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CARDIOPULSE

The Future Treatment of Heart Failure?

Five imaginative predictions for the treatment of Heart Failure by 2028 are proposed by Milton Packer

What will the treatment of heart failure look like in 2028? Tackling such a question would seem impossible or (at the very least) whimsical. Yet, it is always enjoyable to wonder about a world that does not yet exist. Certainly, the intent of making predictions is not to demonstrate one's intellectual prowess. Instead, the goal is to luxuriate in the sheer power of human imagination. Yet, there is one caveat. Realizing that someone might actually read this article a decade from now, it is certainly tempting to make predictions that are so vague that they cannot possibly be shown to be wrong. I will resist that temptation.

Prediction # 1

Heart failure with a preserved ejection fraction will be broken into distinct phenotypes. The most common phenotype—that associated with obesity—will be treated as a neurohormonal disorder.

Our understanding of heart failure with a preserved ejection fraction is changing rapidly. We now understand that most patients with the disorder are obese, and in those individuals, obesity drives both sodium retention and plasma volume expansion. At the same time, the distensibility of the ventricle is impaired by the encroachment of epicardial fat into the pericardial space, and by its association with myocardial fibrosis. Recent work suggests the interplay of several endogenous hormonal factors in the genesis of these derangements, including the adipokines (leptin and adiponectin) and the sodium-retaining and profibrotic actions of aldosterone and neprilysin. It seems likely that sodium-glucose cotransporter 2 (SGLT2) inhibitors can also ameliorate the plasma volume expansion, visceral adiposity, and myocardial fibrotic processes. I predict that combinations of inhibitors of leptin, aldosterone, neprilysin, and SGLT2 will be the mainstay of the treatment for many of these patients. These drugs will have a major impact in reducing the morbidity and mortality of this disorder.

It is also likely that other distinct phenotypes of heart failure with a preserved ejection fraction will be individually characterized, including those involving the accumulation of collagen and amyloid in the heart, which can act to limit the ability of the ventricle to dilate in response to sodium retention and plasma volume expansion. These may be amenable to treatments that enhance the degradation of inelastic fibrils, and thus restore ventricular distensibility. The pericardium may also act as an important constraint in some individuals, suggesting the possibility that a limited pericardial resection may allow the elderly heart to enlarge sufficiently to maintain its normal function. Surgical procedures might also include ways of enhancing the lysis of epicardial fat, whose inflammation may play a role in promoting fibrosis of the underlying myocardium.

Prediction # 2

The next wave of new pharmacological agents for heart failure with a reduced ejection fraction will focus on drugs that induce the cellular housekeeping process of autophagy.

We have made enormous progress in the treatment of patients with chronic heart failure associated with a reduced ejection fraction, and current trials may yet identify additional agents that can reduce morbidity and mortality. Yet, potentially the most important molecular pathway for modulating the evolution of heart failure is autophagy. Autophagy is the biological process that cells use to degrade cytoplasmic contents for quality control, survival for short-term energy needs, catabolism, and recycling. It plays a critical role in cellular remodelling, and impairment of its function prevents cells for adapting to genetic and environmental stress. Abnormalities of this cellular housekeeping process appear to underlie the genesis of many chronic and progressive disorders, including cancer, chronic inflammatory diseases, and neurodegenerative disorders. Dysfunction of autophagic flux leads to the accumulation of cellular debris and its potentially toxic consequences.

Importantly, an insufficient or dysfunctional response of the autophagosome-lysosome pathway to pressure or volume overload appears to contribute to maladaptive cardiac remodelling and to heart failure. Autophagy can promote the engulfment and degradation of injured mitochondria (a process known as mitophagy) and can prevent the accumulation of unwanted lipids, misfolded proteins, and other deleterious by-products. Consequently, the enhancement of autophagy may be critical in minimizing oxidative stress, inflammation, and cellular injury and allowing adaptive reshaping of cardiomyocyte structure and function. Parenteral agents that induce autophagy have been developed, and orally-active (and potentially organ-specific) agents are on the horizon.

