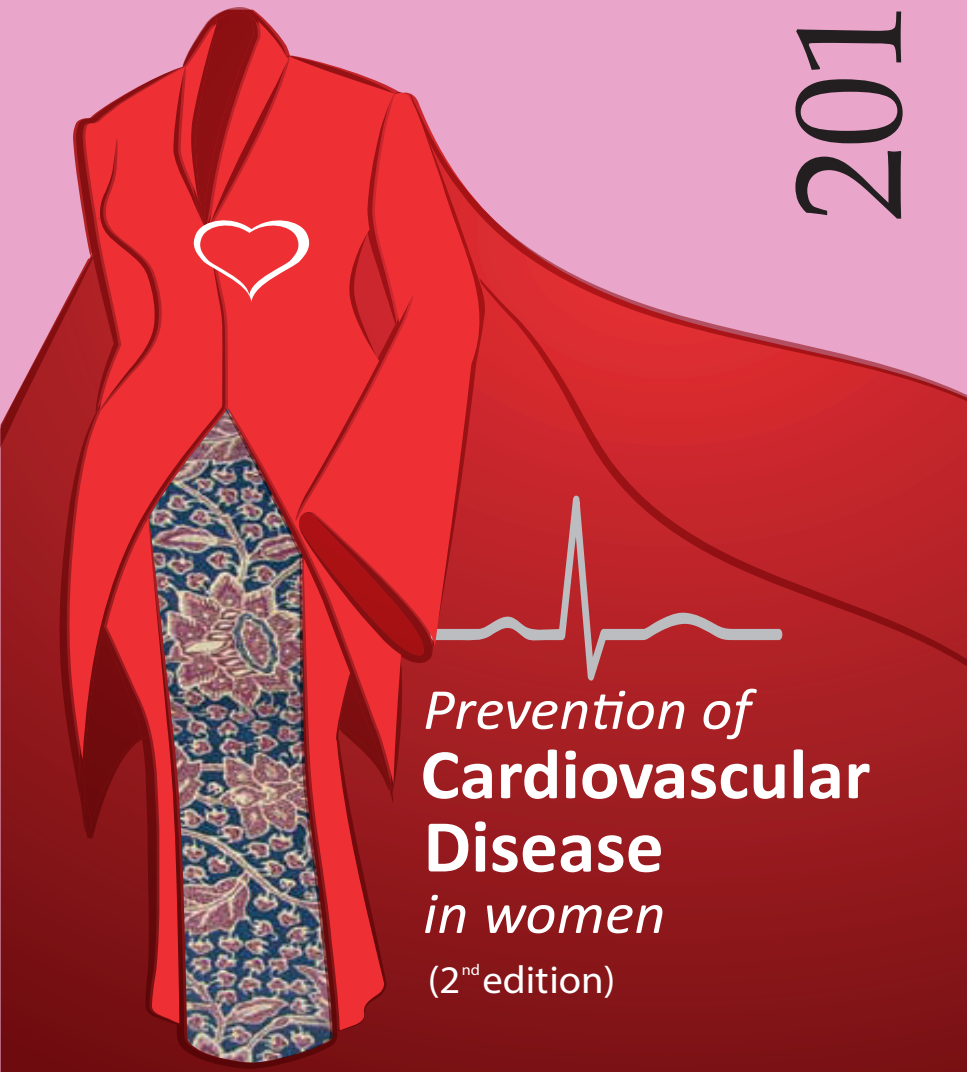
CLINICAL PRACTICE GUIDELINES

2016



Prevention of **Cardiovascular Disease** *in women*

(2nd edition)

Ministry of Health Malaysia

Academy of Medicine Malaysia

National Heart Association of Malaysia

STATEMENT OF INTENT

This guideline was developed to be a guide for best clinical practice in the management of cardiovascular diseases in women, based on the best available evidence at the time of development. Specific attempts were made to use local data and publications to ensure local relevance. Adherence to this guideline does not necessarily lead to the best clinical outcome in individual patient care. Every health care provider is responsible for the management of his/her unique patient based on the clinical presentation and management options available locally.

REVIEW OF THE GUIDELINE

This guideline is issued in 2016 and will be reviewed in 2021 or earlier if important new evidence becomes available.

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Available on the following websites:

http://www.moh.gov.my
http://www.acadmed.org.my

This is an update to the Clinical Practice Guidelines on Prevention of Heart Disease in Women published in 2008. This CPG supersedes the previous CPG.

FOREWORD BY THE DIRECTOR-GENERAL OF THE MINISTRY OF HEALTH MALAYSIA

Cardiovascular disease, till this day, remains the primary cause of mortality globally. Although it affects both genders, a greater emphasis appears to be placed on male patients, who appear to develop the disease at an earlier age compared to females. However, it is also known the incidence of cardiovascular disease in females rapidly rises to match males after menopause. From the National Cardiovascular Disease Registry in Malaysia (2011-2013), it was demonstrated that female patients had a higher in-hospital and 30-day mortality for acute coronary syndrome compared to male patients. Such statistics demand a greater focus being placed, not only on the diagnosis and treatment, but critically on the prevention of cardiovascular disease in women in our country.

Malaysia has a rising prevalence of cardiovascular risk factors in the population. Diabetes, hypertension and dyslipidaemia afflict both gender groups. Coupled with smoking and other non-communicable cardiovascular risk factors, it is important to place equal emphasis on both gender groups in the effort to prevent cardiovascular disease. The Ministry of Health is committed towards reducing the rates of non-communicable diseases, including those leading to cardiovascular disease, and these Guidelines form an important reference point to all stakeholders.

The advent of newer diagnostic and therapeutic strategies has also provided the opportunity to improve prevention of cardiovascular disease, including in women. Techniques such as multislice computed tomography of the coronary arteries and cardiac magnetic resonance imaging provide the clinician greater options for disease detection, yet each has its limitations. Contemporary strategies such as these will enhance the capacity of the clinician to improve both primary and secondary prevention of cardiovascular disease, augmenting established strategies such as the exercise stress test. Research in cardiovascular medicine has accelerated in recent years, and with such a rapidly expanding evidence base, these updated Guidelines are timely.

I am therefore grateful to the writing committee chaired by Tan Sri Dato' Seri Robaayah, who has no doubt put countless hours into the preparation of this Clinical Practice Guidelines, which is now in its second edition. While publication becomes a useful companion for clinicians, I hope it inspires more women to the field of cardiovascular medicine.

Datuk Dr Noor Hisham Abdullah
Director-General of Health Malaysia

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International Reviewers

"Let me congratulate you and your colleagues both on the initial Clinical Practice Guideline and on undertaking a very ambitious and extensive revision. This is a scholarly document, well referenced, and a major strength is the inclusion of Malaysian data – highly relevant to the clinical practice in your country as it derives from your population."

Nanette K. Wenger, MD, MACC, MACP, FAHA

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SUMMARY

- Cardiovascular disease (CVD), heart disease and strokes, is the main cause of death among women in Malaysia. It is 2 ½ times more common as a cause of death than all cancers combined.
- The pathophysiological mechanisms contributing to myocardial ischemia in women are varied and maybe multiple. Women with angina may have:
  - Atherosclerotic obstructive Coronary Heart Disease (CHD)- (coronary lesions > 50% luminal narrowing)
  - Non-obstructive CHD (≥ 20% and < 50% luminal narrowing). The prognosis of these patients is not benign. It is worse if myocardial ischemia is documented.
  - Normal coronary arteries (Cardiac Syndrome X) - (< 20% luminal narrowing)
- Other unique gender specific cardiac issues include:
  - Takotsubo Cardiomyopathy
  - Spontaneous coronary artery dissections
- Presenting symptoms for CHD and stroke in women may be both typical and sometimes atypical.
- Prognosis for women following a myocardial infarction (MI) and stroke is poorer than in men.
- Other diseases that are associated with increased cardiovascular (CV) risk in women include:
  - connective tissue diseases (especially rheumatoid arthritis, systemic lupus erythematosus (SLE) and systemic vasculitis) and the drugs that are used to treat these diseases
  - chemotherapy and radiation induced cardio toxicity
  - infections such as influenza, periodontal disease and human immunodeficiency virus (HIV)
  - obstructive sleep apnea (OSA)
- Increased awareness, early detection with appropriate investigations and management is important.
- All women above the age of 40 years should know their CVD risk.
- Assessment of CVD risk involves:
  - ***History:*** Looking for symptoms suggestive of CHD or CHD Equivalents, family history of premature CHD, smoking status, physical activity
  - ***Physical Examination:*** Height, weight, body mass index (BMI), waist circumference, pulses, blood pressure (BP)
  - ***Investigations:*** Blood glucose, lipid profile

- Risk Classification helps to identify **High Risk** women and to guide intensity of risk reduction efforts and the need for pharmacotherapy. Women may be classified according to their CVD risk (Table 1, pg 8) as:
  - ***High Risk***
  - ***At Risk***
  - ***Optimal Risk***
- Risk classification can also be done using the The Framingham Risk Score (FRS) in Table 2 (pg 9 & 10). The AHA/ACC pooled Risk Equations may also be used although in 2 retrospective studies, the FRS was a better estimate of CV risk in our local population. The 2013 ACC/AHA Atherosclerotic Cardiovascular Disease (ASCVD) Risk calculator (Table 3, pg 11) is also available at www.cvriskcalculator.com.
- Prevention of CVD involves a healthy lifestyle and risk factor reduction – the targets of risk factor reduction will depend on the individual's CVD risk. (Tables 4 & 5, pg 12 & 14)
  - ***High Risk:*** Intensive risk factor reduction with lifestyle and pharmacological measures to achieve target levels.
  - ***At Risk:*** Non pharmacological intervention with diet and physical activity. If targets not achieved, pharmacological therapy is indicated.
  - ***Optimal Risk:*** Continue with healthy lifestyle measures
- To ensure compliance to the guidelines, periodic audit of simple parameters should be done. Suggested audit parameters are documentation in the medical records of the individual's:
  - CVD risk
  - Height, weight, waist circumference and BMI and the desirable values.
  - BP
  - Lipid values
  - Fasting glucose and glycated haemoglobin A1c (HbA1c) levels
- The Audit of Clinical Diabetes (Green Book) by the *Unit Penyakit Kardiovaskular dan Diabetes* may be used as a guide.

Table 1: Classification of CVD Risk in Women*

High Risk	Established CHD and/or CHD Equivalents which are: • Cerebrovascular disease • Peripheral arterial disease (PAD) • Abdominal aortic aneurysm (AAA) • Diabetes mellitus (DM) • End stage or chronic kidney disease • Multiple risk factors that confer a 10 year CVD risk of > 20% using FRS (Table 2, pg 9 & 10)
At Risk	1 major risk factor for CVD including: • Family history of premature CVD (CVD at age < 55 years in male relative and < 65 years in female relative) • Total cholesterol ≥ 5.2 mmol/L, HDL-C < 1.2 mmol/l, or treated for dyslipidaemia • Systolic blood pressure (SBP) ≥ 120 mmHg, diastolic blood pressure (DBP) ≥ 80 mmHg, or treated hypertension • Cigarette smoking • Physical inactivity • Obesity especially central obesity • Metabolic syndrome • Evidence of advanced subclinical atherosclerosis (e.g. coronary calcification, carotid plaque, or thickened Intima Medial Thickness (IMT)) • History of preeclampsia, gestational diabetes, or pregnancy-induced hypertension • Systemic autoimmune collagen-vascular disease (e.g. lupus or rheumatoid arthritis)
Optimal Risk	10 year CVD risk of < 10% using FRS. Having a healthy lifestyle with no risk factors • Total cholesterol (TC) < 5.2 mmol/L (untreated) • BP < 120/< 80 mmHg (untreated) • Fasting blood glucose < 6.1 mmol/L (untreated) • BMI < 23 kg/m^2 • Abstinence from smoking • Physical activity at goal for adults > 20 years of age: ➢ ≥ 150 min/week moderate intensity, ➢ ≥ 75 min/week vigorous intensity, or combination

**Adapted from the Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women-2011 Update A Guideline From the American Heart Association*

Table 2: Framingham Risk Score for Asessment of CVD Risk*

Table 2A: CVD Points for Women

Points	Age,y	HDL-C	TC	SBP (not treated)	SBP (treated)	Smoker	Diabetes
-3				<120			
-2		1.6+					
-1		1.3-1.6			<120		
0	30-34	1.2-<1.3	<4.2	120-129		No	No
1		0.9-<1.2	4.2-<5.2	130-139			
2	35-39	<0.9		140-149	120-129		
3			5.2-<6.3		130-139	Yes	
4	40-44		6.3-<7.4	150-159			Yes
5	45-49		>7.4	160+	140-149		
6					150-159		
7	50-54				160+		
8	55-59						
9	60-64						
10	65-69						
11	70-74						
12	75+						
Points allotted							

Grand Total: _____ points

** D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB.General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743.*

Table 2B: CVD Risk for Women*

Total Points	10 year Risk %	Total Points	10 year Risk %
≤ -2	< 1	10	6.3
-1	1.0	11	7.3
0	1.2	12	8.6
1	1.5	13	10.0
2	1.7	14	11.7
3	2.0	15	13.7
4	2.4	16	15.9
5	2.8	17	18.5
6	3.3	18	21.5
7	3.9	19	24.8
8	4.5	20	28.5
9	5.3	21+	> 30

Table 2C: Heart Age/ Vascular Age for Women*

Points	Heart age, y
< 1	<30
1	31
2	34
3	36
4	39
5	42
6	45
7	48
8	51
9	55
10	59
11	64
12	68
13	73
14	79
15+	> 80

To determine a women's 10 year CVD risk, calculate in order:

- Grand Total CVD points (Table 2A)
- 10 year Risk of CVD (Table 2B)
- Heart Age/ Vascular Age for Women (Table 2C)

**D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB.General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743.*

Table 3: 2013 ACC/AHA Atherosclerotic Cardiovascular Disease Risk Calculator

Risk Factor	Units	Patient's Value	Acceptable range of values	Optimal Values
Sex	M(males) or F(females)		M or F	
Age	years		20-79	
Race	AA(African Americans) WH(Whites and others)		AA or WH	
Total Cholesterol	mg/dL		130-320	170
HDL cholesterol	mg/dL		20-100	50
Systolic BP	mmHg		90-200	110
Treatment for BP	Y (Yes); N (For No)		Y or N	N
Diabetes	Y (Yes); N (For No)		Y (Yes); N (For No)	N
Smoker	Y (Yes); N (For No)		Y (Yes); N (For No)	N

The 2013 ACC/AHA Atherosclerotic Cardiovascular Disease (ASCVD) Risk calculator is available at www.cvriskcalculator.com. It gives the 10 year risk of developing ASCVD (non fatal MI, cardiac death, fatal and non fatal stroke) as well as the lifetime risk of developing ASCVD of an individual at age 50 years with the same risk factors.

Table 4: General Recommendations for Prevention of CVD in Women

Recommendations		Grade of Recommendation/ Level of Evidence
Nutrition	• Know one's daily calorie requirements. • Home cooked meals are preferable. • Diet should encompass all food groups. Eat more fruits, vegetables, whole grain cereals and bread, fish especially oily fish rich in omega-3 fatty acids (such as *ikan tenggiri, carp*), lean meat, nuts and legumes, low fat milk and cheese, skinless poultry, non-tropical vegetable oils. • A high fiber diet: 20-30 gm/day • Eat more complex carbohydrates-whole grains, peas, beans, lentils. Whole grains should form 50% of total grain intake. • Naturally occurring sugars are preferred. Avoid sweets and sucrose -sweetened beverages. • Reduce daily salt intake to approximately 1-1¼ teaspoon salt. • Replace saturated and *trans*-fats with monounsaturated and polyunsaturated fats.	I, B
Physical Activity	• Exercise for at least 30 - 45 minutes, 5 times a week. Women who need to lose weight or sustain weight loss should exercise more.	I, B
Weight maintenance /reduction	• Ideal BMI for Asian women is 18.5 - < 23 kg/m^2 and ideal waist circumference is ≤ 80 cm (31.5 inches). ➢ Assess BMI and waist circumference at each visit. ➢ Encourage a weight reduction of 0.5 - 1 kg/week in the overweight and obese. The initial goal should be to reduce body weight to < 10% of baseline within 6 months.	I, C I, B

Recommendations		Grade of Recommendation/ Level of Evidence
Cigarette Smoking	• Women should abstain/stop smoking	I, B
Drug Therapy		
Aspirin (75-100mg daily)	• For secondary prevention • For primary prevention, aspirin use should be individualized weighing the benefit versus the risk of bleeding	I, A I, A
Anticoagulation for Atrial Fibrillation (AF)	• Non valvular AF and CHA_2DS_2-VASc score*: ➢ ≥ 2 - anticoagulate with ▪ warfarin or ▪ Novel Oral Anti-Coagulants (NOAC)** ➢ 1 - consideration for anticoagulation should be individualized (either no anti thrombotics, oral anticoagulants or aspirin alone) • < 65 years of age with lone AF and those with CHA_2DS_2-VASc of 0, anti thrombotics may be omitted • Valvular AF: anticoagulate with warfain to maintain INR 2.0-3.0	 I, A I, B IIa, C IIa, B I, B

** CHA_2DS_2-VASc score: Table 15, pg 86*

*** Novel Oral Anti-Coagulants: dabigratan, rivaroxaban, apixaban. These agents do not require monitoring of INR but the antidote for reversal may become available locally in future.*

Table 5: Targets of Treatment of Specific Risk Factors

Targets of Specific Risk Factors		Grade of Recommendation/ Level of Evidence
Dyslipidemia	**Low density lipoprotein cholesterol (LDL-C):** This should be the target of therapy. Treatment targets will depend on a woman's CVD Risk Classification (Table 1, pg 8): ***High Risk:*** Patients with established CHD or CHD Equivalents LDL-C Goal: < 2.6 mmol/L (the lower the better) (*or* a reduction of at least 50% if the baseline LDL-C is between 2.6-5.1 mmol/L) < 1.8 mmol/L in diabetics with CVD (*or* a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L)	 I, A I, A
Blood Pressure*	***At Risk & Optimal Risk*** < 3.0 mmol/L	-
	< 140/90 mmHg in most women < 80 years of age	I, A
	< 150/90 mmHg in most women > 80 years of age	I, A
	In the presence of the following co-morbidity, target BP should be:	
	➢ renal impairment (CKD): < 140/90 mmHg	I, A
	➢ proteinuria of < 1 g/24 hr: < 140/90 mmHg	I, A
	➢ proteinuria of > 1 g/24 hr: < 130/80 mmHg	I, A
	➢ post MI and heart failure: < 130/80 mmHg	I, C
	➢ secondary prevention of lacunar stroke: < 130/80 mmHg	IIa, B
**Diabetes ** **	Pre-prandial blood sugar or fasting: 4.4 – 7.0 mmol/L***	I, C
	Post prandial blood sugar (90 mins after a meal): 4.4 – 8.5 mmol/L***	I, C
	HbA1c: ≤ 6.5%***	I, A
	Blood Pressure: ≤ 135/75 mmHg	I, B
	LDL-cholesterol: < 2.6 mmol/L (the lower the better) < 1.8 mmol/L in diabetics with CVD	 I, A I, A
	HDL-cholesterol: > 1.2 mmol/L	
	Triglycerides: < 1.7 mmol/L	

** Malaysian Clinical Practice Guidelines on Hypertension, 4th ed 2013. Available at www.acadmed.com.my*
*** Malaysian Clinical Practice Guidelines on Management of Type 2 Diabetes Mellitus, 5th Ed 2015. Available at www.acadmed.org.my*
****Glycaemic target should be individualised depending on the patient's profile to minimise risk of hypoglycaemia*

RATIONALE AND PROCESS OF GUIDELINE DEVELOPMENT

Rationale:

CVD is an important cause of morbidity and mortality in Malaysian women. Unfortunately many women and most healthcare professionals have the misconception that CVD is not a woman's disease and that it is a disease that only affects men.

