Prognostic Value of ECG in Diabetes Mellitus: The Danger of "Knowing Too Much"

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Type 2 diabetes mellitus (DM2) is a disease with an increasingly high prevalence leading to a rise in cardiovascular risk. Around 75% of patients with DM2 die with some sort of cardiovascular disorder, such as myocardial infarction or stroke. Indeed, the future increase in DM2, as a consequence of the rise in obesity with which DM2 is pathophysiologically associated, will be one of the main causes of the increase in cardiovascular death and disease in both developed and developing countries over the coming decades.[1] Furthermore, the presence of diabetes largely determines the treatment pattern of major cardiovascular diseases,[2] thus enhancing its role in cardiovascular disorders.

Since Haffner et al[3] noted that the cardiovascular risk in a patient with DM2 was similar to that of a patient without diabetes but who had suffered a myocardial infarction, it has been established that DM2 is associated with an equivalent risk to that of coronary heart disease ($\geq 2\%$ annually). In fact, the AHA[4] and the ESC[5] both consider DM2 as an equivalent of coronary heart disease and have recommended similar strategies and aims to those of secondary prevention. In spite of this consensus, however, certain controversy still exists about the cardiovascular risk of DM2.

This controversy stems from the studies by Evans et al,[6] who showed that the risk in patients with recently diagnosed DM2 is lower than that of persons who have already had a myocardial infarction. Since the publication of this report, frequent studies have appeared in support of one or other of the conclusions in an attempt to shed light on or take importance away from such a profound debate. The fact that a large part of the information published is in favor of a similar risk in both populations,[7] including among Spanish patients with diabetes,[8] has been of little use. Some authors have demonstrated something logical that is often not included in the debate: the importance of the time of

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evolution of DM2 in these patients and the clinical symptoms of coronary heart disease with which its risk is compared (angina, myocardial infarction, etc). It is logical to suppose that a longer development time of DM2 corresponds to a greater cardiovascular risk, just as we know that the risk for stable angina is not the same as the risk for unstable angina or myocardial infarction—which in turn is associated with various subgroups of risk, despite the fact that all are clinical manifestations of coronary disease, and thus require secondary prevention measures. Some authors have shown that the risk in DM2 is greater than that of patients diagnosed with angina and slightly less than that of patients with myocardial infarction, with which it equates after 7-12 years of follow-up.[9] Obviously, the follow-up period required to equate the risk of patients with DM2 with that of patients who have coronary heart disease varies and depends on concomitant diseases. We know that recently diagnosed DM2 in persons who have hypertension (and a vast number of diabetics do have hypertension) is associated with a similar cardiovascular risk to that of persons with previously known DM2 (VALIANT study)[10] and substantially increases the risk in hypertensive patients (VALUE study).[11]

Barr et al[12] recently reported on a prospective study of an Australian cohort of 10 428 patients who were followed-up for a mean of 5.2 years. They found that, after adjusting for traditional risk factors, mortality was higher among the patients with any type of glucose metabolism disorder than in normal persons. The patients with previously known DM2 had 2-fold mortality to that of persons who had recently diagnosed DM2, and that worsening of fasting glucose tolerance or impaired fasting glucose was associated with 50%-60% greater mortality than that of the general population. In fact, 65% of all cardiovascular deaths in this population occurred in persons who had some type of baseline glucose metabolism disorder, which gives some idea of the importance of maximizing cardiovascular prevention measures in these subjects. Nevertheless, and in spite of all this information, the doubts remain and the main consequence of this debate is that this confusion results in lack of action, and most patients with DM2 fail to have their many risk factors sufficiently controlled, with the resulting associated prognostic implications.[13]

Electrocardiography (ECG) is a simple, economic technique that has proven to be of great diagnostic and

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prognostic use in certain prevalent diseases, such as coronary heart disease and hypertension,[14,15] although its prognostic usefulness in other populations (eg, the general population) is rather more limited. However, little information is available about the prognostic value of ECG in patients with DM2, especially for the detection of asymptomatic coronary heart disease.[16] The Q waves of necrosis, abnormalities in repolarization, increases in voltage indicative of enlargement of the chambers and various arrhythmias are the electrocardiographic parameters most often associated with the prognosis in different populations.[13,14] The American Diabetes Association recommends an exercise stress test in patients with DM2 who also have ECG abnormalities compatible with coronary artery disease, more so if they have symptoms, although in this clinical setting other diagnostic techniques are more useful, such as a perfusion study, stress echocardiography or multislice tomography.[17]

In this issue of the *Revista Española de Cardiología*, de Santiago et al[18] analyze the prognostic value of ECG in a group of 221 patients with DM2 with no known cardiovascular disease, followed up for 5.9 years. They conclude that ECG abnormalities can predict the onset of cardiovascular events in patients with DM2 more precisely than traditional risk factors (hypertension, smoking, hypercholesterolemia, age, sex). The study is interesting and well carried out, for which the authors are to be congratulated, as are all those who strive to better their knowledge about the diseases they treat and about which they have to take daily decisions. I firmly believe that this is an initiative we should all applaud and encourage as far as we can.

