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PILLARS OF EVIDENCE SUPPORT FUTURE HEART FAILURE DISCOVERIES

СТЪЛБОВЕТЕ НА ДОКАЗАТЕЛСТВАТА СА ГАРАНЦИЯ ЗА БЪДЕЩИТЕ ОТКРИТИЯ ОТНОСНО СЪРДЕЧНАТА НЕДОСТАТЪЧНОСТ

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Dr. Marc A. Pfeffer, a graduate of Rockford College in Rockford, Illinois, received both his doctorate in physiology and biophysics and his medical degree from the University of Oklahoma in Oklahoma City. He completed his internship, residency and clinical fellowship at the Peter Bent Brigham Hospital, Harvard Medical School in Boston. Dr. Pfeffer is currently the Distinguished Dzaou Professor of Medicine at Harvard Medical School, and Senior Physician in the Cardiovascular Division at the Brigham and Women's Hospital in Boston. A noted researcher, Dr. Pfeffer, along with his late wife, Dr. Janice Pfeffer, and Eugene Braunwald MD, is credited with



Д-р Марк А. Пфeфeр e възпитаник на Рокфорд Колидж в Рокфорд, Илинойс, получава докторска степен по физиология и биофизика и медицинска степен от University of Oklahoma в Оклахома Сити. Завършва стажа, докторантурата и клиничната си специалност в болница Harvard Medical School in Boston, Harvard Medical School in Boston. Понастоящем д-р Пфeфeр e високоуважаван и ценен професор по медицина в Harvard Medical School и старши лекар в Отделението по сърдечно-съдови заболявания в Brigham and Women's Hospital в Бостън. Известен изследовател, д-р Пфeфeр, съвместно с покойната си съпруга – д-р Janice Pfeffer, и с д-р Eugene Braunwald, се считат за

introducing the concept that angiotensin-converting enzyme inhibitors (ACEIs) could attenuate adverse ventricular remodelling following myocardial infarction and that this use would result in a prolongation of survival and other clinical benefits. Since this initial discovery, he has had a principal role in several practice-changing clinical outcome trials. An internationally recognized expert in the field of cardiology, Dr. Pfeffer was recognized by Science Watch as having the most 'Hot Papers' (highly cited) in all of clinical medicine and was listed as one of the highly influential biomedical researchers of 1996-2011 in the European Journal of Clinical Investigation. He is the recipient of the William Harvey Award of the American Society of Hypertension, the Okamoto Award from Japan's Vascular Disease Research Foundation, the American Heart Association Clinical Research Prize and the James B. Herrick Award. The Distinguished Scientist Awards from both the American Heart Association as well as the American College of Cardiology. The Lifetime Achievement Award from both the Heart Failure Society of America and the Heart Failure Association of the European Congress of Cardiology. The Gold Medal Award from the European Society of Cardiology in 2018. Dr. Pfeffer has Honorary Doctoral Degrees from Sahlgrenska Academy and the University of Gothenburg, Sweden, from the University of Glasgow, Scotland and from UCLouvain University in Belgium.

основоположниците на концепцията, че инхибиторите на ангиотензин-конвертиращия ензим (ACEi) могат да намалят неблагоприятното камерно ремоделиране след миокарден инфаркт и че подобна употребата би довела до удължаване на преживяемостта и други клинични ползи за болния. След това първоначално откритие той има основна роля в няколко клинични изпитания, променящи практиката. Международно признат експерт в областта на кардиологията д-р Пфeфeр e титулуван от Science Watch за автор на едни от "най-горещите" статии (силно цитиран) в цялата клинична медицина и e посочен като един от биомедицинските изследователи през периода 1996-2011 г. с най-силно влияние според European Journal of Clinical Investigation. Той e носител на редица награди като: "Уилям Харви" на Американското общество за хипертония, "Окамото" на Японската фондация за изследване на съдовите заболявания, наградата на Американската асоциация за сърдечни заболявания и наградата "Джеймс Б. Херик". Лауряд e на наградите за отличен учен както на Американската сърдечна асоциация, така и на Американската колегия по кардиология. Присъдена му e награда за цялостна дейност от Американското общество за сърдечна недостатъчност и Асоциацията за сърдечна недостатъчност на Европейския конгрес по кардиология, както и златен медал от Европейското кардиологично дружество през 2018 г. Д-р Пфeфeр има почетни докторски степени от Академията Sahlgrenska и Университета в Гьотеборг, Швеция, от Университета в Глазгоу, Шотландия и от Университета UCLouvain в Белгия.

