Cardiovascular Risk in Malaysia: causes, consequences and prevention

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Cardiovascular Risk in Malaysia:

causes, consequences and prevention

Hartvaatziekte risico in Maleisië: oorzaken, gevolgen en preventie
(met een samenvatting in het Nederlands)
'Risiko Kardiovaskular di Malaysia: penyebab, akibat dan pencegahan'
(dengan ringkasan dalam Bahasa Malaysia)

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door

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te Petaling Jaya (Maleisië)

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Manuscripts based on the studies presented in this thesis

Chapter 2.1

Selvarajah S, Haniff J, Kaur G, Guat Hiong T, Chee Cheong K, Lim CM, Bots ML. Clustering of cardiovascular risk factors in a middle-income country: a call for urgency. European Journal of Preventive Cardiology 2012 Jan 24 [Epub ahead of print.]

Chapter 2.2

AG Nuur Amalina, H Jamaiyah, S Selvarajah for the NHMS Cohort Study group. Geographical variation of cardiovascular risk factors in Malaysia. Medical Journal of Malaysia 2012; 67: 31-38.

Chapter 3.1

Selvarajah S, Fong AYY, Selvaraj G, Haniff J, Uiterwaal C.S.P.M. and Bots ML. An Asian Validation of the TIMI risk score for ST-Segment Elevation Myocardial Infarction. PLoS ONE published 16 Jul 2012 10.1371/journal.pone.0040249.

Chapter 3.2

Selvarajah S, Haniff J, Kaur G, Guat Hiong T, Chee Cheong K, van der Graaf Y , Bots ML for the NHMS Cohort Study group. Comparison of the Framingham Risk Score, SCORE and WHO/ISH risk prediction models in an Asian population. Submitted.

Chapter 4.1

Selvarajah S, van der Graaf Y, Visseren FL, Bots ML; SMART study group. Cardiovascular risk factor treatment targets and renal complications in high risk vascular patients: a cohort study. BMC Cardiovascular Disorders 2011 Jul 5;11(1) 40.

Chapter 4.2

Selvarajah S, Fong AYY, Selvaraj G, Haniff J, Hairi NN, Bulgiba A and Bots ML. Impact of cardiac-care variation on ST-Elevation Myocardial Infarction outcomes. Submitted.

Chapter 4.3

Selvarajah S, Haniff J, Kaur G, Guat Hiong T, Chee Cheong K, Bujang A, Bots ML. Identification of effective screening strategies for cardiovascular disease prevention in a developing country: using cardiovascular risk-estimation and risk-reduction tools for policy recommendations. In revision BMC Cardiovascular Disorders.

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Chapter 1

Introduction

When I was a medical student in the late 1990's, information on cardiovascular disease prevalence, incidence, risk factors and prognosis were based on studies conducted in western countries. Medical journals were not easy to come by and the provision of the internet/ online access was not widespread. Practicing clinical medicine in the early 2000's, first in the general hospital in the city I lived in, and subsequently in a rural small hospital opened my eyes to the epidemiological transition occurring in my country. Men were being admitted with acute myocardial infarctions in their early 40's. Women in the rural areas were being diagnosed with Type 2 diabetes mellitus in their 20's. The traditional risk factors for these conditions, such as (older) age and family history were not applicable to a wide range of patients. Aside from this, those practicing clinical medicine in the rural areas (where there are no specialists stationed) were not exposed to continuous medical education on a regular basis due to the shortage of human resource as well as availability of courses. This led to the slower expansion of knowledge of the epidemiologic transition that was engulfing developing countries and Malaysia. Till the late 2000's, higher budget allocations and more emphasis was still placed on tackling infectious and vector-borne diseases, such as HIV/ AIDS and dengue instead of cardiovascular risk-factors and disease.

Currently, it is well-known that cardiovascular disease forms the greatest morbidity and mortality worldwide and disproportionately affects low and middle-income developing countries.(1-3) Cardiovascular disease as the 'disease of affluence' no longer applies. Studies have shown that now, large increases in cardiovascular risk factors occur at earlier stages of a country's economic development (4) and cardiovascular risk is increased more in the lower socio-economic group. (5, 6) Aside from this, in developing countries, cardiovascular morbidity and mortality tends to affect the (younger) working adults.(3) This causes a significant burden to the economy. The cost of cardiovascular morbidity and mortality is also exorbitant, with up to USD298 billion spent in the United States in 2008 for cardiovascular disease related conditions.(7) However, resources committed to the prevention and management of cardiovascular disease in developing countries are far lower than in developed countries. In 2011, low and middle-income countries spent 25 times less per capita on healthcare.(8) With a larger proportion of communicable diseases endemic in low and middle-income countries, the disparity in amounts spent on cardiovascular disease may be more than that.

In Malaysia, up to 39% of the population belongs to the lower socio-economic category, 65% of the general population access healthcare from public-funded healthcare facilities and up to 83% of hospitalizations occur in public-funded hospitals.(9) With only 4.75% of the gross domestic product (GDP), equivalent to USD13.21 billion spent on healthcare in 2011(10), resources are scarce. To tackle the increasing burden of cardiovascular diseases and its healthcare costs to the

country, the government has initiated a 'National Strategic Plan' for the prevention and management of non-communicable diseases.(11) In tandem with this, there are plans for healthcare reform and a greater call for accountability for patient outcomes. In order to make the national strategic plan and healthcare reform successful, a better understanding of the burden of cardiovascular risk, disease and its consequences in Malaysia will be essential.

Outline of this thesis

This thesis attempts to provide an evidence base to help tackle the burden of cardiovascular disease in Malaysia. Here we investigate the full spectrum of cardiovascular epidemiology from the causes of cardiovascular disease to its consequences and finally, its prevention.

The first part of this thesis (**Chapter 2**) focuses on the burden of cardiovascular risk factors in the country. **Chapter 2.1** describes the clustering of cardiovascular risk factors and the identification of high-risk subgroups, using a nationwide population-based survey of 34,505 people in Malaysia. **Chapter 2.2** describes the geographical distribution of cardiovascular risk factors in the country with the aim of identifying higher-risk regions or states. **Chapter 3** covers aspects of risk stratification and prediction in cardiovascular disease. **Chapter 3.1** validates a prognostic model for mortality risk in myocardial infarctions; specifically the Thrombolysis-In-Myocardial-Infarction risk score in patients with ST-segment elevation myocardial infarction and **Chapter 3.2** compares a variety of risk prediction models in primary care. The last portion of this thesis **(Chapter 4)** focuses on prevention of cardiovascular disease and its complications. **Chapter 4.1** assesses the effects of achieving cardiovascular risk-factor treatment targets on reduction of renal complications. **Chapter 4.2** reviews the effects of cardiac-care provision and reperfusion strategies in preventing mortality in patients with myocardial infarctions. **Chapter 4.3** identifies effective screening strategies for the early detection of high cardiovascular-risk patients in its effort to prevent cardiovascular disease.

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Chapter 2

Causes

Chapter 2.1

Clustering of cardiovascular risk factors in a middle-income country: a call for urgency

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Gurpreet Kaur,Tee Guat Hiong, Kee Chee Cheong,Chiao Mei Lim
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Abstract

Background

This study aimed to estimate the prevalence of cardiovascular risk factors and its clustering. The findings are to help shape the Malaysian future healthcare planning for cardiovascular disease prevention and management.

Methods

Data from a nationally representative cross-sectional survey was used. The survey was conducted via a face-to-face interview using a standardised questionnaire. A total of 37,906 eligible participants aged 18 years and older was identified, of whom 34,505 (91%) participated. Focus was on hypertension, hyperglycaemia (diabetes and impaired fasting glucose), hypercholesterolaemia and central obesity.

Results

Overall, 63% (95% confidence limits 62, 65%) of the participants had at least one cardiovascular risk factor, 33% (32, 35%) had two or more and 14% (12, 15%) had three risk factors or more. The prevalence of hypertension, hyperglycaemia, hypercholesterolaemia and central obesity were 38%, 15%, 24% and 37%, respectively. Women were more likely to have a higher number of cardiovascular risk factors for most age groups; adjusted odds ratios ranging from 1.1 (0.91, 1.32) to 1.26 (1.12, 1.43) for the presence of one risk factor and 1.07 (0.91, 1.32) to 2.00 (1.78, 2.25) for two or more risk factors.

Conclusions

Cardiovascular risk-factor clustering provides a clear impression of the true burden of cardiovascular disease risk in the population. Women displayed higher prevalence and a younger age shift in clustering was seen. These findings signal the presence of a cardiovascular epidemic in an upcoming middle-income country and provide evidence that drastic measures have to be taken to safeguard the health of the nation.

Introduction

Malaysia, a multi-ethnic, middle-income country has enjoyed economic stability and substantial growth in the past three decades.(1) It has a good healthcare system, with private and public coverage that provides access to almost 98 percent of the population.(2) With recent increased urbanisation and globalisation, there has been anecdotal evidence of rapid changes in health of the Malaysian population. These include trends towards a younger age at first myocardial infarction (3), higher cardiovascular mortality than in developed countries (4) and increasing prevalence of cardiovascular risk factors.(5) In addition, there is compelling evidence that rural communities are increasingly displaying alarming proportions of cardiovascular risk factors. (5)

In the past thirty years, there have been regular National Health and Morbidity Surveys into the prevalence of chronic diseases, patterns and costs of health care utilisation. Results were used to provide health care programme planners and policy makers with information on the burden of a wide variety of risk factors and diseases, including obesity, hypertension, diabetes mellitus and hypercholesterolaemia.(2,6) However, there are no reports on the burden of combinations of these cardiovascular risk factors, although these are required to help shape the country'sfuture healthcare planning for the prevention and managementof cardiovascular disease.

This study specifically addressed the following questions; 1) Where is Malaysia in terms of cardiovascular risk factor prevalence on a global scale? 2) What is the extent of cardiovascular risk factor clustering and are there high risk subgroups by gender, age groups, or urban/rural location.

Methods

Study population

This study utilises data from the National Health and Morbidity Survey (NHMS III) conducted in 2006. The NHMS is a non-institutionalised, nationally representative population based survey held every ten years that assesses various aspects of health care.

Sampling strategy

The NHMS III used a two-stage stratified random sampling strategy proportionate to the population size. The sampling frame was obtained from the Department of Statistics, Malaysia. Malaysia is divided geographically into Enumeration Blocks (EB) with 80-120 living quarters (LQ) each. The EB and the LQ formed the sampling unit at the first and second stage respectively. All persons in an LQ were included in this survey. In total, 2150 EB's and 17 251 LQ's were randomly sampled.

Data collection

Data was collected via a face-to-face interview using a bi-lingual (Malay language and English) pre-coded questionnaire. All interviewers were centrally trained. Visits were carried out up to three times to ensure response, both at the household and individual level. Non responders were individuals who did not respond to any question. The survey was funded by the Ministry of Health Malaysia and ethics approval was obtained from the Medical Research and Ethics Committee, Ministry of Health, Malaysia. Written informed consent was obtained from all participants.

Cardiovascular risk factors

Anthropometric measurements

Height and body weight were measured without shoes to the nearest 0.1 centimetre and kilogramme respectively. Body mass index (BMI) was calculated as weight divided by height squared (kg/m2). Waist circumference was measured at the midpoint between the inferior margin of the last rib and the iliac crest to the nearest 0.1 centimetre. Central obesity was determined using cut points recommended by the International Diabetes Federation for Asians (7); 90 centimetres for males and 80 centimetres for females.

Hypertension

Systolic and diastolic blood pressure were taken at rest, 15 minutes apart using the Omron Blood Pressure Monitor Model HEM-907 with an appropriate cuff size. The average of two readings was used. Hypertension was indicated when systolic blood pressure was more or equal to 140 mmHg and/or diastolic blood pressure was more or equal to 90 mmHg (8), or if anti-hypertensive medication was used. Newly diagnosed or known diabetics were hypertensive if systolic blood pressure was more or equal to 130 mmHg and/or diastolic blood pressure more or equal to 80 mmHg.(8)

Hypercholesterolemia

Total cholesterol levels were measured after an overnight fast using the Roche Accutrend GC machine. Hypercholesterolemia was defined as a total cholesterol level of more or equal to 5.2 mmol/l(9) or use of lipid lowering drugs.

Diabetes mellitus and Impaired fasting glucose

Participants without self-reporting of diabetes had a fasting glucose test using the Accutrend GC, Roche Diagnostic glucometer. Those with a fasting glucose of more or equal to 5.6mmol/l and less than 6.1 mmol/l were diagnosed as having impaired fasting glucose and those with more or equal to 6.1mmol/l were considered to be diabetic. (10)

Additional risk factors.

Race was categorized as Malay, Chinese, Asian-Indian and others. Smoking status was determined using the Center for Disease Control and Prevention, Atlanta (CDC) classification. Current smokers were those who smoked 100 or more cigarettes in their lifetime, and smoked daily or for some days in the previous month. Ex-smokers were those who had smoked 100 or more cigarettes in their lifetime, but had not smoked in the one month prior to the survey. Education was determined as completed years of formal education, categorised as no education, primary education (six years), secondary education (seven to 12 years) and tertiary education (more than 12 years). Income was based on self-reported average household monthly income in Malaysian Ringgit (MYR); categorized as less than MYR2000 (low), between MYR 2000 and MYR 3999 (middle) and MYR4000 or more (high).

Statistical analyses

Prevalence estimates are given overall, by age and gender. Complex survey analyses were employed, with the two stages of random sampling used as stratification variables. Appropriate sampling weights were adjusted for non-response. Further age and sex adjusted weights were used to produce correct estimations of the Malaysian adult population. Variance estimation was calculated using the Taylor linearization method.

Differences between gender for categorical variables were tested using Pearson's chi square test, adjusted for design effect (*F* statistic). Group differences between males and females for continuous variables were estimated using an adjusted Wald test (*F* statistic). A multivariable logistic regression model was used to determine risk associations between gender, age groups and residence location with individual cardiovascular risk factors. The model was adjusted for confounders determined a priori; race, smoking status, education and income level, and other cardiovascular risk factors. Clustering was defined as having two or more risk factors.

For all analyses, p values less than 0.05 were considered statistically significant. Analyses were performed using PASW Statistics version 18.0 for Windows (SPSS Inc., Chicago, IL,USA) and Stata Statistical Software : Release 11.0 (College Station, TX: Stata Corporation LP).

Results

The sampling strategy identified 37 906 eligible participants 18 years and above. Of those sampled, 1 828 (4.8%) were not available after three visits and 1 400 (3.7%) refused to participate. Of the 34 678 participants available, 34 505 (91%) with demographic variables were included in this study. Mean age was 40.4 years, 55.2% were women and the racial distribution reflects the Malaysian population (Table 1).

Prevalence
Overall, 63% (62, 65%) of the participants had at least one cardiovascular risk factor, 33% (32, 35%) had two or more risk factors and 14% (12, 15%) had three risk factors or more. Of the total population 52% (50, 53%) had manifest metabolic changes with either hypertension, hypercholesterolemia, diabetes mellitus or impaired fasting glucose or any combination of the above. Amongst those centrally obese, 68% (66, 70%) had one or more of these cardiovascular risk factors.

Gender
The lack of education was higher in women compared to men (13.6% versus 5.6%) (Table 1). The prevalence of obesity in women was almost 20% higher than that in men. Clustering of cardiovascular risk factors was more common in women: 36% (35, 38%) of women had two or more cardiovascular risk factors compared to only 30% (28, 33%) of men.

At every age, women were more likely than men to have elevated cardiovascular risk factors. For ages 30 to 44, the adjusted OR for one risk factor was 1.10 (0.91, 1.32) and the adjusted OR for 2 or more risk factors was 1.07 (0.91, 1.32). For ages ages 45 to 54, the adjusted OR for one risk factor was 1.23 (1.02, 1.49) and the adjusted OR for 2 or more risk factors was 1.44 (1.15, 1.8). For ages 55 and above, the adjusted OR for one risk factor was 1.26 (1.12, 1.43) and the adjusted OR for 2 or more risk factors was 2.00 (1.78, 2.25). For ages between 18 and 29 years, the adjusted OR for one risk factor was 1.16 (1.03, 1.30).

Age
Overall, 39% (37, 40%) of those younger than 30 years had at least one cardiovascular risk factor. The prevalence of at least one cardiovascular risk factor increased with age: for ages 30-44, 62% (60, 63%), for ages 45-54, 80% (79, 82%) and for ages 55 years or above, 89% (87, 90) (Table 2).

Urban or rural residence
In both rural and urban locations 63% of the population had one or more cardiovascular risk factors. Compared to urban locations, rural locations did not have a higher clustering of cardiovascular risk factors (adjusted OR 0.96 (0.83, 1.1)).

Discussion
Our study provides the first estimates of cardiovascular risk factor clustering among the adult population in Malaysia, and suggests that the cardiovascular disease epidemic has already begun. Two thirds of the population had at least one cardiovascular risk factor and at least one third had two or more risk factors. There

was a high prevalence of risk factor clustering among the younger adults in both men and women.

Table 1 - Baseline characteristics and prevalence of cardiovascular risk factors of study participants

Variables	Overall	Male	Female	p value
n	34505	15445	19060	
Age	40.4 (0.04)	40.1 (0.05)	40.7 (0.04)	<0.001
Race				0.332
Malay	50.7	50.4	50.9	
Chinese	26.5	26.5	26.6	
Asian Indian	7.7	7.6	7.7	
Others	15.2	15.6	14.8	
Residence				0.002
Urban	61.6	60.4	62.9	
Rural	38.4	39.6	37.1	
Education level				0.000
Tertiary	10.9	11.6	10.1	
Secondary	51.7	54	49.3	
Primary	27.9	28.8	27	
Household income				0.160
<MYR2000	60.9	60.2	61.6	
MYR2000-3999	25.3	25.4	25.1	
≥MYR4000	13.9	14.4	13.3	
Smoking status				<0.001
Current	23.7 (22, 25.4)	45.7 (42.4, 49.0)	1.6 (1.2, 2.2)	
Ever	5.4 (4.8, 6.1)	10.0 (9.0, 11.2)	0.8 (0.6, 1.1)	
Systolic blood pressure (mmHg)	131 (0.7)	133 (0.6)	130 (0.8)	<0.001
Diastolic blood pressure (mmHg)	80 (0.3)	80 (0.2)	80 (0.4)	0.162
Total cholesterol (mmol/l)	4.58 (0.04)	4.5 (0.04)	4.66 (0.04)	<0.001
Waist circumference (cm)	81.4 (0.3)	83.4 (0.5)	79.4 (0.2)	<0.001
BMI (kg/m^2)	24.5 (0.1)	24.2 (0.2)	24.9 (0.1)	<0.001
Central obesity	37.2 (35.4, 39)	28.6 (26.0, 31.4)	45.7 (44.4, 47.0)	<0.001
Hypertension	37.6 (35.6, 39.5)	38.3 (36.2, 40.4)	36.8 (34.7, 39.0)	0.055
Hypercholesterolemia	23.5 (21.4, 25.7)	21.2 (19.1, 23.5)	25.8 (23.6, 28.2)	<0.001
Diabetes	10.7 (9.8, 11.7)	10.8 (9.6, 12.1)	10.6 (9.8, 11.4)	<0.001
Impaired fasting glucose	4.3 (3.7, 4.9)	5.1 (4.4, 5.8)	3.5 (3.0, 4.0)	<0.001
Number of cardiovascular risk factors*				<0.001
0	36.6 (35.3, 37.9)	39.5 (37.5, 41.4)	33.8 (32.4, 35.1)	
1	30.1 (29.4, 30.8)	30.3 (29.4, 31.1)	29.8 (28.9, 30.8)	
2	19.8 (19.2, 20.5)	19.2 (18.2, 20.3)	20.4 (19.4, 21.4)	
3	10.6 (9.6, 11.6)	8.9 (7.8, 10.1)	12.3 (11.3, 13.4)	
4	2.9 (2.6, 3.3)	2.1 (1.8, 2.5)	3.7 (3.3, 4.1)	

BMI, Body Mass Index; * Cardiovascular risk factors are hyperglycaemia (diabetes or impaired fasting glucose), hypertension, hypercholesterolemia and central obesity

Data are % for categorical variables, mean (se) for continuous variables & prevalence (95%CI) for risk factors

P value is for the comparison between men and women, unadjusted.

The implications of our findings are important. Firstly, despite current health care prevention programmes, the burden of cardiovascular risk is on the rise. Compared to the NHMS survey in 1996, the prevalence of hypertension and diabetes increased by 15.5% and 6.3% respectively, and 27% had two or more cardiovascular risk factors in those aged 30 years and older.(11,12) Some may be due to definition changes, as they used a cut-off for diabetes of 7.8 mmol/l and a Western body mass index cut-off for overweight.(13) Elevated cardiovascular risk factors substantially increase the risk of cardiovascular disease and mortality both individually and on a population level.(14,15) A higher risk factor prevalence translates into higher numbers with established cardiovascular disease and events, leading to increased use of healthcare services, reduced labour productivity and economic consequences. These consequences are likely to occur in the very near future.

Secondly, risk factor clustering is alarmingly higher in women than in men. This might be contributed to by increased central obesity, calling for introduction of gender-specific targeted measures to prevent further obesity and to reduce overweight (currently 46% of the population). We know that a reduction in waist circumference by as little as three centimetres produces significant beneficial effects on cardiovascular risk factors (16) leading to risk reduction. Although these results were found in a Caucasian population, they also apply to our population because relations between cardiovascular risk factors and disease are similar for Asians and Caucasian populations.(17)

Thirdly, with 40% of 30 year olds having at least one risk factor and 11% having two risk factors or more, the younger age shift in cardiovascular risk factors clustering paints a dire picture of healthcare consumption if nothing is done to target the young. This is especially relevant for Malaysia given the broad based population structure.

Lastly, our data indicated that clustering is similar in the urban and the rural population. However, current health care facilities and professionals are concentrated in urban areas and better developed states. There is a disparity of primary care facilities by up to four times (2.94 versus 0.73 facilities per 10,000 population) (18) and hospitals up to 6.5 times (0.26 versus 0.04 facilities per 10,000 population).(19) For health care professionals, this disparity can be as great as 17 times (21.08 versus 1.24 doctors per 10,000 population, unpublished data). This imbalance will have to be addressed, as both rural and urban areas need equal attention.

Malaysia's closest neighbouring countries are Thailand and Singapore. Thailand has a higher prevalence of cardiovascular risk factors. Thailand has reported a 44%

prevalence of central obesity, 22% of hypertension, 63% of hypercholesterolemia, 10% of diabetes and 50% of impaired fasting glucose among those 35 years and older.(20) They reported a similarly increased prevalence of obesity among women with 52 % compared to men (19%). However, these findings may be attributed to an older and more aging population structure.(21) Singapore, on the other hand has a lower prevalence of risk factors; hypertension 24%, hypercholesterolemia 18% and diabetes 8%.(22) After the implementation of it's National Healthy Lifestyle Campaign in 1992 a reduction in prevalence of hypertension by four percent, hypercholesterolemia by eight percent and diabetes by two percent was found.(22) Malaysia also began its Healthy Lifestyle Campaign in 1991 (unpublished reports), yet has not seen a decrease in prevalence of cardiovascular risk factors.

On a global scale, Malaysia has a higher prevalence of hypertension than the United States of America (38 versus 30%) (23) , a comparable rate of diabetes (10.7 %) (24), but a lower rate of overweight and obesity (37 versus 52% - Western cut-offs for abdominal obesity is used in the US).(25) Although having a similar rate of hypercholesterolemia (26%), the cut-off value used by the US is higher (6.2mmol/l).(24) Forty five percent of the US population has either hypertension, diabetes or hypercholesterolemia. In comparison to European countries, Malaysia has a higher prevalence of diabetes except for Switzerland (11.2%) and Germany (11.8%).(26) Malaysia has a lower prevalence of hypertension than the average in Europe (44%). (27)

Based on our results, government policy makers and programme planners have to radically modify the healthcare system to enable risk factor prevention in those not already at risk, and to provide optimal primary and secondary preventive measures to those currently at risk. Currently, the national cardiovascular prevention and management policy focuses on environmental, lifestyle and clinical interventions.(6) There is a wealth of evidence suggesting that policy interventions, which achieve population-wide improvements through lifestyle changes, pharmacological treatment of risk factors in primary prevention and application of evidence based treatment in secondary prevention are effective, potentially cost saving and can achieve substantial and rapid reductions in cardiovascular disease.(14,28,29)

When resources are scarce and drastic changes are needed, the approach taken should be the one that can produce swift changes and is most cost effective. Evidence obtained from high income countries has shown that a comprehensive population based prevention strategy that promotes tobacco control and a healthier lifestyle (28,29) results in a rapid decline of cardiovascular disease incidence.(30) In a lower income country, such approaches may not be as successful due to poorer enforcement (31) and possibly lower participations rates.(32) In addition, a recent

study in an emerging economy country such as Argentina on the cost-effectiveness of cardiovascular disease prevention strategies showed that treatment of hypertension and hypercholesterolemia had a much higher disability adjusted life year (DALY) saved than enforced salt reduction in bread and mass media campaigns for tobacco cessation.(33) The incremental cost-effectiveness ratio (ICER) per DALY saved was $2909 for pharmacological treatment of hypertension and $3187 for the mass media campaigns for tobacco cessation. A polypill strategy for high risk populations had an ICER per DALY saved of -$247. This suggests that for Malaysia, a polypill strategy (34), may be an option that needs careful consideration, while awaiting environmental policy changes to be implemented by intergovernmental agencies.(6) Further studies on economic implications of increased cardiovascular risk factor clustering and cost-effectiveness of different prevention strategies are warranted, to help guide the allocation of resources to prevention and treatment strategies.

Limitations

We may have underestimated the diabetes prevelance since we did not use the current WHO guidelines suggesting a two hour postprandial glucose level of an Oral Glucose Tolerance Test (OGTT). Blood pressure measurements were determined using an automated digital monitor that was regularly calibrated. However, the auscultatory method recommended in guidelines was not used.(8) No information was avialable on serum lipids, most likely leading to an underestimation of prevalence of risk factor clustering. Finally as we are unable to estimate population levels on physical activity and dietary habits, it would be difficult to recommend specific actions on these behavioural components.

In conclusion, this study confirms the presence of a cardiovascular epidemic in Malaysia and provides evidence that drastic measures have to be undertaken to safeguard the health of the nation.

NHMS Cohort Study Group

Members of the NHMS Cohort Study group are Adam Bujang, Premaa Supramaniam and Tassha Hilda Adnan.

Table 2 - Prevalence of cardiovascular risk factors, clustering and it's risk association with age and sex

	Males				
Risk factors	**18-29**	**30-44**	**45-54**	**≥ 55**	p for trends
n	4,195	4,831	2,929	3,492	
Prevalence					
Hypertension	19 (16, 22)	30 (28, 33)	51 (48, 54)	70 (67, 72)	<0.001
Hypercholesterolemia	9 (8, 10)	21 (18, 24)	31 (28, 35)	31 (27, 35)	<0.001
Diabetes mellitus	3 (2, 4)	7 (6, 8)	18 (15, 20)	22 (19, 26)	<0.001
Impaired fasting glucose	4 (3, 5)	6 (5, 8)	6 (5, 7)	5 (4, 6)	0.003
Central obesity	17 (15, 19)	29 (25, 33)	37 (34, 41)	39 (36, 41)	<0.001
Number of cardiovascular risk factors					
≥ 1	38 (35, 40)	58 (56, 61)	77 (74, 79)	85 (83, 86)	<0.001
≥ 2 (clustering)	12 (10, 14)	25 (23, 28)	44 (40, 48)	54 (50, 58)	<0.001
Association					
Adjusted					
Hypertension	1.00	1.43 (1.24, 1.65)	2.77 (2.36, 3.25)	5.79 (4.9, 6.83)	<0.001
Hypercholesterolemia	1.00	2.49 (2.14, 2.9)	3.97 (3.43, 4.6)	4.03 (3.19, 5.09)	<0.001
Diabetes mellitus	1.00	2.08 (1.66, 2.61)	5.18 (3.8, 7.07)	6.73 (4.73, 9.58)	<0.001
Impaired fasting glucose	1.00	1.15 (0.93, 1.42)	1.19 (0.87, 1.62)	1.16 (0.83, 1.64)	0.374
Central obesity	1.00	1.59 (1.41, 1.8)	1.89 (1.65, 2.16)	2.16 (1.9, 2.47)	<0.001
Number of cardiovascular risk factors*					
1	1.00	1.94 (1.78, 2.11)	3.44 (3.05, 3.88)	4.9 (4.38, 5.49)	<0.001
≥ 2 (clustering)	1.00	3.39 (2.89, 3.99)	10.71 (8.81, 13.02)	21.51 (18.14, 25.5)	<0.001

	Females				
Risk factors	**18-29**	**30-44**	**45-54**	**≥ 55**	p for trends
n	5,128	6,272	3,687	3,973	
Prevalence					
Hypertension	9 (8, 11)	28 (25, 31)	54 (51, 57)	75 (71, 77)	<0.001
Hypercholesterolemia	12 (10, 14)	21 (19, 24)	34 (32, 37)	45 (41, 49)	<0.001
Diabetes mellitus	2 (1, 2)	7 (6, 8)	16 (15, 18)	24 (22, 27)	<0.001
Impaired fasting glucose	2 (1, 3)	3 (3, 4)	4 (4, 5)	5 (4, 6)	<0.001
Central obesity	27 (25, 28)	48 (46, 50)	60 (57, 62)	58 (56, 61)	<0.001
Number of cardiovascular risk factors					
≥ 1	40 (38, 42)	65 (63, 67)	84 (82, 85)	92 (90, 93)	<0.001
≥ 2 (clustering)	10 (9, 11)	30 (28, 32)	54 (51, 58)	69 (66, 72)	<0.001
Association					
Adjusted					
Hypertension	1.00	2.66 (2.31, 3.05)	6.29 (5.55, 7.14)	13.8 (12.19, 15.62)	<0.001
Hypercholesterolemia	1.00	1.67 (1.46, 1.92)	2.88 (2.45, 3.39)	4.43 (3.75, 5.23)	<0.001
Diabetes mellitus	1.00	2.68 (2.1, 3.42)	5.47 (4.18, 7.16)	8.25 (6.05, 11.24)	<0.001
Impaired fasting glucose	1.00	1.46 (1.13, 1.88)	2 (1.4, 2.87)	2.82 (1.87, 4.25)	<0.001
Central obesity	1.00	1.95 (1.74, 2.19)	2.43 (2.09, 2.83)	2.21 (1.84, 2.66)	<0.001
Number of cardiovascular risk factors*					
1	1.00	2.05 (1.85, 2.26)	3.5 (2.99, 4.1)	5.26 (4.47, 6.2)	<0.001
≥ 2 (clustering)	1.00	5.17 (4.5, 5.93)	18.27 (15.19, 21.97)	41.85 (34.76, 50.38)	<0.001

* Cardiovascular risk factors are hyperglycaemia (diabetes or impaired fasting glucose), hypertension, hypercholesterolemia and central obesity
Data are prevalence (95% confidence interval) and OR (95% CI) for associations

Adjusted for: smoking, race, income, education level, residence (urban/rural) & other cardiovascular risk factors

*Adjusted for: smoking, race, income, education level & residence (urban/rural)

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Chapter 2.2

Geographical variation of cardiovascular risk factors in Malaysia

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Abstract

The purpose of this study was to describe differences in cardiovascular risk factor prevalences and clustering patterns among the states and federal territories of Malaysia. Risk factors considered were abdominal obesity, diabetes, hypertension, hypercholesterolemia and smoking. Using data from the third National Health and Morbidity Survey (NMHS III) in 2006, we estimated the states and federal territories risk factor prevalences and clustering patterns to map the cardiovascular burden distribution in Malaysia. There was a clear geographical variation in the distribution of the individual risk factors as well as in its clustering with remarkable impact seen in Peninsular Malaysia. Perlis, Kedah and Kelantan were the most affected states overall.

