Phase 4 Studies in Heart Failure - What is Done and What is Needed?

Pupalan Iyngkaran1,*, Danny Liew2, Peter McDonald3, Merlin C. Thomas4, Christopher Reid5, Derek Chew6 and David L. Hare7

1Cardiologist & Senior Lecturer NT Medical School, Flinders University; 2Chair Clinical Epidemiology University of Melbourne and Director of the Melbourne EpiCentre; 3Medical Director Heart Transplant Program, St Vincent’s Hospital, Sydney, Professor of Medicine, UNSW, Head Transplantation Research Laboratory, Victor Chang Cardiac Research Institute and Visiting Cardiologist, Condobolin Aboriginal Health Service, Condobolin, NSW; 4NHMRC Senior Research Fellow Baker IDI Heart and Diabetes Institute, Melbourne Victoria 3004, Australia; 5Cardiovascular epidemiologist and Assoc. Director of the Monash Centre of Cardiovascular Research and Education in Therapeutics; 6Regional Director of Cardiology, Southern Adelaide Local Health Network, Flinders Medical Centre, Head of the Flinders Clinical Trial Centre, and Chair of the Statewide Cardiology; 7Coordinator, Cardiovascular Research, University of Melbourne; Director of Heart Failure Services, Austin Health, Melbourne, Australia

Abstract: Congestive heart failure (CHF) therapeutics is generated through a well-described evidence generating process. Phases 1 – 3 of this process are required prior to approval and widespread clinical use. Phase 3 in almost all cases is a methodologically sound randomized controlled trial (RCT). After this phase it is generally accepted that the treatment has a significant, independent and prognostically beneficial effect on the pathophysiological process. A major criticism of RCTs is the population to whom the result is applicable. When this population is significantly different from the trial cohort the external validity comes into question. Should the continuation of the evidence generating process continue these problems might be identified. Post marketing surveillance through phase 4 and comparative effectiveness studies through phase 5 trials are often underperformed in comparison to the RCT. These processes can help identify remote adverse events and define new hypotheses for community level benefits. This review is aimed at exploring the post-marketing scene for CHF therapeutics from an Australian health system perspective. We explore the phases of clinical trials, the level of evidence currently available and options for ensuring greater accountability for community level CHF clinical outcomes.

Keywords (MeSH): Clinical Trial, Congestive heart failure, Drug Surveillance, Review, Phase IV, Post-marketing Surveillance.

INTRODUCTION

Clinical evidence is the process of generating data that can be translated for safe and acceptable clinical use. Clinical audit is the process of generating data that can inform if the implementations of clinical evidence are benefiting the population being treated [1, 2]. In congestive heart failure (CHF), many drugs that are approved by the therapeutics goods administration (TGA) and subsequently accepted onto the national pharmaceutical benefits scheme (PBS) would have undergone a large multicenter randomized controlled trial (RCT). Drugs are then subsidized based on criteria where only a CHF patient can receive a HF class beta-blocker (β), angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor antagonist (ATRA). For arguments sake, should another class of medication be shown to be beneficial for comorbidities such as diabetes or renal failure, but not proven in CHF, this medication can be provided to one group but not the other. In addition this process fails to recognize a host of other real-world considerations [2-5]. In theory this issue can be negated should phase 4 studies be given equal priority to the RCT from which the guidelines for use and administration are derived. Some unanswered questions include who is responsible for post-marketing surveillance, what is the most cost-effective means to do so [6-12], and what is the argument for CHF? CHF is a chronic condition with high morbidity, mortality and cost, needing multicomponent management including lifelong medication, polypharmacy and often without cure. Comorbidities are present at onset in nearly half or will develop at some point in all. Numerous factors can affect response to therapies including age, sex, ethnicity, body size, family history, smoking status, diseases in excretory organs,
disease severity, drug interactions and compliance. Many of these patients are not represented in the major RCT’s [3, 4]. The clinical evidence is largely generated in a controlled setting but subsequently distributed into an uncontrolled environment. Thus there are a broad range of clinical questions to be factored, and not to forget costs which equates to 1-2% of health budgets [13, 14]. The purpose of this review is to explore the area of post-marketing research, the types of studies that provide evidence to influence practice, and the requirements needed for adequate monitoring of CHF. It is hoped that these discussions will raise the importance for the need to continue to monitor the implementation of therapies at the community level.

PHASES AND COST OF EVIDENCE GENERATION

Development of therapeutics and evidence to determine their safety, efficacy and effectiveness is generated and translated through a series of steps. Clinical evidence is generated from the ‘bench to the bedside’ through phases 0 - 3 and perfected from ‘bedside to beyond’ with phase 4 and 5 [13]. The ‘bench’ is often referenced with context to experimental research, usually in animals that form the foundation for first in man studies. ‘Translation’, as defined by The National Center for Advancing Translational Sciences (NCATS), is the process that brings the bench observation into the clinical domain to help improve the health of individuals and their communities, and encompasses all facets from, diagnostics, therapeutics, to medical procedures and even behavioral changes. At the heart of all this is the search for efficacy, effectiveness and quality [1, 2, 15-18]. Box 1 explores these steps in greater detail.

Preclinical Studies

In-vivo and in-vitro testing with non-human subjects is often the first step in development of novel therapies. Wide dose ranges, efficacy, toxicology, as well as improved pathophysiologic understanding are established. An important point established is the No Observable Adverse Effect Levels (NOAEL), which is used to determine initial first-in-man drug dosage and status for development as investigational new drug (IND). This so-called non-clinical phase in drug development is largely done by private industry where much of the knowledge is not published, although standards are adhered to [18-20]. Examples of preclinical development by academia which were open to scrutiny can be seen with mineralocorticoid antagonist and the ATRA - losartan [21, 22], which will be discussed later. There remain concerns however about the adequacy of reporting and ‘fit for purpose’ of many studies to inform clinical practice or policy [23-25]. It is our view that preclinical studies should be viewed twofold: firstly, studies that bring a novel therapy into the clinical domain (mainly industry); and secondly, studies that evolve from new hypothesis following post-marketing surveillance (mainly academia). This type of indication can form the basis for equivalence studies or expansion of an indication of drug within a class [15, 16, 26-33].

Clinical Studies

1. Phase 0 Studies: First-in-man studies, using an IND and microdosing techniques to determine/evaluate pre-liminary mechanism of action, target modulation as well as pharmacokinetic and dynamic relationships and similarities with preclinical studies. One in four drugs fail to progress [26, 27].

2. Phase 1 studies: Often healthy volunteers, to assess safety, tolerability and additional pharmacokinetics and pharmacodynamics e.g. dose range, maximum tolerated dose, and early insights into efficacy is derived.

3. Phase 2 studies: Testing of biological activity and efficacy of treatment at various dose ranges – leading to establishment of treating protocols. Often conducted as case series and occasionally with a randomized design. Surrogate endpoints (often biological markers) or short-term clinical well being can also be ascertained.

4. Phase 3 studies: Conduct of a clinical trial to test ‘treatment efficacy’. All aspects of the research design are optimized and controlled (internal validity is of primary importance), resulting in the best possible surrogate for laboratory like environment where the maximum potential of the treatment can assessed (against current commonly used agents or placebo), while removing all confounders (provides risk-benefit analysis).

Post-marketing Surveillance

1. Phase 4 Studies: Post approval studies or ‘pharma-covigilance’, aimed at determining ‘treatment effectiveness’ or the maximum benefit in the real world or day-to-day clinical practice. Often underutilized in regards to extension of benefit when there is less than usual clinical support, in minority communities or clients with comorbidities. External validity is of primary importance. Technical support for the monitoring that come from regulatory authorities or sponsoring companies.

2. Phase 5 Studies: Translational research in reference to who benefits from the treatment and the cost or cost-effectiveness/equivalence.

The Cost and Considerations in Drug Development

Impetus for innovation in new treatments factors in cost, risk and the protracted process from discovery to approval. Costs from development to approval have escalated by 145% since 2003 to $2.6 billion US dollars. Further $312 million is spent on post approval development. On average, only 3 in 10 drugs recuperate the investment costs, which are not helped by issues such as loss of patent protection. For CHF therapeutics, clinical trialing averages 5.2 years, approval phase 1.7 years without including preclinical development coupled with high attrition rates (Box 2) [30-32].