This Clinical Practice Guidelines (CPG) on the Prevention of Cardiovascular Disease in Women is the second edition. The first edition was published in 2008. This CPG has been drawn up by a committee appointed by the National Heart Association of Malaysia, Ministry of Health and the Academy of Medicine. It comprises of cardiologists, endocrinologists and general physicians from the government and private sectors and the Universities.

Objectives:

The objectives of these guidelines is to:

- Increase awareness regarding cardiovascular disease in women among healthcare providers
- Improve the detection and management of women with cardiovascular disease
- Update healthcare providers on women's cardiovascular health
- Develop a preventive strategy for cardiovascular disease in women

Process:

The previous CPG published in 2008 was used as a base. In addition to the previous clinical questions that needed to be updated, the Expert Panel formulated new questions that needed to be addressed. These clinical questions were then divided into sections and each member was assigned one or more topics.

A review of current medical literature on Cardiovascular Disease in Women and Women's Heart Health from 2008 (the date of the last CPG) till 30th August 2015 was performed. Literature search was carried out using the following electronic databases – PubMed and Cochrane Database of Systemic Reviews.

The following MeSH terms or free text terms were used either singly or in combination:

"Cardiovascular disease in women", "Heart disease in women", "Myocardial infarction in women", "Coronary heart disease in women", "Stroke in women", "Hypertension in women", "Dyslipidaemia in women", "Combined oral contraceptives", "Hormone replacement therapy".

The search was filtered to clinical trials and reviews, involving humans and published in the English language. The relevant articles were carefully selected from this huge list. In addition, the reference lists of all relevant articles retrieved were searched to identify further studies. Experts in the field were also contacted to obtain further information. International guidelines - the American Heart Association/American College of Cardiology (AHA/ACC) and European Society of Cardiology - were also studied. All literature retrieved were appraised by members of the Expert Panel and all statements and recommendations made were collectively agreed by the group. The grading of evidence and the level of recommendation used in this CPG was adapted from the AHA/ACC and the European Society of Cardiology (pg. 18).

After much discussion, the draft was then drawn up and submitted to the Technical Advisory Committee for Clinical Practice Guidelines, Ministry of Health Malaysia and key health personnel in the major hospitals of the Ministry of Health and the private sector for review and feedback.

Clinical Questions Addressed:

Are there gender specific differences in the;
- epidemiology of cardiovascular disease?
- risk factors for cardiovascular disease?
- clinical presentation of cardiovascular disease (ie heart disease and strokes) resulting in diagnostic difficulties?
- management of women with cardiovascular disease (ie heart disease and strokes)?
- prevention (both primary and secondary) of cardiovascular disease?

Target Group:

These guideline are directed at all healthcare providers treating women – general practitioners, general and family physicians, cardiologists, endocrinologists and gynaecologists.

Target Population:

It is developed to prevent cardiovascular disease (heart disease and strokes) in women of all ages.

Period of Validity of the Guidelines:

These guidelines need to be revised at least every 5 years to keep abreast with recent developments and knowledge that is being learnt regarding women's health.

Implementation of the Guidelines:

The implementation of the recommendations of a CPG is part of good clinical governance. To ensure successful implementation of this CPG we suggest:

- Increasing public awareness of cardiovascular disease in general and educating them on the importance of knowing their individual cardiovascular risk
- Continuous medical education and training of healthcare providers on methods of cardiovascular risk assessment and the implementation of appropriate preventative strategies depending on each individual's risk status
- Clinical audit by individual hospitals, units and general practices to ensure compliance. (see Section 7, pg 87 & 88)

GRADES OF RECOMMENDATION	
I	Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful and/or effective.
II	Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure/therapy.
II-a	Weight of evidence/opinion is in favour of its usefulness/efficacy.
II-b	Usefulness/efficacy is less well established by evidence/opinion.
III	Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/ effective and in some cases may be harmful.

LEVELS OF EVIDENCE	
A	Data derived from multiple randomized clinical trials or meta analyses.
B	Data derived from a single randomized clinical trial or large non randomized studies.
C	Only consensus of opinions of experts, case studies or standard of care.

Adapted from the American College of Cardiology Foundation/ American Heart Association and the European Society of Cardiology

(Available at: http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing-_Committees and at http://www.escardio.org/guidelines-surveys/escguidelines/about/Pages/rules-writing.aspx).

TABLE OF CONTENTS

ABBREVIATION

AAA	Abdominal aortic aneurysm
ABI	Ankle brachial index
ACEI	Angiotensin-converting enzyme inhibitors
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHA/ACC	American Heart Association/American College of Cardiology
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CAST	Cardiac arrhythmia suppression trial
CHD	Coronary heart disease
CMR	Cardiac magnetic resonance
COC	Combined oral contraceptive
CPAP	Continuous positive airway pressure
CPG	Clinical practice guideline
CT	Computed tomographic
CTA	Computed tomographic angiography
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ET/EPT	Menopausal hormone therapy
FRS	Framingham risk score
GTT	Glucose tolerance test
HbA1c	Glycated haemoglobin A1c
HDL-C	High density lipoprotein cholesterol
HF	Heart failure
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRT	Hormone replacement therapy
IDF	International Diabetes Federation
IFG	Impaired fasting glycaemia
IGT	Impaired glucose tolerance
IHD	Ischemic heart disease
IMT	Intima medial thickness
LBBB	Left bundle branch block

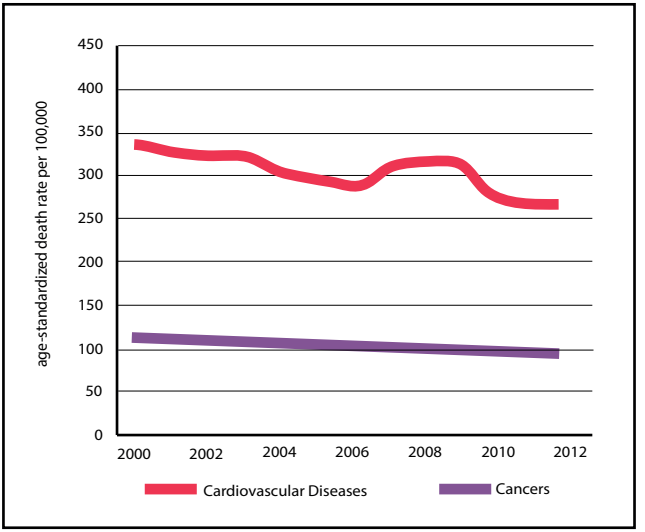
ABBREVIATION

LCD	Low-calorie diet
LDL-C	Low density lipoprotein cholesterol
Lp(a)	Lipoprotein a
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
Met S	Metabolic syndrome
MI	Myocardial infarction
MRA	Magnetic resonance angiogram
MSSM	Metabolic Syndrome Study of Malaysia
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NCEP-ATPIII	National Cholesterol Education Program Adult Treatment Panel III
NHMS	National Health and Morbidity Survey
NOAC	Novel oral anti-coagulant therapy
NVCD-ACS	National Cardiovascular Disease Database-Acute Coronary Syndrome
OGTT	Oral glucose tolerance test
OSA	Obstructive sleep apnoea
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PCOS	Polycystic ovarian syndrome
PD	Periodontal disease
PET	Positron emission tomography
RR	Relative risk
SBP	Systolic blood pressure
SCAD	Spontaneous coronary artery dissection
SCD	Sudden cardiac death
SLE	Systemic lupus erythematosus
SPECT	Single-photon emission computed tomography
STEMI	ST elevation myocardial infarction
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TCM	Takotsubo cardiomyopathy
TG	Triglyceride
TIA	Transient ischemic attack
US	United States
VLCD	Very low-calorie diet
VT	Ventricular tachycardia
VTE	Venous thromboembolism
WHO	World Health Organization
WISE	Women's Ischemia Syndrome Evaluation

1. THE SCOPE OF THE PROBLEM

CVD is the main cause of death among women worldwide including South East Asia and Malaysia.[1] It is 2 ½ times more common as a cause of death in Malaysian women than all cancers combined.[1,2] (Figure 1)

Figure 1: Age-standardised death rates among women due to Cardiovascular Disease and all Cancers Combined in Malaysia (2000 – 2012)



From : World Health Organization. Noncommunicable diseases country profiles 2014. July 2014. WHO Document Production Services, Geneva, Switzerland

The Malaysian National Cardiovascular Disease Database—Acute Coronary Syndrome (NCVD-ACS) Registry showed that Malaysian women presenting with Acute Coronary Syndrome (ACS) were older and more likely to have co-morbidity such as diabetes, hypertension, previous heart failure, and strokes than men.[3] They were less likely to receive evidence based medications-aspirin, β-blockers, angiotensin-converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB)- and undergo coronary angiography and percutaneous coronary intervention. There were no gender differences in the in-hospital mortality in all spectrums of ACS but following ST Elevation Myocardial Infarction (STEMI) women had almost twice the in-hospital mortality when compared to men (15.0% vs. 8.1%, respectively, $p< 0.0001$).[3]

A similar trend has also been observed in other countries where the in-hospital and early post MI mortality was shown to be greater in women than in men.[4-11] Even after one year, the mortality rate after an MI was higher in women than in men.[5]

Similarly, following a stroke, women are more likely to die than men.[12] Those who survive have a poorer long term outcome and a lower quality of life.[13] Stroke is the most important cause of death in women worldwide.[14] It is the most important cause of disability and the second most common cause of dementia after Alzheimer's disease.[12,15] At age 65, women have a higher lifetime risk of Alzheimer's than men.[15]

These facts are not well appreciated by both the general public and health care professionals who often regard CVD as a problem that only affect men. In 2 surveys carried out 2 years apart among middle-aged urban Malaysian female office workers and other professionals, more than two thirds of women surveyed said that cancer was the main cause of death among women.[16] A contemporary study done in Spain and the United States (US) found that only 35% and 55% of women respectively below the age of 55 years perceived themselves at risk of heart disease before their index MI.[17]

This lack of awareness has contributed to:

- failure in providing adequate information and health promotion to the public regarding CVD in women. Only about 25% and 48% of women in Spain and the US respectively, were told by their healthcare providers before their index MI that they were at risk and less than 50% of them were told about heart disease and how to modify their risk[17]
- less screening for risk factors that contribute to CVD in women
- high threshold for diagnosis and management of these risk factors
- lower rates of diagnosis of CVD in women
- lower usage of appropriate medications and interventions for treating women with CVD

Women with heart disease often present atypically and tend to have less chest pain.[18] Typical symptoms of an ACS however, are as important in women as in men.[18,19] General feelings of illness, fearfulness and nausea were more common in women.[18,20] Other atypical presentations include breathlessness and fatigue. Due to their atypical presentations, women are often not appropriately triaged in the emergency room resulting in a delay in the diagnosis and treatment.[18,20] This has adverse consequences on their prognosis.

This CPG highlights the important gender differences in CVD. There are differences in the clinical presentation, predisposing risk factors and the presence of co-morbidity in women. The accuracy of diagnostic tests and physiologic responses to exercise differ. Cultural norms, socioeconomic and psychological factors all affect the way women respond to their illness. All these factors have an impact on the management of CVD in women.

This CPG provides evidence based recommendations focusing on preventing CVD in women. Cardiovascular disease often strikes without warning, underscoring the importance of prevention. The impact of the different risk factors on CVD in women, the role of lifestyle changes and the use of appropriate drug therapies in the prevention of CVD are discussed. Decision making however, should be individualized and based on sound clinical judgment.

2. TYPES OF CARDIOVASCULAR DISEASE

Men and women have similar lifetime risks of CVD at age 55 years. There are however, considerable differences in the first manifestation.[21] Men are more likely to develop CHD as a first event, while women are more likely to have a stroke or heart failure (HF) as their first event, although these manifestations tend to appear when they are older.[21]

2.1. Coronary Heart Disease

2.1.1. Presenting Symptoms

In general, women present with CHD 10 to 20 years later than men.[22-26] Before menopause, the prevalence of CHD is low.[25]

There are gender differences in the symptoms at presentation.[18,20,22] Angina pectoris is an earlier and more common presentation in women as compared to men who more often present with MI.[27] Women often have atypical presentations.[27] In addition to chest pain or discomfort, women also have a lot of non chest related pain symptoms. Compared to men, women's symptoms are more often precipitated by mental or emotional stress and less frequently by exertion.[27]

The prodromal symptoms of an MI may also be atypical e.g. shortness of breath, sleep disturbances, diaphoresis, epigastric pain and fatigue.[28,29] However, when presenting as an ACS, there are no gender differences where women may also have typical symptoms (acute chest pain associated with sweating).[18,19]

Women presenting with an MI tend to have more atherosclerotic plaque erosions than plaque rupture.[30] In autopsy studies, plaque erosions accounted for about 25% of MI.[30] Most of these erosive lesions have a thick fibrous cap and do not have a necrotic core. In a series of patients who presented with MI and underwent aspiration thromboectomy followed by optical coherence studies, the residual lesion showed relatively minor luminal narrowing.[31] Most of these patients were younger individuals including premenopausal women and smokers.[31]

Following an MI, women have worse outcomes irrespective of age.,[11,32,33] More women had sudden cardiac death (SCD) before their arrival in hospital and almost two thirds of women who died suddenly had no previous symptoms.[26,34]

Paradoxically, women tend to have lower prevalence of obstructive coronary disease but more symptoms, ischemia and adverse outcomes.[26,35,36] It has been postulated that this could be due to abnormal coronary vasomotor reactivity, microvascular dysfunction, distal coronary erosion/embolization and non obstructive coronary disease.[26,37] In view of the varied pathophysiology of heart disease in women, a more appropriate term would be Ischemic Heart Disease (IHD) rather than CHD.

Studies seem to suggest that the adverse outcomes seen in women could be due to their baseline risk and clinical characteristics rather than to gender dependent factors or to bias in therapies.[38]

2.1.2. Risk Factors

The lifetime risk for CHD is generally lower in females and depends on their risk profile. At age of 55 years, with an optimal risk factor profile, lifetime risk for CHD is 3.6% for men and < 1% in women; with ≥ 2 risk factors, it is 37.5% in men and 18.3% for women.[39] In one study, women were found to experience the combined end point of CV death, MI, stroke and HF hospitalization, an average of 5.7 years later than men of similar risk profiles. For MI there was a delay of 10.7 years.[23]

There are important gender-related differences in the prevalence and outcome of cardiac risk factors (section 4, pg 52). Generally, women with CHD are more likely to be obese and have type 2 diabetes when compared to men.[17,18,26] Elderly hypertensive women and young female smokers are especially at risk for CHD.

Risk assessment can be used to raise awareness of CVD, educate patients about their CV risk, prompt lifestyle changes, guide therapy, and predict both 10-year and lifetime risk of CVD.[40] (section 5, pg 72)

2.1.3. Diagnosis and Investigations

Women with chest pain are less likely to be referred for appropriate investigations due to the following:

- patient factors
  - differences in presenting symptoms[27-29]
  - cultural norms – passive nature, fearfulness, anxiety, denial, self-sacrifice and care giver roles
  - co-morbidity e.g. arthritis, obesity
  - age
- physician factors
  - lack of awareness and misconceptions

Investigations for diagnosing CHD include non-invasive and invasive tests. There are important gender differences in the sensitivity and specificity of the various non-invasive tests.

2.1.3.1. Functional tests for ischemia

Conventional exercise stress testing has a lower diagnostic accuracy in women for obstructive CHD. The sensitivity is 31-71% and specificity is about 66 to 78% in women and about 80% for both in men.[18,41,42] This is partly due to:

- lower CHD prevalence in pre-menopausal women and thus a lower pre-test probability of disease
- poor exercise tolerance resulting in failure to achieve an adequate level of stress
- presence of baseline electrocardiogram (ECG) abnormalities making interpretation difficult

Despite these limitations, a normal stress ECG at adequate workloads in women with intermediate probability of CHD is a good indication that there is no significant obstructive lesion.[41,41] An exercise stress test, however, does not detect myocardial ischemia in women with non- obstructive coronary lesions.

Due to the limitations of exercise stress testing, stress echocardiography (exercise or dobutamine) and stress Single-Photon Emission Computed Tomography (SPECT) have been recommended in women. Both these tests can detect myocardial ischemia in the presence of obstructive and non-obstructive coronary lesions.[42] They also have higher specificity.[43] The diagnostic accuracy of SPECT however, can be reduced in women by both breast tissue and obesity, resulting in false-positives, especially in the anterior myocardial segments.

Cardiac Magnetic Resonance (CMR) is a newer imaging tool to investigate CHD in women. It has superior spatial resolution and does not use ionizing radiation unlike SPECT.[44] The prognostic implications of stress CMR using either adenosine or dobutamine is being investigated in women. A negative stress CMR study is associated with very low risk of CV death and MI.[45]

2.1.3.2. Other Imaging Modalities

Computed tomographic (CT) Coronary Calcium scoring and CT coronary angiography are increasingly being utilized in the diagnosis of CHD in women. Calcium scoring has been shown to improve CV risk prediction.[46-49]

The presence of coronary calcium redefined a group of women improperly labelled as low risk by Framingham criteria.[46,47]

A calcium score of ≥300 was associated with a 6.7% and 8.6% absolute risk of CHD and CVD respectively over a 3.75 year period as compared to women with undetectable calcium.[46] However, a more recent analysis showed that the presence of any calcium together with traditional risk factors (MESA-Score) provided a better estimate of 10 year CHD risk[50] (for MESA-Score see www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx).

