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The paradigmatic case of Tsimane natives and their very low prevalence of coronary heart disease

Kaplan H, Thompson RC, Trumble BC, Wann LS, Allam AH, Beheim B, et al. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. **Lancet 2017;389:1730-9. http://doi.org/f96tbd**

Traditional coronary risk factors explain more than 90% of the risk taken into account for presenting with coronary heart disease. Atherosclerotic disease has been defined as a Western civilization disease, with a strong influence of lifestyle (inadequate diet, physical inactivity) in the presentation of these risk factors; and it is demonstrated that a "healthy" behavior is associated to marked decrease in the incidence of vascular events, even in the population at greater risk. The THLHP project has been conducting research for years in the Tsimane community (16,000 indigenous Bolivians living in pre-industrial conditions, in thatched roof huts, without electricity, sewage or drinking water, who obtain their food from spear or bow hunting, fishing and fruit and vegetable harvesting). The hypothesis of the study was that these Indians' lifestyle would be determinant of low prevalence of coronary heart disease despite the activation of inflammatory phenomena, mainly due to the high prevalence of infectious diseases.

The study randomly selected 1,214 men and women participants over 40 years of age. Anthropometric measurements and laboratory tests were performed and computed tomography was done to determine the coronary calcium score. Finally, a total of 705 individuals were analyzed, not differing in age, blood pressure, and total body fat content from those who did not participate, thus ensuring the representativeness of the sample. Mean age was 57.6 years and 50% were women. The prevalence of risk factors was very low: 6% of obesity, 5% of hypertension, 0% of diabetes, and 9% with LDL cholesterol >130 mg/dl. Smoking was present in 28% of cases, but the average consumption was 10 cigarettes per month. In contrast, the prevalence of inflammation markers was high: 23% had white cell blood count above 10,700 / mm3, 27% had elevated erythrocyte sedimentation rates and 48% had C-reactive protein levels above 3 mg/dl.

The calcium score was surprisingly low: it was 0 in 85% of cases, between 0 and 100 in 13% of cases and only greater than 100 in 2% of cases. These figures were compared with data available from other cohorts, including that of the MESA study exploring similar data in a multiethnic population of the United States. Comparison by age groups showed a significant difference in the time coronary atherosclerotic disease becomes manifest: the Tsimanes reach a calcium score >0 24 years later, and above 100 28 years later than their American counterpart. Between the ages of 65 and 74 years, 72% of the Tsimane population has a calcium score of 0, compared to 36% of participants in the MESA study, and only 8% of the Tsimane community has a calcium score >100, compared to 34% in the MESA study. In the multivariate analysis, age, male gender and inflammation markers were predictors of having a calcium score >0, but the whole model explained only 19% of the variation (age and sex accounted for 14%, and inflammatory markers for 5%). The data presented indicate that the Tsimane community has the lowest known prevalence of coronary heart disease in the world, even lower than that of Japanese women, so far considered to be carriers of the lowest values.

The case of Tsimane natives has several points that deserve to be highlighted. Firstly, lifestyle (diet with only 14% fat, 72% unprocessed carbohydrates, and rich in fiber; daily physical activity of 6-7 hours in men and 6 in women) appears clearly linked to a very low prevalence of traditional risk factors. Is that enough to explain finding such a scant presence of coronary artery disease? Genetic or environmental factors may be mentioned, but it is interesting to note that since 2011 when they began to use motorized canoes and stopped paddling to make their river crossings, the average LDL cholesterol rose by almost 20 mg/dl. Despite the high prevalence of inflammatory factors, coronary disease is very rare, suggesting that the role that is attributed to inflammation as a precursor of atherosclerosis may be real but in the presence of a favorable substrate, such as high plasma lipids or hypertension. And another point to outline: most of the deaths occur in the community around the age of 70 years. Lifestyle that impresses healthy for our eyes, used to focus on atherosclerosis, may not be so healthy. Lack of drinking water and electricity, high prevalence of infectious and inflammatory phenomena are undoubtedly factors that limit life expectancy. How to achieve progress without falling into the diseases of civilization? Perhaps the Tsimane natives could also be a test bench in this respect, if adequate policies were implemented and there evolution followed-up.

