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SECURE study: advantages of the administration of a polypill in secondary prevention of cardiovascular events

Castellano JM, Pocock SJ, Bhatt DL, Quesada AJ, Owen R, Fernandez -Ortiz A et al. Polypill Strategy in Secondary Cardiovascular Prevention. **N Engl J Med 2022;387:967-77. https://doi.org/10.1056/NEJMoa2208275.**

Cardiovascular disease is the leading cause of death and complications worldwide. Despite the existence of different effective pharmacological measures in the field of secondary prevention, the incidence of new ischemic events after an index event remains high. Lack of adherence to treatment is one of the most important causes, and its incidence is estimated at around 50%. Inadequate adherence to prescribed treatment is associated with worse outcomes. Among the measures proposed to overcome this problem is the adoption of a polypill, which, by bringing together the drugs indicated for prevention in a single tablet, simplifies their administration. A recent meta-analysis demonstrated the advantage of using a polypill in primary prevention. We now know the results of the SECURE study, which explored the usefulness of the strategy in secondary prevention.

SECURE was a multicenter, phase 3, randomized, controlled study in which elderly patients with a history of acute myocardial infarction (AMI) were assigned to a strategy based on the polypill, versus a usual strategy of administering the indicated therapy for secondary prevention. It was carried out in 113 centers in Spain, France, Germany, Poland, the Czech Republic and Hungary. Patients had to have a history of type 1 AMI according to the Universal Classification (plaque rupture or erosion and thrombosis, with or without ST-segment elevation) and be >75 years old, or ≥65 years old with at least one of the the following conditions: diabetes, glomerular filtration rate between 30 and 60 mL/min/1.73 m^2, or history of AMI, coronary revascularization or cerebrovascular accident (CVA). Patients receiving oral anticoagulation and those in whom a revascularization procedure was scheduled were excluded. The patients were randomly assigned to receive usual pharmacological treatment according to the practice guidelines of the European Society of Cardiology, or a polypill, AAR40, in three presentations, containing aspirin 100 mg, atorvastatin 40 mg and ramipril in doses of 2.5, 5 or 10 mg. In patients who had not previously been receiving angiotensin-converting enzyme inhibitors (ACEI), treatment was started with the polypill containing 2.5 mg of ramipril. In those who had already received prior treatment with ACEI, the polypill with the equivalent dose of ramipril was used. The goal was to reach ramipril 10 mg. If the treating physician wanted to decrease the dose of atorvastatin, he could switch to the AAR20 preparation, similar to the AAR 40 preparations, but with 20 mg of atorvastatin. Face-to-face follow-up was planned at 6, 12, and 24 months, with telephone calls at 18, 36, and 48 months. Adherence was evaluated with Morisky's 8-point scale. The study's primary endpoint was a composite of cardiovascular death, nonfatal type 1 MI, nonfatal stroke, or urgent revascularization. The main secondary end point, a composite similar to the primary, but without considering urgent revascularization. End points were also each of the components separately, and adherence at 2 years.

The study was designed for noninferiority, and the upper end of the 97.5% CI of the HR of the relationship between polypill and conventional treatment, set at a value of 1.373, was assumed as the noninferiority margin (that is, it was assumed until 37.3% excess in presentation of the primary end point, to accept non-inferiority). If non-inferiority was demonstrated, a superiority test could then be performed. If superiority was demonstrated for the primary endpoint, it could then be explored for the secondary endpoint. Considering an estimated incidence of the primary end point of 7.2% per year, it was considered that with 3206 patients with a minimum of 2 years of follow-up, there would be 90% power to reject the null hypothesis of non-inferiority, and 80% power to detect a 21% reduction in the primary endpoint, with a 5% loss to follow-up and a p-value of 0.05. The estimate was later changed to an expected incidence of the primary endpoint in the control arm of 7.7%, so that, with 2514 patients, there would be 78% power to detect superiority. An intention-to- treat analysis was proposed, and, additionally, a per-protocol analysis for the primary and primary secondary endpoints.

Between August 2016 and December 2019, 2466 patients were included in the study, 1237 in the polypill arm. The median time from AMI to inclusion was 8 days. The mean age was 76 years, 31% were women, 77.9% had hypertension, 57.4% diabetes, and 51.3% had a history of smoking. On admission, mean systolic blood pressure (SBP) was 129.1 mm Hg and mean LDL cholesterol was 89.2 mg/dL. In the polypill arm, 91.7% received the preparation with 40 mg of atorvastatin, compared to 40.4% who used a high-intensity statin in the usual treatment arm. In this arm, 98.7% received aspirin (by design, all received aspirin in the polypill arm); and a second antiplatelet agent was used in more than 90% of the cases in both arms.

Adherence was greater in the polypill group: at 6 months 70.6% vs 62.7% (RR 1.13, 95% CI 1.06-1.20) and at 2 years 74.1% vs 63.2% (RR 1.17, 95% CI 1.10-1.25). The median duration of follow-up was 3 years. During it, the incidence of the primary endpoint was 9.5% in the polypill arm versus 12.7% in the usual treatment arm (HR 0.76, 95% CI 0.60-0.96; p < 0.001 for non-inferiority and 0.02 for superiority). The incidence of the primary secondary endpoint was 8.2% vs. 11.7% respectively (HR 0.70, 95% CI 0.54-0.90; p=0.005). Although all components of the composite endpoint contributed to the results, the significant reduction in cardiovascular death stands out: 3.9% vs. 5.8%, HR 0.67, 95% CI 0.47-0.97. There was no significant reduction in death from all causes. There was no difference in the incidence of adverse events (32.7% vs. 31.6%) or non-fatal serious adverse events (19.2% vs. 18.2%).