The fundamental principles regarding the major advances in the use of pharmacologic agents to prevent and treat heart failure are deeply rooted in the results of robust clinical outcome data generated from major randomized controlled clinical trials. This rich heritage of outcome trials has provided the critical data used to progressively improve clinical practice and prognosis. The primary efficacy endpoint of the initial placebo-controlled trials was rates of death from all causes. The demonstration of a survival benefit with the angiotensin converting enzyme inhibitor (ACEi) enalapril in two trials established it as a foundation therapy for patients with heart failure [1, 2, 3]. The concurrent demonstration of a reduction in both the risk of death as well as the development of symptomatic heart failure in patients experiencing an acute myocardial infarction with other agents in this class solidified broad use ACEi for both the management and prevention of heart failure [4, 5, 6].

The next major therapeutic advance, use of beta blockers in patients with symptomatic heart failure and reduced ejection fraction (HFrEF), was at first counter-intuitive. Indeed, the prevailing concept at the time was that augmented sympathetic activity was a necessary compensation for the impaired heart and that inhibition would exacerbate the deteriorated pathophysiologic state. It is in this context, that the three major independent placebo-controlled beta blocker mortality trials, each demonstrating a greater than 30% reduction in rates of death, should be considered both field advancing as well as concept expanding [7, 8, 9]. The impressive magnitude of the improvement in survival was even more remarkable since these major reductions in rates of death were for the most part, achieved in those already benefiting from use of an ACEi. This “on top of” additive approach to testing potential therapeutic advances became an important hallmark of heart failure clinical trials.

The next major advance in the care of patients with HFrEF was the demonstration that an aldosterone antagonist could also improve prognosis. Although the Randomized Aldactone Evaluation Study (RALES) trial showed a clear survival benefit with the use of spironolactone on top of an ACEi, this placebo-controlled trial was conducted before there was definitive evidence of a concomitant survival benefit with beta blockers [10]. As such, there was only a small proportion of these patients on both an ACEi and beta blocker at baseline. This resulted in a lingering question as to whether the observed benefit of spironolactone was a true advance “on top of” the two established therapies. This concern was partially addressed in Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), with the demonstration of a survival benefit of eplerenone, another mineralocorticoid antagonist, in a high-risk myocardial infarction population [11]. The demonstration of a reduction in

deaths with the use of eplerenone was achieved with substantial use of both ACEi and beta blockers at baseline. Although highly supportive of the three-drug regimen, many wanted more direct evidence of the safety and benefits in patients with symptomatic heart failure before adopting this triple therapy approach. This apparent data gap was appropriately filled with the results of the EMPHASIS-HF trial that showed a clear benefit of the addition of eplerenone in reducing the composite endpoint of cardiovascular death and hospitalizations for heart failure “on top of” both ACEi and beta blockers in a population with symptomatic heart failure [12]. Treating physicians were reassured that the three proven classes of pharmacologic therapies for HFrEF when used collectively resulted in the best clinical outcomes.

This pattern of acknowledging aspects with sufficient uncertainties to warrant a focused major randomized trial has resulted in expansions in the evidence-based direction for clinical practice with international guidelines being updated and modified to reflect the meaningful advances in patient care. This high bar of testing new therapies “on top of” optimal care with other proven agents also applied to the trials of electrophysiologic devices such as implantable cardiac defibrillator and cardiac resynchronization therapy [13, 14, 15]. As a result of the comprehensive background therapies in the pivotal trials, the favorable impact demonstrated by use of these devices in the appropriate patient populations had more immediate clinical relevance.

