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Should antialdosterone drugs be used in heart failure with preserved ejection fraction? The TOPCAT trial

Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Clagget B, et al. Spironolactone for heart failure with preserved ejection fraction. **N Engl J Med 2014;370:1383-92. http://doi.org/sq6**

Neurohumoral antagonists decrease mortality in heart failure (HF) with reduced ejection fraction (HFREF). However, results are far from being similar in heart failure with preserved ejection fraction (HF-PEF). Different randomized studies with angiotensin II converting enzyme inhibitors and antagonists were unable to improve the outcome. The hypothesis that this result could ameliorate with an aldosterone antagonist was the aim of the TOPCAT trial.

Patients were eligible if they had at least one sign and symptom of heart failure (HF), left ventricular ejection fraction (LVEF) $\geq$ 45%, systolic blood pressure <140 mm Hg (or $\leq$ 160 mmHg in hypertensive patients treated with at least 3 drugs), and fulfilled one of the following conditions: history of hospitalization for HF within the previous year, or elevated brain natriuretic peptide (BNP) ($\geq$ 100 pg/ml) or N-terminal pro-BNP (NT-proBNP) ($\geq$ 360 pg/ml). They were randomly assigned to spironolactone (S) from an initial dose of 15 mg daily to a maximum dose of 45 mg daily, or placebo. The primary endpoint was the composite of death from cardiovascular causes, resuscitated cardiac arrest or hospitalization for HF.

A total of 3445 patients from 6 countries (123 in Argentina), with median age of 68.7 years and median LVEF of 56%, were included in the study; 71.5% because they had been hospitalized within the previous year, and 28.5% due to elevated natriuretic peptide levels. Mean S dose was 25 mg daily. In the 3.3-year follow-up interval there were no differences in the primary endpoint: 5.9 events per 100 person-years with S vs. 6.6 events per 100 person-years with placebo [HR 0.89, 95% CI 0.77-1.04; p = 0.14]. The separate analysis of each primary endpoint component showed no difference in death from cardiovascular causes (2.8% vs. 3.1%, HR 0.89, 95% CI 0.73-1.12; p = 0.35), but a significant difference in hospitalization for HF (3.8% vs. 4.6%. HR 0.83, 95% CI 0.69-0.99; p=0.04). In the subgroup analysis, over 22 planned comparisons, there were only differences according to the origin of the inclusion in the study: S did not reduce the primary endpoint of patients who entered the study due to previous hospitalization for HF (HR 1.01, 95% CI 0.84-1.21; p=0.92), but reduced events in those incorporated for elevated natriuretic peptides (HR 0.65, 95% CI 0.49-0.87; p=0.003). Similarly, the intervention appeared to be effective in patients enrolled in America, but not in Eastern Europe (almost all these patients were included due to hospitalization in the previous year). As in other studies, S administration was associated with increased hyperkalemia and reduced hypokalemia.

The TOPCAT trial confirmed what we had assumed: as HFPEF occurs mainly in elderly people who have a high rate of comorbidities, it was hardly expected that a single intervention aimed to inhibit neurohumoral activity (barely one of the involved mechanisms and seldom the most important) would significantly improve the outcome. The differences in results according to the cause of enrollment cannot be clearly explained: patients included not for previous hospitalization but for elevated BNP and NT-proBNP were in average 6 years older, with slightly worse renal function and slightly lower kalemia, but none of these criteria was in turn a predictor of improved response. Taking into account the possibility of more complications with increasing age and renal dysfunction, and considering that at best, less than one hospitalization for HF per 100 patient-years was prevented, abstaining from regularly using anti aldosterone drugs in HFPEF seems a sensible option. More exhaustive analyses with as yet unreported data would help to define if there is a subgroup of patients who could benefit from their administration.

Renal denervation therapy in patients with resistant hypertension does not achieve the expected results: the SIMPLICITY-HTN 3 trial.

