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Renal stenting does not improve the prognosis of atherosclerotic renal artery stenosis

Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. **N Engl J Med 2014;370:13-22. http://doi.org/rrt**

Renal artery stenosis (RAS) has been linked to the development or persistence of hypertension (HT) and ischemic nephropathy. Although uncontrolled case reports have suggested that renal stenting (RS) could decrease blood pressure and improve renal function, randomized clinical trials such as the ASTRAL and STAR studies have not confirmed this assumption. However, no studies to date have been performed to explore the effect of RS on clinical endpoints.

The CORAL study included patients with RAS of atherosclerotic origin with systolic hypertension treated with at least two antihypertensive agents, glomerular filtration rate ≤ 60 ml/min/1.73 m2, or both. Injury of at least one of the renal arteries had to be present. A renal angiography for the diagnosis of acute RAS (damage between 80% and 99 %, or between 60 % and 79 % with systolic gradient ≥ 20 mm Hg) was initially required, but then other diagnostic methods were admitted. Patients with creatinine ≥ 4 mg/dL, those with non-ischemic renal failure, RAS cases due to fibromuscular dysplasia and patients with lesions that could not be treated with a single stent were excluded from the study. All patients had to receive the best medical treatment (candesartan with or without hydrochlorothiazide and the combination agent amlodipine - atorvastatin) to maintain BP below 140-90 mm Hg (130-80 mm Hg in patients with diabetes or renal failure). They were randomized in a 1:1 ratio to RS plus medical treatment or medical therapy alone. The primary endpoint was a composite of major cardiovascular or renal events: death, myocardial infarction, stroke, hospitalization for congestive heart failure, renal failure progression and need for permanent dialysis.

The study included 947 patients (459 in the RS group and the rest in the medical treatment group). Mean age was 69 years and 50% were women. Mean systolic BP was 150 mm Hg. The average number of antihypertensive drugs used was 2.1. In the RS group, a stent was placed in 94.6 % of patients and renal stenosis was reduced from 68 ± 11 % to 16 ± 8%. In the median follow-up of 43 months, the primary endpoint occurred in 35.1% of patients in the RS group and in 35.8% in the medical treatment group (p = 0.58). There was also no difference in any of the endpoints considered separately. In the longitudinal follow-up a slightly greater reduction in BP was observed with stenting (2.3 mm Hg, 95% CI 0.2 to 4.4 mm Hg), but this did not translate into less need for medication. In fact, average antihypertensive drugs administered at the end of the study were 3.3 and 3.5 in the RS and medical therapy alone groups, respectively.

The CORAL study, designed to demonstrate the benefit of RS, ends by exposing the strength of medical treatment. It points out that RS does not improve the outcome of patients with ischemic RAS receiving adequate medical therapy. This conclusion should not be extrapolated to patients with fibromuscular dysplasia, to younger patients and to those in whom the procedure has been shown to be useful.

Coffee consumption and cardiovascular events: the importance of moderation

Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. **Circulation 2014;129:643-59. http://doi.org/rrv**

Coffee is one of the most consumed beverages worldwide. Publications related to its relationship with cardiovascular events have yielded conflicting results, from positive association in case-control studies to non- linear association in meta-analyses of prospective cohort studies. However, the possibility of a non-linear association between consumption and incidence of events remains open. A meta-analysis of published prospective studies on the subject was performed to explore this possibility.

This meta-analysis included 36 studies published between 1966 and 2013 (34 cohort-studies, 1 cohort-case and 1 nested control case) involving a total of 1,283,685 participants. The end point was incidence of cardiovascular events, including mortality, coronary events, stroke and heart failure. Median follow-up was 10 years. Compared with people with very low or no coffee consumption (median 0 cups daily), the RR for low consumption (median of 1.5 cups per day) was 0.89 (95 % CI 0.84 to 0.94), for intermediate consumption (average of 3.5 cups per day) it was 0.85 (95% CI 0.80-0.90) and for high consumption (median 5 cups daily) 0.95 (95% CI 0.87 to 1.03). There was no interaction with age, gender, history of hypertension or myocardial infarction, type of coffee (caffeinated or decaffeinated) or smoking. A closer analysis established the presence of a non-linear U-shaped association between coffee consumption and the incidence of the primary endpoint. Thus, compared with no coffee consumption, the RR associated with consuming a daily cup was 0.95 (95% CI 0.93-0.97), it gradually descended consuming up to 4 cups (RR 0.88, 95% CI 0.83-0.93 %) and then increased again, reaching 0.93 (95% CI 0.85 to 1.03) with 7 cups daily. As shown, con-

sumption was not associated with excess risk in any case, and moderate drinking seemed to have a protective effect.

