Cardiovascular Disease Taskforce Report

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AIM

1. This report outlines the recommendations of the Cardiovascular Disease (CVD) Taskforce and includes an overview of the CVD research landscape, proposed focus areas, industry alignment needs, and desired outcomes of CVD disease research in Singapore.

BACKGROUND

2. Globally, cardiovascular disease – pathologies of the heart, blood vessels and the vascular system of the brain – is the leading cause of death. It has no geographic, gender or socio-economic boundaries. According to the World Health Organisation, CVD caused 17.5 million deaths in 2012, representing over 30% of all global deaths.[1] By 2030, it is projected that 23.6 million people will die from CVD, mainly from heart disease and stroke.[2] The breakdown of global causes of death and CVD deaths is shown in Figure 1.

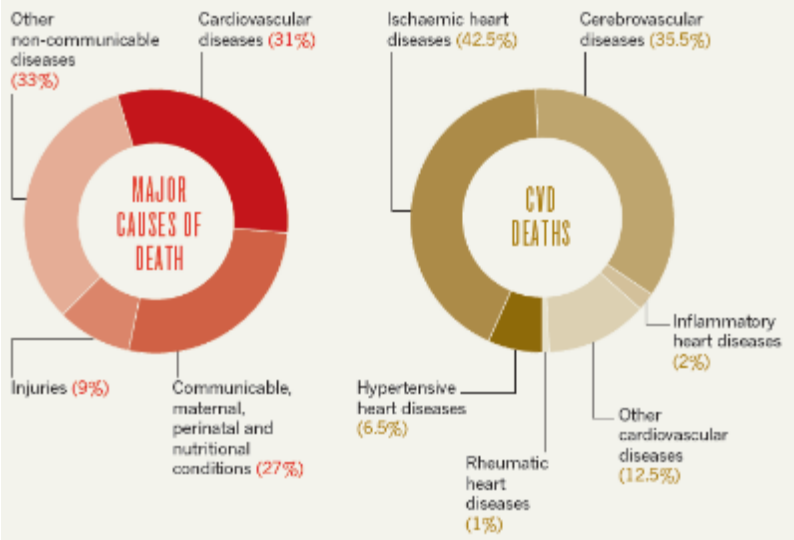

Figure 1: Breakdown of global causes of death and CVD deaths

3. In Singapore, CVD accounted for nearly 30% of all deaths in 2015, which equates to 16 CVD deaths per day.[3] As shown in Figure 2, by Disability-Adjusted Life Years (DALYs)[4], CVD was the top disease burden in Singapore, responsible for ~20% of the total disease and injury burden in 2010.[5] Of this, ischaemic heart disease (53% of CV burden) and stroke (34% of CV burden) were the main contributors (Figure 3).

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[1] Cardiovascular diseases Fact Sheet (reviewed September 2016), WHO
[2] Cannon, B. (2013). Cardiovascular disease: Biochemistry to behaviour. *Nature, 493*(7434). doi:10.1038/493s2a
[3] Source: MOH (http://www.myheart.org.sg/article/about-the-heart-and-heart-disease/statistics/singapore/75)
[4] Disability-adjusted life year (DALY) is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death.
[5] Singapore Burden of Disease Study 2010, MOH

Others include hypertensive heart disease, inflammatory heart disease, and aortic aneurysms (less than 5% of CVD burden each). Also, there are more than 1800 Out-of-Hospital Cardiac Arrests (OHCA) annually in Singapore.[6]

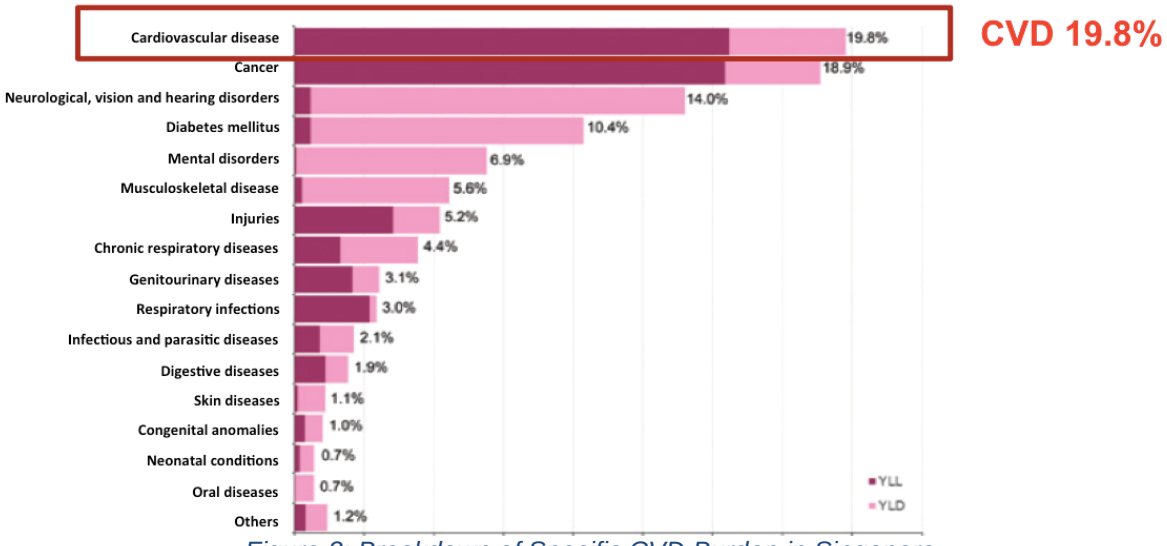
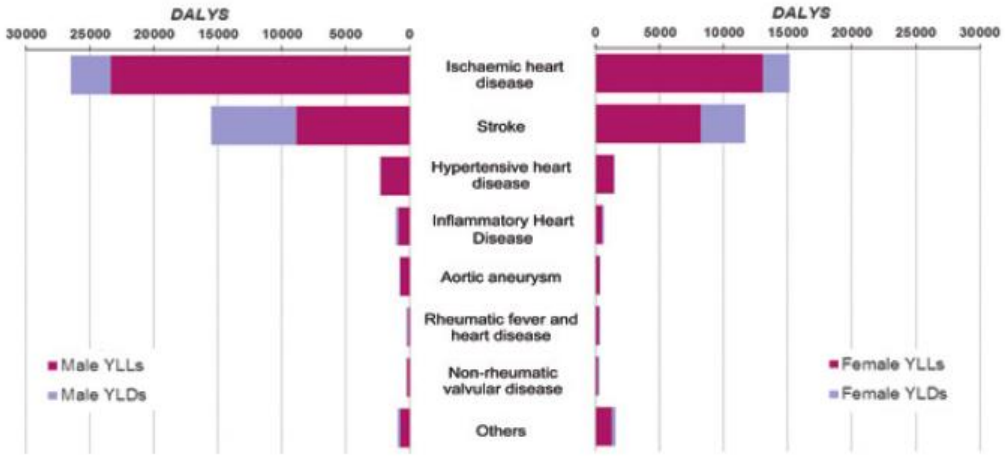


