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A meta-analysis confirms the effects of walking on cardiovascular prognosis

Paluch AE, Bajpai S, Ballin M, Bassett DR, Buford TW, Carnethon MR, et al. Prospective Association of Daily Steps With Cardiovascular Disease: A Harmonized Meta-Analysis. **Circulation 2023;147:122-31. https://doi.org/10.1161/CIRCULATIONAHA.122.061288.**

Countless observational studies have associated physical activity with improved vital prognosis and a reduced risk of diabetes mellitus, malignancies, and cardiovascular disease, among others. In fact, clinical practice guidelines for cardiovascular prevention recommend vigorous physical activity or moderate activity for at least 75 minutes a week or 150 minutes a week, respectively. Walking is certainly the most accessible, manageable, and simple form of physical activity. It is widely acknowledged that 10 000 daily steps are the target to improve life expectancy in terms of both quantity and quality. In 2022, Paluch et al. published a meta-analysis of 15 observational studies in 47 471 adults with a median follow-up of 7.1 years. The population was divided into quartiles according to the daily number of steps, with a median of 3553, 5801, 7842, and 10 901 for the first, second, third and fourth quartiles, respectively. As compared to the lowest quartile, the hazard ratio (HR) adjusted for all-cause mortality was 0.60 (95% CI [confidence interval] 0.51-0.71) for the second quartile, 0.55 (95% CI 0.49-0.62) for the third quartile, and 0.47 (95% CI 0.39-0.57) for the fourth quartile. The mortality risk was gradually reduced in ≥60-year adults with an increasing number of up to 6000-8000 steps a day, and in <60-year-olds with up to 8000-10 000 daily steps. When adjusting for the daily number of steps, the association between a higher frequency of steps and mortality diminished, though still remarkable for a daily walk reaching 30 minutes and 60 minutes; however, there was no significant association between the time spent walking at 40 steps/min or faster, or 100 steps/min or faster.

The same group of authors has now published a meta-analysis focused on defining the relationship between a daily walk and cardiovascular risk, including 8 studies of 20 152 participants (mean age 63.2±12.4 years; 52% females) followed for a mean of 6.2 years (range 2.8 to 12.6 years). Seven of these studies are also part of the previous meta-analysis. Each of the studies used a device (pedometer, accelerometer) to prospectively measure the number of daily steps for 3 to 7 days, according to the study, and this was averaged to define the daily number of steps. The incidence of fatal or non-fatal cardiovascular events was reported in every case. A cardiovascular event was any cardiac episode, a stroke, or heart failure (HF).

Among participants aged ≥60 years old (7 studies, 12 741 participants), the median number of daily steps was 4323. When divided into quartiles, the median number of steps was 1811 for the lowest quartile, and 3823, 5520 and 9259 for the second, third and fourth quartiles, respectively. The annual incidence of cardiovascular events was 1.93%. In a multivariate analysis including age, sex, time spent using the device, race/ethnic group, education or income, body mass index, as well as lifestyle-specific variables (e.g., smoking, alcohol), hypertension, diabetes mellitus, dyslipidemia, chronic conditions, and general medical condition, there was a significant association with a higher number of steps leading to better cardiovascular prognosis. Relative to the first quartile, the HR (95% CI) for cardiovascular events was 0.80 (0.69-0.93) for the second quartile, 0.62 (0.52-0.74) for the third quartile, and 0.51 (0.41-0.63) for the fourth quartile. There was a curvilinear relationship between the number of steps and risk reduction, with a steeper slope for steps 2000 to 6000 that was later attenuated.

For those aged <60 (4 studies, 7411 participants), the median of daily steps was 6911, and 3128, 5464, 7857, and 11,463 for the first to fourth quartiles, respectively. The annual incidence of cardiovascular events was 0.51%. The multivariate model showed no significant incidence of the number of steps on cardiovascular prognosis for the second, third or fourth quartiles versus the lowest quartile.