Coffee intake exerts different acute or chronic effects. Accordingly, it immediately generates vasoconstriction and may increase blood pressure, and in fact, some short-term studies have reported a transient increase in the risk of infarction, stroke and sudden death associated with its intake. Moreover, non-filtered coffee may increase cholesterol levels. In contrast, on a long-term basis increased sensitivity to insulin, with reduced incidence of type 2 diabetes and systemic inflammation markers have been observed. The results of this publication, with long-term follow-up and adjusted for some traditional confounders, may show the balance between harmful and beneficial effects of coffee, with the most favorable combination when consumption is moderate. The limitations are those inherent to any meta-analysis of observational studies, including the presence of residual confounders beyond the covariates considered. Furthermore, as they are non-intervention studies, there are no grounds for establishing a causal relationship.

Valve repair versus replacement for ischemic mitral regurgitation: what is better?

Acker MA, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. **N Engl J Med 2014;370:23-32. http://doi.org/rrw**

Acute functional ischemic mitral regurgitation (IMR) is associated with an increased mortality risk, mainly caused by papillary muscle migration, especially of the posterolateral muscle. Annular dilation and reduced closing forces do not play an important role. Numerous publications have indicated that repair is better than replacement in mitral regurgitation surgical treatment, mainly because it preserves ventricular function and in some series due to its better clinical outcome. However, repair advantages do not seem so clear in the case of IMR. A recently published randomized study confirms these suspicions.

The study included patients with chronic and acute IMR, with effective regurgitant orifice (ERO) ≥ 0.4 cm^2 in whom surgical resolution was decided, with or without associated coronary revascularization. If ERO was < 0.4 cm^2 other severity echocardiographic parameters (left chamber size, pulmonary venous flow, and the width of the vena contracta, among others) were required. Structural valve involvement or papillary muscle rupture cases were excluded. Patients were randomly assigned to repair (with rigid or semi-rigid annuloplasty) or replacement with preservation of subvalvular apparatus. The primary endpoint was left ventricular end-systolic volume index (LVESVI) variation at 12 months. A mean LVESVI of 100 ml/m^2 estimated at baseline, with 20 ml/m^2 reduction in the repair group and 35 ml/m2 in the replacement group would require 250 patients to find a significant difference. The incidence of various clinical events, from death to clinical worsening and need for new surgery, was considered as secondary end point.

The study included 251 patients (126 in the repair group); 61.7 % were men and mean age was almost 69 years. Mean LVESVI was 61 ± 26 ml/m^2 in the repair group and 65 ± 27 ml/m^2 in the replacement group. The average ERO was nearly 0.4 cm^2 in both groups. There was concomitant coronary revascularization in 73.8 % of patients with valve repair and in 75.2 % of those with valve replacement. There was no significant difference in LVESVI in survivors at 12-months, with a decrease of 6.6 ml/m^2 and 6.8 ml/m^2, respectively. Neither did the event rate differ: 14.3 % mortality with repair surgery and 17.6% with replacement. The occurrence of recurrent MR was higher in the repair group: 32.6 % vs. 2.3%, $p < 0.001$.

This study has the advantage of being randomized, preventing the selection bias present in many series, which could have defined the most favorable outcome for patients with valve repair, as generally, those undergoing replacement are older and with a higher rate of comorbidity. The fact that the replacement was performed with chordal sparing may also account for the similar evolution of both groups. The number of patients included seems appropriate to explore the differences in LVESVI, but it is certainly insufficient to confirm the lack of difference in clinical outcome. A better initial but perhaps worse long-term evolution might be hypothesized with repair surgery, given the 30% recurrences. Therefore, a longer follow-up of a larger number of patients is needed to arrive to definitive conclusions.

