A CALL TO ACTION FOR NEW GLOBAL APPROACHES TO CARDIOVASCULAR DISEASE DRUG SOLUTIONS

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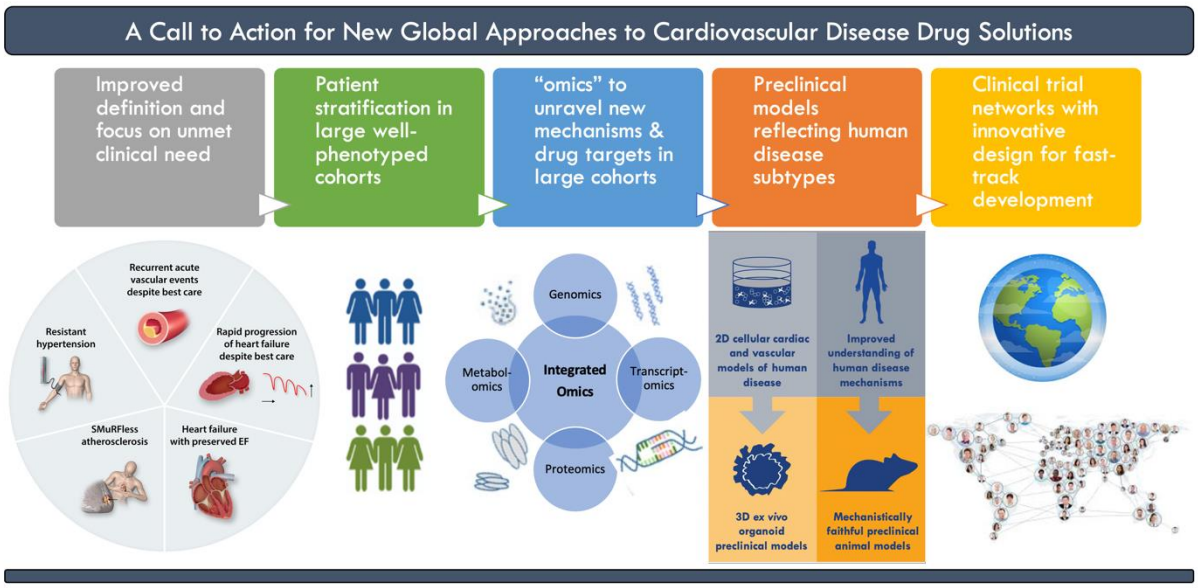
Short title: Global Call to Action for CVD Drug Solutions

Key words: drug discovery, pharmacotherapy, cardiovascular, organoids, precision medicine

Graphical Abstract



Abstract

Whilst we continue to wrestle with the immense challenge of implementing equitable access to established evidence-based treatments, there remain substantial gaps in our pharmacotherapy armament for common forms of cardiovascular disease including coronary and peripheral arterial disease, heart failure, hypertension and arrhythmia. We need to continue to invest in the development of new approaches for the discovery and rigorous assessment of new therapies. Currently, the time and cost to progress from lead compound/product identification to the clinic, and the success rate in getting there reduces the incentive for industry to invest, despite the substantial burden of disease and potential size of market. There are tremendous opportunities with improved phenotyping of patients currently batched together in syndromic "buckets". Use of advanced imaging and molecular markers may allow stratification of patients in a manner more aligned to biological mechanisms that can, in turn be targeted by specific approaches developed using high throughput molecular technologies. Unbiased "omic" approaches enhance the possibility of discovering completely new mechanisms in such groups. Furthermore, advances in drug discovery platforms, and models to study efficacy and toxicity more relevant to the human disease are valuable. Reimagining the relationship between discovery, translation and implementation will help reverse the trend away from investment in the cardiovascular space, establishing innovative platforms and approaches across the full spectrum of therapeutic development.

Keywords: therapeutic target, drug discovery, precision medicine, multi-omics, atherosclerosis, heart failure

Introduction

Cardiovascular disease is the leading cause of death globally, with an ongoing rapid rise in low and middle income countries[1, 2]. Initiatives to improve equitable access to and implementation of established effective therapies (e.g. statins) continue to be an international challenge. However, there remain substantial gaps in our pharmacotherapy armament for common forms of cardiovascular disease, including coronary and peripheral arterial disease, heart failure, hypertension and arrhythmia. Collaborative efforts to tackle access and affordability issues need to be combined with initiatives to accelerate new therapeutic discovery and development. Integration of health economic analyses at all stages of the development and trial pipeline, that take into consideration the "payer's" perspective relevant to the different jurisdictions, is a critical factor for successful and equitable implementation. Currently the time and cost to progress from lead compound/product identification to the clinic, and the success rate in getting there reduces the incentive for industry to invest, despite the substantial burden of disease and potential market size. Re-imagining the relationship between discovery, translation and implementation is required to rapidly reverse these trends. This can be achieved by establishing innovative platforms and approaches across the full spectrum of therapeutic development, and re-establishing a thriving and impactful sector capable of discovering and translating new solutions.