Introduction

Cardiovascular disease (CVD) is the number one cause of death worldwide. Of 17.1 million deaths of CVD reported in 2004, 82% were from low and middle income countries.(1) In Malaysia, the National Health and Morbidity Surveys (NHMS) report alarming increases in traditional cardiovascular risk factors prevalences. National prevalences of hypertension and diabetes in adults >30 years increased considerably from 29.9% to 42.6% and 8.3% to 14.9% respectively in a 10 year period.(2) A particularly sharp increase was seen in the prevalence of obesity which rose from 4.4% to 14% in the same time period. This shows more and more Malaysians are at risk of acquiring cardiovascular disease.

Presence of multiple risk factors in one patient ie clustering of risk factors has been associated with increased risk in heart related diseases.(3,4) In the United States, the Behavioural Risk Factor Surveillance System (BRFSS) for the year 1994 reported that 18.0% of adults had at least two risk factors.(5) A higher proportion of clustering was reported in China; 45.9% of adults aged 35-74 years.(6) In 1996, Malaysia had 27.0% of cardiovascular risk factor clusters among adults aged 30 and above in one national study.(7) Recent reports from two single centre studies showed higher proportions of risk factor clustering in Malaysia; up to 93%.(8,9) Though this might not be representative on a national level, it suggests an increased rate of risk factor clustering. With the escalating prevalence of individual risk factors, this amplifies the cardiovascular disease burden in Malaysia.

Years of research demonstrated that cardiovascular disease burden is not distributed equally. Many reports show different risk profiles exist for sub-populations with demographic variations.(6,10-12) Geographically, evident variations in cardiovascular risk profiles were reported among provinces in Canada (10), among women in cities of United States (13) and between southern and northern populations of China.(6) In Malaysia, the cardiovascular risk profile variation and distribution is not well-reported. Many of the reports were done at the district, division (8,14) or state level.(15,16) Hence, they provide limited information in understanding the overall picture of cardiovascular disease burden in Malaysia.

It is important to determine the geographical variation in cardiovascular risk factor profile and its clustering in Malaysia. Such information can be used by programme planners to identify high risk regions or states that require more resources or interventions to help reduce the burden of these risk factors.(13) The goal of this study is to describe the geographical variation of the following modifiable risk factors: hypertension, diabetes, hypercholesterolemia, abdominal obesity and smoking, and its clustering in Malaysia.

Materials and Methods

The NHMS III is a household survey conducted by the Institute of Public Health, Ministry of Health Malaysia in the year 2006. This survey involved a structured questionnaire that covered general household, socio-demographic, load of illnesses, health utilisation, cost and specific health problems. Included in the protocol also were general anthropometric measurements, blood pressure, and capillary blood measurements. All measurements were conducted by trained nurses or officers. Written informed consent forms were signed by the participants before the questionnaire was administered. NHMS III employed a multi-stage stratified sampling design proportionate to the population size throughout all states in Malaysia. A detailed account of the procedures can be found elsewhere.(2)

States included were Perlis, Kedah, Kelantan, Melaka, Johor, Negeri Sembilan, Pulau Pinang, Perak, Pahang, Terengganu, Selangor, Federal Territory of Kuala Lumpur from the Peninsular and Sabah, Sarawak and Federal Territories of Labuan from East Malaysia. Where relevant, geographical variation in the Peninsular was described according to regional boundaries; West Coast (Perlis, Kedah, Pulau Pinang, Perak, Negeri Sembilan, Melaka, Selangor and Kuala Lumpur), East Coast (Kelantan, Terengganu and Pahang) and South (Johor).

Cardiovascular Risk Factors

Cardiovascular risk factors included in this study were hypertension, diabetes, hypercholesterolemia, abdominal obesity and smoking. Clustering was defined as co-existence of at least two cardiovascular risk factors. Relevant information for respondents aged 20 years and above was abstracted out from the NHMS III dataset for this study. The main outcomes measured were prevalence and clustering of cardiovascular risk factors among the various states.

Hypertension

Systolic and diastolic blood pressures were measured using Omron Digital Automatic Blood Pressure Monitor Model HEM-907. Two readings were taken for both diastolic and systolic blood pressure, 15 minutes apart. The average was used as recorded blood pressure values. Respondents were considered hypertensive if their average reading was ≥140 mmHg for systolic and/or ≥90 mmHg for diastolic blood pressure (17), or were on blood pressure lowering drugs, or were self reported to be hypertensive.

Diabetes

Blood glucose was checked by the finger prick method after 8 to 10 hours overnight fast using the Accutrend GC machine. Only respondents who claimed to be non diabetics were tested for their glucose level after obtaining written consent.

Diabetics were either respondents who had been diagnosed with diabetes in the past, or were taking anti-diabetic medication or had their fasting blood glucose level higher than 6.1 mmol/l.(18)

Hypercholesterolemia
Blood lipid was measured with Accutrend GC machine in all respondents who agreed to be tested. Respondents were considered hypercholesterolemia if their blood total cholesterol was ≥5.2 mmol/l (19), or were previously diagnosed with hypercholesterolemic by a medical doctor or paramedic.

Abdominal Obesity
Waist circumference was measured at the midpoint between the inferior margin of the last rib and the crest of the ilium in all respondents. Measurements were done to the nearest 0.1 centimetre using a Seca 200 measuring tape following a verbal permission. Cut-off points of 80 centimetres for females and 90 centimetres for males were used to determined abdominal obesity as recommended by the International Diabetes Foundation (IDF).(20)

Smoking
Current smokers were based on the CDC definition; participants who reported to have smoked 100 or more cigarettes in a lifetime and smoked daily or some days in the past one month.

Statistical Analysis
Analysis was done using STATA 10 and accounted for the complex sampling design. Survey Sample Analysis was used to obtain means, proportions and 95% Confidence Intervals (CI) for all risk factors reported in this paper. Both crude and adjusted prevalences were presented. Prevalences were adjusted for age and gender using the Malaysian 2006 census to obtain the weights.

Crude prevalences were mapped to illustrate the cardiovascular risk factor burden distribution in Malaysia. Maps were created using Epi Map interface in Epi Info (TM) 3.5.1 software. Choropleth maps were generated for each risk factor based on state boundaries, and risk factor prevalences were divided into tertiles, each representing the first, second and third 33.3% of the prevalence values in ascending order. The tertiles were different for each risk factor, and were referred to as low, medium and high categories respectively. For hypertension, prevalence of 0 to 34.7%, 34.8 to 42.2% and above 42.2% were referred as low, medium and high categories. In case of diabetes, low, medium and high categories were 0 to 8.7%, 8.8 to 12.3% and 12.4 and above respectively. Abdominal obesity prevalence of 0 to 38.8%, 38.9 to 42.8% and above 42.8% were described as low, medium and high

categories. For hypercholesterolemia 0 to 21.4%, 21.5 to 31.5% and above 31.5% were low, medium and high categories respectively. Lastly, for smoking, prevalence of 0 to 21.3%, 21.4 to 26.7% and above 26.7% were referred to as low, medium and high categories.

Results

Study Sample

Overall, there were 32 796 eligible adults aged above 20 years in the NHMS III survey. Out of these, 32 789 records were obtained for diabetes, 32 172 for smoking, 32 719 for hypertension, and 32 796 for hypercholesterolemia and abdominal obesity. Baseline characteristics of the study sample are described in Table I.

National prevalences of hypertension, diabetes, hypercholesterolemia, smoking and abdominal obesity for adults aged 20 years and above were 39.6%, 11.9%, 23.7%, 22.0 % and 40.9%. Nationally, risk factor clusters were seen in 43.2% of our samples who had at least two risk factors of the five considered. Additionally, 19.1% had clustering of the drug modifiable risk factors; hypertension, diabetes and hypercholesterolemia.

Geographical distribution of cardiovascular risk factors

Prevalence of risk factors varied remarkably between states (Table II). Each risk factor had a different distribution over the 13 states and two federal territories of Malaysia. Overall, Peninsular Malaysia showed greater risk factor prevalences compared to East Malaysia.

The prevalence of hypertension ranged from 27.2% in Kuala Lumpur to 49.8% in Perlis. In addition to its high prevalence, hypertension distribution also displayed an alarming pattern as majority states were either in the high or medium category (Figure 1-A). Overall, only Kuala Lumpur and Selangor of the Malaysian Peninsular had low prevalences of hypertension. Diabetes, with lower prevalence of 5.1% in Sabah to 15.9% in N. Sembilan showed a similar high overall distribution (Figure 1-B). Geographically, for hypertension and diabetes, states of high prevalence highly overlapped. These include majority of states in the West Coast. Kuala Lumpur and Selangor however, had high prevalence of diabetes but low prevalence of hypertension. The East Coast states were less affected by both risk factors.

Smoking, hypercholesterolemia and abdominal obesity demonstrated less severe overall burden. However, the crude prevalences of these risk factors were high. Abdominal obesity especially, showed high proportions ranged from 34.9% in

Table I: Baseline characteristics of study respondents of the third National Health and Morbidity Survey (2006).

Characteristic	Mean
Age (year)[a]	42.88 (0.50)
Gender [b]	
Male	44.6 (43.7,45.4)
Female	55.4 (54.6,56.3)
Ethnicity [b]	
Malay	54.7 (45.6,63.6)
Chinese	20.6 (16.4,25.5)
Indian	8.3 (5.4,12.6)
Other Bumiputera	11.4 (4.6,25.3)
Others	5.1 (3.5, 7.3)
Residence [b]	
Urban	59.4 (45.1,72.4)
Rural	40.6 (27.6,54.9)
Education Level [b]	
None	11.4 (8.3,14.4)
Primary	29.9 (27.2,32.6)
Secondary	48.5 (46.0,51.0)
Tertiary	10.3 (6.8,13.7)
Waist Circumference [a]	82.12 (0.30)
Male	84.19 (0.40)
Female	80.45 (0.27)
Blood Pressure (mmHg)[a]	
Systolic	133.02 (0.87)
Diastolic	80.95 (0.31)
Total Cholesterol [a]	4.64 (0.05)

[a] Continuous variable reported as means and standard errors
[b] Categorical variable reported as means and 95% confidence interval

Sabah to 46.8% in Melaka. Especially affected by abdominal obesity were Kuala Lumpur, Selangor, Melaka and N. Sembilan and Perlis from the West Coast (Figure 1-C). Hypercholesterolemia prevalence arrayed in a wide continuum of 11.3% in Sabah to 41.7% in Perlis. High prevalence states were Perlis, Kedah and Kelantan and Terengganu from the East Coast region (Figure 1-D). The rest of the Peninsular were in the medium category. For smoking, prevalences were relatively low, ranging from 15.9% in Kuala Lumpur to 32.2% in Perlis. The East Coast region and Perlis showed high prevalence of smoking (Figure 1-E). Perlis as an individual state was highly prevalent in all five risk factors.

Table II: Prevalence of cardiovascular risk factors in 15 states and federal territories of Malaysia

States	% (95% CI) Prevalence				
	Hypertension	Diabetes	Abdominal Obesity	Hypercholesterolemia	Smoking
Crude					
Johor	37.0 (29.4,45.3)	11.7 (10.2,13.5)	39.7 (39.5,39.9)	24.6(23.2,25.9)	20.9 (20.0,21.8)
Kedah	47.0 (42.3,51.8)	14.3 (13.5,15.1)	41.2 (38.5,44.0)	31.9 (29.4,34.4)	26.1 (20.8,32.3)
Kelantan	45.6 (43.2,48.0)	12.2 (9.0,16.4)	36.6 (31.4,42.0)	32.8 (32.2,33.3)	28.0 (24.1,32.2)
Melaka	46.7 (40.1,53.4)	15.4(13.3,17.7)	46.8 (40.9,52.7)	28.1 (27.8,28.5)	20.0 (18.8,21.3)
N.Sembilan	43.5 (36.6,50.8)	15.9 (15.4,16.3)	44.4 (42.4,46.4)	25.6 (25.0,26.2)	23.8 (17.7,31.1)
Pahang	41.7 (34.6,49.1)	12.6 (12.4,12.8)	40.5 (39.2,41.8)	27.5 (23.8,31.5)	27.4 (21.7,34.0)
Pulau Pinang	43.5 (39.9,47.1)	15.2 (15.1,15.4)	42.0 (39.7,44.3)	22.0 (21.9,22.2)	18.6 (16.6,21.0)
Perak	47.4 (42.3,52.5)	13.1 (12.0,14.3)	40.7 (39.5,42.0)	26.9 (25.4,28.5)	21.4 (16.4,27.5)
Perlis	49.8 (46.1,53.6)	14.3 (12.5,16.3)	45.7 (40.8,50.7)	41.7 (40.3,43.2)	32.2 (30.9,33.5)
Selangor	34.0 (32.2,35.8)	12.5 (12.4,12.7)	44.3 (43.2,45.4)	23.0 (22.1,23.9)	18.3 (17.2,19.5)
Terengganu	38.5 (33.7,43.6)	11.6 (10.1,13.4)	41.6 (36.9,46.3)	32.5 (31.3,33.7)	27.3 (24.0,30.7)
Sabah	36.8 (31.9,41.9)	5.1 (3.7, 7.1)	34.9 (29.3,41.1)	11.3 (8.2,15.4)	24.5 (20.4,29.0)
Sarawak	40.3 (39.5,41.0)	10.2 (7.8,13.2)	40.2 (35.9,44.6)	19.7 (19.1,20.3)	19.7 (16.3,23.6)
Kuala Lumpur	27.2 (27.2,27.2)	13.0 (13.0,13.0)	43.8 (43.8,43.8)	18.5 (18.5,18.5)	15.9(15.9,15.9)
Labuan	37.7 (37.6,37.8)	8.3 (8.2, 8.4)	39.9 (35.5,45.1)	19.0 (12.5,27.8)	22.0 (20.1,24.1)

CI = Confidence Interval

* Crude prevalence was adjusted for age and sex with reference to 2006 Malaysian census.

Adjusted*					
Johor	31.8 (28.5,35.2)	9.9 (9.4,10.5)	36.5 (34.9,38.1)	22.5 (22.0,23.0)	25.1 (24.0,26.2)
Kedah	38.9 (36.5,41.4)	11.2 (10.5,12.0)	37.0 (34.7,39.3)	28.2 (26.6,29.8)	30.4 (26.3,34.9)
Kelantan	37.9 (35.4,40.6)	9.9 (7.7,12.7)	32.7 (28.4,37.4)	29.8(29.8,29.9)	31.8 (28.3,35.4)
Melaka	40.1 (36.4,44.0)	12.5(9.7,16.0)	42.7 (37.1,48.6)	25.1 (24.2,26.0)	25.5 (23.3,27.8)
N.Sembilan	35.7 (31.4,40.2)	12.8 (11.2,14.5)	39.1 (37.0,41.3)	22.5 (21.8,23.2)	28.3 (22.2,35.4)
Pahang	36.9 (34.8,39.0)	11.0 (9.7,12.4)	37.4 (35.0,39.9)	25.8 (23.7,28.1)	29.2 (23.8,35.2)
Pulau Pinang	38.2 (34.6,41.9)	12.5 (12.3,12.6)	38.4 (36.4,40.5)	19.5 (19.2,19.9)	22.5 (19.8,25.5)
Perak	37.2 (33.1,41.5)	9.8 (8.8,10.8)	34.3 (32.5,36.2)	22.8 (22.7,22.8)	25.3 (21.5,29.6)
Perlis	41.8 (40.7,42.9)	11.8 (11.6,12.0)	42.4 (38.1,46.8)	38.8 (35.3,42.5)	35.2 (35.0,35.5)
Selangor	32.2 (30.6,33.9)	11.5 (11.4,11.7)	41.8 (40.5,43.0)	21.7 (20.9,22.5)	22.4 (21.7,23.1)
Terengganu	33.6 (32.1,35.1)	9.9 (8.0,12.2)	38.1 (32.8,43.7)	29.4 (29.2,29.5)	30.6 (27.7,33.7)
Sabah	37.5 (33.4,41.8)	5.2 (3.6, 7.6)	33.9 (28.7,39.6)	11.4 (8.3,15.5)	28.1 (25.8,30.4)
Sarawak	35.6 (32.1,39.2)	9.0 (6.2,13.0)	37.3 (32.4,42.5)	18.0 (17.8,18.1)	23.5 (19.9,27.6)
Kuala Lumpur	26.8(26.8,26.8)	12.9 (12.9,12.9)	42.3 (42.3,42.3)	17.6 (17.6,17.6)	18.2 (18.2,18.2)
Labuan	39.6 (39.6,39.6)	8.4 (7.2, 9.7)	40.5 (36.2,45.0)	19.3 (12.9,27.7)	23.2 (21.3,25.2)

CI = Confidence Interval

* Crude prevalence was adjusted for age and sex with reference to 2006 Malaysian census.

Table III: Prevalence of cardiovascular risk factor clustering in 15 states and federal territories of Malaysia

States	% (95% CI‡) Prevalence		
	RF§ = 0	RF§ =1	RF§ ≥2
Crude			
Johor	24.7 (21.7,28.0)	34.7 (33.4,36.0)	40.6 (36.2,45.1)
Kedah	18.9 (17.0,21.1)	30.0 (28.7,31.4)	51.1 (47.7,54.4)
Kelantan	18.9 (17.7,20.1)	32.3 (30.1,34.5)	48.9 (47.9,49.8)
Melaka	20.0 (14.9,26.4)	29.9 (28.9,30.9)	50.1 (45.4,54.9)
N.Sembilan	20.6 (17.3,24.4)	30.5 (29.6,31.5)	48.9 (44.4,53.4)
Pahang	21.2 (15.8,27.9)	32.9 (32.5,33.3)	45.9 (39.5,52.3)
Pulau Pinang	24.4 (21.8,27.2)	31.8 (30.8,32.8)	43.8 (40.1,47.5)
Perak	20.6 (17.0,24.8)	32.5 (32.0,32.9)	46.9 (43.5,50.4)
Perlis	13.5 (12.7,14.8)	26.4 (24.8,28.1)	60.1 (59.3,60.8)
Selangor	27.0 (26.2,27.9)	33.3 (32.8,33.7)	39.7 (39.3,40.2)
Terengganu	19.8 (18.2,21.5)	34.4 (32.9,36.0)	45.8 (42.6,49.0)
Sabah	29.9 (28.7,31.1)	38.2 (36.1,40.4)	31.9 (30.9,32.9)
Sarawak	24.6 (23.4,25.8)	36.1 (34.0,38.3)	39.3 (38.4,40.3)
Kuala Lumpur	30.7 (30.7,30.7)	35.3 (35.3,35.3)	34.0 (34.0,34.0)
Labuan	25.4 (23.7,27.3)	37.8 (35.5,40.1)	36.8 (36.3,37.3)
Adjusted*			
Johor	26.6 (25.6,27.5)	36.5 (36.4,36.7)	36.9 (36.2,37.7)
Kedah	22.6 (21.4,23.8)	32.4 (32.1,32.8)	45.0 (43.5,46.6)
Kelantan	21.5 (20.4,22.7)	35.5 (34.1,36.9)	43.0 (42.8,43.2)
Melaka	22.0 (18.2,26.4)	32.7 (31.2,34.3)	45.2 (42.7,47.8)
N.Sembilan	24.1 (21.1,27.2)	33.6 (32.9,34.3)	42.4 (40.1,44.7)
Pahang	23.5 (20.4,27.0)	34.6 (33.4,35.8)	41.9 (39.8,44.1)
Pulau Pinang	26.9 (23.8,30.4)	33.6 (33.5,33.7)	39.5 (36.2,43.0)
Perak	25.8 (23.6,28.2)	36.0 (35.7,36.2)	38.2 (36.2,40.3)
Perlis	16.2 (15.0,17.5)	29.9 (27.9,31.9)	54.0 (50.7,57.2)
Selangor	27.3 (26.6,28.1)	34.1 (33.4,34.7)	38.6 (38.6,38.7)
Terengganu	21.5 (21.3,21.8)	37.1 (36.6,37.7)	41.4 (41.1,41.7)
Sabah	27.7 (27.4,27.9)	39.0 (37.2,40.9)	33.3 (31.7,35.0)
Sarawak	26.5 (25.3,27.6)	37.3 (34.9,39.6)	36.3 (32.9,39.9)
Kuala Lumpur	30.9 (30.9,30.9)	35.4 (35.4,35.4)	33.7 (33.7,33.7)
Labuan	23.8 (21.1,26.8)	37.9 (35.3,40.6)	38.3 (38.1,38.5)

‡CI = Confidence Interval
§RF = any of Hypertension, Hypercholesterolemia, Diabetes, Abdominal Obesity and Smoking.
* Crude prevalence was adjusted for age and sex with reference to 2006 Malaysian census.

After adjusting for age and sex, a general reduction by 2-5% for prevalences were observed in all risk factors except smoking. Instead, smoking prevalences increased for majority of the states by 1-5% (Table II, lower panel).

Geographical variation in cardiovascular risk factor clusters

The prevalence of having at least one risk factor was high among the respondents. About 69% in Kuala Lumpur to 87% in Perlis had at least one risk factor; smoking, diabetes, hypertension, hypercholesterolemia or abdominal obesity (Table III).

Cardiovascular risk factor clusters were consistently seen in all states and federal territories. Again, the Peninsular showed higher overall prevalence of clustering. The prevalences varied across the states ranging from the lowest of 31.9 % in Sabah to the highest of 60.1% in Perlis. Of all 15 states and federal territories considered, Perlis (60.1%) and Kedah (51.1%) had high prevalence of cardiovascular risk factor clusters (Figure 2). Melaka was in the medium category, but had a prevalence of 50.1% that was at the border of high and medium category. Adjusting for age and sex reduced the prevalence of clusters by 1-9%.

Geographical variation in drug-modifiable risk factors

Drug modifiable risk factors were a combination of diabetes, hypertension or hypercholesterolemia. High proportions, ranging from 32.2% in Perlis to 70.4% in Kuala Lumpur had at least diabetes, hypertension or hypercholesterolemia (Table IV).

The Peninsular showed greater prevalence of hypertension, hypercholesterolemia or diabetes cluster overall. Perlis led by 32.2%, followed by Kedah, Kelantan and Melaka (Figure 3). Lowest prevalence was seen in Sabah at 8.9%. It is interesting to note that Melaka and Kelantan were highly prevalent in hypertension, hypercholesterolemia or diabetes, but not for all five risk factor clustering (Figure 2 and 3).

Among all states, Melaka had the highest prevalence of having all three drug-modifiable risk factors at 4.8%, followed by Terengganu 4.2%, Kelantan 4.0%, Kedah and Perak 3.9%. Adjusting for age and sex reduced the drug-modifiable cluster prevalence by 1-9%.

Discussion

Results from our study illustrate a worrying pattern of cardiovascular risk factor distribution at the national, regional and state levels. The Malaysian Peninsular is highly burdened by risk factor clustering, driven largely by drug-modifiable risk factors. Considering only the high prevalence states; at least one-fifth of the Peninsular population need social, lifestyle or medical interventions to control their cardiovascular risk factors. Moreover, this high burden was mainly seen in the poorer states of the Peninsular, including Perlis, Kedah and Kelantan.

Table IV: Prevalence of diabetes, hypertension or hypercholesterolemia clustering in 15 states and federal territories of Malaysia

States	% (95% CI‡) Prevalence		
	RF§ = 0	RF§ =1	RF§≥2
Crude			
Johor	47.2 (41.5,53.0)	35.0 (33.2,36.8)	17.8 (14.2,22.2)
Kedah	37.6 (35.4,39.9)	35.5 (34.5,36.5)	26.9 (23.8,30.3)
Kelantan	38.3 (37.0,39.7)	36.7 (33.8,39.8)	25.0 (23.4,26.6)
Melaka	39.9 (35.4,44.6)	34.7 (30.3,39.4)	25.4 (25.4,25.4)
N.Sembilan	41.4 (36.2,46.7)	35.9 (33.2,38.7)	22.7 (20.4,25.3)
Pahang	43.2 (36.7,50.0)	35.1 (32.1,38.2)	21.7 (18.3,25.6)
Pulau Pinang	43.6 (41.7,45.5)	35.0 (34.3,35.6)	21.5 (20.2,22.8)
Perak	39.9 (34.8,45.3)	36.7 (32.2,41.5)	23.4 (22.8,24.1)
Perlis	29.6 (26.0,33.4)	38.2 (28.4,49.1)	32.2 (25.8,39.4)
Selangor	50.5 (48.5,52.5)	32.1 (30.9,33.4)	17.4 (16.6,18.1)
Terengganu	44.0 (40.0,48.1)	33.4 (31.1,35.9)	22.6 (20.9,24.3)
Sabah	56.7 (54.6,58.7)	34.4 (30.7,38.4)	8.9 (7.2,10.9)
Sarawak	47.3 (46.9,47.7)	37.1 (37.1,37.2)	15.6 (15.2,15.9)
Kuala Lumpur	56.8 (56.8,56.8)	29.9 (29.9,29.9)	13.3 (13.3,13.3)
Labuan	51.8 (47.4,56.2)	32.8 (30.8,34.8)	15.4 (13.2,18.0)
Adjusted*			
Johor	52.3 (50.7,53.9)	33.3 (32.8,35.1)	14.4 (13.3,15.5)
Kedah	45.3 (44.7,46.0)	33.9 (32.8,35.1)	20.7 (19.0,22.6)
Kelantan	45.4 (43.6,47.1)	34.7 (32.4,37.0)	20.0 (19.5,20.5)
Melaka	46.2 (43.9,48.5)	33.4 (29.6,37.4)	20.4 (18.8,22.1)
N.Sembilan	49.2 (46.4,52.0)	33.3 (31.8,34.9)	17.5 (16.3,18.8)
Pahang	47.5 (45.5,49.6)	33.9 (32.2,35.7)	18.6 (18.2,18.9)
Pulau Pinang	45.0 (47.3,50.6)	34.1 (33.6,34.5)	16.9 (15.8,18.2)
Perak	49.6 (45.6,53.5)	33.9 (29.8,38.2)	16.6 (16.3,16.9)
Perlis	35.1 (27.4,43.7)	38.9 (29.3,49.4)	26.0 (24.1,28.0)
Selangor	52.7 (50.8,54.5)	31.5 (30.2,32.7)	15.9 (15.3,16.5)
Terengganu	49.2 (48.2,50.2)	32.1 (30.8,33.4)	18.7 (18.4,19.0)
Sabah	55.9 (54.6,57.3)	35.0 (31.6,38.5)	09.1 (07.2,11.5)
Sarawak	52.1 (47.7,56.4)	34.8 (32.3,37.4)	13.1 (11.4,15.1)
Kuala Lumpur	57.6 (57.6,57.6)	29.6 (29.6,29.6)	12.9 (12.9,12.9)
Labuan	49.9 (45.2,54.6)	34.5 (33.0,36.0)	15.7 (12.7,19.1)

‡CI = Confidence Interval
§RF = any of Hypertension, Hypercholesterolemia, Diabetes.
* Crude prevalence was adjusted for age and sex with reference to 2006 Malaysian census.

Our results suggest that cardiovascular risk factor clustering is very common. Concerted efforts of the policy makers, public health professionals and clinicians are needed to cope with this health burden. Prevention, detection and treatment of cardiovascular risk factor clustering should be an important component of the national strategy. National strategic health planning should also consider the overall higher cardiovascular risk factor burden in the Peninsular, and account for the higher risks seen in the poorer states. This is essential because the prevalence of clustering is high and has increased. In 1996, 27% of adults aged 30 and above had at least two risk factors of obesity, hypertension, diabetes or hypercholesterolemia.(7) The higher prevalence of clusters seen in our younger sample makes it necessary to address this issue to reduce the future burden of CVD nationally.

Additionally, allocation of healthcare resources should be fully utilised to cater to the communities' needs. As such, institution of public health measures in accordance to the demand is an important aspect. From our study, by the burden of risk factors, Perlis, Kedah, Kelantan and Melaka appear to be the most in need compared to other states. Previously, the EUROASPIRE II study showed similar geographical variation in burden distribution and attributed it to differential access of the communities to comprehensive prevention and treatment programmes.(21) It may be likely that these four states are facing similar issues. Hence, improved public health strategies that tailor to the needs would improve the populations of Perlis, Kedah, Kelantan and Melaka's access to better prevention and treatment programmes.

Maximum support should be given to primary prevention effort at all levels. This is important as effective prevention programmes can potentially reduce the future burden of intensive and expensive pharmacotherapies for hypertension, diabetes and hypercholesterolemia in the population.(22) Emphasis on risk factor screening as a public health strategy is important, because at least half of the hypertensive and hypercholesterolemic participants in NHMS III were not aware of their diagnosis.(2) Consequently, accessibility to early screening in the four states should be evaluated and improved if found lacking. In addition, effective behavioural preventive strategies should be established. Interventions of healthy lifestyle, diet and exercise have shown improved coronary heart disease risk and reduced incidence rate of diabetes.(23,24) Involvement of communities' institutions and agencies at the district and state level are important in the implementation of these strategies. Their participation will allow prevention strategies to be tailored to specific community needs. Besides, it facilitates community wide behavioural change.(22) Encouraging results have been described with involvement of religious organizations (25), schools (26) and worksite (27) in such intervention programmes.

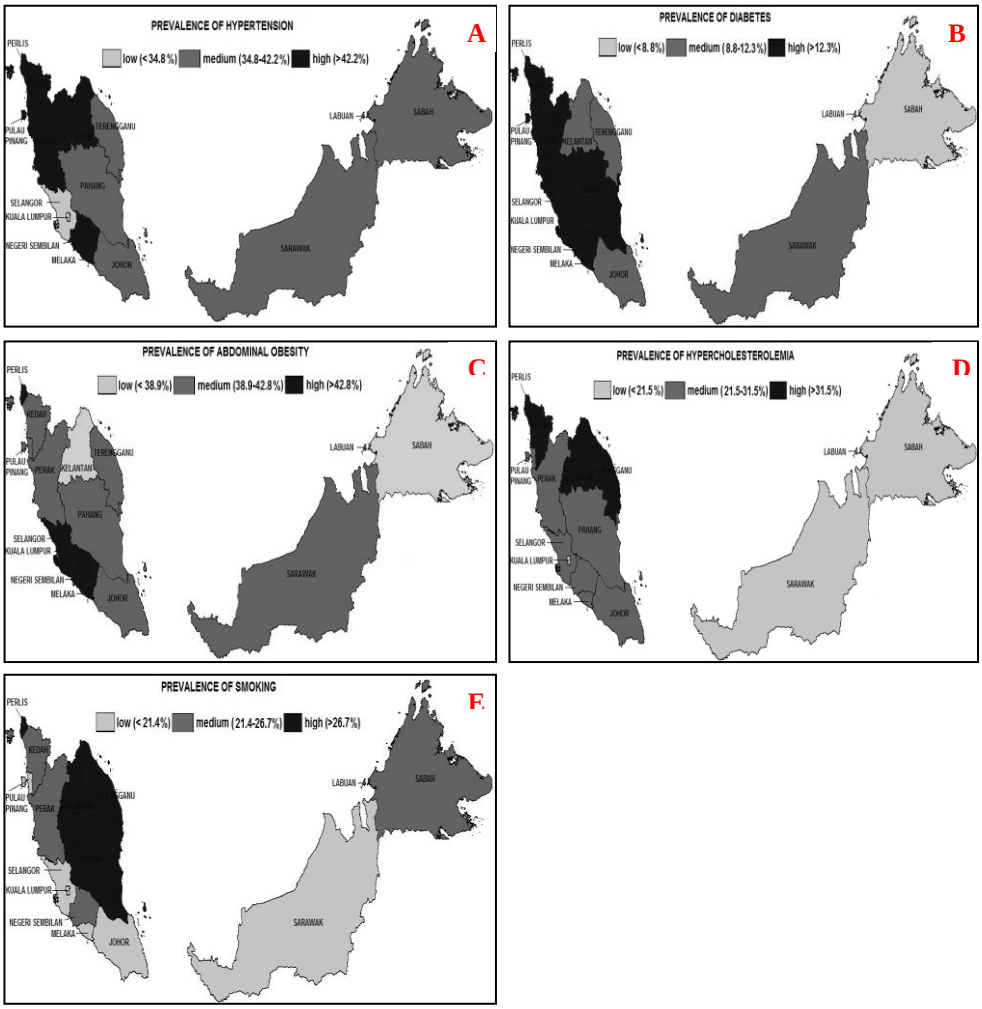

Figure 1: Geographical distribution of cardiovascular risk factors in states and federal territories of Malaysia.

