College of Family Physicians Singapore

The Singapore Family Physician

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Cardiometabolic Risk Update

With risk coming from multiple directions, add on a multi-dimensional lipid therapy.

TREDAPTIVE®† sends lipids in the right direction.

Significant improvements with 2 g/40 mg when added to a statin (P < 0.001)[1,a,b]

n=469
Placebo-adjusted values

TREDAPTIVE® (ER niacin/laropiprant, MSD) is indicated for the treatment of dyslipidemia, particularly in patients with combined mixed dyslipidemia (characterized by elevated levels of LDL-C and TG and low HDL-C) and in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial).

TREDAPTIVE should be used in patients in combination with HMG-CoA reductase inhibitors (statins), when the cholesterol lowering effect of statin monotherapy is inadequate. It can be used as monotherapy only in patients in whom statins are considered inappropriate or not tolerated. Diet or other non-pharmacological treatments (eg, exercise, eight reduction) should be continued during therapy with TREDAPTIVE.

SELECTED SAFETY INFORMATION

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients.
- Significant or unexplained hepatic dysfunction.
- Active peptic ulcer disease.
- Arterial bleeding.

PRECAUTIONS

Hepatic Effects: Switching from immediate-release (crystalline) niacin to TREDAPTIVE has not been studied. However, cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have switched from immediate-release niacin to sustained-release (modified-release, timed-release) niacin products at equivalent doses. Therefore, patients switching from immediate-release niacin to TREDAPTIVE should be initiated at the 1 g/20 mg dose.

TREDAPTIVE should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

Niacin products have been associated with abnormal liver function tests. Liver function tests are recommended before initiation, every 6 to 12 weeks for the first year, and periodically (eg, semi-annually) thereafter. Should an increase in ALT or AST of ≥ 3 X ULN persist, reduction of dose or withdrawal of TREDAPTIVE is recommended.

Effect on Skeletal Muscle: Rare cases of myopathy/rhabdomyolysis have been associated with concomitant administration of lipid-altering doses (≥1 g/day) of niacin and statins.

Physicians contemplating combined therapy with statins and TREDAPTIVE should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and when the dosage of either drug is increased. Periodic serum CK should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

In an ongoing, double-blind, randomized cardiovascular outcomes trial conducted in China, the United Kingdom and Scandinavia, an interim analysis by the independent safety monitoring committee revealed that the incidence of myopathy among approximately 4700 UK/Scandinavian patients treated with TREDAPTIVE 2 g/40 mg coadministered with either simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg is similar to the overall incidence of 0.08% reported in the prescribing information for simvastatin 40 mg. However, in approximately 3900 Chinese patients in the same treatment arm, the incidence is higher than expected (approximately 0.9%).

Because the incidence of myopathy is higher than expected in Chinese patients, caution should be used when treating Chinese patients with TREDAPTIVE coadministered with simvastatin or ezetimibe/simvastatin (particularly simvastatin doses of 40 mg or higher). Chinese patients should not received TREDAPTIVE with simvastatin 80 mg or ezetimibe/simvastatin 10/80 mg.

Niacin preparations have been associated with increases in fasting blood glucose levels. Diabetic or potentially diabetic patients should be observed closely. Adjustment of diet and/or hypoglycemic therapy may be necessary.

TREDAPTIVE should be used with caution in patients with renal dysfunction, acute coronary syndrome or with gout (or predisposed to gout). As with other niacin products, TREDAPTIVE was associated with a small reduction in platelet count in a clinical trial. Patients undergoing surgery should be carefully evaluated.

SIDE EFFECTS

In clinical trials, TREDAPTIVE is generally well tolerated. Adverse reactions have usually been mild and transient.

Cutaneous flushing (redness, warmth, itching, or tingling) is the most common side effect of TREDAPTIVE. In a pool of four active- or placebo-controlled clinical trials (N=4747, n=2548 taking TREDAPTIVE), flushing was reported by the investigator as a possibly, probably, or definitely drug-related adverse reaction in 12.3% of patients taking TREDAPTIVE

Other side effects reported in ≥1% of patients treated with TREDAPTIVE for up to one year (with or without a statin) include: diarrhea, dyspepsia, nausea, vomiting, feeling hot, dizziness, headache, paresthesia, erythema, pruritus, rash and urticaria.

An apparent hypersensitivity reaction has been reported (<1%) characterized by multiple symptoms that may include: angioedema, pruritus, erythema, paresthesia, loss of consciousness, vomiting, urticaria, flushing, dyspnea, nausea, incontinence of urine and stool, cold sweats, shivering, chills, increased blood pressure, lip swelling, burning sensation, drug eruption, arthralgia, leg swelling, and tachycardia.

In controlled clinical studies, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3X ULN, consecutive) and CK was 1.0% and 0.3%, respectively, for patients treated with TREDAPTIVE with or without a statin.

Please consult the full Prescribing Information enclosed before initiating therapy

Data from a study of TREDAPTIVE 2 g/40mg relative to placebo. The primary end point was safety and LDL-C percent change from baseline across weeks 12 to 24. Patients (N=1,613); mean age: 58 years) were randomized to TREDAPTIVE 1 g/20 mg (n=800), ER niacin 1 g (n=543) or placebo (n=270) for 4 weeks; patients then advanced directly to TREDAPTIVE 2 g/40 mg, ER niacin 2g and placebo, respectively, for a total treatment duration of 24 weeks.[1]

[a] Each tablet of TREDAPTIVE contains 1 g of extended-release niacin plus 20 mg of laropiprant, a novel flushing pathway inhibitor.[2]

[b] Patients received the following statins: atorvastatin (29%), simvastatin (54%), other statins (pravastatin, fluvastatin, rosuvastatin, lovastatin; 17%). Nine percent of statin patients were taking ezetimibe. Baseline values for the entire cohort were LDL-C, 113.5 mg/dL (2.9 mmol/L) (mean);HDL-C, 50.8 mg/dL (1.3 mmol/L) (mean) and TG, 127.0 mg/DL (1.4 mmol/L) (median).[1]

[c] Mean percent change from statin-treated baseline.

[d] Mean percent change from statin-treated baseline.

References: 1. Maccubbin D, Bayes HE, Olsson AG, et al. Lipid-modifying efficacy and tolerability of extended-release niacin/laropiprant in patients with primary hypercholesterolaemia or mixed dyslipidaemia. Int J Clin Pract. 2008;62:1959-1970. 2. Local Product Circular.

Tredaptive®
(ER niacin/laropiprant, MSD) tablets
Multidimensional Lipid Therapy

MSD
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150 Beach Road, #31-00 Gateway West, Singapore (189720)
Tel: 6508 8400 Fax: 6296 0005

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MANAGEMENT OF METABOLIC SYNDROME

Adj Asst Prof (Dr) Tan Ngiap Chuan

SFP2011; 37(4) (Supp 2): 3

In Singapore, the prevalence of obesity and type 2 diabetes mellitus (T2DM) have risen to 10.8% and 11.6% respectively in 2010. This steep increase in these metabolic disorders contribute to atherosclerosis and end-organ complications such as coronary heart disease, stroke and peripheral vascular disease. Increasingly these chronic and complex patients will be managed by primary care physicians, as continuity of care for them is vital to ensure good outcomes.

This issue of SFP provides an insight and update on new developments in areas of therapeutics and surgery. In treating dyslipidemia, Niacin in extended formulations and in combination with prostaglandin D2 receptor antagonist (Laropiprant) are available to reduce its side-effects. CETP inhibitors are new class of drugs for raising HDL-cholesterol, which show promise when used with simvastatin.

Recent studies have thrown more light on the role of dual renin-angiotensin-aldosterone system (RAAS) blockade, the effect of ARB on the development of T2DM and the efficiency of the single pill combination drugs in anti-hypertensive treatment.

Incretin mimetics and DPP-4 are now added to our armamentarium to combat T2DM. Incretin-based therapy has been introduced into the treatment algorithms in European and American guidelines. With lesson learnt from the previous use of rosiglitazone, we have to watch the safety data of these new drugs diligently.

Metabolic surgery is an increasingly popular treatment option, targeting at those patients with both obesity (BMI_> 32.5 kg/m^2) and metabolic disorders. This bariatric surgery includes both restrictive and by-pass type of procedures. Notwithstanding the remarkable effects of metabolic surgery on T2DM, hypertension, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnoea and even on cancer and mortality, they are invasive, life-changing procedure with known risks and complications. Patients should be informed about the restriction on eating ability and their commitment to regular reviews and surveillance for nutritional deficiencies.

Primary care physicians (PCP) should interpret the data from these recent clinical trials carefully, inform their patients of the options available locally and offer to share what is known about the advantages of these new treatments and their potential adverse effects and complications. It is important for PCP to negotiate with patients on mutually agreed goals of treatment, so as to treat these diseases to evidence-based targets. Only with such productive interactions between the prepared and proactive PCP and the informed activated patients, that we expect the outcomes of managing these metabolic disorders to be favorable. With that, we are confident that PCP in Singapore will be capable of delivering effective chronic care to these patients at risk and trim the burden of these diseases.

TAN NGIAP CHUAN, Honorary Editor, Singapore Family Physician

Distance Learning Course on "Cardiometabolic Risk Update"

- Overview of "Cardiometabolic Risk Update"
- Unit 1 : Cardiometabolic Risk Update – A 2011 Perspective
- Unit 2 : Rationale for Combination Therapy in Lipid Management Strategy
- Unit 3 : Treating Dyslipidemia in the High-risk Group Patients- Current Management and Future Approach
- Unit 4 : How Do Incretin-Based Therapies Fit Into the Treatment Algorithm?
- Unit 5 : Metabolic Surgery: A New Approach in the Treatment of Metabolic Disease of the 21st Century
- Unit 6 : Rethinking the Strategies in Hypertension Management

OVERVIEW OF "CARDIOMETABOLIC RISK UPDATE" FAMILY PRACTICE SKILLS COURSE

A/Prof Goh Lee Gan

SFP2011: 37(4) (Supp 2): 5-6

INTRODUCTION

The rising prevalence of cardiometabolic diseases is a worldwide problem, including Singapore. The educational aim of this Family Practice Skills Course is to update primary care physicians on the identification, risk stratification and effective management of its continuum of risks so that the cardiometabolic endpoints of cardiovascular diseases and diabetes can be effectively controlled, treated and complications prevented. The College thanks Merck Sharp & Dohme (I.A.) Corp. (Singapore Branch) for sponsoring this Family Practice Skills Course.

COURSE OUTLINE AND CME POINTS

This Family Practice Skills Course is made up of the following components. You can choose to participate in one or more parts of it. The CME points that will be awarded are also indicated below.

Components and CME Points

- Distance Learning Course – 6 units (6 Core FM CME points upon attaining a minimum pass grade of 60% in Distance Learning Online MCQ Assessment).
- 2 Seminars (2 Core FM CME points per seminar).
- 2 Workshops (1 Core FM CME point per workshop).
- 10 Readings – read 5 out of 10 recommended journals (maximum of 5 CME points for the whole CME year).

Distance Learning Course

Unit 1: Cardiometabolic Risk Update – A 2011 Perspective
A/Prof Goh Lee Gan

Unit 2 : Rationale for Combination Therapy in Lipid Management Strategy
Dr Raymond Lee

Unit 3 : Treating Dyslipidemia in the High-risk Group Patients- Current Management and Future Approach
Dr Yong Quek Wei

Unit 4 : How Do Incretin-Based Therapies Fit Into the Treatment Algorithm?
Dr Chia Su-Ynn

Unit 5 : Metabolic Surgery: A New Approach in the Treatment of Metabolic Disease of the 21st Century
Dr Tham Kwang Wei, Dr Daniel Wai Chun Hang, Dr Alvin Eng Hock Kim, Dr Shanker Pasupathy

Unit 6 : Rethinking the Strategies in Hypertension Management
Dr Akira Wu

COURSE TOPIC DETAILS

Unit 1: Cardiometabolic Risk Update – A 2011 Perspective

- Introduction
- Cardiometabolic Risk, metabolic syndrome and risk stratification
- Pathophysiology of cardiometabolic risk
- Epidemiology of cardiometabolic risk in populations & population subgroups
- Interventions to reduce cardiometabolic risk
- Conclusions

Unit 2: Rationale for Combination Therapy in Lipid Management Strategy

- Introduction
- Prevalence of mixed dyslipidemia
- Residual cardiovascular risk
- Fibrates
- Niacin
- CETP inhibitors
- Prescription omega-3 fatty acid

Unit 3: Treating Dyslipidemia in the High-risk Group Patients- Current Management and Future Approach

- Introduction
- Reduction of LDL-Cholesterol Levels
- Non-HDL-Cholesterol as secondary target of therapy
- Raising HDL-Cholesterol Levels
- Combination therapies

Unit 4: How Do Incretin-Based Therapies Fit Into the Treatment Algorithm?

- What are "incretins" and what is their relevance to diabetes?
- What is incretin-based therapy?
- What are the potential advantages of incretin-based therapy?
- What are the potential disadvantages of incretin-based therapy?
- How does incretin-based therapy fit into the current treatment algorithms?

GOH LEE GAN, Associate Professor, Division of Family Medicine, University Medicine Cluster, National University Health System
Senior Consultant, Institute of Family Medicine, College of Family Physicians Singapore

Unit 5: Metabolic Surgery: A New Approach in the Treatment of Metabolic Disease of the 21st Century

- Introduction
- Types of interventions
- Metabolic effects of metabolic surgery (MBS)
- Effect of MBS on Type 2 Diabetes Mellitus
- Effect of MBS on hypertension
- Effect of MBS on lipids
- Effect of MBS on Non-Alcoholic Fatty Liver Disease (NAFLD)
- Effect of MBS on Obstructive Sleep Apnoea (OSA)
- Effect of MBS on cancer
- Mortality outcomes
- Indications for metabolic surgery

Unit 6: Rethinking the Strategies in Hypertension Management

- Introduction
- Etiologic consideration
- Pre-hypertension
- New challenges in blood pressure goals
- Dual RAAS blockade
- Hypertension and new-onset diabetes
- Single pill combinations

FACE-TO-FACE SESSIONS

Seminar 1: 22 October 2011
2.00pm – 4.15pm

Unit 1 : Cardiometabolic Risk Update – A 2011 Perspective
A/Prof Goh Lee Gan

Unit 2 : Rationale for Combination Therapy in Lipid Management Strategy
Dr Raymond Lee

Unit 3 : Treating Dyslipidemia in the High-risk Group Patients-Current Management and Future Approach
Dr Yong Quek Wei

Workshop 1: 22 October 2011
4.30pm – 5.45pm

Screening & Risk Assessment for Cardiometabolic Patients
Dr Yong Quek Wei

Seminar 2: 23 October 2011
2.00pm – 4.15pm

Unit 4 : How Do Incretin-Based Therapies Fit Into the Treatment Algorithm?
Dr Chia Su-Ynn

Unit 5 : Metabolic Surgery: A New Approach in the Treatment of Metabolic Disease of the 21st Century
Dr Tham Kwang Wei

Unit 6 : Rethinking the Strategies in Hypertension Management
Dr Akira Wu

Workshop 2: 23 October 2011
4.30pm – 5.45pm

Managing the Obese and Other Problems
Ms Teo Soo Lay

THE DPP-4* INHIBITOR AVAILABLE IN OVER
86 COUNTRIES

POWERFUL RESULTS. PROVEN EXPERIENCE.

Janumet
(sitagliptin/metformin, MSD)

Once daily
Januvia
(sitagliptin, MSD)

For patients with type-2 diabetes mellitus:

JANUMET is indicated as initial therapy in adult patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise do not provide adequate glycemic control. JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin. JANUMET is also indicated in combination with a sulfonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus inadequately controlled with any two of the three agents: metformin, sitagliptin, or a sulfonylurea. JANUMET is indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in patients when insulin and metformin alone do not provide adequate glycemic control.

JANUVIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus as initial therapy, alone or in combination with metformin. JANUVIA is indicated in combination with metformin, sulfonylurea, PPARγ agonist, metformin and a sulfonylurea when the current regimen, with diet and exercise does not provide adequate glycemic control. JANUVIA is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycemic control.

Before initiating therapy, please consult the locally approved full Prescribing Information.

MSD DIABETES

*DPP-4 = dipeptidyl peptidase-4.