Figure 3: Breakdown of Specific CVD Burden in Singapore

The percentage refers to the proportion of total DALYs contributed by the respective broad cause group.

Figure 2: Singapore Burden of Disease Study 2010, MO



4. With CVD being the largest contributor to global mortality, accounting for nearly half of the 36 million annual deaths due to non-communicable disease (NCD), the United Nations set key targets to reach by 2025 to reduce the risk of premature NCD

[6] Lai H, Choong CV, Fook-Chong S, Ng YY, Finkelstein EA, Haaland B, Goh ES, Leong BSH, Gan HN, Foo D, Tham LP, Charles R, Ong MEH. Interventional Strategies Associated with Improvements in Survival for Out-of-hospital Cardiac Arrests in Singapore over 10 years. Resuscitation 2015; 89(2015):155-161.

death by 25% by 2025 ("25 by 25"). This target, as well as 8 additional targets addressing modifiable risk factors and committing to the use of essential medicines, technologies, and drug therapies to prevent heart attacks and strokes, have been adopted as part of a global monitoring framework and included in the WHO's Global Action Plan for the Prevention and Control of NCDs 2013-2020. The Global Cardiovascular Disease Task Force[7] coordinates and shapes national approaches to reaching the United Nations 2025 targets.

5. When considering outcomes for CVD, the benefits of a given therapy may not be realized because of a range of implementation barriers. In its 2001 landmark publication "Crossing the Quality Chasm", the US Institute of Medicine highlighted the reality that "the health care system … falls short in its ability to translate knowledge into practice"[8]. Research leaders stressed the need to identify effective community-based implementation strategies to successfully navigate the National Institutes of Health Roadmap for Research.[9] This highlights the need for high quality research in the community but also the need to develop local knowledge in CVD in order to translate through implementation. In Singapore, more CVD research is needed as a first step so that we can better understand the problems and only then can meaningful implementation be considered.

CURRENT LOCAL CVD RESEARCH LANDSCAPE

6. Even though CVD is the largest contributor to the disease burden of Singapore[10], research funding in this area has been under-funded compared to other domains. This situation warrants rapid remediation especially in view of (1) the "uptick" in myocardial infarction in the 30-60 year old demographic over the last 10 years, and (2) the establishment of a cadre of internationally respected talent in CVD research in Singapore over the last 5-10 years.

7. There are 2 major strategic programmes being funded in Singapore at present in CVD research. These promote Singapore's growing thought leadership particularly in heart failure in Asia (Table 1).

[7] The Global Cardiovascular Disease Taskforce is led by the World Heart Federation and comprises the American Heart Association, American College of Cardiology Foundation, European Society of Cardiology and European Heart Network, as well as representations from the African Heart Network, Asia Pacific Heart Network, Asia Pacific Society of Cardiology, Inter-American Heart Foundation, Inter-American Society of Cardiology, and Pan African Society of Cardiology.

[8] Institute of Medicine, Committee on the Quality of Health Care in America. Crossing the Quality Chasm. A New Health System for the 21st Century. Washington, DC: National Academy Press; 2001

[9] Westfall JM, Mold J, Fagnan L. Practice-based research--"Blue Highways" on the NIH roadmap. JAMA. 2007;297(4):403-6

