Trial. *Circulation* 2021.

In patients with severe aortic stenosis (AS), defined as aortic jet velocity  $> 4$  m/s which corresponds to a mean transaortic gradient  $\geq 40$  mm Hg and aortic valve area  $\leq 1$  cm<sup>2</sup> or  $< 0.6$  cm<sup>2</sup>/m<sup>2</sup>, the presence of symptoms is a clear indication of aortic valve replacement to improve the adverse short and long-term outcomes. In asymptomatic patients with severe AS, watchful waiting has been the traditional recommendation, especially because in truly asymptomatic patients with severe AS the annual risk of sudden death does not exceed 1%, which is lower or the same as the risk of operative



mortality. Several risk markers have been suggested to identify asymptomatic patients with severe AS that could benefit from an earlier indication of surgery: left ventricular ejection fraction (LVEF) < 50% not attributable to other causes, elevated natriuretic peptide levels or the development of pulmonary hypertension in the absence of other causes, late enhancement on cardiac magnetic resonance imaging, or an abnormal exercise stress test due to the development of symptoms or fall in blood pressure. Furthermore, the practice guidelines recommend aortic valve replacement in asymptomatic severe AS associated with another cardiac condition that requires surgery. In asymptomatic patients with very severe aortic stenosis (peak velocity > 5-5.5 m/s) aortic valve replacement is indicated. In all these cases, the level of evidence is B, based on cohort studies, or C, derived from consensus, and there was no strong evidence emerging from randomized trials until 2020, when the RECOVERY trial, a multicenter study performed in Korea, was published, and was then commented in the Argentine Journal of Cardiology (Rev Argent Cardiol 2020; 88:83-91). This randomized, open-label trial included patients with very severe AS, defined as an aortic-valve area  $\leq 0.75$  cm<sup>2</sup> with either a peak aortic jet velocity  $\geq 4.5$  m/s or a mean transaortic gradient  $\geq 50$  mm Hg. To be included, patients should be free from angina, dyspnea or syncope and had LVEF  $\geq 50\%$ . Exercise testing was selectively performed to evaluate patients with nonspecific symptoms. A total of 145 patients were included; mean age was 64.2 years, 49% were men and mean LVEF was 64.8%. The cause of AS was a bicuspid aortic valve in 61%, degenerative valvular disease in 33%, and rheumatic valvular disease in 6%. The mean aortic-valve area was  $0.63 \pm 0.09$  cm<sup>2</sup> and the mean peak aortic jet velocity was  $5.1 \pm 0.5$  m/s. Patients were assigned to early surgery or follow-up and surgery in case they became symptomatic. There was no operative mortality. Of the 72 patients assigned to conservative care, 74% underwent surgical aortic valve replacement or transcatheter aortic valve replacement (1 patient) during follow-up. During a median follow-up of 6.2 years, cardiovascular mortality was 1% in the early surgery group and 15% in the conservative group (HR, 0.09; 95% CI, 0.01-0.67). The cumulative incidence of cardiovascular mortality was 1% at both 4 and 8 years in the early surgery group, as compared with 6% at 4 years and 26% at 8 years in the conservative care group. All-cause mortality was 7% in the early surgery group vs. 21% in the conservative care group (HR, 0.33). The incidence of hospitalization for heart failure was 0% in the early surgery group vs. 11% in the conservative care group.

A similar study conducted in 9 centers in Europe, the AVATAR trial, has been recently published. The study included patients with severe aortic stenosis and excluded those with a history of angina, syncope or dyspnea, LVEF < 50%, peak aortic jet velocity > 5.5 m/s; significant mitral valve disease, severe aortic regurgitation, dilatation of the ascending aorta > 5

cm, previous cardiac surgery, atrial fibrillation, lung disease or limited life expectancy < 3 years. Exercise testing was performed in all candidates (either stress electrocardiography or stress echocardiography), and those who developed symptoms, fall in systolic blood pressure > 20 mm Hg or signs of myocardial ischemia were also excluded. Patients were randomly assigned to early surgical aortic valve repair or watchful waiting, and those patients in the watchful waiting arm were referred for surgery in case of onset of symptoms, if LVEF decreased to less than 50%, or if the peak aortic jet velocity increased each year by more than 0.3 m/s. The primary end point was a composite of all-cause mortality or major adverse cardiovascular events (MACE): acute myocardial infarction (AMI), stroke or heart failure (HF) hospitalization needing intravenous treatment with diuretics or inotropic drugs. The investigators assumed a 2-year enrollment duration, a 9% event rate at 12-months in the conservative care arm, and that 312 patients would be necessary to demonstrate (with power 80% and  $p < 0.05$ ) a decrease of event rates by 5.5% per year with an event rate of 3.5% in the early surgery arm.