**JANUVIA and JANUMET are indicated for triple therapy in type 2 diabetes mellitus.

UNIT NO. 1

CARDIOMETABOLIC RISK UPDATE – A 2011 PERSPECTIVE

A/Prof Goh Lee Gan

ABSTRACT

The rising prevalence of cardiometabolic diseases is a worldwide problem, including Singapore. In 2010, the prevalence of obesity and type 2 diabetes mellitus (T2DM) had risen to 10.8% and 11.6% respectively. In 2009, of the 17,101 deaths (100%), ischaemic heart disease, cerebrovascular disease, and diabetes mellitus contributed respectively 19.2%, 8%, and 1.7% - making a total of 28.9% from cardiometabolic deaths. Cardiometabolic risk may be defined as a continuum of risks ranging from behaviour related factors, on to high risk diseases of the deadly quartet (hypertension, diabetes, hyperlipidemia, and obesity), and cardiovascular and metabolic endpoints. The pathophysicolgical basis of cardiometabolic risk is complex. The mechanisms responsible for the cardiometabolic syndrome are not entirely known, but it is likely that multi-organ insulin resistance, which is a common feature of the cardiometabolic syndrome, is involved. Low grade inflammation and dysfunction of high-density lipoprotein and its apolipoproteins are main drivers of cardiometabolic risk. Population studies in China and India provide insights on the development of cardiometabolic disease. PCOS, erectile dysfunction, antipsychotic medications related weight gain need to be addressed too as cardiometabolic problems. Interventions to reduce cardiometabolic risk include: health behaviour modification, pharmacological and surgical interventions, and avoidance of over-consumption of fructose sweetened beverages.

Keywords: Cardiometabolic risk; Metabolic syndrome; Risk stratification; Global risk assessment; Multi-organ insulin resistance; Health behaviour modification; Surgical intervention; Pharmacological intervention; Fructose; Erectile dysfunction; PCOS

SFP2011; 37(4) (Supp 2): 8-12

INTRODUCTION

The rising prevalence of cardiometabolic diseases is a worldwide problem, including Singapore. In 2010, the prevalence of obesity and type 2 diabetes mellitus (T2DM) had risen to 10.8% and 11.6% respectively. In 2009, of the 17,101 deaths (100%), ischaemic heart disease, cerebrovascular disease, and diabetes mellitus contributed respectively 19.2%, 8%, and 1.7% - making a total of 28.9% from cardiometabolic deaths.

A PUBMED search using the keywords of "cardiometabolic disease" for review papers published in the last 3 years were shortlisted and reviewed for information on concepts, identification, and management of cardiometabolic risk.

GOH LEE GAN, Associate Professor, Division of Family Medicine, University Medicine Cluster, National University Health System, Senior Consultant, Institute of Family Medicine, College of Family Physicians Singapore

CARDIOMETABOLIC RISK, METABOLIC SYNDROME AND RISK STRATIFICATION

Definition

Cardiometabolic risk may be defined as a continuum of risks ranging from behaviour related factors, on to high risk diseases of the deadly quartet (hypertension, diabetes, hyperlipidemia, and obesity), and cardiovascular and metabolic endpoints[2].

Overlapping concepts

The concepts of "cardiometabolic risk" and "metabolic syndrome" and the process of "risk stratification" overlap, and all relate to the atherogenic process and development of type 2 diabetes, an important cardiovascular (CV) risk factor. This situation has led to confusion as to what these terms and concepts really mean and how they can best be used to improve our understanding of cardiovascular disease (CVD) treatment and prevention [1].

The following are proposals offered by a national workgroup on cardiometabolic risks in Canada [1, 2]:

- The term "cardiometabolic risk" or "global cardiometabolic risk" be considered to represent the comprehensive catalogue of factors that contribute to the development of both CVD and type 2 diabetes. Each of these factors increases the risk of CV mortality and mortality to some extent, but the term "global cardiometabolic risk" is mainly intended to encourage consideration of factors that go beyond the set of traditional risk factors and that include new or emerging risk factors. The term is intended to be used to catalogue the sources of risk, but not to quantify risk in either absolute or relative terms.

- The term "metabolic syndrome" be considered to represent a specific subset of "cardiometabolic risks" that, when clustered together, impart a relative increase in risk of CVD and development of type 2 diabetes. Metabolic syndrome has been shown to increase overall lifetime CVD risk by about 1.5 – 2-fold [3, 4].

- The term "risk assessment" or "global risk assessment" be

used to describe a process that mathematically weighs the presence or absence of risk factors, as well as their severity, to calculate an absolute CV risk by using validated algorithms derived from long-term observational studies in large patient cohorts.

Cardiometabolic risk screening [1]

The goal of cardiometabolic risk screening is to develop, through identification of the significant traditional and nontraditional risk factors, a comprehensive understanding of a patient's risk for cardiometabolic events, thereby enabling appropriate individual preventive measures to be taken. Information to be collected should include the items listed in Figure 1.

Such an assessment should be taken:

- When any traditional CV risk factor (e.g., hypertension, or dyslipidemia) is first identified, or

- In patients who are overweight or obese (especially if abdominally obese).

Calculation of absolute cardiometabolic risk

The calculation of absolute cardiometabolic risk is done by means of a validated algorithm such as Framingham Risk score, followed by appraisal for the presence or absence of "metabolic syndrome", may help identify patients whose risk might be underestimated through sole consideration of traditional risk factors and who might warrant more comprehensive or intensive intervention, including prompt initiation of health behaviour changes. The Singapore version of the Framingham Risk Score and its use in this context is described in the MOH Clinical Practice Guidelines 1/2011 (March 2011) [5].

PATHOPHYSIOLOGY OF CARDIOMETABOLIC RISK

The pathophysicolgical basis of cardiometabolic risk is complex. The mechanisms responsible for the cardiometabolic syndrome is not entirely known, but it is likely that multi-organ insulin resistance, which is a common feature of the cardiometabolic syndrome, is involved [5, 6].

Alterations in free fatty acid metabolism: These are likely to be a major factor involved in the pathogenesis of hyperglycemia and dyslipidemia associated with the cardiometabolic syndrome. Excessive release of free fatty acids from adipose tissue into plasma and increased plasma free fatty acid concentration can impair the ability of insulin to stimulate muscle glucose uptake and suppress glucose production.

In addition, increased free fatty acid delivery to the liver can increase hepatic very low-density lipoprotein triglyceride production and plasma triglyceride concentration. An increase in plasma triglycerides increases the transfer of triglycerides from very low-density protein to high-density protein lipoprotein clearance and decreased plasma high-density lipoprotein concentration

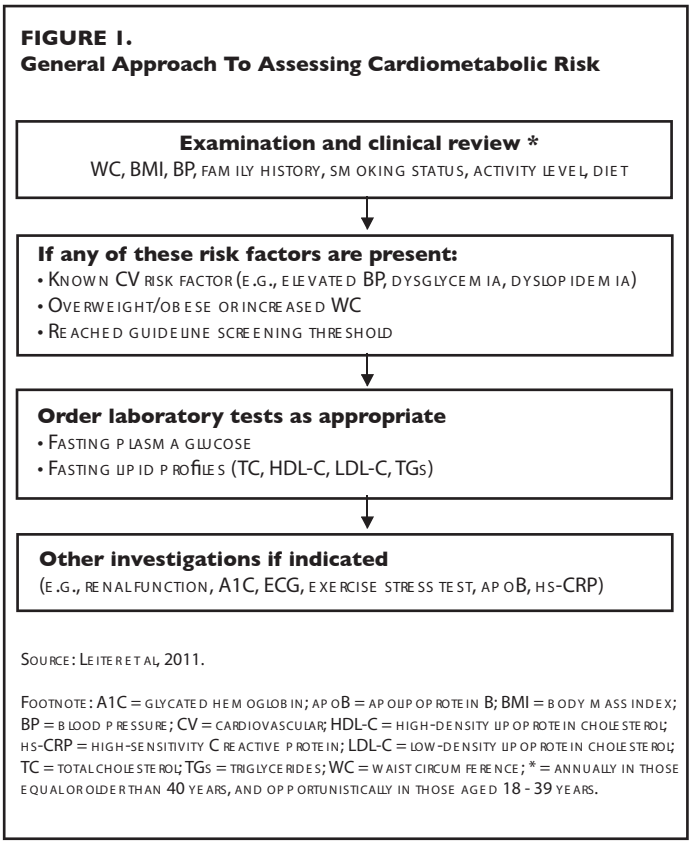
Abdominal adipose tissue: Excess abdominal fat mass, particularly visceral (intraperitoneal) fat, is associated with insulin resistance. It has been hypothesised that fatty acids released during lipolysis of visceral adipose tissue are an important cause of insulin resistance because these fatty acids enter the portal vein and are delivered directly to the liver [5].

Ectopic fat: Ectopic accumulation of fat in liver and muscle cells is associated with insulin resistance in those tissues.

Increased blood pressure: The relationship between insulin resistance and hypertension is well established [7, 5]. Fatty acids themselves can cause vasoconstriction. Additionally, insulin resistance can increase blood pressure because insulin is a vasodilator, and hyperinsulinemia increases renal sodium reabsorption. Persons who are insulin-resistant tend to lose the vasodilatory effect of insulin but preserve the renal effect on sodium reabsorption, and sodium reabsorption is increased in persons with cardiometabolic syndrome.

Low grade inflammation and dysfunction of high-density lipoprotein and its apolipoproteins are major drivers of cardiometabolic risk: Dysfunction of high density lipoprotein (HDL) particles that even become proinflammatory or lose atheroprotective properties is closely linked to obesity. The great impact in public health of the dysfunction of protective serum proteins requires individual clinical recognition, appropriate preventive measures, and delineation of management, including with anti-inflammatory drugs [8].

FIGURE 1.
General Approach To Assessing Cardiometabolic Risk



Source: Leiter et al, 2011.

Footnote: A1C = glycated hemoglobin; apoB = apolipoprotein B; BMI = body mass index; BP = blood pressure; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C reactive protein; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TGs = triglycerides; WC = waist circumference; * = annually in those equal or older than 40 years, and opportunistically in those aged 18 - 39 years.

Exposure to suboptimal nutrition during critical periods of development: Evidence from both epidemiological and experimental animal studies now demonstrates that metabolic syndrome onset is increasingly likely following exposure to suboptimal nutrition during critical periods of development, as observed in maternal obesity. Thus, the developmental priming of the metabolic syndrome provides a common origin for this multifactorial disorder [9, 10].

Moving beyond weight loss in nonalcholic fatty liver disease (NAFLD): Epidemiologic data now show an independent relationship between liver fat, physical activity, and fitness, and a growing body of longitudinal research demonstrates that increased physical activity participation per se significantly reduces hepatic steatosis and serum aminotransferases in individuals with NAFLD, independent of weight loss [11].

EPIDEMIOLOGY OF CARDIOMETABOLIC RISK IN POPULATIONS & POPULATION SUBGROUPS

Insights from population studies

Several population studies have highlighted the rising prevalence of cardiometabolic risks and a study of the developments in these countries will be useful in a better understanding of the population control measures necessary.

China: A study from China highlights the rising incidence of cardiovascular diseae fueled by an epidemic of cardiometabolic risk factors. While hypertension and smoking have received considerable spotlight, little attention has been given to obesity, diabetes, and metabolic syndrome [14].

India: The prevalence of obesity and the metabolic syndrome is rapidly increasing in India and other south Asian countries, leading to increased morbidity and mortality due to type 2 diabetes and cardiovascular disease. The main drivers are rapid nutrition, lifestyle, and socioeconomic transitions, consequent to increasing affluence, urbanisation, mechanisation, and rural to urban migration. Less investigated determinants of the metabolic syndrome include psychological stress in urban setting, genetic predisposition, adverse perinatal environment, and childhood "catch up" obesity [15].

Women and polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is of clinical and public health importance as it is very common, affecting up to one in five women of reproductive age. It has significant and diverse clinical implications including reproductive (infertility, hyperandrogenism, hirsutism), metabolic (insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, adverse cardiovascular risk profiles) and psychological features (increased anxiety, depression and worsened quality of life). Polycystic ovary syndrome is a heterogeneous condition and, as such, clinical and research agendas are broad and involve many disciplines [16].

Metformin has been introduced as a therapeutic option in PCOS, targeting of cardiometabolic and reproductive abnormalities on the basis of its action on the reduction of glucose levels and the attenuation of insulin resistance. The use of metformin in pregnant women with PCOS is another of its positive features. Overall, available data supports the therapeutic usefulness of metformin on cardiometabolic risk and reproduction assistance in PCOS women [17].

Modest weight loss of 5% to 10% of initial body weight has been demonstrated to improve many of the features of PCOS. Management should focus on support, education, addressing psychological factors and strongly emphasising healthy lifestyle with targeted medical therapy as required. Monitoring and management of long-term metabolic complications is also an important part of routine clinical care [16].

Men and Erectile dysfunction

Erectile dysfunction (ED) is a marker of increased cardiovascular (CVS) risk. In younger men with ED, the Framingham risk assessment has inadequate sensitivity. There is a need to develop a more sensitive risk-stratification protocol for this population. The presence of ED should prompt assessment of cardiac risk and aggressive risk factor treatment. Available risk assessment factors should initially be used to stratify each patient. ED patients younger than 60 years of age and with no clinical CVD are at risk of CAD events (>10%) and should undergo further risk assessment. Additional tests of arterial damage and biomarkers may aid in refinement of risk for future cardiac events [18].

Mental health patients and related weight gain from antipsychotic medications

Antipsychotic-related weight gain and metabolic effects are a critical outcome for patients requiring these medications. Across 32 studies including 1482 subjects, 15 different medications were tested and compared with placebo. Metformin was found to have the greatest weight loss {N=7, n=334, -2.94 kg [confidence interval (CI: -4.89, -0.99)]} [19].

INTERVENTIONS TO REDUCE CARDIOMETABOLIC RISK

Health behaviour modification

Health behaviour modification is recommended as the primary treatment strategy for the management of cardiometabolic risk and should include simultaneous counselling regarding physical activity, smoking cessation, caloric intake, and diet composition, as these are associated with improvements on all cardiometabolic risk factors [3].

The magnitude of improvement in these variables appears to

be dependent on baseline values, with greater improvements reported among those with the greatest disturbances. Improvements in cardiometabolic risk factors tend to be more pronounced when a modest reduction in body weight is achieved, significant improvements are also observed even in the absence of significant weight change. Moderate-intensity exercise for 30 to 60 minutes on most days of the week, together with a moderate reduction in caloric intake (500 kcal/day), can result in significant reductions in cardiometabolic risk. The long-term benefit of health behaviour interventions requires sustained efforts in compliance and adherence.

Pharmacologic and surgical interventions

While health behaviour interventions are the primary strategy to reduce cardiometabolic risk, adjunctive pharmacologic therapy or surgery may be required. The majority of pharmacologic interventions to reduce cardiometabolic risk also apply to the patient with diabetes, since most patients with diabetes have increased cardiometabolic risk.

Weight loss: For patients with a BMI ≥ 30 kg/m^2, or those with a BMI ≥ 27 kg/m^2 plus CV risk factors and/or impaired glucose tolerance (IGT), guidelines recommend that weight-loss medications can be considered if weight loss is <0.5 kg (1 lb) per week after health behaviour changes have been attempted for 3 to 6 months. There are currently no data to show that weight reduction induced by medications results in improved clinical outcomes.

Bariatric surgery has been shown to lower all-cause mortality by 24% to 40% because of a reduction in deaths from myocardial infarction (MI), diabetes, and cancer, as well as prevention of the development of diabetes in patients with severe obesity. Currently, bariatric surgery can be considered in Caucasians with BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 plus comorbid conditions, in whom efforts at medical therapy have failed and who have an acceptable operative risk. The corresponding BMI cut-offs for Asians will be 37.5 and 32.5 to 37.4 respectively [3].

Obesity in DM: Obesity is a well known risk factor for type 2 diabetes mellitus. Individuals with type 2 diabetes mellitus are at risk for weight gain as a result of multiple influences, including sedentary lifestyle, high-calorie diet, diabetes medications, sociocultural factors, chronic medical and psychiatric illnesses, and a dysregulated enteroendocrine axis. Because both diabetes mellitus and obesity predispose patients to abnormal cardiometabolic profiles and increased cardiovascular disease, management of diabetes mellitus should focus on weight management and optimising cardiometabolic parameters, concomitant with glycemic control. Lifestyle modification incorporating healthy, calorie-appropriate diets and increased physical activity, in addition to metformin, are central components to diabetes management and weight management. These interventions have been shown to improve body weight, glycemic control, and overall cardiometabolic profile. The weight-neutral and weight-losing diabetes medications include metformin, alpha-glucosidase inhibitors, glucagon-like peptide-1 analogs, dipeptidyl peptidase-4 inhibitors, and amylin analogs. It is essential that providers understand the metabolic and weight effects of diabetes medications in order to develop strategies for managing diabetes mellitus while helping patients maintain or lose weight in order to improve their overall health outcomes [20].

Optimise BP: Clinical trials have not specifically evaluated BP lowering in individuals solely with cardiometabolic risk. However, in patients with cardiometabolic risk associated with dysglycemia, it may be advisable to use agents that may be associated with improvement of glucose metabolism [ie, renin-angiotensin-aldosterone system (RAAS) inhibitors] or antihypertensive drugs that are metabolically neutral [ie, calcium channel blockers (CCBs)] [3].