Revealing data on myocardial infarction with normal coronary arteries

Lindahl B, Baron T, Erlinge D, Hadziosmanovic N, Nordenskjöld A, Gard A, et al. Medical Therapy for Secondary Prevention and Long-Term Outcome in Patients With Myocardial Infarction With Nonobstructive Coronary Artery Disease. **Circulation 2017;135:1481-9. http://doi.org/f9r8pg**

Acute myocardial infarction (AMI) with coronary arteries without angiographically obstructive lesions (understood as those ≥ 50%) is universally known by its acronym in English, MINOCA. The prevalence of MINOCA in different cohorts has ranged from 5% to 10% of total AMI. Treatment guidelines, due to the lack of randomized studies, do not establish clear treatment guidelines for patients who have presented with MINOCA. In Sweden, the SWEDEHEART registry records all hospitalizations for AMI where angiography has been performed. This, together with the obligatory registration of the vital evolution of patients, pharmacological prescriptions, and use of resources has allowed us to define in this publication the characteristic profile of the patients with MINOCA, the treatment established and the prognosis.

Between 2003 and 2013, the SWEDEHEART registry included 199,162 AMI out of which 9,466 cases were MINOCA (8%). For the present report, focused on describing long term evolution and the influence of treatment on prognosis, patients who died in the first 30 days were excluded, leaving 9,136 patients for the analysis. Mean age was 65.6±11.7 years, and 61% were women. Fifty eight percent of patients were hypertensive, and 16% were diabetic. At discharge, 90.1% was prescribed with aspirin (dual antiplatelet therapy in 66.4% of cases), 83.4%, with beta blockers, 64.1% with renin-angiotensin system inhibitors or antagonists (RASA) and 84.5% with statins. At a mean follow-up of 4.1 years, 23.9% experienced at least one major cardiac event (MCE): 13.4% died, 7.1% had an AMI, 4.3% had a stroke, and 6.4% were hospitalized for heart failure.

In an observational study, the administration of the different treatments depends on patients' characteristics and on doctors' decision. To define treatment influence in the evolution after discharge, regardless of the baseline characteristics that could have led to adopt it, a propensity score was constructed by logistic regression for each of the interventions, defining the independent predictors of use for each of the drugs. Each patient had a score that indicated the probability of being treated with each specific medication. Patients with the same propensity score were then matched for each analysis; among them, some were actually treated with the drug in question and some were not. This analysis (which attempts to mimic a randomized study) showed that the use of RASA was associated with a significant reduction of MCE (HR 0.82, 95% CI 0.73-0.93), similarly to the use of statins (HR 0.77, 95% CI 0.68-0.87). Treatment with beta-blockers was associated with a reduction in the limit of MCE significance (HR 0.86, 95% CI 0.74-1.01), while the use of dual antiplatelet therapy did not influence disease progression (HR 0, 90, 95% CI 0.74-1.08). When analyzing specific endpoints, RASA did not significantly reduce any of the events separately; statins achieved a significant reduction in overall and cardiovascular mortality and stroke mortality; beta-blockers a significant reduction in overall mortality and AMI; and dual antiplatelet therapy had no favorable effect on any of the endpoints, and was associated with an excess of bleeding events, which did not reach significance.

The SWEDEHEART registry data are extremely interesting. The prevalence of MINOCA is similar to that of other cohort studies. We may regret not having the information about the prevalence of patients with truly disease-free coronary arteries, compared with those with non-obstructive coronary artery disease. Similarly, we do not know if there were among the cases some with myocarditis, or Takotsubo heart disease. The analysis of the medication effect does not come from a randomized study, but from observational data paired by propensity score, so that the presence of some residual confounder cannot be excluded. However, the observed results allow us to advance in some pathophysiological hypotheses. Statins have stabilizing action on the coronary plaque and attenuate endothelial dysfunction. It is possible that some MINOCA cases are due to active atherosclerotic disease despite not being in an obstructive range. Renin-angiotensin system antagonists modulate neurohormonal activation and may have been particularly useful in cases of ventricular dysfunction. Beta-blockers decreased mortality; was it also by effect in cases of worse ventricular function, or by neurohormonal attenuation? Finally, aspirin and dual antiplatelet therapy failure opens a question mark on the role of thrombus formation in this group of patients. We can assume, with little risk of being mistaken, that MINOCA is a heterogeneous entity, with different mechanisms at play in different patients. Additional information on new records or interventional studies may help to further clarify this point.

