

JORGE THIERER ^{MTSAC}

Physical activity and anger or emotional upset are triggers of acute myocardial infarction. The INTERHEART study

Smyth A, O'Donnell M, Lamelas P, Teo K, Rangarajan S, Yusuf S. Physical activity and anger or emotional upset as triggers of acute myocardial infarction: The INTERHEART Study. *Circulation* 2016;134:1059-67. <http://doi.org/bwxw>

Physical exertion, anger, and emotional upset have been reported as triggers of acute myocardial infarction (AMI) in publications with small sample sizes and completed primarily in one country or geographical region. The INTERHEART study, published in 2004, was a case-control study that explored the determinants of a first AMI in 15,152 cases and 14,820 controls in 262 centers across 52 countries. A recently published sub-analysis confirms both triggers as independent predictors.

A total of 12,461 cases with AMI were considered in the primary analysis. The participants were interrogated if they had been engaged in heavy physical exertion and if they had been angry or emotionally upset during the hour before the onset of symptoms (case period) and at the same hour on the previous day (control period). In this way, each patient acted as his/her own control. The results were adjusted for age, sex, diabetes, hypertension, smoking habits, angina, stroke and the INTERHEART risk score, which defines the risk of cardiovascular events. For the analysis of the influence of physical exertion, baseline level of physical activity was considered. For the analysis of emotional upset, chronic stress, depression, and level of education were also considered.

Physical exertion was reported by 13.6% of participants during the hour before the onset of symptoms and 9.1% at the same hour on the previous day. The adjusted OR of AMI associated with physical exertion was 2.31 (99% CI, 1.96–2.72). There was no significant difference in the presence of traditional risk factors between those who were and those who were not engaged in heavy physical activity, and there was no interaction between intense physical activity and any of the confounding variables mentioned.

Anger or emotional upset was reported by 14.4% of participants during the hour before the onset of symptoms and 9.9% during the same hour on the previous day. The adjusted OR of AMI associated with anger or emotional upset was 2.44 (99% CI, 2.06–2.89). There was no significant difference in the presence of traditional risk factors between those who felt anger or were emotionally upset and those who were not, and there was no interaction with any of the confounding

variables mentioned.

The presence of both triggers (physical exertion and emotional upset) was associated with an adjusted OR of 3.05 (99% CI, 2.29–4.07). There was no effect modification by geographical region or previous treatment with the usual cardiovascular medication for either trigger.

In a traditional case-control analysis, and considering all the participants of the INTERHEART study, (cases with data of the hour before the onset of symptoms and controls with data of the last 24 hours before inclusion), the adjusted OR of AMI associated with physical exertion was 3.08 and the adjusted OR associated with anger or emotional upset was 2.41.

This publication confirms that in a large and widely distributed population, both triggers evaluated (reported by 1 in 7 cases) are independent predictors of AMI. The underlying mechanisms of these triggers may be neurohumoral activation, vasoconstriction, increased heart rate and endothelial dysfunction. In any case, these pathophysiological consequences cannot be inferred from these data. The information presented is not an argument against physical activity, but a signal to prevent heavy physical exertion. As in any case-control study, the main limitation of this study is inherent to the presence of design biases, particularly recall bias: although only cases were considered in the main analysis, participants could have a different perception of what happened in the hour before AMI compared with the previous day.

Lone atrial fibrillation: an expression of heart disease?

Wijesurendra RS, Liu A, Eichhorn C, Ariga R, Levelt E, Clarke WT, et al. Lone atrial fibrillation is associated with impaired left ventricular energetics that persists despite successful catheter ablation. *Circulation* 2016;134:1068-81. <http://doi.org/bwxx>

Traditionally, atrial fibrillation (AF) is associated with the presence of risk factors or structural cardiomyopathy, and is a predictor of embolic events, AMI and death. The association with heart failure is bidirectional. Atrial fibrillation generates ventricular dysfunction by different mechanisms (irregularity of the RR intervals, loss of the atrial kick, increased neurohormonal activation, oxidative stress and fibrosis, and inadequate management of intracellular calcium). However, there has not been a clear demonstration that strategies designed to restore sinus rhythm provide prognostic benefit compared with heart rate control. Different reasons (toxicity of antiarrhythmic medications, underlying disease, etc.) have been advo-

cated to explain this fact. Catheter-ablation may avoid the effects associated with the medication.