Optimise lipid levels: In patients with cardiometabolic risk with a moderate or high Framingham Risk Score, treatment should be initiated with a statin to reduce low-density lipoprotein cholesterol (LDL-C) by at least 50% and to <2.0 mmol/L. Apo B levels are a better measurement of lipid-related risk in these patients, and the target level for treatment is <0.8 g/L in high-risk and moderate-risk individuals. There is a large residual risk for patients at high risk for CVD and these should be treated [3].

Optimise blood glucose levels, prevent progression to diabetes, and manage hyperglycemia: While health behaviour modification, with weight loss and increased physical activity, is the most effective, pharmacotherapy can also be considered to prevent progression to type 2 diabetes [3].

Consumption of fructose sweetened beverages: Such has increased steadily over the past century and with this increase has come more and more reports associating their use with the risk of overweight, diabetes and cardiometabolic disease. In a meta-analysis of the relationship between soft drink consumption and cardiometabolic risk, there was a 24% overall increased risk comparing the top and bottom quantiles of consumption. Several factors might account for this increased risk, including increased carbohydrate load and increased amounts of dietary fructose. Fructose acutely increases thermogenesis, triglycerides and lipogenesis as well as blood pressure [21].

CONCLUSIONS

- "Global cardiometabolic risk" is an umbrella term for a comprehensive list of existing and emerging factors that predict CVD and/ or type 2 diabetes.
- A risk stratification approach ensures that a best approach is taken to reduce cardiometabolic disease.

- Interventions to reduce cardiometabolic risk can take place simultaneously at the levels of health behaviour modification, interventions directed at weight control, blood pressure control, blood sugar control, as well as management of CVD and metabolic endpoints.

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LEARNING POINTS

- **Cardiometabolic risk may be defined as a continuum of risks ranging from behaviour related factors, on to high risk diseases of the deadly quartet (hypertension, diabetes, hyperlipidemia and obesity) and cardiovascular and metabolic endpoints.**
- **The mechanisms responsible for the cardiometabolic syndrome is not entirely known, but it is likely that multi-organ insulin resistance, which is a common feature of the cardiometabolic syndrome, is involved.**
- **Low grade inflammation and dysfunction of high-density lipoprotein and its apolipoproteins are main drivers of cardiometabolic risk.**
- **PCOS, erectile dysfunction, antipsychotic medications related weight gain need to addressed too as cardiometabolic problems.**
- **Interventions to reduce cardiometabolic risk includes: health behaviour modification, pharmacological and surgical interventions and avoidance of over-consumption of fructose sweetened beverages.**

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ARCOXIA is contraindicated in patients with the following:

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- Established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease (including patients who have recently undergone coronary artery bypass graft surgery or angioplasty)
- Hypertension whose blood pressure has not been adequately controlled
- Active peptic ulceration or gastro-intestinal (GI) bleeding
- Severe hepatic dysfunction (Child-Pugh score >9)
- Estimated creatinine clearance <30 ml/min
- Developed signs of asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria following the administration of acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs)
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PRECAUTIONS

Cardiovascular effects

- Selective COX-2 inhibitors may be associated with an increased risk of thrombotic events (Especially myocardial infarction and stroke), relative to placebo and some NSAIDs (naproxen). As the cardiovascular risks of selective COX-2 inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used.

Fluid retention, oedema and hypertension

- Fluid retention, edema, and hypertension have been observed in patients taking ARCOXIA. ARCOXIA may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Special attention should be paid to blood pressure monitoring during treatment with ARCOXIA. If blood pressure rises significantly, alternative treatment should be considered.

Renal effects

- In patients with advanced renal disease, treatment with ARCOXIA is not recommended. If therapy with ARCOXIA must be initiated in such patients, close monitoring of the patient's renal function is advisable.

General

- Medically appropriate supervision should be maintained when using ARCOXIA in the elderly and in patients with renal, hepatic, or cardiac dysfunction.
- Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving ARCOXIA.

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In clinical studies the following undesirable effects were reported at an incidence greater than placebo in patients with OA, RA, chronic low back pain or ankylosing spondylitis treated with ARCOXIA 30mg, 60 mg or 90 mg for up to 12 weeks or in the MEDAL Program studies: Oedema, fluid retention, dizziness, headache, hypertension, gastro-intestinal disorders (e.g. abdominal pain, flatulence, heartburn), diarrhoea, dyspepsia, epigastric discomfort, nausea, asthenia/fatigue, flu-like disease, increased ALT, and increased AST.

Rare but serious side effects reported from clinical trials and post-marketing experience include: hypersensitivity and anaphylactic reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, myocardial infarction, cerebrovascular accident, hypertensive crisis, congestive heart failure, and gastro-intestinal perforation and bleeding.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; RA = rheumatoid arthritis.

Please see the Prescribing Information, including contraindications and precautions, before prescribing ARCOXIA.

[a]Study Summary: A randomized, double-blind, placebo- and active-comparator-controlled, parallel-group, dose-ranging trial enrolled 398 men and women 16 years of age and older with moderate-to-severe pain following extraction of 2 or more third molars, at least one of which was partially embedded in mandibular bone. Treatment consisted of ARCOXIA 60 mg (n=75), 120 mg (n=76), 180 mg (n=74), and 240 mg (n=76) once daily, ibuprofen 400 mg once daily (n=48), or placebo (n=49). Using a dairy card, patients reported pain intensity and pain relief for 24 hours after dosing. Onset of analgesia was determined with 2 patient-controlled stopwatches; the first stopwatch was stopped when patient achieved perceptible pain relief, and the second was stopped when patient achieved meaningful pain relief. The primary end point was total pain relief over 8 hours. Onset of analgesia occurred as early as 24 minutes after dosing in at least 50% of patients taking ARCOXIA 120 mg. Analgesia persisted as long as 24 hours after dosing in 72% of patients taking ARCOXIA 120 mg.

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UNIT NO. 2

RATIONALE FOR COMBINATION THERAPY IN LIPID MANAGEMENT STRATEGY

Dr Raymond Lee

ABSTRACT

Due to the increasing prevalence of obesity and Type II diabetes mellitus (DM), mixed dyslipidemia characterised by high triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C) and small dense low-density lipoprotein cholesterol (LDL-C) particles is becoming increasingly common [1].

The primary goal of lipid treatment is to reduce LDL-C to target levels. However, residual cardiovascular risk remains even after achievement LDL-C goal in high risk patients on statin treatment.

This residual risk may be due in part to persistently low HDL-C and high TG. Combination therapy of statins with fibrates, niacin or prescription omega-3 fatty acids may reduce this risk.

Keywords: Dyslipidemia; Combination Therapy; Residual cardiovascular risk

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INTRODUCTION

Mixed dyslipidemia (atherogenic dyslipidemia) characterised by high TG, low HDL-C and small dense LDL-C particles is the most common dyslipidemia in metabolic syndrome and Type II DM. ATP III recognises low HDL-C as a major risk factor and elevated TG and small dense LDL-C as emerging risk factors for cardiovascular disease (CVD) [2].

Patients with mixed dyslipidemia are at higher risk for CVD. In a post-hoc analysis of the 4S trial[3], patients in the lowest HDL-C (< 39mg/dL) and highest TG (> 159mg/dL) quartiles had the highest incidence of CVD in the placebo group and these patients had the largest benefit when treated with statin compared to the general 4S population. It is therefore important to consider additional therapies to reduce the CVD risk associated with mixed dyslipidemia.

PREVALENCE OF MIXED DYSLIPIDEMIA

With the adoption of Western lifestyles and increasing affluence, the twin global pandemics of obesity and Type II DM are on the rise in Asia. In Singapore, the prevalence of DM is about 9% [4]. Almost 50% of all adults in Singapore have a BMI above 23 kg/m^2 and 14% have a BMI of more than 27.5kg/m^2 [5]. Consequently, mixed dyslipidemia is fast becoming the predominant lipid abnormality in our population.

RESIDUAL CARDIOVASCULAR RISK

Statins have been shown to reduce CVD mortality in both primary and secondary prevention, mainly by lowering LDL-C [6, 7]. However, significant residual cardiovascular risk remains. In a meta-analysis by Baigent et al, 14.1% of patients treated with a statin, had further or recurrent CVD events over a 5-year period, and this risk was even higher in patients with established coronary artery disease (CAD) or CAD risk equivalents, such as DM [8].

Hence, there is a need for additional treatment of mixed dyslipidemia in high risk patients already on statins at target LDL-C. Lifestyle modification which includes interventions aimed at weight loss through diet and exercise, followed by weight maintenance that employs low saturated fat intake remains the cornerstone of management [9]. In high risk patients, adjunctive pharmacotherapy with fibrates, niacin or prescription omega-3 fatty acids may be beneficial.

While there are clearly defined targets for LDL-C (< 100mg/dL for high risk and < 70mg/dL for very high risk) 10, no specific targets for HDL- C and TG have been determined in clinical trials. The following have been suggested as desirable therapeutic targets: HDL-C > 40mg/dL (men) and > 50mg/dL (women) and TG < 150mg/dL.

FIBRATES

Fibrates are peroxisome proliferator-activated receptor (PPAR) alpha agonists. PPAR alpha is a nuclear transcription factor which binds to retinoid X receptor (RXR) to modulate gene expression that influences fatty acid oxidation, lipid metabolism and inflammation[11]. Fenofibrate and gemfibrozil decreases TG's by 20 to 30% and increases HDL-C by 5 to 10%, depending on baseline levels [12, 13].

In the Helsinki Heart Study[12], men with TG > 204mg/dL, HDL-C < 40mg/dL and body mass index (BMI) > 26kg/m^2 who were treated with gemfibrozil had a 78% relative risk reduction in CAD. Similarly, in the FIELD study [13], the greatest effect of fenofibrate on CVD risk was observed in subjects with mixed dyslipidemia, where there was a 27% relative risk reduction.

While there is efficacy data to suggest that combination treatment with statin and fibrate may have additional CVD benefit, until recently, there is no clinical outcome study to test this hypothesis. There is also a safety concern with the addition of fibrates to statins, as they both have skeletal muscle adverse

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effects. When used in combination with statins, the number of rhabdomyolysis reports was approximately 15 times lower for fenofibrate than for gemfibrozil [14]. Overall, it is much safer to combine fenofibrate with statin than with gemfibrozil.

The ACCORD-Lipid trial [15] published last year evaluated CVD outcomes in 5000 diabetic subjects randomised to receive either simvastatin plus fenofibrate or simvasatin plus placebo, in which all subjects were at LDL-C goal. The results showed that fenofibrate plus statins did not reduce CVD events more than statins alone. However, in the subgroup of patients with baseline levels of TG $\geq$204 mg/dL and HDL -C $\leq$34 mg/dL, there was a trend towards lower CVD event rates.

To further define the role of combination treatment with statin and fibrate, the FDA advisory panel recently recommended that a new trial of fenofibrate in diabetic patients who have met their LDL-C goal on a statin but still have high TG and low HDL -C, where patients should be randomised to fenofibrate plus a statin or placebo plus a statin should be conducted.

The combination of statin with ABT-335, which is the choline salt of fenofibrate is also currently being evaluated in a number of surrogate and clinical end-point trials.

NIACIN

Niacin is the most effective agent currently available for raising HDL-C. In addition to increasing HDL-C (20 to 25%), it also lowers LDL-C (10 to 15%), TG (15 to 25%) and lipoprotein (a)(15 to 20%) [16]. Niacin raises HDL-C by stimulating apo A1 production in the liver. The immediate release formulation of niacin was frequently associated with cutaneous flushing which limited its use. The introduction of extended release formulations (ER-niacin) and recently, formulations which contain the prostaglandin D2 receptor antagonist (laropiprant) has significantly reduced niacin-induced cutaneous flushing and improved its tolerability.

The Coronary Drug Project [17] is the only niacin monotherapy outcomes study, and was done in 1119 men with a previous MI randomised to niacin (immediate release formulation) or placebo. At the end of 5 years the niacin group had a 14% reduction in coronary death and non-fatal MI, and at the end of 9 years, an 11% reduction in all-cause mortality, due to a reduction in CAD mortality by 12%.

The HATS trial [18] was a randomised placebo controlled study which enrolled 160 patients with CAD and used quantitative coronary angiographic stenosis as the primary endpoint. It showed that in the placebo group, coronary stenosis progressed by 3.9% while in the simvastatin-niacin combination, there was regression by 0.4%.

The ARBITER-6 HALTS trial published in 2009 [19] was a randomised study which enrolled 360 patients with CAD and used regression of carotid-intima media thickness as the primary endpoint. It showed that while regression in the carotid-intima media thickness was seen in the simvastatin-niacin combination, no change was seen in the simvastatin-ezetimibe group.

However, the AIM-HIGH trial, which was the first randomised clinical outcome trial to compare ER-niacin combined with simvastatin versus simvastatin alone in 3,300 patients, with known CVD and mixed dyslipidemia was halted prematurely this year, 18 months ahead of schedule, because ER-niacin offered no additional protection against CVD events compared to simvastatin monotherapy in this patient population.

The HPS-2-THRIVE which is another large randomised clinical outcome trial comparing ER-niacin (plus laropiprant) combined with simvastatin versus simvastatin alone in 20,000 patients with known CVD (albeit a higher risk population than AIM-HIGH) and who are at LDL-C target is still ongoing, with results expected in 2013. It is hoped that the results of this trial would clarify the role of combination treatment of statin with niacin in high risk patients with mixed dyslipidemia.

CETP INHIBITORS

CETP inhibitors are a new class of drugs for raising HDL-C. CETP facilitates transfer of cholesterol from HDL to LDL and VLDL. Inhibition of CETP has been shown to increase HDL-C by 80 to 138% [20, 21].

The ILLUMINATE trial [20] was the first randomised clinical outcome trial with a CETP inhibitor. It compared torcetrapib combined with atorvastatin versus atorvastatin alone in 15,000 patients with known CVD, but was halted prematurely because of an increased CVD mortality in subjects who received torcetrapib, attributed to an off-target effect of torcetrapib on raising the blood pressure.

There has been renewed interest in CETP inhibitors after results of the DEFINE trial were published last year [21]. This was a randomised safety and efficacy trial which compared a new CETP inhibitor anacetrapib combined with simvastatin versus simvastatin alone in 1,623 patients with known CVD. The results showed that subjects who received anacetrapib had a 138% increase in HDL-C and a 36% decrease in LDL-C, but no increase in the blood pressure or CVD mortality.

The REVEAL HPS-3 TIMI 55 trial is an ongoing large randomised clinical outcome trial in 15,000 patients with known CVD to assess whether the combination of anacetrapib with simvastatin would reduce CVD events compared to simvastatin alone, with results expected in 2015.

PRESCRIPTION OMEGA-3 FATTY ACID

Omega-3 fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] are components of fish oil and the Mediterranean diet, and have been used to lower TG. Omega-3 fatty acids at pharmacologic doses (>2g/day) reduce VLDL concentration by unknown mechanisms. Fish oil reduces TG by

30%, but has minimal effects on other lipoproteins [22].

Although a recent Japanese study in patients with hypercholesterolemia reported a 19% reduction in CVD events, the data remain inconclusive and their clinical efficacy appears to be related to non-lipid effects [23].

CONCLUSIONS

The mixed dyslipidemia (atherogenic dyslipidemia) associated with DM and the metabolic syndrome (high TG, low HDL-C and small dense LDL-C) contributes to CVD risk. The primary goal of lipid therapy is to reduce LDL-C to targets with statins.

However, residual CVD risk remains after achievement of LDL-C goal in patients with CVD who are on statin treatment. This residual risk may be due to persistently low HDL-C and elevated TG. Combination lipid therapy of statins with fibrates, niacin or omega-3 fatty acids may reduce this risk, especially in high risk individuals.

To date, clinical trials are yet to demonstrate that combination lipid therapy could provide additional reduction of CVD events in high risk patients, compared to statin alone.

