

JORGE THIERER <sup>MTSAC</sup>**Cardiovascular rehabilitation programs: Less benefit than expected? A meta-analysis**

Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane Systematic Review and Meta-Analysis. **J Am Coll Cardiol** 2016;**67**:1-12. <http://doi.org/bdxz>

Cardiovascular rehabilitation (CR) is a Class I indication for coronary patients according to the practice guidelines of the main cardiology societies of the world. The intervention has physical activity as its cornerstone, but it also includes advice on lifestyle and risk factor modifications, and psychosocial support. The first meta-analyses of its use were published over 20 years ago and consistently showed decreased mortality. But some objections can be made: many studies were small or of poor methodological quality, the vast majority were post-acute myocardial infarction (AMI) patients, so other forms or manifestations of coronary artery disease were under-represented, and finally, it is true that the pharmacological and non-pharmacological treatment has progressed so much in recent decades that it may be wondered whether CR maintains its ability to improve prognosis.

The present meta-analysis tried to salvage these criticisms. It included all randomized studies published from 1970 to mid-2014 in which a CR strategy based on exercise (supervised or not, in outpatients or inpatients, at the hospital, institutional or home setting), with or without educational or psychosocial associated intervention, was compared with a strategy that could involve regular treatment or interventions, as long as exercise was not included. A minimum of 6-month follow-up was established, and at least one of the following endpoints in the evolution of patients had to be reported: all-cause or cardiovascular mortality, need for revascularization, AMI, hospitalization, quality of life or costs.

Sixty-three studies involving 14,486 patients were included. Median age was 56 years and less than 15% were women. In almost half of the studies only post-AMI patients were included; in the rest, the population was more varied, including post-revascularization or stable angina patients. In 24 studies, CR consisted only of exercise and in the rest there were other associated interventions. Exercise was generally aerobic, the weekly frequency ranged from 1 to

7 times and the duration of each session between 20 and 90 minutes. Median duration of the program was 6 months and median follow-up 12 months.

In 47 studies reporting all-cause mortality (n=12,455), this showed no difference with CR: RR 0.96, 95% CI 0.88-1.04. In 27 studies (n=7,469) reporting cardiovascular mortality, proven benefit was found for CR: RR 0.74, 95% CI 0.64-0.86. Cardiovascular rehabilitation was not associated with reduced risk of AMI or need for revascularization, but was associated with reduced hospitalization (15 studies, 3,030 patients, RR 0.82, 95% CI 0.70-0.96). A stratified analysis failed to show difference in the results according to type of patient, pathology, type of intervention, duration or total dose of exercise administered. In the majority of the 20 studies reporting quality of life there was an improvement in some of the scales measuring it, but due to the heterogeneity of the instruments used a formal meta-analysis was not possible. Cost data were dissimilar.

*The results of this meta-analysis suggest cardiovascular mortality and hospitalization reduction. A decrease in all-cause mortality or revascularization procedures is not revealed. This leads us to consider that the mechanisms at play perhaps do not specifically involve the coronary anatomy and function. It should be noted that in general the reporting quality of the study data was not good, and that a median follow-up of 12 months may be scarce to notice effect on all-cause mortality. It is also true that the inclusion of more recent studies, including a population with less impaired ventricular function, better medical treatment and more successful interventions may have contributed to dilute the beneficial effect of exercise on hard points. It is regrettable that we do not have a more complete analysis regarding the influence on quality of life. The different results in cost issues could lead us to focus efforts in more complex programs, with greater supervision and institutional participation in higher risk patients.*

**Atrial fibrillation has a more detrimental effect on women**

Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. **BMJ** 2016;**532**:h7013. <http://doi.org/bdx2>