Pharmacotherapies for smoking habit cessation: network meta-analysis of adverse cardiovascular effects

Mills EJ, Thorlund K, Eapen S, Wu P, Prochaska JJ. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. **Circulation 2014;129:28-41. http://doi.org/rrx**

There are three first-line drug treatments employed for smoking cessation: nicotine replacement therapy (NRT), bupropion and varenicline. On each of these, questions have been posed concerning their safe use and increased incidence of cardiovascular and cerebrovascular events. In general, each of these treatments has been compared with placebo, while studies comparing these agents between them are scarce. A network meta-analysis was performed considering all the randomized clinical trials published in each of the above therapies, to examine the direct (head-to-head studies) and indirect evidence of the comparative safety of different treatments.

The selection included 63 trials (30508 patients), 58 two-armed, 3 three-armed and 2 four-armed. The analysis included the following comparisons: 21 trials

of RNT vs. placebo or control, 27 of bupropion vs. placebo, 18 of varenicline vs. placebo, 3 of RNT vs. bupropion, 1 of NRT vs. varenicline and 2 of varenicline vs. bupropion. All cardiovascular events (CVE) and specifically major adverse cardiovascular events (MACE): death and myocardial infarction and nonfatal stroke were considered as end-points. The median treatment time was 12 weeks and median follow-up was 1 year. Due to the Bayesian network meta-analysis employed, the results are not reported with the traditional 95 % CI, but with 95% CrI (credible interval).

a) Head-to-head comparison: the comparison of NRT vs. placebo was associated with an increased risk of overall CVE (RR 1.81, 95% CI 1.35-2.43), mainly tachycardia and palpitations, but not with MACE (RR 1.38, 95% CI 0.58-3.26). Bupropion vs. placebo evidenced no increased risk of overall CVE (RR 1.03, 95% CI 0.71 to 1.50) but it definitely showed a tendency to exert a protective effect with regard to MACE: RR 0.57, 95% CI 0.31-1.04 %. Varenicline compared with placebo showed no significant association with overall CVE (RR 1.24, 95% CI 0.85-1.81) and specifically with MACE (RR 1.44, 95% CI 0.73-2.83). With much broader 95 % CI, given the small number of patients involved, the comparison between the various agents showed no increased risk of events in any comparison between them.

b) Network meta-analysis: NRT compared with placebo was associated with an increased risk of overall CVE and showed a tendency to excess risk of MACE (RR 1.95, 95% CrI 0.92 to 4.30). Bupropion versus placebo showed no increased risk of overall events and in contrast exerted a protective effect with respect to MACE (RR 0.45, 95% CrI 0.21 to 0.85). Varenicline compared with placebo showed no significant association with overall CVE and in particular with MACE. In the comparison between different agents, bupropion appeared safer than NRT both for overall CVE (RR 0.43, 95% CrI 0.19-0.91) and for MACE (RR 0.23, 95% CrI 0.08-0.63), and also appeared safer than varenicline regarding MACE (RR 0.33, 95% CrI 0.16 to 0.87).

This meta-analysis confirms that none of the aforementioned therapies significantly increased incidence of MACE. The use of "network " technology can achieve results impossible to accomplish with traditional analysis. However, we must consider possible limitations: lack of information in some studies on endpoint security and the wide confidence intervals for some of the association measurements fail to ensure the absence of risk. In this analysis, bupropion appears safer than the other alternatives with regards to MACE; this should be confirmed in prospective studies. Actually, recent large observational registers (with the biases inherent to this type of study) do not match these results. The greater or lesser risk of events of an intervention over another must also be seen in the context of their degree of effectiveness in achieving the initial objective, given the risk of MACE that the smoking habit persistence entails.

Anticoagulation in pulmonary arterial hypertension: in the absence of clinical trial ...

Olsson KM, Delcroix M, Ghofrani HA, Tiede H, Huscher D, Speich R, et al. Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). **Circulation 2014;129:57-65. http://doi.org/rrz**

Treatment with oral anticoagulation (OAC) in pulmonary arterial hypertension (PAH) is still under debate. It is indicated in practice guidelines for idiopathic PAH (IPAH) based on pathological studies showing thrombotic lesions in the pulmonary vasculature, and retrospective or prospective non-randomized studies with small numbers of patients suggesting improved survival with OAC. In other forms of PAH (secondary to collagen vascular disease, congenital cardiomyopathies, etc.), the indication is even more diffuse and almost left to individual criteria. It should also be noted that these forms of PAH occur in patients with increased bleeding risk, elderly patients, and with a higher rate of comorbidity. In this context, the COMPERA register of pulmonary hypertension launched in seven European countries, which included 4069 patients between 2007 and 2013, provides valuable information.