A new electrocardiographic criterion of left ventricular hypertrophy seems superior to the traditional ones

Peguero JG, Lo Presti S, Perez J, Issa O, Brenes JC, Tolentino A et al. Electrocardiographic Criteria for the Diagnosis of Left Ventricular Hypertrophy. **J Am Coll Cardiol 2017; 69:1694-703. http://doi.org/f9z3c3**

Numerous electrocardiography (ECG) criteria allow the diagnosis of left ventricular hypertrophy (LVH). Among the most common are the Cornell index (RavL+S V3 >2.8 mV in males and > 2 mV in

females) and the Sokolow and Lyon index (R in V5 or V6+S V1 ≥3.5 mV). In general, they stand out for their specificity, but their sensitivity is poor. A new criterion is added to the previous ones, and their authors sustain that it preserves the specificity of those mentioned above and significantly increases the sensitivity.

The data derivation set consisted of 94 patients hospitalized between August and September 2013, half of them due to a hypertensive crisis and the other half normotensive hospitalized for various causes, in whom ECG and echocardiogram were performed. With the data of septal and posterior wall thickness and internal LV diameter, the left ventricular mass was defined using the Devereaux formula. Mass indexed by body surface area >115 g/m2 in men and 95 g/m2 in women was defined as LVH. Two authors read the ECG of all patients, without knowing the echocardiographic data, and measured the amplitude of the R and S waves of all leads. For each of them and for the usual criteria already mentioned, they defined the sensitivity (St) and specificity (Sp) for the diagnosis of LVH, and based on these data, the area under the corresponding ROC curve (which indicates the ability to adequately discriminate the presence of LVH between true positives and false positives). As a novel ECG criterion the authors proposed the sum of the deepest S wave amplitude (Sd) in any ECG lead, plus the amplitude of the S wave in V4. They established as cut-off value to define LVH a sum >2mV in women and >2.8 mV in men.

Diagnosis based only on RV5 amplitude showed a ROC area of only 0.53 (p=NS) and that based on the amplitude of RV6, a ROC area of 0.57 (p=NS). Instead, the amplitude of S V4 had a ROC area of 0.78 (p <0.001), and that of Sd a ROC area of 0.80 (p <0.001). The Sokolow index St was only 23%, but with 97% Sp. The Cornell index had 40% St and 91% Sp. In contrast to these traditional criteria, the Sd+S V4 criterion presented 70% St and 89% Sp (with no significant difference with the Sp of the other indexes mentioned) and a ROC area of 0.85. It was the only one of all examined indices in which there was no significant discrepancy with the echocardiographic diagnosis.

The findings were corroborated in a derivation set of 122 patients in whom ECG and echocardiogram were performed between January and February 2014. Compared with the patients in the first derivation set, they were older (68 vs. 54 years) and with higher prevalence of hypertension and diabetes. In general, the St of the criteria was lower and this was true both for the traditional indices (the Sokolow index showed 14% St and 99% Sp, Cornell's index had 31% St and 99% Sp) and for the new criterion: Sd+SV4, which evidenced 57% St and 90% Sp. However, their ROC area was again high (0.80, p <0.001). Working together with both cohorts, the Sd+S V4 criterion showed 62% St and 90% Sp, the best combination of all the explored ones.

