In Translation

The Newsletter of the International Society for Cardiovascular Translational Research

Vol 1/No 2

In Memoriam: Glen Nelson

Glen Nelson, MD, 79, a beloved member of the board of directors of the International Society for Cardiovascular Translational Research, died of congestive heart failure May 14. He had been seeking treatment in Egypt at the time of his death.

"Glen Nelson was truly ahead of his time — a pioneer not just in the field of cardiology but in business and in melding the two, translating discovery into practical use. His inspiration was at the heart of our society. He also was a dear friend, and we will miss him tremendously," said ISCTR President **Nabil Dib, MD**.

Barely one month prior to his passing, at the annual symposium in Chicago, the ISCTR had presented the first Glen and Marilyn Nelson Award for Cardiovascular Innovation and Translational Research in honor of Dr. Nelson's numerous contributions to the field.

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First Nelson Award Presented at Annual Symposium in Chicago

The creation of the Glen and Marilyn Nelson Award for Cardiovascular Innovation and Translational Research came about, according to ISCTR Vice President **Anthony DeMaria, MD, MACC**, because the society strove to "establish an award that personified the translation of cardiovascular discoveries to the bedside."

He noted both **Glen Nelson**'s transition from surgeon to executive with Medtronic, helping getting devices designed, tested, and put into practice, and **Marilyn Nelson**'s leadership in medicine as chair of the Mayo Clinic board as part of the impetus for the naming of the award.

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In This Issue

Meeting of the Minds

The Ninth Annual Symposium for the International Society for Cardiovascular Translational Research was held April 4 in Chicago in conjunction with the 65th Annual Scientific Sessions of the American College of Cardiology. The symposium was preceded by a meeting of the ISCTR Scientific Advisory Board, the group that assists the board with guiding the strategies that move our organization and profession forward.

The symposium that followed was unique in that it was the first time our organization presented the Glen and Marilyn Nelson Award for Cardiovascular Innovation and Translational Research and the recipient was none other than the individual whose name is practically synonymous with cardiovascular translational research, **Eugene Braunwald, MD**. Dr. Braunwald also presented a highly anticipated keynote address. We offer highlights of his talk starting on page 6; you also can view it in its entirety on our web site.

Following Dr. Braunwald's enlightening discussion of the successful collaboration between academia and industry to produce one of the first successful agents to treat heart failure making it to market in more than a decade, a variety of international experts addressed a number of critical topics in cardiovascular translational research. In one segment, three current and former regulators provided their perspectives of how their agencies embrace innovation, offering insights that will help innovators in the future. In upcoming issues of *In Translation*, we will provide a round-up of the different presentations from the annual meeting.

It is bittersweet that this meeting will be known for the inaugural awarding of what we consider our highest honor, the Glen and Marilyn Nelson Award for Cardiovascular Innovation and Translational Research, given the truly sad news that Glen passed away on May 14. Glen was truly a giant both as a professional and as a friend. He grabbed life with a gusto and he was fortunate indeed to find a life partner in Marilyn who shared his enthusiasm for discovery and for mentoring to grow new generations of innovators. We offer a short look back at Glen's life starting on page 1 and send our deepest condolences to Marilyn, their children Diana, Curtis, and Wendy, and 9 grandchildren.

In Memoriam: Glen Nelson

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Glen Nelson was born March 28, 1937, in Minneapolis, Minnesota. His parents, Ralph and Edna Mae Nelson, where both pharmacists, and Glen's first job, at age 10, was clerking in his parents' neighborhood drugstore.

He received his bachelor of arts in 1959 from Harvard; while there, he met Marilyn Carlson — who had graduated from the same high school as Glen back in Minnesota — at a mixer at Smith College. They married 2 years later upon Marilyn's graduation from Smith.

Glen earned his MD from the University of Minnesota. From 1975 through 1986, he performed general surgery at Park Nicollet Medical Center, a large multispecialty group practice, where he became President and CEO. He also helped launch American MedCenters in the mid-1980s.

In 1986, Glen became vice chairman of Medtronic, Inc. When asked to describe the transition from medical doctor to business executive, Glen noted that "As a surgeon, you save one life at a time, but with medical devices, you know you are saving so many more."

Glen and Marilyn Nelson at the White House

Others saw that transition as a natural extension for Glen. According to Bill Kling, President Emeritus of American Public Media and Minnesota Public Radio, "Glen Nelson was a very successful business executive, serving as vice chair of Medtronic during the years when its growth and product development were at its peak. Glen had a lot to do with that success. He was a leader who was extremely curious about technology and how it could combine with medicine for the betterment of the health of the people of the world. That was the thing with Glen. His curiosity. His willingness to take risks in the hope that something significant would develop. His willingness to listen carefully to what others had to offer. Those attributes made him a rare executive."

