Bedside–to-Bench Translational Research for Chronic Heart Failure: Creating an Agenda for Clients Who Do Not Meet Trial Enrollment Criteria

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Supplementary Issue: Heart Failure: An Exploration of Recent Advances in Research and Treatment

ABSTRACT: Congestive heart failure (CHF) is a chronic condition usually without cure. Significant developments, particularly those addressing pathophysiology, mainly started at the bench. This approach has seen many clinical observations initially explored at the bench, subsequently being trialed at the bedside, and eventually translated into clinical practice. This evidence, however, has several limitations, importantly the generalizability or external validity. We now acknowledge that clinical management of CHF is more complicated than merely translating bench-to-bedside evidence in a linear fashion. This review aims to help explore this evolving area from an Australian perspective. We describe the continuation of research once core evidence is established and describe how clinician–scientist collaboration with a bedside-to-bench view can help enhance evidence translation and generalizability. We describe why an extension of the available evidence or generating new evidence is occasionally needed to address the increasingly diverse cohort of patients. Finally, we explore some of the tools used by basic scientists and clinicians to develop evidence and describe the ones we feel may be most beneficial.

KEYWORDS: bedside to bench, comorbidities, heart failure, indigenous australians, translational research, validity

SUPPLEMENT: Heart Failure: An Exploration of Recent Advances in Research and Treatment

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Introduction

Congestive heart failure (CHF) care has benefited greatly from the translational sciences. The National Center for Advancing Translational Sciences (NCATS) defines *translation* as the process of turning observations in the laboratory and clinic into interventions that improve the health of individuals and the public, from diagnostics and therapeutics to medical procedures and behavioral changes, and *translational sciences* as the investigative field focused on understanding the scientific and operational principles in the translational process.[1] The term *bench-to-bedside* describes the first arm of this complex process. The term *bench* is often used in reference to experimental research, usually before direct human involvement, that builds the evidence to inspire first in human studies. Bench can be used to better understand pathophysiological basis for diseases. It can then be used to study the effects of a ligand (drug) in altering the maladaptive process for improved outcomes. During these stages, many aspects from safety to efficacy are also tested. When sufficient evidence is generated, the studies gradually move toward human subjects. When a ligand or drug has safely passed through the defining trial phases and is available for clinicians to use in their practice, this is described as *bedside* translational research. Hence the term *bench-to-bedside*.

The process described is one directional, where the other arm *bedside-to-bench* is often forgotten. Woolf highlights that this second part focuses on closing health gaps by studying systems of care from issues such as access and organizational factors to client factors such as informed choices and behavioral changes. This part strengthens organizational delivery of health care, clients informed uptake, and relationships between the health systems, health provider, and patient.[2] In this review, we describe this forgotten process and discuss its relevance for collaborative posttranslational research between two health populations, those who fit the randomized controlled trial (RCT) demography and those who do not. Often, these are also patients living outside urban areas who suffer with comorbidities or access to health services. We have previously described

avenues for purely clinical collaboration and described the infrastructure, demographic, and key clinical issues.[3–9] We thus explore key diagnostic and therapeutic areas to help maximize and/or broaden the therapeutic efficacy for our clients.

Defining Key Areas to Study

In our region, the three priority bedside issues that stand out are CHF with the comorbidities diabetes mellitus (DM) and renal impairment (RI) and CHF in minority groups (eg, Australia's indigenous population). We feel that significant findings in these areas could be *game changers* in not only advancing a scientific understanding but also having significant clinical value in outcomes. These clients have significantly increased risk. What we know thus far suggests:

1. CHF remains a significant problem although system-wide improvements are noted. There are significant heterogeneity with gaps in CHF best practice, including service availability and delivery and uptake of pharmacotherapy across the continuum of care.[3–8,10–18]
2. Comorbidities add greater complexity to the treatment plan, both in care delivery and therapeutic regimes. DM is a leading cause of ill health, and RI remains the single greatest determinant of poor heart failure (HF) outcomes.[15,19–24]
3. Indigenous Australians have not shared the same positive outcomes. They lag in all prognostic indices as well as uptake or implementation of novel therapies. As a group, solid prospective data are lacking and implementable research findings are also lacking.[3,8,25–36]
4. Trial enrollment excludes at least those with moderate RI and diabetes with complications and indigenous groups, outright or with strict run-in periods. Medication side effects, extra class interactions, and pill burden are poorly factored in RCT or guidelines.[5,6]
5. Posttranslational research for evidence to simplify therapeutic regimes or to improve efficacy is also lacking.[5,6]

Understanding and addressing translational blocks is also important. Such blocks can take two forms: first, preventing basic research findings being tested in a clinical setting; and second, preventing proven interventions from becoming standard practice; are both mainly administrative issues. Collaborative groups that are generating regional data stand greater advantage in lobbying for changes.[7] In regional settings, sometimes translational efforts are too effective in that they are rapidly implemented without due consideration for external validity. Such groups can also balance how consensus is derived to solve regional issues. Further discussions, which are beyond the scope of this review, can be found at Sung et al and NCATS website.[1,37]

Key requirements to start include a multidisciplinary and highly collaborative group focusing on agreed research themes into diagnostic tools, medicines, procedures, policies, and education (Fig. 1). Difficulties in setting this up may partly explain the failures for more robust posttranslational work. Individual health systems will need to prioritize within these choices and secure such alliances. The American National Institutes of Health (NIH) has emphasized on such collaborations, and through its subsidiary, NCATS, has ensured that there is a dedicated focus to translate proven strategies within the community quicker.[37,38] The practice of medicine has changed so much that as chronic illnesses became more complex, treatment guidelines have become more rigid. Moving from the bedside-to-bench could reduce some of this rigidity by refining the existing evidence.