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LEARNING POINTS

- **Mixed dyslipidemia (high TG, low HDL-C and small dense LDL-C) is becoming increasingly common due to the increased prevalence of DM and metabolic syndrome, and is associated with a high CVD risk.**
- **The primary goal of lipid therapy is to reduce LDL-C to targets with statins [< 100mg/dL for high risk (established CAD or CAD risk equivalent e.g DM) and < 70mg/dL for very high risk (e.g acute coronary syndrome)].**
- **Treatment of mixed dyslipidemia may reduce the significant residual CVD risk that remains even after achievement of LDL-C goal in high risk patients on statin treatment.**
- **Lifestyle modification which includes interventions aimed at weight loss through diet and exercise, followed by weight maintenance that employs low saturated fat intake remains the cornerstone of management of mixed dyslipidemia.**
- **Combination lipid therapy is indicated in high risk patients on maximal doses of statins who have achieved the LDL-C goal, but have persistently low HDL-C and/or high TG, in spite of lifestyle modification.**
- **The choice of which drug to add on to the statin depends on which is the predominant lipid abnormality: If low HDL-C is predominant, niacin could be added; If high TG is predominant, either omega-3 fatty acids or fibrate could be added.**

UNIT NO. 3

TREATING DYSLIPIDEMIA IN THE HIGH-RISK GROUP PATIENTS- CURRENT MANAGEMENT AND FUTURE APPROACH

Dr. Yong Quek Wei

ABSTRACT

Dyslipidemia is an important etiologic component to cerebrovascular, peripheral vascular and coronary heart disease worldwide, including Singapore. Most studies have shown that the 10% of the population with the highest LDL levels account for only 20-30% of the CHD events. Conversely 70-80% of CHD events occur in patients with so-called "normal" or "near-normal" levels. Standard guidelines therapy 5-6 years ago focus treatment only on those with very high cholesterol levels and ignore this large group of the people with "normal "or mildly raised cholesterol levels. New approaches in last few years include more intensive lowering of LDL-cholesterol levels, reducing triglycerides/non-HDL components and raising the high-density lipoprotein (HDL)-cholesterol level. In 2006, a target of <70 mg/dL LDL goal has became a "reasonable goal" in the guidelines for secondary prevention. High triglycerides or too-low HDL-cholesterol, also contribute to CHD risk and these lipid abnormalities often cluster with other risk factors, including obesity, insulin resistance, hyperglycemia, and hypertension (metabolic syndrome). Such patients are considered to have mixed, or atherogenic dyslipidemia, and include those with metabolic syndrome and type 2 diabetes. In patients whose triglyceride levels remain high (>200 mg/dL) or HDL-cholesterol levels low (<40 mg/dL) even after they have achieved their LDL-cholesterol goals, the NCEP ATP III guidelines recommend non−HDL-cholesterol as a secondary target of therapy. Combination therapies using fibrates seemed appealing and two ongoing trials are comparing combination therapy (statin with either niacin or a fibrate) to assess the incremental benefit of combination therapy.

Keywords: High-risk patients, residual cardiovascular risks, statin therapy, fibrate therapy, LDL-cholesterol, non-HDL-cholesterol, combination therapy

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INTRODUCTION

This article reviews the current state of treatment of dyslipidemia in the high-risk patients in light of latest trials and how to reduce the residual cardiovascular risks that frequently remains.

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Dyslipidemia is an important etiologic component to cerebrovascular, peripheral vascular and coronary heart disease worldwide [1]. These diseases contribute significantly to mortality and morbidity locally. They also have a huge negative impact on healthcare resources in developed and developing countries. Lipid lowering agents especially statin therapy have reduced morbidity and mortality rates from CHD remarkably over the last few decades. They act by lowering low-density lipoprotein (LDL)-cholesterol level, increasing HDL–cholesterol levels, modifying other atherogenic particles and reduce vessels inflammation. However despite these gains, CHD continues to be a major threat and substantial unmet residual risk remains.

Moreover, most studies have shown that the 10% of the population with the highest LDL levels account for only 20-30% of the CHD events. Conversely 70-80% of CHD events occur in patients with so-called "normal" or "near-normal" levels. Hence, standard guidelines therapy 5-6 years ago that focus treatment only on those with very high cholesterol levels will ignore this large group of the people (with "normal" or mildly raised cholesterol levels) destined to suffer a CHD event. New approaches in last few years include more intensive lowering of LDL-cholesterol levels, reducing triglycerides/non-HDL components and raising the high-density lipoprotein (HDL)-cholesterol level. However, not all approaches have reaped the desired benefits. Novel agents to modify other atherogenic components as well as reduce inflammatory causal components and improve endothelial function are in the development and some are now undergoing clinical trials.

REDUCTION OF LDL-CHOLESTEROL LEVELS

For the past few decades, reduction of LDL levels has remained the main objective of lipid therapy. Almost all guidelines (ACC, AHA, ESC , National Cholesterol Education Program and Ministry of Health, Singapore guidelines) has all these while target the reduction of serum levels of LDL-cholesterol as the cornerstone of lipid therapy, for primary and secondary prevention. This approach is clinically valid and has been corroborated by the results of numerous randomised clinical trials [6, 7, 8]. Recently the Cholesterol Treatment Trialists' (CTT) Collaborators Study has affirmed this approach of dyslipiademia treatment. This large meta-analysis of more than 90,000 patients confirmed the central role of lowering LDL cholesterol [6]. In this meta-analysis of 14 large-scale statin trials, a 1-mmol/L reduction in LDL-cholesterol reduced the incidence of major coronary event by 23% and the incidence of CHD death by 19% over 5 years. In the high-risk group with pre-existing CHD, a 1-mmol/L (or 38 mg/dL) reduction in LDL-death by 19% over 5 years. In the high-risk group with death by 19% over 5

years. In the high-risk group with pre-existing CHD, a 1-mmol/L (or 38 mg/dL) reduction in LDL-cholesterol reduces 14 deaths per 1000 subjects. The benefit is seen regardless of baseline LDL-cholesterol levels i.e. benefit is still obtained when statin is given when the baseline levels were low by previous conventional treatment guidelines i.e. <2.6 mmol/l (or 100 mg/dL). Of note is that greatest benefit was achieved in the high-risk and very-high-risk groups. This group comprised patients with diabetes, known CAD, those with peripheral arterial disease and those older than 75 years. In fact long-term follow-up monitoring has shown that lowering LDL-cholesterol in this high risk group continued to reduce cardiovascular events for 10 years after the study has ended, thus alluding to the long-term salutary effects of statin therapy.

However, how low a level should LDL cholesterol be reduced remains highly contentious. Observational and experimental studies have shown that the relationship between cholesterol and CHD mortality has no apparent lower threshold, and that the physiologic normal level for LDL-cholesterol in some societies especially Asian countries may be lower than that seen in Western countries [4]. In some studies done in urban Chinese population e.g. amongst native Beijing city dwellers and even amongst local population, the mean baseline total cholesterol level was lower compared to western populations, and likewise a lower rate of deaths were attributed to CHD [4]. Nonetheless there is an independent and strongly positive relationship between total cholesterol and risk of CHD death [7], starting at a level as low as 150-mg/dL total cholesterol level. A similar relationship was seen in LDL-cholesterol level with acute events occurring even at levels of 90-100 mg/dL. Other studies have indicated that the physiologic norm for LDL-cholesterol levels should be in the range of 50 to 65 mg/dL. Serum total cholesterol concentrations in newborn healthy babies have been reported to be in the 100-140 mg/dL range [9]. These levels are also frequently seen in some healthy native hunter aboriginal groups and in vegan populations. In these groups, the prevalence of CHD is low compared to western populations.

Hence, low LDL-cholesterol level in the long run does equate to a lower atherosclerotic disease risk and studies have affirmed that lowering LDL cholesterol in high risk groups by drugs seem to confer the same effect. Invasive angiographic data from statin clinical trials indicate that atherosclerosis does not progress when LDL-cholesterol levels are maintained at <70 mg/dL [20], while other data suggest that CHD event rates could be minimised at LDL-cholesterol levels of <60 mg/dL for primary prevention and at levels as low as <30 mg/dL for secondary prevention.

Hence, recent clinical trials have compared more intensive and less intensive statin regimens in high-risk subjects, and found that lower LDL-cholesterol values achieved by more intensive regimens produced higher benefits. In the Treating to New Targets (TNT) trial patients with stable CHD and mean baseline LDL-cholesterol levels of 98 mg/dL, comparing the use of atorvastatin 10 mg/day to atorvastatin 80 mg/day, those in the high-dose 80 mg/day group achieved a mean LDL-cholesterol level of 77 mg/dL, which translate into a 22% reduction in risk of a major cardiovascular event (P<. 001) and a significant 25% reductions in stroke and cerebrovascular events[16]. Likewise in the PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial and Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, patients who had been hospitalised for acute MI were randomly assigned to atorvastatin 80 mg/day or pravastatin 40 mg/day for 2 years. The patients' median LDL-cholesterol levels fell from 106 mg/dL at baseline to 62 mg/dL in the intensive high dose therapy group and to 95 mg/dL in the standard pravastatin therapy group. At 2 years, the primary end point of cardiovascular events was 16% lower (P=. 005) in patients on intensive therapy, and the greatest benefit is seen in those with baseline LDL-cholesterol levels of at least 125 mg/dL or less. However, favorable outcomes were more closely related to the on-treatment levels of LDL-cholesterol and C-reactive protein than to the specific agent used. Hence both trials show that in high-risk patients, a LDL-cholesterol level of very low levels of 60 to 80 mg/dL results in better outcomes than regimens that achieve LDL-cholesterol levels of approximately 100 mg/dL.

Treatment amongst hyperintensive[12,14] and the elderly[15] patients suggest treatment strategy currently used in middled-aged people should equally apply to these groups.

In this era of global and instant connectivity amongst researchers, clinical trials' findings should rightly be assimilated into guidelines as soon as possible. However since most guidelines are updated only once every 4- 5 years, earlier updating of guidelines or insertion of addendums should be done by the cardiology and advisory societies as needed. In the 2002 NCEP Adult Treatment Panel III (ATP III) guidelines the then recommended LDL-cholesterol goals depend on the patient's level of risk, with <100 mg/dL as the goal for those in the highest risk category [2]. This is further corroborated by the Heart Protection Study (HPS) where patients achieved a mean LDL-cholesterol level of 89 mg/dL, and a "highly significant" 18% reduction in coronary deaths (P=. 0005) was achieved, even in individuals who entered the study with baseline LDL-cholesterol level of <116 mg/dL[13]. No threshold effect was found. For that reason, the investigators suggested that reducing LDL-cholesterol further to very low levels might produce greater reductions in cardiovascular events. Hence in the 2004 NCEP guidelines update, they suggest that for CHD patients in the "very-high-risk" group, a target of <70 mg/dL LDL goal is an "optional target level". This "very-high-risk" group includes those with established cardiovascular disease and additional risk factors such as diabetes mellitus, continued cigarette smoking, metabolic syndrome, renal failure and acute coronary syndrome.

In 2006, a target of <70 mg/dL LDL goal has became a "reasonable goal" in the guidelines for secondary prevention jointly issued by the American Heart Association and the American College of Cardiology[5]. It states that a goal of <70 mg/dL is "reasonable" for all patients with CHD and other clinical forms of atherosclerotic disease, even for those whose baseline LDL-cholesterol level is between 70 and 100 mg/dL [5].

Likewise, abundant data from prospective trials have revealed a strong and direct relationship between on-treatment LDL level and rate of atherosclerotic progression. These randomised controlled trials show that whether patients were on statin therapy or placebo, the rate of angiographic progression of atherosclerosis was closely related to the LDL levels and in a few studies inversely related to HDL levels. In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) trial which used 80 mg/day atorvastatin versus 40 mg/day pravastatin patients with a mean baseline LDL of 150 mg/dl. Atorvastatin reduced LDL by 50% to a mean LDL of 76 mg/dl compared with a 27% drop to a mean of 110 mg/dl on pravastatin. The carotid intima-media thickness regressed 0.038 mm in the atorvastatin group compared with a mean progression of 0.026 mm in the pravastatin group (p = 0.021).

The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) [19] trial compared the effects on atheroma volume, as measured by intracoronary intra-vascular ultrasound, using intensive (atorvastatin 80 mg/day) vs. moderate (pravastatin 40 mg/day). In the intensive treatment group, which a mean LDL-cholesterol level of 79 mg/dL was achieved, a 0.4% reduction in atheroma volume was seen. This indicated no disease progression from baseline and a significantly lower progression rate (P=.02). By contrast, the group on moderate treatment that achieved a mean LDL-cholesterol level of 110 mg/dL had a 2.7% increase in atheroma volume, indicating progression of atheroma / plaque volume. Both of these trials demonstrated the inadequacy of LDL reduction to current goals of <100mg/dl.

In the ASTEROID study[20], (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden,) the effect of rosuvastatin 40 mg/day on coronary disease progression was again assessed by intravascular ultrasound at baseline and after 2 years of treatment. The results showed a regression in the mean change in percent atheroma volume (–0.98%, compared with baseline P<.001). The investigators attributed disease regression to intensive statin treatment (a very low mean LDL-cholesterol level together with significantly increased HDL-cholesterol levels up to 49 mg/dL, up 5% from baseline.

However in a very controversial study in patients with familial hypercholesterolemia utilising ultrasound measurements of carotid intima-media thickness, lowered LDL-cholesterol levels did not result in regression of atherosclerosis in contrast to the ARBITER study. In this Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, groups using simvastatin 80 mg plus ezetimibe 10 mg compared with simvastatin 80 mg alone did not demonstrate any difference of carotid intima-media thickness. Despite significant 16.5% greater lowering of LDL-cholesterol with combination therapy (P<.01), no difference was observed in both groups. This negative study was attributed to a different study population disease profile by some experts [21].

However in recent years, some experts have cautioned against a severe reduction of cholesterol levels to very low levels. As cholesterol is an essential component of the cell membrane/ tissue regeneration process and an obligate precursor for bile acid, steroid hormone, and vitamin D synthesis. It is likely that a physiologically ideal range of blood cholesterol exists above and below which adverse health consequences might be expected. Although individuals with chronic illnesses and malignancies, often develop depressed LDL levels as a result of malnutrition or hypermetabolism, epidemiologic studies show that people with naturally low LDL levels are associated with improved longevity. This is seen in some Asian countries and closed communities. Needless to say, having a naturally low cholesterol level in a healthy person and artificially inducing a low cholesterol level using drugs in a diseased state is two different pathophysiologic process. Thus given the physiologic importance of cholesterol, the very low cholesterol levels artificially achieved with intensive statin therapy in some trials has raised certain issues about the safety of high dose regimens. So far, the cumulative experience with statin therapy shows impressive cardiovascular benefits that are directly proportional to LDL lowering with no increase in adverse events such as malignancy or non-cardiovascular mortality [6,7]. The incidence of the two principal adverse effects commonly attributed to statins — liver and muscle toxicity — rise modestly as a function of dose and type of statin utilised but not in relationship to the on-treatment LDL level. In the PROVE IT-TIMI 22 trial where patients whose LDL-cholesterol levels had dropped to 40 mg/dL or lower, there were fewer cardiovascular events in this group compared with the patients with LDL-cholesterol levels between 80 and 100 mg/dL, and no relationship was found between this low level and adverse events over 24 months[11]. Similarly, the TNT study group found that the lowest quintile (LDL<64 mg/dL, mean 54 mg/dL) had the lowest event rate, without a difference in adverse events over 5 years[8,17]. However, some cholesterol expert maintain that little is known about the side effects of taking statins at higher doses for long periods as most trials follow-up patients for less than 5 years and use of intensive regimens has only been instituted in western countries only recently and in relatively small numbers. Animal studies 10 years ago have already shown that the equivalent of high dose statins in humans in the long term does induce a degenerative myopathy and neuropathy state. Recent findings have prompted the Food and Drug Administration to recommend that the use

simvastatin 80 mg / highest approved dose be sharply curtailed because of the risk of myopathy. Moreover a lot of trials do not address issues of "non-quantifiable" or "subtle" side effects like aches and pains, mental and neurological derangements such as depression, sleep disturbance, severe irritability and memory loss.

NON-HDL-CHOLESTEROL AS SECONDARY TARGET OF THERAPY

It is also clear from the statin clinical trials that cardiovascular events occur even after LDL-cholesterol is optimally treated. In fact current treatment regimens reduces only about 25-35% of all cardiovascular events over an average of 5 years. Unmet risks of 60-70% still exist despite statin therapy. Other lipid components e.g. high triglycerides or too-low HDL-cholesterol, also contribute to CHD risk [3.] These lipid abnormalities often cluster with other risk factors, including obesity, insulin resistance, hyperglycemia, and hypertension (metabolic syndrome) [27]. Such patients are considered to have mixed, or atherogenic dyslipidemia, and include those with metabolic syndrome and type 2 diabetes [3]. In patients whose triglyceride levels remain high (>200 mg/dL) or HDL-cholesterol levels low (<40 mg/dL) even after they have achieved their LDL-cholesterol goals, the NCEP ATP III guidelines recommend non–HDL-cholesterol as a secondary target of therapy. Non–HDL-cholesterol (calculated as total cholesterol minus HDL-cholesterol) is a measure of all the atherogenic lipids i.e. apolipoprotein B-containing lipoproteins (LDL), intermediate-density lipo-protein [IDL], and very-low-density lipoprotein [VLDL]).

In mixed dyslipidemia, the LDL particles are usually smaller and the calculated LDL-cholesterol content does not reflect the increased particle number. Several observational studies suggest that non–HDL-cholesterol is a better predictor of risk than LDL-cholesterol level [4] and higher and denser LDL particle numbers may reflect the pathogenicity of cholesterol better than the absolute LDL-cholesterol levels.

In the TNT and IDEAL (Incremental Decrease in End Points through Aggressive Lipid Lowering) trials, where LDL-cholesterol levels were positively associated with cardiovascular outcome [8, 10], that relationship turned out to be less significant than the relationship with non–HDL-cholesterol and apolipoprotein B. The ratio of total cholesterol to HDL Total/HDL) and the ratio of apolipoprotein B to apolipoprotein A-I were each more strongly associated with outcome than any of the individual lipoprotein parameters.