Bhatt DL, Kandzari DE, O'Neill WW, D´Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. **N Engl J Med 2014;370:1393-401. http://doi.org/sq7**

It is well known that sympathetic activation is essential in the pathophysiology of hypertension (HT), especially in severe cases. Therefore, decades ago, sympathectomy was proposed as an alternative therapy for resistant cases. In recent years, renal denervation has emerged as an optional treatment, and self-controlled or nonrandomized controlled studies suggest that it is a choice in cases of resistant severe HT, as they have shown significant reduction of blood pressure.

The SIMPLICITY-HTN 3 trial selected patients with resistant severe HT (systolic blood pressure (BP) $\geq$ 160 mmHg in the office and $\geq$ 135 mmHg in the 24-hour ambulatory blood pressure monitoring) despite adequate doses of at least three drugs, one of which had to be a diuretic. Exclusion criteria were secondary HT, more than one hospitalization within the previous year, renal artery stenosis > 50%, renal artery diameter < 4 mm, a treatable segment < 20 mm in length, or renal artery aneurysm.

All patients underwent renal angiography. Radio-frequency denervation was performed in a 2:1 ratio, i.e. for every 3 patients 2 effectively underwent denervation and the other patient was a sham control. The trial was kept blinded for patients and those involved in BP follow-up. The primary efficacy endpoint was mean change at 6 months in office systolic BP with respect to control, with a superiority margin of 5 mm Hg; and the secondary endpoint was the change in mean 24-hour ambulatory systolic BP with respect to control, with a superiority margin of 2 mm Hg. The primary safety endpoint was a composite of death from any cause, a thrombotic event with target organ injury, end-stage renal failure, hypertensive crisis within 30 days, vascular complications or new renal artery stenosis > 70%.

A total of 535 patients were enrolled in the trial, with mean age 57.3 years and an average of five antihypertensive medications, four at maximum doses. At 6 months, there was no difference in the primary efficacy endpoint (a decrease of 14.1 ± 23.9 mm Hg in the active treatment group vs. a decrease of 11.7 ± 25.9 mm Hg in the control group, for a difference of only 2.4 mm Hg between both groups; p = 0.26), nor in the secondary endpoint (a decrease of 6.7 ± 15.1 mm Hg in the active treatment group vs. a decrease of 4.8 ± 17.2 mm Hg in the control group, for a difference that did not reach 2 mm Hg; p = 0.26). The rate of adverse events was low: 1.4% with active treatment and 0.6% in control.

Two types of previous studies showed a clear effect of renal denervation: a) non-randomized self-controlled studies, where the improvement could be due to regression to the mean, which is expected for repeated measures, and b) randomized controlled, but not blinded studies. This study demonstrates the importance of random intervention assignment and blinded event assessment, and questions the relevance of sympathetic activation in the pathophysiology of resistant severe HT. It points out the importance of the placebo effect, supporting the influence of the nervous system on BP. It cannot be disregarded that control patients could have adhered more strictly to medication and diet, convinced of having received an efficient noninvasive treatment. Interestingly, the intervention was inefficient in Black patients and effective in the rest (p = 0.09 for interaction), indicating that different mechanisms and treatment response may be expected in different patients. This study reduces the enthusiasm for renal denervation, and additional studies or analyses are required to know if it should be recommended, and to whom.

Elevated heart rate: a risk factor for the development of heart failure

Opdahl A, Ambale Venkatesh B, Fernandes VR, Wu CO, Nasir K, Choi EY, et al. Resting heart rate as predictor for left ventricular dysfunction and heart failure: MESA (Multi-Ethnic Study of Atherosclerosis).

Elevated resting heart rate (RHR) is associated with the incidence of cardiovascular events and cardiac and non-cardiac death. From a pathophysiological perspective, RHR is related to the prevalence of hypertension, diabetes and atherosclerosis. New evidence suggests its novel association with the incidence of heart failures (HF).

Between 2000 and 2002, the observational MESA trial incorporated 6814 multi-ethnic participants from six United States communities, free from cardiovascular disease at inclusion, and with ages ranging from 45 to 84 years. They underwent a magnetic resonance imaging (MRI) study, which was repeated in a subgroup of subjects 5 years later. The study was directed to explore the association between basal clinical and paraclinical variables with the development of atherosclerotic disease and different types of events.

