## Two randomized studies on the role of aspirin for primary prevention of cardiovascular and cerebrovascular events

Rothwell PM, Cook NR, Gaziano JM, Price JF, Belch JF, Roncaglioni MC, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. Lancet. Published Online August 26, 2018 http://doi.org/ctqd

The ASCEND Study Collaborative Group. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med Published online August 26, 2018, at NEJM.org. http://doi.org/ctks

Use of aspirin for primary prevention of cardiovascular and cerebrovascular events is controversial in low to moderate risk patients. Although studies prior to 2005 suggested its usefulness, doubts were cast by later studies, mainly because the reduction of vascular events was balanced by excess bleeding, from epistaxis to severe cases of digestive and cerebral hemorrhage. Consequently, different treatment guidelines provide contradictory recommendations.

The ARRIVE trial, presented at the recent Congress of the European Society of Cardiology, tried to clary this query. This is a multicenter, randomized, double-blind study, exploring the effect of 100 mg enteric-coated aspirin in patients at moderate risk of coronary heart events ( $10-20 \%$ at 10 years according to different risk calculators, which implies $20-30 \%$ of cardiovascular and cerebrovascular events), compared with placebo. The study included men of $\geq 55$ years of age and women of $\geq 60$ years, considering the following risk factors: a) total cholesterol levels $>200 \mathrm{mg} / \mathrm{dl}$ and LDL-cholesterol $>130 \mathrm{mg} / \mathrm{dl}$ in men and $>240 \mathrm{mg} / \mathrm{dl}$ and $>160 \mathrm{mg} / \mathrm{dl}$, respectively, in women; b) HDL-cholesterol $<40 \mathrm{mg} / \mathrm{dl}$; c) smoking in the last 12 months; d) hypertension, with systolic blood pressure $>140 \mathrm{mmHg}$ or antihypertensive treatment; and e) family history of cardiovascular disease. Diabetic patients were excluded from the study. Men were required to have between 2 and 4 of the above-mentioned risk factors and women 3 or more. Patients with previous cardiovascular or cerebrovascular event, those with clear indication of antiplatelet therapy and those with increased bleeding risk or treated with anticoagulants or non-steroidal anti-inflammatory drugs were excluded from the study. The primary endpoint was the incidence of cardiovascular death, non-fatal stroke and non-fatal myocardial infarction (AMI). A 5-year follow-up was initially planned, with an expected event rate of $13.4 \%$ in the placebo group and $11.4 \%$ in the aspirin group. During the study, the low observed event rate led to an extension of the follow-up period to 6 years and to expand the primary endpoint, incorporating the incidence of
unstable angina and transient ischemic attack (TIA).
The study was conducted between 2007 and 2016 in 501 centers of 7 countries (Germany, Ireland, Italy, Poland, Spain, the United Kingdom and the United States of America). It included 12,546 patients (6,270 in the aspirin group), with median follow-up of 5 years. Mean age was 63.9 years and $70.3 \%$ were men. Among the total number of patients, $28.7 \%$ were smokers, $58 \%$ had high total cholesterol, $45 \%$ high LDL-cholesterol and more than $60 \%$ were hypertensive. Forty-three percent of patients were receiving statins. Mean 10-year risk of vascular events according to the ACC/AHA risk calculator was $17.3 \%$ and the 10 -year risk of coronary heart events according to the Framingham score was $14 \%$. Results were analyzed by intention-to-treat, and also by per-protocol analysis (considering patients who had adhered to treatment at least $60 \%$ of the time). At the mean follow-up of 5 years, the incidence of the expanded primary endpoint was $4.29 \%$ in the aspirin group and $4.48 \%$ in the placebo group ( $\mathrm{p}=\mathrm{NS}$ ) in the intention-to-treat analysis. Neither was there difference in any endpoint considered separately. The incidence of fatal and non-fatal AMI was $1.52 \%$ and $1.78 \%$ in the aspirin and placebo groups, respectively, and that of cardiovascular death was $0.6 \%$ in both groups. In the per-protocol analysis, however, the values were more favorable for aspirin: the incidence of the composite endpoint was $3.4 \%$ vs. $4.19 \%$ ( $p=0.07$ ), that of fatal or non-fatal AMI was $0.98 \%$ vs. $1.84 \% ~(\mathrm{p}=0.0014)$ and that of non-fatal AMI alone was $0.84 \%$ vs. $1.53 \%$ ( $p=0.0056$ ). The incidence of cardiovascular mortality was again similar in both groups, between $0.6 \%$ and $0.7 \%$. Regarding medication-associated adverse events, the incidence was greater with aspirin: $16.7 \%$ vs. $13.5 \%$, with higher prevalence of dyspepsia, epistaxis, gastroesophageal reflux and epigastralgia. The incidence of gastrointestinal bleeding was $0.24 \%$ vs. $0.03 \%$, and the incidence of hemorrhagic stroke was slightly above $0.1 \%$ in both groups.