In Rev Argent Cardiol 2021, vol 89 (5), we comment on a meta-analysis of individual data from 3 large, randomized studies that explored the use of the polypill in primary prevention (with some differences in components): PolyIran, TIPS-3, and HOPE-3. In total, it included 18 162 participants, half women, with a mean age of 63 years; 49.8% were hypertensive, 23.4% were smokers or former smokers, and 19.4% had diabetes. Mean SBP was 137.7 mm Hg and mean LDL cholesterol 121.7 mg/dL. The primary endpoint of the study was a composite of cardiovascular death, AMI, stroke, or any revascularization procedure. Compared to the control, at a mean of 2.1 years, mean LDL cholesterol was 22 mg/dL lower, and at 5 years mean SBP was 4.7 mm Hg lower in the polypill arm. In a median follow-up of 5 years, the primary endpoint occurred in 3% of the intervention arm and 4.9% of the control arm (HR 0.62; 95% CI 0.53-0.73; p<0.001). The number needed to treat (NNT) to prevent one event was 52 over 5 years. The effects of greater magnitude were reduction of AMI, stroke and need of revascularization, in all cases with HR between 0.52 and 0.59; for cardiovascular death, the HR was 0.65, 95% CI 0.52-0.81. There were no differences in death from all causes. In the aspirin stratum, the incidence of the primary endpoint was 2.6% in the intervention arm and 4.8% in the control arm (HR 0.53, 95% CI 0.41-0.67) with an NNT at 5 years of 37. The main differences were in AMI, stroke, and cardiovascular death, with no difference in death from all causes. In the non-aspirin stratum, the incidence of the primary end point was 3.3% in the intervention arm and 4.9% in the control arm (HR 0.68, 95% CI 0.57-0.81), and the NNT at 5 years it was 66. The main differences were in AMI, stroke, and revascularization, with no difference in all-cause death.

The SECURE study clearly presents differences with those mentioned: it is a secondary prevention study, with patients 13 years older, with a higher prevalence of risk factors. It is logical, for these reasons, that the incidence of major events has been higher in SECURE; it is paradoxical that the baseline figures for BP and LDL cholesterol have been lower than in the primary prevention studies, but surely more frequent prior treatment can explain the difference. As in the studies cited, the polypill is triumphant over its comparator; but some doubts arise regarding the responsible mechanisms. In SECURE, as we saw, adherence was 10% higher with the polypill than with drugs administered individually; we would have expected, therefore, lower levels of LDL cholesterol and BP in this arm. However, this did not happen. At 2 years, the same BP was verified in both arms (135.2/74.8 mm Hg with polypill, 135.5/74.9 mm Hg with usual treatment) and the same happened with LDL cholesterol (67.7 vs. 67.2 mg/dL). Therefore, the greater adherence does not seem to have resulted in better control of the most important risk factors (when this is one of the arguments most frequently put forward to justify the use of the preparation); and, in turn, despite similar figures for BP and LDL cholesterol, the evolution of the patients was better with the polypill. Two facts that still await an answer. The authors mention the possibility that the beneficial effect is actually due to the pleiotropic effects of statins and ACEI (argument that has been repeated for many years, without convincing evidence that this is the real responsible for the better evolution, although a possible role should not be dismissed either); and because greater adherence also implies greater use of aspirin, included in the polypill, and which has a precise indication in secondary prevention. Some voices have been heard that, given the lack of a solid response to the doubts raised, the results are meaningless. We believe that the evidence accumulated with thousands of patients in primary and secondary prevention is a very good reason to justify the use of the polypill, if access to treatment is facilitated.

Back to the beginning: the administration of antihypertensive medication in the evening is not better than in the morning. TIME study

Mackenzie IS, Rogers A, Poulter NR, Williams B, Brown MJ, Webb DJ et al. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomized, open-label, blinded-endpoint clinical trial. **Lancet 2022;400:1417-25. https://doi.org/10.1016/S0140-6736(22)01786-X.**

Blood pressure (BP) normally follows a circadian rhythm, with values falling at night and rising on awakening in the morning. This pattern is called a dipper pattern. When this drop in blood pressure is reduced or absent, or, on the contrary, nighttime blood pressure is higher than daytime blood pressure, the risk of adverse cardiovascular events is greater. This has led to different clinical trials testing changing the usual schedule for administering antihypertensive medication, going from the traditional morning administration to an evening administration, to ensure a better night-time drop in blood pressure. In some

trials, this change has resulted in better blood pressure control over 24 hours, and a Spanish group has shown in the Hygia Chronotherapy study a significant reduction in adverse cardiovascular events by taking the treatment administration schedule from morning to night. Some however have questioned the results of the Hygia study, and have argued that the observed effect is exaggerated. Added to this is the fear of a higher incidence of complications when administering drugs at night (falls, stroke), and it is also pointed out that adherence to treatment is lower when administration is left for dinner time or when to go to bed. All of these reasons led to a new clinical trial, the TIME study.

TIME was a randomized, controlled, open-label, parallel-group study with blinded adjudication of events. It was carried out in Great Britain, and included hypertensive patients, treated with at least one drug administered once a day. Patients who received the medication more than once a day, or who worked at night, were excluded. They were randomly assigned in a 1:1 ratio to receive the treatment between 6:00 and 10:00 h, or between 20:00 and 00:00 h. The study did not require face-to-face visits. All the administrative procedures, including the allocation of the schedule for taking the medication, were carried out through an electronic platform. Those taking diuretics were suggested to take them at 18:00 to prevent nocturia. Questionnaires were sent to patients on a regular basis, in the first month after random assignment, and every 3 months thereafter. Each patient was questioned about adherence to treatment, and the incidence of adverse events (digestive intolerance, dizziness, falls, fractures, nocturia, insomnia, etc.). Those who had a home blood pressure measurement device were invited to submit regular blood pressure records. The primary endpoint was the incidence of vascular death and nonfatal acute myocardial infarction (AMI) or stroke. Initially, it was estimated that, in 10 269 participants followed up for 5 years, 631 events would be verified, necessary to demonstrate, with 80% power and $p < 0.05$, a 20% reduction in the primary end point in the evening administration arm compared to the morning. But the low incidence of events led to an increase in the necessary population to almost 20,000 patients. The analysis was done by intention to treat.