Medtronic Dedication

That sentiment was echoed by former Medtronic CEO Bill George, who called Glen "the smartest and wisest person I have ever worked with" and credited him with helping Medtronic broaden its focus beyond cardiac rhythm disease.

When Glen retired from Medtronic in 2002, he formed GDN Holdings, focusing his medical, business, and strategic expertise on health care start-ups. He was a leader in the widespread adoption of the retail clinic concept, serving as chairman of MinuteClinic from its inception until its acquisition by CVS. Glen was viewed as a thought leader in health care and served as a board member advising more than 20 companies over time. He also was a founding member of the board of Carlson,

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the privately held company founded by his father-in-law, Curt Carlson.

Glen's life was far more than medicine, however. He served on and chaired boards for such distinguished groups as Minnesota Public Radio (MPR) and Harvard University Dean's Council. During his time as chair of MPR, he worked closely with Mr. Kling in overseeing the fundraising and design and construction of the new MPR building that opened in 2006, replete with futuristic technology and contemporary production studios.

As Minnesota Public Radio's Kling said, "Glen didn't have to do any of what he did. He didn't need to give so much of himself and of his resources to the community. He didn't need to create more new companies. He didn't need to mentor me or the MPR|APM management nor lead our Board. He didn't do it for glory. He did it because those were his values."

Glen also had a sense of adventure that melded into his urgency to help others where one might find him organizing and leading a trip to Africa to distribute hearing aids to hearing impaired children in rural villages.

Those who were fortunate to know Glen also knew that despite all of his extraordinary accomplishments — the greatest of which he might say was making the Harvard football team — he was by nature a family man who gave much of himself and was steadfast in his commitment to and delight in his family.

Glen and Marilyn made family — their two daughters and one son and nine grandchildren and step-grandchildren — the center of their lives, hosting holiday celebrations, attending school "grandparent" days and Minnesota Wild hockey games and providing unconditional love to all — probably his greatest legacy.

Nelson Family

Nelson Award

Nelson Award

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The award itself, a tall crystal globe on a strong pedestal, represents the international nature of the society as well as translational medicine itself, given that advances in medicine are meant to touch every bedside no matter where in the world disease must be defeated. Crystal was chosen both for the beauty of medicine as a force for well-being and the transparent nature of science in working towards solutions for all.

A full-size replica of the award was given to the Nelsons in appreciation for their contributions to medicine and support for the goals of the ISCTR.

The inaugural honor was awarded to **Eugene Braunwald, MD, MACC, MACP**, the Distinguished Hersey Professor of Medicine at Harvard Medical School and the founding Chairman of the TIMI Study Group at the Brigham and Women's Hospital.

For the past 30 years, Dr. Braunwald and TIMI colleagues demonstrated improved patient survival with a patent coronary artery, which led to the widely accepted "open artery hypotheses." They were the first to show the benefit of preventing adverse remodeling of an infarcted ventricle with ACE inhibition. In the PROVE-IT TIMI 2 Trial, in 2004, they demonstrated the benefit of more intensive reduction of LDL in high-risk coronary artery disease patients, which has changed practice guidelines and favorably affects the lives of millions. *Science Watch* listed Dr. Braunwald as the most frequently cited author in cardiology.

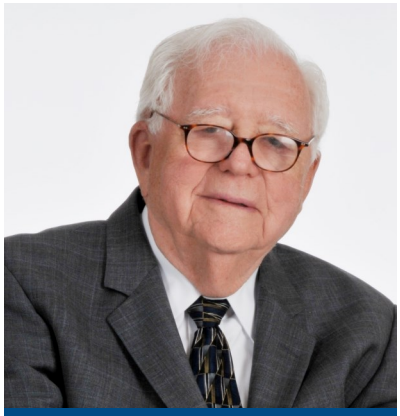
After receiving the award, Dr. Braunwald presented the keynote address at the ISCTR symposium.

