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An image is worth a thousand words: the VIPVIZA study

Naslund U, Ng N, Lundgren A, Fharm E, Gronlund C, Johansson H, et al. Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA): a pragmatic, open-label, randomised controlled trial. **Lancet 2019;393:133-42. http://doi.org/gfkw52**

The primary prevention of vascular disease depends on a series of well-known measures: physical activity, healthy diet, no smoking, and adequate hypertension, dyslipidemia and abnormal glucose metabolism treatment. However, adherence to a favorable conduct is poor despite doctors and patients have all the supposedly necessary information. Is it really so? Will there be data that, known by doctors and patients, serve to improve this prospect? The VIPVIZA study presents an original approach to the problem.

In the county of Västerbotten, in Sweden, the VIP primary prevention program is in force, focusing on people aged 40, 50 or 60 years who are screened for risk factors, an individual interview to motivate the adoption of healthy conducts and pharmacological prevention of cardiovascular disease according to treatment guidelines. In the context of this program, the pragmatic, open-label, randomized, controlled VIPVIZA study was carried out, in which the endpoints were evaluated by researchers blinded to the intervention group (PROBE design). Individuals aged 40 years who had at least one family member less than 60 years with cardiovascular disease; 50-year-old persons with at least one risk factor, or a family member under 60 years with cardiovascular disease; and 60-year-old persons without any necessary additional criteria, were included in the study. An interview, risk factor assessment and clinical and laboratory measurements were conducted in each subject. A carotid ultrasound study was also performed to define myointimal thickness and presence of plaques. In each case, the corresponding value was defined by 2 risk scores: Framingham and SCORE.

In the intervention group, participants and their primary care physicians were given a graphic representation of their carotid study findings. The relationship between vascular age calculated from myointimal thickness and chronological age was plotted on a color scale: green if the vascular age was 10 years less than the chronological age, red if it was 10 years older and yellow or orange if the situation was intermediate, closer to a favorable (yellow) or unfavorable (orange) condition. In addition, the report presented a circle that could be red (presence of plaque) or green (absence). And finally, a stylized image of the carotid artery was presented, where the myointimal thickness and the location of red plaques were drawn with the same color scale. The participants of this group were also provided with an explanatory text, and at 2 to 4 weeks a nurse made a phone call to confirm that they had understood the information and to answer their questions. At 6 months, the same procedure was repeated. In the control group, none of these actions was carried out. The primary endpoint of the study was the change in risk scores at 1 year. Secondary endpoints were variations in blood pressure, lipids, blood glucose and treatment.

Between 2013 and 2016, 3,532 participants were included, 1,749 of them in the intervention group. Fifty-three percent were women, 8% were 40 years old, 28% were 50 years and 64% were 60 years. Fifty-two per cent were hypertensive and 5% diabetic, 93% were dyslipidemic and only 12% regular or occasional tobacco smokers. The average value of the Framingham score was 12.9, with 48% of participants with an estimated risk at 10 years <10%, 33% with an estimated risk ≥10% and <20% and the rest with a risk ≥20%. The average value of SCORE was 1.28, with 55% of patients at low risk, 43% at moderate risk and the rest at high or very high risk. Carotid plaque was present in 45% of participants, and the mean myointimal thickness was 0.74 mm. In the vascular age scale, 8% corresponded to green, 19% to yellow (favorable conditions); 30% to orange and 43% to red.

Among initially included subjects, 3,175 completed the follow-up year. Those who dropped out tended to be somewhat younger, and specifically in the intervention group, with a higher prevalence of obesity and smoking. After 1 year, there was a significant difference in the Framingham score (mean of 12.2 in the intervention group and 13.3 in the control group, p=0.0017), with a 5% drop in the intervention group and an increase of 3% in control group. In the case of SCORE there was aslight increase in both groups, with final scores of 1.42 in the intervention group and 1.58 in the control group (p=0.010). There was reduction in total cholesterol and LDL in both groups, but significantly greater in the intervention group after adjusting for age, gender and educational attainment, a result that was accompanied by greater use of lipid-lowering drugs. Although there was a trend to more favorable evolution of blood pressure and weight in the intervention group, the difference was not significant.