Atrial fibrillation (AF) is a predictor of stroke and mortality in men and women. We know that some risk factors exert a different influence according to gender: thus, for example, diabetes is a stronger predictor of stroke and coronary heart disease in women. In the case of AF, the information is contradictory. Let us recall that the CHA<sub>2</sub>DS<sub>2</sub>-VASc score in the female gender implies an additional risk of stroke, but this could be due to the fact that in the general population, independently of AF, the pattern of covariates as predictor of stroke is different in men and women. The authors of this report conducted a meta-analysis of observational cohort studies in which there were men and women, a minimum of 50 individuals with AF and 50 without AF, and a minimum 6-month follow-up. The objective was to define whether AF involves more risk of any of these events in women. Only studies reporting the incidence of events (all-cause or cardiovascular mortality, fatal and nonfatal stroke, myocardial infarction, heart failure, peripheral vascular or renal disease) by gender and presence or absence of AF were included, adjusting for age (women were older in all series) and baseline presence of cardiovascular disease. Postoperative AF was excluded and there were no language restrictions.

Thirty studies with 4,371,714 participants were included, 1.5% of whom had AF. The presence of AF involved increased risk of events in men and women regarding sinus rhythm, but this was relatively higher in women than men: a) all-cause mortality: RR 1.12, 95% CI 1.07-1.17; b) cardiovascular mortality: RR 1.93, 95% CI 1.44-2.60; c) stroke: RR 1.99, 95% CI 1.46-2.71; and d) heart failure: RR 1.16, 95% CI 1.07-1.27. In terms of events per 1,000 patients per year, the presence of AF in women vs. men meant an excess of 1.8 deaths, 3.1 strokes and 6.1 heart failures, in all cases with statistical significance.

*Although AF is a universal predictor of poor outcome, in this meta-analysis it appears clearly linked to higher risk in women than in men. Why? Several theories can be put forward. Probably women receive less anticoagulant treatment: this has been confirmed in some cohorts, but not in others. It is likely that the electrical response to antiarrhythmic therapy is different in them, with increased risk of serious arrhythmias. Perhaps adjusting for baseline cardiovascular disease has not been adequate due to disease underreporting in women. Finally, residual confounding, the Achilles heel of observational studies, should not be ruled out: i.e. factors not considered, associated to gender regardless of AF, are truly responsible for the differences found. In conclusion, we cannot establish with certainty the reason of excess risk of AF in women; however, we can see a call for an intensive search of hazardous conditions and*

*a treatment that should meet the highest standards.*

### **Renin-angiotensin system inhibition in diabetic hypertensive patients: no longer imperative for all?**

Bangalore S, Fakhri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. **BMJ** 2016;352:i438. <http://doi.org/bdx3>

Diabetes is associated to greater prevalence of hypertension and activation of the renin-angiotensin system. Large randomized studies, as HOPE and EUROPA, in which ramipril and perindopril, respectively, were compared with placebo showed the beneficial effect of renin-angiotensin system antagonists (RASA) in diabetic patients, beyond the decrease in blood pressure. However, some doubts have emerged. Should RASA be preferred to other families of anti-hypertensive drugs in all diabetics, or is the benefit effective in those with microalbuminuria or proteinuria? Thus, while some practice guidelines consider RASA as the drugs of choice in diabetic patients, others claim that any antihypertensive agent can be used.

Bangalore et al. performed a meta-analysis of randomized studies (at least 100 patients with at least 1 year follow-up) in which RASA were compared with other antihypertensive agents in diabetics or patients with abnormal fasting glucose. They excluded heart failure studies, those comparing RASA with placebo, or in which angiotensin-converting enzyme inhibitors (ACEI) were compared with angiotensin II receptor blockers (ARBs). Endpoints were all-cause mortality, cardiovascular mortality and each of the usual cardiovascular events, separately.

Nineteen studies were selected with a total of 25,4141 diabetic patients and mean follow-up of 3.8 years. Most studies compared RASA with calcium blockers, only 3 with diuretics and 2 with beta-blockers. Seventeen studies enrolled hypertensive patients, and the other two, normotensive patients. In 14 studies, the RASA used was an ACEI. Compared with other agents, RASA did not reduce the incidence of all-cause and cardiovascular mortality, stroke, myocardial infarction or end-stage renal failure. Renin-angiotensin system antagonists were only superior to calcium blockers in terms of reduction in heart failure incidence: RR 0.78, 95% CI 0.70-0.88.

