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CHARTING AND NAVIGATING THE “SCYLLA AND CHARYBDIS” CONUNDRUM OF OUR AGEING HEARTS – HEART FAILURE & ATRIAL FIBRILLATION



Henry Fuseli's painting of Odysseus choosing the unpalatable choice between Scylla and Charybdis, circa 1794/6 (Public Domain)

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Submitted in fulfilment of the requirements for the **Doctor of Medical Science**



School of Medicine, Sydney, NSW, Australia

March 2023

DECLARATION

To the best of the candidate's knowledge, this thesis contains no material previously published by another person, except where due acknowledgement has been made. This includes the portfolio of published, peer-reviewed manuscripts that form the basis for the thesis where the candidate is listed as the first and/or senior corresponding author.

This thesis is the candidate's own work and contains no material which has been accepted for the award of any other degree or diploma in any institution.

HUMAN ETHICS

The research projects presented and reported in this thesis were conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007, updated 2018). Ethics approval was granted by all relevant Human Research Ethics Committees in Australia, UK, USA, Sweden, and South Africa.

SIMON STEWART

30TH MARCH 2023

ABSTRACT

Residing on opposite sides of the Strait of Messina between Sicily and Calabria, *Scylla* and *Charybdis* were mythical sea monsters (one a fearsome creature, the other a deadly whirlpool) described by Homer. For anyone seeking to navigate that narrow and treacherous passage, avoid one of these lethal threats and you would be devoured by the other. For many populations around the world, the conundrum of successfully preventing and/or treating heart failure (HF) to increase longevity, only to increase the probability that it will increase the number of people living with and dying from atrial fibrillation (AF), represents a conundrum of *Scylla* and *Charybdis* dimensions. So how did this happen? In the late 20th Century, heart disease was characterised by a predominance of middle-aged men suffering often fatal acute coronary events. However, this pattern began to change due to the combination of two key factors. Firstly, in high-income countries at least, there were increasingly successful attempts to prevent and treat acute coronary events (thereby reducing premature mortality rates). Secondly, the vanguard of the *Post-War Baby Boomer* generation had reached their sixth decade of life, with more to come. Thus, more people were living longer with an ageing/damaged heart and those numbers would inevitably rise.

The first manifestation of this phenomenon was an increasing number of HF cases (well before a noticeable increase in AF cases). This mandated increasing recognition that HF was a discrete physical entity/syndrome that needed to be more widely recognised. This trend (rising HF cases) meant that the main burden of heart disease was shifting from the fifth/sixth decade of life with a male predominance, to the seventh/eighth decade of life affecting both men and women. Unless urgently addressed, it seemed clear that HF cases would overwhelm future health care services. At this point in time, AF attracted far less scrutiny because case numbers remained low. However, fuelled by the inevitable wave of ageing *Baby Boomers*, combined with successful attempts to prolong the lives of those affected by “earlier” forms of heart disease (including HF), it was inevitable, therefore, that more people would be successfully reaching their eight/ninth decade of life. Thus, the perfect “recipe” for a rising tide of AF had emerged.

So does every individual face a *Scylla* and *Charybdis* choice between HF and AF – of course not! However, as a society in successfully recognising and treating a rising epidemic of HF, we inevitably fuelled (as some of us were predicting) a consequential epidemic of AF. In simple terms, unless we could “cure” heart disease – we had no choice in a classical *Scylla* and *Charybdis* conundrum, by solving/avoiding one problem and then creating/running into, another. Thus, as with HF 10-20 years earlier, AF has since challenged health care systems to cope with the demands it places on all healthcare services. Concurrent to the rise of AF, HF now represents a sustained threat to the heart health of successfully ageing populations worldwide (creating a “twin epidemic”), with AF and HF often occurring in the same person.

It is within this context, that this thesis describes two closely related portfolios of research (comprising >100 primary and topic-related, original reports) that were instrumental in – **1)** Describing the evolving burden of disease imposed by HF and AF, **2)** Developing targeted, multidisciplinary management programs with the capacity to simultaneously reduce the risk of recurrent hospitalisation and prolong the lives of vulnerable people affected by one or both of these deadly/disabling conditions, and **3)** Considering their broader impact in vulnerable/disadvantaged communities and regions of the world (from Central Australia to Sub-Saharan Africa).

In addition to describing how this portfolio of research represents a *cogent investigation* of two critical aspects of HF and AF (i.e., what is the pattern of disease and how can its impact from an individual to societal perspective be attenuated?), this thesis outlines the concrete impact these research reports have made in our collective awareness, understanding and response to them.

My own (small) contribution to this field of research includes a series of important studies generating new knowledge (e.g., the prognostic impact and economic burden of HF and AF) and trials of HF and AF management that have directly influenced the provision and design of new health programs and services. Consistent with this impact, the 33 original research studies presented in this thesis have attracted >100 individual citations in Expert Clinical Guidelines/Consensus Reports over the last 20 years.

FOREWORD

Fulfilling the criteria for the award of a *Doctor of Medical Science* administered by the *University of Notre Dame Australia*, this thesis provides a critical appraisal of a body of research undertaken and led by me over a 20-year period. Following the completion of my PhD within the Department of Medicine at the University of Adelaide ("*Optimising therapeutic efficacy in acute and chronic cardiac disease states*") under the wonderful supervision of Professor John Horowitz (Head/Professor of Cardiology at the Queen Elizabeth Hospital) and Professor John Marley (Head/Professor of General Practice), I was awarded the 1999 *National Heart Foundation of Australia Overseas Ralph Reader Fellowship*.

With great fortune, the Ralph Reader Fellowship led me to the University of Glasgow, Scotland under the mentorship/tutelage of Professor John McMurray (now one of the world's most influential and respected Cardiologists). During my Fellowship I also worked with other luminaries in the fields of cardiology/public health – including Professors Simon Capewell, Jill Pell, David Hole, and Caroline Morrison.

My time at the University of Glasgow (noting that I proudly remain an active collaborator and Visiting Professor with Professor McMurray and his team) represents the starting point for the body of work presented in this thesis. When I landed in Glasgow in 1999, I had already had a strong interest in the clinical management of **heart failure**. By the time I returned to Professor John Horowitz's group in 2002, I had developed a further (intense) interest in the burden of disease imposed by *heart failure*. As a prospective component of my Fellowship (prompted by Professor Horowitz), I also extended my interest in developing and adapting clinical management programs to the emerging problem of **atrial fibrillation**.

When comparing notes with the parallel experience of the late, great Professor Henry Krum (who also returned home to Australia after working with Professor Milton Packer in the USA), I realise how much better it would have been for my career if I had stayed in the UK (for the recognition and opportunities it would have generated). Until I joined the *Baker Heart Institute* as Head of Preventative Cardiology in 2007, I struggled to gain any traction (or research project funding) back home in Australia. Nevertheless, through the support of an *Inaugural NHMRC Career Development Award* and then successively more senior NHMRC Fellowships (culminating in a *Senior Principal Research Fellowship* 15 years later), I persisted in developing my own research program/team focussed on *heart failure* and *atrial fibrillation*.

Not surprisingly (given its genesis/origin), the portfolio of research presented in this thesis has many international components – stretching from Sweden in Northern Europe to Soweto in South Africa. I've been extremely fortunate to collaborate with amazing people like Professors Karen Sliwa (Director of the *Cape Heart Institute*/Immediate Past-President of the *World Heart Federation*) and Ana Mocumbi (Non-Communicable Disease Lead, Instituto Nacional de Saúde, *Mozambique Ministry of Health*).

Given the above context (good fortune, geographically disperse research projects and a myriad of collaborations and opportunities not necessarily conducive to creating a linear narrative), I've deliberately sought to present a set of primary manuscripts with three key characteristics – **1)** I was the 1st or last/senior author, **2)** When combined (even if out-of-synch in terms of timing) they form a cogent narrative focussed on *heart failure* and *atrial fibrillation*, and **3)** Each report has had a proven impact on our wider understanding of these conditions and/or changed clinical practice.

No research is perfect. Thus, in linking each manuscript, I have been mindful of the imperative to present a balanced and critical account of each study and how it built on previous research (either my own or someone else's). If there is just one lesson, I've learned in my research journey, it is that the goal of truly understanding and responding to complex phenomena such as *heart failure* and *atrial fibrillation* will only end when we've eliminated disease and created the "eternal" heart. I hope this lesson is reflected in this thesis! Ironically, therefore, after fretting early in my career whether I'd still have anything to research once heart disease had been "cured" (remembering the early hype around stem cells, regeneration and near immortality!), I can confidently predict that conditions like *heart failure* and *atrial fibrillation* will continue to confound and challenge us for many more years to come.

Simon Stewart March 2023

ACKNOWLEDGEMENTS

I hope it is entirely clear from the Foreword, that I recognise and owe much of my research career success to the senior people (many of whom are named above) who have mentored and supported me. I've also been blessed with amazing research teams. Some members of these teams, like the late Ms. Ana Nadonza, Ms. Nerolie Stickland, and Dr Kai Chan, are deserving as much credit as me for the work we've collectively produced. I've also been blessed with "visionary" PhD students like Professor Geoff Strange who've created their own career path and taken me on the journey with them. I'm eternally grateful for everyone who has collaborated and supported me along the way.

It would be rare for anyone at my career stage to be good at listening and taking advice. This is especially true for someone writing a thesis about their beloved research – and I'm no exception! For their patience and forbearance of my peculiar writing style and penchant for long sentences, I'd like to warmly thank Professors Jim Codde and David Playford for helping me to compile this thesis. Both have been instrumental in me being able to complete this labour of love.