With these sequential improvements in therapies, estimated mortality rates for stable patients with heart failure declined. As such, the sample size needed for a randomized trial of a new intervention to have sufficient statistical power using death as primary outcome became prohibitively large. Recent trials of stable patients with symptomatic heart failure and reduced ejection fraction generally adopted the composite of cardiovascular death and hospitalization for heart failure as a more feasible though still clinically relevant and important primary outcome measure, with deaths as a key secondary measure [16].

The heart failure community maintained these high clinical outcome standards for efficacy because of an earlier lesson that surrogate outcomes, although attractive in drug discovery and development, proved to be unreliable in terms of predicting clinical outcome responses to a seemingly promising therapy. The inotropic agents by definition improved contractile state and thereby measures such as ejection fraction and abnormal hemodynamic variables. Surprisingly, and regrettably, the larger placebo controlled clinical outcome trials testing safety and efficacy of these positive inotropic agents demonstrated worrisome increases in rates of death with the active therapy [17, 18, 19]. In this setting, prognosis improving effectiveness and

safety have been sustained hallmarks of major heart failure trials.

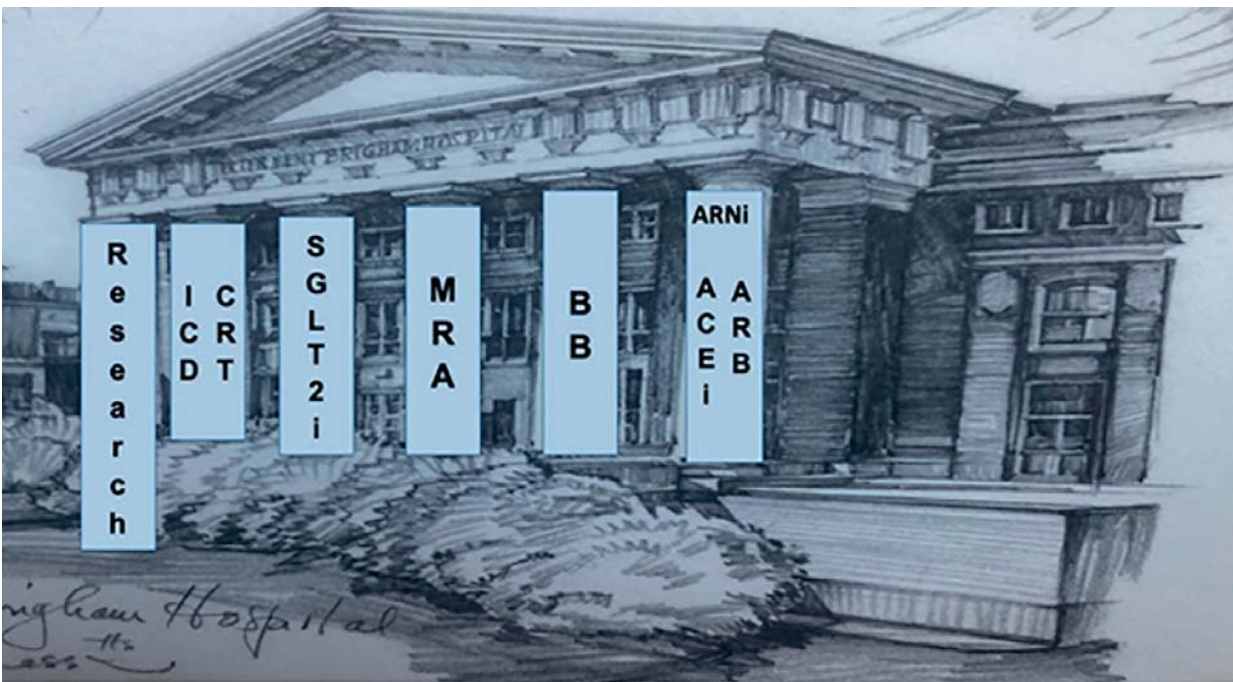
As these high standards were maintained, it is notable that in the past 7 years two new classes of heart failure therapies have emerged with sufficient clinical outcome data further improving prognosis to warrant updated guideline recommendations [20, 21]. A novel combination of an angiotensin receptor blocker with a neprilysin inhibitor (ARNI) more specifically, valsartan and sacubitril, was proven in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) to be superior to enalapril in reducing the primary composite of cardiovascular death and hospitalizations of heart failure [22]. The effectiveness of sacubitril/valsartan over a proven dose of the ACEi was also demonstrated for rates of cardiovascular and deaths from all causes. This was the first major clinical outcome trial in heart failure generating the evidence to recommend use of one agent, sacubitril/valsartan as a replacement (either an ACEi or ARB) rather than an add on. In effect, to obtain the benefit, an effective therapy had to be stopped to start an even more effective one. This advance in heart failure treatment strengthened one of the three existing pillars to improve outcomes (Figure 1).