In symptomatic patients with low or intermediate pre-test probability and low or zero calcium score, CT angiography accurately rules out obstructive CHD. Care should be taken to adhere to radiation safety guidelines.

However, in patients with known CHD and/or extensive coronary calcification and/or high pre-test probability of CHD, an invasive coronary angiogram is superior for diagnostic accuracy.[47]

2.1.3.3. Conventional/Invasive Coronary Angiography

Women are less likely to be offered invasive coronary angiography in view of their atypical symptoms. When performed appropriately, coronary angiography is associated with a similar low complication rate in both gender. Its underutilization in women results in under-diagnosis, suboptimal treatment and poorer long term outcome.

In women, atheromatous plaques tend to be distributed diffusely, rather than in clumps. As such, coronary angiographic studies in women tend to be misinterpreted as “normal”.[26] Autopsy studies in young people who were certified as having ischemic heart disease as a cause of death, showed that fewer women had obstructive CHD despite pathological evidence of an MI (obstructive CHD in this study, was defined as ≥ 75% cross-sectional area stenosis in an epicardial vessel or ≥ 50% left main).[35]

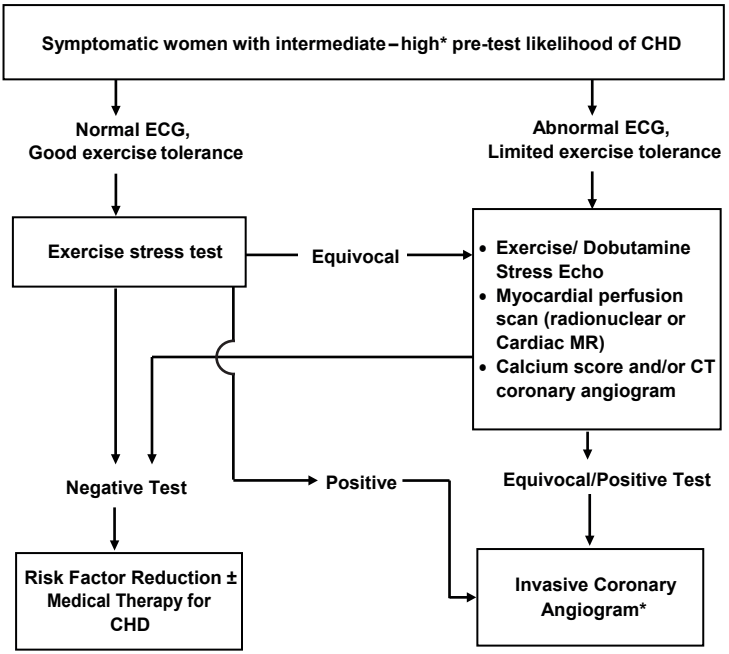
In a substudy of the WISE registry, intravascular coronary ultrasound showed that almost 80% of women who had “normal” coronary arteries by conventional coronary angiogram, had evidence of atherosclerosis involving more than 40% of the interrogated vessel length and 73% had positive remodeling with preserved lumen size.[51] These patients were classified as having non-obstructive CHD.

2.1.4. Management

Evidence based data on the management of CHD in women are limited because they are generally under-represented in the randomized controlled trials. Available data however, suggests that most of the benefits seen in men can be extrapolated to women.

Women with CHD should be treated in the same manner as in men.

Figure 2: Algorithm for the investigation of women suspected of CHD



**In individuals with typical symptoms and a high pre-test likelihood of CHD, an invasive coronary angiogram may be the initial investigation of choice (please refer to Appropriate Use Criteria for Investigations and Revascularization in CAD 2015 (1st edition): available at www.acadmed.org.my)*

Symptomatic women with low pre-test probability of CHD should undergo a clinical examination, screening for CV risk factors, resting ECG, and if necessary, an exercise stress test may be considered.

2.1.5. Unique Gender Specific Cardiac Issues

2.1.5.1. Non-obstructive CHD

Definitions for non obstructive CHD differ. According to the Veteran Affairs Clinical Assessment Reporting, and Tracking (CART) Program, based on the coronary angiographic findings, non-obstructive CHD may be defined as:[52]

- coronary artery stenosis ≥ 20% but < 50% in the left main coronary artery
- a stenosis ≥ 20% but < 70% in any other epicardial coronary artery

In the WISE study, non-obstructive CHD was defined as at least one coronary stenosis ≥ 20% but < 50% luminal narrowing while obstructive CHD was coronary stenosis ≥ 50%.[37] A < 20% luminal narrowing was defined as "Normal". Persons with non-obstructive CHD may have atheromatous plaques occurring in "clumps" with positive remodelling or as diffuse involvement of the vessel wall.[35,51]

Non-obstructive CHD is more common in women.[37,53] Patients with non-obstructive CHD may present as stable angina, ACS and sudden death.[37]

The prognosis of this condition is not benign. Compared to persons with no apparent coronary lesions (< 20% luminal narrowing) non-obstructive CHD was associated with significantly higher risk of MI and all cause mortality in both gender.[37,54]

In the WISE study, symptomatic women with non-obstructive CHD but who had exercise induced myocardial ischemia documented by MRI had a 3 year event rate of 43% when compared to 13% in symptomatic women with no demonstrable myocardial ischemia.[55]

In a systemic review, 7% of patients presenting with MI had non-obstructive coronary arteries.[56] A third of patients presented with STEMI and two-thirds with NSTEMI. About 40% of the patients were women with a mean age of 54 years. Compared with MI due to obstructive coronary artery disease, these patients tended to be younger, females and have less hyperlipidemia. The one-year all-cause mortality in patients with MI due to non-obstructive disease was 4.7% compared to 6.7% for those with MI and obstructive coronary arteries.[56]

Non-obstructive CHD is associated with limitations in flow reserve at the coronary microvascular level.

However, little is known about the pathophysiological mechanisms contributing to myocardial ischemia in these subjects. The etiology appears diverse, multifactorial and may involve more than one mechanism.[57,58]

2.1.5.1.1. Management

There are no randomized trials on optimal prevention and treatment strategies for non obstructive CHD. In patients with evidence of atherosclerosis, statins and ACE-I have been beneficial against progression of disease in short term trials.[37] β-blockers have been shown to give more relief of angina compared to calcium channel blockers. Imipramine has also been shown to provide symptom relief.[37]

2.1.5.2. Cardiac Syndrome X

Cardiac Syndrome X is angina in the absence of obstructive CHD (< 20% luminal narrowing). There is however, a wide variation and lack of consensus on its definition.[59] There is also considerable overlap with non-obstructive CHD.[59]

A proposed more precise definition of Cardiac Syndrome X entails the following criteria:[60-62]

- Exercise-induced, angina-like chest discomfort
- ST-segment depression during spontaneous or stress-induced typical chest pain
- Normal epicardial coronary arteries at angiography
- No spontaneous or inducible epicardial coronary artery spasm upon egonovine or acetylcholine provocation
- Absence of cardiac or systemic diseases associated with microvascular dysfunction such as hypertrophic cardiomyopathy or diabetes

Recently a modified definition that includes evidence of ischemia in any form of functional testing (exercise stress test, stress echocardiography, SPECT, CMR, positron emission tomography, [PET] or intracoronary Doppler ultrasound) has been proposed.[60,61]

There are several groups of patients who have angina-like chest pain and normal coronary arteries at angiography but fail to meet one of the above criteria. Examples include those with angina predominantly at rest, those with diabetes or hypertension, or those with lack of ST depression on ECG during angina.

It remains unclear whether the pathogenesis of angina in these patients is the same as in patients who fall under the strict definition of Cardiac Syndrome X.[60]

Cardiac Syndrome X is more common in women than men; about 70% of patients are women who are approaching or are post-menopausal.[60,62,63] About 50% of women undergoing coronary angiography for chest pain do not have major obstructive CHD.[64] In early CHD, men have higher degrees of atheroma and epicardial endothelial dysfunction, whereas women have more disease of the microvasculature.[65]

In symptomatic patients with "normal" coronary arteries, further tests for myocardial ischemia (stress contrast echocardiogram or preferably myocardial perfusion scans such as CMR/SPECT) may be warranted.

There are several theories on the aetiology of Cardiac Syndrome X. Two factors that may be involved are:

- Microvascular dysfunction. About 50% of women with chest pain have evidence of microvascular dysfunction,[66-68] but only about 20% to 25% showed signs of ischaemia[55,67,69]
- Enhanced pain perception[70,71]

A recent study however, found that there were no gender differences in the prevalence of coronary microvascular dysfunction.[72] An accompanying editorial questioned if the fundamental pathophysiology of ischemic heart disease is different between the sexes.[73] It raised the hypothesis that sex-based disparities in the prevalence and combination of known risk factors may be the cause for the different manifestations of disease in women compared with men.[73]

Patients with Cardiac Syndrome X generally have a good prognosis - overall major cardiac event rate of MI and CVD death 0-3.8% over 5 years.[74] As many as 55% of patients however, often continue to suffer recurrent chest pain even with treatment.[74]

It is important to distinguish between women with angina and normal coronaries- luminal narrowing of < 20% - (Cardiac Syndrome X) and those with non- obstructive CHD.

The WISE study showed that the 5 -year cardiac event rate for MI and CVD death were significantly different ($P \leq 0.002$) in the 3 subgroups:[75]

- 16% for women with angina and non-obstructive CHD (stenosis < 50%)
- 7.9% for women with angina and normal coronary arteries (Cardiac Syndrome X)
- 2.4% for the asymptomatic control group

Women with non-obstructive CHD and documented myocardial ischemia have a poorer prognosis.[55,76] Women with Syndrome X and severe endothelial dysfunction have a 30% increased risk of developing CHD at 10 years.[63,77-80]

2.1.5.2.1. Management

Patients with Cardiac Syndrome X are at increased CV risk.[77-80] Thus, emphasis should be towards prevention by modification of CV risk factors and control of chest pain.

Management of patients with chest pain includes:

- Nitrates – only half of all Cardiac Syndrome X patients respond to nitrates.[64] Occasionally, the chest pain may be GTN resistant.
- Calcium channel blockers such as verapamil and nifedipine[64,81]
- β-blockers[61,64,81]
- Ranolazine[82]

Although there have been a number of other different treatment strategies that have been studied in coronary microvascular angina such as ACEI (quinapril), phosphodiesterase inhibitors (sildenafil), statins and calcium channel blockers (diltiazem), a recent systemic review found little data to support any of these therapies.[83] These were however very small short term studies.

2.1.5.3. Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy (TCM) is a transient cardiac syndrome that is characterized by left ventricular apical akinesis, electrocardiographic changes of MI, minimal rise in cardiac biomarkers and absence of significant obstructive coronary artery disease. Almost 90% of cases occur in women with the mean age of 67 years.[84]

Common presenting symptoms are acute chest pain and dyspnoea almost always (85% of cases) precitated by an emotionally or physically stressful event. These symptoms are often indistinguishable from an ACS.

The modified Mayo Clinic criteria for the diagnosis of TCM includes:[85,86]

- Transient hypokinesis, dyskinesis, or akinesis of the left ventricular midsegments, with or without apical involvement; the regional wall-motion abnormalities extend beyond a single epicardial vascular distribution, and a stressful trigger is often, but not always, present
- Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture
- New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin level
- Absence of pheochromocytoma or myocarditis

The underlying etiology is unknown but is likely related to release of catecholamines, both locally in the myocardium and in the circulation.

2.1.5.3.1. Management

Treatment is mainly supportive. About 5% of patients may develop LV thrombus and require anticoagulation.[87]

The prognosis is excellent with almost 95% having complete recovery within 4-8 weeks.[84] The most common complication is heart failure. Treatment of heart failure is as outlined in section 2.1.5.6.1, pg 41. About 3.5% of patients however, suffer a recurrence of TCM.[84]

2.1.5.4. Spontaneous Coronary Dissection

Spontaneous Coronary Artery Dissection (SCAD) is a very rare condition with an incidence of 0.07-1.1% of all coronary angiograms performed.[88] The prevalence may be as high as 24% in women < 50 years of age who present with MI.[89] It affects predominantly young females - 70-80% are women and the mean age at presentation was 42 years.[88,90] In one series however, 62.3% of women who had SCAD were post menopausal.[91]

They usually present as an ACS – almost 50% as STEMI. Some may present as Sudden Cardiac Death. The left anterior descending artery is the commonest vessel affected in women and the right coronary artery in men.[88] In about 25% of patients, there may be multivessel involvement.[88]

Classically, patients with SCAD fall into the following groups:[90]

- Peripartum- about a third of cases occur in the third trimester or early post partum period[92]

- Atherosclerotic – about a third have underlying atherosclerotic plaque rupture
- Others – vasculitis, Ehler's Danlos, Fibromuscular dysplasia, connective tissue disease such as systemic lupus erythematosis and certain conditions such as vigorous exercise, prolonged sneezing or cocaine abuse.
- Idiopathic

The diagnosis is often difficult and made only after coronary angiography. The index of suspicion should be high if a young woman without the traditional risk factors presents with an MI.

2.1.5.4.1. Management

There are no guidelines available on treatment of SCAD. In patients presenting with MI:

- Fibrinolytic therapy is contraindicated.
- A conservative approach is the treatment of choice if the patient is stable, without chest pains and the coronary vessel is open with TIMI 3 flow.
- Primary Percutaneous Coronary Intervention (PCI) should be considered if the patient has ongoing pain, hemodynamic instability and/or flow limitation in a large epicardial vessel with a large area of myocardium at risk. The technical success of PCI and the long term results in patients with SCAD are much lower than in patients with atherosclerotic disease.[88,91]
- Coronary artery bypass grafting maybe more appropriate if the SCAD involves the left main coronary artery or multiple coronary arteries.

The in hospital and 1 year mortality is about 1-4%.[91] Predictors of poor prognosis include female sex and late treatment. Patients presenting in the post partum period had the worst prognosis.[91]

2.1.5.5. Cardiac Arrhythmias

Women tend to have a higher prevalence of sick sinus syndrome, inappropriate sinus tachycardia, atrioventricular nodal re-entry tachycardia, idiopathic right ventricular tachycardia and arrhythmic events in the long QT syndrome.[93]

Atrial Fibrillation (AF) is the most common supraventricular arrhythmia. It is 1.5 more frequent in men than women but in those over 70 years old, the prevalence is similar in both gender probably because of the longer average lifetime of women.[94,95] Women are more likely to experience an impaired quality of life with longer and more symptomatic episodes and frequent recurrences.[96,97] In subjects older than 75 years of age, female sex has been associated with an additional risk of stroke.[98] A recent study found that patients with non valvular AF had a high prevalence of left ventricular hypertrophy (LVH), which was related to female gender, older age, hypertension, and previous MI.[99] There is also a strong association between AF and obstructive sleep apnoea (OSA).[100]

Women have a lower propensity to ventricular arrhythmias. However, women with CHD have been noted to have more easily inducible ventricular arrhythmias[101,102] and those with congestive heart failure have a higher frequency of non-sustained ventricular tachycardia (VT).[103]

Women have faster resting heart rates yet longer QTc intervals.[94,104,105] They are more prone to develop torsades de pointes during administration of cardiovascular drugs that prolong cardiac repolarization (QT interval).[106,107]

In the Cardiac Arrhythmia Suppression Trial (CAST) study[108] two factors significantly increased the hazard ratio (HR) for arrhythmic death or resuscitated cardiac arrest in non-randomized patients given anti-arrhythmic drugs. These were:

- Female gender (HR 4.7, $p < 0.05$) and
- Electrocardiographic abnormalities (such as VT, proarrhythmia, widened QRS complex, heart block, bradycardia)

The incidence of SCD is lower in women than in men.[109-112] Female survivors of cardiac arrest are less likely to have underlying CHD and more likely to have other forms of heart disease or structurally normal hearts.[109,111,113]

However, in women with a previous MI, the risk of SCD is 2-fold higher and in those with heart failure, it is 5 times higher than in men.[111,113,114] Women who do suffer SCD are less likely to have a left ventricular ejection fraction (LVEF) < 35% documented prior to SCD.[111]

2.1.5.5.1. Management

Women should be treated in a similar manner as men. Women with AF benefit from both rate and rhythm control and anticoagulants for prophylaxis against thrombo-embolism. Anticoagulants are however underused in older women.[96] There are a number of safety issues with the use of warfarin in women necessitating close monitoring. These include:

- higher risk of major bleeding[96]
- female gender being an independent risk factor for not being in the therapeutic range of warfarin[115]
- even within the therapeutic range of warfarin, women remain at a higher risk of stroke[115]

The newer novel oral anticoagulants appear to be more efficacious and safer in women.[116] (Section 6.2.5.1, pg 85)

Catheter ablation for AF appears to have similar results in both gender although few women have been recruited in the trials.

Caution should be exercised in the use of anti-arrhythmic drug therapy in women because of the danger of pro-arrhythmia.[106-108] Registry data indicate that women benefit from implantable cardioverter defibrillator similar to men[117] although several previous meta-analysis suggest that the survival benefit in women in the primary prevention trials did not reach statistically significant levels. Women however were under-represented in these trials only constituting about 15-30% of the study population. This may have contributed to bias.[118,119]

2.1.5.6. Heart failure

Common aetiologies of HF in women include hypertension, CHD and valvular heart disease. Hypertension increases the risk of developing HF almost 3-fold in women as compared to 2-fold in men.[120,121] Women developing HF are more likely to be older, hypertensive and have preserved left ventricular systolic function and less CHD.[122-124] Women with prior MI are at a higher risk of developing HF than men.[125] The risk of death is also higher in women who develop HF post MI.[125]

The risk of HF in diabetic women is also much higher - almost 3-fold – when compared to non-diabetics.[126] Obesity is also a risk factor for HF conferring a risk that is twice that of subjects of normal weight.