*The preferential indication of RASA in diabetic hypertensive patients is supported by: a) initial small studies in patients with microalbuminuria in whom there was evidence of greater renoprotective effect, with significant reduction in the incidence of proteinuria and renal dysfunction, and b) larger*

*dimension studies with clinical endpoints, in which they were compared with placebo. But it is true that placebo is not a hypertension treatment, and not all diabetics have microalbuminuria or kidney disease. Some studies in which RASA were compared with other drugs (for example, the IDNT study comparing irbesartan with amlodipine) evidenced reduction of renal dysfunction worsening, considered as double creatinine levels, but not of hard endpoints. This meta-analysis, which included patients free from renal involvement, questions the preference of RASA over other type of drugs in all diabetic hypertensive patients. We do not know if this will be the final recommendation (it is, for example, what the European Societies of Cardiology and Hypertension sustain), but the truth is that something we regarded as an unquestionable truth is again put into question. It is not the first time that Bangalore publishes a meta-analysis with disruptive data (let us remember his findings on the lack of betablocker efficacy in the treatment of hypertension, with increased diabetes risk). In the case of diabetic patients with incipient or marked renal involvement, RASA seem, at least for now, to preserve their place.*

### **Statins used before non-cardiac surgery reduce perioperative cardiovascular events**

Berwanger O, Le Manach Y, Suzumura EA, Biccarrd B, Srinathan SK, Szczeklik W, et al. Association between pre-operative statin use and major cardiovascular complications among patients undergoing non-cardiac surgery: the VISION study. **Eur Heart J** 2016;37:177-85. <http://doi.org/bdx4>

Approximately 5% of the 200 million patients subjected annually to non-cardiac surgery present a cardiovascular complication during the first 30 days after surgery. There are no universally accepted measures to reduce this risk. Some small observational studies suggest that use of statins in the pre-operative period might be useful in this sense. The VISION study was an observational, prospective cohort study conducted in the 5 continents, including over 40,000 patients of at least 45 years of age undergoing non-cardiac surgery, to define perioperative outcome and associated prognostic variables. Fourth generation troponin T (TnT) was assessed in the first 16,081 patients, with a cut-off value  $\geq 0.03$  ng/ml to establish myocardial injury (MI). Among them, 15,478 patients with analyzable data are the basis of this study.

Its main purpose was to evaluate the effect of preoperative use of statins (at some point during the 7 days prior to surgery) on the primary composite endpoint of all-cause mortality, myocardial injury (with two TnT measurements at 6-12 h and 3 days

after surgery, excluding cases in which a non-cardiac increase was assumed) and stroke at 30 days. Secondary endpoints were each of the primary endpoint components, sepsis and pneumonia.

Among the included patients, 24.3% received statins before surgery. As expected, patients treated with statins differed from untreated ones: they were older, with greater prevalence of risk factors, history of coronary heart disease and heart failure, and with concomitant treatment, including aspirin, betablockers, renin-angiotensin system antagonists (RASA) and calcium blockers. Therefore, to isolate the effect of statins, a propensity score for the use of statins was built, defining by logistic regression the variables significantly associated to the prescription of these drugs. Thus, each patient had a specific score, whether treated or not with statins. Subsequently, treated and untreated patients were matched by similar propensity score, in 1 treated vs. 1 or 2 untreated ratio. Two groups were defined, with similar propensity score to receive treatment; one of the groups was effectively treated (n=2,845) and the other not (n=4,492). Use of propensity score tries to reproduce a randomized study, assuming that those who receive or not treatment initially have the same probability of being assigned to one or the other group. Nonetheless, patients of the treated group had higher burden of coronary heart disease, diabetes and peripheral vascular disease, as well as more treatment with aspirin and RASA.