Where are we now?

Whilst there have previously been limited specific data on development of cardiovascular drugs, and factors associated with success of new therapies in clinical trials, Hwang and colleagues have provided an excellent quantitative analysis of the field[3]. Prior to this, reports had anecdotally suggested that the number of new cardiovascular drugs approved by the US Food and Drug Administration (FDA) had recently declined[4, 5], and that there was a

contraction in the pool of drugs under development targeting cardiovascular disease[6]. Using the large commercial database of drug development activity (Citeline Pharmaprojects, Informa plc), Hwang et al were able to quantify the rate and ultimate success of translation along the pipeline of over 50,000 products for all diseases, and to compare the rates among disease states, as well as examine factors associated with success. These data confirmed that the number of new cardiovascular drugs entering clinical trials at all stages of development declined between 1990 and 2012 (compared with cancer which increased). Many cardiovascular drugs in development were targeted against modifiable risk factors and previously proven mechanisms addressing these risks including antihypertensive agents, lipid modifying agents, and anticoagulants. However, 50% of cardiovascular drugs entering phase III trials between 1990 and 2012 were categorised as targeting novel biological pathways, with this rate of novelty increasing over the time period. Most clinical trials for cardiovascular drugs were sponsored by large pharmaceutical companies. Smaller companies were observed to be active, but more focussed on rarer forms of cardiovascular disease. In all three phases of study, the proportion of cardiovascular trials sponsored by large pharmaceutical companies compared to small- or medium-sized companies was significantly greater than that for non-cardiovascular trials[3].

At the center of the disparity between cardiology and oncology is the lack of routine clinical access to tissue in cardiac and vascular diseases which has led to disease classifications and thus clinical trials focused to a large extent on phenotypes that aggregate relevant visible properties. These phenotypes, while often linked by final common pathways, typically reflect heterogeneous underlying etiologies and thus responses to intervention. Therefore, efforts in cardiology (and other specialties) to reclassify or stratify diseases based on discrete pathogenetic mechanisms have been proposed as one rational approach to resolving the trend away from cardiovascular therapeutic development. Identification of

etiologically homogeneous subgroups of patients (endotypes) within a heterogeneous population is a goal of stratified medicine but remains a challenging. For instance, Type 1 myocardial infarction is a phenotype which is caused by different endotypes needing different forms of therapy[7], which may not be readily defined by current techniques. Similarly, angina is a phenotype which is caused by different endotypes[8], but we have tended to focus only on the endotypes for which we have efficient interventions (i.e. macrovascular obstruction).

This, and some of the additional challenges and potential solutions are outlined below and summarised in Table 1.

Table 1. Challenges and potential solutions for accelerating drug discovery and translation in the cardiovascular space.

Challenges	**Potential solutions**
Historic tendency to target biological mechanisms which have empirically been shown to influence overall outcomes, rather than definitive disease mechanisms (necessary and sufficient) identified in a discrete subset. Thus ~50% agents entering phase III clinical trials still target BP, lipids and coagulation[3], with limited novel therapeutic targets beyond these.	Identification of definitively causal (not association) novel targets and pathways from robust studies of increasingly homogeneous phenotypic subsets through improved use of molecular and advanced imaging and clinical markers. Increasing proportion of CVD drugs entering phase III trials targeting novel causal biologic pathways[3, 9]
Limitations in methods that target known signalling pathways involved in disease processes	Advances in drug design platforms will accelerate translation of complex mechanistic knowledge to new therapies.
Poor translation of safety and efficacy parameters from preclinical models (especially rodents) to humans	Development of mechanistically faithful human ex-vivo cardiac and vascular organoids, and the creation of similarly robust animal models that do not just mimic the human condition, but rather reflect the definitive mechanisms, and the burden of co-morbidities and age.
Lack of rigor in some preclinical research (e.g. single centre, not blinding or randomising, no protocol publication, over emphasis of findings) contributes to well-recognised limited reproducibility	Leadership and cultural shift to increased rigor, broader sharing of successes or failures and empiric evaluation of the translatability of the relevant models. Multicentre research networks for pre-clinical testing.
Challenges with respect to demonstrating efficacy in long term follow-up phase III cardiovascular outcome (MACE) trials which are large and expensive relative to other disciplines such as	Sub-phenotyping of cardiovascular patients (e.g. advanced imaging, or "omics") to permit more precise targeting of therapies based on biological