Unfortunately, my father Tom Stewart (the reason why I chose Glasgow over Boston, San Francisco, or Gothenburg for my Post-Doctoral Fellowship), never witnessed me gain a PhD or, hopefully, this higher degree. It strikes me that his witty twist on a simple label ("*Simple Simon*") into "*It's not so Simple Simon*" neatly describes my complex clinical and academic career. Nevertheless, his memory and legacy (never to be forgotten) is, and always will be, a central motivation to my research endeavours. I can only honour him properly by striving to make a difference and supporting others who seek to do the same – regardless of where they come or their circumstances. Despite all her health challenges, my mother, Jo Stewart, was still here to inspire me with her fierce intellect and support for her "boys". She played an integral role in my achieving a PhD in the first instance. Subsequently, I was grateful for the opportunity to explain how I had written and completed my thesis ready for evaluation. Thus, providing her with further concrete evidence that her sacrifices to give us a new life in Australia were still being honoured. Sadly, she died before I could share the good news about my being awarded the degree. Nevertheless - "*top of the world Ma!*".

"*This one is important!*". I can't count how many times I said this to my wife Tania as I burned through yet another evening and night finishing one of the manuscripts included in this thesis. There is really no excuse for my single-mindedness and journeying so far away from home T. However, I sincerely hope you understand why I'm so driven towards answering the next question (and the one beyond)! Regardless, I couldn't have achieved anything without your love and support and this thesis (dedicated to you and the girls) is just as much your creation as mine.

By the same token, I never had the opportunity to truly explain to my three daughters why I was absent (physically or mentally distracted) so often when they were growing up. Laura, Amy and Sarah, the fact that you grew-up to be such amazingly talented, accomplished, and caring young women is more credit to yourselves and your mum than anything I ever did. Regardless, I'm so very proud of you and the career choices you've made. I hope this thesis at least allows you to understand me a little better. If ever I worry, that I'm not working hard enough or not doing something for the right reason, I have you (and your grandfather) to thank for driving me on. I'm truly inspired and honoured to be your father.

LIST OF THESIS PUBLICATIONS

1. McMurray JJ, **STEWART S**. Epidemiology, aetiology, and prognosis of heart failure. *Heart*. 2000;83:596-602.
2. **STEWART S**, MacIntyre K, Hole DJ, Capewell S and McMurray JJ. **More 'malignant' than cancer? Five-year survival following a first admission for heart failure.** *Eur J Heart Fail*. 2001;3:315-22.
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 30. Ball J, Carrington MJ, McMurray JJ, **STEWART S**. **Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century.** *Int J Cardiol.* 2013;167:1807-24.
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INTELLECTUAL CONTRIBUTION & LEADERSHIP

APPENDIX I provides the details of the 12 peer-reviewed funding schemes (from prestigious career Fellowships to substantive program of research grants) that directly relate to these 33 selected manuscripts.

A key component of a good proportion of this portfolio, is the co-authorship of PhD candidates under my principal/co- supervision. Many were supported by their own prestigious post-graduate scholarships. I am fortunate to have navigated 20 such candidates to completion in the past 20 years. Many of these early career researchers were initially funded by the *National Heart Foundation of Australia* and/or *National Health & Medical Research Council of Australia*. Moreover, many now hold senior academic appointments (at last count at least 5 are full Professors) through which they lead their own research teams and undertake impactful research programs.

When selecting the 33 primary/original research manuscripts to compile this thesis and survive the scrutiny of expert peer-review, I consciously decided to apply a combination of the following criteria, in respect to unequivocally demonstrating my intellectual contribution/leadership of each output -

- A. Being listed as the first/primary author or last/senior corresponding author of the manuscript.
- B. Conducting the described research/project as the primary recipient/ Principal Investigator of the peer-reviewed funding that supported the research being described.
- C. Demonstrated leadership of large multidisciplinary research teams such as the *WHICH? Trial* and *SAFETY Trial* and *Heart of Soweto Study* Investigators, to successfully complete (and report on) large-scale disease surveillance and pragmatic health service intervention studies.

APPENDIX II contains all 34 of the primary manuscripts that have been carefully selected to form the core of this portfolio of research. They comprise a key review of the HF literature co-authored by me with the inspirational Professor John McMurray and published in *Heart* in 2000 plus 33 original research papers spanning 20 years thereafter. A further 78 co-authored manuscripts that support the results and interpretation of study findings of these primary reports have been added as references and are highlighted in the **REFERENCES**.

PLACING THIS PORTFOLIO OF RESEARCH INTO MY CAREER CONTEXT

During my research career as a clinician/scientist/health services researcher who has spanned multiple disciplines (basic science, nursing, cardiology, medicine, clinical trials, public health, epidemiology, and health economics), I've been privileged to publish more than 400 research articles, more than 1000 research abstracts and authored/edited (all as senior author/editor) ten books.

My current *Scopus h-index (March 2023) stands at 69 from 420 listed papers and ~22,000 citations.* I am proud that this important metric is not inflated by guidelines or “group” research papers where I have minimal intellectual control or input. Thus, as reflected in the portfolio of research informing this thesis, most of my highly cited, original research reports were led and written by me.

RESEARCH IMPACT

As was succinctly commented to me when compiling this portfolio of research – “*it is one thing to be highly cited, it's another to be impactful and make a difference*”. Indeed, the conditions for this award are clear in that the published body of research must –

- a. **Represent a significant advance in knowledge** (*in this case, our understanding of the evolving epidemiology/burden of disease and optimal management of heart failure and atrial fibrillation*).
- b. **Given rise to significant debate amongst recognised scholars** (*in this case, generating numerous editorials and high citations from subsequent research projects and reviews of the literature*).
- c. **Have directly changed the direction of research or practice in a newer generation of scholars** (*in this case, contributing to an expanded focus on heart failure as a truly “malignant” syndrome and pioneering dedicated health services, identifying atrial fibrillation as a rising public health threat requiring dedicated care programs AND highlighting the increasing intersection between these two deadly and disabling conditions*).

In framing the clinical impact of my portfolio of research **TABLE 1** and **TABLE 2**, specifically identify the **>50 individual guideline/expert consensus reports** that have referenced the 33 original research reports that form the core of this thesis. To date, my research has informed **>200** expert documents. This includes current clinical guidelines published by the *European Society of Cardiology, American Heart Association* and *Cardiac Society of Australia & New Zealand*.

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INTRODUCTION

In the late 20th Century/early 21st Century there was a growing realisation among clinicians and epidemiologists alike that the syndrome heart failure (HF) was placing an increasing burden on health care systems worldwide.¹ However, in many jurisdictions, including the UK, the clinical entity “*heart failure*” was poorly defined and documented.¹ This was exacerbated by the fact it could not be placed on a death certificate as a contributory cause of death.¹ Moreover, the definition of HF was evolving in tandem with the growing armoury of neurohormonal agents being successfully (and unsuccessfully) trialled to improve health outcomes.¹

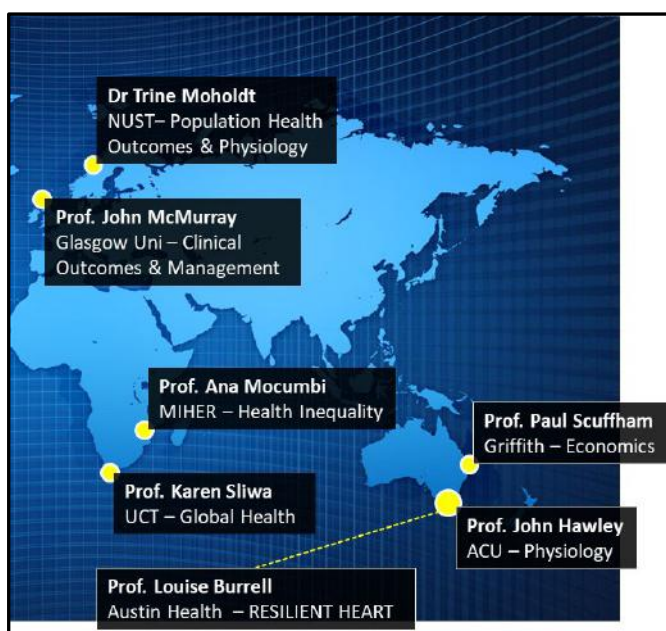
As summarised in **FIGURE 1**, arising from an expert review paper¹ that was published in the 12 months following the completion of my PhD in collaboration with the host of my *National Heart Foundation of Australia Overseas Ralph Reader Fellowship* (Professor John McMurray, University of Glasgow, Scotland, UK), over nearly two decades I completed and published an integrated portfolio of **22 original research manuscripts** that focussed on –

1. Understanding the evolving burden and impact of ***all forms heart failure*** and,
2. Further developing clinical management strategies that would attenuate the high rates of morbidity and mortality among those hospitalised with this deadly and disabling syndrome.¹⁻²³

Although HF was already the focus of considerable interest (both in terms of its burden and optimal treatment/management), this was clearly not the case for atrial fibrillation (AF). It is notable that in early clinical trials focussing on HF, AF was barely mentioned. Moreover, pre-existing cases were being treated with “blunt” therapeutics such as warfarin and sotalol. However, as shown in **FIGURE 2**, after considering the key dynamics of how HF had developed into a substantive health issue (due to the progressive ageing of high-income populations within which an increasing component of individuals were living with cardiac risk factors and/or survived an acute coronary event), I/we published a closely related portfolio of **10 original research manuscripts** focussed on –