TNT data also shows that HDL-cholesterol levels in patients receiving statins does predict major cardiovascular events. Among subjects with LDL-cholesterol levels <70 mg/dL, those in the higher HDL-cholesterol levels were at less risk for major cardiovascular events [9]. These analyses support the concept that there is residual CHD risk after optimal statin treatment and that the easily obtained non–HDL-cholesterol and HDL-cholesterol levels per se are predictive of that risk [22, 23].

The ATP III recommended goal for non–HDL-cholesterol is 30 mg/dL above the LDL goal. Thus, a high-risk person whose LDL-cholesterol goal is <100 mg/dL would have a non–HDL-cholesterol goal of <130 mg/dL. ATP III recommends lowering non–HDL-cholesterol by intensifying statin therapy to further reduce LDL as well as considering the addition of niacin or a fibrate to further decrease VLDL and triglycerides. Fish oil supplements with Omega-3 fatty acids at a sufficient dose (3-4 g/d of ecosapentanoic acid and decosahexanoic acid) can reduce triglycerides as monotherapy, or when added to statins. Likewise the 2008 consensus conference report from the American Diabetes Association and the American College of Cardiology states that in patients with high cardiometabolic risk, measurements of total atherogenic particles are better [25]. These measurements include non–HDL-cholesterol, apolipoprotein B, and the number of LDL particles identified by nuclear magnetic resonance. In individuals in the highest-risk category (known clinical cardiovascular disease or diabetes plus one or more CHD risk factors in addition to dyslipidemia), they recommend a non –HDL-cholesterol goal of <100 mg/dL and an apolipoprotein B goal of <80 mg/dL [18].

RAISING HDL-CHOLESTEROL LEVELS

Another approach widely pursued by investigators nowadays is to raise HDL cholesterol levels. The validity of raising HDL-cholesterol is supported by epidemiological evidence [26,28,33] showing an inverse relationship between HDL-cholesterol levels and cardio-vascular risk: an increase of 1 mg/dL in HDL-cholesterol is associated with a 2% to 3% decrease in risk of cardiovascular disease. An analysis of data from the Framingham study, the Coronary Primary Prevention Trial, and Multiple Risk Factor Intervention Trial indicates that for every 0.025 mmol/L rise in HDL, the risk of CHD decreases 2% in men and 3% in women. This compares favourably with LDL where a decrease of 1 mg/dL in LDL-cholesterol is associated with only a 1% decrease in risk of cardiovascular disease.

Findings from INTERHEART, a global case control study of heart attack involving 52 countries, imply that even in patients with low levels of LDL cholesterol, if the level of HDL cholesterol is not sufficiently high, there remains an increased risk of further cardiovascular events. Therapeutic lifestyle changes, such as weight loss, exercise, and smoking cessation are effective at increasing HDL-cholesterol and these interventions are always encouraged. Most statins increase HDL-cholesterol only modestly (5-10%), with rosuvastatin generally producing the largest increases [29]. Currently, the most efficacious HDL-raising drug is niacin. As monotherapy, niacin can increase HDL-cholesterol by 15% to 35%. Increases as high as 40-50% have been reported when used in combination with statins. The problem with niacin is that it often causes flushing and other unpleasant side effects especially GI side effects. This cause some

20% of patients to discontinue therapy especially when high doses are used. Extended-release formulations cause less flushing than immediate-release forms of niacin, and specific flush-reducing agents (laropiprant) are used in combination pills to improve tolerance.

Fibrates can also increase HDL-cholesterol by 8% to 35% by activating the nuclear transcription factor peroxisome proliferator-activated receptor-α (PPAR) [3]. The Veterans Affairs HDL Intervention Trial (VA-HIT) 34 studied the effects of gemfibrozil in men with CHD and HDL-cholesterol <40 mg/dL. After a median follow-up of 5 years, gemfibrozil raised HDL-cholesterol by 6% more than placebo and lowered triglycerides by 31% more (P<.001for both), but did not affect levels of LDL-cholesterol. Compared to placebo, gemfibrozil treatment reduced the risk of CHD death and nonfatal myocardial infarction by 22% (P=.006). In post hoc analysis, each 5-mg/dL increase in HDL-cholesterol was associated with an 11% decrease in the risk of these CHD events. The Helsinki Heart Study reported similar results with gemfibrozil in population without CHD. Small studies using rosuvastatin and fenofibrate and atorvastatin and fenofibrate have shown positive effects on dyslipidemia. Gemfibrozil may be associated with increased risks of myositis, whereas fenofibrate combined with statins has not shown this effect.

COMBINATION THERAPIES

Hence combination therapies using fibrates seemed appealing and two ongoing trials are comparing combination therapy (statin with either niacin or a fibrate) with statin therapy to assess the incremental benefit of combination therapy. AIM-HIGH (Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides and Impact on Global Health outcomes) is a 5-year study in 3300 patients with vascular disease and low HDL-cholesterol. This study is designed to find out whether lowering LDL to <80 mg/dL with simvastatin plus niacin can delay the time to a first major cardiovascular event compared to simvastatin therapy alone.

The 6-year ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) randomises patients with type 2 diabetes into 2 groups, 1 receiving statin-fibrate combination therapy and the other statin monotherapy. ACCORD is designed to find out whether raising HDL-cholesterol and lowering triglycerides with targeted reductions in LDL-cholesterol will improve CHD outcomes more than LDL lowering alone. These trials are not completed and findings are highly anticipated.

Omega-3 fatty acids are also sometimes used in conjunction with simvastatin and dietary counselling to improve non-HDL-C and other lipoprotein parameters to a greater extent than simvastatin alone[24]. Their effect on HDL-C is minimal.

Other HDL cholesterol raisers have initially proved disappointing. The first CETP inhibitor, Torcetrapib [31], which had been shown to increase HDL-cholesterol by >50% in early clinical trials [30]. However, a clinical outcomes trial comparing torcetrapib and atorvastatin with atorvastatin alone was stopped early because the combination therapy was associated with a higher incidence of adverse events including strokes and total mortality. Significant increases in average systolic blood pressure with torcetrapib were reported. Further, substantial HDL-cholesterol increases of 54% to 61% achieved with torcetrapib in 2 surrogate outcomes trials did not have a beneficial effect on atherosclerosis. Other CETP inhibitors are currently in development that, investigators hope, will not have the adverse effects associated with torcetrapib [32]. Additional investigative approaches for increasing HDL-cholesterol levels such as apolipoprotein A1-Milano[34], apolipoprotein A1-mimetic peptides, and phospholipid-directed therapies are in development.

CONCLUSIONS

Most studies have shown that the 10% of the population with the highest LDL levels account for only 20-30% of the CHD events. Conversely 70-80% of CHD events occur in patients with so-called "normal" or "near-normal" levels. In patients whose triglyceride levels remain high (>200 mg/dL) or HDL-cholesterol levels low (<40 mg/dL) even after they have achieved their LDL-cholesterol goals, the NCEP ATP III guidelines recommend non–HDL-cholesterol as a secondary target of therapy. Combination therapies using fibrates seemed appealing and two ongoing trials are comparing combination therapy (statin with either niacin or a fibrate) with statin therapy to assess the incremental benefit of combination therapy.

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LEARNING POINTS

- **Some 70-80% of CHD events occur in patients with so-called "normal" or "near-normal" levels.**
- **High triglycerides or too-low HDL-cholesterol, also contribute to CHD risk and these lipid abnormalities often cluster with other risk factors, including obesity, insulin resistance, hyperglycemia, and hypertension (metabolic syndrome).**
- **In patients whose triglyceride levels remain high (>200 mg/dL) or HDL-cholesterol levels low (<40 mg/dL) even after they have achieved their LDL-cholesterol goals, the NCEP ATP III guidelines recommend non−HDL-cholesterol as a secondary target of therapy.**
- **Combination therapies using fibrates seemed appealing and two ongoing trials are comparing combination therapy (statin with either niacin or a fibrate) to assess the incremental benefit of combination therapy.**

UNIT NO. 4

HOW DO INCRETIN-BASED THERAPIES FIT INTO THE TREATMENT ALGORITHM?

Dr Chia Su-Ynn

ABSTRACT

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), termed "incretins," are gut-derived peptide hormones released from intestinal K and L cells into the bloodstream in response to ingested nutrients. They greatly augment the insulin response of the pancreas to an oral glucose load. In patients with T2DM, particularly those with more long standing disease and poorer glycemic control (HbA_{1c}~8-9%), the GLP-1 response to glucose and mixed meal challenges is decreased, but GIP secretion is unchanged when compared to healthy subjects. Also, acute GLP-1 administration is able to increase insulin secretion to normal levels and to lower plasma glucose effectively in these patients. The main drawback with GLP-1 is its short half-life (~1–2 min for the intact, biologically active form). For this reason, GLP-1 analogues, also known as "incretin mimetics" (e.g., exenatide and liraglutide) with considerably longer half-lives were developed. All incretin mimetics are peptides and need to be administered by subcutaneous injection. Exenatide has a half-life of ~3 h and has been approved for administration (twice-daily injections) to type 2 diabetic patients inadequately controlled with oral antidiabetic agents, and lowers Hb A1c by about 0.7-1%. Liraglutide has a half-life of 12–14 h (suitable for once-daily administration) and can lower HbA1c between 1-1.5%. GLP-1 analogues provoke significant weight loss, which is especially important when considered against the weight gain associated with, e.g., sulfonylureas, TZDs, and insulin. DPP4 inhibitors, which are oral agents that inhibit the breakdown of endogenous GLP-1, also lower HbA1c levels. They are well tolerated, weight neutral, and have a very low risk of hypoglycemia. Based on these advantages, incretin-based therapies have been mentioned in recent treatment algorithms for the treatment of type 2 diabetes.

Keywords: Incretin-based therapy; diabetes mellitus

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WHAT ARE "INCRETINS" AND WHAT IS THEIR RELEVANCE TO DIABETES?

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), termed "incretins," are gut-derived peptide hormones released from intestinal K and L cells into the bloodstream in response to ingested nutrients. They greatly augment the insulin response of the pancreas to an oral glucose load, an effect not seen with an intravenous glucose infusion. These incretins increase insulin secretion in a glucose-dependent manner through activation of their specific receptors on ß-cells.

In patients with T2DM, particularly those with more long standing disease and poorer glycemic control (HbA_{1c} ~8–9%), the GLP-1 response to glucose and mixed meal challenges is decreased, whereas GIP secretion is unchanged when compared to healthy subjects. However, acute GLP-1 administration is able to increase insulin secretion to normal levels and to lower plasma glucose effectively in these patients (Chia et al 2008)[1]. Additional beneficial effects of GLP-1 on endocrine pancreatic islets are that it *1*) supports the synthesis of proinsulin to replenish insulin stores in ß-cells; *2*) reduces the rate of ß-cell apoptosis when islets are incubated in a toxic environment (glucotoxicity, lipotoxicity, cytotoxic cytokines); and *3*) promotes differentiation of precursor cells with the ability to develop into ß-cells and proliferation of ß-cell lines, and in whole animals (rodent studies), this leads to an increased ß-cell mass within a few days or weeks. Furthermore, GLP-1 can lower glucagon concentrations, i.e., induce ß-cells to respond again to the inhibitory action of hyperglycemia, while leaving the counterregulatory glucagon responses undisturbed, as in the case of hypoglycemia (Nauck et al 2009)[2]. Additional activities of GLP-1 are the deceleration of gastric emptying, which slows the entry of nutrients into the circulation after meals, a reduction in appetite, and earlier induction of satiety, leading to weight reduction with chronic exposure. Renal effects (promotion of sodium and water excretion, as well as neuro- and cardioprotective properties of GLP-1, have also been described. In contrast, exogenous GIP, even at supraphysiological doses, has markedly reduced insulinotropic actions with little or no glucose-lowering effects in T2DM. Therefore, therapeutic strategies for T2DM within the incretin field focused on the use of GLP-1, and not GIP (Drucker et al 2006)[3].

WHAT IS INCRETIN-BASED THERAPY?

The main drawback with GLP-1 is its short half-life (~1–2 min for the intact, biologically active form) caused by rapid proteolytic degradation and inactivation through the ubiquitous enzyme DPP-4 and renal elimination, making it difficult to use therapeutically. For this reason, **GLP-1 analogues, also known**

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as "incretin mimetics" (e.g., exenatide and liraglutide) with considerably longer half-lives were developed. A common feature of all incretin mimetics is that they are peptides and need to be administered by subcutaneous injection. They bind to and activate the GLP-1 receptor and display the full array of biological (antidiabetic) activity known for/characteristic of (CTT) Collaborators Study has affirmed this approach of dyslipiademia treatment. This large meta-analysis of more than 90,000 patients confirmed the central role of lowering LDL cholesterol 6. In this meta-analysis of 14 large-scale statin trials, a 1-mmol/L reduction in LDL-cholesterol reduced the incidence of major coronary event by 23% and the incidence of CHD death by 19% over 5 years. In the high-risk group with pre-existing CHD, a 1-mmol/L (or 38 mg/dL) reduction in LDL-activate the GLP-1 receptor and display the full array of biological (antidiabetic) activity known for/characteristic of GLP-1. Within the group of incretin mimetics, differences are seen with respect to amino acid homology in comparison to native human GLP-1, and in pharmacokinetic characteristics, such as elimination of half-lives, and so forth. Novel attempts have aimed at developing compounds, or preparations, with a longer duration of action, and less frequent administration (e.g. once-weekly). The two available forms of incretin mimetics currently available are exenatide and liraglutide. Exenatide is a synthetic form of a natural peptide found in the saliva of Heloderma suspectum (a big venomous lizard found in the USA and Mexico) with amino acid sequence homology with GLP-1. Exenatide has a half-life of ~3 h and has been approved for administration (twice-daily injections) to type 2 diabetic patients inadequately controlled by oral antidiabetic agent, and has been shown to lower Hb A1c by about 0.7-1% (Nielsen et al 2004)[4]. Recently developed liraglutide, synthesised by attaching a free fatty acid to a slightly modified GLP-1 molecule, is characterised by a half-life of 12–14 h (suitable for once-daily administration) and can lower HbA1c between 1-1.5%.

Another method of exploiting the antidiabetic potential of GLP-1 is by **inhibiting its proteolytic degradation and inactivation through the action of DPP-4**. Several agents have been identified that are able to inhibit DPP-4 activity (in serum) by >85% and preserve GLP-1 secreted from endogenous sources (mainly in response to meal ingestion) in its intact biologically active forms, thus leading to doubled or tripled incremental responses (Ahren et al 2004)[5]. Sitagliptin, vildagliptin, alogliptin and saxagliptin have been approved as DPP4-inhibitors. All these agents, in general, have a modest HbA1c-lowering effect between 0.5-1% (Renee et al 2007)[6].

WHAT ARE THE POTENTIAL ADVANTAGES OF INCRETIN-BASED THERAPY?

One of the most significant advantages is the glucose-dependent nature of its insulinotropic effects, which means that incretin-based therapies amplify physiologic insulin secretion and are associated with very low rates of hypoglycemia. In addition to this, incretin-based therapies do not cause weight gain. In fact, GLP-1 analogues provoke significant weight loss, which is especially important when considered against the weight gain associated with, e.g., sulfonylureas, thiazolidenideones (TZDs), and insulin. DPP-4 inhibitors are weight neutral (Renee et al 2007)[6] .Post prandial glucose excursions are also significantly reduced with incretin-based therapy, probably in part due to their effect at modulating glucagon secretion.

Additional novel features include possible positive effects of some incretin-based therapies on the β-cell. This has been shown in several animal models and in-vitro studies on islet cells, but clinical data is scarce. GLP-1 analogues improve some parameters of β-cell function during treatment; however, this effect has not been shown to be sustained one year after treatment with exenatide (Bunck et al 2009)[7]. Even less data regarding beta cell preservation is available with DPP4-inhibitors.

Some mechanistic studies have even suggested the cardio-protective activity of GLP-1. Similar effects may be present with GLP-1 analogues. Clinical trials have shown effects of exenatide and liraglutide on surrogate cardiovascular parameters such as systolic blood pressure, triglycerides, and brain natriuretic peptide (Ban et al 2008)[8]. Long-term studies proving cardiovascular benefit are necessary for both incretin mimetics and DPP-4 inhibitors.

WHAT ARE THE POTENTIAL DISADVANTAGES OF INCRETIN-BASED THERAPY?

Dose-dependent nausea and vomiting are the most frequently reported adverse events with incretin-mimetics, particularly with exenatide. Up to 57% may have nausea and 17% vomiting, which generally peaks during the initial 8 weeks of treatment and declines thereafter. Liraglutide seems to have lower rates of gastrointestinal complaints. Some cases of pancreatitis have been reported with incretin-mimetic therapy, but it is not clear whether they have occurred at a higher rate than expected for an obese type 2 diabetic population. A somewhat higher rate of nasopharyngitis may be seen in patients on DPP4 inhibitors, and occasional elevations in liver enzymes have been reported with vildagliptin. Overall however, DPP4 inhibitors are very well tolerated, with low absolute rates of adverse events (Renee et al 2007)[6].

