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LEADER Trial: Liraglutide reduces mortality in patients with type 2 diabetes

Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. **N Engl J Med 2016 [Epub ahead of print].**

Type 2 diabetes is associated with increased risk of macrovascular and microvascular complications. Treatment with different types of glucose-lowering drugs has shown to decrease consistently microvascular complications. The reduction of major cardiovascular events has been shown only after prolonged follow-up with commonly used drugs. Recently, the EMPA-REG study evidenced the beneficial effect of empaglifozin, a renal sodium glucose cotransporter inhibitor, by reducing the incidence of total cardiovascular mortality and heart failure. Now, the LEADER trial (randomized, multicenter, double-blind, placebo-controlled study) brings into consideration an agent with different action, liraglutide (L), a GLP-1 analogue.

As in the EMPA-REG study, a population of patients with type 2 diabetes (with glycosylated hemoglobin, HbA1c ≥7%) and high cardiovascular risk was selected: a) patients over 50 years of age with at least one of the following clinical conditions: cardiovascular disease, cerebrovascular or peripheral vascular disease, glomerular filtration rate <60 ml/min/1.73 m2, or functional class II-III heart failure; or b) patients above 60 years of age with one risk factor: microalbuminuria or proteinuria, hypertension with left ventricular hypertrophy, ventricular systolic or diastolic dysfunction, or ankle-brachial index <0.9. Patients could be with or without previous hypoglycemic treatment, but use of rapid-acting insulin, GLP-1 agonists or DPP-4 inhibitors, or pramlintide were exclusion criteria. In addition, patients with history of type 2 multiple endocrine neoplasia or medullary thyroid cancer (due to excess risk of these diseases in animal models with L), or major cardiovascular or cerebrovascular event in the last 14 days were also excluded. The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction (AMI) or nonfatal stroke. A hierarchical non-inferiority analysis was planned (setting as non-inferiority margin the upper limit of the HR 95% CI in 1.3; that is, accepting excess risk of up to 30%), which, if positive, admitted the performance of a superiority analysis. An exploratory analysis of other endpoints was also conducted: one extended study (the primary endpoint plus revascularization or hospitalization for unstable angina or heart failure), all-cause death, and a composite of nephropathy (onset of macroalbuminuria, doubling of creatinine levels, filtration rate drop to <45 ml/min/1.73 m2 or need for dialysis) and retinopathy (need for photocoagulation, vitreous hemorrhage, blindness). A minimum follow-up of 42 months was postulated.

The study included 9,340 patients assigned to receive L or placebo in a 1:1 ratio. Nearly all patients had established cardiovascular or renal disease. Mean diabetes duration was 12.8 years and mean HbA1c was 8.7% at the time of inclusion. At a median follow-up of 3.8 years, the primary endpoint occurred in 13% of cases with L and 14.9% with placebo (HR 0.87, 95% CI 0.78-0.97, p<0.001 for non-inferiority and 0.01 for superiority). There was significantly lower cardiovascular mortality (4.75% vs. 6%, HR 0.78, 95% CI 0.66-0.93) and overall mortality (8.2% vs. 9.6%, HR 0.85, 95% CI 0.74-0.97) with L. Survival curves separated after 18 months. The incidence of the extended endpoint was also lower (20.3% vs. 22%), and there was a non-significant trend towards reduction in the incidence of AMI or stroke. A significant reduction in microvascular events was verified due to a reduction in the incidence of nephropathy (5.7% vs. 7.2%), while there was a non-significant trend to increase retinal pathology (2.3% vs. 2%). The use of L was associated with an average decrease in weight of 2.3 kg, and slight changes in blood pressure (1.2 mmHg average drop in systolic blood pressure and 0.6 mmHg increase of diastolic blood pressure) and a heart rate increase of 3 beats per minute.