[10] Singapore Burden of Disease Study 2010, MOH

Table 1. Strategic cardiovascular research programmes in Singapore

Grant	Programme Title	Members
NMRC TCR Flagship, 2014 - 2018	Genetic predilection, epigenetic change, microRNA profiling and experimental therapies in heart failure. Aims: To improve understanding of role of inherited and epigenetic factors for risk and progression of heart failure, through genetic and epigenetic studies and the identification of specific gene products, with a view to improving prediction of heart failure and identifying new treatments.	Lead PI: Arthur Mark Richards (NUHCS) Theme PIs: Liu Jianjun (GIS) Roger Foo (NUHCS) Colin Lawson Stewart (IMB)
A*STAR BMRC SPF, 2015 - 2017	Asian network in Translational Research and Cardiovascular Trials (ATTRaCT**)** Aims: To build on Singapore's competitive advantages in advanced cardiac imaging, genetic and molecular studies to develop an integrated "one- stop" platform spanning from human to large and small animal models, dedicated to deepening our understanding of CVD progression in heart. failure.	Programme Lead: Carolyn Lam (NHCS) Theme Leads: Imaging: Patrick Cozzone (SBIC) Genetics/Epigenetics: Roger Foo (GIS) Biomarkers & Immunology: Arthur Mark Richards (NUHCS)

8. ATTRaCT is a translational cardiovascular research programme that integrates efforts from basic and clinical scientists in multiple institutes in Singapore. It is a consortium of research institutions comprising both our national heart centres, A*STAR (SBIC, GIS, IMCB, SIgN, CIRC), SingHealth (STIIC) and NUS. ATTRaCT leverages on the Singapore-led Asian-HF Registry and the NUHCS-led national Heart Failure network by obtaining its clinical subjects through the network's collaborating hospitals from within Singapore (NUH, NHCS, TTSH, CGH, KTPH, SGH).

CARDIOVASCULAR COHORTS

9. There are several prospective observational cardiovascular cohort studies in progress, including regional registries. Established in 2012, the Asian-HF Registry is the first academic-led prospective multinational Asian registry of >6,000 patients with symptomatic heart failure including both HFrEF and HFpEF, involving 45 centres across 11 Asian regions (Korea, Thailand, Indonesia, Philippines, India, Japan, Malaysia, Hong Kong, China, Taiwan and Singapore). It was established for the broad purpose of determining the mortality burden of HF in Asian patients, and to define the burden and risk factors of sudden cardiac deaths, as well as sociocultural barriers to

preventive device therapy. The study also aims to study the genetic variants associated with HFrEF versus HFpEF in the Asian cohort.

10. Over the last 15 years, the Pan-Asian Resuscitation Outcomes Study (PAROS) group has conducted a research implementation programme to strengthen the chain of survival upon cardiac arrest. The national cardiac arrest registry was started in 2001, and from 2001 to 2012 has been able to show significant improvement in OHCA survival to discharge from 2.5% to 11.0%. In 2010, the PAROS Clinical Research Network (PAROS-CRN) expanded the OHCA registry to collect information on OHCA in the Asia Pacific. Supported by the Singapore Clinical Research Institute (SCRI), the network now comprises investigators from 15 countries across Asia, including Japan, Singapore, South Korea, Malaysia, Taiwan, Thailand, and UAE-Dubai.[11]

11. The Cardiovascular Research Institute (CVRI) and NUHCS have deployed Centre Grant and STaR Award resources to establish island-wide collaborative recruitment of CVD cohorts in heart failure ("SHOP" and "ATTRaCT"), heart valve disease ("SAVIOUR") and coronary heart disease ("IMMACULATE"). More recently at NHCS, a large and very deeply phenotyped cohort of population controls has been established ("SingHEART") to understand pre-disease and to predict disease based in the SingHealth/Duke-NUS Precision Medicine Institute (PRISM) at NHCS.

CARDIOVASCULAR RESEARCH EXPERTISE

12. Singapore's CVD researchers are mostly concentrated in the research institutes of our national heart centres (CVRI and NHRIS), with specific expertise also residing in our Restructured Hospitals, SCDF, A*STAR RIs and universities. The research includes CV biomarkers (CVRI), CV genetics/epigenetics (GIS, NHRIS, Duke-NUS), stem cells (GIS, IMB, NHRIS), CV imaging (SBIC, CIRC), animal models of heart disease (CVRI, SBIC, NUS, NHRIS), biosensors for CV applications (NUS, IME), and cardiac simulation modelling (IHPC, NHCS).

13. In addition, three Senior Translational Research (STaR) award holders, Prof Mark Richards, Director, Cardiovascular Research Institute (CVRI) NUHS, Prof Stuart Cook, Director, National Heart Research Institute (NHCS) and Prof John Chambers, Prof of Cardiovascular Epidemiology, Lee Kong Chian School of Medicine (NTU) work in cardiovascular research. Prof Richards, a world expert on biomarkers in cardiovascular disease, has a record of translating biomarker discovery to the clinic and market (including the most widely used heart failure biomarker world-wide, NT-proBNP), currently researches post-ischemic adverse remodelling of the cardiac left ventricle and methods to improve post-myocardial infarction outcomes. Prof Cook is a world expert in the genetics, genomics and cardiovascular magnetic resonance analysis of heart muscle disease who has implemented his research in Singapore into

[11] More information about the PAROS network can be found at http://www.scri.edu.sg/index.php/paros-clinical-research-network.

clinical practise and set up new clinical services in cardiac MRI and genetics (serving HSA and DSO) at NHCS, translated from research. Prof Chambers, a molecular epigenetic expert focuses on identifying mechanisms underlying high rates of diabetes and cardiovascular disease amongst South Asians, and developing new strategies for prediction and prevention of these major diseases.