HOW DOES INCRETIN-BASED THERAPY FIT INTO THE CURRENT TREATMENT ALGORITHMS?

This new class of medication is a welcome addition to our existing pharmacological therapies against Type 2 diabetes and its associated severe morbidity and mortality. Meta-analyses have shown that incretin-based therapy in adults with Type 2 diabetes is moderately effective in improving glycemia, with greater reductions in postprandial glucose. This preferential improvement of postprandial glycemia addresses an important limitation of currently available pharmacologic therapies and provides an alternative to our limited options for targeting post-prandial glycemia. In contrast to nearly all available hypoglycemic agents which cause weight gain, GLP-1 analogues have a favorable effect, and DPP4 inhibitors a neutral effect on weight.

As such, the main advantages which incretin-based therapies offer over traditional oral agents and insulin, is in terms of both convenience and reduced side effects, especially with regard to the expected frequency of hypoglycemia and weight gain. Based on these, incretin-based therapies have been mentioned in recent treatment algorithms for the treatment of type 2 diabetes.

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have published a joint treatment recommendation with an algorithm for the stepwise escalation of therapeutic steps in the course of type 2 diabetes. Based on evidence from clinical studies and on available cost-effectiveness data, they divided therapy into Tiers 1 ("well-validated therapy") and 2 ("less-well validated therapy"). Tier 1 therapy included lifestyle modification with initial metformin monotherapy, followed by the addition of basal insulin or sulphonylurea if glycemic goals were not met. Incretin-mimetics and DPP-4 inhibitors were not included in the first tier of this algorithm because of their generally still limited clinical data and/or relative expense. Instead, they were included in Tier 2 of " less well-validated therapy" to be considered in selected clinical settings, including obese patients or those with a low tolerance for hypoglycemia (Nathan et al 2009)[9].

The American Association of Clinical Endocrinologists (AACE) also published a treatment algorithm for patients with Type 2 diabetes. Their approach was slightly different from that adopted by the ADA/EASD algorithm. The AACE panel gave issues like patient compliance and adverse events such as hypoglycemia and weight gain higher priority over expense or long term clinical data. As such, incretin based therapy was elevated to first line therapy alongside more established players like metformin, sulphonylureas, thiazolidinediones and alpha glucosidase inhibitors (Rodbard et al 2009)[10].

CONCLUSIONS

While new medications are often prized and quickly embraced, recent experiences with other drugs like rosiglitazone may have taught us a lesson of caution with newer agents which still have limited clinical data on long term effectiveness and safety. On the other hand, incretin-based therapy has shown to date that it certainly has several distinct physiologic and therapeutic advantages over currently available therapy. As such, it is rapidly becoming a very valuable addition to our armamentarium in our fight against the multifactorial and complex disease that is diabetes. At the end of the day, all the guidelines, despite their differences, reinforce the need of an individualised treatment approach for patients with Type 2 diabetes. As clinicians, it remains our call as to whether incretin-based therapy will be beneficial to each of our individual patients.

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LEARNING POINTS

- **Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), termed "incretins," are gut-derived peptide hormones.**
- **Acute GLP-1 administration is able to increase insulin secretion to normal levels and to lower plasma glucose effectively in patients with Type 2 Diabetes**
- **The main drawback with GLP-1 is its short half-life (~1–2 min for the intact, biologically active form) and for this reason, GLP-1 analogues, also known as "incretin mimetics" (e.g., exenatide and liraglutide) with considerably longer half-lives were developed. All incretin mimetics are peptides and need to be administered by subcutaneous injection.**
- **DPP4 inhibitors, which prevent the breakdown of endogenous GLP-1, can also enhance GLP-1 levels and help lower plasma glucose.**
- **GLP-1 analogues provoke significant weight loss, which is especially important when considered against the weight gain associated with, e.g., sulfonylureas, TZDs, and insulin, while DPP4 inhibitors are weight neutral.**
- **The glucose-lowering effect of incretin based therapy is glucose dependent; in other words, the risk of hypoglycemia is very low.**
- **Based on these advantages, incretin-based therapies have been mentioned in recent treatment algorithms for the treatment of Type 2 Diabetes.**

UNIT NO. 5

METABOLIC SURGERY: A NEW APPROACH IN THE TREATMENT OF METABOLIC DISEASE OF THE 21ST CENTURY

Dr Tham Kwang Wei, Dr Daniel Wai Chun Hang, Dr Alvin Eng Hock Kim, Dr Shanker Pasupathy

ABSTRACT

Metabolic surgery is "the operative manipulation of a normal organ or organ system to achieve a biological result for potential health gain" [1]. More recently, it has been applied to describe the stunning reversal of metabolic disorders noted after bariatric (weight loss) surgery. Indeed, the improvement in conditions such as type 2 diabetes mellitus, hypertension, dyslipidaemia and non-alcoholic fatty liver disease have been so dramatic that national obesity surgery societies have quickly added "metabolic" to their names to capitalise on the health benefits of these procedures. These recent findings, well-documented over the past 2 decades, have added a new dimension to bariatric surgery which hitherto was focused on weight loss, giving rise to the present specialty of metabolic-bariatric surgery (MBS). This paper looks at the various types of metabolic surgical interventions and analyses the purported benefits in improving each of these obesity-related metabolic disorders. The appropriate indications for surgery and possible complications arising are also discussed.

Keywords: metabolic bariatric surgery, weight loss, diabetes, remission, mortality

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INTRODUCTION

The rise in obesity world-wide is paralleled by a steep rise in metabolic disorders such as type [2] diabetes mellitus (T2DM), hypertension, dyslipidaemia, stroke, sleep apnoea and non-alcoholic fatty liver disease (NAFLD) [2]. In Singapore, a rise in the prevalence of obesity (defined as a body-mass index {BMI} $\geq$30kg/m^2) from 6.9% in 2004 to 10.8% in 2010, saw a parallel increase in the T2DM prevalence of a similar magnitude – from 8.9% to 11.6%.

The postulate that obesity, and in particular, visceral adiposity, is correlated to metabolic diseases was conceptualised in the "Syndrome X"[3], now more commonly known as the metabolic syndrome. All these conditions contribute to atherosclerosis resulting in end-organ complications such as coronary artery disease, stroke, and peripheral vascular disease. The microvascular complications of T2DM also result in retinopathy, nephropathy and neuropathy.

There is much evidence for a critical link between obesity and metabolic disease, and a rise in BMI is positively correlated with a rise in mortality[4]. Fortunately, intensive lifestyle intervention with successful weight loss can markedly improve glycaemic and lipid profiles and cardiovascular risk in diabetic patients[5]. Weight loss can even prevent or delay the development of T2DM in susceptible individuals[6]. Similar benefits are observed after weight-loss (bariatric) surgery. In Dr Pories' landmark study in 1995, 83% of the obese diabetic patients who had a gastric bypass underwent "remission" of T2DM, without need for diabetic medication while nearly all patients with impaired glucose tolerance (IGT) never went on to develop diabetes[7].

Further evidence from the bariatric surgery literature gave rise to the awareness in the 1990s that weight loss surgery was in fact more significant in treating metabolic disorders than obesity itself! As a result, the specialty has been renamed in many centres across the globe as metabolic-bariatric surgery (MBS). MBS is growing at an exponential rate, partly due to the widespread adoption of newer, minimally invasive (laparoscopic or key-hole) surgical techniques and the use of less aggressive interventions such as gastric banding, which avoid any cutting or stapling of the stomach.

We discuss the types of surgical interventions, the benefits of MBS as well as its risks and complications. Last but not least, the selection of the suitable patient along with the appropriate intervention is of critical consideration.

TYPES OF INTERVENTIONS

The surgical options for treating metabolic disease arise from

traditional bariatric surgical procedures [8]. They may be divided into 2 categories according to their mechanism of action: a) restrictive and b) bypass-type (malabsorptive) procedures.

Early attempts at metabolic surgery involved intestinal bypass in an attempt to interrupt the entero-hepatic circulation of cholesterol and bile acids to treat severe hypercholesterolemia [9]. However, these procedures are less commonly performed today due to the potential for severe protein-loss and nutritional deficiencies, and safe and effective lipid-lowering medications are now available.

Restrictive procedures result in a smaller gastric reserve hence limiting intake and are gradually gaining traction among both patients and surgeons as they are less complex than the bypass-type procedures, and are less likely to require life-long vitamin and nutrient supplementation. Laparoscopic adjustable gastric banding (LAGB) (Figure 1) involves the placement of an inflatable balloon around the proximal circumference of the stomach resulting in a gastric pouch of 30 ml, thus increasing the sensation of satiety in patients. Laparoscopic sleeve gastrectomy (LSG) (Figure 2) involves the reduction of stomach volume to approximately 15% of its original capacity by resecting the greater curve.

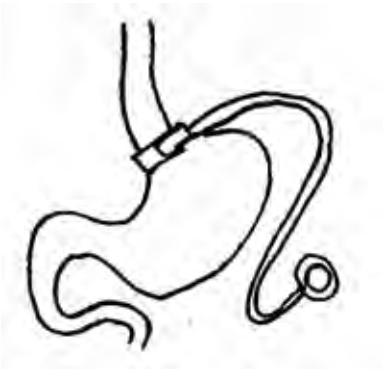

Figure 1. Adjustable gastric band

Figure 2. Sleeve gastrectomy

The most commonly performed bypass-type operation today is the laparoscopic Roux-en-Y gastric bypass (LRYGB) (Figure 3). This is a combined restrictive-malabsorptive procedure which essentially works by (a) reducing the functional stomach to approximately 30ml or less; (b) delaying gastric emptying by reducing the gastric outlet to approximately 1 cm or less; (c) bypassing the foregut with a 40-150 cm Roux-en-Y gastrojejunostomy, causing reduced nutrient absorption. Depending on the length of the bypassed intestine, there is a risk for malnutrition, in particular of vitamin B12, iron, calcium, and 25-vitamin D. Therefore, patients require lifelong vitamin and mineral supplementation. More extensive bypass-type procedures include bilio-pancreatic diversion (BPD) and BPD with duodenal switch (BPD-DS), which result in the largest amount of weight loss, but are associated with higher operative mortality and risk of nutritional deficiencies due to the longer intestine bypassed.

Figure 3. Roux-en-Y gastric bypass

Weight loss is greater with the bypasses compared with the restrictive procedures. It is greatest typically at 1-2 years and mostly sustained at 10-15 years. Unlike medical therapy, weight loss with MBS is durable. Compared with control subjects, patients with MBS had an average (absolute) weight loss of 23.4% and 16.1% from baseline at 2 and 10 years respectively while the control group had a weight gain of 0.1% and 1.6%. Typical weight losses at about 2 years in the subgroups are: gastric bypass 32% and gastric banding 20%. After 10 years, most of the weight lost is still sustained with weight losses from baseline stabilised at 25% and 14%, respectively[10]. In comparison to banding and bypass, LSG is a relatively new technique and performed widely as a stand-alone weight-loss procedure only in the last 5 years.[11] Long term data on durability of weight loss and impact on metabolic co-morbidities is not yet available for the gastric sleeve procedure.

Pure "metabolic" surgery, i.e. interventions that seek to change physiology without achieving weight loss, and therefore applicable to normal weight individuals - such as endoluminal sleeves, gastric electro-stimulation, duodeno-jejunal bypass and ileal transposition[12-14] - are still considered to be at the

experimental stage and will not be discussed further in this article.

METABOLIC EFFECTS OF MBS

Metabolic surgery aims to effect physiologic changes to either improve or "reverse" the various components of the metabolic syndrome, thereby reducing the risk of cardiovascular complications long-term. With durable weight loss and permanent changes to gastrointestinal anatomy, the beneficial effects of metabolic surgery on the various cardiovascular risks are noted to be sustained as well.

EFFECT OF MBS ON TYPE 2 DIABETES MELLITUS

The greatest metabolic risk associated with obesity is T2DM, a progressive disorder characterised by insulin resistance, which is largely as a result of visceral obesity, and concomitant impaired insulin secretion.

A large body of evidence suggests that MBS results in remission of T2DM, defined as normal sugars without the use of DM medications, the degree of which is proportional to the extent of excess weight loss, with LAGB having the least (56.7%) and LRYGB and BPD/DS seeing the highest rates of remission (80.3% & 95.1% respectively) (Table I). This remission is sustained in about half of these patients up to 10 years while matched obese controls on medical weight loss treatment are at a 4-fold higher risk of developing diabetes[16]. The benefits of IGT reversal to normoglycaemia after MBS (~99% of subjects) are also noted to be sustained over the 14-year period of the study by Pories et al [7].

Multiple mechanisms are responsible for this phenomenon, including restriction of caloric intake with resultant weight loss. However, early remission of DM has been reported even before significant weight loss has taken place[7], triggering postulated mechanisms that MBS invokes altered foregut and hindgut hormonal balances independent of weight loss. Proponents of gastric bypass are convinced that bypass of the duodenum has a positive impact on glucose metabolism by diminishing inhibitory peptides from the duodenum ("anti-incretins") which oppose the effects of incretin hormones such as glucagon-like peptide[1] (GLP-1) this is called the "foregut hypothesis". After bypass procedures, the increased transit time of food passage leads to rapid delivery of nutrients to the hindgut with accelerated/early and enhanced secretion of GLP-1, which is increased by 40% (the "hindgut hypothesis") [17].

LRYGB and LSG have been used in clinical studies for the treatment of T2DM in non-obese patients and early results show that while it is effective in some, the benefit is lower than that observed in obese patients [18,19].

EFFECT OF MBS ON HYPERTENSION

Similarly, hypertension is noted to improve or resolve in about 79% of patients after MBS. In 66% of patients, normal blood pressures are attained without need for medications[20]. These effects are greatest at 1-2 years and somewhat sustained at 10 years though with a drift back to baseline in the long-term [16]. Potential mechanisms of MBS on hypertension include a reduction in visceral adiposity which in turn reduces the inflammatory cytokines like tumour necrosis factor and the interleukins. A reduction in peri-renal fat may also play a part in reducing intravascular volume via renin [21].

Table I: T2DM resolution after various metabolic surgery procedures

	Total	Gastric Banding	Gastroplasty	Gastric Bypass	BPD/DS
% EBWL	55.9	46.2	55.5	59.7	63.6
% Resolved overall	78.1	56.7	79.7	80.3	95.1
% Resolved <2 y	80.3	55.0	81.4	81.6	94.0
% Resolved ≥2 y	74.6	58.3	77.5	70.9	95.9

Adapted from Buchwald H et al. [15]

Excess weight is the weight difference between one's current weight and one's weight based on the population-designated ideal BMI. In this series, the mean excess weight loss (EWL) is 61.2 per cent, with greater weight loss with the bypass procedures (63.6% for BPD/DS) than with the restrictive procedures (47.5% for gastric banding).

EFFECT OF MBS ON LIPIDS

Obesity and insulin resistance is associated with dyslipidaemia in the form of lower high density lipoprotein (HDL)-cholesterol, hypertriglyceridemia (TG), and low density lipoprotein (LDL) particles that are small and dense[22]. Individuals with such dyslipidaemia have much higher cardiovascular risk than those without[23]. Metabolic and bariatric surgery (MBS) reverses this dyslipidaemia by increasing the HDL-c and lowering the TG [24,25], as well as reduction of the small-dense LDL particle [26]. MBS has been shown to reduce cardiovascular mortality in prospective studies [27] and the favourable lipid changes have certainly contributed to it [28]. Interestingly, this improvement is correlated more with the decrease of insulin resistance rather than the extent of weight loss alone [24], suggesting that the beneficial effects of MBS on lipids work through tackling insulin resistance.

EFFECT OF MBS ON NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

NAFLD encompasses a spectrum of liver disorders starting with simple steatosis, then progressing to non-alcoholic steatohepatitis (NASH) and finally cirrhosis. It has become the most common chronic liver disorder in the general population affecting up to 35% of urbanised Asians [29]. The prevalence of NAFLD is high in the overweight (67%) and obese (91%), with insulin resistance as one of the key elements in its pathogenesis [30]. Simple steatosis is rather benign, but NASH is associated with much higher risk of progression to cirrhosis[31]. The dramatic weight loss and reduction of insulin resistance also ameliorate the early stages of NAFLD, improving simple steatosis in 92%, NASH 81% and fibrosis 69.5%, with 70% chance of complete resolution of NASH [32]. The complication rate of MBS in patients with compensated cirrhosis is 2.2 times that of patients without, but patients with decompensated cirrhosis had a complication rate 21.2 times [33]. Long time data is not yet available for patients with cirrhosis, but it is clear that MBS should be performed before patients with cirrhosis become decompensated.