Adverse events with L revealed an increase of pancreatic cancer (0.3% vs. 0.1%, p=0.06), but fewer prostate neoplasms or leukemias; thus, no significant difference in tumor incidence was observed. There was also an excess of gallstones. At 3-year follow-up, HbA1c had decreased by 0.4% in the L branch. With L there was less need to add another hypoglycemic drug to achieve glucose targets in each patient, resulting in lower incidence of overall and severe forms of hypoglycemia (2.4% vs. 3.3%, p=0.02).

The LEADER trial shows a new agent capable of modifying the prognosis of type 2 diabetic patients with risk factors or established vascular damage. Analogs of GLP-1 generate increased insulin secretion, reduced glucagon secretion, decreased intestinal motility and increased satiety. However, in the ELIXA trial, another GLP-1 analogue, lixisenatide, did not show the ability to improve the prognosis seen with liraglutide. It is impossible not to think of empaglifozin and the results seen in the EMPA-REG study. The population included in the LEADER trial appears a priori to be sicker: (HbA1c 8.7% vs. 8%, almost 15% incidence of the primary endpoint vs. slightly over 12% in the EMPA-REG study in similar periods). The mechanisms of action also seem to be different: in the EMPA-REG study the survival curves of empaglifozin and placebo separated almost from the beginning for cardiovascular mortality and at 1 year for overall mortality; there was no difference in the incidence of AMI, but there was a significant reduction in the incidence of heart failure. In the LEADER trial the survival curves separated at a later point, and there was a trend to reduce the incidence of AMI. These data suggest a pre-

dominantly hemodynamic mechanism for empaglifozin (which acts as an osmotic diuretic) and metabolic mechanism in the case of liraglutide. Future studies should define the most suitable profile for each patient, whether both agents can coexist in treating patients with existing vascular damage, and whether their employment may be implemented earlier.

Use of candesartan prevents the development of cardiotoxicity in patients undergoing chemotherapy. The PRADA trial.

Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. **Eur Heart J 2016;37:1671-80. http://doi.org/bm3f**

Breast cancer chemotherapy (QT) with anthracycline and in HER-2 positive patients with trastuzumab, may be complicated by the presence of asymptomatic left ventricular dysfunction or clinical heart failure. Several animal studies, or observational or randomized small sample size studies in humans have suggested that the use of neurohormonal antagonists could prevent ventricular damage. The single-center Norwegian PRADA trial aimed to confirm this hypothesis. This was a randomized, placebo-controlled study, with a 2x2 factorial design. Patients with breast cancer without prior cardiovascular disease who were directed to treatment with 5-fluorouracil, epirubicin and cyclophosphamide (FEC scheme) after surgery, were randomly assigned to one of 4 branches: candesartan (C) at a dose of 32 mg daily and metoprolol succinate (M) at a dose of 100 mg daily; C and M placebo; M and C placebo; or both drug placebo. Patients underwent physical examination, blood tests measuring troponin I and B natriuretic peptide (BNP), ECG and cardiac magnetic resonance (CMR), before initiating QT, after the first cycle of anthracyclines and at the end of treatment. In patients who then received trastuzumab or radiotherapy, new assessments were made after the end of the additional treatment. Tissue Doppler echocardiography was also performed at the beginning and at the end of the study. The primary endpoint was left ventricular ejection fraction change (LVEF) evaluated by CMR.

Thirty patients were included in the C-M branch and 32 in each of the other three branches. Average age was around 50 years; all received the FEC scheme, and almost 80% additional treatment with taxanes, slightly over 20% with trastuzumab and 65% radiotherapy. Treatment with neurohormonal antagonists started before QT initiation. The mean baseline LVEF ranged between 62% and 64% in the four groups. During follow-up no patient developed clinical heart failure. Since there was no interaction between M and C on any endpoint, patients receiving C (with M or M placebo) could be compared with those who did not. Patients treated with C had lower LVEF reduction: 0.8% vs. 2.6%, p=0.026. The effect of C on LVEF did not depend on its effect on blood pressure. No effect on diastolic function or on biomarker values was verified. In all groups there was slight increase of troponin I. There were no differences according to age subgroups, mass index or additional treatment with trastuzumab or radiotherapy.