This substudy highlights the effect of baseline RHR and its relationship with the incidence of clinical HF and ventricular dysfunction. Five thousand participants with technically assessable MRI were divided into quartiles according to RHR: 36-56, 57-62, 63-69 and 70-130 beats/minute, with clinical HF assessment at follow-up. In 942 participants with MRI repeated at 5 years, differences in contractility were assessed by LVEF and circumferential strain changes. Compared with participants in the lowest quartile (mean HR of 52 ± 4 beats/minute), those in the highest quartile (mean HR of 76 ± 6 beats/minute) were more frequently women and diabetic participants, with higher body mass index and diastolic blood pressure, and slightly lower LVEF and circumferential strain. In the median 7-year follow-up, 2.2% of participants developed HF. After adjusting for demographic variables, coronary disease risk factors, treatment and echocardiographic variables, HRH was an independent predictor of HF. Results showed that for 1 beat/minute increase in RHR, there was a 4% greater risk of HF (95% CI 2%-6%). Considering RHR quartiles as categories, the adjusted hazard ratio with respect to the lowest quartile was 2.62 (95% CI 1.41-4.87) for the second quartile, 2.57 (95% CI 1.36-4.89) for the third quartile and 3.76 (95% CI 2-7.07) for the highest quartile. Resting HR was an independent predictor of coronary disease or obstructive pulmonary disease and positively associated with the decrease in LVEF and circumferential stress.

It is well known that tachycardiomyopathy, in which HR is persistently elevated, generally in the context of supraventricular arrhythmia, may generate ventricular dysfunction. The present work goes a step forward: it shows that in subjects without HF, a "normal" RHR (let us remember that mean HR in the highest quartile was 76 ± 6 beats/min) increases its incidence. Elevated HR is associated with greater neurohumoral and inflammatory activation, and patholo-

gies as anemia, hyperthyroidism, respiratory disease and renal dysfunction which predispose to HF. Furthermore, elevated HR generates deleterious effects per se: increase in hemodynamic load, altered arterial geometry, increased frictional stress and myocardial O2 consumption (with higher risk of atherosclerotic disease and ischemia), in addition to extracellular matrix disruption, myocyte loss, high energy phosphate depletion and calcium mismanagement. Probably, many coexisting mechanisms explain the study findings. The multivariate analysis seems to establish a causal relationship, but it is not possible to confirm it clearly. And a question is left floating: should RHR, as other risk factors, be a therapeutic goal in primary prevention?

Coronary risk factors are associated with cognitive impairment already in midlife

Yaffe K, Vittinghoff E, Pletcher MJ, Hoang TD, Launer LJ, Whitmer R, et al. Early adult to midlife cardiovascular risk factors and cognitive function. **Circulation 2014;129:1560-7.http://doi.org/sq8**

Numerous observational studies have shown the association between coronary risk factors (CRF) in midlife and late-life cognitive impairment. But does this association occur earlier, so that greater prevalence of CRF in young subjects and greater cumulative exposure throughout the years results in worse cognitive function already in midlife?

The CARDIA trial included 5115 subjects between 18 and 30 years from four North American cities between 1985 and 1986. Blood pressure (BP), fasting blood sugar and plasma cholesterol were measured at baseline and repeated throughout the years. The expected follow-up interval was 25 years, and three cognitive tests were performed in the last visit, exploring memory, attention, psychomotor velocity and executive function.

The substudy presented here includes the 3381 subjects who completed the 25-year follow- up period, had at least two CRF measurements and completed the cognitive tests. Their mean age was 50 years and 84% had an educational level above secondary school. Mean systolic and diastolic BP, blood glucose and cholesterol were 119.7 and 74.8 mmHg, 99.5 and 192.1 mg/dl, respectively.