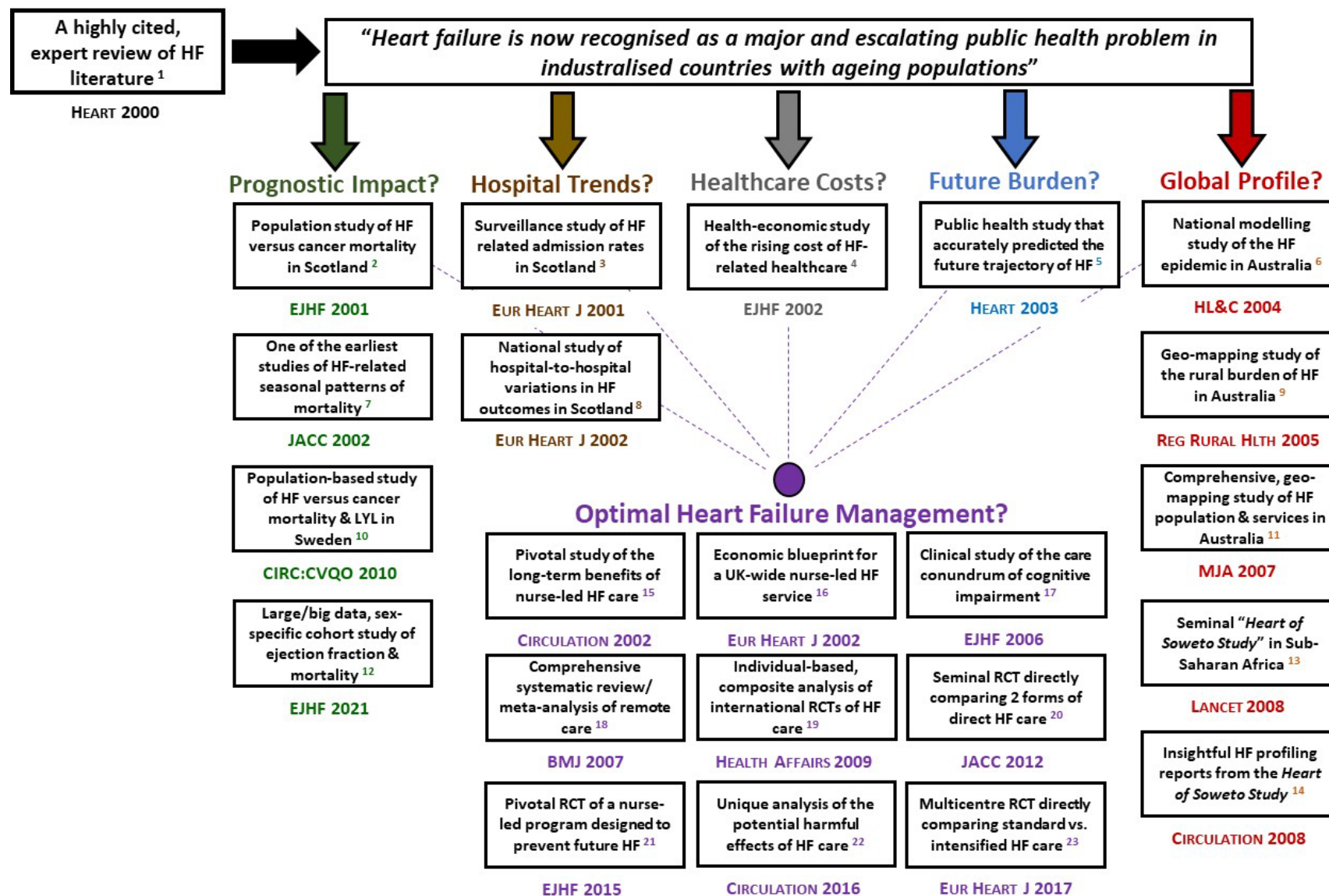
1. Charting the emerging threat and impact of ***all forms of atrial fibrillation*** and,
2. Developing new clinical strategies that would specifically attenuate the high-rates of morbidity and mortality among those hospitalised with chronic forms of AF.²⁴⁻³⁴

As with many complex research programs shaped by data availability, the formation of opportunistic collaborations and, critically, funding to conduct key studies, both portfolios of research are not completely linear in their progression of ideas, concepts, and findings. Critically, however, nearly every discrete project and publication described below has been highly cited in the literature (as of March 2022, collectively they have attracted >10,000 *Scopus Citations*) – thereby shaping the literature in return.



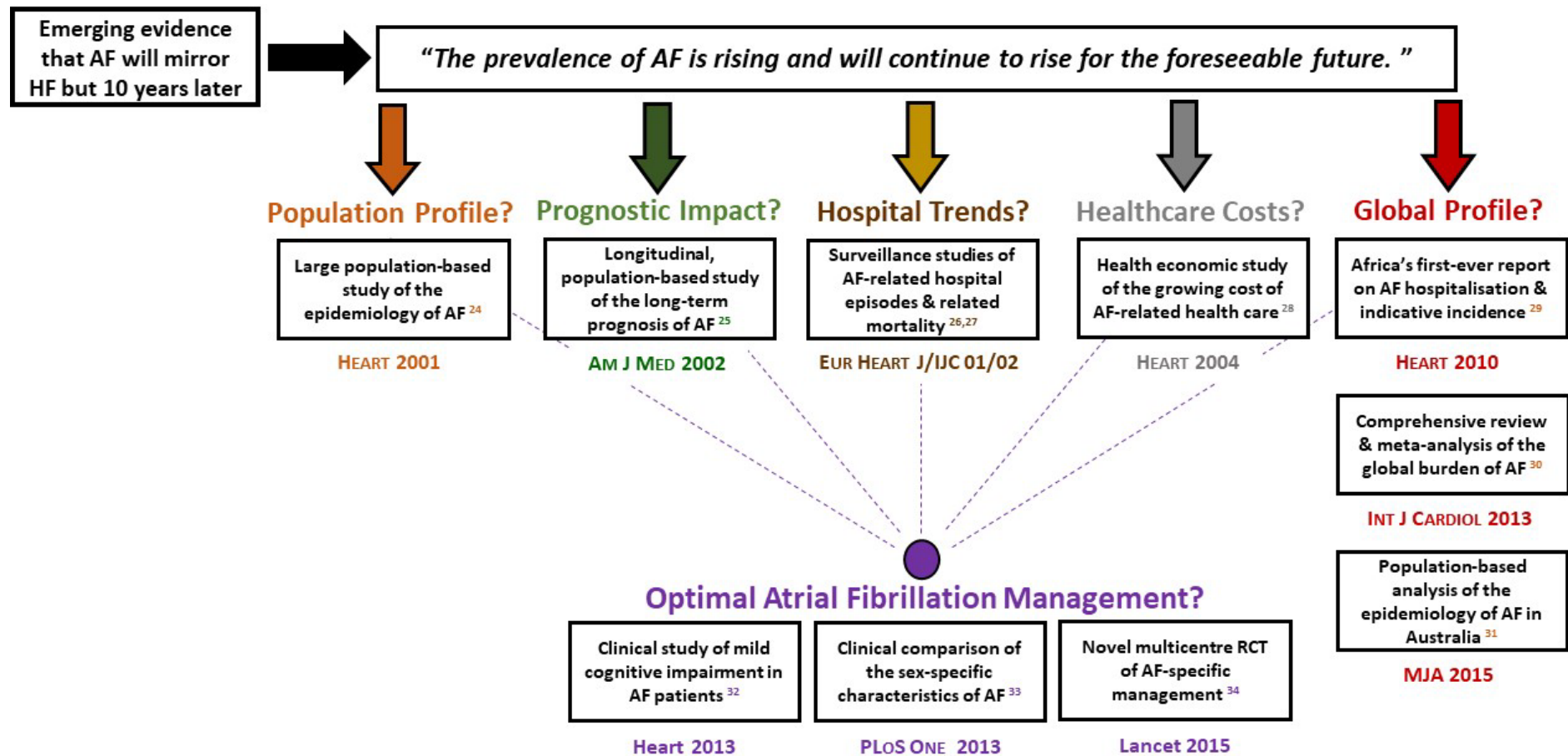
Testament to the international collaborations and partnerships (as represented by the image on the left) underlying this research, the portfolios of research summarised in **FIGURES 1 AND 2** have been cited close to 100 times in expert guidelines/peer reports on a global basis (see **TABLES 1 AND 2**). This includes clinical guidelines for the contemporary management of HF and AF as currently recommended by the *European Society of Cardiology (ESC)*³⁵, *American Heart Association (AHA)*³⁶ and *Cardiac Society of Australia and New Zealand (CSANZ)*.³⁷

FIGURE 1 – A PORTFOLIO OF ORIGINAL RESEARCH REPORTS EXAMINING AND RESPONDING TO THE EVOLVING BURDEN OF HEART FAILURE IN THE 21ST CENTURY.



LEGEND Within the thesis, six broad sections (comprising 22 key publications) relating to the epidemiological profile, burden and management of HF are presented. Each section/reference is colour coded.

FIGURE 2 – A PARALLEL PORTFOLIO OF ORIGINAL RESEARCH REPORTS IDENTIFYING AND RESPONDING TO THE EVOLVING BURDEN OF AF IN THE 21ST CENTURY.



LEGEND Within the thesis, six broad sections (comprising 10 key publications) relating to AF are presented. Each section/reference is colour coded.

Material not shown due to copyright

CONCLUSIONS: Over a 20-year period, we conducted a range of pragmatic trials and analyses focussed on the benefits (and potential adverse effects) of multidisciplinary HF management. Pragmatic RCTs were conducted in the UK¹⁷⁰, Hong Kong¹⁷¹ and Australia.²³ Similarly, international collaborations collated and synthesised outcome data from across the globe. A key focus of my research program (ongoing) is the translation of evidence into cost-effective and sustainable health services. It also involves monitoring health systems to determine if the evidence around HF management is being appropriately applied. In parallel to our evolving knowledge around the detection and treatment of HF (the definition and clinical scope of which is continually changing), we have re-tested the contemporary efficacy of our original approaches to HF management, including our own. Recent findings suggest that our old models of care need to be updated to accommodate a more challenging HF patient population and the environment in which they live.¹⁶⁹ Consequently, new, more innovative approaches to care are being developed and tested in a new generation of appropriately powered RCTs (from Africa to Australia).

TRANSLATIONAL IMPACT – GREATER HF AWARENESS & DEDICATED MANAGEMENT PROGRAMS

Of the 22 research manuscripts presented in this portfolio of research in HF, 16 (73%) were published in highly prestigious journals with an impact factor >10. This includes the *British Medical Journal*, *The Lancet*, *Circulation*, *Journal of the American College of Cardiology* and *European Heart Journal* and the *European Journal of Heart Failure*. Two manuscripts are the 1st and 3rd most cited research articles in the journal's history.