Limitations of this study need mentioning. Firstly, it should be considered that results reported here may not strictly represent each state's performance as only general Malaysian age and sex weight were used for standardization, not each state-specific age and sex weight. Secondly, measurements of blood pressure, and glucose and cholesterol levels were captured in one day. No measures were taken to ensure reading consistency after the one day period. In this study, glucose level was measured in respondents following an instruction of fasting 8-10 hours. However, it cannot be guaranteed all respondents adhered to the instructions given.

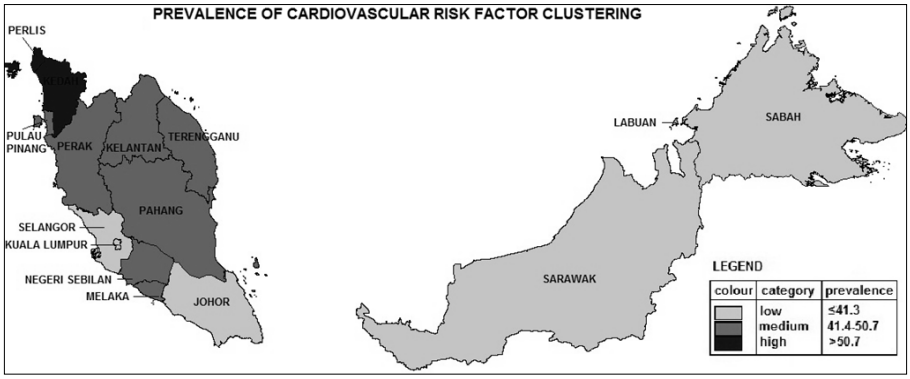

Figure 2: Geographical distribution of cardiovascular risk factor clusters in states and federal territories of Malaysia.

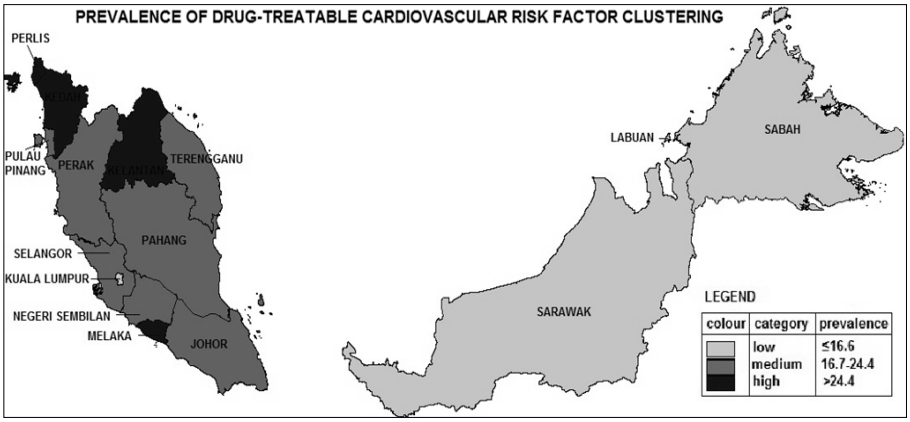

Figure 3: Geographical distribution of diabetes, hypertension or hypercholesterolemia clusters in states and federal territories of Malaysia.

In conclusion, this study provides a glimpse of the geographical mapping of cardiovascular risk factor burden nationally, conferred by the five risk factors mentioned. It shows that variation in cardiovascular risk factor distribution exists among the states and federal territories of Malaysia. Drastic measures at policy, community and clinical levels should be taken to address the rising burden seen in the country.

NHMS Cohort Study group

Members of the NHMS Cohort study group are Gurpreet Kaur, Tee Guat Hiong, Kee Chee Chiong, Lim Chiao Mei, Adam Bujang, Premaa Supramaniam and Tassha Hilda Adnan.

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Chapter 3

Consequences

Chapter 3.1

An Asian Validation of the TIMI risk score for ST-Segment Elevation Myocardial Infarction

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Abstract

Background

Risk stratification in ST-elevation myocardial infarction (STEMI) is important, such that the most resource intensive strategy is used to achieve the greatest clinical benefit. This is essential in developing countries with wide variation in health care facilities, scarce resources and increasing burden of cardiovascular diseases. This study sought to validate the Thrombolysis In Myocardial Infarction (TIMI) risk score for STEMI in a multi-ethnic developing country.

Methods

Data from a national, prospective, observational registry of acute coronary syndromes was used. The TIMI risk score was evaluated in 4701 patients who presented with STEMI. Model discrimination and calibration was tested in the overall population and in subgroups of patients that were at higher risk of mortality; i.e., diabetics and those with renal impairment.

Results

Compared to the TIMI population, this study population was younger, had more chronic conditions, more severe index events and received treatment later. The TIMI risk score was strongly associated with 30-day mortality. Discrimination was good for the overall study population (c statistic 0.785) and in the high risk subgroups; diabetics (c statistic 0.764) and renal impairment (c statistic 0.761). Calibration was good for the overall study population and diabetics, with $\chi 2$ goodness of fit test p value of 0.936 and 0.983 respectively, but poor for those with renal impairment, $\chi 2$ goodness of fit test p value of 0.006.

Conclusions

The TIMI risk score is valid and can be used for risk stratification of STEMI patients for better targeted treatment.

Introduction

Risk stratification is important in acute coronary syndromes (ACS). It provides information to both patients and clinicians on the possible prognosis and serves as a guide to aggressiveness of treatment.(1,2) ST-segment elevation myocardial infarction (STEMI) forms the severest spectrum of ACS (3) and the best clinical outcomes are achieved when the primary percutaneous coronary intervention (PCI) strategy is applied.(4, 5)

In developing countries, where there is a wide variation of healthcare service provision, it is often challenging to provide the best treatment strategies recommended in international guidelines. In this respect, risk stratification of patients with STEMI takes on greater importance, especially for those at the highest risk strata, such that the most resource intensive strategies can be applied to achieve the greatest clinical benefit.

The Thrombolysis In Myocardial Infarction (TIMI) risk score was developed as a bedside tool to stratify STEMI patients eligible for reperfusion by their mortality risk.(6) This low cost risk estimation may be very suitable for use in developing countries. It was developed in a clinical trial population, and has been validated in non-selected Western patient populations.(7, 8) The TIMI risk score has shown to provide good discrimination in predicting mortality at 30 days and even up to 365 days. This offers some evidence for its clinical applicability in risk stratification and prognostication. However, it is not known how the TIMI risk score performs in a population with many characteristic differences from the population the risk score was derived from, in the era where an early invasive strategy for re-vascularisation is becoming more common. In Malaysia, patients presenting with STEMI are younger, have a much higher prevalence of diabetes, hypertension and renal failure, and present later to medical care than their western counterparts.(9)

In this study, we studied whether the TIMI risk score can be applied, i.e., results in adequate risk assessment, in a multi-ethnic Malaysian population presenting with STEMI. We also sought to determine if the TIMI risk score was useful prognostically in subgroups of patients with diseases that are more prevalent in the country and at higher risk of mortality; diabetics (10) and those with renal impairment.(11)

Methods

The National Cardiovascular Disease Database (NCVD) in Malaysia is an on-going observational prospective registry of patients who present with ACS. It commenced on the 1st of January 2006. Patient recruitment occurs at 16 hospitals with varying facilities; 14 from the Ministry of Health, 1 university hospital and the National

Heart Institute of Malaysia. All patients aged 18 and above with ACS at these sites have details of their past medical history, presenting symptoms, in-patient clinical care and health outcomes till 1 year post ACS recorded.

Ethics Statement

The NCVD is registered in the National Medical Research Register of Malaysia (ID: NMRR-07-38-164) and received ethical approval from the Ministry of Health Medical Research and Ethics Committee. A waiver of informed consent was obtained from the Ministry of Health Medical Research and Ethics Committee. Instead, a public notice is displayed at all sites and patients are given the option to opt out of the NCVD.

This study made use of anonymized data from patients who presented with STEMI registered from 1st January 2006 till 31st December 2008 with follow up details recorded till 31st December 2009.

The diagnosis of STEMI is based on the following; signs and symptoms of ACS (chest pain or overwhelming shortness of breath), elevated serum cardiac biomarkers and an ST elevation in contiguous leads of the electrocardiogram or the development of a new left bundle branch block (LBBB).(12) All clinical care given to patients presenting with STEMI was at the discretion of the treating physician or cardiologist at the respective sites. Diabetes mellitus (DM) status was determined based on self report, or use of blood sugar lowering agents (oral or insulin). Renal impairment was determined based on medically documented reports of moderate to severe chronic kidney disease (CKD); CKD Stage 3 and above (e-GFR below 60 ml/min). For this study, a previous medical history that was noted to be 'not known' or 'not recorded' was classified as absent.

The TIMI risk score for STEMI was developed using the study population from the Intravenous nPA for Treatment of Infarcting Myocardium Early II (InTIME II) trial.(13) The study population of the InTIME II trial will be referred to as the 'TIMI development' population for this study. The elements of the TIMI risk score are age, systolic blood pressure, heart rate, Killip classification, infarct location or left bundle branch block, history of diabetes, hypertension or angina pectoris, weight and time to treatment. The TIMI STEMI scoring mechanism has been published.(6) For this study, the TIMI risk score is slightly modified for 'time to treatment' variable. Time to treatment is defined as time from presentation (not symptom onset) to reperfusion, either via thrombolytics (door-to-needle time) or primary percutaneous coronary intervention (door-to-balloon time). Those who did not receive reperfusion therapy for the following reasons; missed thrombolysis

(12.6%), thrombolysis was contraindicated (4%) or patient refused treatment (0.2%), were given a score of 1 for time to treatment.

The outcome of interest was 30-day mortality. Details on mortality were obtained via hospital records and a 30-day follow up phone call to the patient/relatives. Confirmation of mortality is done yearly via record linkages with the Malaysian National Registration Department for deaths in the country. The IBM® InfoSphere® QualityStage (http://www-01.ibm.com/software/data/infosphere/qualitystage/) was used for record matching purposes. Rule sets for record matching were prepared based on some of the methods available in the software (such as 'String character or phrase comparison', 'Phonemic name comparison', 'Specialised numeric comparisons', 'Absolute difference comparison', etc). The rule sets were implemented for key identifier fields such as name, identification card number, year and month of birth. Accurate record linkages are possible because all Malaysians have a unique numerical identification number. This unique identification number is used for all official matters; including hospital and clinic visit registrations, as well as death registration.

Missing data was checked to determine if it was Missing At Random using the separate variance *t* test. Seven variables with missing values were imputed. Those with missing values of <5% (age 0.1%, systolic blood pressure 1.1%, heart rate at presentation 2%, sex 2.2% and smoking status 4.9%) were imputed using mean or median values where applicable. Two variables with >5% missing (time to treatment, 23.9% and weight, 36.1%) were imputed using single imputation with a random error term method.

A multivariable logistic regression model was used to determine the risk association of the TIMI risk score and 30-day mortality. Odds ratios (OR) and its 95% confidence intervals (95% CI) are reported. All variables included in the original TIMI development set model were included in the validation model.(6)

Validity of the TIMI risk score was tested using discrimination and calibration. Discrimination was assessed using the concordance statistic (*c* statistic) which is equivalent to the area under the Receiver Operating Characteristic (ROC) curve. A *c* statistic value of >0.75 is considered good discrimination. Calibration was determined graphically by plotting the observed 30-day mortality rates with the predicted rates which were determined from the observed mortality rates from the TIMI risk score development set. A chi square goodness-of-fit test was used to determine if the observed mortality rates differed significantly from the expected.(14) A p value of <0.05 was considered to be statistically significant. All

analyses were performed using SPSS Statistics Version 17.0 for Windows (SPSS Inc., Chicago, Il, USA).

Results

There were 10682 patients registered in the NCVD registry for ACS from 1st January 2006 till 31st December 2008. Of these, 478 (4.5%) did not have a diagnosis for type of ACS; STEMI, non-STEMI or unstable angina. There were 4701 patients diagnosed with STEMI. Among them, 36.3% had diabetes mellitus and 3.3% had renal impairment. Among those with STEMI, 72.7% were given thrombolysis reperfusion therapy (97.7% streptokinase) and 6.8% had primary PCI. The remainder had either missed thrombolysis (12.6%), or thrombolysis was contraindicated (4%), patient refused thrombolysis (0.2%) or data was missing (3.5%).

Baseline characteristics of the study population and TIMI score derivation population are shown in Table 1. Overall, patients presenting with STEMI in this validation set were younger; only 25% of them being older than 65 years of age, except for those with renal impairment (41%). The population in this study had more chronic conditions such as diabetes, hypertension, prior angina and history of cerebrovascular disease. Presenting characteristics at time of myocardial infarction were also more severe. Higher proportions of the study population had poorer Killip classes, high heart rates (>100 beats per minute) and low systolic blood pressures (<100 mmHg).

The diabetics comprised of more Indian patients than the overall study population, had more females and had higher rates of hypertension, prior myocardial infarctions and renal impairment. Compared to others in the study population, patients with renal impairment were of older age, had more severe disease (diabetes, hypertension, prior myocardial infarctions, documented coronary artery disease) and presented with more severe heart failure at the time of myocardial infarction.

The 30-day mortality rate for the study population was 11.1%, of which 9.4% was attributed to in-hospital mortality. The 30-day mortality rate for the TIMI development population was 6.7% (6). The overall mortality rate among diabetics and those with renal impairment was 14% and 27.6% respectively.

Table 2 presents the risk associations of 30-day mortality for each characteristic used in the TIMI risk score calculation. The risk associations were similar between this validation set and the development set for all characteristics except for age older than 75 years and weight.

Table 1. Baseline characteristics of patient populations from TIMI Score development set and study set.

Variables	Overall Population	Diabetics	Renal imp	TIMI score development pop
n	**4701**	**1707**	**156**	**15060**
Demographics				
Age (years)	56 (48, 65)	57 (50, 65)	63 (54, 70)	62 (52, 70)
> 75 y	7	6.7	10.9	13.7
65 -74 y	18	18.9	30.1	28.1
Female	15.1	22.4	28.8	24.7
Weight (kg)	67 (58, 77)	68 (58, 79)	62 (53, 76)	77 (69, 86)
< 67 kg	49.4	47.5	63.5	19.2
Race				
Malay	52.9	49.3	44.2	NA
Chinese	20.3	16.9	25.6	NA
Indian	18.2	26.8	17.3	NA
Others	8.6	7	12.8	NA
Risk factors				
Smoking status				
Current	50.8	38.9	24.4	44.7
Past	20.1	21.4	26.9	26.4
Never	29.1	39.7	48.7	28.4
Diabetes	36.3	100	62.8	13.9
History of hypertension	48.4	67.8	79.5	30.4
Renal impairment (Mod- severe)	3.3	5.7	NA	NA
Cardiovascular history				
Prior myocardial infarction	9.6	12.5	23.1	16
Peripheral vascular disease	0.3	0.5	3.2	5.2
Cerebrovascular disease	2.7	4	8.3	1
Prior angina	51.7	55.1	52.6	21.2
Documented CAD >50%	5.7	8.9	16.7	7.2
Diabetes/ HPT/Prior angina	79.2	100	94.2	47.6
Medications at presentation				
β-blockers	12.9	18.3	31.4	15.6
Calcium channel blockers	5.1	8.2	21.2	15.7
Lipid lowering	16.6	25.1	42.9	9.3
Anti-arrhythmic	1.9	2.3	3.2	1.3
Presenting characteristics				
Infarct location				
Anterior or LBBB	59.1	60.3	57.7	42.7
Inferior	45.4	44.4	46.2	56.9
Killip class II - IV	28.9	31.8	44.2	12.6
Heart rate (bpm)	80 (68, 96)	85 (71, 100)	89 (69, 108)	74 (63, 86)
Heart rate > 100 bpm	17.8	23.3	30.1	7.7
Systolic blood pressure (mmHg)	133 (115, 152)	134 (115, 156)	134 (113, 160)	140 (122, 155)
Systolic BP < 100 mmHg	8.5	8.1	7.7	2.6
Time to treatment > 4 hours	35.9	37.6	51.3	24.3

Data are % for categorical variables and median (interquartile range) for continuous variables
CAD, coronary artery disease, HPT, hypertension, LBB, left bundle branch block
NA, not available/not applicable

Table 2. TIMI risk score, characteristics and risk of 30-day mortality

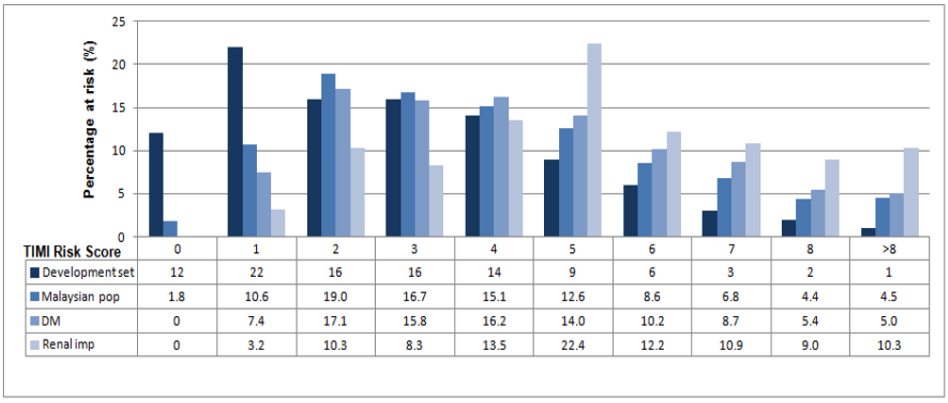
Characteristics	TIMI risk score *	TIMI Adjusted OR (95% CI) *	Malaysian Adjusted OR (95% CI)
Age ≥ 75 years	3; 2 (65-74)	2.7 (2.2 - 3.2)	6.1 (4.5 - 8.3)
Systolic blood pressure < 100 mmHg	3	2.7 (1.9 - 3.8)	4.3 (3.3 - 5.6)
Heart rate > 100 bpm	2	2.3 (1.9 - 2.8)	2.7 (2.2 - 3.4)
Killip class II - IV	2	2.3 (1.9 - 2.7)	2.8 (2.3 - 3.5)
Anterior MI or LBB	1	1.6 (1.4 - 1.9)	1.3 (1 - 1.6)
Weight < 67 kg	1	1.4 (1.2 - 1.7)	0.8 (0.6 - 1)
Time to treatment > 4 hours	1	1.4 (1.2 - 1.6)	1.3 (1.1 - 1.7)
** Diabetes		1.4 (1.2 - 1.7)	1.4 (1.1 - 1.7)
**History of HPT	1	1.3 (1.1 - 1.5)	1.2 (0.9 - 1.5)
**Prior angina		1.4 (1.1 - 1.6)	0.9 (0.7 - 1.1)

MI indicates myocardial infarction, LBB, left bundle branch block, HPT, hypertension
Other variables adjusted in the model: never smoked, prior MI, peripheral arterial disease, anti-arrhythmic medication, lipid lowering drugs and female sex

* obtained from Morrow et al (6)

** Diabetes, HPT and prior angina combined has a risk score of 1

Figure 1 depicts the distribution of the TIMI risk score for the TIMI development population and the Malaysian validation population. It clearly shows a difference in the risk distribution, with the Malaysian population having higher proportions of intermediate risk (TIMI risk score 4–6) and high risk categories (TIMI risk score of ≥7), including the diabetic and renal impairment subgroups.

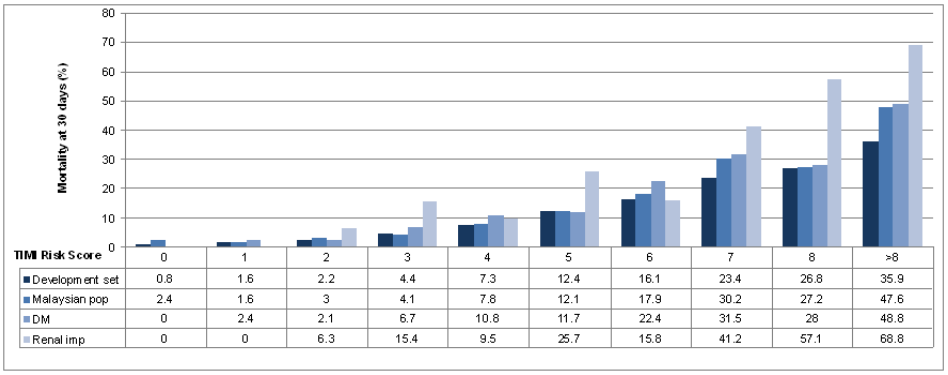


TIMI Risk Score	0	1	2	3	4	5	6	7	8	>8
Developmentset	12	22	16	16	14	9	6	3	2	1
Malaysian pop	1.8	10.6	19.0	16.7	15.1	12.6	8.6	6.8	4.4	4.5
DM	0	7.4	17.1	15.8	16.2	14.0	10.2	8.7	5.4	5.0
Renal imp	0	3.2	10.3	8.3	13.5	22.4	12.2	10.9	9.0	10.3

Figure 1: Percentage at risk by the TIMI risk score for the TIMI risk score development population, Malaysian STEMI population, as well as diabetic (DM) and renal impairment sub-groups.

There was a strong association of increasing risk of 30-day mortality with each increasing TIMI risk score for the study population, *p* value of <0.001 (Figure 2). This was consistent for the diabetic and renal impairment subgroups (*p* values <0.001 for tests of trend). The mortality rate for each risk score ranged from 2.4 to 100% from the lowest TIMI risk score (0) to the highest (13). For diabetics, the

mortality rate ranged from 2.4 to 72.7% from the lowest TIMI risk score (0) to the highest (11) and for those with renal impairment, it ranged from 0 to 100% (risk score 0 to 11).



TIMI Risk Score	0	1	2	3	4	5	6	7	8	>8
Development set	0.8	1.6	2.2	4.4	7.3	12.4	16.1	23.4	26.8	35.9
Malaysian pop	2.4	1.6	3	4.1	7.8	12.1	17.9	30.2	27.2	47.6
DM	0	2.4	2.1	6.7	10.8	11.7	22.4	31.5	28	48.8
Renal imp	0	0	6.3	15.4	9.5	25.7	15.8	41.2	57.1	68.8

Figure 2: Mortality rate at 30 days for the TIMI risk score development, Malaysian STEMI population, as well as diabetic (DM) and renal impairment sub-groups.

Discrimination for the TIMI risk score for this study population was good, *c* statistic 0.785 (95% confidence limit 0.77, 0.81) and also performed better than the original development set (*c* statistic 0.779) (6). This good discrimination was consistent in both the diabetic and renal impairment subgroups; c statistic 0.764 (0.73, 0.80) and 0.761 (0.68, 0.85) respectively. Calibration of the TIMI risk score was good for the overall study population and diabetics (Figure 2) with a $\chi 2$ goodness-of-fit test p value of 0.936 and 0.983 respectively. However, there was poor calibration for the renal impairment subgroup; $\chi 2$ goodness-of-fit test p value of 0.006.

Discussion

Our study provides a fully independent external validation of the TIMI risk score, which includes geographic and temporal validation. It confirms that the TIMI risk score can be used to accurately risk stratify patients presenting with ST-elevation myocardial infarction in Malaysia, despite having more severe presenting characteristics than the original TIMI risk score population. Aside from that, risk stratification worked well for high risk groups prevalent in Malaysia; the diabetics and those with renal impairment.

Although the management options for patients with STEMI are well established (4,15,16), our findings are important. Firstly, clinicians managing life-threatening STEMI conditions can accurately risk stratify patients and discriminate those who are more likely to benefit from primary PCI or thrombolytics, depending on the resources available at hand. A recent pooled meta-analysis confirmed that absolute risk reduction for mortality using thrombolytics or primary PCI depended on the patient's baseline risk.(17) Other studies have shown that in low risk patients,

fibrinolysis (18) and even conservative therapy (19) performed as well as primary PCI for 30-day mortality. Therefore, the use of the TIMI risk score in Malaysia may help improve the use of limited resources through better targeted treatment for higher risk patients.

Secondly, it is beneficial to clinicians in the Malaysian setting to be able to use an existing risk score for stratification instead of developing a new tool. There have been various studies developing new scores or identifying additional biomarkers which utilize resource intensive or time-consuming investigations such as C-Reactive Protein (20), B-type natriuretic peptide (21), creatinine (GRACE risk score) (22,23) and platelet function.(24) The validation of this risk score which uses signs, symptoms and investigations readily done at the time of presentation provides an efficient inexpensive tool for risk stratification. This is essential in developing countries where publicly funded health care systems cater to the majority of the population.(25)

Finally, our findings are also relevant to government policy makers and fund holders who are involved in providing care for patients with STEMI. For Malaysia, there is a relative lack of hospitals with cardiac care facilities adequately equipped and resourced for primary PCIs, compared to developed countries.(26,27) At present, heavily subsided public-access cardiac care facilities exist primarily in large urban areas. The validation of the TIMI risk stratification score in the Malaysian population can provide policy makers and fund holders with information on the distribution of high-risk STEMI patients. Regions with higher numbers/proportions of high-risk patients may benefit from the addition of primary PCI resources at existing facilities. We believe risk stratification can be used to support the process of healthcare planning in Malaysia, from the perspective of STEMI management.

The TIMI risk score for STEMI patients has been validated in Western populations.(7,8) It has even been compared to different risk scores for STEMI such as the CADILLAC, GRACE and PAMI score and has been shown to have high prognostic accuracy.(28,29) Our findings confirm the validity of the TIMI risk score in STEMI for an Asian multi-ethnic population.

This study has various strengths. Firstly, it is a prospective multi-centre study with its population comprising of various ethnic groups such as the Malays, Chinese and Indians, which comprise of ethnicities of a large part of Asia. Secondly, this study population comprised a broad spectrum of STEMI patients unlike those found in clinical trials. Thirdly, mortality events were reconfirmed by linkages with the National Registration Department for deaths. Therefore, even for patients lost to follow-up, information on mortality was still recorded in the database.

The TIMI risk score development population consisted of STEMI patients undergoing a clinical trial comparing lanetoplase versus alteplase. It is worth noting that in our study population, the majority of patients (73%) had reperfusion therapy by fibrinolytics (mainly streptokinase) with a relatively low rate of primary PCIs (<7%) as the first line of management for STEMI. Our findings suggest that the TIMI risk score covers the more important variables that affect short term prognosis, irrespective of the type of treatment given. Our management of STEMI is consistent with that in other developing countries.(30) While major improvements to our healthcare system is planned, such as improving human resource (experienced, trained cardiologists), physical and financial infrastructure (31), reperfusion using the fibrinolytic strategy remains the mainstay of STEMI management in Malaysia. Therefore our findings are relevant to our country and may be to others at a similar evolutionary stage of cardiovascular healthcare provision.

Our study had a high percentage of missing values for two variables used in the TIMI risk score; time to treatment and weight. Studies have shown that complete case analysis leads to biased estimates of risk relations (32,33), hence imputation was used. Both these variables have a low score of one and are independent of each other. Therefore, we anticipate any misclassification of one of the variables to be a non-differential misclassification bias. In other words, the TIMI risk score can still be used for risk stratification (relative ranking), but it may not accurately predict mortality rates by the different risk scores.

The poor calibration seen in the renal impairment subgroup is probably due to the small sample size of 156 patients and thus limits its interpretation. Further validation in this subgroup is warranted. However, this poor calibration seen is consistent with published findings of the TIMI risk score validation in non-STEMI patients.(34)

The higher overall mortality rate observed in our validation population compared to the TIMI development population is due to the larger proportion of high risk patients and their higher mortality rates. This higher mortality rate seen among the high-risk strata needs to be investigated further.

In conclusion, the TIMI risk score is relevant and may be of benefit in improving clinical care through better targeted treatment, for patients presenting with ST-segment elevation myocardial infarction in Malaysia.

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Chapter 3.2

Comparison of the Framingham Risk Score, SCORE and WHO/ISH risk prediction models in an Asian population

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Abstract

Background

Cardiovascular risk prediction models are used in clinical practice to identify and treat high risk populations as well as to communicate risk effectively. Most prediction models have been developed in high income societies. We assessed the validity and utility of four cardiovascular risk-prediction models in an Asian population of an emerging middle-income country.

Methods

Data from a national population-based survey of 14 983 participants aged 40 to 65 years was used. The Framingham Risk Score (FRS), high and low risk SCORE (Systematic COronary Risk Evaluation) and the World Health Organization /International Society of Hypertension (WHO/ISH) models were assessed. The outcome of interest was cardiovascular mortality. Discrimination of all four models and calibration of the SCORE models were assessed.

Results

Overall, there was a high proportion of participants with cardiovascular risk factors. The FRS and SCORE models show similar trends in risk stratification and good agreement in risk categorisation. The WHO/ISH had a disproportionately large amount of low risk populations and showed poor agreement with other models. The FRS and both SCORE models showed good discrimination for cardiovascular mortality rates. The WHO/ISH model showed poor discrimination. Calibration of the SCORE-high model was good overall and for men, $\chi 2$ goodness-of-fit test p value of 0.345 and 0.057 respectively, but underestimated for women, $\chi 2$ goodness-of-fit test p value of <0.001.

Conclusions

The FRS and both SCORE models, but not the WHO/ISH model can be used to accurately identify high cardiovascular risk in the Malaysian population for both men and women.

Introduction

Cardiovascular risk prediction models are important in the prevention and management of cardiovascular diseases. These models are used in clinical practice to identify and treat high-risk populations as well as to communicate risk effectively.(1) Currently, there are three cardiovascular risk prediction models recommended in the Malaysian clinical practice guidelines for the prevention of cardiovascular diseases; the Framingham Risk Score (FRS), SCORE (Systematic COronary Risk Evaluation) and the World Health Organization /International Society of Hypertension (WHO/ISH) models.(2)

There are various concerns when adopting a risk prediction model for the clinical assessment of a patient to determine treatment options. First, is the risk score applicable to the local patient setting? It is well known that the underlying incidence of disease and prevalence of its risk factors determines the suitability of any risk prediction score. Secondly, can the risk prediction model be calibrated? In other words, can it be fully assessed of its clinical utility to predict risk accurately in the local patient setting? Unfortunately, developing countries often lack the information on cardiovascular events that are required for a full calibration of cardiovascular risk prediction models.

In Malaysia, a middle-income multi-ethnic developing country, both factors discussed above are applicable. Thus, these questions remain; 1) Are all the recommended cardiovascular risk prediction scores applicable in the Asian patient setting? 2) Do they accurately stratify risks? With these concerns in mind, we sought to compare the cardiovascular risk prediction models that are recommended in local clinical practice guidelines; the FRS, high and low risk SCORE and WHO/ISH risk-prediction models.

Methods

The population dataset from the 2006 National Health and Morbidity Survey (NHMS) was used in this study. The NHMS was a nationwide cross-sectional population-based survey that assessed cardiovascular risk factors among other health and social indicators. Details of the study have been published elsewhere and the measurement of cardiovascular risk factors have been descibed in detail.(3) For this study, all NHMS participants aged between 40-65 years were selected to ensure comparability between the different risk models assessed.

Ethics approval was obtained from the Malaysian Medical Research and Ethics Committee (NMRR ID- 10-731-6916).

Cardiovascular risk prediction models

Four cardiovascular risk prediction models were assessed; the FRS for global cardiovascular risk, SCORE – high-cardiovascular risk region (SCORE-high), SCORE – low-cardiovascular risk region (SCORE-low), and the WHO/ISH – Western Pacific Region B. A summary of the risk prediction models are given in Appendix A.

The FRS (4), SCORE (5) and WHO/ISH (6) models use information on age, sex, systolic blood pressure and smoking. The SCORE and WHO/ISH models includes information on total cholesterol whereas the FRS model in the present study uses body mass index instead of the ratio of total and HDL cholesterol. This is because the NHMS did not collect information on HDL cholesterol. Both the FRS and WHO/ISH include diabetes in the model.