Taking as reference the group with both placebos which had a LVEF drop of 2.9%, the group treated with C and M placebo had significant lower LVEF reduction (0.9%, p=0.025), whereas in the group treated with C and M, the reduction only showed a trend towards statistical significance (0.6%, p=0.075). Conversely, when both groups treated with M were compared with those that did not receive it, there was no difference in LVEF: drop of 1.6% vs. 1.8%. In those treated with M a minimal increase in the E/e' ratio and BNP was observed. There were no serious adverse events and both C and M were well tolerated.

The strength of this study lies in the use of the gold standard method to assess LVEF: CMR. It shows that even in patients without previous cardiovascular involvement, treatment with anthracyclines is associated with LVEF reduction of 2%-3%. Since the study has no follow-up, the consequence of this reduction, which obviously has not the same impact in all patients, could not be established. In fact, large observational studies show that the use of anthracyclines is associated with clinical heart failure during follow-up in only a number of patients. The differences between the effects of C and M may have different causes, from a possible effect of M generating slight reduction in LVEF in patients without previous heart disease, to a mere chance effect. Studies with a higher number of patients and longer follow-up will generate greater certainty.

Adolescent obesity and mortality in midlife

Twig G, Yaniv G, Levine H, Leiba A, Goldberger N, Derazne E, et al. Body-mass index in 2.3 million adolescents and cardiovascular death in adulthood. **N Engl J Med 2016;374:2430-40. http://doi.org/bm3g**

Obesity in early life has been associated with increased risk of cardiovascular mortality in adulthood, but the strength of the association is not clear, nor is the body mass index (BMI) that marks the threshold from which risk increases. An Israeli large-scale epidemiological study attempts to answer these questions.

Between 1967 and 2010, 2,298,130 adolescents between 16 and 19 years (60% male) were subjected to medical examination prior to admission to compulsory military service. Mean BMI was 21.1 in men and women, ranging between 12 and 47 in both sexes. The following categories of BMI according to distribution percentiles were considered: <5 (underweight), 5-24 (reference category), 25-49, 50-74, 75-84, 85-94 (overweight): and ≥ 95 (obese). The association of each category with the incidence of cardiovascular (coronary or cerebrovascular etiology or sudden death), non-cardiovascular and overall death was assessed during follow-up up to June 2011. A multivariate analysis was performed adjusting for age, gender, birth year, educational attainment and socioeconomic level.

Follow-up was 25,959,547 person-years for men and 16,337,460 for women, during which 32,127 deaths were established, of which only 2,918 (9.1%) were cardiovas-

cular, which is logical due to the age of those who died, 38.9 years on average.

In the multivariate analysis, compared with the reference category, being underweight was associated with 5% excess risk of overall and non-cardiovascular death, but not of cardiovascular death. Cardiovascular death risk began to increase significantly, compared with the reference category, in the category comprised between percentiles 50 and 74 (HR 1.32, 95% CI 1.18-1.48) and it continued to increase until in obese people it reached a HR of 3.46, 95% CI 2.93-4.10. The risk of death from coronary heart disease began to grow in the category between percentiles 50 and 74 (HR 1.49, 95% CI 1.27-1.76) and climbed to a HR of 4.89 (95% CI 3.91-6.12) in obese people. Risk of death from stroke and sudden death became significantly higher than in the reference category in percentiles 75-84, with excess risk that barely exceeded 40% and peaked in the obese. The risk of overall and non-cardiovascular death also began to grow significantly between percentiles 50 and 74, with HR values of 1.04 and 1.06, reaching 1.54 and 1.68 respectively in obese people. The association with cardiovascular death was evident at 10-year follow-up (HR 2.1), but was even more marked at 30-40 years (HR 4.1).

When absolute values instead of percentiles were considered, having a BMI between 20 and 22.4 was associated with a significant 20% excess risk of coronary death compared with a BMI between 17.5 and 19.9 kg/m2, and a BMI of 22.5 kg/m2 indicated increased risk of death from stroke and sudden death.