EFFECT OF MBS ON OBSTRUCTIVE SLEEP APNOEA (OSA)

OSA is estimated to affect 25% of the general population but as high as 45% in the obese and 70% in patients going for MBS [34] and implicated in the aetiology of hypertension and the progression of diabetes, pulmonary hypertension, atrial fibrillation and congestive heart failure [35]. It may worsen weight gain through reduced activity and increased appetite [36]. Bariatric surgery reduces apnoea hypopnoea index (AHI) from 55 to 16 events per hour with an average reduction of body mass index (BMI) of 15 kg/m^2 [34].

EFFECT OF MBS ON CANCER

Overweight and obesity is estimated to account for 20% of all cancers [37]. Obesity leads to insulin resistance, hyperleptinaemia, increased plasminogen activator inhibitor-1, increased endogenous sex hormones, chronic inflammation and decreased adiponectin levels are all thought to contribute to the increased risk [38]. Indeed, MBS decreases cancer mortality by 60%[27] and cancer incidence by 33%[39] probably by reversing a lot of the effects of obesity.

MORTALITY OUTCOMES

Despite the higher risks morbidly obese patients pose during surgery, the mortality rates related to MBS are reportedly low at 0.1% to 2.0%, with greater risks with the more drastic bypass procedures. Common causes of death are pulmonary embolism and anastomotic leaks [8,40]. In the long-term, MBS has been shown to reduce mortality. In the landmark Swedish Obese Subjects (SOS) study, a well-matched, prospective study which followed 2010 obese subjects who have undergone MBS and their 2037 matched controls treated medically over 16 years, there was an overall relative reduction in mortality of 34% in MBS subjects, with most of the reduction in cardiovascular and cancer-related deaths [10].

INDICATIONS FOR METABOLIC SURGERY

There is no doubt that MBS benefits morbidly obese patients with multiple features of the metabolic syndrome in the long-term with mortality reductions [10, 27]. For patients suffering from T2DM, the sustained effect of MBS on glycaemic control is so dramatic that the American Diabetes Association and the International Diabetes Federation have recommended that MBS may be considered a treatment option in carefully selected patients with a BMI $\geq$30kg/m^2 and in whom glycemic control is suboptimal despite currently available pharmacotherapy[41, 42]. The Singapore Ministry of Health's 2004 Clinical Practice Guidelines on obesity allows for MBS at a BMI of $\geq$ 32.5kg/m^2 in people with obesity-related conditions like T2DM, dyslipidaemia, OSA and hypertension.

Bariatric surgery is a life-changing procedure associated with known risks and complications. Patients should be well informed about the restriction on eating ability and must be prepared to commit to life-long follow-up to treat and prevent potential complications such as nutrient deficiencies. Generally, there are relatively few contraindications for MBS (e.g. unstable coronary artery disease, active cancer with limited life expectancy). However, often overlooked are psychosocial factors such as low socioeconomic status, limited social support, unrealistic expectations and disordered eating habits (e.g. binge eating), which are associated with a suboptimal outcome and should be carefully screened for and dealt with along with the medical and surgical aspects of MBS. Hence for best long-term outcomes, the patient should be cared for by a trained multi-disciplinary team and patients must realistically understand this.

CONCLUSIONS

1) MBS is an effective, durable and safe treatment modality for metabolic diseases, in particular T2DM.

2) Furthermore, reduced mortality particularly related to T2DM, CVD and cancer, has been observed in the long-term.

3) However, careful patient selection with long-term management and close monitoring by an experienced and trained multi-disciplinary team should be considered mandatory to minimise the risks and maximise the benefits of MBS in these appropriately selected patients.

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LEARNING POINTS

- **Metabolic bariatric surgery (MBS) is effective, durable and safe treatment modality for metabolic diseases in the morbidly obese, in particular T2DM.**
- **In the long term metabolic bariatric surgery results in reduced mortality particularly related to T2DM, CVD and cancer.**
- **The surgical procedures for treating metabolic disease are divided into: (a) restrictive and (b) bypass-type (malabsorptive) procedures.**
- **Restrictive procedures are gradually gaining acceptance among both patients and surgeons as they are less complex than the bypass-type procedures and are less likely to require life-long vitamin and nutrient supplements.**
- **According to the Singapore Ministry of Health's 2004 Clinical Practice Guidelines on obesity, MBS is indicated for patients with BMI $\geq$32.5kg/m^2 with T2DM and /or other obesity related co-morbidities.**
- **The International Diabetes Federation (IDF) recommends that MBS may be considered a treatment option in carefully selected patients with a BMI $\geq$30kg/m^2 (Asian BMI $\geq$27.5kg/m^2) in whom glycemic control is suboptimal despite currently available pharmacotherapy.**

UNIT NO. 6

RETHINKING THE STRATEGIES IN HYPERTENSION MANAGEMENT

Dr Akira Wu

ABSTRACT

The prevalence rates of hypertension are expected to increase globally. Hypertension accounts for the majority of stroke and at least half of heart attacks. Blood pressure lowering results in significant reduction in coronary artery disease events and stroke. Therapeutic intervention in high normal blood pressure delays the onset of hypertension but its long term benefits are uncertain. In hypertension with co-morbidities, the lower achievable blood pressure may not be better in view of concerns over the J curve effect of excessive blood pressure reduction. Hypertension predisposes to the onset of diabetes which may be accelerated by certain classes of anti-hypertensive agents, namely diuretics or beta-blockers. In the very elderly, the cardiovascular benefits of blood pressure lowering can be substantial. Improved cardiovascular outcomes are achieved by combination therapies which have clearly demonstrated pronounced blood pressure lowering and higher control rates. Certain drug components of the combination therapy may be preferred to improve cardiovascular outcomes. Dual renin-angiotensin aldosterone system blockade should not be routinely used but is indicated for hypertensive patients without heart severe heart failure or chronic renal disease with heavy proteinuria. The many advantages of single pill combination therapy will improve the overall management of hypertension.

Keywords: Etiologic consideration; Dual RAAS blockade; Diabetes; Single pill combination therapy

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INTRODUCTION

Approximately 26.4% of the adult population worldwide had hypertension in 2000, and this is expected to increase to 29.2% by 2025[1]. Hypertension accounts for approximately two-thirds of all strokes and 50% of heart attacks. There was a 22% reduction in coronary heart disease (CHD) events and a 41% reduction in stroke for a systolic BP reduction of 10 mm Hg or diastolic BP reduction of 5mmHg[2]. The slope of the relationship between blood pressure (BP) and stroke in individuals of the Asia-Pacific region is steeper than that observed in western populations[3]. It is anticipated that a better control of hypertension among Asians might have substantial beneficial effects on the cardiovascular morbidity and mortality. Unfortunately, blood pressure control rates are far from optimal in most populations [4, 5]. This mini-review will highlight some recent developments in hypertension research that may influence our strategies in improving management of hypertension.

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ETIOLOGIC CONSIDERATION

Although 90% of hypertension is essential or idiopathic, the rest is caused by kidney disease, vascular (arterial) stenosis, endocrinopathies, obesity and poly-pharmacy. An integral part of the assessment for hypertension should include the patient's cardiovascular (CV) risk and co-morbidities, and target organ involvement in the heart (LVH) or in the kidney (proteinuria). Some of the key patho-physiologic considerations which may influence therapeutic approach, are volume regulation (sodium and fluid balance, ADH, aldosterone etc), sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), vasoactive substances such as nitric oxide, prostaglandins, endothelin, endothelium-derived hyperpolarising factor (EDHF), associated co-morbidities such as obesity, sleep apnoea, and genetic factors. The kidney plays a pivotal role in salt and water intake and excretion which have a direct influence on volume status. The INTERSALT Study confirmed a direct relationship between sodium and mean blood pressure [6]. Hypertensive patients can have chronically increased levels of renin despite feedback mechanisms [7]. Aldosterone promotes hypertension by sodium retention contributing to volume expansion, up-regulation of angiotensin II (Ang II) receptors and potentiation of pressor responses of Ang II [8]. Over-activity of the sympathetic nervous system may contribute to hypertension. Alpha 1, alpha 2 and beta receptors mediate cellular responses to catecholamines. Activation of alpha 1 receptors results in vasoconstriction contributing to increased blood pressure [9]. Vasoactive substances synthesised in the vascular wall also play a vital role in the pathogenesis of hypertension. The key vasoactive substances are nitric oxide (vasodilation), prostaglandins (vaso-constriction), enthothelin I (ET)-1 which counters the effects of nitric oxide and EDHF which is vasodilating [10]. Some of the important co-morbidities in hypertensive patients are obesity and insulin resistance [11].

PRE-HYPERTENSION

Pre-hypertension is defined by JNC-7 as the blood-pressure range of 120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic [12]. The condition heralds arterial hypertension and thus may be considered a starting point in the cardiovascular

disease continuum. Pre-hypertension is associated with excess morbidity and death from cerebrovascular causes [13, 14]. Unfortunately, current preventive strategies which aim at preventing the progressive rise in blood pressure using the recommended lifestyle modifications are weak.

Two trials [15, 16] involving pre-hypertensive individuals showed an angiotensin-converting enzyme inhibitor (ACEI) and an angiotensin receptor blocker (ARB) were able to lower blood pressure below 140/90 mmHg during therapy. However, blood pressure of most subjects rose above 140/90 mmHg following cessation of the drug. Pre-hypertension remains a useful designation to identify individuals at high risk of developing hypertension so that measures can be undertaken to prevent the disease from developing.

NEW CHALLENGES IN BLOOD PRESSURE GOALS

Most guidelines for the initiation of antihypertensive therapy advocate the target BP < 140/90 mmHg for patients with or without risk factors or target organ damage, or less than 130/80 mmHg for patients with diabetes or chronic kidney disease (CKD). However, there are some concerns over the possible existence of J-curve for lowering blood pressure too excessively in patients with pre-existing coronary artery disease [17, 18].

In patients with isolated systolic hypertension, an increase in stroke was observed when diastolic pressures were brought down from 90 mmHg to below 65 mmHg. CKD patients had an increase in strokes when systolic blood pressure was lowered below 120 mmHg [19]. Other studies [20, 21] have shown that systolic blood pressures of less than 120 mm Hg and diastolic blood pressures of less than 60 mm Hg have been associated with increased mortality. On the other hand, patients with pre-existing cerebrovascular disease had the greatest protection against recurrence if the systolic blood pressure was reduced below 120 mmHg [22]. The findings of a meta-analysis of seven randomised, controlled trials suggest the increased risk for events observed in patients with low blood pressure was not related to antihypertensive treatment. Poor health conditions leading to low blood pressure and an increased risk for death probably explain the J-curve [23].

Reduction of BP in patients with hypertension (>140/90 mmHg) and diabetes is known to reduce the risk of cardiovascular events [24, 25, 26]. An old mantra of hypertension management is that "the lower the blood pressure, the better". However, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [27] of diabetic patients with hypertension, no significant difference in risk of nonfatal MI or cardiovascular-related death was observed when comparing the intensive-therapy (SBP < 120 mmHg) and standard-therapy (SBP < 140 mmHg) groups. However, a significant 42% reduced risk of total stroke and 38% reduced risk of nonfatal stroke were observed with intensive therapy. Significant adverse events attributed to antihypertensive therapy were significantly more frequent in the intensive treatment group. The ACCORD investigators concluded that their results provide no evidence that intensive BP control reduces the rate of a composite of major cardiovascular events, such as hypotension (most significant), bradycardia and hyperkalaemia. Adverse laboratory measures include hypokalaemia, increased serum creatinine and decreased glomerular filtration rate. Other adverse clinical measures were decreased high density lipoprotein and increased triglyceride.

Similarly, in The International Verapamil SR/ Trandolapril (INVEST) study [28], no difference was seen in diabetic patients with coronary artery disease when comparing the tight-control (SBP <130 mmHg) and usual-control (SBP 130 to < 140 mmHg) groups with regard to the rate of the primary outcome (first occurrence of all-cause death, nonfatal MI, or nonfatal stroke). However, a significant 8% increase was seen in the relative risk of all-cause mortality in the group with tight systolic control BP (P = 0.04), suggesting a J-shaped curve for the relationship between systolic blood pressure and mortality [29].

Furthermore, a retrospective analysis of outcomes in 25,588 high-risk subjects in ONTARGET [30] revealed no relationship between in-trial systolic blood pressure reduction and risk of myocardial infarction, heart failure, and cardiovascular mortality. On the basis of available evidence from placebo-controlled trials, randomised trials, and achieved BP analyses, it would appear that the target BP levels recommended in current guidelines (<130/80 mmHg) are not supported for the prevention of macrovascular outcomes in patients with diabetes.

The ongoing NIH-sponsored Systolic Blood Pressure Intervention trial (SPRINT) [31] will test the hypothesis that lowering of systolic blood pressure to <120 mmHg compared to <140 mmHg is more effective in reducing cardiovascular events in 9,250 high risk subjects with CKD, older age (> 55 years) or underlying cardiovascular disease.

In elderly patients (80 years or older) with hypertension (SBP >160 mmHg), the HYVET study [32] showed that reducing SBP to ≈143.5/75.4 mm Hg with active treatment and to 158.5/84 mm Hg with placebo resulted in a 39% significant reduction in the risk of fatal stroke. The active treatment studied was indapamide SR (1.5mg). Also, Perindopril 2-4mg was added when necessary, in order to achieve target blood pressure of SBP 150mmHg and DBP 80mmHg. There was also an impressive 64% reduction in the rate of heart failure, which was highly significant. The study was stopped prematurely after a median follow-up of 1.8 years because of a significant reduction in all-cause mortality of 21% in favour of active treatment. The HYVET study has provided unequivocal evidence that the benefits of BP lowering in the very elderly can be very substantial.

DUAL RAAS BLOCKADE

Several studies have suggested that combining an ARB with an ACEI may provide a more complete blockade of the RAAS in the treatment of diabetic and non-diabetic nephropathy and essential hypertension; in particular, it may lower BP and proteinuria further than monotherapy [33, 34]. In patients with high CV risk, ACEI and ARB are virtually identical in providing CV protection as shown in the ONTARGET study [35].

However, the renal data from the ONTARGET study suggest that an ACEI/ARB combination has no advantages and should not be routinely used for hypertensive patients without severe heart failure or chronic renal disease with heavy proteinuria. The combined treatment with an ACEI and an ARB worsened renal outcome despite lowering proteinuria to a greater extent. Furthermore, the study has limited generalisation to the general diabetic nephropathy population, considering that only 13% had microalbuminuria and 31% were normotensive.

In the meantime, the addition of an ARB should be considered for patients with heart failure due to reduced left ventricular ejection fraction who have persistent symptoms, or a progressive worsening of symptoms, despite therapy with an ACE inhibitor and a β-blocker [36]. A recent trial found that of the 1750 patients (5.4% of the study population) who received combination therapy, 86.4% did not have trial-established indications such as heart failure or proteinuria [37].

Combining a direct renin inhibitor (DRI) with an ACEI or an ARB has been shown to produce additional blood pressure [38] or albuminuria [39] reductions respectively. The long-term benefits of combining a DRI and an ARB in diabetic patients with high CV and renal risk should be known when the results of ALTITUDE study [40] are available in the near future.

HYPERTENSION AND NEW-ONSET DIABETES

Individuals with hypertension are at increased risk of developing diabetes. Antihypertensive agents have a variable influence on the rate of development of diabetes with diuretics and beta-blockers accelerating, and ARBs slowing the process; calcium channel blockers (CCBs) appear neutral [41]. Whether or not drug-related, hypertensive patients who develop new-onset diabetes are at high cardiovascular risk [42].

A recent meta-analysis used 11 randomised, placebo-controlled clinical trials, with a total of 84,363 patients, to study whether the administration of ACEIs or ARBs reduced the incidence of new-onset diabetes[43]. The results showed that ARBs significantly reduced diabetes incidence (OR, 0.8; CI, 0.8-0.9; P < .01). Incidence was also lower for ACEIs (OR, 0.8; CI, 0.7-1.0) but was only marginally significant (P = .07). The findings of the this meta-analysis are consistent with the 2 trials, DREAM [44] and NAVIGATOR [45] which found lower but non-statistically significant diabetes incidence with ACEIs, and significantly lower incidence with ARBs. Pre-treatment plasma glucose is by far the most important predictor of new-onset diabetes and its excessive risk of CV events [46, 47]. Multi-factorial intervention remains the primary goal in patients at high risk of developing diabetes.

SINGLE PILL COMBINATIONS

In complicated hypertension, more than 2 antihypertensive agents were usually required to reach goal BP levels as specified in various trials (ALLHAT, LIFE, ASCOT) on hypertension [48, 49, 50]. JNC7 was the first guideline advocating first-line combination therapy for those subjects requiring ≥ 20/10mmHg blood pressure reduction (stage 2 hypertension) [51].

The recognition of the need for several drugs to achieve control led to the development of single-pill combination therapies involving almost all newer classes of antihypertensive agents. Single pill combinations offer many advantages which include ease of administration, minimisation of side effects due to lower doses of component drugs, synergistic mechanisms of drug actions, and improved compliance. The other advantage of single pill combinations is to provide the opportunity for early achievement of blood pressure goals to impact positively on CV outcome as shown in the VALUE trial [52].

