

JORGE THIERER

An interesting analysis on the determinants of cardiovascular disease and mortality. The PURE Study

A, Hystad P, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study.

Lancet. 2020;395:795-808.

It is estimated that a third of the deaths worldwide are of cardiovascular origin. The PURE study is a prospective cohort study designed to provide contemporary information on the prevalence of risk factors and socioeconomic conditions, and their relationship with different cardiovascular outcomes. In the present study, the associations and the population attributable fraction (PAF) of 14 modifiable risk factors with cardiovascular disease and mortality were precisely quantified and compared. The study included 4 high-income countries (HI): Canada, Sweden, Saudi Arabia, and the United Arab Emirates; 12 middle income countries (MI): Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, Palestine, the Philippines, Poland, Turkey and South Africa; and 5 with low income (LI): Bangladesh, India, Pakistan, Tanzania and Zimbabwe. In the participating countries, urban and rural communities were chosen using pre-specified criteria. Within each community, households and individuals were selected by sampling to avoid selection bias. The analysis was performed on those included who had had at least one follow-up visit. Potentially modifiable, behavioral, metabolic and environmental risk factors were considered. Behavioral risk factors were tobacco use, alcohol consumption, diet quality, physical activity, and sodium intake. Metabolic factors considered were high blood pressure, dysglycemia or history of diabetes, non-HDL cholesterol, and abdominal obesity measured using the waist-hip ratio. Additionally, environmental pollution, grip strength measured with a dynamometer, educational level and the presence of depressive symptoms were considered. The primary endpoint was a composite of cardiovascular events: cardiovascular death, myocardial infarction (AMI), stroke and heart failure (HF), and all-cause death.

Between January 2005 and December 2016, 155,722 participants between 35 and 70 years of age were included in the study, with a median follow-up of 9.5 years. Mean age was 50.2 years, and 58.3% were women; 52.6% lived in urban areas, 20.4% were current tobacco users, and 4.2% consumed moderate and 1.9% large amounts of alcohol. In 18.5% of cases participants reported low physical activity, 11.3%, symptoms consistent with depression, 39.4% had high blood pressure and 10.2%, diabetes. Mean non-HDL chole-

sterol was 142 mg/dL and mean body mass index (BMI) 25.7 kg/m². During follow-up, the following outcomes were reported: 10,234 deaths (2,917, less than 30%, due to cardiovascular disease), 7,980 cases of cardiovascular disease, 3,559 AMI and 3,577 strokes.

Low income and MI countries had more individuals from rural areas, and a slightly lower average age in relation to those with HI. Primary education was the highest level achieved by most participants in LI countries (54%), and in a minority of participants in HI countries (13.2%). Among the latter, 58% had tertiary or university education. Diet was healthier in HI countries, but they also had the highest history of smoking or alcohol consumption. Mean BMI, waist-to-hip ratio and non-HDL cholesterol were higher among HI countries, there was a higher prevalence of hypertension in MI countries (with a strong influence of China), and of diabetes in LI countries. Air pollution was also higher in LI countries.

The behavioral risk factor most strongly associated with cardiovascular disease was tobacco use, followed by low physical activity and poor diet quality. Among metabolic risk factors, the strongest association with cardiovascular disease corresponded to hypertension, followed by diabetes, elevated non-HDL cholesterol and increased waist-hip ratio. Low levels of education, depression, low grip strength, and household air pollution were also associated with an increased risk of cardiovascular disease. Hypertension was the highest risk factor for stroke, while diabetes, non-HDL cholesterol, and current tobacco use were stronger risk factors for AMI. Metabolic risk factors tended to have greater association with cardiovascular death compared with non-cardiovascular death. Approximately 71% of PAF for cardiovascular disease, 79% for AMI, and 65% for stroke were attributed to individual and family risk factors. Risk factors contributed to a higher proportion of PAF for cardiovascular disease in LI countries.

In the general cohort, hypertension was the highest population risk factor for cardiovascular disease (PAF of 22.3%), followed by high non-HDL cholesterol, environmental pollution, smoking, poor diet quality, abdominal obesity, and diabetes (each contributed with 5%-10% PAF for cardiovascular disease). Hypertension was the risk factor with the highest PAF for stroke (greater than 30%), followed by household air pollution and poor diet (each with PAF around 10%). Regarding AMI, the risk factor with the highest PAF (above 15%) was elevation of non-HDL cholesterol, followed by hypertension, smoking, and abdominal obesity, each with PAF close to 10%.

