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A large cohort study demonstrates the added value of ambulatory blood pressure compared with blood pressure measured in the clinic

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24-hour ambulatory blood pressure monitoring (ABPM) adds information to clinic blood pressure (BP); however, clinic blood BP is the standard to define the presence of hypertension (HT). In that sense, the guidelines recommend ABPM in special situations. Evidence demonstrates that ABPM could add prognostic information to clinic BP data; yet, as this evidence is derived mainly from studies with limited number of events, these conclusions are not conclusive. On the other hand, the predictive value of the defined patterns of HT is not clearly established.

A prospective study conducted on a large cohort in Spain clarifies both issues. The cohort included 63,910 patients evaluated with ABPM between 2004 and 2014. The reasons for ABPM included suspected white-coat HT, refractory or resistant HT, high-risk HT, and labile or borderline HT, as well as assessment of drug-treatment efficacy and study of the circadian BP pattern. Clinic BP was defined as the mean of two readings after the patient had been resting in a seated position for 5 minutes, with the use of validated oscillometric devices in 85% of patients or calibrated mercury sphygmomanometers in 15% of the cases. Ambulatory blood-pressure monitoring was performed with validated, automated devices that were programmed to record BP at 20-minute intervals during the day and at 30-minute intervals during the night. The mean of all the recordings was used to define 24-hour BP values, mean readings during the waking times to define daytime BP and mean readings during sleeping times to define nighttime BP.

Hypertension phenotypes in untreated patients were defined as white-coat HT (clinic systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, whereas ABPM corresponding values were <130 mmHg and <80 mmHg, respectively), masked HT (clinic SBP <140 mmHg and DBP <90 mmHg and ABPM corresponding values were ≥130 mmHg or ≥80 mmHg, respectively), sustained HT (clinic SBP ≥140 mmHg or DBP ≥90 mmHg and ABPM corresponding values were ≥130 mmHg or ≥80 mmHg, respectively), and normotension (clinic SBP <140 mmHg and DBP <90 mmHg and ABPM corresponding values were <130 mmHg and <80 mmHg, respectively).

In treated patients, the corresponding categories *were white-coat uncontrolled HT, masked uncontrolled HT, sustained uncontrolled HT, and controlled HT,* respectively.

The authors defined the association with long-term prognosis of clinic and ambulatory BP. as well as of HT phenotypes, based on data from the National Institute of Statistics. Median follow-up was 4.7 years.

Mean age was 58 years and 58% were men. Mean body mass index was 29.3 kg/m2. History of cardiovascular disease was present in 11% of participants. Mean clinic BP was 147.9 ± 18.8 /86.7 ± 11.6 mmHg. Mean ABPM values were 129.2 ± 13.7 /76.5 ± 10.1 mmHg (daytime BP 132.3 /79.4 mmHg, nighttime BP 120.2/68.4 mmHg).

At the moment of inclusion, 40.2% of the patients were not taking antihypertensive medications. The prevalence HT phenotypes were as follows: normotension 16.4%, white-coat HT 25.9%, masked HT 8.9%% and sustained HT 48.8%. Among treated patients, the prevalence of controlled HT, uncontrolled white-coat HT, uncontrolled masked HT and uncontrolled sustained HT was 17.6%, 28.9%, 8% and 45.5%, respectively.

After adjustment for age, sex and risk factors, the HR for all-cause and cardiovascular mortality was 1.54 per 1-standard deviation (SD) increase in clinic SBP. Excess risk was lower per 1-SD increase in clinic DBP (HR = 1.02) and was only significant for all-cause mortality. However, after additional adjustment for SBP and DBP in 24-hour ABPM, clinic BP lost much of its predictive power; HR = 1.02 for SBP and 0.89 for DBP (significant only for all-cause mortality).

After adjustment for age, sex and risk factors, the HR for all-cause and cardiovascular mortality was 1.55 and 1.58, respectively, per 1-SD increase in SBP and DBP in ABPM (24-hour BP, daytime BP and nighttime BP). After additional adjustment for clinic SBP and DBP, the risk did not vary, except for daytime DBP, which lost statistical significance. The models including ABPM showed better discriminative performance than those which used clinic BP.

Using normotension as the reference phenotype, and after adjustment for age, sex, risk factors and number of drugs used, controlled HT was associated with better outcome in terms of all-cause mortality compared with the other HT phenotypes. On the other hand, the other controlled and uncontrolled HT phenotypes were associated with adverse outcome, with HR between 1.3 and 2.9 (the worse outcome was associated with masked HT in untreated patients). After adding clinic SBP and DBP to the predictive model, the favorable outcome of controlled HT and the adverse outcome of uncontrolled white-coat HT were

lost. Masked HT in treated and untreated patients was the HT phenotype associated with the greatest risk (HR 1.96 and 2.83, respectively). As masked HT is relatively less prevalent (8.9% in untreated patients and 8% in treated patients), the population attributable fraction (fraction of mortality in the population that could be attributed to the disease) was lower than that of sustained HT in treated and untreated patients (prevalence between 45% and 50%).

This large study with adequate follow-up shows the importance of ABPM and suggests that, beyond defining BP patterns or evaluating the response to treatment, ABPM provides better prognostic information than clinic BP measurement. In addition, other interesting information is provided. Systolic BP is more determining than DBP. The risk of white-coat HT is not similar to that of normotension, as many physicians and doctors believe, probably because it shows a pattern of response to daily stress of which clinic HT is just a manifestation. The adverse outcome associated with unmasked HT (which can be only diagnosed with ABPM or home BP measurement) is undoubtedly related with poor follow-up and treatment. Clearly, the high population weight is still in patients with sustained HT and remains as the most important source of events due to the great prevalence of this type of HT.

