

JORGE THIERER ^{MTSAC}

Renin-angiotensin system antagonists might reduce mortality in heart failure with preserved ejection fraction

For heart failure with preserved ejection fraction (HFPEF), there is yet no evidence available of therapies reducing mortality. Three randomized clinical trials (RCTs), CHARM preserved, PEP-CHF and I-Preserve, investigated the role of renin-angiotensin system antagonists (RASAs) -angiotensin II receptor blockers (ACEIs) and angiotensin II receptor blockers (ARBs) - in this setting and failed to show positive results. Data from a Swedish registry was quite different. (1)

Between 2000 and 2011, of 41791 patients discharged from hospitals and outpatient clinics with diagnosis of HF, 16216 (38.8%) had HFPEF, defined as EF > 40%. Of these patients, 12543 (77%) received ACEIs, ARBs or both. Compared to untreated patients, those receiving this therapy were younger and had better functional class and lower creatinine and NT-proBNP levels; yet, EF was lower (EF < 50%, 53% vs. 36%). Mortality at 1 and 5 years was significantly lower in treated vs. untreated patients (14% vs. 31% and 45% vs. 68%, respectively).

As patients treated with RAS antagonists were less compromised and thus had a better expected prognosis, propensity scores for RAS antagonist use were derived from independent predictors. Patients treated or not were then matched 1:1 according to propensity score to avoid significant differences in the baseline characteristics to yield 3329 patients pairs of patients (one patient treated and one untreated in each pair). Mortality at 1 year was lower in treated patients (23% vs. 28%) and at 5 years (64% vs. 66%), HR 0.91, 95% CI 0.85-0.98; p = 0.008. Reduction in mortality rate was observed in patients with EF < 50% but not in those with higher EF.

A priori, patients included in this registry had worse prognosis compared to those included in the aforementioned RCTs as they were older, had more comorbidities and higher NT-proBNP levels. Therefore, it may be possible that the benefit of RASA therapy is evident in a population with HFPEF and comorbid conditions. However, as the interventions of an observational study are non-randomized, the presence of unknown confounders responsible of the effect observed cannot be excluded. The definition of HRPEF is open to debate, as an EF near 40% implies impairment of the contractile function, a clinical scenario in which RASAs improve the outcome. This study demonstrates that the issue is not resolved and that RASAs might be beneficial for patients with HF and EF between 40% and 50%.

Changes in implantable cardioverter defibrillators programming: reduction in inappropriate therapy and mortality

The implantable cardioverter-defibrillator (ICD) reduces total mortality in primary prevention among patients with severe impairment of the ejection fraction (EF). About one-third of patients receive inappropriate device-delivered therapy activated by a supra-ventricular tachyarrhythmia. Inappropriate therapy is associated with increased mortality, either by producing myocardial damage or by occurring in more compromised patients.

The MADIT-RIT trial (2) included patients who met approved guidelines for primary prevention with an ICD or cardiac resynchronization therapy device. Patients were randomly assigned to receive an ICD with one of three programming configurations for the detection of arrhythmia (antitachycardia pacing followed by shock therapy if pacing did not terminate the detected tachyarrhythmia). In the conventional-therapy group (n = 514), energy was delivered with a 2.5-second delay when the heart rate was of 170 to 199 beats per minute and with a 1.0-second delay when the heart rate was of 200 beats per minute. Patients in the high-rate group (n = 500) received a device programmed to a monitor-only zone between 170 and 199 beats per minute and to a therapy zone beginning at 200 beats per minute, after a 2.5-second monitoring delay. Patients in the delayed-therapy group (n = 486) received a device programmed to three detection zones: one at 170 to 199 beats per minute, with rhythm detection on and a 60-second delay; a second tachyarrhythmia-detection zone beginning at 200 beats per minute, with rhythm detection on and a 12-second delay; and a third zone at 250 beats per minute or higher, with a 2.5-second delay.