Between 2015 and 2020, 157 patients were included. Mean age was 67 years and 57% were men. The cause of AS was degenerative valvular disease in 84.7% of the patients, bicuspid aortic valve in 14%, and rheumatic valvular disease in 1.3%. The mean aortic valve area was  $0.73$  cm<sup>2</sup>/m<sup>2</sup>, the mean peak aortic jet velocity was 4.5 m/s and the STS PROM score was 1.7%. Of the 78 patients assigned to the early surgery arm, surgical aortic valve replacement was performed in 92%; more than 50% of the patients received a mechanical valve and 47% received a bioprosthetic valve, and concomitant coronary artery bypass grafting was performed in 4%. Operative mortality was 1.4%. Of the 79 patients assigned to the conservative care arm, 31% underwent aortic valve replacement during follow-up, 40% of patients received a mechanical valve and concomitant coronary artery bypass grafting was performed in 2 cases. Median follow-up was 28 months in the early surgery group and 35 months in the conservative care group. The primary end point at 3 years was 15.2% in the early surgery group and 34.7% in the conservative care group (HR, 0.46; 95% CI, 0.23 - 0.90). Similarly, the incidence of MACE was lower, 20.5% vs. 41.8%.

*The AVATAR trial confirms that, in patients with asymptomatic severe AS, early surgical aortic valve replacement improves their outcomes. There are some differences with the RECOVERY study: exercise testing was systematically performed to all the patients, thus there is greater certainty that the patients included were truly asymptomatic. Aortic stenosis was less severe than in the RECOVERY study, as the aortic valve area was larger, and the peak aortic jet velocity was lower. In the conservative care arm of the RECOVERY study, the need for aortic valve replacement at follow-up was 74%, and was 31% in AVATAR study; nevertheless, it is true that the mean follow-up periods*

were significantly different: just over 6 years in the RECOVERY study, and 2.5 years in the AVATAR study. In both studies we can conclude that the favorable outcomes start with a very low operative mortality, which is an essential requirement for recommending early surgery. The duration of the study is noteworthy: it took 5 years to include 157 patients (as it was an event-driven study, 35 events were necessary to finish it). Let us recall that the investigators calculated that it was necessary to enroll 312 patients during 2 years (156 per year) and that finally the number included during 5 years was the number expected for 1 year. This reflects the low inclination to consider asymptomatic patients with severe AS for surgery. Perhaps spreading the results of these studies, the publication of other similar studies and observational data, and some type of recommendation in the practice guidelines will contribute to making the practice more common. Finally, we shall repeat the question we asked when we commented on the RECOVERY trial: *¿will the observation of better outcome with early intervention be extended to indicate percutaneous aortic valve implantation in patients like those considered in the AVATAR trial?*

#### **Treatment of hypertension reduces the incidence of diabetes. Two meta-analyses and one mendelian randomization study.**

Nazarzadeh M, Bidel Z, Canoy D, Copland E, Wamil M, Majert J et al. Blood pressure lowering and risk of new-onset type 2 diabetes: an individual participant data meta-analysis. *Lancet* 2021;398:1803-10. [https://doi.org/10.1016/S0140-6736\(21\)01920-6](https://doi.org/10.1016/S0140-6736(21)01920-6)

Although we usually refer to vascular risk factors as separate entities, we know that they are strongly associated with each other. Patients with one vascular risk factor are more likely to be affected by the presence of another risk factor or more than one. For example, we know from data from a meta-analysis of observational studies with 4.7 million participants, that each 20 mm Hg higher systolic blood pressure (SBP) is associated with a 77% increased risk of diabetes mellitus (DM). As whenever 2 conditions coexist, we can ask ourselves if one of them is (at least partially) responsible for the development of the other, if both share a common background, or if this coincidence occurs by chance. We are aware that patients with diabetes usually have hypertension: we attribute this phenomenon to underlying obesity, vascular stiffness, neurohormonal activation, and renal dysfunction, among other causes. Our intuition does not suggest reverse causation: hypertension (HTN) predisposes to the onset of diabetes. A study by the BPLTTC (Blood Pressure Lowering Treatment Trialists' Collaboration) group, a collaboration of principal investigators and trialists of major randomized clinical trials of pharmacological treatment of hypertension, provides relevant information in this regard.