Diabetes is a high risk factor for the incidence of vascular events. The recommendation of using aspirin in primary prevention of diabetic patients has suffered the same ups and downs that in non-diabetic patients, from a warm recommendation to its complete rejection, due to the balance between beneficial effects and excess bleeding. The ARRIVE trial, commented above, explored the effect of low-dose aspirin in primary prevention, but excluded diabetic patients. The ASCEND trial, also presented at the European Congress of Cardiology, considered its use specifically in this population. It included diabetic patients above 40 years of age, free from cardiovascular or cerebrovascular disease at study inclusion. This was a randomized study, with $2 \times 2$ factorial design, in which patients were assigned to receive on the one hand enteric-coated aspirin $100 \mathrm{mg} /$ daily or placebo, and on the other 1 gram of omega- 3 acids/daily or placebo. The primary efficacy endpoint was a compos-
ite of cardiovascular death, non-fatal stroke (except for hemorrhagic stroke) and non-fatal AMI. Same as in the ARRIVE trial, TIA was later added to increase the low incidence of events and achieve greater statistical power. The primary safety endpoint was the incidence of major bleeding (cerebral, ocular, digestive or other), considering an annual risk of events ranging from $1.2 \%$ to $1.3 \%$. It was assumed that at least 15,000 patients followed-up for 7.5 years would detect with a power of $90 \%$ a $15 \%$ reduction in the incidence of the primary endpoint.

Between 2005 and 2011, 15,480 patients were included in the study, with mean age of 63 years and $62.5 \%$ men. Median diabetes duration was 7 years, $61 \%$ of patients were hypertensive and $75 \%$ were receiving statins. During the mean follow-up of 7.4 years, $30 \%$ of patients abandoned the assigned regimen in both groups. A reduction in the primary endpoint was verified with aspirin: $8.5 \%$ vs. $9.6 \%$ (RR 0.88, 95 CI $0.79-0.97$ ). There was no significant reduction of any separate risk component. The effect was focused on the first 5 years. The incidence of major bleeding was higher in the aspirin group: $4.1 \%$ vs. $3.2 \%$ (RR 1.29 , $95 \%$ CI 1.09-1.52). Among major bleedings, 41.3\% were gastrointestinal, $21.1 \%$ ocular, 17.2 intracranial and the rest had other locations. It was necessary to treat 91 patients to prevent a major vascular event, and 112 patients to generate major bleeding.

The ARRIVE trial provides some data for analysis. Firstly, it shows the difficulty of accurately predicting cardiovascular risk. In a population with a 10-year calculated risk of $17 \%$, real risk ranged between $8 \%$ and 9\% (the 5-year incidence was between $4 \%$ and $4.5 \%$ ). Real risk was clearly inferior to that predicted. This is a deficit generally faced by clinical prediction rules: their predictive capacity decreases when they are used in other spatial (different patient profile from a biological perspective, concomitant diseases, socioeconomic conditions) and temporal (different diagnostic strategies and change in the co-treatment pattern) contexts. The ability of aspirin to reduce the incidence of AMI in patients who comply with treatment is confirmed, although it should be borne in mind that the per-protocol analysis does not have the purity of the intention-to treat analysis, as it breaks the advantage of randomization. Lack of effect on neurological events and total mortality is also verified, as well as excess of some adverse events, including low rate of non-fatal gastrointestinal bleeding. The final decision for the use of aspirin in primary prevention of low-risk patients depends on the patient profile and should be agreed with his physician. It is clear that the initially posed question (usefulness of aspirin in patients at 10\% and 20\% risk of events at 10 years) was not answered by the ARRIVE trial.

The ASCEND trial added to already known results: decrease in the incidence of vascular events (1.1\% reduction in absolute terms) balanced by an increase in the incidence of severe bleeding (absolute increase of 0.9\%). This almost identity between both effects was similarly verified in different event risk strata at 5 years: $<5 \%, 5$ to $<10 \%, \geq 10 \%$. It should be remarked that the annual incidence of the primary endpoint in the placebo group was greater in this trial (1.3\%) than in the ARRIVE
study ( $0.9 \%$ ) even when in the latter the final endpoint also included unstable angina. This result confirms the prognostic weight entailed by diabetes. If the risk of bleeding were not significantly increased by aspirin, there would surely be more reasons for its indication. In this sense, it should be recalled that a little over $40 \%$ of bleeding episodes corresponded to the digestive tract, and that use of proton pump inhibitors was prescribed in only $25 \%$ of patients. In diabetic patients in whom the risk of events is high, the concomitant use of aspirin and drugs preventing gastrointestinal bleeding could contribute to find a better risk-benefit relationship.

