UNIT NO. 6

UPDATE ON MANAGEMENT OF CORONARY ARTERY DISEASE RISK FACTORS: PHARMACOLOGICAL STRATEGY

Dr Raymond Lee

ABSTRACT

Cardiovascular disease (CVD), which includes coronary artery disease (CAD), stroke, and peripheral vascular disease is by far the leading cause of death in the United States and most developed countries, including Singapore[1].

The majority of known risk factors for CVD are modifiable by specific preventive measures. In the worldwide INTERHEART study of patients from 52 countries, nine potentially modifiable risk factors accounted for over 90% of the population attributable risk of a first MI[2]. These included smoking, dyslipidaemia, hypertension, diabetes, abdominal obesity, psychosocial factors, daily consumption of fruits and vegetables, regular alcohol consumption, and regular physical activity.

Hence, the following CVD risk factors are modifiable and should be considered as therapeutic targets for primary prevention of CVD in all adults:

- **Smoking**
- **Hypertension**
- **Diet**
- **Dyslipidaemia**
- **Physical inactivity**
- **Obesity**
- **Diabetes mellitus (CAD risk equivalent)**

Furthermore, aspirin is recommended for primary prevention of CVD by the third United States Preventive Services Task Force (USPSTF) for men and women whose 10-year risk of a first CHD event is six percent or greater as determined by the Framingham risk score, as well as by the American Heart Association for men and women whose 10-year risk is 10 percent or greater[3].

In this review, we will focus on the updates in the guidelines and pharmacotherapy of hypertension and dyslipidaemia. Diabetes mellitus is considered a CAD risk equivalent and the American Diabetes Association Guidelines recommend that all diabetics should be on Aspirin and should have their LDL cholesterol treated to NCEP-ATP III target of < 100mg/dL[4].

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RAYMOND LEE KOK KEONG, Consultant Cardiologist, Department of Cardiology, Tan Tock Seng Hospital

WHAT IS HYPERTENSION AND WHY IS IT IMPORTANT?

Any definition of hypertension is arbitrary. Consensus from published guidelines is that hypertension is defined at a BP of ≥140/90mmHg (i.e. either systolic BP ≥140mmHg or diastolic BP ≥90mmHg).

Hypertension is a well-established risk factor for adverse cardiovascular outcomes, including CAD, CAD mortality, stroke, congestive heart failure, and sudden death[5]. Systolic blood pressure is at least as powerful a coronary risk factor as diastolic blood pressure[6] and isolated systolic hypertension is an established major hazard for CAD and stroke[7].

The co-existence of other modifiable risk factors (e.g. elevated cholesterol, smoking, impaired glucose metabolism) and non-modifiable risk factors (e.g. old age, history of CVD, male gender) dramatically increases the CVD risk associated with any given blood pressure (BP)[8].

Lifestyle modifications – the best first step

A healthier lifestyle, by lowering BP and CVD risk, may reduce, delay or remove the need for long-term drug therapy in some patients. As such, all hypertension guidelines recommend that lifestyle interventions should form an integral part of the management of hypertension, either alone or in addition to drug therapy, depending on how severely BP is raised (Table 1)[9].

Table 1: Lifestyle modifications to prevent and manage hypertension*

Modification range†	Recommendation	Approximate SBP reduction
Weight reduction	Maintain normal body weight (BMI 18.5-24.9kg/m2)	5-20mmHg/10kg
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low fat dairy products with reduced total and saturated fat content	8-14mmHg
Dietary sodium restriction	Reduce dietary sodium to no more than 100mmol/day (2.4g sodium or 6g sodium chloride)	2-8mmHg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week)	4-9mmHg
Moderation of alcohol consumption	Limit consumption to not more than 2 drinks (24oz beer, 10oz wine or 3oz 80-proof whiskey per day in most men and no more than 1 drink per day in women and lighter weight persons	2-4mmHg

DASH indicates dietary approaches to stop hypertension
**For overall cardiovascular risk reduction, stop smoking*
†The effects of implementing these modifications are dose and time dependent and could be greater for some individuals
Source: JNC VII

DRUG TREATMENT OF HYPERTENSION – WHEN TO START, WHICH AGENT TO USE AND WHAT SHOULD THE TARGET BP BE?