A second consideration, in technical aspects clinical trials can be highlighted by several examples. Firstly, Krum et al highlighted the concepts of ‘regression to the truth’ and reaching of pharmacological ‘threshold’ as possibilities. Supporting these arguments is the translation of surrogate markers to clinical outcomes which many question as unreli-able. Highlighting failure of 3 drugs it was noted that short-term hemodynamic parameters and exercise tolerance...
### Box 1. Phases of Clinical Trials

| Phase      | Primary goal                                                                                     | Dose                                           | Patient monitor                          | Sample Size | Notes                                                                                                                                 |
|------------|--------------------------------------------------------------------------------------------------|------------------------------------------------|------------------------------------------|-------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Preclinical| Testing of drug in non-human subjects, to gather efficacy, toxicity and pharmacokinetic information | Unrestricted                                   | A graduate level researcher (Ph.D.)       | Not applicable (in vitro and in vivo only) | Criticisms about quality of published material |
| Phase 0    | Pharmacodynamics and pharmacokinetics, particularly oral bioavailability and half-life of the drug | Limited, very small or sub-therapeutic dosing, only to achieve target modulation, thus less risk of toxicity | Clinical researcher                       | 10-15       | No therapeutic intent often skipped for phase I                                                                                 |
| Phase I    | First administration of new treatment Primary goal: to determine maximum tolerated dose (MTD)     | Multiple dosing starting sub-therapeutic with dose escalation aimed at establishing safety and toxicity | Clinical researcher                       | 20-100      | Primary goals: to evaluate mechanism of action/target modulation; assess PK/PD relationships; optimize target assay                    |
| Phase II   | Early Trial in patients                                                                          | Therapeutic dose                               | Clinical researcher                       | 100-300     | Safety – is further investigation warranted?                                                                                         |
| Phase III  | Large scale comparison versus standard treatment                                                 | Therapeutic dose                               | Clinical researcher and personal physician | 300-3000+   | Efficacy – dose ranging, adverse events, pathophysiologic insights                                                                  |
| Phase IV   | Post-marketing surveillance – monitoring in clinical practice                                    | Therapeutic dose                               | Personal physician                       |             | Determines a drug's therapeutic effect; at this point, the drug is presumed to have some effect                                    |
| Phase V    | Translational research                                                                           | No dosing                                      | None                                     | All reported use | Research on data collected                                                      |

Edited from Ref 1, 2, 13, 14
measures were divergent from longer-term outcome measures [26]. Secondly, there are also a significant number of good drugs that fail due to outdated and poor clinical trial design. This old paradigm established in the 1960s was designed to answer one question, at one site, and from one single trial [33]. While we have moved on in size and sites, the efficiency quota for real-world applications remains wanting. Part of this highlights the greater needs for planning in phase II testing, which could involve standardizing surrogate biomarkers or even health economics, in conjunction with many other new developments [34-40]. In this complex mix it is worth asking again, what is translatable evidence, who is now responsible for discovering, marketing, surveillance, translating and increasing the external validity of therapeutics?

WHAT IS THE EVIDENCE FOR PHASE 4 STUDIES IN HEART FAILURE?

Post-marketing studies in CHF have either been surveillance of one agent or prospective audits of clinical care. These studies can be extrapolated to represent phase-4 studies as clinical guidelines and a robust range of therapeutics have been established; although they do not answer all the relevant phase 4 points. Pooled data have gone on to consolidate on the efficacy of these agents and clinical audits have shown effectiveness but also highlighted important gaps. We have initially provided a quick synopsis of novel therapies in the pipeline to contextualize the value for ongoing trials to establish new therapies. These data are presented:

**Novel Therapies**

Studies expanding the clinical utility of beta-blockers (β), ACE-I, ATRA and mineralocorticoid receptor antagonists (MRAs) have been key developments. These agents alter pathophysiology, improve hemodynamics, symptoms and clinical outcomes. The majority of therapies have targeted patients with systolic HF. In-contrast options for acute decompensated heart failure (ADHF) and HF with preserved ejection fraction treatments have not altered significantly. Many promising agents including inotropes and selective vasodilators actually increased mortality. Other agents tried without influencing morbidity and mortality, including endothelin-1 (ET-1) antagonists, antioxidants, vasopeptide inhibitors and cytokine inhibitors. There are a number of therapeutic targets on the horizon (see tables in references), which await exploration or positive results [40, 41].
Clinical Databases and Health Systems Intervention Studies

International prospective databases, not targeted at any particular therapeutic agent, have highlighted: higher short term mortality, early readmissions, variable intensity of follow-up from primary to tertiary care, patients who would not qualify for RCTs outright, multiple concomitant comorbidities, diverse ethnic-socio-cultural-geographical demographics, lower use of echocardiography and therapeutics; which are different to the setting of most clinical trials. When the diagnosis of ADHF is made, there is greater implementation of guideline therapeutics, but not so in renal failure of all grades. There is also great variation in practice [42-49]. The major health systems intervention studies, OPTIMIZE-HF and IMPROVE-HF showed that inpatient and outpatient care can be improved by addressing care delivery [50, 51]. Asian pacific databases from Japan showed similar characteristics but with greater use of ARB and longer hospital stays (median 21 days) [48, 49]. In other parts of the Asia-Pacific, retrospective case reviews highlighted gradients across mature countries of more severe clinical symptoms and signs at younger ages, less frequent use of echocardiography and prognostic therapeutics [52], however common traditional risk factors posed equal risks regardless [53].

Specific examples for Australia are presented in Box 3 [54-86]. There is no published evidence of a comprehensive prospective CHF audit. Discussions on Indigenous Australians are presented elsewhere [87]. There are however national and selective state based data to suggest that many aspects of comprehensive CHF care are comparable or better than internationally published standards particularly in mortality and utilization of best practice. Morbidity, hospitalizations and cost remain major issues. There is heterogeneity in care delivery peaking at capital cities and stagnating in rural areas. Lower socio-economic status and Indigenous groups also lag in outcomes. Important gaps that have not been adequately studied are comorbidities, polypharmacy, greater role for nurse lead care, self-care and roll out of technology [5]. There remain potentially important questions on effectiveness, cost effectiveness and perhaps efficacy.

Systematic Reviews and Meta-Analysis of Prognostic Therapeutics

ββ with proven benefits include carvedilol, bisoprolol, metoprolol XR and in the elderly nebivolol. Chatterjee et al, compared different ββ head to head and noted no difference in mortality, discontinuation or improvements in left ventricular ejection fraction (LVEF). This appears globally and in real world clinical practice. It is accepted that the magnitude of heart rate reduction using HF class ββ’s are vital [88-90]. It remains unclear: the extra class benefits and role of vasodilator ββ’s for the lifelong use in HF with comorbidities; prescription consistency, tolerability and compliance outside urban areas; and pharmaco genomics in some groups in Australia [3-5, 91-95].

The story is more complicated for renin angiotensin aldosterone system (RAAS) blockers. ACEIs are first line therapies for treatment or prevention of CHF, hypertension, diabetes, renal impairment, vascular bed atherosclerosis, either as the primary disease, comorbidity, with or without end organ disease from the earliest stages to the more advanced. ARBs, were introduced as an alternative with lower side effects such as cough, greater tolerance and perhaps now efficacy approaching ACEI, and with arguments for greater cost effectiveness. There remain important physiological differences between the 2 classes of drugs from primary action, pleiotropic effects, other extra-class benefits and contextual race responses [96-123]. When we look at selective examples for ACE-I, there are some who argue that one agent such as perindopril could be superior in its class [124]. In studies such as Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALL-HAT) and Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, African American patients receiving lisinopril or losartan had higher relative risk of CHF [125].

The ONTARGET trial and the study of Telmisartan in CHF and hemodialysis has raised important questions of the growing benefit of ARB at least for the agent in question. With additional data on tolerability across all racial profiles, pharmacological stability, pleiotropic effects for all comorbidities, questions can be asked as to whether the therapeutic paradigm could be widened when patients not meeting trial conditions are being treated [125-133]. Finally, aldosterone antagonists are now proven therapy for all classes of CHF, and the guidelines to follow suit. The main difference between 2 established agents is the sexual side-effect profile, potential for adverse drug interactions and cost benefit when all factors are considered [134-136]. These points highlight that there are still posttranslational factors that remained unresolved with RAAS blockers.