HF and Diabetes

Diabetes independently increases HF risk by two–five times and mortality hazards by 30–60% once HF develops. The majority of cases is associated with one other HF risk factor such as dyslipidemia, hypertension, mood disorders, obesity, or RI, which adds incremental risk. Insulin resistance (IR) and hyperglycemia contribute indirectly by atherosclerosis and directly via diabetic cardiomyopathies. In diabetic hearts, cardiomyocytes under conditions of increased cellular metabolic needs and altered energy substrate supply are unable to switch from free fatty acid to glycolysis for more efficient energetics.[39] The principal focus in CHF is to ensure good glycemic control. Intensive glucose control runs the risk of hypoglycemia and rebound sympathetic system activation and imprinting of adverse metabolic memory. Out of three large RCTs Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veteran Affairs Diabetes Trial (VADT), the former was stopped early because of increased mortality, while the other two failed to show improved outcomes in the intensive arm. Closer scrutiny showed greater hypoglycemic events and access of weight gain with intensive treatment. Of further interest in the ADVANCE study where participants actually lost weight and hypoglycemic events were only 1% greater between strategies, there was a significant reduction in major macrovascular or microvascular events.[40–46] To achieve good control, it is thus imperative that we ensure the accuracy of monitoring and safety of standard diabetic and HF therapeutics when diabetes exists as a comorbidity.

Improving diagnostics. Accurate prediction of diabetic control is vital. Factors affecting erythropoiesis (iron and vitamin B12, erythropoietin, chronic liver disease) and glycation (alcoholism, aspirin, vitamin supplements), altering hemoglobin and erythrocyte half-life or interfering with assay (hypertriglyceridemia, alcoholism), all prevalent in our region, can interfere with HbA1c reliability for assessing the adequacy of glycemic control, leading to poor control.[47] It is important in this setting that clinicians continue to utilize plasma glucose diaries of clients. An interesting consideration is glycated albumin, which reflects a shorter term glycemic control within

one to two weeks. In three studies with diabetics on dialysis, fasting glucose and glycated albumin were 30–40% greater than HbA1c, which underestimated control. Further analysis is needed before committing to this approach as serum albumin is equally affected by RI and chronic disease states.[48,49] Exploring glycation of other cell lines that are relatively unaffected by the above factors is another area to explore. However, the point that glycemic control, the most important marker of adequate DM care, could be altered by clinical states, lifestyle factors, and drugs is vital to consider.

Improving therapeutics. Iatrogenic hyperinsulinemia with sulfonylureas or insulin is associated with weight gain, hypoglycemia, lipid imbalances, and potential cellular toxicity.[50,51] Sulfonylureas increase insulin secretion by inhibiting adenosine triphosphate (ATP)-dependent potassium (K_{ATP}) channels, blocking the myocardial K_{ATP} channels, interfering with cardioprotective ischemic preconditioning, and reducing resulting infarct sizes. Prospective data from Danish registry also raise concerns for sulfonylureas in some diabetics with ischemic cardiovascular disease.[52] Metformin, a biguanide that reduces hepatic glucose secretion and improves insulin resistance, is associated with a 40% risk reduction in cardiovascular events, however is cautioned in severe HF because of concerns of lactic acidosis. Thiazolidinediones improve insulin sensitivity without hypoglycemic risk by activation of peroxisome proliferator-activated (PPAR)-γ with other nonglycemic effects, including anti-inflammatory and improved lipid profiles via PPAR-α/γ. In clinical practice, rosiglitazone and pioglitazone increased peripheral edema and the risk of new or worsening HF. The etiology is speculated as follows: low-level PPAR-γ expressed in myocardium with metabolic syndromes when blocked leads to hypertrophy and overexpression-dilated cardiomyopathy; altered fluid and sodium reabsorption in distal collecting ducts lead to fluid retention.[39,53,54]

Other newer agents have issues of weight gain and significant hypoglycemia but suffer from lack of convincing data for diabetes, HF outcomes, and high cost. The dipeptidyl peptidase-4 inhibitors (DPP-4) prolong circulation of gastrointestinal incretins, which stimulate pancreatic insulin release. DPP-4 has other functions that suggest theoretical benefits in HF. In two of the three major RCTs, there were excess HF hospitalizations, while no trial showed superiority to placebo. We still await results from two studies.[55] SGLT2 inhibitors of the sodium-dependent glucose cotransporter in the proximal tubule reduce weight that, could potentially interact with loop diuretics and have other safety issues such as urinary tract sepsis and cancer risk.[56]