The electrical voltage that is the basis for ECG diagnosis of LVH depends fundamentally, but not only, on ventricular mass. Active and passive electrical conditions, the distance from the ventricular cavity to the electrode, the interposition of muscle and breasts, interstitial fibrosis, and the presence of deposit material, are all factors that act to define the voltage. Daily variations in the surface ECG of the same individual have also been described. Therefore, the choice of a variable lead, the one of deepest S wave, either in the limbs or precordial leads, recognizes this source of variability. It is striking that the best ECG criterion for defining LVH consists of the voltage addition of 2 S waves, and does not consider any R wave. This may be due to the fact that the depolarization of the LV free wall is better represented by the terminal part of the QRS complex. Some caution, however, should be exerted: the S (which is the maximum advantage of the new criterion with respect to the traditional ones, somewhat more specific) was lower in the derivation set than in the validation set. It was enough to maintain its preeminence over the usual criteria, but new assessments in other populations could give a definitive conclusion about this new criterion. And for the end, and beyond validation: It is a good thing that in this age of so much complex and expensive measurements, a group of enthusiasts have come up with something new and useful (because determining the presence of LVH has consequences on treatment and prognosis) using 2 methods widely disseminated and accessible: the ECG and the two-dimensional echocardiogram! Something complex is not always necessary to do good research.

Risk factors for developing aortic stenosis are the traditional cardiovascular risk factors

Yan AT, Koh M, Chan KK, Guo H, Alter DA, Austin PC, et al. Association Between Cardiovascular Risk Factors and Aortic Stenosis: The CANHEART Aortic Stenosis Study. **J Am Coll Cardiol 2017;69:1523-32. http://doi.org/f9tsk5**

The pathogenesis of degenerative aortic stenosis (AS) has not been sufficiently clarified. To the traditional conception limited to talk about wear and tear of biological material, observational evidence on the role of deposition of lipid material, inflammation, and production of osteopontin has been added. Cross-sectional studies have indicated the association between AS and cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia, but until now there has not been strong evidence of prospective longitudinal cohort studies confirming the temporal relationship of these factors with the development of heart valve disease.

The CANHEART study is a large Canadian project, collecting individual data from 17 population registers, vital statistics, universal health insurance, prevalence of various pathologies and pharmacological prescriptions. With information from several of these registries we evaluated the incidence of AS and

its predisposing factors in the Ontario region. All health insurance beneficiaries who were aged at least 65 years on April 1, 2002, with no history of heart valve disease, coronary disease, arrhythmia, heart failure, or cerebrovascular disease were selected. Those who had been hospitalized for angina, syncope, or shock were excluded in case those symptoms were due to AS. This cohort was prospectively followed-up and the study endpoint was the incidence of severe AS, clinically manifested by hospitalization or need for surgery.

A total of 1,120,108 persons were included; at a median follow-up of 13 years 20,995 (1.9%) developed severe AS. Compared with the remaining cohort, they were slightly older (median 75 vs. 73 years), with a higher prevalence of male gender and coronary risk factors. This coincided with greater use of cardiovascular medication. The mortality of this group during follow-up was higher: 60% vs. 41.7%. The incidence of severe AS was 144.2/105/year, higher in men than in women (168 vs. 127/105/year, respectively). There was a clear gradient between the presence of three major cardiovascular risk factors (hypertension, diabetes and dyslipidemia) and the incidence of severe AS: 95.8/105/year in those without any of the three risk factors, 154.7/105/year with a risk factor; 200.2/105/year with two and 234.2/105/year with the presence of the three risk factors.

Age (HR 1.71 per decade of life), male gender (HR 1.53), hypertension (HR 1.71), diabetes (HR 1.49) and dyslipidemia, although with less strength of association (HR 1.17) were independent predictors of severe AS. Longer duration of diabetes or hypertension was associated with an increased risk of presenting heart valve disease. The same was not true of dyslipidemia. Hypertension was associated with the highest attributable risk: 23.4%, followed by diabetes (5.6%) and dyslipidemia (4.4%). The joint presence of the three risk factors explained 34.4% of the population risk.