UNDERSTANDING THE CONSIDERATION AND CONTEXT FOR TRANSLATING AND EXTENDING THE EVIDENCE THE BASE

Generating evidence and interpreting evidence are mostly independent processes. This independence also means that regulatory bodies have no control over the breadth and depth of evidence presented when regulating for populations. Thus the three important questions of efficacy, effectiveness and cost-effectiveness are not always available. A combination of structured guidelines and judgement are needed. Let’s explore some important points:

What Constitutes Translatable Evidence?

There are no agreed rules on how evidence is interpreted and choices made for a particular agent, a class, extra class benefits, the primary disease treated, should there be evidence for competing agents within a class, physiological targets as primary mode for decision making, the role of pill burden and the auditing of off-label use in Australian clinical practice. An important correlation can be made where physiological effects are used in device guidelines but not in therapeutics. There is an established process to translate controlled evidence from RCT to the clinical domain regulated by the pharmaceutical governing authorities in each country. Further scrutiny, more related to cost-efficacy, are made by formularies in treating institutions. Thus the vast majority of practitioners have no say in the process. We do however see selective publications, uncontrolled for bias, voicing
## Box 3. Australian Data for Heart Failure.

| Theme           | Data Source Reference | Positive Findings                                                                 | Negative Findings                                                                 | Notes                              |
|-----------------|-----------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------|
| Databases       | Prospective Registries [52-60] | - Risk factors contribute equally to HF death regardless of SES or race          | - Underutilization of HF therapies in pts undergoing PCI                         | Unrepresentative demographics      |
|                 |                       | - No significant gender differences in HF management                             | - Many clinical HF cases remained undiagnosed                                     | Limited data                      |
|                 |                       | - Higher EF but more severe NYHA class among women                               | - Majority of LV dysfunction in preclinical stage                                 | Extrapolation from non HF dedicated registries |
|                 |                       |                                                                                  | - Suboptimal prognostic HF therapeutics post MI                                  | Aging data                        |
|                 |                       |                                                                                  | - Increased prevalence of CHF, and significantly lower use of diagnostic and therapeutics in rural areas. |                                   |
| Data Linkage    | [62-68]               | - Similar outcomes in male, females and elderly in WA                            | - Remote areas, variable access to care and Indigenous pts to care poorer outcomes | Overall admissions and mortality from national data, other data predominately from 2 states |
|                 |                       | - Encouraging declines in overall HF mortality, and index admissions overall     | - Growing burden of HF hospitalization of non-ischemic etiology                   | WA - probably accurate data with previously published validation of methodology |
|                 |                       | - Prognostic therapies well utilized with demonstrated benefits in improved long-term survival | - High mortality persists particularly in high risk groups                        | Modelling and statistical techniques used to extrapolate data is some cases    |
|                 |                       | - Decline incidence and improvement in survival early onset HF after Min in WA  | - Cost and acute bed occupancy remains significant more so in elderly (NSW)       |                                   |
|                 |                       | - No Increase in late-onset HF mortality in WA                                   | - Echocardiography underutilized                                                 |                                   |
| Retrospective Reviews | [52, 70-74]     | - Comparable standard of care to international best practice achievable          | - Poor outcomes related to SES                                                   | Prospective data needed           |
|                 |                       | - Collaborative medicines review effective in delaying time to next HF hospitalization |                                                                                  | Efficient measures are needed to deliver comprehensive care                  |
| Intervention    | Surveys [78-81]       | - High intensity CHF MP applying more evidence based interventions improve outcomes | - Inequitable access and distribution of CHF MP, particularly outside capital cities | Improvements have been made in information availability and distribution via NHF, since these publications |
|                 |                       |                                                                                  | - Substantial heterogeneity between CHF MP                                       | No national credentialing process for CHF MP’s                                |
|                 |                       |                                                                                  | - Dissemination of written information suboptimal                                |                                   |
| Patient Contact | [80]                  | - Nurse lead care in CHF MP’s supplemented by technology can improves outcomes increase compliance | - Numerous unaddressed issues for acceptance, staffing, remuneration, protocols and standards in allied health lead and technology assisted care | Nurse-lead and technology assisted care previously discussed (5, 104) |
|                 |                       |                                                                                  | - Self-care findings variable                                                     | Well thought out studies on integrating self-care, allied health staffed and technology assisted CHP MP’s needed |
|                 |                       |                                                                                  |                                                                                  | Mental health and depression data lacking                                      |
preference for particular agents or combinations. These perhaps reflect observations made from clinical experiences from a broader cohort of patients.

Are there Examples of Heterogeneity of Practice where the Evidence could be Interpreted Differently?

Variations in clinical responses of blood pressure lowering medications between white and black patients have been noted from early studies and subsequent meta-analysis. These highlighted favorable responses to calcium channel blockers (CCB) and diuretics over ACEI and β-blockers. Poorer outcomes were later noted with Lisinopril (ALLHAT) and Losartan (LIFE) studies. Additional benefit with isosorbid and hydralazine, and preliminary evidence for lower frequency of responsive genotype to metoprolol in blacks, adds impetus for new thinking that variations in either physiology or response do exist. Some of these points are gradually making it into the guidelines [137]. The question remaining is what other ethnic groups is this relevant to? Thus this remains a dilemma faced by many physicians who are treating patients of diverse ethnicities. Another example is the role of pharmacotherapy post myocardial infarction (MI) when the LVEF is >40%. Reperfusion therapy remains first line at many smaller and remote centers. Reperfusion injury is recognized, and remains inadequately addressed. The CCBs, verapamil and diltiazem, were shown to prevent no-reflow/slow-flow and wall motion index when given pre-thrombolytics. Verapamil use post MI may improve mortality, reduce reinfarction and reduce late onset HF [138-140]. While the study numbers were small the results are worth considering. Development in acute interventions shaped acute therapies in major centers with clear reductions in all forms of HF. However in many smaller or remote centers late onset HF rates are unclear. Overall as these newer therapies have superseded thrombolytics, this type of thinking is no longer reflecting in the guidelines.

Finally, omega-3 an essential lipid had early data showing benefit in CHF, MI and reducing sudden cardiac deaths [141]. Subsequent studies and pooled data where not encouraging. In one study, over 12,536 diabetic patients aged 50 years and older, were followed for mean 6.2 years. These patients were given a low dose of 1 g of n-3 fatty acids (containing 465 mg of eicosapentaenoic acid [EPA] and 375 mg of docosahexaenoic acid [DHA]) and no dietary restriction. No blood levels for EPA or DHA were tested. There was no difference in major outcomes between the groups [142, 143]. The evidence also tells us that dietary sources of omega-3 and blood levels predict outcomes [144, 145]. How does one safely negotiate this? There have been trials that support, others that do not, meta-analyses in favor and others against. In Australia the Heart Foundation provided a position on omega-3 in 2008. The national Pharmaceutical Benefits Scheme did not endorse this perhaps reflecting the lack of cost benefit from these negative studies. It is however clear there are differences in all the studies, and the questions looked at in the meta-analyses. How do we approach this for our patients, who can’t meet the dietary requirements, with more advanced disease, more comorbidities, or unable to tolerate all best practice medications?

Interpreting Clinical Trials and Meta-Analysis

Clinical experiments are valid if a cause and effect is established with all biases accounted. The most powerful evidence-generating tool is the Randomized Control Trial (RCT) and evidence syntheses tool are systematic reviews and metaanalyses. To ensure biases are controlled, criteria are placed for the internal validity. The resulting finding allows causal inference for any finding to the population enrolled in that study. In time, a pool of knowledge will accumulate. Systematic reviews are publications that include studies from a defined period, sometimes ranking them, with a well formulated clinical question, systematic and reproducible methodologies, thus establishing the weight of this scientific evidence. As described by Robey “A fundamental tenet of science holds that the best estimate of a population characteristic is the pool of all valid and independently obtained estimates of that characteristic. Therefore, a meta-analysis achieving a positive outcome forms very strong evidence of treatment efficacy”. This principle is based on the RCT’s findings that estimate the size of the treatment effect, which can then be mathematically integrated to estimate the average or common effect. When data pooling is not feasible results are presented as number of studies in support or against or ‘vote counting’ [31, 146-148].