The VIPVIZA study extends and gives greater external validity to similar studies with fewer patients performed only in tobacco patients or diabetics. Although the result obtained with the intervention seems modest (1 point in the Framingham score), given that

it is a low intensity strategy and simple to carry out, which can induce behavioral modifications sustained over time and therefore able to generate changes in the incidence of clinical events (something that this study fails to demonstrate), its usefulness seems indisputable. Formal cost-effectiveness analyses may help define their relevance. "Seeing" vascular damage, rather than simply reading or hearing it, seems to contribute to achieve a significant modification in the lipid profile, and a trend to changes in weight and blood pressure. The most notable effects are obtained among patients with the highest burden of disease.

In view of this success, it is logical to ask a few questions: is the achievement due to changes in the eating habits, to the increase in physical activity, or to changes in pharmacological treatment? And, above all: which behavior is modified faced with the graphic representation of vascular disease? That of patients, who take charge of the problem and initiate a behavioral change? Or that of the doctors, who despite all their theoretical knowledge and the help of treatment guidelines, are impelled to improve their therapeutic practice when challenged by the profusion of reds and oranges?

Vaccination against influenza benefits patients with heart failure

Modin D, Jorgensen ME, Gislason G, Jensen JS, Kober L, Claggett B, et al. Influenza Vaccine in Heart Failure. **Circulation 2019; 139: 575-86. http://doi.org/c2z5**

There is well known association between influenza virus infection and higher risk of presenting acute coronary syndromes. The incidence of influenza can also complicate the prognosis of patients with heart failure. However, guidelines for the treatment of heart failure do not make influenza vaccination a class I indication, perhaps because there is no firm evidence from randomized studies. Until this evidence arrives (a clinical trial is under development) we can rely on observational study findings. We have just learned the data of a large Danish registry. In Denmark there is a single Registry of outpatients and inpatients that can be associated with vital statistics and dispensed medication registries. The entire population has public health coverage and the administration of influenza vaccine is free for all people with cardiovascular disease. In the study here discussed, all patients in whom heart failure was diagnosed between 2003 and 2015 were considered. After excluding those who died within the first 30 days of diagnosis, a population of 134,048 patients was defined, determining whether or not they had received at least once the influenza vaccine after diagnosing heart failure, the number of times they had been vaccinated and the time of the year when the vaccine had been administered. The final endpoint of the study was all-cause mortality and cardiovascular mortality.

Median follow-up was 3.7 years, during which 58% of patients received at least once the influenza vaccine. Follow-up was complete in 99.8% of the patients. In 98% of cases, the vaccine was administered between the months of September and December corresponding to the autumn of the Northern hemisphere. Patients who received the vaccine were somewhat older, with a higher prevalence of male sex, comorbidities and greater use of cardiovascular medication. In the unadjusted analysis, having received the vaccine was associated with a significant excess of risk of total and cardiovascular mortality (28% and 26%, respectively). However, adjusting for the presence of the described confounders (age, gender, comorbidities and baseline medication), it was found that the administration of at least one shot of the influenza vaccine was associated with a reduction in the risk of total and cardiovascular mortality, in both cases of 18% ($p < 0.001$). If the vaccine was received every year the follow-up risk reduction was 19%. If the frequency was less than once a year, the reduction was significant but lower, 13% for total mortality and 8% for cardiovascular mortality. Risk reduction was greater for those vaccinated in September and October than for those who received the vaccine in November or December. There was a minimal but significant reduction, of approximately 4%, in the incidence of pneumonia in patients who received the vaccine.

The reasons why influenza can worsen the prognosis of heart failure are varied. The infection can, like any other, generate inflammatory and neurohormonal activation and increase myocardial oxygen consumption. It has been shown that there is a higher incidence of coronary events after infection with the influenza virus. Viral aggression may result, among other things, in myocarditis that may often be fatal when it generates contractile depression in patients who already have compromised ventricular function. Influenza can open the pathway to bacterial respiratory infections that may worsen the condition. In this context, these registry's findings are not unexpected, because there is already evidence of randomized studies on the beneficial effect of vaccination in cardiovascular patients without heart failure. It may also be that vaccination for influenza is a marker of better treatment in general: a patient who receives indication for vaccination may also be a patient in which more attention is paid to other aspects of the disease and in which the quality of the care received is greater. Nevertheless, until not having data to the contrary, the conclusion is to always bear in mind, and especially in the forthcoming autumn, the benefits that vaccination against influenza seems to offer in cardiovascular patients, especially in those with heart failure, in terms of a very significant reduction in mortality, of around 25%.