Patients with PAH diagnosis since May 2007, presenting with right heart catheterization data, mean pulmonary artery pressure ≥ 25 mm Hg and pulmonary capillary wedge pressure ≤15 mm Hg, were selected for this analysis Two groups were formed, according to whether they had received or not, partial or total OAC during follow-up. The primary endpoint was survival at 3 years. From the 1283 patients selected for this study (800 with IPAH and the rest with other forms of PAH), 738 (58 %) received OAC (55.7 % throughout follow-up, 23.3 % for > 75 % of the time and the rest for shorter periods). Considering the whole group, there was no significant difference in survival at 3 years (74.2% with OAC, 69.6 % without OAC, p = 0.14).

Among patients with IPAH, 66 % received OAC. Although with a similar age, gender and functional class to that of patients without OAC, anticoagulated patients often had worse hemodynamics and more frequently a combination of specific drug therapy for PAH (endothelin blockers, phosphodiesterase-5 inhibitors and prostanoids). At 3 years, survival of patients with OAC was higher: 76.9 % vs. 66.3 %, p = 0.006. In multivariate analysis, OAC was an independent predictor of survival, along with female gender, age and functional class. Combination therapy was not a predictor of better outcome in this analysis. In a sub-analysis of 168 pairs of patients with and without OAC, matched for age, gender, functional class and pulmonary resistance (but who persisted in treatment asymmetry), the difference in survival was maintained in favor of

anticoagulated patients.

Among the 483 patients with other forms of PAH, 43% received OAC. Though OAC patients had more severe disease, there was no difference in mortality. In the specific subgroup of patients with PAH secondary to scleroderma (n = 208) 50% received OAC with worse survival at 3 years (62.7 % vs. 73.7 %), but with no significant difference. However, in the multivariate analysis OAC showed a tendency to associate with increased mortality: HR 1.82, 95% CI 0.94 -3.54, p = 0.08.

A large randomized study of OAC in PAH is still missing, will it ever be accomplished? Meanwhile, the data in this registry, with the inherent limitations, seem to support anticoagulation therapy in patients with IPAH. Beyond statistical adjustment, the role that the different prevalence of specific therapy may actually have in patients with and without OAC still remains to be defined: does it contribute to a better prognosis of the former; does it express better quality of care or more frequent monitoring and therefore less risk of complications? The interpretation of findings in patients with other forms of PAH is more complex, but the association of OAC with worse outcome in patients with scleroderma calls for attention. Whether for causal reasons or worse disease expression, it suggests a cautious attitude towards OAC indication.

Do statins decrease contrast-induced acute kidney injury? The PRATO-ACS study

Leoncini M, Toso A, Maioli M, Tropeano F, Villani S, Bellandi F. Early high-dose rosuvastatin for contrast-induced nephropathy prevention in acute coronary syndrome: Results from the PRATO-ACS Study (Protective Effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome). **J Am Coll Cardiol 2014;63:71-9. http://doi.org/rr2**

Contrast-induced acute kidney injury (CI-AKI) is a possible complication of diagnostic or therapeutic procedures using iodine-based contrast media. Its incidence varies according to patient characteristics, underlying condition, procedure, osmolarity and contrast volume. Pre-procedural and post-procedural hydration and use of the lowest amount of isosmolar or low osmolarity contrast media are common measures to prevent it. Different observational and interventional studies have suggested that statins, through as yet unclear mechanisms (anti-inflammatory, antioxidant, antithrombotic), and with greater effect with higher vs. lower doses, can reduce the incidence of CI-AKI.

