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How many daily steps are necessary to improve cardiovascular prognosis? Data from a meta-analysis

Stens NA, Bakker EA, Manas A, Buffart LM, Ortega FB, Lee DC et al. Relationship of Daily Step Counts to All-Cause Mortality and Cardiovascular Events. **J Am Coll Cardiol 2023;82:1483-94. https://doi.org/10.1016/j.jacc.2023.07.029.**

Different observational studies and meta-analyses have confirmed the relationship between regular physical activity and vital prognosis, and specifically with cardiovascular prognosis. We are referring not to sporting activity, but simply to walking. A greater number of daily steps is associated with a lower incidence of cardiovascular disease (CVD) and frailty, and longer survival. The metric is simple: it is not about measuring the distance traveled but about counting the steps. Different devices (pedometers, accelerometers) and applications on cell phones (which accompany us throughout our daily lives) allow us to carry out this task. Although many publications have exposed the aforementioned association, it is not entirely clear what is the minimum number of steps necessary to improve the prognosis, and what other factors linked to walking have an impact. For this reason, a systematic review and meta-analysis was carried out to answer these questions.

Prospective cohort studies published in English were considered, which included participants at least 18 years old, free of CVD at the beginning of the study, and in which an objective measurement of the number of daily steps had been made for each participant with accelerometers or pedometers, and the relationship between step count and total mortality and the incidence of CVD (acute myocardial infarction, stroke, heart failure) during follow-up would have been established.

Twelve studies were included. In 11 of them (n= 111 309) the relationship between the number of steps and all-cause mortality was explored; in 4 (n=102 191) the relationship between walking speed and mortality; and in 4 (n= 85 261) the relationship between the number of steps and the incidence of CVD.

The relationship of the number of daily steps with prognosis was evaluated in 2 ways. One, with the generation of 3 categories or tertiles (each with its median and interquartile range, IQR) in which the prognosis of the intermediate and high tertiles with respect to the low one was explored. The other, considering the number of steps as a continuous variable. In this case, 2000 steps per day were taken as the reference value, and the number of steps (up to a maximum of 16 000) with which the lowest adjusted hazard ratio (aHR) for the incidence of events was achieved was explored.

In a median follow-up of 77.8 months, considering the lowest tertile (median 3166 daily steps, IQR 2375-4191) as the reference, the intermediate tertile (median 6000, IQR 5392-6775) was associated with an aHR of 0.65 (95% CI 0.56-0.72) for all-cause mortality; and the upper tertile (median 10 000, IQR 8,843-11,082) with an aHR of 0.50 (95% CI 0.42-0.60). For CVD incidence, in a median follow-up of 72.9 months, compared to the lowest tertile (median 2022, IQR 1468-2885), the intermediate tertile (median 5737, IQR 5449-6000) was associated with an aHR of 0. 58 (95% CI 0.46-0.63); and the upper tertile (median 11 000, IQR 9923-12 024) with an aHR of 0.42 (95% CI 0.33-0.53)

In the analysis of steps as a continuous variable, for all-cause mortality, a significant risk reduction with respect to a reference of 2000 steps per day began at 2517 steps, with an aHR of 0.92 (95% CI 0.84-0.999), and the maximum reduction was reached at 8763 steps, with aHR 0.40 (95% CI 0.38-0.43) above which there was no longer a statistically significant gain. For the incidence of CVD, the risk reduction with respect to a reference of 2000 steps per day began at 2735 steps, with an aHR of 0.89 (95% CI 0.79-0.999) and the maximum reduction was reached with 7126 steps, with aHR 0.49 (95% CI 0.45-0.55) above which there was no longer a statistically significant gain.

Beyond the number of steps, the cadence or walking speed also influenced the prognosis. Regarding a low speed (median of 29 steps/minute), an intermediate speed (median of 63 steps/minute) and a high speed (median of 88 steps/minute) were associated with an aHR of 0.67 (95% CI 0.56-0.80) and 0.62 (95% CI 0.40-0.97) for all-cause mortality, respectively.

Studies using hip-worn accelerometers showed greater risk reduction than those using wrist-worn accelerometers or pedometers.