A comment that cannot be ignored is that of the healthy envy generated by the ability to associate data from national registries and obtain relevant clinical information, especially when evidence from observational studies is not available. In this sense, the certainty that we are very far from this reality and pos-

sibilities, should be no reason for discouragement, but a strong injection of enthusiasm to reverse the state of affairs that dominates today in which ignoring what we do and how we are doing it seems to be the rule in most cases.

Troponin elevation is not an innocent phenomenon, even when an acute coronary syndrome is ruled out.

Eggers KM, Jernberg T, Lindahl B. Cardiac Troponin Elevation in Patients without a Specific Diagnosis. **J Am Coll Cardiol 2019; 73: 1-9. http://doi.org/c2z6**

The assessment of troponin levels of cardiac origin plays a fundamental role in patients with chest pain, in whom it is essential for the diagnostic certification of an acute coronary syndrome and to guide therapeutic decisions. A value above the 99th percentile is considered as expression of myocardial injury, and if there is compatible clinical evidence, of acute myocardial infarction (AMI). Phenomena not due to plaque accidents (embolism or coronary spasm and microvascular disease) also generate increased troponin plasma levels, as well as myocarditis and Takotsubo syndrome. There are other conditions in which troponin measurement contributes to define the severity of the disease and can also guide certain treatments, such as pulmonary embolism, pulmonary hypertension and heart failure. But on many occasions the presentation of patients at the emergency department, with more or less clear symptoms and with troponin elevation above the 99th percentile does not produce any definite diagnosis, and this elevation is then left without a clear explanation. It is common then that we use terms such as "troponinitis", which means a high troponin level for unknown reason, indicating a laboratory alteration that seems to involve no risk. Is it really so?

We have already referred to the Swedish SWEDEHEART registry on other occasions. It is a national registry in which all patients admitted to coronary care units are included due to a presumed acute coronary syndrome. Data from more than 100 variables are prospectively collected to describe the presentation, treatment and evolution patterns of these patients. An analysis of this registry allows us to unravel the meaning of the alleged "troponinitis". All patients admitted between 2003 and 2015 that were discharged without a specific diagnosis of acute coronary syndrome were included in the analysis. Patients were divided into 4 categories: those with a troponin level ≤99th percentile of the reagent used in each case for troponin T or I assessment and those with higher levels than the established cutoff value, divided into increasing tertiles according to the level reached. The association of troponin levels with the outcome was specifically studied in 3 cohorts: 1) patients without previous cardiovascular disease; 2) patients who also had glomerular filtration ≥60 ml/min/1.73 m2; and 3) patients who in the previous conditions had a left ventricular ejection fraction >50% and absence of coronary disease defined by lesions ≥50%.

The study population consisted of 48,872 patients, 95% of whom had consulted for acute chest pain. The diagnosis at discharge was nonspecific chest pain in 79% of cases and observation due to suspected acute myocardial infarction (AMI) in 16%. Overall, 20.1% of the patients had troponin levels above the 99th percentile (18.2% in cohort 1, 17.2% in cohort 2 and 30.1% in cohort 3). Age, prevalence of risk factors (except smoking) and of established cardiovascular disease was greater the higher the troponin levels. In patients in whom an echocardiogram was performed, a greater prevalence of ventricular dysfunction was found when these values were higher. In a median follow-up of 4.9 years, 15.4% of patients experienced one significant adverse event, mainly all-cause mortality, AMI or hospitalization due to heart failure. The risk of presenting one of these events increased stepwise according to the strata of troponin levels. Thus, for example, for an annual mortality of 2.2% in the entire cohort, the annual incidence was 1.8% in those with troponin levels below the 99th percentile, and 2.8%, 4% and 7.6% in tertiles 1, 2 and 3, respectively. The difference between the upper tertile and the two lower ones was especially notable in the cohort of patients without cardiovascular, kidney or coronary heart disease and with preserved ejection fraction, in which the HR for major events was 1.25 (p: NS), 1 26 (p: NS) and 3.57 for tertiles 1, 2 and 3 compared with patients with normal troponin values.

The association of elevated troponin levels with worse prognosis has already been reported in different clinical conditions. To those already mentioned at the beginning of this comment we can add similar examples in the case of peripheral vascular disease, atrial fibrillation, non-cardiac disease (for example, in cases of respiratory distress or sepsis) and also in the general population. Thus, for example, in people older than 65 years without evident cardiovascular disease, slight elevations of troponin indicate a greater risk of events. Thus, we should not be surprised by the findings of this study. Let us clearly note how the highest troponin levels correspond to people who, although not undergoing an acute coronary syndrome at the time of consultation (not for the current diagnostic criteria), have a higher burden of cardiovascular disease. Does that elevation point out to more compromised patients, for example with chronic heart disease or incipient kidney damage, in whom at the time of consultation "nothing acute is happening", or to subtle clinical conditions, which we are still unable to read as acute?