Pooled research studies are among the simplest forms of post marketing research that address efficacy. The role of
systematic reviews and meta-analyses in clinical practice has however varied [149-162]. Berlin et al. argues that a large RCT will always be required to influence regulatory bodies. As it is not often possible to replicate studies, nor should they be encouraged, pooling data often has differences from the start. So, meta-analyses can perhaps play a complementary role by strengthening support for the evidence. Thus pooled data should be considered among the strongest sources for post-marketing evidence, however on their own should not be used to derive clinical decisions.

What are Important Considerations for Designing Post-Marketing Evidence?

In the examples mentioned above, pooled data can provide a synopsis of evidence that has already been generated; audits address community level efficacy or potential gaps and health services intervention efficacy and cost effectiveness. In most health systems there are a number of these fundamental questions. Four important points should be factored before exploring suitable studies:

1. **Generalization**: As clinicians, we are keen to see that the efficacy observed in the more selected populations of clinical trials is confirmed in the less restricted populations of registries. With audits, the real problem is the lack of randomization.

2. **Value for the patient and health system**: Clinical practice should be an exercise in finding value. Clinicians may value harder outcomes while patients may value quality of life. Nevertheless, the exercise of pursuing value leads one to the point of choosing therapies with the most value, and therefore into the realm of cost-effectiveness.

3. **Extending the choice between therapies**: Given the historical sequence of the developing evidence base, analyses of formal studies to explore the utility of older therapies in the context of established newer therapies are always needed. This is important for valuing the incremental value of each therapy when one must choose, either at a patient or health service level.

4. **Health systems change**: All innovations in diagnosis and therapy require a commensurate adaptive change in clinical and health service delivery if the promised benefits are to be realized. Studying the health clinical and health service determinants of effective translation therefore is also an important goal.

The crux of phase 4/5 studies is to identify if treatments efficacy can be replicated in the community and the cost. To achieve this value we also need information to compare. For example, with therapeutics the benefits of an agent in a class for the patient with the disease, combinations of disease
Box 5. Interpreting clinical trials.

Basic principles guide evidence generation and interpretation. Two common abbreviations, FINER and PICO, can be used to explore the relevance of trials and data pooling research. More specifically the top boxes present the common terminology, factors relevant to internal and external validity and interpreting clinical trials. The REAIM framework bottom left addresses important points in translational research (Adapted from ref 4, 151-159).

processes and variations in demographics. The phase 3 study will usually only answer the first of those possibilities. Extending the evidence can occur by auditing data when implemented in the community, controlled comparative effectiveness studies which are bound by cost and time constraints of RCT, or animal data, which is discussed below. The most important prerequisite is obtaining enough of the right information to inform. There are no right or wrong trial designs for this line of work. As there are more tools including mathematical modelling [163, 164] or quasi-intervention, the process could be less rigorous than RCT. There will also be situations where trial level evidence is unambiguously needed to answer the questions. It remains unclear how observational, non-randomised, pseudorandomized trial level or low powered evidence will be interpreted. Good communication between research-clinical-administrative arms is the first and most important step in phase 4 research. It is fair to say most systems have not found valid solutions for all these issues.
Animal Models to Aid Post-Marketing Research

Well-designed animal studies could bridge hypotheses gaps in post-marketing studies. The introduction of phase 0 studies in 2006 is a promising step to speed up preclinical evidence. Similarly such methods could be devised prior to constructing post marketing intervention studies. Firstly finding ways to reduce sample sizes with novel early surrogate markers for clinical endpoints [165, 166]. Secondly, advancing gaps in the development of complex comorbid HF models and in standardizing the reporting of animal work [33, 40, 167]. One such initiative in Spain aims to address regional issues [168]. There is still a long way to go, but these gaps are not insurmountable and more collaborative work is needed.

MOVING FORWARD

Post-translational research should provide a ‘real-world’ picture of therapeutics e.g. there is often an understated appreciated difference between efficacy and effectiveness. A therapy may be highly efficacious in RCTs, but not at all effective nor cost-effective. From this perspective, phase 4 research could perhaps be more difficult than the primary evidence generating process, as it equally involves both evidence gathering or generation, with an implementation goal. With the latter, there is always the concern of when the evidence will be considered enough, to be translatable. An understanding among health systems is thus important. Some of the points we to consider are:

Understanding Scientific Decision Making and Process of Care:

- It is important to get a grasp on how the health profession views evidence, its strengths and weaknesses and what is considered implementable. This can be done by a survey among health professionals and administrators.

Evidence Gathering

- **Snapshots or Audits**: provide an opportunity to gauge problems broadly and are good bridge to more focused audits. It requires funding and collaboration, and can be opt in or out. Mathematical modelling, pseudo-randomisation techniques such as regression adjustment, propensity matching, inverse probability weighting and instrument variables can improve bias but require general understanding with an implementation arm.

- **Key Performance Indicators and Case Report Forms**: It is important to ensure those who will be using the information agree on the data to be collected. Surrogate endpoints in HF have been notoriously unreliable and this continues as a work in progress. Krumholtz et al and other groups from the ACC have published important work on this [30]. Local agreement on suitable surrogate endpoints may be important.

Evidence Generation

- Development of protocols for post-marketing intervention and non-inferiority studies involving minority communities or other demographics where small sample sizes are inevitable

- **Development of new biomarkers and risk scores**: – as it is not feasible to wait the course for events to develop as in the original RCTs, this point becomes important. Linking database may be the important first step and efforts to simplify these processes are also important post-translational endeavors.

- **Development of new treatment protocols or options**: Extending the scope of treatment for a class of drugs or for a disease can be beneficial for patients with genetic predispositions, comorbidities or for other reasons. This evidence is particularly difficult to generate, as they are rarely supported by industry, or difficult to implement from questions on the robustness of investigator generated research and the standardizing and translating of animal data. It is the first two aspects that local health systems need to address and standards to be agreed on.

- **Development of new service delivery protocols or options**: Often health care can be improved by ensuring, what is known is delivered and patients comply, as noted by the OPTIMIZE-HF study [68]. Other examples here are nurse delivered care, self-care and the use of technology. In this line of research many studies look to achieve hard endpoints such has mortality. It is important that standards be derived for suitable endpoints for non-drug research as the goals here are predominately to improve service, reduce cost and increase compliance [168]. The standardizations of these endpoints are important to establish to ensure smooth translation of findings.

Evidence Translation

- **The core team**: Health administration eventually decides the policy standing on any finding. It is important to negotiate this earlier in the process than later. As the robustness of evidence sways decisions in most cases, working with the specialty to find ways to standardize and increase the translational flavor of investigator initiated research is important.

- **Rural and remote evidence**: It is often in these communities that disparities in health and outcomes are noted. It is also the most difficult community to build evidence for. All the points cited apply here.

- **Ease of access for clinical trials**: the importance of this point is often understated. Extending the ability to conduct trials across more centers improves the clinical infrastructure and in the longer run will aid all aspects of clinical care. Sharing of staff is another advantage.

CONCLUSIONS

The evidence generating process provides a lot of emphasis for phases 0 to 3. In this the greatest weight is usually provided to RCT’s in phase 3. These trials provide the most significant answers which are however limited to one (or very few) questions within a controlled group. The forgotten posttranslational arm that aims to address unanswered questions at the community level requires greater emphasis.
Regular studies of the process of care that inform efficacy, effectiveness or cost effectiveness are the main focus of this phase. Ensuring the evidence indeed applies and finding better ways to do things is vital. Early in the process, industry requires support and facilitation in running studies. Equally post-trial studies are initiatives which should reciprocally receive industry support. Thus all these parties have roles to play in phase 4 studies. While initially it may be difficult to gauge which endeavors will tax the system greatly, which are feasible, which are efficacious and the cost, in the long term, however, understanding the many dimensions of implemented new treatments will provide the most important surrogate information to assess and administer for all major health systems performance indicators including overall costs, utility of services including readmissions and also long-term community wellbeing.

DISCLOSURES

Author has won independent and governmental research funding. None pose a conflict of interest for this review.