This study included all primary and secondary prevention trials that used a specific class or classes of

antihypertensive drugs versus placebo or other classes of blood pressure lowering medications, that had at least 1000 persons-years of followup in each randomly allocated arm. All the participants with a known diagnosis of diabetes at baseline or trials conducted in patients with prevalent diabetes were excluded. For placebo-controlled trials, the active arm was considered as the intervention, and for trials that compared two or more drug classes, the arm with the greater systolic blood pressure reduction was considered as the intervention and the other as the control group. Two meta-analyses were conducted.

The first was individual participant data meta-analysis that considers the information from each participant in each study, and not the aggregated data per study, which increases statistical power, the accuracy of the measures of association and allows for the analysis of subgroups, even if they were not reported as such in the original studies. This meta-analysis considered 145 939 participants in 19 studies; 60.6% were men; 65 042 corresponded to the intervention arm and 80 887 to the control arm. A little more than 57% of the patients in the intervention arm had overweight or obesity, 20% had renal dysfunction, 25% cerebrovascular disease and 27% ischemic heart disease. Over a median follow-up of 4.5 years, the incidence rate for developing new-onset type 2 DM per 1000 person years was 15.94 in the intervention arm and 16.4 in the control arm. For each 5 mm Hg reduction in SBP, the reduction in risk for type 2 DM was of 11% (HR 0.89; 95% CI, 0.84–0.95).

The second meta-analysis, a network meta-analysis, considered the comparisons drug vs. placebo and drug vs. drug/s from different studies. If one study compared drug A vs. placebo, and another study compared drug A vs. drug B, the network meta-analysis allows estimating the effect of drug B vs. placebo from the effect measures of each study, even if such a comparison had never been carried out. The same is true to estimate the effect of one drug versus another. In other words, part of the results depends on direct evidence (comparisons actually carried out in clinical trials) and part on indirect evidence (results inferred from a succession of comparisons of different branches of different studies that were not actually compared within a trial). This meta-analysis considered data from 22 studies, 8 comparing drug vs. placebo and 14 comparing drug vs. drug/s. Compared with placebo, angiotensin-converting enzyme inhibitors (ACEIs) reduced the risk of type 2 DM by 16% (RR, 0.84; 95% CI, 0.76–0.93; 59% direct evidence) and angiotensin II receptor blockers (ARBs) produced a similar reduction (RR, 0.84; 95% CI, 0.76–0.92, 60% direct evidence). There was no effect for calcium channel blockers whereas beta blockers (BBs) (RR, 1.48; 95% CI, 1.27–1.72, 0% direct evidence) and thiazide diuretics (RR, 1.20; 95% CI, 1.07–1.35; 2% direct evidence) increased the risk.

A complementary analysis used mendelian ran-

domization investigation, a type of analysis that we mentioned in *Rev Argent Cardiol* 2021; 89: 479-487. As we have already commented, this type of study is based on the idea that our genetic endowment is randomly assigned to each of us, and that this endowment does not depend on any environmental factor, acquired or confounder. If certain genes are linked to a defined exposure, but not to an event or outcome, and it is clearly demonstrated that the individuals with those genes are more likely to present that event, that means that the exposure is linked to the outcome beyond any confounder. Mendelian randomization analysis confirmed that each 5 mm Hg genetically influenced lower SBP was associated with a lower risk of type 2 DM, a decrease in the risk with ACEIs and ARBs, null effect with calcium channel blockers, and an increased risk with BBs. There was no statistical power to confirm greater risk for thiazide diuretics.