Beyond not being able to demonstrate an event at the time of the assessment, it is clear that the elevation of troponin above the 99th percentile defines myocardial injury, and therefore, is not an innocent phenomenon. If the conduct is clear when the clinical condition of acute coronary syndrome is present, how to behave when the etiological diagnosis is not available? The findings of this Registry clearly suggest that

close monitoring, the performance of complementary examinations (images, evocative tests) and the intensive treatment of risk factors and associated conditions is essential. The term "troponinitis" should only be a way of describing our ignorance.

The presence of sleeping disorders is associated with a higher prevalence of subclinical atherosclerosis.

Dominguez F, Fuster V, Fernandez-Alvira JM, Fernandez-Friera L, Lopez-Melgar B, Blanco-Rojo R, et al. Association of Sleep Duration and Quality with Subclinical Atherosclerosis. **J Am Coll Cardiol 2019; 73: 134-44. http://doi.org/c2z7**

Sleeping disorders have been associated with cardiovascular disease. When the duration of sleep is short, the prevalence of obesity, hypertension and diabetes is higher. Some publications indicate that there is also implicit risk when the duration of sleep is very long. Some reports have remarked that in people with sleeping disorders the risk of atherosclerotic disease, coronary heart disease and stroke is higher. But most of these publications rely on questionnaires or self-report. Dr. Valentín Fuster has generated in Santander a prospective cohort study, the PESA CNIC, which includes Banco de Santander employees from 40 to 54 years of age, free of clinically manifested cardiovascular disease at the time of inclusion. A recent analysis confirms the association of sleeping disorders with the presence of objectively demonstrated subclinical atherosclerosis.

Individuals with obstructive sleep apnea were excluded from the analysis. Baseline data, risk factors and other clinical and laboratory variables of interest were available for the study. All participants were subjected to an actigraphy study. This procedure consists in placing an accelerometer on the patient, usually in the wrist of the non-dominant arm, although it can also be in one leg or, as in the case of this study, in the waist. The device remains in place for no less than 5 days (7 in the study we are discussing). By detecting the body movements and their intensity, it allows to define the times of the sleep-wake cycle, the total amount of daily hours destined to sleeping and the sleep quality, when analyzing its fragmentation. A value of 7 to 8 hours per day was defined as a category of reference or normal sleep duration. A duration of sleep <6 hours was considered very short sleep (VSS), 6 to 7 hours short sleep (SS) and >8 hours long sleep (LS). The measurement of sleep fragmentation was divided into quintiles, and the lowest quintile (the one with the least fragmentation) was taken as reference. A three-dimensional vascular Doppler was performed in all participants to define the presence of atherosclerotic plaques in the carotid and femoral territory, and a non-contrast computed tomography was also carried out to determine in each case the presence of coronary calcification and the Agatson score. .

A total of 3,974 participants (62.6% men) with mean age of 45.8±4.3 years were included in the study. Only 30.7% had sleep duration lasting between 7 and 8 hours a day; 27% presented VSS, 38.3% SS and 4% LS. Participants with VSS and SS were older, with a higher prevalence of cardiovascular risk factors and greater risk at 10 and 30 years estimated by the Framingham score. Similarly, the quintile with greater sleep fragmentation had more advanced age, and higher prevalence of hypertension and smoking.

Participants with VSS presented an excess risk of 27% (p=0.008) of being within the highest tertile of plaque burden, and tendency to have more affected territories. This association was independent of age, gender, vascular risk factors, education, marital status or tendency to present sleep apnea assessed by an ad hoc questionnaire. Participants with greater sleep fragmentation presented greater extent of atherosclerotic disease. Although there were no differences between the different categories of sleep duration with respect to caloric intake, participants with VSS had higher alcohol intake, and both in these and in those with SS greater consumption of caffeine. This was also verified among subjects with very fragmented sleep. People with VSS had higher values of C-reactive protein, although the association was lost in the multivariate analysis. There was no association of sleep duration with the presence of coronary calcium. Presenting LS was linked with a higher plaque burden among women but not in men.