Use of preoperative statins appeared associated with lower incidence of the primary endpoint (RR 0.83, 95% CI 0.73-0.95, with absolute 2% reduction), all-cause mortality (RR 0.58, 95% CI 0.40-0.83), cardiovascular mortality (RR 0.42, 95% CI 0.23-0.76), myocardial injury (RR 0.86, 95% CI 0.73-0.98), sepsis and pneumonia. The effect was significantly higher in diabetic than in non-diabetic patients.

*This is an observational study. As in any such study, there is the possibility of bias. It is clear that patients who for some reason receive statins have a different profile than those who do not receive them: more risk factors and history of cardiovascular diseases. We should therefore assume in them greater risk of an ischemic event in a stressful situation, such as surgery. Use of a propensity score tries to overcome this marked initial disparity to establish a "fairer" comparison with untreated patients. It should be noticed that despite all the efforts differences persisted in the population matched by this score, with greater cardiovascular burden in treated patients. What is remarkable is that despite these differences, statins appeared as protective agents: those not treated with statins had more events. Why? One possibility is residual confounding. Despite matching, there may be factors associated to the outcome that were not con-*

sidered. That is the difference between random assignment (both known and unknown characteristics are equally distributed) and adjusting only by known variables. But, attempting to understand results, we can ask ourselves other questions: Were there among the untreated group patients with statin indication who were not receiving them for intolerance, ignorance or error, and it was in them where the worse outcome was concentrated? Or the incidence of ischemic events in a stressful situation is unpredictable and we can think in a universal recommendation of statins in the preoperative period of non-cardiac surgery? A patient at risk should already be treated, regardless of whether or not he is going to be operated. A randomized study in patients without primary indication of statins will contribute to clarify this point.

### **Atrial fibrillation and heart failure: temporal association and reciprocal influence. An analysis of the Framingham registry.**

Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, et al. Atrial Fibrillation Begets Heart Failure and Vice Versa: Temporal Associations and Differences in Preserved Versus Reduced Ejection Fraction. *Circulation* 2016;133:484-92. <http://doi.org/bdx5>

Atrial fibrillation (AF) and heart failure (HF) have a series of common features. Their incidence and prevalence increase with each decade of life, both are strong predictors of hard events and frequent cause of hospitalization, and threaten to become an epidemic in a relatively near future.

But, in addition, it is worth pointing out that their evolution does not correspond to unrelated phenomena. On the contrary, they are concurrent in an important number of patients, and each has been described as a comorbidity of the other. If so, what is the temporal relationship between AF and HF? Which precedes which, and what is their individual role in the prognosis of the other entity? Researchers of the Framingham registry had already published some information in this regard, but a new report contributes to provide more precision and strengthen some impressions.

As we recall, the Framingham registry consisted of an original cohort, with individuals included in the 1940-1949 decade (n=5,209), and a cohort of its descendants recruited at the beginning of the 70s. (n=5,124). The present analysis included patients with incident AF or HF (new cases) between 1980 and 2012.

In that period, 1,166 patients developed HF, 44% with reduced ejection fraction (REF <45%), 41% with preserved EF (PEF ≥45%), and in the rest EF

was not classified. Thirty-eight percent of patients did not develop AF, either before or after HF, 32% had AF before developing HF, in 18% AF and HF were concurrent (AF within 30 days of HF diagnosis) and in 12% AF was diagnosed more than a month after HF occurrence. Atrial fibrillation was more prevalent in patients with HFPEF than in those with HFREF (32% vs. 23%), as well as presenting AF at some stage of HF evolution (62% vs. 55%). The annual incidence of HF was significantly higher in patients with prevalent AF compared with those without AF (3.14% vs. 0.48%). After adjusting for age, sex, coronary risk factors and history of cardiovascular disease, prevalent AF was predictor of HFPEF (HR 2.3, 95% CI 1.5-3.7) but not of HFREF (HR 1.3, 95% CI 0.8-2.1). Conversely, AF not present at the onset of HF but incident at some stage of evolution was predictor of HFREF and not of HFPEF. Also in multivariate analysis, and compared with the absence of AF during all the follow-up period, prevalent and incident AF were independent predictors of greater mortality in patients with new-onset HF. When patients with HFPEF and HFREF were considered separately, the worse prognosis was observed in patients with incident AF, but not in those with prevalent AF.