This study has some limitations associated with daily practice. Clinic BP (and, thus, HT pattern after obtaining the results of ABPM) was defined as the average of only two readings within the same clinic visit. What would have happened if BP was determined based on BP readings in two or three clinic visits? Would the added value of ABPM be the same? There is no data on medication during the follow-up period. The prognosis at five years is established from a baseline determination. Perhaps another determination during the follow-up period could have refined the diagnosis. There is a selection bias from inclusion criteria: only patients with clinical indication for ABPM were included, and this is reasonable due to the observational nature of the study. Beyond these observations, this study provides important information which makes us think about the need of complementing clinic BP readings with ambulatory or home BP monitoring in all the patients.

Is the prognostic impact of intensive therapy to reduce LDL-cholesterol according to baseline values lower? A meta-analysis of randomized trials over the past 25 years

Navarese EP, Robinson JG, Kowalewski M, Kolodziejczak M, Andreotti F, Bliden K, et al. Association Between Baseline LDL-C Level and Total and Cardiovascular Mortality After LDL-C Lowering: A Systematic Review and Meta-analysis. **JAMA 2018;319:1566-79. http://doi.org/cpqn**

The stated aphorism "the lower, the better" in reference to lipid lowering therapy is still valid and LDL-cholesterol (LDL-C) levels seems to have no bottom at the moment of defining the ability to achieve better outcome.

However, previous studies comparing moderate-intensity versus high intensity statin therapy, or adding ezetimibe to conventional treatment, or adding a PCSK9-inhibiting monoclonal antibody for further lowering LDL-C, have failed to demonstrate reduction in mortality. For this reason, the following meta-analysis was performed to further explore this phenomenon.

The study included 34 trials involving 270,288 patients analyzing all-cause mortality and cardiovascular mortality, 32 of which (258,333 patients) evaluated major adverse cardiovascular events (MACE). In 26 trials, the patients received statin monotherapy; in 3 trials, statin and ezetimibe; and in 5 trials, statin and PCSK9-inhibiting monoclonal antibodies. Eight trials were conducted in primary prevention, 16 in secondary prevention, and 10 in both primary and secondary prevention. Mean baseline LDL-C level decreased over time (192 mg/dL in the WOSCOPS trial and 92 mg/dL in the FOURIER trial). Median follow-up was 3.9 years (from 0.6 years in the SPIRE1 trial and 0.9 years in the OSLER program to 6.7 years in the SEARCH trial). More intensive therapy was defined as the more potent pharmacologic strategy in each study (statin in the trials vs. placebo, high-dose statin in those trials comparing doses, statin in combination with non-statin therapies using either ezetimibe or a PCSK9-inhibiting monoclonal antibody vs. statins alone) while less intensive therapy corresponded to the control group of the original trial.

Overall, intensive therapy was associated with a 9% (95% CI: 4% - 12%) reduction in mortality rate for each 40 mg/dL higher baseline LDL-C level which means an absolute reduction of mortality of 1 incident case per 1000 person-years. The overall risk reduction in cardiovascular mortality across the 34 trials was 8%, but varied with baseline LDL-C. In the trials with baseline LDL-C levels of 160 mg/dL (4S, WOSCOPS, GREACE), risk reduction was 28% (95% CI: 16%-38%), with an absolute risk reduction in mortality of 4.3 incident cases per 1000 person-years. Risk reduction was 9% (95% CI: 4%-14%) in those with baseline LDL-C levels between 130 and 159 mg/dL, 12% (95% CI: 2% - 11%) when baseline LDL-C levels were between 100 and 129 mg/dL and 0% when baseline LDL-C levels were <100 mg/dL.

Statistical heterogeneity was present in the trials with baseline LDL-C levels of 100 to 129 mg/dL, depending on therapy intensity: risk reduction with more versus less intensive therapy was 12% in statin trials and 62% in PCSK9-inhibiting monoclonal antibody trials. The addition of ezetimibe to statin therapy in the SHARP trial did not show risk reduction. The reduction of all-cause mortality depended on the magnitude of LDL-C lowering: it was minimal in the studies with reduction <35 mg/dL and at the limit of significance. All-cause mortality was associated with a 10% risk reduction in the trials with LDL-C reduction of 35 to 65 mg/dL and 30% in the trials with LDL-C

reduction greater than 65 mg/dL, but without significant difference for interaction (p = 0.11).

The results of cardiovascular mortality risk were similar to all-cause mortality, with a risk reduction of 14% per 40 mg/dL increase in baseline LDL-C with more intensive therapy but only when baseline LDL-C levels were ≥100mg/dL. More intensive LDL-C lowering strategy was associated with a significant reduction in the risk for myocardial infarction (MI) across all baseline LDL-C values (10% per 40 mg/dL increase in baseline LDL-C) depending on the case: 16% in trials with baseline LDL-C levels <100 mg/dL and 36% in those with baseline LDL-C levels ≥160 mg/dL. There was a uniform reduction in the risk for cerebrovascular events with intensive treatment, independent of baseline LDL-C levels and a significant reduction of 9% in the risk for revascularization procedures per 40 mg/dL increase in baseline LDL-C levels. If we consider major cardiovascular events as a whole, a 10% reduction was achieved with more intensive treatment versus less intensive treatment per 40 mg/dL increase in baseline LDL-C levels, and in this case the reduction was significant over all values, but again, it was less pronounced in the studies with baseline C-LDL <100 mg/dL.