In the analysis adjusted by age, sex, race and education, higher cumulative systolic BP was associated with worse results in the three cognitive tests, and higher cumulative diastolic BP was negatively associated with all cognitive parameters except verbal memory. Subsequent adjustment for diabetes, smoking habit and body mass index did not change the outcome. Cumulative effects of blood glucose were also associated with worse results in the tests, but statistical significance was lost after adjustment for diabetes. In the case of cholesterol, the association was less consistent: the multivariate analysis only showed a statistically significant relationship with verbal memory.

Although in the non-adjusted analysis, exposure to the whole range of CRF was associated with cognitive impairment, after adjustment for age, sex, race and education, the association was only significant for systolic BP $\geq$ 120 mm Hg, diastolic BP $\geq$ 80 mm Hg, fasting blood glucose $\geq$ 100 mg/dl and cholesterol $\geq$ 200 mg/dl.

There are numerous mechanisms involved in CRF which may affect cognitive function: inflammation, oxidative stress, enhanced ischemia and structural brain damage (associated with greater amyloid deposition) especially at the subcortical level. The limitation of this study was lack of baseline cognition, precluding assessment of its changes with CRF. The separate effect of CRF was small, but the coexistence of two or more factors indicates, as with cardiovascular and cerebrovascular events, a group at greater risk. The greatest merit of the publication is pointing out that the impairing effect starts at an early stage, is evident already in midlife and is greater with longer exposure. This is another reason to insist in CRF prevention and control measures.

Let´s Walk! Possible association of physical activity with better prognosis in patients with impaired glucose tolerance. A NAVIGATOR substudy

Yates T, Haffner SM , Schulte PJ, Thomas L , et al. Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): a cohort analysis. **Lancet 2014, 383:1059-66. http://doi.org/qpv**

Changes in diet and increased physical activity decrease the incidence of diabetes in high-risk individuals with impaired glucose tolerance. It was not clear until now that in these patients a more intense physical activity would translate into lower cardiovascular risk. The NAVIGATOR study post hoc analysis provides evidence in this respect.

NAVIGATOR was a multicenter, randomized, placebo-controlled trial with a 2x2 factorial design, in which patients with impaired glucose tolerance, aged $\geq$ 50 years and with cardiovascular disease, or aged $\geq$ 55 years and with at least an additional risk factor, were allocated to receive nateglinide, valsartan, both or none. It included 9306 patients between 2002 and 2004, with a mean follow-up of 6 years. All patients were included in a change of lifestyle program in order to reduce weight by 5% or more and a performance of at least 150 minutes of physical activity per week. Patients were handed a pedometer to be used for 7 consecutive days to measure the number of steps taken per day at baseline and at one year. A combined endpoint of cardiovascular death, myocardial infarction, and nonfatal stroke was considered. Change in physical activity was considered as the difference between the average daily steps taken at 12 months and at the initial measurement.

Four groups were defined according to the

activity during the year: the group that decreased ≥ 1500 steps/day, the one that decreased 0-1500 steps/day, the one that increased 1-1500 steps/day and the one that increased > 1500 steps/day. The prognostic value of this change for the primary endpoint was explored, adjusting for baseline demographic, clinical and laboratory characteristics, treatment assigned in the study, additional drug treatment, baseline body mass index and its change at 12 months, changes in glomerular filtration rate and incidence of unstable angina at one year.

Since baseline ambulatory activity data were unavailable in 25% of cases and activity at 12 months in 45%, missing data were calculated by complex statistical procedures. The analysis included data from 9018 patients. In the entire cohort there was no significant change in ambulatory activity, but of course there were those within the cohort who increased, maintained or decreased their activity. Multivariate analysis showed that baseline activity already had prognostic value: the HR for the primary endpoint per each difference of 2000 additional daily steps was 0.90, (95% CI 0.84-0.96; p = 0.002); and a change in the activity representing an increase from baseline of 2000 steps/day at one year was associated with a HR of 0.92, (95% CI 0.86 to 0.99, p = 0.035). Each of the determinations had independent prognostic value.