The monitoring of this cohort is highlighted by the monumental number of individuals and follow-up time. The large sample size allowed the authors to clarify relations previously undefined as the relationship of obesity with death of cerebrovascular origin. Due to the nature of the target population it is clear that follow-up reaches middle age and does not extend beyond, when the number of deaths of vascular origin specifically increases. It proves that BMI values considered normal are already associated with excess risk. Its weaknesses are failure to correct or adjust for important confounders, such as smoking, dyslipidemia, diabetes or physical activity level. Moreover, because a new BMI determination in young adulthood was not repeated during follow-up, it is not clear whether the poor prognosis associated with excess weight depends on alterations already present in adolescence or if in fact that early BMI projects in an even higher BMI in adulthood, really responsible for the poor outcome.

Coronary revascularization in patients with ventricular dysfunction: equal prognosis with angioplasty or surgery.

Bangalore S, Guo Y, Samadashvili Z, Blecker S, Hannan EL. Revascularization in patients with multivessel coronary artery disease and severe left ventricular systolic dysfunction: everolimus-eluting stents versus coronary artery bypass graft surgery. **Circulation 2016;133:2132-40. http://doi.org/bm3h**

A surgical option is generally considered when significant ischemia is detected in a patient with severe ventricular dysfunction and proposed revascularization procedure. In fact the most important practice guidelines in such cases recommend surgery (CABG) and leave out the possibility of coronary angioplasty (CA), or assign it a lower strength indication. In patients with poor ventricular function, CA has not been compared in randomized studies with medical treatment or CABG, as has occurred in patients with preserved ventricular function. To fill this knowledge gap in order to take appropriate decisions, the authors of this study considered all patients with left ventricular ejection fraction (LVEF) ≤35% and at least two-vessel coronary heart disease (with lesions >70% in each one) subjected to CABG as single procedure or CA with everolimus eluting stent between January 2008 and December 2011 in the state New York, where all revascularization procedures are compulsorily registered. Patients with main coronary artery lesion >50%, acute myocardial infarction (AMI) in the last 24 hours, previous cardiac surgery, non-everolimus eluting stent implantation, revascularization in the last year or unstable hemodynamic condition were excluded. The primary endpoint was total mortality at 30 days and secondary endpoints were periprocedural or remote AMI, stroke, or repeated revascularization at the long-term follow-up.

The study selected 3,265 patients undergoing CABG and 1,351 referred for CA. The former were 1 year younger, with a higher prevalence of men, cerebrovascular disease, lung disease, and three-vessel disease (71% vs. 33%). Therefore, a propensity score was proposed to balance both populations. The score is constructed using logistic regression that establishes which variables are independently associated with the performance of a particular procedure. Each patient then has a score that establishes his propensity to be treated in a certain way (for example, be subjected to CABG) regardless of whether he has finally been treated one way or another. The next step is to form pairs of patients having the same or only very slightly different score, so that in each pair of patients one has received a treatment and the other the alternative procedure. The aim of matching patients by their propensity score is to compare two groups with a similar average propensity to a particular treatment; one group treated effectively with the procedure in question and the other with an alternative method. The final purpose is to imitate what would have happened in a randomized study, where regardless having similar baseline variables, some receive a treatment and others receive another intervention or behave as control.

Thus, 1,063 pairs of patients with equal prevalence of each of the baseline variables were defined, with 1,063 patients subjected to CABG and 1,063 to CA (slightly over 41% with three-vessel disease, 7% with LVEF <20%, 35% with LVEF between 20% and 29%, and the rest with LVEF between 30% and 35%). At 30 days there was no difference in mortality, AMI, or need for new procedure, but there was lower incidence of stroke with CA (0.1% vs. 1.8%, p=0.004).