For both the FRS and SCORE models, the originally developed and validated predictors and coefficients were used to calculate the predicted cardiovascular risk in the present study. The cardiovascular risk prediction for the FRS was calculated using the Framingham equations for general cardiovascular risk provided online (http://www.framinghamheartstudy.org/risk/gencardio.html.). Risk estimations for the SCORE models were calculated using the regression equations provided by Conroy et al.(5) Estimated risks were multiplied by three in diabetic men and by five in diabetic women.(7) Both SCORE models were used, that for populations at high and that for low cardiovascular disease risk populations. This is because it is unknown which model would perform better in Malaysia. The WHO/ISH risk prediction model does not provide regression equations that can estimate individual absolute risk. It has risk charts with five categories of risk. Each subject's risk category was calculated.

Cardiovascular risk stratification

For each model, cardiovascular risk was stratified into three categories; low, intermediate and high cardiovascular risk. High cardiovascular risk was defined as ten-year risk $\geq 20\%$, $\geq 5\%$ and $\geq 30\%$ for the FRS, SCORE and WHO/ISH models, respectively. Low risk was defined as $< 10\%$ for the FRS and WHO/ISH models and $<1\%$ for both the SCORE models. All other values were in the intermediate risk group.

Agreement between risk categorization was determined using the kappa statistic. K values ≥ 0.81, 0.61-0.80, 0.41-0.60, 0.21-0.40, and ≤ 0.20 are interpreted as excellent, good, moderate, fair and poor respectively.(8)

Outcome of interest for model performance

The 5-year risk of cardiovascular mortality was the outcome of interest in this study. Non-fatal cardiovascular events were not considered, because despite a relatively good healthcare system, estimates of incidence of coronary heart disease, stroke and other cardiovascular events assessed by many cardiovascular risk prediction models cannot be obtained. Cardiovascular causes of death were fatal events described in the International Classification of Diseases (ICD)-10 codes I10-I15 (hypertensive diseases), I20-25 (ischaemic heart diseases), I60-I69 (cerebrovascular diseases), I70 and I71(other atherosclerosis).

Mortality data from the years 2006 till 2010 for the NHMS population were obtained via record linkages with the Malaysian National Registration Department. All Malaysians have a unique numerical identification number given at birth by the National Registration Department. This unique identification number is used for all official matters, including death registrations. The IBM® InfoSphere® QualityStage (http://www-01.ibm.com/software/data/infosphere/qualitystage/) was used for record matching purposes.

Statistical analyses

Missing data was reviewed and determined if it was missing at random. Imputation was performed since several studies have indicated that complete case analyses leads to biased results.(9,10) Continuous variables with ≤ 2% missing were imputed using mean or median values where applicable. Single imputation using a linear regression with a random error term was done for total cholesterol (7% missing).

Model performance

Validity of prediction models were assessed based on discrimination and calibration of the models. Discrimination is the ability to categorise those with and without disease based on predictive values. Calibration is the measure of how accurately the predicted risks match the observed risks. Utility of the models in this study was based on discrimination alone for two models, the FRS and WHO/ISH. Calibration was not determined because these models estimate the 10-year risk of fatal and non-fatal cardiovascular events. In our study, only fatal cardiovascular events were available.

Discrimination

Discrimination was assessed using the area under the Receiver Operating Characteristic (ROC) curve. A value of > 0.75 was considered good discrimination. Model comparisons were statistically tested for differences in the area under the ROC. This method has been proven acceptable for comparing ordinal tests (11) (WHO/ISH) with continuous tests (FRS and SCORE).

Calibration

Model calibration was done for two models; SCORE-high and SCORE-low. To enable calibration, the numbers of 5-year observed mortality events were doubled to obtain 10-year mortality events. Calibration was assessed tabularly and statistically using a chi square goodness-of-fit test to determine if the observed mortality rates differed significantly from the expected.(12) Groupings of the predicted risk were based on the seven categories provided by the SCORE charts (13); <1%, 1%, 2%, 3-4%, 5-9%, 10-14% and ≥15%.

Sensitivity analyses

Due to the low percentage of medically certified deaths in the country, 57% in 2010 (14), we conducted sensitivity analyses for model discrimination using all-cause mortality rates.

For all analyses, p values less than 0.05 were considered statistically significant. Analyses were performed using SPSS Statistics Version 17.0 for Windows (SPSS Inc., Chicago, Il, USA) and Stata Statistical Software : Release 11.0 (College Station, TX: Stata Corporation LP).

Results

There were a total of 14983 participants aged between 40 to 65 years, and 45.4% of them were men. The 5-year all-cause and cardiovascular mortality rate was 3.4% (509 events) and 1.1% (165 events) respectively. Cardiovascular risk factors were prevalent; hypertension (55.2%), hypercholesterolemia (33.9%), diabetes (17.8%), and overweight (40.4%) and obesity (32%). Among the men, 42% were currently smoking, 53% had hypertension, 31% had hypercholesterolemia, 17% had diabetes, 44% were overweight and 25% were obese. Among the women, 2% were current smokers, 57% had hypertension, 37% had hypercholesterolemia, 18% had diabetes, 37% were overweight and 38% were obese.

Cardiovascular risk stratification and mortality distribution

Figure 1 depicts the distribution of the cardiovascular risk categories for the FRS, SCORE and WHO/ISH risk-prediction models. In men, all score models except the WHO/ISH model showed similar trends in risk stratification. Despite the high proportions of cardiovascular risk factors prevalent in this study population, the WHO/ISH model classified almost 90% in the low cardiovascular risk category. Among the women, all models showed similar trends. However, as with men, the WHO/ISH model had the highest classification of low risk populations. The 5-year cardiovascular mortality rates for all models increased as cardiovascular risk increased (Figure 2). They showed similar trends for both men and women for all

models. However, in women, cardiovascular mortality rates among the intermediate and high risk categories of the WHO/ISH model were almost similar.

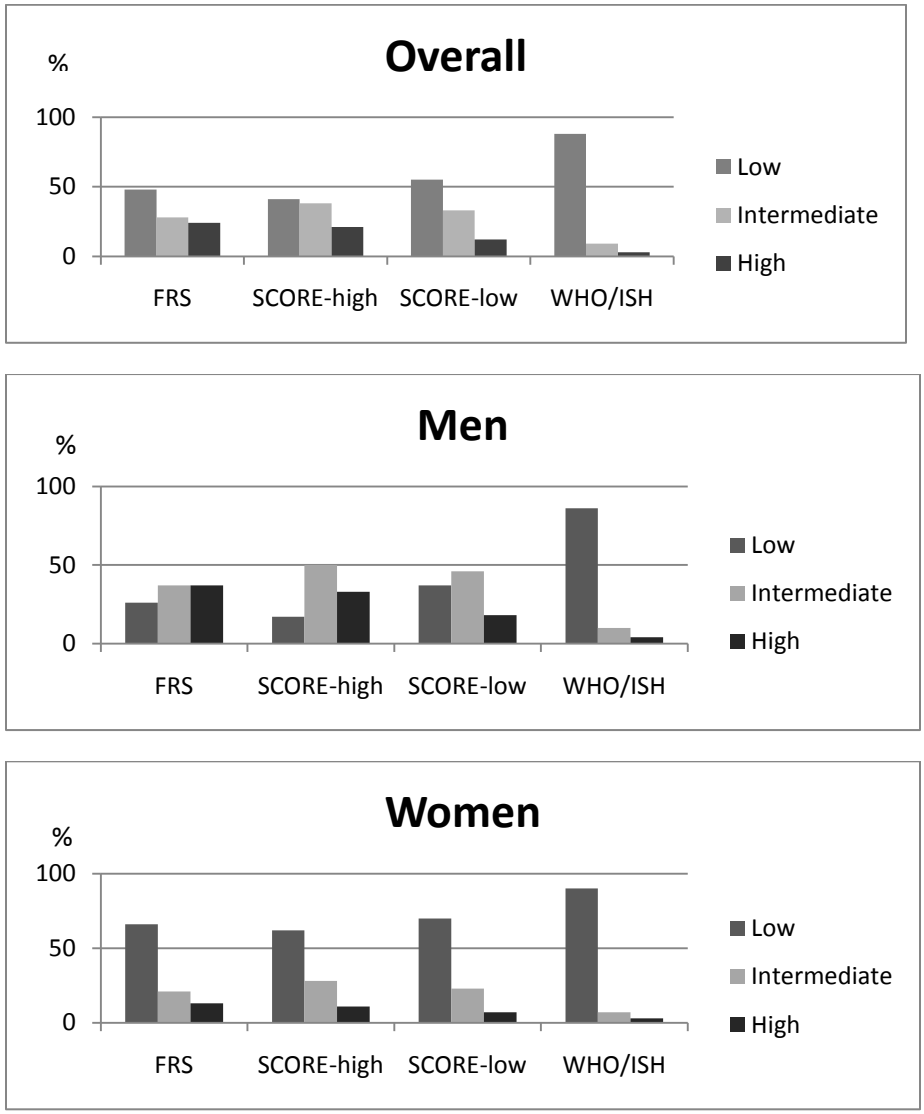
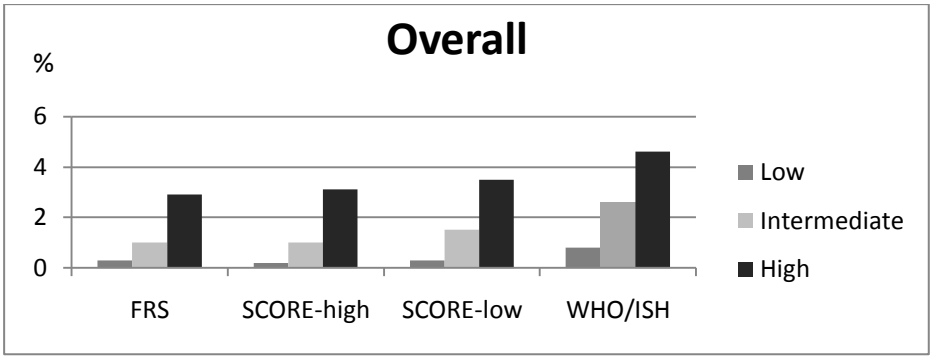
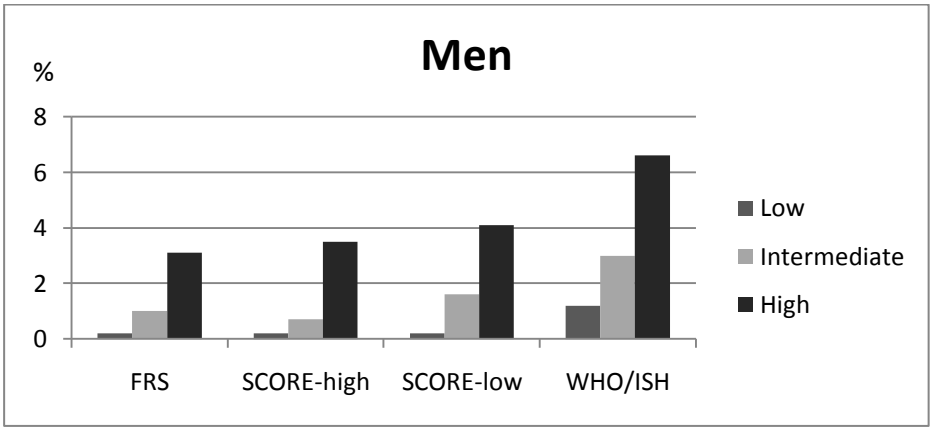


Figure 1 - Comparison of cardiovascular risk categories for the Framingham Risk Score, SCORE and WHO/ISH risk prediction models (y-axis reflect percentage of individuals)





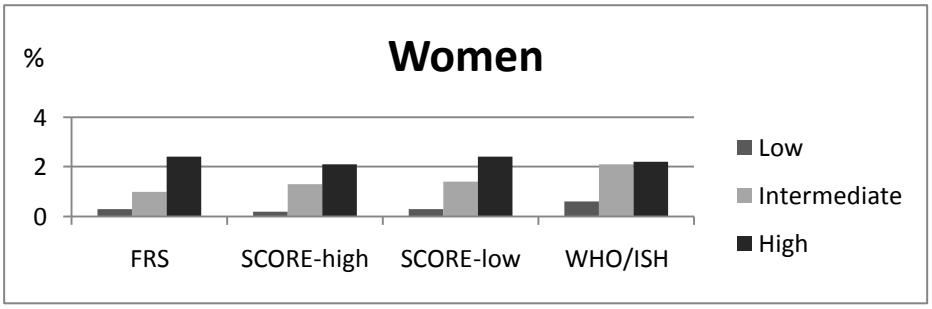


Figure 2 -5-year cardiovascular mortality rate (y-axis, percentage) by the Framingham Risk Score, SCORE and WHO/ISH risk prediction models

Table 1 - Agreement of cardiovascular risk categorisation for the Framingham Risk Score, SCORE and WHO/ISH risk prediction models

Models	Both high or both low (n)	Both high (n)	First model* high / comparator low (n)	First model* low/ comparator high (n)	k
FRS* and SCORE - high					
Overall	8605	2773	3	0	0.71
Men	3132	2051	0	0	0.68
Women	5473	722	3	0	0.66
FRS* and SCORE - low					
Overall	8549	1719	26	0	0.61
Men	2889	1193	11	0	0.52
Women	5660	526	15	0	0.63
FRS* and WHO/ISH					
Overall	7613	445	2075	3	0.13
Men	2015	257	1618	0	0.04
Women	5598	188	457	3	0.23
SCORE - high* and WHO/ISH					
Overall	6544	418	1780	9	0.09
Men	1397	248	1377	0	0.01
Women	5147	170	403	9	0.18
SCORE - low* and WHO/ISH					
Overall	8489	387	643	16	0.16
Men	2711	239	450	0	0.09
Women	5778	148	193	16	0.24

Comparison of cardiovascular risk-prediction models

The agreement for risk categorisation between the FRS and SCORE models was good, with better agreement with the SCORE-high model (Table 1). There was poor agreement between all models with the WHO/ISH model. The WHO/ISH model classified about 5% of the study population as high-risk patients and thus missed high numbers of cardiovascular mortality.

Model performance

The FRS, SCORE-high and SCORE-low all show good discrimination for cardiovascular mortality rates (Table 2). The WHO/ISH model shows poor discrimination overall, for men and for women. Model comparisons for area under the curve show a p value of <0.0001 overall, as well as for men and women. The WHO/ISH model was statistically significantly different from the FRS, SCORE-high and SCORE-low models.

Table 2 - Sensitivity, specificity, discriminative ability and optimal thresholds for the FRS, SCORE and WHO/ISH models for 5-year cardiovascular mortality

Models	Cut-off	Sensitivity	Specificity	AUC (95% CI)	**Sensitivity analyses AUC
FRS					
Overall	>20%	61.8	76.8	0.768 (0.734, 0.802)	0.721 (0.698, 0.744)
Men	>20%	72.6	63.6	0.751 (0.708, 0.795)	0.727 (0.697, 0.756)
Women	>20%	42.4	87.7	0.758 (0.702, 0.815)	0.707 (0.672, 0.742)
SCORE-high					
Overall	>5%	59.4	79.4	0.774 (0.741, 0.807)	0.741 (0.72, 0.763)
Men	>5%	74.5	67.4	0.768 (0.726, 0.809)	0.747 (0.719, 0.776)
Women	>5%	32.2	89.3	0.763 (0.711, 0.815)	0.736 (0.704, 0.768)
SCORE-low					
Overall	>5%	38.2	88.5	0.775 (0.742, 0.807)	0.744 (0.723, 0.766)
Men	>5%	46.2	82.8	0.768 (0.726, 0.81)	0.748 (0.719, 0.777)
Women	>5%	23.7	93.1	0.761 (0.709, 0.813)	0.736 (0.703, 0.768)
WHO/ISH					
Overall	>30%	13.3	96.9	0.613 (0.564, 0.662)	0.6 (0.572, 0.628)
Men	>30%	16.0	96.4	0.617 (0.556, 0.678)	0.625 (0.588, 0.662)
Women	>30%	8.5	97.3	0.597 (0.516, 0.678)	0.563 (0.522, 0.605)

** AUC (95%CI) for 5-year all-cause mortality

AUC, area under the receiver operating curve

Calibration of the SCORE-high model was good for the overall study population and men, (Table 3) with a 2 goodness -of-fit test p value of 0.345 and 0.057 respectively. However, there was poor calibration for the SCORE-high model for women and the SCORE-low for men and women; 2 goodness -of-fit test p value of <0.001.

Table 3 - Observed and predicted cardiovascular mortality rates for SCORE-high and SCORE-low cardiovascular risk prediction models, by risk groups as defined by the SCORE charts

Expected SCORE 10-year CV mortality rates, by SCORE chart categories	Observed* SCORE-high 10-year CV mortality rates			Observed* SCORE-low 10-year CV mortality rates		
	Overall	Men	Women	Overall	Men	Women
<1%	0.39	0.35	0.40	0.61	0.48	0.66
1%	1.49	0.70	2.47	2.11	2.03	2.22
2%	2.06	1.99	2.19	3.14	2.69	3.95
3-4%	2.58	2.07	3.52	5.02	6.09	2.89
5-9%	4.50	5.11	2.98	5.68	5.33	6.43
10-14%	6.86	5.89	9.18	8.33	11.86	1.61
15%	9.13	11.49	2.69	10.53	14.08	3.64

* Estimated by doubling 5-year cardiovascular mortality events

CV, cardiovascular

Discussion

Our study confirmed that the FRS and both SCORE models, but not the WHO/ISH model can be used to discriminate cardiovascular risk in the Malaysian population for both men and women. The SCORE-high model accurately predicts mortality risk in men but not in women.

The findings of this study are important. It shows that not all cardiovascular risk prediction models can identify high-risk individuals accurately despite having similar variables in the model. This strongly suggests that prior to adoption into clinical practice, these clinical models have to be assessed for its utility.

Prediction models in limited resource settings such as in developing countries have a very important role. The model cut-off point should sufficiently distinguish between the high and low-cardiovascular risk so as to optimize treatment for those who will benefit the most.(12) Currently, the FRS, SCORE and WHO/ISH models are recommended in the Malaysian clinical practice guidelines for the prevention and management of cardiovascular disease. However, we have shown that the WHO/ISH model categorises most people into the low cardiovascular risk group. Thus, using the WHO/ISH risk prediction model would under-identify high-risk individuals leading to higher rates of under-treatment. This is detrimental to the prevention and control of cardiovascular disease in the country since resources would be spent on screening yet high risk individuals would be misclassified.

The cardiovascular risk scores assessed in this study are contemporary models used in other countries. The Framingham risk score was developed from a single cohort study, all Caucasians, and has been assessed and validated in many populations. In some European, Australian and Middle Eastern populations, it discriminates patients well but it overestimates the absolute cardiovascular risk.(15-17) A different version of the FRS risk prediction model has been validated in a Chinese population. Similarly, it accurately stratifies risk but overestimates the absolute cardiovascular disease risk.(18) In the Thai population, the FRS has been recalibrated.(19) The SCORE models were developed from a variety of cohort studies from different European countries, in individuals mostly of Caucasians origin.(5) This was to ensure representativeness of the different background risks in the region; hence the high and low cardiovascular risk SCORE charts. They used the ‘hard’ end-points of fatal cardiovascular disease. This was because definitions of cardiovascular events used in the various cohorts were different, but a previous study confirmed that the ratio of ‘hard’ to ‘soft’ end-points were similar in high and low cardiovascular risk regions.(20) The SCORE models have been validated.(21-23) The WHO/ISH risk prediction model is the only model not based on actual cohort studies. The model was developed based on a hypothetical cohort that was assigned values of cardiovascular risk factors using estimates of risk-factor

prevalence of the various regions. Calculation of absolute risk of cardiovascular events was based on incidence rates estimated from other WHO studies. These WHO/ISH models created for the Asian and African regions have not been assessed as yet.

Many of the components of the cardiovascular risk prediction models used in this study are similar. The FRS and SCORE models showed good discrimination probably because they were developed from real patient populations. The slightly better performance of the SCORE models compared to the FRS may be due to total cholesterol levels. The FRS model in this study used body mass index instead of total/ HDL cholesterol ratio. However, although the WHO/ISH model included total cholesterol levels, it underperformed compared to the other models tested.

The calibrated SCORE-high model for men shows that there is an available risk prediction model which can accurately stratify and predict cardiovascular risk. In a country such as ours, the SCORE models would be a better option, as recalibration can be easily accomplished in future as mortality data is easily available. The poor calibration seen for women will have to be assessed further. There are three possible explanations for the poor calibration. Women in South-East Asian countries have shown low cardiovascular causes of mortality compared to other countries (24) and this may be similar for Malaysia. Or, cardiovascular causes of mortality may be under-recognised in Malaysian women as in other South-East Asian countries.(25) Or, the number of events seen among women in the present study was low, thus limiting true calibration.

Our study has limitations. The accuracy of mortality reporting in the country is unknown. However, there are up to three sources of mortality reporting to the National Registration Department; via the police, the healthcare facility (if pronounced dead in this setting) and the next-of-kin. As in other developing countries, the percentage of medically-certified deaths is low with only 57% in 2010.(14) This percentage differs according to state/ region in the country.(26) However, it is likely that the percentage of medically-certified deaths is non-differentially related to the cause of death. Thus, although the absolute rates of cardiovascular deaths may change, the percentage of cardiovascular deaths will not.

The FRS model which includes the total cholesterol/HDL cholesterol ratio is more widely used in cardiovascular risk-prediction. It is unknown how the more commonly used FRS model would have performed in our population.

In conclusion, our study highlighted that it is crucial to assess cardiovascular risk-prediction models as not all are created equal. Only the FRS and SCORE models are applicable for use in clinical practice for the identification of patients at high

cardiovascular risk in Malaysia. The high-risk SCORE model should be recommended because of its ease of recalibration, if needed in the future.

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Appendix A - Characteristics of the FRS, SCORE and WHO/ISH risk prediction models

Characteristics	**Framingham Risk Score (FRS)**	**SCORE (Systematic COronary Risk Evaluation)**	**World Health Organization/ International Society of Hypertension (WHO/ISH)**
Data source	Cohort studies: Framingham Heart Study and Framingham Offspring Study.	Pooled cohort studies	Hypothetical cohort s for different regions
Population	General population in Framingham, Massachusetts, United States of America	12 cohort studies (population and occupational cohorts) from 11 European countries	Not applicable
Age range	30–75	40–65	40–79
Variables	Age, gender, body-mass-index OR total cholesterol & HDL cholesterol, SBP, smoking status, diabetes, hypertensive treatment.	Age, gender, total cholesterol, SBP, smoking status.	Age, gender, with or without total cholesterol, SBP, smoking status, diabetes.
Endpoints	10-Year risk of Cardiovascular events (coronary death, myocardial infarction, coronary insufficiency, angina, ischaemic stroke, haemorrhagic stroke, transient ischaemic attack, peripheral artery disease, heart failure)	10-Year risk of Cardiovascular mortality (ICD -9 codes 401-414, 426-443, 798.1 and 798.2. Non-atherosclerotic deaths were excluded – 426.7, 429.0, 430.0, 432.1, 437.3, 437.4, 437.5.)	10-Year risk of Cardiovascular events (coronary heart disease, stroke, other atherosclerotic disease)
Scoring mechanism	Online calculator/ Risk equations online	Online calculator/ charts Risk equations online Versions: High- and low-risk countries	Charts Versions: Regions

Chapter 4

Preventions

Chapter 4.1

Cardiovascular risk factor treatment targets and renal complications in high risk vascular patients: a cohort study

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Abstract

Background
To determine if recommended treatment targets, as specified in clinical practice guidelines for the management of cardiovascular disease, reduces the risk of renal complications in high risk patient populations.

Methods
This was a cohort study. Participants in Utrecht, The Netherlands either at risk of, or had cardiovascular disease were recruited. Cardiovascular treatment targets were achievement of control in systolic and diastolic blood pressure, total and low-density cholesterol, and treatment of albuminuria. Outcome measures were time to development of end stage renal failure or symptomatic renal atherosclerotic disease requiring intervention.

Results
The cohort consisted of 7,208 participants; 1,759 diabetics and 4,859 with clinically manifest vascular disease. The median age was 57 years and 67% were male. Overall, 29% of the cohort achieved the treatment target for systolic blood pressure, 39% for diastolic blood pressure, 28% for total cholesterol, 31% for LDL cholesterol and 78% for albuminuria. The incidence rate for end stage renal failure and renal atherosclerotic disease reduced linearly with each additional treatment target achieved (p value less than 0.001). Achievement of any two treatment targets reduced the risk of renal complications, hazard ratio 0.46 (95% CI 0.26-0.82). For patients with clinically manifest vascular disease and diabetes, the hazard ratios were 0.56 (95% CI 0.28 – 1.12) and 0.28 (95%CI 0.10 – 0.79) respectively.

Conclusions
Clinical guidelines for cardiovascular disease management do reduce risk of renal complications in high risk patients. Benefits are seen with attainment of any two treatment targets.

Background

Current clinical practice guidelines for the management of patients with diabetes, hypertension and other atherosclerotic risk factors are geared to the prevention of cardiovascular disease and its complications.(1-3) However, cardiovascular diseases are not the only complications that can arise. Renal complications such as renal atherosclerotic disease (4) and end stage renal failure (ESRF) are of equal importance (5-9) though not as common.

There are few studies looking at the effects of combined cardiovascular treatment targets on renal complications; most are aimed at cardiovascular complications for which the targets were derived for. The risk of renal complications is low (10) despite the high prevalence of diabetes and hypertension (11, 12), and is usually confined to those with a genetic predisposition.(13, 14) In clinical practice, these complications arise after a long duration of disease and/ or treatment.(15) In the meantime, these patients undergo the same clinical management as those who are not predisposed to renal diseases. Studies of natural history of reno-atherosclerotic disease have shown that control of blood pressure do not necessarily prevent the progression of renal disease.(16) Therefore, it is relevant to determine whether the current clinical guidelines which have treatment targets geared for cardiovascular disease reduce the risk of renal complications.

This study will evaluate if the current 2007 European treatment guidelines for the prevention of cardiovascular disease concomitantly reduces the risk of renal complications in patients at high risk of vascular diseases. We assessed whether there is an inverse dose-response risk for renal complications by the number of treatment targets achieved or if there is an optimal number instead. We also determined if there are differences in targets to be achieved for two high risk patient groups; diabetics and those with clinically manifest vascular disease.

Methods

Study design and population

The Second Manifestations of ARTerial disease (SMART) study is a prospective cohort study that is conducted in the University Medical Centre (UMC) Utrecht. It commenced in September 1996 and is currently on-going. Patients aged 18 to 80 years with clinically manifest atherosclerotic vascular disease, newly referred to the UMC are invited to participate. Diseases that qualify for enrolment are internal carotid artery stenosis, transient ischemic attack, minor stroke, peripheral arterial disease, diabetic foot, angina pectoris, myocardial infarction, abdominal aortic aneurysm, and renal artery stenosis. Those treated for cardiovascular risk factors, including hyperlipidaemia, diabetes mellitus, hypertension and renal insufficiency are also recruited. Patients with terminal cancer, dependent in their daily activities

or not fluent in Dutch are excluded. All cohort members are followed up for a minimum of three years using biannual questionnaires.

The study was approved by the UMC Utrecht Institutional Review Board, which is approved by the Dutch Central Committee for research involving human subjects. The study was conducted in accordance with principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. The rationale and design of the SMART study have been described elsewhere.(17)

The current study selected all patients without end stage renal failure at baseline, recruited from September 1996 till February 2008. Every patient who was enrolled in the SMART study had physical examinations at baseline. Blood pressure was measured using a sphygmomanometer on both upper arms. The measurement was repeated on the arm with the highest value. The maximal value was used in this study.

Hypertension was diagnosed based on a systolic blood pressure of more or equal to 140 mm Hg and/or a diastolic blood pressure of more or equal to 90 mm Hg or being treated with two or more anti-hypertensive medications. Diabetes was determined based on self- report, hyperglycaemia at baseline (>7.0mmol L^{-1}), glycated haemoglobin (HbA1c) of more than 7% or being treated with glucose lowering therapy.

Clinical measurements

The exposure of interest was number of cardiovascular risk factor treatment targets achieved at baseline. Treatment targets were defined according to the 2007 European guidelines (18) for high risk patients and were limited to the management of risk factors that were modifiable using drug therapy. Targets were systolic and diastolic blood pressure, total cholesterol and low density lipoprotein (LDL) and albuminuria. For albuminuria status, the target to achieve was no micro-albuminuria. For those with albuminuria (micro-albuminuria or proteinuria), the desired target was the appropriate choice of therapy for albuminuria; treatment with either an angiotensin-converting enzyme inhibitor (ACEI) or angiontensin II receptor blocker (ARB). The choice of renin-angiotensin system (RAS) inhibitor use as a treatment goal is due to its effects on albuminuria, independent of blood pressure lowering. RAS inhibitors either improve albuminuria by reducing excretion (regression or stabilization)(19-21) or by delaying the time to progression.(22) Diabetics had an additional target; HbA1c. Patients had a maximum of five targets to achieve whereas those with diabetes had six. Table 1 depicts the treatment targets for this study. In the final analysis, the treatment

categories were condensed to five categories; ≤ 1: those who had none or only one target achieved, 2, 3, 4, ≥5 those who had five and/or all targets achieved.

Biochemical measurements

The biochemical assays measured in this study has been described in detail previously.(17) In summary, a venous blood sample was taken to determine lipid, glucose and creatinine levels. Plasma total cholesterol, triglycerides, glucose and creatinine were measured using a commercial enzymatic dry chemistry kit (Johnson and Johnson). HDL-cholesterol in plasma was determined using a commercial enzymatic kit (Boehringer-Mannheim) after precipitation of LDL and very low density lipoprotein (VLDL) with sodium phosphotungstate magnesium chloride. LDL-cholesterol was calculated using the Friedewald formula.

A urine sample was collected to measure micro-albuminuria and creatinine excretion. Creatinine was measured using a commercial enzymatic dry chemistry kit (Johnson and Johnson) and micro-albuminuria was determined with immunoturbidimetric assays (Boehringer-Mannheim).

Table 1 – Cardiovascular risk factor treatment targets

	Treatment targets	
Risk factor	**All patients without Diabetes**	**Diabetes mellitus**
Systolic blood pressure (mm Hg)	< 130	< 130
Diastolic blood pressure (mm Hg)	< 80	< 80
Total cholesterol (mmol L^{-1})	< 4.5	< 4.5
Low density lipoprotein (mmol L^{-1})	< 2.5	< 2.5
HbA1c (%)	-	< 6.5
Microalbuminuria and proteinuria	Treatment with ACEI/ARB or No proteinuria	Treatment with ACEI/ARB (Any albuminuric state)

ACEI : angiotensin-converting enzyme inhibitor
ARB : angiontensin II receptor blocker

Primary outcome

Renal outcomes were defined as a composite endpoint consisting of end stage renal failure requiring renal replacement therapy and reno-atherosclerotic disease requiring intervention; either arterial stenting or bypass grafting. Time to any renal endpoint was the outcome of interest.

During the follow up period, outcomes were determined through questionnaires biannually. Participants provided information on hospitalization and clinic visits. Original source documents were reviewed if a hospitalization or clinic visit was reported. All hospital discharge letters and results of related laboratory and

radiological examinations were collected. Each event was classified according to a standard operating procedure. All endpoints were adjudicated by three members of the SMART Endpoint Committee, comprising of physicians from different departments.

The participants were followed up till death or refusal to participate.

Statistical analysis
Analysis was performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Baseline data displayed was calculated using a general linear model for continuous variables adjusted for age and sex. P values for trends across the five treatment target groups were estimated using Mantel Haenszel's $\chi 2$. Ordinal data was tested using ordinal tests (Kendall's tau).