In this context, the PRATO-ACS study incorporated patients with acute coronary syndrome without ST-segment elevation, naïve to statin treatment and who were scheduled for an early invasive procedure. They all received aspirin, clopidogrel and non-fractionated heparin, N-acetyl cysteine and a hydration program with 1ml/kg/h saline solution 12 hours before and up to 12 hours after the angiography. Patients were randomly assigned to: a) rosuvastatin 40 mg on admission, followed by 20 mg/day during hospitalization and after discharge, or b) no statin treatment prior to angiography and atorvastatin 40 mg/day at discharge. The primary endpoint was CI-AKI defined by an increase in creatinine ≥ 25% or ≥ 0.5 mg/dl compared with baseline, 72 hours after receiving iodinated contrast. Patients ≥70 years, with diabetes, left ventricular ejection fraction (LVEF) ≤ 45% or creatinine clearance ≤ 60 ml/min were considered at high risk of CI-AKI. Secondary endpoints were incidence of CI-AKI with other definitions, cardiovascular and renal adverse events at 30 days, and death or non-fatal infarction at 6 months.

The study included 504 patients with mean age of 66 years. Sixty-five percent of patients were men and 21% were diabetic. Slightly more than 33% of patients had LVEF ≤ 45%, and almost 42% creatinine clearance ≤ 60 ml/min. Seventy-one percent of patients presented high risk for CI-AKI. Angiography was performed in 66% of patients. The CI-AKI incidence was 6.7% in the early statin arm vs. 15.1% in the control arm, with an OR adjusted by age, coronary risk factors and for CI-AKI and procedure-associated variables of 0.38, 95% CI 0.20-0.71; p = 0.003. Results were more marked in patients with worse LVEF and renal function. Similar results were obtained with other definitions of CI-AKI. The incidence of cardiac and renal adverse events at 30 days was lower with early statins [3.5% vs. 7.9% (p = 0.036)] and at 6 months this group showed a tendency of lower infarction and death [3.6% vs. 7.2% (p = 0.07)]

Use of statins seems clearly indicated to prevent CI-AKI compared with other not clearly confirmed strategies. Although there was already observational evidence of this benefit, the PRATO-ACS has the merit of being a randomized study, with the novelty of an evaluation performed in the context of acute coronary syndrome. Results suggest that statins should be used early if an invasive strategy is scheduled. No superiority could be ascribed to rosuvastatin (hydrophilic) over other lipophilic statins, as atorvastatin, due to lack of head to-head-comparisons. Nevertheless, it seems that higher doses are needed, since in addition to this study, other studies comparing low vs. high doses of other statins showed better results at higher doses. It is not clear what dose should be administered in the case of patients already receiving statins.

Cardiac failure: the role of renal impairment

Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. **Eur Heart J 2014;35:455-69. http://doi.org/rr3**

Cohort and meta-analysis studies have shown that

chronic renal failure (CRF) and worsening renal function (WRF) are predictors of poor outcome in heart failure (HF). A recently published meta-analysis confirms and quantifies this association in detail.

The meta-analysis included 85 studies of patients with acute or chronic HF. Among these studies, 57 (1,076,104 patients) explored the prognostic value of CRF, identified in most studies by glomerular filtration rate < 60 ml/min, and in the remaining studies, defined according to creatinine, cystatin C values or international codification. Prevalence of CRF was 32%. After a follow-up period of almost 1 year in acute HF studies and a little over 2 years and a half in those of chronic HF, mortality rate with or without CRF was 16% and 11%, respectively (OR 2.34, 95% CI 2.20-2,50; p < 0.001). The effect was slightly higher in acute HF. However, results were very heterogeneous, and subsequent analyses revealed that the prognostic value of CRF increases with higher diuretic use. Also, in patients with preserved EF, the OR in studies with mean EF < 30%, between 30% and 40% and > 40% was 2, 2.56 and 3.22, respectively.

The remaining 28 studies (49890 patients) investigated the incidence of HF in the prognosis of WRF during follow-up, generally defined by an increase in creatinine > 0.3 mg/dl, and occasionally by other absolute or percent cut-off values, or the decrease in glomerular filtration rate. The incidence of WRF was 35%. After a monitoring period of 14 months in acute HF studies, and over 19 months in chronic HF, mortality with and without WRF was 36% and 32% (OR 1.81, 95% CI 1.55-2.12; p < 0,001). The effect was slightly lower in acute HF studies. Age, hypertension, diabetes, diuretic use and above all baseline CRF were independent predictors of WRF.