Between 2011 and 2018, 21 104 patients were included in the study (10 503 in the evening arm). The mean age was 65.1 years, 42.5% were women, and 12.9% had a cardiovascular history. Mean systolic blood pressure was 135 mm Hg and diastolic 79 mm Hg. The median follow-up was 5.2 years, and the maximum follow-up was 9.3 years. Just over 4% of patients in both arms died before the end of follow-up. Of the 53.6% of patients who reported the usual time for taking their medication before their random assignment, more than 85% did so in the morning. During the study, 11.6% of the patients abandoned the active follow-up of questionnaire responses; almost 63% of them belonged to the evening arm.

The primary endpoint occurred in 3.4% of the evening arm (0.69 events/100 patient years) and 3.7% of the morning arm (0.72 events/100 patient years), without significant difference. There was no difference according to the different prespecified subgroups, nor in the incidence of the different components of the primary end point. At some point of follow-up 30.7% of the participants reported non-adherence to treatment, at a mean of 1.7 years from randomization; lack of adherence was greater in the evening arm (39% vs. 22.5%, $p<0.0001$); at the last visit, 19.8% were non-adherent vs. 7.1%. The evening arm had a slightly lower incidence of falls (21.1% vs. 22.2%, $p=0.048$) and adverse events in general (69.2% vs. 70.5%, $p=0.041$), but there was not a difference in fractures, hospitalization for fractures or glaucoma exacerbation. About 80% of the slightly more than 11 000 patients who reported having a home blood pressure measurement device, submitted at least one blood pressure report: morning blood pressure (usually taken between 8:00 and 9:00 a.m.).) was lower (1.8 mm Hg for systolic and 0.4 mm Hg for diastolic) and the afternoon was higher in the arm that received treatment in the evening; in contrast, in the group with morning treatment, evening blood pressure was lower (1.1 mm Hg lower for systolic and 0.9 mm Hg for diastolic blood pressure).

In Rev Argent Cardiol 2020, vol 88 (6), we presented the results of the Hygia Chronotherapy study, with 19 084 hypertensive patients, with a mean age of 60.5 years; 55.6% men; 24%, diabetics, and 29% with impaired renal function. Follow-up and control were done with ambulatory blood pressure monitoring (ABPM). Mean office BP was 149/86 mmHg, and in the ABPM 131/77 mm Hg; 49.3% had a non-dipper pattern. Patients were randomly assigned to receive treatment in the morning after waking up or in the evening before going to sleep. In a median follow-up of 6.3 years, in ABPM, mean BPs were lower in the night arm (124.3/72.2 mmHg vs. 125.6/73.1 mmHg). This was achieved by reducing the nocturnal mean SBP (114 mmHg vs. 118 mmHg) and DBP (64 mmHg vs. 66 mmHg), with no difference in daytime figures. In the overnight arm, there was a notable decrease in the risk of major cardiovascular events (HR 0.55; 95% CI 0.50-0.61), all-cause mortality (45% reduction), cardiovascular mortality (reduction in 56%) and each of the individual components of the end point (from 34% for the risk of acute myocardial infarction, to 61% for the risk of hemorrhagic stroke).

However, much criticism was leveled at the way the study had been conducted. It was questioned whether the rules of a randomized study had been met; the cleanliness of the procedures was questioned, the way of adjudicating the events was doubted. It was hypothesized that Hygia actually recruited patients from previous studies. The abrupt increase in the number of participants was discussed, from the 5 000 initially proposed to the more than 19 000 finally included. The ABPM was also discussed as a valid way of evaluating

the results, and specifically the control device used in the study, and the very low rate of reported measurement errors, which do not coincide with usual practice.

In the midst of this controversy, the TIME study represents a new blow to the defenders of the nocturnal administration of the medication, since it calls into question its benefit. Unlike Hygia Chronotherapy, the design of the study or the way of carrying it out has not been discussed in academic circles. This is a clearly pragmatic study: a behavior was indicated to the patients and its consequences were verified. Precisely this condition also implies dealing with a certain lack of information: there is data on the behavior of blood pressure in around 40% of the patients (80% of the little more than half that had a home blood pressure measurement device). Sending the data depended on the willingness of the patients to participate, and was greater in older patients, with a greater amount of antihypertensive drugs. In the patients of the evening arm, the abandonment of sending forms was greater, and therefore the rate of associated complications may be underestimated. In any case, it does not appear that any of these differences have substantially influenced the results. A statement from the International Society of Hypertension published just over a month ago supports the need to achieve adequate 24-hour BP control and recommends morning administration of long-acting medications in a single dose as preferential. As always in medicine, we understand that a precise study of the conditions of each patient and the individual behavior of BP is essential to implement the best administration scheme in each case; the routine administration of antihypertensive treatment at evening-night has certainly lost steam, due to the stated reasons for doubting the Hygia results, and the strength of the TIME study data.