The reasons why sleep disorders are associated with a greater presence of atherosclerotic disease are varied: higher prevalence of risk factors, more neurohormonal and inflammatory activation, alteration in the levels of growth hormone, and greater insulin resistance. Some researchers have highlighted the association of SS with obesity. In this report, a greater consumption of coffee and alcohol have also been noted as pathogenic factors. A point that seems essential is that this association is independent of the presence of obstructive sleep apnea, which in turn is clearly related to the increase in sympathetic tone, and higher risk of hypertension, coronary events, heart failure and arrhythmia. The association with the presence of plaque, but not with the calcium score may simply represent the finding of early stage atherosclerosis (do not forget the average age of 45 years). One limitation of the study is the use of actigraphy instead of polysomnography, which is the gold standard for exploring sleep disorders, but it is no less true that this method of study is more economical, allowing studies with a large number of subjects; moreover, a good association with polysomnographic findings has been demonstrated.

Now, what does short duration sleep actually express? Is it the result of the individual genetic expression? Is the relationship with metabolic alterations causal, uni- or bidirectional? Or does it reveal a certain psychic and behavioral environment, which, just as it alters sleep, also damages the endothelium? Are short sleep and vascular disease two independent results of greater stress? The complex relationship of sleep with

atherosclerosis is yet another expression of the brain-heart interaction, and much remains to be understood. Meanwhile, and in the absence of randomized trials, ensuring a good sleep hygiene and habits that tend to its adequate duration seems to be an advice that surely does not cause harm, and is potentially beneficial.

Coronary angioplasty guided by fractional flow reserve measurement decreases the risk of events in stable patients. A meta-analysis of individual data.

Zimmermann FM, Omerovic E, Fournier S, Kelbaek H, Johnson NP, Rothenbuhler M, et al. Fractional flow reserve-guided percutaneous coronary intervention vs. medical therapy for patients with stable coronary lesions: meta-analysis of individual patient data. **Eur Heart J 2019; 40: 180-6. http://doi.org/c2z8**

In recent years the assessment of fractional flow reserve (FFR) has emerged as the gold standard to define the hemodynamic involvement of intermediate coronary lesions (40-90% stenosis) when there is no evidence of ischemia in an evocative test. In the case of stable coronary lesions, if the value of FFR is ≤0.80, it is understood that catheter revascularization offers a better prognosis than medical treatment, considering a composite endpoint of death, acute myocardial infarction (AMI) and need for new revascularization. However, in the different randomized studies, this improvement has been achieved specifically at the expense of a reduction in the need for revascularization, without clear evidence of a reduction in AMI or death. Since studies comparing FFR-guided revascularization with medical treatment are open-label, it is possible that revascularization may be indicated more frequently if symptoms appear in patients in the medical treatment group, i.e., there could be a bias in favor of the FFR arm when considering the need for new revascularization as an endpoint. The question that persists is whether a strategy guided by FFR can effectively reduce the incidence of death or AMI.

To answer this question, a meta-analysis of individual data was carried out considering the three large studies that compared two strategies, FFR-guided coronary angioplasty vs. medical treatment, in hemodynamically stable patients with stable lesions. The three studies were FAME 2, which included chronic coronary patients; and DANAMI-3-PRIMULTI and Compare Acute, which included patients with ST-segment elevation AMI, in whom after treating the unstable lesion responsible for AMI, the rest of the coronary tree was evaluated, and if other stable lesions were detected, they were randomly assigned to FFR-guided angioplasty or medical treatment. A total of 2,400 patients were considered; among them, 1,056 underwent FFR-guided angioplasty. There was no difference in baseline characteristics between both strategies. In the FAME 2 study, all patients had FFR ≤0.80. In contrast, 31% of patients in the DANAMI 3 PRIMULTI trial had negative FFR in all lesions, and 49% of patients were in the same situation in the Compare Acute trial.

In a median follow-up of 35 months, there was 28% reduction in the incidence of cardiac death or AMI in the FFR-guided group (HR 0.72, 95% CI 0.54-0.96, p=0.02). The estimated incidence at 5 years was 16.4% with medical treatment and 10.3% in the FFR-guided group. The difference was specifically due to a lower incidence of AMI (HR 0.70, 95% CI 0.51-0.97), with no difference in the incidence of cardiovascular death or all-cause mortality. The benefit was evident in patients in whom there was at least one lesion with FFR ≤0.80, that is, in those in whom the determination led to coronary angioplasty. There was no difference according to the presentation (stable coronary lesion vs. AMI). A non-significant excess risk of the endpoint was verified in the first 7 days after the procedure with the FFR-guided strategy (HR 1.94, 95% CI 0.84-4.42), followed by a marked reduction since day 8 (HR 0.62, 95% CI 0.46-0.85). This interaction between treatment and the incidence of the endpoint was basically defined by the risk of AMI, higher with the invasive strategy in the first week and lower after it.

