

# Strategies to Prevent Cardiovascular Disease in Singapore: A Call to Action

*A joint statement of the Singapore Heart Foundation, Singapore Cardiac Society and Chapter of Cardiologists of the Academy of Medicine, Singapore.*



## TABLE OF CONTENTS

<b>02</b>	<b>ABOUT THIS REPORT</b>
<b>03</b>	<b>SUMMARY</b>
<b>04</b>	<b>INTRODUCTION</b>
<b>07</b>	<b>CALL-TO-ACTION TO PREVENT CARDIOVASCULAR DISEASE IN SINGAPORE: HEALTHIER HEART SG</b>
<b>09</b>	<b>CALL TO UPDATE THE STANDARDS OF CARE</b>
<b>10</b>	<i>Lifestyle interventions</i>
<b>11</b>	<i>Hypertension</i>
<b>12</b>	<i>Dyslipidaemia</i>
<b>14</b>	<i>Diabetes mellitus</i>
<b>15</b>	<i>Obesity</i>
<b>15</b>	<i>Smoking cessation</i>
<b>16</b>	<b>PATIENT EDUCATION THROUGH COOPERATION WITH COMMUNITY PARTNERS</b>
<b>18</b>	<b>SUPPORT FOR INTEGRATED CARE</b>
<b>21</b>	<b>REFERENCES</b>

## About this report

*Call to Action to Prevent Cardiovascular Disease in Singapore* is a whitepaper published at the Annals of the Academy of Medicine Singapore (2024, vol. 53, pp. 23-33)<sup>1</sup>. This version also provides updated data from the 2021 Singapore Myocardial Infarction Registry, the 2021 Singapore Stroke Registry, the 2022 National Population Health Survey and the 2023 Agency for Clinical Effectiveness Clinical Guidance for Hypertension..

This whitepaper is a joint statement of the Singapore Heart Foundation, Singapore Cardiac Society and Chapter of Cardiologists of the Academy of Medicine, Singapore.

We would like to thank the original authors for contributing their time and insight:

- Jack Wei Chieh Tan<sup>1-6</sup> MBBS, MMed (Int Med), FRCP (Edin), FAMS
- Tee Joo Yeo<sup>4,5,7,8</sup> MBBS, MMed (Int Med), MRCP (UK), FESC
- Doreen SY Tan<sup>7,9</sup> PharmD, BSc(Pharm)
- Terrance Siang Jin Chua<sup>1,2,4-6</sup> MBBS, MMed (Int Med), FRCP (Lond), FACC
- Khung Keong Yeo<sup>1-3,5,6</sup> MBBS, FAMS, FAHA, FESC, FACC, FASPC
- Natalie Si Ya Koh<sup>1-3</sup> MBBS, MMed (Int Med), MRCP (UK)
- Tavintharan Subramaniam<sup>10,11</sup> MBBS, FRCP (Edin), FAMS
- Yew Seng Kwan<sup>12</sup> MBBS, MMed (FM), FCFPS
- Michael Chun Leng Lim<sup>6,13</sup> MBBS, MMed (Int Med), FRCP (Edin), FAMS
- Lip Ping Low<sup>4,14</sup> MBBS, FRACP (Int Med), FAMS
- Huay Cheem Tan<sup>4-8</sup> MBBS, MMed (Int Med), FRCP (Edin), FAMS

<sup>1</sup>Department of Cardiology, National Heart Centre Singapore, Singapore; <sup>2</sup>Duke-NUS Medical School, Singapore; <sup>3</sup>Department of Cardiology, Sengkang General Hospital, Singapore; <sup>4</sup>Singapore Heart Foundation; <sup>5</sup>Singapore Cardiac Society; <sup>6</sup>Chapter of Cardiologists, College of Physicians, Academy of Medicine, Singapore; <sup>7</sup>Department of Cardiology, National University Heart Centre Singapore, Singapore; <sup>8</sup>Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; <sup>9</sup>Department of Pharmacy and Pharmaceutical Science, National University of Singapore, Singapore; <sup>10</sup>Diabetes Centre, Admiralty Medical Centre, Singapore; <sup>11</sup>Department of Medicine, Khoo Teck Puat Hospital, Singapore; <sup>12</sup>National University Polyclinics, Singapore; <sup>13</sup>Royal Heart, Stroke and Cancer Centre, Singapore; <sup>14</sup>Low Cardiology Clinic, Singapore.

The front cover was designed using assets from Freepik.com.

---

<sup>1</sup> Under Creative Commons Licence CC BY-NC-SA 4.0. <https://creativecommons.org/licenses/by-nc-sa/4.0/>

## SUMMARY

In 2022, the Minister for Health of Singapore launched Healthier SG, a national strategy in championing the shift towards a population health approach. In relation to this, the Singapore Heart Foundation conducted a series of roundtable discussions, also attended by representatives of the Singapore Cardiac Society and the Chapter of Cardiologists of the Academy of Medicine Singapore. During the meetings, the authors formulated interventions supportive of Healthier SG that specifically aimed to uplift the state of cardiovascular (CV) preventive care in Singapore.

In support of Healthier SG, the authors propose a three-pronged approach (“Healthier Heart SG”) to augment the success of Healthier SG in achieving good CV outcomes. This proposal includes the following components: (1) a call to update the standards of care in addressing the 5 main modifiable risk factors of cardiovascular disease (CVD); (2) patient education through cooperation between healthcare professionals and community partners for a whole-of-system approach; and (3) support for integrated care, including access to cardiac rehabilitation in the community, improved referral processes and access to nutrition/dietetics counselling and tobacco cessation, optimal use of information technology, and continued CV research.

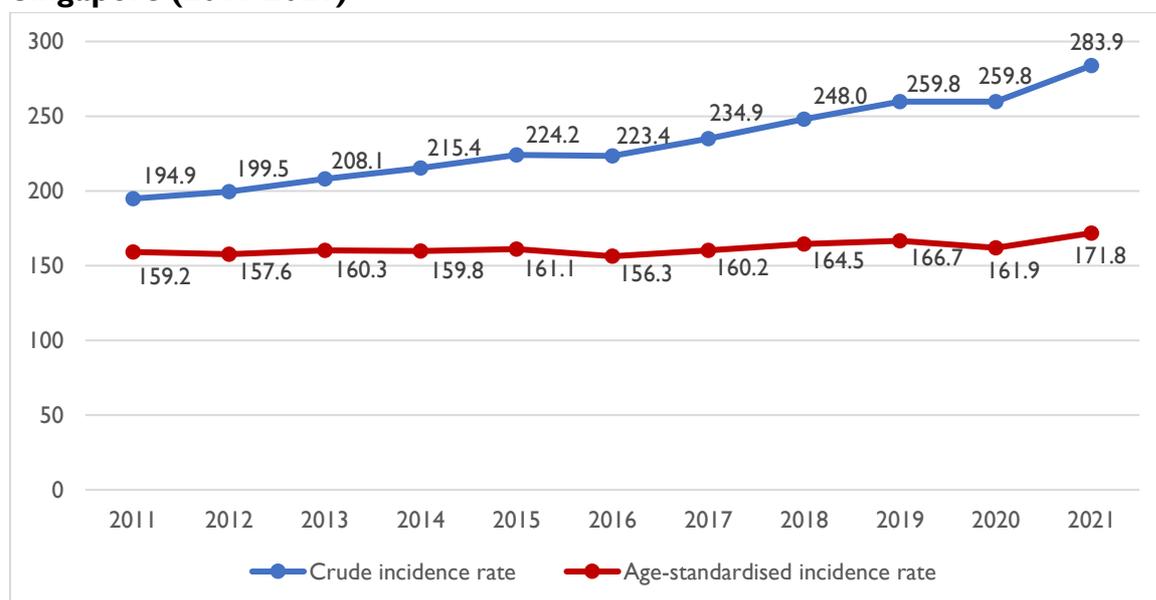
Healthier Heart SG would bring the standards of care and CV care delivery in Singapore closer to achieving the vision of proactive prevention of CVD and CV morbidity and mortality. This can only be achieved through the concerted efforts of healthcare professionals, policymakers and community partners, coupled with the cooperation of community members.