Invasive strategy in acute coronary syndromes without elevation of the ST segment. ¿Early or delayed? The last meta-analysis

Kite TA, Kurmani SA, Bountziouka V, Cooper NJ, Lock ST, Gale CP et al. Timing of invasive strategy in non-ST-elevation acute coronary syndrome: a meta-analysis of randomized controlled trials. **Eur Heart J 2022;43: 3148-61. https://doi.org/10.1093/eurheartj/ehac213.**

In the context of non-ST-segment elevation acute coronary syndromes (NSTEACS), an invasive strategy is recommended by all clinical practice guidelines for most patients. There is not so much uniformity about the best moment to establish it. An initial plaque stabilization strategy with antithrombotic agents and statins has been proposed, with deferred coronary angiography, but also an early invasive strategy in order to jugulate the present ischemia and reduce the risk of total vessel occlusion. Two meta-analyses (years 2016 and 2017) of 10 and 8 randomized studies (the latter with individual data analysis) did not show an advantage for an early invasive strategy compared to a delayed one. Since then, new studies have been published, and long-term follow-up results of some of the previous studies have become known. For this reason, a new meta-analysis has just been published.

Randomized studies were included that had compared early and delayed invasive strategies in patients with NSTEACS, with a minimum follow-up of 30 days and all-cause mortality data reporting. Studies comparing a routine invasive strategy with a selective invasive or conservative strategy were excluded. Seventeen studies were included, with 10 209 patients (5 215 in the early invasive arm and the rest in the delayed arm). The median time to angiography in the early invasive arm was 3.43 hours, and in the delayed arm 41.3 hours. There was heterogeneity in baseline characteristics and definition of endpoints. In most of the studies, after angiography, percutaneous coronary intervention (PCI), surgery or medical treatment was decided, except in 4, in which all patients underwent PCI. The median follow-up was 12 months.

For the analysis of all-cause mortality, 16 studies were considered, with 10 155 patients. There was no difference in its incidence, with RR 0.90, 95% CI 0.78-1.04. There was no heterogeneity in the results. In 6 of the studies, the median time to angiography in the deferred branch was <24 hours. Even after excluding these studies, there was no difference between the two strategies. Fifteen studies analyzed the incidence of acute myocardial infarction (AMI) and 13 of recurrent ischemia. No difference was found in the incidence of AMI, but there was a difference in recurrent ischemia in favor of the early invasive strategy (RR 0.57, 95% CI 0.40-0.81), although with high heterogeneity in the results. No difference was seen in the incidence of heart failure, stroke, or major bleeding; the length of hospital stay was shorter in the early invasive branch (median 22 hours less).

Clinical practice guidelines agree in recommending an immediate invasive strategy (within 2 hours of presentation) in patients with NSTEACS at very high risk. Who are these patients? Those with hemodynamic instability, heart failure or cardiogenic shock, malignant ventricular arrhythmia, recurrent or refractory pain, mechanical complications, or extensive ST-segment changes (depression > 1 mm/ 6 leads, with elevation in aVR or V1). These patients have been excluded from randomized studies comparing an early versus a delayed invasive strategy. In general terms, the meta-analysis that we are commenting on, despite notably increasing the number of patients considered (more than 10 000 compared to 6 400 in the most numerous of the previous ones), does not substantially change the concepts that we handle. There is no advantage for an early invasive strategy (within 24 hours) compared to the delayed one if we consider all patients, in terms of hard endpoints (death, AMI; major bleeding). The reduction in recurrent ischemia is remarkable, but it should be noted that it is a softer point, with hetero-

geneity in its definition and evaluation in the different studies. The decrease of one day in the duration of hospitalization is obvious, because it is little less than the difference in the moment of implementation of the invasive strategy. An individual patient data meta-analysis published in 2017 by Jobs et al. in Lancet, on 8 studies and 5334 patients (half of the studies and patients than the current one) suggested that the subgroups of NSTEACS patients who especially benefited from an early invasive strategy were those with elevated cardiac biomarkers at baseline (HR 0.76 , 95% CI 0.58-0.99), diabetes (HR 0.67, 95% CI 0.45-0.99), those over 75 years of age (HR 0.65, 95% CI 0.46-0.93), or with a GRACE score > 140 (HR 0.70, 95% CI 0.52-0.95), although the interaction tests were not conclusive. In fact, troponin elevation, a GRACE score > 140, and dynamic ST-segment changes in adjacent leads are currently recommended criteria to define high risk and thus early invasive behavior. It is worth remembering two things: that the evidence to which we refer comes almost entirely from studies in which conventional troponin T was used, not ultrasensitive; and that the cited GRACE score arises from the model to predict hospital mortality in patients with ACS, and not from those used for other endpoints, in which case the result obtained could differ, and lead to different behaviors. More recent studies are being carried out to prospectively define the use of this cut-off value.

As a limitation of this meta-analysis, we can mention that it is not one of individual patient data, which could have contributed to better define risk subgroups in which an early invasive strategy offered advantages, over and above the criteria already mentioned; therefore, its value is essentially confirming what has already been established, rather than a source of change and improvement.

Differences in the prevalence of cardiovascular risk factors, temporal evolution and prognosis between men and women. A sub-analysis of the PURE Registry

Walli-Attaei M, Rosengren A, Rangarajan S, Breet Y, Abdul-Razak S, Sharief WA et al. Metabolic, behavioral, and psychosocial risk factors and cardiovascular disease in women compared with men in 21 high-income, middle-income, and low-income countries: an analysis of the PURE study. **Lancet 2022;400: 811-21. https://doi.org/10.1016/S0140-6736(22)01441-6.**

A series of metabolic, behavioral, and socioeconomic factors are associated with an increased risk of cardiovascular disease. The association does not always have the same strength in men as in women. For example, it has been pointed out that hypertension (HTN), diabetes (DM) and smoking are associated with a higher risk in women than in men. But it is true that these data come from high-income countries (HIC). The burden of risk factors is higher in low (LIC)- and middle-income countries (MIC), and information from them is scarcer. The PURE study (Prospective Urban Rural Epidemiology) is a prospective cohort study, which at different stages included people from countries with different income levels, and from urban and rural locations, with the purpose of reflecting the existing heterogeneity in the distribution of risk factors and their association with the incidence of cardiovascular events in the world population. In the analysis that we present, the relationship of these factors with cardiovascular evolution in men and women is explored.