After a series of clinical trials failed to demonstrate that in stable lesions an invasive conduct can reduce a hard endpoint (death or AMI), this meta-analysis suggests that this is indeed the case. A series of considerations must be formulated in order to better understand this finding. Firstly, each of the previous studies had, due to the number of patients included, little power to detect a significant effect (approximately 25% power to detect 30% reduction in a composite endpoint of death or AMI). Due to the number of patients considered, this meta-analysis had much greater power, of about 65%. Secondly, many of the previous studies were carried out with bare-metal stent grafts, and not drug-eluting stents as considered in this meta-analysis. On the other hand, and this is not a minor fact, in many of these studies the conduct was decided based on angiographic findings, without an FFR-guided approach. And, finally, even in studies with FFR, there was a high proportion of patients in whom although all the lesions were negative FFR, an angioplasty was nevertheless carried out. The last study of these characteristics is the ORBITA trial, with 29% of patients with lesions of these characteristics.

In the meta-analysis we present, risk reduction was 28%, basically due to a reduction in the risk of AMI. But if we consider the cases in which angioplasty was performed due to the presence of a lesion with FFR ≤0.80, the risk reduction increases to 38%. This seems to be the group of patients in whom it is possible to expect an advantage with an invasive approach: angioplasty defined by the finding of decreased FFR, expressing a lesion that imposes true jeopardy of the territory irrigated by the involved artery. It is important to bear in mind that in the first 7 days the procedure imposes a greater risk than following medical treatment (something similar to what happens when heart surgery is compared with medication in stable

patients, and the risk is greater in the course of the first month with the invasive treatment). And a detail to take into account is the most frequent administration of double anti-aggregation therapy in the group of patients undergoing FFR, 99% vs. 82%, which may have contributed to the different outcome. A randomized study currently underway, the ISCHEMIA trial, will undoubtedly shed more light on the subject.

A meta-analysis of aspirin for primary prevention. Will it be the final one?

Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-analysis. **JAMA 2019;321:277-87. http://doi.org/gft2vs**

Use of aspirin for secondary prevention of cardiovascular and cerebrovascular events is unquestionable. For primary prevention, however, conflicting results have been obtained regarding a possible favorable balance between prevention of ischemic events and the incidence of bleeding attributable to the medication. A meta-analysis performed in 2009 with 95,000 patients established a relative 12% reduction in a composite endpoint of cardiovascular death, acute myocardial infarction (AMI) and stroke, at the expense of 30% increased risk of bleeding. Another meta-analysis in 2012, with more than 100,000 patients confirmed the reduction of adverse events, especially AMI, but again with significant increase of bleeding. Treatment guideline recommendations are not uniform. Recently, the ARRIVE study in patients with 10% and 20% estimated risk of events at 10 years (although the real incidence was below 10%) could not demonstrate a significant reduction of ischemic events, but found greater incidence of hemorrhagic incidents. Along the same line, in the ASCEND study in diabetic patients, use of aspirin for primary prevention evidenced reduction of cardiovascular and cerebrovascular events, though with a similar increase of bleeding episodes. In the ASPREE study, use of aspirin for primary prevention in patients ≥70 years (≥65 years if they were Hispanic or black patients) was associated with the same incidence of major adverse cardiovascular events (fatal or non-fatal myocardial infarction or fatal or non-fatal stroke) as in the placebo group. Aspirin produced excess risk of major bleeding and all-cause mortality, mainly due to the increased risk of death for cancer.

We now know the results of a new meta-analysis that incorporated the cited studies to the already known information. It considered 13 randomized studies with a total of 164,225 participants (47.2 % men) with median follow-up of 5 years. Nine studies were placebo-controlled, double-blind studies and four were open-label studies comparing aspirin use vs. non-use.