## INTRODUCTION

Despite the success of Singapore’s public health systems in providing medical care through the country, there is still much to be achieved in terms of optimising the cardiovascular (CV) health of its 5.5 million residents. According to the 2019 Global Burden of Disease report, while the incidence rate of stroke and the mortality rates for both stroke and ischaemic heart disease (IHD) are decreasing in Singapore, the incidence of IHD is increasing.<sup>1</sup>

Also, the Singapore Myocardial Infarction Registry (SMIR) reported that the number of acute myocardial infarction episodes increased from 7344 in 2010 to 11,631 in 2020 and the age-standardised incidence rate (ASIR) also increased slightly from 194.5 to 207.0 per 100,000 population during this period.<sup>2</sup> The more recent 2021 SMIR data showed a continued increase in the incidence of myocardial infarction (**Fig. 1**).<sup>3</sup>

**Fig. 1. Incidence rate of acute myocardial infarction (per 100,000 population) in Singapore (2011-2021)**

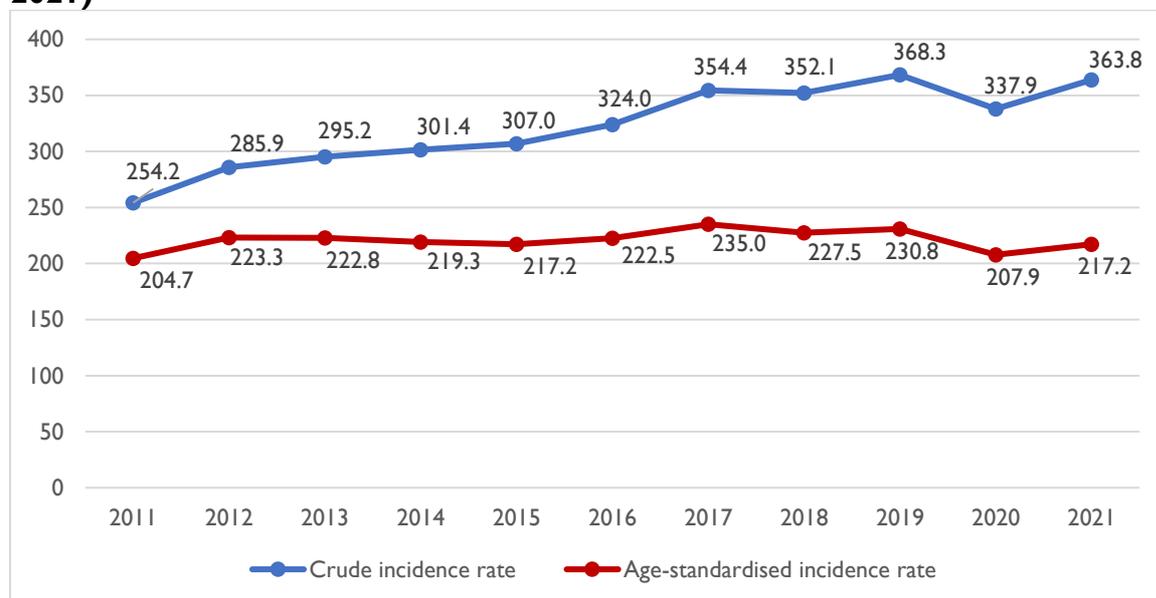


Source: Singapore Myocardial Infarction Registry 2021

Similarly, the Singapore Stroke Registry showed that the number of strokes increased from 5890 episodes in 2010 to 8846 episodes in 2020 (ASIR slightly rising from 158.0 to 165.2 per 100,000 population during this period).<sup>4</sup>

Mirroring the trends of myocardial infarction, the recent 2021 Singapore Stroke Registry data showed a continued increase in the incidence of myocardial infarction (**Fig. 2**).<sup>5</sup>

**Fig. 2. Incidence rate of stroke (per 100,000 population) in Singapore (2011-2021)**



Source: Singapore Stroke Registry 2021.

Peripheral arterial disease, another associated cardiovascular condition, also affects up to 8% of residents and is a major cause of limb loss in Singapore.<sup>6,7</sup>

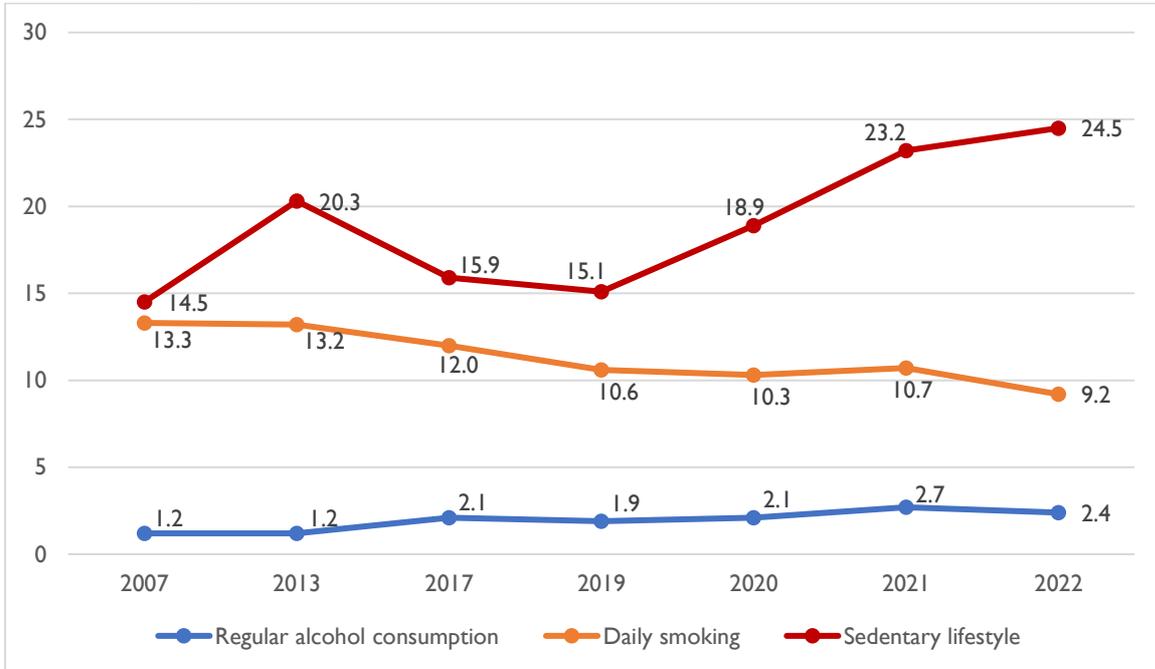
The estimated annual direct and indirect costs of IHD in Singapore are USD 2.2 billion and 1.4 billion, respectively; the respective figures for stroke are USD 1.2 billion and 2.8 billion.<sup>8</sup> Overall, these costs represent almost 2% of the annual GDP of the country.

The increasing trend in IHD and myocardial infarction incidence could partly be explained by the increasing prevalence of several modifiable CV risk factors, as reported in the National Population Health Survey 2020. In this report, the following trends were observed:<sup>9</sup>

- Decline in proportion who met World Health Organization-recommended guidelines for physical activity
- Increase in the prevalence rates of non-communicable diseases—hypertension, diabetes and high blood cholesterol
- Increase in the proportion of residents with high-risk body mass index (BMI  $\geq 27.5$  kg/m<sup>2</sup>)