Lone AF is considered a purely electrical phenomenon that is not associated with underlying heart disease. Thus, one may expect that, even when the mechanisms already mentioned may produce some degree of left ventricular dysfunction, restoration of sinus rhythm may fully correct it.

The authors of this article selected patients with paroxysmal or persistent lone AF (excluding any cardiac or extra cardiac condition associated with risk of AF) undergoing first-time catheter ablation, and compared them with controls in sinus rhythm. Cases and controls were studied within 4 weeks before the ablation procedure, after it (median of 20 hours), and between 6 and 9 months after the procedure. All the patients were evaluated with Doppler echocardiography measuring peak systolic circumferential strain, cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement and phosphorus-31 magnetic resonance spectroscopy to assess ventricular energetics through the phosphocreatine/ATP ratio. Atrial fibrillation burden was determined by 7-day Holter monitoring. Fifty-three cases (median time from the first diagnosis was 3.7 years) and 25 controls were included.

Mean age was between 60 and 65 years and slightly over 70% were men. There was no difference between cases and controls in end-diastolic dimension, but although left ventricular ejection fraction (LVEF) was within normal ranges, it was significantly lower in cases: 61% (persistent AF 54%, paroxysmal AF 64%) vs. 71% in controls. Circumferential strain was also lower in cases: -15% vs. -18%. Left ventricular mass and diastolic function was similar in both groups. Late gadolinium enhancement was an infrequent finding: 15% in cases vs. 8% in controls. The phosphocreatine/ATP ratio was lower in cases, regardless of the type of AF and of whether patients had sinus rhythm or AF at the moment of ablation.

Ablation was performed in 51 patients. Forty-eight of them were evaluated at 20 hours: 24 who underwent ablation in sinus rhythm persisted with sinus rhythm, and of the 24 patients with AF at the time of ablation, 3 persisted with AF and, 21 presented sinus rhythm. There was no significant overall change in LVEF which remained in 61% in this first visit, but a slight increase was seen in the subgroup of patients with restored sinus rhythm ($7\% \pm 10\%$).

Holter-determined AF burden during follow-up was 0%. However, at the final visit (6 to 9 months after the procedure), no significant left ventricular function improvement was generally found. An analysis of patients who were in AF at the moment of ablation, recovered sinus rhythm after the procedure and remained in sinus rhythm, showed a significant improvement in LVEF: 55% before ablation, 60% at 20 hours, and 64% at the final visit. Nevertheless, LVEF was lower than in the control group. There was no

change in LVEF in any of the patients who were in sinus rhythm before the procedure. Myocardial energetics, as determined by the phosphocreatine/ATP ratio, did not improve at 6-9 months compared with the one before the procedure in any of the subgroups considered.

Despite the low number of patients included, this study allows to explore in depth the pathophysiology of ventricular dysfunction generated specifically by AF. As we see, left ventricular function, evaluated by different methods, is slightly but significantly impaired in patients with persistent or paroxysmal AF compared with healthy controls. Left ventricular function improves in patients in whom sinus rhythm was restored, but is still lower than in controls. Myocardial metabolism remains impaired, without cellular energetic improvement. These findings raise the possibility of two sources of ventricular dysfunction: one caused specifically by AF that improves when AF terminates, and another that is independent of AF and persists in spite of treatment. It can be speculated that even left ventricular dysfunction may be responsible for the development of AF. In this case, lone AF would be the consequence of an underlying cardiomyopathy, an initial manifestation of a subtle involvement. Unfortunately, the follow-up period was not long enough to rule out the possibility of late ventricular function recovery; nevertheless, this study opens the door to the possibility of considering lone AF not as lonely as we think.