Mean EF was of 26% and 93% were receiving beta blockers. Compared to the conventional-therapy group, high-rate group and delayed-therapy group showed a reduction of 79% and 76%, respectively, in the incidence of inappropriate therapy (p < 0.001 in both groups) pacing after a mean follow-up of 1.4 years, particularly by reducing the episodes of antitachycardia. Also, mortality decreased by 55%, in the high-rate group (p = 0.01) and by 46% in the delayed-therapy group (p = 0.06). In addition, appropriate antitachycardia pacing (triggered by ventricular tachycardia) was significantly less frequent in both groups, a finding that suggests that many episodes of arrhythmia that would have terminated spontaneously were treated prematurely in the conventional-therapy group.

This significant study contributes to clarify the mechanisms and the consequences of electrical therapy and demonstrates that programming detection and treatment of ventricular arrhythmia significantly improves the outcome of patients.

Failure of adding a renin inhibitor to treatment with other renin-angiotensin system antagonist in diabetic patients

Patients with type 2 diabetes have high risk of renal and cardiovascular complications. Treatment with ACEIs and ARBs is indicated in these patients, with benefits extending beyond blood-pressure lowering. Although it may be presumed that the combination of both drugs may offer greater benefit, data from previous studies in diabetic and non-diabetic populations did not support this hypothesis. The lack of benefit could be due to aldosterone escape and renin activation.

The ALTITUDE study (3) was a randomized, double-blind, placebo-controlled trial that evaluated the effect of a renin inhibitor, aliskiren (300 mg daily), as an adjunct to an ACEI or ARB in patients with type 2 diabetes. The primary end point was a composite of cardiovascular death, cardiac arrest with resuscitation, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, end-stage renal disease, death attributable to kidney failure and the need for dialysis or doubling of the baseline serum creatinine level.

Between 2007 and 2010 4,274 patients were included in the aliskiren group and 4,287 in the placebo group. Mean age was 65.5 years, 94.5% had hypertension and 42.3% had a cardiovascular disease other than hypertension.

At the second interim analysis, performed when two-thirds of the events had occurred, the independent data and safety monitoring committee ordered the termination of the study, based on the lack of difference in the primary outcomes during a mean follow-up of 32.9 months (18.3% in aliskiren, 17.1% in placebo; $p = 0.12$), with a trend towards greater cardiovascular events in the aliskiren group (13.8% vs. 12.6% in placebo; $p = 0.09$). Adverse events were more evident in the aliskiren group (potassium level > 6 mEq/L: 11.2% vs. 7.2%; hypotension 12.1% vs. 8.3%, both with $p < 0.001$) and were the cause of discontinuing therapy.

This study is part of the RCTs and meta-analyses which do not recommend dual renin-angiotensin blockade as this therapy does not improve the outcome and increases the incidence of complications. Compared to previous studies, the novelty of this trial is that it was terminated before being completed as the event rate was greater, yet not significant, in the active treatment group.

Surgery remains the best revascularization option for diabetic patients with multivessel coronary artery disease

The results of large randomized trials conducted in patients with diabetes showed better outcome in those who underwent coronary artery bypass graft surgery (CABGS) than among those who underwent percutaneous coronary intervention (PCI). However, these data come from the analysis of subgroups and the difference lies in the need for repeated revascularization. In addition, both approaches show continuous improvement in terms of technique and materials used.

The FREEDOM trial (4) randomized diabetic patients with at least two-vessel coronary artery disease without left main coronary stenosis to compare the effectiveness of PCI using drug eluting stents to CABGS (best with arterial revascularization). The primary outcome was a composite of death from any cause, nonfatal myocardial infarction, and nonfatal stroke. The study enrolled 1900 patients between 2005 and 2010. The mean age was 63.1 years, and 83% of patients had three-vessel disease. The patients included were of low to intermediate risk (median EuroSCORE of 2, mean LVEF of 66%, and median SYNTAX score of 26). Sirolimus-eluting and paclitaxel-eluting stents were used in more than 90% of the cases. Mean number of graft vessels was of 2.9 and the left internal mammary artery was used in 94.4% of cases.