*Through which mechanisms HTN could favor new-onset DM? For many of the same reasons we initially mentioned to explain reverse causation: HTN is associated with endothelial dysfunction, inflammation, and neurohormonal activation, all of which in turn promote an increase in insulin resistance. Previous studies had already demonstrated that the presence of left ventricular hypertrophy in hypertensive patients is a predictor of DM; the meta-analysis mentioned at the beginning of this comment had quantified this relationship. As we know, observational studies are an important source of information, but they are subject to residual confounding. The publication commented has several merits. It presents a meta-analysis of randomized studies including many patients (which noticeably decreases the risk of confounding factors); the use of individual participant data is considered the gold standard; and it demonstrates that the reduction of exposure (SBP) reduces the incidence of the outcome (DM), which supports the idea of causality. We obviously acknowledge that the genesis of DM is multi-causal, and that it includes genetic, dietary and environmental factors; but the finding of the relationship described opens the door to a new preventive measure. Reducing SBP adds a new favorable effect. The mendelian randomization analysis confirms the association between the reduction in blood pressure and the risk of DM. However, some comments should be made.*

*In several analyses made by the BPLTTC group that we have presented, many of the favorable effects of antihypertensive treatment occur throughout the different values of SBP, ranging from normal to elevated levels. In this case we do not observe such analysis, and it would be appropriate to count with it. The incidence of DM is often reported from clinical data and is not based on a prospectively designed laboratory testing monitoring. In any case, the data are consistent among the studies carried out with different methods of collecting the information.*

*The information on the effect of the different antihypertensive drugs and the incidence of DM is not new.*

*In a meta-analysis published in the Lancet in 2007 using thiazide diuretics as a reference, Elliot et al. had already shown a significant reduction in the incidence of DM with ACEIs, ARBs and calcium antagonists in the treatment of HTN. In 2004, Shekelle et al. had demonstrated the ability of ACEIs and ARBs to reduce the incidence of DM in the treatment of heart failure. Different mechanisms have been suggested: preservation of beta-cell function or an increased insulin sensitivity, and a direct effect favoring insulin action in the cell, by blocking angiotensin II. Treatment with nonselective beta-blockers or poorly selective beta 1 blockers enhances alpha 1 activity, leading to vasoconstriction and decreased blood flow to the muscles, resulting in insulin resistance. Nonselective beta-blockers may decrease the first phase of insulin secretion from pancreatic beta cells which has been suggested as an important predictor of type 2 DM. Finally, sympathetic activation stimulates glyconeogenesis and inhibits glycogen synthesis in the liver. This effect depends on the stimulation of alpha-2 receptors; treatment with beta blockers could enhance alpha activity and contribute to the presence of type 2 DM. Carvedilol, a non-selective BB, but also with alpha 1-blocking properties has been also found to reduce insulin resistance. The GEMINI and the COMET trials demonstrated that carvedilol reduced the incidence of DM compared with metoprolol, a selective beta-1 blocker. Therefore, the results of the meta-analysis about higher risk of DM using BBs should be considered but bearing in mind that the studies in HTN were mainly performed with non-selective BBs, or poorly selective beta1 blockers. Finally, in the case of thiazide diuretics, the higher incidence of DM seems to be linked to lower potassium levels, with increased release of aldosterone.*

*And all that has been said unflinchingly raises a question: ¿is BP reduction the condition that inevitably reduces the incidence of DM, or does it depend on how it is achieved? Is a 5 mm Hg-reduction with ACEIs or ARBs the same as with thiazide diuretics, atenolol or nifedipine? Evidently not, and the success of antihypertensive treatment (in terms of reducing the incidence of DM) will depend not only on blood pressure levels, but also on the agent used*

#### **Microvascular angina: clinical presentation, diagnosis, treatment and prognosis. The COVADIS registry**

Shimokawa H, Suda A, Takahashi J, Berry C, Camici PG, Crea F et al. Clinical characteristics and prognosis of patients with microvascular angina: an international and prospective cohort study by the Coronary Vasomotor Disorders International Study (COVADIS) Group. *Eur Heart J* 2021;42:4592-4600. <https://doi.org/10.1093/eurheartj/ehab282>.

Up to 50% of coronary angiographies performed in patients with chest pain do not reveal coronary obstructive disease (lumen reduction >50%). Therefore, in these cases, angina is attributed to functional



disorders: epicardial artery spasm, or microvascular dysfunction, assumed as an exaggerated susceptibility of coronary microcirculation that results in spasm, or decreased ability of microvascular vasodilation, with consequent ischemia. The term microvascular angina is used in cases of angina or ischemia due to microvascular coronary dysfunction. The Coronary Vasomotor Disorders International Study Group (COVADIS) has postulated 4 diagnostic criteria for microvascular angina: 1) signs or symptoms of myocardial ischemia; 2) absence of obstructive coronary artery disease in coronary angiography or computed tomography angiography; 3) objective evidence of ischemia in resting or exercise stress ECG and/or in single-photon emission computed tomography (SPECT), positron-emission tomography (PET), cardiac magnetic resonance imaging (CMR), or echo-stress; and 4) evidence of microvascular dysfunction either noninvasively (coronary flow reserve assessment with PET, CMR, or Doppler echocardiographic assessment of anterior descending artery flow reserve velocity) or invasively (with coronary flow reserve and microvascular resistance measurement, demonstration of slow flow in the coronary angiography and/or acetylcholine test generating symptoms and ECG changes, without epicardial coronary spasm).