In the long-term, mortality was similar, but a difference was verified according to the number of involved vessels, with a trend to excess mortality with CA in patients with three-vessel disease (HR 1.60, 95% CI 0.84-3

05) and to lower mortality in patients with two-vessel disease (HR 0.67, 95% CI 0.44-1.03), with p=0.03 for interaction. The risk of AMI was higher with CA (HR 2.16, 95% CI 1.42-3.28), mainly due to events in patients with three-vessel disease (HR 6, p=0.02) or with incomplete revascularization (HR 3.1, p<0.0001). The need for repeat revascularization (HR 2.54, 95% CI 1.88-3.14) was also higher with CA, regardless of the number of vessels or of complete or incomplete revascularization. Conversely, the risk of stroke was lower (HR 0.57, 95% CI 0.33-0.97), with a similar trend in all subgroups analyzed.

Despite the use of a propensity score, this study does not have the force of a randomized trial. Randomized allocation ensures that known and unknown baseline characteristics are equally distributed among those receiving the study treatment and those who do not. Nevertheless, in the absence of such a study, the data presented allow a glimpse of the possible role of CA in patients with severe ventricular dysfunction. The results of this comparison are similar to those conducted in patients with preserved function: there is no difference in mortality, stroke risk is higher with CABG, and need for repeated procedures is greater with CA. On the other hand, the increased risk of AMI with CA in patients with coronary artery disease and more extensive incomplete revascularization should be considered. Until better information is available, patients with two-vessel disease, history of cerebrovascular disease and in whom complete revascularization may be proposed, would be the best CA candidates in the context of severe ventricular dysfunction.

Does the type of atrial fibrillation impact on thromboembolic risk and mortality?

Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. **Eur Heart J 2016;37:1591-602. http://doi.org/bm3j**

The risk of thromboembolic events in patients with atrial fibrillation (AF) is usually predicted on the basis of patient characteristics and not on AF. For example, the CHA2DS2 VASc score takes into account the presence of heart failure or systolic dysfunction, hypertension, age, diabetes, history of stroke, previous vascular disease and female gender. It is irrelevant whether the AF to which we refer is paroxysmal (PAF) or non-paroxysmal (NPAF), persistent or permanent. But is this approach correct? This question is put forward by a systematic review and subsequent meta-analysis.

All studies published in indexed journals that had reported the outcome of patients according to the type of AF were considered. Finally, 10 randomized and 2 observational studies published between 1990 and 2015, with a total of 99,996 patients were included in the analysis. Follow-up ranged between 1 and 2.8 years, mean age was between 62 and 73 years and the proportion of women between 27% and 43%. On average, the annual unadjusted risk of thromboembolism was 2.17% for NPAF and 1.5% for PAF (RR 1.35, 95% CI 1.17-1.57). The information to adjust risk by the presence of the CHA2DS2 VASc score components was available in slightly over 58,000 patients. The adjusted RR did not differ from the unadjusted one: 1.38, 95% CI 1.19-1.60. Non-paroxysmal atrial fibrillation involved increased risk of stroke in anticoagulated or not anticoagulated patients, but the RR was higher in the latter: 1.69 vs. 1.27.

In the six studies with available data, NPAF was also associated with higher annual mortality: 3.89% vs. 2.79%, RR 1.46, 95% CI 1.25-1.70. The four studies where a multivariate analysis could be performed resulted in RR for total mortality of 1.21 (95% CI 1.08-1.36). There were no differences in bleeding risk between the two forms of AF.

This analysis strongly suggests that AF does not imply a risk only defined by the patient's variables: the type of AF also impacts on the probability of thromboembolism or death. The cause of this differential association depending on PAF or NPAF goes beyond the components of the CHA2DS2 VASc score. Are NPAF patients sicker? Are they patients who starting with PAF have worsened more their ventricular function? Is their renal function worse? Or does the type of AF itself play an important role in defining the risk of stroke and death? In any case, it is clear that we should exercise extreme care for the patient with episodes of PAF not to progress to NPAF: either because his overall condition has worsened or because NPAF imposes worse prognosis per se, his fate will be more adverse. Meanwhile, there are insufficient data to pose a different anticoagulant scheme in one or the other form of AF.