This meta-analysis confirms the beneficial prognostic effect of walking. It is interesting to note that the necessary dose of walking to improve prognosis seems to be lower than what is usually mentioned. We have all heard and read advice about the 10 000 steps a day that should be taken to improve cardiovascular prognosis. It is worth noting that this figure comes from an advertising campaign, but, as we see, it is not based on epidemiological data. We see that, with respect to 2000 steps per day, an increase from only 500 to 700 steps already implies a significant reduction in mortality and the incidence of CVD; and that the maximum reduction is achieved with around 8700 and 7100 steps respec-

tively. The involved mechanisms undoubtedly include improvement in exercise capacity, reduction of endothelial dysfunction, attenuation of inflammatory activation, neurohormonal activation and insulin resistance, weight loss, better control of blood pressure, delay in the onset of diabetes and cancer.

A strength of this meta-analysis is the large number of observations and the robustness of the statistical procedures used. As a limitation, it can be stated that we are dealing with observational studies, in which, beyond the known baseline characteristics that allow the generation of adjusted HR, there may be residual confusion due to characteristics not taken into account that explain the different walking capacity and are responsible for the phenomenon. In any case, the strength of the association makes it very unlikely that there are unconsidered confounders of significance. The possibility of reverse causality can also be raised: it is not that walking more improves the prognosis, but that those who are less sick and have a better prognosis walk more. In this sense, it is worth highlighting that 10 of the 12 studies excluded reverse causality by removing the first 1 to 3 years of follow-up in the sensitivity analysis, so the sickest patients were not taken into account, and the relationship of more steps with better prognosis remained. So we must insist on walking as a simple measure in the general population to improve vital prognosis. We can obtain profit already with small increments. Every step counts.

The sense of lowering LDL cholesterol in primary prevention in adults at least 70 years old. Results of a Danish observational study

Andersson NW, Corn G, Dohlmann TL, Melbye M, Wohlfahrt J, Lund M. LDL-C Reduction With Lipid-Lowering Therapy for Primary Prevention of Major Vascular Events Among Older Individuals. **J Am Coll Cardiol 2023;82:1381-91. https://doi.org/10.1016/j.jacc.2023.07.027.**

Meta-analyses of LDL cholesterol reduction studies with lipid-lowering drugs demonstrate a 22% reduction in the risk of major cardiovascular events for every 1 mmol/L (38.66 mg/dL) reduction. People over 70 or 75 years are exposed to a higher cardiovascular risk; however, they are underrepresented in clinical trials . The level of evidence and the strength of recommendation to use statins in primary prevention in this age segment are lower than in younger patients, and the controversy over the usefulness of implementing the treatment in older adults is periodically reactivated. A large Danish observational study addressed the problem.

It took data from different administrative, pharmaceutical, laboratory and health registries in Denmark, taking advantage of the fact that in that country each individual has a personal identification number that is shared by the different registries. A cohort of people at least 50 years old was generated, who had started lipid-lowering treatment (statins alone or combined with other drugs) for primary prevention of CVD between January 1, 2008 and October 31, 2017. The index date was considered that of the first medication prescription. Patients had to have an LDL cholesterol determination within 6 months prior to the index date, and another within a year after. They must have survived at least 1 year after the index date. The primary endpoint of the study was the incidence of hospitalization due to CVD (acute coronary syndrome, nonhemorrhagic stroke, or revascularization procedure), and secondary endpoints were the primary components and all-cause mortality. Older patients (OP) were considered those at least 70 years old. The start of follow-up was taken one year after the index date. The study included 65 190 patients, 16 035 of which (24.6%) were OP. Their average age was 75.4 years, and 57.5% were women. Patients under 70 years of age had a mean age of 60.2 years, and 53% were women. The OP logically had a higher prevalence of comorbidities and frailty. Most patients across the age range used moderate intensity statin treatment (77.4% of the PM; 79.4% of the youngest); most of the remainder used high-intensity statins.