The primary endpoint was a composite of cardiovascular death, non-fatal AMI and non-fatal stroke, and its annual incidence was 5.7‰ in the aspirin group and 6.1‰ in the control group, with a HR of 0.89 (95% CI 0.84-0.95) and a number needed to treat (NNT) of 265 patients to prevent a major event. Use of aspirin was not associated with reduction of all-cause cardiovascular death. It was associated with reduction of AMI (HR 0.85 with NNT of 361) and ischemic stroke (HR 0.81 with NNT of 540), but not of all-cause stroke. Parallel to the use of aspirin, there was increased annual risk of bleeding: 2.3‰ vs. 1.6‰ in the control group (HR 1.43; 95% CI 1.30-1.56). The number needed to harm (NNH), i.e. to generate an excess major bleeding was 210. The risk of hemorrhagic stroke was greater with aspirin (HR 1.34, NNH 927), as well as that of gastrointestinal bleeding (HR 1.56, NNH 334). In studies where estimated risk of major events at 10 years was <10%, use of aspirin was associated with a reduction in the composite outcome, with a NNT of 297 patients; in studies with estimated risk ≥10%, aspirin was also associated with reduction of the composite outcome, with a NNT of 196. In both populations, aspirin increased the risk of major bleeding, with a NNH of 249 and 152, respectively. Balance between NNT to decrease a major event (153) and NNH to generate excess bleeding (12) was also reported among diabetic patients. No excess risk for cancer or death for this cause could be demonstrated.

Another meta-analysis on aspirin for primary prevention, and there are…. However, after three significant studies on the subject were published last year, its arrival was unavoidable.

We have thus recent data with a more precise quantification of expected benefits and harms, without changes in the previous concept: an almost perfect balance between one and the other, so that the decision will continue to be, as up to now, individual. Perhaps, in patients with great risk burden and small propensity to bleeding, aspirin will find its place in primary prevention. What is clear is that its use cannot be postulated as an extended strategy. Maybe the most remarkable result is that aspirin seems not to be linked to the incidence of cancer: it neither decreases its occurrence, as sustained by other studies, nor increases it, as suggested by the ASPREE study.

A new concept in heart failure: the presence of endotypes

Tromp J, Ouwerkerk W, Demissei BG, Anker SD, Cleland JG, Dickstein K et al. Novel endotypes in heart failure: effects on guideline-directed medical therapy. **Eur Heart J 2018;39:4269-76. http://doi.org/gd46jc**

Heart failure treatment, as that of any other disease, relies on a series of recommendations, some based on the results of randomized studies, and most on empirical considerations. Treatment guidelines of scientific societies define the strength and the level of evidence for each recommendation. However, it is clear that applying the same measures do not yield the same results in all patients, despite being suggested in

the guidelines. For each intervention, some patients respond more or less; they are responders or non-responders. This differential response can be attributed to different factors: baseline clinical conditions, presence of comorbidities, facilitators and barriers. The concept of a personalized medicine, beyond the recommendations "for everybody or nobody" responds to this reality.

Along this line of reasoning a recent publication introduces the concept of endotypes in heart failure. It considered patients from the BIOSTAT-CHF study, including two cohorts. The derivation cohort consisted of patients with recent-onset or progressive heart failure, with left ventricular ejection fraction (LVEF) ≤40% or elevated natriuretic peptide levels (BNP >400 pg/ml or NT pro-BNP >2000 pg/ml), from 69 centers in 11 European countries, either untreated, or treated with <50% of the recommended dose of angiotensin converting enzyme inhibitors (ACEI) and/or betablockers (BB). The validation cohort consisted of patients with similar characteristics to the former, from 6 centers in Scotland. Ninety-two cardiovascular biomarkers were measured in each patient to identify by means of complex statistical procedures, including principal component analysis, 6 subgroups of mutually exclusive patterns of biomarker levels (clusters). These groups or endotypes were defined in the derivation cohort (1,802 patients) and their existence was confirmed in the validation cohort (813 patients).

The 6 endotypes of the derivation cohort presented a number of patients ranging between 80 (endotype 5) and 435 (endotype 2). An area under the ROC curve was outlined for each of the biomarkers which defined an endotype, in many case with a value <0.78. NT pro-BNP was among the three biomarkers with highest ROC area in 3 of the 6 endotypes. As can be deduced, most biomarkers considered are not usually measured in cardiological practice. Endotype 1 patients were the youngest and less sick patients (predominantly FC I-II, with mild signs and symptoms). Endotype 2 patients presented greater prevalence of anemia and kidney dysfunction, those with endotype 3 exhibited more frequently ischemic etiology, and those with endotype 4 had more severe signs and symptoms of heart failure and the highest levels of natriuretic peptides. In turn, endotype 5 patients showed more frequently anemia and those with endotype 6 the greatest prevalence of hypertension. At the end of a 21-month follow-up period, the incidence of the composite outcome of death or hospitalization for heart failure was highest for endotype 4 (48%) and lowest for endotype 1 (24%). Following adjustment for a clinical risk score considering usual variables (age, blood urea nitrogen, hemoglobin, NT pro-BNP and use of BB at the time of inclusion), endotype 4 had still the worst prognosis for the composite outcome and endotypes 2 and 4 had the greatest mortality. Overall, the endotype classification displayed worse performance than the clinical score to discriminate prognosis, with areas under the ROC curve of 0.61 and 0.71, respectively.