The study is interesting and provides relevant conclusions, although certain of the results and assumptions are rather unexpected. Of surprise in the univariate analysis was that neither hypercholesterolemia nor smoking were associated with cardiovascular complications. I do not know whether the lack of consideration of the treatment followed by the patients (lipid lowering drugs, antihypertensive agents, etc) influenced the results, but I do believe it an important limitation not to take into account the effect of treatment over the years when determining the specific weight of each risk factor. Treatment with statins is known to reduce mortality by 30%-40% over a 5-year follow-up in patients with a high cardiovascular risk, such as diabetics; this would be more than sufficient to "dilute" any negative influence of cholesterol on mortality. The case of smoking is also difficult to understand, and the data provided by the authors fail to be of much help: in Figure 1 it appears that smoking has a protective effect (cardiovascular complications are less common in smokers, although only absolute figures are given rather than percentages), whilst Table 3 shows the risk to be slightly, albeit not significantly, increased in the smokers. How many continued without smoking and how many quit smoking during the follow-up is difficult to determine, which

might explain these contradictory findings with the information that we have about smoking being an important risk factor in patients with DM2, for both myocardial infarction and intermittent claudication. Moreover, of note is the fact that no consideration is given to the time during which the patients had had DM2 prior to inclusion in the study, given the already mentioned influence of this factor on cardiovascular risk.

One "false" or skewed conclusion that could be drawn from the study by de Santiago et al[18] is that the patients with DM2 could be divided into 2 large risk groups according to their baseline ECG: 1 group (normal baseline ECG) with such a low risk that no "aggressive" preventive measures are required and another high risk group (abnormal ECG), in whom "more aggressive" preventive measures should be taken. Although it is difficult to determine the exact complications depending on whether the patients had a normal or an abnormal ECG as presented by the authors, it is tempting to calculate the 10-year cardiovascular risk for both groups of patients. This "estimation" would mean that the group with no ECG abnormalities would have a 10-year risk of approximately 10%, well below the 20% that would be considered a high risk, and thus they would not need any aggressive preventive measures. Before succumbing to the temptation of doing these calculations, however, and thus of drawing conclusions, we should recall that 53 (24%) patients were lost to follow-up or refused it and that we do not, therefore, have information about the baseline ECG of these patients nor of whether they had any complications. That is to say, we cannot rule out the possibility that their baseline ECG was normal but that they had complications, which would alter our conclusions. Additionally, neither do we know about the ECG of the 191 diabetic patients who already had cardiovascular disease at the start of the study. This means, then, that the study provides the information that it does, which is not scarce nor of little importance, but at the same time no more than it can do given the inherent design limitations.

Accordingly, I do not wholly agree with the conclusion drawn by the authors that their findings could "be of practical interest to select populations in whom prevention should be more aggressive." This, together with the fact that in the text DM2 is considered another "independent cardiovascular risk factor," and not an equivalent to coronary risk, may lead the reader to adopt the false idea that only those diabetic patients who have baseline ECG abnormalities require strict control of cardiovascular risk factors, rather than all diabetic patients, as indicated in the current clinical practice guidelines and the data that back them up. Doing this would deprive a high-risk population of the necessary preventive measures, which would increase the cardiovascular complications in the more long-term future than the strict follow-up period of the study, as indicated by the fact that the ECG changed and became abnormal –with the prognostic implications demonstrated by the authors– with a rate of 4.4% at 1 year (44.4% at 10 years).

Scientific curiosity and the love of truth should lead us to continue searching for knowledge about diseases such as DM2, which will cause an important increase in cardiovascular risk over the coming decades, and for this we should be grateful for the study. However, we must avoid the risk of taking precipitated decisions based on partial and scarce information; that is, the danger of "knowing too much" or, better still, believing that we know enough. Just like Horne Fisher, the curious character in the tale of *The man who knew too much* by Gilbert K. Chesterton, we should act with caution and not take the first appearances as final, as often after an apparent evidence there may be other elements, not initially taken into account, that may substantially modify our first impression. The information provided by de Santiago et al[18] is important for a better understanding of the cardiovascular risk in patients with diabetes, but it is not enough to change our clinical practice. "Only the truth will make us free" and allow us to take the most suitable decisions in each case and for each patient. This study is 1 more step towards the scientific truth we pursue, but I believe that we are still far from uncovering it and we must avoid the danger of confusing it with illusions.

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