Regarding all-cause mortality, among the behavioral risk factors, tobacco consumption showed the

strongest association, followed by high alcohol consumption, low physical activity and poor diet; among the metabolic risk factors, diabetes was the strongest risk factor, followed by hypertension and abdominal obesity. Compared with the lowest non-HDL cholesterol tertile, the top two tertiles were associated with lower risk of death. This striking finding can be attributed to reverse causality. Educational level and household air pollution were strongly associated with an increased risk of death. In LI countries, low educational level and alcohol consumption had the strongest associations with total mortality, while in those with HI, smoking showed the strongest association.

In 75% of cases, total deaths were attributable to risk factors at an individual and family level. Low education had the highest PAF for death in the general population, closely followed by tobacco use, low grip strength, and a poor diet (each contributes >10% of PAF for death). Hypertension, household air pollution and diabetes contributed between 5% and 10% of PAF for death in the general population. Tobacco use was the highest risk factor for non-cardiovascular death, closely followed by low education, low grip strength, poor diet and domestic pollution.

This large epidemiological study confirms, in principle, previous information on the differences between countries with different income levels regarding risk factors for cardiovascular and global disease. In this sense, it once again demonstrates that HI countries are those with the highest BMI and, in parallel, those with the healthiest diet but the highest obesity (these findings seem opposed). And despite the higher prevalence of obesity there is a lower prevalence of diabetes than in those with LI, demonstrating the multi-causality of this pathology.

The study ratifies the importance of traditional risk factors to determine the risk of cardiovascular disease. Considered independently from the behavioral, metabolic, or environmental classification, the factors with the highest hazard ratio (HR) for cardiovascular disease are hypertension (HR 2), diabetes (HR 1.74), and current smoking (HR 1.69). But one thing is HR and another is PAF; HR expresses the strength of association of a variable with the outcome and the excess risk in the individual patient when the variable is present compared to the strength of association when it is not present; while PAF expresses the relative weight of each variable to define the outcome in the population. So, due to its very widespread condition, high blood pressure has high PAF (>20%), while diabetes, second in the ranking by HR, falls to the eighth place, and household air pollution rises to the third position.

The study also shows how high blood pressure is by far the most important population risk factor for stroke, and non-HDL cholesterol for AMI. And how, when PAF is considered no longer for cardiovascular disease but for death from that origin, hypertension (which again presents the highest PAF) is followed by low educational level, low grip strength, poor diet and

pollution, while smoking, diabetes and high non-HDL cholesterol have lower values. This confirms the role that environmental and socioeconomic factors have in conditioning disease burden.

But cardiovascular deaths are less than 30% of the total. And when we refer to non-cardiovascular deaths, which represent the majority, smoking displaces hypertension from the first place, but the following four positions correspond again to the factors cited in the same order as for cardiovascular death. And if we think in all-cause mortality, low educational level climbs to the first place.

The PURE study has the enormous merit of reflecting the relative weight of different risk factors in the development of cardiovascular disease, its associated mortality and all-cause death in different countries worldwide. It allows us to reflect on phenomena which, as cardiologists, we sometimes do not consider. It is everyone's responsibility, each from his/her own place, to take this information into account and work together to achieve a healthier world for everyone. Because, we should bear in mind, the study refers to modifiable risk factors.

Vericiguat in heart failure with reduced ejection fraction: a new therapeutic alternative? The VICTORIA study

Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernández AF, Butler J, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. **N Engl J Med.** 2020. DOI: 10.1056/NEJMoa1915928

The VICTORIA study, recently presented at the ACC 2020 Congress, was a multinational, double-blind, randomized, placebo-controlled trial designed to demonstrate the beneficial effect of vericiguat, a stimulant of soluble guanylyl cyclase (sGC), in patients with heart failure and reduced left ventricular ejection fraction (LVEF), with recently worsening conditions. It included patients aged ≥ 18 years, with heart failure in functional class (FC) II to IV, LVEF <45% and systolic blood pressure ≥ 100 mmHg. They should have BNP ≥ 300 pg/mL or NT pro-BNP ≥ 1000 pg/mL in sinus rhythm, and values of at least 500 pg/mL or 1600 pg/mL, respectively, in atrial fibrillation. Moreover, patients should have presented hospitalization for heart failure in the last 6 months or need for intravenous diuretics in the last 3 months and optimal medical treatment.

After a screening period of up to 30 days, without run in, patients were randomized in a 1:1 ratio to vericiguat (at an initial dose of 2.5 mg daily, with the aim of reaching 10 mg daily) or placebo. The primary endpoint was a composite of cardiovascular death and first hospitalization for heart failure, and secondary endpoints were the components of the primary endpoint, the total number of hospitalizations for heart failure, and all-cause mortality.