Alcohol septal ablation in hypertrophic cardiomyopathy. Results from the European registry

Veselka J, Jensen MK, Liebregts M, Januska J, Krejci J, Bartel T, et al. Long-term clinical outcome after alcohol septal ablation for obstructive hypertrophic cardiomyopathy: results from the Euro-ASA registry. **Eur Heart J 2016;37:1517-23. http://doi.org/bm3k**

Alcohol septal ablation (ASA) for the treatment of septal obstructive hypertrophic cardiomyopathy (HCM) has been used for 20 years in symptomatic FC III-IV cases despite full medical treatment. The concerns about its extended use include the possible long-term incidence of ventricular dysfunction and heart failure (due to the generation of septal necrosis by the procedure), the elevated rate of atrioventricular block (AVB), requiring definitive pacemaker, and poor understanding of the beneficial effects' persistence in the long-term. The publication of the Euro-ASA registry helps to answer some of these issues.

The registry includes 1,275 consecutive patients (49% women, mean age 58±14 years) treated with ASA in 10 tertiary referral hospitals from seven European countries (Germany, Austria, Czech Republic, the Netherlands, Poland, Denmark and Norway) between 1996 and 2015. They were patients with severely symptomatic HCM, with maximum provoked gradient ≥50 mmHg in the absence of severe mitral valve disease or other condition that would justify surgery. During the study period in the mentioned centers, 250 patients were primarily subjected to myectomy.

Patients were symptomatic mainly due to dyspnea

(mean FC 2.9±0.5); maximum gradient in the left ventricular outflow tract was 67±36 mmHg, mean septum thickness 20 mm and mean left ventricular ejection fraction (LVEF) 70%.

A median dose of 2 ml alcohol was used for ASA and in 90% of cases the dose ranged between 1 and 3 ml. Electric cardioversion was required in 1.3% of patients due to malignant ventricular arrhythmia within 48 hours of the procedure, 37% presented complete AVB within 30 days and a third of these patients required definitive pacemaker implantation. Thirty-day mortality was 1%.

In the long-term follow-up (median 3.9 years) during which clinical and echocardiographic data could be obtained in 1,254 patients, mean FC was 1.6±0.7, mean septum thickness had decreased to 15 mmm and mean gradient to 16±21 mmHg. Mean LVEF remained at 66%. Eighty-six percent of patients had improved at least one FC. The dose of alcohol used was linearly correlated with gradient reduction, but it was also associated with complete AVB: 32% when the dose ranged between 0.4 and 1.4 ml, and 43% when it spanned between 3 and 11 ml. The lower the septum thickness in the last check-up, the greater the fall in gradient, and lower gradients during follow-up were associated with improved FC. Five percent of patients required pacemaker implantation during their outcome, 7% new ASA and 3% underwent myectomy.

Survival analysis was performed during a mean follow-up of 5.7 years. All-cause mortality was 2.42% per year. Independent predictors of mortality risk were: age (6% excess per year) and FC (50% excess for each increasing FC) at the time of ASA, septum thickness before the procedure (5% excess per mm), and left ventricular outflow tract gradient in the last follow-up measurement (1% excess per mm). The incidence of sudden or cardiovascular death was 1.16% per year and that of all-cause death plus appropriate defibrillator discharge was 2.84% per year.