Obese women are at higher risk of developing HF than obese men. (HR: 2.12 vs 1.90).[127] However, in patients with established systolic HF, there appears to be an obesity paradox – survival appears better in patients with higher BMI.[128-131]

Left ventricular diastolic dysfunction is more common in women due to the effects of prolonged hypertension and diabetes. In addition, women develop CHD and HF later in life and have more age-related changes in the heart, such as poor diastolic performance at that time.[122-124]

The prognosis of women with HF is generally better than that of men.[124,132-134] However if the aetiology of HF is ischaemia related, the prognosis is similar.[124,125]

2.1.5.6.1. Management

Women with HF have similar benefits as men with evidence based therapy such as ACEI/ ARB, β-blockers and mineralocorticoid inhibitors. Registry data show that women with HF and left bundle branch block (LBBB) requiring cardiac resynchronisation therapy benefit as much as men although few women have been enrolled in the randomized clinical trials.[135]

Women who are overweight and obese should reduce weight although there is limited data to support its benefit in HF.[131]

2.2. Cerebrovascular disease

2.2.1. Epidemiology

Stroke is now the leading cause of death in women worldwide and has been projected to remain an important cause of mortality till 2030.[14,136] However in the US and UK, it is the second most important cause of death after CHD.[22,137] Women have a higher lifetime risk of stroke than men and are on average about 4 years older at stroke onset than men.[23,138,139] (≈ 75 years compared with 71 years) In younger and middle-aged groups, age-specific incidence rates of stroke in women are much lower than men but in the older age groups (> 75 years), incidence rates are approximately equal or even higher than in men.[140,141] Women are more likely to die or have disability following a stroke than men.[12,13] This could be due to their older age at presentation and their pre-stroke disability which is greater than that of men.[13]

2.2.2. Presenting Symptoms

In general, there are no gender differences in the clinical presentation of stroke although women report a higher frequency of headache and facial sensory deficits and men have more prodromal symptoms and gait disturbances.[142-144]

2.2.3. Risk Factors

Women and men share many common risk factors for stroke although there are gender differences in the prevalence of the different risk factors.[145] (Table 6, pg 43) Women are more likely to have AF and hypertension, whereas men are more likely to have a history of CHD, MI, peripheral arterial disease, diabetes, alcohol and tobacco use.[146,147] Diabetes and metabolic syndrome (Met S) have a greater effect on stroke risk in women.[148,149]

Other stroke risk factors include:-

- AF
- Carotid artery disease
- Transient ischaemic attacks
- Family history of premature stroke- Ischemic strokes tend to occur in families.[150,151] A meta – analysis found that female probands were more likely to have a positive family history of stroke in any parent than were male probands and were also more likely to have a history of stroke in their mothers than fathers[152,153]
- Previous history of stroke[154,155]

2.2.3.1. Special Issues for Stroke in Women

Women also face additional gender specific risk factors. (Table 6, pg 43) These include:

- Oal contraceptive use[156,157]
- Oestrogen therapy/ Oestrogen Progesterone Therapy (ET/ EPT)[158]
- Pregnancy[159,160]
- Migraine[161-163]

2.2.3.1.1. Oral Contraceptive Use (Section 4.12.1, pg 67)

2.2.3.1.2. Hormone Replacement Therapy (Section 4.12.2 pg 68)

2.2.3.1.3. Pregnancy

Pregnancy increases the risk of a stroke in women due to:

- Pregnancy-induced hypertension
- increased blood coagulability
- postpartum haemorrhage with hypotension

The incidence of stroke, both ischaemic and haemorrhagic, is markedly increased in the postpartum period.[159,160]

Table 6: Sex Specific Stroke Risk Factors*

Risk Factor	Sex-Specific Risk Factors	Risk Factors That Are Stronger or More Prevalent in Women	Risk Factors With Similar Prevalence in Men and Women but Unknown Difference in Impact
Pregnancy	X		
Preeclampsia	X		
Gestational diabetes	X		
Oral contraceptive use	X		
Postmenopausal hormone use	X		
Changes in hormonal status	X		
Migraine with aura		X	
Atrial fibrillation		X	
Diabetes mellitus		X	
Hypertension		X	
Physical inactivity			X
Age			X
Prior CVD			X
Obesity			X
Diet			X
Smoking			X
Metabolic syndrome			X
Depression		X	
Psychosocial stress		X	

**Adapted from Bushnell C et al. AHA/ASA Guideline. Guidelines for the Prevention of Stroke in Women. A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2014; 45: 1545-1588.*

2.2.3.1.4. Migraine

Women are more likely to suffer from migraine. Migraine with visual aura increases the risk of stroke.[161-163] This risk is higher in current cigarette smokers and current users of oral contraceptives.[163]

2.2.4. Diagnosis and Management

Most studies have found no gender differences in terms of stroke types, although some studies have found an increase in subarachnoid and cardio-embolic strokes in females.[13]

There are no gender differences in the way strokes are diagnosed and managed. Please refer to Malaysian CPG on Management of Ischemic Stroke (2012).

2.3. Peripheral Arterial Disease

The prevalence of peripheral arterial disease (PAD) is lower in women under 50 years of age but it increases with age and in those over 80 years, the prevalence is as high as in men. Even for the same disease states, women have poorer prognosis with event rates that are higher than men especially when the ankle brachial index (ABI) is low.[164-167] Women have an increased risk of MI, cardiovascular and total mortality.[165-167] They also have faster functional decline and greater mobility loss than men with PAD.[168]

2.3.1. Presenting Symptoms

The classical symptom of PAD is intermittent claudication. Women with PAD however, tend to be asymptomatic or present with atypical symptoms.[164,166]

2.3.2. Diagnosis

The ABI is an independent and significant indicator of mortality.[166] Measurement of the ABI index using a Doppler ultrasound, detects about 3-5 times more cases than history alone.[166] In patients, especially in those with diabetes, the hardened arterial wall may lead to incompressibility of the vessel and cause erroneous readings.

The following women, symptomatic and asymptomatic, should be screened for PAD.[164,169]

- Those with exertional leg symptoms
- The elderly (above the age of 70 years)
- Those above the age of 50 years with any atherosclerotic risk factor (smoking, diabetes, hypertension, elevated cholesterols)
- Diabetics who are 49 years old or younger or who have any of these atherosclerotic risk factors
- Subjects with a 10 year CVD risk of 10-20% (FRS, Table 2, pg 9 & 10)

These women should be screened by history and clinical examination of the foot pulses. The diagnosis of PAD may be objectively confirmed by the measurement of the ABI by Doppler ultrasound. The presence of PAD indicates a high risk individual and alters the intensity of risk factor modification.

2.3.3. Management

Patients with intermittent claudication should undergo a supervised exercise program to improve symptoms of claudication and exercise performance.[164] Women however, respond less well to exercise training.

Treatment options include medical therapy, angioplasty and surgery. Patients with PAD whether symptomatic or not, should be treated as aggressively as patients with CHD with risk factor modification, anti-platelet agents (aspirin or clopidogrel) statins, β-blockers and ACEI.[170-181]

After adjusting for risk factors, the following drugs have been found to be beneficial in reducing mortality:[170]

- Statins HR; 0.46
- β-blockers HR = 0. 68
- Aspirin HR = 0.72
- ACEI HR = 0.80

A phosphodiesterase III inhibitor (cilostazol) has been shown to improve exercise performance and quality of life in symptomatic patients but there is no data that it results in a reduction of adverse cardiovascular events.[182,183]

The use of β-blockers has previously been discouraged in the presence of PAD because of the possibility of worsening limb ischaemia.

However a meta-analysis has shown that these drugs can be safely used in stable patients with mild to moderate symptoms of PAD.[180] A more recent review showed that β-blockers do not adversely affect walking distance, calf blood flow, calf vascular resistance and skin temperature in persons with intermittent claudication although most of the trials done were small, of poor quality and done more than 20 years ago.[180] Thus the presence of stable PAD is not a contraindication for the use of β-blockers in patients with CHD.

Symptomatic patients should be considered for intervention – angioplasty or surgery. The diagnosis can be confirmed with either a magnetic resonance angiogram (MRA) or CT angiography (CTA) prior to intervention. Women tend to have higher morbidity and mortality after open surgical procedures.[184,185]

2.4. Aortic Atherosclerosis and Thoracic or Abdominal Aortic Aneurysm

2.4.1. Presenting Symptoms

Aortic atherosclerosis is usually asymptomatic and was noted in 38% of women.[186] Aortic aneurysms are uncommon in women. The prevalence ranges from 0.6 to 1.4% which is about 15% of that seen in men. Women present seven to ten years later than men.[187] Most AAA- related deaths occur before 80 years of age in men and after 80 years of age in women.[187]

2.4.2. Diagnosis

There is no evidence that routine screening is beneficial in women. If an aortic aneurysm is suspected diagnostic tests include ultrasound, CTA and/or MRA.[187]

2.4.3. Management

The goal of management of aortic aneurysms is to prevent rupture. This involves aggressive risk factor control, adequate β-blockade and serial imaging for progression.

The general guidelines for the management of AAA are:[187]

- Small aneurysm (4 cm or smaller)
  - Conservative therapy with periodic ultrasound examinations to assess progression

- Medium sized aneurysm (between 4 cm and 5.5 cm)
  - Treatment of this condition is still unclear. Closer and more frequent monitoring for progression is recommended
- Large (5.5 cm or larger), fast-growing aneurysm (more than 0.5 cm over six months) or symptomatic (leaking, tender or painful)
  - Surgical or endovascular repair is recommended

Key Messages:

- CVD (heart disease and strokes) is the main cause of death among women in Malaysia.
- The pathophysiological mechanisms contributing to myocardial ischemia in women are varied and maybe multiple.
- Women with angina may have :
  - Obstructive CHD (coronary lesions > 50% luminal narrowing)
  - Non-obstructive CHD (≥ 20% and < 50% luminal narrowing).The prognosis is worse if myocardial ischemia is documented.
  - Normal coronary arteries- (< 20% luminal narrowing)- (Cardiac Syndrome X)
- Presenting symptoms for CHD and stroke in women may be both typical and sometimes atypical.
- Prognosis for women following an MI and stroke is poorer than men.
- Increased awareness, early detection with appropriate investigations and management is important.

3. OTHER DISEASES WITH INCREASED RISK FOR CARDIOVASCULAR DISEASE

3.1. Connective Tissue Disease and the Heart

Patients with connective tissue disease especially SLE, rheumatoid arthritis and systemic vasculitis are at increased risk for CVD.[188-193] This excess risk of premature CVD is seen most commonly in SLE where CVD is the third most common cause of death.[188] The CVD risk is 5-6 times greater in women especially in those aged 35-44 years where the risk may be as high as 50 times the general population.[189,190] The causes are multifactorial and include increased prevalence of the traditional risk factors, impaired endothelial function, systemic inflammation and the presence of autoantibodies such as anti-phospholipid antibodies and lupus anticoagulant which are associated with increased thrombotic risk.[188,191]

Cardiovascular manifestations of rheumatological diseases include:

- Myocardial- congestive heart failure, LVH, diastolic dysfunction, myocardial fibrosis, amyloidosis
- Pericardial – pericardial effusion, pericarditis
- Valvular – Libman-Sacks vegetation, valvular regurgitation, valvular nodules
- Arrhythmic – SCD, ventricular arrhythmias, supraventricular arrhythmias, atrioventricular block
- Vascular – atherosclerosis, arterial stiffness, vasculitis, thrombosis

Patients with connective tissue disease should have their CV risk assessed and have their CV risk factors addressed according to guidelines. Some of the drugs used for the treatment of these rheumatological disorders may have cardiac effects which also have to be addressed.[194-197]

3.2. Cancer and the Heart

Chemotherapeutic agents have potential cardiotoxicity. In symptomatic patients, chemotherapy-induced cardiotoxicity is defined as a decrease in LVEF by ≥ 5% to < 55%. In asymptomatic individuals, it is defined as a decrease in LVEF by ≥ 10% to < 55%.[198] Cardiotoxicity may be:

- Irreversible – type 1 (e.g. anthracycline induced toxicity)
- Reversible – type 2 (e.g. herceptin induced toxicity)

Vascular toxicity is a recognized side-effect of some chemotherapeutic agents especially the tyrosine kinase inhibitor. This includes serious arterial thrombotic events such as acute MI, stroke and acute ischemic limb.[199]

Radiation also causes significant cardiac toxicity after a long latent period even more so if the doses exceed 30 Gy.[200] Radiation-induced heart disease, to date, remains significant as most patients currently seen are those who had higher exposures 20-30 years ago.[201] Radiation also induces and accelerates atherosclerosis on top of traditional risk factors.[202,203]

For the management of patients on potentially cardiotoxic chemotherapeutic agents, see Appendix 1, pg 89. Women who had chemotherapy or radiation therapy in the past and who are now pregnant or planning to get pregnant should be evaluated by a cardiologist, as the pregnancy can unmask a cardiomyopathy.[199]

3.3. Infections and the Heart

3.3.1. Influenza

Clinical trials have shown an association between a recent respiratory infection and acute MI.[204] In a recent study done in UK and Hong Kong, there was strong evidence for a link between influenza and MI associated deaths and hospitalizations in both regions.[205] A meta-analysis of 5 published randomized clinical trials of 6735 patients showed that influenza vaccination was associated with a lower risk of composite cardiovascular events.[206] The greatest treatment effect was seen among the highest-risk patients with more active coronary disease. In a case-control study done in Australia, influenza did not predict MI but vaccination was found to be protective.[207] This protective effect is comparable to that of currently accepted therapies for secondary prevention of MI.

It is advisable that high risk CVD patients receive annual influenza vaccination. However, to date, there is no supportive epidemiological data from tropical regions.

3.3.2. Periodontal Disease

A number of observational studies have shown that there is an association between periodontal disease (PD) and CVD although the evidence for a causal relationship is still controversial.

Treatment of PD has been shown to result in improvement in surrogate markers of inflammation and endothelial function but there is no data that it can prevent CVD.[208-210]

Maintaining good dental hygiene and regular dental visits are recommended.

3.3.3. Human Immunodeficiency Virus

Studies have shown that HIV infected individuals of both gender, are at increased risk of premature CVD.[211-214] Atherosclerosis tends to be diffuse, circumferential and is often accelerated.[215-219] The reasons for this increased CVD risk are multifactorial and includes systemic immune activation resulting in endothelial activation and atherosclerosis, metabolic derangements due to anti-retroviral therapy and also the high prevalence of traditional risk factors such as smoking and obesity in these patients.[220-222] This increased CVD risk persists even after adjustment for Framingham risk factors, other co morbidities and substance use.

All HIV infected individuals should be encouraged to adopt a healthy lifestyle with CV risk factor modifications.

3.4. Obstructive Sleep Apnoea (OSA)

OSA is a sleep disorder associated with high blood pressure, CVD, and/or obesity. Observational studies seem to suggest a causal relationship between OSA and CVD although the data is not conclusive.[223,224]

It occurs more frequently in men than women - due to differences in obesity and the distribution of adipose tissue, upper-airway anatomy and muscle function, control of ventilation, and the effect of sex hormones and leptin.[224-226]

It is likely that OSA may be underdiagnosed in women.[227] Observational studies indicate that untreated severe OSA is an independent predictor of cardiovascular mortality in women.[228] However, there are no randomised controlled trials to support this.

Management of OSA includes general measures such as weight reduction, avoidance of alcohol and sedative drugs in the evening.[224] The use of continuous positive airway pressure (CPAP) improves quality of life, reduces apnoeic spells, daytime somnolence, and blood pressure. The benefits of CPAP in preventing CVD remains unresolved.[224,227,229]

Registry data indicate that CPAP is associated with reduced all-cause mortality in middle-aged and elderly men but there was no significant effect in women.[228] However, a recent randomized trial in patients with systolic heart failure found that adaptive servo-ventilation actually increased all cause and cardiovascular mortality.[230]

Key Messages:

Other diseases that that are associated with an increased CV Risk in women include:

- Connective tissue diseases (especially rheumatoid arthritis, SLE and systemic vasculitis) and the drugs that are used to treat these diseases
- Chemotherapy and radiation induced cardio toxicity
- Infections such as influenza, peridontal disease and HIV
- Obstructive Sleep Apnoea

4. CARDIOVASCULAR RISK FACTORS

4.1. Personal History of CHD and/or CHD equivalents

Persons with established CVD are at high risk for recurrent vascular events. In the GRACE registry, the 6 month risk of CV death and major CV event rate after an ACS, was 5-8% and 15-20% respectively.[231] A study done in England showed that following the first MI, the risk of a recurrent MI was highest during the first year and the cumulative risk increased gradually thereafter. For women, the 1 and 7 year cumulative risk was 7.2% and 16.2% respectively which were higher than that in men (5.6% and 13.9% respectively).[30] Older age, no revascularization procedures, and the presence of comorbidities were associated with a higher recurrence risk.[30]

In patients with stable CHD, the 1 year rate of CV death was 1.9% and the rate of CV death, MI or stroke was 4.5%.[232] Following a stroke, the risk of a recurrent stroke was 8% and the risk of death 4.5%. The rates continued to increase steadily up to 4 years.[154,155]

Persons with CHD Equivalents are also at high risk for CV events. This includes:

- Cerebrovascular disease
- Peripheral arterial disease
- Type 2 diabetes mellitus (T2DM)
- Multiple risk factors that confer a 10 year FRS of > 20%[233]

The presence of vascular disease in any one of the vascular beds usually indicates co-existing disease in other parts of the vascular tree. Hence it is imperative to assess all vascular beds.

4.2. Age (and Menopause)

The age-specific incidence rates for CHD in women are lower than in men at every age.[22,234-237] The onset of CHD may be delayed by about 10 years in women.[23,24,25]

Atherosclerosis starts in early adolescence and progresses throughout a woman's lifetime, the rate of progression depending upon the presence and severity of the risk factors. In mid-life, a woman's risk for CVD increases dramatically. This is due to:-

- the effect of increasing age, an effect that is also similarly observed in men

- the hormonal imbalances that occur with the menopause, and
- an increase in the prevalence of risk factors for heart disease often seen in mid-life such as:-
  - obesity and changes in body fat distribution and storage from the hips to the waist- gynaecoid (subcutaneous fat) to an android (abdominal obesity) pattern
  - physical inactivity
  - dyslipidaemia
  - hypertension
  - worsening glucose tolerance/ insulin resistance
  - lifestyle change associated with an increase in risk factors

It is still not clear if this increase in the prevalence of risk factors is due to oestrogen deficiency or part of the "ageing" process.