Baseline LDL-C levels were associated with the effect of intensive therapy on all-cause mortality and cardiovascular mortality. Probably, this may explain the fact that the most recent publications have not demonstrated reduction in all-cause mortality. Clearly, this effect depends on baseline values and on the magnitude of LDL-C lowering. Greater lowering can be achieved when baseline values are higher, when the follow-up period is longer and when the agent is more potent (let us think of the difference between PCSK9-inhibiting monoclonal antibodies and statins in patients with moderate LDL-C levels). The ODISSEY OUTCOMES trial, which has been recently published, was of longer duration than the FOURIER trial, and included patients with baseline LDL-C levels of 87 mg/dL. The study demonstrated mortality risk reduction particularly in patients with LDL-C levels >100 mg/dL. This meta-analysis focuses on absolute reductions of LDL-C levels. It would have been interesting to observe the effect in terms of the percent reduction achieved.

The lack of effect on all-cause mortality in the trials with baseline LDL-C values <100 mg/dL should not make us forget that although all-cause mortality was not reduced, more intensive therapy was associated with less risk for MI, revascularization and MACE in the same trials. Of importance, this is not a meta-analysis of individual data. The figures analyzed are those reported by the studies, each as a summary measure of all patient assessments included in each study. Therefore, comparing studies is not the same as comparing patients, and the background and concomitant treatment play a key role: in fact, the reality and the use of aspirin in the 4S and WOSCOPS was very different from the FOURIER trial. The result of the analysis should not be taken as an expression of intensive therapy futility in patients with lower LDL-C values, but as an important factor in deciding whether this intensity will involve the use of very expensive medications. Finally, patients' risk does not rely only on LDL-C levels but on a complete profile. Undoubtedly, efforts should focus on high-risk patients with more florid history, although LDL-C levels seem to be "controlled".

We should find different blood pressure targets according to the risk profile: a sub-analysis of the SPRINT trial

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The SPRINT trial was a randomized, open-label and controlled study that compared two treatment strategies in hypertensive patients to achieve a systolic blood pressure (SBP) treatment goal <140 mmHg (standard treatment, ST) or a SBP treatment goal <120 mmHg (intensive treatment, IT). The study included patients >50 years old with SBP between 130 and 180 mmHg with at least one of the following high risk criteria for cardiovascular events: history of clinical or subclinical cardiovascular disease (except for stroke), a Framingham risk-score of at least 15% at 10 years, chronic kidney failure with glomerular filtration rate between 20 and 59 ml/min/1.73 m2 or aged 75 years or older. Patients with diabetes and stroke were excluded from the study. The primary outcome was a composite of myocardial infarction (MI), acute coronary syndrome not resulting in MI, stroke, acute decompensated heart failure (HF), or cardiovascular mortality.

The attending physicians were free to choose drug therapy in each treatment group, but were encouraged to use evidence-based medications. In the ST group, the SBP treatment goal was initially between 135 and 139 mmHg; when lower values were observed during follow-up, the doses of the treatment introduced were reduced. The study began in 2010 and enrollment ended in 2013 with 9,361 patients. The study was stopped in August 2015 after a mean follow-up of 3.26 years due to recommendation of the Data and Safety Monitoring Board. Mean age of the participants was 68 years (28% were 75 years or older), 64% were men and 28% had chronic kidney failure. Mean BP at the beginning of the study was 139.7/78.1 mmHg. Patients randomized to the ST group achieved a mean SBP of 134.6 mmHg throughout the study while those in the IT group achieved a mean SBP of 121.5 mmHg, with a mean number of antihypertensive drugs of 1.8 and 2.8, respectively.

The incidence of the primary outcome was 1.65% per year in the IT group and 2.19% per year in the ST group (HR 0.75; 95% CI: 0.64-0.89), and this difference was statistically significant after the first year. There were no significant differences in the incidence

of MI or stroke, but the rate of acute HF, cardiovascular mortality and all-cause mortality was significantly different. Patients with kidney failure on inclusion (>28%) did not have different outcome. The incidence of serious adverse events was not significantly different, but the incidence of hypotension, syncope and kidney failure was significant; in all cases, between 2% and 4% in the IT group and between 1.5% and 2.5% in the ST group.

Based on these results, the 2017 ACC/AHA guideline lowered BP values to 130/80 mmHg to define hypertension and recommended intensive treatment in patients with an estimated 10-year atherosclerotic cardiovascular disease risk of 10% or higher to achieve SPB <130 mm Hg. The discussion on this suggestion included considerations on how BP was measured in the SPRINT trial (three BP measurements with the use of an automated measurement system while the patient was seated and after 5-minute rest without the presence of a physician, an unusual situation in daily practice). As BP values measured with this device are between 5 and 10 mmHg below office BP values, SBP <120 mmHg corresponds to values <130/80 mmHg in usual practice. However, one question that emerges is that generalizing BP targets below the traditional value of 140/90 mmHg can lead to higher incidence of adverse events related with the medication.

The authors of the publication here presented worked with the individual patient-data of the SPRINT database. Subject-specific estimates of the 10-year ACC/AHA cardiovascular disease risk were determined using the risk prediction equations from the ACC/AHA Guideline on the Assessment of Cardiovascular Risk. The SPRINT population was then stratified into quartiles based on 10-year risk. The risk of presenting the primary outcome and serious adverse events was defined for each quartile according to the data of the SPRINT study. Then, the benefit-to-harm ratio of implementing IT versus ST was determined. The first quartile corresponded to a 10-year baseline risk of major events <11.5%; the second, to those with risk between 11.5% and 18.1%; the third to those between 18.2% and 28.9% and the fourth to those with risk >28.9%. Risk increased as age, SBP and kidney dysfunction increased, and cholesterol values and body mass index decreased. Mean SBP was 133 mmHg in the first quartile and 146 mmHg in the fourth; 17.3% of the patients >75 years were in the fourth quartile and 79.8% in the fourth.