With the lack of novel therapeutic agents, we must ensure greater metabolic safety with established HF therapies. The angiotensin receptor blocker (ARB) and partial PPAR-γ agonist telmisartan has been shown to improve insulin sensitivity greater than any other ARB, with other positive PPAR-γ effects. In addition, it is better tolerated and more efficacious in preventing HF than most angiotensin-converting enzyme inhibitors (ACE-Is) and drugs in its class. This and other findings have encouraged researchers to question the degree and site of blockade as the next step in elucidating PPAR-γ and HF.[57–59] This agent and partial PPAR-γ blockade are worthy of greater review. Vasodilatory beta-blockers (ββ) have superiority in the metabolic syndrome.[19] Nebivolol with the highest β1 selectivity is also an agonist of β3-adrenergic receptor via activation of NO synthase pathways. This receptor has been shown in animal models to exert positive inotropy with adverse effects on glucose and lipid metabolism. This has however not translated into human studies.[60–64] Finally, high-dose statin has been associated with higher diabetic risk.[65] It was noted from the genetic data of more than 220,000 individuals from 43 studies that this related partially to HMGCR inhibition.[66] With the availability of ezetimibe and positive data from Study of Heart and Renal Protection (SHARP),[67] this option could be factored. While individually the clinical effect of these points could vary in significance, the cumulative effects need to be better clarified, as evidence generated could allow for more choices.

HF and RI

CHF and RI contribute to the pathophysiology of the other alone or when they co-exist in the various forms of the cardiorenal syndrome (CRS). The epidemiology, mechanisms for disease and management are well documented.[20–22,68,69] RI is the greatest risk for poorer CHF outcomes in all stages and with all types of associations. The priority is to ensure that at-risk patients are identified and offered timely screening and access to therapies that delay onset or progression and for those already suffering with the CRS, measures to optimize management.

Improving diagnostics. Current risk factor scoring [eg, General Surgery Acute Kidney Injury (AKI) Risk Index] and AKI diagnosis based on conventional urine and serum markers (eg, RIFLE, AKIN, and KDIGO) appear adequate for most of our clients, although some questions remain for subsets of CHF and indigenous patients. In CHF, as renal perfusion is affected by many factors, and with the single-nephron GFR, which contributes to overall renal function (RF) often functioning at capacity, the risk for AKI is greater. In the hospital setting, the serum creatinine (SCr)-based estimated glomerular filtration rate (eGFR) is a retrospective (delays of over 48 hours) and inaccurate tool for both functional and renal injury information from which to make clinical decisions.[21] Maple-Brown et al found that the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula outperformed several established eGFR equations, but had a greater bias in diabetics with normal RF.[70] In a separate study, they identified albuminuria as a potentially better prognostic marker than low eGFR in randomly selected individuals.[71] Under