Even more recently, a new class of agents, sodium glucose cotransporter-2 inhibitors (SGLT2i) have robustly demonstrated that the addition of a fourth

agent can lead to even further major incremental improvements in outcomes of patients with heart failure. This important discovery has serendipitous origins. In response to regulatory concerns about new classes of glucose lowering drugs for the treatment of type 2 diabetes possibly augmenting risks of myocardial infarction, large outcomes trials had to be conducted to provide some assurance of cardiovascular safety [23]. More specifically, placebo-controlled trials were required to show that the upper limit of the 95% confidence interval for the composite of cardiovascular death, myocardial infarction and stroke could be used to exclude 30% harm.

This led to a spurt of major randomized trials of the new potential agents developed to reduce glucose which now had to target patients with diabetes plus additional risk enhancing factors in order to have sufficient clinical events to establish the required safety confidence interval. In this process of assessing cardiovascular safety, several SGLT2i showed a surprising reduction in reports of heart failure hospitalizations [24, 25, 26]. It must be acknowledged that heart failure was not a component of the regulatory cardiovascular safety endpoint and that the baseline status of heart failure with respect to left ventricular ejection fraction was not carefully evaluated. Nevertheless, the signal of a potential beneficial impact on heart failure events could not be ignored.

With this impetus, major randomized trials of SGLT2i were promptly launched in patients with heart



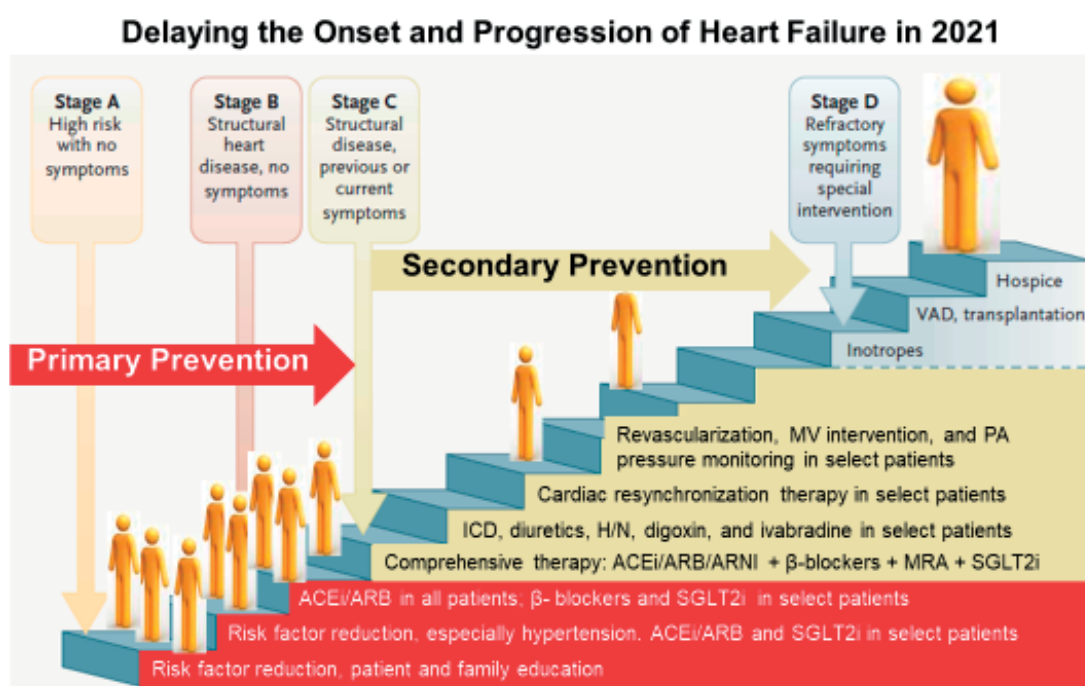
Legend: The framework for progression of heart failure therapies is firmly supported by four classes of pharmacologic agents. One firm pillar for electrophysiologic devices and, most importantly, one pillar for future discoveries that build on prior existing advances.