Low diastolic blood pressure is associated with myocardial damage and is an adverse prognostic marker. A subanalysis of the ARIC study

McEvoy JW, Chen Y, Rawlings A, Hoogeveen RC, Balantyne CM, Blumenthal RS, et al. Diastolic blood pressure, subclinical myocardial damage, and cardiac events: Implications for blood pressure control. *J Am Coll Cardiol* 2016;68:1713-22. <http://doi.org/bwxx>

On the field of hypertension (HTN), attention focuses on systolic blood pressure (SBP) in terms of prognosis and treatment targets. Diastolic blood pressure (DBP) is usually overlooked. Several studies have demonstrated that the association between DBP and outcome can be represented as a J-curve. A recent analysis of the ARIC study stresses the idea of risk associated with excessive drop in DPB.

The prospective ARIC study evaluated the prevalence and incidence of risk factors, atherosclerosis and cardiovascular disease in a cohort of white and black persons from the United States. The study included 15,792 men and women aged between 45 to 64 years between 1987 and 1989. The participants attended four additional visits: visit 2 between 1990 and 1992, visit 3 between 1993 and 1995, visit 4 between 1996 and 1998 and visit 5 between 2011 and 2013. This subanalysis focuses on 11,565 persons without cardiovascular disease at visit 2, when, apart from the usual

determinations, high-sensitivity cardiac troponin-T (hs-cTnT) was measured. A cutoff value of 14 pg/ml was established to consider the presence of myocardial damage. Six categories of DBP were defined: <60, 60-69, 70-79, 80-89, 90-99, and ≥ 100 mmHg. The participants with lower DBP tended to be older, female, and white, had lower BMI, SBP and less frequent use of antihypertensive therapy. Compared with persons with baseline DBP between 80 to 89 mmHg, the multivariate analysis adjusted by demographic characteristics, SBP, risk factors and treatment showed that the probability of having elevated hs-cTnT was higher in those with DBP <60 mmHg (OR 2.24, 95% CI 1.22-4.10) and DBP between 60 and 69 mmHg (OR 1.52; 95% CI 1.00-2.32). Also compared with having a DBP of 80 to 89 mmHg, the estimated annual increase in hs-cTnT between visits 2 and 4 was 1.45 pg/ml per year higher in the DBP <60 mmHg group, 0.95 pg/ml per year higher in the DBP 60 to 69 mmHg group, and 0.85 pg/ml per year higher in the DBP 70 to 79 mmHg group.

For the same DBP categories, and consistent with the incidence of myocardial damage, the prevalence of coronary artery disease was higher in the lowest DBP categories: with adjusted HR of 1.49 (95% CI: 1.20-1.85) among persons with DBP <60 mmHg, 1.23 (95% CI: 1.05-1.44) for persons with DBP between 60-69 mmHg and 1.20 (95% CI: 1.05-1.37) for those with DBP between 70 and 79 mmHg. Lower DBP (<60 mmHg) was also an independent predictor of mortality: HR 1.32 (95% CI: 1.13-1.55). Of importance, low DBP was associated with higher incidence of coronary events in those with elevated hs-cTnT at the initial visit, and the risk associated with DBP <60 mmHg was seen in those with SBP >120 mmHg (in other words, pulse pressure >60 mmHg). As expected, low DBP was not associated with higher incidence of stroke.

The findings of this study confirm the association of very low DBP values with adverse outcome, as low DBP was cross-sectionally associated with higher prevalence of elevated hs-cTnT, as an expression of myocardial damage, and was prospectively associated with higher elevation of hs-cTnT and incidence of events. Other studies had already pointed out that both elevated and very low DBP levels predict poor prognosis. These findings support these data. As coronary perfusion takes place mostly during diastole, it is not surprising that a significant reduction in DBP is associated with greater prevalence and incidence of myocardial damage and poor outcome. Although SBP increases and DBP decreases with aging, the prognostic value of DBP was independent of age. The predictive value of low DBP was seen among those with higher SBP, and, therefore, with higher pulse pressure. Traditionally, a pulse pressure >65 mmHg has been associated with adverse outcome; the data from this study (higher risk when pulse pressure is >60 mmHg) confirms this statement, particularly due more to low DBP than to high SBP.