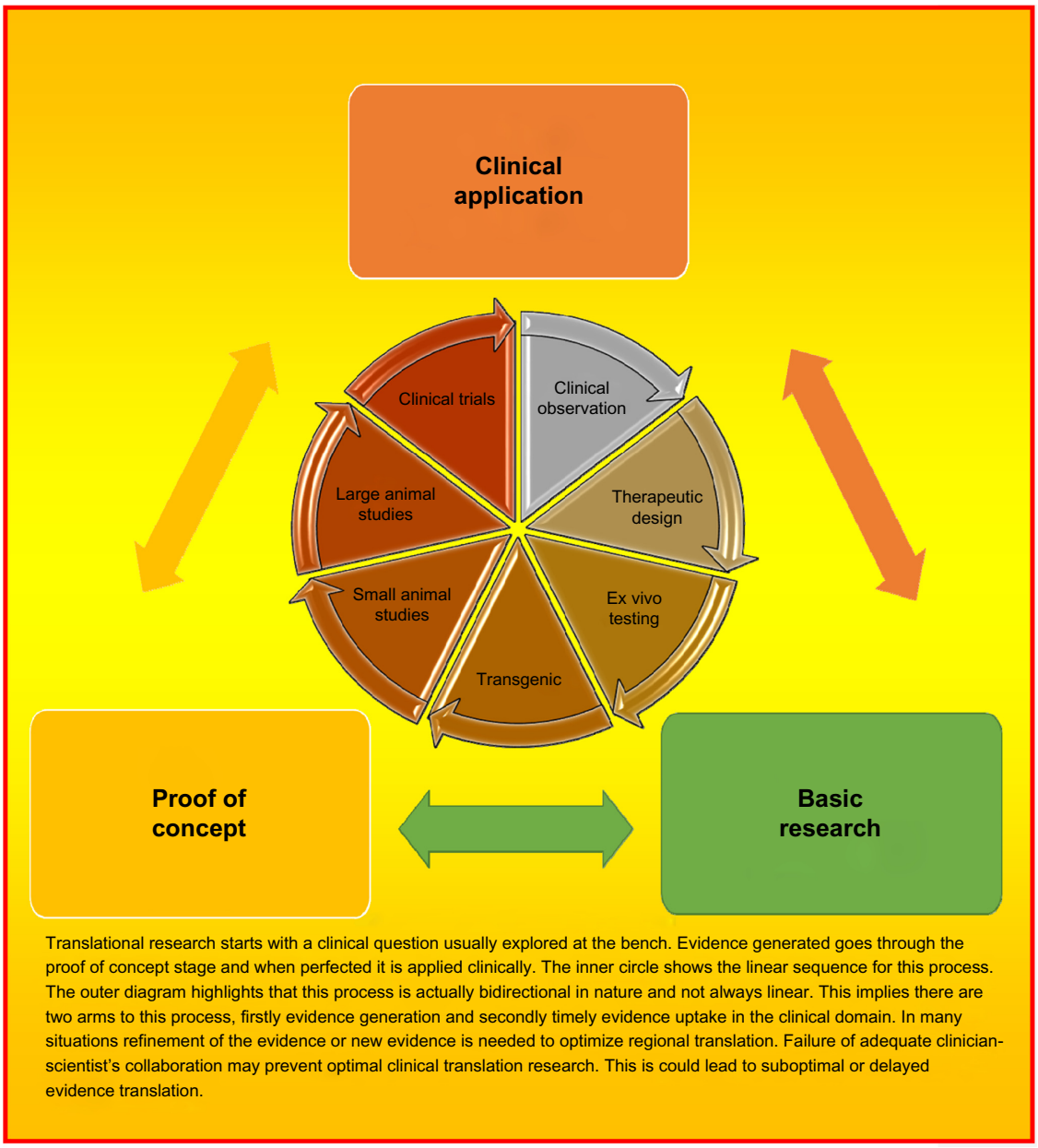


Figure 1. Conventional model of evidence generation and translation.

prescription also remains a major problem in the CRS, and this in return contributes to poor outcomes.[72,73] A reliable and accurate marker will help improve prescribing of prognostic CHF therapeutics by increasing the confidence of physicians.

Cystatin-C (Cys-C) is a low molecular weight proteinase inhibitor protein that is synthesized and released into plasma by all nucleated cells at a constant rate. Thus, it is not affected by individual patient characteristics such as age, race, and weight. It is freely filtered through the glomerulus and completely reabsorbed in the proximal tubules. Of interest, Cys-C is accurate in diabetics with mild-to-moderate RI, in contrast to SCr-based equations as highlighted by Maple-Brown et al. For CHF, it is superior to SCr-based eGFR formulae and has the added advantage of providing prognostic data. Finally, it can be easily measured from blood samples without complex equations and should be factored as a biomarker for accurate RF estimation in moderately reduced eGFR (60–90 mL/minute/1.73 m^2), in the elderly and selected minority groups.[21,35,74]

Neutrophil gelatinase-associated lipocalin (NGAL) is a low molecular weight protein that is upregulated and secreted early into urine, in response to various acute renal tubular injuries. Levels are elevated within 2 hours in both urine and blood. It offers additional information in prognosis and the need for more intensive cardiac or renal care. It is also evolving into an important marker for the early diagnosis and risk stratification of CHF and acute decompensated HF. Cost factors, diagnostic protocols, and issues surrounding reference ranges are some of the challenges prior to mainstream use. The availability of

troponin (cTn), brain natriuretic peptide (BNP), Cys-C, and NGAL as point-of-care testing (POCT) biomarkers adds to its appeal in a wide range of situations from improved emergency triage to increasing confidence for earlier renal referrals or introducing therapies and subsequent monitoring.[21,75] A learning curve is expected in implementing cost-effective protocols and understanding routine baseline and disease reference ranges. This could be part of the translational issues to address.

Improving therapeutics. The therapeutic priority remains translating best practice for renin-angiotensin-aldosterone-system (RAAS) and adrenergic system modulators where pathophysiology contributes to many of the adverse features.[5,6,19–21,73,76–78] Finding avenues to improve compliance by reducing medication dosing, preventing adverse drug effects, and enhancing QOL is a priority. We have previously highlighted reasoning to consider wider availability and appeal for certain drugs: RAAS modulators, eg, telmisartan, perindopril, and eplerenone; ββ; nebivolol; and once daily carvedilol.[6] Telmisartan remains the only RAAS agent with proven benefit in HF with end-stage renal failure (RI).[79] Its preventive capacity matches the best ACE-I, ramipril, and is better tolerated, an encouraging finding for long-term users. RAAS blockade also exerts renoprotective effects independent of blood pressure lowering. An ARB with glucose lowering potential, renal anti-inflammatory, antioxidants, and 24 hours blood pressure could be promising.[80–82]

Sympathetic nervous system activation (SNSA) is autonomous and deleterious in RI[19] and ββ improve outcomes.[83] A recent finding has even suggested that sympathetic nervous system (SNS) blockade could be more important than RAAS blockade for hypertension in dialysis-dependent RI.[84] However, with conventional ββ prescriptions at 20–30%, partly from fear of reduced cardiac output, reduced renal perfusion or less significant antihypertensive effects, vasodilatory ββ need further emphasis. In fact, there is evidence for nephroprotection and improved HF endpoints in the CRS, including hemodialysis.[6,86–88] Nebivolol, although less well explored than carvedilol, is safe,[89] efficacious, and potentially equivalent to telmisartan for hypertension[90] and could improve renal function in some.[91,92] The novel invasive renal artery denervation is also important to explore.[93] Statin use often encourages the highest doses, targeting greatest LDL reduction. A wide range of QOL and safety issues exists; however, a relatively underexplored area remains, its effects on RF. Several recent publications have raised concerns for AKI in high potency station, particularly if there is a predisposition.[94] This coincides with the SHARP study that highlighted the safety and efficacy of simvastatin plus ezetimibe in ESRD.[67] Exploring a wider role for vytorin is a consideration to reduce high-dose statins in selected cases.

