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## Direct renin inhibitor failure in the treatment of heart failure. Is the neurohumoral model exhausted?

Gheorghiade M, Bohm M, Greene SJ, et al. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial. **JAMA 2013;309:1125-35.**

Renin-angiotensin-aldosterone system (RAAS) antagonists have shown their usefulness in the treatment of chronic heart failure (CHF), but may promote the renin escape phenomenon with partial loss of the expected treatment effect. Direct renin inhibitors are designed to overcome this phenomenon. Aliskiren is one the drugs that has shown some neurohumoral benefits in CHF patients. Hospitalization for HF is a condition with great RAAS activation, high risk of mortality and short term rehospitalization.

ASTRONAUT was a multicenter, randomized, double blind, placebo-controlled study, evaluating aliskiren during hospitalization for decompensated CHF. Inclusion criteria were LVEF ≤ 40%, BNP ≥ 400 pg/ml or NT-proBNP ≥ 1600 pg/ml, glomerular filtration rate ≥ 40 ml/min/1.73 m2, sodium ≥ 130 meq/l, potassium ≤ 5 meq/l, and hemodynamic stability not requiring vasoactive drugs (except nitrates) after admission. Patients were randomly assigned to either aliskiren (150 and then 300 mg daily) or placebo. Treatment was initiated during hospitalization and patients were followed-up after discharge for a maximum of 12 months. The primary end point was cardiovascular death or HF hospitalization at 6 months. Secondary end points were the same events at 12 months, all-cause mortality at 6 and 12 months, BNP and quality of life. In total, 1615 patients (808 in the aliskiren group and 807 in the placebo group) with mean age 64.6 years and mean EF 28%, were included in the study between 2009 and 2011. At randomization, 96% of patients were receiving diuretics, 82% beta-blockers, 84% angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and 57% mineralocorticoid receptor antagonists.

No significant differences were found for the primary end point (24.9% with aliskiren, 26.5% with placebo), and neither in cardiovascular death rate or HF rehospitalization at 12 months (35% vs. 37.3%) nor in any of the individual end points. Aliskiren treatment was associated with higher hyperkalemia, hypotension and renal failure rates. An interesting finding was the interaction between treatment and diabetes: in diabetic patients aliskiren was associated with greater incidence of cardiovascular death or HF rehospitalization (hazard ratio (HR) 1.16, 95% CI 0.91-1.47) and to excess of all-cause mortality (HR 1.64, 95% CI 1.15-2.33), while in non-diabetics opposite results were found (HR 0.80, 95% CI 0.64-0.99; and HR 0.69, 95% CI 0.50-0.94, respectively). These data replicate the ALTITUDE study findings (commented in a previous issue), which was discontinued due to greater incidence of adverse events in diabetic patients treated with aliskiren.

*The results of the ASTRONAUT study do not encourage widespread use of renin blockers in patients with decompensated HF and specifically confirm that they should not be recommended in diabetic patients. It is possible that the hyporeninemia present in these patients might contribute to explain the adverse outcome with this type of drugs.*

## Sildenafil does not improve exercise capacity in heart failure with preserved ejection fraction

Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. **JAMA 2013;309:1268-77.**

Phosphodiesterase-5 (PDE 5) metabolizes nitric oxide and GMPc, second messenger of natriuretic peptides. Pre-clinical studies show that its inhibition by drugs such as sildenafil improves endothelial function, inducing vasodilation and reversal of cardiac and vascular remodeling. Existing evidence indicates that sildenafil improves exercise capacity in patients with primary pulmonary hypertension or heart failure (HF) with reduced ejection fraction. There is, however, scarce experience in HF with preserved ejection fraction (PEF), a condition whose prognosis has not yet been improved by any intervention.

The multicenter, randomized, placebo-controlled RELAX study evaluated the hypothesis that sildenafil PDE 5 inhibition in HFPEF patients would improve their functional capacity. Inclusion criteria were history of HF, EF ≥ 50%, O2 consumption in cardiopulmonary test ≤ 60% than that predicted for sex and age, and NT-proBNP ≥ 400 pg/ml or evidence of elevated LV filling pressure. The primary end point was the change in exercise capacity after 24 weeks of treatment, and the secondary end point a composite of clinical events (death, hospitalization, and change in quality of life). A total of 216 patients were randomly allocated to sildenafil (20 mg every 8 hours during the first 12 weeks and then 60 mg every 8 hours) or placebo. Median age was 69 years, and median EF (60%),



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oxygen consumption (11.7 ml/kg/min) and systolic pulmonary pressure (41 mm Hg) were obtained at baseline. Eighty-six percent of patients were receiving diuretics, 76% beta blockers and 70% renin-angiotensin system blockers or antagonists.

