Being a cardiologist looking in the mirror of prognosis assessment: who am I, a wizard or a mathematician?

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Heart failure (HF) prognostic assessment has been, is and will be a major unmet need in the field of medicine. Indeed, it is never precise enough and never enough specific at an individual patient level. As a matter of facts, when a HF patient, or their relatives, asks a medical doctor to estimate his prognosis, he became something between a wizard who looks into a glass-ball and a mathematician who applies artificial intelligence produces and complicated algorithms. For years we have been looking for a magic number able to predict the future. We started from left ventricular ejection fraction - the lower the worst -, and we end up understanding that HF patients with preserved ejection fraction carry a worst prognosis than their reduced ejection fraction counterparts. We than looked at natriuretic peptides, discovering how they can be very good for diagnosis, but very poor for prognosis. From exercise evaluation we obtained the NYHA classification, which is however very subjective and imprecise. Putting our HF patients on a bike, we derived metabolic parameters as peak oxygen intake (VO_2) and ventilation over CO_2 production (VE/VCO_2) slope which have independent and additive prognostic capacity [1]. At this regard, D. Mancini in the 80' suggested a fix peak VO_2 cutoff of 14 ml/min/kg for poor and good prognosis, as a black-and-white issue [2]. This value has been reduced to 12 ml/min/kg in patients treated with β-blockers [3]. The prognostic power of peak VO_2 is thereafter remained but its meaning has changed. Indeed, reanalyzing the data of the MECKI score register which now includes >8000 low ejection fraction HF patients who underwent cardiopulmonary exercise test, we can group cases according to when the test has been done in first place: before 2003 (n=1224), between 2003 and 2008 (n=2056), between 2009 and 2014 (n=3269), and between 2015 and 2021 (n=1511). As reported in the graph (Figure 1), the prognostic meaning of our metabolic values changes from patients studied before 2003 and those studied between 2015 and 2020. When we presented a similar analysis a few years ago, a very interesting accompanying editorial by Levy and Dardas [4] showed that, although in many studies a correlation between peak VO_2 and prognosis was clear, in the overall picture it was much less evident. Of note, the prognosis improved in most recent studies confirming the concept that the prognostic meaning of peak VO_2 varied with time (Figure 2). So, albeit peak VO_2 is the so called "gold standard" for cardiovascular performance evaluation, its prognostic meaning is time

dependent and, honestly, less clear. The same applies to VE/VCO_2, prompting a reflection on how the robustness of all our cutoffs may rust over time.

The HF population is a *potpourri* of different phenotypes, etiologies, comorbidities and treatments. Given this complexity, the scientific community built several scores in the last years. At the beginning, they were used for definition of a disease when a single clear diagnostic element was not present. We used, for examples, a multivariable score to define the presence of cardiac involvement in case of rheumatic fever, but the same concept has been applied to a variety of diseases. Then, scores were introduced for prognosis. I count >100 different scores in chronic HF meaning that none of them was 100% perfect. As a matter of facts, despite performing better that the single variables, scores are rarely used in clinical practice. Why? A possible explanation is that several numbers, often not immediately available, are needed to build a score. The modern medicine, which can provide us everything stat, will probably overcome this limit, but how much it will immediately increase the utilization of scores remains to be demonstrated (or foreseen by a wizard!). Moreover, scores suffer for the same time-dependent effect we previously described for peak VO_2. If we calculate a MECKI score of 5, which means originally a 5% risk of the combined event of cardiovascular death, urgent heart transplant or left ventricle assist device implantation, we move from a true observation of events in 14% of cases, to 6.3%, 5.4% and 4.5% events at two years in patients evaluated before 2003, between 2003 and 2008, between 2008 and 2014 and between 2015 and 2020, respectively (figure 2).

One of the major negative issues when looking for a prognostic parameter for HF prognosis, either a number derived from a single variable or from a score, is that it provides an instantaneous picture and we pretend that this evaluation keeps its meaning intact during the following months or years. However, as we well know from clinical practice, with time several events can occur, treatment and follow-up strategies may change, and intercurrent events may happen, such as anemia, atrial fibrillation, major arrhythmias or a new acute cardiovascular accident. Clearly, at this point of the story, the original picture does not apply to the new condition anymore. Moreover, with time HF may spontaneously improve or deteriorate, and this is precisely the reason

why, more than the value of variables taken in a single timepoint, their dynamic changes assume the greatest importance. This, for instance, has been demonstrated for the MECKI score population [5].

In the present issue of the European Journal of Preventive Cardiology a new score for mortality risk prediction after acute myocardial infarction is presented by Wohlfart et al [6], performing a little better than the previous GRACE score [7]. This is a very well done and interesting report, but - somebody may argue – we are just dealing with another score that nobody will use. However, in this new score, named the PragueMi score, HF signs and symptoms are included and, most importantly, they are not evaluated only as an instantaneous picture of signs and symptoms, but also the HF signs and symptoms evolution in the last two weeks. So, albeit in an informal way, the concept of HF evolution or as it is named in a more fashion way "HF trajectory" is included. This may be seen as a minor change, but it is, in our opinion, extremely important since it introduces in HF scores the concept that dynamic changes over the time may play a major role in HF prognosis. In a time when wizards are lacking in many areas, this represents a significant step forward for a scientific and accurate prognostic evaluation of our patients.