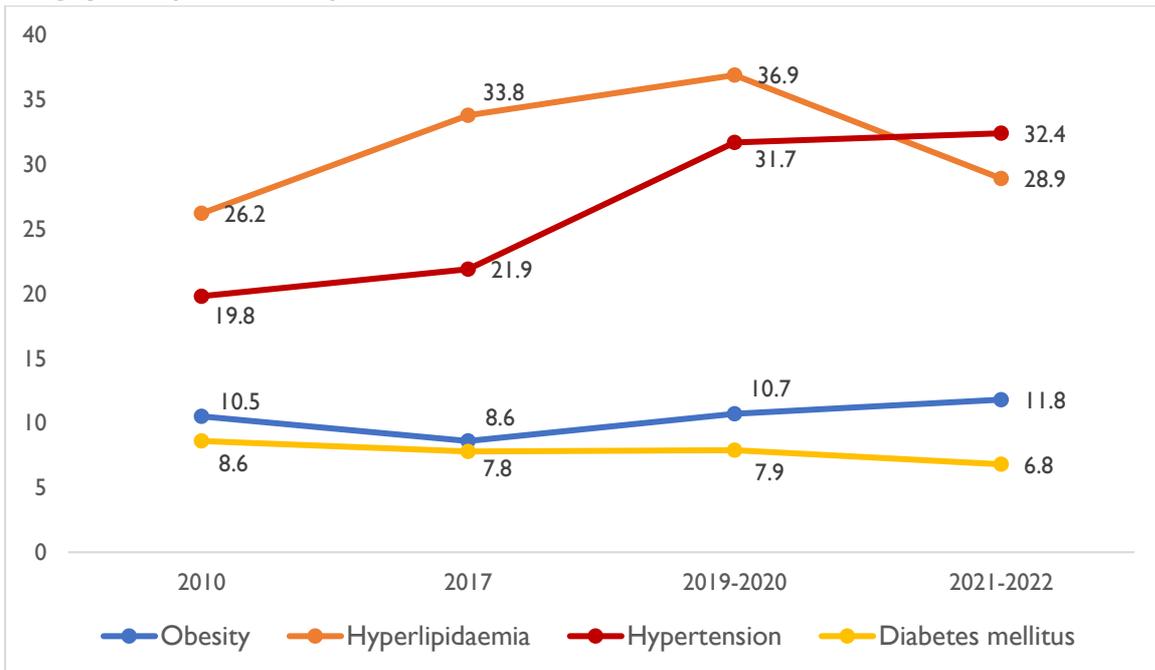
The more recent National Population Health Survey (2022) showed a continued worsening of some CV risk factors, particularly alcohol drinking, sedentary lifestyle, hypertension and obesity (**Fig. 3 and Fig. 4**).<sup>10</sup>

**Fig. 3. Prevalence (%) of lifestyle-related cardiovascular risk factors among adults in Singapore (2007-2022)**



Source: National Population Health Survey (2022)

**Fig. 4. Prevalence (%) of comorbid cardiovascular risk factors among adults in Singapore (2010-2022)**



Source: National Population Health Survey (2022)

The increase in these risk factors may also partly explain the increasing trends for atrial fibrillation (an established cause of ischaemic stroke) which steadily rose in prevalence among stroke patients, from 15.8% in 2005 to 25.2% in 2016 before declining slightly to 19.2% in 2020.<sup>4,11</sup> It is important to underscore that the atherosclerotic CV diseases such as ischaemic heart disease, cerebrovascular disease and peripheral arterial disease all share risk factors with atrial fibrillation.

Given these trends, there is a need to prevent CV disease, especially the first episode of myocardial infarction and stroke among residents of Singapore. In this call-to-action paper endorsed by the Singapore Heart Foundation (SHF), Singapore Cardiac Society (SCS) and the Chapter of Cardiologists of the Academy of Medicine, Singapore (AMS), the authors propose a strategy and framework for the prevention of CV disease in Singapore.

#### METHODOLOGY

The SHF conducted roundtable discussions, which were attended by representatives of the SCS and the Chapter of Cardiologists of the AMS, on 21 August 2021, 22 May 2021, 8 July 2022, 25 November 2022 and 08 July 2023. During the meetings, the authors reviewed the HealthierSG white paper, the burden of CVD in Singapore, and the current state of delivery of CV preventive healthcare in Singapore, including the local guidelines on the management of hypertension, dyslipidaemia, diabetes mellitus, smoking and physical activity. During the roundtable discussion, the authors also formulated interventions supportive of Healthier SG that specifically aimed to uplift the state of CV preventive care in Singapore.

#### **CALL-TO-ACTION TO PREVENT CV DISEASE IN SINGAPORE: HEALTHIER HEART SG**

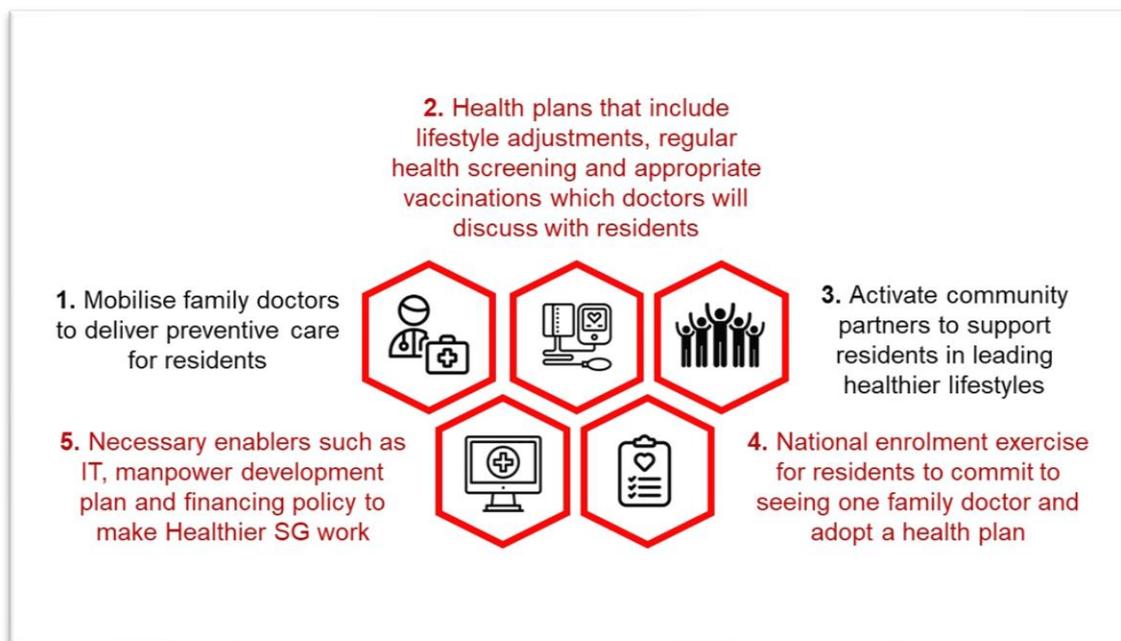
In 2022, the Minister for Health of Singapore launched Healthier SG, a national strategy in championing the shift towards a population health approach. This strategy aims to shift the emphasis from reactively caring for those who are sick, to proactively preventing individuals from developing chronic diseases such as atherosclerotic CV disease, which could lead to myocardial infarction or stroke.

With Healthier SG, chronic diseases could be prevented by reshaping the health-seeking behaviour and lifestyle of Singapore residents. This would be done by anchoring Singapore residents with a family doctor, fostering community support for healthier lifestyles, and developing the appropriate policies and other enablers (e.g., Healthy 365 app, which is

currently used for the National Steps Challenge and the Eat Drink Shop Healthy Challenge). Healthier SG has 5 key features (**Fig. 4**):<sup>12</sup>

1. Mobilise family doctors to deliver holistic preventive care for residents, and to build stronger longer-term relationships;
2. Develop health interventions that include lifestyle adjustments, regular health screening and appropriate vaccinations;
3. Activate community partners to support residents in leading healthier lifestyles
4. Launch a national enrolment exercise for residents to commit to seeing one family doctor and adopt a health plan
5. Set up necessary enablers such as IT, manpower development plan and financing policy to make Healthier SG work.