ABBREVIATIONS

ACE-I = angiotensin converting enzyme inhibitor
ADHF = acute decompensated heart failure
ARB = angiotensin receptor blocker
ββ = beta-blocker
CCB = calcium channel blockers
CHF = chronic Heart Failure
IND = investigational new drug
HF = heart failure
LVEF = left ventricular ejection fraction
MI = myocardial infarction
MRAs = mineralocorticoid receptor antagonists
NOAEL = No Observable Adverse Effect Levels
RAAS = renin angiotensin aldosterone system
TGA = therapeutics goods administration

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Friedlm A, Furberg CD. DeMets DL. Fundamentals of Clinical Trials. 4th ed. 2010, XVIII, 445 p.
[2] Antman EM, Part 1 – Critical Evaluation of Clinical Trials Fundamentals of Cardiovascular Disease in Braunwald’s Heart Disease A Textbook of Cardiovascular Medicine 10th Edn EDN Mann DL, Zipes DP, Libby P, Bonow RO. Elsevier.
[3] Iyngkaran P, Majoni W, Sanders P, et al. Northern Territory Perspectives on Heart Failure With Comorbidities – Understanding Trial Validity and Exploring Collaborative Opportunities to

Broaden the Evidence Base. Heart Lung Circ 2014; pii: S1443-9506(14)00821-X.

[4] Iyngkaran P, Thomas M, Sander P, et al. Do we need a Wider Therapeutic Paradigm for Heart Failure with Comorbidities? - A Remote Australian Perspective. Health Care Curr Rev 2013; 1: 106.

[5] Iyngkaran P, Harris M, Ilton M, et al. Implementing guideline based heart failure care in the Northern Territory: Challenges and Solutions. Heart Lung Circ 2014; 23(5): 391-406.

[6] Kesselheim AS, Green MD, Avorn J. Who is now responsible for discovering and warning about adverse effects of generic drugs?. JAMA 2013; 310(10): 1023-4.

[7] Vlahović-Palčevsk V, Mezentser D. Postmarketing surveillance. Handb Exp Pharmacol 2011; 205: 339-51.

[8] Crowther M. Phase 4 research: what happens when the rubber meets the road? Hematology Am Soc Hematol Educ Program 2013; 2013: 15-8.

[9] Chen BK, Yang YT. Post-marketing surveillance of prescription drug safety: past, present, and future. J Legal Med 2013; 34(2): 193-213.

[10] Iyngkaran P, Beneby G. Phase 4 Trials in Heart Failure – A Social and Corporate Responsibility. World J Met (accepted 14th Feb 2015).

[11] Kramer DB, Tan YT, Sato C, Kesselheim AS. Ensuring medical device effectiveness and safety; a cross–national comparison of approaches to regulation. Food Drug Law J 2014; 69(1): 1-23.

[12] Maro JC, Brown JS, Kullendorf M. Medical product safety surveillance: how many databases to use? Epidemiology 2013; 24(5): 692-9.

[13] Robey RR. A five-phase model for clinical-outcome research. J Commun Disord 2004; 37: 401-11.

[14] Rohilla A, Singh RK, Sharma D, Keshari R, Kushnoor A. Phases of clinical trials: a review. IJPCBS 2013; 3(3): 700-3.

[15] Iyngkaran P, Thomas M. Bedside to Bench Translational Research for Heart Failure – Creating an agenda for Urban and Remote Australia. Clinical Medicine Insights: Cardiology 2014 (accepted 10th March 2014)

[16] http://www.ncats.nih.gov/about/about.html

[17] Woof SH. The Meaning of Translational Research and Why It Matters. JAMA 2008; 299(2): 211-3.

[18] Brodniewicz T, GryNkiewicz G. Preclinical Drug Development. Acta Pol Pharm Drug Res 2010; 67(6): 579-86.

[19] http://www.ich.org/products/guidelines.html ? when accessed

[20] Bauersachs J, Fraccarollo D. Pre-clinical data on involvement of mineralocorticoid receptor activation in healing and remodeling post-myocardial infarction. Eur Heart J Suppl 2011; 13(Supplement B): B10-4.

[21] Timmermans PB, Wong PC, Chiu AT, Smith RD. The preclinical basis of the therapeutic evaluation of losartan. J Hypertens Suppl 1995; 13(1): S1-13.

[22] Begley CG, Ioannidis JP. Reproducibility in Science: Improving the Standard for Basic and Preclinical Research. Circ Res 2015; 116(1): 116-26.

[23] Kilkenny C, Parsons N, Kadyzewskei E, et al. Survey of the Quality of Experimental Design, Statistical Analysis and Reporting of Research Using Animals. PLoS ONE 2009; 4: e7824.

[24] Simera I, Moher D, Hoey J, Schulz K, Altman DG. A catalogue of reporting guidelines for health research. Eur J Clin Invest 2010; 40: 35-53.

[25] Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving Bioscience Research Reporting: The ARRIVE Guidelines. PLoS ONE 2009; 4: e7824.

[26] Krum H, Tonkin A. Why do phase III trials of promising heart failure drugs often fail? The contribution of "regression to the truth". J Card Fail 2003; 9(5): 364-7.

[27] Coloma PM. Phase 0 clinical trials: theoretical and practical implications in oncologic drug development. Open Access J Clin Trials 2013; 5: 119-26.

[28] DeMets DL. Design of phase II trials in congestive heart failure. Am Heart J 2000; 139(4): S207-10.

[29] Packer M. Current perspectives on the design of phase II trials of new drugs for the treatment of heart failure. Am Heart J 2000; 139: 5202-6.

[30] Kaitin KI. Deconstructing the drug development process: the new face of innovation. Clin Pharmacol Ther 2010; 87(3): 356-61.
Phase 4 Studies in Heart Failure - What is Done and What is Needed?

Morgan S, Grootendorst P, Lexchin J, Cunningham C, Greyson D. The cost of drug development: A systematic review. Health Policy 2011; 100: 4-17.

Mullin R. Tufts Study Finds Big Rise In Cost Of Drug Development. C&EN 2014; http://cen.acs.org/articles/92/web/2014/11/Tufts-Study-Finds-Big-Rise.html

Leford H. Translational research: 4 ways to fix the clinical trial. Nature 2011; 477(7366): 526-8.

Neaton JD, Gray G, Zuckerman BD, Konstam MA. Surrogate end points in heart failure trials. Am Heart J 2003; 145(2): S67–70.

Neaton JD, Gray G, Zuckerman BD, Konstam MA. Key Issues in End Point Selection for Heart Failure Trials: Composite End Points. J Card Fail 2005; 11(8): 567-75.

Mark DB, Simons TA. Economic end points in Phase II trials. Am Heart J 2000: 139: 155-7.

Anand IS, Florea VG, Fisher L. Surrogate end points in heart failure. J Am Coll Cardiol 2002; 39: 1414-21.

Gheorghide M, Vaduganathan, Shah SJ. Evaluative Framework for Phase II Studies in Patients With Heart Failure and Preserved Ejection Fraction. JCHF 2013; 1(2): 123-6.

Shah SJ, Fonarow GC, Gheorghide M, Lang RM. Phase II trials in heart failure: the role of cardiovascular imaging. Am Heart J 2011; 162: 3-15.

Tamargo J, López-Sendón J. Novel therapeutic targets for the treatment of heart failure. Nat Rev Drug Discov 2011; 10(7): 536-50.

Kaye DM, Krum H. Drug discovery for heart failure: a new era or the end of the pipeline? Nat Rev Drug Discov 2007; 6(2): 127-39.

Fonarow GC. Epidemiology and risk stratification in acute heart failure. Am Heart J 2008; 155(2): 200-7.

McLean AS, Ellis CK, Coats AJ. The epidemiology of heart failure in Australia. Int J Cardiol 2007; 118(3): 370-4.

Cleland JG, Swedberg K, Folkhå F, et al. Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology: The EuroHeart Failure Survey programme – a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur J Heart Fail 2003; 24: 462-63.

Niinemets MS, Brutsaert D, Dickstein K, et al. on behalf of the EuroHeart Survey Investigators. Heart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006; 27: 2725-36.

Heywood JT, Fonarow GC, Costanzo MR, et al. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. J Card Fail 2007; 13: 422-30.

Fonarow GC, Yancy CW, Albert NM, et al. Heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. Circ Heart Fail 2008; 1(2): 98-106.

Sato N, Kajimoto K, Asai K, et al. Admission time, variability in clinical characteristics, and in-hospital outcomes in acute heart failure. Ann Intern Med 2007; 147: 1493-502.