oncology (where putative surrogates such as reduced tumour size are acceptable).	mechanisms, increased therapeutic effect sizes and consequent reduction in clinical trial sample sizes. Staged regulatory models which include: • Use of validated mechanistic endpoints for initial registration • Subsequent phase III clinical trials to determine efficacy with respect to MACE and safety • Real world clinical trial capacity to continue to examine both efficacy and safety Innovative trial designs including health care system/registry enrolled phase 3 trials (E.g. SWEDEHEART, Orion 4, Astra-Zeneca, Farxiga fast-tracked by FDA for heart failure following acute MI[10])
Justifiable reliance on RCT as the dominant method of proving efficacy and safety of a new pharmaceutical	Increased uptake of innovative, more efficient study designs including A/B testing or formal randomisation within the .electronic medical record.
Paucity of repositioning strategies	Systematic assessment of existing non-cardiovascular drugs, testing their potential for repurposing for cardiovascular conditions
Slow innovation cycle in cardiovascular medicine	Strategies and incentives to promote the efficient implementation of interventions that are already known to work- with a focus on equity.
Apathy in the community, government and private insurance companies - that cardiovascular disease is all "solved" and that we have effective treatments	Raise awareness of the significant health and economic burden of cardiovascular diseases within the community. Particular focus on the many groups that are susceptible to disease progression and clinical events despite current evidence-based management
Identifying meaningful outcomes for patients	Rigorous application of patient reported outcome and patient reported experience measures

Residual risk and "missing" biology

Many medications in cardiovascular disease have been identified through serendipity, for example, none of the major classes of drug treatment for heart failure (renin-angiotensin-aldosterone inhibitors, beta blockers, SGLT2 inhibitors), were initially developed for the syndrome. Not surprisingly, drugs discovered in this manner do not appear to address all of the pathophysiologic components of the diseases which they are now used to treat. For example, up to 27% of ST-elevation MI patients do not exhibit traditional modifiable risk factors[11, 12], and a substantial proportion of patients with coronary artery disease (CAD)

progress rapidly to recurrent acute events despite optimal medical management[13]. The recent successful trial addressing the residual risk driven by inflammation (CANTOS[14] and LoDoCo2[15]) are good examples of how cardiovascular risk can be further reduced addressing non traditional risk factors. A major limitation of these trials, however, is that they have included the broad population of patients with cardiovascular disease rather than the "endotype" susceptible to an anti-inflammatory treatment[16].

There is significant potential to address these gaps through systematic reappraisal of the mechanisms of the constituent disorders, and the application of proven methods of drug discovery to the resultant novel mechanistically robust targets. For quite some time cardiovascular discovery efforts have been dominated by a multitude of signalling pathways, emerging from large-scale profiling technologies, which while they often provide molecular phenotyping[17], often lie downstream of the actual causal factors and in many instances may represent compensatory pathways, at least partially explaining the mixed results that have been observed. For example, of the >150 genetic loci reproducibly associated with CAD to date, very few are thought to act via traditional risk factors[18]. Pipelines focused on discoveries from genome-wide association studies (GWAS) have been employed by a number of the leading Pharma companies for over a decade, but new causal pathways and successful interventions based on such targets have been slow to emerge.

Technology to target novel biology

The technologies to efficiently develop new therapeutics once definitive targets have been identified are maturing and approaches including in silico screening, fragment-based drug discovery and tagged libraries have changed the pace of modern drug discovery[19]. An expanded tool kit of molecular targeting through cell, gene, RNA, peptide, and protein (including antibody) therapies and nanoparticle technology provide further diversity of

approaches and enhance the likelihood of success against any target[20, 21]. RNA and gene therapies offer remarkable specificity and safety profiles with successful 'platform' approaches to therapeutic development, for example, the siRNA Inclisiran (Novartis) represents a powerful approach to sustained inhibition of PCSK9 to reduce LDL-cholesterol. The top 10 (2019) highest growing pharmaceutical companies that are using artificial intelligence (AI) or machine learning for drug discovery have been recently reviewed[22].

Patients with recurrent events despite best evidence-based care- an opportunity for novel agents

The current unmet need in cardiovascular disease is exemplified by the substantial number of individuals who develop disease or progress despite best practice treatment. Examples include resistant hypertension (estimated to be ~10% of the hypertensive population) and those with advanced atherosclerosis and acute MI, but no elevation in Standard Modifiable cardiovascular Risk Factors ("SMuRF"-less; between 15-30% of ST elevation MI [11, 12]). A key goal is to define those individuals at risk of rapid cardiovascular disease progression, in a manner similar to metastatic malignancy, where new agents can be rapidly tested in small sample sizes due to higher event rate. This approach permits elucidation of novel biological mechanisms not currently addressed by existing agents (**Figure 1**). For instance, recent data suggests that failure of plaque healing might help explain recurrent acute coronary events and might become a new therapeutic target[23]. A consensus definition of those who rapidly progress to have recurrent events for atherosclerosis, heart failure or other disorders, despite best evidence-based therapies may also provide enhanced opportunities to define underlying mechanisms, and to augment the power for targeted therapeutic studies. Similarly, angina or myocardial infarction without obstructive coronary disease, a cause of substantial morbidity with unmet need, might usefully be defined using population level diagnostics for coronary

microvascular dysfunction which could then drive rigorous mechanistic studies and improved targeted therapies[24].