The incidence of the primary outcome was greater in patients with higher baseline risk in both treatment groups. Within quartiles, the risk was lower in the IT group, with a HR <1 in the four quartiles compared with ST, but reached statistical significance only in the fourth quartile. The necessary intention- to-treat (ITT) number to prevent one event decreased from 91 in the first quartile to 38 in the fourth. The HR for all-cause mortality was always <1 and did not reach statistical significance in any of the four quartiles, but the ITT number decreased from 333 in the first quartile to 45 in the fourth.

The incidence of adverse events also increased when baseline risk increased, but the higher risk of using IT was lower in the higher quartiles, so that the number needed to harm (NNH) increased from 62 in the first quartile to 250 in the fourth quartile.

The predictive model of benefit-to-harm ratio demonstrated ratios of 0.50, 0.78, 2.13, and 4.80, for the first, second, third, and fourth quartiles, respectively A benefit-to- harm ratio <1 suggests greater harm than benefit; conversely, a benefit-to- harm ratio >1 means greater benefit than harm. For the authors, this analysis suggests that intensive treatment is only justified in patients as those of the SPRINT trial with a 10-year risk ≥18.2%.

This meta-analysis offers sufficient material for discussion. Firstly, this is a post hoc meta-analysis that was not specified as an objective when the study was initiated. From this viewpoint, we can consider it an observational study in the population included in the randomized trial. Nevertheless, most of the risk variables were equally distributed in the two treatment strategies in each quartile. Blood pressure targets according to age deserve special consideration. In general, such targets can be higher in elderly patients. The analysis of the SPRINT trial seems to be in the opposite direction: 97% of those >75 years were in quartiles 3 and 4, in which IT offered the greatest benefit-to-harm ratio.

The concept of baseline cardiovascular risk, common when referring to lipid-lowering treatment (to the point that treatment intensity is based on cardiovascular risk in some guidelines), is not common when referring to antihypertensive treatment. However, it seems reasonable to think that as blood pressure is only one of the risk markers and determinant of events in patients with HT, it would be appropriate to establish a more intensive treatment depending on the probability of benefit or harm. And going even further, it seems sensible to think about the proper treatment according to the pattern of baseline variables. Finally, these findings support the concept of personalized medicine tailored to therapeutic targets.

Real-world evidence about the benefit of sodium glucose co-transporter 2 inhibitors in type 2 diabetes mellitus patients: the EASEL registry

Udell JA, Yuan Z, Rush T, Sicignano NM, Galitz M, Rosenthal N. Cardiovascular Outcomes and Risks After Initiation of a Sodium Glucose Cotransporter 2 Inhibitor: Results From the EASEL Population-Based Cohort Study (Evidence for Cardiovascular Outcomes With Sodium Glucose Cotransporter 2 Inhibitors in the Real World). **Circulation 2018;137:1450-59. http://doi.org/gdc4cd**

Sodium glucose co-transporter 2 inhibitors (SGLT2i) are a new class of agents used to treat diabetes. They promote osmotic diuresis and generate glycosuria and natriuresis. These agents reduce circulating glycated hemoglobin A1c to the same extent as other drugs, promote negative caloric balance, reduce body fat

and epicardial fat and induce weight loss. They also attenuate arterial wall stiffness and produce a mild reduction in blood pressure levels. They have anti-inflammatory and antifibrotic effects. Sodium glucose co-transporter 2 inhibitors increase HDL-cholesterol levels, have renoprotective effects (by reducing intraglomerular pressure and glomerular hyperfiltration) and reduce albuminuria progression. They reduce plasma volume due to their natriuretic effect.

So far, we are aware of two large randomized trials evaluating this group of agents. The EMPA REG trial showed that empagliflozin was associated with reduction in all-cause mortality and hospitalization for heart failure (HHF) in type 2 diabetes patients with established cardiovascular disease. In the CANVAS Program trial, the use of canagliflozin in similar patients but with a slightly better prognosis reduced the composite outcome of major cardiovascular adverse events and HHF without a significant reduction in all-cause mortality. Both studies evaluated the ability of these drugs to slow the onset of impaired renal function. The CANVAS Program trial reported increased risk for below-knee limb amputation but the reason remained unclear and was even suggested being probably due to chance.

Another large observational study was the CVD-REAL, which included type 2 diabetes patients with lower prevalence of cardiovascular disease. In these patients, the use of SGLT2i (particularly canglifozin and dapaglifozin) reduced HHF by 39% and all-cause mortality by 51% compared with other antihyperglycemic drugs.

The EASEL study is now available. This retrospective cohort study was conducted in the context of the U.S. Department of Defense. The Department of Defense health system gives care to 10 million beneficiaries and has prospective information about demographic and clinical baseline characteristics and treatments used. These data can be associated with prescription of medications over time and vital outcome.

Initially, the study considered all patients with type 2 diabetes with prescription of a new antihyperglycemic agent between April 2013 and December 2016. A new antihyperglycemic agent was considered as the one that had not been indicated within the year before the prescription and no prior exposure to any medication within the same medication class had been made. Overall, 111,576 new users of an antihyperglycemic agent with established cardiovascular disease were identified, among which 13,757 were new users of an SGLT2i and 97,819 of a non-SGLT2i antihyperglycemic agent, excluding metformine. Because patients receiving SGLT2i were younger and had lower incidence of cardiovascular disease and comorbidities, a propensity score was used to compare these groups based on independent predictors for prescribing SGLT2i. Approximately 1,000 variables were considered to generate the new score. Using this score, patients were paired in a 1:1 ratio and 12,629 pairs with similar baseline characteristics were defined. Mean age was 66 years and 44% were women. Approximately 23% had history of heart failure, 16% had history of acute myocardial infarction (AMI) and almost 11% had history of stroke. The mean duration of diabetes was 5.6 years. Among SGLT2i therapies, 58.1% patients initiated treatment with canagliflozin, 26.4% with empagliflozin, and the rest used dapagliflozin.