Systolic blood pressure variability has a strong association with the incidence of major cardiovascular events

Gosmanova EO, Mikkelsen MK, Molnar MZ, Lu JL, Yessayan LT, Kalantar-Zadeh K, et al. Association of systolic blood pressure variability with mortality, coronary heart disease, stroke, and renal disease. **J Am Coll Cardiol** 2016;68:1375-86. <http://doi.org/bwx2>

Systolic blood pressure (SBP) elevation is a strong predictor of cardiovascular and cerebrovascular events, renal function impairment and mortality. The values of SBP do not remain steady over time, but instead fluctuate in the short term (daily and seasonally) and in the long term (with aging, antihypertensive therapy used and adherence to this treatment, etc.). These fluctuations are not random and respond to patterns that can be explained. Visit-to-visit variability (VVV) of SBP has been mentioned as a stronger predictor of events than isolated measurements. Previous studies were focused on assessing only selected outcomes and included high-risk subgroups with a small number of BP measurements. A recent study from the Veteran Administration of the United States surprises for the amount of observations and robust conclusions.

The study included 2,865,157 patients with creatinine clearance ≥ 60 ml/min/1.73 m² at a first visit between 2004 and 2006 and at least 8 SBP records during follow-up. Visit-to-visit variability was assessed as standard deviation (SD) of SBP measurements until death, last visit or end of study (July 2013). Mean age was 60 years, 94% were men and 78% were white. Mean SBP was 130 \pm 18 mmHg. Four VVV quartiles were defined according to SBP SD: <10.3; 10.3-12.7; 12.8-15.5 and 15.6 mmHg. Patients with higher VVV were older, had lower income, higher prevalence of comorbidities and greater use of antihypertensive medications. Higher mean SBP was associated with higher VVV: from 127 mmHg in the lowest quartile to 142 mmHg in the highest quartile.

Mean follow-up was 8 years. In a model adjusted for age, sex, systolic and diastolic blood pressure, comorbidities, socioeconomic and educational level, medication and adherence to treatment, higher VVV (considering the lowest quartile as reference) was associated with: a) higher incidence of coronary artery disease, with HR of 2.1 for quartile 2, 3.6 for quartile 3 and 5.9 for quartile 4; b) higher incidence of stroke, with HR of 2 for quartile 2, 3.6 for quartile 3 and 6.6 for quartile 4; c) higher incidence of end-stage renal disease, with HR of 1.3 for quartile 2, 2.6 for quartile 3 and 10.6 for quartile 4; and d) higher mortality, with HR of 1.1 for quartile 2, 1.3 for quartile 3 and 1.8 for quartile 4. In all cases, the p value was <0.05. These findings were reproduced in all the subgroups analyzed, except for the association between mortality and VVV in patients with heart failure, where higher VVV was associated with better survival.

The reasons behind SBP VVV include changes in the elastic properties of blood vessels and aortic distensibility related with aging, disturbed baroreflex function, genetic and environmental factors, antihypertensive treatment and nonadherence to BP medications. Although the association between higher VVV with higher SBP is expected, it is also true that more complex methods of measurement point to their independent character. In turn, increased VVV is associated with greater endothelial dysfunction and pulse wave velocity, implying higher risk of vascular disease and hence, more events. A meta-analysis of 389 randomized controlled trials of antihypertensive medications demonstrated that calcium channel blockers and nonloop diuretic agents were associated with reduction of SBP VVV, whereas beta blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were associated with increase in SBP VVV. The Veterans study was observational; therefore, inferences about the causality cannot be made. The study emphasizes the importance of a phenomenon seen in daily practice: significant variations in longitudinal blood pressure measurements might identify a high-risk population in which the reversible causes of such variations should be investigated.

Pulmonary embolism: a cause of syncope rarely considered

Prandoni P, Lensing AW, Prins MH, Ciammaichella M, Perlati M, Mumoli N, et al. Prevalence of pulmonary embolism among patients hospitalized for syncope. *N Engl J Med* 2016;375:1524-31. <http://doi.org/bwx3>

Although pulmonary embolism (PE) is included as a potential cause of syncope in most textbooks, it is rarely considered in this condition. An Italian study has reported that PE is more common than we expected.