14. Cardiovascular researchers who are recipients of human capital awards are listed in Table 2.

Table 2: Cardiovascular investigators who have received human capital awards from 2010-2016

Award	**Awardee**
Singapore Translational Research Investigator Award (STaR)	Arthur Mark Richards (NUHS) Stuart Cook (NHCS) John Chambers (NTU)
Clinician Scientist Award (Senior Investigator)	Roger Foo (NUHS) Carolyn Lam (NHCS) Tazeen Jafar (Duke-NUS) Raymond Seet (NUHS) Derek Hausenloy (Duke-NUS) Marcus Ong (SGH) Paul Yen (Duke-NUS)
Clinician Scientist Award (Investigator)	Raymond Seet (NUHS) Chester Drum (NUHS) Vijay Sharma Kumar (NUHS) Marcus Ong (SGH) Ronald Lee (NUHS) Mark Chan (NUHS)
Transition Award	Ronald Lee (NUHS) Calvin Chin (NHCS) Angela Koh (NHCS) Poh Kian Keong (NUHS)

INTERNATIONAL CVD RESEARCH LANDSCAPE

15. CVD research is one of five areas of 'Translational research in other major diseases' in the European Commission's Seventh Framework Programme (FP7 2007-2013). During the first five years of FP7, 25 collaborative cardiovascular disease research projects were funded under this part of the HEALTH programme with a total EU contribution of over €163 M. Research in CVD continues under Horizon 2020, which is the biggest EU Research and Innovation programme to date with nearly €80 B of funding available over 7 years (2014 to 2020). The aims are to attract private investment and deliver more discoveries and world-firsts by translating ideas from the lab to the market.

16. CarTarDis, CVgenes@target and TransCard are ongoing EU FP7 cardiovascular projects that have received approximately €18 M in funding. The 3

consortia comprise researchers from academia, SME's and big pharma from 15 European countries and have the following aims:

a) CarTarDis - Identify and clinically validate targets that are suitable to start pharmaceutical drug screening and further development.
b) CVgenes@target - Exploitation of genomic variants affecting coronary artery disease and stroke risk for therapeutic intervention.
c) Transcard - Translating disease into cardiovascular health by identifying new targets for pharmaceutical intervention.

17. In the USA, the NIH FY2017 budget estimate for the Heart and Vascular Diseases programme is USD $1.739 B. Current NIH research focuses on elucidating new biological pathways, new treatment and prevention models, dissecting the genetic vs. environmental contributions, developing and understanding the value of new diagnostic and imaging tests, resolving the contributing role of social networks to disease, and enhancing device technologies for treatment.

INDUSTRY INTEREST

18. In Singapore, initiatives like the IMMACULATE studies in post-myocardial infarction ventricular remodeling, the SHOP heart failure cohort, the Asian-HF Registry and the ATTRaCT programme have garnered industry collaborations with companies that are interested in understanding the pathophysiology of ventricular remodeling and heart failure (including heart failure with preserved ejection fraction (HFpEF)) in the Asian population as well as finding new therapies and diagnostics for heart failure. These companies include Boston Scientific, AstraZeneca, Bayer HealthCare, Thermo Fisher Scientific, MSD, Philips Medical Systems, and Hitachi Aloka Medica.

19. In a workshop conducted for representatives from the CVD industry in Singapore in January 2017, the following feedback was obtained from the medtech and pharma/in-vitro diagnostic sectors:

19.1 Medtech

a. The general agreement was that Class 1 and 2 medical devices and biomarkers for in-vitro diagnostics are sweet spots for Singapore to pursue for commercialization but are extremely competitive with many big players, academic and commercial, active in this area. There is strong interest to understand how CVD interlink with diabetes and hypertension (macrovascular vs microvascular).

b. The industry also agreed on the need to establish a pan-Asian phenotype for various CVD with in-depth characteristic baseline information, which programmes like ATTRaCT could help to fill. They concurred that a registry could provide additional information on the Asian market to develop better therapy/devices.

c. It was suggested that Singapore could leverage on existing solutions that were readily available from the industry for some of the challenges identified, using schemes such as pay for performance.

d. It was noted that Singapore needed to improve its articulation of the unmet needs in CVD to industry, as well as better engage with industry in developing the new innovations arising from our research institutions.

e. It was unanimously agreed that the workshop was one of the few forums that brought together key stakeholders from the industry, public institutions, VCs and funding agencies to facilitate cross talk amongst them.

19.2 Pharma/In-vitro Diagnostics

a. The pharma industry is interested in new molecules (including genetic, circulating and imaging biomarkers for inclusion in diagnostic-therapy coupling strategies ["theranostics"] as well as new drugs), repurposing existing drugs and extending indications for drugs within CVD.

b. A clear common theme from both industry and the research community is the intent to move into the disease prevention space in terms of predictive phenotyping and biomarkers, placing greater focus on CVD risk factors and including primary care institutions in CVD research activities. This includes focus on disease interception, consumer insights and studies of pre-disease.

c. Project champions are key drivers of industry collaboration projects but their relatively low number in Singapore needs to be increased to fully capitalise on the resources and human capital in both national heart centres. This includes expanding the pool of clinician scientists as well as changing mind-sets of researchers to be less averse to risk-taking.

d. Better integration and support is needed for initiatives such as large scale capture and exploitation of "big data" (e.g. the "Singcloud" initiative), which should be a nationwide effort.

SELECTION OF RESEARCH FOCUS AREAS

20. In August 2016, a workshop was organized by the HBMS CVD Taskforce to engage the community of CVD thought leaders and researchers on developing a plan for the future direction of CVD research in Singapore.