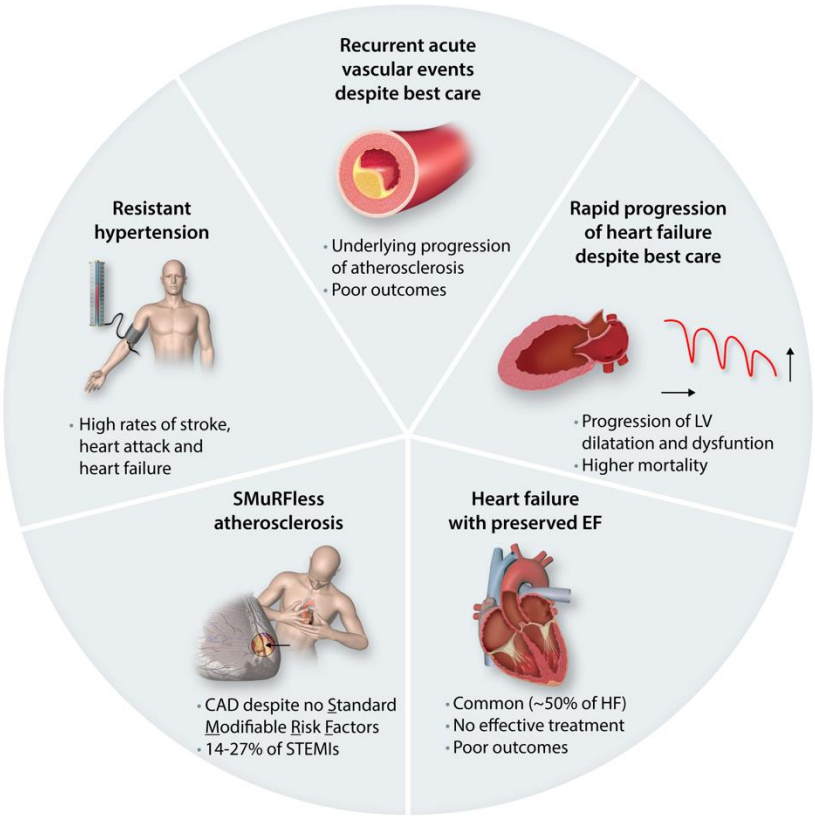


Figure 1. Schematic representation and summary of 5 patient groups with unmet need for new therapeutic approaches.

Precision medicine and drug development

Common disease states impacting cardiovascular health, driving morbidity and mortality such as atherosclerosis and heart failure, are multi-factorial, and have been shown to consist of many different sub-groups each presumed to be driven by a distinct predominant mechanism (as yet unknown). An extreme example is the syndrome of heart failure which is divided into subgroups based on systolic function- reduced ejection fraction (HFrEF) versus preserved ejection fraction (HFpEF). Interestingly, HFrEF patients, with widely diverse

aetiologies- from prior myocardial infarction, to chronic ischemia, to inflammatory and infiltrative conditions, and through to dilated cardiomyopathy of uncertain aetiology, all appear to gain some benefit from the same neurohormonal agents. In contrast, clinical trials of patients with HFpEF have been consistently neutral[25]. This may partly relate to the even more broad spectrum of phenotype cluster, which not only includes individuals with bona fide physiologic abnormalities of relaxation e.g. cardiac amyloidosis and restrictive cardiomyopathy, but also an amalgam of conditions where non-cardiac comorbidities and abnormalities contribute, and the only cardiac abnormalities may be changes in load dependent indices of diastolic physiology which may represent a range of disorders from deconditioning to poorly treated hypertension[26, 27]. A similarly complex spectrum of "phenotypes" and aetiologies, regarding individual patterns of response to classic risk factors, likely exists for atherosclerosis[28]. Better stratification by underlying mechanistic markers will be required to make the next advances in the prevention and treatment of these conditions.

Current clinical trials, and subsequently guidelines, of necessity tend to "bundle" patients together based on the aggregated syndromes referred to above. Whilst the evidence-based treatment likely acts on common parts of the pathway, and some pharmaceutical companies would prefer to design validation phases to provide as "wide" a market as possible, this may hinder larger leaps relevant to smaller more etiologically pure sub-groups. Advances in disease stratification tools (including molecular and advanced imaging technologies) to identify more specific patient populations will help to unravel new mechanisms in these sub-groups, and lead to better targeting of new therapies. Ultimately, these same mechanisms will also be useful to identify potential novel endpoints that will also accelerate subsequent focused clinical trials. In other words, time has perhaps come to give more emphasis to "splitting" rather than "lumping".