ISCTR 9th Annual Symposium Highlights

Keynote Address:

The Path to an Angiotensin Receptor Antagonist-Neprilysin Inhibitor in the Treatment of Heart Failure: A Triumph of Academic-Industry Collaboration

The first Glen and Marilyn Nelson Award for Cardiovascular Innovation and Translational Research was awarded to ***Eugene Braunwald, MD, MACC, MACP****, for his contributions to innovation in translational research in cardiology and beyond. After accepting the award, Dr. Braunwald presented the keynote address of the ISCTR 9th Annual Symposium.*



Eugene Braunwald, MD

Dr. Braunwald chose as the topic of his keynote address the development of the new drug Entresto®, an agent formerly known as LCZ696 that is used to treat heart failure (HF). He did so because he considered its creation and approval to be "a triumph of academic-industry collaboration. And that's what translation is all about – it's to diminish that barrier."

He noted that it was exactly 2 years prior, on the last day of the 2014 American College of Cardiology meeting, that Novartis Corporation had announced that its clinical trial in patients with congestive HF had been stopped early by the data and safety monitoring board because of overwhelming efficacy. Given the need for new therapies in heart failure, Dr. Braunwald was interested in finding out more about the drug, and his research into the research leading up to its development became the basis of his address.

Thus the dual goals of Dr. Braunwald's presentation were to:

- Present the history of the physiologic and clinical advances that led to the first angiotensin receptor-neprilysin inhibitor (ARNI).
- Use this achievement as a "case study" that demonstrates the necessity of devoting efforts of both academia and industry to advance science and to improve medical care.

The full presentation on the aforementioned PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial) trial came at the 2014 European Society of Cardiology meeting in August 2014 and published simultaneously in the *New England Journal of Medicine*.[1] In a brief summary, Dr. Braunwald noted that PARADIGM-HF was the largest heart failure trial ever conducted (N = 8,442), comparing the study drug to the angiotensin-converting enzyme (ACE) inhibitor enalapril; it demonstrated a significant benefit in its primary composite endpoint of cardiovascular death or HF hospitalization – the hazard ratio was 0.80 – as well as both of those outcomes separately (**Figure 1**).

Death from any cause also was significantly lower with the study drug (17.0% vs. 19.8%; HR: 0.84; p<0.001). As Dr. Braunwald noted, the fact that LCZ696 also reduced total mortality is "very rare even in drugs that we accept to be outstanding drugs. We see cardiovascular mortality, but we see that that gets diluted by non-CV mortalities. So it's rare to see total mortality and here it is. So this was really very exciting."

Adding to the excitement, he said, was that the new agent also reduced the number of patients who went to intensive care, who went onto cardiac transplantation, who required assisted circulation, who showed deterioration in renal function, and more, calling it "a grand slam home run across the board."

In the Beginning

Dr. Braunwald then went back to the point where the story began: 1896 and academia with Swedish professor of physiology, **Robert Tigerstedt, MD**, who pulverized the kidneys of rabbits and injected that eluate from the pulverization into other rabbits.[2] The result of the first of several experiments showed that "within 80 seconds, there

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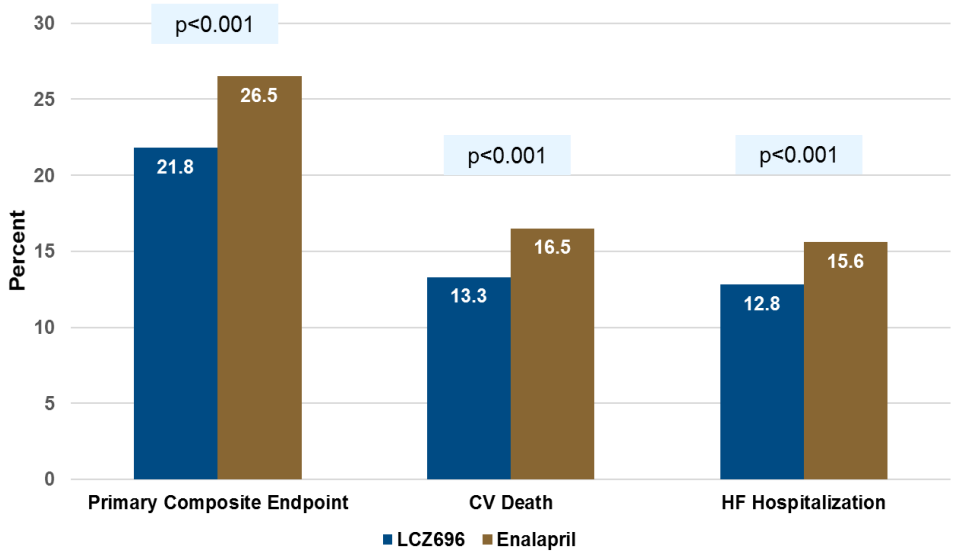

Figure 1 **PARADIGM-HF: Primary and Component Endpoints**

was a rise in mean arterial pressure from 62 to 67 mm Hg to 100 mm Hg, an increase by about 50%. Although not knowing exactly what had been extracted, Dr. Tigerstedt dubbed it renin because it came from the kidney.