Pharmacotherapy should be instituted when lifestyle modification fails to achieve the desired BP target or when there is evidence of target organ damage or associated high risk features (see Figure 1). The following are important risk factors for hypertensive patients:

- Left ventricular hypertrophy
- Type 2 diabetes mellitus
- Peripheral artery disease
- Previous stroke or TIA
- Male sex
- Age ≥ 55 years
- Microalbuminuria
- Smoking
- Premature family history of CAD
- Ratio of plasma total cholesterol/HDL-cholesterol ≥ 6

A range of effective antihypertensive drugs from different pharmacological classes can be considered for the treatment of hypertension. On an individual patient basis, some drugs may be more effective and/or have a more tolerable side-effect profile than others.

Acceptable classes of agents for initial pharmacologic treatment of hypertension include:

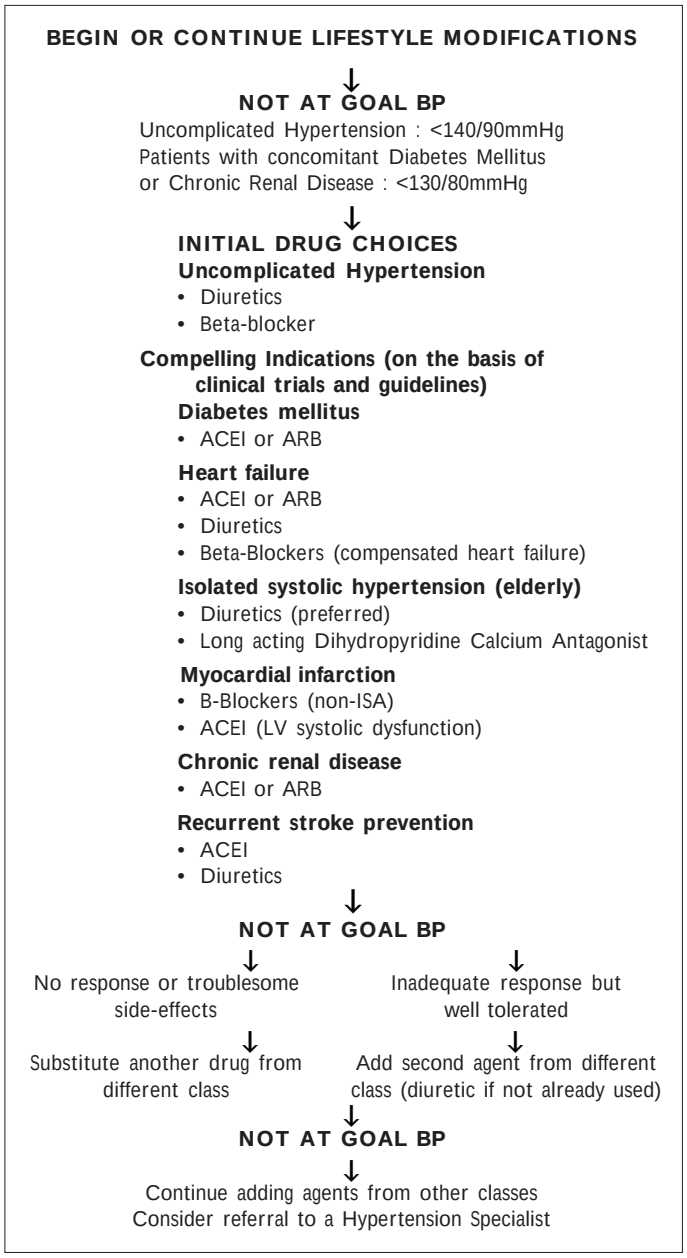
- Diuretics
- Beta-blockers
- ACE-inhibitors
- Angiotensin receptor blockers (ARBs)
- Calcium antagonists
- Alpha-beta blockers
- Peripheral alpha-blockers

Of paramount importance for reducing CVD risk is the degree of BP reduction achieved. Although there may be some benefits for particular drug classes in specific patient groups, in general, there is little evidence of clinically significant, drug-specific effects to distinguish the efficacy of drugs within or between classes when their BP lowering effect is taken into account. Therefore, choice of antihypertensive should be based on individual patient factors (e.g. comorbidities), side-effect profiles, and costs.