## Smoking cessation: weight gain, higher incidence of type 2 diabetes and lower mortality

Hu Y, Zong G, Liu G, Wang M, Rosner B, Pan A, et al. Smoking Cessation, Weight Change, Type 2 Diabetes, and Mortality. N Engl J Med 2018;379:623-32. http://doi.org/gdz6mw

It is well known that smoking cessation entails many times weight gain. Quitting smoking undoubtedly contributes to improve the vital prognosis by decreasing the incidence of cardiovascular events and cancer; but weight gain, due to excess food consumption that appears as a way of compensating abandoning the habit, operates in the reverse sense. Among other harmful effects, weight gain induces diabetes in susceptible persons, increasing cardiovascular risk. How does this algebraic sum of abandoned and emergent risk factors finally translate in the vital prognosis?

Approximately three decades ago, 3 cohort studies were initiated including health professionals: the NHS, NHS-II and HPFS studies. Each of them collected baseline data on different medical conditions, and during follow-up questionnaires were sent in cycles every two years to update the information. The authors of the publication here commented used collectively the data from the 3 studies (because of their similar design) and focused their analysis on smoking, weight change, incidence of diabetes and vital status. Subjects who had reported were smokers in the previous cycle but were non-smokers in the current one were identified in each cycle. Those who had abandoned smoking were classified in three mutually excluding categories: subjects transiently quitting the habit (after reporting having abandoned smoking in one cycle, defined themselves as smokers in the following one); recent ex-smokers (those who has quitted smoking in 2 to 6 previous years); and ex-smokers with more than 6 years of tobacco cessation. On the other hand, the study focused on weight change at 6 years ( since after 6 years of quitting smoking, the trajectory of weight change is similar to that of non-smokers) and participants were categorized as the ones who did not gain or decreased weight, those that gained 5 kg , between 5.1 and 10 kg or more than 10 kg . Based on questionnaires, the diet and physical activity, as well as the incidence of diabetes, cardiovascular mortality and all-cause mortality was established for all participants in a follow-up period that extended up to 2012 or 2013 depending on the study. Data from 162,807 participants and from 170,723 observations
were used to analyze the incidence of diabetes and mortality, respectively.

Mean follow-up was 19.6 years. Taking current smokers as reference, recent ex-smokers had excess risk of developing type 2 diabetes, with a HR adjusted for age, sex, ethnicity, risk factors, diet and physical activity of 1.22 ( $95 \%$ CI 1.12-1.32). This excess risk was modulated by weight gain in the study period. No weight gain was observed in $27 \%$ of cases; in $37 \%$ weight gain was up to 5 kg ; in $22 \%$ between 5 and 10 kg and in $14 \%>10 \mathrm{~kg}$. An increased risk of $8 \%$, $15 \%, 35 \%$ and $59 \%$ was found according the aforementioned categories, from absence of weight gain to $>10 \mathrm{~kg}$ increase, which was significant for the last two. Risk peaked between 5 and 7 years after smoking cessation, and then gradually decreased, reaching the same risk of a non-smoker after 30 years. Among exsmokers with more than 6 years of smoking abandonment there was no excess risk of developing diabetes.

However, despite this excess risk of diabetes, recent ex-smokers, compared with current smokers, evidenced a significant decrease in the risk of cardiovascular mortality, (HR 0.48; 95\% CI 0.41-0.56) and all-cause mortality (HR 0.58; 95\% CI 0.54-0.62). This risk reduction was seen in all the categories of weight gain, and was also observed among ex-smokers with more than 6 years of smoking cessation, both for cardiovascular mortality (HR 0.50) as all-cause mortality (HR 0.57).

This study shows that weight gain after quitting smoking, present in the majority of individuals (more than $70 \%$ of cases in this combined cohort) is associated with excess risk of presenting diabetes, clearly related to the magnitude of the weight increase. Effectively, $68 \%$ of the risk of diabetes was explained by weight gain in a multivariate analysis. And even so, there was a clear reduction of mortality risk in those who quitted smoking, compared with those that continued with the habit. Although it is true that some specific errors in the classification could have been made (weight increase and the incidence of diabetes were self-reported), the amount of observations and the extended follow-up period are strong arguments to trust the conclusions of the study. Smoking is a strong predictor of mortality, and weight gain seems in the end to be a lesser evil, an unwanted consequence of having abandoned smoking, which does not darken (even with the excess risk of diabetes) the advantage of having quitted. Nevertheless, we should not fall in the danger of underestimating the increased risk of diabetes, with its load of microvascular disease, quality of life impairment and increased costs for the healthcare system. And to end, we should remember that the category with lower risk of events was that of non-smokers, with HR 0.72 (95\%CI 0.68-0.76) for diabetes, 0.34 ( $95 \%$ CI 0.32-0.37) for cardiovascular mortality and 0.35 (95\% CI 0.34-0.37) for all-cause mortality.