Little happened in this field of inquiry until a 1934 paper by **Harry Goldblatt, MD**, and colleagues from Western Reserve University (now Case Western Reserve University) in Cleveland created experimental hypertension by clamping a renal artery to produce renal ischemia from the so-called Goldblatt kidney.[3]

About 6 years later, according to Dr. Braunwald, came the first significant industry contribution to our body of knowledge regarding rise in blood pressure, courtesy of **Irvine Page, MD**, and **OM Helmer, PhD**, investigators with the Lilly Laboratory for Clinical Research in Indianapolis. They actually isolated the "crystalline pressor substance" that resulted from the reaction between renin and renin-activator coming from the liver, and dubbed the substance angiotonin, what we now call angiotensin.[4]

The next leap back to academic contributions might have actually made more than a few people jump: **Sérgio Ferreira, MD**, professor of pharmacology at the University of São Paulo in Brazil, worked with Bothrops Jararaca, a pit viper from southern Brazil, and "found a factor in its saliva; he called it BPF, or bradykinin-potentiating factor. Bradykinin is a naturally occurring polypeptide vasodilator. And by activating bradykinin release that was part of the venom of the snake, he saw massive vasodilatation."[5]

Dr. Ferreira continued his work with BPF in London, and 5 years later published in *Nature* that BPF "inhibits the peptidase that converts angiotensin I into angiotensin II"[6] – demonstrating a parallel between bradykinin potentiation and ACE inhibition, somewhat of a "double whammy for vasodilatation," stressed Dr. Braunwald. Industry then took up this important work and a new class of orally active antihypertensive agents was born in the Squibb laboratory of Ondetti and Cushman: angiotensin-converting enzyme inhibitors,[7] the first being captopril.

As Dr. Braunwald noted, "So you see the transition – first, discovering there is a pressor substance that comes out of the kidney, and that it's somehow related to snake venom in a peculiar way, and then these two factors are pooled together, and industry comes up with a drug."

Captopril performed well in trials; for example, Dr. Braunwald studied it with **Mark Pfeffer, MD, PhD**, and others in the SAVE (Survival and Ventricular Enlargement) trial where it improved survival and reduced mortality and morbidity in post-MI patients with left ventricular dysfunction.[8] Despite the positive results in this and other studies, captopril itself "didn't really make it big in industry because it was a TID drug and it was aimed primarily for patients with hypertension. And hypertension, in contrast to heart failure, is a silent disease, it's a silent killer. And while you can get people to take their medicines once a day and those people who brush their teeth in the morning and in the evening, you can get them to take a pill twice a day if they're feeling well. It's hard to get them to take it three times a day," Dr. Braunwald explained.

Development on other ACE inhibitors continued, and Merck's initial contribution was enalapril, which is still used today, and was the focus of the landmark CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) trial.[9] So influential is this trial that the 1987 *New England Journal of Medicine* article discussing results has been cited nearly 2,600 times since publication. It was also a development that Dr. Braunwald felt reflected contributions from both academia and industry in translating the work from the bench to the bedside.

This randomized, double-blind, placebo-controlled trial was conducted in "very sick, class IV heart failure patients with very high mortality – it was

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62% in 1 year, so these were very sick patients – and it was reduced by 27%," Dr. Braunwald said (**Figure 2**). "This was not an 8,500-patient trial like PARADIGM, but it was a trial of about 250 patients and that really was enough for this drug to be approved by the FDA for indications not only for hypertension, but also for severe heart failure. So that made a lot of progress."

The Art of the Atrium

While developments in ACE inhibition were unfolding, so too were discoveries impacting other areas of the heart. Dr. Braunwald pointed to the work of **Adolfo DeBold, PhD**, trained in biochemistry, physiology, and pharmacology and affiliated with Queens University in Ontario, Canada. Similar to Dr. Tigerstedt's experiments, Dr. de Bold created a crude extract of atrial myocardium and intravenously injected it in rats, producing a "rapid and potent natriuretic response."[10] Dr. de Bold, however, took his research further and faster than Dr. Tigerstedt, discovering granules in the kidney that produced what he called atrial natriuretic factor (ANF), known today as atrial natriuretic peptide (ANP).