Confounders were selected a priori for testing based on literature. Variables selected were age, sex, waist circumference, history of coronary artery disease, cerebrovascular disease, peripheral arterial disease and renal disease, smoking status (never, former, current), alcohol consumption (never, ever, recently stopped, current), haemoglobin levels, albuminuria status (no, micro-albuminuria, overt proteinuria) and estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula. These were then determined to be included in the final model if there was a change in the hazard ratio (HR) estimate of more than 10 percent when compared to the crude estimate.(23) Medication was seen as not confounders in this study because the type and number of drugs used were primarily to achieve treatment targets. Medications which had independent action on renal function such as ACEIs and ARBs were already included as a treatment target for albuminuria.

A multivariate Cox proportional hazards model was used to determine the association between the number of treatment targets achieved and the risk of renal complications. Hazard ratios and the 95% confidence intervals were calculated for each number of treatment targets achieved, with the category of one or less targets achieved as reference. The likelihood ratio test was used to determine the significance of the variables included in the model. A p value of less than 0.05 (two tailed) was considered to be statistically significant. Analysis was performed with two adjustments; 1) adjustment for statistically significant confounders 2) adjustment for statistically significant confounders, age and sex. For participants from the whole cohort, the significant confounders were hypertension, albuminuria, eGFR and haemoglobin levels. For those with clinically manifest vascular disease, the confounders were hypertension, albuminuria and eGFR levels. Only eGFR and haemoglobin were significant confounders for participants with diabetes. The Wald

test was used to determine if treatment targets were significant as a linear variable. A p value of less than 0.05 was considered to be statistically significant.

The assessment of hazard ratios for individual treatment targets was done at a quantitative level. There was a statistically significant correlation between systolic and diastolic blood pressure. Pearson's correlation coefficient *r* was 0.68 with a p value of less than 0.001 (two tailed). There was stronger correlation between total cholesterol and LDL levels, Spearman's correlation coefficient *rho* 0.88 was statistically significant at a p value of less than 0.001 (two tailed). When testing the hazard ratios at the risk factor level, due to the high correlation between these variables, only one from each set of these factors was chosen; systolic blood pressure and LDL. Both systolic blood pressure and LDL cholesterol levels are the more important treatment targets for the prevention of cardiovascular disease.(24, 25) Cox proportional hazards assumptions were tested visually using hazard and *Log Minus Log* (LML) plots.

Incidence rates were calculated using the number of events, divided by the total person time in years. The time period is calculated from baseline till event, death or loss to follow up.

Missing data was reviewed to determine if it was Missing At Random. Those missing at less than one percent were imputed using mean or median values where applicable. Single imputation using a linear regression with an error term was done for other variables. This was done for four variables; albuminuria (6.2% missing), LDL (6.9% missing), waist circumference (17.6% missing) and HbA1c for diabetics (38.1% missing).

Results

Between September 1996 and February 2008, 7,292 participants were enrolled in the SMART study cohort. Of these, the 84 participants who had end stage renal failure at baseline were excluded from this study. At the end of the study period, 670 had died and 253 were lost to follow up. The median duration for follow up was 4.21 years (IQR 2.08–7.11).

Table 2—Clinical profile and end points of study population according to number of cardiovascular risk factor treatment targets achieved at baseline

	Treatment Targets Achieved					
Characteristics	**≤1**	**2**	**3**	**4**	**≥5**	**p value for trends**
n	2813	1652	1785	593	365	
Age (years)[a]	57 (49,66)	57 (48,66)	56 (47,64)	58 (50,66)	55 (46,64)	
Male sex	65.6 (1845)	65.9 (1088)	67.3 (1202)	73.9 (438)	75.1 (274)	0.001
Smoking						
Current	32.1 (902)	33.7 (556)	30.3 (541)	29.3 (174)	30.7 (112)	
Former	41.7 (1174)	42.3 (698)	45.2 (806)	43.8 (260)	46.3 (169)	
Never	26.2 (737)	24.1 (398)	24.5 (438)	26.8 (159)	23 (84)	
Packyears	18 ± 0.36	19 ± 0.46	18 ± 0.45	18 ± 0.77	17 ± 0.99	
Alcohol consumption						0.001
Never	20.8 (584)	21.7 (358)	19.9 (355)	18.2 (108)	18.1 (66)	
Ever	9.7 (273)	9 (148)	9.8 (175)	10.8 (64)	12.9 (47)	
Recently stopped	29.5 (831)	28.5 (470)	23.1 (412)	16.5 (98)	14.2 (52)	
Current	40 (1125)	40.9 (676)	47.2 (843)	54.5 (323)	54.8 (200)	
History of:						
Coronary artery disease	26.5 (745)	36.7 (607)	49 (875)	63.4 (376)	71 (259)	0.001
Cerebrovascular disease	19.9 (561)	20.8 (343)	17.9 (319)	18.4 (109)	15.6 (57)	0.027
Peripheral arterial disease	16.8 (472)	17.1 (283)	13 (232)	8.4 (50)	7.9 (29)	0.001
Previous kidney disease	2.6 (74)	2.7 (44)	2.7 (48)	4.9 (29)	3.6 (13)	
Any of the above	56.7 (1595)	64.5 (1065)	71.8 (1281)	82.1 (487)	87.1 (318)	0.001
BMI (kg m^{-2})	27 ± 0.08	27 ± 0.11	27 ± 0.10	27 ± 0.18	26 ± 0.23	0.001
Waist circumference (cm)	95 ± 0.22	94 ± 0.29	93 ± 0.28	94 ± 0.49	92 ± 0.62	0.001
Systolic BP (mm Hg)	154 ± 0.34	141 ± 0.44	135 ± 0.43	130 ± 0.74	119 ± 0.95	0.001
Diastolic BP (mm Hg)	91 ± 0.20	82 ± 0.26	79 ± 0.25	75 ± 0.44	71 ± 0.56	0.001
S. Glucose (mmol L^{-1})	6.5 ± 0.04	6.6 ± 0.06	6.1 ± 0.05	6.6 ± 0.09	5.9 ± 0.12	0.001
HbA1c (%)	6.1 ± 0.02	6.2 ± 0.03	5.9 ± 0.03	6.1 ± 0.05	5.8 ± 0.06	0.001
Total cholesterol (mmol L^{-1})	5.95 ± 0.02	5.45 ± 0.03	4.87 ± 0.03	4.02 ± 0.05	3.76 ± 0.06	0.001
HDL cholesterol (mmol L^{-1})	1.28 ± 0.01	1.25 ± 0.01	1.25 ± 0.01	1.24 ± 0.02	1.20 ± 0.02	0.001
LDL cholesterol (mmolL^{-1})	3.75 ± 0.02	3.23 ± 0.03	2.84 ± 0.03	2.04 ± 0.05	1.95 ± 0.06	0.001
Triglycerides (mmol L^{-1})	2.05 ± 0.04	2.16 ± 0.05	1.74 ± 0.05	1.65 ± 0.09	1.38 ± 0.11	0.001

Creatinine (µmol L^{-1})	92.3 ± 0.87	93.9 ± 1.13	92.1 ± 1.09	91.6 ± 1.88	93.1 ± 2.40	
Microalbuminuria	21.9 (616)	16.5 (272)	9.7 (174)	13.8 (82)	7.9 (29)	0.001
Proteinuria	3.6 (102)	2.8 (46)	1.4 (25)	1.9 (11)	0.8 (3)	
eGFR (mL min^{-1} 1.73m^{-2})	78.1 ± 0.33	77.6 ± 0.43	77.9 ± 0.41	78.7 ± 0.71	78.1 ± 0.91	
Haemoglobin (mmol L^{-1})	9.0 ± 0.01	8.8 ± 0.02	8.8 ± 0.02	8.7 ± 0.03	8.6 ± 0.04	0.001
Patients with Hypertension	84.9 (2387)	62.3 (1029)	54.2 (968)	55.3 (328)	41.4 (151)	0.001
Duration of hypertension (years)	6.0 ± 0.19	5.1 ± 0.24	4.8 ± 0.23	5.5 ± 0.40	4.5 ± 0.51	0.001
Use of BP lowering drugs	62.2 (1749)	61.8 (1021)	64.8 (1157)	75.9 (450)	79.2 (289)	0.001
Type of BP lowering drugs						
-blockers	29.6 (834)	36 (594)	42.7 (762)	50.9 (302)	60.8 (222)	0.001
Diuretics	18.3 (516)	16.6 (274)	16.6 (296)	22.8 (135)	16.4 (60)	
ACE inhibitors	20.5 (576)	22.8 (377)	26.8 (478)	33.1 (196)	32.3 (118)	0.001
ARBs	7.2 (203)	6.6 (109)	7.1 (126)	11.5 (68)	8.5 (31)	
Calcium channel blockers	15.2 (428)	15.7 (260)	16.1 (288)	20.2 (120)	18.1 (66)	0.015
Number of BP lowering drugs						0.001
1	27.3 (768)	26.8 (443)	26.3 (470)	28.8 (171)	37.5 (137)	
2	18.3 (515)	18.9 (313)	22.7 (406)	27 (160)	24.7 (90)	
3	7.6 (214)	9.1 (151)	10.2 (182)	13.8 (82)	14.8 (54)	
≥ *4*	1.8 (51)	2.1 (33)	2.1 (36)	3.9 (23)	1.4 (5)	
Use of Lipid lowering drugs	32.7 (920)	43.6 (721)	57 (1017)	72.7 (431)	77.3 (282)	0.001
Patients with Diabetes	24.4 (686)	28.8 (475)	17.8 (318)	34.7 (206)	20.3 (74)	
Duration of diabetes (years)	1.4 ± 0.09	1.8 ± 0.12	1.3 ± 0.12	2.2 ± 0.21	1.3 ± 0.26	
Use of oral anticoagulants	43.1 (1211)	51.7 (854)	60 (1071)	74.5 (442)	77.3 (282)	0.001
Endpoints						
End stage renal failure	35	14	5	2	1	
Reno-atherosclerotic disease	15	3	5	1	0	
Number of total events	50	17	10	3	1	
Total person years	14209	8195	7766	2205	1218	
Incidence rate per 1000 population	3.52	2.07	1.29	1.36	0.82	< 0.001

Continuous variables are expressed as age and sex adjusted means with SE; categorical variables are expressed as percentages with numbers in parenthesis; [a]median with interquartile range

Characteristics of the participants

The cohort consisted of 7,208 participants. There were 4,859 (67.4%) with clinically manifest vascular disease and 1,759 (24.4%) diabetics, both conditions not mutually exclusive. Other participants had risk factors without clinical evidence of atherosclerotic disease. The median age was 57 years (IQR 48 – 66) and 67.2% were male. Overall, 29.1% of the cohort fulfilled the treatment target for systolic blood pressure, 38.5% for diastolic blood pressure, 28.2% for total cholesterol, 30.7% for LDL cholesterol and 77.9% for albuminuria. About 47% of those prescribed beta blockers had ischaemic heart disease. Only 12% of those prescribed beta blockers were due to hypertension.

Table 2 summarizes the baseline characteristics of the whole cohort. Those who achieved all five targets were more likely to be male, had more often a previous history of coronary artery disease, consumed alcohol, had lower levels of triglycerides and micro-albuminuria or proteinuria was less common.

Among those with clinically manifest vascular disease, 29.2% achieved the systolic blood pressure treatment target, 43.3% the diastolic blood pressure target, 33.7% the total cholesterol target, 34.8% the LDL target and 78.9 % the appropriate treatment target for albuminuria. Among the diabetic participants, 24.6% achieved the systolic blood pressure treatment target, 38.1% the diastolic blood pressure target, 33.9% the total cholesterol target, 38.2% the LDL target, 41% achieved appropriate treatment of albuminuria and 26.9% achieved the HbA1c target. The diabetics had poorer control of blood pressure and less use of RAS inhibitors for the treatment of albuminuria than the general cohort.

Primary objective

At the end of the follow up period, there were 81 renal endpoints (Table 2). The unadjusted incidence rate for renal endpoints was 2.41 per 1,000 person-years. There were 57 renal endpoints for end stage renal failure with an incidence rate of 1.7 per 1,000 person-years. For renal atherosclerotic disease, there were 24 events with an incidence rate of 0.71 per 1,000 person-years. There was a statistically significant linear trend (p value less than 0.001) for incidence rate reduction with increasing target achievement.

The attainment of two or more treatment targets at baseline decreased the unadjusted risk of renal endpoint development for all groups except the diabetics (Table 3). The decreased unadjusted risks were statistically significant for trends. After adjustment for confounding variables such as age, sex, eGFR, albuminuria

Table 3 – Hazard ratios of renal endpoints by number of cardiovascular risk factor treatment targets achieved

	All			Clinically Manifest Vascular Disease			Diabetes		
	HR	(95% CI)	p for trends	HR	(95% CI)	p for trends	HR	(95% CI)	p for trends
n	7208			4859			1759		
number of events	81			52			28		
Renal endpoint									
Model 1 (crude)									
Targets achieved									
≤1	1.00		0.001	1.00		0.0001	1.00		0.704
2	0.59	(0.34, 1.02)		0.51	(0.26, 1.00)		0.69	(0.27, 1.81)	
3	0.36	(0.18, 0.71)		0.23	(0.09,0.59)		1.09	(0.39, 3.05)	
4	0.37	(0.12, 1.19)		0.29	(0.07, 1.22)		0.99	(0.29, 3.47)	
≥5	0.22	(0.03, 1.59)		0	0		0	0	
Model 2 adjusted	a			b			c		
Targets achieved									
≤1	1.00		0.018	1.00		0.021	1.00		0.174
2	0.49	(0.28, 0.86)		0.58	(0.29, 1.14)		0.37	(0.13, 1.00)	
3	0.54	(0.27, 1.09)		0.38	(0.15, 0.99)		0.62	(0.22, 1.80)	
4	0.46	(0.14, 1.51)		0.64	(0.15, 2.69)		0.54	(0.15, 1.99)	
≥5	0.42	(0.06, 3.11)		0	0		0	0	
Model 3 adjusted[d]									
Targets achieved									
≤1	1.00		0.013	1.00		0.018	1.00		0.107
2	0.46	(0.26, 0.82)		0.56	(0.28, 1.12)		0.28	(0.10, 0.79)	
3	0.51	(0.26, 1.03)		0.36	(0.14, 0.95)		0.39	(0.12, 1.26)	
4	0.49	(0.15, 1.60)		0.63	(0.15, 2.67)		0.56	(0.16, 2.01)	
≥5	0.37	(0.05, 2.76)		0	0		0	0	
Risk factors [e]									
SBP (per mmHg)	1.02	(1.01, 1.03)		1.02	(1.01, 1.03)		1.03	(1.01, 1.05)	
LDL (per mmol/L)	1.26	(1.04, 1.53)		1.31	(1.02, 1.68)		1.21	(0.83, 1.75)	
Treatment for albuminuria	0.90	(0.57, 1.43)		0.97	(0.55, 1.70)		0.58	(0.24, 1.39)	
HbA1c (per %)	1.18	(1.01, 1.38)		1.20	(0.96, 1.49)		1.44	(1.12, 1.84)	

[a]adjusted for hypertension, albuminuria, eGFR and haemoglobin levels, [b]adjusted for hypertension, albuminuria and eGFR levels
[c]adjusted for eGFR and haemoglobin levels, [d]adjusted for Model 2 + age and sex
[e]adjusted for age, sex, hypertension, albuminuria, eGFR and haemoglobin level

status, haemoglobin and hypertension, the hazard ratios for renal endpoints remained statistically significant for trends in the overall cohort and for those with clinically manifest vascular disease.

Secondary objective
When individual cardiovascular risk factors were compared, there was an increased risk of developing any renal endpoint for each increase in unit of systolic blood pressure, LDL and HbA1c levels. The hazard ratios for all risk factors were similar for all subgroups of patients, except for the hazard ratio of HbA1c among diabetics. Each unit increase in HbA1c levels suggests a higher rate of increase in the hazard ratio for renal complications in diabetics, than in the general cohort or in those with clinically manifest vascular disease.

Discussion
In this cohort study, we studied whether the attainment of treatment targets established for the prevention of cardiovascular disease would concomitantly reduce the rate of renal complications. Based on the current 2007 European clinical practice guidelines, we observed that the achievement of any two or more treatment targets at baseline do reduce the rates of renal complications, for patients at high risk of atherosclerotic disease and for those with clinically manifest vascular disease. Although this observation was not statistically significant for diabetics, it may be clinically beneficial. A previous study of diabetics showed a decline in renal complications if three or more treatment targets were achieved.(26) With increasing treatment targets achieved, a lower haemoglobin concentration level was seen. However, it was not associated with poorer outcomes. This may be a result of more liberal use of RAS inhibitors, which decreases erythropoiesis.(27) There was no optimal number of cardiovascular risk factor treatment targets to achieve. The risk of renal complications decreased linearly as more targets were attained; consistent with the notion that no J-curve exists for renal outcomes.

There are distinct differences between the diabetic and clinically manifest vascular disease population cohorts. Primarily, the decreased hazard ratios for renal outcomes in diabetics were only observed after the model was adjusted for renal confounders such as eGFR and haemoglobin levels. This may be because once chronic renal disease has set in, achievement of treatment targets alone is insufficient to reduce or retard the rate of complications in diabetics. This was not the case for those with manifest vascular disease, where there was a consistent reduced risk of renal complications even with non-adjustment for renal confounders. The second distinct difference is, there does not appear to be a gradient decreased hazard ratio for diabetics as the number of treatment targets

achieved increased. A previous study of treatment targets and cardiovascular outcomes in diabetics showed a graded response.(28)

The low percentage of participants achieving treatment targets is consistent with other countries. In a Swedish study, only 17% of their hypertensive population had achieved a systolic blood pressure target of less than 140 mmHg and 64% achieved the diastolic blood pressure target of less than 90 mmHg.(29) In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, which was a multi country randomized control trial, only 16.3% had achieved the total cholesterol target of less than 5.0 mmol/l at baseline.(30) In the United Kingdom, only 19.7% and 26.9% achieved blood pressure and cholesterol targets respectively.(31) More patients achieving the target for diastolic blood pressure than for systolic blood pressure is also consistent with other studies.(29) This is probably reflective of older, stiffer arteries which is expected in high risk patients, and not because therapies used were more effective in lowering diastolic blood pressure.

Looking at the individual cardiovascular risk factor levels, the findings amongst the study population is consistent with current literature. With increasing systolic blood pressure (32), LDL and HbA1c, the risk for renal complications increases statistically significantly. Considering the similar risks for renal complications in all cohort groups with increasing systolic blood pressure and LDL levels, the treatment of HbA1c levels is crucial in diabetics. The non-significant decreased hazard ratio seen in all patient groups for the treatment of albuminuria may be due to two reasons; suboptimal dosing or discontinuation of medication due to non-response to blood pressure lowering with ACEI or ARB use. Inadequate dosing of ACEI or ARB's causes less anti-albuminuric activity thus there is suboptimal reduction in albuminuria. Aside from this, non-response to blood pressure reduction does not mitigate the effects of anti-albuminuric activity; therefore discontinuation of these drugs increases the risk of renal endpoints.(33)

This study has a few limitations. The number of treatment targets achieved was determined only at baseline. Over the entire duration of follow up, patients may fluctuate between different categories of targets achieved, depending on clinical management received.

The duration of follow up may be insufficient for ESRF development in many patients. In the UKPDS study, development of renal endpoints occurred in only 0.8% after a median of 10 years.(34) Aside from this, the number of events that occurred was small, 81 in total and in diabetics 28. This may explain the lack of power in proving statistical significance, except for the tests for trends. A longer follow up duration would provide more accurate estimates and therefore stronger

evidence. Nevertheless, this study had a total sample size of 7,208 participants with a sum of 33, 593 person-years of follow up. This is sizable.

Another key strength of this study is the use of hard endpoints; end stage renal failure and symptomatic renal vascular disease requiring intervention. We did not use surrogate endpoints such as rate of GFR decline because in diabetics and in other patient populations, the calculated GFR using the MDRD formula underestimates the rate of renal function loss.(35-37) It also becomes inaccurate as renal function improves; real GFR can fluctuate between 35 to 90 mL min^{-1} $1.73m^{-2}$ for an eGFR of 60 mL min^{-1} $1.73m^{-2}$.(38) Aside from this, stabilization or regression of renal function decline has been known to occur in patients treated with ACEI despite having severe GFRs.(39) In this study, the maximum survival time for an eGFR of less than 15 mL min^{-1} $1.73m^{-2}$ was 6.27 years.

These hard endpoints reflect different pathophysiological mechanisms. End stage renal failure may be caused by both micro and macrovascular changes whereas renal vascular disease is caused by macrovascular changes. Despite these differing pathophysiological mechanisms, these findings are suggestive that the same treatment targets reduce their risk of development.

Conclusions

This study shows that current clinical practice guideline targets for the prevention of cardiovascular disease are useful in concomitantly reducing the risk of renal complications; in any patient population at high risk for vascular diseases. If more patients can be adequately treated to achieve the cardiovascular risk factor treatment targets, there will be important reductions in renal complications.

SMART Study Group

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Chapter 4.2

Impact of cardiac care variation on ST- Elevation Myocardial Infarction outcomes

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Abstract

Aims
Developing countries have wide variations in cardiac-care provision due to limited resources. This causes challenges in providing the best reperfusion strategy for patients with ST-Elevation Myocardial Infarction (STEMI). We assessed the impact of variation in cardiac-care provision and reperfusion strategies on patient outcomes.

Methods
Data from a prospective national registry of acute coronary syndromes was used. The 30-day all-cause mortality in 4562 patients with STEMI was assessed by 1) cardiac-care provision (specialist versus non-specialist centres) and 2) primary reperfusion therapy (thrombolysis or primary percutaneous coronary intervention (P-PCI)). All patients were risk stratified by their disease severity using the Thrombolysis-In-Myocardial-Infarction (TIMI) risk score.

Results
Patients presenting with STEMI in specialist and non-specialist cardiac-care facilities had similar severity. 68.3% and 73.2% of patients in specialist and non-specialist cardiac-care facilities were given acute reperfusion therapy. Timely reperfusion was low; 24% versus 31.1% respectively for in-hospital fibrinolysis, and 27.5% for P-PCI. Specialist centres had a statistically significant higher use of evidence-based treatments. The adjusted 30-day mortality rate was 13% (95% confidence interval: 8 - 19) and 12% (95%CI: 5 - 18) for specialist and non-specialist cardiac-care facilities (p value 0.63). Adjusted 30-day mortality for in-hospital fibrinolytics and P-PCI was 7% (95%CI: 5 -9) and 7% (95%CI: 3 -11) respectively (p value 0.75).

Conclusions
Variation in cardiac-care provision and reperfusion strategy did not adversely affect patient outcomes. However, to further improve cardiac-care, increased evidence-based resources, improvement in quality of P-PCI care and reduction in door-to-reperfusion times should be achieved.

Introduction

The primary aim of acute ST-elevation myocardial infarction (STEMI) management is to achieve early and complete reperfusion of the blocked artery. The prognosis of STEMI depends on a variety of factors, among these; severity of presentation, time from presentation to primary treatment and choice of reperfusion therapy.(1) Studies have conclusively proven that patient outcomes for STEMI improve with use of evidence-based treatment (2) and timely reperfusion.(3)

In developing countries, there is a wide variation in cardiac-care provision (4, 5) and there are challenges to providing the best reperfusion strategy as recommended by international guidelines. The current recommended reperfusion strategy for STEMI is the Percutaneous Coronary Intervention (PCI).(6) Malaysia, a middle-income developing country, has a dual public and private healthcare system, whereby up to 65% of the population is serviced by the public system.(7) The challenges faced are limited resources and a relative lack of specialist cardiac-care centres (8) having primary-PCI (P-PCI) facilities for STEMI management.

As in many other developing countries, the primary reperfusion strategy is thrombolytic therapy, mainly streptokinase.(4, 5, 8) At present, public-funded cardiac-care facilities equipped for P-PCI exist mainly in the larger, more economically developed urban areas. This study aimed to assess the impact of variation in cardiac-care provision and reperfusion strategies on patient outcomes.

Methods

Study population

The National Cardiovascular Disease Database –Acute Coronary Syndrome Registry (NCVD-ACS) in Malaysia is a prospective registry of patients who present with acute coronary syndrome (ACS) and it commenced in January of 2006. Patient recruitment occurs at 16 hospitals with varying cardiac facilities, 15 of which are publicly funded; 14 from the Ministry of Health (MOH), one university hospital and the corporatised National Heart Institute of Malaysia. The 14 MOH hospitals represent the general hospitals in all the states of Malaysia, including the main tertiary referral centre of the country. Of these 16 participating sites, six provide specialist cardiac-care services and have on-site P-PCI and cardiac surgical services. The remaining ten sites are non-specialist cardiac-care facilities. Their cardiac-care services are run by general physicians and do not have on-site P-PCI or cardiac surgical back-up. These differences in cardiac-care provision are due to financial and human resource constraints faced by the public healthcare service. There are no private-for-profit centres reporting to the NCVD-ACS.

Details of past medical history, presenting symptoms, reperfusion therapy, in-hospital clinical care and health outcomes till one year post ACS are recorded for all

patients aged 18 and above. Ethics approval for the NCVD-ACS was obtained from the Ministry of Health Medical Research and Ethics Committee (MREC). A waiver of informed consent was approved by the MREC. As an alternative, a public notice is displayed at all sites and patients are given the option to opt out of the NCVD-ACS. This study complies with the Declaration of Helsinki.

Anonymised data from patients who were registered from 1st January 2006 till 31st December 2008 with 30-day follow-up data were used. For this study, all patients presenting with STEMI were selected.

Clinical details

The diagnosis and confirmation of STEMI was based on the following; signs and symptoms of ACS (chest pain or overwhelming shortness of breath), elevated serum cardiac biomarkers and an ST elevation in contiguous leads of the electrocardiogram or the development of a new left bundle-branch block (LBBB). Clinical care provided was at the discretion of the treating physician or cardiologist. A previous medical history stated to be 'not known' or 'not recorded' in the registry records was classified as absent for the purposes of analysis in this study.

Severity of STEMI presentation

Risk stratification by severity of STEMI presentation was done using the TIMI risk score for STEMI. This risk score has been validated for Malaysia.(9) The TIMI risk score consists of the following components; age, systolic blood pressure, heart rate, Killip classification, infarct location or LBBB, history of diabetes, hypertension or angina pectoris, weight and time-to-reperfusion (thrombolytics or P-PCI). The time-to-reperfusion was modified for the Malaysian population to be door-to-needle time or door-to-balloon time, instead of symptom-to-reperfusion time due to insufficient information on symptom-to-time to presentation. Patients who did not undergo any reperfusion strategy were given a score of 1. The TIMI STEMI scoring mechanism has been published (10) and is given in the Appendix. Scores of ≤ 3, 4-6 and ≥ 7 are in the low, intermediate and high risk categories, respectively.

Patient outcomes

The clinical outcome of interest was 30-day all-cause mortality, which includes in-hospital mortality. Mortality details were obtained via hospital records and phone calls to the patient/relatives after 30-days. Annual confirmation of mortality for the NCVD-ACS is done through record linkages with the Malaysian National Registration Department for deaths. The IBM® InfoSphere® QualityStage (http://www-01.ibm.com/software/data/infosphere/qualitystage/) was used for record matching purposes. Rule sets for record matching were prepared based on methods available in the software. These were executed for key identifier variables

such as name, identification card number, year and month of birth. All Malaysians have a unique numerical identification number, thereby enabling accurate record linkages.

Outcomes comparisons were analysed for cardiac-care provision and acute reperfusion therapies:

1) Cardiac care provision; specialist cardiac-care versus non-specialist cardiac-care facilities
2) Acute reperfusion therapies; thrombolytics (pre- and in-hospital), P-PCI and conservative clinical management

Statistical analyses

Data analyses that ignores missing data (complete case analysis) has been shown to give biased results, therefore we imputed missing data.(11, 12) Missing data was reviewed to determine if it was Missing At Random prior to imputation. Five variables with missing values <5% had mean or median values imputed; age 0.1%, systolic blood pressure 1.0%, heart rate at presentation 1.9%, sex 2.1% and smoking status 4.1%. Two variables; door-to-reperfusion time, 21.6% and weight, 36.0% were imputed using single imputation with a random error term method. For sensitivity analyses, we ran a complete case analysis, which did not materially change the results (direction and statistical significance) of this study.

Baseline differences between patients presenting at facilities with and without specialist cardiac-care services were determined using an unequal variance t-test for continuous variables and a Pearson's chi-square test for categorical variables. *P* values for differences in severity of STEMI presentation by cardiac-care provision and reperfusion therapies were tested using Wilcoxon Mann-Whitney tests.

Comparisons of primary acute reperfusion therapies and crude mortality rates by cardiac-care provision were tested using Pearson's chi-square test. Comparisons of in-hospital treatment and adjusted mortality rates were assessed using the Generalized Estimation Equations (GEE) to adjust for clustering effects of cardiac care facilities. An independent working model structure was used. Adjusted mortality rates were obtained using the estimated marginal means and differences were tested using the Wald chi-square tests. Comparisons of overall and in-hospital fibrinolysis 30-day mortality rates for cardiac-care facilities were adjusted for STEMI severity (described by TIMI risk score).(13) For centre mortality comparisons for pre-hospital fibrinolysis, conservative therapy, as well as reperfusion strategy comparisons for specialist cardiac-care facilities, 30-day mortality rates were adjusted for STEMI severity as a linear term due to the small number of events.

Two sided p values less than 0.05 were considered statistically significant. All analyses were performed using SPSS Statistics Version 17.0 for Windows (SPSS Inc., Chicago, Il, USA).

Results

There were 4701 patients registered with STEMI, of which 139 (2.96 %) were excluded because there was no information on their primary reperfusion therapy. 54.8% of them presented to specialist cardiac-care facilities. 75% were given fibrinolytics (12% pre-hospital and 63% in-hospital fibrinolytics), 7.6% had P-PCI and the remainder received conservative management. Streptokinase formed up to 97.7% of fibrinolytics given in-hospital.

Baseline characteristics

The median age for those presenting with STEMI was 56 (IQR 48, 65) and up to 85% were males (Table 1). The racial distribution was not representative of the Malaysian population, with >11% higher proportion of Indians than the general population, and a much lower proportion of other races.

Those presenting at specialist cardiac-care facilities had more chronic diseases such as hypertension, diabetes and renal impairment, had higher proportions of patients with a documented history of coronary artery disease of >50% and prior myocardial infarctions, as well as higher proportions of beta-blocker and lipid-lowering drug use.

Severity of presentation, reperfusion therapy and in-hospital clinical management

Despite higher proportions of severe disease among STEMI patients presenting to specialist cardiac-care facilities, there was no statistical difference in severity of STEMI presentation, as described by the TIMI risk score (Table 1). There were similar proportions of low, intermediate and high risk STEMI patients presenting to both specialist and non-specialist cardiac-care facilities respectively.