In the overall population, the HR (95% CI) for females in the final adjusted model was 0.81 (0.62-1.04) in the second quartile, 0.68 (0.48-0.97) in the third quartile, and 0.51 (0.35-0.76) in the fourth quartile, as compared to the first. For males, values were 0.76 (0.63-0.90), 0.63 (0.52-0.76), and 0.68 (0.51-0.89). For both males and females, there was a curvilinear relationship between the number of steps and cardiovascular prognosis, with a steeper slope of risk reduction of up to 8000 steps that was then attenuated.

An important aspect of this publication is the curvilinear association between the distance walked and the effect on events reduction. Particularly in those aged 60 or older, increasing the walk from 2000 to 6000 steps provides many advantages, and a median of about 9000 steps reduces cardiovascular risk to a half. Therefore, an initial increase is highly beneficial, while persistence and increased exercise help to reinforce and improve results. There is no need to achieve 10 000 steps to gain any benefits! Why does the effect become less evident in younger individuals? Probably

because incidence of cardiovascular disease is much lower in this population (4 times lower than annual incidence in this meta-analysis), and therefore, the time needed to experience some kind of effect must be much longer. Evaluating the effect on body weight, or emergence of hypertension or diabetes mellitus may evidence a very much suspected effect. It is worth noting that the effect of steps in this meta-analysis using devices is more powerful to determine the effort made than in analyses based on self-reporting, possibly since the former tend to be more objective. As with every observational study, there are limitations. Is the effect of walking due to the activity itself (with the whole array of favorable consequences, such as reduced endothelial dysfunction, reduced neurohormonal and inflammatory activation, and improved cardiopulmonary capacity)? Or is walking an expression of lower rates of baseline disease (whether cardiovascular or not) and part of a healthier lifestyle including more self-care and better eating habits, etc.? There is always a risk of residual confounding. This meta-analysis is also limited by lack of individual data and a distinction of the effects on each of the components of the cardiovascular compound. In any case, walking only require time, proper outfit, and footwear, and most of all, being willing to walk. The cost-benefit ratio has rarely been clearer. So, let's walk!

Cardiovascular rehabilitation and the effects on secondary prevention of coronary events. A meta-analysis

Dibben GO, Faulkner J, Oldridge N, Rees K, Thompson DR, Zwisler AD et al. Exercise-based cardiac rehabilitation for coronary heart disease: a meta-analysis. **Lancet 2022;400:1417-25. Eur Heart J 2023;44:452-69. https://doi.org/10.1093/eurheartj/ehac747.**

Cardiovascular rehabilitation (CR) has a Class I indication in the international guidelines for coronary disease management. Recently, an updated meta-analysis was published; this analysis was conducted according to the Cochrane Collaboration guidelines to evaluate the effect of exercise-based CR for patients with coronary artery disease on overall and cardiovascular mortality, events, quality of life, and cost-effectiveness. The Cochrane meta-analysis, released in 2016, had included 63 randomized trials until June 2014. This update added 22 studies published from 2016 to September 2020. There are 85 studies in 23 430 patients with a history of acute myocardial infarction (AMI), coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA), angina or coronary angiography with significant injuries who were randomized to exercise-based CR alone (45% of studies) or who had received some additional psychosocial or educational intervention (the remaining 55%), or control (no exercise, or routine care), and monitoring for at least 6 months. The endpoints were all-cause mortality and cardiovascular death, AMI, CABG, PTCA, and all-cause and cardiovascular hospitalization.

The median age of participants was 56; the median length of intervention was 6 months, with a median follow-up of 12 months. The frequency of intervention in the studies ranged from 1 to 7 times a week; sessions lasted 20 to 90 minutes, intensity went from 50% to 90% of the highest heart rate and 50% to 95% of aerobic capacity. Exercise was done at home in 21 studies. The effect of the intervention was reported at the longest follow-up as the continuous mean, and it was classified after 6-12 months, 12-36 months, and >36 months. According to Cochrane classification, the risk of bias (matters relative to deficits in randomization, follow-up, blinded events, selective report) was generally low or uncertain. Based on GRADE, a reference framework to assess the quality of evidence, during 6-12 months of follow-up (the most commonly reported period), it was moderate for all endpoints, except for CABG (high) and cardiovascular hospitalization (low).