HF and Indigenous Populations

The problems remain bad for Australia's indigenous community. There is little evidence of any significant inroads.[95] Lack of accurate prospective data also makes it difficult to gauge the size of the problem[3,8]; We thus speculate that in many cases HF is more severe, less well treated, occur at younger ages, and associate with more comorbidities. There also remain gaps in critical services and disease demographics.[3,11,14,15,24–36,96–117] Let us start by defining some of the confounders:

1. first, a higher percentage of clients who would not qualify for RCT inclusion because of severity of illness of perhaps exclusions after the run-in period[5];
2. second, lack of culturally appropriate information,[99] follow-up services,[100] and prescribing flexibility exploring simpler dosing regimes, intervals and even pill size and characteristics.[3,5,6,100–106];
3. third, differences in illness phenotypes and therapeutic responses such as genetic polymorphisms and epigenetic factors[107–110];
4. fourth, improved risk stratification and scoring systems that factor in indigenous specific risks, including comorbidities, demographics, geography, and genetics[111–117];
5. fifth, critically ill patients who do not qualify for life-saving therapies for whom experimental therapies may benefit[96]; and
6. finally, community and social stigma for novel research.[3,118]

On the first three points, most would agree that applying the physiological principles of therapy is vital. Using such principals to widen the therapeutic paradigm has not, however, translated into the guidelines. There also remain gaps in the evidence to actually support deviating from established guidelines. What this has done is seen medications dispensed often without due consideration of the patient's pill burden, pill size, side effects, and potential effects on comorbidities. Thus, the concept of keeping it simple is an issue that the bench could address. Proper models that reflect the characteristics for indigenous communities are lacking. Such models could explore the following:

1. *Pharmaceutical design:* Presenting with a chronic illness has not only altered the quality of life but also the way of life. The ease of carrying, storing and taking medications could impact on compliance.
2. *Alternate prognostic drugs within a class:* animal models to assess potential therapies with favorable pharmacodynamics and kinetic profiles, adverse drug interactions (eg, cytochrome modulation), and extra class effects. Examples include vasodilatory ββ in metabolic CRS. Nebivolol and carvedilol are examples where receptor selectivity and extra class effects have been shown to improve metabolic control, renal blood flow, and comorbidities.[19] Carvedilol, dosing is twice daily, while nebivolol is off patent and is difficult to explore in a clinical trial.[4] Developing suitable

bench model for these could save on cost and logistics. Examples for RAAS blockade and other therapies were highlighted earlier.

3. *Genetic polymorphisms:* better genetic understanding will allow us to personalize medicines better and minimize side effects, although it is not intended for fine-tuning in every situation. How we select clients remains an area to review. Data will certainly add to the pool of knowledge.[119]

On the fourth point, novel proteomic and genomic research would in principal be timely. From a diagnostic perspective, what is needed are markers that signal whole system well-being, not disease or organ specific, both early and accurately. This is important: first, as screening will detect many factors associated with poorer outcomes and following one disease-specific marker may provide false and lead time biases for other comorbidities; second, resource and service shortfall issues may require greater information at each interaction; and finally, to determine if a novel clinical therapy is achieving the desired outcome without waiting for several years as in most RCTs. The Strong Heart Study identified baseline electrocardiogram (ECG) changes, a multitude of cardiac morphological changes, and established novel biomarkers, to name a few, with poorer outcomes.[110,112–117] Potential avenues to explore:

1. *Novel risk scoring and biomarkers:* combining datasets should be priority, although such data are lacking. Telomere studies may be one option as they reflect physiological aging and a fingerprint of whole system's effects of illnesses.[119–128] This can be compared to disease-specific markers left ventricular ejection fraction (LVEF) (cardiac parameter) or HbA1c. Personalized medicine requires understanding the gene–transcriptome–proteome path (Fig. 2). This is an inexact science, for eg, mRNA levels do not correlate necessarily with protein levels. We are thus yet to define the specific questions, backed with scientific rigor, while addressing infrastructure issues. An area that could be important is understanding micro changes in plasma protein levels. It does appear that the 22 most abundant proteins such as albumin and immunoglobulins make up 99% of the plasma. The remainder of the tens of thousands are a combination, including intracellular and cell membrane proteins indicating cell turnover. The metabolome measuring protein <2 kDa could be used to detect certain components. An example of interest is in chronic obstructive airways disease, where levels of protein turnover were increased.[129] Could this be used to detect general levels of health? The issue of whether the genome, proteome, or metabolome is best studied is thus important.[130–132]
2. *Biopsychosocial factors in decision making:* it is vital we tie an understanding of the social, psychological, and biological factors that dictate a clients' decision analysis. Communities have to be approached in advance and the benefits advocated, so the research is translational.