Women who experience early menopause are at increased CVD risk. When compared to those with a natural menopause, women with:

- early menopause--before their 46th birthday--are twice as likely to suffer from CHD and stroke. This finding is independent of age, race/ethnicity and traditional risk factors.[238]
- endogenous oestrogen deficiency had more than 7-fold increase in coronary artery disease (CAD) risk in the Women's Ischemia Syndrome Evaluation (WISE) study.[239]

Other studies have also shown that menopause before the age of 50, either spontaneous or surgically induced, is associated with an increased risk of CVD.[240,241] This risk is mainly for CHD and not stroke. This increased risk was significant even after controlling for age and smoking.[240]

The incidence rates of CHD are 2-3 times higher in postmenopausal women than for those women of the same age who have not yet undergone menopause.[25] In the Nurse's Health Study though, this risk associated with natural menopause disappeared after adjusting for age and cigarette smoking.[240] At present, it is still unclear if the postmenopausal state per se is a risk factor for CVD.[242,243]

The association between menopause and the risk of stroke is conflicting. In the Framingham Heart study, women with natural menopause before 42 years of age had twice the risk of ischemic stroke when compared to women who attained natural menopause after 42 years of age.[244] However, in the Nurse's Health Study, there was no association between age at natural menopause and risk of ischemic or haemorrhagic stroke.[245]

Another finding that is consistent with the theory that the menopausal state per se may not be directly responsible for the increase in CVD risk is the lack of benefit of HRT in both primary[246,247] and secondary prevention trials.[248-250] A recent randomized trial however, found that HRT given early after menopause and continued for 10 years had beneficial cardiac effects without any apparent increase in cancer, venous thromboembolism (VTE) or stroke.[251]

The current recommendation supports the use of HRT at the lowest oestrogen dose and for the shortest duration in women with vasomotor symptoms (hot flushes/flashes/night sweats) and genitourinary symptoms (vaginal dryness or discharge, pain, burning or itching, urinary frequency, recurrent urinary tract infections) up to the age of 60 years.[252]

HRT is not recommended for the prevention of any chronic illness.

4.3. Family History of Premature CVD

The presence of CVD (CHD and stroke) in first degree relatives (parent or sibling) before 55 years in men and 65 years in women is an independent risk factor for future CVD.[253-257] This risk is increased:

- when the affected individual is a first degree relative
- the higher the number of family members with CVD
- the younger the age at which family members develop CVD
- if the affected individual is an identical twin

In one study, the odds ratio of developing a future MI was:[258]

- 1.67 when one parent had MI *after* age 50
- 2.36 when one parent had MI *before* age 50
- 2.90 when both parents had MI *after* age 50
- 6.56 when both parents had MI *before* age 50

Some studies found that maternal history of MI at any age was more strongly associated with MI in the offspring than was paternal history of MI.[259,260] History of MI in second degree relatives also increases an individual's risk of a future MI.[261] Parental history of premature stroke also increases the risk of stroke in the offspring.[150,151]

Individuals with a family history of premature CHD or stroke should have their global CVD risk assessed and the appropriate preventive strategies implemented.[262,263]

4.4. Dyslipidaemia

Lipoprotein levels are similar in pre-pubertal girls and boys. After puberty,[264]

- HDL-C levels remain higher in women compared to men
- LDL-C and non HDL-C levels are lower in young and middle-aged women

After the menopause,[264]

- TC levels increase
- LDL-C levels rise and may exceed that of age-matched men
- LDL-C particle size shifts towards smaller dense particles
- HDL-C levels remain constant
- greater postprandial rises in lipoprotein levels after standardized fat meals
- lipoprotein a [Lp(a)] also increases with age

The effect of HRT on lipids will depend on the hormone composition and route of administration. Generally when given orally HRT tends to:

- decrease LDL-C
- decrease Lp(a)
- increase HDL-C
- increase TG

When compared to men:

- low HDL-C rather than high LDL-C is more predictive of CVD risk.[265,266] This suggest that the protective effect of HDL may be diminished as women transition in menopause[267]
- high TG is important as a CVD risk factor in older women especially at levels above 4.5 mmol/L[268-271]
- TC appears to be associated with CVD only in premenopausal women or at very high levels (> 6.9 mmol/L)[271]
- Lp(a) is a determinant of CVD in both premenopausal and post-menopausal women under the age of 66 years[272]

Women with increasing obesity, metabolic syndrome and/or diabetes tend to have lower HDL-C, higher TG and a greater proportion of LDL phenotype B (small dense LDL particles). This atherogenic lipoprotein profile associated with diabetes is more pronounced in women than men and may contribute to their increased CVD risk.[273,274]

In Malaysia, the prevalence of hypercholesterolemia (defined as total cholesterol ≥ 5.2 mmol/L) has been on a rising trend. It has increased from 20.7% (2006) in the National Health and Morbidity Survey III (NHMS III) to 32.6% in 2011 (NHMS IV) with a further increase to 47.7% in 2015 (NHMS V).[275] In both NHMS IV and NHMS V, the prevalence was significantly higher among females (40.2% and 52.2% respectively).[275]

4.5. Hypertension

In Malaysia, according to the NHMS V (2015) 29.7% of women above the age of 18 have hypertension.[275] The prevalence rises with increasing age, reaching a prevalence of 75.4% in those aged 70-74 years. There was no significant gender difference.[275]

In both men and women, BP tends to increase with age. Epidemiological studies from the US have shown that before the age of 60, women have lower systolic and diastolic BP than men.[276] After the age of 60 years, women have a much steeper rise in SBP.[277] At the age of 60 years, over 80% of women are hypertensive.[278]

Isolated systolic hypertension is more common in older women than men.[279] This age-related rise in BP, particularly systolic BP and pulse pressure, contributes substantially to the age-related increase in CVD and HF in middle-aged and elderly women.[277]

Hypertension is more common after the menopause. Postmenopausal women are more than twice as likely to have hypertension as premenopausal women even after adjustment for age and BMI.[280]

Hypertension and LVH are both stronger predictors for CVD, HF, CHD and stroke mortality in women than in men.[281-283]

Hypertension is a leading risk factor for stroke in both men and women, with a relative risk (RR) ratio of 4. For every 7.5 mmHg increase in diastolic BP, the stroke risk increases by 46%.[284] In the elderly, SBP is a more important CVD risk factor than DBP and should be the principal target of therapy.[285] An increase in SBP by 20 mmHg is associated with a two fold increase in the rate of death from stroke, CHD and other vascular causes.[286]

The cause of hypertension in both men and women is usually primary. Some causes of secondary hypertension are more common in women e.g. fibromuscular renal artery stenosis.[287]

Women tend to have more labile BP and a higher prevalence of white coat hypertension than men.[288] Women are also more likely to be salt sensitive and have low renin, high volume hypertension than men.[289]

Combined oral contraceptive (COC) use may cause a small but detectable increase in BP.[290] A small percentage of women develop frank hypertension. A family history of hypertension, pre-existing pregnancy-induced hypertension, occult renal disease, obesity, age > 35 years, COC dosage, composition and duration of use increase susceptibility to COC-induced hypertension.[290] This usually resolves within 3 months of the withdrawal of the COC.[291] COC induced hypertension appears to be related to the progesterogenic, not the estrogenic, potency of the preparation.[292] Hypertension due to COC is likely the most frequent cause of secondary hypertension in young women.[293] Women on COC should have their BP monitored periodically.

In contrast, HRT as either oral or transdermal oestrogen alone or in combination with a progestin, has neutral effects or may lower the BP in normotensive and in hypertensive women.[290]

Factors that predispose to pregnancy-induced hypertension also predispose to CVD in later life. Thus long term follow-up of these patients is advisable.[294] (section 4.12.3, pg 69)

4.6. Diabetes Mellitus/Pre-diabetes

4.6.1. Diabetes Mellitus

The most recent NHMS V 2015 found that the prevalence of DM among adults 18 years and above was 17.5%.[275] The prevalence increases with increasing age, from 5.5% in the 18-19 years age group to 39.1% among the 70-74 years age group. In adults age 30 years and above the prevalence had increased from 8.3% in 1996[295] (NHMS II) to 20.8% (NHMS IV).[297] (Table 7, pg 58) Among adults above the age of 18 years old, the prevalence was highest in the Indians (22.1%) followed by Malays (14.6%) and Chinese (12.0%).[275] There remains no gender difference observed. (Women 18.3% vs men 16.7%)[244] T2DM accounts for > 95% of the local diabetic population.[298]

Table 7: Prevalence of diabetes in adults 30 years and above*

National Health & Morbidity Survey	NHMS II[295] 1996	NHMS III[296] 2006	NHMS IV[297] 2011
Prevalence of Diabetes Mellitus in Adults 30 Years and Above	8.3%	14.9%	20.8%

**NHMS V not included because data only available for adults 18 years and above. There was no significant gender differences in the prevalence of diabetes noted in all 3 surveys.*

DM eliminates the "female advantage" of a lower CHD prevalence.[299]

Women with diabetes are at increased risk for all-cause, cardiac and CHD mortality.[300,301] The CHD mortality in diabetic women is 2 - 5 times that of non-diabetic women.[302-304] Even in insulin treated diabetics < 30 years of age, the CVD mortality in women is higher than that of diabetic men.[301,304]

A recent large analysis showed that women with diabetes are 44% more likely to develop CHD than men.[305-307] This increased incidence cannot be explained by sex differences in pharmacotherapy alone. The overall relative risk of fatal CHD was significantly greater among diabetic women (RR: 3.50) than among diabetic men (RR: 2.06).[308] The relative risk for fatal CHD associated with diabetes was 50% higher in women than it was in men.[308]

In the last 3 decades, CV deaths have remained unchanged for diabetic women while outcomes for non-diabetic women and men (non-diabetic as well as diabetic) have improved. This has been shown to be due to disparities in preventive care and intensity of risk reduction.[309]

4.6.2. Pre-diabetes/Gestational

Pre-diabetes includes:
- Impaired Fasting Glycaemia (IFG)
- Impaired Glucose Tolerance (IGT)
- Combined IFG and IGT

DM and pre-diabetes can be diagnosed by using fasting or random plasma glucose, oral glucose tolerance test (OGTT) or HbA1c (Table 8 & 9, pg 59).

In asymptomatic individuals, any 2 abnormal values performed on 2 different days are required to make the diagnosis of diabetes. In symptomatic individuals, a single abnormal value is adequate.

Table 8: Diagnosis of Pre-Diabetes and T2DM*

Plasma glucose (mmol/L)	T2DM	Prediabetes	
		IFG	IGT
Fasting	≥ 7.0	≥ 6.1 – 6.9	-
2 hr post-OGTT	≥ 11.1	-	7.8 - 11.0

**Diagnosis of DM: for symptomatic patients, a single abnormal value is adequate; for asymptomatic individuals, 2 abnormal values are required*

Table 9: Diagnosis of Pre-diabetes and T2DM* based on HbA1c

	Normal	Pre-diabetes (ADA/WHO)	T2DM (ADA[310]/ WHO)[311]	T2DM (Malaysian CPG 2015)[312-314]
HbA1c%	< 5.6	5.6-6.4**	≥ 6.5	≥ 6.3
mmol/mol[278,279,280,281,282]	< 38	38-48***	≥ 48	≥ 45

** Diagnosis of DM: for symptomatic patients, a single abnormal value is adequate; for asymptomatic individuals, 2 abnormal values are required*
*** < 6.3% according to Malaysian CPG for Management of Type 2 Diabetes Mellitus 5th Ed, 2015[314]*
**** < 45mmol/mol according to Malaysian CPG for Management of Type 2 Diabetes Mellitus 5th Ed, 2015[314]*

International guidelines recommend the use of an HbA1c of ≥ 6.5% for the diagnosis of diabetes.[310,311] Based on the Metabolic Syndrome Study of Malaysia (MSSM) 2009, an HbA1c level of 6.3% was found to give the maximal acceptable sum of specificity and sensitivity of 97% and 42.5% respectively in diagnosing diabetes.[311,312] Using an HbA1c of 6.5% for diagnosing diabetes in the local population however, leads to a lower unacceptable sensitivity of 36.7%.[312,313]

Pre-diabetes (dysglycaemia) is also associated with increased CVD risk and events.[315,316]

Women with a prior history of gestational DM, a big baby (birth weight > 4 kg) or a diagnosis of polycystic ovarian syndrome are at high risk of developing glucose intolerance/ T2DM and Metabolic Syndrome (Met S). They should be screened at regular intervals for diabetes as well as other CVD risk factors.

4.7. Metabolic Syndrome

Met S is a constellation of risk factors that includes the following criteria:

- abdominal obesity (waist circumference ≥ 80 cm / 31.5 inches)
- elevated fasting TG (≥ 1.7 mmol/L)
- low HDL-C (≤ 1.29 mmol/L) ;
- hypertension (BP ≥ 130 and/or ≥ 85 mmHg)
- T2DM/ IFG/ IGT

There are 2 main definitions for the Met S:

- International Diabetes Federation (IDF) 2005[317]
- National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII-Harmonized Criteria)[233,318]

The difference is that in the IDF definition, abdominal obesity is the mandatory parameter with presence of 2 other criteria for the diagnosis, whereas for the NCEP/ ATP III, any ≥ 3 out of 5 criteria are adequate.

In Malaysia, Met S is higher in urban areas, females, Indians and with increasing age.[319,320] In general, the risk for Met S rises with increasing age. This effect is more marked in women than men, particularly after the menopause. Menopause causes an increase in total adiposity and a redistribution of fat to the abdominal region.[321,322] In a prospective clinical study of older women followed up for more than 6 years, it was found that Met S and high waist-to-hip ratio were associated with increased risk of CV events.[323]

The 'clustering' of metabolic abnormalities that occur in the same individual appears to confer increased risk of future development of CVD and T2DM. The presence of any one of the components should trigger further screening for the other associated CV risk factors.

Unfortunately, the value of Met S as a scientific concept remains controversial. Although several epidemiologic studies have identified an increased risk of CVD in individuals with Met S,[324-330] the presence of Met S does not predict an elevated CHD risk beyond the sum of its components.[327,331]

The traditional risk assessment algorithms are recommended to quantify global CVD risk.

Excess abdominal adipose tissue is associated with insulin resistance, creating an atherogenic inflammatory milieu, characterized by high levels of C-reactive protein and other inflammatory markers (e.g., fibrinogen, plasminogen activator inhibitor-1, cytokines, and adhesion molecules).[323-332] Epidemiologic studies have shown a positive correlation between levels of these biomarkers and CVD risk.

Non-alcoholic fatty liver disease (NAFLD), in particular, NASH (non-alcoholic steatohepatitis), is considered the hepatic manifestation of the metabolic syndrome.[333] Recent data suggest that NAFLD is linked to increased CV risk and is an independent CV risk predictor.[334,335]

4.8. Overweight/ Obesity

Overweight/ obesity increases CVD risk. With increasing body mass, both CHD mortality and all-cause mortality are increased.[336,337] A recent study showed a higher BMI, particularly ≥ 30, is also associated with a greater risk of SCD and it appeared to be a stronger risk factor in middle aged rather than older women.[338] Many CVD risk factors (such as dyslipidaemia, glucose intolerance and hypertension) are associated with obesity. With increasing degrees of overweight/ obesity, there is an increased likelihood of developing these risk factors.

In Malaysia, in just 9 years from 2006 to 2015, there was a further increase in the prevalence of obese and overweight males and females (Table 10, pg 61 and Figure 3A and B, pg 62).[296,339] The prevalence of obesity is higher in Malaysian women than men.[275]

Table 10: Prevalence of Overweight/Obesity in NHMS III[296] (2006) and NHMS V[275] (2015)

Adults	Overweight BMI 25 – 29.9 kg/m²		Obese BMI > 30kg/m²	
	NHMS III[296]	NHMS V[275]	NHMS III[296]	NHMS V[275]
Males	29.7%	31.6%	10.0%	15.0%
Females	28.6%	28.3%	17.4%	20.6%
Overall	29.1%	30.0%	14.0%	17.7%

The prevalence shown above uses the international definition of overweight/ obesity. This is to allow comparison between the NHMS III and NHMS V. The Asia Pacific definition[340] for overweight/ obesity uses different cut-off points i.e. overweight > 23 to < 25 kgm^2; obese > 25 kgm^2. The reason for this lower cut-off points is because Asians have a higher CVD risk at lower BMI.[341,342] Furthermore, Asians also have a higher abdominal adiposity compared to Caucasians for the same BMI.[343]

Figure 3A: Prevalence of Obesity according to Gender in NHMS III (2006)[296] vs NHMS V (2015)[275]

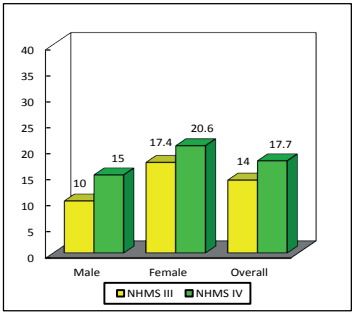
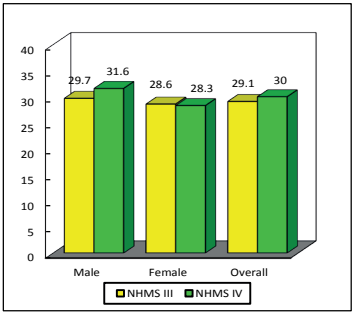


Figure 3B: Prevalence of Overweight according to Gender in NHMS III (2006)[296] vs NHMS V (2015)[275]



With increasing age, there is an increased prevalence of overweight and obese individuals especially in females. For any given BMI, women have more total body fat.

Waist circumference correlates better with abdominal fat content than BMI. Gender specific waist circumference cut-off points for CVD risk have been established. In Asians, a waist circumference of ≥ 80 cm in women raises CVD risk.[317]

Weight gain during adulthood is associated with a significantly increased risk of CHD, independent of physical activity level.[344] In a large prospective study in women, those who gained substantial weight after age 18 were at significantly increased risk of CHD, T2DM and total mortality compared with women who remained within 2.3 kg (5 lbs) of weight at age 18.[345] For each increase in body weight of approximately 1 kg, the risk of CHD mortality increases by 1-1.5%.[346]

Although obesity is associated with CHD risk and weight loss has been shown to be beneficial, studies regarding weight cycling (repeated weight loss and weight gain of 5 to 10 lbs) have been equivocal, and this remains controversial.[347-350] For benefits of weight loss, see Table 11, pg 63. These are seen in addition to psychological, physical and other metabolic benefits.

Table 11: Beneficial effects of a 10% weight loss in the obese individual[351]

Mortality	>20% ↓ total >30% ↓ diabetes related >40% ↓ obesity related cancer
Blood Pressure	10 mmHg ↓ systolic 20 mmHg ↓ diastolic
Diabetes	30-50% ↓ in fasting glucose 50% ↓ in developing diabetes 15% ↓ in HBA1c
Lipids	10% ↓ total cholesterol 15% ↓ LDL-cholesterol 30% ↓ triglycerides 8% ↑ HDL-cholesterol

4.9. Polycystic Ovarian Syndrome

Polycystic Ovarian Syndrome (PCOS) is a common hormonal disorder affecting women in the reproductive age, with features of androgen excess, ovulatory dysfunction and polycystic changes in the ovaries.[352] This condition is often associated with insulin resistance and CV risk factors such as central adiposity, glucose intolerance (prediabetes and diabetes), hypertension and dyslipidaemia.