Prediction # 3

Unless major changes take place in the pricing or uptake of new pharmaceuticals, drug development for heart failure will cease. The risks and expense of new drug development for these patients will exceed the likelihood of a meaningful return on investment.

Regardless of our skills in elucidating the biological pathways that drive the development of chronic heart failure, the acceptance of novel drugs by physicians in the community has been poor, and the lack of implementation is likely to continue unless major structural changes are made in the delivery of health care to the millions of people with chronic diseases. The life expectancy of most patients with heart failure is currently limited not by the lack of effective treatments, but a lack of access to drugs that are known to be effective. The slow and ineffectual uptake of mineralocorticoid receptor antagonists and neprilysin inhibitors by physicians who treat most patients with heart failure offers us an important reality test.

The cost of developing a new drug for chronic heart failure is enormous, given the need for long-term large-scale randomized controlled clinical trials to demonstrate efficacy and safety. No surrogate endpoints have emerged, and none are likely to be identified in the future. As a result, a sponsor must make a substantial financial commitment that carries a major risk of failure. Such a commitment is feasible only if a drug—once shown to be successful—will be rapidly adopted in clinical practice. However, our current system of healthcare delivery discourages (rather than encourages) the adoption of new pharmaceutical agents, regardless of their utility.

To hedge against the risk of slow adoption, pharmaceutical companies overprice their products in the hope of generating an immediate financial return that will offset the costs of drug development. This overpricing is then countered by healthcare systems that place administrative impediments to further slow the adoption of the new treatments, thus motivating even higher initial prices by the manufacturer. The current model of resource allocation will simply not allow premium pricing for new drugs for common diseases that are typically treated (even unsatisfactorily) with inexpensive generic agents. As a result, sponsors will direct their efforts to rare diseases that can be genetically characterized and targeted in the hope that someone will agree to pay.

The development of new drugs for common diseases in the community—including heart failure, diabetes, and arthritis—will not be financially viable and will cease. We have already nearly stopped developing novel drugs for acute heart failure; the shutting down of innovative efforts in chronic heart failure is simply the next step.

Prediction # 4

Most patients with chronic heart failure will be managed by specialist practitioners who will not be cardiologists and may not be physicians.

The number of patients with chronic heart failure worldwide is staggering and will continue to increase as the population ages and patients survive ischaemic injury that was previously lethal. Furthermore, the drugs being currently developed for the treatment of many common diseases (cancer, diabetes, and arthritis) are likely to further increase the risk of heart failure. At the same time, the complexity of managing patients with heart failure has grown to the point that such a task is currently out of the reach of most physicians.

The appropriate treatment of patients with a reduced ejection fraction in the current era—which will be multiplied by the complexity of managing patients with a preserved ejection fraction in the future—cannot be achieved by the available pool of cardiologists. There are too few of us, and our attention span for caring for patients with chronic diseases is limited. Once the diagnosis is made, the clinical challenge is to orchestrate a wide range of therapeutic options in a timely and skilful manner. This can best be done by specially-trained trained nurse practitioners who will focus exclusively on patients with chronic heart failure.

In the next decade, healthcare systems will need to truly define the role of a physician along with that of other healthcare professionals. For most chronic disorders that require complex and ever-changing therapeutic regimens, the diagnostic skills of the physician may not be needed and may be best directed elsewhere.

In my own experience, nurse practitioners are often far better than many cardiologists at titrating appropriate drug therapy for heart failure. My confidence in them greatly exceeds my confidence in non-specialists who typically care for most patients with heart failure in the community.

For many chronic diseases requiring complex long-term management, a physician-based healthcare delivery system may no longer be feasible or even desirable.

Prediction # 5

Cell- and gene-based treatments will fail, but because of advances in mechanical devices that provide effective circulatory support, no one with adequate financial resources will die of heart failure involuntarily.

Although cardiologists are understandably fascinated with the potential of regenerative therapy, this approach has not generated successes outside of cardiology, and the challenges of regeneration in the heart are much greater. The obstacles are formidable. We do not know what to deliver; we do not know how to do it; we do not know how to retain it in the heart; and we certainly cannot control what happens even if we were to generate new cells. For all we know, the new cells that we create will turn into fibroblasts rather than functional cardiomyocytes; that would be the ultimate alchemist's nightmare!