Among those presenting to specialist cardiac-care facilities, 68.3% of them received acute reperfusion therapy (either fibrinolytics, 54.5% or P-PCI, 13.8%) compared to 73.2% presenting to non-specialist cardiac-care facilities (Table 2), p value 0.4. Specialist cardiac-care facilities received a 5.2% higher proportion of referred patients treated with pre-hospital fibrinolytics than non-specialist cardiac-care facilities. Overall, timely reperfusion of <30minutes of door-to-needle time for fibrinolytic therapy and <90 minutes of door-to-balloon time for P-PCI was very low; about 1 in 4 respectively. However about two-thirds of patients received reperfusion in < 240 minutes, irrespective of type of facility. Specialist cardiac-care facilities had a significantly lower proportion of timely reperfusion for fibrinolytic

Table 1 - Baseline characteristics of study population overall and by type of cardiac care facility

Variables	Overall Population	Specialist Cardiac care facilities	Non cardiac care facilities	*p value
n	**4562**	**2501**	**2061**	
Demographics				
Age (years)	56 (48, 65)	56 (48, 65)	56 (48, 65)	0.32
Female	15.1	15.2	15.1	
Weight (kg)	67 (58, 77)	67 (59, 76)	68 (57, 78)	0.12
Race				0.001
Malay	53	43.7	64.3	
Chinese	20.3	27	12.2	
Indian	18.2	21.3	14.4	
Others	8.4	8	9	
Risk factors				
Smoking status				0.001
Current	51	50.9	51.1	
Past	19.7	18	21.7	
Never	29.4	31.1	27.2	
Diabetes	36.5	38.4	34.2	0.003
History of hypertension	48.9	51.1	46.2	0.001
Renal impairment (Mod- severe)	3.2	4	2.2	0.001
Cardiovascular history				
Prior myocardial infarction	9.5	11.6	6.9	0.001
Peripheral vascular disease	0.3	0.3	0.3	0.86
Cerebrovascular disease	2.7	3	2.5	0.32
Prior angina	52.4	52	52.9	0.52
Documented CAD >50%	5.6	8.4	2.3	0.001
Diabetes/ HPT/Prior angina	79.8	79.8	79.9	0.94
Medications at presentation				
-blockers	13	16.2	9	0.001
Calcium channel blockers	5.1	5.8	4.2	0.02
Lipid lowering	16.7	19.5	13.3	<0.001
Anti-arrhythmic	1.8	2	1.7	0.51
Presenting characteristics				
Infarct location				
Anterior or LBBB	59.7	58.9	60.7	0.23
Inferior	46	46.1	45.9	0.89
Killip class II - IV	29.2	30.5	27.7	0.04
Heart rate > 100 bpm	17.7	17.4	18	0.56
Systolic BP < 100 mmHg	8.4	8.6	8.1	0.58
TIMI risk score	4 (2,5)	4 (2,5)	4 (2,5)	0.66
TIMI risk score categories				0.90
Low risk (score 3)	48	48.1	47.8	
Intermediate risk (score 4-6)	36.4	36.3	36.6	
High risk (score 7)	15.6	15.6	15.6	

Data are % for categorical variables and median (interquartile range) for continuous variables
* for comparison between type of facilities

Table 2 - Reperfusion strategies, in-hospital medication and patient outcomes by type of cardiac care facility

Variables	Specialist Cardiac care facilities	Non cardiac care facilities	p value
Intervention	**2501**	**2061**	
Fibrinolytics given inhospital	54.5 (1363)	73.2 (1509)	<0.001
Prehospital Fibrinolytics given	14.4 (359)	9.2 (190)	<0.001
Primary PCI	13.8 (346)	NA	
No emergency reperfusion	17.3 (433)	17.4 (359)	0.93
Door to reperfusion > 4 hours	35.6 (891)	34.7 (716)	0.53
Door to needle time <30mins *	24 (327)	31.1 (469)	<0.001
Door to balloon time <90mins	27.5 (95)	NA	
In-hospital Medication			
Aspirin	96.3 (2408)	90.7 (1870)	0.001
ADP antagonist	85 (2127)	48.7 (1004)	0.03
GlycoProtein Receptor inhibitor	5.4 (134)	1.3 (27)	0.002
Unfractionated heparin†	15.3 (382)	4.3 (88)	0.006
Low Molecular Weight Heparin†	27.3 (683)	43.1 (889)	0.08
Statin	93.8 (2345)	86.4 (1780)	<0.001
other Lipid lowering agent	3 (75)	5.6 (116)	0.04
Beta Blocker	71.3 (1782)	56.2 (1159)	0.001
Calcium Channel Blocker	8.2 (204)	5.4 (112)	0.07
Diuretics	25.6 (641)	25.5 (525)	0.97
ACE-Inhibitors	56.5 (1413)	58.3 (1202)	0.81
Angiotensin-II Receptor Blockers	5.5 (137)	3.9 (81)	0.35
Anti arrhythmic agents	7.6 (189)	8.2 (168)	0.77
30-day mortality rates			
Prehospital Fibrinolytics given			
Crude death rate	12.5 (45)	8.4 (16)	0.83
Adjusted death rate‡	9 (7, 11)	7 (4, 9)	0.18
Fibrinolytics given inhospital			
Crude death rate	9.5 (130)	8.9 (134)	0.78
Adjusted death rate‡	10 (7, 14)	9 (4, 14)	0.68
Primary PCI			
Crude death rate	11.8 (41)	NA	
Adjusted death rate‡	7 (3, 11)	NA	
No emergency reperfusion Rx			
Crude death rate	17.1 (74)	16.2 (58)	0.66
Adjusted death rate‡	12 (10, 15)	11 (3, 19)	0.77

Data are % (n), Adjusted death rate, % (95%CI)

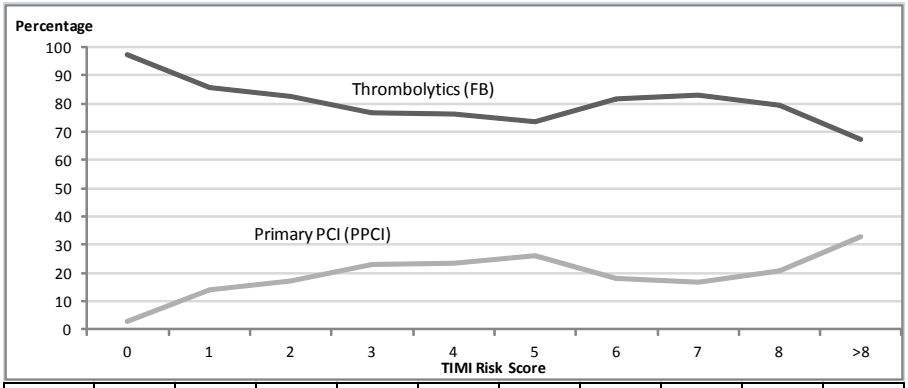
* In-hospital fibrinolytics

†FB use included in GEE model

‡Adjusted for TIMI risk score

therapy compared to non-specialist facilities (Table 2). There were significant differences in in-hospital drug prescription by type of cardiac-care facility. There were consistently higher use of aspirin, ADP antagonists, beta blockers, statins, and unfractionated heparin in the specialist cardiac-care facilities. However, there was a lower use of low-molecular weight heparin.

As seen in Figure 1, with increasing severity of STEMI presentation, the proportion of patients receiving P-PCI increased from 2.8% for TIMI risk score 0 to 32.7% for TIMI risk score of >8 (p value for trends < 0.001).



TIMI risk score	0	1	2	3	4	5	6	7	8	>8
FB (n)	35	199	305	218	196	149	112	74	38	37
PPCI (n)	1	33	64	66	61	53	25	15	10	18

Figure 1: Choice of in-hospital primary reperfusion therapy by severity of ST-Elevation Myocardial Infarction presentation for specialist cardiac care facilities

Patient outcomes by cardiac-care provision and reperfusion strategy

The unadjusted all-cause 30-day mortality rate for STEMI patients was 10.9%, with 11.6% and 10.1% (p value 0.11) among the specialist and non-specialist cardiac-care facilities respectively. Figure 2 depicts the overall mortality by severity of STEMI presentation. Mortality rates ranged from 2.8% to 49.6%.

Table 2 depicts the crude and adjusted mortality rates for cardiac-care facilities by their acute reperfusion strategies. Those who did not receive acute reperfusion therapy had the worst prognosis. However, there were no significant differences in mortality risk by centres; adjusted OR 1.12 (95%CI: 0.51 - 2.46). Up to 87% of 30-day mortality was attributed to in-hospital mortality; 7.8% mortality rate for in-hospital fibrinolysis and 10.8% for P-PCI.

Figure 2a and Figure 2b depicts the prognosis of patients stratified by their severity of STEMI presentation.

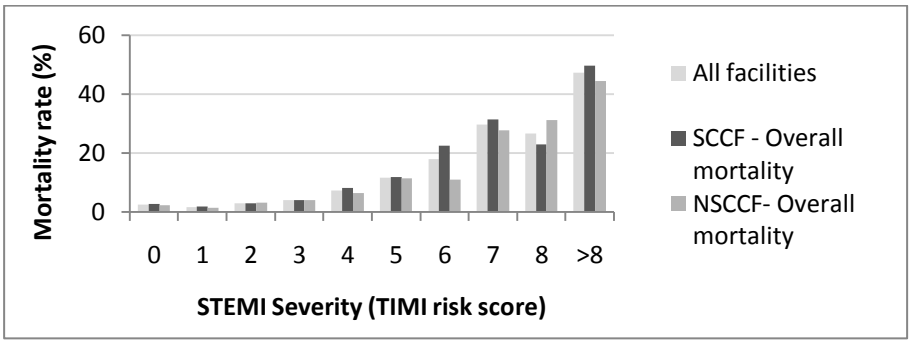


Figure 2a: 30-day mortality rates by ST-Elevation Myocardial Infarction severity for types of cardiac care facilities

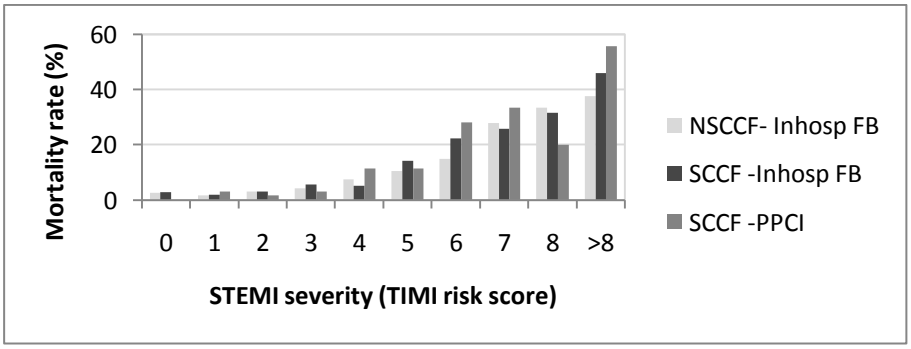


Figure 2b: 30-day mortality rates by ST-Elevation Myocardial Infarction severity for reperfusion strategies by types of cardiac care facilities

Figure legends: SCCF – Specialist cardiac care facilities, NSCCF – Non-specialist cardiac care facilities, FB – Fibrinolysis, P-PCI – Primary Percutaneous Coronary Intervention.

Patient outcomes by reperfusion strategy for specialist cardiac-care facilities

In specialist cardiac-care centres, where both fibrinolytics and P-PCI are offered, the crude 30-day mortality of P-PCI was higher than fibrinolytics. However, once adjusted for the TIMI risk score, there was no difference in adjusted mortality rates; P-PCI 7% (95%CI: 3 - 11) and in-hospital FB 7% (95%CI: 5 - 9) respectively, p value 0.75. Patient outcomes were also similar by risk groups. The adjusted mortality rates for P-PCI and in-hospital FB for the low risk category was 2% (95%CI: 0 -5) and 3 (95%CI: 2 - 5) respectively. For the intermediate risk group, adjusted mortality rates were 14% (95%CI: 5 - 22) and 11% (95%CI: 7 - 15), and for the high risk group, 35% (95%CI: 30 - 41) and 33% (95%CI: 24 - 42) respectively.

Discussion

This study was the first assessment of STEMI outcomes by cardiac-care provision and reperfusion strategy in the country. Our findings showed that 1) non-specialist cardiac-care facilities achieved patient outcomes that were not inferior to those in specialist cardiac-care facilities; and 2) thrombolytic therapy as the primary reperfusion strategy gave similar patient outcomes to P-PCI for all risk categories.

Our study demonstrated that despite international recommendations for P-PCI as the reperfusion strategy of choice (6), P-PCI did not perform better than thrombolytics in our country. This is conflicting with predominant medical literature, where P-PCIs improve survival compared to thrombolytics for every stage of risk, and especially for those at high risk.(14) This may be due to the very low volumes performed by each centre. Six centres performing 346 P-PCIs over the course of three years is unlikely to enhance percutaneous coronary interventional skills for acute presentations. Our findings highlight the need to enhance P-PCI care in existing facilities, either by increasing the volume of P-PCI use (15), or by improving the training of interventional cardiologists. This is imperative because performing P-PCIs is a complex undertaking compared to the far simpler administration of thrombolytics.

Aside from this, policymakers and clinicians need to tailor cardiac-care planning and patient care according to local situations. Other studies looking into hospital variation in care and outcomes have demonstrated that non-tertiary/ community hospitals without PCI facilities can perform as well as tertiary cardiac-care centres.(16-18) In our setting, non-specialist cardiac-care facilities provided similar patient outcomes than specialist cardiac-care facilities. This is informative. Non-specialist cardiac-care facilities are mainly located in the less-economically developed states and are usually of relatively smaller size than their counterparts in more economically developed states. The smaller sizes of these facilities may have contributed to shorter door-to-treatment times observed. Perhaps the addition of P-PCI capacity in these hospitals may further improve current patient outcomes.

Overall, there were high proportions of reperfusion therapy (68-73%) and good in-hospital STEMI management. However, timely reperfusion as recommended by international (6) and local (19) clinical guidelines was provided in only slightly more than 25% of in-hospital cases. This highlights a need to focus on aspects that can reduce door-to-reperfusion times for the remaining 75% of patients.

Other studies involving developing countries showed lower 30-day mortality rates for STEMI; 8.6% in the Indian CREATE study (5) and 5% in the ACCESS study on patients from African, Latin American and Middle Eastern countries.(4) The higher

mortality rates observed in our study may be due to three factors. Firstly, despite similar younger ages of presentation and a very high male preponderance, our patient population had more risk factors; higher current smokers, diabetics and hypertensives than the CREATE patient population and a 20% higher proportion with prior angina than the ACCESS study population. Our population also had more severe index events with a higher proportion of patients presenting with poorer Killip classes. Secondly, the lower mortality rate seen in the ACCESS study may be due to a higher rate of P-PCI; 25.5%.(4) A third factor may be timelier reperfusion. Data from CREATE showed a lower mortality rate despite having similar P-PCI rates (8%).(5) However, up to 50% of their patients had reperfusion within 50 minutes. When comparing our mortality rates with studies which involved similar risk stratification, our patient outcomes are better. When stratified by the TIMI risk score, our patient population showed better mortality rates for each risk category than the Canadian EFFECT study cohort (20), with almost a 20% reduced mortality rate for the highest risk category, 47% versus 68%. The EFFECT study however used the simpler non-specific TIMI risk index for risk stratification.

The clinical management of STEMI in our country was good. The acute reperfusion rate of 82.6% is higher than reperfusion rates of 71% found in GRACE (21) and other developing countries (64.5%).(4) For patients given thrombolytic therapy in other developing countries, up to 15% are given tissue-plasminogen activators (t-PA).(4) In our patient population, 98% were given streptokinase. Our mortality rate of 9.2% is consistent with mortality rates for streptokinase, 10% and t-PA, 9% found in a meta-analysis of trials comparing thrombolytics and P-PCIs.(22) However, our P-PCI mortality rate is higher than the 7% found in Keeley et al's meta-analysis (22) and the 5% observed in West et al's study on low-volume P-PCI centres in England and Wales.(23) It is not known how our patient population differs in baseline characteristics and severity of STEMI presentation with Keeley et al's study. However, the patient population in West et al's study had less chronic diseases such as hypertension, diabetes and renal failure, and had better door-to-balloon times, with 61% being treated within one hour.

The lack of superiority for P-PCI compared to thrombolytics in our setting is not isolated. Three of the largest trials comparing P-PCI's and thrombolytics (24-26), did not find P-PCI superior for all-cause mortality, only a combined end-point of death, non-fatal re-infarction and stroke. In the meta-analysis of P-PCI and thrombolytics confirming P-PCI superiority (22), the analysis was not weighted by trial size. Thus, smaller-sized trials with significant benefits had equal weight as larger trials without. Aside from this, only 27% of those receiving P-PCI had timely reperfusion in our setting. It is well known that timeliness is important for successful reperfusion.(27) Poorer outcomes have been demonstrated for each 10-

minute delay in door-to-balloon times (28,29) and its benefits over thrombolysis could even be nullified if delays exceeded 100 minutes (30), or 71 minutes depending on the patient's baseline characteristics.(31) Also, time delays for P-PCI's are prognostically more important in high-risk patients (28) and in our patient setting, more high-risk patients were treated with P-PCI's. Survival benefits of P-PCI's over thrombolytics in low-risk patients have been shown to be unfavourable if delays to P-PCI's are expected and immediate thrombolysis is possible.(32) In our study, up to 50% of STEMI patients fell into the low-risk category and more than 85% of them were treated with thrombolytics. All these factors may explain the improved outcomes of patients receiving thrombolytics in our setting.

Our study is not without limitations. Firstly, our study involved hospitals which volunteered to join the NCVD-ACS and did not have any private healthcare facilities, or smaller rural public hospitals. The centres studied may not necessarily be representative of all hospitals in the country. However, all the important larger publicly-funded hospitals in the country were included. A recent study on patient registry recruitment identified a biased mortality rate (increased by three-fold) when non-registry selected patients were analysed.(33) The NCVD-ACS included all consecutive patients, thus patient outcomes in this study are valid.

Secondly, differences in patient outcomes seen between the two reperfusion strategies may have been affected by residual risk factors not identified by the TIMI risk score or the baseline characteristic differences. Nevertheless, we feel that this has been minimized because the TIMI risk score has been validated in our patient population.(9) It also shares many variables as other risk scores (34), five of them by the most-used risk score for STEMI; GRACE risk score.

Thirdly, we were unable to assess symptom-to-door time. This would have affected the adjusted mortality rates observed. However, in assessing the variability in provision and reperfusion strategies of STEMI care, identifying modifiable processes is paramount. Unlike symptom-to-door time, reducing door-to-reperfusion time is directly under the purview of the hospital administration and clinicians. Fourthly, in assessing mortality rates by STEMI severity for P-PCI and pre-hospital fibrinolytics, the total number of events were small, 41 and 61 in total respectively. This limited the strength of conclusions in comparing these two reperfusion strategies by severity of STEMI presentation. Lastly, the data used for this study was available in mid-2009. Since then, improvements in patient outcomes may have occurred. However, as these findings represent the first description of STEMI outcomes by cardiac-care provision and reperfusion strategies, at the least it provides a baseline for the impact and quality of patient care in the country.

In conclusion, variation in cardiac-care provision did not adversely impact prognosis. Patients with STEMI in Malaysia received good acute cardiac-care in both specialist and non-specialist facilities, with similar outcomes despite poorer resources in the latter. Patients also had similar prognoses with thrombolytic therapy compared to P-PCI. This suggests that, the planning of future cardiac-care services should include 1) increased provision of evidence-based resources (including P-PCI care) for non-specialist cardiac-care centres, 2) methods to improve the quality of P-PCI care and 3) measures to reduce door-to-reperfusion time.

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Appendix - Clinical variables of the TIMI Risk Score

#	Clinical variables	Points
1	Age, years	
	≥ 75	3
	65 - 74	2
2	History of diabetes, hypertension or angina	1
3	Systolic Blood Pressure < 100mmHg	3
4	Heart rate > 100 beats/minute	2
5	Killip class II - IV	2
6	Weight < 67 kg	1
7	Anterior ST-elevation or Left bundle branch block	1
8	Time to reperfusion treatment> 4 hours	1
	Total possible points	**14**

Chapter 4.3

Identification of effective screening strategies for cardiovascular disease prevention in a developing country: using cardiovascular risk-estimation and risk-reduction tools for policy recommendations

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Abstract

Background
Recent increases in cardiovascular risk-factor prevalences have led to new national policy recommendations of general community screening for primary prevention of cardiovascular disease. This study assessed whether the current national policy recommendation of general community screening was optimal, by comparing the effectiveness and impact of various cardiovascular screening strategies.

Methods
Data from a national population based survey of 24 270 participants aged 30 to 74 was used. Five screening strategies were modelled for the overall population and by gender; the general community and four age cut-off points. Screening strategies were assessed based on the ability to detect high cardiovascular risk populations (effectiveness), incremental effectiveness, impact on cardiovascular event prevention and cost of screening.

Results
26.7% (95% confidence limits 25.7, 27.7) were at high cardiovascular risk, men 34.7% (33.6, 35.8) and women 18.9% (17.8, 20). General community screening covered 100% of the high risk populations, and resulted in one high-risk individual detected for every 3.7 people screened with an estimated cost of USD60. Screening men of all ages identified one high-risk individual for every 2.9 persons screened, for USD46. Screening women identified one high-risk individual for every 5.3 persons screened, costing USD85. For screening women to be as effective as men, the target age for screening was 50 and above, with one high-risk individual detected for every 2.7 persons screened, costing USD43.

Conclusions
Targeted gender- and age-specific screening strategies would ensure more optimal utilisation of scarce resources compared to the current policy recommendations of general community screening.

Introduction

Malaysia is one of the many developing countries in the world that has undergone epidemiologic and demographic transition. Recent national health reports showed a rising prevalence of several risk factors (1) and worrying clustering of cardiovascular risk factors.(2) However, information on risk factor prevalence alone is insufficient to provide adequate knowledge on the risk of future cardiovascular events. It is well known that a constellation of low to moderately elevated risk factors can confer a higher cardiovascular risk in an individual than just one highly elevated risk factor.(3,4) For example, a 45 year old male smoker, non diabetic with a total cholesterol level (TC) of 5.4 mmol/l, systolic blood pressure (SBP) of 150mmHg and a HDL cholesterol level of 1.2 mmol/l has an overall 10-year cardiovascular disease risk of 17% compared to 8.9% of a 50 year old non smoker, non diabetic who has a SBP of 180mmHg, total cholesterol of 4.3mmol/l and HDL of 1.9mmol/l (using the Framingham Risk Score). Therefore, cardiovascular risk estimation is an important component of estimating the overall effects of risk factors.

Recently, the Ministry of Health, Malaysia developed a national strategic plan to tackle the burgeoning increase in cardiovascular risk factors and disease. Among the various strategies and key activities planned are screening strategies to identify individuals at high cardiovascular risk to institute early clinical management. The two proposed strategies are: 1) to start community based risk factor screening (covering the general population) and 2) to make policy and regulation changes to include compulsory screening for all employees aged 40 and above.(5)

However, before the implementation of national policies, the most effective screening strategy should be identified. In this study, we hope to answer three questions; 1) what is the distribution of overall cardiovascular risk in Malaysia, 2) What are the more effective screening strategies to identify high-risk populations and 3) what are the impact (numbers of cardiovascular events prevented) and estimated costs for these strategies.

Methods

Study population

This study used data from the National Health and Morbidity Survey (NHMS III) conducted in 2006. The NHMS is a national population based survey held every ten years, that assesses various aspects of health care, including burden of disease, health care utilisation and costs. The NHMS III used a two-stage stratified random sampling strategy proportionate to the population size of Malaysia. All data were collected via a face-to-face interview using a bi-lingual (Malay language and English) pre-coded questionnaire. The NHMS III was funded by the Ministry of

Health Malaysia and ethics approval was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia. Written informed consent was obtained from all participants prior to the interview and examinations. Details of this survey have been published previously.(1) Survey participants aged 30 to 74 years were selected for this study.

Overall cardiovascular risk

Overall cardiovascular risk was estimated using the Framingham Risk Score (FRS) for general cardiovascular disease (10-year risk).(6) Events of this risk score are coronary death, myocardial infarction, coronary insufficiency, angina, ischaemic stroke, haemorrhagic stroke, transient ischaemic attack, peripheral artery disease and heart failure. The FRS used a simple office-based non-laboratory set of variables. We used the formula with body mass index (BMI) as a substitute for total and high-density lipoprotein (HDL) cholesterol levels, because in the NHMS III, HDL cholesterol levels were not measured. The variables were logarithm of age, logarithm of BMI, logarithm of SBP (with different regression coefficients for treated or untreated high blood pressure), smoking and diabetes mellitus (website: http://www.framinghamheartstudy.org/risk/gencardio.html).

An example is given below:

The 10-year risk of cardiovascular disease for men who were not treated for hypertension was calculated as $1\text{-}0.88431^{\exp((3.11296*\text{logage}) + (0.79277*\text{logBMI}) + (1.85508*\text{logUntreatedSBP}) + (0.70953*\text{smoking}) + (0.53160*\text{diabetes}) - 23.9388)}$

Framingham risk definitions

High risk individuals were defined as those whose 10-year risk of cardiovascular disease was more or equal to 20%. Those at intermediate risk were between 10 to 20% and low risk was less than 10%.

Statistical analyses

A complex survey analysis weighted for non-response, as well as population age and sex demographics, was used to produce correct estimations for the Malaysian population. Prevalences, screening coverage and detection rates of populations at high cardiovascular risk were estimated.

Prevalence estimates for demographics and cardiovascular risk factors were given by the Framingham risk categories, as well as overall. Variance was estimated using the Taylor linearization method.(7) Group differences between risk categories for continuous variables were estimated using an adjusted Wald test (*F* statistic). Differences between the risk categories for categorical variables were tested using Pearson's chi square test, adjusted for design effect (*F* statistic).

For all analyses, p values less than 0.05 were considered statistically significant. Analyses were performed using Stata Statistical Software : Release 11.0 (College Station, TX: Stata Corporation LP).

Simulated screening strategies

For the purpose of this study, only community screening was assessed, because this strategy will be funded by the government, and it encompasses the entire population. The screening strategies chosen for simulation in this study were based on incremental five year age cut-offs. Stratification by gender was included to determine if gender-specific screening strategies were required. The coverage, effectiveness and impact of screening strategies were simulated for:

1. The general community (aged 30 and above)
2. Those aged 35 and above
3. Those aged 40 and above
4. Those aged 45 and above
5. Those aged 50 and above

Effectiveness

Effectiveness was assessed as the ability of a screening strategy to identify individuals of high cardiovascular risk as classified by the FRS. Comparisons of effectiveness were determined using the numbers needed to screen (NNS) to detect one high-risk individual. Incremental effectiveness was determined as the additional number of individuals needed to be screened to detect one high-risk individual. Strategies were compared with a lower age cut-off for screening eligibility.

Impact

The impact of each screening strategy was assessed by the NNS to prevent one cardiovascular event among individuals at high risk. The number of cardiovascular events prevented was determined using the following formula (8):

Number of cardiovascular events prevented=N x Cardiovascular disease rate x (1-((1- pd x pu x pc x RRR)$_{int\ 1}$ x -(1- pd x pu x pc x RRR)$_{int\ 2}$ x …x -((1- pd x pu x pc x RRR)$_{int\ n}$)

Where,

N = number of high-risk people in respective screening strategy

Cardiovascular disease rate = average FRS score for respective screening strategy

pd = proportion of high-risk people with disease/ risk factor requiring intervention

pu = proportion of high-risk people with disease/ risk factor requiring intervention that take up the intervention

pc = proportion of adequacy of control /adherence to intervention

RRR = relative risk reduction achieved with intervention (9-12)

The interventions that were assessed in the simulation models were antihypertensive, lipid lowering and glucose lowering drugs, and smoking cessation therapies.

Table 1 depicts the proportion of individuals with a cardiovascular risk factor who decide to accept treatment, the proportion adhering to treatment and the relative risk reduction for those adhering to treatment.

Table 1 - Proportion of uptake and adherence to treatment, and relative risk reductions for cardiovascular interventions.

Therapy/ Intervention	Uptake proportion (%) *	Proportion adhering (%) †	RRR ‡
Antihypertensives	87.5	26.3	0.22
Lipid lowering drugs	44.1	69	0.22
Hypoglycaemic agents	85.8	29.3	0.1
Smoking cessation	70.6	*9.3	0.36

*,† from the NHMS III (1)

‡ from meta-analysis on effects on interventions on CVD events (9-12)

RRR Relative risk reduction

Cost

Cost estimations for each screening strategy were calculated using the Malaysian Medical Association's Schedule of Fees (13). The recommended fee for screening is Malaysian Ringgit (MYR) 50.00 (about USD16.00).

Assumptions

Those who do not adhere to therapies have the same 10-year risk of cardiovascular disease as those untreated. All interventions are independent of each other and there are no additive nor multiplicative effects.

Results

There were 24 270 participants from the NHMS III survey between the ages 30 to 74 years. Women made up 55.2% of the population (13 393 participants).

Distribution of overall cardiovascular risk (Table 2)

26.7% (95% confidence limits 25.7, 27.7) were in the high risk category, 20.3% (19.8, 20.9) were at intermediate risk and 53% (51.8, 54.1) were in the low risk category. Among those in the low risk category, a quarter had hypertension and almost 40% were centrally obese.

Table 2 - Characteristics of study participants by their overall cardiovascular risk

Variables	Overall	Low risk	Intermediate risk	High risk	p value
Age	49.4 (0.01)	48.4 (0.03)	49.7 (0.03)	52.9 (0.13)	
Male sex	49.6	40	55	64.3	<0.001
Race					0.0079
Malay	48.4	47.2	48.3	50.9	
Chinese	29.6	28.3	30.3	31.5	
Asian Indian	7.8	7.9	8.2	7.4	
Others	14.2	16.6	13.2	10.1	
Residence					0.0071
Urban	60.8	64.3	58	55.8	
Rural	39.2	35.7	42	44.2	
Education (Years of schooling)					<0.001
Tertiary (≥ 13 years)	7.8	11.1	5.8	2.8	
Secondary (7-12 years)	41.7	54.3	33.7	22.9	
Primary (≤6 years)	35.4	26.4	40.9	49	
Household income					<0.001
<RM2000	62.4	57.1	64.4	71.4	
RM2000-3999	23.9	26.3	23.1	19.8	
≥RM4000	13.7	16.6	12.5	8.8	
Prevalences of CV risk factors					
Smoking	22.2 (20.3, 24.3)	16.6 (14.8, 18.5)	25.9 (23.8, 28.0)	30.7 (27.7, 33.8)	<0.001
Central obesity	44.6 (42.6, 46.5)	38.4 (36.7, 40.2)	48.5 (45, 51.9)	53.8 (51, 56.5)	<0.001
Hypertension	50.1 (48.1, 52.2)	26.1 (24.4, 28.1)	64.3 (62.2, 66.5)	87 (85.9, 88)	<0.001
Hypercholesterolemia	30.3 (27.7, 33)	23.2 (21.0, 25.5)	35.9 (32.6, 39.3)	40.1 (36.8, 43.6)	<0.001
Diabetes	15.2 (13.8, 16.7)	4 (3.4, 4.6)	15.4 (13.7, 17.3)	37.3 (33.7, 41)	<0.001

Data are % for categorical variables, mean (se) for continuous variables & prevalence (95%CI) for risk factors

CV Cardiovascular

Smoking; Current smokers who smoked ≥100 cigarettes in their lifetime, and smoked daily or for some days in the previous month.

Central obesity; Men, 90 cm and women, 80 cm (21)

Hypertension; SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg (22), or use of anti-hypertensive medication.

Hypercholesterolemia; Total cholesterol level ≥ 5.2 mmol/l (23) or use of lipid lowering drugs.

Diabetes; Fasting glucose ≥ 6.1mmol/l (24) or self reported to be diabetic

Overall, 34.7% (33.6, 35.8) in men and 18.9% (17.8, 20) among women (p=0.0001).were considered at high risk. For every age group, there were far more men at high risk of cardiovascular disease (Figure 1). The prevalence of high risk was similar in urban and rural areas (Figure 2).

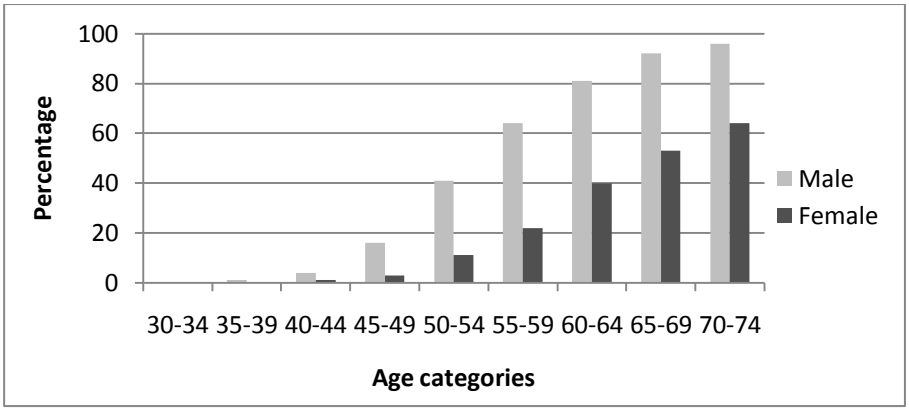

Figure 1 - Proportion of males and females with high overall cardiovascular risk (>= 20% ten year risk) by age categories.