**Fig. 4. Five features of Healthier SG.**



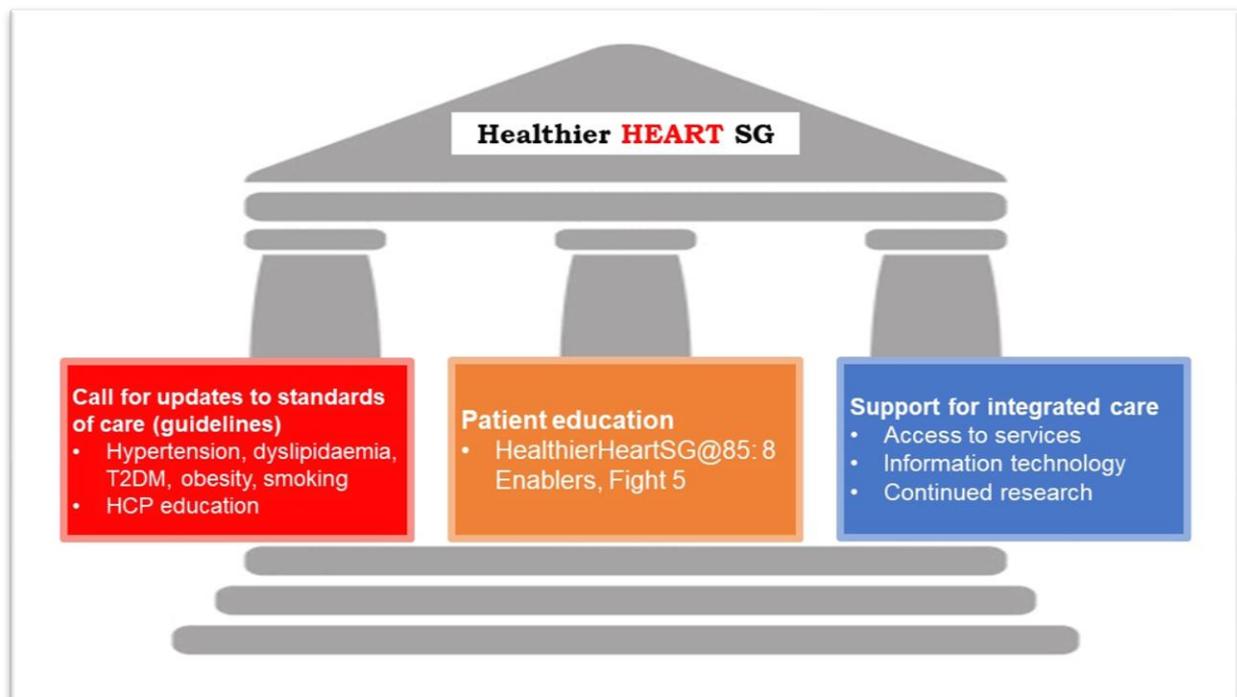
Source: White Paper on Healthier SG (2022) and Tan et al. *Annals Acad Med Singap* 2024;53:23-33. Creative Commons Licence CC BY-NC-SA 4.0.

In this call-to-action paper, the Singapore Heart Foundation, Singapore Cardiac Society and the Chapter of Cardiologists of the Academy of Medicine, Singapore, express full support for the Healthier SG strategy and agree that a population health approach is also needed to prevent CVD and its complications, especially the first occurrence of myocardial infarction or stroke, among Singapore residents.

In line with Healthier SG, the authors propose a three-pronged approach (i.e., Healthier Heart SG; **Fig. 5**) to augment the success of Healthier SG in achieving good CV outcomes. This proposal includes the following components:

- A call to update the standards of care in addressing the five main modifiable risk factors of CVD, namely, hypertension, dyslipidaemia, type 2 diabetes mellitus (T2DM), obesity and smoking.
- Patient education through cooperation between healthcare professionals and community partners for a whole-of-system approach (to support features 1, 2 and 4 of Healthier SG; Fig. 1)
- Support for integrated care (as part of Healthier SG features 1, 2, 4 and 5; Fig. 1).

**Fig. 5. Healthier Heart SG: A three-pronged approach to the success of Healthier SG towards heart health.**



HCP: healthcare professionals; T2DM: type 2 diabetes mellitus.

Source: Tan et al. *Annals Acad Med Singap* 2024;53:23-33. Creative Commons Licence CC BY-NC-SA 4.0.

### **CALL TO UPDATE THE STANDARDS OF CARE**

The Ministry of Health Singapore published clinical practice guidelines (CPG) for hypertension (2017), dyslipidaemia (2016), obesity (2016) and tobacco use (2013), which are used as the standard of care by many primary care practitioners in Singapore.<sup>13-16</sup> In 2017, the Agency for Clinical Effectiveness (part of the Ministry of Health Singapore) took over

the publication of clinical guidelines and released guidance for prediabetes and diabetes the same year. Apart from prediabetes (updated in 2021)<sup>17</sup>, diabetes (updated in 2022 for basal insulin and 2023 for non-insulin medications)<sup>18,19</sup>, dyslipidaemia (updated 2023)<sup>20</sup> and hypertension (published in December 2023)<sup>21</sup>, all the other aforementioned guidelines have yet to be updated.

On 15th December 2023, the committees of the Agency for Clinical Effectiveness (ACE) clinical guidance and the CPG for the management of lipids (led by the Chapter of Cardiologists, College of Physicians, Academy of Medicine, Singapore) jointly released the latest ACE clinical guidance (ACG) and Singapore CPG (SCPG) for the management of lipids.<sup>20</sup> Both committees had cross representation and worked closely to ensure that both guidance documents were consistent. The ACG document is focused on the management of lipids by primary care physicians whereas the CPG is a more comprehensive document that caters for both primary care physicians and specialists.

As volumes of clinical evidence have emerged to justify newer treatments to attain lower targets and international guidelines have since adjusted their recommendations and treatment targets, the various Singapore guidelines also need to be updated to reflect current evidence and international standards of care. This paper aims to highlight the areas of care that need to be addressed to update the standards of care to control these 5 risk factors.

Importantly, the treatment of the 5 aforementioned CV risk factors may vary depending on the baseline CV risk of the patient. Hence, the authors recommend a baseline CV risk assessment for all patients to at least categorise each patient as having low/moderate-, high-, or very-high CV risk. Clinicians may use any of the various CV risk factor calculators currently available to achieve this.<sup>22-24</sup>

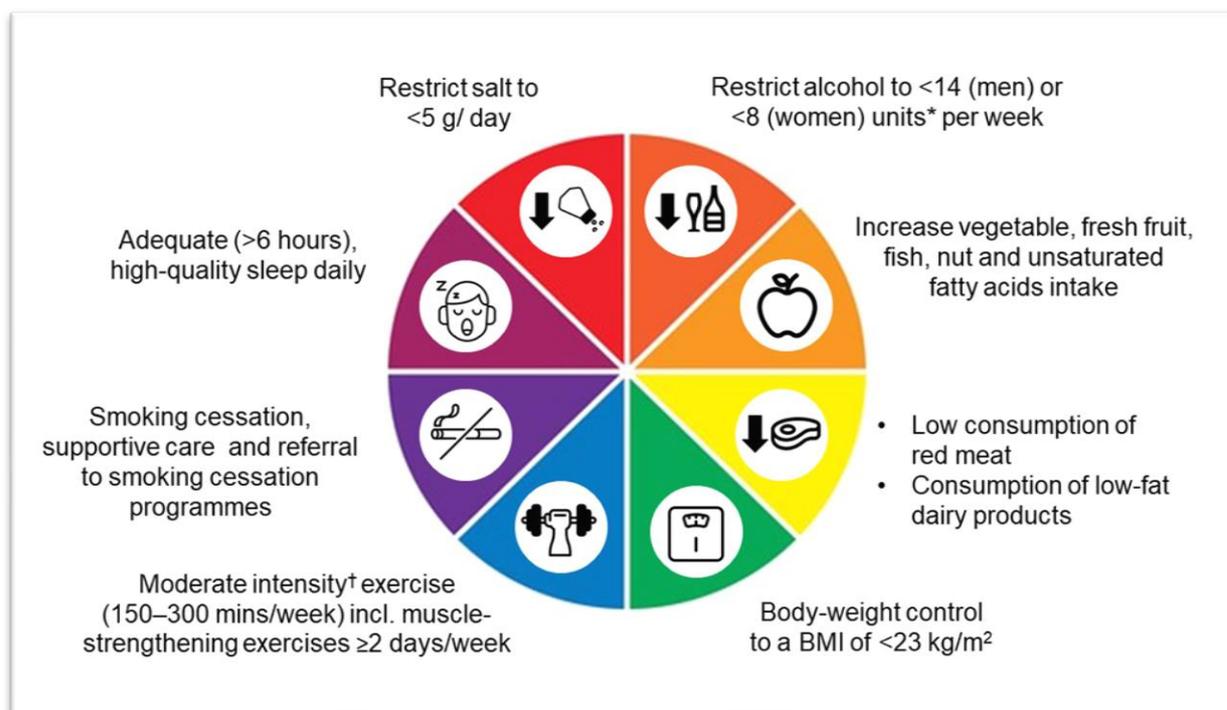
### ***Lifestyle interventions***

Lifestyle interventions remain the cornerstone of a population-based approach to reducing CVD. The authors recommend establishing the following as the necessary lifestyle interventions to reduce CV risk in all adult Singapore residents (see also **Fig. 6**):<sup>13-21,25-28</sup>

1. Avoidance of excessive salt intake >5 g per day
2. Alcohol restriction to less than 14 units (men) or 8 units (women) per week (1 unit is equal to half a glass [125 mL] of wine or a glass [250 mL] of beer)
3. Increased consumption of vegetables, fresh fruits, fish, nuts and unsaturated fatty acids
4. Low consumption of red meat, and consumption of low-fat dairy products
5. Body-weight control to a body mass index (BMI) of <23 kg/m<sup>2</sup>

6. Exercise (moderate intensity) for 150–300 minutes per week. Include muscle-strengthening exercises at least 2 days per week.
7. Smoking and vaping avoidance (smoking cessation, supportive care and referral to smoking cessation programmes)
8. Adequate (>6 hours), high-quality sleep daily

**Fig. 6. Lifestyle interventions to lower CV risk among adult Singapore residents.**



\* 1 unit is equal to half a glass (125 mL) of wine or 1 glass (250 mL) of beer.