The median reduction in LDL cholesterol was 1.7 mmol/L (65.7 mg/dL) in both age groups, which represented a decrease of 45.2% in the OP and 43.6% in the youngest. During a median follow-up of 2.5 years, the incidence of major cardiovascular events was 13.4 ‰ annually among the OP and 7.1 ‰ in the younger ones. The risk reduction per 1 mmol/L (adjusted for age, sex, socioeconomic status, LDL cholesterol, intensity of lipid-lowering treatment, comorbidity and co-treatment) was similar in both groups: an HR of 0.77 (95% CI 0. 71-0.83) in the OP and 0.76 (95% CI 0.71-0.80) in the youngest, p= 0.79. There was no reduction in all-cause mortality in either of the 2 groups. Considering a cut-off value of 75 years, the results were similar.

A meta-analysis by Gencer et al that we discussed in Rev Argent Cardiol 2020;88:566-575, already reported in 29 randomized studies that tested statins, ezetimibe and/or PCSK9 inhibitors in 244 090 patients, of which 21 492 (8.8%) were at least 75 years old. Primary and secondary prevention studies were included. Among those ≥75 years, the effect of active or more intensive treatment implied an RR for major events of 0.74 (95% CI 0.61-0.89) for each decrease in LDL cholesterol of 1 mmol/L. The effect was similar to that achieved in those under 75 years (RR 0.75). But a limitation of this meta-analysis was that only a quarter of the events corresponded to primary prevention, which reduced the strength of the evidence in this condition in elderly patients.

But it is also true that many of these randomized studies date back one to two decades, and it is certain that the population profile has varied. On the other hand, due to the inclusion and exclusion criteria, it is feasible that the elderly patients included were the healthiest, with a lower rate of comorbidity and frailty, and therefore with a lower baseline risk. In this sense, this large observational study offers data from a contemporary cohort. Limitations include , as always, the possibility of residual confusion typical of any observa-

tional study, and the lack of data that would have been important in the multivariate analysis: blood pressure, blood glucose, body mass index. An ongoing randomized study, STAREE, may contribute to clarifying the effect of statin treatment in primary prevention in aged > 70 years. Until its results are known, this Danish registry strongly suggests that older people should not be excluded from the benefit of such therapy.

Predictors of improvement in left ventricular ejection fraction in heart failure after atrial fibrillation ablation

Bergonti M, Ascione C, Marcon L, Pambrun T, Della Rocca DG, Ferrero TG et al. Left ventricular functional recovery after atrial fibrillation catheter ablation in heart failure: a prediction model. **Eur Heart J 2023;44:3327-35. https://doi.org/10.1093/eurheartj/ehad428**

Heart failure (HF) and atrial fibrillation (AF) are two conditions that frequently coexist. Each of them favors the appearance of the other and conditions its treatment. Although initially the studies of rhythm control and frequency control of AF in patients with HF yielded similar results, the appearance of AF catheter ablation demonstrated the ability to significantly improve the prognosis in selected patients. A meta-analysis by Chen et al that we discussed in Rev Argent Cardiol 2020;88:469-476 showed that AF catheter ablation in HF patients lowers mortality and hospitalization and generates an average improvement in left ventricular ejection fraction (LVEF) of almost 7 points. However, who are the patients in whom we can expect this improvement, and therefore, those in whom it is most advisable to carry out the procedure, remains a matter of doubt. The ANTWOORD study, published in 2022, developed a score predictive of LVEF improvement after AF catheter ablation in patients with HF, called the Antwerp score. This score was validated internally, and we now know of an external validation study.

This is a multicenter, retrospective study with patients with HF and LVEF < 50% from 8 referral centers to which they were sent for catheter ablation of their AF. The primary end point was LVEF recovery one year after the procedure (between 9 and 15 months). Responders were defined as patients with LVEF between 40% and 50% who had achieved an LVEF > 50% after ablation, and those with initial LVEF < 40% who had ≥ 10% increase and LVEF > 40% in the follow-up. The predictive capacity of the previously developed score was considered. It takes into account the following variables: a) known etiology (2 points); b) QRS > 120 msec (2 points); c) indexed left atrial volume > 50 mL/m 2 (1 point) and d) paroxysmal AF (1 point). The higher the score, the lower the probability of LVEF recovery.