Study results are plausible from a physiological point of view, since exercise attenuates insulin resistance and neurohormonal and inflammatory activation. It progresses in comparison to other studies by having objectified physical activity, and by the careful and fairly complete account of the patients' baseline characteristics. The limitations to consider are: a) the imputation strategy in a high proportion of cases (meaning that the number of step values are not real but predicted by complex equations based on baseline characteristics and on the evolution of each case); b) patients were not blinded to the pedometer measurements; therefore, their outcome could lead to other behavioral changes that could contribute to a better prognosis and c) because of the observational nature of the data, it cannot be completely excluded that the different evolution is at least partially due to omitted factors. While awaiting data from randomized studies, this is the best available evidence on physical activity and its relationship to prognosis in individuals with impaired glucose tolerance. Although still not definitive, for the reasons exposed, we consider it is enough for the title recommendation.

Increased body mass index and its relationship with cardiovascular and cerebrovascular events. Meta analysis of 97 studies in 1,800,000 patients.

Lu Y, Hajifathalian K , Ezzati M , Woodward M , Rimm EB , Danaei G. Metabolic Mediators of the effects of body- mass index , overweight , and obesity on coronary heart disease and stroke : a pooled analysis of 97 prospective cohorts with 1.8 million participants.

Lancet 2014, 383:970-83. http://doi.org/f2qmmj

Increased body mass index (BMI) which results in overweight (BMI between 25 and < 30) and obesity (BMI ≥ 30) is a clear risk factor for the occurrence of cardiovascular and cerebrovascular events. Much of its deleterious effects are mediated by hypertension (HT), increased cholesterol and alterations in carbohydrate metabolism. Although there are clear measures to treat HT and lower cholesterol levels, with the ability to improve vascular prognosis, this does not occur with obesity. Diets do not seem effective in the long-term, pharmacological measures generally do not have an adequate safety profile and surgery is reserved for severe cases.

This study presents an analysis of 97 prospective cohort studies conducted between 1948 and 2005 in different countries of Asia, Europe, America and Oceania, with 1,800,000 participants. They all had baseline evaluation of BMI and at least one of the risk mediators associated with it (blood pressure, cholesterol or glucose, either measured continuously or categorically) as well as coronary event and stroke assessment in at least 1 year follow-up. Subjects with BMI <20 were excluded from the study. The analysis was adjusted for age, gender, smoking habit and other additional factors according to data available in each cohort.

Median follow-up was 13.3 years, with range between 2.7 and 55.7 years. Each increase of 5 points in BMI was associated with an adjusted HR of 1.27 (1.23 -1.31) for coronary events and of 1.18 (95% CI 1.14 to 1.22) for stroke. After adjustment for HT, the HR for coronary events was 1.19 (95% CI 1.16 -1.22) and for stroke 1.06 (95% CI 1.03-1.09). Adjustment for dysglycemia produced a HR for coronary events of 1.23 (95% CI 1.19 to 1.27) and of 1.13 (95% CI 1.09 to 1.18) for stroke. Adjustment for the three mediators reduced the HR for coronary events to 1.15 (95% CI 1.12 to 1.18) and 1.04 for stroke (95% 1.01-1.08). Overweight was associated with an excess risk of 26% for coronary events and of 13% for stroke and being obese with an excess risk of 69% and 47% respectively.

Hypertension accounted for 31% of coronary risk associated to obesity, and 65% of stroke risk. The association of the three mediators explained 46% of coronary risk and 76% of stroke risk when BMI was assessed continuously. In the case of overweight, the association of the three mediators explained 50 % of coronary risk and 98% of stroke risk, and in obesity 44% of coronary risk and 69% of stroke risk. This implies that the risk per se due to increased BMI, regardless of mediators, is greater with increasing overweight.

This meta-analysis has the great merit of having considered studies conducted in different populations over almost 60 years, with a number of observations that ensures risk quantification accuracy. It allows defining the contribution of increased BMI to a poor vascular prognosis, regardless of known risk factors,

which, strictly speaking, can only be considered mediators if their occurrence is subsequent to the increase in BMI. It confirms the role of HT in the genesis of stroke, but it turns on a warning light by attributing overweight and obesity half of the possibility of coronary risk. It is clear that, considering the lack of success of many of the strategies adopted to lose weight, avoiding gaining weight and maintaining an optimum bodyweight is vital to lower cardiovascular risk.