The importance of having vascular risk factors in the normal range in the context of type 2 diabetes Rawshani A, Rawshani A, Franzen S, Sattar N, Eliasson B, Svensson AM, et al. Risk Factors, Mortality,
and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2018; 379: 633-44. http:// doi.org/gd2xw2

Type 2 diabetes is a strong risk factor for the incidence of microvascular and macrovascular events, and higher mortality. This can be attributed to different causes: the higher prevalence of risk factors, the presence of more extensive and intense atherosclerotic disease, sub-treatment, the existence of a specific heart disease, etc. The Steno 2 study has already shown that an intensive management of traditional risk factors accompanied by lifestyle changes significantly improves the prognosis of type 2 diabetic patients, but there is no contemporary data about this finding. The data from the Swedish Diabetes Registry, confirmed what we assumed. The analysis presented here considered patients with type 2 diabetes treated with diet, hypoglycemic drugs and/or insulin (the latter only in those over 40 years of age) with at least one registry between 1998 and 2012. Each patient was matched by age, sex and county with 5 non-diabetic controls randomly selected from the Swedish population. Two diabetic cohorts were defined. The first one excluded those with a history of stroke, acute myocardial infarction (AMI), amputation, dialysis or kidney transplantation, and body mass index (BMI) $<18.5 \mathrm{~kg} / \mathrm{m} 2$. The second considered the same exclusion criteria, but added history of coronary heart disease, atrial fibrillation (AF) and heart failure (CHF). Five factors were employed to define the risk of each patient: glycosylated hemoglobin (HbA1c) $\geq 7 \%$; systolic blood pressure (SBP) $\geq 140 \mathrm{mmHg}$ or diastolic blood pressure $\geq 80 \mathrm{mmHg}$; LDL-cholesterol $\geq 97$ $\mathrm{mg} / \mathrm{dl}$; serum albumin, and current smoking. In non-diabetic subjects (important data to partially understand the results), risk factor data was not available. Survival curves were defined according to age: $<55,55-<65,65-$ $<80$, and $\geq 80$ years. The risk for all-cause mortality, fatal or non-fatal AMI, fatal or non-fatal stroke, and hospitalization due to CHF was defined for each age category.

The study included 271,174 type 2 diabetic patients and $1,355,870$ control subjects and complete data was available in 96,673 diabetic patients. Mean age was 60.6 years, and $49.4 \%$ were women. Only $5 \%$ of the patients had none of the risk factors considered; $23 \%$ had $1,41 \%$ had $2,25 \%$ had 3 , and the rest 4 or 5 . Median follow-up was 5.7 years, during which $13.9 \%$ of diabetic patients and $10.1 \%$ of controls died. Overall, a diabetic without additional risk factors, which implies $\mathrm{HbA1c}$ $<7 \%$, without hypertension, dyslipidemia, smoking or kidney damage, had excess risk of mortality of only $6 \%$ compared with a non-diabetic control. Taking control subjects as reference, the presence of a growing number of risk factors in each age category was associated with a growing excess in the incidence of each of the endpoints. For example, among diabetic patients aged $55-<65$ years, the presence of $0,1,2,3,4$ or 5 conditions was associated with a HR for mortality of 1.15, $1.23,1.32,1.53,2.53$ and 3.88. In turn, age was inversely associated with the excess risk that diabetes with
more or less concomitant risk factors entails: the risk of events was always lower for those $\geq 80$ years, and progressively increased as age decreased. Thus, a diabetic patient without any of the risk factors considered had, at 80 years, the same mortality risk as a non-diabetic individual of the same age. Conversely, a diabetic patient of less than 55 years with the 5 risk factors, had, compared with a non-diabetic of the same age, a HR of 4.99. The mentioned associations were similar for the final endpoints of AMI and stroke. In the case of CHF, the mere presence of diabetes already implied a significant excess risk of hospitalization after 65 years of age.

The 5 most potent predictors of mortality among type 2 diabetic patients were, in order of importance, smoking, physical activity, marital status, HbA1c level and use of statins. For AMI, the predictors were HbA1c, SBP, LDL-cholesterol, physical activity and smoking; for stroke, these were HbA1c, SBP, diabetes duration, physical activity and AF. Finally, predictors for hospitalization due to CHF were AF, BMI, kidney dysfunction and HbA1c.

This analysis of the Swedish Registry provides already known data: in diabetic patients, higher HbA1c values, and the presence of traditional risk factors, imply worse outcome. Risk factors act synergistically, and a greater number progressively worsen the prognosis. Some points deserve special comment. As in this registry there was no data on the presence of risk factors among non-diabetics, it is clear that we cannot define the independent effect of diabetes. As already mentioned, the prognostic weight of the diabetic condition was lower as age increased. As we become older, the prevalence of vascular risk factors increases. It is therefore feasible that in non-diabetic older people the prevalence of concomitant diseases has approached that of diabetics, thus attenuating the difference that the diabetic condition implies. When comparing an 80-year-old diabetic person with a non-diabetic one, it is more likely that the prevalence of the other risk factors will not be so different between them. In younger people, the prevalence of risk factors is significantly higher among diabetic patients (they are generally hypertensive, dyslipidemic, more obese and sedentary) than among those who are not. When a 50-year-old diabetic is compared with someone of the same age who is not diabetic, it is much more likely that, in addition, the prevalence of the other risk factors will be very different.