Consistent with the overall significance of the research being presented in these papers, combined they have accumulated **>4,500 Scopus citations** (~180 cites per paper) with a **mean field-weighted citation index of 6.27** (topic rather than discipline profile). Critically, the importance of an early report focussing on seasonal patterns of HF events took many years to be recognised (hence it's low FWCI calculated over the first 3 years of publication). By the same token, due to the predominant reliance on external guidelines, the African-specific reports (whilst highly influential) are unlikely to be cited until the framework of African research expands and clinical guidelines based on African-led findings are published.

As outlined in **TABLE 1***, nearly all papers have specifically informed the expert clinical guidelines (28 individual citations), expert consensus statements (10 individual citations) and expert position statements/reports (18 individual citations). These cover the following regions:

- Sub-Saharan Africa - *Pan-African Society of Cardiology* [PASCAR]),
- Australia - *National Heart Foundation of Australia* [NHFA]/*Cardiac Society of Australia and New Zealand* (CSANZ),
- Europe – *European Society of Cardiology* (ESC) and its *Heart Failure Association* [HFA]),
- Latin America and North America - *American Heart Association* (AHA), *American College of Cardiology* (ACC) and *Heart Failure Society of America* [HFSa])
- Global – Lancet Commission reports

Overall, these papers have attracted **66 individual citations in these highly influential documents** (by mid-2022). At the most fundamental level, my program of research has contributed to the development of a new role for nurses (the *Specialist HF Nurse*) and new *Multidisciplinary HF Management* programs delivering care to those affected by HF worldwide – the challenge being to extend such coverage to disadvantaged/low-resource regions (e.g., Sub-Saharan Africa) and ensure these programs are adapted to remain cost-effective.

TABLE 1 summarises the bibliometric profile and inclusion in expert guidelines of each manuscript groups into the categories described in **FIGURE 1**.

TABLE 1 – A PORTFOLIO OF RESEARCH REPORTS ON THE EVOLVING BURDEN & MANAGEMENT OF HF

Title	Journal [Year]	SS	Scopus Cites	FWCI/Centile	Significance of the report to HF awareness/management	Guidelines/Expert Consensus & Positions
DEFINING THE PROGNOSTIC IMPLICATIONS & BURDEN OF HEART FAILURE						
More malignant than cancer? Five-year survival following a first admission for HF	<i>European Journal of Heart Failure</i> [2001]	1st	838	11.22/99 th	Report on the prognostic impact of HF relative to the most common forms of cancer. It remains the <u>most cited research paper</u> in the history of the highly prestigious <i>European Journal of Heart Failure</i> .	<ul style="list-style-type: none"> ▪ 2019 Italian Society of Cardiology Consensus Statement ▪ 2017 Austrian Cardiology Society Position Statement ▪ 2015 EHRA Consensus Statement ▪ 2014 Polish Clinical Forum on Cardiac Imaging ▪ 2012 ESC HF guidelines ▪ 2011 Brazilian Cardio-oncology guidelines ▪ 2010 ESC HF guidelines ▪ 2008 Italian Cardiology Society guidelines ▪ 2008 ESC HF guidelines ▪ 2006 HFSA guidelines ▪ 2005 ESC Position Paper
HF in a cold climate: Seasonal variation in HF-related morbidity & mortality	<i>Journal of the American College of Cardiology</i> [2002]	1st	159	1.54/81 st *	Early, report on the seasonal impact on HF-related events – most citations have appeared in the last decade. It now forms the initial rationale for a MRFF-funded RCT - the RESILIENCE Trial.	<ul style="list-style-type: none"> ▪ 2020 Family Practice (US) guidelines ▪ 2011 ESC guidelines
Population impact of HF & the most common forms of cancer: A study 1 162 309 hospital cases in Sweden (1988 to 2004)	<i>Circulation: CV Quality & Outcomes</i> [2010]	1st	158	3.31/81	One of the largest population studies of HF-related mortality (versus cancer) ever reported. It quantified (for the first-time) the number of life-years-lost due to HF among men and women within a whole population.	<ul style="list-style-type: none"> ▪ 2017 Austrian Cardiology Society ▪ 2011 ESC guideline
Ejection fraction & mortality: a nationwide register-based cohort study of 499 153 women & men	<i>European Journal of Heart Failure</i> [2021]	1st	11	5.50/99 th	Largest-ever patient cohort study of its kind to date. It has contributed to a paradigm change in the interpretation of ejection fraction levels and the risk of mortality on a sex-specific basis with calls to revisit sex-specific thresholds of risk according to VEF levels and a reinterpretation of clinical trial outcomes	<ul style="list-style-type: none"> ▪ 2021 ESC guidelines
EXAMINING THE EVOLVING PATTERN OF HEART FAILURE-RELATED HOSPITAL ADMISSIONS & OUTCOMES						
Trends in hospitalization for HF in Scotland, 1990-1996: An epidemic that has reached its peak?	<i>European Heart Journal</i> [2001]	1st	195	7.94/98 th	A controversial report on the peaking of admissions with a primary diagnosis of HF (but not secondary diagnosis) in Scotland - subsequently replicated by equivalent studies worldwide	
Substantial between-hospital variation in outcome following first emergency admission for HF	<i>European Heart Journal</i> [2002]	1st	29	0.92 / 71 st	Highly controversial and debated study within Scotland/UK that framed calls for the application of multidisciplinary HF management programs to address wide variations in HF-related outcomes	<ul style="list-style-type: none"> ▪ 2005 Latin American guidelines
QUANTIFYING THE INCREASING COST-BURDEN OF HEART FAILURE TO THE HEALTH CARE SYSTEMS OF HIGH-INCOME COUNTRIES						
The current cost of heart failure to the National Health Service in the UK	<i>European Journal of Heart Failure</i> [2002]	1st	450	6.71/98 th	One of the <u>top 5 most cited research papers</u> in the history of the highly prestigious <i>European Journal of Heart Failure</i> , this was the first study compare & contrast the cost of HF within the same health service a decade apart. Findings showed the increasing economic burden of HF -subsequently replicated by other studies worldwide	<ul style="list-style-type: none"> ▪ 2017 Position Statement Austrian Cardiology Society ▪ 2012 ESC HF guidelines ▪ 2010 ESC HF guidelines ▪ 2009 Italian Cardiology Society HF guidelines ▪ 2008 ESC HF guidelines
PROJECTING THE FUTURE BURDEN OF DISEASE IMPOSED BY AN EVOLVING EPIDEMIC OF HEART FAILURE						
Heart failure and the aging population: An increasing burden in the 21 st Century	<i>Heart</i> [2003]	1st	296	5.50/96 th	A study that challenged pre-existing/alarming warnings of an exponential rise in HF cases & the associated burden of disease. Study findings suggesting a more modest (~25%	<ul style="list-style-type: none"> ▪ 2012 German National HF guidelines ▪ 2008 AHA guidelines ▪ 2006 ESC guidelines

					increase) and plateauing burden of disease were subsequently proven more accurate.	
CLOSING KEY KNOWLEDGE GAPS ON THE PATTERN OF HF: FROM AUSTRALIA TO SUB-SAHARAN AFRICA						
Uncovering a hidden epidemic: A study of the current burden of heart failure in Australia	<i>Heart Lung & Circulation</i> [2004]	Last	50	1.40/79 th	Australia relies on very poor & often misleading (e.g., asking the public if they have swollen ankles or HF). This study was the first quantify the burden of HF using the best available data at the time.	<ul style="list-style-type: none"> 2010 NHFA/CSANZ guidelines 2010 AIS Position Statement 2006 NHFA/CSANZ guidelines
Chronic heart failure beyond city limits	<i>Rural & Remote Health</i> [2005]	Last	16	1.05/73 rd	Contemporary national health surveys in Australia focussed on urban populations. This study was the first to demonstrate a disproportionate burden of HF cases in rural Australia (due to socio-economic factors) - subsequently confirmed by other studies.	
Inequitable provision of optimal services for patients with chronic heart failure: A national geo-mapping study	<i>Medical Journal of Australia</i> [2007]	Last	53	3.11/92 nd	A geo-mapping study that built on the findings of the above report – demonstrating a mismatch between HF cases and available clinical services/expert care. It also led to the innovative CARDIAC-ARIA tool	<ul style="list-style-type: none"> 2014 NHFA/CSANZ Consensus Statement 2010 NHFA/CSANZ guidelines
Cardiometabolic risk and disease in Indigenous Australians: The Heart of the Heart Study	<i>International Journal of Cardiology</i> [2014]	Last	30	1.49/81 st *	This was a study of the antecedents and epidemiological profile (reported in a separate manuscript as part of a PhD program) of HF and other forms of chronic heart disease within the Indigenous communities of Central Australia	
Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study	<i>The Lancet</i> [2008]	Last	282	15.53/99 th *	This paradigm-changing report challenged the conventional wisdom that heart disease and, specifically HF, was almost non-existent in Sub-Saharan Africa.	<ul style="list-style-type: none"> 2020 ESC/HFSA Position Paper 2020 PASCAR Position Paper 2019 AHA Heart diseases & stroke statistics 2018 AHA Heart diseases & stroke statistics 2017 AHA Heart diseases & stroke statistics 2016 AHA Heart diseases & stroke statistics
Predominance of heart failure in the heart of Soweto study cohort: Emerging challenges for urban African communities	<i>Circulation</i> [2008]	1st	127	2.39/89 th *	Published as the same time as the primary <i>Heart of Soweto</i> primary report, this study characterised the large volume of HF cases (many with hypertension as well as right-sided aetiology) in a large urban African community in epidemiological transition.	<ul style="list-style-type: none"> 2021 Lancet Commission on Women & Cardiovascular Disease 2020 Lancet Commission on Poverty & Non-Communicable Diseases
ESTABLISHING AND THEN EXPLORING THE BENEFITS & PITFALLS OF HEART FAILURE MANAGEMENT PROGRAMS						
An economic analysis of specialist heart failure nurse management in the UK: Can we afford not to implement it?	<i>European Heart Journal</i> [2002]	1st	82	2.58/90 th	Arising from my trials of HF management (PhD program) & the world-first <i>Glasgow Heart Failure Nurse Liaison Service</i> I helped to establish, this paper modelled the cost-benefits of applying a UK-wide HF service – the results of which were then implemented by, the <i>British Heart Foundation</i> .	<ul style="list-style-type: none"> 2019 German Cardiac Society Position Paper 2017 ESC/HFSA Position Paper 2011 ESC Position Paper
Home-based intervention in congestive heart failure: long-term implications on readmission and survival	<i>Circulation</i> [2002]	1st	250	7.08/98 th	Arising from my trials of HF management (PhD program) this report demonstrated that the initial benefits of this kind of program (previously shown to be effective in the short-term) were sustained over the longer-term.	<ul style="list-style-type: none"> 2017 Austrian Society of Cardiology Consensus 2016 Spanish Society of Cardiology Consensus 2009 German Society of Cardiology Guidelines 2008 HFSA Consensus 2006 HFSA Guidelines 2005 Latin American HF Guidelines