Between 2016 and 2018, 6,857 patients were

screened and 5,050 were included in the study: 2,526, in the vericiguat branch and 2,524, in the placebo branch. Mean age was 67 years, 76% were men and 67% had been hospitalized for decompensated heart failure in the last 3 months. Mean LVEF was $28.9\% \pm 8.3\%$, and 85% had LVEF $<40\%$. In 59% of cases subjects were in FC II, 39.7% in FC III, and 1.3%, in FC IV. The prevalence of comorbidities was high: 52.7% had atrial fibrillation or flutter and 47% had diabetes. Median NT pro-BNP was 2,826 pg/mL. At the beginning of the study, 93% of the patients were receiving beta-blockers, 73% renin angiotensin inhibitors or antagonists, 70% anti-aldosterone agents and 15% with sacubitril/valsartan). In 32% of cases, patients had an implanted cardioverter defibrillator or resynchronizer.

Median follow-up was 10.8 months. The primary endpoint of cardiovascular death or first hospitalization for heart failure occurred in 35.5% in the vericiguat branch and 38.5% in the placebo branch (HR 0.90, 95% CI 0.82-0.98, $p=0.02$), which corresponds to an annual incidence of 33.6% and 37.8%, respectively. The difference between both branches was in the reduction of first hospitalization for heart failure (25.9% vs. 29.1% annually; HR 0.90 95% CI 0.81-1) and in the reduction of the total number of hospitalizations for heart failure (38.3% vs. 42.4% annually; HR 0.91, 95% CI 0.84-0.99, $p=0.02$). There was no significant decrease in cardiovascular death (12.9% vs. 13.9% annually) or in all-cause mortality (16% vs. 16.9% annually). The results were consistent in subgroup analyses, except for age (for the primary endpoint, HR 0.84 in those <75 years of age, and HR 1.04 in those ≥ 75 years), and baseline values of NT pro-BNP (HR between 0.73 and 0.82 for the lower 3 quartiles and HR 1.16 for the highest quartile, with values $>5,314$ pg/mL). In both cases, the interaction test was significant.

Regarding the incidence of adverse events, there was no significant difference in the two events of greatest interest: hypotension (9.1% vs. 7.9%) or syncope (4% vs. 3.5%). The incidence of anemia was higher with vericiguat (7.6% vs. 5.7%).

The VICTORIA study enrolled more severe patients than its immediate predecessors, the PARADIGM HF and DAPA HF trials. Patients were only slightly older than in those studies, with similar male prevalence, and comparable LVEF. But due to hospitalization or emergency treatment in the previous months and higher natriuretic peptide levels, it had a higher prevalence of patients in FC III-IV (41% vs. just under 33% in the DAPA HF trial and almost 25% in the PARADIGM-HF study), and pro-BNP NT levels between 75% and 95% higher than in the PARADIGM HF and DAPA HF trials, respectively. Therefore, the evolution of the patients was clearly worse than in these studies, with an annual incidence of hospitalization for heart failure between 3 and 4 times greater than in the PARADIGM HF and DAPA HF trials, and almost double cardiovascular and total mortality. The effect of the intervention

was clearly noticeable in the reduction of hospitalization for heart failure, with a smaller reduction in relative terms (10% in VICTORIA, 21% in PARADIGM and 30% in DAPA HF), but due to the higher incidence of events in the VICTORIA study, as it was sicker population, it resulted in absolute terms with a similar reduction than the DAPA HF trial (almost 3% per year) and higher than that of the PARADIGM HF trial (just over 1% per year). But enthusiasm is lessened by the lack of effect on cardiovascular or total mortality, unlike the other studies cited. The authors postulate that the short follow-up period prevented the probable effect on mortality from being evident. But looking at the Kaplan Meier survival curves, some separation between drug and placebo seems to emerge only after two years. From an effective intervention to reduce mortality we would expect an earlier, more evident separation effect. Perhaps, despite its manifest importance, the sGC/cGMP cascade fails to define the vital prognosis when other pathways are adequately covered in advanced heart failure. In an era marked by the proliferation of alternatives, but also by the increase in costs, it is clear that we should initially focus on drugs that decrease mortality. Tending to an extension in the use of these agents, which also reduce hospitalization, is the clearest option. For patients who do not respond adequately to these strategies, for those who have a torpid course despite them, and for those who do not tolerate them or have contraindications for their use, vericiguat now appears as an option to consider, although an analysis of costs looms as essential to define their place in the therapeutic strategy.