Numerous factors have been associated with the development of aortic stenosis in research studies with laboratory animals: the association of genetic predisposition, neurohormonal activation, joint action of terminal glycosylated products, inflammation, endothelial dysfunction and metalloproteinases. This observational cohort study has the enormous merit of presenting data of more than one million persons, and solidly demonstrating the association of the risk factors that we link with vascular disease, with the genesis of AS. Thus, AS definitely acquires the character of a systemic disease, probably avoidable in many cases. Some additional observations: only AS that generated hospitalization or surgery was considered, implying that the number of patients affected by heart valve disease must be greater than the nearly 2% mentioned. Previous randomized studies had shown failure of statin therapy to prevent worsening or progression of AS. This study offers a reason: of all the factors considered, and although statistically significant, the one with the lowest strength of association was precisely dyslipidemia, being the only one of the three in which the exposure time had no impact. One out of every three cases of severe AS can be attributed to the combination of the three factors considered. This means that much remains to be explained. In this sense, genetic susceptibility factors, and ageing may be more responsible. In the meantime, an adequate control of pressure levels seems to be a measure that can contribute to decrease the incidence of AS in the population.

Socioeconomic status: the ignored player when talking about cardiovascular risk and prognosis

Stringhini S, Carmeli C, Jokela M, Avendaño M, Muennig P, Guida F, et al. Socioeconomic status and the 25 x 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1.7 million men and women. **Lancet 2017;389:1229-37. http://doi.org/bzzj**

The purpose of the World Health Organization (WHO) of reducing by 25% the mortality attributable to non-communicable diseases by 2025 focuses on 7 conditions upon which action may be taken: hypertension, diabetes, obesity, sedentary lifestyle, excessive consumption of sodium and alcohol, and smoking. The members of the Lifepath project, authors of the present work, rightly point out that the socioeconomic condition, clearly linked to these factors and in turn with the prognosis, is not mentioned as an equally reversible condition.

In order to compare the influence of socioeconomic status on prognosis with that exerted by the factors considered in the 25 x 25 initiative, they analysed the data from 48 cohort studies carried out between 1965 and 2009 in seven WHO member countries (United States, United Kingdom, France, Italy, Portugal, Switzerland and Australia). The data on occupational level had been collected as surrogate of socioeconomic status and had a minimum of 3 years follow-up. According to the occupation and following the European Socioeconomic Classification, three levels were defined: high (corresponding to professionals and managers, high ranking clerks, high positions in service and sales area), intermediate (small employers and self-employed workers, farmers, supervisors and technicians) and low (lower-ranking positions in offices, services and sales, semi-skilled and unskilled workers). Of all the factors considered in the 25 x 25 initiative only the data of salt consumption was lacking.

A total of 1,751,479 individuals were considered, with mean age of 47.8 years, 54% women and a mean follow-up of 13.3 years. On average, 41.4% of males and 27.1% of females had low level and 32.5% of males and 26.1% of females had high level of occupational status. At follow-up, 15.2% of men with low occupational status died, compared to 11.5% of those in the upper level; among women, the corresponding figures were 9.4% and 6.8%. Taking high occupational level

as a reference, mortality HR adjusted for age, marital status and race or ethnicity was 1.42 for men and 1.34 for women in the intermediate level, in all cases with $p < 0.05$. In this analysis, the risk of belonging to the low socioeconomic status was greater than that due to obesity and hypertension.

In a more complex analysis that was adjusted not only by the conditions mentioned, but also by the factors considered in the 25 x 25 initiative, low occupational level compared to high level implied a HR for overall mortality of 1.26 (95% CI 1.21-1.32). This risk was only clearly exceeded by smoking (HR 2.21, 95% CI 2.10-2.33) and diabetes (HR 1.73, 95% CI 1.60-1.88); it did not show significant differences in relation to the risk caused by sedentary lifestyle, alcohol consumption and hypertension and was significantly higher than that due to obesity (HR 1.05, 95% CI 0.97-1.14). Life expectancy at 40 years of age, consideron 85 years as temporal horizon, was reduced in 2 years because of low socioeconomic status, 2.6 years for men and 1.5 years for women. These values were higher than those due to alcoholism, hypertension and obesity.