"All of us have circulating ANP, but those of us who are not in heart failure have extremely low levels. When I say low levels, it has a half-life; you can synthesize it. If you inject ANP into normal people, it has a half-life of 2 to 3 minutes. So you have to figure out what happens to this ANP because there was certainly enough left in the atrial myocardium of rats to produce a prolonged natriuresis and I can say also vasodilatation," said Dr. Braunwald.

He then noted the contributions from academia of Kenny, who discovered an enzyme that hydrolyzes human ANP,[11] and Roques, who led a group that developed a closely related enzyme.[12] "So now we have a new system. We have a natriuretic peptide system, we know that the natriuretic peptide has a potent physiologic action, we know that there is an enzyme that is present in our kidneys that degrades the peptide and we now are beginning to see a blocker of that enzyme. So if we wanted more ANP circulating, then we would like to block this," Dr. Braunwald noted.

He continued that heart failure, "in the simplest sense, produces atrial distension, which, as shown by de Bold, results in more release of ANP." However, the neutral endpopeptidase (NEP) present in the kidney and other tissues degrades ANP, reducing its effects. Conversely, a NEP inhibitor prevents such degradation (**Figure 3**). "And that's where the NI in ARNI comes from. If you antagonize the neutral endopeptidase, you're blocking the degradation of ANP and you're raising the concentration of ANP, which should be a good thing theoretically."

Interest from industry also was high, and at the turn of the century, Bristol-

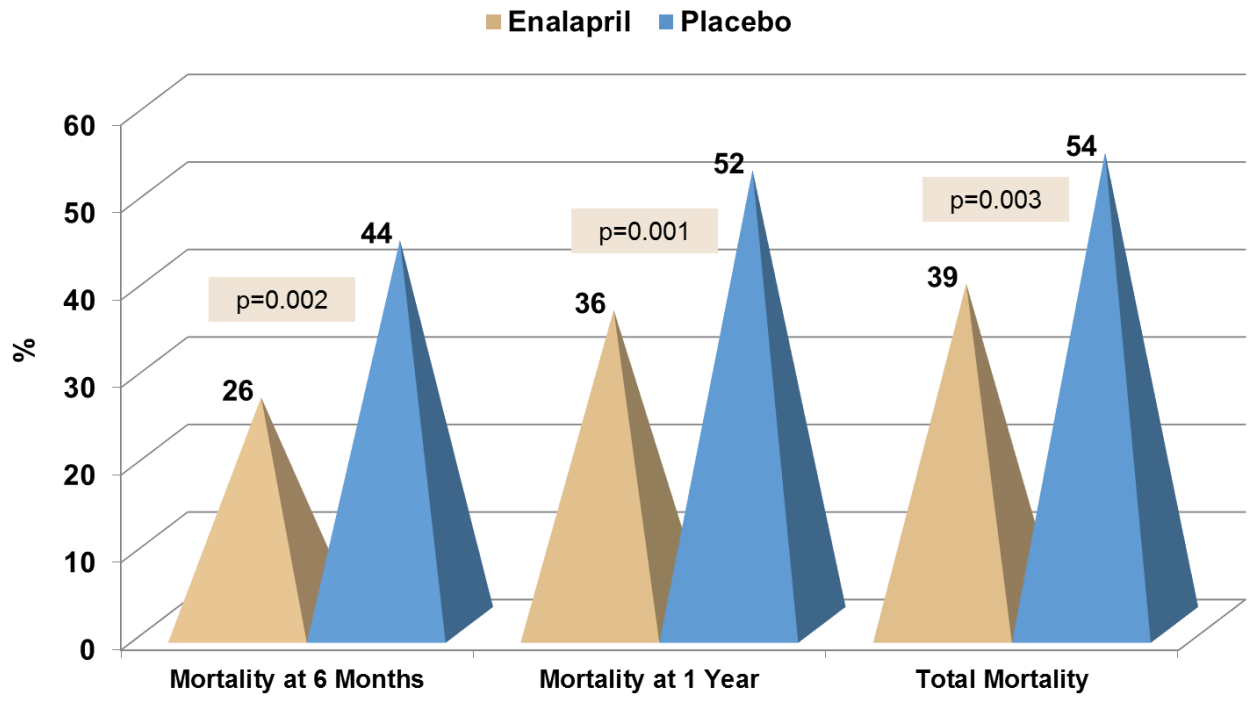

Figure 2 CONSENSUS: Mortality

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Myer-Squibb combined inhibitors of ACE, NEP, and a third enzyme (aminopeptidase) into omapatrilat, which was shown to be extremely effective in lowering blood pressure and was developed primarily as an antihypertensive. The effectiveness seen came from the fact the drug not only lowered blood pressure because of the ACE inhibitor, "but you also have part of the molecule that inhibits the degradation of ANP, so you decrease the amount of angiotensin II and you increase the concentration of the natriuretic peptides," Dr. Braunwald noted. The industry speculation was that omapatrilat would be a blockbuster drug, generating $2 billion annually.