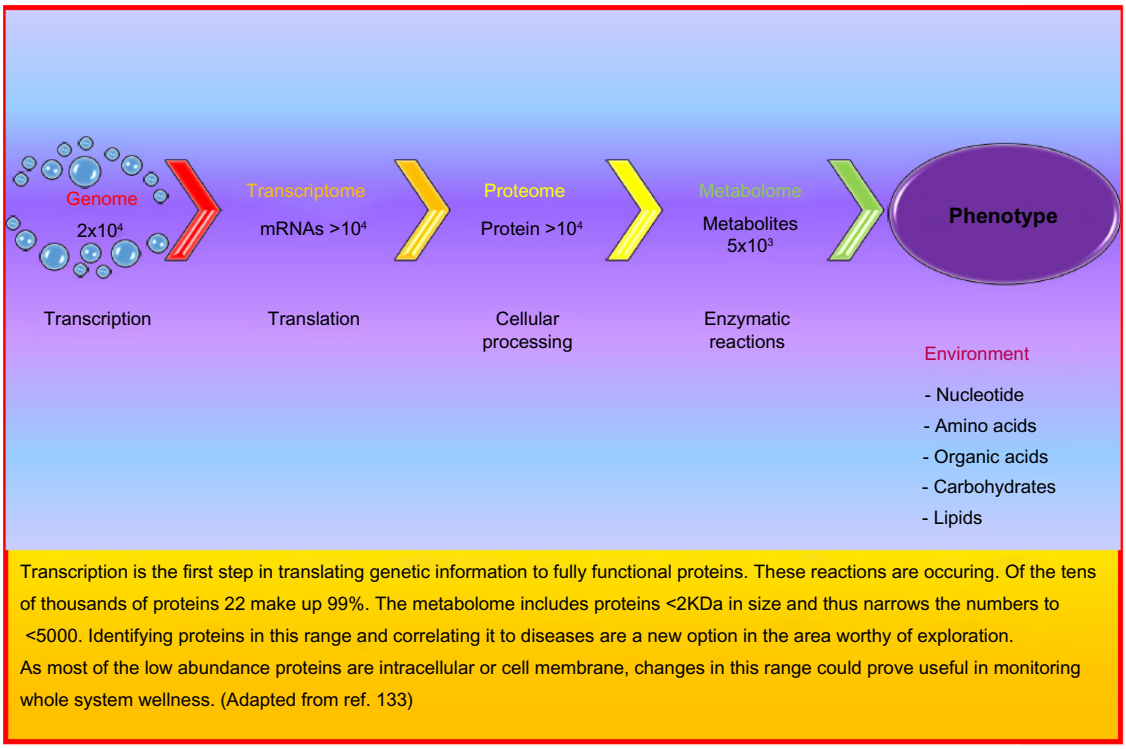


Figure 2. The gene protein highway.

3. *Models to help define the right questions:* it still remains unclear if specific groups would greater benefit from directly assessing the proteome or genome. From studies on biomarkers like troponin, we find good generalizability. These sorts of physiological understanding could be universal. In more selective cases of receptor or cytochrome system polymorphisms, there could be benefit. We are yet to define the role polymorphic alleles play in accelerating or slowing disease or responses to therapeutics for indigenous clients. The family health history (FHH) assessment highlights one such approach.[133,134] Systematically identifying targets through consensus could also be useful.

On the fifth point, there has only been a handful of heart transplants for indigenous Australians and few presently get worked up for such defining therapies. Device-based therapies have benefited; however, the distance from treatment centers prevents the very best of outcomes when combined pharmacological and device support is implemented. Introducing novel therapies or ideas should be factored (Fig. 3). Exploring a wider role for cellular or gene-based therapies has shown promise. Improvements in cardiac function approaching double digits have been reported. In addition to disease-specific benefits, evidence is also developing for a wide pleiotropic effect. The ability to replacing lost and aging cells, with wide systemic effects (autocrine and paracrine effects, improved eGFR, reduced inflammation, improved DM), makes this form of therapy more attractive for clients who are not on the best available *game changing* therapies and for critical ill HF patients, even for a short period during their recovery. Many questions about the type of cell, delivery methods, and frequency will undoubtedly remain, but is not a cause for hindrance.[135–149]

Finally, the National Health Medical Research Council (NHMRC) and other position statements for research in indigenous populations are well established. Respecting codes of conduct and defining questions that are perhaps potential *game changers* and presenting these to indigenous communities, even if they sit on the boundaries of cultural acceptance, should thus be explored. How these issues are defined will remain difficult. It is however fair to say that the spirit coming from the research team is important. The paradigm will undoubtedly change, but we should allow this to occur at its natural speed and volition.[118,150] In summary, with escalating costs, workforce issues, and complex nature of multidisciplinary care, may not entirely address the basic factors like compliance.[151] Efficiency and simplicity is an important goal and is achievable by fine-tuning available evidence with contextual planning of potential novel options.