It is remarkable how the medical literature but also the great initiatives to reduce cardiovascular risk tend to focus on individual behaviors and ignore social factors. As if unfavorable socioeconomic conditions could not be modified, as if measures could not be taken to significantly reduce inequity. This extraordinary meta-analysis demonstrates the unequivocal role that belonging to low-income sectors plays in determining not only cardiovascular prognosis, but also cancer mortality and overall mortality. There is often an easy explanation: the poorest sectors have a worse prognosis because they eat worse, consume more alcohol, have less time to do physical activity, and smoke more. This analysis shows that regardless of the risk factors we are accustomed to blame, those with lower resources do worse. Can we assume, with a low risk of error, that poorer access to the health system, economic limitation in the treatment instituted, lack of knowledge due to lack of information, extensive and unchangeable working hours, greater distances to care sites, are also prognosis determinants? However, it seems that for many decision makers all these conditions are the same as age: you cannot fight them. We recall a publication already discussed in this section, in Rev Argent Cardiol 2015; vol 83 nro 6 (Kivimaki et al, Lancet 2015; 386:1739): upon finding that excessive working days are associated with an increased risk of stroke, the authors concluded that more emphasis should be placed on risk factors, rather than asking whether something could be done to improve working conditions. A whole way of seeing the world. And for the end: remember that this meta-analysis refers to people with work! What is the risk of those who have no work? Serious initiatives and precise health policies should not ignore these data, and encourage an approach that also includes the mentioned factors.

Imaging and diagnosis of ischemia: which is the best method?

Danad I, Szymonifka J, Twisk JW, Norgaard BL, Zarins CK, Knaapen P, et al. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. **Eur Heart J 2017;38:991-8. http://doi.org/f93k98**

In our daily practice, we resort to different methods for the diagnosis of coronary heart disease with functional consequences. The severity of a lesion found in the coronary angiography (CA) or the coronary computed tomography angiography (CCTA) does not bear an exact correlation with its facility to generate ischemia. Thus, in our daily practice we employ methods to define its presence, such as stress echocardiography (SE), single photon emission computed tomography (SPECT), cardiac magnetic resonance imaging (MRI) or fractional flow reserve derived from CCTA. Fractional flow reserve (FFR) defined in the context of coronary angiography, measures the pressure gradient generated by a lesion, and is a tool that helps decision making in the case of finding lesions in the CA. Its value theoretically ranges between 0 (complete absence) and 1 (normal FFR). A cut-off value <0.80 is generally assumed to define the presence of ischemia, and effectively, its assessment is considered the gold standard to identify it.

A recently published meta-analysis establishes the diagnostic performance of the different methods mentioned, considering FFR as reference. The authors performed a systematic review of all the studies published in English between 2002 and 2015, evaluating diagnostic methods of coronary heart disease responsible for ischemia and which had contemplated FFR as reference in at least 75% of patients, arteries or segments considered. Sensitivity (St), specificity (Sp) and diagnostic odds ratio (DOR), understood as the ability to discriminate between coronary heart disease with or without repercussion (the higher the DOR, the better the discriminating capacity) was defined for each method. Twenty-three studies including at least one of the methods considered met the meta-analysis criteria, with 1,696 individuals and 4,740 arteries studied. Hemodynamically significant coronary heart disease was defined by FFR in 42% of patients and 34% of vessels.

In the patient-based analysis, the greatest St (90%) corresponded to CCTA, fractional flow reserve derived from CCTA and MRI. Conversely, St for CA was 69%, 70% for SPECT and 77% for SE. The highest Sp was 94% for MRI, followed by SPECT with 78%, and the lowest corresponded to CCTA with only 39%. The greatest DOR was 92 for MRI, very far from the ones for SE and SPECT (in both cases near 9) and that for CCTA, almost 7.

In the artery-based analysis, the highest St corresponded to CCTA and MRI, 91% in both cases, and the lowest to SPECT, with 57%. The greatest Sp was the one for MRI (85%) and the lowliest that of CCTA (58%). Again, the highest DOR was the one for MRI.