CR did not affect all-cause mortality (reported in 60 studies) in none of the follow-up periods. Out of 33 studies reporting cardiovascular mortality, events occurred in 26 trials, where CR was associated with a relative risk (RR) of 0.74, a 95% CI 0.64–0.86 in the longest follow-up, and a number needed to treat (NNT) of 37. However, 6-12 months of follow-up showed no significant difference.

The incidence of AMI was reported in 42 studies, and events were experienced in 39 of these. CR was associated with a RR (95% CI) of 0.82 (0.70–0.96), and a NNT of 100. This reduction was due to the decrease observed after 6 to 12 months (RR 0.72) and >36 months (RR 0.67), while no difference was noted after 12-36 months. There was no difference as regards the incidence of CABG or PTCA, with or without CR. Twenty-two studies reported incidence of all-cause hospitalization, and 21 studies had events, where CR was shown with a RR (95% CI) of 0.77 (0.67-0.89) and a NNT of 37. There were no effects on cardiovascular mortality. Six studies evaluating the effect on SF-36 questionary, and 20 out of 32 trials including other methods of measurement reported improved quality of life. The difference in costs versus traditional care was heterogeneous in 8 cost studies, and a significant difference was found in one of them. Only 3 studies reported an acceptable cost-effectiveness ratio.

The relevance of this meta-analysis lies in the number of patients enrolled and its contemporaneous nature, making it possible to extend evidence to CR in the setting of the latest pharmacologic treatment. Another advantage is the inclusion of 21 studies in low to moderate income countries, where the effect of the intervention was no different from that in high-income nations. Results are generally reliable and confirm reduced cardiovascular mortality and AMI incidence, as well as all-cause hospitalization. However, they are not very clear concerning cost-effectiveness, and the effect

on quality-of-life scores, though significant in many trials, is not always clinically relevant. The heterogeneous population, the background heart condition, schedules, the amount of exercise, etc. may impact on a lack of uniform results. In addition, in half of the cases, follow-up lasted less than 12 months. As above stated, the effects of CR cannot be ascribed only to the physical activity it entails, unless we consider that taking part in a CR program also involves closer contact with the healthcare system, and a higher possibility of identifying manageable impairments, and that in more than half of the studies, CR involved psychosocial or educational support as well. Anyway, CR appears to be a positive intervention for secondary prevention of coronary artery disease, and it seems increasingly wrong to leave it out, at least when deciding treatment for many of our patients.

High-sensitive troponin T and NT-proBNP in SPRINT study: it is not always as expected

Berry JD, Chen H, Nambi V, Ambrosius WT, Ascher SB, Shlipak MG et al. Effect of Intensive Blood Pressure Control on Troponin and Natriuretic Peptide Levels: Findings From SPRINT. **Circulation 2023;147:310-23. https://doi.org/10.1161/CIRCULATIONAHA.122.059960.**

The use of biomarkers in cardiovascular disease is here to stay. The two biomarkers most commonly used in daily practice and in the context of interventional studies are undoubtedly high-sensitive troponin, T or I, and natriuretic peptides, BNP or NT-proBNP. Troponin expresses myocardial injury; it is an essential part of the diagnosis of acute coronary syndromes, but, in addition, its acute or chronic elevation indicates worse prognosis in a variety of conditions, from peripheral artery disease to atrial fibrillation, in respiratory diseases or in the non-cardiac surgery postoperative period. Natriuretic peptides are elevated as an expression of increased wall stress in both ventricles; they are usually associated with elevated filling pressures, but they also increase in the context of renal dysfunction, general cardiovascular involvement, and activation of inflammatory events. They are used in the differential diagnosis of dyspnea of cardiac versus respiratory origin in acute conditions, in the characterization and follow-up of the response to treatment of chronic heart failure, in determining the severity of valvular heart disease, and so on. A generalized concept is that the increase in any of both biomarkers implies greater cardiovascular involvement and is associated with worse outcome. Another concept is that treatments that improve cardiovascular prognosis should generate a reduction in both biomarker values, or at least not increase them.