The rate of ACEI uptitration was low for endotype 4 and high for endotypes 3 and 6. The rate of uptitration to recommended target dose of BB was low for endotype 6 and high for endotypes 1 and 5 after adjusting for ACEI uptitration. But what was really interesting was the prognostic response to BB uptitration in the different endotypes. Uptitration of BB was beneficial in endotype 6, neutral in endotype 5 and harmful in endotype 2.

This is a very interesting study from a physiopatological viewpoint: it points out that heart failure can adopt diverse humoral patterns, which translate into patterns of response to medication, and even in a different prognosis. Knowing the values of these biomarker combinations may thus contribute to a better patient characterization. But we can forward some comments that will dampen our initial enthusiasm. Firstly, many of the cited biomarkers are far from being accessible or even known (for example, who has ever heard about chitotriosidase 1, with the greatest area under the ROC curve to define endotype 5? In a setting where it is sometimes difficult to have access to natriuretic peptides, the definition of patterns based on biomarkers that can only be measured in the context of research studies has no practical value. Secondly, even when the determinations could be carried out, it would be necessary to consider a cost analysis, which we assume might provide not very favorable results, especially if we take into account an essential data: the area under the ROC curve to classify endotypes is poor (0.61) and below the reference clinical model, built with usual variables.

Then? The endotype concept looks attractive, but should be refined to be truly useful. In the progress of physiopathological knowledge we cannot still appreciate the reason for the association of these patterns with the outcome. Models considering more accessible and explicable variables would be preferable. But it is also true that what today is enigmatic may tomorrow be a new way of understanding the etiopathogenesis of disease and the adoption of more appropriate conducts.

Which is the best anti-anginal drug? A systematic review

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Nitrates, betablockers and calcium antagonists are often used for the standard treatment of chronic stable angina. In fact, long-acting nitrates started to be used in 1867, propranolol was introduced in 1964 and calcium antagonists in 1975. These are considered first-line drugs for the treatment of this disease. In the last decades, other drugs, considered as second-line treatments have been incorporated: ivabradine, ranolazine, trimetazidine and nicorandil, some of which are not available in our country. However, in the era

of evidence-based medicine, what is the corroboration to recommend any of these drugs over others, and on what basis?

A systematic review questions many of our assumptions. The search was based on randomized studies published in English comparing two drugs of different families, with a minimum of 100 patients with chronic stable angina (50 per group) and minimal follow-up of 1 week. As there are no studies in this context with hard events as the final outcome, the review considered the effect on the time of exercise. Only 13 studies met these criteria, 9 which enrolled between 50 and 150 patients per group (a total of 1,611 patients) and 4 with more than 150 patients per group (a total of 2,818 patients). Only one study comparing metoprolol and nifedipine evidenced superiority of the former with respect to the time to the first millimeter of ST-segment depression, but not with respect to the total exercise time. None of the remaining 12 studies demonstrated superiority of any anti-anginal drug over others.

In the context of evidence-based cardiology, it is especially remarkable that the treatment of one of the most frequent and extended diseases is a fertile field for empirical therapy and assumptions. Physiopathological considerations and perhaps the years they have been used and habit make some of these drugs seem superior to others, without clear demonstration of phenomena that justify their preeminence as a therapeutic resource. This neither means that they should be rejected or that we should automatically prefer others; but it is always good to know why we do what we do, and on what basis. Proportional studies are still lacking in the context of chronic stable angina. Perhaps, the extended use of aspirin, statins and percutaneous or surgical revascularization make it impossible to demonstrate that in a chronic and stable disease with low rate of events, an anti-anginal drug may have effect on hard events. But more specific physiopathological studies taking into consideration the different mechanisms involved might help us to adopt more accurate decisions in the future.