Prognostic importance of cognitive impairment in chronic heart failure patients: Does specialist management make a difference?	<i>European Journal of Heart Failure</i> [2010]	Last	76	4.41/96 th	Despite growing support for HF management programs world-wide, this paper (for the first-time) identified the pitfalls associated with implementing such programs among those with cognitive impairment (including those with HF & chronic pulmonary disease).	<ul style="list-style-type: none"> ▪ 2015 American HF Association Position Paper ▪ 2011 ESC/HFSA Guidelines
Telemonitoring or structured telephone support programmes for patients with chronic heart failure: Systematic review and meta-analysis	<i>British Medical Journal</i> [2007]	1st	485	37.67/99 th	Following the publication of this meta-analysis of HF programs (of which I was the 2 nd author), this report focused on the evidence supporting the remote management of HF. Along with the original meta-analysis [R] and a series of related reports derived from this analysis, this has shaped the application of HF programs worldwide.	<ul style="list-style-type: none"> ▪ 2013 ACCF/AHA HF guidelines ▪ 2009 ACCF/AHA HF guidelines ▪ 2008 ESC guidelines
What works in chronic care management: The case of heart failure	<i>Health Affairs</i> [2009]	Last	185	13.99/99 th	Addressing the inherent limitations of meta-analysis of scientific reports, this was a global collaboration that combined individual RCT profiling and outcome data from <u>studies of HF management led by worldwide experts</u> – producing a service-defining recommendation that in-person, multidisciplinary HF teams produced the best health outcomes.	<ul style="list-style-type: none"> ▪ 2015 EHRA Consensus Statement ▪ 2013 ACC/AHA HF Guidelines ▪ 2012 ESC guidelines
Impact of home versus clinic-based management of chronic heart failure: The WHICH? (Which heart failure intervention is most cost-effective & consumer friendly in reducing hospital care) multicentre, randomized trial	<i>Journal of the American College of Cardiology</i> [2012]	1st	103	3.25/93 rd	This RCT (funded by the NHMRC of Australia), was the first to compare two forms of HF management head-to-head. Initially underpowered to detect program differences, longer-term follow-up showed the superiority of the home-based intervention, whilst patients also preferred home-based management.	<ul style="list-style-type: none"> ▪ 2014 ESC Position Statement ▪ 2016 NHFA/CSANZ HF guidelines
Impact of a nurse-led home and clinic-based secondary prevention programme to prevent progressive cardiac dysfunction in high-risk individuals: The Nurse-led Intervention for Less Chronic Heart Failure (NIL-CHF) randomized controlled study	<i>European Journal of Heart Failure</i> [2015]	1st	18	1.45/80 th	Funded by the NHMRC of Australia, this was <u>first study of its kind</u> (complementing one other trial in primary care) to determine if it's possible to prevent HF in high-risk individuals via multidisciplinary care & surveillance. Although initially negative, the original and subsequent long-term follow-up identified the potential to prevent disease progression in high-risk individuals.	<ul style="list-style-type: none"> ▪ 2021 ESC/HFSA Position Paper
Impact of nurse-led multidisciplinary home-based intervention on event-free survival across the spectrum of chronic heart disease	<i>Circulation</i> [2016]	1st	24	1.62/83 rd	Funded by the NHMRC of Australia, this was a composite analysis of 4 RCTs of home-based disease management (including patients with HF). This study demonstrated, <u>for the first-time</u> , the potential harmful effects of this type of intervention among younger and older patients with chronic heart disease (often with malignant multimorbidity) requiring new perspectives on how care should be delivered to such individuals.	<ul style="list-style-type: none"> ▪ 2018 American Practitioner Nurse Association Consensus Statement
Standard versus intensified management of heart failure to reduce healthcare costs: Results of a multicentre, randomized controlled trial	<i>European Heart Journal</i> [2016]	Last	16	1.17/75 th	Funded by the NHMRC of Australia, this multicentre RCT compared an intensified versus standardised approach to HF management of those living in both urban and rural settings – no difference between the two groups being found.	<ul style="list-style-type: none"> ▪ 2021 ESC/HFSA Position Paper

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This new clinical reality mandates a re-evaluation of many longstanding hospital avoidance programs to determine if they are still “fit for purpose”.¹²¹ There is a cogent argument that they should be modified to suit the needs of modern-day patient populations. It also mandates the development of new approaches to care. It is for this reason we are conducting the MRFF-funded RESILIENCE Trial to reduce external provocations to the cardiopulmonary health of high-risk patients affected by a combination of CAD, AF and/or HF – rather than focussing on AF alone.^{166, 167}

CONCLUSIONS: Despite a wealth of clinical to public health data (some of which has been presented in this portfolio of research) to characterise the evolving characteristics and burden of AF, the evidence in support of AF-specific management programs remains under-developed. This might be rectified with the publication of further RCTs (such as the HELP-AF Study) and the potential to then generate meta-analyses from multiple RCTs with a large volume of endpoints/outcomes. At the very least, ongoing efforts to address “seasonal” vulnerability (as described above) will automatically identify individuals living with chronic AF at high-risk of recurrently hospitalisation and premature mortality. This approach (individual rather than disease specific) is the better new/old approach to provide incremental health benefits within a growing patient population presenting to hospital with a combination of AF and/or HF and other forms of multimorbidity.

TRANSLATIONAL IMPACT – GREATER AWARENESS & DEDICATED MANAGEMENT PROGRAMS FOR ATRIAL FIBRILLATION

In stark contrast to the HF portfolio, of the 10 AF-focussed manuscripts described above (all presenting primary research outputs), only 2 (20%) were published in journals with an impact factor >10. Despite this, reflective of the latent/delayed recognition of these reports, combined they have accumulated ~**2,900 Scopus citations** (~290 cites per paper) with a **mean field-weighted citation index of 6.19** (topic rather than discipline profile).

Overall, all 10 of these papers have specifically informed the expert clinical guidelines (23 individual citations), expert consensus statements (11 individual citations) and expert position statements/reports (5 individual citations). These cover the following regions:

- Sub-Saharan Africa - *Pan-African Society of Cardiology* [PASCAR]),
- Australia/Asia-Pacific - *National Heart Foundation of Australia* [NHFA]/*Cardiac Society of Australia and New Zealand* (CSANZ), *Pan-Pacific Heart Rhythm Society*
- Europe – *European Society of Cardiology* (ESC) and its *Heart Failure Association* [HFA]),
- Latin America and North America - *American Heart Association* (AHA), *American College of Cardiology* (ACC) and *Heart Failure Society of America* [HFSA])
- Global – Lancet Commission reports

Overall, these papers have attracted **44 individual citations in these documents** (by mid-2022). At the most fundamental level, my program of research, whilst having a lesser (to date) impact in respect to triggering coordinated AF management, still played an important role in highlighting the rising individual to economic burden of AF – high health expenditure being one the main drivers of health service and commercial innovations.

TABLE 2 (PAGES 61-62) summarises the bibliometric profile and inclusion in expert guidelines of each manuscript groups into the categories described in **FIGURE 2**.