No significant differences were found for the primary end point (median of O2 consumption change was 0.2 ml/kg/min in both groups), the number of adverse events, diastolic function, pulmonary pressure or ventricular mass assessed at 24 weeks. Unexpectedly, NT-proBNP, endothelin, creatinine and uric acid showed modest, though significantly increased values.

*Slightly increased pulmonary pressure and normal right ventricular function in study patients could be among the main reasons for this failure. It is possible that the main sildenafil effect lies in its ability to generate pulmonary vasodilation, with more evident clinical benefit when pulmonary hypertension becomes, at least moderately, more prevalent. Another failed attempt in HFPEF patients: use of PDE 5 inhibitors does not seem to be justified in these patients. New studies in HFPEF patients with significantly elevated pulmonary pressure will shed more light on this topic.*

## Correction of anemia with darbepoetin: an inefficient measure in heart failure

Swedberg K, Young JB, Anand IS, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. **N Engl J Med 2013;368:1210-9**

Anemia is a frequent condition in heart failure with preserved ejection fraction (HFPEF). It is associated with worse quality of life, lower functional capacity and poor prognosis. The cause of this condition is unknown, but may be related to absolute or relative erythropoietin deficiency or resistance. Small studies have shown that erythropoiesis stimulating agents (ESA) may improve functional capacity.

The multicenter RED-HF study was designed to test the hypothesis that darbepoetin, an ESA agent, improves the outcomes in HFPEF patients with non-iron-deficiency anemia. Patients with LVEF ≤ 40%, FC II to IV, hemoglobin values between 9 and 12 g/dl, transferrin saturation ≥15%, creatinine ≤ 3 mg/dl and arterial pressure ≤ 160/100 mm Hg were included in the study. They were randomly assigned to receive subcutaneous injection of darbepoetin alfa, 0.75 $\mu$g/kg every 2 weeks to achieve a stable hemoglobin level of 13 g/dl, after which the frequency was lowered to monthly injections, or placebo. If at any time during follow-up transferrin saturation fell below 20%, oral or intravenous iron could be administered. The primary end point was a composite of death from any cause or hospitalization due to worsening HF. Secondary end points were the composite of cardiovascular death or hospitalization for worsening HF, or death from any cause.

Recruitment took longer than expected, and instead of the 2600 patients planned initially, 2278 were included in the study (1136 in the study drug group and 1142 in the placebo group) between 2006 and 2012. Median age was 72 years and median EF was 31%. Sixty-five percent of patients were in FC III-IV. Median hemoglobin was 11.2 g/dl and that of saturated transferring, 24%. Mean follow-up was 28 months. Median hemoglobin attained in the darbepoetin group was 13 g/dl and in the placebo group, 11.5 g/dl ($p< 0.001$). The proportion of patients receiving oral or intravenous iron was above 70% in both groups, without significant differences between them. The need for transfusion was higher in the placebo group: 16.5% vs. 10.9% ($p< 0.001$).

There was no significant difference in the primary end point outcome (50.7% with darbepoetin, 49.5% with placebo) or in any of the secondary end points. The quality of life score improved slightly more in the darbepoetin group but without clinical relevance. Thromboembolic events were more frequent with the active treatment (13.5% vs. 10%, $p = 0.009$), mainly ischemic stroke (4.5% vs. 2.8%, $p = 0.03$).

*The RED-HF study suggests that non-iron-deficient anemia in the context of HFPEF is more a risk marker than a true therapeutic target. It cannot be ruled out, however, that in patients with more severe conditions (hemoglobin < 9) ESA agents might be beneficial, though this assumption needs to be confirmed.*

## Fibrinolysis or primary percutaneous intervention in ST-segment elevation acute myocardial infarction

Armstrong PW, Gershlick AH, Goldstein P, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. **N Engl J Med 2013;368:1379-87.**

Primary percutaneous intervention (PCI) is the preferred reperfusion strategy for ST-segment elevation myocardial infarction (STEMI). However, different factors, ranging from symptom onset to hospital admission delay or logistic issues affect its execution within recommended times. This results in increased morbidity and mortality.