The PESIT study included patients hospitalized for syncope, defined as abrupt transient loss of consciousness of short duration (<1 minute) and spontaneous resolution, and after having ruled out obvious causes such as epileptic seizure, stroke, and head trauma. Reasons for hospital admission were trauma related to falls, severe coexisting comorbidities, failure to identify an explanation for the syncope, or a high probability of cardiac syncope. A detailed medical record was obtained in all cases. All the patients underwent a thorough physical examination, ECG, arterial blood gas testing, D-dimer assay, and when considered necessary, tilt testing, echocardiography and 24-hour Holter monitoring. The pretest clinical probability of PE was defined according to the Wells score, which establishes high or low PE probability according to the following criteria: clinical signs or symptoms of deep-vein thrombosis (DVT), alternative diagnosis less likely than PE, heart rate >100 beats/min, prolonged immobilization or surgery in the previous 4 weeks, previous PE, hemoptysis and active cancer. In

patients who had a low pretest clinical probability of PE and a negative D-dimer assay, no further testing was performed. In patients who had a high pretest clinical probability, a positive D-dimer assay, or both, computed tomography pulmonary angiography or ventilation-perfusion lung scan (V/Q) was performed.

Between March 2012 and October 2014, a total of 2,584 patients sought medical advice because of syncope in the 11 participating centers. Among the 717 patients (27.7%) who were admitted, 560 patients with a first episode of syncope who were not receiving ongoing anticoagulation therapy were included in the study. In 330 of the 560 patients (59%), a diagnosis of PE was ruled out on the basis of the Wells score and a negative D-dimer assay. In the remaining 230 patients (41%), 58.7% had a positive D-dimer assay, 1.3% a high pretest clinical probability and 40% both conditions. In these patients, 180 underwent computed tomography angiography and PE was diagnosed in 72 (40%), and two thirds of them presented a main pulmonary artery or lobar artery involvement. Forty-nine of the 230 patients underwent V/Q lung scanning and PE was diagnosed in 24 (49%). One patient died before testing and the autopsy certified PE. Hence, PE was confirmed in 97 of patients (in 42.2% of those with suspected PE and in 17.3% of all those admitted for syncope). Although the prevalence of data suggestive of PE (tachypnea, hypotension, signs of DVT and cancer) was higher in patients with confirmed PE, almost one fourth of the patients with diagnosis of PE did not have clinical manifestations. Pulmonary embolism was detected in 25.4% of the patients who had syncope of undefined origin compared with 12.7% of the patients who were regarded as having a potential alternative explanation for syncope.

The presence of PE as a cause of syncope in patients with unclear causes is not systematically investigated. The main merit of this study is the use of a systematic protocol to search for PE. It is worth mentioning that the study included patients with a first episode of syncope who were not receiving ongoing anticoagulant therapy. In this population, PE was confirmed in approximately one of every 6 patients. These findings cannot be extrapolated to patients with several episodes of syncope or receiving anticoagulants. The high prevalence of PE as a cause of syncope suggests that this diagnosis should be undoubtedly considered. This is an interesting coexistence of two elusive conditions: one with a high proportion of cases of unexplained origin, and another that remains without diagnosis in a significant proportion of cases.

BNP is an important predictor of risk in patients with degenerative mitral regurgitation

Clavel MA, Tribouilloy C, Vanoverschelde JL, Pizarro R, Suri RM, Szymanski C, et al. Association of B-type natriuretic peptide with survival in patients with degenerative mitral regurgitation. *J Am Coll Cardiol* 2016;68:1297-307. <http://doi.org/bwx4>

In degenerative mitral regurgitation (DMR), surgery is indicated in the presence of symptoms and a left ventricular ejection fraction (LVEF) >30%, or in asymptomatic patients with a relatively preserved LVEF (between 30% and 60%), left ventricular end-systolic diameter (LVESD) >40 or 45 mm, atrial fibrillation (AF) or pulmonary hypertension. Adequate timing of surgical treatment is controversial, as the parameters usually used for surgical referral are also predictors of long-term adverse outcome, independently of initial successful repair. Previous studies have reported that B-type natriuretic peptide (BNP) assessment may contribute to define the severity of MR and its prognosis. We present a prospective cohort study performed in four centers from Europe and America, including the Hospital Italiano in our country.