Between July 2015 and December 2018, the COVADIS group carried out an international registry (Japan, United States of America, United Kingdom, Spain, Italy, and Australia) of patients with definite (met the 4 criteria) or suspected (met criteria 1 and 2, but only one of 3 and 4) microvascular angina. The primary endpoint was a composite of cardiovascular death, non-fatal acute myocardial infarction or stroke, and hospitalization for unstable angina or heart failure. A total of 704 patients were included in the study, but only 686 had follow-up data, constituting the study population of the publication here commented. Among these patients, 362 (52.8%) had a condition with definite diagnosis and the rest with probable diagnosis. Mean age was 61 years, and 64% were women. In 61% of cases, patients were of Caucasian, 29% Asian, and 6% Hispanic ethnicity. Fifty-two percent of patients were hypertensive and the same percentage presented dyslipidemia, 17% were diabetic and 16% were current smokers. A total of 34% of cases had history of coronary artery disease (more women than men), but only 9% had history of coronary angioplasty (more men than women). Predominant symptoms were chest pain or discomfort (68%), especially at rest (36%), and stress dyspnea (18%). Twenty-six percent of cases evidenced ECG changes during the anginal episode and among them 90% had ST-segment depression. There was objective evidence of myocardial ischemia (diagnostic criterion 3) in 59% of patients, more frequently diagnosed in a treadmill or echocardiographic stress test. Objective evidence of microvascular dysfunction (diagnostic criterion 4) was found in 89% of cases: 42% microvascular spasm, 35%

reduced vasodilator reserve, 14% increased microvascular resistance and 6% slow flow at coronary angiography. In 38% of cases, acetylcholine testing revealed concomitant epicardial coronary spasm. Treatment consisted of statins in 62% of cases, nitrates in 43%, calcium antagonists in 36% and betablockers also in 36% of cases.

During a median follow-up of 398 days, the annual incidence of the composite primary endpoint was 7.7%, mainly hospitalization for unstable angina (5.9%), with low incidence of cardiovascular mortality (1%) or non-fatal myocardial infarction (0.5%). After propensity score matching, no ethnical or gender differences were found. History of hypertension or coronary artery disease were the only independent predictors of events.

*Angina or myocardial ischemia without obstructive coronary artery disease has been acknowledged for decades. Today, this condition is known as ischemia with nonobstructive coronary arteries (INOCA), and we know that it is present in two-thirds of women and one-third of men with chest pain or other manifestations of myocardial ischemia. In these conditions, the predominant mechanism can be epicardial coronary spasm or microvascular dysfunction. In different INOCA series the condition has been attributed to microvascular angina (which in 1973 was termed cardiac syndrome X) in slightly over 50% of cases, epicardial coronary spasm in approximately 20% and mixed forms in another 20%. Coronary microcirculation is composed of pre-arteriolar vessels, arterioles and capillaries. It is important to recognize that current imaging methods do not allow viewing the microvascular anatomy, so the definition of microvascular disease is basically functional. In daily practice we associate coronary flow and ischemia mainly with epicardial coronary circulation abnormalities, which is visible. However, it is in the microcirculation where coronary flow is chiefly regulated, by endothelial-dependent (associated with shear stress and nitric oxide vasodilator and endothelin and thromboxane vasoconstrictor actions), endothelial-independent (changes in intraluminal pressure mediated by myogenic receptors generating vasodilation when the luminal diameter decreases and vasoconstriction when it increases) and metabolic mechanisms. Endothelial dysfunction is the underlying disorder in most cases of microvascular angina, and its main origin are inflammatory processes, with neurohormonal activation also playing a part. Many times we forget the essential role of microcirculation, perhaps because "we do not see it"; and to complicate things further, we must recall that epicardial coronary disease frequently coexists with microvascular disease, and that microvascular coronary disease may be present and be either symptomatic or asymptomatic, beyond chest pain, in hypertensive heart disease, hypertrophic cardiomyopathy, aortic stenosis, heart failure with preserved ejection fraction, diabetes and chronic kidney disease, all conditions in which there is ventricular hy-*