It is worth pointing out that in all the analyses, CA presented St around 70% and Sp close to 67%. An essential general characteristic of results was their heterogeneity, influenced, depending on the case, by age, presence of diabetes or hypertension and publication year (which suggests differences as the learning curve progresses for the implementation of the most recent methods).

This meta-analysis suggests various comments. In the first place, CA St and Sp near 70%: these do not seem adequate figures for a procedure acknowledged for a long time as the gold standard. In lesions considered as non-significant and in lesions which, on the contrary, are contemplated as severe, and "clearly" generators of ischemia, we may commit errors if we assume presence or absence of functional impact solely on the anatomical features. Moreover, the diagnostic methods we usually employ (SE, SPECT) seem to have a higher diagnostic performance than CA, but only slightly higher. In this context, MRI appears as a method of high St and Sp, and a diagnostic capacity very superior to that of traditional methods. As limitation we must mention lack of apparatuses in wide areas, cost, and deficient understanding of its usefulness by vast sectors of treating physicians. Fractional flow reserve assessment, as the gold standard, is an invasive procedure and yet inaccessible for many systems. Its measurement in the context of CCTA could be a solution, but the available information is still scarce. Nevertheless, there are some limitations in this publication. The role of positron emission computed tomography (PET) was not considered. Some of the comparisons included a small number of patients (for example, the comparison between MRI and FFR is based on only 70 cases). In some studies FFR assessment was decided after knowing the coronary anatomy, which may produce bias. And speaking about bias, we may wonder if some FFR comparisons were not published for different reasons, among them, not very encouraging results for some of the methods evaluated. However, the information presented is the richest known so far; it is possible that technical improvements, learning curves of new techniques, evaluation of non-considered populations, will all modify the figures presented. At the same time, the greater diffusion and cost reduction of the best performing methods will contribute to a more efficient diagnostic practice.

Two revealing analyses on the usefulness and safety of dual antiplatelet therapy

Palmerini T, Della Riva D, Benedetto U, Bacchi Reggiani L, Feres F, Abizaid A, et al. Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients. **Eur Heart J 2017;38:1034-43. http://doi.org/f9z3c3**

Costa F, van Klaveren D, James S et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. **Lancet 2017;389:1025-1034. http://doi.org/f9tm77**

Dual antiplatelet therapy (DAT) with aspirin and a P2Y12 receptor inhibitor is the rule after coronary angioplasty with stent implantation, and in the context of acute coronary syndrome (ACS) with or without stent placement. The necessary DAT duration is still debated, according to the clinical condition, type of stent, bare-metal or drug-eluting (DES), and the balance between the risk of new ischemic events and the risk of complications, especially bleeding. We present two studies with interesting data.

The first study is a new meta-analysis including clinical trials in stable patients or with ACS, with an implanted DES and randomly assigned to short DAT (3-6 months) vs. extended DAT ≥ 1 year (with the data censored at one year to define the effect up to that moment). This was a meta-analysis of individual data, which increases the reliability of conclusions. A network meta-analysis method was used, which allows establishing comparisons among different groups of interest even when there has been no direct comparison between studies.

Six randomized studies were included, with a total of 11,473 patients; 41.5% with ACS (two-thirds with negative biomarkers) and 58.5% stable patients. As expected, ACS patients had greater risk of presenting with acute myocardial infarction (AMI) or definite or probable stent thrombosis at one year (HR 1.5, 95% CI 1.12-2). In the intention-to-treat analysis, short DAT was not associated to a different rate of events than extended DAT at one-year follow-up (HR 1.15, 95% CI 0.88-1.51, p=NS). However, a closer analysis showed a trend to different results according to the clinical condition. In the context of ACS, short DAT was associated to higher risk of AMI or stent thrombosis compared with extended DAT (HR 1.48, 95% CI 0.98-1.22, p=0.059). Conversely, there were no differences among stable patients (HR 0.93, 95% CI 0.65-1.35). However, the difference was consistent for the risk of bleeding; short DAT was associated to lower risk of major bleeding (HR 0.50, 95% CI 0.30-0.83) and all-cause bleeding (HR 0.67, 95% CI 0.47-0.91) without influence of the clinical condition leading to angioplasty. A per-protocol analysis (where only patients in each branch which effectively meet the assigned treatment are considered) showed similar results.