The countries were classified as HIC, MIC and LIC according to the 2006 World Bank classification.

The metabolic risk factors considered were hypertension, systolic blood pressure (SBP), diabetes, fasting glucose, waist-to-hip ratio, abdominal obesity, and non-HDL cholesterol. Behavioral risk factors include smoking, alcohol consumption, physical activity (self-reported and taken on a MeTS scale per week, with a cut-off value of 600) and diet (assessed with PURE score). Psychosocial risk factors considered were symptoms of depression and a low level of education (primary or less). Grip strength (assessed with a dynamometer) and household pollution (defined by cooking with kerosene or solid fuels) were added as risk factors to be analyzed. The primary endpoint was the incidence of major cardiovascular events, a composite of cardiovascular death, nonfatal acute myocardial infarction (AMI), nonfatal stroke, and heart failure. The secondary endpoint included the top three.

Of all PURE participants, 155 724 were selected for this analysis, aged between 35 and 70 years, with no history of cardiovascular disease, with at least 3 years of follow-up. Of these, 58.4% were women, with a mean age of 49.8 years at admission, compared to 50.8 years for men. At entry, just over 37% of both men and women lived in HIC, or in the top half according to income level of MIC (Argentina, Brazil, Canada, Chile, Malaysia, Poland, Saudi Arabia, South Africa, Sweden, Turkey, and United Arab Emirates), and the rest in lower-income MIC, or LIC (Bangladesh, China, Colombia, India, Iran, Pakistan, Palestine, the Philippines, Tanzania, and Zimbabwe). Just under half of the men and women lived in rural communities.

Median follow-up was 10.1 years. During it, 4.7% of women and 7.6% of men reached the primary endpoint, with an age-standardized annual incidence of 5 ‰ for women and 8.2 ‰ for men. SBP and blood glucose levels increased with age and tended to be lower in women; the waist-hip ratio was significantly lower in women, while non-HDL cholesterol increased with age in women but not in men. In men, the prevalence of smoking, alcohol consumption and poor physical activity was higher; in women, the presence of depression and lower educational level. In both sexes, diet, grip strength and exposure to pollution were similar. Total and LDL cholesterol levels were higher between 35 and 44 years of age in men, similar in both sexes

between 45 and 54 years of age, and higher in women from 55 years of age. Triglyceride values were higher in men up to 54 years of age, and similar to those of women from 55 years of age.

Let us now go to the strength of association of each of the risk factors with cardiovascular evolution. Among metabolic factors, the strength of association with outcome was similar for all of them between men and women, except for non-HDL cholesterol, which was a stronger predictor in men (HR 1.28 in men, 1.11 in women, p =0.0037). The elevation of total cholesterol (≥200 mg/dL), LDL cholesterol (≥130 mg/dL) and triglycerides (≥150 mg/dL) did not imply an increased risk in women (HR 1.01 in all cases) but yes in men (HR 1.19 for triglycerides, 1.26 for LDL cholesterol and 1.30 for total cholesterol). There was a tendency to greater weight for smoking in men (HR 1.30 vs 1.15 in women, p=0.06). Lower-quality diet was a heavier risk factor in women, depression in men. The association of risk factors with evolution was similar in all country income levels. The population attributable fraction, PAF, (how much of cardiovascular disease in the population can be attributed to each risk factor) was similar for hypertension in men and women, as well as in the case of diabetes; but obesity and a poor-quality diet were associated with higher PAF in women, and smoking and elevated LDL cholesterol with higher PAF in men. In the case of AMI, PAF was similar in men and women for the risk factors considered as a whole: 69.1% in women, 68.3% in men; in the case of stroke, PAF was much lower in women; 47.1% vs 63.1% in men; for cardiovascular death, the difference in PAF was negligible: 79.3% vs 82.5%.

This analysis of the PURE registry ratifies some previous concepts about the differences in cardiovascular profile and evolution between men and women and puts others into question. It confirms that the overall cardiovascular prognosis is worse in men, who have a worse profile of risk factors from an earlier stage, with higher figures (significantly or with a trend) of blood pressure, lipids and glycemia. In men, smoking and alcoholism prevalence is higher; symptoms of depression and lower educational level are more frequent in women. The passing of the years tends to attenuate the differences; even the numbers of LDL cholesterol end up being higher in women. The association of metabolic factors with prognosis in PURE is similar in men and women, except for dyslipidemia, which weighs more in men. This is consistent with a meta-analysis showing that a 1 mmol/l (38.6 mg/dL) reduction in LDL cholesterol reduces the risk of cardiovascular events by 15% in women, but by 28% in men. Where we found a discrepancy with respect to previous data is in the relative weight of diabetes in determining risk. Meta-analysis with almost 1 million patients confirms the higher risk of cardiovascular mortality that diabetes entails in women than in men in the entire age range, especially between 35 and 65 years. Similarly, smoking had been identified as a greater risk factor in women than in men, and in PURE an opposite trend was verified. It is interesting that alcohol consumption appears as a protective factor, more in women than in men. It should be noted, however, that this refers specifically to cardiovascular risk, and does not exempt alcohol from the increased risk of cancer, accidents, and all-cause mortality.