Another issue that should be emphasized is the prognostic weight of HbA1c and SBP. It is clear that the higher their values, the worse the prognosis. But it is not possible distinguish those who spontaneously have values closer to normal from those who achieve it with medication. Different studies have suggested that an intensive hypoglycemic regimen is not associated with better outcome, among other things due to the adverse effects of medication. And although with contradictory data, studies of intensive BP control in diabetics have suggested similar conclusions. There seems to be a coincidence that in younger patients, with a shorter duration of diabetes and less damage to the target organ, a
more intensive treatment is more indicated. It is striking that a diabetic without any of the mentioned factors evolves almost similarly as a non-diabetic subject, except for the development of heart failure. It cannot be inferred from the study if this corresponds to diabetics treated intensively, or in fact to "less diabetic" diabetics, or to patients in early stages of the disease, younger and with a very low prevalence of other risk factors.

## Greater cardiovascular health and lower incidence of dementia

Samieri C, Perier MC, Gaye B, Proust-Lima C, Helmer C, Dartigues JF, et al. Association of Cardiovascular Health Level in Older Age With Cognitive Decline and Incident Dementia. JAMA 2018; 320: 657-64. http:// doi.org/gd5zsv

Different publications have linked the presence of traditional cardiovascular risk factors (obesity, hypertension, dyslipidemia, diabetes) with a higher incidence of dementia and cognitive decline, as well as that of a "healthy" behavior (not smoking, diet rich in fruits, vegetables and grains, exercise) resulting in a decrease of these phenomena. But there is not much in the medical literature about the combination of these factors and the quantification of the effect on their incidence.

An instrument developed by the American Heart Association allows us to jointly consider the 7 behaviors or conditions cited, which, when present, imply good cardiovascular health. For each one, 3 levels can be considered: low, intermediate or high. A low level implies undesirable values or behaviors: active smoking, low level of physical activity, blood pressure (BP) $>140-90$ mmHg , cholesterol $>240 \mathrm{mg} / \mathrm{dl}$, fasting blood glucose $>126 \mathrm{mg} / \mathrm{dl},<1$ daily serving of fruits and vegetables, < 2 servings of fish per week, and body mass index (BMI) $>30 \mathrm{~kg} / \mathrm{m} 2$. A high level corresponds to not smoking or having stopped smoking for at least in the 12 previous months, doing physical activity on a regular basis, BP $<120-80 \mathrm{mmHg}$, cholesterol $<200 \mathrm{mg} /$ dl, fasting blood glucose $<100 \mathrm{mg} / \mathrm{dl}$ without need for treatment, a diet with at least 1 daily serving of fruits and vegetables and at least 2 servings of fish per week, and BMI $<25 \mathrm{~kg} /$ m2. An intermediate level corresponds to values and conditions between the two levels mentioned. The scale is awarded 0 points for each component in low level, 1 for intermediate level and 2 for high level, so that the score ranges between 0 (the worst level of cardiovascular health) and 14 (the best).

The 3 C study was a prospective cohort study that included 9,294 participants aged $\geq 65$ years, between 1999 and 2000. It was carried out in 3 French cities: Bordeaux ( $\mathrm{n}=2,104$ ), Dijon ( $\mathrm{n}=4,931$ ) and Montpellier ( $\mathrm{n}=2,259$ ). Baseline sociodemographic, health, medication, lifestyle, etc. data were collected. The analysis we present focused on the emergence of dementia at follow-up. For this particular analysis, those with already established cardiovascular disease or dementia were excluded. The number of risk factors cited in the AHA scale (between 0 and 7) and the specific score of the scale (between 0 and 14) was defined
for each patient. To describe the prevalence and incidence of dementia and cognitive impairment, each participant was administered a series of neurocognitive tests (the Mini Mental State Examination, tests of verbal semantic fluency, memory, attention and executive behavior), followed by a neurological exam. The final decision was reached by a neurological committee that examined all the results without knowing the state of cardiovascular health. These tests and the corresponding diagnosis were carried out every 2 to 3 years until the end of the follow-up period (2012 in Dijon and 2016 in the other 2 cities).

A total of 6,624 individuals free of cardiovascular disease and dementia at the beginning of follow-up, who had at least 1 cognitive evaluation at follow-up, participated in this study. Mean age was 73.7 years, and $63.4 \%$ were women. At the beginning of the study, $36.4 \%$ had between 0 and 2 risk factors at optimal level; $57.1 \% 3$ or 4 risk factors at optimal level and only $6.5 \%$ between 5 and 7 factors at that level. At a mean follow-up of 8.5 years, the incidence of dementia was $1.32 \%$ per year. There was a clear relationship with the number of risk factors present. In those with only 0 or 1 factor at the optimal level, the incidence was $1.76 \%$ per year. With 2 risk factors at high-level, the incidence fell to $1.50 \%$ per year and so on until reaching 6 or 7 high-level factors, where the incidence was $0.80 \%$ per year. In multivariate analysis the incidence of dementia fell by $8 \%$ for each point of increase in the AHA scale. Considering income and occupation, the results were similar.