TABLE 2 – A PORTFOLIO OF RESEARCH REPORTS ON THE EVOLVING BURDEN & MANAGEMENT OF AF

Title	Journal [Year]	SS	Scopus Cites	FWCI/ Centile	Significance of the report to HF awareness/management	Guidelines/Expert Consensus & Positions
POPULATION PROFILE OF AF						
Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley Study	<i>Heart</i> [2001]	1st	502	2.92/ 92 nd	It took many years for the importance of this report to be recognised – it represents one of the first-ever population studies of the incidence and prevalence of AF.	<ul style="list-style-type: none"> ▪ 2017 EHRA guidelines ▪ 2013 French Society of Geriatrics and Gerontology guidelines ▪ 2010 ESC guidelines ▪ 2004 Swiss Cardiology Society guidelines
PROGNOSTIC IMPACT OF AF						
A population-based study of the long-term risks associated with atrial fibrillation: 20-Year follow-up of the Renfrew/Paisley Study	<i>American Journal of Medicine</i> [2002]	1st	1,183	8.66/ 98 th	<p>This is a <u>paradigm-changing population-based longitudinal research report</u> that redefined the prognostic implications of AF. Despite winning a major population research prize at the American Heart Association’s Scientific meeting, as with the “more malignant than cancer” HF report, there was a reluctance by the major medical journals to publish anything that hadn’t been derived from the Framingham Heart Study. Its importance was finally recognised when for two iterations of the major AF guidelines, it was first reference quoted to underline the importance of recognising the public health threat and need for expert clinical management of AF.</p> <p>This is the <u>most cited</u> paper published by the <i>American Journal of Medicine</i> in 2002.</p>	<ul style="list-style-type: none"> ▪ 2020 ESC guidelines ▪ 2020 EHRA/APHRs guidelines ▪ 2019 ACC/AAT/AHA guidelines ▪ 2018 European Society of Hypertension Position Paper ▪ 2016 ESC guidelines ▪ 2014 AHA/ACC guidelines ▪ 2013 French Society of Geriatrics and Gerontology Consensus Statement ▪ 2012 HRS/EHRA Consensus Statement ▪ 2012 Polish Cardiac Society Consensus Statement ▪ 2011 ACC/ACC guidelines ▪ 2010 ESC guidelines ▪ 2009 Canadian Hypertension Education guidelines ▪ 2009 AFNET-EHRA Consensus Statement ▪ 2009 Japanese Hypertension Society guidelines ▪ 2007 HRS/EHRA Consensus Statement ▪ 2006 ACC/AHA/ESC guidelines
TRENDS IN AF-RELATED HOSPITAL ADMISSIONS						
Trends in hospital activity, morbidity and case fatality related to atrial fibrillation in Scotland, 1986-1996	<i>European Heart Journal</i> [2001]	1st	129	3.03/ 91 st	This report was the first-ever analysis of long-term trends in AF-related hospital activity and outcomes. Like those studies focussing on HF, it led to several studies focussing on seasonal patterns of admission and the future burden of disease.	<ul style="list-style-type: none"> ▪ 2011 ACC/AHA guidelines ▪ 2006 ACC/AHA guidelines
Trends in case-fatality in 22,938 patients admitted for the first time with atrial fibrillation in Scotland, 1986-1995	<i>International Journal of Cardiology</i>	1 st	37	1.44/ 80 th	This follow-up report (to that above), provided a granular age-and sex-specific analysis of de novo/incident admissions with AF in Scotland – showing that the future burden of disease would increase as the population progressively aged.	<ul style="list-style-type: none"> ▪ 2012 Polish Cardiac Society guidelines
COST-BURDEN OF AN EMERGING EPIDEMIC OF AF						
Cost of an emerging epidemic: An economic analysis of atrial fibrillation in the UK	<i>Heart</i> [2004]	1st	437	11.22/ 99 th	This report represents the first-ever analysis of the economic burden of AF. Up until its publication there was little appreciation of the growing health burden of AF. Many similar reports have now been generated from around the world. It is the <u>most cited</u> paper published by the <i>Heart</i> in 2004	<ul style="list-style-type: none"> ▪ 2022 Asia Pacific HRS guidelines ▪ 2020 Canadian CV Society guidelines ▪ 2018 NHFA guidelines ▪ 2017 WHF AF Roadmap ▪ 2016 ESC guidelines ▪ 2011 AIAC guidelines ▪ 2011 ACCF/AHA guidelines ▪ 2006 ACC/AHA/ESC guidelines

EPIDEMIOLOGICAL FEATURES OF AF – A GLOBAL PERSPECTIVE						
Predisposing factors and incidence of newly diagnosed atrial fibrillation in an urban African community: Insights from the Heart of Soweto Study	<i>Heart</i> [2010]	Last	51	1.80/ 84 th *	Arising from the paradigm-changing <i>Heart of Soweto Study</i> , that redefined the modern spectrum of heart disease in the region, this represents an early and therefore important <u>study of AF in Sub-Saharan Africa</u> .	<ul style="list-style-type: none"> ▪ 2021 Lancet Commission on Women & Cardiovascular Disease ▪ 2020 Lancet Commission on Poverty & Non-Communicable Diseases ▪ 2020 PASCAR Position Paper
Atrial fibrillation: Profile and burden of an evolving epidemic in the 21st century	<i>International Journal of Cardiology</i> [2013]	Last	394	10.19/ 99 th	This report represents one of the most comprehensive systematic reviews and meta-analyses of AF ever reported. It provides pooled analyses of every aspect of the population characteristics and health burden of AF in high-income countries, whilst highlighting the paucity of data in low-income regions of the world.	<ul style="list-style-type: none"> ▪ 2017 EHRA Consensus Statement ▪ 2015 EHRA Consensus Statement
Estimating the current and future prevalence of atrial fibrillation in the Australian adult population	<i>Medical Journal of Australia</i> [2015]	Last	61	11.22/ 99 th	This is one of the first report in Australia to examine the current and future burden of AF.	<ul style="list-style-type: none"> ▪ 2019 Italian Society of Cardiology Consensus Statement ▪ 2017 Austrian Cardiology Society Position Statement ▪ 2015 EHRA Consensus Statement
ESTABLISHING THE CASE FOR ATRIAL FIBRILLATION-SPECIFIC MANAGEMENT PROGRAMS						
Mild cognitive impairment in high-risk patients with chronic atrial fibrillation: A forgotten component of clinical management?	<i>Heart</i> [2013]	Last	60	2.25/ 88 th	An insightful clinical report that led to recommendation that all inpatients chronic AF should be screened for cognitive impairment, with consequential implications on the education and post-discharge management of these cases.	<ul style="list-style-type: none"> ▪ 2016 ESC guidelines ▪ 2016 EIPAAHA Consensus Statement
Women Versus Men with Chronic Atrial Fibrillation: Insights from the Standard Versus Atrial Fibrillation spEcific managemenT studY (SAFETY)	<i>PLoS ONE</i> [2013]	Last	52	0.90/ 68 th	Arising from the SAFETY Trial this study generated important data on the clinical differences between men and women affected by AF.	<ul style="list-style-type: none"> ▪ 2020 Canadian CV Society guidelines ▪ 2016 ESC guidelines ▪ 2016 EIPAAHA Consensus Statement
Standard versus atrial fibrillation-specific management strategy (SAFETY) to reduce recurrent admission and prolong survival: Pragmatic, multicentre, randomised controlled trial	<i>The Lancet</i> [2015]	1 st	87	9.67/ 99 th	Analogous to the RCT on HF management (published in <i>The Lancet</i> as part of my PhD), this study provided concrete evidence to support nurse-led multidisciplinary AF-specific management to simultaneously reduce hospital admissions and prolong survival in those patients with AF but not HF – hence its simultaneous presentation at the 2015 AHA Scientific Meeting and simultaneous publication in <i>The Lancet</i> .	<ul style="list-style-type: none"> ▪ 2020 ESC guidelines ▪ 2018 NHFA/CSANZ guidelines ▪ 2016 ESC guidelines ▪ 2016 EHRA Consensus Statement ▪ 2015 EHRA Consensus Statement

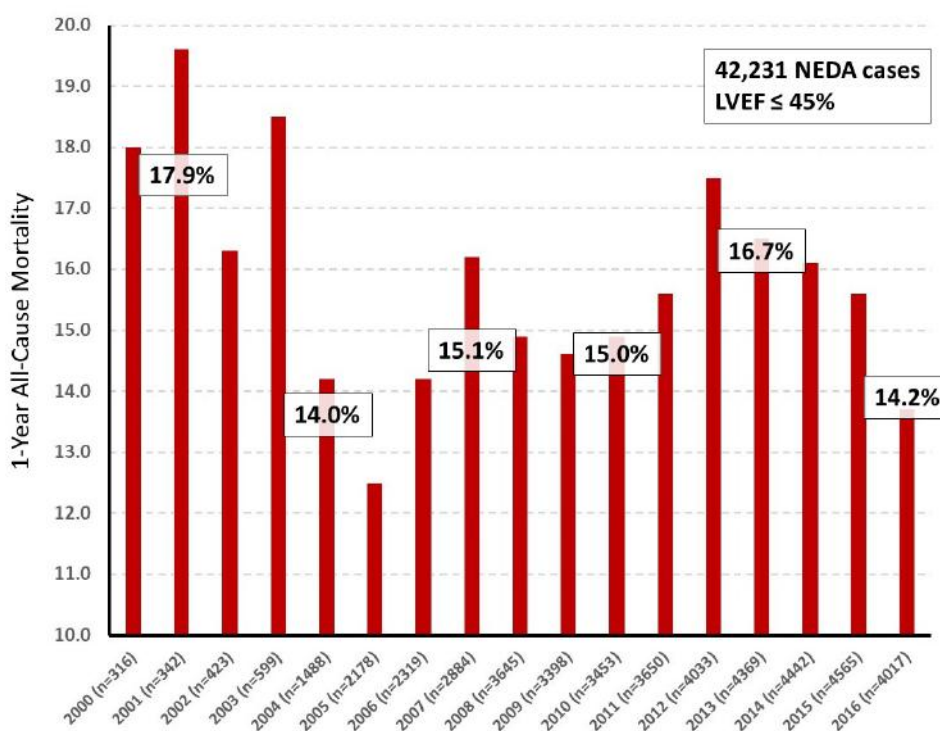
THESIS CONCLUSIONS

When the first of the 33 manuscripts comprising this portfolio of research was published, it would have been difficult to justify labelling HF and AF as the “*Scylla and Charybdis*” of chronic heart disease. Even with poetic license (noting the need for such a strategy when applying perfectly elegant mythologies and metaphors to the imperfect world of public health/clinical care), one might argue that this label is still not justified – particularly when an increasing number of individuals in high-income countries are achieving relatively heart healthy longevity. However, all the data presented in this manuscript suggest that –

1. Even if the rate of *de novo* HF is declining (there is no real data to support this at a time when its definition is being expanded), due to better management of common antecedents such as acute coronary syndromes, paradoxically the overall volume of people entering old age at risk of developing the syndrome will remain high. Critically, antecedent risk in the form of sedentary behaviours, metabolic diseases, and hypertension, along with improving management of acute coronary syndromes remain at historical highs. **Thus, the modern-day epidemic of HF that emerged in the late 20th Century, will be sustained well into the foreseeable future.**
2. Following on from the initial rise of HF, AF has since emerged as the new cardiac epidemic in the 21st Century. **There is no sign (yet) that it has reached its peak.** Like HF, there is a paradoxical twist to the dynamics of this epidemic given that – **a)** The prevalence of AF naturally rises with advancing age (due to the “ageing heart” effect) in the absence of any substantive disease and, **b)** It is far more likely to occur in those individuals who reach older age with pre-existing risk factors and/or established forms of heart disease (the most notable one being HF).