† Can talk in phrases or short sentences but cannot sing.

Source: White Paper on Healthier SG (2022) and Tan et al. *Annals Acad Med Singap* 2024;53:23-33. Creative Commons Licence CC BY-NC-SA 4.0.

### **Hypertension**

Singapore's CPG for hypertension was published in 2017. It indicates that the target blood pressure (BP) was <140/90 mmHg in patients aged under 80 years.<sup>13</sup> In contrast, the 2018 European Society of Cardiology (ESC) guidelines target a BP of <140/90 mmHg in all patients, and may be lowered to <130/80 mmHg or lower in most patients, provided that the treatment is well tolerated.<sup>29</sup> The 2023 ACG for Hypertension updated the treatment targets to <140/90 mmHg for patients with low to intermediate CV risk (consider lower, i.e., <130/80, as tolerated); and <130/80 mmHg for those with high to very high CV risk

(e.g., patients with CVD, chronic kidney disease, diabetes mellitus, hypertension-mediated organ damage, or a risk score >20%.<sup>20</sup>

Areas that need attention include the role of comorbidities in treatment decisions, the use of ambulatory blood pressure (BP) monitoring, and updates in the use of pharmacotherapy, including the role of combination therapy in the overall treatment algorithm. The key messages proposed by the authors regarding the control of hypertension, which may be considered in the updating of the standards of care, are shown in Box 1.

#### Box 1. Key messages on hypertension.

1. All adult patients should have their BP properly measured according to the appropriate steps at every clinic visit. Home BP monitoring is also recommended.
2. Lifestyle interventions remain the first-line treatment in hypertensive patients with low/moderate CV risk without evidence of hypertension mediated organ damage (HMOD). However, lifestyle interventions plus antihypertensive medications should be instituted in hypertensive patients with HMOD or high/very-high CV risk.
3. The target diastolic BP is below 80 mmHg for most patients. Provided treatment is well tolerated, the target systolic BP is 130–139 mmHg for patients aged 65 years or older. Treatment should be cautiously uptitrated to target BP in patients aged older than 80 years. Systolic BP below 120–129 mmHg is reasonable for most patients younger than 65 years.
4. Most patients will require combination therapy (i.e., an angiotensin-converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB], combined with a CCB and/or a thiazide/thiazide-like diuretic) to achieve BP control. Low-dose combination therapy may be considered as an initial treatment strategy.
5. Treatment should be escalated accordingly to achieve BP control within 3 months of treatment initiation. BP control should be monitored by at least weekly home monitoring or via telemonitoring.

#### ***Dyslipidaemia***

The latest SCPG on the management of lipids<sup>20</sup> was published in December 2023 and was formulated to provide an evidence-based, cost-effective approach towards the management of lipids.

The new guidance indicates a low-density lipoprotein cholesterol (LDL-c) of <1.8 mmol/L for patients with very high risk (established atherosclerotic cardiovascular disease or ASCVD) and a LDL-c of <1.4 mmol/L for very high risk patients with a history of acute

coronary syndrome (ACS). This differs slightly with the guidance of a LDL-c <1.4 mmol/L and at least a 50% reduction from baseline for very high risk patients in the 2019 ESC guidelines and the 2021 Asian Pacific Society of Cardiology consensus statements.<sup>20,30,31</sup> The SCPG uses a different risk classification – an updated 2023 Singapore Modified Framingham Risk Score risk calculator – which has been adapted for local use.

The SCPG recommendation of a LDL target of <1.8 mmol/L for high-risk patients (DM with additional risk factors, familial hypercholesterolemia [FH] and calculated risk of >20% 10-year risk) is comparable to a target LDL-c of <1.8 mmol/L and at least a 50% reduction from baseline in patients at high risk as indicated in the European and Asian Pacific guidance documents. However, in patients with chronic kidney disease (CKD) in the high risk category, the SCPG recommends a target LDL-c of <2.6 mmol/L based on current evidence. The latest SCPG also provides updated guidance on the screening and treatment of patients with FH.

The latest CPG also provides guidance on the rate of treatment intensification, the role of combination therapy and novel strategies, and the optimal treatment for special populations including those with comorbid conditions. Box 2 summarises the key messages proposed by the authors regarding the control of dyslipidaemia, which has been considered in the updating of the standards of care.

#### Box 2. Key messages on dyslipidaemia.

1. Cardiovascular risk assessment including lipid screening (total cholesterol, triglycerides, LDL-c and HDL-c) should be routinely performed in adults aged 40 years or more.
2. Lifestyle interventions should be the first-line treatment for dyslipidaemia in patients with low or moderate CV risk and should always accompany lipid-lowering therapy.
3. LDL-c treatment should aim for a target on-treatment level at least <1.8 mmol/l (very high risk or high risk) or <1.4 mmol/l (post-ACS patients), while aiming for LDL-c <2.6 mmol/L for moderate risk. In individuals at low risk, an LDL-c goal <3.4 mmol/L may be considered .
4. For very high CV risk post-ACS patients, treatment should be intensified within 4 to 6 weeks in those who do not achieve treatment targets.
5. Lipoprotein(a) measurement may be considered at least once in each adult person's lifetime, especially those with family history of premature ASCVD.

### **Diabetes mellitus**

The CPG for diabetes mellitus (2014) has been withdrawn.<sup>32</sup> Since its withdrawal, several developments have already taken place in the field of diabetes mellitus management, including the increased recognition of the harms of hypoglycaemia and the importance of individualised treatment targets, as well as the publication of multiple CV outcome trial results in various patient subpopulations.<sup>33</sup>

In 2017, the ACE issued a clinical guidance on initiating basal insulin, which has been updated in 2022.<sup>18</sup> ACE also published a clinical guidance on personalising management of T2DM with non-insulin medications, which has been updated in June 2023, incorporating most of the recent developments in T2DM management.<sup>19</sup>

Box 3 summarises the key messages proposed by the authors regarding the control of diabetes mellitus. These key messages align with the 2023 ACE clinical guidance as well as the 2021 ACE clinical guidance on the management of prediabetes.<sup>17,19</sup>

#### **Box 3. Key messages on diabetes mellitus.**

1. Patients with prediabetes should be monitored closely and counselled regarding lifestyle interventions.
2. Lifestyle interventions and weight management should be the foundational treatment for all patients with type 2 diabetes.
3. Where possible, optimal glucose control is defined as HbA1c (glycated haemoglobin) of below 7%.
4. Hypoglycaemia should be avoided. Hence, a less stringent HbA1c target (<8%) may be appropriate in patients with advanced age, limited lifespan and comorbidities that predispose to hypoglycaemia.
5. SGLT2is have demonstrated CV outcome benefits in patients with high CV risk including those with established CV disease. An SGLT2i (sodium-glucose cotransporter-2 inhibitor) is recommended in patients with T2DM with high CV risk, including those with established CV disease.
6. GLP-1Ras (glucagon-like peptide-1 receptor agonist) with proven CV outcome benefits may also be considered in patients with established CVD and in those with CKD with increased CV risk. Cost is a concern with this group of medications.
7. Cardiovascular risk factor management is key in patients with diabetes. Management of lipids, blood pressure and smoking as detailed in Key messages in Box 1, 2 and 5 are required to reduce CV risk and disease in these patients

## Obesity

Singapore's CPG on the management of obesity was published in 2016 and most of the recommendations in this document remain relevant and valid.<sup>15</sup> Nonetheless, given the multifaceted nature of obesity management, there may be a need to simplify the recommendations to facilitate its implementation in primary care. Box 4 summarises the key messages proposed by the authors regarding the control of obesity, which may be considered in the updating of the standards of care.