Mood disturbances, mostly severe depression, are prevalent in women with PCOS and contribute to impaired quality of life, fatigue, sleep disturbances, phobia, appetite changes, and binge eating resulting in higher BMI and greater insulin resistance and CVD risk factors than non-depressed women with PCOS.[353]

Women with PCOS often have subclinical, early coronary and other vascular disease documented by coronary angiography, carotid artery scanning and coronary artery calcium measurement.[354-356] Echocardiographic abnormalities include increased left atrial size and left ventricular mass index, lower left ventricular ejection fraction and diastolic dysfunction.[357,358]

The WISE Study found that women with PCOS have higher CV event rates, multivessel CVD and lower survival compared with non-PCOS women.[359]

All women with PCOS should have CV risk assessed as follows[360]

- Family history of early CVD
- Cigarette smoking
- Waist circumference and BMI at each clinic visit
- Complete lipid profile every 2 years or sooner if weight gain occurs
- OGTT every 2 years or sooner if additional risk factors are identified
- BP check at each clinic visit
- Assess for OSA
- Assess for depression, anxiety, and quality of life

Women with PCOS with obesity, cigarette smoking, dyslipidaemia, hypertension, impaired glucose tolerance, and subclinical vascular disease are at risk, whereas those with Met S and/or T2DM are at high risk for CVD.[360]

For overweight/ obese women with PCOS, a 5–10% weight loss should be targeted. This can be achieved with lifestyle modification and behavioural techniques.[361] The long-term goal should be a 10 to 20% weight loss and a waist circumference of < 80 cm.[362]

4.10. Smoking

Smoking is a very important cardiac risk factor in both men and women. This risk is dose related. In women, even with minimal use, CVD risk is elevated (RR: 2.4 for 1.4 cigarettes/ day).[363,364] The risks associated with smoking are consistently higher in women than in men and are not age dependent.[365] The risk of CHD begins to decline within months of smoking cessation and reaches the level of persons who have never smoked within 3 to 5 years.[363] Cigarettes can induce an unfavourable lipid profile, increase inflammation, thrombosis and oxidative stress. As a result women, especially premenopausal women, lose their “natural” protection against atherosclerotic vascular disease.

In Malaysia, only about 1% of women smoke.[366] In NHMS V there was however a small but significant increase to 1.4%.[275]

Young women who smoke and use COC have a very high CVD risk. They have more than 5-fold increase in the risk of MI when compared to COC users who do not smoke.[367,368] Women smokers above the age of 34 years who use COC are at especially high risk.[369]

Women switching to “low yield” cigarettes with reduced tar, nicotine, and carbon monoxide have the same CVD risk as those who smoke higher-yield brands.[370]

Smoking also increases the risk of developing diabetes by 30–40%. There is a positive dose-response relationship between the number of cigarettes smoked and the risk of developing diabetes.[340]

Non smokers exposed to secondhand smoke increase their risk of developing:[371,372]

- CHD by 25-30%
- Stroke by 20-30%
- Lung cancer by 20-30%

The scientific evidence indicates that there is no risk-free level of exposure to secondhand smoke.[372]

4.11. Physical Activity

Epidemiological studies have shown that low physical activity is a strong and independent risk factor for both CVD (both CHD and stroke) and all-cause mortality.[373-375]

Physical activity includes:

- Leisure-time physical activity defined as:
  - high: participation in recreational sports (e.g. running, jogging, gymnastics, swimming or heavy gardening) or in intense training or sports competitions for at least 3 hours a week
  - moderate: walking, cycling or practicing some other form of light exercise (gardening) at least 4 hours per week
  - low: reading, watching TV or working in the household without much physical activity
- Occupational physical activity defined as:
  - high: lots of walking and lifting at work, taking the stairs or walking uphill (e.g. industrial work and farm work)
  - moderate: walking quite a lot at work without lifting or carrying heavy objects (e.g. store assistant, light industrial worker)
  - low: mostly sedentary work without much walking (e.g. secretary, working in an office)

- Commuting activity defined as:
  - high: more than 30 min physical exercise (e.g. walking every day while getting to work and back home)
  - moderate: exercising (e.g. walking between 15 and 30 min daily on the way to work and back home)
  - low: exercising less than 15 min daily (e.g. motorized transport, no walking or cycling)

Moderate and high levels of leisure-time and/ or occupational physical activity or high levels of commuting activity in women are associated with reduced CVD (CHD and stroke) and all-cause mortality[376-379] and 10 year risk of CHD.[380]

However even light-to-moderate activity is associated with lower cardiac risk in women. Walking for at least 1 hour per week predicted lower CHD risk. Time spent walking was more important than walking pace.[381] A recent large study showed that any physical activity was beneficial compared to inactivity in reducing CV risk.[381] Among active women, moderate physical activity 4-6 times per week had the best CV risk reduction compared to those who exercised daily.[382]

These benefits of physical activity were seen in all women irrespective of the baseline CHD risk.[383,384] A structured, moderate-intensity physical activity program was found to be beneficial even in sedentary men and women aged 70 to 89 years.[385]

Obesity is often associated with physical inactivity and both independently contribute to the development of CHD in women. Being physically active attenuates moderately but does not eliminate the adverse effects of obesity on cardiac risk. Being lean does not counteract the increased risk of CHD associated with physical inactivity. The lowest risk of CHD is observed among physically active, lean women.[344]

When compared to women who had a BMI of 18.5 to 24.9 kg/m^2 and were physically active (exercise ≥ 3.5 hours/week), the RR of CHD were[386]:

- 3.44 for women who were obese (BMI ≥ 30 kg/m^2) and sedentary (exercise < 1 hour/week)
- 2.48 for women who were active but obese
- 1.48 for women who had a healthy weight but were sedentary

A BMI of > 25 kg/m^2 and < 3.5 hours of exercise per week accounts for 59% deaths due to CVD.[386]

Overweight/obese is associated with far greater increases in the risk of developing T2DM than being unfit or inactive. Higher levels of physical activity does not ameliorate this risk.[387]

Women who are physically active tend to have a more favourable CVD risk profile. Physical fitness is independently associated with lower TG, higher HDL-C, lower TC/HDL-C ratio, lower BP and lower cigarette smoking.[383]

4.12. Others

4.12.1. Combined Oral Contraceptives

Observational studies have shown that COC are associated with an increased risk of VTE, stroke and MI.[369,388,389] The CV risk was greater in smokers.[369,390] These early studies however, had numerous potential biases.[391]

Second (2nd) and 3rd generation pills seem to have slightly different risk profiles. VTE seems to be somewhat more prevalent with 3rd generation pills, the risk of non-fatal VTE being increased by about 2 fold (or about 3 cases for every 10,000 users).[392,393] (Appendix 2, pg 91)

The risk of stroke and MI appears higher among 2nd generation COC pills.[369,389,393-395] The overall incidence of MI was found to be increased at least 2-fold, the risk of ischemic stroke by approximately 2-fold and that of haemorrhagic stroke by about 1.5-fold among current users of COCs.[388,393,396] Studies comparing the stroke risk of users of 2nd and 3rd generation COCs however, are not consistent and have shown mixed results.[157,391,397] Currently, 1st generation pills are hardly used.

There is however, no data available for the newest generation COC (4th generation) as well as for the non-oral routes (topical and vaginal).[388]

Current or prior use of low-dose COC is not associated with a significant increased risk of MI in healthy non-smokers. Women who smoke heavily however, are at high risk of MI.[395,398,399] This risk was independent of the formulation or dose of oestrogen used.

The CV risk of COCs is increased if the women is diabetic, obese, smokes, or has hypertension. Before prescribing COCs, it is important to screen for CV risk factors and have them optimally controlled.

The WHO have published a medical eligibility criteria for COC use. They have advised against the use of COCs in persons with:[400]

- Breast feeding < 6 weeks post-partum
- < 21 days post-partum with other risk factors for VTE
- Smoking ≥ 15 cigarettes a day
- Uncontrolled BP (systolic ≥ 160 or diastolic ≥ 100 mmHg)
- Any vascular disease
- Prior or current history of pulmonary embolism or VTE
- Known thrombogenic factors
- Recent surgery with prolonged immobilization
- History of CHD or stroke
- Valvular heart disease complicated by pulmonary hypertension, atrial fibrillation and/or infective endocarditis
- SLE with positive (or unknown) anti-phospholipid antibodies
- Migraine with aura

Use of COC is not usually recommended unless other more appropriate methods are not available or not acceptable in persons:[400]

- > 6 weeks < 6 months post-partum
- > 21 days < 42 days with other risk factors for VTE
- With multiple risk factors for CVD
- With hypertension
- With migraine without aura but age ≥ 35 years

4.12.2. Oestrogen Therapy/ Oestrogen Progesterone Therapy

Menopausal hormone therapy (ET/ EPT) does not protect post-menopausal women against CVD, and may even cause an increased risk of stroke.[250,252] There is no evidence that ET/ EPT has any protective effects against death from any cause, and specifically death from CVD, non-fatal MI or angina, either in healthy women or women with pre-existing heart disease. Instead there a small increased risk of stroke in post-menopausal women.[250]

There is some evidence that women who start treatment within the first 10 years of their menopause, seemed to have a small protection against death and MI, with no increased risk of stroke.[251] However, even in this group, the risk of deep vein thrombosis (DVT) is increased. This apparent benefit in preventing CVD in younger women should be considered alongside other possible benefits and emerging evidence of harm, including the risk of breast cancer, ovarian cancer, and DVT.

Absolute excess risk per 10,000 women treated with an ET/EPT combination for a year, were:[246]

- 5 fewer hip fractures
- 6 fewer colorectal cancers
- 7 more CHD events
- 8 more strokes
- 8 more pulmonary emboli
- 8 more invasive breast cancers.

There was a trend that women who initiated hormone therapy closer to menopause tended to have reduced CHD risk and total mortality compared with those more distant from menopause.[401] For the ET only pill, per 10 000 person-years, there was an absolute:[402]

- excess risk of 12 additional strokes
- risk reduction of 6 fewer hip fractures

Earlier studies showed that the risk of stroke was elevated regardless of years since menopause.[401]

Menopausal hormone therapy is not recommended either for primary or secondary prevention of CVD.[403,404] It should only be used for symptomatic relief of bothersome vasomotor symptoms using the lowest oestrogen dose and for the shortest duration of time up to age 60.[252]

In women with high CV risk, non-hormonal therapy is recommended. For women with moderate risk of CVD, transdermal estradiol alone is recommended as 1st line in women without a uterus or combined with micronized progesterone for women with uterus.[252]

4.12.3. Pre-eclampsia/Pregnancy

Pregnancy is a cardiovascular and metabolic “stress test”. A history of preeclampsia, gestational diabetes or pregnancy-induced hypertension puts a woman “at risk” of CVD.[294]

Women with preeclampsia have 2 times the risk of subsequent ischemic heart disease, stroke and venous thromboembolic events in the next 5 - 15 years.[294]

Following pre-eclampsia, women are at an increased risk of CVD.[294] The RR for the following are increased:

- hypertension by 3.70
- CHD by 2.16
- stroke by 1.81
- VTE by 1.79
- overall mortality by 1.49

It is not known if this association is due to a common cause for pre-eclampsia and CVD, an effect of pre-eclampsia on disease development, or both.

It is important that such women be referred for risk factor monitoring and control in the years after pregnancy.

4.12.4. Alcohol

There is J shaped curve between alcohol intake and a variety of adverse health outcomes.[405] Low levels of alcohol intake have been found to reduce all-cause mortality in both men and women. In non-pregnant women this should not exceed 1 drink (10 g/day) per day.[405-407] At moderate to high levels, the risk of death is higher in women than in men, probably owing to increasing risk of cancer and both haemorrhagic and ischemic strokes.[408,409] Heavy consumption of alcohol (3 or more drinks a day) is also related to hypertriglyceridemia, uncontrolled hypertension, congestive heart failure and liver disease.

When men and women consume the same amount of alcohol, women experience higher blood alcohol concentrations. This is because women metabolize ethanol differently and have a lower gastric alcohol dehydrogenase activity, resulting in higher blood ethanol levels. Pregnant women are advised to refrain from alcohol consumption. (Appendix 3, pg 93).

The benefits of alcohol appear to be related to its antithrombotic properties and its ability to increase HDL levels.[410] Wine (ethanol with antioxidants) exhibits significantly higher anti-inflammatory effects than gin (ethanol without polyphenols), and thus in general, wine should be preferred to liquor or beer. Regular drinking is associated with better outcomes than occasional (binge)/weekly drinking.[410]

4.12.5. Depression

CVD and depression often co-exist. Patients with CVD have more depression than the general population and persons with depression are also more likely to eventually develop CVD and have a higher mortality rate than the general population.[411] Clinical depression/depressive symptoms are associated with adverse CV outcomes.[412-414]

Depression is more common in women than men.[415] Depressive symptoms in women ≤ 55 years predicted the presence of CHD and increased risk of death when compared to men and older women.[416] Patients with depression are 6 times more likely to die within 6 months post MI and this increased risk persists for at least 18 months.[416] In this study, depression was more common in women than men.[417] Major depression is also a risk factor for HF in older women but not men.[418]

Coronary patients with clinically significant depression can be safely and effectively treated with psychotherapy[411,419-421] or selective serotonin re-uptake inhibitors,[422,423] although evidence for a beneficial effect on cardiac endpoints is inconclusive. Care must be taken with the use of the older anti-depressants as they may cause arrhythmias. A prudent approach at present is to offer patients with clinically significant depression or anxiety, treatment with psychotherapy and antidepressant/ anxiolytic medication. Those not accepting treatment should be followed closely, and treatment offered again if symptoms persist for 4 – 6 weeks.

Key Messages:

CV risk factors in women include:

- Non-modifiable factors – increasing age, family history of premature CVD
- Modifiable factors:
  - hypertension – especially systolic blood pressure
  - dyslipidemia – high LDL-C, low HDL-C, high fasting TG
  - diabetes mellitus and pre-diabetes
  - metabolic syndrome
  - obesity
  - Polycystic Ovary Syndrome
  - Smoking
  - Physical inactivity
  - Others–Combined Oral Contraceptives, Oestrogen Therapy/ Oestrogen Progesterone Therapy, pre-eclampsia, alcohol, depression

5. TOTAL CARDIOVASCULAR RISK ASSESSMENT

All asymptomatic apparently healthy women ≥ 40 years of age should have their CV risk assessed. Women with established CV risk factors or family history of premature CVD can be assessed at a younger age. This should be an integral component of periodic health examinations of all women in addition to their regular gynaecological and breast examinations. Women can do this CV risk assessment in government clinics for a nominal fee.

CV risk refers to the likelihood of a woman developing a CV event, fatal or non-fatal, over a defined period of time. Determining an individual's CVD risk would help:

- identify high risk women
- guide the intensity of preventive strategies. Women at high risk should undergo intensive lifestyle interventions and where appropriate, drug therapies
- improve physician recognition, detection and treatment of risk factors

Ideally, the CV risk model should be based on data derived from the local population. Currently, we do not have such a CV risk score. The risk score that is widely used in Malaysia is the Framingham general CVD risk score tool for primary care that assesses the 10 year risk of developing CVD.[424] (Table 2, pg 9 & 10) It provides sex-specific CVD risk scores and allows for the calculation of an individual's heart/vascular age.

The FRS has the advantage of being derived from a population that had received no or little treatment at the start and during the study.[425] It is also simple and easy to use – an important feature if healthcare providers are to use it routinely.[426] It may however underestimate risk in women. The FRS has been validated in a multi ethnic local population in 2 retrospective studies.[427,428]

Other risk models include:

- **Framingham Risk Score** - by The National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)[233]-This assesses the 10 year risk of developing CHD (cardiac death, MI) only.
- **SCORE** system developed by the European Society of Cardiology.[429] This system predicts the occurrence of a first fatal CVD event and allows the estimation of total CVD risk projected to age 60.

- **WHO/ ISH Cardiovascular Risk Prediction Charts**- these predict fatal and non fatal CVD[430]
- **QRISK1 & QRISK2** (risk score using the QRESEARCH database) is a CVD risk prediction algorithm formulated in the United Kingdom (UK)- this predicts fatal and non fatal CVD events[431,432]
- **ASSIGN** (Assessing cardiovascular risk using SIGN guidelines) based on a Scottish population[433]
- **2013 ACC/ AHA risk calculator** (Table 3, pg 11)[434] - this risk model assesses the 10 year risk of Atherosclerotic Cardiovascular Disease (ASCVD)–both cardiac death, non fatal MI and fatal and non fatal strokes–in adults 40-79 years of age. It has the advantage that it is gender specific. In a local study, however, this risk model overestimated risk in the Malaysian population.[435]

The FRS has been validated in white and black American men and women but may not be that predictive in other populations.[436,437] It also has its limitations in women because it focuses on short term (10 year) risk of MI and CHD mortality.[438] Although women have a low absolute risk of CVD, due to their longer life expectancy, the average lifetime risk in women is substantial (approaching 1 in 2)[439]

For these reasons, in women, we advocate the risk classification in Table 1, pg 8. It is adapted from the American guidelines and incorporates the Framingham general CVD risk score tool.[440] It provides a more holistic approach to CV risk assessment in women. Sometimes, however, it may be necessary to juggle multiple guidelines and risk models to evaluate CVD risk and decide on the intensity of primary prevention strategies in women.[441]

The risk model outlined in Table 1, pg 8 does not include newer risk factors such as hs-CRP and other biomarkers. In addition, it does not include investigations such as resting ECG, calcium scoring, ABI etc.

These newer risk factors may provide incremental information to traditional risk factor assessment in certain asymptomatic individuals at intermediate CVD risk. Their presence would elevate the individual to a higher CVD risk, indicating the need for more aggressive preventive strategies. Studies done to date, however, have failed to show an improvement in the accuracy of CV risk prediction when these parameters are added to the traditional risk factors. Routine screening for these risk factors is thus not recommended.[442]

From an early age, all women should know their levels and significance of their risk factors.
All women above the age of 40 years should know their global CVD risk. (Table 1, pg 8)

Assessment of CVD risk involves:

- **History:** Looking for symptoms suggestive of CHD or CHD Equivalents, family history of premature CHD, smoking status, physical activity
- **Physical Examination:** Height, weight, BMI, waist circumference, pulses, BP
- **Investigations:** Blood glucose, lipid profile

The following additional investigations may be reasonable in "**At Risk**" (intermediate risk) women to risk stratify them further:

IIa, B • Microalbuminuria in the presence of hypertension and diabetes[442]

IIa, C • Resting ECG in the presence of hypertension and diabetes

Women with established CVD (CHD and CHD Equivalents) are at **High Risk** of a future vascular event. They have a risk of a recurrence of their angina or the occurrence of death that is 1.5 to 15 times that of the general population.[231,232] These High Risk women should have the most intensive lifestyle intervention and appropriate drug therapies.