New anticoagulants: efficacy and safety. Meta-analysis of four large randomized trials in the context of non-valvular atrial fibrillation

Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of oral anticoagulants with warfarin in new patients with atrial fibrillation: a meta- analysis of randomized trials. **Lancet 2014, 383:955-62. http://doi.org/f2qmmh**

Four new oral anticoagulants (NACO) have been compared with warfarin (W) in the context of non-valvular atrial fibrillation (AF): a direct thrombin inhibitor, dabigatran (D) in the RE-LY trial, and three inhibitors of the Xa factor: apixaban (A) in the ARISTOTLE trial, rivaroxaban (R) in the ROCKET AF trial and edoxaban (E) in the ENGAGE trial. At present, the publication of a meta-analysis of the 4 studies accurately quantifies the effect of NACO on patient outcome.

The meta-analysis considered 42411 patients with NACO and 29272 patients with W. Overall average patient age was 71.5 years and almost 38% were women without much difference between studies. Overall baseline CHADS2 score showed that 17% of patients had a 0-1 value, but while in the RE-LY and ARISTOTLE trials the percentage of patients varied between 31% and 34 % according to the arm, it was 0 % in the ROCKET trial and <1% in ENGAGE trial. The median time in therapeutic range (TTR) for patients of the W arm was 65%, but in the ROCKET trial it was 58 %, ranging between 66% and 68% in the other three studies.

As known, 2 daily doses of D were assessed in the RE-LY trial: 150 mg and 110 mg every 12 hours; and in the ENGAGE trial two schemes were also considered: 60 mg or 30 mg of E daily. The other 2 studies tested a single dose of the respective NACO. To avoid mixing the effects of high and low doses, 2 analyses were performed: both considered the single doses of A and R compared to W; also, in one analysis, high doses of D and E were considered and in the other the low doses.

a) Analysis of A and R and high doses of D and E: NACO compared with W decreased the primary endpoint of stroke and systemic embolism: RR 0.81 (95% CI 0.73-0.91; p < 0.0001). This was achieved at the expense of hemorrhagic stroke (RR 0.49, 95% CI 0.38 -0.64; p < 0.0001) with no reduction in ischemic stroke. Reduced total mortality (RR 0.90, 95%

CI 0.85-0.95; p = 0.0003 and intracranial hemorrhage (RR 0.48, 95% CI 0.39 to 59; p < 0.0001) were shown. There was no heterogeneity for these outcomes between individual studies. Increased gastrointestinal bleeding was verified(RR 1.25, 95% CI 1.01 to 1.55; p = 0.043), but at the same time there was a tendency to decrease total bleeding (RR 0.86, 95% CI 0.73-1.00; p = 0.06), with strong heterogeneity between studies: patent reduction with A and E, and lack of effect with D and R.

There was no significant difference in the effectiveness of NACO compared with W according to age dichotomized in 75 years, gender, renal function and CHADS2 score or that TTR in those treated with W was < 66% or ≥ 66. This last condition did influence the reduction of bleeding, significant in those centers in which TTR was < 66%, and not in those with a higher value.

b) Analysis of A and R, and low doses of D and E: NACO compared with W did not reduce the primary endpoint of stroke and systemic embolism: (RR 1.03, 95% CI 0.84 -1, 27; p = 0.74). There was a reduction of hemorrhagic stroke (RR 0.33, 95% CI 0.23 -0.46; p < 0.0001), but increased risk of ischemic stroke (RR 1.28, 95% CI 1.02 -1.60; p = 0.045) and acute myocardial infarction (RR 1.25, 95% CI 1.04 -1.50; p = 0.019). Reduction in total mortality (RR 0.89, 95% CI 0.83 -0.96; p = 0.003) and intracranial hemorrhage (RR 0.31, 95% CI 0.24 -0.41; p <0.0001) was verified. No increase in gastrointestinal bleeding was observed and there was a strong tendency to reduction of total bleeding, (RR 0.65, 95% CI 0, 43-1.00; p = 0.05).