Furthermore, treating hypertension should not be viewed in isolation and other interventions, such as statins and aspirin, should be considered, where appropriate, based on patient's history of CVD or an assessment of the global CVD risk.

Another important consideration is that in a substantial proportion of patients with hypertension (up to 60%), monotherapy often does not achieve the target BP. Indeed, most hypertension trials have patients on more than one medication. In the HOT trial involving 18,790 patients receiving antihypertensive agents to titrate DBP down to ≤ 80mm Hg, 77% were on two agents and 24% were on three agents[10]. Hence, the initial choice of anti-hypertensive drug may not be so important, as most patients will end up needing at least two drugs.

Figure 1. An algorithm for starting anti-hypertensive drug therapy and the treatment goals



WHAT IS NEW IN THE GUIDELINES FOR TREATMENT OF HYPERTENSION?

A recent statement by the American Heart Association has recommended changes to both the drug therapy recommendations for primary prevention in uncomplicated hypertension and also the target BP for "high risk" hypertensive patients, especially those with established CAD, or who are at high risk of developing CAD[11].

In keeping with recent European Hypertension Society guidelines, beta-blockers are no longer recommended for blood

pressure control in the primary prevention group. Many comparative clinical trials have shown that for preventing both stroke and CAD complications, beta-blockers are inferior to newer classes of drugs like ACE inhibitors, angiotensin-receptor blockers, or calcium channel blockers[12,13]. However, once there is established occlusive CAD, with symptoms like angina or acute MI, or heart failure due to LV systolic dysfunction, then beta-blockers are recommended.

The JNC seventh report currently recommends that the lower target of < 130/80 mm Hg be used in patients with diabetes mellitus or chronic renal disease. The new statement suggests this group should be broadened to include men and women with established CAD in different forms (stable angina; unstable angina/non-ST elevation MI; ST-elevation MI; heart failure secondary to CAD), or who are at high risk of developing CAD [CAD-risk equivalent (carotid disease, peripheral artery disease, or abdominal aortic aneurysm) or a ten-year Framingham risk score ≥ 10%]. In patients with heart failure, the target BP should be even lower (< 120/80 mm Hg), although blood pressure lowering should be slow. An update of the guidelines for treatment targets in hypertension is shown below.

- General CAD prevention in uncomplicated hypertension
  – **< 140/90 mmHg**
- Known CAD or high CAD risk (Peripheral artery disease, cerebrovascular disease, 10-year Framingham risk score ≥ 10%,)
  – **< 130/80 mmHg** (previously confined to diabetes mellitus or chronic renal disease in JNC VII guidelines)
- Heart failure
  – **< 120/80 mmHg**

DYSLIPIDAEMIA

In the past three decades, numerous clinical and epidemiologic studies have shown repeatedly that an elevated blood cholesterol level is one of the major modifiable risk factors associated with the development of atherosclerosis and CAD[14]. In particular, these studies have demonstrated that low-density lipoprotein (LDL) cholesterol is the primary lipoprotein mediating atherosclerosis. A low level of high-density lipoprotein (HDL) cholesterol has also been implicated in CAD[15].

Lifestyle modifications – the essential first step

As with hypertension, lifestyle modification which encompasses diet, physical activity, and weight loss remains the cornerstone of treatment of hypercholesterolemia. The NCEP-ATP III guidelines stress the importance of non-pharmacologic treatment but recognize its limitations by reducing the trial of these modalities from six months to 12 weeks before considering the use of medications to assist in achieving recommended LDL goals[16].

The distribution of the fat allowance has been altered to recognise the value of monounsaturated and polyunsaturated fatty acids. By replacing saturated fats (cheese, whole milk, red meat) with monounsaturated fats (olive, canola oil) and polyunsaturated fats (corn oil, peanuts), LDL is reduced. Although replacing saturated fats with a high-carbohydrate diet results in lower LDL levels, it has the adverse effect of raising triglycerides and lowering HDL. Saturated and trans-unsaturated fatty acids should be avoided.