21. Key observations with respect to CVD in Singapore were highlighted: an earlier age of onset with more severe disease; a more severe degree of disease for a given level of apparent risk than in the West; ethnic disparities in long-term outcomes, increasing incidence of OHCA in Singapore whereas it has plateaued in the West.

22. Multi-system macro-vascular disease-associated end organ events for myocardial infarction, heart failure, stroke, aortic aneurysm/rupture and peripheral arterial disease (amputations) were established as key focus areas for CVD research in Singapore. In particular, the aim to delay onset and reduce complications of macro-vascular disease (coronary, cerebral, aortic and peripheral).

23. Singapore's differentiating factors and strengths in CVD research were identified as:

a. Multi-ethnicity;
b. High disease burden;
c. Younger onset of CVD;
d. High Incidence of hypertension and diabetes;
e. Established and growing expertise in CVD research that is recognised internationally as important and competitive;
f. High degree of collaboration and potential of integration of electronic health data across the spectrum of disease (from primary care, pre-hospital care, acute care, tertiary care and step down care);
g. Access to large parallel Western cohorts via senior researchers at NHCS and NUHCS;
h. Existing, active and productive collaborations between the two Heart Centres

RECOMMENDED RESEARCH PRIORITY AREAS FOR OPEN FUND LARGE COLLABORATIVE GRANT (OF-LCG)

24. For the Open Fund Large Collaborative Grant (OF-LCG), the CVD Taskforce has recommended a total of 3 themes and their respective challenge statements to be as follows:

1) Macrovascular disease: myocardial infarction and chronic coronary heart disease

Challenge Statement:

To support the of long-term goals of (i) delaying the average age of onset of acute coronary syndromes and acute heart failure events by 5 years within the next 5-10 years; (ii) reducing 30-days post-MI mortality by 30% over the next 5 years and (iii) doubling survival from Out-of-Hospital Cardiac Arrest over the next 5 years from 11% to 22%.

2) Stroke

Challenge Statement:

To support the long-term goals of (i) reducing the incidence of stroke by 20% in 10 years; (ii) reducing mortality and morbidity from stroke by 20%.

3) Macrovascular disease: aortic and peripheral arterial disease

Challenge Statement:

To support the long-term goals of (i) delaying the average age of onset of aortic and peripheral artery disease by 5 years within the next 5-10 years; (ii) reducing the number of surgical arterial interventions required for macrovascular disease by 20% within the next 10 years, and (iii) establishing accurate documentation of the disease burden.

The goals of all three themes go hand-in-hand with efforts from MOH and healthcare institutions to promote screening of CVD risk factors (e.g. hypertension, diabetes, BMI, sex, age, obesity, diet, lipids) from age 40 in Singapore.

FIVE YEAR ROADMAP FOR CVD RESEARCH IN SINGAPORE

(I) RESEARCH PRIORITY AREAS

25. While the Taskforce has recommended three priority themes for the OF-LCG, the Taskforce would like to emphasise that not all available research funding for CVD should be allocated to these areas. There are many other research areas which afford opportunities to benefit Singapore, and should be considered for funding through other national or industry schemes. In the following paragraphs the Taskforce recommends priority areas with respective outlines of associated suggested research strategies. Current CVD research initiatives, as tabled in this report, including research extending from assessment of premorbid risk through to investigation of established heart failure, should be assessed in light of the overall findings of this Taskforce and the possibility of an expanded scope remain possible where appropriate.

26. *Risk stratification of CVD by ethnicity, genetics, epigenetics, circulating biomarkers, advanced imaging, advanced wearable vital signs monitoring and data analytics.* This priority area can be addressed through systematic cohort studies securing data on CV risk factors from a multi-ethnic cohort over a period of several years during transition from young adulthood to middle age. The trajectory of evolution of each risk factor should be documented and the association of temporal increments

in risk investigated in parallel with genetic, epigenetic, circulating biomarker and imaging changes acquired. Preferably such studies should emulate protocols in non-Singaporean cohorts contemporaneously recruiting elsewhere to allow inter-ethnic, East/West comparisons. Advanced wearable monitoring and data analytics incorporating Machine Learning algorithms also show potential to improve risk stratification strategies for acute disease.

27. *Biology of multi-system macro-vascular disease (coronary, cerebral, aortic, peripheral).* Elucidation of the biology of premature arterial disease in Singapore should claim urgent priority. Myocardial infarction, stroke and peripheral ischaemia leading to limb loss all appear to be more prevalent than in the West. The risk of macrovascular events in the presence of a risk factor, especially diabetes, is greater than in the west. With respect to diabetes, which is an obviously over-represented risk factor in Singapore, work is needed to investigate the pathobiology of macrovascular disease to complement the current Diabetes-dedicated OF-LCG proposal addressing microvascular disease. Deaths in diabetes are most commonly due to macrovascular events. Standard clinical epidemiology of peripheral vascular disease in Singapore needs to be defined. First steps could include establishment of registries. This should be supplemented by clinical investigation of genetics, epigenetics and markers in parallel with basic science exploration of in vitro and animal vascular disease models of the more common local macrovascular dysfunctions and finally therapeutic trials of novel interventions. The same principles apply to programmes addressing coronary and cerebral disease with application of common systems biology platforms across the anatomical categories of arterial disease.