In considering the first point/conclusion, it’s worth considering the temporal pattern of cases presenting with an LVEF <45% and their subsequent 1-year mortality captured by NEDA - **FIGURE 57**. Over a prolonged period, the survival profile of such cases has improved. However, dynamics such as the age, sex, diagnostic and investigative thresholds, new therapeutics and even variability in outcomes (depending on which institutions contributed to NEDA cases over that period) confound simple interpretation of these data. The only thing we can say with (some) certainty, is that despite some gains in survival overall, there appears to be a “steady state” of individuals being investigated with impaired systolic function. Such data will provide a rich line of enquiry as NEDA expands to include more cases (>1 million from >40 Australian centres), hospital episodes and therapeutic data (including new treatment strategies).

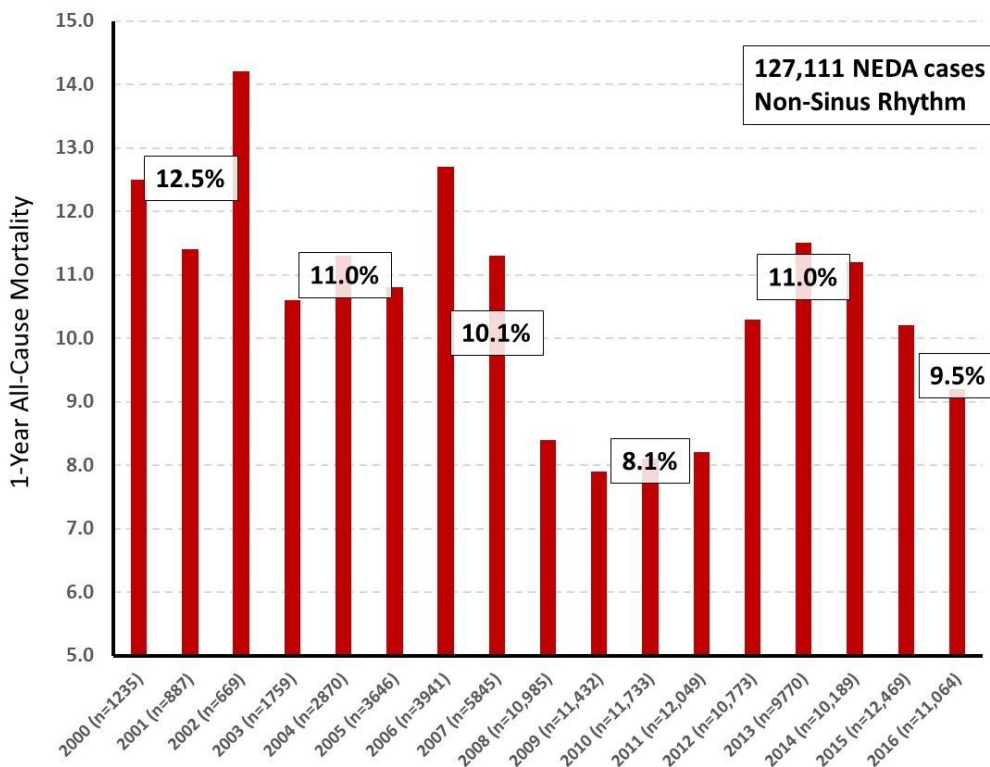
FIGURE 57 – TEMPORAL TRENDS IN 1-YEAR ALL-CAUSE MORTALITY IN NEDA CASES WITH LVEF ≤45%



Legend: The insert boxes show 1-year mortality averaged over 3 years (2000-02 to 2015-17)

Similarly, when considering the second point/conclusion, it's worth considering the temporal pattern of cases presenting in non-sinus rhythm (an imperfect surrogate for individuals in AF during their echocardiogram) and their subsequent 1-year mortality captured by NEDA - **FIGURE 58**. Once again, without more detailed analyses/accurate identification of AF cases (something that will be addressed once NEDA integrates linked data to hospital episodes and treatment data), these data are difficult to interpret. Once again however, despite a myriad of potential confounders and positive survival trends, the volume of individuals presenting with potential AF in Australia remains high. Thus, the underlying tension to optimally prevent and manage AF will remain high for the foreseeable future.

FIGURE 58 – TEMPORAL TRENDS IN 1-YEAR ALL-CAUSE MORTALITY IN NEDA CASES NOT IN SINUS RHYTHM



Legend: The insert boxes show 1-year mortality averaged over 3 years (2000-02 to 2015-17)

Thus, no matter how we might seek to safely *navigate* our increasingly at-risk populations to old age without provoking the rise of costly, debilitating, and deadly forms of heart dysfunction at an early age, we are inevitably placing them at risk of the twin threats HF and AF. Optimal disease management programs based on the highest levels of evidence (including appropriately powered RCTs and robust meta-analyses) do offer some hope – particularly those designed to optimise the management of high-risk individuals hospitalised with HF and/or AF. New pharmacological agents typically require real-world health service capacity to replicate what was achieved in the trials that proved their worth. This typically includes more cautious up-titration and safety monitoring than first anticipated. However, generating additional gains within an increasingly older and more complex patient cardiac population with HF and AF is increasingly challenging.

Final Conclusions. Paradoxically, we are the victims of our own success and relative wealth. We've largely overcome the dangers of middle-age - although the recent spate of high-profile sudden cardiac deaths/events in men aged in their 50's is a sobering reminder that it still exists (especially in middle-aged men who chose to smoke!). Many more people are now entering old age. However, they are typically entering it with antecedent risk for developing chronic forms of heart disease. Thus, HF and AF represent the *Scylla & Charybdis* of this new world. Having emerged in the clinical to public consciousness separately (around 10 years apart to reflect their different natural history/disease trajectory), they've now merged and pose a twin threat to millions of people globally. This mandates more nuanced thinking about the triggers of events and how we might prolong the lives of those affected. This will include the challenge of maintaining good quality of life for those affected whilst not provoking more debilitating and costly hospital episodes.

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APPENDIX I – COMPETITIVE FUNDING SUPPORTING THIS PORTFOLIO OF RESEARCH

TIMEFRAME	RESEARCH FUNDING	PORTFOLIO OUTPUT
1999-2002	<p>SIMON STEWART 1998 NATIONAL HEART FOUNDATION RALPH READER POST-DOCTORAL OVERSEAS MEDICAL RESEARCH FELLOWSHIP (University of Glasgow, Scotland)</p>	<ul style="list-style-type: none"> ❖ McMurray JJ, STEWART S. Epidemiology, aetiology, and prognosis of heart failure. <i>Heart</i> 2000; 83(5): 596-602. ❖ STEWART S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. <i>Eur J Heart Fail</i> 2001; 3(3): 315-22. ❖ STEWART S, MacIntyre K, MacLeod MM, Bailey AE, Capewell S, McMurray JJ. Trends in hospitalization for heart failure in Scotland, 1990-1996. An epidemic that has reached its peak? <i>Eur Heart J</i> 2001; 22(3): 209-17. ❖ STEWART S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. <i>Heart</i> 2001; 86(5): 516-21. ❖ STEWART S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK. <i>Eur J Heart Fail</i> 2002; 4(3): 361-71. ❖ STEWART S, MacIntyre K, Capewell S, McMurray JJ. Heart failure and the aging population: an increasing burden in the 21st century? <i>Heart</i> 2003; 89(1): 49-53. ❖ STEWART S, McIntyre K, Capewell S, McMurray JJ. Heart failure in a cold climate. Seasonal variation in heart failure-related morbidity and mortality. <i>J Am Coll Cardiol</i> 2002; 39(5): 760-6. ❖ STEWART S, Demers C, Murdoch DR, et al. Substantial between-hospital variation in outcome following first emergency admission for heart failure. <i>Eur Heart J</i> 2002; 23(8): 650-7. ❖ STEWART S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. <i>Am J Med</i> 2002; 113(5): 359-64. ❖ STEWART S, MacIntyre K, Chalmers JW, et al. Trends in case-fatality in 22968 patients admitted for the first time with atrial fibrillation in Scotland, 1986-1995. <i>Int J Cardiol</i> 2002; 82(3): 229-36.
2002-2006	<p>SIMON STEWART NATIONAL HEALTH & MEDICAL RESEARCH COUNCIL OF AUSTRALIA CAREER DEVELOPMENT RESEARCH AWARD (University of South Australia/University of Queensland, Australia)</p>	<ul style="list-style-type: none"> ❖ STEWART S, Murphy NF, Walker A, McGuire A, McMurray JJ. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. <i>Heart</i> 2004; 90(3): 286-92. ❖ 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. <i>Heart Lung Circ</i> 2004; 13(3): 266-73.