This publication by the authors of PURE confirms the value of large observational studies and the importance of thinking about the different exposure of men and women to risk factors and their specific impact. When the association with outcomes matches that seen in other studies, we can view it as confirmatory data. When there are discrepancies, we understand that we can doubt. How to define if the truth lies in this Registry, or in those that show another reality? Just as we have understood that randomized studies are a biased sample of reality, we must recognize that Registries are too: each one has its own inclusion and exclusion criteria, which define a specific population in each case (for example, here we talk of people between 35 and 70 years old), their definitions, their specific mechanisms to access information, their monitoring methods. The undoubted merit of the article is to emphasize that men and women are not the same; that we must learn to recognize biological, socioeconomic, and behavioral differences. There are still no specific indications in the cardiovascular disease guidelines that differentiate behaviors according to sex. Without going so far, it is desirable that at least special considerations be made in the most notable cases, when it comes to finding the best treatment in each case.

Antibiotic prophylaxis of infective endocarditis: when and how. Data from a large population registry.

Thornhill MH, Gibson TB, Yoon F, Dayer MJ, Prendergast BD, Lockhart PB et al. Antibiotic Prophylaxis Against Infective Endocarditis Before Invasive Dental Procedures. **J Am Coll Cardiol 2022;80:1029-41. https://doi.org/10.1016/j.jacc.2022.06.030.**

Infective endocarditis (IE) is an entity associated with high mortality and complications. Thirty to 40% of IE episodes caused by oral streptococci are attributed to invasive dental procedures (IDP). Already in 1955, the AHA established the indication of antibiotic prophylaxis (AP) in case of performing a IDP. However, the true efficacy of AP to prevent IE in this context has never been tested in a clinical trial, and it has even been postulated that the risk of IE may be greater in situations not strictly related to IDPs, but simply to tooth brushing, or chewing, in conditions of poor oral hygiene. The risk of promoting antibiotic resistance in the face of uncontrolled antibiotic use led regulatory agencies to promote the use of AP only in the case of IDP in patients at high risk of IE, and even in Great Britain, AP was discouraged. A retrospective analysis of a large Medicare database in the US, linked to one

of dental procedures among its beneficiaries, helps to clarify the issue.

It included individuals aged at least 18 years, with data from both databases, related for at least 16 months. All hospitalizations for IE between 2000 and 2015 were identified. It was defined in each case if the patient had a high risk of IE (previous history of IE, prosthetic heart valve, valve repair with prosthetic material, unrepaired cyanotic congenital heart disease, congenital heart disease with palliative shunts or conduits, congenital heart defect completely repaired with prosthetic material or device, during the first 6 months after the procedure), moderate (rheumatic heart disease, non-rheumatic valve disease, congenital valvular anomalies, hypertrophic cardiomyopathy), or low/unknown. The dental procedures carried out were classified as a) IDPs: those that involve the manipulation of the gingival tissue or the periapical region of the teeth, or perforation of the oral mucosa (extractions, surgical procedures, supragingival or subgingival scaling or deep cleaning), and endodontic procedures; that is, those procedures that the AHA recommends "should" be covered by AP; b) intermediate dental procedures, those restorative dental procedures that may require AP only if there is gingival manipulation, and c) non-invasive procedures, for example routine dental examination, dental X-rays, or placement of removable prostheses or orthodontics, for which AP is not recommended . For each visit, the most invasive procedure was considered as the index; in a treatment that required several visits, each one was considered independently. An episode of IE was considered new if it was separated by at least 6 months from a previous one. In each case of dental procedure, the incidence of IE was considered in the 30 days and 4 months after the procedure. The crude incidence of IE in each risk group was adjusted for age, sex, and the Charlson comorbidity index.

Of 7 951 972 enrolled in coverage, 0.46% had a high risk of IE; 7.09% moderate risk, and the rest low or unknown risk. In total, 3774 people (475 cases per million) were hospitalized for IE; 34.2% with high risk of IE, 22% with moderate risk and 43.8% with low/unknown risk. The adjusted incidence of IE in the 30 days after a dental procedure was 467.6; 24.2 and 3.8 per million people, respectively. In patients at high risk of IE, and taking non-invasive procedures as a reference, overall, intermediate procedures or IDPs did not imply a significant increase in the risk of IE; but specifically, extractions (OR 9.22) and surgical procedures (OR 20.18) marked high-risk situations. In patients with moderate risk of IE, and taking non-invasive procedures as a reference, intermediate procedures and IDPs did not imply a significant increase in the risk of IE; but again extractions (OR 3.25) were associated with excess risk. And among patients with low/unknown risk, the situation was repeated: in general, intermediate procedures or IDPs did not score significantly higher than non-invasive procedures, but extractions (OR 2.41) and surgical procedures (OR 3 .74) marked situations of significant risk.

AP was prescribed in 32.6%, 9.5%, and 2.9% of IDPs in patients at high, moderate, and low risk for IE, respectively. The most used antibiotics were amoxicillin 2 g (75% of cases) and clindamycin 600 mg (in 17%). AP significantly reduced the incidence of IE in the case of IDPs in high-risk patients (OR 0.38, 95% CI 0.22-0.62), especially in extractions (OR 0.13) and other surgical procedures (OR 0.09). There was no effect of AP in lower risk patients, or in intermediate or non-invasive procedures.