28. *Behavioural modification strategies and interventions, incl. monitoring of outcomes.* Rigorous documentation of relevant behaviours (exercise, diet, smoking, alcohol, exposure to sedentary hours, sleep quality, perceived stress etc.) in representative samples of the young to middle aged demographic is required. The relationship of the behaviours and life style factors to levels of cardiovascular risk and actual end organ event rates should be established. This can be supplemented with interrogation by systems biology (“‘omics”). Programmes of behavioural modification should be trialled in controlled fashion and assessed rigorously for efficacy. Health services research and implementation science will be important to support to drive this strategy. Promising strategies on behaviour modification can be tested using multi-centre implementation trials.

29. *Develop platforms that transects multi-system macrovascular cardiovascular and neurovascular diseases.* Efforts in the pre-morbid population should overlap and “talk” to work conducted in those with defined risk (but free of overt disease) and likewise characterization and therapeutic trials of the population with established CVD should be informed by the work conducted in earlier stage CVD. In this way, the trajectory from health to risk to disease can be understood and points of intervention more readily identified. Implementation barriers to current best practice guidelines should

be documented and then addressed in prospective trials linked to national registries, to be able to show improved outcomes across cardiovascular and neurovascular diseases.

30. *Development of platforms to develop new therapeutic candidates or device prototypes to a state of "Readiness" for clinical testing.* Singapore requires a vibrant enabling ecosystem for therapeutic clinical trials in cardiovascular disease. Discovery of candidate therapeutics and engineered devices should be supported, their rigorous preclinical assessment facilitated, and finally a pathway to partnership with pharma and the medical devices companies, enabling conduct of phase 1-3 clinical trials is needed. Trials of anti-risk cardio-protective pharmacotherapy with a lower recruitment age than currently customary in the west or in western-based guidelines should be considered.

31. National Priority Health Resource: National population cohort study to definitively characterize the Asian disease phenotype. The major diseases in Singapore have features in their presentation, disease progression and therapeutic outcomes that are unique from those in the West, and have been collectively referred to via a vague term "Asian Phenotype". This "Asian phenotype" has been a recurring rationale to justify numerous very expensive population cohort studies to provide for a more precise understanding and targeted approach towards the prevention and treatment of diseases in Singapore. In fact, a running theme in 4 of the 5 priority research areas for CVD is the need for rigorous and large socio-clinical epidemiological studies and highly curated biobanks that are representative of our multi-ethnic population.

32. As such, it may be timely for Singapore to consider developing a comprehensive, nationwide Framingham-like cohort study. Unlike the Framingham study, this cohort study will have the breadth and depth to cut across the five major disease groups in Singapore, and provide data and biological samples to support epidemiological studies, biomarker discovery and genetic/epigenetic predisposition to diseases. It will be unprecedented.

33. This cohort study will be a large and expensive national undertaking and will require design inputs from all taskforces to ensure a broad relevance. However, the cost will probably not exceed that of past numerous cohort studies and of the many that are being proposed. To minimize disruptions caused by institutional boundaries and operations, this undertaking can be split between SingHealth and National Health clusters. Funds (equivalent to ~2 LCGs) will be disbursed to each cluster for quarterly completion of the target size for the clusters i.e. the first 25% of the funds will be disbursed for the first 25% of the target size and the next 25% will be disbursed on completion of the first 25%. The more efficient cluster that completes their task should use undisbursed funds to complete the national target size. Access to socio-clinical epidemiological data, genetic/epigenetic sequences, and biobanks could be regulated by a steering committee.

INDIVIDUAL RESEARCH GRANT

34. IRGs provide bottom up, investigator-led funding and are a very important component of the grant environment. It must provide sufficient room for serendipity yet must have productive scientific output. KPIs should be metrics to measure quantity and quality of the science such as the number and citation index of publications as well as the innovative or novelty of the science measured by patents granted and licensed. One of the greatest predictors of future outputs is previous performance and there should be scrutiny of the quality of the PI in the proposed field of research and a five-year H-index should be included as part of the application. PIs' CVs for IRG submissions should list their 5 most important papers over the previous 10 years on which they are first (or co-first) or last (or co-last or corresponding) author along with the citations for those papers. This would help with discerning the quality of the applicants.

(II) ROADBLOCKS AND RECOMMENDATIONS

35. Overall implementation, funding, and central data and care coordination needs to be improved. The Taskforce recommends the following measure to address current impediments to research:

i. Hospitals and Ministry to sustain PDPA- and HIPAA HL7-compliant efforts to facilitate linking the patients, data, research and appropriate industry involvement. Barriers to sharing of research data across public as well as private institutions should be addressed. This includes challenges relating to interoperability, uniform coding of patient information, and dealing with privacy and security concerns.

ii. Allow co-leadership between institutions to facilitate synergy in developing a seamless integrated infrastructure with minimal redundancy. For example, the OF-LCG could be co-led on equal terms by both national heart centres. The traditional single lead PI model in grants often acts as a barrier to collaboration among institutional equals especially for projects that benefit from a team approach.

iii. Adequate funding to encourage innovation and creativity through investigator-driven high-risk disruptive research. CVD research has been underfunded compared to other therapeutic areas despite it being the top disease burden in Singapore with several areas being unmet needs.

36. The CVD Taskforce recommends the following five-year roadmap, broadly categorised in three areas: (i) Governance and Structure; (ii) Research Capabilities and Funding; and (iii) Talent and Others.