Median follow-up time in an intention-to-treat analysis was 1.6 years. The incidence rate of all-cause mortality or HHF was 1.73% vs. 3.01% among new users of SGLT2i and non-SGLT2i antihyperglycemic agents, respectively (HR 0.57, 95% CI: 0.50-0.65). All-cause mortality and HHF were lower among new users of SGLT2i (HR 0.57, 95% CI: 0.49-0.66 and HR 0.57, 95% CI: 0.45-0.73, respectively). An early separation of the curves for both events was observed from the beginning of treatment. The rate of the composite of all-cause mortality, nonfatal MI, and nonfatal stroke was also lower (HR 0.67; 95% CI: 0.60-0.75) at the expense of a reduction in mortality and a trend toward reduction in non-fatal MI (HR 0.81; 95% CI 0.64-1.03). Along with these beneficial effects, the rate of below-knee amputation was higher with SGLT2i (0.17% vs. 0.09% HR 1.99, 95% CI: 1.12-3.51). The incidence seemed to be greater with canagliflozin (0.19%) than with empagliflozin (0.12%) or dapagliflozin (0.09%), but a formal comparison was not made due to the low number of cases.

An as-treated analysis (only with those patients taking the medication when the event occurred) showed similar results to those of the intention-to-treat analysis.

The EASEL registry confirms the results of the CVD-REAL registry in a slightly sicker population. The magnitude of the reduction in mortality is similar. The final end points showing the superiority of SGLT2i versus other treatments are the same as those of the randomized trials: all-cause mortality and HHF. Further research of the physiopathololgy is needed to clarify the mechanism of action of the phenomena involved in the reduction of mortality and HHF. Attributing all the effect to osmotic diuresis seems to be too simplistic. The mechanisms involved with attenuation of endothelial dysfunction, the interaction with the myocardial sodium-hydrogen exchanger and a certain anti-inflammatory effect are reasons that may contribute in this regard, but none of them are exclusive. The registry confirms the higher risk of below-knee amputation, and although this event does not have sufficient power, it was more common with canaglifozin.

Finally, we must remember that in this registry patients were matched by a propensity score constructed from a known set of variables, and we cannot assume, as in a randomized trial, that the unknown variables are equally distributed. However, the fact that it is not a randomized trial constitutes the strength of the study, as it provides unselected, real-world patients. The coincidence of findings between the clinical trials and the registries allows the most common doubts in this case. At this point in time and with similar results

obtained in clinical trials and observational studies in type 2 diabetics with different baseline profiles and risk for cardiovascular events, it seems difficult to disregard these drugs as first-line therapy.

Not all antihyperglycemic agents ensure the same outcome. A network meta-analysis comparing sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors.

Zheng SL, Roddick AJ, Aghar-Jaffar R, Shun-Shin MJ, Francis D, Oliver N, et al. Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis. **JAMA 2018;319:1580-91. http://doi.org/gdftpx**

Dipeptidyl peptidase 4 (DPP-4) inhibitors are among the most commonly used drugs for the treatment of diabetes. Over the past years, other agents have emerged, as sodium-glucose cotransporter 2 inhibitors (SGLT-2i) and glucagon-like peptide 1 (GLP-1) agonists. Traditionally, the evaluation of the response to any of the agents used for the treatment of diabetes is based on hypoglycemia and the incidence of macrovascular and microvascular events. However, the use of SGLT-2i and some GLP-1 agonists has been associated with reduction in mortality, changing the focus on the objectives of using new antihyperglycemic drugs. We present a network meta-analysis comparing the use of the three types of drugs and their effect on all-cause mortality in type 2 diabetes mellitus patients.

A network meta-analysis includes the studies that evaluate the therapeutic agents considered and allows making direct and indirect comparisons between them. In this way, it provides information from studies that actually compared agents with one another, but also from studies where the drugs were compared with a common comparator (placebo, another drug or no treatment), thus increasing the number of observations. For example, when comparing A with B, the analysis uses information from studies comparing A vs. B, but also A vs. C and B vs. C, to obtain more information about the effect of A and B indirectly and increase the power of the comparison.

This meta-analysis included trials published in English in which one agent belonging to any of the three family of drugs was compared with any of the three or with placebo or no treatment in studies with at least 1-year follow-up period and which provided information about mortality (even if it was not a primary outcome of the study).

A total 236 articles comprising 258 comparisons and 176,310 patients with mean follow-up of 1.7 years were included in the meta-analysis. Only 23 studies represented direct comparisons: 14 trials compared a GLP-1 agonist with a DPP-4 inhibitor (7,748 patients), 8 trials compared a DPP-4 inhibitor with an SGLT-2i, and 1 trial compared a GLP-1 agonist with a SGLT-2i (458 patients). Most of the participants were involved in comparisons between any agent and placebo or no treatment control.

Among the 236 studies included, 9 were designed as cardiovascular outcome trials and enrolled almost half (87,162) of the participants: EMPAREG (empagliflozin), CANVAS (canagliflozin), ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN 6 (semaglutide), EXSCEL (exenatide), SAVOR TIMI 53 (saxagliptin), EXAMINE (alogliptin) and TECOS (sitagliptin). In the different comparisons, 51% to 58% of cases comprised men; mean age was 53 to 58 years and HbA1c was between 8% and 8.2%.

SGLT-2 inhibitors (HR, 0.80; 95% CI, 0.71 to 0.89) and GLP-1 agonists (HR, 0.88; 95% CI, 0.81 to 0.94) were associated with significantly lower all-cause mortality. DPP-4 inhibitors were not significantly associated with lower all-cause mortality (HR, 1.02; 95% CI, 0.94 to 1.11). Compared with DPP-4 inhibitors, SGLT-2i (HR, 0.78) and GLP-1 agonists (HR, 0,86) demonstrated significant reduction in all-cause mortality. There were no significant differences between SGLT-2i and GLP-1 agonists. The same conclusions were obtained for cardiovascular mortality. For individual drugs, only empagliflozin, liraglutide and exenatide demonstrated reduction of all-cause mortality.