In another type of analysis, the 3774 episodes of IE were specifically considered, and the relationship between dental procedures in the previous month and what had occurred in the 12 months prior to that month was evaluated. A significant association was verified between IDPs in the previous 30 days and hospitalization for IE (OR 2, 95% CI 1.59-2.52)

This one that we present is another observational study of enormous value, which helps to suggest behaviors in a condition that will hardly be explored in randomized studies. A first fact to note: the IE risk classification works. In the Medicare population (> 65 years, or younger, with disabilities), less than 0.5% are at high risk, but they generate a third of all hospitalized IE (more than 60 times what is expected under the null hypothesis). Seven percent have moderate risk, and cause just over 20% of cases (3 times expected); and from the rest (more than 92%), of low or unknown risk, comes a little less than half of the cases (half of what would be expected if the risk were the same in the 3 categories). Extractions and oral surgery have been implicated in increased risk of IE among high-risk patients; if, overall, the IDPs did not show a significant association with the incidence of IE, this was because the deep cleaning procedures unexpectedly presented a negative association with this incidence. The authors hypothesize that patients who undergo deep dental cleaning comply more strictly with oral hygiene, and this may reduce the risk, while in general extractions are more urgent procedures, with less time to get the mouth subjected to an intervention without risk. Even with lower overall risk, extractions in low- or intermediate-risk patients and surgery in low-risk patients implied a significant excess risk of IE. AP use was low: it was 3.7% overall, and even in IDPs in high-risk patients (the riskiest combination), it did not reach 33%. Even so, the beneficial effect of AP in this type of patient was confirmed, which supports the recommendation of the AHA and the ESC. Numerous *limitations can be cited, the most important being the lack of microbiological data and the fact that the prescription of AP is based on administrative data: it cannot be stated with certainty whether each time it was indicated it was actually administered, and whether when it was not indicated some patients did not access it by other means (for example, because they had antibiotics at*

home, and received a verbal indication). Finally, a figure that emerges from a survey among dentists in the US: 63% understand that it is the clinician or the cardiologist who should indicate the AP, not the dentist (perhaps understanding they are the ones who can define a patient's IE risk before a dental procedure); only 30% believe that the conditions and procedures that must receive AP are sufficiently clear. In daily practice we frequently receive the dentist's request to decide on the type and dose of AP. Knowing the above data helps us to be less doubtful and make fewer mistakes when doing so.

New demonstration of the effect of gliflozins in patients with kidney failure: the EMPA-KIDNEY study

Empa -Kidney Collaborative Group, Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ et al. Empagliflozin in Patients with Chronic Kidney Disease. **N Engl J Med 2022. https://doi.org/10.1056/NEJMoa2204233.**

In the last months of 2020, we knew the results of DAPA CKD study, which included patients at least 18 years old, with or without diabetes, with an estimated glomerular filtration rate between 25 and 75 mL/min/1.73 m 2 and a urinary albumin-creatinine ratio (UACR) between 200 mg/g and 5000 mg/g. They had to be medicated with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) at the maximum tolerated dose. Patients with type I diabetes, polycystic kidney disease, advanced heart failure, and those with vascular events or revascularization in the last 2 months were excluded. Patients were randomly assigned in a double-blind manner to dapagliflozin 10 mg daily or placebo. The primary endpoint was a composite of: a) drop in estimated glomerular filtration rate ≥50%; b) end-stage renal failure (filtrate rate <15 mL/min/1.73 m^2 sustained for at least 28 days, need for dialysis for at least 20 days or kidney transplant; c) death of cardiovascular or renal origin. Secondary endpoints were a renal endpoint, composed of those already mentioned, except cardiovascular death; a composite of cardiovascular death or hospitalization for heart failure; and death from any cause. In February 2017, the first patient was included, and in March 2020, when 4304 patients had been randomly assigned and 408 end points had occurred (60% of those planned), the study was suspended due to the notorious superiority of the dapagliflozin arm. Patients mean age was 62 years, 67% were men, 67.5% had diabetes, 10.9% heart failure; mean systolic blood pressure was 137 mmHg. Ninety-seven percent were treated with ACEIs or ARBs. Mean estimated glomerular filtration rate was 43 mL/min/1.73 m^2, and the median UACR was 950 mg/g. The incidence of the primary endpoint was 9.2% in the dapagliflozin arm and 14.5% in the placebo arm (HR 0.61, 95% CI 0.51-0.72, p = 0.000000028). There was a highly significant reduction in the drop in estimated glomerular filtration rate ≥50% (HR 0.53; 95% CI 0.42-0.67) and in the incidence of end-stage renal failure (HR 0.64; 95% CI 0 .50-0.82), both due to a drop in the incidence of filtration <15 mL/min/1.73 m^2 and the need for dialysis for at least 20 d (HR 0.66; 95% CI 0.48 -0.90). The mean annual drop in glomerular filtration rate was 2.86 mL/min/1.73 m^2 in the dapagliflozin arm and 3.79 mL/min / 1.73 m^2 in the placebo arm, an annual difference of 0.93 mL/min/1.73 m 2 (95% CI 0.61-1.25 mL/min/1.73 m^2). There was a significant reduction in the renal end point (6.6% vs 11.3%, HR 0.56; 95% CI 0.45-0.68, p = 0.000000018); of the composite of cardiovascular death and heart failure hospitalization (4.6% vs. 6.4%, HR 0.71; 95% CI 0.55-0.92, p = 0.0089) and of death from all causes (4.7% vs. 6.8%, HR 0.69; 95% CI 0.53-0.88, p = 0.0035). In subgroup analysis, there were no differences according to age, sex, diabetes, glomerular filtration rate or albumin-creatinine ratio. The incidence of serious adverse events was lower in the dapagliflozin arm. The incidence of significant hypoglycemia also differed (0.7% vs. 1.3%, p = 0.03).