Despite all the uses above mentioned, the use of troponin or natriuretic peptides in the context of arterial hypertension is infrequent, and information on their usefulness in this condition is scarce. A subanalysis of the SPRINT study challenges some of the assumptions that have been made. As we all know, the SPRINT study was a randomized, open-label, controlled study that compared two strategies in hypertensive patients: to achieve a systolic blood pressure (SBP) <140 mmHg (standard treatment, ST) or <120 mmHg (intensive treatment, IT). It included patients with SBP between 130 and 180 mmHg, >50 years old and with at least one cardiovascular risk criterion: previous clinical or subclinical cardiovascular disease, except stroke; 10-year event risk according to the Framingham score of at least 15%; glomerular filtration rate between 20 and 59 mL/min/1.73 m2; ≥75 years old. Patients with diabetes were excluded. The primary endpoint was a composite of acute myocardial infarction (AMI), other acute coronary syndromes, stroke, acute decompensated heart failure (HF), and cardiovascular death. A total of 9361 patients were enrolled, with a mean follow-up of 3.26 years. The annual incidence of primary endpoint was 1.65% in the IT arm and 2.19% in the ST arm (HR 0.75, 95% CI 0.64-0.89), with no significant difference in the incidence of AMI or stroke, but significant differences in the incidence of acute HF (HR 0.62, 95% CI 0.45-0.84), cardiovascular death (HR 0.57, 95% CI 0.38-0.85) and all-cause death (1.03% vs. 1.40% per year, HR 0.73, 95% CI: 0.60-0.90).

A substudy of SPRINT including patients with baseline and 1-year measurements of high-sensitive troponin T (hsTnT) and NT-proBNP has just been published. The study aimed to evaluate the relationship of the changes in both biomarkers (1-year minus baseline) with the primary endpoint of all-cause death and incidence of HF, and the secondary endpoint of the other cardiovascular events. Such change was analyzed as a continuous variable and as a categorical variable. In each case, the analysis was stratified based on the baseline value. The minimum detection value for hsTnT was 6 ng/L. Participants with undetectable hsTnT at baseline (<6 ng/L), were classified at follow-up as patients with incident hsTnT elevation (≥6 ng/L at 1 year) or patients with no change (<6 ng/L). Participants with baseline levels ≥6 ng/L, were classified at follow-up they into 3 mutually exclusive categories: decrease (decrease ≥50%), increase (increase ≥50%), or no change (change <50% from baseline). The minimum NT-proBNP detection value was 5 pg/mL, but the cutoff value for the analysis was 125 pg/mL, as it is considered the one that in clinical practice divides normal from elevated values. For patients with baseline NT-proBNP values <125 pg/mL, changes were classified as increase (increase ≥50% up to a value ≥125 pg/mL), decrease (decrease ≥50%), or no change (change <50% in either direction). For those with baseline NT-proBNP values ≥125 pg/mL, changes were also classified as increase (increase ≥50%), decrease (decrease ≥50% up to a value <125 pg/mL), or no change (change <50 %).