Physical inactivity is an independent risk factor, raising the risk of a cardiovascular event two-fold[17]. Aerobic exercise raises HDL levels and lowers triglyceride levels. When it results in weight loss, it contributes to LDL reduction. Weight loss also improves insulin sensitivity and serum glucose uptake, reducing the risk of diabetes. Cigarette smoking remains a cardiovascular risk factor. Patients who stop smoking can expect an increase of up to 30 percent in their HDL levels[18]. A recommended therapeutic lifestyle changes diet is shown (Table 2).

DRUG TREATMENT OF HYPERCHOLESTEROLEMIA – WHEN TO START, WHICH AGENT TO USE AND WHAT SHOULD THE THERAPEUTIC TARGETS BE?

As indicated by NCEP-ATP III guidelines, failure of therapeutic lifestyle changes (TLC) to modify LDL cholesterol levels or the presence of high CAD risk levels (CAD and CAD-risk equivalents) warrants the use of drug therapy. Despite its use, particular attention to TLC should always be maintained and reinforced by the physician[16].

The extent of LDL-lowering therapy depends on the patient's CAD risk. Patients are classified in one of three categories of risk: (a) CAD and CAD-risk equivalents, (b) two or more risk factors (further delineated by a Framingham risk score of 10 to 20 percent versus 10 percent or less), or (c) zero or one risk factor. Patients with diabetes mellitus, carotid disease, peripheral artery disease, abdominal aortic aneurysm and those with a 10-year cardiac event risk of 20 percent or greater are considered CAD-risk equivalents.

Table 2: Nutrient composition of the therapeutic lifestyle changes diet

Nutrient	Recommended intake
Saturated fat*	<7 percent of total calories
Polyunsaturated fat	Up to 10 percent of total calories
Monounsaturated fat	Up to 20 percent of total calories
Carbohydrates†	25 to 35 percent of total calories
Protein	50 to 60 percent of total calories
Fiber	20 to 30 g per day
Total fat	Approximately 15 percent of total calories
Cholesterol	<200 mg per day
Total calories‡	Balance energy intake and expenditure to maintain desirable body weight

* *Avoid trans fatty acids as well because they increase LDL and lower HDL cholesterol levels*

† *Carbohydrates should be derived from foods rich in complex carbohydrates, including whole grains, fruits, and vegetables*

‡ *Daily energy expenditure should include at least moderate physical activity.*

Source: NCEP-ATPIII

Table 3: LDL cholesterol goals for the different risk categories

Risk category	LDL goal	LDL level at which to initiate TLC	LDL level at which to consider drug therapy
CHD or CHD risk equivalent (10-year risk >20 percent)	<100 mg/dL (2.60 mmol/L)	>=100 mg/dL	>=130 mg/dL (at 100 to 129 mg/dL, drug optional)*
2 or more risk factors (10-year risk <20 percent)	<130 mg/dL (3.35 mmol/L)	>=130 mg/dL	>=130 mg/dL for 10-year risk of 10 to 20 percent; >=160 mg/dL for 10-year risk of <10 percent
0 to 1 risk factor†	<160 mg/dL (4.15 mmol/L)	>=160 mg/dL	>=190 mg/dL (at 160 to 189 mg/dL, LDL-lowering drug optional)

** If an LDL cholesterol level of <100 mg per dL cannot be achieved by therapeutic lifestyle changes, some authorities recommend use of LDL-lowering drugs in this category. Others prefer using drugs that primarily modify triglycerides and HDL (i.e., nicotinic acid or fibrate). Clinical judgment also may call for deferring drug therapy in this subcategory*

† People with zero to one risk factor almost always have a 10-year risk <10 percent; thus, 10-year risk assessment is not necessary in this group.

Source: NCEP-ATPIII

Studies have shown that LDL-C is closely related to CAD events. Virtually all large scale randomised trials of statins in both primary and secondary prevention have demonstrated clinical benefits on CAD, with a direct relationship between lower LDL cholesterol levels and reduced risk for major CAD events[19-21].

Once LDL cholesterol is at a target level, physicians are advised to address the metabolic syndrome and hypertriglyceridemia.

LDL cholesterol goals for the different risk categories is shown (Table 3). Several drugs have specific effects on lipoprotein metabolism. A list of the current classes of drugs and their associated lipid-altering effects is shown (Table 4).

Is HDL cholesterol important?