Even if we were to be successful, how many patients would be eligible for such an intervention? Cell- or gene-based treatments are not likely to be either inexpensive or non-invasive, thus dramatically limiting their applicability to most patients with chronic heart failure. We cannot currently ensure that most patients with heart failure receive treatment with a mineralocorticoid receptor antagonist, which is given once daily by mouth and is incredibly affordable. Imagine performing an invasive procedure (perhaps even multiple times) to deliver an enormously expensive product with a skill that few can provide and even fewer can afford. It just will not happen.

However, the talents of our colleagues in engineering should not be underestimated. They have shown an incredible ability to deliver devices that can provide reliable circulatory support, and the safety and practicality of these machines advances every year. It seems likely that long-term ambulatory circulatory support with a mechanical device can be achieved both effectively and safely, at least for the few with the resources to pay for them. The success and cost of these devices will dramatically increase the chasm between those with and those without the financial wherewithal to pay.

I imagine—within the next 10 years—no wealthy person will ever die of heart failure, unless they willingly make the decision to do so. Cardiac immortality will be within reach of the very few who are able and would elect to make that intriguing moral choice.

So here are my five predictions for 2028. How many will prove to be correct? That is not the question that matters. The choices we need to make for the next decade is not whether cardiology advances, but whether society as a whole will benefit from our innovation. I have no doubt about the former, but I am deeply concerned about the latter.

The inequalities in healthcare are so vast that we may soon be able to make some very wealthy people live forever—but to what end?

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Conflict of interest: M. Packer has recently consulted for Admittance, Amgen, AstraZeneca, Bayer, BioControl, Boehringer Ingelheim, Cardiorentis, Celyad, Daiichi Sankyo, Novartis, NovoNordisk, Relypsa, Sanofi, Takeda and ZS Pharma.

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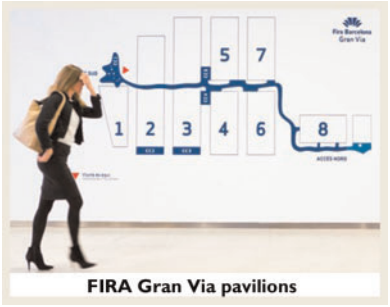
ESC Annual Congress 2017 news. . . .I

ESC Congress Barcelona 2017

Probably the best ESC Congress-ever, took place in the FIRA Gran Via, Barcelona in 2017, a modern very functional Congress Centre with eight pavilions



FIRA Gran Via pavilions

Photo © ESC

FIRA Gran Via

The recent ESC Congress in Barcelona brought together more than 31 700 healthcare professionals from 153 countries to the beautiful capital of Catalonia. Barcelona is certainly a very creative, modern, and cosmopolitan city of Spain. The large FIRA Centre provides excellent congress facilities. The FIRA Congress Centre is well located and the logistics including transport facilities such as a well-functioning metro network and affordable taxi transfer from the city to the Congress Centre made access much easier. The congress attracted more than 500 journalists and the coverage of the scientific news in the more traditional media press and television, and also in the new social media was excellent. Therefore, the exciting scientific news presented at the Congress was broadcast not only to the cardiovascular community but also to the public, which is very important for preventing heart disease and for optimal care of cardiac patients.

The ESC Congress in Barcelona is the world's largest cardiovascular congress with over 500 expert sessions and more than 4500

abstracts contributing to the advancement of cardiovascular medicine worldwide.

The ESC Congress Programme Committee chaired by Professor Stephan Achenbach, Germany and the ESC staff succeeded in organizing outstanding days in Barcelona. The theme of the meeting was '40 years of PCI' and there were several interesting sessions on the history of PCI and new interesting discoveries in the field of coronary angioplasty. Also live-in-a-box cases and exciting panel discussions of great educational value were contributing to a lively atmosphere. This year there was a large area showing interesting new tools for digital health—a rapidly expanding area.