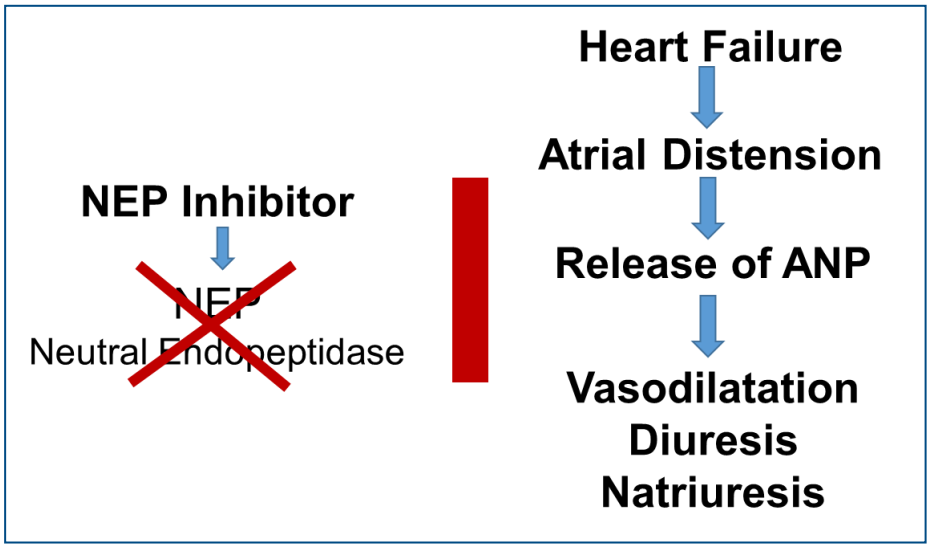

Figure 3 **Natriuretic Peptide System**

In a very large international phase III trial of 25,302 patients with untreated or uncontrolled hypertension, the OCTAVE (Omapatrilat Cardiovascular Treatment vs. Enalapril) investigators not only compared the blood pressure-lowering effects of the agents, but also took a closer look at incidence of angioedema that had been seen in previous trials.[13] And they found that omapatrilat did indeed reduce blood pressure significantly versus enalapril and produced a higher incidence of angioedema – 2.17% of the overall population on the study drug, a rate that tripled in black patients. At this level, "this is a dangerous complication. It's not just an allergy; these people get obstruction of the upper airways," Dr. Braunwald said.

With that, the FDA dropped it from likely review and Bristol-Myers-Squibb shut down research and development. Development of similar combinations of an ACE inhibitor and a neprilysin inhibitor at other pharmaceutical companies also stopped abruptly.

Why did this occur? Dr. Braunwald pointed to the fact that ACE inhibitors are bradykinin-potentiating factors, and neprilysin inhibitors also increase bradykinin concentration. Adding the drugs together set the stage for the dangerously heightened incidence of angioedema.

The Ascent of ARNI

Approximately 2 years later, industry revisited the issue when two scientists at Novartis applied for a patent for a molecule complex similar to omapatrilat but with a basic yet important difference: an angiotensin receptor blocker (ARB) was substituted for the ACE inhibitor. "So now you are back to the risk of a single whammy. A very, very simple concept – but brilliant," Dr. Braunwald noted.

The first human application of LCZ696 was in hypertension, with a comparison of the combination of the ARB valsartan and NEP inhibitor sacubitril (then called AHU377; both of which Novartis manufactured) to valsartan alone.[14] Valsartan versus sacubitril, both as monotherapies, produced about the same modest reduction in systolic blood pressure, but the combination produced an additive effect and more significant drop, particularly as doses of both agents rose. Taking all effects into account, the investigators stayed with valsartan 160 mg in the 200 mg dose of Entresto.