There is increasing evidence for the role of HDL cholesterol in predicting CAD events. The AFCAPS/TexCAPS study correlated a six percent increase in HDL cholesterol levels with a reduction of first acute major coronary events in men and women with baseline average LDL cholesterol levels and below-average HDL cholesterol levels[19].

Similarly, The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) also demonstrated the benefit of raising HDL levels[20]. In this study, HDL levels increased by six percent, triglyceride levels decreased by 31 percent, and coronary events decreased by 22 percent with gemfibrozil therapy, compared with placebo. Analyses of the data revealed a correlation between rising HDL levels and lower coronary event rates. This was not consistently true across the spectrum of baseline triglyceride levels, suggesting that HDL was the primary element responsible for the positive outcome.

Table 4: Characteristics of drugs affecting lipoprotein metabolism

Agents	Effects on LDL	Effects on HDL	Effects on triglycerides
Bile acid sequestrants	↓↓↓	↑/minimal	None
Fibric acids	↓	↑↑↑	↓↓↓↓
Nicotinic acid	↓↓	↑↑↑↑	↓↓↓
Statins	↓↓↓↓	↑↑	↓↓
Ezetimibe*	↓↓↓	↔	↔

** Ezetimibe is a novel, selective cholesterol absorption inhibitor.*

Hypertriglyceridaemia

The NCEP-ATP III recognises the increasing number of studies correlating elevated triglyceride levels with increased CAD risk. Diet and exercise are the primary modes of treating hypertriglyceridaemia. If indicated, nicotinic acid and fibric acid derivatives are the most efficacious in lowering triglyceride levels. Triglyceride reduction is a secondary benefit of statins (the primary benefit being LDL cholesterol reduction)(Table 5).

Metabolic syndrome

The NCEP-ATP III panel recognises the importance of metabolic syndrome (also known as syndrome X) as a secondary target of therapy after recommended LDL levels are achieved. Metabolic syndrome, or insulin resistance syndrome, is defined

Table 5: ATP III classification of triglyceride levels and treatment strategies

Classification	Serum level	Treatment strategy
Normal	<150 mg/dL (170 mmol/L)	None
Borderline-high	150 to 199 mg/dL (170 to 2.25 mmol/L)	Achieve target goal for LDL cholesterol; emphasize weight reduction and physical activity
High	200 to 499 mg/dL (2.26 to 5.64 mmol/L)	Achieve target goal for LDL cholesterol; institute weight reduction and physical activity; use drug therapy to achieve non- HDL goal*
Very high	>=500 mg/dL (5.65 mmol/L)	Primary goal is triglyceride lowering followed by LDL lowering†

** There are two approaches to drug therapy: (1) intensify therapy with LDL-lowering drug or (2) nicotinic acid or fibrate can be added. Non-HDL = LDL + VLDL. The non-HDL goal is 30 mg per dL higher than the LDL goal.*

† The approach to triglyceride lowering is a diet very low in fat (¾15 percent of calorie intake), weight reduction, increased physical activity and, usually, a triglyceride-lowering drug (fibrate or nicotinic acid).

Source: NCEP-ATPIII

as a cluster of abnormalities that include obesity, hypertension, dyslipidaemia, and type 2 diabetes; it is associated with insulin resistance and compensatory hyperinsulinemia[23].

In particular, insulin resistance has been found in persons with low levels of HDL cholesterol and high levels of very low-density lipoprotein (VLDL) cholesterol and triglycerides[24]. Because insulin resistance is often a precursor to the development of this syndrome, identification and potential treatment of insulin-resistant patients has been suggested as a means of preventing some or all components of the syndrome. However, measurement of fasting insulin levels is not standard practice at this time; criteria for normal and abnormal values have not yet been established.

The diagnosis of metabolic syndrome can be made when three or more of the risk determinants are present, as outlined in Table 6. These determinants can be measured readily in clinical practice. The treatment of metabolic syndrome is two-fold: (a) reduce the underlying causes (i.e. obesity and physical inactivity), and (b) treat the associated lipid and non-lipid risk factors.

Table 6: Clinical Diagnosis of Metabolic Syndrome

Risk factor	Defining level
Abdominal obesity (waist circumference)	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglyceride level	>=150 mg/dL (170 mmol/L)
HDL cholesterol	
Men	<40 mg/dL (1.05 mmol/L)
Women	<50 mg/dL (1.30 mmol/L)
Blood pressure	>=130/>=85 mm Hg
Fasting glucose	>=110 mg/dL

WHAT IS NEW IN THE GUIDELINES FOR TREATMENT OF HYPERCHOLESTEROLEMIA?