		<ul style="list-style-type: none"> ❖ Clark RA, McLennan S, Eckert K, Dawson A, Wilkinson D, STEWART S. Chronic heart failure beyond city limits. <i>Rural Remote Health</i> 2005; 5(4): 443. ❖ McLennan SN, Pearson SA, Cameron J, STEWART S. Prognostic importance of cognitive impairment in chronic heart failure patients: does specialist management make a difference? <i>Eur J Heart Fail</i> 2006; 8(5): 494-501.
2007-2011	<p>SIMON STEWART, J HOROWITZ, T MARWICK, P SCUFFHAM, P DAVIDSON, P MACDONALD, H KRUM, C REID NATIONAL HEALTH & MEDICAL RESEARCH COUNCIL OF AUSTRALIA HEALTH SERVICES RESEARCH GRANT FOR THE WHICH INTERVENTION IS MOST COST-EFFECTIVE& CONSUMER FRIENDLY IN HEART FAILURE (WHICH?) TRIAL (Baker Heart Research Institute, Australia)</p>	<ul style="list-style-type: none"> ❖ STEWART S, Carrington MJ, Marwick TH, et al. Impact of home versus clinic-based management of chronic heart failure: the WHICH? (Which Heart Failure Intervention Is Most Cost-Effective & Consumer Friendly in Reducing Hospital Care) multicenter, randomized trial. <i>J Am Coll Cardiol</i> 2012; 60(14): 1239-48.
2007-2009	<p>SIMON STEWART, A TONKIN, D WILKINSON, R CLARK, J MILLIGAN, P ASTLES AUSTRALIAN RESEARCH COUNCIL OF AUSTRALIA LINKAGE GRANT FOR THE CARDIAC-ARIA PROJECT (University of South Australia/University of Adelaide/AlphaPharm Australia Pty Ltd, Australia)</p>	<ul style="list-style-type: none"> ❖ Clark RA, Driscoll A, Nottage J, et al, STEWART S. Inequitable provision of optimal services for patients with chronic heart failure: a national geo-mapping study. <i>Med J Aust</i> 2007; 186(4): 169-73. ❖ Clark RA, Inglis SC, McAlister FA, Cleland JG, STEWART S. Telemonitoring or structured telephone support programmes for patients with chronic heart failure: systematic review and meta-analysis. <i>BMJ</i> 2007; 34(7600): 942.
2008-2012	<p>SIMON STEWART NATIONAL HEALTH & MEDICAL RESEARCH COUNCIL OF AUSTRALIA SENIOR RESEARCH FELLOWSHIP (Baker Heart Research Institute, Australia)</p>	<ul style="list-style-type: none"> ❖ Sliwa K, Wilkinson D, Hansen C, et al, STEWART S. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. <i>Lancet</i> 2008; 371(9616): 915-22. ❖ STEWART S, Wilkinson D, Hansen C, et al. Predominance of heart failure in the Heart of Soweto Study cohort: emerging challenges for urban African communities. <i>Circulation</i> 2008; 118(23): 2360-67 ❖ Sochalski J, Jaarsma T, Krumholz HM, et al, STEWART S. What works in chronic care management: the case of heart failure. <i>Health Aff (Millwood)</i> 2009; 28(1): 179-89. ❖ STEWART S, Carrington M, Pretorius S, Methusi P, Sliwa K. Standing at the crossroads between new and historically prevalent heart disease: effects of migration and socio-economic factors in the Heart of Soweto cohort study. <i>Eur Heart J</i> 2011; 32(4): 492-9.
2008-2012	<p>SIMON STEWART, G JENNINGS, P BERGIN, B DE COURTEN, G LEE, M CARRINGTON, C WONG NATIONAL HEALTH & MEDICAL RESEARCH COUNCIL OF AUSTRALIA PROJECT RESEARCH GRANT FOR THE NURSE-LED INTERVENTION FOR LESS CHRONIC HEART FAILURE (NIL-CHF) STUDY (Baker Heart Research Institute, Australia)</p>	<ul style="list-style-type: none"> ❖ STEWART S, Chan YK, Wong C, et al. Impact of a nurse-led home and clinic-based secondary prevention programme to prevent progressive cardiac dysfunction in high-risk individuals: the Nurse-led Intervention for Less Chronic Heart Failure (NIL-CHF) randomized controlled study. <i>Eur J Heart Fail</i> 2015; 17(6): 620-30.

2009-2013	<p>SIMON STEWART, D THOMPSON, W ABHAYARATNA NATIONAL HEALTH & MEDICAL RESEARCH COUNCIL OF AUSTRALIA - PROGRAM OF RESEARCH GRANT FOR “INTEGRATION OF RISK EVALUATION IN CARDIOVASCULAR DISEASE MANAGEMENT PROGRAMS” (Baker Heart Research Institute, Australia)</p>	<ul style="list-style-type: none"> ❖ Ball J, Carrington MJ, McMurray JJ, STEWART S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. <i>Int J Cardiol</i> 2013; 167(5): 1807-24. ❖ Ball J, Thompson DR, Ski CF, Carrington MJ, Gerber T, STEWART S. Estimating the current and future prevalence of atrial fibrillation in the Australian adult population. <i>Med J Aust</i> 2015; 202(1): 32-5. ❖ Ball J, Carrington MJ, STEWART S. Mild cognitive impairment in high-risk patients with chronic atrial fibrillation: a forgotten component of clinical management? <i>Heart</i> 2013; 99(8): 542-7. ❖ Ball J, Carrington MJ, Wood KA, STEWART S, Investigators S. Women versus men with chronic atrial fibrillation: insights from the Standard versus Atrial Fibrillation spEcific management studY (SAFETY). <i>PLoS One</i> 2013; 8(5): e65795. ❖ STEWART S, Ball J, Horowitz JD, et al. Standard versus atrial fibrillation-specific management strategy (SAFETY) to reduce recurrent admission and prolong survival: pragmatic, multicentre, randomised controlled trial. <i>Lancet</i> 2015; 385(9970): 775-84.
2012-2016	<p>SIMON STEWART, J HOROWITZ, M CARRINGTON, P SCUFFHAM, C WONG, P NEWTON, A RISCHBIETH NATIONAL HEALTH & MEDICAL RESEARCH COUNCIL OF AUSTRALIA HEALTH SERVICES PROJECT GRANT FOR THE WHICH INTERVENTION IS MOST COST-EFFECTIVE IN HEART FAILURE (WHICH 2?) TRIAL (Baker Heart Research Institute, Australia)</p>	<ul style="list-style-type: none"> ❖ Scuffham PA, Ball J, Horowitz JD, et al, STEWART S. Standard vs. intensified management of heart failure to reduce healthcare costs: results of a multicentre, randomized controlled trial. <i>Eur Heart J</i> 2017; 38(30): 2340-8.
2012-2017	<p>SIMON STEWART, A BROWN, DR THOMPSON, N STOCKS, P SCUFFHAM, M CARRINGTON, K SLIWA, G MAGUIRE NATIONAL HEALTH & MEDICAL RESEARCH COUNCIL OF AUSTRALIA – CENTRE OF RESEARCH EXCELLENCE TO REDUCE INEQUALITY IN HEART DISEASE (Baker Heart & Diabetes Research Institute/Mary MacKillop Health Services Research Institute, Australia)</p>	<ul style="list-style-type: none"> ❖ STEWART S, Chan YK, Wong C, et al. Impact of a nurse-led home and clinic-based secondary prevention programme to prevent progressive cardiac dysfunction in high-risk individuals: the Nurse-led Intervention for Less Chronic Heart Failure (NIL-CHF) randomized controlled study. <i>Eur J Heart Fail</i> 2015; 17(6): 620-30. ❖ STEWART S, Wiley JF, Ball J, et al. Impact of Nurse-Led, Multidisciplinary Home-Based Intervention on Event-Free Survival Across the Spectrum of Chronic Heart Disease: Composite Analysis of Health Outcomes in 1226 Patients From 3 Randomized Trials. <i>Circulation</i> 2016; 133(19): 1867-77. ❖ STEWART S, Ball J, Horowitz JD, et al. Standard versus atrial fibrillation-specific management strategy (SAFETY) to reduce recurrent admission and prolong survival: pragmatic, multicentre, randomised controlled trial. <i>Lancet</i> 2015; 385(9970): 775-84.
2013-2017	<p>SIMON STEWART</p>	<ul style="list-style-type: none"> ❖ Ball J, Carrington MJ, McMurray JJ, STEWART S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. <i>Int J Cardiol</i> 2013; 167(5): 1807-24.

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2014-2018	<p>SIMON STEWART, D THOMPSON, L BURRELL NATIONAL HEALTH & MEDICAL RESEARCH COUNCIL OF AUSTRALIA - PROGRAM OF RESEARCH GRANT FOR “OPTIMISING HEART DISEASE PREVENTION & MANAGEMENT” (Baker Heart & Diabetes Research Institute/Mary MacKillop Health Services Research Institute, Australia)</p>	<ul style="list-style-type: none"> ❖ STEWART S, Ball J, Horowitz JD, et al. Standard versus atrial fibrillation-specific management strategy (SAFETY) to reduce recurrent admission and prolong survival: pragmatic, multicentre, randomised controlled trial. <i>Lancet</i> 2015; 385(9970): 775-84. ❖ STEWART S, Chan YK, Wong C, et al. Impact of a nurse-led home and clinic-based secondary prevention programme to prevent progressive cardiac dysfunction in high-risk individuals: the Nurse-led Intervention for Less Chronic Heart Failure (NIL-CHF) randomized controlled study. <i>Eur J Heart Fail</i> 2015; 17(6): 620-30. ❖ STEWART S, Wiley JF, Ball J, et al. Impact of Nurse-Led, Multidisciplinary Home-Based Intervention on Event-Free Survival Across the Spectrum of Chronic Heart Disease: Composite Analysis of Health Outcomes in 1226 Patients From 3 Randomized Trials. <i>Circulation</i> 2016; 133(19): 1867-77. ❖ STEWART S, Ball J, Horowitz JD, et al. Standard versus atrial fibrillation-specific management strategy (SAFETY) to reduce recurrent admission and prolong survival: pragmatic, multicentre, randomised controlled trial. <i>Lancet</i> 2015; 385(9970): 775-84.
2019-2024	<p>SIMON STEWART NATIONAL HEALTH & MEDICAL RESEARCH COUNCIL OF AUSTRALIA SENIOR PRINCIPAL RESEARCH FELLOWSHIP (Torrens University Australia/University of Notre Dame Australia, Australia)</p>	<ul style="list-style-type: none"> ❖ Strange G, Playford D, Scalia GM, et al, STEWART S. Change in ejection fraction and long-term mortality in adults referred for echocardiography. <i>Eur J Heart Fail</i> 2021; 23(4): 555-63.

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