Recommendation 1: To establish leadership and mechanisms to address CVD research needs, translate research into health and economic outcomes, and improve coordination.

37. The CVD TF recommends a coordinated effort from all institutes engaged in CV research in Singapore to provide platforms allowing translation of research from bench to beside. To provide leadership and research direction for the key stakeholders in the 2 heart centres are working closely together to coordinate efforts and achieve maximum positive outcomes for Singapore. The co-chairmanship of the CVD TF is a good example of productive collaboration between the directors of the 2 heart centres.

38. To address CVD research needs in a holistic and unbiased matter; the TF recommends tapping on an international advisory board covering both heart centres. This can be most efficiently achieved by leveraging upon our existing international advisory boards [i.e. Centre Grant Scientific Advisory Boards (SABs)].

39. In addition, a network of dedicated staff to coordinate operationalization of the CVD research effort is required. This team should work closely with the advisory board and the research community to determine the operational needs of the entire translational CV research landscape. They should have the technical knowledge to review research findings and facilitate their translation into clinical applications. More importantly the team must assist the research leadership to secure funding for high priority projects. The team should also be an enabler; communicating with regulators and policy makers and resolving roadblocks. The team must be able to engage effectively with researchers and enable partnerships and collaboration. This could include fostering formal and informal communication within the research community to encourage regular engagement and alignment. This platform should also be extended to the industry to ensure that the research will be more likely adopted by industry.

Recommendation 2: To ensure good balance in distribution of research funds.

40. Despite being the top contributor to Singapore's burden of disease, CVD research funding still lags behind that for other disciplines including cancer, infectious diseases, neurological & sense disorders and diabetes. As such, the Taskforce recommends an increase in CVD research funding. In particular, a better balance in the distribution of resources to address unmet needs in specific types of CVD.

41. Furthermore, funding should also be allocated to establish a strong mechanism (including a standing internationally respected SAB) that would be widely used by the cardiovascular research community and funding agencies to review core research capabilities/platforms as well as grant applications and execution.

Recommendation 3: To build research capabilities in social science for CVD.

42. It is evident that CVD has an important lifestyle/behavioural component and research efforts in understanding these aspects of CVD and social/ public health factors are important. These areas include (I) smoking, (ii) diet, (iii) exercise, (iv) assorted disease interventions including behaviour modification and enhancement of treatment adherence.

43. Data acquisition in, patient compliance and post-hospital care is currently inadequate within in the healthcare system. It is critical to set up programmes to achieve centralized capture of out-of-hospital data to allow design and audit of programmes to reduce hospital admissions. This requires partnerships between members of the digital health industry and public health researchers.

44. Major efforts are required to incentivize Singaporeans to undertake regular screening for cardiovascular risk factors at 40 years of age onwards. Despite the existence of guidelines for health screening from the Health & Promotion Board, these are inadequate as there is currently poor data on screening compliance rates or response to results from screening. As such, the taskforce recommends emphasis on promoting health screening for CVD risk factors (hypertension, diabetes, smoking, BMI, age, sex, obesity, unhealthy diet, lipids) at age 40, including access to smoking counselling and institution of life style and pharmaceutical measures in accord with evidence-based guidelines. At present, the ministry of health (MOH) and Health Promotion Board (HPB) are supporting Screen for Life (SFL) programme by enhancing subsidies to encourage more locals to go for health screenings. Singaporeans are entitled to selected screening services at only a small cost ($0 - $5)[12]. One of the screening services is for cardiovascular risk conditions including obesity, diabetes high blood pressure and high blood cholesterol. MOH and HPB should continue such efforts, and work with Singapore Heart Foundation in this, in order to ensure Singaporeans are better diagnosed and treated earlier to secure better health outcomes.

Recommendation 4: To address issues around PDPA- and HIPAA HL7-compliant in CVD research

45. Personal data protection and data compliance needs to be addressed quickly and effectively to avoid impeding CVD research in Singapore. The national taskforces are aware that there have been efforts made by the MOH and its respective stakeholders in addressing these issues. The CVD taskforce supports sustaining PDPA- and HIPAA HL7-compliant efforts to facilitate hospitals in linking the patients, data, research institutes and appropriate industry involvement together.

Recommendation 5: Build regional research networks

[12] https://www.healthhub.sg/programmes/61/Screen_for_Life

46. Strengthening regional research networks can accelerate research driven innovation and improve patient outcomes as well as secure a position for Singapore as the cardiovascular translational research hub for Asia. The Asian-HF registry, which was set up to gather real world data on the demographics and risk factors of heart failure patients from 11 Asian regions is an example of the benefits of such a collaboration that enables comparison study of the differences across geographical regions, ethnicities, and regional income levels. Other examples include the 'SMART ACS" trial the "SLEEP and STENT", the parallel SHOP (SG) and the PEOPLE (NZ) heart failure studies which in aggregate have recruited thousands of patients into multi-centre, multi-national studies.

47. Greater collaboration can be facilitated by organising international workshops, roundtables or conferences to encourage networking. Funding agencies may also consider expanding the proportion of funding provided to support research conducted overseas if where a national advantage applies.

48. Participation in global cardiovascular initiatives will increase transnational collaborative and cross-disciplinary interaction. Researchers should be encouraged and assisted in applying for international R&D funding, e.g. Wellcome Trust, Fondation Leducq. Funding agencies should be open to developing joint-funding schemes with funders outside of Singapore [e.g. Wellcome Trust, British Heart Foundation, ERA-CVD, NIH, NHMRS (Australia) and HRC (Zew Zealand)] as that will allow research groups to provide complementary skills and facilities to accelerate research outputs of multi-national relevance.