Regarding hsTnT, out of 9361 patients, 8828 and

8027 had baseline (median 9.4 ng/L and 99th percentile 48.6 ng/L) and 1-year (median 9.5 ng/L and 99th percentile 53 ng/L) measurements, respectively. A total of 21.2% of patients had undetectable hsTnT value at baseline; of these, 20.3% had a value ≥6 ng/L at 1 year. Among the 78.8 % of patients with hsTnT ≥6 ng/L at baseline, there was no significant change in 89.4%, decrease in 6.1% and increase in 4.5%. Increased hs-TnT was associated with male sex, older age, higher baseline SBP, and worse renal function. In patients with increased hsTnT, the mean annual change in glomerular filtration rate was -8.9 mL/min/1.73m², compared to an increase of 1.7 mL/min/1.73m² in those with decreased hsTnT. There was no variation in diuretic use throughout follow-up in those patients with decreased hsTnT. Belonging to the IT arm was more frequent in those in whom hsTnT increased (60.8%) than in those in whom it decreased (43.7%). In multivariate analysis, when considering clinical characteristics and the initial value of hsTnT, IT was associated with a significant 3% increase in biomarker values, but when considering the change in glomerular filtration rate, the difference between IT and ST disappeared. In mediation analysis, 96% of the effect of IT with respect to the increase in hsTnT was explained by the change in glomerular filtration rate.

Regarding NT-proBNP, 8836 had baseline measurements (median of 86 pg/mL, 38.2% with values ≥125 pg/mL) and 8040 had measurements at 1 year (median of 82 pg/mL, 37.4% with values ≥125 pg/mL). A total of 62.6% had values <125 pg/mL at baseline; of these, 11% had an increase, 17.7% had a decrease, and 71.3% had no significant change. Among the 37.4% of patients with NT-proBNP ≥125 pg/mL, 16.7% had an increase, 12.9% had a decrease, and 70.3% had no significant change. Increased NT-proBNP was associated with older age, worse renal function and lower SPB. Glomerular filtration rate declined in all groups, with only small differences according to baseline and direction of NT-proBNP change; but SBP reduction was higher in those with decreased NT-proBNP (>20 mmHg) than in those with increased NT-proBNP (about 11 mmHg). In patients with decreased NT-proBNP, diuretic use increased over the year. In contrast to hsTnT, IT was associated with a significant 10% decrease in NT-proBNP values, even when adjusting for changes in glomerular filtration rate. When adjusting for changes in SBP, the effect difference between IT and ST on NT-proBNP disappeared.

Both increases in hsTnT and NT-proBNP were associated with higher incidence of all-cause death and incidence of HF. In formal mediation analyses, changes in NT-proBNP explained 15.4% of the treatment effect on HF incidence, and 10.4% of the effect on the composite endpoint. In contrast, changes in hsTnT did not contribute to explain the treatment effect.

The substudy we are considering provides very interesting conclusions. It confirms that in the follow-up of patients with arterial hypertension, treatment has certain effects on the two most frequently used biomarkers, but they are not always as expected. Initially, both appear to be strongly linked to prognosis. But we have noted that the IT, associated with better evolution in the study, has a counterintuitive effect on hsTnT: in more than 80% of the cases there is no significant variation (when improved prognosis would have been expected to be associated with a reduction in the values), and, in fact, when hsTnT is considered as a continuous variable, its values increase. It is true that the increase is small (overall 3%), and that it is diluted when considering the variations in glomerular filtration rate. It could also be thought of the effect of IT by reducing diastolic BP (DBP) and thus generating coronary hypoperfusion, as an alternative hypothesis for the increase in troponin. However, in the multivariate analysis, the changes in DBP do not explain the changes in hsTnT. The increase is then the result of the treatment effect on renal function. Finally, this goes along with the fact that it is not possible to verify an independent influence of the biomarker on the prognosis in hypertension treatment. Therefore, is hsTnT useful for monitoring the effect of antihypertensive treatment?

In contrast, the effect of the IT on NT-proBNP is remarkable (10% decrease), independent of changes in glomerular filtration rate, and clearly associated with the effect on BP. In this case, we found no differences between what has been expected and what has been found. This decrease generates a reduction in wall stress and filling pressures. Moreover, in the mediation analysis, changes in the biomarker influence on patients' life course.