Due to the number of patients and follow-up period, this meta-analysis is the most solid proof of the importance of renal impairment as HF marker and prognostic factor. Renal dysfunction expresses greater prevalence of traditional risk factors, higher vascular injury and coronary disease and greater hemodynamic impairment. Patients with renal dysfunction generally present higher filling pressures and reduced cardiac output, added to usually being badly medicated. We could then state that it points to sicker patients. Moreover, renal impairment per se generates poor prognosis due to activation of neurohumoral and inflammatory phenomena and anemia. Consequently, renal function impairment is not only an expression of more illness, but an independent risk factor of poor prognosis.

Effect of renin-angiotensin system antagonists on mortality of nondialysis-dependent patients with chronic kidney disease

Molnar MZ, Kalantar-Zadeh K, Lott EH, Lu JL, Malakauskas SM, Ma JZ, et al. Angiotensin-converting enzyme inhibitor, Angiotensin receptor blocker use, and mortality in patients with chronic kidney disease. **J Am Coll Cardiol 2014;63:650-8. http://doi.org/rr4**

Cardiovascular morbidity and mortality are significantly higher in patients with chronic kidney disease (CKD) than in those not presenting this condition. Many of these patients have hypertension, diabetes, coronary disease or heart failure, all conditions in which renin-angiotensin system antagonists (RASA), whether angiotensin-converting enzyme inhibitors or angiotensin II antagonists, have been shown to improve the prognosis by reducing the incidence of events, and in some specific cases, mortality. Furthermore, in the context of CKD, use of RASA is associated with delayed progression of renal function impairment. However, it is not yet clear whether in nondialysis-dependent CKD RASA specifically reduce mortality. A cohort study carried out by the United States Veteran Association tried to answer this question.

The study included 141,413 patients between 2004 and 2006, with nondialysis-dependent CKD (glomerular filtration rate < 60 ml/min/1.73 m2, or higher values, but with overt microalbuminuria) not treated with RASA prior to admission. Mean age was almost 75 years, 22% of patients were diabetic and mean glomerular filtration rate was 50 ± 13 ml/min/1.73 m2. In the year after entering the register, 18% of patients initiated treatment with RASA. Compared with the rest of the patients, treated patients were younger, with more history of hypertension and higher arterial pressure, and greater prevalence of diabetes, coronary disease and heart failure. In the multivariate analysis, lower age, male gender, better renal function and the aforementioned comorbidities were independent predictors of RASA treatment initiation. Therefore, with these independent predictors the authors built a propensity score to receive RASA. Subsequently, an analysis was performed matching treated and non-treated patients with similar propensity scores in a 1:1 ratio (to obtain baseline characteristics that were not significantly different). This analysis resulted in 20247 pairs of patients. In a median follow-up of 4.7 years, treatment with RASA was significantly associated with lower mortality in a) "an intention to treat" analysis, considering all patients who initiated treatment as effectively treated, even though they had afterwards abandoned it (HR 0.81, 95% CI 0.78-0.84) and b) an analysis according to real treatment, where a more complex statistical model is used to consider the period of time in which a patient is effectively treated and the changes in conditions that may lead to treatment modification (OR 0.37, 95% CI 0.34-0.41). This analysis seems to be nearer to the real effect if we consider that only 8.4% of patients receiving treatment were treated with RASA during 100% of the follow-up period, 17% for more than 90% of follow-up and only 66% for more than 50% of the time. Renin-angiotensin system antagonists were associated with improved outcome independently of age, race, glomerular filtration rate, arterial pressure, serum potassium or heart failure. There was interaction with diabetes, with a

much greater effect in case this was present.

This study has the merit of answering a hitherto unresolved question. The reason for decreased mortality with RASA in the context of CKD is still unclear, but we may assume an effect on hypertrophy, remodeling, heart failure and renal function. Not having collected data on the evolution of renal function and hospitalizations limits the understanding of observed results. Matching by propensity score and use of complex analysis models are tools to overcome what appears to be the main limitation: lack of a randomized study. We must recall that in a great number of patients we do not use RASA precisely because we think that decreased renal function prevents it. Study results seem to justify a more liberal indication, without abandoning close and careful monitoring.

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