*peritrophy and it is complex to sustain whether it precedes or is consequence of the microvascular disease. The presence of traditional vascular risk factors only in part of the patients; the often poorly clear symptoms; the fact that it is a diffuse or patchy phenomenon, without clear anatomical distribution; the need for invasive tests to rule out spasm; the frequent coexistence with epicardial coronary disease in which we can rely to explain the symptoms; the disorder affecting predominantly women, in whom the angina characteristics differ from those traditionally described in a mainly male population; and the lack of firm evidence on the most efficient treatment, are all condition that may blur patient diagnosis and evolution.*

*The COVADIS registry has several favorable points. It is the first large international registry of microvascular angina. It allows confirming some of the traditionally cited characteristics in local studies with a much lower number of patients, regarding gender, symptoms, and forms of presentation. It is based on solid and objective criteria, and allows to discriminate responsible mechanisms. It demonstrates that the prognosis is not as innocent as it sustains, although 90% of outcomes are hospitalizations for unstable angina. What can we regret? That concomitant clinical conditions are not reported, and that follow-up has been relatively short, with a median slightly over one year. But it is undoubtedly a great step forward in the undertaking of adequately characterizing a much more prevalent condition than we presume.*

*Finally, we urge the readers to examine the Consensus for the diagnosis and treatment of MINOCA (Myocardial infarction with nonobstructive coronary arteries), of the Argentine Society of Cardiology Multidisciplinary Working Group, whose abridged version we publish in this same issue or the Journal. It refers to the other central entity in the range of nonobstructive coronary conditions, and honors national cardiology.*

### **Sacubitril/valsartan is not superior to ramipril in acute myocardial infarction with ventricular dysfunction or heart failure: The PARADISE:MI study**

Pfeffer MA, Claggett B, Lewis EF, Granger CB, Kober L, Maggioni AP et al. Angiotensin Receptor-Neprilysin Inhibition in Acute Myocardial Infarction. *N Engl J Med* 2021;385:1845-55. <https://doi.org/10.1056/NEJMoa2104508>.

Almost 30 years ago, angiotensin-converting enzyme inhibitors (ACEI) demonstrated their protective role when administered early after an acute myocardial infarction (AMI) with reduced left ventricular ejection fraction (LVEF) or heart failure (HF). The SAVE (in 1992, captopril between 3 and 16 days in AMI with LVEF  $\leq 40\%$  but without manifest HF), AIRE (in 1993, ramipril between 3 and 10 days in AMI with clinical or radiological signs of HF) and TRACE (in 1995, trandolapril between 3 and 7 days in AMI with

echocardiographic criteria indicating LVEF  $\leq 35\%$ ) studies demonstrated in 5966 patients, with a mean LVEF of 32% and median follow-up of 31 months, that ACEI reduced all-cause death from 29.1% to 23.4% (OR 0.74; 95% CI 0.66-0.83). Angiotensin-converting enzyme inhibitors also significantly decreased the incidence of reinfarction and rehospitalization for HF. Later, the VALIANT study (in 2003) in patients with AMI and clinical evidence of HF, LVEF  $\leq 35\%$  or 40% according to the method used, or both, compared the use of captopril, an angiotensin II-receptor blocker (ARB), valsartan, or their combination. It included 14 703 patients, with mean LVEF 35%. At a median follow-up of slightly over 24 months, all-cause mortality was similar (around 19%) in the 3 groups, as well as incidence of cardiovascular death and HF. Hypotension was more frequent with valsartan, and cough with captopril, while the combination presented the greatest incidence of adverse events. All this evidence supported ACEI and alternatively ARBs to become first-line treatment drugs in patients with AMI and reduced LVEF and/or HF.