### Box 4. Key messages on obesity.

1. A target BMI of 18.5 – 23 kg/m<sup>2</sup> is recommended among adults.
2. In patients with BMI >23 kg/m<sup>2</sup>, waist circumference should be measured in addition to BMI. Measure blood pressure in both arms, fasting glucose or glycated hemoglobin and lipid profile to determine cardiometabolic risk and, where appropriate, alanine aminotransferase to screen for nonalcoholic fatty liver disease in people living with obesity.
3. Adults living with obesity should receive individualised medical nutrition therapy provided by a registered dietitian (when available) to improve weight outcomes (body weight, BMI), waist circumference and glycaemic control, and achieve established lipid and blood pressure targets.
4. Moderate intensity exercise (150–300 minutes per week) is recommended. This should include moderate- or vigorous-intensity muscle-strengthening activity, at least 2 days per week. For those aged over 50 years, include multi-component physical activity that emphasises strength and functional balance at least 3 days of the week at a moderate or greater intensity.
5. Pharmacotherapy for weight loss can be used for persons with BMI ≥ 30 kg/m<sup>2</sup> or BMI ≥ 27 kg/m<sup>2</sup> with T2DM or adiposity-related complications, in conjunction with medical nutrition therapy, physical activity and psychological interventions. Referral to an obesity specialist may also be considered in patients with BMI >40 kg/m<sup>2</sup> or >35 kg/m<sup>2</sup> plus ≥1 obesity-related comorbidity to assess suitability for metabolic bariatric surgery.

## Smoking

The Singapore CPG on the treatment of tobacco use and dependence was published in 2013.<sup>16</sup> While these guidelines rightly advocate the use of behavioral therapy in conjunction with pharmacotherapy, the latter is largely based on nicotine replacement therapy (NRT). In contrast, more recent guidelines have shifted to the use of varenicline as the backbone of pharmacotherapy.<sup>34</sup> Varenicline is not currently available in Singapore. Box 5 summarises the

key messages proposed by the authors regarding the control of tobacco use and dependence, which may be considered in the updating of the standards of care.

**Box 5. Key messages on tobacco cessation.**

1. Current smokers should be advised to stop smoking during routine consultations at least once a year.
2. Current smokers should be informed of smoking cessation resources available in the community, such as free smoking cessation counselling at community pharmacies. If deemed suitable, pharmacists may prescribe nicotine replacement therapy.
3. Current smokers should be offered a referral to a specialist clinic or other specialist service, record the response to that advice, and arrange follow-up where appropriate.
4. Efforts at smoking cessation should be supported by behavioural support from specialist clinics. Self-help materials and telephone counselling may also be offered.

Finally, the authors call for a comprehensive healthcare professional education programme to cascade the updated standards of care and emphasise the importance of achieving treatment targets across all CV risk factors. This programme can utilise various media, including publications, seminars, webinars, podcasts and periodic scientific meetings.

**PATIENT EDUCATION THROUGH COOPERATION WITH COMMUNITY PARTNERS**

In 2021, a nationwide population-based survey assessed the knowledge of Singaporeans regarding heart disease and preventive measures. The survey found that while 88.4% recognised CVD as one of the 3 leading causes of mortality in Singapore, more than a third (37.2%) had a low or moderate knowledge scores regarding the risk factors of heart disease.<sup>35</sup>

Furthermore, many patients were not able to identify the following behaviours as promoting heart health: maintain a healthy BP (32%), get adequate sleep (32%), increase fruits and vegetable consumption (32%), reduce dietary cholesterol intake (42%), reduce sugar intake (45%), regular physical exercise (45%), reduce sodium intake (48%), reduce stress (49%), lose weight (56%), moderate alcohol consumption (62%), visit doctor for regular test for heart disease (63%) and quit smoking (91%). Another 2021 national survey on cholesterol and cholesterol-lowering medications found that many Singaporeans had misconceptions regarding the efficacy, safety and proper usage of statins.<sup>36</sup>

To address the urgent need to increase the knowledge on heart health and encourage heart-healthy behaviour throughout the population, the authors propose a comprehensive patient education campaign (i.e., 8 Enablers to Fight 5) that outlines 8 action points to control the 5 main modifiable CV risk factors (**Fig. 7**).

**Fig. 7. Healthier Heart SG@85 (8 enablers to fight 5).**



\*<120-129/80 mmHg for <65 years old; <130-130/80 mmHg for ≥65 years old. †Consult your healthcare professional for your specific target cholesterol level. Source: White Paper on Healthier SG (2022) and Tan et al. Annals Acad Med Singap 2024;53:23-33. Creative Commons Licence CC BY-NC-SA 4.0.

This campaign, which would be spearheaded by the Singapore Heart Foundation with the support of the Singapore Cardiac Society and the Chapter of Cardiologists of the Academy of Medicine, Singapore, should also be the main venue to cascade the details of the updated standards of care to the community and to combat the proliferation of myths, misconceptions and fake news regarding heart disease and treatments for CV risk factors.<sup>35-37</sup>

The programme would address the underlying values and hesitations of the population of Singapore regarding heart health to ensure high uptake and adoption. To ensure high penetration, the programme would include a wide array of media, including traditional mass media, social media, and digital and live events such as webinars podcasts and periodic seminars. The Heart Week, held every September, can serve as a culminating activity for year-round educational campaigns.

Beyond the information overload on health, the challenge is to help an ageing population, those with lower socio-economic status and those with lower health literacy use digital tools—to make healthier choices and to ensure compliance with medication and avoidance of drug-drug interaction. Importantly, authors recognise that healthy lifestyle choices and the avoidance of risk factors such as smoking develop at a young age and are affected by lifestyle choices made by other family members.<sup>38-41</sup> Therefore, even though the burden of CV disease increases with advancing age, individuals in the paediatric age group would also be targets for education on healthy lifestyles and risk reduction. Specific topics such as targeted cascade screening for FH may also be delivered to a younger target audience, all within the framework of the 8 Enablers to Fight 5 campaign.

### **SUPPORT FOR INTEGRATED CARE**

The authors underscore that CVD is a multifactorial disease and its outcomes depend on long-term behavioural change, long-term medical care and regular monitoring of overall risk. Hence, we fully support the Healthier SG initiatives to mobilise family doctors to deliver preventive care, push for lifestyle adjustments and regular health screening, activate community partners to support healthier lifestyles, and ensure residents commit to seeing one family doctor and adopt a health plan.

In terms of providing access to necessary CV care, this would also include access to cardiac rehabilitation (i.e., interventions to optimise the physical, mental and social conditions of patients with chronic or post-acute CVD to live a productive life)<sup>42</sup> in the community as well as improved referral processes and access to nutrition/dietetics counselling and tobacco cessation, as well as the necessary financial structures to subsidise these services.

In line with this, the authors support initiatives that encourage continuity of care, such as CareHub, a transition programme developed in the National University Health System (NUHS).<sup>43</sup> This programme assigns each patient to a coordinator, who works with the patient and family members to coordinate a tailored multidisciplinary post-discharge care plan.<sup>8</sup>

Second, the authors fully support the Healthier SG to strengthen the necessary enablers to ensure the optimal delivery of care across the population. To us, this includes the optimal use of information technology and continued CV research. We encourage policymakers and stakeholders to maximise the use of information technology across the various aspects of healthcare management. Specifically, we encourage the use of digital technology in the areas shown in **Box 6**.