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Figure legend

Figure 1: Changes of risk according to time of enrolment in the current MECKI score population.

Figure 2:

Mortality rate vs. peak VO_2 in 6 published trials. In each trial a strong correlation between mortality and peak VO_2 was observed. However, considering all studies together the correlation was weaker. The reason is likely the different time of the studies as deducible from the year of studies publication. Modified from Levy and Dardas [4] with permission.

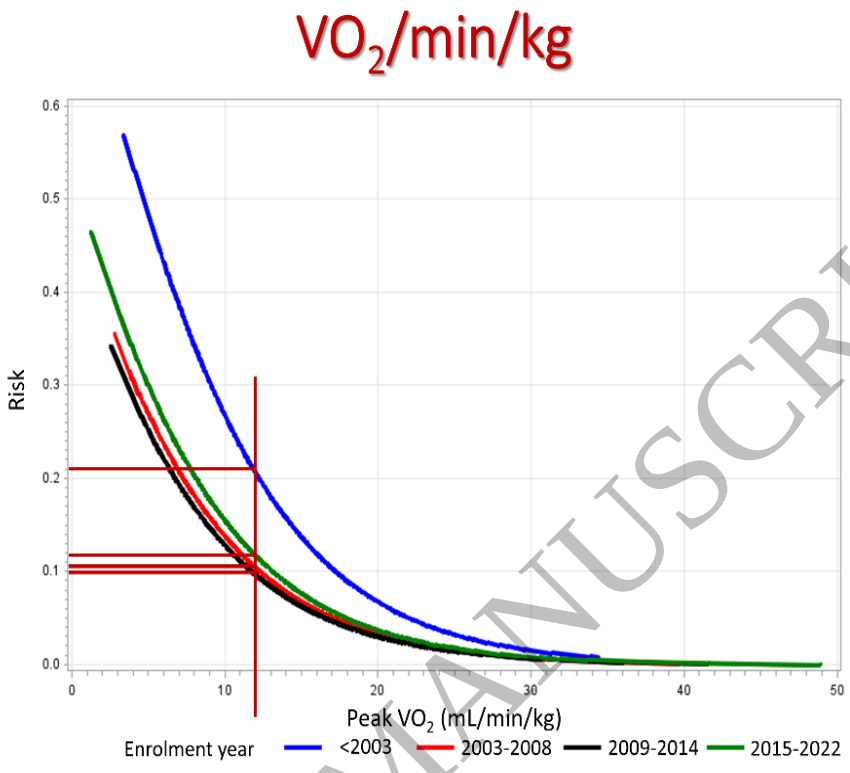

Figure 1
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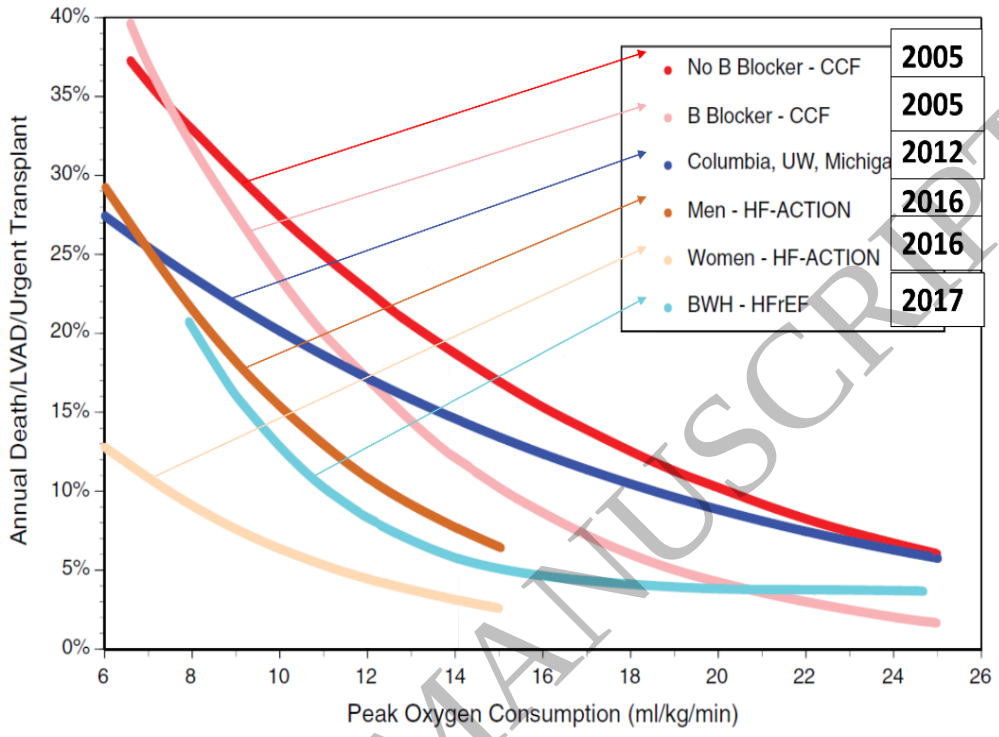

Figure 2
170x96 mm (x DPI)