In the middle of the past decade, we knew the results of the PARADIGM-HF study. In 8442 ambulatory patients with HF and mean LVEF of 29%, a new therapeutic agent, sacubitril/valsartan (SV), which adds to the angiotensin II blocking action neprilysin inhibition, thus attenuating natriuretic peptide degradation, showed, when compared with an ACEI (enalapril), reduced admission for HF, cardiovascular mortality and all-cause mortality. And, later, the PIONEER-HF study, in 881 patients hospitalized for HF with median LVEF of 24%, confirmed a higher reduction of NT-pro BNP levels with SV compared with enalapril and, in an exploratory way, better outcome. As a logical corollary, the mandatory question was: Would SV be better than ACEI in the context of AMI with HF or reduced LVEF, reproducing what had been demonstrated in ambulatory or hospitalized patients with HF and reduced LVEF? The answer to this question was given in the PARADISE-MI study.

PARADISE-MI was a randomized, international, multicenter, double-blind study testing whether SV was superior to ramipril in the ability to reduce the risk of cardiovascular death or HF incidence in patients that, without history of HF, were coursing AMI within the first 0.5 to 7 days, associated with reduced LVEF ( $\leq 40\%$ ), clinically or radiologically-defined pulmonary congestion requiring intravenous treatment, or both conditions; and that presented at least one of eight factors known to be linked to worse prognosis: age  $\geq 70$  years, diabetes, previous AMI, estimated glomerular filtration rate  $< 60$  ml/min/1.73 m<sup>2</sup>, atrial fibrillation, LVEF  $< 30\%$  associated with index AMI, Killip and Kimball III-IV, or ST-segment elevation AMI without reperfusion within 24 hours of presentation. Patients who required intravenous drugs in the 24 hours prior to randomization, and those with estimated glomerular filtration rate  $< 30$  ml/min/1,73 m<sup>2</sup>,



serum potassium  $>5.2$  mmol/L, history of angioedema or inability to take ACEI or ARBs were excluded from the study. Patients were randomly assigned in a 1:1 ratio to SV (dose of 50, 100 or 200 mg twice daily) or ramipril (1.25 mg, 2.5 mg or 5 mg twice daily). In each case the doses were left to the discretion of the treating physician, and were adjusted with the idea of reaching the maximum tolerated dose. The primary endpoint was a composite of cardiovascular death or HF incidence (hospitalization or ambulatory episode treated with intravenous or intensified sustained oral diuretic treatment). Secondary endpoints were hierarchically evaluated: cardiovascular death or hospitalization for HF; outpatient incident HF or requiring hospitalization; a composite of cardiovascular death, non-fatal AMI and non-fatal stroke; and total number of non-fatal cardiovascular events. The trial was guided by the number of events. It was established that 708 primary endpoint events would yield 80% power to detect a HR of 0.81 (19% reduction) for the primary endpoint, with a two-tailed  $p < 0.05$ ; and 592 events of cardiovascular death or hospitalization for HF would provide 77% power to detect a HR of 0.80 for the secondary endpoint. A necessary sample size of 4650 patients followed-up for 19 months was estimated; but after reviewing the incidence of events in the interim analysis, this number was raised to 5650. The COVID-19 pandemic motivated an additional intermediate analysis, when 80% primary endpoint events had occurred, with  $p < 0.01$ . Finally, a  $p$  value of 0.0484 was defined for the primary endpoint analysis, and in the hierarchical analysis the formal search of statistical significance ended with the first non significant result.

Between December 2016 and March 2020, 5661 patients were included and effectively analyzed, 2830 in the SV group. Mean age was 63.7 years, and 24.1% were women. Patients were randomized at a mean of 4.3 days after AMI presentation. In 16% of cases, patients had previous AMI and another 16% had history of some coronary artery revascularization procedure. Mean LVEF was 36.5%; 81.4% of patients had LVEF  $< 40\%$ ; 54% presented signs of pulmonary congestion, and slightly over 50% had one or more additional increased risk factors. Admission Killip and Kimball was  $> I$  in marginally over 56% of cases. The index AMI coursed with ST-segment elevation in 76% of cases, and the location was anterior in 68% and inferior in 18%. Some reperfusion procedure was attempted in 89% of cases, and 88% received an angioplasty. Pharmacological treatment was dual-antiplatelet therapy in 92% of patients, betablockers in 85%, anti-aldosterone agents in 41%, statins in 95%, and in the days prior to randomization, before being discontinued, ACEI or ARBs in 78%.