In the same period 1,737 patients developed AF. Most of them, around 63%, did not present HF either before or after developing AF, 8% had previous HF, in 12% AF and HF were concurrent and in 17% HF was diagnosed more than a month after the occurrence of AF (half of them with HFPEF). The annual incidence of AF was significantly higher in patients with prevalent HF compared with those without HF (4.78% vs. 0.79%). After adjusting for age, sex, coronary risk factors and history of cardiovascular disease, both prevalent and incident HF doubled the risk of new-onset AF. Also in multivariate analysis, and compared with the absence of HF during all the follow-up period, prevalent HFPEF (HR 1.8, 95% CI 1.4-2.4) and HFREF (HR 2.7, 95% CI 2.1-3.5) were independent predictors of higher mortality in patients with new-onset AF. In the case of incident HFPEF and HFREF, their association with higher mortality in patients with new-onset AF was similar (HR 2.3 in both cases).

*As can be seen, these data reveal strong association between AF and HF. More than 60% of patients with HF develop AF at some stage of the progression, in most cases before. Almost 40% of patients who develop AF have HF at some point, more frequently after. This temporal sequence, in which it is more frequent for AF to precede HF (due to remodeling and loss of atrial contraction with decreased cardiac output, caused by tachycardiomyopathy with irregular RR intervals, among other phenomena) reveals the*

*importance of adopting measures to prevent the latter in patients with AF. Each of the pathologies casts a shadow on the prognosis of the other. Atrial fibrillation and HF are intimately linked. They respond to common causes, feed and stimulate each other. To approach the treatment of one forgetting the other can only lead to failure. Undoubtedly, progress in the genetic understanding of both pathologies will demonstrate that the link between them is even greater than we assume.*

### **A meta-analysis reveals the benefit of achieving a more pronounced decrease of blood pressure in high risk patients**

Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. **Lancet** 2016;387:435-43. <http://doi.org/bdx6>

The last hypertension (HTN) treatment guidelines consider an index BP of 140/90 mmHg for patients suffering from diabetes, coronary heart disease, and with history of cerebrovascular or renal disease. However, approximately half of cardiovascular events in this group, which is the one at highest risk, occur in patients with blood pressure values below the ones mentioned. Therefore, is more intensive treatment of HTN justified?

The present meta-analysis included (in a systematic review of the literature since 1950) randomized studies of antihypertensive treatment in which 2BP or pressure decrease objectives were compared between an intensively treated group (IT) and another with less intensive treatment. Follow-up had to be at least 6 months. Nineteen studies were defined, with 44,989 patients and mean follow-up of 3.8 years. Two studies were in diabetic patients without HTN, and the remaining 17 included hypertensive patients mostly with diabetes, cardiovascular or renal disease. Average BP at study initiation was 159/92 mmHg. In most early studies, index BP in the IT group was 140-150/85-90 mmHg. In more recent studies, index systolic BP was 20-30 mmHg lower. At the end of follow-up, average BP attained was 140/81 mmHg with the less intensive treatment and 133/76 mmHg with IT.

Intensive treatment was associated with a decrease in the composite endpoint of cardiovascular death, stroke, acute myocardial infarction (AMI) or heart failure (HF), with RR 0.76, 95% Ci 0.78-0.96. There was also reduction of AMI (RR 0.87, 95% CI 0.76-1), stroke (RR 0.78, 95% CI 0.68-0.90), progression of albuminuria and retinopathy. No decrease was observed in the incidence of end-stage renal disease, HF, all-cause or cardiovascular mortality.