When compared with the control groups (HR, 0.62), DPP-4 inhibitors (HR, 0.55), and GLP-1 agonists (HR, 0.67), SGLT-2i were associated with reduced heart failure events. There were no significant differences between GLP-1 agonists and controls, but when the different GLP-1 agonists were compared with one another, the incidence of heart failure was lower with GLP-1 (HR, 0.82).

Only SGLT-2i were associated with reduction in all MIs (HR, 0.86) and nonfatal MIs (HR, 0.84).

For hypoglycemia, SGLT-2i (HR, 1.24), DPP-4 inhibitors (HR, 1.29) and GLP-1 agonists (HR, 1.44), were all associated with an increased risk but there were no significant differences for major hypoglycemia. Sodium-glucose cotransporter 2 inhibitors were associated with a reduction in serious adverse events between 8% and 10% compared with the control groups and the other drug classes. On the contrary, GLP-1 agonists were associated with an increased risk.

In a sub-analysis considering only the 9 studies with cardiovascular events as primary outcomes, the results were similar, except that SGLT-2i were not associated with reduction of MI and GLP-1 antagonists did not reduce the incidence of HF compared with DPP-4 inhibitors.

Network meta-analyses are a fantastic tool for generating information about comparisons that have never been made in a clinical trial. From this perspective, they provide invaluable information. As with any meta-analysis, publication bias favoring studies with positive results may be possible, but the fact that so many studies and comparisons are considered makes this possibility very remote. As this meta-analysis uses

data from studies and not from individual patients, the conclusions may not have sufficient power. Of interest, SGLT-2i and GLP 1 antagonists again demonstrate significant reductions in all-cause mortality compared with DPP-4 inhibitors, the agents most commonly used in the treatment of type 2 diabetes, and that the latter have no effect on mortality when compared with control or placebo.

A new paradigm is growing in the treatment of diabetes: the importance of a drug is no longer measured by its ability to reduce glycated hemoglobin A1c but by its actual ability to reduce cardiovascular events. Does this mean that DPP-4 inhibitors or other drugs that do not improve the outcome will be removed from standard therapy? Definitely not, but certainly, at the time of deciding, DPP-4 inhibitors will become antihyperglycemic agents used as combination therapy rather than as first-line treatment in many cases. We should not forget the benefit produced by the usual treatment on microvascular disease. Finally, we should wait for studies exploring SGLT-2i in combination with GLP-1 antagonists in high-risk patients. Will their effects be additive?

A new evaluation of NT-proBNP performance for the diagnosis of heart failure: the ICON RELOADED study

Januzzi JL, Jr., Chen-Tournoux AA, Christenson RH, Doros G, Hollander JE, Levy PD et al. N-Terminal Pro-B-Type Natriuretic Peptide in the Emergency Department: The ICON-RELOADED Study. **J Am Coll Cardiol 2018;71:1191-200. http://doi.org/gc74t3**

Measurement of N-terminal pro–B-type natriuretic peptide (NT-proBNP) is mentioned as a resource to consider for the diagnosis of acute heart failure (HF). However, the strength of this recommendation is not the same for all the societies of cardiology. The European Society of Cardiology (ESC) considers measurement of NT-proBNP a class I, level of evidence A recommendation in patients with acute HF to rule out non-cardiac causes of acute dyspnea. For the AHA/ACC, the indication is also IA, especially when there is uncertainty about the diagnosis. On the contrary, for the Argentine Society of Cardiology (SAC) it is a class IIaB indication. Furthermore, the cutoff points for excluding or confirming the diagnosis vary according to the context. The ESC recommends a cutoff point of 300 pg/ml to exclude the diagnosis. The Food and Drug Administration (FDA) considers cutoffs for NT-proBNP of 125 for patients <75 years and 450 pg/ml for those >75 years.

For several years, two observational studies, ICON and PRIDE, suggested optimal diagnostic cutoff points of 450, 900, and 1,800 pg/ml for age categories <50, 50 to 75, and >75 years, respectively, not to exclude but to confirm acute HF. However, these cutoffs were not validated and, probably, the epidemiology of acute HF could have varied in such a way that it may not be useful nowadays. The ICON RELOADED study was performed between 2015 and 2016 to validate the cutoff points identified in both studies in 19 centers of the United States and Canada. The study considered the age-specific rule-in cutoff points previously mentioned for the diagnosis of acute HF and a rule-out cutoff point of 300 pg/ml to exclude the diagnosis. The specificity and positive predictive value (PPV) for the rule-in cutoff points, as well as the sensitivity and negative predictive value (NPV) for the rule-out cutoff values were calculated. The expected prevalence of acute HF was 50% with a PPV of 85 and a NPV of 98.5%.

A total of 1,461 patients who sought medical care at the emergency department were included. A clinical events adjudication committee, blinded to NT-proBNP results independently reviewed and adjudicated the diagnosis of acute HF based on data from the medical records, physical examination and complementary tests. Mean age was 56.4 years, 49.1% were female, 63.3% had hypertension and almost 25% had history of myocardial infarction. The prevalence of acute HF was only 19%, lower than expected. Median NT-proBNP levels were significantly different in patients with and without acute HF: 2,844 pg/ml vs. 98 pg/ml, respectively ($p<0.0001$).