The open-label, prospective, randomized, parallel-group, multicenter STREAM study evaluated whether thrombolytic therapy (TT), coupled to antiplatelet and anticoagulant therapy provides a clinical outcome comparable to that of PCI in patients with STEMI who present within 3 hours of symptom onset and who cannot undergo PCI within one hour after medical contact. A strong emphasis was placed on prehospital randomization. Tecneteplase was used in the TT group, with doses between 30 and 50 mg according to body weight. A coronary angiography was planned within 6 to 24 hours, but in the event of thrombolytic treatment failure, rescue angioplasty was performed immediately. Concomitant therapy in both groups included enoxaparin, clopidogrel and aspirin. The

primary end point was a composite of death, shock, heart failure or reinfarction at 30 days.

Between 2008 and 2012, 1892 patients with mean age 59.7 years, 94% of whom were in Killip class I were included in the study. The infarction was inferior in 50% of cases and anterior in the rest of the cases. Medians of symptoms-first medical contact and symptoms-randomization times were not significantly different between TT and PCI: 62 vs. 61 min and 91 vs. 92 min, respectively. Symptoms-onset of reperfusion therapy delay was lower in the TT group: 100 vs. 178 min ($p<0.001$); for patients randomized in the ambulance setting, this delay was 96 vs. 165 min and for those assigned to a group at the hospital, 13 vs. 230 min. Thirty-six percent of patients in the TT group required rescue angioplasty, with a delay in arriving to the cath-lab of 2.2 hours and a median of 17 hours for the remaining 64% of patients. Overall, 80% of patients in the TT group underwent percutaneous intervention compared to 89.8% in the PCI group ($p<0.001$). The primary end point showed no significant differences between TT and PCI groups (12.4% vs., 14.3%, $p=0.21$), but a higher trend of heart failure and shock in the TT group. Stroke was significantly more frequent in the TT group (1.6% vs. 0.5%), especially hemorrhagic stroke and in patients 75 years of age or older, leading to tecneteplase dose reduction in this age group during the course of the study.

*The results of the STREAM study suggest that, in the study conditions, TT with tecneteplase is comparable to PCI, with slightly increased risk of intracranial bleeding. It cannot be ruled out, however, that these results are due to the high rate of post-thrombolysis intervention, and neither can they be extrapolated to patients presenting 3 hours after symptom onset, or those that can undergo PCI within one hour of the first medical contact.*

## Farewell to aspirin in patients with oral anticoagulation therapy submitted to percutaneous coronary intervention?

Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of Clopidogrel With or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomized, controlled trial. **Lancet 2013, 381:1107-15.**

Oral anticoagulation (OAC) is the treatment of choice for patients with mechanical valves and for the majority of those with atrial fibrillation. In 20 to 30% of cases coronary angioplasty requires the use of aspirin (ASA) and clopidogrel (C). Triple therapy (TT) with OAC, ASA plus C is associated with high bleeding rate. Since OAC and C discontinuation increase the risk of thromboembolic events and stent thrombosis, respectively, the WOEST study authors analyzed whether in these patients a dual therapy (DT) with OAC and C would not be superior to TT.

The open-label, multicenter, randomized WOEST study included patients with OAC indication for at least 1 year after study initiation, undergoing percutaneous coronary intervention (PCI) and without contraindication for antiplatelet therapy. They were randomly assigned to TT or DT. In both cases, INR of 2 was the proposed target. Clopidogrel was administered, whenever possible, in doses of 75 mg at least 5 days prior to PCI, a loading dose of 300 mg, 24 hours, or 600 mg, 4 hours prior to the intervention, followed by 75 mg daily. In patients with no prior treatment, 320 mg of ASA were administered in the TT group 24 hours prior to PCI followed by a dose of 80 to 100 mg daily. In the case of bare-metal stents, antiplatelet therapy was administered for 1 month which could extend to 1 year; in the case of drug-eluting stents antiplatelet therapy was indicated for 1 year. The primary end point was any bleeding within 1 year. Secondary end points were a composite of death, myocardial infarction, revascularization of the treated vessel and stent thrombosis, and each of them analyzed separately.