There was no difference according to mean baseline BP, or BP attained in the control group. The absolute reduction of events was greater in studies with higher baseline risk. Thus, in studies in which all patients had vascular or renal disease, or were diabetic, the annual rate of major events was 2.9% and the necessary-to-treat number of cases to avoid an event was 94; in the remaining studies, the annual rate of major events was 0.9% and the necessary-to-treat number to avoid an event was 186. Although there was no difference in the general incidence of adverse events, IT was associated with excess severe hypotension (annual 0.3% vs. 0.1%).

*This meta-analysis shows the advantage of not being satisfied with BP values around 140/90 mmHg, even when the population considered has target organ injury. The idea that lower values can be associated to severe adverse events might be due to a reverse causality phenomenon (sicker patients, with higher incidence of events, have lower BP, and it is not a lower BP the cause of that adverse outcome). The fact of having worked with summary study data, and not individual data, prevents having more precision on the underlying disease and the results achieved. In the previous issue of the Journal we presented the results of the SPRINT study. Let us recall that this study excluded diabetic patients or with previous stroke, that do take part in the meta-analysis. Moreover, mean systolic BP attained in the IT group of that study (121 mmHg) was clearly lower than the one reached with IT in this meta-analysis (133 mmHg). Patients with less comorbidities and a lower achieved BP may explain why the SPRINT study evidenced decreased HF, cardiovascular and all-cause mortality, and this meta-analysis did not.*

### **Elevated resting heart rate predicts the development of hypertension**

Aladin AI, Al Rifai M, Rasool SH, Keteyian SJ, Brawner CA, Michos ED, et al. The Association of Resting Heart Rate and Incident Hypertension: The Henry Ford Hospital Exercise Testing (FIT) Project. **Am J Hypertens** 2016;29:251-7. <http://doi.org/bdx7>

Different studies have associated elevated resting heart rate (ERHR) to worse prognosis in healthy persons or with cardiovascular disease. Thus, ERHR has been related to higher risk of coronary events, heart failure and mortality. The mechanisms involved are manifold. Elevated resting heart rate can be assumed as the expression of greater neurohumoral and inflammatory activation, anemia or other metabolic disorders (in which case it is an epiphenomenon) or as its ability to generate greater vascular endothelial friction stress and risk of plaque

rupture, as well as ventricular dysfunction. A new association seems to be confirmed in the study presented here: the role of ERHR as predictor of hypertension (HTN) prevalence.

This is a retrospective cohort study carried out in Michigan, considering non-hypertensive patients with sinus rhythm who underwent an exercise test between 1991 and 2009. Baseline HR was assessed at exercise testing onset, and patients were divided into 3 groups according to its value: <70, 70-85 and > 85 beats/minute. The latter group was considered as ERHR. A total of 21,873 patients were included in the study, 14.7% of whom presented ERHR. Compared with the rest, patients with ERHR were somewhat younger, with greater prevalence of women and diabetes, and slightly higher systolic and diastolic blood pressure (BP). In the exercise stress test, they exhibited lower capacity.

Median follow-up was 4.4 years. The annual HTN incidence (BP >140/90 mmHg) was 6.3%, 7% and 8.1% for groups with HR <70, 70-85 and >85 beats/minute, respectively. After adjusting for age, sex, race, coronary risk factors, initial systolic and diastolic BP and exercise capacity in the stress test, the ERHR group presented 15% excess risk of developing HTN (95% CI 8-23%) compared with those who had baseline HR <70 beats/minute. Each 10 beat/minute increase in the initial HR was associated to 4% increase in the incidence of HTN. Age behaved as effect modifier: the higher risk of presenting HTN associated to ERHR was present in patients younger than 60 years, and not in older ones.