Patients were enrolled in this study if they had DMR detected by echocardiography, and had BNP measured at the time of echocardiography. Patients were excluded if they presented with mitral stenosis, concomitant aortic valve disease or congenital heart disease, AF with rapid ventricular response, contraindication to surgery, severe comorbidity, and endocarditis or pericarditis. BNP was considered in three categories: within normal ranges for sex and age, BNP measured divided by the upper limit of normal for age and sex (BNP ratio) ≤ 1 to ≤ 4 , and BNP ratio >4 . The decision of how to treat each patient was left at the discretion of the treating physician. All patients who underwent mitral valve surgery within 3 months after baseline echocardiographic evaluation were classified as the surgical treatment (ST) group, and the rest were classified as the medical treatment (MT) group. In the MT group, patients who underwent surgery after 3 months of medical follow-up were censored at the time of surgery.

Finally, 1,331 patients were included; mean age was 64 years and 66% were men. Degenerative mitral regurgitation was grade 3 in 31% of cases and grade 4 in 64%. BNP ratio was normal in 50% of cases, between 1 and 4 in 36% and >4 in 14%. Forty-two percent of patients belonged to the ST group and 58% to the MT group. Patients in the ST group had more symptoms, MR was more severe, had fewer comorbidities, and larger ventricular diameters and left atrial volume. Mean BNP ratio was higher in these patients: 1.1 versus 0.9.

After a mean follow-up of 5.1 years, natural log transformations of BNP and BNP ratio were predictors of mortality. After adjusting for age, sex, comorbidities, renal function, type of surgery and LVEF, BNP lost predictive capacity, whereas BNP ratio remained an independent predictor of mortality but with interaction with the type of treatment. BNP ratio had prognostic value in the context of MT. Compared with patients with normal BNP ratio (≤ 1), the adjusted HR for mortality in those with BNP ratio between >1 and ≤ 4 was 2.28 (95% CI, 1.45-3.68) and 3.71 (95% CI, 2.14-6.53) for those with BNP ratio

>4 . BNP ratio was an independent predictor among symptomatic patients under MT, but also in patients without symptoms when no other triggers prompting surgery were present.

On the contrary, BNP ratio did not help to define prognosis in patients with ST (96% undergoing valve repair).

The prognostic value of elevated natriuretic peptides in the general population and in several conditions, particularly heart failure, is undeniable. BNP elevation is the expression of higher end-diastolic wall stress. Different factors (age, sex, renal function, extent of cardiovascular and cerebrovascular disease, anemia and supraventricular arrhythmias) have an influence on the expected value in each case. The merit of the present study is that it did not focus on the absolute value of BNP but on its relationship with the maximal normal value for each patient. Therefore, a high BNP ratio adjusted for the factors mentioned refers to a real elevation associated with the severity of MR, which explains its independent prognostic value. An interesting aspect of BNP ratio is its ability to predict outcome in patients with asymptomatic DMR and without the traditional criteria for surgical referral. Is it time to consider routine measurement of BNP in this context? Will it be a new criterion to indicate surgery? It must be borne in mind that neither any of the usual criteria nor BNP have been validated in randomized trials for decision-making. As in this case, their value arises from observational studies; yet, it is worth discussing what to do if evidence of better quality does never appear. It is clear that the results of the surgical groups should be taken into account at the moment of decision-making. Finally, ST eliminated the prognostic value of BNP, suggesting that the pathophysiological cycle of disease progression ends with surgery.

Non-steroidal anti-inflammatory drugs and risk of heart failure: an analysis of over 8 million users

Arfe A, Scotti L, Varas-Lorenzo C, Nicotra F, Zambon A, Kollhorst B, et al. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. **BMJ** 2016;**354**:i4857. <http://doi.org/bw48>

The use of both traditional non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX2 inhibitors has been associated with higher risk of heart failure (HF). In fact, current guidelines limit the use of NSAIDs in patients with heart failure. A large meta-analysis of over 600 randomized trials showed that NSAIDs produced a 2-fold increase in the risk of HF compared with placebo. Nevertheless, there is still limited information on whether this effect is common to all NSAIDs and on their dose-response relationships. Therefore, in order to answer these questions, the authors of the study here presented developed a case-control study within a project aimed at evaluating the safety of NSAIDs and their adverse gastroin-

testinal and cardiovascular effects.