Fonarow GC, Yancy CW, Albert NM, et al. Improving the use of evidence-based heart failure therapies in the outpatient setting: the IMPROVE HF performance improvement registry. Am Heart J 2007; 154(1): 12-38.

Atherton JJ, Hayward CS, Wan Ahmad WA, et al. ADHERE International-Asia Pacific Scientific Advisory Committee. Patient characteristics from a regional multicenter database of acute decompensated heart failure in Asia Pacific (ADHERE International-Asia Pacific). J Card Fail 2012; 18(1): 82-8.

Huxley RR, Barzi F, Woo J, et al. Asia Pacific Cohort Studies Collaboration. A comparison of risk factors for mortality from heart failure in Asian and non-Asian populations: an overview of individual participant data from 32 prospective cohorts from the Asia-Pacific Region. BMC Cardiovasc Disord 2014; 14: 61.

Lu KJ, Yan BP, Ajani AE, et al. Melbourne Interventional Group. Impact of concomitant heart failure on outcomes in patients undergoing percutaneous coronary interventions: analysis of the Melbourne Interventional Group registry. Eur J Heart Fail 2011; 13(4): 416-22.

Tobing D, French J, Varigos J, Meehan A, Bilbain B, Krum H, Post-MI Audit Group. Do patients with heart failure appropriately undergo invasive procedures post-myocardial infarction? Results from a prospective multicentre study. Intern Med J 2008; 38(11): 945-51.

Ng AC, Wong HS, Yong AS, Sindone AP. Impact of gender on outcomes in chronic systolic heart failure. Int J Cardiol 2007; 117(2): 214-21.

Krum H, Meehan A, Varigos J, Loane PR, Bilbain B. Does the presence of heart failure alter prescribing of drug therapy after myocardial infarction? A multicentre study. MJA 2006; 185: 191-4.

Abhayaratna WP, Smith WT, Becker NG, Marwick TH, Jeffery IM, McGill DA. Prevalence of heart failure and systolic ventricular dysfunction in older Australians: the Canberra Heart Study. Med J Aust 2006; 184(4): 151-4.

Clark RA, Eckert KA, Stewart S, et al. Rural and urban differentials in primary care management of chronic heart failure: new data from the CASE study. Med J Aust 2005; 183(9): 515-20.

Krum H, Mill J, Fruehwald F, et al. Tolerability of beta-blockers in elderly patients with chronic heart failure: the COLA II study. Eur J Heart Fail 2006; 8(3): 302-7.

Krum H, Tonkin AM, Currie R, et al. Chronic heart failure in Australian general practice. The Cardiac Awareness Survey and Evaluation (CASE) Study. Med J Aust 2001; 174: 439-44.

Teng TH, Katzenellenbogen JM, Hung J, et al. Rural-urban differentials in 30-day and 1-year mortality following first-ever heart failure hospitalisation in Western Australia: a population-based study using data linkage. BMJ Open 2014; 4(5): e004724.

Teng TH, Katzenellenbogen JM, Thompson SC, et al. Incidence of first heart failure hospitalisation and mortality in Aboriginal and non-Aboriginal patients in Western Australia, 2000-2009. Int J Cardiol 2014; 173(1): 110-7.

Close GR, Newton PJ, Fung SC, et al. Socioeconomic status and heart failure in Sydney. Heart Lung Circ 2014; 23(4): 320-4.

Hung J, Teng TH, Finn J, et al. Trends from 1996 to 2007 in incidence and mortality outcomes of heart failure after acute myocardial infarction: a population-based study of 20,812 patients with first acute myocardial infarction in Western Australia. J Am Heart Assoc 2013; 2(5): e000172.

Robertson J, McElduff P, Pearson SA, Henry DA, Inder KJ, Attia JR. The health services burden of heart failure: an analysis using linked population health data-sets. BMC Health Serv Res 2012; 12: 103.

Teng TH, Hung J, Knuiman M, et al. Trends in long-term cardiovascular mortality and morbidity in men and women with heart failure of ischemic versus non-ischemic aetiology in Western Australia between 1990 and 2005. Int J Cardiol 2012; 158(3): 405-10.

Teng TH, Hung J, Finn J. The effect of evidence-based medication use on long-term survival in patients hospitalised for heart failure in Western Australia. Med J Aust 2010; 192(6): 106-5.

Najafi F, Jamrozik K, Dobos AJ. Understanding the ‘epidemic of heart failure’: a systematic review of trends in determinants of heart failure. Eur J Heart Fail 2009; 11(5): 472-9.

Najafi F, Dobos AJ, Hobbs M, Jamrozik K. Late-onset heart failure after myocardial infarction: trends in incidence and survival. Eur J Heart Fail 2008; 10(8): 765-71.

Najafi F, Dobos AJ, Hobbs M, Jamrozik K. Temporal trends in the frequency and longer-term outcome of heart failure complicating myocardial infarction. Eur J Heart Fail 2007; 9(9): 879-85.

Najafi F, Dobos AJ, Jamrozik K. Recent changes in heart failure hospitalisations in Australia. Eur J Heart Fail 2007; 9(3): 228-33.

Najafi F, Dobos AJ, Jamrozik K. Mortality from heart failure increasing in Australia? An analysis of official data on mortality for 1997-2003. Bull World Health Organ 2006; 84(9): 722-8.

Roughhead EE, Barratt JD, Ramsay E, et al. The effectiveness of collaborative medicine reviews in delaying time to next hospitalization for patients with heart failure in the practice setting: results of a cohort study. Circ Heart Fail 2009; 2(5): 424-8.
[75] Clark RA, McLennan S, Eckert K, Dawson A, Wilkinson D, Stewart S. Chronic heart failure beyond city limits. Rural Remote Health 2005; 5(4): 443.

[76] Clark RA, McLennan S, Dawson A, Wilkinson D, Stewart S. Uncovering a hidden epidemic: a study of the current burden of heart failure in Australia. Heart Lung Circ 2004; 13(3): 266-73.

[77] Driscoll A, Tonkin A, Stewart S, et al. Complexity of management and health outcomes in a prospective cohort study of 573 heart failure patients in Australia: does more equal less? J Clin Nurs 2013; 22(11-12): 1629-38.

[78] Clark RA, Driscoll A. Access and quality of heart failure management programs in Australia. Aust Crit Care 2009; 22(3): 111-6.

[79] Vity A, Phillips SM, Semple SJ. Quality and availability of consumer information on heart failure in Australia. BMC Health Serv Res 2008; 8: 255.

[80] Clark RA, Driscoll A, Nottage J, et al. Inequitable provision of optimal services for patients with chronic heart failure: a national geo-mapping study. Med J Aust 2007; 186(4): 169-73.

[81] Driscoll A, Worrall-Carter L, McLennan S, Dawson A, O'Reilly J, Stewart S. Heterogeneity of heart failure management programs in Australia. Eur J Cardiovasc Nurs 2006; 5(1): 75-82.

[82] Clark RA, Yallop JJ, Piterman L, et al. CHAT Study Team. Adherence, acceptance and acceptance of elderly chronic heart failure patients to receiving healthcare via telephone-monitoring. Eur J Heart Fail 2007; 9(11): 1104-11.

[83] Page K, Marwick TH, Lee R, et al. National Heart Foundation of Australia. A systematic approach to chronic heart failure care: a consensus statement. Med J Aust 2014; 201(3): 146-50.

[84] Krum H, Jelinek MV, Stewart S, et al. Guidelines for the prevention, detection, and management of people with chronic heart failure in Australia. Med J Aust 2011; 194: 405-9.

[85] Henry K, Michael VJ, Simon S, et al. on behalf of the CHF Guidelines Core Writers., Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006. Med J Aust 2006; 185(10): 540-56.

[86] Teng TH, Finn J, Hung J, Geelhoed E, Hobbs M. A validation study: how effective is the Hospital Morbidity Data as a surveillance tool for heart failure in Western Australia? Aust N Z J Public Health 2008; 32(5): 405-7.

[87] Iyngkaran P, Kangaharan N, Zimmet H, et al. Heart Failure in Minority Populations - Impediments to Optimal Treatment in Australasian Aborigines. Curr Card Rev 2016; in press.