This registry presents some invaluable data for clinical practice: in expert hands, mortality associated with ASA is low. Increasing doses of alcohol are associated with more marked gradient reduction, but greater risk of complete AVB. Therefore, according to the authors of this study, doses between 1.5 and 2.5 ml would afford the most adequate balance between the resolution of the problem and complications. In fact, almost 1 out of 8 patients requires definitive pacemaker implantation. The long-term follow-up does not show ventricular function impairment or increased risk of heart failure, and the remote prognosis is good. Long-term survival is similar to that of myectomy series. It is important (with the aforementioned provisions) to attempt the best possible gradient reduction, as this is measured during follow-up as predictor of remote mortality. What objections can be made to this report? This registry presents data from highly specialized referral centers: actually, at most there are two centers per participating country; therefore, this statistics might not apply to interventions performed by less experimented treating teams or with lower number of procedures. There is still lack of randomized myectomy studies vs. ASA, and of any of these procedures vs. optimal medical treatment, perhaps due to difficult patient recruitment with adequate conditions allowing their randomized assignment to one group or the other. Let us remember that in 20 years and in 7 countries, slightly over 1,500 patients were considered for both invasive treatments, and that there are conditions which a priori imply preference for one or the other (less basal hypertrophy, higher papillary muscle hypertrophy and larger leaflets favoring surgery, with reverse conditions favoring ASA) and which therefore hamper randomization.

A headache: the risk of migraine in women

Kurth T, Winter AC, Eliassen AH, Dushkes R, Mukamal KJ, Rimm EB, et al. Migraine and risk of cardiovascular disease in women: prospective cohort study. **BMJ 2016;353:i2610. http://doi.org/bm3m**

Approximately one fifth of the population has migraine at some point in lifetime, a condition affecting women 3 to 4 times more frequently than men. Migraine has been associated with increased risk of stroke, and although the causes are not yet clear, endothelial dysfunction, susceptibility to thrombotic events, the underlying causes of inflammatory disease and greater prevalence of vascular risk factors are mentioned as explanation for this relationship. If the association between migraine and stroke is real, migraine could also be a predictor of adverse cardiovascular events. The analysis presented here based on the Second Nurse Health Study tests this hypothesis. The study cohort was established in 1989 and included 116,430 nurses aged between 25 to 42 years in the United States.

Eight hundred and eighty-nine women presenting with cardiovascular disease at the time of inclusion were excluded, leaving 115,541 nurses for the analysis. Presence of migraine was verified at baseline history taking in 1,989 cases and in two follow-up questionnaires in 1193 and 1995. No information was collected on the presence of aura or frequency of migraine episodes. The primary endpoint was death of cardiovascular origin, nonfatal acute myocardial infarction (AMI) and nonfatal stroke.

At baseline medical history, 17,531 nurses (15.2%) reported suffering from migraine. They presented greater prevalence of hypertension, dyslipidemia, current smoking, family history of AMI, body mass index, use of hormone replacement therapy and contraceptives, as well as greater use of aspirin, paracetamol and other non-steroidal anti-inflammatory agents. Follow-up extended up to 2011. After adjusting for age and all the above-mentioned factors, women with migraine were at greater risk of the primary endpoint (HR 1.50, 95% CI 1.33-1.69) and of each of its components (HR of 1.37 for cardiovascular death, 1.39 for nonfatal AMI and 1.62 for nonfatal stroke). They were also at greater risk of angina or need for revascularization, with a HR of 1.73.

Previous studies with a lower number of persons had already pointed out the relationship between migraine and stroke; however, the association with other manifestations of cardiovascular disease was less clear. The Women's Health Study showed the link between migraine and cardiovascular risk in women above 45 years, and mainly for migraines presenting with aura. This registry extends the risk to younger women. It has been pointed

out that this excess risk could be due to greater prevalence of risk factors and family history in women affected by migraine, but the independence of these factors, emerging from the multivariate analysis compels the search for other causes. Genetic factors? Residual confusion due to ignored conditions? The main strength of this study lies in the number of observations and the length of the follow-up period. Perhaps its greatest weakness is not having recorded the accompanying aura and the frequency of these episodes (although it is possible that they were mainly reported by women with usual or frequent migraine to remember it). Some lines of investigation have been opened (statins, vitamin D) but still without clear results. In the meantime, it is evident that the complaint of frequent headaches should not be disregarded, and that it deserves at least a closer clinical follow-up.