AI and machine learning approaches are being used to better cluster patient populations and derive more tightly circumscribed patient cohorts. This patient segmentation may derive patient endotypes, but this will likely require a systematic improvement in the information content of phenotypic assessment. Both unsupervised and supervised machine learning approaches are currently being used to better characterize patients with heart failure and those who have had a stroke. Among these efforts are electronic health record-based explorations of several million patients with longitudinal follow-up data (up to 7 years) in a collaboration with the Broad Institute at Harvard and MIT, Boston, MA, US, as well as with Sensyne Health in Oxford, UK. The American Heart Association have also invested substantially in the Precision Medicine Initiative. The resulting datasets offer the opportunity to train models against discrete outcomes and then validate these in prospectively collected data from Randomized Controlled Trials (RCT). Such approaches aim to improve inclusion or exclusion of patients in future clinical trials targeting more distinctly stratified patient cohorts, but ultimately definitive new biology will be required to define new targets.

A more immediate application of genomics to drug development, is the relatively simpler application of pharmacogenomics, where variants at a specific locus are known to alter the metabolism or response to therapeutic agents. There has been mixed support for such an approach from Pharma yet targeting drugs to specific mechanisms in individuals might streamline development pathways with smaller trials and ultimately lead to higher efficacy and safety as well as better outcomes for patients. In the case of clopidogrel, warfarin and statins, drugs already well-established, the literature has become sufficiently strong that guidelines are now available to help implement the use of genetic information to guide treatment with these therapies[29]. The cost effectiveness of implementing these insights has been difficult to prove, and so the prospective development and validation of new therapies for patients with specific genotypes has not been broadly undertaken.

Neglected forms of cardiovascular disease contributing to the burden of disease in low- and middle-income countries

It is estimated by the World Health Organization that 75% of the burden of cardiovascular disease across the globe is found in low- and middle- income countries[30]. Whilst a major component of this is shared with higher-income countries- in regard to ischemic heart disease, cerebrovascular disease and hypertension, neglected tropical diseases and other infections associated with poverty account for a significant proportion of these cardiovascular categories[31, 32]. It is well recognised that tackling these conditions, such as rheumatic heart disease, endomyocardial fibrosis and Chagas Disease require public health and policy solutions and equitable implementation of existing evidence. However, there are many stages of the disease where new drug therapies are urgently needed, working with governments and clinicians to consider pragmatic issues around delivery and affordability at all stages of development.

Advances in in vitro human models of cardiovascular disease

Pharmacological studies have long been a centrepiece of nonclinical drug evaluation prior to *in vivo* studies. Well-defined cellular models enabling investigators to screen chemical compound libraries and drug candidates have then been selected for secondary validation screens. Perhaps more than other organs, there is a need for *in vitro* models that better represent the human heart to understand cellular mechanisms and to test new therapies[33]. Several teams around the world have made recent progress on this front by moving from 2D monolayer cultures to 3D spheroids, organoids, or microphysiological systems. This includes both primary cardiac myocytes, or induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs), along with co-culturing approaches which incorporate endothelial cells[34], and cardiac fibroblasts[35]. Such approaches not only enhance the modelling of human heart

behaviour, but also prolong the survival of human cardiac myocytes in culture[36]. For example, Mei and colleagues have established a model of myocardial infarction in human cardiac organoids that utilises both hypoxia and noradrenaline and recapitulates pathological metabolic, fibrosis, and calcium handling changes at the transcriptomic, structural and functional level[31]. Hudson and team have developed a bioengineered human cardiac organoid platform which provides functional contractile tissue with biological properties similar to native heart tissue. Moreover, the team have applied this model to screen small molecules with pro-regenerative potential, demonstrating that whilst some small molecules were pro-regenerative, they had the unintended side effect of decreasing contractility[32]. Similarly, Takeda et al., have demonstrated the potential of 3D cardiac tissue derived from human iPSC-CMs, to screen for drug-induced cardiotoxicity[37]. Such approaches have the potential to support early drug screening and tackle the biggest gaps in our drug armament, but it will be vital to improve the uniformity of the organoids at the scale necessary for empiric screening, and proof of translatability remains a challenge for all preclinical models in the cardiovascular space. If successful, this will be a major step forward in overcoming the limitations related to our minimal access to the tissues and cells at the centre of the disease.

In vivo translational models

Robust demonstration of both proof-of-mechanism and efficacy in animal disease models is a critical step in drug development that must be achieved prior to progression to human trials. The cardiovascular field is littered with numerous examples of therapies that show great promise in preclinical studies yet fail during the clinical trial phase. A major challenge for cardiovascular drug development, that is shared by other disease groups, is the failure of many small animal (usually rodent) models to fully reproduce human diseases. For example, rodents are particularly resistant to the development of atherosclerosis, and even more so to

the development of unstable plaques. While the reasons for this are not fully understood, they are at least partly related to fundamental species differences in hemodynamics, lifespan, lipid metabolism (e.g. absence of the cholesteryl ester transfer (CETP) gene in rodents)[38] and immune function[39]. Similar difficulties in adequately replicating disease parameters in animal models for other human cardiovascular pathologies, including cardiac arrhythmias (where species differences in cardiac electro-mechanical coupling confound model development[40]), HFpEF, and resistant hypertension, have plagued translation of discovery research into the clinic. Typically, cardiovascular disease models are agnostic to the actual disease mechanisms in humans, not least because there is insufficient information available regarding the biology in humans as a result of the logistical challenges of obtaining human cardiac and vascular disease tissues.