[88] Chatterjee S, Biondi-Zoccai G, Abbate A, et al. Benefits of β-blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. BMJ 2013; 346: 155.

[89] Flannery G, Gehrig-Mills R, Billah B, Krum H. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. Am J Cardiol 2008; 101(6): 865-9.

[90] McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. Ann Intern Med 2009; 150: 784-94.

[91] Iyngkaran P, Anavekar N, Majoni W, Thomas MC. The role and management of sympathetic overactivity in cardiovascular and renal complications of diabetes. J Intern Med 2013; 39(4): 290-8.

[92] Lazarus DL, Jackevicius CA, Behlouli H, Johansen H, Pilote L. Population-based analysis of class effect of β blockers in heart failure. Am J Cardiol 2011; 107: 1196-202.

[93] Go AS, Yang J, Gurwitz JH, Hsu J, Lane K, Platt R. Comparative effectiveness of different beta-adrenergic antagonists on mortality among adults with heart failure in clinical practice. Arch Intern Med 2008; 168: 2415-21.

[94] Dulin BR, Haas SJ, Abraham WT, Krum H. Do elderly systolic heart failure patients benefit from beta blockers to the same extent as the non-elderly? Meta-analysis of >12,000 patients in large-scale clinical trials. Am J Cardiol 2005; 95(7): 896-8.

[95] Fitzgerald AA, Powers JD, Ho PM, et al. Impact of medication nonadherence on hospitalizations and mortality in heart failure. J Card Fail 2011; 17: 664-9.

[96] Shibata MC, Tsuyuki RT, Wiebe N. The effects of angiotensin receptor blockers on mortality and morbidity in heart failure: a systematic review. Int J Clin Pract 2008; 62(9): 1397-402.

[97] Munger MA. Use of Angiotensin receptor blockers in cardiovascular protection: current evidence and future directions. P T 2011; 36(1): 22-40.

[98] Abdulla J, Pogue J, Abildstrom SZ, et al. Effect of angiotensin-converting enzyme inhibition on functional class in patients with chronic heart failure and left ventricular systolic dysfunction--a meta-analysis. Eur J Heart Fail 2006; 8(1): 90-6.

[99] Li EC, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. Cochrane Database Syst Rev 2014; 8: CD009096.

[100] Wu HY, Huang JW, Lin HJ, et al. Comparative effectiveness of renin-angiotensin system blockers and other antihypertensive drugs for treating patients with diabetes: systematic review and bayesian network meta-analysis. BMJ 2013; 347: f6008.

[101] Matchar DB, McCrory DC, Orlando LA, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. Ann Intern Med 2008; 148(1): 16-29.

[102] van Vark LC, Bertrand M, Akkerhuis KM, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. Eur Heart J 2012; 33(16): 2088-97.

[103] Cheng J, Zhang W, Zhang X, et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: a meta-analysis. JAMA Intern Med 2014; 174(5): 773-85.

[104] Nakao YM, Teramukai S, Tanaka S, et al. Effects of renin-angiotensin system blockers on cardiovascular outcomes in patients with diabetes mellitus: A systematic review and meta-analysis. Diabetes Res Clin Pract 2012; 96(1): 68-75.

[105] Hirst JA, Taylor KS, Stevens RJ, et al. The impact of renin-angiotensin-aldosterone system inhibitors on Type 1 and Type 2 diabetic patients with and without early diabetic nephropathy. Kidney Int 2012; 81(7): 674-83.

[106] Vejakama P, Thakkinstian A, Lerrattanathanon D, Ingsathit A, Ngarukkos C, Attia J. Renoprotective effects of renin-angiotensin system blockade in type 2 diabetic patients: a systematic review and network meta-analysis. Diabetologia 2012; 55(3): 566-78.

[107] Geng DF, Jin DM, Wu W, Liang YD, Wang JF. Angiotensin converting enzyme inhibitors for prevention of new-onset type 2 diabetes mellitus: a meta-analysis of 72,128 patients. Int J Cardiol 2013; 167(6): 2605-10.

[108] Tocci G, Paneni F, Falano F, et al. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and diabetes: a meta-analysis of placebo-controlled clinical trials. Am J Hypertens 2011; 24(5): 582-90.

[109] Al-Mallah M, Khawaja O, Sinno M, Alzohaili O, Samra AB. Do angiotensin converting enzyme inhibitors or angiotensin receptor blocker prevent diabetes mellitus? A meta-analysis. Cardiol J 2010; 17(5): 448-56.

[110] Huang Y, Zhou Q, Haaijer-Ruskamp FM, Postma MJ. Economic evaluations of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in type 2 diabetic nephropathy: a systematic review. BMC Nephrol 2014; 15: 105.

[111] Yang LY, Ge X, Wang YL, et al. Angiotensin receptor blockers reduce left ventricular hypertrophy in dialysis patients: a meta-analysis. Am J Med Sci 2013; 345(1): 1-9.

[112] Balamuthusamy S, Srinivasan L, Verma M, et al. Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis. Am J Heart J 2008; 155(5): 791-805.

[113] Savarese G, Costanzo P, Cleland JG, et al. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. J Am Coll Cardiol 2013; 61(2): 131-42.

[114] Al-Mallah MH, Tielehay IM, Abdel-Latif AA, Weaver WD. Angiotensin-converting enzyme inhibitors in coronary artery disease: new insights from randomized controlled trials. J Am Coll Cardiol 2006; 47(8): 1576-83.

[115] Danchin N, Cucherat M, Thuillez C, Durand E, Kadri Z, Steg PG. Angiotensin-converting enzyme inhibitors in patients with coronary artery disease and absence of heart failure or left ventricular sys-
tolic dysfunction: an overview of long-term randomized controlled trials. Arch Intern Med 2006; 166(7): 787-96.

[116] Powers BJ, Coe tyaux RR, Dolor RJ, et al. Updated report on comparative effectiveness of ACE inhibitors, ARBs, and direct renin inhibitors for patients with essential hypertension: much more data, little new information. J Gen Intern Med 2012; 27(6): 716-29.

[117] Caldeira D, David C, Sampaio C. Tolerability of angiotensin-converting enzyme blockers in patients with intolerance to angiotensin-converting enzyme inhibitors: a systematic review and meta-analysis. Am J Cardiovasc Drugs 2012; 12(4): 263-77.

[118] Kronish IM, Woodward M, Sergie Z, Godegebe G, Falzon L, Mann DM. Meta-analysis: impact of drug class on adherence to antihypertensives. Circulation 2011; 123(15): 1611-21.

[119] Stafylas PC, Sarafidis PA, Grekas DM, Lasaridis AN. A cost-effectiveness analysis of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in diabetic nephropathy. J Clin Hypertens (Greenwich) 2007; 9(10): 751-9.

[120] Peck RN, Smart LR, Beier R, et al. Difference in blood pressure response to ACE-Inhibitor monotherapy between black and white adults with arterial hypertension: a meta-analysis of 13 clinical trials. BMC Nephrol 2013; 14: 201.

[121] McDowell SE, Coleman JJ, Fener RE. Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. BMJ 2006; 332(7551): 1077-81.

[122] Brewster LM, van Montfrans GA, Kleijnen J. Systematic review of antihypertensive drug therapy in black patients. Ann Intern Med 2004; 141(8): 6142.

[123] Snyman JR, Wessels F. Perindopril: do randomised, controlled trials support an ACE inhibitor class effect? A meta-analysis of clinical trials. Cardiovasc J Afr 2009; 20(2): 127-34.

[124] Ferdinand KC. Recommendations for the management of special populations: racial and ethnic populations. Am J Hypertens 2003; 16(11 Pt 2): 505-48.

[125] Verdecchia P, Angeli F, Gentile G, Mazzotta G, Rebaldi G. Telmisartan for the reduction of cardiovascular morbidity and mortality. Expert Rev Clin Pharmacol 2011; 4(2): 151-61.

[126] Akhrass PR, McFarlane SI. Telmisartan and cardioprotection. Vasc Health Risk Manag 2011; 7: 677-83.

[127] Takagi H, Umemoto T, All-Literature Investigation of Cardiovascular Evidence Group. A meta-analysis of randomized trials of telmisartan versus active controls for insulin resistance in hypertensive patients. J Am Soc Hypertens 2014; 8(8): 578-92.