Whole-grain cereal consumption and prognosis

Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. **BMJ 2016;353:i2716. http://doi.org/bm3n**

Different cohort studies have associated whole grain cereal consumption with better long-term prognosis and lower risk of cardiovascular and cerebrovascular events. Enhanced glycemic control, reduced cholesterol levels, lower weight increase and decreased inflammatory events are among the reasons for this benefit. We know that whole grain cereals are the main source of fiber, that the endosperm and germ (removed during the refinement process) provide carbohydrates, proteins, energy, vitamins and micronutrients. The main sources of whole grain cereals vary according to the region: bread in Scandinavia, bread and cereals for breakfast in North America, corn, sorghum and rice in Africa and rice in Asia. Different clinical practice guidelines recommend their consumption, but in many cases there is no precision on the amount that should be eaten or if there is a dose-response relationship. Neither is there definite information on other causes of death beyond vascular disease. We present a systematic review and meta-analysis providing relevant information on these subjects.

Forty-five cohort studies were included in the study (20 from Europe, 16 from the United States, and 9 from Asia) reporting the association between cereal consumption and prognosis, in populations ranging between 245,012 and 705,253 persons. A helping of whole grain cereals was assumed as 30 grams, a helping of pasta as 150 grams, and of rice as 167 grams, based on the proportion of each type of rice (white or whole grain) used in different studies and their weight when cooked. The association with prognosis was explored considering at least three consumption categories (low, medium or high) or consumption as continuous variable.

The association between whole grain cereal intake and the incidence of coronary heart disease was reported in seven cohort studies (n=316,491). The RR for high vs. low consumption was 0.79 (95% CI 0.73-0.86) and for each 90 grams per day increase it was 0.81 (95% CI 0.75-0.87). Although the reduction was higher for the first 90 grams, a dose-response relationship was found up to 210 grams per day. The improvement in prognosis was verified for whole grain bread, whole grain cereals and bran, and not for white bread or refined cereals. Six studies (n=245,012) reported the association between whole grain cereal consumption with a reduced trend in the incidence of stroke. The RR for high vs. low intake was 0.87 (95% CI 0.71-1.05) and for each 90 grams per day increase it was 0.88 (95% CI 0.75-1.03). No dose-response correlation was found beyond 120-150 grams per day. A clear association between a type of cereal and improved prognosis could not be established. Ten studies (n=704,317) reported the association of whole grain cereal consumption with the incidence of cardiovascular disease. The RR for high vs. low consumption was 0.84 (95% CI 0.80-0.87) and for each 90 grams per day increase it was 0.78 (95% CI 0.73-0.85). Although the reduction was higher for the first 50 grams, a dose-response relationship was found up to 200 grams per day. Again, whole grain cereals were related with better prognosis.

In 10 studies analyzing all-cause mortality (n=705,253), RR for high vs. low consumption was 0.82 (95% CI 0.77-0.88) and for each 90 grams per day increase this was 0.83 (95% CI 0.77-0.90); although the reduction was greater with the initial doses, a dose-response relationship was found up to 225 grams per day. The improvement in prognosis was verified for whole grain cereals, but total cereal consumption (high vs. low) also showed association with decreased mortality, as well as the intake of refined cereals (although with weaker correlation). Whole grain cereal consumption was related with lower incidence of death for cancer (between 11% and 15% risk reduction), diabetes, and respiratory and infectious diseases.

This meta-analysis has de merit of setting definitive figures to the benefit that can be expected from consuming whole grain cereals. It shows that benefits are already obtained at low intake, but at the same time evidences that much more can be achieved with higher intake. It suggests that the replacement of the amount of refined cereals consumed by whole grain cereals would generate a positive effect. As limitation, it should be noted that in some of these associations (especially with mortality) heterogeneous results were reported among studies. Perhaps the way of determining the daily amount of cereal intake and the different types and forms of presentation may have influenced this heterogeneity. It is also possible that whole grain cereal consumption indicates a population more concerned with their health status, with greater self-care, more physical activity and better socioeconomic level. Many of the studies considered here adjusted for these variable and nevertheless, the association with better prognosis persisted. Increasing the presence of whole grain cereals in the daily diet appears as a public health need.