Five hundred and sixty three patients (279 in the DT group and 284 in the TT group), with a mean age of 70 years were analyzed. Sixty-nine percent of patients had atrial fibrillation, 11% mechanical valve and the remaining 20% had another OAC indication. In 27.5% of patients the indication for PCI was acute coronary syndrome. After 1 year, 92.5% of patients in the DT group were still treated with OAC and 80.6% with C therapy, whereas in the TT group, 91.2% were treated with OAC, 78% with C and 66.5% with ASA therapy. The primary end point occurred in 19.4% patients of the DT group and in 44.4% of the TT group (HR 0.36, 95% CI 0.26 to 0.50, $p<0.0001$), at the expense of mild to moderate bleeding according to different scales (TIMI, GUSTO, BARC). There was no difference in intracranial bleeding but it was confirmed in other organs, mainly cutaneous and gastrointestinal. The composite secondary end point occurred in 11.1% of patients in the DT group and in 17.6% in the TT group (adjusted HR 0.56, 95% CI 0.35-0.91, $p<0.05$), with difference in mortality favoring DT: 2.5% vs. 6.3%, $p = 0.027$.

*The bleeding rate in WOEST was greater than that reported in registries or other studies, perhaps because bleeding was the prospectively defined end point. The lower bleeding rate with DT, with no excess of thromboembolic events suggests that ASA is not necessary in anticoagulated patients who undergo stent implantation. However, the study was designed to test superiority in the primary end point and not non-inferiority in the secondary end points, so that conclusions in that respect may not be definitive.*

## Off-pump versus on-pump coronary-artery bypass grafting: absence of substantial differences.

Lamy A, Devereaux PJ, Prabhakaran D, et al. Effects

of off-pump and on-pump coronary-artery bypass grafting at 1 year. N Engl J Med 2013, 368:1179-88.
Diegeler A, Borgermann J, Kappert U, et al. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. **N Engl J Med 2013, 368:1189-98.**

Coronary artery bypass grafting (CABG) has been traditionally carried out with cardiopulmonary bypass (CPB) and is associated with 2% operative mortality and 5 to 7% major complications. In the last decade off-pump CABG has become increasingly frequent and with less associated morbidity according to its advocates. Overall, observational studies comparing both types of surgery present with selection bias that could explain the better performance in some of these off-pump CABG studies. However, randomized studies (ROOBY with 2203 patients and DOORS with 900) have not confirmed these findings, probably due to lack of statistical power. Two recent publications seem to confirm the lack of significant difference between the two forms of approach.

The CORONARY trial was the largest study to prospectively analyze the benefit of off-pump or on-pump CABG surgery. It included 4752 patients scheduled to undergo CABG and who met one or more of the following criteria: age ≥ 70 years, peripheral vascular disease or stroke, carotid stenosis ≥ 70% or renal failure. Patients less than 70 years had meet at least one of the following criteria: diabetes, EF ≤ 35%, need for emergency surgery or history of recent smoking. Only experienced surgeons could participate (at least 100 CABG of each type to his credit). The average age of the patients was 67.6 years. One-month results had already been published showing no difference in the composite end point of death, myocardial infarction, stroke, or new renal failure requiring dialysis, and with greater need for repeated revascularization and lower incidence of bleeding and renal or respiratory failure in off-pump CABG. We now know that at 1 year follow-up there was still no difference in the end point (12.1% in off-pump CABG, 13.3% in on-pump CABG, p = 0.24) or in the need for repeated revascularization. There was also no difference in cognitive function.

The German GOPCABE study included 2394 patients over 75 years (mean age 78.5 years). Its design was similar to that of the CORONARY study with a combined primary end point that added repeated revascularization to the previous study events. Again, there was no significant difference in the incidence of the composite end point between off-pump and on-pump CABG at 30 days (7.8% vs. 8.2%) or at 1 year (13.1% vs. 14%). As in the previous case the need for repeated revascularization was higher at 30 days but not at 1 year in off-pump CABG.

*Overall, both studies have similar results and strongly suggest that there is no reason to prefer one approach over the other in CABG. The experience of each surgical group and patient individual characteristics may tip the scales in either sense.*

## Beneficial effect of the Mediterranean diet in primary prevention of vascular events in high-risk patients

Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. **N Engl J Med 2013, 368:1279-90**

Numerous observational and some intervention studies have shown the beneficial effects of the Mediterranean diet (MD) for secondary prevention and reduction of cardiovascular events. The traditional MD is rich in olive oil, fruits, nuts, vegetables and grains, with moderate amount of fish, chicken and wine and low intake of dairy products, red or processed meat and sweets. A recently published Spanish study explored the beneficial effects of two different MD compared to a control diet in primary prevention.