**Box 6. Areas where digital technologies can be utilized.**

- **Electronic Health Records (EHR) and Health Information Exchange (HEI) technology** to improve efficiency at the point of care and facilitate efficient data sharing and collaboration among healthcare professionals.<sup>44</sup>
- **Telemedicine and Remote Monitoring** through video conferencing, wearable technology and mobile apps to provide more complete or real-time health monitoring information and improve accessibility to care, especially among certain disadvantaged patients, such as those with mobility problems.<sup>44-47</sup>
- **Decision support systems** such as risk assessment tools, clinical calculators and digital management algorithms to aid in making evidence-based decisions for individualised cardiovascular preventive care.<sup>44,45</sup>
- **Patient tools** such as mobile health apps to track physical activity, monitor dietary habits and sleep patterns, and provide reminders for medication adherence.<sup>44,45</sup>
- **Health education and awareness** through websites, apps, online portals and curated social media to disseminate information on risk factor control, healthy lifestyle choices, and the importance of regular screenings.<sup>44,45</sup>
- **Data analytics and predictive modelling** to identify patterns in cardiovascular events to predict future trends, which may be used to develop targeted prevention strategies, and allocate resources effectively.<sup>44</sup>

The authors acknowledge that digital facilities, such as [www.HealthHub.sg](http://www.HealthHub.sg) and the Healthy 365 mobile app, are already in place.<sup>48,49</sup> The authors also note that Healthier SG aims to provide a one-off grant to family doctors involved to offset the costs of information technology adoption “to facilitate sharing of clinical notes, monitoring of patient outcomes, collation and sharing of data.”<sup>12</sup>

In addition, understanding that research may be a costly but invaluable investment, we call for support for the continuation of CV research, including current initiatives such as the Singapore Cardiovascular Longitudinal Outcomes Database (SingCLOUD) and the SMIR. Singapore is already participating in several multicentre collaborative researches, such as INTERASPIRE<sup>50</sup>, the international survey of coronary patients, their cardiometabolic, renal and biomarker status, and the quality of preventive care delivered in all WHO regions; and the Acute Myocardial Infarction: Allied Health-Oriented, Patient-Centred Technology-Enabled (AMI-HOPE), which is supported by the Ministry of Health Singapore. Hopefully, these initiatives may help to address some of the knowledge gaps and serve to ultimately improve the delivery of CV care throughout the population.

Specifically, we call on the various academic and healthcare institutions (public and private) to consider implementing of the types of research shown in Box 7.

#### Box 7. Proposed priority research

- **Clinical-focused research** that includes patient-reported outcomes, pharmacovigilance and pharmacoepidemiology;
- **Research on quality performance/improvement** and other action research programmes that explore process efficiency;
- **Socioeconomic impact** of care and interventions; and
- **Research on patient activation, attrition and fallout**, and **the values and perceptions** of key stakeholders.

These types of research will provide information that is meaningful to patients and healthcare providers and will help improve healthcare delivery and efficiency, which may potentially improve individual and population-wide health outcomes.

The authors applaud efforts of Healthier SG to improve access to care, such as the full subsidy of nationally recommended screenings for Singapore citizens, waiver of co-payment when using their national medical savings scheme MediSave for chronic care management, the introduction of a new Community Health Assist Scheme (CHAS) drug subsidy tier for selected chronic disease management drugs, and the leveraging of the health points system under the National Steps Challenge to offer rewards to residents for enrolling and completing their first consultation and for leading active and healthy lifestyles.<sup>12</sup>

Several Singapore studies have consistently reported that the costs of screening and treatment are major barriers to both access to CV care.<sup>37,51-53</sup> The aforementioned

initiatives under Healthier SG will encourage Singapore residents, especially those with less financial resources, to comply with medical advice.

Finally, the authors acknowledge that establishing population CV health requires overcoming several challenges in the implementation of national programmes, such as the need to rally support as well as coordinate the programmes' multiple stakeholders.

We also acknowledge that access to CV care and the adoption of healthy lifestyle choices go beyond the health system and are strongly influenced by personal factors (e.g., willpower and self-regulation), interpersonal factors (e.g., influence from family and peers) and environmental factors (e.g., situational factors; culture, traditions and customs; and major national/international events).<sup>47</sup>

## CONCLUSION

With CVD a leading cause of morbidity and mortality in Singapore, the success of Healthier SG is largely dependent on the control of CVD and its risk factors. Healthier Heart SG and its three-pronged approach would bring the standards of care and CV care delivery in Singapore closer to achieving the vision of proactive prevention of CVD and CV morbidity and mortality. This can only be achieved through the concerted efforts of healthcare professionals, policymakers and community partners, coupled with the cooperation of community members.

## REFERENCES

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396:1204-1222.
2. National Registry of Diseases Office. Singapore Myocardial Infarction Registry Annual Report 2020. [https://nrdo.gov.sg/docs/librariesprovider3/default-document-library/smir-web-report-2020.pdf?sfvrsn=585f8334\\_1](https://nrdo.gov.sg/docs/librariesprovider3/default-document-library/smir-web-report-2020.pdf?sfvrsn=585f8334_1). Accessed 12 March 2023.
3. National Registry of Diseases Office. Singapore Myocardial Infarction Registry Annual Report 2021. [https://www.nrdo.gov.sg/docs/librariesprovider3/default-document-library/smir-annual-report-2021-\(web\)\\_final.pdf?sfvrsn=3418ed95\\_0](https://www.nrdo.gov.sg/docs/librariesprovider3/default-document-library/smir-annual-report-2021-(web)_final.pdf?sfvrsn=3418ed95_0). Accessed 05 April 2024.
4. National Registry of Diseases Office. Singapore Stroke Registry Annual Report 2020. [https://www.nrdo.gov.sg/docs/librariesprovider3/default-document-library/ssr-web-report-2020c544bb698cf04ad1aaaa7a1472296132.pdf?sfvrsn=33b4f18a\\_0](https://www.nrdo.gov.sg/docs/librariesprovider3/default-document-library/ssr-web-report-2020c544bb698cf04ad1aaaa7a1472296132.pdf?sfvrsn=33b4f18a_0). Accessed 8 July 2023.
5. National Registry of Diseases Office. Singapore Stroke Registry Annual Report 2021. [https://nrdo.gov.sg/docs/librariesprovider3/default-document-library/ssr-annual-report-2021\\_web.pdf?sfvrsn=7d63ee29\\_0](https://nrdo.gov.sg/docs/librariesprovider3/default-document-library/ssr-annual-report-2021_web.pdf?sfvrsn=7d63ee29_0). Accessed 05 April 2024.
6. Yeo TC, Chan YH, Low LP, et al. Risk factor profile and treatment patterns of patients with atherothrombosis in Singapore: insight from the REACH Registry. *Ann Acad Med Singap* 2008;37:365-371.
7. Subramaniam T, Nang EE, Lim SC, et al. Distribution of ankle-brachial index and the risk factors of peripheral artery disease in a multi-ethnic Asian population. *Vasc Med* 2011;16:87-95.