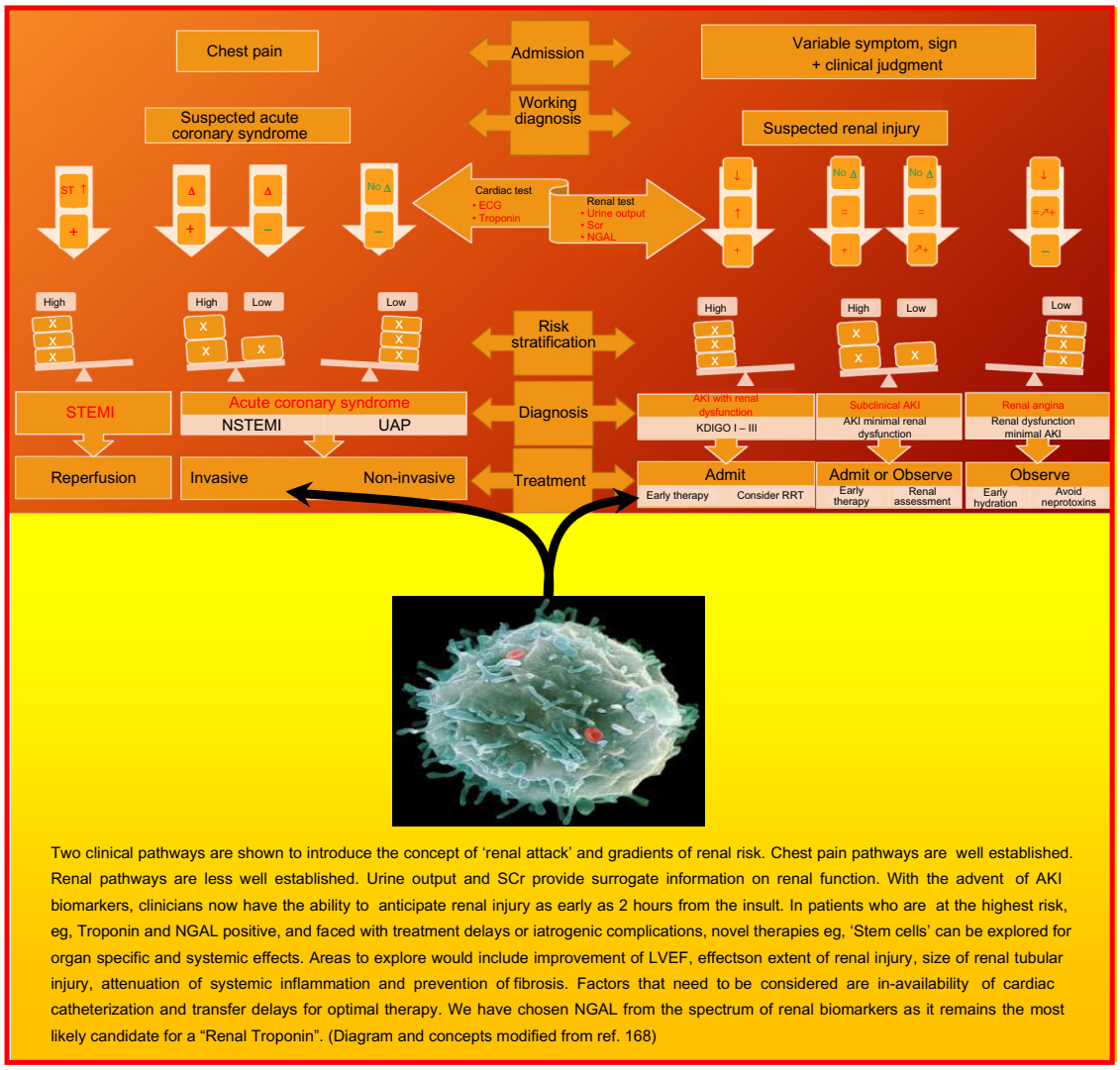
Models for CHF Translation

Databases to pool available resources and to develop suitable models to test novel ideas are at the heart of these discussions. Many remain unconvinced of the boundaries between evidence from animal work and human clinical translation at least when developed by public academia, although this is the pathway usually behind closed doors, for drug manufacturing in the private sector. Let us explore both these points.

Expanding regional client data and collaboration. There have been a few endeavors to collect and generate data on proteomics and genomics. The current health system is focused on delivery, and in the vast majority of cases, this has been at a high standard. Thus, the mood for resources to be diverted into such niche areas is not there. In addition, the cost and lack of translation of this science further supports this reasoning. The Framingham study, however, reflects what systems can gain with correct planning. In the current era, it is easier to share knowledge and link datasets to extract information with data mining. This is the simplest method for finding newer surrogate markers of risk. This translational block in many systems is usually administrative. An innovative progress in the area is the freely available Human Protein Atlas that collects and stores information on healthy human tissues that then can be used to identify biomarkers in non-failing hearts.[152] Understanding whether the identified protein is relevant, we can then use animal models through collaboration with heart banks such as the Sydney Heart Bank, which has stored more than 500 hearts over 20 years.[153] It is important that health professionals and systems continue to invest in these types of thinking and store samples where an uncommon event is noted even if no current studies are thought of presently.

Expanding regional diagnostic and therapeutic evidence. It is important again for systems to plan how they are going to gain the evidence using suitable bench models. Such models can be used to understand cellular changes with disease and how they are influenced by the therapies we deliver. In the first part, a strong set of guidelines is needed to shape similar strengths that are seen from the RCT. We had previously discussed the internal validity questions for clinical studies.[5] Similarly, a strong foundation is needed for standardizing animal work and ensuring high rates of translation to clinical work. Many continue to question the adequacy of reporting in biomedical research, with Kilkenny et al using the term *fit for purpose* to describe the limited value of many studies as agents to actually inform clinical practice or policy. Specifically, nearly half of the 271 surveyed studies reported objectives and hypothesis and more than two-thirds did not report measures to reduce bias or statistics.[154,155] Similar to other checklists for RCT,[156] the Animals in Research: Reporting In Vivo Experiments (ARRIVE) guidelines for reporting in vivo experiments are based on the CONSORT statement for RCT and provide a strong platform to plan research.