Recommendation 6: Talent building

49. To secure future excellent cardiovascular research in Singapore, we need a greater talent pool (especially MD-PhDs) specialising in: basic mechanistic science, epigenetics/genetics/genomics, medical devices, socio-behavioural sciences, public health, health economics/health services research, applied biostatistics/ computational biology/bioinformatics/big data analysis.

50. More could be done to increase awareness of NMRC's human capital and talent development awards among our researchers, as well as provide funding schemes for MD-PhD/PhD students to undertake post-doctoral training overseas in basic and clinical research. Local postgraduate programmes for MD/MD-PhD/PhD e.g. Summer Research Programme, could also be set up to build up our local capabilities in specific areas of cardiovascular research. The newly established Social Science Research Council (SSRC) may be a good partner for building up talents in health services research.

51. A constant constraint in our hospitals is the lack of biostatistical expertise to support clinical and translational research. Efforts to attract and retain biostatisticians

often lose out to other industries due to the poorer job prospects and salary in the hospitals. Some steps towards mitigating this could include developing a clear hospital career path for biostatisticians and the provision of a funding mechanism beyond the current pay-scale. Embedding experts (e.g. from universities and A*STAR) inside each clinical institution will also provide a more continuous biostatistics resource regardless of fluctuations in funding and research directions.

CONCLUSION

52. In Singapore, CVD accounted for nearly 30% of all deaths in 2015, which equates to 16 CVD deaths per day.[13] By Disability-Adjusted Life Years (DALYs), CVD was the contributor to Singapore's overall burden of disease. Of this, ischaemic heart disease (53% of CV burden) and stroke (34% of CV burden) were the main contributors. It is apparent that much of this morbidity and mortality occurs earlier than observed in western jurisdictions.

53. Problem areas are readily identified and have multi-system macro-vascular disease as a common factor. This underlies the common occurrence of adverse end organ events (myocardial infarction and heart failure; stroke) at a relatively young age. Cardiovascular risk is prevalent (hypertension, metabolic syndrome, dyslipidaemia and diabetes) and these are associated with more severe end organ disease for given risk factor burden than in the West. There are ethnic differences in disease burden. It is possible lifestyle factors Including nutrition (diet), exercise, smoking and psychosocial stress are important. Cultural attitudes to treatment adherence may be important. A seamless set of national research projects covering the biology and sociology of CVD from risk to established disease and health services research is proposed in the road map outlined above.

54. Despite being the top disease burden in Singapore and having the strong foundation of research talent which has built up in this domain over the last 5-10 years, funding for CVD still lags far behind other disciplines such as cancer, infectious diseases, neurological & sense disorders and diabetes. To build momentum and retain internationally competitive talent in CVD research, this imbalance must be corrected. A better balance in the distribution of funding to the different types of cardiovascular diseases is also needed to address the unmet needs of CVD in Singapore.

[13] Source: MOH (http://www.myheart.org.sg/article/about-the-heart-and-heart disease/statistics/singapore/75)

ANNEX – COMPOSITION OF CARDIOVASCULAR DISEASE TASKFORCE

S/N	**Name**	**Designation**
1	Prof Stuart Cook **(Co-Chair)**	Director, National Heart Research Institute Singapore
2	Prof Mark Richards **(Co-Chair)**	Director, Cardiovascular Research Institute, National University Health System
3	Assoc Prof Philip Wong En Hou	Deputy Director, National Heart Research Institute Singapore; Senior Consultant, Dept of Cardiology, National Heart Centre Singapore
4	Assoc Prof Mark Chan Yan Yee	Senior Consultant, Dept of Cardiology, National University Heart Centre Singapore
5	Assoc Prof Theodoros Kofidis	Senior Consultant, Department of Cardiac, Thoracic & Vascular Surgery, National University Heart Centre Singapore
6	Assoc Prof Roger Foo Sik Yin	Senior Investigator, Genome Institute of Singapore, A*STAR; Senior Consultant, Dept of Cardiology, National University Heart Centre Singapore
7	Adj Assoc Prof Lim Sai Kiang	Research Director, Institute of Medical Biology, A*STAR
8	Assoc Prof Marcus Ong Eng Hock	Senior Consultant, Department of Emergency Medicine; Head, Data Analytics, Health Services Research Centre (HSRC) SingHealth Services; Associate Director, Health Services and Systems Research (HSSR) Duke-NUS Medical School
9	Adj Assoc Prof Chan Kay Fei	Senior Consultant, Dept of Rehabilitation Medicine, Tan Tock Seng Hospital
10	Adj Assoc Prof Tan Teng Hong	Head & Senior Consultant, Dept of Paediatric Subspecialties, Cardiology Service, KK Women's and Children's Hospital
11	Dr Ignatius Rasiah	Adjunct Professor, National University of Ireland, Galway (Formerly VP for Breakthrough Platforms, Medtronic)
12	Assoc Prof Joanne Yoong Su-Yin	Director, Centre for Health Services and Policy Research, Saw Swee Hock School of Public Health, National University of Singapore
13	Adj Assoc Prof Ching Chi Keong	Senior Consultant, National Heart Centre Singapore
14	Dr Tan Ngiap Chuan	Director of Research, SingHealth Polyclinics