The analysis included 605 patients treated between 2010 and 2021, with a mean age of 61 years, 24% women. In just over half of the cases the procedure consisted of pulmonary vein ablation as the only treatment, in the rest there was another associated practice. Seventy percent were responders, with LVEF increased by an average of 19.6 ± 9.6%. Non-responders did not change their LVEF: 0.3 ± 5.7%. Responders were more frequently men, somewhat younger, with fewer comorbidities, less need for electrical therapy devices, smaller left atrial and ventricular volume, narrower QRS (mean 102 vs 127 msec), less frequently known etiology and less frequent paroxysmal AF. The median (IQR) Antwerp score was 1 (0-2) in responders vs. 4 (3-5) in non-responders. At a median follow-up of 440 days (316-728) responders less frequently experienced recurrence of atrial arrhythmia (30.6 vs. 51.5%), specific recurrence of persistent AF (9.6 vs. 34.1%), hospitalization for HF (3.8 vs 30.1%), death or heart transplant (1.5 vs 11.5%), and on the contrary, more frequently reverse remodeling, with a drop of at least 15% in the left ventricle end systolic volume (48.8 vs 9.6%). In all cases the differences were statistically significant. The score had excellent external validation. In those with a score ≤ 2 the LVEF recovery rate was 90%; in those with score ≥ 5, 14%; in those with an intermediate score, 47%.

When deciding on AF catheter ablation in the context of HF with reduced LVEF, the question always arises about choosing the appropriate candidate. The procedure success depends greatly on the baseline clinical and paraclinical characteristics. That is why treatment guidelines always talk about "selected patients." The study we present contributes to an adequate selection of the cases with the greatest feasibility of success. The known etiology variable refers to the fact that a cause for the decrease in LVEF can be identified, beyond AF. If this etiology (ischemic, non-ischemic, infiltrative, etc.) is present, it is less likely that AF ablation will significantly improve LVEF. If it is not, we can be more confident in its increase by eradicating AF. Atrial dilation and widened QRS imply installed structural damage, and therefore a lower possibility of success. Note that the atrial volume considered as the cut-off value is very high (50 mL/m 2), which increases the specificity and therefore the positive predictive value. Paroxysmal AF signals electrical instability due to the presence of triggers and a predisposed substrate. The presence of the 4 variables of the score suggests being pessimistic when expecting success of the procedure. Its absence, on the contrary, allows us to trust in a favorable result.

It is worth noting that responders (two-thirds of the total) had a 30% AF or atrial flutter recurrence rate, despite which their prognosis was much better than that of non-responders, with a combined end point of death/transplant that was 10 times lower. This coincides with the concept that a reduction in AF burden > 50% is associated with reverse remodeling and a better prognosis. The recurrence of AF is not, then, per se, a sign of failure of the procedure. But it must be clear that we cannot, in this observational study, attribute the better evolution only to the successful AF ablation. The responders were, in fact, younger, less sick, with a narrower QRS

and a clearly lower Antwerp score. Stronger evidence of the relationship between AF ablation and prognosis in patients with advanced HF undoubtedly arises from a randomized study such as Castle -HTx, which we discussed in the previous issue.

Cardiovascular risk attributable to newly diagnosed type 2 diabetes

Gyldenkerne C, Mortensen MB, Kahlert J, Thrane PG, Warnakula Olesen KK, Sorensen HT et al. 10-Year Cardiovascular Risk in Patients With Newly Diagnosed Type 2 Diabetes Mellitus. **J Am Coll Cardiol 2023;82:1583-94. https://doi.org/10.1016/j.jacc.2023.08.015**