HF models are well described with pros and cons for small and large animal models. Transgenic, which adds further science, is worth mentioning but not the scope of this paper.[157] Mouse models are attractive to studying the



Two clinical pathways are shown to introduce the concept of 'renal attack' and gradients of renal risk. Chest pain pathways are well established. Renal pathways are less well established. Urine output and SCr provide surrogate information on renal function. With the advent of AKI biomarkers, clinicians now have the ability to anticipate renal injury as early as 2 hours from the insult. In patients who are at the highest risk, eg, Troponin and NGAL positive, and faced with treatment delays or iatrogenic complications, novel therapies eg, 'Stem cells' can be explored for organ specific and systemic effects. Areas to explore would include improvement of LVEF, effectson extent of renal injury, size of renal tubular injury, attenuation of systemic inflammation and prevention of fibrosis. Factors that need to be considered are in-availability of cardiac catheterization and transfer delays for optimal therapy. We have chosen NGAL from the spectrum of renal biomarkers as it remains the most likely candidate for a "Renal Troponin". (Diagram and concepts modified from ref. 168)

Figure 3. Hypothetical scenarios for novel biomarkers and therapeutics trials.

molecular basis of HF.[158] However, rodent and human hearts differ physically in architecture, protein expression, contractile apparatus (differing in predominant myosin isoforms), adrenergic receptor ratios, and stem cell populations and physiologically in heart rates, oxygen consumption, contractility, and response to loss of regulatory proteins. Large animal models of HF better approximate human anatomy and physiology. In fact, studies with a matrix metalloproteinase inhibitor and levosimendan transitioned from such models,[159] and the evolving areas of cellular therapies.[160] The pig model of balloon occlusion of the left anterior descending produces predictable infarct sizes, and similar coronary circulation and collateral development, size, and cardiac physiology to human beings makes this an attractive model for postinfarction remodeling and dilated cardiomyopathy development, progression, and response to therapies. This model requires skilled personnel, surgical facilities, and specialized equipment and is costly. Chronic pacing of the left atrium or ventricle produces a reliable and reproducible model of DCM and chronic HF. Deciding on the best model of surgical, pharmacological, or electrically induced organ damage is still unclear but should be explored based on the question and outcome desired and actual survival of the animals.[161–164]

Comorbidity models are more difficult to design as they may create the physiological environment for a short period but does not necessarily standardize the severity or factor the chronology of events in human beings. For diabetes, pancreatic toxicity produces insulin-dependent diabetes and potential cardiomyocyte toxicity, while an overfeeding model produces insulin resistance (IR) but is confounded by hyperlipidemia in rodents. Genetically engineered models of IR produce rapid progression of CM, for understanding IR on myocytes; however, many other features do not reflect patterns in human beings. Furthermore, large animal models are lacking.[165,166] Similarly in the CRS, only a few rodent models are established. These are surgical, uninephrectomy or subtotal nephrectomy producing mild to severe RI, or acute

pharmacologically induced changes to the heart or kidney. In contrast, human CRS is often a chronic process over years. Genetic manipulation is an avenue that is being considered.[167] It is thus even more vital that we understand and develop the surrogates for specific organ damage to standardize a baseline and monitor progress. Finally, to achieve all this, we feel that there has to be greater clinician–scientist collaboration. Greater efforts also have to be made to publish detailed methods of the work, as is done in clinical studies, particularly if they are aimed to go on to inform clinical practice or clinical trial in human beings.

Factors bridging basic and clinical research. In Australia, funding is competitive thus, research groups tend to work in silos. There are, however, institutions like the Baker IDI Heart and Diabetes Institute where basic and clinical researchers are under the same roof. Even without such formal links, for a working system, it is vital that basic and clinician researchers team up with full-time clinicians, so there is a direct link between science and patients and vice versa.[5] Training colleges and governing bodies could start by creating regulations for accountability. The process of questioning will lead to a need for solutions and perhaps greater interaction between those generating and those translating evidence.

Conclusions

CHF best practice does not stop at the RCT. There are a whole range of factors at play to ensure the communities we care for receive the greatest benefit from their treatments. Much of this will relate to enhancing translational research in the clinical domain. Some of it will require more basic research. This second phase, *bedside-to-bench* translational research, is also important and is often overlooked. While bench-to-bedside approaches, rightly, target universal appeal, posttranslational research, the second phase of translation or *bedside-to-bench* approach is more likely targeted. It is vital, however, that we also recognize that the science for this aspect is evolving and in many areas poorly developed and perhaps conjectural. It is thus important we focus on what is known and gradually develop what is unclear. The most viable option at this stage would be to find evidence to broaden the therapeutic paradigm for drugs within a class that show additional extra class benefits. In conjunction, we need to refine methods to perform and report animal work and gradually transition to larger animal models. The more novel ideas could potentially be incorporated into an agenda and the feasibility monitored. Thus, many questions remain on how we best move forward. For our region, we see this as an opportunity to close important gaps while trying to find solutions to keep a lid on costs and ensure that population-level CHF best practice is achievable.

Abbreviations

AKI: acute kidney injury
EF: ejection fraction, surrogate for cardiac function
EKG: electrocardiogram
NGAL: neutrophil gelatinase-associated lipocalin
NSTEMI: non-ST elevation myocardial infarction
ST: segments
STEMI: ST elevation myocardial infarction
Sym: symptom
UAP: unstable angina pectoris
UO: urine output.
Symbols: ↑: increased
↓: decreased
↗: trend
+: positive
−: negative
±: equivocal
Δ: changes
≈↗+: range from equivocal to positive.[168]

Disclosures

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Author Contributions

Wrote the first draft of the manuscript: PI. Contributed to the writing of the manuscript: PI, MT. Agree with manuscript results and conclusions: PI, MT. Jointly developed the structure and arguments for the paper: PI, MT. Made critical revisions and approved final version: MT. Both authors reviewed and approved of the final manuscript.

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