The median follow-up time was 3.8 years. The rate of the primary outcome was significantly lower in the CABGS group: at 5 years 18.7% vs. 26.6% ($p = 0.005$), with lower mortality rate (10.9% vs. 16.3%; $p = 0.049$) and nonfatal AMI (6% vs. 13.9%; $p < 0.001$). Yet, the incidence of stroke was greater (5.2% vs. 2.4%; $p = 0.03$) at 30 days. The need for repeated revascularization was greater in the PCI group: at 1 year 12.6% vs. 4.8%; $p < 0.001$. A significant divergence of the survival curves was seen after 2 years. The differences were consistent in the different subgroups of SYNTAX score, number of vessels, kidney function or type of stent.

The FREEDOM trial confirmed that CABGS was superior to PCI in patients with diabetes and advanced coronary artery disease. The study reaffirms that the need for new revascularization is low with surgery, demonstrates the reduction in nonfatal AMI and confirms the greater risk of stroke. So far, CABGS should be indicated to patients with diabetes and multivessel disease eligible for revascularization until new techniques show other results.

Does surgery for atrial fibrillation improve the outcome of patients?

So far, surgical treatment for atrial fibrillation (AF) has only been explored in trials with few patients with mitral valve disease and without mid and long-term

results. The PRAGUE-12 trial (5) was an open, randomized multicenter clinical trial including patients with coronary and/or valve disease and paroxysmal, persistent or permanent AF documented at least twice in the previous 6 months. Patients were randomly assigned to surgery combined with left atrial ablation (group A, n = 117) or to surgery without left atrial ablation (group B, n = 107). Cryo-ablation was used in more than 95% of cases.

The primary efficacy outcome was the sinus rhythm presence (without any AF episode) during a 24 h electrocardiogram (ECG) after 1 year. The primary safety outcome was the combined endpoint of death, AMI, stroke or need for dialysis at 30 days.

The type of AF was permanent in half of the cases, paroxysmal in a quarter and persistent in the remaining quarter. The mean age was 70 years. The mitral valve was involved in surgery in 49.5% of group A and in 42.8% of patients of group B. At the moment of surgery, 77.8% of group A patients and 65.4% of group B patients were in AF (p = ns).

There were no differences in operative mortality (5.1% vs. 4.7%) or complications. The duration of surgery was 20 minutes longer in group A (p = 0.003). There were no significant differences in pharmacological treatment at discharge or during follow-up. A 24h Holter-ECG was performed 1 year after surgery in 93 patients in group A and in 76 in group B; the primary outcome was present in 60.2% of group A patients vs. 35.5% of group B (p = 0.002). No difference was found in the incidence of major events at 30 days or at 1 year.

The merit of this study is being a randomized trial including the largest number of patients up to the present and evaluating long-term results with a 24 h Holter-ECG. Yet, follow-ups were not completed in all patients and the need for performing a more thorough electrocardiographic monitoring to define the usefulness of the procedure are weak points to consider. Although the efficacy of the procedure was demonstrated, the study failed to demonstrate improved outcome and thus its implementation as standard strategy cannot be recommended.

There is no place for polyunsaturated fatty acids for prevention of post-operative atrial fibrillation

Postoperative atrial fibrillation or flutter occurs in one-third of patients after cardiac surgery, even in those taking beta blockers and antiarrhythmic agents. Evidence from experimental studies and from non-controlled open studies with small sample sizes has suggested that long-chain n-3 polyunsaturated fatty acids (PUFAs) may reduce the incidence of AF following cardiac surgery.