Although type 2 diabetes is a universally recognized cardiovascular risk factor, the bulk of the information comes from patients with a long history of the disease. There is a paucity of data on the cardiovascular prognosis of patients with type 2 diabetes of less than 10 years' duration, and in fact it is accepted that this short duration of disease may not imply a high risk of events. To clarify this situation, a cohort study was carried out in Denmark in which patients with type 2 diabetes recently diagnosed between January 2006 and December 2013 were matched by age and sex in a 1:3 ratio with people free of diabetes . All those (with or without diabetes) who had established cardiovascular disease (CVD) were excluded from the study. This finally led to a ratio of people with vs without diabetes of 1 to 2.7. The primary endpoint of the study was CVD incidence: CV death, nonfatal acute myocardial infarction, and nonfatal stroke. The analysis considered the competing risk of non-CV death for the CV death end point, and that of unrelated death for non-fatal cardiovascular events. Follow-up began with the diagnosis of type 2 diabetes, and extended to a maximum of 10 years, the incidence of any of the end points, or December 31, 2013, whichever came first.

Finally, 142 857 people with recently diagnosed diabetes and 388 410 individuals from the general population, all free of CVD, were included. The median age of the population was 60 years. Patients with diabetes had a higher prevalence of comorbidities and were prescribed more medication. In patients with diabetes, metformin was used in 69% of women and 67% of men, and statins were used in 35.7% of women and 38.5% of men. Logically, due to the inclusion period, the use of gliflozins and GLP-1 agonists was 0 or close to 0. In the age range of up to 49 years, patients with diabetes presented a diagnosis of obesity more frequently than at older ages, and they were prescribed fewer statins and antihypertensive medications.

At a median (IQR) follow-up of 8.1 years (6.3-10) the incidence of CVD was 12% among patients with diabetes and 9.3% in those without diabetes. The risk of CVD increased from 2% in those under 40 years to 30% in those 80 years or older. The HR considering the competing risk of non-CV death decreased with increasing age, from 2.59 in those < 40 years to 1.08 in those ≥ 80 years. For any CVD risk percentile, patients with diabetes reached it at a younger age. For example, a 10-year CVD risk of 5% was achieved in men with newly diagnosed type 2 diabetes at age 43, and in men without diabetes at age 55. In the case of women, they reached a 10-year risk of 5% at age 51 if they had diabetes, and at age 61 if they did not. Progressively higher risks were logically reached at older ages, and coincided with a smaller age difference between people with and without diabetes. In all age groups, the CVD risk of patients with newly diagnosed diabetes was higher in men than in women, especially in the youngest (in < 40 years, 4% in men, 1.3% in women) but extending to the most advanced ages (in those ≥ 80 years 30.3% in men vs 29.8% in women). The 10-year all-cause death risk was 25% among patients with diabetes and 16% in those without diabetes, primarily attributable to non-cardiovascular death.

This Danish study shares with the one we discussed about lowering LDL cholesterol the fact of being based on national registries of medical and administrative data. It allows us to elucidate what happens with recently diagnosed type 2 diabetes, and how it influences prognostic determination. It is worth noting that, in absolute values, logically the risk of CVD in patients with newly diagnosed type 2 diabetes is greater as age increases; but that the risk relationship between a patient with and without diabetes decreases as age increases. Higher risk of events, but with lower weight of the diabetes condition in older patients; logical if we consider that the older they are, the greater the presence of other risk factors in patients without diabetes, so that their difference with a patient with diabetes tends to decrease. On the other hand, the presence of type 2 diabetes in young patients goes hand in hand with obesity and smoking. This combination, added to a lower prescription of statins and antihypertensives, may help explain the excess risk of CVD in them compared to their counterparts without diabetes.

The strengths of the study are that it is a contemporary cohort, with excellent quality of prospectively collected data, and the number of observations. Weaknesses include not having data on smoking, alcohol consumption, blood pressure, LDL cholesterol nor HbA1c figures. In the comparison of patients with and without diabetes, it was not possible to adjust for the presence of other cardiovascular risk factors. The authors maintain that, in any case, this allows us to consider the excess risk that a patient has when diagnosed with diabetes, with all the risk factors that this entails.

In conclusion, newly diagnosed diabetes implies excess risk of CVD already in the first 10 years of diagnosis. This excess risk is even greater in relative terms the younger the patients are, especially men. This information should be considered when choosing treatment: statins, gliflozins, GLP-1 agonists (to be taken into account if we recall the higher prevalence of obesity in this subgroup)