Women **At Risk** should have their global risk for CVD reduced by lifestyle modification and drug treatment, where appropriate. If CVD is suspected, they should undergo the relevant diagnostic tests and treatment.

Women at **Optimal Risk** should be encouraged to continue their healthy lifestyle and to maintain their ideal weight.

Key Messages:

- All women above the age of 40 years should know their CVD risk.
- Assessment of CVD risk involves: (Table 1, pg 8)
  - ***History:*** Looking for symptoms suggestive of CHD or CHD Equivalents, family history of premature CHD, smoking status, physical activity.
  - ***Physical Examination:*** Height, weight, BMI, waist circumference, pulses, BP.
  - ***Investigations:*** Blood sugar, lipid profile.
- Prevention of CVD involves: (Table 2 & 3, pg 9-11)
  - ***High Risk:*** Intensive risk factor reduction with lifestyle and pharmacological measures to achieve target levels.
  - ***At Risk:*** non pharmacological intervention with diet and physical activity. If targets not achieved, pharmacological therapy is indicated.
  - ***Optimal Risk:*** Continue with healthy lifestyle measures.

6. RECOMMENDATIONS FOR PREVENTION OF CVD IN WOMEN

The *INTERHEART* study found that 9 potentially modifiable factors accounted for 96% of the population attributable risk of a first MI in women compared to 93% among men.[24,443] These 9 modifiable risk factors include dyslipidaemia, hypertension, diabetes, smoking, abdominal obesity, psychosocial factors, regular physical exercise, daily consumption of fruits and vegetables and regular alcohol consumption.[24] Hypertension, diabetes, alcohol intake, and physical activity were more strongly associated with MI in women compared to men.[24] Generally risk factors were more strongly associated with acute MI in younger (< 60 years) compared to older (≥ 60 years) women and men.[24]

In Malaysia, according to the NHMS IV (2011), almost half of women > 30 years are hypertensive, a third are obese and have high cholesterols and a fifth have diabetes.[296] An earlier survey (NHMS III 2006) showed that women displayed a higher prevalence and a younger age shift in CV risk factor clustering.[444]

It was estimated that 90% of CHD events occurred in people with at least 1 CV risk factor.[445] Borderline CV risk factors contribute incrementally to this CVD risk.[445] As the number of risk factors increase, the CV risk also increases and survival decreases.[440]

Thus it is important to assess the global CVD risk since mildly raised levels of several risk factors, in the long term, will result in increased global CVD risk. All CVD risk factors should be identified and managed aggressively according to guidelines.

6.1. General Recommendations

The following healthy lifestyle measures are important in all women. By adopting a healthy lifestyle, women can reduce their CVD risk by as much as 55%.[440] A healthy life style has been shown to reduce the risk of heart failure in post-menopausal women even in the absence of antecedent CAD, hypertension and diabetes.[446]

6.1.1. Nutrition

IIa, C Knowing how much calories one needs a day is a good start for healthy living.

This depends on several factors such as age, gender, BMI and level of physical activity. Home cooked meals are preferable to eating out.

A diet encompassing food from all the food groups is recommended. Healthy food choices that reduce CVD risk should be encouraged.[446-454]

General recommendations should fit in with the local culture. Energy intake should be adjusted to avoid overweight/ obesity.

I, B

Encourage:[455]

- fruits
- vegetables
- whole grain cereals and bread
- fish especially oily fish rich in omega-3 fatty acids (such as *ikan tenggiri, carp*)
- lean meat
- nuts and legumes
- low fat milk and cheese
- skinless poultry
- non-tropical vegetable oils – canola oil, olive oil, peanut oil, sesame oil, vegetable oils (combination of corn/soybeans and/or sunflower seeds)[455]

I, B

Limit the intake of saturated fats and trans-fat as it increases the LDL-C. Replace saturated fats with monounsaturated and polyunsaturated fats whilst still maintaining a nutritionally calorie adjusted diet. Reduce total fat < 30% of energy, of which < 1/3 should be saturated.[456,457]

I, B

Carbohydrates are either refined or complex. Complex carbohydrates (e.g. whole grains, peas, beans, lentils) are the preferred choice as they are digested more slowly and supply a steady release of energy.[455] Refined grains, such as white rice and white flour that have been processed, are deficient in many nutrients and fibre unless enriched. Fibre makes one feel full and satisfied longer and discourages over-eating.

I, B

The effect of dietary soluble fiber on serum cholesterol levels has been extensively studied. Intakes of 9 to 16.5 g/day of a variety of soluble fibers (mostly psyllium and guar) produced net reductions in serum total and LDL cholesterol levels of 5.5% to 11% and 3.2% to 12.1%, respectively.[458]

Sweets and sucrose-sweetened beverages should be discouraged. Naturally occurring sugars are preferable. A Mediterranean type diet which is rich in fruits, vegetables and nuts is encouraged.

Nutritional recommendations should be individualized depending on risk factors – dyslipidaemia, hypertension, diabetes and obesity. It is recommended that a qualified dietitian be involved in dietary counselling and education.

All high risk patients should be referred to a registered dietitian for further nutrition assessment, diagnosis, intervention, monitoring and evaluation. Dietitians are also available through the Malaysian Dietitians Association (MDA) website: www.dietitians.org.my

I, A Some hypertensive patients (especially the elderly) are sensitive to salt. In general, reduce daily salt intake to approximately 1- 1¼ tsp salt.[459,460] This can be achieved by reducing salt in cooking and by not adding table salt or soy sauce. Choose fresh or frozen unsalted foods as processed food is generally high in salt.

IIa, B In women with CHD, omega-3-fatty-acid (>1 gm/day) has been found to be beneficial.[452,454]

Healthy eating focuses on filling:

- ½ the plate with fruits and vegetables
- ¼ the plate with lean protein prepared with healthy cooking methods
- the remaining ¼ with grains and starches preferably whole grains.

6.1.2. Physical activity

I, B Women should be encouraged to exercise for at least 30 minutes on most days of the week.[344,373,374,381,461] Women who need to lose weight or sustain weight loss should exercise more.

Before engaging on an exercise program, women should be assessed by qualified trainers/healthcare providers. However even small increases in physical activity is beneficial.[381] This will include activities such as:

- walking 1 hour per week (about 10-15 minutes a day)
- using stairs instead of the lift or escalator
- parking some distance away and walking

6.1.3. Weight maintenance/ reduction

I, B Ideal BMI for Asian women is 18.5 - < 23 kg/m^2 and ideal waist circumference is ≤ 80 cm (31.5 inches).[317,340]

Weight control can be achieved by restriction of total calorie intake and regular physical activity.

6.1.4. Cigarette smoking

I, B Women should not smoke and should avoid secondhand smoke.[462] There is no data at present on the secondhand effects of e-cigarettes.

6.1.5. Aspirin

I, A Aspirin (75 mg-150 mg OD) is indicated for secondary prevention in all women with CVD.[463,464]

For primary prevention, in a large study, aspirin was found to be beneficial in women > 65 years.[465] Aspirin lowered the risk of stroke without affecting the risk of non-fatal MI and CV death.[465]

I, A However a more recent meta-analysis found that aspirin was of uncertain net value in primary prevention in both gender. The reduction in occlusive events needs to be weighed against the risk of major bleeding.[466-468]

I, A For patients with diabetes, the recommendations of the AHA/ACC are:[469]

- Low-dose (75–162 mg/d) aspirin use for prevention is reasonable for adults with diabetes and no previous history of vascular disease who are at increased CVD risk (10 year risk of CVD events over 10%) and who are not at increased risk for bleeding. These include women over age 60 years who have 1 or more of the following additional major risk factors: smoking, hypertension, dyslipidaemia, family history of premature CVD, and albuminuria

- Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (women < 60 years with no major additional CVD risk factors; 10-year CVD risk < 5%) as the potential adverse effects from bleeding offset the potential benefits
- Low-dose (75–162 mg/d) aspirin use for prevention might be considered for those with diabetes at intermediate CVD risk (younger patients with 1 or more risk factors, or older patients with no risk factors, or patients with 10-year CVD risk of 5–10%) until further research is available.

6.2. Treatment of Specific Risk Factors

Aggressive risk factor reduction should be instituted in all **High Risk** patients.

6.2.1. Dyslipidaemia

The primary target of therapy is LDL-C.[470-479]

In women especially in diabetics, low HDL-C and high TG are also important risk factors and are the secondary targets of therapy.[471,480]

6.2.1.1. Targets of therapy

Table 12: Targets of Therapy in Dyslipidaemia

	High Risk	At Risk & Optimal Risk
LDL-C	High Risk: Patients with established CHD or CHD Equivalents LDL-C Goal: < 2.6 mmol/L** (or a reduction of at least 50% if the baseline LDL-C is between 2.6-5.1mmol/L) < 1.8 mmol/l in diabetics with CVD (or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L)	<3.0 mmol/L

***the lower the better*

6.2.1.2. Management of Dyslipidaemia: Primary Prevention

I, C The cornerstone of management of women **At Risk** and **Optimal Risk** is lifestyle modification with advice on a healthy diet and physical activity.

I, C Women at risk who do not achieve their target levels should be considered for pharmacological intervention.

Meta-analysis consistently show that primary prevention with statin therapy improves survival and reduces CV events in both gender.[479-482]

Women with genetic dyslipidaemias such as familial hypercholesterolemia with very high levels of TC or LDL-C may be considered for lipid lowering therapy from the outset.

6.2.1.3. Management of Dyslipidaemia: Secondary Prevention

I, A Numerous studies on secondary prevention have shown that women have similar benefits on CVD outcomes as men.[470,471,473,481]

I, A These High Risk women should have statin therapy.[470,472,473,481]

I, C Statins should not be used in women who are pregnant, intend to become pregnant or who are breast feeding.

6.2.2. Hypertension

6.2.2.1. Targets of Therapy

I, A The target BP in most patients < 80 years of age, should be < 140/90 mmHg.[482] In patients > 80 years, the target should be < 150/90 mmHg.[482] In the presence of target organ damage, a lower BP maybe considered especially in younger patients.[482] (Table 13, pg 82)

I, B In diabetics, the target BP is < 135/75 mmHg.[314]

I, A In the presence of microalbuminuria/proteinuria, ACEI/ARBs are the first choice.[314]

The guidelines recognize that the risk of target organ damage extends to BP below this level and the true threshold for CVD risk should be flexible and dependent on the total risk of the individual. A recent study showed that in persons over the age of 50 years and without diabetes, a lower BP of 120/80 mmHG was associated with improved survival and cardiac outcomes. A lower BP target was however, associated with an increase in adverse effects (syncope, hypotension, electrolyte problems and acute kidney injury or failure).[483]

Table 13: Blood Pressure Targets in the Different Risk Groups *

< 140/90 mmHg in most women < 80 years of age	I,A
< 150/90 mmHg in women > 80 years of age	I,A
In the presence of the following co-morbidity, target BP should be:	
➢ renal impairment (CKD): < 140/90 mmHg	I,A
➢ proteinuria of <1g/24hr: < 140/90 mmHg	I,A
➢ proteinuria of >1g/24hr: < 130/80 mmHg	I,A
➢ post MI and heart failure: < 130/< 80 mmHg	I,C
➢ secondary prevention of lacunar stroke: < 130/80 mmHG	II a, B

**Malaysian Clinical Practice Guidelines on Hypertension, 4th ed 2013. available at www.acadmed.com.my*

Blood Pressure control in women may be challenging. In the Women's Health Initiative, 64% of hypertensive women were treated with drugs but BP control was only achieved in 36% with the lowest rates of control in the oldest groups.[484] This was mainly because of the difficulty of controlling systolic BP.[484] Women are also more sensitive to a number of anti-hypertensive medications.

For recommended pharmacotherapy refer Appendix 4C, pg 95.

6.2.2.2. Gender Specific issues

The benefits of treating hypertension has been shown in both gender although some gender specific differences have been seen in the clinical trials. An earlier subgroup meta-analysis showed that in men, antihypertensive treatment reduced all categories of events while in women it was statistically significant only for stroke and major CV events. In absolute terms, the benefit in women was seen primarily for strokes; in men, treatment prevented as many coronary events as strokes.[485-487]

However, a more recent large meta- analysis found that there were no gender differences on the primary outcome of total major cardiovascular events. There was also no evidence that different anti-hypertensive regimens based on ACEI, calcium antagonists, ARBs, or diuretics/β-blockers were more effective in one gender than the other.[488]

Current guidelines for the treatment of hypertension are not gender specific. There are however some gender differences. Diuretics were associated with better blood pressure control than any of the other drug classes as monotherapy.[489,490] Women are:

- less likely than men to have BP controlled with lifestyle interventions alone[488,489]
- less successful in losing weight [489,490]
- more sensitive and more likely to respond to salt restriction[491,492]
- more likely to develop hyponatraemia and/or hypokalaemia associated with diuretic therapy[493]
- less likely to respond to β-blockers[490]
- more likely to develop pedal oedema with calcium channel blockers[490]
- twice as likely as men to develop ACEI induced cough[494]

Special issues in women:

- pre-conception counselling is important in young women with hypertension
- women in the reproductive age should preferably avoid ACEI and ARBs
- in pregnancy, the drugs of choice are methyldopa, nifedipine and labetolol
- weight loss and reduced sodium intake is beneficial in reducing blood pressure in older women[488]

6.2.3. Diabetes

6.2.3.1. Targets of therapy

Table 14: Targets of Therapy in Diabetes*

	Unit	Target	Grade, Level
Glycemic Control	HbA1c	≤ 6.5%**	**I, A**
	Fasting or Pre-prandial blood sugar	4.4 - 7.0 mmol/L**	-
	Post prandial blood sugar (90 mins after a meal)	4.4 - 8.5 mmol/L**	-
BP		≤ 135/75 mmHg	**I, B**
Lipids	LDL-C	≤ 2.6 mmol/L ≤ 1.8 mmol/L in the presence of CVD *or* a reduction of at least 50% if the baseline LDL-C is between 2.6-5.1mmol/L	**I, A** **I, A** **-**
	TG	≤ 1.7 mmol/L	
	HDL-C	> 1.2 mmol/L	

**Malaysian CPG for Management of Type 2 Diabetes Mellitus, 5th Ed 2015.*[314]
***Glycemic targets needs to be individualised depending on the patient's profile*

Specific local guidelines for the management of diabetic complications (CPGs on Diabetes Nephropathy 2006, Diabetes Retinopathy and Diabetic Foot 2004) are also available at the website – *www.acadmed.org.my*.

6.2.4. Overweight and Obesity

Treatment of overweight and obesity can be achieved through a variety of modalities which include:

- changes in dietary composition
- low-calorie diet (LCD)
- very low-calorie diet (VLCD)
- physical activity

- behaviour therapy
- drug therapy
- bariatric surgery

Certain weight loss therapies may be inappropriate in the following circumstances:

- serious, acute psychiatric illness
- pregnancy or lactation

6.2.4.1. Overall Goals for Weight Loss Management

I, B
- 10% loss of the initial body weight is associated with significant health benefits (Table 3, pg 11)[350,495]
- Overweight/ obese women who lose weight intentionally over a year, have been shown to have significantly reduced mortality rates[496]
- Maintain lower weight over the long-term. It is better to maintain a moderate loss over the long-term than it is to achieve a greater weight loss that cannot be maintained
- Prevent weight regain

6.2.5. Others

6.2.5.1. Anticoagulant

I, A Patients with non valvular AF irrespective of whether the pattern is paroxysmal, persistent or permanent should be considered for anticoagulation depending on their CHA_2DS_2-VASc score.[497]

The CHA_2DS_2-VASc score is calculated as in Table 15, pg 86.

The rate of stroke is 0.2, 1.3, and 2.2% per year for CHA_2DS_2-VASc scores of 0, 1, and 2 respectively.[497] Patients with a CHA_2DS_2-VASc score of 2 or more, should be considered for anticoagulation with:

I, A
- warfarin or

I, B
- NOAC[497]

IIa, C In those with a CHA_2DS_2-VASc score of 1, consideration for anticoagulant therapy should be individualized.[497,498]

IIa, B Patients who are < 65 years of age with lone AF (strictly defined, irrespective of gender) and those with CHA_2DS_2-VASc of 0, have very low absolute stroke risk. It may be reasonable not to consider these group of individuals for antithrombotic treatment.[497,498]

The NOAC's have been shown to be safer and more efficacious in women.[116] The risk of bleeding, renal function and patient preferences must however be taken into consideration before initiating therapy.

I, B In patients with AF secondary to valvular heart disease, warfarin is the agent of choice.[497]

Table 15: CHA_2DS_2-VASc score

	CHA_2DS_2-VASc SCORE
Congestive Heart Failure	1
Hypertension	1
Age > 75 years	2
Diabetes Mellitus	1
Prior Stroke or TIA or thromboembolism	2
Vascular Disease	1
Age 64-74 years	1
Female gender	1

6.2.5.2. Supplements

There is no evidence that the following supplements are useful in preventing CVD in women:

III, A 1. Antioxidant vitamin supplements (e.g. vitamin E,C & beta carotene)[499-502]

III, A 2. Folic acid[503,504]

II, B Omega-3 fatty acid consumption in the form of fish or in capsule form (e.g. EPA 1800 mg/day) may be helpful in women with hypercholesterolemia and/or triglyceridaemia.[505] It has not been shown to be helpful in the primary prevention of CHD.[506-508]

7. ADHERENCE, COMPLIANCE AND QUALITY ASSURANCE

It has been well documented that there is a lack of adherence to cardiovascular preventive therapy. This is due to:

- Healthcare providers not:
  - counselling patients on healthy dietary practices, weight management and regular exercise
  - risk stratifying patients
  - initiating appropriate treatment when necessary
  - achieving treatment goals
  - checking on drug compliance
- Patient - non compliance to medical advice and drug therapy

Lack of adherence threatens the success of the guideline recommendation and implementation. More importantly, lack of adherence leads to missed opportunity for the risk reducing benefits of the treatment, thus creating enormous costs to the health system for treating CV events that could have been prevented.

To improve adherence and compliance the following are recommended:

- Patient:
  - Simplify medication regimens using wherever possible drugs with a single daily or twice daily dosing
  - Give clear instructions
  - Encourage the support of the family
  - Involve patients in their care through self-monitoring
- Healthcare providers:
  - Practise effective preventive strategies in accordance with clinical guidelines
  - Educate patients to participate in their preventive care
  - Use mass media for patient education
  - Standardize reference values in all laboratories to recommended Malaysian guidelines
  - Where available, the patient should be referred to the Medication Therapy Adherence Clinic (MTAC) to improve compliance to therapy.