Practices that are routine in clinical research such as *a priori* sample size and power calculations, randomisation, blinding, and the use of appropriate statistical analyses, were frequently overlooked in preclinical studies, particularly in academic research. Other factors such as clearly defined inclusion and exclusion criteria, littermate controls, full disclosure of all collected data, and confirmation of findings across multiple labs, have historically often been lacking in academia[41-43]. Many cardiovascular models are 'accelerated', for example employing animal models in which the disease phenotype of e.g. atherosclerosis or heart failure develops over weeks rather than months to years, and/or utilising young animals despite the fact that in humans most cardiovascular diseases present during middle age or beyond. Similarly, many therapies are tested in remarkably few genotypes before clinical use, so that relatively rare adverse events may not be detected. Likewise, cardiovascular morbidities seldom present in isolation from other co-morbidities, yet few studies focus on animal models that combine multiple diseases (e.g. superimposing comorbidities such as obesity or hypertension onto the model of interest). Finally, the overwhelming majority of

animal studies only use males and thus likely fail to model key disease mechanisms present in females, failing to represent half of the patients for whom these therapies are intended in the real world.

How can the field be improved? First and foremost is the need for rigorous mechanistically faithful models for the indication of interest. Attention to those models which have proven translatability for safety and efficacy in previous drug development programs would also be useful[42]. Where there are no mechanistic models, efforts are likely best focused on human studies to define causal mechanisms. In many instances there is also a need for large animal models, as a bridge between rodent studies and human trials, but here too the need for mechanistic representation cannot be overstated. Finally, closer attention must be paid to best practice in experimental design. In this regard, guidelines such as ARRIVE (Animal Research: Reporting of In Vivo Experiments)[44] and STAIR (Stroke Therapy Academic Industry Roundtable)[45], modelled after the CONSORT (Consolidated Standards for Reporting Trials) statement for clinical research, provide an excellent roadmap. As such, a template flow diagram for reporting animal use and analysis in preclinical studies has been developed[41], the Consolidated Standards of Animal Experiment ReporTing (CONSAERT) template.

Choosing the right models and the right endpoints, as well as empirically defining the extent to which the modeled biology and response to intervention translate into humans, should be a quantitative metric for filing with regulatory agencies to move toward clinical studies. This requirement would also enable such data to be made public in a protected manner, thus enabling progressive optimization of the drug development process.

Transition to a staged approach for approval of therapies based on clinically and mechanistically relevant measures of benefit and safety

The high bar that the cardiovascular field has set, with primary endpoints focussed on mortality in sharp contrast with oncology in which surrogate end points are frequently accepted, creates an unfortunate backlash of disincentivising investment due to high costs, and high risk. Whilst being careful not to lower the ultimate bar, collaborative effort to identify reproducible markers of benefit and safety that could be tested in a staged approach, may be required to ensure efficiency of the cycle, and ongoing investment in the development of cardiovascular drugs. A focus on what is important to the patient, as well as on the biology underlying a more precise disease taxonomy, will be important.

In 2015 the FDA approved alirocumab and evolocumab, monoclonal antibodies to PCSK9, for high risk patients, prior to the large cardiovascular outcome trials being completed[3] due to their benefit on lipid profiles in those who were already maximally treated. This is not dissimilar to the pathway that the diabetic field has taken as required by FDA regarding glucose-lowering treatments, and the oncology field with cancer "shrinkage". In each instance there is a substantial tension between such limited approval and the need for demonstration of definitive benefit and avoidance of harm for patients in terms of morbidity and mortality. Innovation in patient-reported or functional endpoints can be accelerated with the arrival of wearables and other new technologies. There is some potential for advances in non-invasive imaging of the myocardium (e.g. post-contrast myocardial T1 mapping for cardiac fibrosis[46]) and atherosclerosis (e.g. serial CT coronary angiography and plaque characterisation[47]) to enhance the power of early phase trials for relevant drugs, but it will be vital to improve the rigorous mapping of such metrics onto meaningful patient outcomes. The "hard" endpoints required for new agents for management of myocardial infarction, heart failure, or most primary prevention drugs is a consequence of prior adverse outcomes when such putative surrogates were employed. Improving our approaches to defining and testing new endpoints will be a central requirement to advance cardiovascular drug discovery. The

advent of real-world tools and large-scale analytics may aid this process, but here again increased information content will likely be necessary to escape the constraints of existing disease nosology and the resultant decades of downstream selection bias. Regulatory agencies have strong track records responding to patient-centred outcomes, and the cardiology community is actively increasing the use of such metrics and novel trial designs to transform the approaches to translational science in the field. A collaborative effort working with regulatory agencies to develop a staged approach may allow for acceleration of efficacious therapies, reducing time and cost, but not rigor and safety.