This analysis, then, sheds light on an infrequent phenomenon, but one which have just seen: the lack of absolute correlation between the treatment effects on surrogate endpoints and the clinical phenomena that such treatment aims at, and generates. A wake-up call to avoid automatic thinking, which does not consider the nuances and interactions between the different factors that condition prognosis.

Congenital long QT syndrome: how to avoid overdiagnosis. A report from the Mayo Clinic

Bains S, Neves R, Bos JM, Giudicessi JR, MacIntyre C, Ackerman MJ. Phenotypes of Overdiagnosed Long QT Syndrome. **J Am Coll Cardiol 2023;81:477-86. https://doi.org/10.1016/j.jacc.2022.11.036.**

Congenital long QT syndrome (LQTS) is characterized by a prolonged QT interval and ventricular arrhythmia primarily caused by adrenergic activation. Mean age of presentation is 14 years. The annual rate of sudden cardiac death (SCD) in untreated asymptomatic LQTS patients is less than 0.5%, a figure that rises to 5% in those with a history of syncope. There are 3 genes indisputably linked to LQTS, which cause the LQTS1, LQTS2 and LQTS3 forms: KCNQ1, KCNH2 and SCN5A, respectively, which are specifi-

cally activated by exercise (LQTS1), emotional stress (LQTS2) and sleep (LQTS3). The diagnosis rests on the ECG, where a QTc ≥480 msec fundamentally, and to a lesser extent also a QTc of 460 to 479 msec in the presence of arrhythmic syncope or cardiac arrest or torsade de pointes; and then a QTc of 450-459 msec in men, or alterations of the T wave, and even less bradycardia according to age are all elements to consider. Clinical (history of syncope with or without stress), familial (family members with a definite diagnosis of LQTS or a history of SCD in a first-degree relative <30 years), and genetic (verifiable pathogenic mutation) findings contribute to the diagnosis. All this information is condensed in the Schwartz score, and a score >3 (QTc ≥ 480 msec by itself already adds 3.5 points, the same as a pathogenic mutation; unexplained syncope, torsade de pointes or a QTc of 460-479 msec in the presence of syncope add up to 2 points) makes a diagnosis of LQTS. It is essential not to be mistaken in the diagnosis, because it implies, depending on the case and the type, the use of antiarrhythmic drugs, the implantation of a cardioverter defibrillator (ICD) or cardiac sympathetic denervation. That is why the publication we are commenting on is so interesting.

The authors, from the Mayo Clinic, explored the records of the arrhythmia clinic database from July 2000 to October 2021 and, of all patients admitted with a diagnosis of LQTS, identified those in whom finally that diagnosis was discarded. Among 1841 patients, this occurred in 290 (16%), 60% women with a mean age of 22±14 years. Twenty per cent of these patients had self-referred to the Clinic, the rest had been referred by a physician. The initial QTc was 504±39 ms. 80% were receiving beta-blockers, and 8% had received an ICD. In 67% of the cases LQTS had been diagnosed for a single reason, in the rest for more than one reason.

What were the reasons that led to an overdiagnosis of LQTS? The authors divided them according to the diagnostic criteria that we cited. Clinical causes were present in 38% of cases. As the sole cause or associated with others, vasovagal syncope was the most frequent. As striking data, mean QTc in the ECG after syncope was 487 msec; the one measured in the consultation at the Clinic was 422 msec. Another frequent clinical cause was a prolongation that was later interpreted as isolated or transient, for different reasons: panic attack, hypokalemia, hypoglycemia, drug action, etc. In 29% of the cases, the error was diagnostic, mainly due to including the U wave in the QT interval, or due to an erroneous measurement in cases of borderline intervals. There were also cases of QT prolongation overestimation in an epinephrine test, or in a tilt test (tests that are done in some cases to unmask occult LQTS). The diagnostic error was genetic in 17% of the cases. Among 290 patients, 196 had undergone a genetic test, which was initially positive in 68 (in two thirds of the cases for variants of uncertain significance, presumably linked to LQTS, and in the rest for "possibly pathogenic" variables). After the authors' analysis, the 68 cases were discarded, as they were deemed irrelevant, the relationship with LQTS was very doubtful, and occurred in the presence of an incompatible clinical condition. Finally, in 16% of the cases the error lay in a misinterpretation of the family history, for example SCD but in the context of an acute myocardial infarction, or a false diagnosis of LQTS in a close relative.