This publication confirms data from other cohort studies, such as the CARDIA and ARIC studies, by demonstrating the strong association between vascular risk factors and the incidence of dementia and cognitive impairment. Those studies focused on a young population. This, in turn, incorporated people older than 65 years of age and obtained similar results. As it is an observational study, it cannot be confirmed with certainty that an improvement of the values considered, at an advanced age, will translate into a decrease in the incidence of dementia; but at least, that reaching this stage of life with controlled risk factors ensures a better evolution in the final years of life not only in relation to cardiovascular events but also regarding the neurological status. The use of the AHA scale to anticipate the incidence of dementia is another example of how a prediction rule created for a specific purpose (in this case, to predict major vascular events) then finds subsidiary uses. Perhaps a scale defined specifically to define the risk of dementia has other components in addition to those cited, and greater predictive capacity.

Relationship between cardiovascular health and circulation and brain structure abnormalities: a study with magnetic resonance imaging

Williamson W, Lewandowski AJ, Forkert ND, Griffanti L, Okell TW, Betts J, et al. Association of Cardiovascular Risk Factors With MRI Indices of Cerebrovascular Structure and Function and White Matter Hyperin-
tensities in Young Adults. JAMA 2018;320:665-73. http://doi.org/gd5qce

Different cohort studies have linked the presence of middle-age cardiovascular risk factors with the incidence of dementia and cognitive deterioration in old age. The publication by Samieri et al. that we discuss in this section shows that even near the end of life, a lower prevalence of these factors is associated with better evolution of long-term cognitive ability. On the other hand, several magnetic resonance imaging (MRI) studies of the brain structure have shown that the presence of lesions at the level of the white matter and brain circulation abnormalities are the anatomical and functional correlates of dementia. These studies have included middle-age and elderly patients, those in whom cognitive deterioration is more frequent. But if vascular risk factors are frequently present in young individuals, will there be an association of these factors with incipient injury at the brain level? A remarkable study that has just been published answers this question.

The study held in Oxford between 2014 and 2016, included individuals between 18 and 40 years of age actively and passively recruited, with heterogeneity in the prevalence of traditional risk factors. Demographic, biochemical, blood pressure, effort capacity and lifestyle data were collected. A scale based on 8 modifiable risk factors, similar to the one used in the work of Samieri et al., was defined. One point was assigned for each factor considered healthy: not smoking or having quitted smoking for at least 6 months, belonging to the highest tertile of regular physical activity, 24-hour blood pressure (BP) monitoring $<130-80 \mathrm{mmHg}$, cholesterol $<200 \mathrm{mg} / \mathrm{dL}$, fasting blood glucose $<100 \mathrm{mg} /$ dL without treatment, body mass index $<25 \mathrm{~kg} / \mathrm{m} 2$, alcohol consumption $<8$ drinks per week and non-hypertensive response in an exercise test, with diastolic BP $<90 \mathrm{mmHg}$. All patients underwent a brain MRI in which presence of lesions in the white matter were detected by their hyperintensity, and vessel density and caliber were studied. One hundred and twentyfive patients were included, and in 52 of them brain flow characteristics were also studied.

The population considered had mean age of $24.7 \pm 5$ years, $49 \%$ were women, $23 \%$ were hypertensive and $15 \%$ were smokers. In multivariate analysis, systolic BP and smoking were significantly associated with lower density and caliber of the vessels, and additionally higher BMI implied lower vascular density. The number of white matter lesions was significantly associated with alcohol consumption, smoking and hypertensive response in the stress test. Taking into account the 8 point scale, each 1 point increase was associated with greater vessel density ( 0.3 vessels/ cm 3 ) and greater caliber ( 8 m ). Similarly, each 1 point increase in the scale involved 1.6 less lesions in the white matter. In the brain flow substudy, lower values and greater slowness were observed associated with higher BMI and specifically lower flow was seen in those treated with antihypertensive medication. Flow
was $2.5 \mathrm{ml} / 100 \mathrm{~g} / \mathrm{min}$ higher for each point increase in the cardiovascular health scale. Greater vessel density was associated with higher brain flow velocity.