The PPV for age-stratified diagnostic cutoffs was not high. The PPV of the cutoff point of 450 pg/ml was 53.6% (n=462) in patients <50 years; for 900 pg/ml, the PPV was 58.4% (n=833) in subjects between 50 and 75 years; and for 1800 pg/ml, the PPV was 62% (n=166) in those >75 years. The performance of the specific cutoff points decreased with age: 0.97, 0.89 and 0.84, respectively. The NPV of 300 pg/ml to exclude the diagnosis of acute HF was 98%. As in previous studies, the value of the age-adjusted NT-proBNP had the highest OR to predict acute HF: 11.8 versus 4.7 for chest radiography findings, 3.95 for peripheral edema, 2.67 for prior HF and 2.56 for rales on lung examination. There was no significant difference in the diagnostic performance to discriminate according to ejection fraction, renal function or sex; yet, it was lower in obese patients and in those with atrial fibrillation. The areas under the curve had good discriminating ability, ranging from 0.96 for subjects <50 years to 0.84 for those >75 years.

The value of natriuretic peptides depends on a number of factors, including the presence or absence of heart failure, renal impairment, anemia, inflammation and extent of cardiovascular disease. Defining different age-specific cutoff points helps to mitigate some of these sources of error: with age, the prevalence of each of these factors increases, and using progressively higher cutoff points helps to achieve greater specificity by reducing the rate of false positive results. However, PPV is not striking, as it ranges from 54% to 62% depending on age, which means that in the presence of values above the corresponding cutoff point, a wrong diagnosis of acute HF will be made in 38% to 46% of the cases. The authors attribute this low PPV to the low prevalence of acute HF, only 19%, but other factors (as those previously mentioned) may be involved.

The study confirms the excellent NPV of NT-proB-

NP to rule out the diagnosis of acute HF: in the presence of low values (<300 pg/ml in this study), we can mostly exclude this diagnosis. We can attribute this high sensitivity to the good area under the curve, even though the specificity is less satisfactory.

NT-proBNP strongly contributes to rule out rather than confirm the diagnosis of acute HF, but the use of differential cutoff points helps to improve its performance. Even if the OR for the diagnosis of HF is greater than the one of traditional findings, only careful interrogation and physical examination, with the help of echocardiography (not considered in this study even though it is not always available in the emergency department) and a correct interpretation of peptides in this context will contribute to minimize possible failure to define the presence or absence of acute HF.

A randomized study with evidence against the use of sildenafil in patients with pulmonary hypertension secondary to left-sided heart failure.

Bermejo J, Yotti R, Garcia-Orta R, Sanchez-Fernandez PL, Castano M, Segovia-Cubero J, et al. Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: a multicenter, double-blind, randomized clinical trial. **Eur Heart J 2018;39:1255-64. http://doi.org/cps6**

The most common cause of pulmonary hypertension (PH) is left heart disease, particularly heart failure with preserved ejection fraction (HFpEF) or heart failure with left ventricular dysfunction (HFLVD) and valvular (mitral or aortic) heart disease (VHD). Regression of PH is frequently incomplete after surgical correction of the valve lesion. And although treatment guidelines do not recommend the use of the specific therapy for pulmonary arterial hypertension (PAH) or PH secondary to pulmonary embolism (as 5-phosphodiesterase inhibitors, endothelin receptor antagonists or prostacyclins), sildenafil, a 5-phosphodiesterase inhibitor, is frequently used for treating this condition.

We present a clinical trial which included patients with persistent PH at least one year after successful surgical valve replacement or valve repair. The patients included had undergone right heart catheterization within one month prior to randomization which demonstrated mean pulmonary arterial pressure (PAP) ≥30 mmHg. In patients in whom recent catheterization data was unavailable but had systolic PAP ≥50mmHg in a screening echocardiographic study, a right heart catheterization procedure was performed. Patients with prosthesis dysfunction or residual VHD, significant renal impairment or life expectancy <2 years were excluded from the study.

Patients were randomly assigned to receive either sildenafil 40 mg three times daily or placebo. The primary endpoint was based on the composite of three elements: clinical events, defined as occurrence of death or hospital admission for HF, functional classification and patient global self-assessment. The composite clinical score classified patient's outcome in three categories: worsened, if he/she presented a clinical event, increased his/her functional class, or self-reported a worse category; improved, if he/she had not suffered a clinical event and his/her functional class had improved or reported improvement in global self-assessment; or unchanged. The score was evaluated at six months after inclusion. The authors estimated proportions of improved, worsened, and unchanged categories to be 15%, 20%, and 65%, respectively. By estimating an absolute 10% increase in the proportion of improvement with sildenafil, the calculated sample size was 354 patients to find with an 80% power a difference with placebo that had $p<0.05$. Over the course of the study, the incidence of the worsened category was higher than expected and the final sample size was re-adjusted to 198 patients.

Between 2009 and 2015, 200 patients were randomly assigned to receive either sildenafil (n=104) or placebo. Median age was 72 years; 47.5% were in functional class II and 43.5% in functional class III. Atrial fibrillation was present in 77% of cases. Right-heart catheterization showed median right atrial pressure of 12 mmHg, median PAP was 38 mmHg, median wedge pulmonary pressure was 23 mmHg and median transpulmonary pressure gradient was 2 mmHg. This pattern is characteristic of post-capillary pulmonary hypertension.

After six months, 33 patients in the sildenafil group worsened their composite score (24 patients with a clinical event), as compared with 14 in the placebo group (12 events). Only 27 patients receiving sildenafil improved their composite clinical score, as compared with 44 patients receiving placebo (OR for sildenifil vs. placebo: 0.39; 95% CI, 0.22–0.67). There were 31 hospitalizations due to HF in the sildenafil group versus 22 in the placebo group ($p=0.035$).

The use of sildenafil in HFpEF has shown contradictory evidence so far. Some studies failed to demonstrate benefits compared with placebo, while other studies reported improvement in exercise performance. The presence of PH has often been suggested as one of the criteria for prescribing sildenafil in heart failure patients. However, this clinical trial opens the door to the idea that, on the contrary, sildenafil could be causing harm to patients with this condition.