And how did rejecting the diagnosis affect the fate of the patients? Of those who were on beta-blockers, 84% stopped receiving them; of those with an ICD, 45% had it removed. A search of all patients and their vital records after passing through the Mayo Clinic revealed only 2 deaths from causes unrelated to LQTS.

The diagnosis of LQTS is of vital importance. This publication emphasizes the false positives of the diagnosis. Clinical and ECG diagnostic errors are frequent causes, and to a lesser extent a misinterpretation of family history or a misreading of genetic test results. Some keys to avoid misunderstandings are: a) adequately distinguish vasovagal syncope (generally preceded by characteristic prodromes) from arrhythmic syncope taking into account that in a vasovagal syncope there may be immediate QT prolongation, so subsequent ECG examination is fundamental; b) be sure not to include the U wave in the QT measurement; c) take into account electrolyte disturbances, drug use, clinical conditions, which may be associated with QT prolongation; d) interpret ECG changes in a clinical context; e) be very precise with the family history to avoid erroneous adjudications; f) it is fundamental to leave genetic diagnosis in the hands of experts who know how to deal with variants of uncertain significance and those associated with doubtful pathogenesis.

The authors emphasize that overdiagnosis generated in their population no less than 500 years of unnecessary drug treatment, and at least (corroborated by subsequent evolution) half of pointless ICD implantations. And it is clear that all this is true. Of course, we must also bear in mind that here we are talking about false positives. Unfortunately, there are no reports of false negatives, those LQTS carriers who never reached the diagnosis. And that error is as burdensome as the one analyzed here. In conclusion, remembering the existence of the syndrome, being alert to the possibility of finding it, and at the same time, ready to avoid misdiagnosis, seems to be the best advice.

Low QRS voltages: a finding with its own weight in the context of cardiac amyloidosis

Cipriani A, De Michieli L, Porcari A, Licchelli L, Sinigiani G, Tini G et al. Low QRS Voltages in Cardiac Amyloidosis: Clinical Correlates and Prognostic Value. **JACC CardioOncol 2022;4:458-70. https://doi.org/10.1016/j.jaccao.2022.08.007.**

The diagnosis of cardiac amyloidosis (CA) relies essentially on imaging methods and laboratory measure-

ments, which allow confirming or ruling out the presence of light chain (AL) amyloidosis or transthyretin (ATTR) amyloidosis based on their results. However, the ECG is still a gateway to diagnosis, and can provide useful information. A series of "red flags" have been indicated in the ECG that should make us suspect the pathology: atrial fibrillation, atrioventricular conduction disorders, P wave alterations, but fundamentally the patent of pseudoinfarction, and the presence of low QRS voltages (LQRSV) coexisting with increased wall thickness in the echocardiogram. And it is true that when, in a patient with heart failure and increased thicknesses on the echocardiogram, the ECG indicates the presence of LQRSV, the presumptive diagnosis of CA immediately arises. Now, what is the prevalence of this finding in patients with CA? What is its significance beyond guiding us in the diagnosis? A recent publication brings the answer to these questions.

This is a retrospective study carried out in 6 Italian referral centers for patients with CA, which included 411 patients (120 with AL, 291 with ATTR) diagnosed between the beginning of 2017 and the end of 2020. ECG, echocardiogram, laboratory tests that included the measurement of natriuretic peptides, and nuclear medicine studies. LQRSV was defined as QRS complexes with an amplitude ≤5 mm in all peripheral leads, including the positive and negative component in each complex. A QRS score was also considered by adding the amplitude of the Q, R and S components, in the limb and precordial leads.