Sensitivity analyses considering only Xa factor inhibitors yielded similar results.

This meta- analysis confirms findings outlined in the individual studies, and offers some novel results. Although it was the secondary endpoint of the study, both high and low doses of D and E together with single doses of A and R, reduced total mortality by approximately 10%. It indicates that the main effect of NACO compared with W is to reduce risk of hemorrhagic stroke by half and by a third considering in the analysis high and low doses of D and E, respectively. However, they are no better than W to reduce ischemic stroke, and even when considering the low doses of D and E, they may increase its incidence and also that of myocardial infarction. A vital chapter is security: beyond the increase in gastrointestinal bleeding when the high doses of D and E are taken into account, there is a strong tendency to reduce total bleeding. Age and renal function do not appear to limit NACO effectiveness. Therefore the use of A, R and high doses of D or E may be considered, preserving low doses of D or E for those patients in whom high risk of bleeding is presumed.

Elevated troponin T indicates worse prognosis in patients with peripheral vascular disease

Linnemann B , Sutter T, Herrmann E , Sixt S , Rastan

A, Schwarzwaelder U, et al. Elevated cardiac troponin T is associated with higher mortality and amputation rates in patients with peripheral arterial disease. **J Am CollCardiol 2014; 63:1529-38. http://doi.org/ f2rdp9**

Elevated troponin T (ETnT) indicates worse prognosis in different clinical settings (acute coronary syndrome, acute and chronic heart failure, and pulmonary embolism, among others), and also in the general population. The present publication highlights its importance in the context of symptomatic peripheral vascular disease (SPVD).

This is a retrospective study of patients during 2007 admitted to a single center in Germany for urgent or elective peripheral endovascular revascularization. Those with medical conditions or procedures that had caused increased troponin T (TnT) in the previous 14 days were excluded. Fourth generation TnT was measured at admission and ETnT was defined as a value > 0.01 ng / ml. A 12-month follow-up was performed. The primary endpoint was death or amputation.

The study comprised 1041 selected patients with mean age of 70.7 ± 10.8 years; 62.7% were men. Elevated TnT was detected in 21.3% of patients, who were older, male, diabetic and with worse renal function than the rest of the patients. In patients with ETnT, SPVD was more severe with more distal involvement; 75.7 % of them had critical limb ischemia versus 30.5 % in patients with normal TnT.

At 1-year follow-up, mortality was 31.7% with ETnT versus 3.9% with normal TnT, (unadjusted HR of 9.87, 95% CI 6.49 -5; p < 0.001). Adjusting for age, renal function, smoking habit, diabetes, critical limb ischemia and excluding patients with electrocardiographic changes suggestive of ischemia, the HR was 8.14 (95% CI 3.77-7.6; p < 0.001). Interestingly, in patients with ETnT the amputation rate per year was also higher: 10.1% vs. 2.4%, (unadjusted HR of 4.92, 95% CI 2.68 -9.03; p < 0.001). After adjusting for the variables mentioned above, except ECG, the correlation with the risk for amputation evidenced only a trend (HR 1.86, 95% CI 0.92 -3.74, p = 0.08), but after further adjustment for ECG changes, statistical significance was recovered, with HR 3.71, 95% CI 1.33-10.3, p = 0.012).

Given the strong association of coronary disease with PVD, the first explanation would be enhanced inflammation and apoptosis, silent ischemia and occlusion of small coronary vessels in patients with more PVD and thus, higher prevalence of ETnT. We might assume that in more serious SPVD (with increased risk of amputation) there is more myocardial injury (expressed by ETnT), and hence higher mortality. A further possible explanation in some cases is that in some skeletal myopathy or rhabdomyolysis TnT of muscular origin may be released into the bloodstream; in this case, ETnT might express severe muscle damage due to PVD, justifying the increased amputation risk. The retrospective, single-center character of the study somewhat reduces the strength of these findings; 95% CIs are wide, decreasing estimation accuracy. Nevertheless, there is a message that should not be ignored: there is more interaction between the coronary arteries and the arteries of the lower limbs than we think.