This study was based on five electronic health databases from four European countries: the Netherlands (1, database, n=2.2 million persons), Italy (2 databases, n=10.4 million persons), Germany (1 database, n=13.7 million persons), and the UK (1 database, n=11.1 million persons). Overall, these databases covered over 37 million people with different time windows of data availability between 1999 and 2010. Among them, a cohort of individuals starting NSAID treatment between 2000 and 2010 was selected. The date of first recorded prescription was defined as the date of cohort entry. Participants were excluded if they had received NSAIDs within the year preceding the date of cohort entry, or had been admitted to hospital with a primary diagnosis of HF in the year before the date of cohort entry, or had received a diagnosis of malignant cancer, with the exception of non-melanoma skin cancers. A nested case-control study was performed within the cohort: cases were all cohort members admitted for HF during follow-up, and each case was matched with up to 100 controls (treated with NSAIDs and who did not develop HF) according to sex, age and date of cohort entry (within 28 days). Twenty-three traditional NSAIDs and 4 selective COX 2 inhibitors were separately considered. Cohort members were classified into three categories of NSAID use according to the time of admission for HF: current (within the previous 14 days), recent (between 15 and 183 days) or past. The intensity of NSAID use was expressed in relation to the corresponding defined daily dose (DDD) for each NSAID and categorized as low (≤ 0.8 DDD), medium (0.9-1.2 DDD), high (1.3-1.9), or very high dose (≥ 2 DDD).

Among nearly 10 million new users of NSAIDs, 92,163 cases of hospital admission due to HF were identified and matched with 8,246,403 controls. Mean age ranged between 76 and 77 years and 45% were men. Compared with controls, cases had more comorbidities (mainly cardiovascular disease) received concomitant drug treatments more often and had history of HF, recorded as either a secondary hospital diagnosis in the previous year or as an outpatient diagnosis (9.1% vs. 2.5%). In addition, 17.4% cases and 14.4% controls were current users of NSAIDs. The most frequently used traditional NSAIDs were diclofenac, nimesulide, and ibuprofen, while the most frequently used COX 2 inhibitors were celecoxib and rofecoxib. Current NSAID users had a higher risk of HF than past users: OR (adjusted for clinical and demographic characteristics) 1.19, 95% CI 1.17-1.22). This higher risk was not similar for all NSAIDs. According to the multivariate analysis, current vs. past use of individual NSAIDs associated with higher risk of HF was observed for ketorolac, indomethacin, piroxicam, diclofenac, ibuprofen, nimesulide, naproxen, rofecoxib and etoricoxib. The OR ranged between 1.16 for naproxen and 1.83 for ketorolac. Conversely, the OR for celecoxib was 0.96. There was no evidence that recent use

of any NSAID was associated with higher risk of HF with respect to past use.

The risk of HF was higher with the use of higher doses of diclofenac, indomethacin, piroxicam, rofecoxib and etoricoxib. For diclofenac, the highest risk was observed with very high doses, with an OR of 2.2 compared with an OR of about 1 for the rest of the doses.

Overall, the association of NSAID use and higher risk of HF has been associated with their vasoconstrictive effect, the ability to antagonize the vasodilation mediated by prostaglandins and to reduce renal function. The main strength of this study is that it was based on electronic databases including a large number of patients, allowing a detailed analysis of each individual drug. The differences observed with each individual drug may be due to the pharmacodynamics and pharmacokinetics of each drug but also with different profiles associated with higher risk of HF among NSAID users that may act as confounders. Of importance, although in many cases the highest risk is seen with high or very high doses, the risk is already high with medium dose of indomethacin. Another aspect to consider is that the admission to hospital with a primary diagnosis of HF was considered as the index event. Then, we may ask ourselves if NSAIDs are also a risk factor for HF not requiring hospitalization, or for HF as a secondary cause for hospitalization. Occasionally, these drugs may be indispensable, in others not, or yes, but at lower doses. We should focus on these situations to prevent new cases of HF.

Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: a meta-analysis.