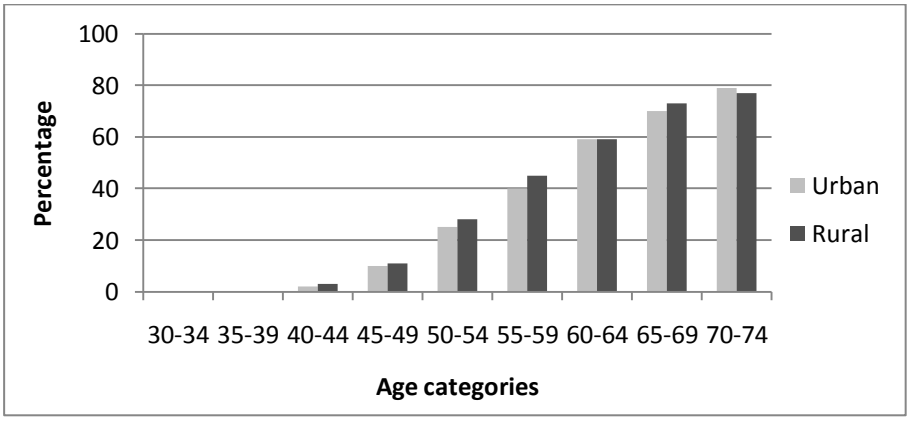

Figure 2 - Proportion of urban and rural populations with high overall cardiovascular risk (>=20% ten year risk) by age categories.

Coverage and detection of populations at high cardiovascular risk

As the cut-off age for screening strategies reduced, more of the general population were eligible for screening (Table 3). However, despite the increase in coverage of 53.3% from the cut-off age of ≥50 to the general community, the coverage of high risk populations only increased by 5.6%. Aside from this, the high risk individuals detected formed smaller proportions of the screened population as the screened populations got larger.

Effectiveness of screening strategies

The NNS to detect one high-risk individual increased as the cut-off age for screening was reduced. By screening the general community, one high-risk individual was detected for every four people screened. Whereas, when only those over age 50 years were screened, one high-risk individual was detected for every

two persons screened (Table 3). Furthermore, the NNS for men among the general community (2.88) was far smaller than the NNS for women (5.30).

Incremental effectiveness of screening strategies (Table 4)
As the screening population was extended (younger ages were included), the additional coverage of high-risk populations decreased, the percentage of additional high-risk individuals detected reduced and the additional number of individuals needed to be screened to detect one high-risk individual increased tremendously. These findings were similar for men and women.

Impact
With general community screening, 187 people have to be screened and treated for 10 years to prevent one cardiovascular event (Table 5). For men, the NNS and treat for 10 years, to prevent a single cardiovascular event was lower than women for all screening strategies.

Cost of screening strategies (Table 5)
The estimated cost of detecting each high-risk individual increased as the screening strategy progressively encompassed younger populations. When comparing the screening strategies of the general community and those aged ≥50 years, the cost for detecting a single high-risk individual slightly more than doubled. The cost of detecting high-risk individuals among men were almost half that of women, for all screening strategies.

Incremental costs (Table 5)
The cost of detecting one additional high-risk individual increased exponentially as the targeted screening population coverage increased incrementally. As younger and younger individuals were screened, the additional cost for detecting one high-risk individual differed significantly among the sexes. For those aged ≥45 years, the incremental cost for detecting an additional high-risk individual among women was 4.7 times that of men. Once the eligibility age of screening reduced to ≥ 35 years, the incremental cost among women was 8.6 times that of men.

Discussion
Our study shows that a targeted cardiovascular risk factor screening strategy would be better than the policy recommendation of screening for all ages at a community level. Defining an age eligibility criteria would be a more cost effective method of identifying high-risk individuals. In addition, our study highlights the need for different screening strategies for men and women due to a significant difference in their overall cardiovascular risk.

Table 3 - Coverage and detection of high cardiovascular risk populations for various screening strategies

	Targeted screening				General community
	≥ age 50	≥ age 45	≥ age 40	≥ age 35	
Overall					
Coverage of population	46.72	58.06	70.13	84.47	100
Coverage of high risk population	94.39	98.71	99.82	100	100
% of high risk individuals - among those screened	53.97	45.42	38.02	31.62	26.71
NNS to detect 1 high risk individual (no.)	1.85	2.20	2.63	3.16	3.74
Males					
Coverage of population	44.36	56.32	68.82	83.95	100
Coverage of high risk population	92.6	98.22	99.75	100	100
% of high risk individuals - among those screened	72.41	60.5	50.28	41.32	34.69
NNS to detect 1 high risk individual (no.)	1.38	1.65	1.99	2.42	2.88
Females					
Coverage of population	49.03	59.76	71.41	84.98	100
Coverage of high risk population	97.61	99.58	99.99	100	100
% of high risk individuals - among those screened	37.59	31.47	26.43	22.22	18.88
NNS to detect 1 high risk individual (no.)	2.66	3.18	3.78	4.50	5.30

All data are in percentage (%) unless otherwise stated

NNS Numbers needed to screen

Table 4 - Incremental coverage and detection of high cardiovascular risk populations for various screening strategie

	Targeted screening				General
	≥ age 50	≥ age 45	≥ age 40	≥ age 35	community
Strategies implemented incrementally*					
Additional % of population screened	-	24.3	20.8	20.4	18.4
Additional coverage of high risk population screened	-	4.32	1.11	0.18	0.00
% of additional high risk individuals detected	-	4.59	1.11	0.17	0.01
Additional NNS to detect 1 high risk individual	-	9.8	41.2	309.7	7168.90
Males					
Additional % of population screened	-	27.0	22.2	22.0	19.1
Additional coverage of high risk population screened	-	5.62	1.53	0.25	0.00
% of additional high risk individuals detected	-	6.08	1.55	0.25	0.01
Additional NNS to detect 1 high risk individual	-	6.1	23.6	176.5	5179.06
Females					
Additional % of population screened	-	21.9	19.5	19.0	17.7
Additional coverage of high risk population screened	-	1.97	0.41	0.01	0.00
% of additional high risk individuals detected	-	2.04	0.36	0.05	0.01
Additional NNS to detect 1 high risk individual	-	28.5	173.4	1525.92	5876.37

* reference screening group is directly to the left of current screening strategy

first reference group (for ages 45)

NNS Numbers needed to screen

Table 5 - Cost, incremental cost and impact of screening strategies

	Targeted screening				General
	≥ age 50 †	≥ age 45	≥ age 40	≥ age 35	community
Overall					
Estimated cost to detect 1 high risk individual, MYR (USD)	92.64 (29.73)	110.08 (35.33)	131.51 (42.2)	158.13 (50.75)	187.2 (60.08)
Incremental cost per additional high risk individual detected, MYR (USD)	- -	490.27 (157.34)	2060.12 (661.14)	15483.29 (4968.96)	358444.85 (115033.65)
NNS to prevent one CV event	62.24	76.14	96.64	123.95	146.73
Males					
Estimated cost to detect 1 high risk individual, MYR (USD)	69.05 (22.16)	82.64 (26.52)	99.44 (31.91)	121.01 (38.84)	144.13 (46.25)
Incremental cost per additional high risk individual detected, MYR (USD)	- -	306.21 (98.27)	1180.58 (378.88)	8825.99 (2832.47)	258952.77 (83104.23)
NNS to prevent one CV event	45.33	57.27	72.96	94.33	112.36
Females					
Estimated cost to detect 1 high risk individual, MYR (USD)	133.01 (42.69)	158.88 (50.99)	189.18 (60.71)	225.02 (72.21)	264.83 (84.99)
Incremental cost per additional high risk individual detected, MYR (USD)	- -	1426.50 (457.8)	8669.32 (2782.19)	76295.96 (24485.23)	293818.47 (94293.47)
NNS to prevent one CV event	85.72	105.59	129.78	165.01	194.20

CV Cardiovascular, NNS Numbers needed to screen, MYR Malaysian Ringgit, USD US Dollar

1.00 USD = 3.11600 MYR; * for incremental costs, reference screening strategy is directly to the left of current screening strategy

† first reference group (for ages 45)

The findings of our study have important implications for policy makers in the prevention and management of cardiovascular disease. Firstly, high rates of cardiovascular risk factors in the country, do not necessarily translate into high overall cardiovascular risk. A previous study on cardiovascular risk factors showed a very high prevalence of hypertension (38%), diabetes (11%), hypercholesterolemia (24%), central obesity (37%) and it's clustering (33%).(2) This was more pronounced in women. Our study showed that overall cardiovascular risk was more severe in men than women, for all ages. Therefore, having identical screening strategies for both sexes may not be necessary or cost-effective.

Secondly, there are various factors which help determine the optimal screening strategy to be recommended; the numbers needed to screen to detect one high-risk individual, its cost and number of cardiovascular events prevented. Our results show that overall, screening the general community would cost twice as much as screening those aged ≥50 but detect high-risk individuals at half the rate. Aside from that, screening the general population would only detect an additionally very small percentage of high-risk individuals.

Thirdly, comparing screening strategies by estimating the incremental cost and effectiveness provides a clearer picture of how much more is paid to identify an additional high-risk individual. By limiting the age for screening to just ≥35 years compared to the general community, the incremental cost spent for detecting one additional high-risk individual can be brought down significantly. Aside from this, the discrepancies in cost are substantial between the sexes. Choosing the optimal screening strategy will depend on the amount policy makers and financiers are willing to pay for each additional high-risk individual detected. Finally, the impact of these strategies clearly show that screening the community only marginally reduces the numbers of cardiovascular events prevented over ten years, when compared to screening those aged 50 and above.

Ideally, the decision to recommend a cardiovascular screening strategy should depend on two factors. First, the ability of the screening strategy to detect the highest proportion of high-risk individuals at an acceptable cost, and second, the ability of healthcare facilities to manage the treatment of these individuals from a financial and human resource perspective. Policy makers and programme planners will have to take these factors into account when deciding the recommended screening strategy for the country. This is especially important for Malaysia where up to 64.5% of the population seek health care from public facilities funded by the government.(1) This study highlighted that the high incremental costs and very low impact for screening the general community may not be justifiable for implementation.

From a public health perspective, this study illustrates that developing countries without available information on, or the resources to obtain information on long term risk of cardiovascular disease and outcomes, can use existing cardiovascular risk scores and global risk-reduction estimates to make informed decisions. While these estimated may not be 100% accurate, they provide a clear picture on the impact of various screening strategies based on observed risk-factor prevalences in the country.

There have been very few studies which have examined the effectiveness and impact of screening strategies for the prevention of cardiovascular diseases using real population data. Chamnan et al (8) assessed the potential impact of various screening strategies in the United Kingdom using data from a single county. They too found that limiting screening to those older than 50 years, or using routine general practice data already available to pre-stratify high-risk individuals were more (cost) effective than screening the general population. For Scotland, Lawson et al found that targeting individuals with a family history of premature cardiovascular disease was the most cost-effective measure.(14) However, their assessment of cost-effectiveness only took into account the cost of screening and identification of high-risk individuals. They did not account for the impact of screening. Our study used data from a nationwide population-based survey and took into consideration the observed treatment uptake and adherence rates. Our study also accounted for the impact of treatment on high-risk individuals for the various screening strategies.

Our study is not without limitations. The Framingham Risk Score has not been validated in our multi-ethnic population. Therefore, it's accuracy in prognostication of risk is unclear. However, it has been shown to accurately risk stratify but overestimate cardiovascular risk in some European, Australian and Middle Eastern populations.(15-17) An earlier version of the FRS algorithm (18) had been validated in a Chinese population. For the Chinese population, it too accurately risk stratifies but overestimates the coronary heart disease risk.(19) If the FRS similarly overestimates cardiovascular risk in Asian populations, the findings of this study are even more important, because for similar risk scores, less cardiovascular events occur in Asians. Thus, screening strategies can be recommended for those with higher Framingham risk scores (eg. 30% and above), or for older age groups because they have higher proportions of high-risk individuals.

Similarly, relative risk reductions for treatment of cardiovascular risk factors have not been assessed in our population. Nevertheless, research has confirmed that risk reduction estimates have been found to be consistent across populations around the

world.(20) In this study, the relative risk reductions were for cardiovascular disease outcomes except for smoking, which was related to mortality.

In our study, the relative risk reduction for each intervention was assumed to be independent of each other. Synergistic effects of multiple drug and lifestyle interventions may be present and most likely will have different impacts for the various screening strategies. However, this may also be true for side effects and complications of treatment, thus the true impact of any treatment strategy may not be so easily determined.

In conclusion, policy recommendations for general cardiovascular screening should be gender-specific with different age group targets. This is to ensure optimal utilisation of scarce resources for the identification of high-risk individuals in the prevention of cardiovascular disease in Malaysia.

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Chapter 5

Discussion

There is a confirmed ongoing cardiovascular epidemic in Malaysia.(1) Cardiovascular risk has grown to enormous proportions (Chapter 2), it disproportionately affects the lower socio-economic group and it has already translated into higher rates of cardiovascular disease severity compared to western populations (Chapter 5). We, namely the Ministry of Health Malaysia (MOH) need to address this urgently and with the appropriate measures in a pragmatic way.

Tackling the cardiovascular epidemic: Why the Ministry of Health Malaysia is unique

Malaysia is an ex-British colony and we inherited its health care system. Malaysia has a dual public and private healthcare system where the Ministry of Health Malaysia (MOH) builds, operates and runs the publicly-funded health care system. Malaysia has 13 states and 3 federal territories. The MOH has healthcare facilities in all of them; 138 hospitals and 2836 clinics in total. The MOH is centrally run with the assistance of the respective state health departments. It is the largest healthcare provider in the country in terms of number of facilities, healthcare personnel and patients. Up to 65% of the Malaysian population access public health care facilities and 83% of the country's hospitalisations occur in public facilities.(2)

The purview of the MOH is not confined to clinical care and public health services. The MOH also creates legislature for health-care related issues (such as tobacco control, food labeling and health care/drug advertising), enforces health-related Acts, licenses healthcare practitioners as well as funds research activities. This puts the MOH in a unique position such that it is actively involved in every part of the healthcare continuum.

Recommended immediate strategies for the Ministry of Health Malaysia

Cardiovascular disease has formed the number one burden of disease in the country since 2000.(3) As of December 2010, cardiovascular disease resulted in 51.68 hospital admissions per 10,000 population.(4) This translates into an estimate of 148,841 hospital admissions for cardiovascular diseases in 2012 based on a total population of 28.8 million. Hospital admissions due to cardiovascular disease are the 'tip of the iceberg' in terms of populations with high cardiovascular risk. Assuming these cardiovascular events occurred in high risk individuals, there are an estimated 5.5 million high cardiovascular risk individuals.(5) This is staggering considering the adult population in Malaysia comprises of about 14.4 million.

One of the biggest challenges faced by developing countries is inadequate resources. The Non-Communicable Disease section under the Disease Control Division creates policies to reduce and manage the burden of cardiovascular disease in the country. The Non-Communicable Disease section consists of four staff-

members; two doctors and two clerks. This is less than the Epidemiological Malaria unit, which consists of five staff members. Malaria, with its incidence rate of just 2.4 per 10,000 population, results in an estimate of 6,912 cases per annum.(6)

The MOH needs to redirect its human (and financial) resources at the level of policy-making to ensure adequate representation of the burden of cardiovascular risk and disease in the country. This will enable the Non-Communicable Disease section to create a better, more forceful team to implement strategies that can drastically reduce the current cardiovascular epidemic.

Developing countries frequently have issues in implementation of policies. For example, to further improve health promotion in the country, in 2006 the MOH created and corporatised the Malaysian Health Promotion Board. Board members include politically appointed representatives from the Ministry of Health, Ministry of Youth and Sports, Ministry of Culture, Arts and Heritage, Ministry of Finance and non-governmental organisations nominated by these respective ministries. The Board's objectives stated in their legislature are - ; 1) to develop the capacity of organisations including health-related and community-based organisations for health promotion; 2) to plan and implement health promotion programmes and activities for the benefit of the community, with a particular focus on youth; 3) to develop and support multi-strategy programmes that promote and support healthy lifestyles and healthy environments through various settings and sectors; 4) to develop and support programmes to improve population health by preventing, reducing or stopping the use of tobacco products; 5) to fund research relevant to health promotion; and 6) to fund and support sporting, recreational and cultural organisations to promote healthy lifestyles and healthy environments.

The current Health Promotion Board's core function has focused on one objective in its legislature; which is to fund and support sporting, recreational and cultural organisations. All fund recipients until 2012 have been youth and sports clubs, to support one-off activities such as health screening days, health promotion talks and recreational activities. The Board should start implementing strategies that focus on all objectives, especially the third objective, which is to develop and support programmes that promote healthy lifestyles and environments through various settings and sectors.

Also, more members should be invited to the Board such as those from the Ministry of Agriculture, Ministry of Housing and Local Government, Ministry of Transport and Ministry of Education. With these members, there will be better opportunities to incorporate healthy living environments and healthy food choices into the daily lives of Malaysians. The Ministry of Housing and Local Government's role will be

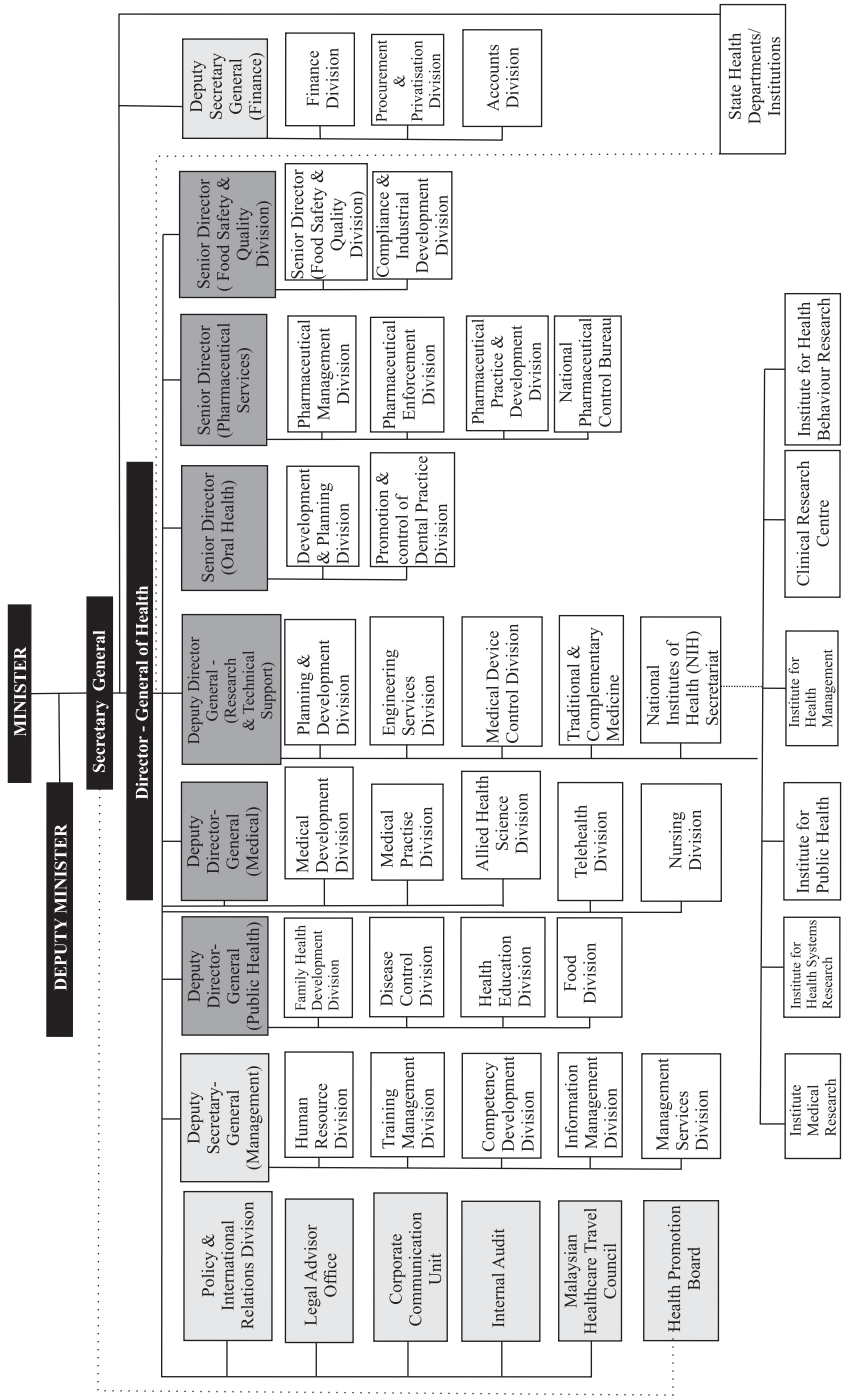

Figure 1: Organisation chart of the Ministry of Health Malaysia

to incorporate healthy living environments into building developments; both new and old. The Ministry of Agriculture can identify mechanisms to promote affordable fresh fruit and vegetables. The Ministry of Education can ensure healthy choices in school canteens, a ban on sales of soft-drinks and more physical activities in schools.

Implementation of cardiovascular policies and programmes should be evidence-based as well as state and community-specific. As shown in Chapter 8, a single cardiovascular screening strategy for the whole country would make inefficient use of existing resources. Chapter 3 showed that there is geographical variation in the prevalence of cardiovascular risk factors in the country. Therefore, the MOH should remove central government control and distribute the management of cardiovascular prevention and control programmes to the respective states. Each state in Malaysia has different cardiovascular disease prevalences, community and culture mix as well as socio-economic conditions. They should have the independence of running cardiovascular disease prevention programmes in a manner suitable for their own population. What works in a rural community, may not work in an urban area and vice versa. What works in East Malaysia will not work in the richest state in West Malaysia. It should not be a 'one size fits all'. There should be dedicated teams to determine, assess and evaluate cardiovascular programmes run at the state level. This should include active assessments of cardiovascular disease events and prognosis. Only with this can we truly delay the progress of the cardiovascular epidemic in Malaysia.

It is well known that health service provision is equally important to health outcomes as effective clinical management.(7) In a developing country such as ours, there is great variation in cardiovascular-care service provision and this can impact patient outcomes in unanticipated ways (Chapter 6). Drug treatment for cardiovascular care is available at a very low flat rate of MYR1.00 (USD0.34) for any number of therapies, both at the primary and secondary level. However, there are more varieties for drug choices for the management of cardiovascular disease at secondary care. This is despite the fact that most patients with high cardiovascular risk are followed-up in primary care clinics. The primary care clinics are the gate-keepers of the health care system. It should be imperative that similar drug therapy options be made for disease-specific conditions instead of location of health service provision. This is to ensure that the best possible treatment strategies are available to patients before they develop cardiovascular disease or acute cardiovascular events.

Future strategies for the prevention of cardiovascular disease

Cardiovascular risk has been established to be mainly due to dietary and lifestyle factors. Dietary and/or lifestyle factors which include physical activity, smoking and alcohol consumption can contribute up to 70% of the development of other cardiovascular risk factors such as abdominal obesity, hypertension, diabetes and hypercholesterolemia.(8-11) Dietary and lifestyle factors and these other modifiable cardiovascular risk factors (abdominal obesity, hypertension, diabetes and hypercholesterolemia) contribute to more than 95% of acute coronary events.(12) Similarly, changes/ improvements in dietary and lifestyle factors reduce cardiovascular morbidity and mortality risk. These changes have been shown to positively affect both people without and with established cardiovascular disease.(13) Mortality risk reductions can be as large as 15-50% in the general population and by 20-45% in those with cardiovascular disease.(14) This magnitude is more than the estimated mortality risk reductions (range 18-26%) seen in drug interventions post cardiovascular events.(14)

It is clear that to tackle the cardiovascular epidemic in the country, dietary and lifestyle changes have to be impressed upon. It is easy for healthcare practitioners to prescribe a good diet and healthy lifestyle to patients as an important component of primary prevention in patients at risk. However, in reality, 'enabling' factors play the most important role in cardiovascular risk prevention. Examples of enabling factors are affordable fresh fruits and vegetables, healthy food choices in school canteens, hostels and universities, no 24-hour fast-food restaurants in housing areas, reduced trans fatty-acids in food sold, walking lanes or jogging tracks in housing areas, playgrounds for children, accessible public parks, designated non-smoking areas, etc. These enabling factors are under the purview of a variety of other ministries in Malaysia, namely the Ministry of Agriculture, Ministry of Housing and Local Government, Economic Planning Unit, Ministry of Education, Ministry of Higher Education, etc. There has to be a concerted, sincere effort from all relevant parties to provide enabling environments for healthy living in Malaysia.

Smoking prevention laws have been enacted since 1976. The Tobacco Control regulation was recently amended in 2010 to expand smoke-free zones to include private workplaces that have centralised air conditioning. However, ideally there should be a blanket ban of smoking in any public place. There should not be any designated smoking zones in public places such as restaurants, pubs, discotheques etc. Smoking bans in public places have been one of the fastest interventions in reducing cardiovascular morbidity. In the state of New York in the United States of America, smoking bans were able to reduce the incidence rates of acute myocardial infarctions by 26% per year.(15) Smoking bans have also shown to reduce smoking prevalence by as much as 6% over two years.

There are various efforts by the government to reduce the economic burden of the population. The government spends up to MYR30 billion (USD 10 billion) on subsidies for staple items. Food items that are subsidised are rice (25% of market price), sugar (19%), cooking oil (43%) and white flour (29%). Out of these four highly subsidised items, sugar, cooking oil and flour are not highly nutritious items.

Subsidies on sugar, cooking oil and flour should be removed and these subsidies should be spent on fresh fruit and vegetables instead. For example, an average Malaysian family of four people (two adults and two children), with a household monthly income of MYR2000 (USD640) will need to spend at least three percent of their monthly income to buy a single type of fruit to have one serving of fruit daily. Recommending five to seven servings of fruit and vegetables will not be affordable for the average family, nor to the lower socio-economic group (where most of the cardiovascular risk is concentrated). Health promotion efforts, dietary counseling or advice by healthcare professionals cannot be translated into practice if fresh fruit and vegetables are not made more affordable.

The role of research in reducing the cardiovascular epidemic in Malaysia

Research should be conducted in areas relevant to the multi-ethnic population in Malaysia. Malaysia has over 30 different ethnic groups encompassing some of the major races in Asia. Ethnic variation in cardiovascular risk factors and treatment has been well established. In Asians, a lower body mass index or waist circumference compared to western populations is associated with higher cardiovascular risk.(16) This is due to higher subcutaneous fat in Asians for the same body mass index or waist circumference.(17) Ethnic differences in response to warfarin therapy are well documented. Asians have the lowest risk of haemorrhage and thromboembolism at lower rates of INR compared to other ethnicities such as whites, blacks and hispanics.(18) Similarly, there were statistically significant higher bleeding complications for Asians compared to whites or Hispanics for the use of clopidogrel in cardiovascular disease.(19)

As seen in chapters 4 and 5, not all western derived risk-stratification scores perform similarly in Asians. Research into ethnic variation in risk stratification, disease prognosis, drug treatment choices and safety will be invaluable in guiding clinical management for the patients in the country.

Malaysia is a country which is rich in bio-diversity and culturally, our multi-ethnic population is very receptive (sometimes more so) to traditional and complementary medicine. A large number of the population consumes traditional and complementary medicine. Sixty-seven percent do this concurrently with western medicine.(20) This is even for those with chronic conditions such as hypertension

(27%)(21) and diabetes (56%).(22) However, more than 90% of these patients do not disclose this information to their health care providers.(20)

Research into traditional and complementary medicine use for cardiovascular diseases is not wide-spread in Malaysia despite its huge potential. Research into medicinal plants and products should be actively encouraged. A recent study on Murraya koenigii (Linn. Spreng (curry leaves) showed a significant dose-dependent decrease in serum urea and creatinine and an increase in plasma anti-oxidant activity in diabetic rats.(23) The bark of *Ougeneinia Oojeinensis* showed anti-diabetic and hypolipidaemic effects. (24) More research into antihypertensive, anti-diabetic, hypolipidaemic and vascular anti-inflammatory medicinal plants is required to provide more viable affordable and perhaps safer alternatives to current treatment regimens.

Can there be rapid changes in the cardiovascular epidemic?

Evidence from international studies confirms that rapid reductions in cardiovascular mortality can be achieved with reductions in cardiovascular risk-factor levels and improved treatment strategies. In Scotland, there was a 30% reduction in cardiovascular mortality between 1975 - 1994; 40% due to cardiovascular treatments and 51% due to reductions in cardiovascular risk-factor levels.(25) In England and Wales, risk factor reductions accounted for 79% of life years gained in 2000 from 1981.(26) An even more remarkable reduction in cardiovascular mortality was seen in Eastern European countries. There were marked reductions in coronary heart disease mortality within 10 years of change in vegetable oil intake (increase in α-linolenic acid).(27)

One of the more important hindrances to implementing strategies that reduce cardiovascular disease risk is the increased costs that accompany them. The financial rewards of investing in health are long-term, and frequently intangible. However, we now know there are many success stories proving that the cardiovascular epidemic can be rapidly curtailed. All we need is to identify the best strategies, tailor them to suit our population and have the commitment to implement and execute them to the best of our abilities.

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Chapter 6

Summary

Cardiovascular disease forms the greatest morbidity and mortality worldwide and disproportionately affects low and middle-income developing countries. Large increases in cardiovascular risk factors occur at earlier stages of a country's economic development and cardiovascular risk is increased more in the lower socio-economic group. In developing countries, cardiovascular morbidity and mortality tends to affect the (younger) working adults and this poses a significant burden to the economy. This thesis attempts to provide current facts and figures to help tackle the burden of cardiovascular disease in Malaysia.

The work presented in this thesis is divided into three parts. **Chapter 2** described the burden of cardiovascular risk factors in the country. **Chapter 3** assessed risk stratification and prediction in cardiovascular disease, and finally, **Chapter 4** focused on prevention of cardiovascular disease and its complications.

Previous national health surveys and anecdotal evidence from the ground showed that the prevalence of cardiovascular risk factors in the general population was high, and on the rising trend. However, these risk factors were always assessed in isolation therefore the total burden of cardiovascular risk was unknown. In **Chapter 2.1**, we described the clustering of cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia and obesity) among the adult population in Malaysia. Overall, 63% (95% confidence interval: 62, 65) had at least one cardiovascular risk factor, 33% (95%CI: 32, 35) had two or more risk factors and 14% (95%CI: 12, 15) had three risk factors or more. Of the total population 52% (95%CI: 50, 53) had manifest metabolic changes with either hypertension, hypercholesterolemia, diabetes mellitus or impaired glucose tolerance or any combination of the above. Thirty-nine percent (95%CI: 37, 40) of those younger than 30 years had at least one cardiovascular risk factor. These findings highlight that despite current health care prevention programmes, the burden of cardiovascular risk is high and affects a large proportion of the young adults. There is a cardiovascular epidemic in Malaysia and drastic measures have to be undertaken to reduce the burden of cardiovascular disease in the country.

Chapter 2.2 described the differences in cardiovascular risk factor prevalences and clustering patterns among the various states and federal territories of Malaysia. Cardiovascular risk factors assessed were hypertension, diabetes, hypercholesterolemia, obesity and smoking. There was geographical variation in the distribution of risk factors as well as its clustering, with very high rates; clustering of two or more risk factors ranged from 31.9 (95%CI: 30.9, 32.9) to 60.1 (95%CI: 59.3, 60.8), driven largely by drug-modifiable risk factors such as hypertension, diabetes and hypercholesterolemia. The higher burden was seen mainly in the poorer states of the Peninsular, especially Perlis, Kedah and Kelantan. Our results can provide useful information for the allocation of health care resources in

accordance to the health care demand by the individual states. Furthermore, it is hoped that our findings may initiate the development of state-specific public health strategies to prevent and manage cardiovascular risk.

In **Chapter 3,** cardiovascular risk prediction and prognosis models were assessed. Risk stratification and prediction is important to support clinical decision making. They predict the individual's probability of developing a pre-specified outcome, and stratifies them by their risk. This is done objectively and in a standardised manner. However, there are concerns when adopting a risk prediction model. These models were all derived from non-Asian populations. Will these risk scores be applicable for use in the local patient setting? The underlying incidence of disease and prevalence of its risk factors determines the suitability of any risk prediction score and thus validation of these models are important prior to adoption.