A key consideration at all phases of research and development of new drug solutions is equality. The exclusion of minority ethnic groups and women, as well as poor representation of low-income countries has been a detriment to the field, and ignores the burden of disease, with ~75-80% of CVD deaths occurring in low and middle- income countries.

There is increasing appreciation of the importance of early engagement with patients and the community in regard to endpoints that are most relevant and important to them. In this regard, it is critical that the cardiovascular sector is proactive in consumer engagement in the design of studies, and in developing innovative measurement of patient-reported outcomes and experiences. Such patient-reported outcomes can be captured electronically or in person through formats ranging from questionnaires to wearable devices and are used to provide a quantifiable record of the patient's lived experience of a disease. The inclusion of such measures as trial endpoints allows for a more comprehensive assessment of the burden of disease and the impact of an intervention[48]. However, for such endpoints to be accepted by regulatory bodies to inform decisions regarding the value and efficacy of the intervention, we need to ensure rigor and reproducibility.

Innovative clinical trial design

One consequence of disease heterogeneity is diminution of the average therapeutic effect. Because of these modest effect sizes, the large-scale, long term follow-up phase III clinical trials needed to demonstrate the effect of interventions on the essential outcomes of CV disease ("hard" cardiovascular endpoints of mortality or combined Major Adverse Cardiovascular Events (MACE)) are expensive and require time for follow-up. Consensus-building between pharmaceutical manufacturers and regulatory bodies, and the inclusion of multiple other stakeholders, to ensure meaningful problems are addressed directly is a key factor for consideration[49]. Diversity of the trial population, specifically with appropriate balance of women and different ethnic groups, could also be significantly improved[49]. At the same time, improved stratification based on precise phenotypes will improve power and success. The estimated cost of a Phase III clinical trial for primary prevention in cardiovascular disease is between $USD250-450 million; approximately 20-times higher than the median estimated cost of Phase III clinical trials overall. Thus, improving the efficiency of cardiovascular trials would be an important step to reinvigorate interest, and to accelerate new drug development and translation at all phases of the pipeline.

The advent of electronic health records and potential for routinely collected medical data to populate virtual registries for heart attacks, heart failure and arrhythmia as examples, are one of a number of opportunities to enhance trial design efficiency and lower costs. Utilization of routinely collected electronic health data will allow self-population of electronic case report form entries to enhance efficiencies of registries and randomized clinical trials. It may also enable the use of additional synthetic or semi-synthetic control arms by matching verum cases with placebo cases from existing patients with the same demographics and baseline characteristics and with an appropriately long enough longitudinal follow-up. Furthermore, the efficient use of electronic medical record data may

enhance the integration of the health system with the research and development (R&D) sector, increasing the proportion of patients with specific conditions participating in trials.

The impact of innovation in clinical studies of novel therapies is evident in Astra Zeneca's testing of Farxiga which has been granted Fast Track Designation in the US for heart failure following acute myocardial infarction leveraging a registry-based trial design[10]. Inclisiran (Novartis), is a further example where health care system data from the UK's National Health System is being used to dramatically reduce trial costs by rapidly identifying patient populations through administrative data. This powerful collaboration among academic institutions, government and industry will accelerate development as well as potential market access through the National Institute for Health and Care Excellence's (NICE) approval programme and a population-level commercial arrangement to make it widely accessible to patients[50]. International networks of clinical trials embedded into efficient health systems with such infrastructure would be a major asset.

Important efficiency gains may be derived from conducting trials directly with the patient-clinican dyad rather than through dedicated trial sites or via specific investigators. This can be further enhanced by utilizing electronic data collection from wearables, and other data collection approaches such as point of care lab tests. Data quality is already dependent on remote monitoring and statistical fraud detection (trained AI algorithms) rather than solely by on-site monitoring visits with source data verification.

Working with key stakeholders towards global solutions

Despite advances in the processes and organisation of clinical guidelines and evidence-based medicine, which would be envisaged to promote the uptake and application of new therapies once proven in large scale Phase III randomised clinical trials, Pharma face a variety of diverse barriers unique to each nation in regard to federal regulatory authorities, and financial

reimbursement policies. This requires a dedicated “army” of strategic company staff members who are often engaged in expensive lobbying with little logical relationship between the chance and rate of success and the clinical unmet need or demonstrated health and economic benefit. Whilst country-specific approaches will be required, moving beyond geographic borders will be essential. As healthcare globalizes, patients are increasingly demanding increased access to the latest innovations and are willing to go beyond their current clinical relationships to gain such access. The solutions likely to be effective in cardiovascular drug development are those seen in oncology where clinical trials are more tightly integrated into clinical care in a much more rapid cycle innovation framework. This will require transformation of the culture of cardiovascular care which often is balkanized on the basis of acuity and revenue for healthcare systems. Such culture change might best be focused on the creation of robust approaches to the implementation of existing proven therapies, which typically are deployed in a highly variable manner even a decade after reaching consensus endorsement by professional society clinical practice guidelines. Resolving these inequities alone would substantially reduce the cost of drug development, long before the advent of novel targets which would be pursued aggressively in tandem.