The study included men between 55 and 80 years, and women between 60 and 80 years with diabetes or with at least 3 of the traditional vascular risk factors. They were randomly assigned to three dietary patterns: a) MD supplemented with extra virgin olive oil (about 1 liter per week) b) MD supplemented with 30 g per day of walnuts, hazelnuts and almonds, c) control diet, low fat but discouraging consumption of olive oil and nuts. No caloric restriction or physical activity promotion was established in any group. The study began in 2003, and initially held quarterly support meetings in MD groups and annual meetings in the control group, until 2006 when the same meeting schedule was established for all the groups. The primary end point was a composite of cardiovascular death, MI and stroke (S). The secondary end points were all the components of the primary end point and death from any cause.

A total of 7447 subjects, 57.5% of whom were female, were enrolled in the study. Mean age was 67 years, mean body mass index 30 kg/m2, 48.5% had diabetes and 82.7% were hypertensive. In July 2011 the study was discontinued after a median follow-up of 4.8 years, when an interim analysis demonstrated a clear difference in favor of MD. The primary end point occurred in 11.2 ‰ of patients per year in the control group, in 8.1 ‰ per year in the MD group supplemented with olive oil (p = 0.009 vs. control) and in 8 ‰ per year in the MD group supplemented with nuts (p = 0.02 vs. control). The incidence of stroke was the only significant difference in the separately evaluated primary end point components: 5.9 ‰ per year in the control group, 4.1 ‰ per year in the MD supplemented with olive oil group (p = 0.03 vs. control) and 3.1 ‰ per year in the MD supplemented with nuts group (p = 0.003 vs. control). Some limitations (different support scheme in the 3 groups during the first years and some slight imbalance in baseline characteristics) were considered in multivariate analysis and after adjustment no significant differences that could modify

the primary conclusion were found.

*Given the open nature of the study, one may wonder whether pharmacological treatment was similar in the 3 groups across the years and if this may have contributed to the results. Nevertheless, with an intervention design, the trial has the benefit of confirming data already emerging from observational studies on the value of MD in primary prevention in patients with moderate to high risk.*

## Biventricular pacing should be chosen in patients with heart failure and depressed ejection fraction requiring permanent pacemaker.

Curtis AB, Worley SJ, Adamson PB, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. **N Engl J Med 2013, 368:1585-93.**

A common topic of controversy in the context of heart failure with depressed ejection fraction (HFDEF) is whether upon the indication of permanent pacing, when it is expected that for most of the time the pacemaker rhythm will prevail, a traditional or a biventricular pacemaker (BP) should be the device of choice. This discussion stems from the fact that sustained right ventricular apical pacing (SRVP) generates a pattern of left bundle branch block with mechanical dyssynchrony that may further impair left ventricular systolic function. Some randomized studies confirm that the risk of hospitalization for heart failure is higher if the pacemaker rhythm is predominant. BP therapy would overcome this complication. So far, there has been no confirmation of this theory, as large randomized trials of resynchronization have excluded patients with specific indication of permanent pacing.

BLOCK-HF was a multicenter, randomized, double-blind study, which included patients with indication of permanent pacing, evidence of second or third degree AV block, or PR ≥ 300 ms at a heart rate > 100 beats/min, and in whom a predominant pacemaker rhythm was thus presumed. An EF ≤ 50%, FC class I to III and no standard indication for resynchronization therapy was required. A biventricular pacemaker was placed (with cardioverter-defibrillator if indicated) and patients were randomly assigned to exclusive BP or SRVP. The primary end point was death from any cause, heart failure emergency treatment with intravenous drugs or an increased rate of end-systolic volume ≥ 15%. Between 2003 and 2011 device implantation was attempted in 809 patients; it was successful in 758 (93.7%) but 691 patients were effectively randomized (349 to BP and 342 to SRVP). Mean EF was 40%, and 73% were in FC class I-II. At mean follow up of 37 months, and only considering those with available stroke volume data, a highly significant difference was found for the primary end point: 45.8% of patients with BP vs. 55.6% with SRVP. The difference in a secondary endpoint of death or hospitalization was also highly significant (32.9% vs. 37.7%)

*The BLOCK HF study has clinical significance, as it clarifies a question that so far had no clear answer on practice guidelines. It confirms the detrimental effect of sustained SVRP in HFDEF patients, and indicates that if the pacemaker rhythm predominates, BP should be preferred.*