[128] Takagi H, Niwa M, Mizuno Y, Goto SN, Umemoto T, ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. Telmisartan as a metabolic sartan: the first meta-analysis of randomized controlled trials in metabolic syndrome. J Am Soc Hypertens 2013; 7(3): 229-35.

[129] Takagi H, Umemoto T. A meta-analysis of randomized controlled trials of telmisartan for flow-mediated dilatation. Hypertens Res 2014; 37(9): 845-51.

[130] Pan G, Zhou X, Zhao J. Effect of telmisartan on atrial fibrillation recurrences in patients with hypertension: a systematic review and meta-analysis. Cardiovasc Ther 2014; 32(4): 184-8.

[131] Parati G, Schumacher H. Blood pressure variability over 24 h: prognostic implications and treatment perspectives. An assessment using the smoothness index with telmisartan-amlodipine monotherapy and combination. Hypertens Res 2014; 37(3): 187-93.

[132] Zhu D, Bays H, Gao P, Mattheus M, Voelker B, Ruiolo LM. Efficacy and tolerability of a single-pill combination of telmisartan 80 mg and hydrochlorothiazide 25 mg according to age, gender, race, hypertension severity, and previous antihypertensive use: planned analyses of a randomized trial. Integr Blood Press Control 2013; 6: 1-14.

[133] Dans AL, Teo K, Gao P, et al. Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial Investigators. In a subgroup of high-risk Asians, telmisartan was non-inferior to ramipril and better tolerated in the prevention of cardiovascular events. PLoS One 2010; 5(12): e13694.

[134] Hu LJ, Chen YQ, Deng SB, Du JL, She Q. Additional use of an aldosterone antagonist in patients with mild to moderate chronic heart failure: a systematic review and meta-analysis. Br J Clin Pharmacol 2013; 75(5): 1202-12.

[135] Phelan D, Thavendiranathan P, Collier P, Marwick TH. Aldosterone antagonists improve ejection fraction and functional capacity independently of functional class: a meta-analysis of randomised controlled trials. Heart 2012; 98(23): 1693-700.

[136] Butler J, Ezekowitz JA, Collins SP, et al. Update on aldosterone antagonists use in heart failure with reduced left ventricular ejection fraction. Heart Failure Society of America Guidelines Committee. J Card Fail 2012; 18(4): 265-81.

[137] Johnson JA. Ethnic Differences in Cardiovascular Drug Response Potential Contribution of Pharmacogenetics. Circulation 2008; 118: 1383-93.

[138] Su Q, Li L, Liu Y. Short-term effect of verapamil on coronary no-reflow associated with percutaneous coronary intervention in patients with acute coronary syndrome: a systematic review and meta-analysis of randomized controlled trials. Clin Cardiol 2013; 36(8): E11-6.

[139] Moukarbel GV, Ayoub CM, Abchee AB. Pharmacological therapy for myocardial reperfusion injury. Curr Opin Pharmacol 2004; 4(2): 147-53.

[140] Opie LH, Yusuf S, Kühler W. Current status of safety and efficacy of calcium channel blockers in cardiovascular diseases: a critical analysis based on 100 studies. Prog Cardiovasc Dis 2000; 43(2): 171-96.

[141] Macchia A, Levantesi G, Franzosi MG, et al. Left ventricular systolic dysfunction, total mortality, and sudden death in patients with myocardial infarction treated with n-3 polyunsaturated fatty acids. Eur J Heart Fail 2007; 9(4): 739-49.

[142] ORIGIN Trial Investigators, Bosch J, Gerstein HC, Dagenais GR, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med 2012; 367(4): 309-18.

[143] Chowdhury R, Stevens S, Gorman D, et al. Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis. BMJ 2012; 345: e6698.

[144] Mozaffarian D, Lemaître RN, King IB, et al. Plasma Phospholipid Long-Chain ω-3 Fatty Acids and Total and Cause-Specific Mortality in Older Adults: A Cohort Study. Ann Intern Med 2013; 158(7): 515-25.

[145] Wilk JB, Tsai MY, Hanson NQ, Gaziano JM, Djoussé L. Plasma and dietary omega-3 fatty acids, fish intake, and heart failure risk in the Physicians’ Health Study. Am J Clin Nutr 2012; 96(4): 882-8.

[146] http://www.phac--phc.gc.ca секб-sectb-drrтб- interpretation-of-the-clinical-evidence.html? Date accessed

[147] https://www.nhmrc.gov.au/_files/nhmrc/publications/attachments/ cp99.pdf? Date accessed

[148] Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011; 343: d4002.

[149] Nikolakopoulou A, Mavridis D, Salanti G. Demystifying fixed and random effects meta-analysis. Evid Based Ment Health 2014; 17(2): 53-7.

[150] Ferreira González I, Urrutia G, Alonso-Coello P. Systematic reviews and meta-analysis: scientific rationale and interpretation. Rev Esp Cardiol 2011; 64(8): 688-96.

[151] Rerkasem K, Rothwell PM. Meta-analysis of small randomized controlled trials in surgery may be unreliable. Br J Surg 2010; 97(4): 466-9.

[152] Perera R, Henehan C. ACP Journal Club. Interpreting meta-analyses in systematic reviews. Ann Intern Med 2009; 150(4): JCC2-2, JCC2-3.

[153] Bath PM, Gray LJ. Systematic reviews as a tool for planning and interpreting trials. Int J Stroke 2009; 4(1): 23-7.

[154] Ioannidis JP. Interpretation of tests of heterogeneity and bias in meta-analysis. J Eval Clin Pract 2008; 14(5): 951-7.

[155] Walker E, Hernandez AV, Kattan MW. Meta-analysis: Its strengths and limitations. Cleve Clin J Med 2008; 75(6): 431-9.

[156] Perera R, Henehan C. Interpreting meta-analysis in systematic reviews. Evid Based Med 2008; 13(3): 67-9.

[157] Reid K. Inter Interpreting and understanding meta-analysis graphs - a practical guide. Aust Fam Physic 2006; 35(8): 635-8.

[158] Greenhalgh T. How to read a paper. Papers that summarise other papers (systematic reviews ad metaanalyses). BMJ 1997; 315: 672-5.

[159] Jackson N. Systematic reviews of health promotion and public health interventions. The Cochrane Health Promotion and Public Health Field. Victorian Health Promotion Foundation, 2005. Available at www.vichealth.vic.gov.au/cochrane.
[160] Hill A, Spittlehouse C. What is critical appraisal? Including: ten questions to help you make sense of a systematic review. Hayward Medical Communications, 2001. Available at www.evidence-based-medicine.co.uk.

[161] Berlin JA, Colditz GA. The role of meta-analysis in the regulatory process for food, drugs, and devices. JAMA 1999; 281: 830-4.

[162] Goehler A, Geisler BP, Manne JM, et al. Decision-analytic models to simulate health outcomes and costs in heart failure: a systematic review. Pharmacoeconomics 2011; 29(9): 753-69.

[163] Ortegan M, Lim S, Chisholm D, Mendis S. Cost effectiveness of strategies to combat cardiovascular disease, diabetes, and tobacco use in sub-Saharan Africa and South East Asia: mathematical modelling study. BMJ 2012; 344: e607.

[164] Ren Y, Fu X, Pan Q, et al. Fast Parameters Estimation in Medication Efficacy Assessment Model for Heart Failure Treatment. Comput Math Methods Med 2012; 2012: 608637.

[165] Lara-Pezzi E, Menasché P, Trouvin JH, et al. Guidelines for Translational Research in Heart Failure. J Cardiovasc Transl Res 2015; 8(1): 3-22.

[166] Alonso-Pulpón L, Borrás X, Brugada J, et al. on behalf of the REDINSCOR researchers. Clinical and Preclinical Heart Failure Research Network (REDINSCOR). Instituto de Salud Carlos III Cooperative Special Topic Research Networks. Rev Esp Cardiol 2008; 61(1): 76-81.

[167] Iyngkaran P, Toukhsati SR, Biddagardi N, Zimmet H, J Atherton J, Hare DL. Technology-assisted congestive heart failure care. Curr Heart Fail Rep 2015; 12(2): 173-86.

[168] Iyngkaran P, Harris M, Connors C, et al. Self Care for Remote Australia. Curr Card Rev May 2016; [Epub ahead of print].