This cross-sectional study has significant findings. As we said, it is known that a higher prevalence of white matter lesions and decreased brain flow are predictors of cognitive deterioration. It is understood that a brain flow $<55 \mathrm{ml} / 100 \mathrm{~g} / \mathrm{min}$ increases almost 3 times the risk of dementia in the elderly population. Notably, in the lower tertile of the cardiovascular health scale of the young people included in this study, the average brain flow had precisely this value. The association of vascular risk markers with greater brain damage in these young people seems to anticipate accurately and be the anatomical correlate of the findings of Samieri et al. in his study with people almost 50 years older, in which a scale quite similar to that of the present study predicts the development of dementia. If the results of the study by Samieri et al. encourage to maximize cardiovascular care in advanced age, those of the study here presented warn about the early risk of brain damage caused by poor control of vascular risk factors in young people. It is true that because this is a cross-sectional study we can talk about temporary association, not causality. A cohort study would be necessary associating MRI findings in young people with greater or lesser incidence of impairment in older age. Do these findings solve the enigma of dementia of vascular origin? They contribute, but we are still far away. Just to keep in mind: the model that links the variables explored with vessel density has a R2 coefficient of determination of only 0.20 , which means that only $20 \%$ of the variation in the density value is explained by the model considered. But it is, for the moment, and if we accept the relationship, the primary objective to which the cannons should be aimed: prevention and work on the risk factors to seek more cardiovascular as well as brain health.

## D-Dimer is a remote predictor of all-cause, cardiovascular and cancer mortality in stable coronary heart disease patients

Simes J, Robledo KP, White HD, Spinoza D, Stewart RA, Sullivan DR, et al. D-dimer Predicts Long-Term Cause-Specific Mortality, Cardiovascular Events and Cancer in Stable Coronary Heart Disease Patients: The LIPID Study. Circulation 2018; 138: 112-23. http://doi.org/ctst

D-Dimer is a degradation product of fibrin, whose increased levels are associated with enhanced risk of arterial and venous thrombosis, especially in patients with vascular disease, and at greater risk for cancer. Less clear is the association with the incidence of mortality for different causes in patients with stable coronary heart disease. A recent analysis of the LIPID study provides relevant information on the subject. The LIPID study included patients between 31 and 75 years of age, with history of acute myocardial infarction (AMI) or hospitalization for unstable angina 5 to 38 months after being recruited, stable since then and with normal values of cholesterol and triglycerides.

They were randomly assigned to pravastatin or placebo. The study endpoint was cardiovascular mortality, non-fatal AMI or non-fatal stroke. As part of the initial assessments (clinical and paraclinical) D-dimer levels were measured. Median follow-up was 6 years, but after the end of the study there was an additional follow-up of 10 years to define total and specific mortality risk for different causes, and 2 additional years to define risk of AMI or stroke. The analysis we present sought to define the independent role of D-dimer as a long-term predictor of death, vascular events and cancer among the study participants.

This substudy included 7,863 patients. D-dimer values were divided into quartiles: $\leq 112,>112-173,>173-$ 273 and $>273 \mathrm{ng} / \mathrm{ml}$. A second D-dimer value was measured at one year, and the variation between the first and second values was also divided into quartiles: $\leq-32,>-32$ to $1,>1-36$ and $>36 \mathrm{ng} / \mathrm{ml}$. Patients with higher D-dimer values were older, with higher prevalence of females, hypertension, renal dysfunction and drug treatment for cardiovascular disease. In them, the values of different biomarkers were greater, including troponin I, C-reactive protein and NT-proBNP.

In the initial 6-year follow-up, and adjusting for more than 30 conditions (risk factors, history of coronary heart disease, laboratory values, treatment) higher D-dimer values were associated with greater incidence of coronary and cardiovascular events, venous thrombotic events, including lung embolism, and total and cardiovascular mortality. The association of D-dimer with total mortality was non-linear, with a marked increase in risk up to values of approximately $400 \mathrm{ng} / \mathrm{ml}$ and a less firm association with higher values. In the 16-year extended follow-up period, multivariate analysis showed that D-dimer was a significant predictor of total, cardiovascular and cancer mortality and mortality for other causes. Belonging to quartile 4 , compared to being in quartile 1 of D-dimer values, was associated with a HR for total mortality of 1.65 ; for cardiovascular mortality of 1.59 ; for cancer mortality of 1.58 , and for non-cardiovascular or cancer mortality of 1.70 . High values of D-dimer were also associated with an increased risk of cancer incidence.

D-dimer is a marker of hypercoagulability and thrombosis. Both conditions are strongly related to the development of cardiovascular and cerebrovascular disease, and thromboembolism. Activation of the coagulation cascade and fibrin formation has been linked to phenomena not only of atherogenesis, but also of angiogenesis, tumor invasion and progression, and metastatic spread. Thus, the association of high values with higher incidence of death due to cardiovascular and total disease during the LIPID study (6 years) should not draw attention. What is more surprising is that a measurement can maintain its predictive value of vascular mortality and neoplasia up to 16 years, even adjusting for a large number of potential confounders. The prediction of non-cardiovascular death or non-cancer causes is also novel. Although it is possible that in fact there has been an error in the classification, and that some of these deaths are actually due to vascular or oncological causes, it should not be forgotten that
thrombosis is linked to phenomena related to rheumatological or renal disease.

Finally, two questions. Should D-dimer be a more usual determination when defining the risk profile of a stable patient? Should a high D-dimer be indication for anticoagulant treatment to modify the prognosis? Or is it a nonspecific marker, which expresses global risk beyond the specific one for thrombosis? Future studies should help to answer both questions.