The network meta-analysis suggested that in the

context of ACS, short 3-month DAT but not 6-month DAT was effectively associated with greater risk of new ischemic events compared with one-year DAT (HR 2.08, 95% CI 1.10-3.93 and HR 1.28, 95% CI 0.73-2.27, respectively). No significant differences were found in stable patients. Both 3-month and 6-month DAT were associated to lower risk of bleeding than one-year DAT

The second publication also refers to the risk of bleeding. Although one of the factors to consider at the moment of deciding DAT duration after stent implantation is the risk of bleeding, there is no validated algorithm to help conduct adoption. The authors of a new PRECISE DAPT score aimed at filling this gap. They considered different randomized studies comparing different DAT durations following coronary stent implantation, generating a bleeding risk score which was then validated with the data from two cohorts of patients treated with coronary angioplasty: one from a large randomized study, the PLATO trial, and the other from a Swiss registry of patients undergoing the same intervention.

The derivation set consisted of 14,963 patients from 8 randomized studies, some of them considered in the analysis of the previous publication. Dual antiplatelet therapy consisted of aspirin and clopidogrel in 88% of cases, and in the remaining cases, 12% aspirin was associated with prasugrel or ticagrelor. The primary endpoint was the occurrence of major or minor TIMI bleeding 7 days after angioplasty, in order to rule out bleeding due to the procedure. Median follow-up was 18 months and the annual bleeding incidence was 1.25%, being major bleeding in more than half of the cases. In the multivariate analysis of patient individual data, 5 independent predictors of bleeding were defined: age, creatinine clearance, hemoglobin, white cell blood count and previous bleeding. Based on these predictors, a prognostic score was built, with an acceptable area under the ROC curve: 0.71 to predict major bleeding and 0.73 to predict any bleeding. The discrimination ability was somewhat lower for the ones treated with prasugrel and higher for those treated with proton pump inhibitors. In the validation set, the area under the ROC curve was 0.70 in the PLATO cohort and 0.66 in the Swiss registry.

The score allowed dividing the patients into risk quartiles (very low, low, moderate and high). Among patients with high risk of bleeding, 12-24 month DAT was associated to a significant excess of bleeding compared with 3-6 month treatments, with an absolute risk difference of 2.6 events per 100 patients treated. Among these high risk patients, there was not a significant reduction in the incidence of ischemic events (acute myocardial infarction, stent thrombosis, stroke or new revascularization), either with extended or short DAT. Conversely, in the three lower risk quartiles the situation was the reverse: there was no difference in the incidence of bleeding between extended and short DAT, but a lower incidence of ischemic events: 1.53 less per 100 patients treated.

The data from both publications support the concept that optimal DAT duration differs according to the patient, his clinical status, and risk of ischemic and bleeding events. The first of these meta-analyses suggests that in stable patients, with elective angioplasty, it is not necessary to extend DAT to one year. On the other hand, in cases which have suffered an ACS, certainly a longer DAT should be preferred, because the risk of a new ischemic event persists. However, the risk of bleeding is always higher the longer the dual treatment and this should also weigh in the decision. In this sense, the PRECISE DAPT score may help to predict risk, and hence aid us in decision making, even when the performance assessed by the ROC curve is not superlative: we will adequately discriminate risk in 2 out of 3 cases. An interesting point is the finding that if the risk of bleeding is high, extended DAT does not provide an advantage for the reduction of ischemic events; this means that the higher risk of hemorrhagic complications could indicate patients in whom, in addition, the benefit of a long therapy to reduce ischemic events would be absent. That is, the possibility of success and that of bleeding are tightly bound. Little by little the body of evidence is ordering the concepts. The point is now to have more precise information so as not to commit errors at the time of deciding a clearly strongly based individual conduct: the patient, his comorbidities, the lesion, the stent type and generation, the circumstance and the procedure outcome, compliance with the treatment and risk of complications.