*The evidence of this retrospective study adds HTN to the unwanted consequences of ERHR. Is HTN secondary to ERHR? This can be suspected understanding that it generates increased vascular stiffness due to endothelial and smooth muscle injury. Moreover, tachycardia and HTN may be the expression of the same underlying phenomenon: the activation of the sympathetic nervous system. In fact, hypertension, diabetes and vascular injury are conditions behind which the shadow of neurohumoral activation is presumed. Hypertension may be an intermediate step in the pathway leading from ERHR to infarction, heart failure and death. That the relationship between ERHR and HTN is evident in persons below 60 years and not in older ones perhaps expresses that the mechanisms responsible for generating HTN vary according to the stage in life, with greater influence of sympathetic tone in younger individuals and vascular stiffness in older ones. It is true that being a retrospective cohort study lessens the robustness of the conclusions, but the agreement with other studies, the biological possibility and the number of observations turn these conclusions worthy of consideration. For all this, ERHR should not be dismissed*

*in the evaluation of our patients' condition.*

### **Uric acid is not a causal factor of cardiovascular disease: a Mendelian randomization study**

Keenan T, Zhao W, Rasheed A, Ho WK, Malik R, Felix JF, et al. Causal Assessment of Serum Urate Levels in Cardiometabolic Diseases Through a Mendelian Randomization Study. **J Am Coll Cardiol** 2016;**67**:407-16. <http://doi.org/bdx8>

Different epidemiological studies have shown increased risk of cardiovascular events in patients with hyperuricemia: up to 25% for diabetes, 6% for coronary heart disease, 17% for ischemic stroke and 19% for heart failure. It is often thought that uric acid has a causal role in the emergence of these pathologies, and that lowering its levels should translate in their reduction. Mendelian randomization studies are based on the randomized distribution of genetic material during meiosis. Some alleles are specifically and selectively associated with a biomarker. In turn, if this biomarker is specifically associated with a disease, there should be statistical association between it and the presence of specific genetic material. The authors of this study based their analysis on this assumption to define the association of uric acid with cardiovascular disease.

They worked with genetic material from different databases with tens of thousands participants, gout cases and controls and different cardiovascular diseases. They defined 28 single nucleotide polymorphisms (SNP) associated with uric acid, and evaluated their association with 50 risk factors and vascular and non-vascular features. This allowed them to discard 14 SNP presenting pleiotropism, i.e. they are statistically related not only with uricemia but with other characteristics or biological markers, and with the 14 "pure" SNP they developed a genetic score. Elevated values of the uric acid genetic score should relate to hyperuricemia, and this can define the risk that elevated uric acid is associated to higher cardiovascular risk.

As result of their investigation the authors confirmed the association between elevated values of the genetic score with hyperuricemia. A genetic score related to an increase of one standard deviation in uric acid levels was associated to gout with OR 5.8 (highly significant), but presented OR around 1 for diabetes, coronary heart disease, heart failure and stroke. And this result was obtained despite having demonstrated the association between hyperuricemia and these pathologies in the study population.

High uric acid levels are related to cardiovascular disease. However, hyperuricemia does not seem to be its causal factor. If this were so, patients would have increase in the genetic condition that shapes

the elevation in uric acid levels. It is possible that the associations evidenced in epidemiological studies are due to residual confounding (not considered factors associated with the cardiovascular disease and the increase in uricemia) or to reverse causality: it is not the elevated uric acid what causes the cardiovascular pathology but the other way round. In fact, for example, the increase in insulin resistance is a factor associated to hyperuricemia.

*Mendelian randomization studies appear as a transcendent resource to support or discard patho-*

*physiological hypotheses and justify or not therapeutic studies. There are limitations: they are not simple to perform, they require adequate technology, resources and thousands of observations. As everything in medicine, their conclusions may not be definitive: new findings of genetic associations could change the risk scores generated. The knowledge they provide (is it justified, as for example, in this case, to postulate a large randomized study with allopurinol in view of the data presented?) validates the enthusiasm they generate.*