Investigators then turned their attention to studying the combination drug in heart failure. The phase II PARAMOUNT (Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction) trial randomized 251 patients with class II-III HF, left ventricular ejection fraction ≥45%, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) >400 pg/ml 1:1 to LCZ696 or valsartan; the primary endpoint was change in NT-proBNP.[15] At 12 weeks, NT-proBNP was significantly reduced with the study drug: LCZ696 at baseline 783 pg/ml decreased to 605 pg/ml at 12 weeks versus 862 pg/ml and 835 pg/ml at the same time points with valsartan (rate of change: 0.77; 95% confidence interval: 0.64-0.92; p=0.005). Systolic blood pressure also decreased significantly with the ARNI.

The same day PARADIGM-HF was stopped after laying to rest the question of Entresto's superiority to enalapril, investigators decided to continue

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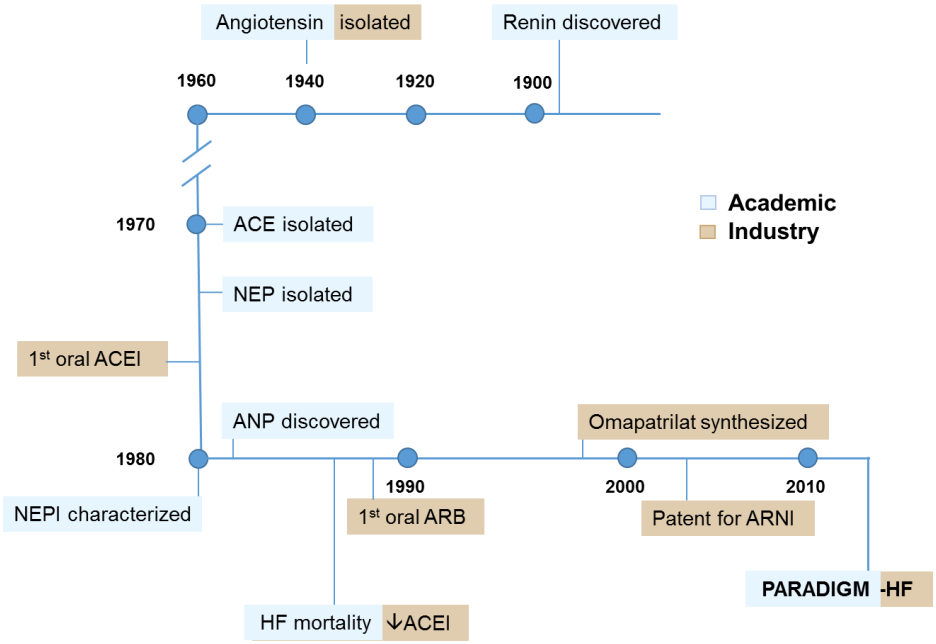

Figure 4 Path to PARADIGM-HF

with its sister trial: PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction), a phase III outcomes trial comparing Entresto and valsartan. It is currently enrolling, with a planned population of ~4,300 patients with HF with preserved ejection fraction. Dr. Braunwald considers PARAGON-HF a true collaboration of academia and industry as "the academics had a great role in the development of this protocol. It's actually simple – there's a run-in period to see if they tolerate valsartan and LCZ696, and then there's randomization. This trial is moving along quite well." Planned follow-up for the study is 5 years.

Dr. Braunwald summed up the keynote address by reviewing the timeline of the ARNI (**Figure 4**), noting that while research and development started slowly, the scale of discovery has changed 4-fold. "Things went very slowly and it is amazing how things have sped up as this thing has developed. And that is because industry and academia are talking to each other and collaborating."

He closed by saying that when it comes to "academic-industry contributions to ARNI, the academics going back really 120 years have provided creativity, experimental excellence, and rigor leading to two important physiologic systems, the renin-angiotensin system and natriuretic peptide system, and their function in health and disease. What has industry contributed? Tremendous ingenuity and great resources for the development and application of the most advanced technology to develop safe drugs and for altering the function of these drugs. And I think that both are required and were key elements on the path to developing this molecule — the whole is obviously much greater than the sum of the parts."

References

1. McMurray JJV, Packer M, Desai AS, et al.; for the PARADIGM-HF Investigators and Committees. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. *N Engl J Med* 2014;371:993-1004.

2. Tigerstedt R, Bergman P. Niere und Kreislauf. *Arch Physiol* 1898;8:223-71.

3. Goldblatt H, Lynch J, Hanzal RF, Summerville WW. Studies on Experimental Hypertension: 1. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia. *J Exp Med* 1934;59:347-79.

4. Page IH, Helmer OM. A Crystalline Pressor Substance (Angiotonin) Resulting from the Reaction Between Renin and Renin-Activator. J *Exp Med* 1940;71:29-42.