8. The Economist Intelligence Unit. The Cost of Inaction: Secondary Prevention of Cardiovascular Disease in Asia-Pacific (2020). [https://impact.economist.com/perspectives/sites/default/files/eiu\\_amgen\\_cvd\\_secondary\\_prevention\\_whitepaper\\_0319.pdf](https://impact.economist.com/perspectives/sites/default/files/eiu_amgen_cvd_secondary_prevention_whitepaper_0319.pdf). Accessed 12 March 2023.
9. National Population Health Survey 2020. <https://www.moh.gov.sg/docs/librariesprovider5/default-document-library/nphs-2020-survey-report.pdf>. Accessed 12 March 2023.
10. National Population Health Survey 2022. [https://hpb.gov.sg/docs/default-source/default-document-library/nphs-2022-survey-report.pdf?sfvrsn=3e8530aa\\_8](https://hpb.gov.sg/docs/default-source/default-document-library/nphs-2022-survey-report.pdf?sfvrsn=3e8530aa_8). Accessed 05 April 2024.
11. Tan BYQ, Tan JTC, Cheah D, et al. Long-Term Trends in Ischemic Stroke Incidence and Risk Factors: Perspectives from an Asian Stroke Registry. *J Stroke* 2020;22:396-399.
12. Ministry of Health Singapore. White Paper on Healthier SG. <https://www.healthiersg.gov.sg/resources/white-paper/>. Accessed 30 Jan 2023.
13. Ministry of Health Singapore. MOH Clinical Practice Guidelines. Hypertension. 1/2017.
14. Ministry of Health Singapore. MOH Clinical Practice Guidelines. Lipids. 2/2016.
15. Ministry of Health Singapore. MOH Clinical Practice Guidelines. Obesity. 1/2016.
16. Ministry of Health Singapore. Treating Tobacco Use and Dependence. HPB-MOH Clinical Practice Guidelines 1/2013.
17. Agency for Care Effectiveness (ACE). Managing pre-diabetes – a growing health concern. Appropriate Care Guide (ACG), Ministry of Health, Singapore. 2021. [https://www.ace-hta.gov.sg/docs/default-source/default-library/managing-pre-diabetes-\(updated-on-27-jul-2021\)c2bfc77474154c2abf623156a4b93002.pdf](https://www.ace-hta.gov.sg/docs/default-source/default-library/managing-pre-diabetes-(updated-on-27-jul-2021)c2bfc77474154c2abf623156a4b93002.pdf). Accessed 12 March 2023.
18. Agency for Care Effectiveness (ACE). Initiating basal insulin in type 2 diabetes mellitus. Appropriate Care Guide (ACG), Ministry of Health, Singapore. 2021. [https://www.ace-hta.gov.sg/docs/default-source/acgs/initiating-basal-insulin-in-t2dm-\(updated-on-10-june-2022\)e789e615718e4371b3353ea5afaa599f.pdf](https://www.ace-hta.gov.sg/docs/default-source/acgs/initiating-basal-insulin-in-t2dm-(updated-on-10-june-2022)e789e615718e4371b3353ea5afaa599f.pdf). Accessed 12 March 2023.
19. Agency for Care Effectiveness (ACE). Type 2 diabetes mellitus – personalising management with non-insulin medications. ACE Clinical Guidance (ACG), Ministry of Health, Singapore. 2023. <https://www.ace-hta.gov.sg/docs/default-source/acgs/acg-t2dm-personalising-medications.pdf>. Accessed 12 March 2023.
20. Chapter of Cardiologists, College of Physicians, Academy of Medicine, Singapore Clinical Practice Guidelines: Management of Lipids. [https://www.ams.edu.sg/view-pdf.aspx?file=media%5c7093\\_fi\\_79.pdf&ofile=AMS+CPG+Management+of+Lipids\\_+FINAL.pdf](https://www.ams.edu.sg/view-pdf.aspx?file=media%5c7093_fi_79.pdf&ofile=AMS+CPG+Management+of+Lipids_+FINAL.pdf). Accessed 22 January 2024.
21. Agency for Care Effectiveness (ACE). Hypertension – tailoring the management plan to optimise blood pressure control. Appropriate Care Guide (ACG), Ministry of Health, Singapore. 2023. [https://www.ace-hta.gov.sg/docs/default-source/acgs/acg-hypertension\\_15dec2023.pdf?sfvrsn=dca0d119\\_10](https://www.ace-hta.gov.sg/docs/default-source/acgs/acg-hypertension_15dec2023.pdf?sfvrsn=dca0d119_10). Accessed 05 April 2024.
22. D'agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743-753.
23. Ueshima H, Sekikawa A, Miura K, et al. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation* 2008;118:2702-2709.
24. Globorisk Risk Charts. <http://www.globorisk.org/risk-charts>. Accessed 12 March 2023.
25. Health Promotion Board. Healthy Living. Singapore: Health Promotion Board. <https://www.hpb.gov.sg/healthy-living>. Accessed 12 March 2023.
26. Singapore Physical Activity Guidelines (SPAG). Singapore: Sport Singapore; 2022.
27. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;74:1376-1414. Erratum in *J Am Coll Cardiol* 2019 ;74:1428-1429. Erratum in *J Am Coll Cardiol* 2020 ;75:840.
28. Lloyd-Jones DM, Allen NB, Anderson CAM, et al. Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association. *Circulation* 2022;146:e18-e43.
29. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021-3104. Erratum in *Eur Heart J* 2019;40:475.
30. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111-188. Erratum in: *Eur Heart J* 2020;41:4255.

31. Koh N, Ference BA, Nicholls SJ, et al. Asian Pacific Society of Cardiology Consensus Recommendations on Dyslipidaemia. *Eur Cardiol* 2021;16:e54.
32. Ministry of Health Singapore. MOH Clinical Practice Guidelines. Diabetes Mellitus. 1/2014 [withdrawn].
33. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2022;65:1925-1966.
34. Leone FT, Zhang Y, Evers-Casey S, et al. Initiating Pharmacologic Treatment in Tobacco-Dependent Adults. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med* 2020;202:e5-e31.
35. Huang Z, Yap QV, Chan YH, et al. Knowledge of Heart Disease, Preventive Behavior and Source of Information in a Multi-ethnic Asian Population: A Population-Based Survey. *J Community Health* 2021;46:31-40.
36. Lim CY, Ho JS, Huang Z, et al. Public perceptions and knowledge of cholesterol management in a multi-ethnic Asian population: A population-based survey. *PLoS One* 2021;16:e0256218.
37. Wee LE, Wong J, Chin RT, et al. Hypertension management and lifestyle changes following screening for hypertension in an Asian low socioeconomic status community: a prospective study. *Ann Acad Med Singap* 2013;42:451-65.
38. August GP, Caprio S, Fennoy I, et al; Endocrine Society. Prevention and treatment of pediatric obesity: an endocrine society clinical practice guideline based on expert opinion. *J Clin Endocrinol Metab* 2008;93:4576-99.
39. Parekh N, Khalife G, Hellmers N, D'Eramo Melkus G. The Healthy Eating and Living Against Noncommunicable Diseases Study: An Innovative Family-Based Intervention. *Diabetes Educ* 2020;46:569-579.
40. Gorga E, Regazzoni V, Bansil S, et al. School and family-based interventions for promoting a healthy lifestyle among children and adolescents in Italy: a systematic review. *J Cardiovasc Med (Hagerstown)* 2016;17:547-55.
41. Back IC, Barros NF, Caramelli B. Lifestyle, inadequate environments in childhood and their effects on adult cardiovascular health. *J Pediatr (Rio J)* 2022;98(Suppl 1):S19-S26.
42. Rehabilitation after cardiovascular diseases, with special emphasis on developing countries: report of a WHO Committee. *World Health Organ Tech Rep Ser* 1993;831:1-122.
43. National University Hospital System. CareHub Hospital to Home. <https://www.nuhs.edu.sg/Care-in-the-Community/Getting-Well/CareHub-Hospital-to-Home/Pages/default.aspx>. Accessed 12 March 2023.
44. Healthcare Information Technology for Cardiovascular Medicine: Telemedicine & Digital Health. Bhatt AB (ed). Switzerland: Springer Cham; 2021.
45. Harky A, Adan A, Mohamed M, et al. Technology and cardiovascular diseases in the era of COVID-19. *J Card Surg* 2020;35:3551-3554.
46. Takahashi EA, Schwamm LH, Adeoye OM, et al. An Overview of Telehealth in the Management of Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation* 2022;146:e558-e568.
47. Maddala R, MacLeod J, McLeish T, et al. The role of digital health in the cardiovascular learning healthcare system. *Front Cardiovasc Med* 2022;9:1008575.
48. Health Hub. [www.HealthHub.sg](http://www.HealthHub.sg). Accessed 9 July 2023.
49. Health Promotion Board. Healthy 365. <https://hpb.gov.sg/healthy-living/healthy-365>. Accessed 9 July 2023.
50. McEvoy JW, Jennings C, Kotseva K, et al. INTERASPIRE: an International Survey of Coronary Patients; Their Cardiometabolic, Renal and Biomarker Status; and the Quality of Preventive Care Delivered in All WHO Regions : In Partnership with the World Heart Federation, European Society of Cardiology, Asia Pacific Society of Cardiology, InterAmerican Society of Cardiology, and PanAfrican Society of Cardiology. *Curr Cardiol Rep* 2021;23:136.
51. Ku CW, Leow SH, Ong LS, et al. Developing a lifestyle intervention program for overweight or obese preconception, pregnant and postpartum women using qualitative methods. *Sci Rep* 2022;12:2511.
52. Subramaniam M, Devi F, AshaRani PV, et al. Barriers and facilitators for adopting a healthy lifestyle in a multi-ethnic population: A qualitative study. *PLoS One* 2022;17:e0277106.
53. Wee LE, Koh GC. Individual and neighborhood social factors of hypertension management in a low-socioeconomic status population: a community-based case-control study in Singapore. *Hypertens Res* 2012;35:295-303.

**Disclosure:** This paper was undertaken by Singapore Heart Foundation through an unrestricted fund from Amgen Biotechnology Singapore Pte Ltd. The funder played no role in the design, data collection, analysis, interpretation or manuscript writing.