At a median follow-up of 22 months, the incidence of the primary endpoint was 11.9% in the SV group vs. 13.2% in the ramipril group, HR 0.90; 95% CI 0.78-1.04;  $p = 0.17$ . As no statistical significance was found

for this difference, all the subsequent secondary endpoint analyses should be considered exploratory. The incidence of cardiovascular death or hospitalization for HF was 10.9% vs. 11.8%; that of cardiovascular death 5.9% vs. 6.7% and of all-cause death 7.5% vs. 8.5%. None of these differences was statistically significant. Neither were there differences for any-cause treatment abandonment, except death, 17.7% vs. 18.3%, nor in the incidence of adverse events forcing the abandonment: 12.8% vs. 13.4%. There was more hypotension with valsartan (28.3% vs. 21.9%) and less cough (9% vs. 13.1%), in both cases with  $p < 0.001$ . The incidence of increased creatinine  $> 2$  mg/dL (5.7% vs. 6%) or of plasma potassium  $> 5.5$  mmol/L (14.2% vs. 12.8%) was not different. At the end of the study, the objective dose of 400 mg SV or 10 mg ramipril was received by 50.8% and 56.7% of patients in each group, respectively.

*The PARADISE-MI study did not achieve the commitment of demonstrating SV superiority over an ACEI in AMI complicated with HF or reduced LVEF. Given the superiority of SV over enalapril in the PARADIGM-HF and PIONEER-HF studies, a similar power effect was expected in the context of AMI (in fact, a primary endpoint reduction of 19% was estimated, similar to the 20% reduction evidenced in PARADIGM-HF). How can we explain the findings?*

*Thirty years ago, ACEI had generated a conclusive effect in patients with AMI and low LVEF. In those studies, 75% of patients were treated with aspirin, 25% with betablockers, and a very low proportion had undergone angioplasty, for example, 17% in the SAVE study. And it was representative of the treatment prevailing at that time that the use of statins and anti-aldosterone drugs was not even mentioned. Mortality at one year was around 17% in the placebo groups. Slightly less than 20 years ago, use of aspirin was 91% in the VALIANT study, but 25% used another antiplatelet agent, 70% received betablockers, use of statins was reported in 34% of cases and a similar percentage received primary or rescue angioplasty. Annual mortality was between 12.3% and 13.3%, according to the groups. And, finally, the PARADISE-MI study presents and excellently treated population: 95% with statins, 92% with dual antiplatelet therapy, 85% with betablockers, and 88% undergoing angioplasty, with drug-eluting stent in almost 90% of cases. And, furthermore, in the first days, before randomization, 78% received ACEI/ARBs. Can we be surprised that in the ramipril group, the annual all-cause mortality has only been 4.5% and cardiovascular mortality 3.6%, and that even the endpoint of cardiovascular death and annual incidence of HF with hospitalization or significant worsening has been inferior to 8%? We can assume that in this context the capacity of SV to demonstrate a difference was inexorably reduced: when the treatment fulfills the best standards, neprilysin inhibition per se is not enough to markedly improve results. We could also recall that mean LVEF was 36.5%; that*

almost 17.1% of patients had LVEF >40%, and an additional 31.9% LVEF between 35% and 40%; and that the most remarkable results with SV had been observed in populations with lower LVEF (29% in PARADIGM-HF and 24% in PIONEER-HF), while they have been much less promising in studies with higher LVEF (for example, PARALLAX or PARAGON-HF). However, subgroup analysis in PARADISE-MI did not show interaction with LVEF.

We can see the PARADISE-MI study as a frustration, because a new therapeutic alternative does not overcome what is known. Alternatively, we can congratulate ourselves for having so many weapons in the context of AMI with HF or reduced LVEF, which have significantly improved the prognosis in the last decades, and thus call attention to their use. The results of the PARADISE-MI study should not be seen as the

denial of the beneficial effects of SV in patients which we should learn to recognize, but as the evidence that a universal strategy of use for all patients with AMI and low LVEF or HF is not sufficiently supported by the data available. In this sense, the study subgroup analysis emerged as an advantage for SV compared with ramipril in patients <65 years and in those undergoing angioplasty. Of course, when the analyses are multiplied, the chance of a false positive increases, so, even in the case of prespecified analyses, they should not be taken as definite evidence. Further studies will have to be performed (in that sense it is impossible to disregard that Marc Pfeffer was the first author of the SAVE study, and 30 years later he is of the PARADISE-MI one, being an example of what is a life dedicated to a study line) and, certainly, using all the good things we have available.