Figure 1

failure to test whether these agents would improve prognosis- not glucose lowering in patients with heart failure. The demonstrations of impressive (25%) reductions in cardiovascular deaths and hospitalizations for heart failure in patients with reduced ejection fraction “on top of” the other three proven effective classes of therapies make use of this fourth pharmacologic class a true advance [25, 26]. The magnitude of these incremental benefits has generated enthusiasm for “quadruple therapy” as the new standard of care [27]. Imputed calculations of combined use of an ARNI, beta-blocker, mineralocorticoid receptor antagonists and SGLT2i offer estimates that use of this comprehensive 4 agent approach could potentially half the morbidity and mortality anticipated for those with HFrEF [28] (Figure 1). The treating physician now has four generally additive classes of therapies to ameliorate the burdens and risks of heart failure, the so called four pillars. For appropriate patients, electrophysiologic devices such as an automatic internal defibrillator and or cardiac resynchronization therapy may offer incremental benefits as the fifth pillar [13, 14, 15]. In my view, it is the sixth pillar for research and education offering the path for future discovery of even more effective preventive and treatment options. The recent SGLT2i experience provides a vivid example of the potential for undiscovered

therapies to promptly go from promising to effective additional prognosis improving “on top of” previously proven agents. We still have much to learn about how broad their favorable impact will be on additional populations. In the near future, we eagerly await the results of two major trials in heart failure with preserved ejection fraction. Pending those results, one could anticipate additional trials aimed at prevention of heart failure in at risk populations.

With multiple effective agents available to reduce morbidity and mortality in those with heart failure, future efforts will also be directed to optimize the benefits while reducing the inherent risks of these pharmacologic agents. Advances in phenotyping, omics, biomarkers and genetics will be incorporated into clinical decision making, ushering in the long-awaited precision medicine approach. The solid historical foundation of robust clinical outcome trials targeting true advances “on top of” existing therapies will serve to continue to improve the opportunities to prevent and treat heart failure (Figure 2). The sixth pillar of new discoveries coupled with more precision and improved implementation ensues that progress will continue in the quest to reduce the personal and societal burdens of heart failure.



Legend: Stages of heart failure and treatment options for systolic heart failure. Stages A+B suggest treatment regimens before the actual appearance of symptomatic heart failure. Adapted from (From Cleland JGF, Pfeffer MA, Clark AL, Januzzi JL, McMurray JJV, Mueller C, Pellicori P, Richards M, Teerlink JR, Zannad F, Bauersachs J. The struggle towards a Universal Definition of Heart Failure-how to proceed? *Eur Heart J*. 2021 42:2331-43). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; H/N, Hydralazine/Isosorbide dinitrate; ICD, implantable cardioverter-defibrillator; SGLT-2, sodium-glucose co-transporter 2; VAD, ventricular assist device. Referral to multidisciplinary group should be considered for stages C+D. Vericiguat and omecamtiv mecarbil may be considered for selected advanced patients.

Figure 2

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