Treatment of depression with escitalopram improves the prognosis in patients after an acute coronary syndrome.
Kim JM, Stewart R, Lee YS, Lee HJ, Kim MC, Kim JW et al. Effect of Escitalopram vs Placebo Treatment for Depression on Long-term Cardiac Outcomes in Patients With Acute Coronary Syndrome: A Randomized Clinical Trial. JAMA 2018; 320: 350-358.

Depression is a highly prevalent condition in patients with cardiovascular disease. It is considered that 30 to $45 \%$ of coronary patients present with depression that in half of the cases is labeled as major depression. The prevalence is particularly high among patients with acute coronary syndrome (ACS). In 50 to $70 \%$ of cases, depression evidenced in this context is actually prior to the coronary event and is a strong predictor of major events, including new ACS and higher mortality. Different studies have been conducted to demonstrate that antidepressant treatment can improve the prognosis in patients with ACS who present depression, including the MIND IT study with mirtazapine, the SADHART study with sertraline and the ENRICHD study with cognitive therapy with or without medication. The results have been generally discouraging, showing only improvement of depressive symptoms, without changing the prognosis with respect to the placebo or control group. We now know the results of a study with escitalopram, which shows for the first time a decrease in the incidence of major cardiovascular events.

This study was conducted in the context of a Na tional Registry of Acute Myocardial Infarction in a South Korea center. Between 2007 and 2013, 4,809 patients who presented with ACS in the two previous weeks were evaluated and after meeting certain exclusion criteria (including severe concomitant disease, age $\geq 85$ years, and uncontrolled hypertension) 1,152 patients were enrolled and underwent Beck's depression inventory. This is a self-administered questionnaire consisting of 21 questions, which allows defining the presence and severity of depression. Those with a questionnaire score $>10$ were submitted to the MINI (Mini International Neuropsychiatric Interview) structured interview, which classifies depression as minor or major. Finally, 300 patients were included in the study, and information related to their interrogation, physical examination, ECG, laboratory and left ventricular ejection fraction (LVEF) was collected. The patients were randomly assigned in a $1: 1$ ratio to escitalopram at an initial dose of $10 \mathrm{mg} /$ day or placebo
for 24 weeks. The primary endpoint was initially the remission of depressive symptoms. The average age of the patients was 60 years, and $60 \%$ were men; $61 \%$ had had an acute myocardial infarction (AMI, 80\% Killip I), and the rest unstable angina. In $56 \%$ of cases patients had major depression. The average LVEF was $61 \%$. Once the study was initiated, the follow-up period was extended for more than 24 weeks, with a combined endpoint of cardiovascular mortality, AMI or need for coronary angioplasty.

Median follow-up was 8.1 years. The incidence of the primary endpoint was $40.9 \%$ in the escitalopram group and $53.6 \%$ in the placebo group (HR 0.69, 95\% CI 0.49-0.96). The difference was mainly in the incidence of AMI (HR 0.54, 95\% CI 0.27-0.96). No difference in mortality or need for revascularization could be demonstrated. The incidence of events was significantly lower in those in whom depression subsided, regardless of whether they had received drug or placebo treatment.

The association of depression with the incidence of cardiovascular and cerebrovascular events has different explanations. There is a higher incidence of endothelial dysfunction, inflammatory activity, increased platelet activation, and autonomic dysfunction in patients with major depression, in addition to behavioral factors such as lack of self-care, less compliance with diet and medication and less physical activity. Although depression is an independent predictor of cardiovascular events and mortality, there is still no current evidence of prognostic improvement with antidepressant treatment. This has questioned the role of depression, and it has been postulated that it is actually an expression of systemic inflammation, a confounder in the relationship between inflammation and cardiovascular disease. However, the study we present contributes to place depression as a causal factor, and not just as a marker. In this sense, the lower incidence of events in patients in whom depression subsided is significant, regardless of the treatment. Is the effect of escitalopram due to a generic effect as antidepressant, or to a particular effect by its action on platelet activation? Let us note that, in fact, a slight risk of hemorrhagic events has been described for serotonin reuptake inhibitors, attributed among other reasons to reduced synthesis of cGMP and to a decrease in the metabolism of non-steroid anti-inflammatory drugs. The increased risk of bleeding may go hand in hand with a decrease in the incidence of ischemic events. In this sense, it is regrettable that there is no description of the adverse effects in the publication. Another possibility is that the treatment has influenced common precursors of depression and coronary heart disease; therefore, more studies are necessary. If it is confirmed that other antidepressant agents with different mechanisms of action achieve the same results, then the relationship of depression with coronary heart disease will be confirmed. If the beneficial effect on cardiovascular prognosis is restricted only to serotonin reuptake inhibitors, it will be more debatable whether this effect is due to treatment of depression or to some specific effect of this type of drugs.