The value of genetics to define the risk of coronary events. Two studies with conflicting results.

Marston NA, Kamanu FK, Nordio F, Gurmu Y, Roselli C, Sever PS, et al. Predicting Benefit From Evolocumab Therapy in Patients With Atherosclerotic Disease Using a Genetic Risk Score: Results From the FOURIER Trial. **Circulation.** 2020;**141:616-23**.

Mosley JD, Gupta DK, Tan J, Yao J, Wells QS, Shaffer CM, et al. Predictive Accuracy of a Polygenic Risk Score Compared With a Clinical Risk Score for Incident Coronary Heart Disease. **JAMA.** 2020;**323:627-35**.

Although traditional clinical risk factors are essential for stratifying cardiovascular risk, it is understood that between 30% and 60% of its variation can be explained by genetic factors. Population association studies have identified many single nucleotide polymorphisms (SNP) that have been associated with an increased risk in the incidence of coronary heart disease, and this information has served to generate scores. We present a subanalysis of the FOURIER study with evolocumab, which explored the prognostic value for major events of a score involving 27 loci, and the effect of this drug according to the score value.

It should be recalled that the FOURIER study was a multinational, randomized, double-blind, placebo-controlled trial that compared evolocumab with placebo in patients with clinically evident cardiovascular atherosclerotic disease, aged 40 to 85 years, with LDL cholesterol ≥ 70 mg/dL or non-HDL ≥ 100 mg/dL, with history of myocardial infarction (AMI), non-hemorrhagic stroke or symptomatic peripheral vascular disease (PVD). In the analysis that we present, a nested cohort study of 14,298 patients was carried out, 7,163 in the evolocumab branch and 7,135 in the placebo branch. There were no clinically relevant differences between participants in the general trial and the genetic substudy. The score with 27 SNP was calculated using the genotype dose for each allele, multiplied by its weight (based on a meta-analysis) and then adding the values of all the variants. In addition, a similar analysis was performed to explore the predictive value of a polygenic risk score with 6,334,602 SNP (PRS-6M). The study endpoint was major coronary artery events (death of coronary origin, AMI and revascularization), and major vascular events (the former plus ischemic stroke). Patients were divided from the lowest to the highest quintile according to the score value, and defined as low risk for quintile 1, intermediate risk for quintiles 2 to 4, and high risk for quintile 5. Median follow-up was 2.3 years.

Mean age was 63 years and 76% were men; 29% were current smokers, 33% had diabetes and 81% hypertension. Median LDL cholesterol was 92 mg/dL. Most patients had history of AMI (82%), stroke (18%) and PVD (15%). Patients in the high genetic risk category were somewhat less likely to have clinical risk factors. They were younger, more frequently female, with less tobacco consumption or diabetes. In them, history of AMI was more frequent than in the lowest categories, while in the latter, history of stroke was more prevalent. There were no marked differences in LDL cholesterol between high (median 94 mg/dL) and low genetic risk (median 91 mg/dL).

The incidence of major vascular events at the 2.5-year follow-up period for the low, intermediate and high genetic risk categories was 10.1%, 11.3% and 13.8%, respectively; and 8%, 9.7%, and 13.2%, respectively, for major coronary artery events. After adjusting for clinical factors, the 27 SNP genetic score was significantly and independently associated with the risk of major vascular events (p trend=0.005) and major coronary events (p trend <0.0001). Those with high genetic risk had an adjusted HR of 1.65 for and 1.37 for major vascular events, while those with intermediate genetic risk had an adjusted HR of 1.23 and 1.14, respectively, with respect to low risk ones.

Regarding the polygenic score with more than 6 million SNP there was a comparable distribution of baseline characteristics; those with high risk had an adjusted HR of 1.55 for major coronary events and 1.31 for major vascular events, while those with intermediate genetic risk had an adjusted HR of 1.26 and 1.16, respectively, with respect to low risk ones.

The greater the genetic risk the greater the effect of evolocumab on major vascular events: the HR of treated vs. control groups, for low, intermediate and high genetic risk was 0.92 (95% CI 0.72-1.18), 0.91 (95% CI 0.79-1.03) and 0.69 (95% CI 0.55-0.86), respectively (p trend=0.07). Similarly, the absolute risk reduction (ARR) was 0.7%, 0.9% and 4%, respectively (p trend=0.04). Treatment with evolocumab reduced the risk of major events in the high-risk category, and led it to that of low genetic risk (9.3% and 9.1%, respectively). In patients without multiple clinical risk factors or high genetic risk, no benefit was observed with evolocumab compared with placebo (HR, 1.02, ARR -0.2%, $p=0.86$). In patients with multiple clinical risk factors, but without high genetic risk, the HR was 0.87 [95% CI 0.75-0.998], $p=0.047$ and the ARR 1.4%, and in those with high genetic risk the HR was 0.69 (95% CI 0.55-0.86, $p=0.0012$) and the ARR 4%, regardless of clinical risk.