Community and government perceptions are often inaccurate, with many believing that much of cardiovascular disease is self-inflicted through poor lifestyle choices, or an inevitable part of ageing. This is compounded by the perception that the current armamentarium of drugs for atherosclerosis and heart failure already provide the entire solution. The remaining large gaps in our understanding and targeting of residual risk and missing mechanisms is ever important. A coordinated strategy engaging patients, clinicians, researchers, regulators and industry needs to be established to focus on strategies for the redesign of the cardiovascular drug discovery and development pipeline. Creating a community which provides a common voice to engage all stakeholders including governments, will be a critical first step and such an

effort might rationally be convened by collaboration across the relevant professional and patient societies.

Next steps and concluding remarks

The COVID-19 Pandemic has provided the community with a poignant example of an acute health problem in urgent need of solutions. Understanding disease spread and individual susceptibility, as well as discovering new treatments and a vaccine are priorities immediately evident to all. The response of researchers from around the globe, working with health care, government leaders and industry, as well as the broader community, demonstrates the committed, diverse and innovative talent that can be mobilized to address our world's major health challenges. The extent of collaboration with industry, including between companies is also unprecedented[51], yet the lack of any pre-existent structures within the biomedical ecosystem for global coordination against a pandemic some 100 years after the last example speaks to the core deficits at play when there is not an immediate temporal imperative to manage a disease. It is important to remember that in the 6 months of COVID-19 to date, based on current statistics, ~9 million individuals around the globe will have died of cardiovascular disease, with the majority from low- and middle- income countries. The time is right to continue the momentum and international collaboration achieved to address COVID-19 and commit to taking similar steps and sustaining these in the fight against our greatest killer (Figure 2). Developing a global approach to transform the drug discovery and translation ecosystem for cardiovascular disease, whilst maintaining efforts towards equitable access to established effective treatments, is an imperative not an option.

Conflict of Interest Statements

Dr. Figtree reports grants from National Health and Medical Research Council (Australia), personal fees from CSL, and grants from Abbott Diagnostic outside the submitted work. In addition, Dr. Figtree has a patent Biomarkers and Oxidative Stress awarded USA May 2017 (US9638699B2) issued to Northern Sydney Local Health District.

Dr. Casadei reports in-kind research support from Roche Diagnostics and iRhythm, outside the submitted work.

Dr. Califf reports personal fees from Verily, Google Health, and Cytokinetics, during the conduct of the study and outside the submitted work.

Dr. Crea reports personal fees from Amgen, Astra Zeneca, Servier, and BMS, outside the submitted work.

Dr. Drummond, Dr Freedman, Dr. Harrison, Dr. Hausenloy, Dr. Hill, Dr. Miura, Dr. Ritchie, Dr. Tomaszewski, and Dr. Xiao have nothing to disclose.

Dr. Guzik reports grants and personal fees from Oxford University Press, grants and personal fees from Bayer AG and Merck, outside the submitted work.

Dr. Januzzi reports grants and personal fees from Roche, grants, personal fees and other contributions from Novartis, grants from Innolife, grants from Applied Therapeutics, personal fees from Abbott, other contributions from Bayer, Siemens, Abbvie, Amgen, and Imbria Pharmaceuticals, during the conduct of the study.

Dr. Kingwell reports other contributions from CSL Ltd, outside the submitted work.

Dr. Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic and Vifor Pharma; has served as consultant or on the

Advisory Board/ Steering Committee/ Executive Committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, Cytokinetics, WebMD Global LLC, Radcliffe Group Ltd and Corpus; and serves as co-founder & non-executive director of Us2.ai.

Dr. MacRae reports grants from NIH, American Heart Association, Verily, Astra Zeneca, Quest Diagnostics, Apple, Pfizer, Bayer, BMS, personal fees from Clarify Health Solutions, Foresite Labs, other contributions from Atman Health, outside the submitted work. In addition, Dr. MacRae has a patent Genetic testing in cardiomyopathies with royalties paid to Partners Health Care, a patent Training cytometry data to refine disease pending, a patent Scalable cellular physiology to refine disease pending, and a patent Annotating small molecule function using phenotypic profiling pending.

Dr. Misselwitz reports other contributions from Bayer AG, outside the submitted work.

Dr. Wu reports grants from National Institutes of Health.

Dr. Zannad reports personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, other contributions from cardiorenal, personal fees from AstraZeneca, Vifor Fresenius, Cardior, Cereno pharmacuetical, Applied Therapeutics, Merck, other contributions from CVCT, personal fees from BAYER, Cellprothera, Owkin, Boehringer, Myokardia, Corvidia, and other contributions from G3 pharmaceuticals, outside the submitted work.

Figure 2. Call to action: collaborative next steps to accelerate discovery, translation and impact in cardiovascular medicine.

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