A 2004 update to the National Cholesterol Education Program's (NCEP) clinical practice guidelines on cholesterol management advises physicians to consider new, more intensive treatment options for people at high and moderately high risk for an MI[25]. These options include setting lower treatment goals for LDL cholesterol and initiating cholesterol-lowering drug therapy at lower LDL thresholds.

Major recommendations in the update include:

High and Very High Risk: For high-risk patients, the overall goal remains an LDL level of less than 100 mg/dL. But for people at very high risk, a group that is considered a "sub-set" of the high-risk category, the update offers a new therapeutic option of treating to under 70 mg/dL. For very high-risk patients whose LDL levels are already below 100 mg/dL, there is also an option to use drug therapy to reach the less than 70 mg/dL goal.

For the overall category of high-risk patients, the update lowers the threshold for drug therapy to an LDL of 100 mg/dL or higher and recommends drug therapy for those high-risk patients whose LDL is 100 to 129 mg/dL. In contrast, ATP III set the threshold for drug therapy for high-risk patients at an LDL of 130 mg/dL or higher, and made drug treatment optional for LDL 100 to 129 mg/dL.

The NCEP defines high-risk patients as those who have coronary heart disease or disease of the blood vessels to the brain or extremities, or diabetes, or multiple (2 or more) risk factors (e.g. smoking, hypertension) that give them a greater than 20 percent chance of having a heart attack within 10 years.

Very high-risk patients are those who have cardiovascular disease together with either multiple risk factors (especially diabetes), or severe and poorly controlled risk factors (e.g. continued smoking), or metabolic syndrome (a constellation of risk factors associated with obesity including high triglycerides and low HDL). Patients hospitalised for acute coronary syndromes such as heart attack are also at very high risk.

Moderately High-Risk: For moderately high-risk patients, the goal remains an LDL under 130 mg/dL, but the update provides a therapeutic option to set a lower LDL goal of under 100 mg/dL and to use drug therapy at LDL levels of 100-129 mg/dL to reach this lower goal. Moderately high-risk patients are those who have multiple (two or more) risk factors for coronary heart disease together with a 10 to 20 percent risk of heart attack within 10 years.

For high-risk or moderately high-risk patients, the report advises that the intensity of LDL-lowering drug therapy be sufficient to achieve at least a 30 to 40 percent reduction in LDL levels. This can be accomplished by taking statins or by combining lower doses of statins with other drugs (bile acid resins, nicotinic acid, or ezetimibe) or with food products containing plant stanol/sterols.

Lower/Moderate Risk: The update did not revise recommendations for lower risk persons: those with moderate risk (two or more risk factors plus an under 10 percent risk of a heart attack in 10 years) or those with zero to one risk factor. According to the report, the absolute benefits for people at the lower levels of risk are less clear cut and the recent clinical trials do not suggest a modification of treatment goals and cut points.

The report emphasises the importance of therapeutic lifestyle changes (TLC)(intensive use of nutrition, physical activity, and weight control) for cholesterol management. Lifestyle changes continue to be an essential part of controlling cholesterol. TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering. Like ATP III, the update addresses and emphasises cholesterol lowering in older persons (age 65 or above). High-risk older persons with established cardiovascular disease are included in the recommendations for intensive LDL-lowering therapy.

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LEARNING POINTS

- **Hypertension and hypercholesterolemia are two major modifiable CVD risk factors and should be considered as therapeutic targets for primary prevention of CVD in all adults. In spite of advances in drug therapy, therapeutic lifestyle changes remain the cornerstone of treatment for both conditions.**
- **Hypertension and hypercholesterolemia should not be regarded as isolated disease processes, but when either is present, should prompt a search for other potentially modifiable CVD risk factors, as part of a global CVD risk evaluation and management strategy.**
- **Recent updates in treatment guidelines have emphasised more aggressive treatment targets for patients with hypertension and hypercholesterolemia with high CAD risk levels (those with established CAD and CAD-risk equivalents).**