The OPERA trial (6) is a double-blind, placebo-controlled, randomized clinical trial evaluating the hypothesis that PUFAs reduce the incidence of post-

operative AF. The study was conducted in 28 centers in three countries: the United States (University of Harvard), Italy (Mario Negri) and Argentina (GESICA Foundation).

A total of 1 1516 patients in sinus rhythm were included and received PUFAs or placebo. Patients received 1-g capsules with preoperative loading of 10 g over 3 to 5 days (or 8 g over 2 days) followed postoperatively by 2 g/d until hospital discharge or postoperative day 10, whichever came first. The primary outcome was occurrence of AF lasting at least 30 seconds detected by continuous electrocardiographic monitoring during at least 5 days.

Mean age was 63.7 years and 7.7% had a history of AF. Mean logisticEuroSCORE was 3.7. Half of the cases had planned valvular surgery. Postoperative medication included beta blockers in 76.9% of cases and amiodarone in 36.9%. There was no difference in the primary outcome (30.7% with placebo, 30% with PUFAs) and in the proportion of sustained or symptomatic AF, number of episodes, adverse events or hospital utilization. When patients were divided in subgroups according to previous intake of fish oil, plasma phospholipids levels or days of loading dose, the analysis did not show any difference.

According to the evidence provided by this trial, there is no place for polyunsaturated fatty acids for prevention of post-operative AF. Future research may be warranted to investigate their role in another setting.

Clopidogrel pretreatment in patients undergoing percutaneous coronary intervention. Systematic review and meta-analysis

Clopidogrel pretreatment in addition to aspirin has proved to reduce ischemic events in patients with stable coronary artery disease after percutaneous coronary intervention and in those with acute coronary syndrome undergoing standard care, fibrinolysis or primary percutaneous coronary intervention.

Although the effect of pretreatment with loading dose of clopidogrel before percutaneous coronary intervention or coronary angiography has been evaluated by several studies, none of them had enough power to detect differences in mortality. A recent meta-analysis (7) evaluated this issue. Six RCTs, two observational analyses of RCTs, and seven observational studies published between 2001 and 2012 were selected. The studies varied in clinical presentation (outpatients or acute coronary syndrome) dose and timing of clopidogrel loading dose.

Pretreatment was defined as the administration of clopidogrel in loading dose of 300 mg or a maintenance dose of 75 mg or more during more than 5 days. The primary efficacy and safety outcomes were all-cause mortality and major bleeding, respectively

Of the 37814 patients included in the meta-analysis, 8608 patients had participated in RCTs. In these patients, clopidogrel pretreatment was not associated with reduction in all-cause mortality (1.54% vs. 1.97%; OR 0.80, 95% CI 0.57-1.11; $p = 0.17$). These results were consistent with those found in the other patients analyzed. Pretreated patients presented a reduction in major coronary events (9.83% vs. 12.35%; OR 0.77, 95% CI 0.66-0.89; $p < 0.001$). In a sensitivity analysis, pretreated patients with ST-segment elevation MI had lower mortality: 1.28% vs. 2.54%; OR 0.5, 95% CI 0.26-0.96; $p = 0.04$.

Pretreatment was not associated with greater risk of major bleeding (3.57% vs. 3.08%; OR 1.18, 95% CI 0.93-1.50; $p = 0.18$).

This meta-analysis demonstrates that clopidogrel pretreatment is not associated with lower risk of mortality or with greater risk of major bleeding. The study confirms a reduction in major coronary events and suggests that the benefit may be greater in ST-segment elevation MI, a finding that should be confirmed by a study specifically designed.

Is it possible to achieve remission of diabetes with lifestyle intervention only?

Type 2 diabetes has been traditionally considered a progressive and incurable disease. However, remission has been observed in some obese patients after bariatric surgery. The Look AHEAD (8) trial evaluated if an intensive lifestyle intervention (ILI) could achieve remission of type 2 diabetes in patients with obesity or overweight.