Siemieniuk RA, Agoritsas T, Manja V, Devji T, Chang Y, Bala MM, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis. *BMJ* 2016;354:i5130. <http://doi.org/bw5w>

Transcatheter aortic valve implantation (TAVI) was compared with surgical aortic valve replacement (SAVR) in patients with symptomatic severe aortic stenosis and intermediate risk (STS score between 4 and 8) in the PARTNER 2 A study, which we commented in this section in a previous issue (*Rev Argent Cardiol* 2016;84:290-296). The results showed non-inferiority for TAVI versus surgery, with a RR of 0.92 (95% CI 0.77-1.09). TAVI was associated with greater incidence of vascular events but with lower risk of major bleeding, atrial fibrillation (AF) or acute renal failure (ARF). There was no significant difference in the indication of definite pacemaker. Specifically in the case of transfemoral approach, there was a significant reduction of the primary endpoint (death or disabling stroke) compared with surgery ($p=0.05$). Since then, some meta-analyses have been published, which also considered other studies in a similar population. Of

interest, the study here presented has the distinctive feature of having considered not only expert opinion but also the opinion of the patients to choose the primary endpoints. The quality of the evidence for each endpoint was evaluated using the GRADE system. The study included randomized controlled trials comparing TAVI with SAVR in patients with symptomatic severe aortic stenosis and a STS risk score <8%: two in the United States (one of them was the PARTNER 2 A) and two in Europe. The studies included 3,179 patients; 54% were men and most were aged over 80 years. Among all the patients who underwent percutaneous TAVI (n=1,308), this was performed by transfemoral access in almost 95% of cases. Among patients who underwent non-percutaneous TAVI (n=269), this was done by transapical access in more than 75% of cases.

At a median follow-up of 2 years, there were no differences in mortality: 20.2% with TAVI versus 21.9% with SAVR (HR 0.86, 95% CI 0.74-1.01). There was a strong trend toward lower incidence of stroke with TAVI (HR 0.81, 95% CI 0.63-1.01) and a reduction in the incidence of ARF (HR 0.48, 95% CI 0.27-0.84).

But each of these outcomes differed when both accesses were separately considered. There was a significant reduction in the incidence of mortality (21%) and ARF with the transfemoral access compared with SAVR, and a strong trend toward lower incidence of stroke. On the contrary, there was a trend toward greater mortality (HR 1.34, 95% CI, 0.91-1.97), stroke (HR 1.67, 95% CI, 0.97-2.87) and ARF (HR 1.54, 95% CI, 0.97-2.87) with the transapical approach. According to the GRADE system, the quality of evidence was moderate or high for each of the findings reported.

Overall, TAVI was associated with a significant reduction in the incidence of bleeding, AF and length of hospitalization (about 3 and 4 fewer days).

But at 2 years, aortic valve reintervention (RR 3.25, 95% CI 1.29-8.14, 7 more per 1000 patients), need of definite pacemaker (RR 2.45, 95% CI 1.17-5.14, 134 more per 1000 patients) and moderate to severe aortic regurgitation were more common in the TAVI group. The incidence of new symptoms of heart failure was also higher (6% excess in absolute terms).

This meta-analysis contributes to demonstrate that we should consider the type of approach at the moment of evaluating the outcomes of TAVI: Compared with SAVR, transfemoral access is associated with lower mortality, ARF and a strong trend toward a reduction in the incidence of stroke. Conversely, the transapical approach is associated with higher risk for each of these outcomes. In this setting, if the transapical approach is the only possible access, the decision to perform the procedure should be thoroughly meditated in patients considered inoperable in daily practice. Overall, bleeding and AF were reduced with TAVI but the need for reintervention and permanent pacemaker implantation was higher (increased risk by about 14%). Some issues should be considered. Firstly, the follow-up period is short to define durability of TAVI valves and the need for long-term reintervention. The risk for reintervention at 2 years seems to be high: which will be the incidence of reintervention at 5 or 10 years? This may not be a limiting issue in very old patients, but for younger patients it may be a reason not to choose TAVI. Secondly, the evidence comes from selected patients and centers, with experienced surgeons. The learning curve, the setting and the presence of comorbidities are decisive factors in the individual case. The technique is still under development and new devices appear; therefore, the results are expected to improve. Finally, we are still waiting for cost-effectiveness studies which may contribute to define the role of TAVI in the treatment of these intermediate-risk patients.