Patients with PAH have different pathological and hemodynamic findings than those with pulmonary hypertension secondary to left-sided heart failure. The pathological findings of PAH occur in the distal pulmonary arteries, with hypertrophy of the media layer, intimal proliferation, adventitia thickening and fibrosis. In addition, right-sided catheterization shows increased pulmonary resistance with normal left ventricular filling pressures. On the other hand, PH secondary to left-sided heart failure presents dilation and thickness of the pulmonary veins, with interstitial edema and alveolar hemorrhage. From a hemodynamic point of view, increased left ventricular filling pressure is the distinct feature, and although pulmonary vascular resistance may be high in certain patients (the

so-called combined precapillary and post capillary PH), this is not sufficient to consider this situation as equivalent to PAH.

Why does sildenafil have a deleterious effect in this scenario? Probably, pulmonary arterial vasodilation produced by sildenafil increases pulmonary venous return to a rigid non-compliant left ventricle with already increased filling pressure, thus worsening the clinical condition. A negative inotropic effect has been also proposed. Regardless, the use of sildenafil in patients with PH secondary to left-sided heart failure seems to be not recommended. Will new evidence against the present evidence emerge?

A new analysis on the use of digoxin and greater risk of mortality.

Lópes RD, Rordorf R, De Ferrari GM, Leonardi S, Thomas L, Wojdyla DM, et al. Digoxin and Mortality in Patients With Atrial Fibrillation. **J Am Coll Cardiol 2018;71:1063-74.http://doi.org/gc52zb**

Over the past years, many publications have reported that the use of digoxin for atrial fibrillation (AF) or heart failure (HF) is associated with higher risk of mortality. This information comes from retrospective cohort studies, or from analyses of randomized trials of other interventions in which a post hoc analysis compared patients treated with digoxin versus untreated patients. Of importance, treatment with digoxin was not randomly assigned in these studies.

The present study is a substudy of the ARISTOTLE trial which compared apixaban with warfarin in AF patients. Among the 17,897 patients with information available on the use of digoxin and HF status, 32.5% were taking digoxin at baseline and 37.4% had HF. Annual mortality was higher in patients treated with digoxin, but after adjustment for baseline characteristics (socio-demographic data, history, AF characteristics, additional therapies, results of laboratory tests and biomarkers) there was no significant difference with placebo (HR, 1.09, 95% CI: 0.96-1.23). This result was observed in patients with or without baseline HF. Baseline serum digoxin concentration was measured in 76% of patients. Median serum digoxin concentrations were significantly higher in patients who died compared with those who survived (median: 0.62 ng/ml vs. 0.55 ng/ml, p <0.0001). For patients with digoxin levels <0.9 ng/ml there was no increased risk of death compared with those not on digoxin, while for patients with levels between 0.9 and 1.2 ng/ml, the HR was 1.16, without statistical significance. For patients with digoxin levels ≥1.2 ng/ml, there was a significant increased risk of death (HR: 1.56; 95% CI: 1.20 to 2.04; p=0.0011) compared with those not on digoxin. For each 0.1-ng/ml increase in baseline serum digoxin concentration, a 4% higher risk of mortality was recorded for patients with or without HF.

Among 12,703 patients not taking digoxin at baseline, 6.9% started digoxin during the study. Of these, 779 patients were matched with 2,337 control participants considering baseline characteristics, clinical status, presence or absence of HF, and the context in which treatment began (outpatient setting or during hospitalization). New digoxin use was associated with a significantly higher risk of mortality during follow-up, with a HR of 1.78, 95% CI: 1.37-2.31 (HR 1.58 in patients with HF and 2.07 in those without HF). New digoxin use was associated with an increased risk of sudden cardiac death, with higher risk from the beginning of the new treatment and a number of patients needed to generate an event at 1 year of 180 and at 2 years of 56. Also, the risk of hospitalization due to HF increased by 70% but only in patients with baseline HF.

This observational study provides similar information to that of previous publications. The fact that the baseline use of digoxin is not associated with increased mortality after adjustment for baseline conditions may have two conflicting explanations. Digoxin may not be a risk factor per se, but just a marker of sicker patients. When this observation is considered in the analysis, the deleterious effect disappears. On the other hand, it may mean that patients who are taking the medication when the clinical trial begins are those who have already survived to the deleterious effect. The association between increased digoxin concentrations and worse outcome indicates a dose-response effect, which is biologically plausible (arrhythmogenic effect of digoxin), and suggests a causal relationship. However, this issue is also a matter of debate: as the determination of digoxin concentration is not randomly assigned, we may infer that slimmer patients with impaired renal function or concomitant diseases are more likely to have higher plasma concentrations.

The evident greater risk of new users supports the theory of the detrimental effect. Of interest, the early separation of the survival curves and, in particular, the significant increase in the risk of sudden death confirm the association of the treatment with the incidence of serious arrhythmias probably due to treatment (as the DIG study, the only randomized study had already demonstrated in patients with HF in sinus rhythm). In contrast, the higher incidence of hospitalization due to HF is less clear (as opposed to the findings of the DIG trial), so we can assume that in fact, and despite statistical adjustment, the use of the drug indicates more compromised patients.

In conclusion, as in all observational studies, we cannot exclude biases after multivariate analysis as well as the presence of non-considered factors (residual confounding). Yet, residual confounding has to be large enough to explain a twofold increase in the risk after analyzing so many variables. And, indeed, it seems unbelievable that we continue quoting these type of studies due to the lack of randomized trials evaluating the potential benefits and harms of digoxin in AF (or in HF, over 20 years after the DIG trial). In the meantime, keeping digoxin concentration <1 mg/ml seems to be reasonable.