Adherence to therapy should be checked periodically. Some suggested audit parameters are as in the Audit of Clinical Diabetes (Green Book) by the *Unit Penyakit Kardiovaskular dan Diabetes* (Appendix 6, pg 100). In addition documentation of the following:

- CVD risk of the women (any CV risk score but the Framingham general CVD risk score tool for primary care is encouraged)
  - Numerator: number of women with CVD risk score documented
  - Denominator: number of women seen at that clinic session
- Patient's weight, waist circumference and BMI and the desirable values.
  - Numerator: number of women with these values documented
  - Denominator: number of women seen at that clinic session
- Blood pressure
  - Numerator: number of women with BP target achieved
  - Denominator: number of women with hypertension seen at that clinic session
- Lipid values
  - Numerator: number of women with LDL-C (or total cholesterol) target achieved
  - Denominator: number of women seen at that clinic session whose LDL-C (or total cholesterol) were measured
- Fasting glucose and HbA1c levels
  - Numerator: number of women with HbA1c (or fasting glucose) target achieved
  - Denominator: number of women with diabetes seen at that clinic session

Target: more than 70% of the medical records should have these data documented.

APPENDIX

APPENDIX 1: CANCER AND THE HEART

Appendix 1A: Cardiotoxicity risk assessment[199]

Medication-related risk	High risk score 4	Anthracyclines, Cyclophosphamide, Ifosfamide, Clofarabine, Herceptin
	Intermediate risk score 2	Docetaxel, Pertuzumab, Sunitinib, Sorafinib
	Low risk score 1	Bevacizumab, Dasatinib, Imatinib, Lapatinib
	Rare risk score 0	Etoposide, Rituximab, Thalidomide
Patient-related risk	Risk score 1 each	• Heart failure or cardiomyopathy • CHD or equivalent (PAD) • Hypertension • Diabetes Mellitus • Prior or recurrent anthracyclines • Prior of recurrent chest radiation • Age < 15, > 65 years • Female gender

Appendix 1B: Cardiotoxicity risk score[199]

Cardiotoxicity Risk Score	Risk Categories
> 6	Very high
5-6	High
3-4	Intermediate
1-2	Low
0	Very low

Appendix 1C: Monitoring recommendations during/after chemotherapy*

Risk Category	Recommendation
Very high risk	TTE with strain before every (other) cycle, end, 3-6 months and 1 year, optional ECG, cTn with TTE during chemotherapy
High risk	TTE with strain every 3 cycles, end, 3-6 months and 1 year after chemotherapy, optional ECG, cTn with TTE during chemotherapy
Intermediate risk	Discuss risk and benefit of medication
Low risk	None, monitoring only
Very low risk	None, monitoring only

TTE: trans-thoracic echocardiography, cTn: cardiac troponins

**Adapted from:*

- *Bovelli D, Plataniotis G, Roila F on behalf of the ESMO Guidelines Working Group. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. Ann Oncol 2010; 21(suppl 5): v277-v282.*
- *Hermann J, Lerman A, Sandhu N et al. Evaluation and management of patients with heart disease and cancer: Cardio-oncology. Mayo Clinic Proceedings 2014; 89(9): 1287-1306.*

Appendix 1D: Treatment recommendations[509-514]

Risk Category	Management
Very high cardiotoxicity risk	Initiate ACEI/ARB, carvedilol and statins, one week prior to chemotherapy and up-titre as tolerated
High cardiotoxicity risk	Initiate ACEI/ARB, carvedilol/nebivolol and statins
Intermediate cardiotoxicity risk	Discuss risk and benefit of medication
Low cardiotoxicity risk	None, monitoring only
Very low cardiotoxicity	None, monitoring only

APPENDIX 2: COMBINED ORAL CONTRACEPTIVE (COC)

Appendix 2A: Combined Oral Contraceptive (COC)

Class of COC*	Progesterone content	Estrogen content
First-generation	Norethynodrel, norethindrone**, norethindrone acetate, or ethynodiol diacetate	containing ≥ 50 µg ethinyl estradiol
Second-generation	Norgestrel or levonorgestrel, norethindrone, norethindrone acetate, ethynodiol diacetate, norgestrel, levonorgestrel, or norgestimate	< 50 µg ethinyl estradiol
Third-generation	Desogestrel, gestodene, or norgestimate	< 50 µg ethinyl estradiol
Fourth-generation	Drospirenone, dienogest, or nomegestrol acetate	< 50 µg ethinyl estradiol

**These terms sometimes refer to the:*

- *timing of the introduction of a product (given both the dose of estrogen and the type of progestin),*
- *timing of the market introduction of the progestin,*
- *structure of the carbon ring from which the progestin is derived (estrane or gonane),*

***also known as norethisterone*

Appendix 2B: Age-Specific Estimates of the Excess Rates of Myocardial Infarcation, Ischemic Stroke, and Venous Thromboembolism Attributable to the Use of Low-Estrogen Oral Contraceptive and Pregnancy-Related Mortality*[515]

Variable	Age		
	20-24 Yr	30-34 Yr	40-44 Yr
No. of excess cases of myocardial infarction and ischemic stroke attributable to oral-contraceptive use (per 100,000 woman-yr of use)**			
Among non-smokers	0.4	0.6	2
Among smokers	1	2	20
Among women with hypertension	4	7	29
No. of pregnancy-related death (per 100,000 live births)	10	12	45
No of excess cases of venous thromboembolism attributable to oral-contraceptive use (per 100,000 woman-yr of use)			
With norethindrone, norethindrone acetate, levonorgestrel, or ethynodiol diacetate	6	9	12
With desogestrel or gestodene	16	23	30

* Low estrogen was defined as less than 50 µg.
**Data are from Farley et al.

From: Farley TM, Collins J, Schlesselman JJ. Hormonal contraception and risk of cardiovascular disease: an international perspective. Contraception 1998;57:211-230

APPENDIX 3: ALCOHOL CONTENT OF COMMON SPIRITS

	**Wine**	**125ml (small glass)**		**175ml (standard glass)**
	12%	2.1 units		1.5 units
	14%	1.75 units		2.45 units
	**Beer**	**Half Pint**	**330ml bottle**	**Pint**
	4%	1.1 units		2.2 units
	5%	1.4 units	1.7 units	2.8 units
	**Spirits**	**25ml (single)**		**50ml (double)**
	40%	1 unit		2 units

Adapted from the UK government guidelines on alcohol consumption

APPENDIX 4: MANAGEMENT OF HYPERTENSION

Appendix 4A: Risk Stratification*

Co-existing Condition / BP Levels (mmHg)	No RF No TOD No TOC	TOD or RF (1-2) No TOC	TOC or RF (≥ 3) or Clinical atherosclerosis	Previous MI or Previous stroke or Diabetes
SBP 130 - 139 and/or DBP 80 - 89	Low	Medium	High	Very high
SBP 140 - 159 and/or DBP 90 - 99	Low	Medium	High	Very high
SBP 160 - 179 and/or DBP 100 - 109	Medium	High	Very high	Very high
SBP > 180 and/or DBP> 110	High	Very high	Very high	Very high

TOD = Target organ damage (LVH, retinopathy, proteinuria)
TOC = Target organ complication (heart failure, renal failure)
RF = additional risk factors (smoking, TC > 6.5 mmol/L, family history of premature vascular disease)
Clinical atherosclerosis (CHD, carotid stenosis, peripheral vascular disease, transient ischaemic attack, stroke)
**Malaysian Clinical Practice Guidelines on Hypertension, 4th ed. 2013*[482]

Appendix 4B: Recommendation for Follow-up Visit based on Initial Blood Pressure Measurements for Adults*

Initial BP (mmHg)			Follow-up recommendation to confirm diagnosis
Systolic		Diastolic	
< 130	and	< 85	Recheck in one year
130 - 139	and	85 - 89	Recheck within 3 - 6 months
40 - 159	and/or	90 - 99	Confirm within two months
160 - 179	and/or	100 - 109	Evaluate within one month and treat it confirmed
180 - 209	and/or	110 - 119	Evaluate within one week and treat it confirmed
≥ 210	and/or	≥ 120	Initiate drug treatment immediately

**Malaysian Clinical Practice Guidelines on Hypertension, 4th ed. 2013*[482]

Appendix 4C: Choice of Anti-Hypertensive Drugs in Patients with Concomitant Conditions*

Concomitant Condition	Diuretics	β-blockers	ACEIs	CCBs	Peripheral α-blockers	ARBs
Diabetes mellitus (without nephropathy)	+	+/-	+++	+	+/-	++
Diabetes mellitus (with nephropathy)	++	+/-	+++	++*	+/-	+++
Gout	+/-	+	+	+	+	++
Dyslipidaemia	+/-	+/-	+	+	+	+
Coronary heart disease	+	+++	+++	++	+	+++
Heart failure	+++	+++	+++#	+@	+	+++
Asthma	+	-	+	+	+	+
Peripheral vascular disease	+	+/-	+	+	+	+
Non-diabetic renal impairment	++	+	+++	+*	+	++
Renal artery stenosis	+	+	++$	+	+	++$
Elderly with no co-morbid conditions	+++	+	+	+++	+/-	+
Very elderly (>80 yrs) with no co-morbid conditions	+++	+	+++	++	+/-	++

The grading recommendation from (+) to (+++) is based on increasing levels of evidence and/or current widely accepted practice

+/- Use with care

- Contraindicated

* Only non-dihydropyridine CCB

\# Metoprolol, bisoprolol, carvedilol, nebivolol – dose needs to be gradually titrated

@ Current evidence available for amlodipine and felodipine only

$ Contraindicated in bilateral renal artery stenosis

**Malaysian Clinical Practice Guidelines on Hypertension, 4th ed. 2013*[482]

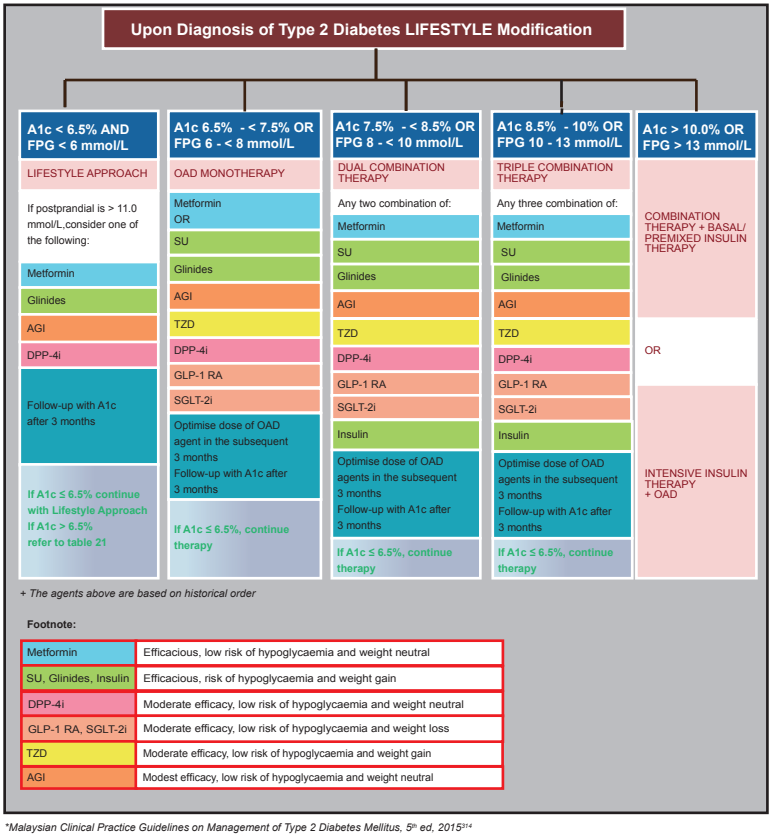
Appendix 4D: Effective Anti-Hypertensive Combinations Used in Outcome Trials*

Effective combination	Patients studied
ACEI + thiazide-like diuretics[516]	Post stroke
ARB + thiazide[517]	Hypertensive with LVH
CCB + ACEIs or β-blocker + thiazide[518]	Patients with CAD
ARB + thiazide or CCb + thiazide [519]	High risk hypertensives
CCB + ACEI[520]	Medium risk hypertensives with no overt vascular diseases
ACEI + thiazide-like diuretics[521]	High risk hypertensives with diabetes
ACEI + CCB[522]	High risk hypertensives
thiazide-like diuretics + ACEI[523]	Very elderly (> 80 years old)

**Malaysian Clinical Practice Guidelines on Hypertension, 4th ed. 2013*[482]

Appendix 5: MANAGEMENT OF TYPE 2 DIABETES MELLITUS

Appendix 5A: Treatment Algorithm for Newly Diagnosed T2DM*



+ The agents above are based on historical order

Footnote:

Metformin	Efficacious, low risk of hypoglycaemia and weight neutral
SU, Glinides, Insulin	Efficacious, risk of hypoglycaemia and weight gain
DPP-4i	Moderate efficacy, low risk of hypoglycaemia and weight neutral
GLP-1 RA, SGLT-2i	Moderate efficacy, low risk of hypoglycaemia and weight loss
TZD	Moderate efficacy, low risk of hypoglycaemia and weight gain
AGI	Modest efficacy, low risk of hypoglycaemia and weight neutral

**Malaysian Clinical Practice Guidelines on Management of Type 2 Diabetes Mellitus, 5th ed, 2015*[314]

Appendix 5B: Treatment Recommendations for Patients on Clinic Follow-up

Glycaemic Control / Current Treatment	A1c 6.5 -< 7.5% or FPG 6 -< 8 mmol/L	A1c 7.5 -< 8.5% or FPG 8-< 10 mmol/L	A1c 8.5-10.0% and FPG 10-13 mmol/L	A1c > 10.0% or FPG > 13 mmol/L
Lifestyle Treatment	Add Metformin (or if metformin cannot be tolerated add either SU/ Glinides/AGI/ TZD/ DPP-4i/ GLP-1 RA/ SGLT2i	Add Metformin and another agent (Dual therapy)	Add Metformin and another 2 agents not used for the dual therapy (Triple therapy)	Dual or Triple therapy + insulin (basal or premixed)
Monotherapy (Metformin preferred)	Add another agent (Dual therapy)	Add 2 agents not used for the dual therapy (Triple therapy)	Dual or Triple therapy + insulin (basal or premixed)	Optimise insulin (basal plus/ multiple premixed) ± OAD
Dual Therapy	Add another agent not used for the dual therapy (Triple therapy)	Dual or Triple therapy + insulin (basal or premixed)	Optimise insulin (basal plus/ multiple premixed) ± OAD	Intensify insulin (basal bolus/ multiple premixed) ± OAD
Triple Therapy	Dual or Triple therapy + insulin (basal or premixed)	Optimise insulin (basal plus/ multiple premixed) ± OAD	Intensify insulin (basal bolus/ multiple premixed) ± OAD	Intensify insulin (basal bolus/ multiple premixed) ± OAD

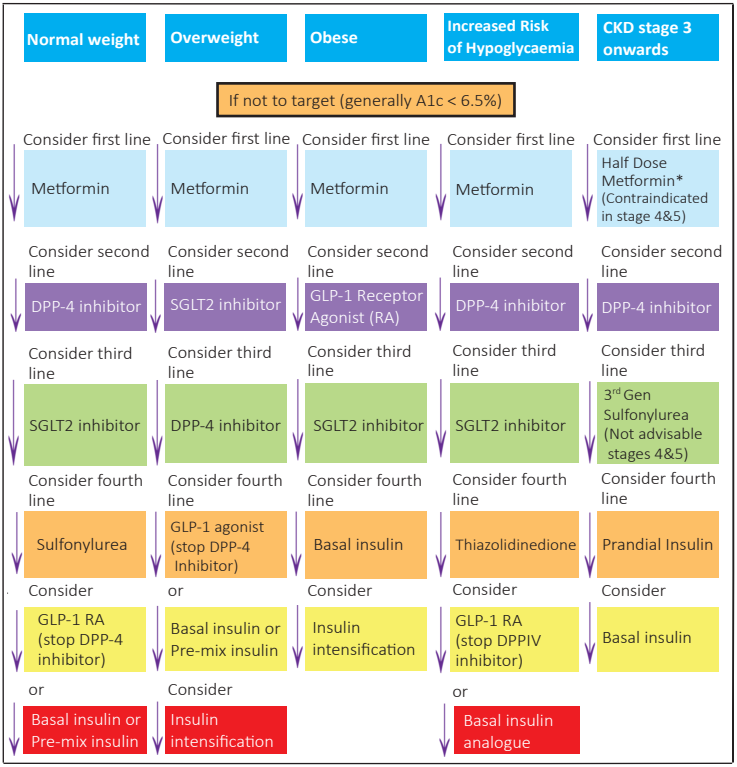
Footnote:

1. *If symptomatic (weight loss, polyuria, etc) at any A1c and FPG level, consider insulin therapy*
2. *Glycaemic target should be individualized however try to achieve as near normal glycaemia without causing hypoglycaemia*
3. *May consider 4th agent (OAD or GLP-1 RA) if A1c ≤ 10%.*

+ intensify involve changing the regimen
+ optimise involve increasing the dose

**Malaysian Clinical Practice Guidelines on Management of Type 2 Diabetes Mellitus, 5th ed, 2015*[314]

Appendix 5C: Recommended Algorithm for Specific Patient Profiles



**Malaysian Clinical Practice Guidelines on Management of Type 2 Diabetes Mellitus, 5th ed, 2015*[314]

Appendix 6: AUDIT OF CLINICAL DIABETES

Buku Rekod Rawatan NCD*

Hospital/ Health Clinic: _____ Type of practice: FMS/ MO/ AMO

Name of patient: _____ IC No: _____

D.O.B:_____ Sex: Male/ Female

Date when diabetes was diagnosed:_____ Ethnic group: _____

*estimated/ presumed*** ☐

Criteria		Result of the most recent examination	Date of the most recent examination	Not done
Height		cm		☐
Weight		kg		☐
Waist circumference		cm		☐
Body Mass Index (BMI)		kg/m^2		☐
Blood Pressure		mmHg		☐
FBS, RBS or 2HPP		mmol/L		☐
HbA_{1C}		%		☐
Lipid profile	TC:	mmol/L		☐
	TG:	mmol/L		☐
	HDL:	mmol/L		☐
	LDL:	mmol/L		☐
Creatinine		µmol/L		☐
Urine microalbumin		Normal/ Abnormal		☐
Urine protein		Present/ Absent		☐
Fundoscopy		Normal/ Abnormal		☐
Examination of feet		Normal/ Abnormal		☐
ECG		Normal/ Abnormal		☐

**This audit form contains only some of the parameters recorded in the Buku Rawatan NCD*
******Estimate/presumed****: If date not known, enter 30/06/yyyy and mark the box.*

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