5. Ferreira SH. A Bradykinin-Potentiating Factor (BPF) Present in the Venom of Bothrops Jararaca. *Br J Pharmacol Chemother* 1965;24:163-9.

6. Ferreira SH, Greene LH, Alabaster VA, Bakhle YS, Vane JR. Activity of various fractions of bradykinin potentiating factor against angiotensin I converting enzyme. *Nature* 1970;225:379-80.

7. Ondetti MA, Rubin B, Cushman DW. Design of specific inhibitors of angiotensin-converting enzyme: new class of orally active antihypertensive agents. *Science* 1977;196:441-4.

8. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669-77.

9. [No authors listed] Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 1987;316:1429-35.

10. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci* 1981;28:89-94.

11. Stephenson SL, Kenny AJ. The hydrolysis of alpha-human atrial natriuretic peptide by pig kidney microvillar membranes is initiated by endopeptidase-24.11. *Biochem J* 1987;243:183-7.

12. Roques BP, Fournié-Zaluski MC, Soroca E, et al. The enkephalinase inhibitor thiorphan shows antinociceptive activity in mice. *Nature* 1980;288:286-8.

13. Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens* 2004;17:103-11.

14. Ruilope LM, Dukat A, Böhm M, Lacourcière Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet* 2010;375:1255-66.

15. Solomon SD, Zile M, Pieske B, et al.; PARAMOUNT Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012;380:1387-95.

Highlight:

Chapter 1.2

To be able to justify spending on new treatment options, economic evaluations of new drugs and devices are critical and can be accomplished either through direct comparison to existing treatment options or predictive modeling for truly novel technology.

A growing phenomenon: the need to make a case for "societal return on investment" to warrant higher reimbursement than reference or existing products. This can be challenging for industry and, more and more, translates to the need for manufacturers to hypothesize and then actually measure improved value over months or years made possible by new devices.

Scientists and others working with independent, credible third parties can help to create a valued and objective position for payer considerations about new device reimbursement. This will become increasingly important as government is able to sponsor only a small fraction of the research needs around device development and health reform pressures will err on the side of choosing technology that comes at a lower cost.

eTextbook: Device Reimbursement

Across the modern era of medicine, the United States leads the world in research and development of new cardiovascular devices and related technology. However, early deployment of such devices typically takes place in other developed nations, and those countries are beginning to assert dominance in the device research arena as well. Why? Factors include increased federal regulatory scrutiny, growing public concern about patient safety, and greater medical liability risk in the U.S.

The second chapter in the first section of the ISCTR's innovative eTextbook focuses on "Investigational and New Cardiovascular Devices: Strategy and Decision-Making for Reimbursement in the Post-Reform Era." While providing a variety of avenues to consider to improve the decision-making process, the book also notes that the U.S. Food and Drug Administration may become an ally in honing such strategies. The concerning trends have the FDA considering ways to transform its policies and perceived regulatory overreach to enable expedited regulatory approval processes and more flexibility in U.S. device innovation and domestic implementation.

Part of that transformation is being driven by and is made possible by the enhanced abilities of health information technologies to track device performance, utilizing registries and real-world data to conduct such tracking across entire patient populations. The hope is these new technologies can expand the sophistication and sensitivity of post-approval studies to monitor both patient safety and device clinical performance, thus streamlining the process for device evaluation and hopefully approval without compromising patient safety.

At the same time, the chapter authors note, necessary and imminent changes are coming to the financing of U.S. health care in order to avert the crippling effects of rising health costs on the economy at-large. Not only does and will reform profoundly impact reimbursement for clinicians, hospitals, and insurers, but it also casts a darkening pall over drug and device development. The always present need to reduce health spending often creates barriers rather than balance in regard to the policy and regulatory changes being considered.

The payer mentality regarding evaluation of new technology often comes down to answering questions such as these (none of which overtly encompass concerns about safety):

"What does this [device] replace in our current list of approved devices?"

"What do we save by permitting use of this device?"

"How does the approval of this [device] affect patient outcomes?"

"What opportunities do we have short- and longer-term to offset other costs?"

These questions are understandable given shrinking reimbursement at the federal level. When this is coupled with the growing trend to allow access to new technology only when information about the outcomes to specified patients has been demonstrated, additional pressures abound for innovators and the delivery system alike. This chapter is focused on understanding the kinds of device reimbursement changes that are in process and offers suggestions about how to turn perceived threats into opportunities, thus promoting ongoing and robust innovation in this space.