Partial remission was defined as achievement of fasting plasma glucose 100-126 mg/dL and HbA1c 5.7-6.5% with no antihyperglycemic medication. Complete remission was defined as achievement of fasting plasma glucose < 100 mg/dL and HbA1c $< 5.7\%$ with no antihyperglycemic medication.

The patients included had a body mass index (BMI) of ≥ 25 or ≥ 27 in diabetics using insulin. Patients with HbA1c $> 11\%$, systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg, or triglycerides > 600 mg/dL were excluded from the trial. The ILI included weekly group and individual counseling in the first 6 months followed by three sessions per month for the second 6 months and twice-monthly contact and regular contact in years 2 to 4. The intention was to reduce calories consumption to 1.200-1.800 kcal/day and to increase physical activity to a target of 175 minutes per week. The standard intervention was an offer of three group sessions per year on diet, physical activity, and social support.

The ILI group consisted on 2 241 participants and 2

262 were assigned to the standard intervention group. Diabetes had a mean duration of 5 years since the diagnosis was made and mean BMI was 35.8. Intensive lifestyle intervention participants lost significantly more weight (8.6% vs. 0.7% at year 1 and 4.7% vs. 0.8% at year 4; $p < 0.001$ for each) and had greater fitness increases. The ILI group was significantly more likely to experience partial or complete diabetes remission: 11.5% vs. 2% at year 1 and 7.3% vs. 2.0% at year 4; $p < 0.001$ for each. Most results corresponded to partial remission, as complete remission was only of 1.3% vs. 0.1% at year 1 and of 0.7% vs. 0.2% at year 4. The shorter duration of the disease, lower HbA1c, absence of insulin requirement and greater weight loss with the diet were independent predictors of success.

This study demonstrates that ILI is associated with partial remission of diabetes without requirement of concomitant medication. The greater benefit is achieved in cases of early diagnosis of with less metabolic impairment. However, the remission rate is modest and decreases as time goes by.

Rev Argent Cardiol 2014;82:73-76. <http://dx.doi.org/10.7775/rac.v82.i1.3767>

REFERENCES

- Lund LH, Benson L, Dahlstrom U, Edner M. Association between use of renin-angiotensin system antagonists and mortality in patients with heart failure and preserved ejection fraction. *JAMA* 2012;308:2108-17. <http://doi.org/kk2>
- Moss AJ, Schuger C, Beck CA, Brown MW, Cannon DS, Daubert JP, et al. Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med* 2012;367:2275-83. <http://doi.org/kk3>
- Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;367:2204-13. <http://doi.org/kk4>
- Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, et al. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;367:2375-84. <http://doi.org/kk5>
- Budera P, Straka Z, Osmancik P, Vanek T, Jelinek S, Hlavicka J, et al. Comparison of cardiac surgery with left atrial surgical ablation vs. cardiac surgery without atrial ablation in patients with coronary and/or valvular heart disease plus atrial fibrillation: final results of the PRAGUE-12 randomized multicentre study. *Eur Heart J* 2012;33:2644-52. <http://doi.org/kk6>
- Mozaffarian D, Marchioli R, Macchia A, Silletta MG, Ferrazzi P, Gardner TJ, et al. Fish oil and postoperative atrial fibrillation: the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) randomized trial. *JAMA* 2012;308:2001-11.
- Bellemain-Appaix A, O'Connor SA, Silvain J, Cucherat M, Beygui F, Barthelemy O, et al. Association of Clopidogrel Pretreatment With Mortality, Cardiovascular Events, and Major Bleeding Among Patients Undergoing Percutaneous Coronary Intervention: A Systematic Review and Meta-analysis. *JAMA* 2012;308:2507-16. <http://doi.org/kk7>
- Gregg EW, Chen H, Wagenknecht LE, Clark JM, Delahanty LM, Bantle J, et al. Association of an Intensive Lifestyle Intervention With Remission of Type 2 Diabetes. *JAMA* 2012;308:2489-96. <http://doi.org/kk8>