The value of the same polygenic score with more than 6 million SNP from the previous publication was tested in another study in subpopulations of two large population-based cohort studies, 4,847 participants from the ARIC study (52.2% women, mean age 61.8 years), and 2,390 from the MESA study (56.4% women, mean age 62.9 years), followed-up from 1986 and 2000, respectively, until 2015 in both cases. The study assessed the ability of the score to predict coronary events (death, non-fatal AMI, and myocardial revascularization), as well as the facility to enrich the prognostic capacity of the mixed population equation postulated by ACC/AHA. Based on this equation, the risk of events at 10 years was defined, and dichotomized as low ($\leq 7.5\%$) or high risk ($> 7.5\%$). In the ARIC cohort study, a median follow-up of 15.5 years reported an incidence of coronary events of 14.4%, and in the MESA study an incidence of 9.5%, with a median follow-up of 14.2 years. In both cases, more than 60% of the events occurred in men.

In the ARIC study, the polygenic score was significantly associated with the incidence of coronary events at follow-up, with a HR of 1.24 for each increase in standard deviation; in the MESA study, the corresponding HR was 1.38. Nevertheless, the discriminative capacity of the score was low; with an area under the curve (AUC) of 0.55 (95% CI 0.52-0.57) in the ARIC study and 0.59 (95% CI 0.53-0.62) in the MESA study. In both cases, adjusting for age and gender brought the AUC to 0.67. Compared to the score, the AUC of the ACC/AHA equation was 0.70 in the ARIC study, and the addition of the polygenic score did not modify it. For the MESA study, the AUC of the ACC/AHA equation was 0.66, and the addition of the polygenic score raised it to 0.68, a non-significant increase.

What was really interesting was the demonstration that adding the genetic score to the ACC/AHA equation prediction was not very effective. In the ARIC study, the ACC/AHA equation characterized 39.2% of patients as low risk and the remaining 60.8% as high

risk. The event rate in both categories was 4.4% and 16.7%, respectively. The addition of the genetic score ended up defining 42.2% as low risk and 57.8% as high risk, with an event rate of 4.4% and 17.3%, respectively, that is, without significant difference with the clinical prediction. The addition of the polygenic score did not lead to a significant change in the net reclassification index (NRI): 1.8%, 95% CI -1.2% to 3.6%. In the MESA study, the results were similar: the genetic score did not improve calibration or reclassification with respect to clinical prediction.

Our relationship with genetics as a tool to define prognosis and make decisions is still slippery. The benefit of genetic determinations is greater in the case of some heart diseases and electrophysiological disorders, but more debatable in the case of coronary heart disease. In fact, when a priori we would suppose greater prognostic usefulness in people with reduced vascular disease, and not so much in the case of secondary prevention, the two studies we have presented challenge our assumption. In a population with established disease, the FOURIER substudy implies that genetic characteristics continue to have value to define the evolution, and that it can even guide in decision-making when it involves high cost, and, hence, more support is necessary to adopt it. This substudy seems to suggest that alternative pathways can be differentiated in the context of established cardiovascular disease: patients with low genetic risk, but with a higher prevalence of

risk factors and patients with high genetic risk, with a lower prevalence of these factors. However, the differences, although statistically significant, are not so noticeable as to be able to establish a rule.

In contrast, in a general population sample, the use of a much broader score does not demonstrate advantages over a simple equation based on age and the prevalence of risk factors. Different scores built on the basis of diverse populations are one reason to explain the discrepancies. The difference between the association of prevalence versus the incidence of coronary heart disease is another reason. The polygenic score works well in demonstrating the presence of disease, but not better than the clinical score when it comes to defining outcome. Perhaps because it is not specific for coronary heart disease, it does not focus on a gene that defines the presence or not of disease, but is broadly inclusive of genes linked to different mechanisms related to atherosclerotic disease, among others. And because the same score can be reached from different genetic backgrounds. To all this, we must add the accessibility to this type of determinations, the costs, etc. Therefore, faced with the uncertainty about its real meaning, and the lack of a clear advantage over the clinic, the use of genetics to define cardiovascular prognosis in the general population seems remote. It may certainly be that gradually, in high-risk populations, and when making very specific decisions, a genetic test can help to define them