Seventy-four percent of the patients were in sinus rhythm. Most were in FC I-II (65% in AL amyloidosis and 78% in ATTR); 169 patients (41%) presented LQRSV (55% with AL, 35% with ATTR, $p < 0.001$). The voltage-to-mass ratio was somewhat lower in the ATTR than in the AL CA, but without significant difference. The prevalence of LQRSV was higher in younger patients, in FC III, with higher values of natriuretic peptides, lower ventricular volume, and more pericardial effusion. In patients with AL CA, LQRSV were also associated with a pseudoinfarction pattern and greater wall thickness on echocardiography. In patients with ATTR CA, LQRSV were less common in stage I of the UK National Amyloidosis Center (NAC) classification, which is defined as NT-proBNP ≤3000 pg./mL and glomerular filtration rate ≥45 mL/min (the stage III corresponds to NT-proBNP > 3000 pg./mL and glomerular filtration rate < 45 mL/min, and stage II to intermediate values). In multivariate analysis, LQRSV were independently associated with younger age, more advanced FC, and higher natriuretic peptides in AL CA, and with pericardial effusion and less tricuspid annular plane systolic excursion (TAPSE) in ATTR CA.

The median follow-up was 33 months. In AL CA, the probability of survival at 40 months was 90% in the group without LQRSV, and 60% in the group with the finding ($p=0.003$). In multivariate analysis, LQRSV were independent predictors of cardiovascular death (HR 1.76; 95% CI 2.41-10.18; $p= 0.031$). In the ATTR CA, the probability of survival at 40 months was 95% in the group without LQRSV, and 80% in the group with the finding ($p=0.009$). In multivariate analysis, LQRSV were independent predictors of cardiovascular death (HR 2.64; 95% CI 1.82-20.17; $p= 0.005$). In this type of CA, the finding of LQRSV added prognostic value to the NAC classification only in stage II, not in I or III.

The refinement of diagnostic methods and the appearance of treatments that can modify the evolution of CA (an entity that until a few years ago had always an ominous prognosis), has led to greater awareness of its presence. There is undoubtedly more CA than we suspect; many cases of hematological disease, aortic stenosis, hypertrophic cardiomyopathy, HF with preserved left ventricular ejection fraction, present with amyloidosis. And, in this context, as we said, the ECG does not confirm or rule out CA, but it can act as an "alarm clock" that leads us to follow a diagnostic path. The publication we are commenting remarks the finding of LQRSV, by demonstrating its prognostic capacity. It is true that LQRSV are not a specific finding of CA: we can find them in chronic obstructive pulmonary disease, marked obesity, large pericardial effusion, and arrhythmogenic cardiomyopathy. For this reason, it is essential to interpret its presence in the clinical context and in light of other complementary studies.

LQRSV are more prevalent in AC AL than in ATTR. Different explanations can be put forward. The mechanisms involved in the gestation of LQRSVs may have to do with a decrease in the myocytes mass (due to necrosis because of a direct toxic effect of the myofibrils, or due to the action of circulating immunoglobulins) or to an infiltration phenomenon that reduces the electrical signal. In AL CA there is more myocardial edema and inflammation in earlier stages, and this may explain the high prevalence of LQRSV. ATTR CA occurs in older patients, with a higher prevalence of age-associated left ventricular hypertrophy, the presence of arterial hypertension or valvular disease, all plausible reasons to justify a lower presence of low QRS voltages. Undoubtedly, systematic cardiac magnetic resonance imaging would have contributed to explain the differences between the two entities. What is clear is that, present in half of the patients with A CAL, and in a third of those with ATTR CA, in both cases the LQRSV indicate sicker patients and have independent prognostic value. So, they should be considered, beyond the anecdotal, as an indicator of greater severity and therefore the need for more advanced therapy.