In **Chapter 3.1**, we validated the Thrombolysis In Myocardial Infarction (TIMI) risk score for patients with St-Elevation Myocardial Infarction (STEMI). The TIMI risk score is used to assess the risk of short-term (30-day) mortality in patients presenting with STEMI. We found that the TIMI risk score accurately stratifies risk and predicts prognosis in patients presenting with STEMI in Malaysia. This is despite Malaysian patients having more severe presenting characteristics than their western counterparts. Aside from that, risk stratification worked well for high risk groups prevalent in Malaysia; diabetics and those with renal impairment. Thus, the TIMI risk score may be of benefit in improving clinical care through better targeted treatment, for patients presenting with ST-segment elevation myocardial infarction in Malaysia.

We assessed four cardiovascular risk-prediction models in the Malaysian population in **Chapter 3.2**. We compared the utility of the Framingham Risk Score (FRS), high and low risk SCORE (Systematic COronary Risk Evaluation) and the World Health Organization /International Society of Hypertension (WHO/ISH) models. Currently, these cardiovascular risk prediction models are recommended in the Malaysian clinical practice guidelines for the prevention of cardiovascular diseases. We compared the models discrimination in risk stratification, by assessing 5-year cardiovascular mortality rates. We found that despite the high proportions of cardiovascular risk factors prevalent in the study population, the WHO/ISH model classified almost 90% in the low cardiovascular risk category. In men, the FRS and SCORE-high models showed similar trends in risk stratification but the WHO/ISH showed a disproportionately large proportion of low risk individuals. In women, all four models had similar trends in risk stratification. However, similarly, the WHO/ISH model had the highest classification of low risk populations. The FRS, SCORE-high and SCORE-low all showed good discrimination for 5-year

cardiovascular mortality rates. The WHO/ISH model showed poor discrimination, for men and for women. Our study confirmed that the FRS and both SCORE models, but not the WHO/ISH model can be used to discriminate cardiovascular risk in the Malaysian population for both men and women.

Chapter 4 addressed the prevention of cardiovascular disease complications and mortality. In **Chapter 4.1**, the effects of achieving cardiovascular risk-factor treatment targets on reduction of renal complications were assessed in patients at high cardiovascular risk in a western population. Cardiovascular treatment targets were achievement of control in systolic and diastolic blood pressure, total and low-density cholesterol, and treatment of albuminuria. Renal complications were development of end stage renal failure or symptomatic renal atherosclerotic disease requiring intervention. We found that the incidence rate for end stage renal failure and renal atherosclerotic disease reduced linearly with each additional treatment target achieved. Achievement of any two treatment targets reduced the risk of renal complications, hazard ratio 0.46 (95% CI: 0.26, 0.82). For patients with clinically manifest vascular disease and diabetes, the hazard ratios were 0.56 (95% CI: 0.28, 1.12) and 0.28 (95%CI: 0.10, 0.79) respectively. Our findings show that current clinical practice guideline targets for the prevention of cardiovascular disease are useful in concomitantly reducing the risk of renal complications; in any patient population at high risk for vascular diseases. Thus, if more patients can be treated to achieve cardiovascular risk-factor treatment targets, there will be important reductions in renal complications.

The prevention of mortality in patients presenting with cardiovascular events such as ST-Elevation Myocardial Infarction depends on a variety of factors. Among these are severity of presentation, time from presentation to primary treatment and choice of reperfusion therapy. The current recommended reperfusion strategy for STEMI is the Percutaneous Coronary Intervention (PCI). In developing countries, there is wide variation in cardiac-care provision and there are challenges to providing the best reperfusion strategy. How this affects the prognosis of STEMI patients is unclear. In **Chapter 4.2**, the effects of cardiac-care provision and reperfusion strategies (primary-PCI and thrombolytics) in preventing mortality for patients presenting with STEMI were assessed in an Asian population. Our findings showed that variation in cardiac-care provision and reperfusion strategy did not adversely affect patient outcomes. Overall, there were high proportions of reperfusion therapy (68-73%) and good in-hospital STEMI management, but low primary-PCI rates of only 7.6%. Timely reperfusion was provided in only slightly more than 25% of in-hospital cases. Patients with STEMI in Malaysia received good acute cardiac-care in both specialist and non-specialist facilities, with similar outcomes despite poorer resources in the latter. Patients also had similar prognoses

with thrombolytic therapy compared to primary-PCI. However, to further improve cardiac-care, increased evidence-based resources, improvement in quality of primary-PCI care and reduction in door-to-reperfusion times should be achieved.

One of the more important strategies of preventing cardiovascular disease is the early identification of cardiovascular risk factors. With early identification through screening and the effective treatment of these risk factors, a significant proportion of cardiovascular events can be prevented or delayed. In **Chapter 4.3**, we identified effective screening strategies for the early detection of high cardiovascular-risk patients in Malaysia. We simulated four screening strategies based on incremental five-year age cut-offs, stratified by gender and compared them to the current policy recommended strategy of general community screening. Our study showed that a targeted cardiovascular risk factor screening strategy would be better than screening for all ages at a community level. Defining an age eligibility criteria would be a more cost effective method of identifying high-risk individuals. In addition, our study highlighted the need for different screening strategies for men and women due to a significant difference in their overall cardiovascular risk.

Lastly, in the discussion, immediate and future strategies for tackling the cardiovascular epidemic in Malaysia were recommended.

Samenvatting

Wereldwijd zijn hart- en vaatziekten belangrijke oorzaken van morbiditeit en mortaliteit. Met name in niet-westerse landen neemt het aantal personen getroffen door hart- en vaatziekten sterk toe en verdringen deze aandoeningen infectieziekten van de eerste plaats als oorzaak voor morbiditeit en mortaliteit. Wanneer landen zich ontwikkelen zien we een sterke toename in cardiovasculaire risicofactoren, in het bijzonder in de lagere sociaal-economische klassen. Vooral de (jongere) werkende volwassenen wordt getroffen door deze aandoeningen met grote consequenties voor de economie van deze landen. De studies in dit proefschrift geven inzicht in de omvang van cardiovasculaire ziekten in Maleisië, maar bieden ook handvatten voor de aanpak ervan.

Dit proefschrift bestaat uit drie delen waarin de onderzoeken besproken worden. In **hoofdstuk 2** wordt de prevalentie beschreven van cardiovasculaire risicofactoren in Maleisië. **Hoofdstuk 3** is gericht op risico-stratificatie en het voorspellen van hart- en vaatziekten. Tot slot wordt in hoofdstuk 4 ingegaan op de preventie van hart- en vaatziekten en de complicaties van deze aandoeningen.

Uit nationale gezondheidsenquêtes en anekdotisch bewijs blijkt dat de prevalentie van cardiovasculaire risicofactoren in de algemene bevolking van Maleisië hoog is en tevens een duidelijk stijgende trend vertoont. Echter, deze risicofactoren zijn altijd voor iedere risicofactor apart beoordeeld, waardoor de totale omvang van het absolute cardiovasculaire risico dus onbekend was. In **hoofdstuk 2.1** beschrijven we hoe de cardiovasculaire risicofactoren (hypertensie, diabetes, hypercholesterolemie en obesitas) onder de volwassen bevolking in Maleisië vaak geclusterd voorkomen. Over het geheel genomen, bleek dat 63% (95% betrouwbaarheidsinterval (BI): 62, 65) van de bevolking ten minste één cardiovasculaire risicofactor had, 33% (95% BI: 32, 35) twee of meer en 14% (95% BI: 12, 15) had drie of meer risicofactoren. Van de totale bevolking had 52% (95% BI: 50, 53) manifeste metabole veranderingen zoals hypertensie, hypercholesterolemie, diabetes mellitus, een verminderde glucosetolerantie of een combinatie van deze veranderingen. In totaal had 39% (95% BI: 37, 40) van de populatie jonger dan 30 jaar minstens één cardiovasculaire risicofactor. Deze bevindingen benadrukken dat, ondanks de huidige preventieprogramma's, de prevalentie van cardiovasculaire risicofactoren hoog is en een groot deel van de jonge volwassenen treft. Er is een cardiovasculaire epidemie in Maleisië gaande en drastische maatregelen moeten worden genomen om de omvang van hart- en vaatziekten in dit land te verminderen.

In **hoofdstuk 2.2** worden de verschillen beschreven in de prevalenties van cardiovasculaire risicofactoren en de clustering van deze risicofactoren in de verschillende staten van de Federatie Maleisië. De cardiovasculaire risicofactoren

zijn hoge bloeddruk, diabetes, hypercholesterolemie, obesitas en roken. Er zijn geografische verschillen in de prevalenties van deze risicofactoren. Daarnaast komen de risicofactoren ook vaak geclusterd voor. Bij 31,9 % (95% BI: 30,9, 32,9) tot 60,1% (95% BI: 59,3, 60,8) is sprake van de aanwezigheid van twee of meer door medicatie te beïnvloeden risicofactoren zoals hoge bloeddruk, diabetes mellitus en hypercholesterolemie. Vooral in de armere delen van het schiereiland, in het bijzonder Perlis, Kedah en Kelantan is er een grotere ziektelast. De resultaten van dit onderzoek zijn onmisbaar als bepaald moet worden of de beschikbare middelen voor gezondheidszorg in overeenstemming zijn met de behoefte van de individuele staten. Verder hopen wij dat deze bevinding een eerste aanzet is voor de ontwikkeling van specifieke strategieën die voor iedere staat van de Federatie Maleisië op maat gemaakt worden om zo de omvang van de cardiovasculaire epidemie te kunnen verminderen.

In **Hoofdstuk 3** worden de bekende cardiovasculaire voorspelmodellen op hun geschiktheid voor de Maleise populatie beoordeeld. Risicostratificatie en het voorspellen van het absoluut cardiovasculair risico is belangrijk voor de ondersteuning van de klinische besluitvorming. De modellen voorspellen de kans op het ontwikkelen van een vooraf gespecificeerde gebeurtenis voor het individu. Dit gebeurt op een gestandaardiseerde manier door gebruik te maken van vast omschreven voorspelregels, waarin diverse risicofactoren worden gekwantificeerd. Echter, de vraag is of de bestaande voorspelmodellen, afgeleid uit westerse populaties, geschikt zijn voor gebruik in Maleisië. De onderliggende incidentie van de ziekte maar ook de prevalentie van risicofactoren bepalen de geschiktheid van een voorspelmodel. Voordat deze modellen in Maleisië worden overgenomen moeten ze dus eerst gevalideerd worden.

In **Hoofdstuk 3.1** hebben we de Trombolyse bij Myocardinfarct (TIMI) risicoscore gevalideerd voor patiënten met een myocardinfarct met ST-elevatie (STEMI). De TIMI risicoscore wordt gebruikt om de kans op sterfte op de korte termijn (binnen 30 dagen) bij patiënten met STEMI te beoordelen. We vonden dat de TIMI risicoscore ook in Maleisië in staat is nauwkeurig het risico op overlijden te voorspellen in patiënten met een STEMI. Dit effect werd gezien, ondanks het feit dat de patiënt in Maleisië zich presenteert met meer symptomen dan zijn/haar westerse tegenhanger. Daarnaast werkte de risicostratificatie in Maleisië goed voor de hoog risicogroepen, zoals diabetici en mensen met een verminderde nierfunctie. Zo kan de TIMI risicoscore gebruikt worden bij het verbeteren van de klinische zorg door gerichtere behandeling van patiënten met een STEMI in Maleisië.

I In **hoofdstuk 3.2** worden vier cardiovasculaire voorspelmodellen gevalideerd in de Maleise bevolking (**hoofdstuk 3.2**). We vergeleken de bruikbaarheid van de

Framingham Risk Score (FRS), de SCORE (Systematic Coronary Risk Evaluation) voor laag en hoog risico populaties en de 'World Health Organization / International Society of Hypertension' (WHO / ISH) modellen. Momenteel worden deze modellen aanbevolen volgens de in Nederland gebruikte richtlijnen voor de preventie van cardiovasculaire ziekten. We vergeleken de modellen met betrekking tot het discriminerend vermogen en de mate waarin de modellen patiënten konden indelen in strata van het cardiovasculair risico. Hierbij werd het vermogen om de 5-jarige cardiovasculaire sterfte te voorspellen getoetst. Ondanks het frequent voorkomen van cardiovasculaire risicofactoren in de onderzoekspopulatie classificeerde het WHO / ISH model bijna 90% in de lage cardiovasculaire risico categorie. Bij mannen vertoonden de FRS en SCORE modellen dezelfde trends, maar de WHO / ISH plaatste een onevenredig deel van de populatie in de laag risico categorie. Bij vrouwen toonden alle vier de modellen dezelfde trends in risicostratificatie als bij mannen. Ook hier plaatste het WHO / ISH model bijna alle vrouwen in de laagste categorie. De FRS en de SCORE modellen lieten een goede discriminatie voor de cardiovasculaire sterfte in 5 jaar zien. Het WHO / ISH-model daarentegen discrimineerde slecht, voor zowel mannen als vrouwen. Onze studie bevestigt dat de FRS en beide SCORE modellen kunnen worden gebruikt om het cardiovasculaire risico van zowel mannen als vrouwen in Maleisië te schatten, in tegenstelling tot het WHO / ISH model.

Hoofdstuk 4 richt zich op preventie van hart- en vaatziekten en de complicaties ervan. In **hoofdstuk 4.1** worden de effecten van het bereiken van cardiovasculaire risicofactor behandeldoelen op de renale complicaties bij patiënten met een hoog cardiovasculair risico beoordeeld. Cardiovasculaire behandeldoelen waren, het onder controle krijgen van de systolische en diastolische bloeddruk, totaal cholesterol en low-density lipoproteïne (LDL)-cholesterol, en de behandeling van eiwit in de urine. Renale complicaties waren de ontwikkeling van een eindstadium nierfalen of symptomatische renale atherosclerose waarvoor een interventie nodig was. We vonden dat de incidentie van terminale nierinsufficiëntie en renale atherosclerose lineair verminderde met elk extra behaald behandeldoel. Het bereiken van twee willekeurige behandeldoelen verminderde het risico van renale complicaties met 54%, hazard ratio (HR): 0,46 (95% BI: 0,26, 0,82). Voor patiënten met klinisch manifest vaatlijden en diabetes mellitus waren de HR 0,56 (95% BI: 0,28, 1,12) en 0,28 (95% BI: 0,10, 0,79) respectievelijk. Onze bevindingen tonen aan dat de huidige behandeldoelen voor de preventie van cardiovasculaire aandoeningen bruikbaar zijn in het gelijktijdig verminderen van het risico op renale complicaties. Indien bij meer patiënten de cardiovasculaire risicofactoren worden behandeld, zullen er derhalve ook minder renale complicaties optreden.

Het voorkómen van sterfte bij patiënten met een myocardinfarct met ST-elevatie is

afhankelijk van een aantal factoren. Dit zijn onder andere de ernst van de symptomen, de tijd tussen de presentatie en de primaire behandeling en de keuze van de reperfusie behandeling. De huidige aanbevolen reperfusie strategie voor STEMI patiënten is percutane coronaire interventie (PCI). In ontwikkelingslanden is er echter grote variatie in de cardiale zorgverlening en is het verstrekken van de beste reperfusie strategie een grote uitdaging. Hoe dit van invloed is op de prognose van patiënten met een STEMI is onduidelijk. In **hoofdstuk 4.2** worden de effecten van de cardiale zorg en de diverse reperfusie strategieën (primaire PCI en trombolyse) op het optreden van sterfte bij patiënten met STEMI beoordeeld. Onze bevindingen laten zien, dat variatie in cardiale zorg en de gekozen reperfusie strategie geen negatieve gevolgen heeft voor de patiënt en de uitkomst niet beïnvloedt. Over het geheel genomen werd er vaak een reperfusie therapie (68-73%) gebruikt en was het management in het ziekenhuis van de STEMI patiënt goed. Er werd echter slechts zelden, bij 7,6% van de patiënten, een primaire PCI toegepast. Tijdige reperfusie was bij iets meer dan 25% van de patiënten in het ziekenhuis mogelijk. Patiënten met een STEMI in Maleisië kregen goede acute cardiale zorg in zowel specialistische als niet-gespecialiseerde voorzieningen met vergelijkbare uitkomsten, ondanks het feit dat bij laatstgenoemde slechtere en minder middelen beschikbaar waren. De prognose na trombolyse en PCI was vergelijkbaar. Echter, om een verdere verbetering van cardiale zorg te bewerkstelligen zijn meer op bewijs gestoelde behandelingen noodzakelijk, moet de kwaliteit van de PCI therapie omhoog en moet de tijd tussen klachten en reperfusie worden verkort.

Een van de belangrijkste middelen voor de preventie van hart- en vaatziekten is de vroegtijdige identificatie van cardiovasculaire risicofactoren. Met vroegtijdige signalering door middel van screening en de effectieve behandeling van deze risicofactoren zou een aanzienlijk deel van cardiovasculaire gebeurtenissen voorkomen of uitgesteld kunnen worden. In **hoofdstuk 4.3**, identificeerden we effectieve screeningsstrategieën voor de vroege opsporing van hoog cardiovasculair-risico patiënten. We simuleerden vier verschillende strategieën gebaseerd op verschillende leeftijdsklassen, gestratificeerd naar geslacht en vergeleken deze met het huidige beleid van populatiescreening. Onze studie toonde aan dat een gerichte cardiovasculaire risicofactor screeningstrategie beter zou zijn op populatieniveau dan screening voor alle leeftijden. Het definiëren van een leeftijdgrens zou een meer kosteneffectieve methode voor het identificeren van hoog-risico individuen zijn. Bovendien toont onze studie aan dat het noodzakelijk is dat er verschillende screeningstrategieën voor mannen en vrouwen zijn, omdat er een groot verschil bestaat in het absoluut globale cardiovasculaire risico tussen beide geslachten.

Ten slotte, worden in de discussie verschillende strategieën voor de aanpak van de cardiovasculaire epidemie in Maleisië aanbevolen.

Ringkasan

Penyakit kardiovaskular merupakan punca morbiditi dan kematian terbesar di seluruh dunia. Kesan penyakit kardiovaskular adalah tidak seimbang dan lebih memudaratkan negara-negara membangun yang berpendapatan rendah dan sederhana. Peningkatan besar faktor-faktor risiko kardiovaskular berlaku di peringkat awal pembangunan ekonomi sesebuah negara, dan risiko kardiovaskular meningkat lebih mendadak dalam kumpulan sosio-ekonomi yang lebih rendah. Di negara-negara membangun, morbiditi kardiovaskular dan kematian lebih menjejaskan golongan dewasa (muda) yang bekerja dan ini membebankan ekonomi negara. Tesis ini adalah hasil penyelidikan yang akan memberi data untuk membantu dalam menangani beban penyakit kardiovaskular di Malaysia.

Hasil penyelidikan yang dibentangkan di dalam tesis ini dibahagikan kepada tiga bahagian. **Bab 2** mengambarkan beban faktor-faktor risiko kardiovaskular di negara ini. **Bab 3** menilaikan stratifikasi risiko dan ramalan dalam penyakit kardiovaskular, dan akhirnya, **Bab 4** tertumpu kepada pencegahan penyakit kardiovaskular dan komplikasinya.

Tinjauan-tinjauan terdahulu kesihatan kebangsaan menunjukkan bahawa kelaziman faktor risiko kardiovaskular dalam populasi Malaysia adalah tinggi dengan 'trend' yang semakin meningkat. Dalam **Bab 2.1**, beban faktor-faktor risiko kardiovaskular digambarkan secara berkelompok (hipertensi, diabetes, hiperkolesterolemia dan obesiti) di kalangan penduduk dewasa di Malaysia. Secara keseluruhan, 63% (95% selang keyakinan: 62, 65) mempunyai sekurang-kurangnya satu faktor risiko kardiovaskular, 33% (95% CI: 32, 35) mempunyai dua atau lebih faktor risiko dan 14% (95% CI: 12, 15) mempunyai tiga atau lebih faktor risiko. Dalam seluruh populasi, 52% (95% CI: 50, 53) mempunyai perubahan metabolik yang nyata, sama-ada hipertensi, hiperkolesterolemia, kencing manis atau toleransi glukosa terjejas atau mana-mana kombinasi faktor-faktorrisiko tersebut. Tiga puluh sembilan peratus (95% CI: 37, 40) dari mereka yang berumur kurang daripada 30 tahun mempunyai sekurang-kurangnya satu faktor risiko kardiovaskular. Penemuan ini menyerlahkan bahawa, walaupun program pencegahan penyakit dan penjagaan kesihatan masih dijalankan, beban risiko kardiovaskular masih tinggi dan memberi kesanke atas sebahagian besar golongan dewasa (muda). Ia adalah jelas menunjukkan terdapat epidemik kardiovaskular di Malaysia dan langkah-langkah drastik perlu diambil untuk mengurangkan beban penyakit kardiovaskular di negara ini.

Bab 2.2 mengambarkan perbezaan dalam prevalens faktor-faktor risiko kardiovaskular dan corak kelompok di negeri-negeri dan wilayah persekutuan Malaysia. Faktor-faktor risiko kardiovaskular yang dinilai ialah tekanan darah tinggi, kencing manis, hiperkolesterolemia, obesiti dan merokok. Terdapat variasi geografi dalam taburan faktor-faktor risiko, dengan kadar yang sangat tinggi;

prevalens dua atau lebih faktor risiko adalah dari 31.9 (95% CI: 30.9, 32.9) hingga 60.1 (95% CI: 59.3, 60.8), sebahagian besarnya didorong oleh faktor-faktor risiko yang boleh dikurangkan dengan ubat-ubatan seperti diabetes, hipertensi dan hiperkolesterolemia. Beban yang lebih tinggi dilihat di negeri-negeri kurang membangun di Semenanjung Malaysia, terutamanya Perlis, Kedah dan Kelantan. Hasil penyelidikan kami boleh memberi maklumat berguna dalam peruntukan sumber penjagaan kesihatan mengikut keperluan setiap kesihatan negeri. Penemuan ini juga diharap dapat membangunkan strategi-strategi kesihatan awam khusus untuk setiap negeri dalam pencegahan dan pengurusan risiko kardiovaskular.

Dalam **Bab 3**, model-model ramalan risiko kardiovaskular dan prognosis dinilai. Stratifikasi risiko dan ramalan adalah penting untuk membuat keputusan klinikal. Model-model ini meramalkan kebarangkalian seseorang individu mendapat penyakit ataupun kejadian yang telah dinyatakan, dan menstratakan mereka mengikut risiko yang diramal. Ini dilakukan secara objektif dan seragam. Walau bagaimanapun, penggunaan model ramalan risiko ini mempunyai limitasi. Adakah skor risiko yang diramalkan selaras dengan apa yang berlaku dalam keadaan pesakit tempatan? Kadar insiden penyakit dan kelaziman faktor risiko menentukan kesesuaian sebarang model ramalan risiko. Dengan itu, pengesahan model ini adalah penting sebelum ia digunakan dalam bidang klinikal.

Dalam **Bab 3.1**, kamimengesahkan Trombolisis Dalam Myocardial Infarction (TIMI) skor risiko untuk pesakit-pesakit yang mengalami serangan jantung ST-Elevation (STEMI). Markah TIMI digunakan untuk menilai risiko jangka pendek kematian (30 hari) bagi pesakit-pesakit yang mengalami STEMI. Kami mendapati bahawa skor TIMI adalah tepat dan sah. Ia menstratifikasikan risiko dan meramalkan prognosis dalam pesakit-pesakit yang mengalami STEMI di Malaysia. Ia masih sah walaupun pesakit-pesakit di Malaysia mempunyai ciri-ciri yang lebih serius daripada pesakit-pesakit di negara barat. Selain daripada itu, stratifikasi risiko berfungsi dengan baik untuk kalangan pesakit yang memang berisiko tinggi di Malaysia; pesakit kencing manis dan mereka yang mempunyai sakit buah pinggang. Oleh itu, skor TIMI mungkin bermanfaat dalam meningkatkan penjagaan klinikal melalui rawatan yang disasarkan, untuk pesakit-pesakit yang mengalami STEMI di Malaysia.

Kami membuat penilaian pada empat model ramalan risiko kardiovaskular di kalangan penduduk Malaysia di dalam **Bab 3.2**. Kami membandingkan utiliti Skor Risiko Framingham (FRS), risiko SCORE (Sistematik Penilaian Risiko koronari) tinggi dan rendah, dan model Pertubuhan Kesihatan Sedunia / Persatuan Antarabangsa Hipertensi (WHO / ISH) . Model ramalan risiko kardiovaskular ini disyorkan dalam garis panduan amalan klinikal Malaysia bagi pencegahan penyakit

kardiovaskular. Kami membandingkan diskriminasi model dalam stratifikasi risiko, dengan menilai kadar kematian 5 tahun akibat penyakit kardiovaskular. Kami mendapati bahawa walaupun faktor risiko kardiovaskular adalah tinggi dalam populasi kajian, model WHO / ISH mengklasifikasikan hampir 90% dalam kategori risiko kardiovaskular rendah. Untuk lelaki, model FRS dan model SCORE tinggi menunjukkan trend yang sama dalam stratifikasi risiko tetapi model WHO / ISH mengklasifikasikan kalangan besar individu sebagai berisiko rendah. Bagi wanita, kesemua empat model mempunyai trend yang sama dalam stratifikasi risiko. Walau bagaimanapun, model WHO / ISH mengklasifikasikan kalangan besar populasi sebagai berisiko rendah. FRS, SCORE tinggi dan SCORE rendah semua menunjukkan diskriminasi yang baik untuk kadar kematian kardiovaskular 5-tahun. Model WHO / ISH tidak menunjukkan diskriminasi yang baik, untuk populasi lelaki dan mahupun wanita. Kajian kami mengesahkan bahawa FRS dan kedua-dua model SCORE, tetapi bukan model WHO / ISH boleh digunakan untuk mendiskriminasi risiko kardiovaskular di kalangan penduduk Malaysia.

Bab 4 adalah tentang pencegahan penyakit kardiovaskular dan komplikasinya. Dalam **Bab 4.1**, kesan mencapai sasaran rawatan faktor-faktor risiko kardiovaskular pada pengurangan komplikasi buah pinggang dinilai dalam pesakit-pesakit kardiovaskular berisiko tinggi. Sasaran rawatan kardiovaskular adalah pencapaian kawalan dalam tekanan darah sistolik dan diastolik, kolesterol dan kolesterol HDL, serta rawatan albuminuria. Komplikasi renal adalah kegagalan buah pinggang peringkat akhir atau gejala penyakit buah pinggang atherosclerotic yang memerlukan rawatan. Kami mendapati bahawa kadar insiden untuk kegagalan buah pinggang peringkat akhir dan penyakit buah pinggang atherosclerotic berkurang secara linear dengan setiap penambahan sasaran rawatan yang dicapai. Pencapaian mana-mana dua sasaran rawatan mengurangkan risiko komplikasi buah pinggang, bahaya nisbah 0.46 (95% CI: 0.26, 0.82). Bagi pesakit dengan penyakit vaskular dan kencing manis, nisbah bahaya adalah 0.56 (95% CI: 0.28, 1.12) dan 0.28 (95% CI: 0.10, 0.79) masing-masing. Penemuan kami menunjukkan sasaran untuk pencegahan penyakit kardiovaskular dalam garis panduan amalan klinikal adalah berguna dalam mengurangkan risiko komplikasi buah pinggang dan juga; untuk semua pesakit yang berisiko tinggi mendapat penyakit-penyakit vaskular. Oleh itu, jika lebih ramai pesakit boleh dirawati dan mencapai sasaran rawatan faktor risiko kardiovaskular, pengurangan komplikasi buah pinggang juga boleh dicapai.

Pencegahan kematian dalam pesakit-pesakit yang mengalami kejadian kardiovaskular seperti serangan jantung ST-elevation (STEMI) bergantung kepada pelbagai faktor. Antaranya ialah tahap serius serangan jantung, masa dari serangan untuk rawatan utama dan pilihan terapi reperfusi. Strategi reperfusi yang disyorkan untuk STEMI adalah 'Percutanoeus Coronary Intervention' (PCI). Di negara-negara

membangun, terdapat variasi dalam peruntukan penjagaan jantung danjuga cabaran untuk menyediakan strategi reperfusi yang terbaik. Bagaimana ia mempengaruhi prognosis pesakit-pesakit STEMI adalah tidak jelas. Dalam **Bab 4.2**, kesan peruntukan penjagaan jantung dan strategi reperfusi (primary-PCI dan thrombolytics) dalam mencegah kematian pesakit STEMI dinilai. Penemuan kami menunjukkan bahawa variasi dalam peruntukan penjagaan jantung dan strategi reperfusi tidak menjejaskan prognosis pesakit. Secara keseluruhan, terapi reperfusi (68-73%) adalah tinggi dan pengurusan STEMI adalah baik di dalam hospital. Walau bagaimanapun, terapi primary-PCI adalah rendah, kadarnya hanya 7.6%. Reperfusi tepat pada masanya telah disediakan dalam hanya 25% daripada kes-kes hospital. Pesakit STEMI di Malaysia menerima penjagaan baik dalam kedua-dua kemudahan pakar dan bukan pakar, dengan prognosis yang sama walaupun bukan pakar kekurangan sumber kemudahan . Pesakit juga mempunyai prognosis yang serupa dengan terapi thrombolytic berbanding primary-PCI. Untuk meningkatkan penjagaan jantung di negara, peningkatan dalam kualiti penjagaan primary-PCI dan pengurangan dalam masa untuk reperfusi harus dicapai.

Salah satu strategi yang penting untuk mencegah penyakit kardiovaskular adalah penyaringan awal faktor-faktor risiko kardiovaskular. Penyaringan awal melalui pemeriksaan dan rawatan yang berkesan untuk faktor-faktor risiko, sebahagian besar penyakit kardiovaskular dan komplikasi boleh dicegah atau ditangguhkan. Dalam **Bab 4.3**, kami telah mengenal pasti strategi saringan yang berkesan untuk pengesanan awal pesakit kardiovaskular berisiko tinggi. Kami simulasikan empat strategi saringan berdasarkan kepada umur, mengikut jantina dan membandingkan strategi-strategi ini dengan strategi dasar negara yang mengesyorkan saringan untuk masyarakat umum. Kajian kami menunjukkan bahawa strategi saringan faktor risiko yang disasarkan mengikut umur tertentu adalah lebih baik daripada saringan bagi semua peringkat umur di kalangan komuniti. Penentuan kriteria kelayakan umur adalah kaedah yang lebih kos efektif untuk mengenalpasti individu-individu yang berisiko tinggi. Di samping itu, kajian kami menekankan keperluan untuk strategi saringan yang berbeza untuk lelaki dan wanita, disebabkan oleh perbezaan ketara dalam risiko keseluruhan kardiovaskular mereka.

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Curriculum Vitae

Sharmini Selvarajah was born March 20th, 1975 in Petaling Jaya, Malaysia. She obtained her medical degree from the University of Malaya in May 2000. She worked as a trainee doctor in the main tertiary referral centre in the country; Kuala Lumpur Hospital. Once she completed her training in August 2011, she was posted to a rural hospital in Selangor. At the end of December 2002, she moved to Clinical Research Centre, Ministry of Health Malaysia and worked on research projects covering health economics and clinical trials. She obtained a World Health Organization fellowship to the Clinical Research Centre at the University of Chicago, Chicago, United States in April 2005. She obtained her Master of Public Health degree (cum laude) from the University of Malaya in June 2006. She was awarded the Asia-link Fellowship and started the research projects presented in this thesis in September 2009. She obtained her Master of Science degree in Clinical Epidemiology from Utrecht University in June 2011. From September 2009 till November 2012 she worked on her PhD thesis with supervision from Professors Yolanda van der Graaf and Michiel L. Bots of the Julius Center for Health Sciences and Primary Care, Utrecht Medical Center, Utrecht University. She is currently a Clinical Epidemiologist working in Clinical Research Centre, Ministry of Health, Malaysia with a focus on cardiovascular disease.