We have just learned about a similar study, corresponding to the same pathology, with empagliflozin, the EMPA-KIDNEY study. It included patients with a glomerular filtration rate between 20 and <45 mL/min/1.73 m^2 with any UACR value, or between 45 and <90 mL/min/1.73 m^2, with an UACR of at least 200 mg/g. Patients had to be receiving ACE inhibitors or ARBs, but could be included if the investigator judged that they would not be tolerated. There was a run-in phase of up to 15 weeks, in which patients received placebo and baseline treatment was consolidated. After at least 6 weeks of run-in, blood and urine samples were taken, and once patients were judged fit, they were randomly assigned to empagliflozin 10 mg or placebo. The primary endpoint was the occurrence of renal disease progression or death from cardiovascular causes. Kidney disease progression was defined as end- stage kidney disease (beginning of maintenance dialysis or kidney transplant), a sustained decrease in filtration rate to less than 10 mL/min/1.73 m^2, a sustained decrease in glomerular filtration rate of at least 40%, or death from renal causes. Secondary endpoints were a composite of cardiovascular death and hospitalization for heart failure, hospitalization from any cause, death from any cause, and a composite of end-stage renal disease and death from any cause. Investigators defined 1070 primary endpoint events to give the study 90% power with p<0.05 2-tailed to demonstrate an 18% reduction with empagliflozin. It was suggested that if, after 624 events, an HR with empagliflozin of 0.778 was found for the primary endpoint (with p<0.0017) and the same HR for the secondary endpoint of terminal renal failure and death from any cause (with p<0.05), the study could be suspended.

Between February 2019 and April 2021, 8 544 patients were screened; 8 184 entered the pre randomization phase, and 6 609 were effectively randomized.

Their mean age was 63.8 years, 66.8% were men, and 46% had diabetes. The mean estimated glomerular filtration rate was 37.3 ± 15.5 mL/min/1.73 m^2, and the median UACR was 329 mg/g. Eighty-five percent were medicated with ACEI or ARB. In March 2022 the interim analysis showed, with 624 events, that the two conditions cited for discontinuing the study had been met. Follow-up was completed in July, with a median of 2 years. At the end of the first year of follow-up, 90% of the patients in both arms had taken more than 80% of the allocated tablets. At the last visit, 16.9% in the empagliflozin arm and 19.4% in the placebo arm had discontinued treatment.

The primary endpoint occurred in 13.1% of the empagliflozin arm and 16.9% of the placebo arm (HR 0.72, 95% CI 0.64-0.82, p<0.001). The rate of first and subsequent hospitalizations for any cause was lower with empagliflozin (24.8 vs. 29.2 hospitalizations per 100 patient-years; HR, 0.86; 95% CI, 0.78-0.95; p=0.003). There was a significant reduction in kidney disease progression (11.6% vs 15.2%, HR 0.71, 95% CI, 0.62-0.81). In contrast, there was no significant decrease in the composite hospitalization for heart failure or cardiovascular death (4% vs. 4.6%), cardiovascular death (1.8% vs. 2.1%) or death from any cause (4.5% vs. 5.1%).

As in all the studies with empagliflozin in different contexts, an attenuation in the drop in glomerular filtration was verified with the use of the drug. Considering the slope from the beginning of the study, the annual difference was 0.75 mL/min/1.73m^2. If the changes from 2 months after randomization are considered, and the initial drop in glomerular filtration rate due to reduced hyperfiltration is ruled out, the difference was greater: 1.37 mL/min/1.73m^2. Overall, in the empagliflozin arm, a reduction in weight of 900 g, in systolic and diastolic blood pressure of 2.6 and 0.5 mm Hg, and in UACR of 19%, compared to placebo, was verified.

We had already verified the nephroprotective effect of gliflozins in studies in diabetes, and in the context of heart failure. The results of EMPA-KIDNEY confirm those of DAPA-CKD regarding its beneficial effect on the evolution of patients with kidney failure. Some differences between the two studies deserve to be highlighted. The presence of diabetes was lower in EMPA-KIDNEY (46% vs 67% in DAPA-CKD). This coincided with a significantly lower UACR in EMPA-KIDNEY (329 mg/g vs 950 mg/g). In contrast, the average glomerular filtration rate was lower (37 vs 43 mL/min/1.73 m^2 *), and, in fact, in DAPA-CKD only 14.5% had < 30 mL/min/1.73* m^2*, compared to 34.5% in EMPA-KIDNEY. Worse glomerular filtration rate, but less albuminuria and diabetes in EMPA-KIDNEY … what could be expected regarding the prognosis?*

The annual incidence of the composite endpoint of worsening renal function, renal death, and cardiovascular death was, in the placebo arms, 7.5% in DAPA-CKD, and 8.9% per year in EMPA-KIDNEY. In both cases the reduction was significant with the tested drug. The incidence of cardiovascular death or hospitalization for heart failure was 3% per year in DAPA-CKD (with a significant reduction of 29% per year with dapagliflozin) and 2.4% in EMPA-KIDNEY (with no significant effect of empagliflozin); cardiovascular death 1.7% in DAPA-CKD and 1.06% in EMPA-KIDNEY (in both cases without significant reduction with gliflozins) and death from all causes 3.1% in DAPA-CKD (with reduction significant with dapagliflozin) and 2.6% in EMPA-KIDNEY (no significant effect of empagliflozin).

In summary, EMPA-KIDNEY patients appear to have had a higher incidence of clinical renal endpoints (but note that the definition was not similar in both studies; in DAPA-CKD a persistent drop in glomerular filtration rate ≥ 50, vs. 40 % in EMPA-KIDNEY) but slightly better cardiovascular and global prognosis than those of DAPA-CKD. Reduction of the primary end point with empagliflozin occurred mainly in patients with UACR > 300 mg/g; 48% of patients had values below. Albuminuria has been shown to be, in different meta-analyses, an even stronger predictor than glomerular filtration rate in the context of kidney failure. It is possible that the lower rate of cardiovascular events in EMPA-KIDNEY compared to DAPA-CKD is associated with a clearly lower UACR, and therefore with a lower chance of demonstrating a significant effect on hospitalization for heart failure or cardiovascular death, and death of all causes. The authors report that a meta-analysis in plan for publication, considering the large studies with gliflozins in kidney failure, confirms an overall reduction of 23% for the composite of cardiovascular death or heart failure and 14% for cardiovascular death. This seems to close the circle on the remarkable effect of this family of drugs in patients with heart failure, diabetes, and kidney failure.