The recently published ACCOMPLISH trial [53] started to address the issue of the impact of different combinations of antihypertensive agents on the outcomes of hypertensive subjects at high risk. This study recruited 11,506 high risk hypertensive patients who were randomised to either ACEI/HCTZ combination or ACEI/CCB combination. The results showed ACEI/CCB was preferable to ACEI/HCTZ in significantly reducing CV events and mortality. In addition, significantly more patients in both arms achieved over 75% control rate with single pill combinations than with free combinations. However, a recent study [54] showed that the ARB/diuretic combination decreased urinary albumin:creatinine ratio (UACR) significantly more than the ARB/CCB combination, and this decrease in UACR was associated with a greater magnitude reduction in sleep SBP. Powerful epidemiological associations with even smaller amounts of albuminuria have been made with the risk of renal failure and cardiovascular events [55, 56].

CONCLUSIONS

In conclusion, the quest for higher rates of blood pressure control continues to be a challenge. Therapeutic reduction of high normal blood pressure delays the onset of hypertension but its long term benefits remain unproven. The ideal blood pressure goals for hypertensive patients remain uncertain as more randomised control trials are needed to address this issue. In the very elderly, the benefits of blood pressure lowering can be substantial. Dual RAAS blockade should only be used in hypertensive patients with certain co-morbidities. The combination of a RAAS blocker with a CCB appears to be an appropriate, and even superior, choice for the treatment of high-risk patients with hypertension. Single pill combinations are certain to play a more important role in the therapeutic management of hypertension.

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LEARNING POINTS

- **Blood pressure lowering results in significant reduction in coronary artery disease events and stroke.**
- **Hypertension predisposes to the onset of diabetes which may be accelerated by certain classes of anti-hypertensive agents, namely diuretics or beta-blockers.**
- **In the very elderly, the cardiovascular benefits of blood pressure lowering can be substantial. Dual renin-angiotensin aldosterone system blockade should not be routinely used but is indicated for hypertensive patients without heart severe heart failure or chronic renal disease with heavy proteinuria.**
- **The advantages of single pill combination therapy in hypertension offer the advantages of ease of administration, minimisation of side effects due to lower doses of component drugs, synergistic mechanisms of drug actions, and improved compliance.**

ASSESSMENT OF 30 MCQs

FPSC NO : 45
MCQs on CARDIOMETABOLIC RISK UPDATE
Submission DEADLINE: 2 December 2011

INSTRUCTIONS

- **To submit answers to the following multiple choice questions, you are required to log on to the College On-line Portal (www.cfps2online.org).**
- **Attempt ALL the following multiple choice questions.**
- **There is only ONE correct answer for each question.**
- **The answers should be submitted to the College of Family Physicians Singapore via the College On-line Portal before the submission deadline stated above.**

1. In 2009, cardiometabolic diseases accounted for X% of the total deaths of 17,101 in Singapore. What is X?

A. 28.9.
B. 30.9.
C. 32.9
D. 34.9.
E. 36.9.

2. About the terms related to cardiometabolic diseases, which of the following statement is CORRECT?

A. "Metabolic syndrome" is specific subset of "cardiometabolic risks" that when clustered together increase overall lifetime cardiovascular risks by 3 fold.
B. "Global cardiometabolic risk" represents the comprehensive catalogue of factors that contribute to the development of both cardiovascular disease (CVD) and Type 2 diabetes.
C. "Risk assessment" describes the relative cardiovascular risk of the patient with regards to cardiometabolic disease
D. "Metabolic syndrome" is a cluster of 5 diseases namely cardiovascular disease, cerebrovascular disease, peripheral arterial disease, chronic renal disease, diabetic retinopathy.
E. "Global cardiometabolic risk" quantifies the risk of cardiometabolic disease in absolute terms.

3. In younger men with erectile dysfunction, the Framingham risk assessment has X sensitivity with regards to cardiovascular risk. What is X?

A. Good.
B. Fairly good.
C. Inadequate.
D. Poor.
E. Excellent.

4. Miss Tan aged 27 is diagnosed to have polycystic ovary syndrome. Which of the following is likely to be present?

A. Pregnancy
B. Alopecia.
C. Downy hair on the face.
D. Hyperandrogenism.
E. Bipolar disorder.

5. A 30-year-old man is on antipsychotic medications and he has put on 10 kg since starting on the medications. Which of the following would result in the greatest weight loss?

A. Thyroxine.
B. Glipzide
C. Niacin.
D. Orlistat.
E. Metformin.

6. In the pharmacological treatment of a patient with mixed dyslipidaemia to reduce cardiovascular mortality, which of the following statement is CORRECT?

A. Fibrates monotherapy is effective for primary prevention
B. Fibrates monotherapy is ineffective for secondary prevention.
C. In patients on niacin, adding a fibrate reduce mortality further.
D. Niacin monotherapy is effective for secondary prevention.
E. In patients treated with a statin, adding a fibrate reduces mortality further.

7. In mixed dyslipidaemia, the primary goal of lipid therapy is to reduce LDL-C to target with X. What is X?

A. Combination of niacin and omega-3 fatty acid.
B. Fibrate.
C. Statin.
D. Niacin.
E. Omega-3 fatty acid.

8. About a defined target for treatment of mixed dyslipidaemia, which of the following is the target to be achieved for the very high risk patient?

A. LDL-cholesterol to 100mg/dL.
B. LDL-cholesterol to less than 70mg/dL.
C. LDL-cholesterol to less than 80mg/dL.
D. HDL-cholesterol to 50mg/dL .
E. Triglycerides to less than150mg/dl.

9. With regards to the use of Fibrates in treatment of dyslipidaemia:

A. In Helsinki Heart study, gemfibrozil had a 50% relative risk reduction in CAD.
B. In the FIELD study, fenofibrate reduced CVD risk by 27% in mixed dyslipidaemia.
C. Combination therapy gives fewer reports of skeletal muscle adverse events.
D. Fenofibrates plus statin reduce more CVD events than statins alone in ACCORD trial with diabetic patients.
E. All of the above are correct.

10. In mixed dyslipidemia, which of the following lipid profile is expected to be present?

A. High TG, High HDL-C, and small dense VLDL-C.
B. High TG, High HDL-C, and big dense VLDL-C.
C. Low TG, low HDL-C, and small dense LDL-C
D. Low TG, low LDL-C, and big dense LDL-C.
E. High TG, low HDL-C, and small dense LDL-C.

11. With regards to coronary heart disease (CHD) events and LDL levels, most studies showed that X% of CHD occur in patients with "normal" or "near normal" LDL levels. What is X?

A. 40-50.
B. 50-60.
C. 60-70.
D. 70-80.
E. 80-90.

12. For the past few decades, in the pharmacological management of dyslipidemia, the reduction of X levels has been the main objective of lipid lowering therapy. What is X?

A. Non-high density lipoprotein cholesterol (non-HDL-cholesterol).
B. Very low density lipoprotein cholesterol (VLDL-cholesterol).
C. High density lipoprotein cholesterol (HDL-cholesterol.
D. Triglyceride.
E. Low density lipoprotein cholesterol. (LDL-Cholesterol)

13. In the patient whose triglycerides level remains high (more than 200 mg/dL), or HDL-cholesterol remains low (less than 40 mg/dL) even if he has achieved his LDL-cholesterol goals, what is the secondary target of therapy?

A. Non-HDL cholesterol level.
B. Triglycerides level.
C. LDL-cholesterol level.
D. Chylo-micron level.
E. VLDL cholesterol level.

14. The treatment of choice for a patient with dyslipidemia and residual cardiac risk is X. What is X?

A. Combination of fibrate and niacin.
B. Combination of statin and niacin.
C. Combination of ACE-Inhibitor and calcium channel blocker.
D. Combination of rostrivastatin and simvastatin.
E. Combination of omega-3 fish oil and simvastatin.

15. Which of the following is a common side effect of niacin?

A. Cough.
B. Postural hypotension.
C. Flushing.
D. Constipation.
E. Urticaria.

16. About incretins, which of the following description is CORRECT?

A. Synthetic hormones manufactured to treat raised blood sugar.
B. Yeast preparations that can lower blood sugar.
C. Gut derived peptide hormones released from intestinal K and L cells.
D. Specific receptors on alpha cells of the pancreas.
E. Herbal preparations that can lower blood sugar.

17. About the action of Glucagon-like peptide-1 (GLP-1), which of the following action is CORRECT?

A. It can increase glucagon secretion.
B. Support the synthesis of proinsulin to replenish insulin stores in alpha cells.
C. It can raise glucagon concentrations.
D. Can increase gastric emptying and induce beta cells to respond to inhibitory action of hyperglycaemia
E. It can increase insulin secretion.

18. About the currently available incretins, which of the following is CORRECT?

A. They have a very long half life of more than 24 hours
B. They are used to treat type I diabetics.
C. They cannot be broken down by proteolytic degration.
D. They naturally and do not need any modifications to change its function for clinical practice
E. They can reduce HbA1C by about 0.7 to 1%.

19. About Incretin-based therapy in people with diabetes:

A. GLP-1 can be potentiated by inhibiting the proteolytic degradation and inactivation through the action of DPP-4.
B. Most DPP-4 inhibitors can lower HbA1C by more than 2%.
C. Causes weight gain like in other oral hypoglycaemics.
D. Pancreatitis is a very common side effect if such therapies.
E. All of the above are correct.

20. About Incretin based therapies, which of the following is CORRECT?

A. Is useful especially for post prandial treatment of hypoglycaemia.
B. GLP-1 analogues have a neutral effect on weight.
C. Is classified as Tier 1 for American Diabetic Association for treatment of Diabetes.
D. The American Association of Clinical Endocrinologists has put incretin based therapy as first line therapeutic agent.
E. ALL of the above are correct.

21. Intensive lifestyle intervention and weight loss can result in X. What is X?

A. Improved thyroid function.
B. Delay of development of Type I Diabetes.
C. Improved glycaemic and lipid profile in people with diabetes.
D. Increased cardiovascular risk in susceptible individuals.
E. ALL of the above are correct.

22. In the various types of Metabolic Bariatric Surgeries (MBS) available nowadays:

A. Restrictive type surgeries tend to be more complex and have more side effects.
B. Bypass type procedures do not require long-term vitamin or nutrient supplementation.
C. Laparoscopic adjustable gastric banding involves the resection of the greater curve of the stomach
D. Bypass type operations nowadays commonly involve restrictive-malabsorptive procedures.
E. Weight loss is greater with the restrictive procedure than the bypass procedure.

23. Metabolic Bariatric Surgery (MBS) has several effects on diabetes mellitus. Which of the following is CORRECT?

A. MBS results in enhanced secretion of GLP-1 by 70%.
B. Laparascopic adjustable gastric banding (LAGB) has the lowest rate of remission of Type 2 diabetes of 20%.
C. MBS results in remission of Type 2 diabetes mellitus.
D. The efficacy of MBS on diabetes is less than 2 years.
E. ALL of the above are correct.

24. The cardiovascular and lipid effects of MBS are several. Which of the following is CORRECT?

A. MBS improves hypertension in more than 95% of patients.
B. MBS results in attainment of blood pressure without need for medications in 66% of patients.
C. MBS increases LDL and reduces HDL.
D. MBS increases TG levels.
E. None of the above is correct.

25. About bariatric surgery, which of the following is CORRECT?

A. Is recommended as an aesthetic procedure.
B. Have minimal risks and unknown complications.
C. No restriction in eating is needed.
D. Lifelong follow-up and monitoring for nutrient deficiency is needed.
E. ALL of the above are correct.

26. With regards to the etiology of hypertension, which of the following is CORRECT?

A. About 10% of the causes are idiopathic.
B. The INTERSALT study confirmed a direct relationship between sodium and mean blood pressure.
C. Aldosterone promotes hypertension by down regulation of angiotensin II receptor.
D. Overactivity of the sympathetic system results in increased blood pressure by promoting volume expansion.
E. ALL of the above are correct.

27. With regards to the control of blood pressure, which of the following is CORRECT?

A. The usual aim is to bring the target BP to less than 130/80 mmHg for patients with or without risk factors or target organ damage.
B. For patients with diabetes or chronic kidney disease the aim is for the blood pressure to be less than 120/70 mmHg.
C. Poor health conditions leading to low blood pressure and an increase risk for death probably explain the J-curve.
D. The findings of a meta-analysis of 7 randomised controlled trials suggest that the increased risk of events observed in patients with low blood pressure was related to anti-hypertensive treatment.
E. ALL of the above are correct.

28. With regards to the results of several currently concluded trials involving treatment of blood pressure, which of the following is CORRECT?

A. ONTARGET retrospective analysis revealed that in trial BP reduction and risk of AMI, heart failure and CV mortality are very closely related.
B. Target BP levels recommended in current guidelines (<130/80 mmHg) are shown in trials to support prevention of macrovascular outcomes in patients with diabetes.
C. The HYVET study showed that showed that for elderly patients, the reduction in BP from >160 mmHg to 143.5/75.4 mmHg with active treatment resulted in 39% reduction in risk of fatal stroke.
D. INVEST study showed that tight control is better than usual control of BP in diabetic patients.
E. ALL of the above are incorrect.

29. With regards to treatment of hypertension and risk of diabetes, which of the following statement is CORRECT?

A. Anti hypertensives do not affect the risk of developing diabetes.
B. Hypertenisve patients who develop diabetes are at high cardiovascular risk.
C. ACE inhibitors significantly reduce incidence of new onset diabetes very much more than ARB.
D. Pre-treatment plasma glucose cannot be used to predict new onset diabetes.
E. All of the above are correct.

30. About the single pill combination therapy in treating hypertension, which of the following is CORRECT?

A. The single pill combination therapy is useful especially for those who require more than or equal 30/15 mmHg BP reduction.
B. The single pill combination therapy usually has fewer side effects due to lower doses of component drugs.
C. ACEI/HCTZ combination appears better than ACEI/CCB in ACCOMPLISH trial to reduce CV events and mortality.
D. The single pill combination therapy has a draw back of greater postural hypotension.
E. ALL of the above are correct.

READINGS

A Selection Of Ten Current Readings On Topics Related To Cardiometabolic Risk Update

A SELECTION OF TEN CURRENT READINGS ON TOPICS RELATED TO CARDIOMETABOLIC RISK UPDATE – available as free full-text

Selection of readings made by A/Prof Goh Lee Gan

READING 1 – Molecular determinants of the cardiometabolic phenotype

de las Fuentes L, de Simone G, Arnett DK, Dávila-Román VG. Molecular determinants of the cardiometabolic phenotype. Endocr Metab Immune Disord Drug Targets. 2010 Jun;10(2):109-23. Review. PubMed PMID: 20384572; PubMed Central PMCID: PMC2887744.

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2887744/pdf/nihms207662.pdf (free full-text)

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ABSTRACT

The metabolic syndrome represents a clustering of risk factors that has been shown to predict adverse cardiovascular outcomes. Although the precise mechanisms contributing to the cardiometabolic syndrome (CMS) remain poorly defined, accumulating evidence identifies two intersecting candidate pathways responsible for inflammation and energy homeostasis in the pathophysiology that underlie cardiometabolic traits. Although currently no pharmacologic interventions specifically target CMS, future drug development efforts should attempt to capitalise on molecular nodes at the intersections of these pathways in the CMS.PMCID: PMC2887744 PMID: 20384572 [PubMed - indexed for MEDLINE]

READING 2 – Prevention of atherosclerosis in overweight/obese patients

Lim S, Despres JP, Koh KK. Prevention of atherosclerosis in overweight/obese patients. - In need of novel multi-targeted approaches-. Circ J. 2011 Apr 25;75(5):1019-27. Epub 2011 Mar 25. Review. PubMed PMID: 21441697.

URL: http://www.jstage.jst.go.jp.libproxy1.nus.edu.sg/article/circj/75/5/1019/_pdf (free full-text)

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ABSTRACT

Obesity has reached epidemic proportions and complications related to obesity contribute substantially to both healthcare costs and mortality. Obesity, particularly when accompanied by an excess of visceral/ectopic fat, is a major risk factor for diseases ranging from insulin resistance, type 2 diabetes, nonalcoholic fatty liver disease, and cardiovascular disease. The epidemic proportions reached by obesity has made these conditions a global problem in human health. Accordingly, preventive and/or therapeutic interventions should be considered in obese patients. Regular physical activity/exercise has numerous beneficial effects on the cardiometabolic risk profile and on the cardiovascular system. However, our current clinical environment is not designed to provide the regular support needed by patients to help them maintain over the long term their improved physical activity/nutritional habits. Because hypertension, dyslipidemia, hyperinsulinemia, and excess visceral adipose tissue are linked by complex reciprocal molecular interactions, it is logical to expect that targeting an interconnected pathway may provide multiple benefits. At this stage, combined therapy of statins or PPAR agonists and

renin-angiotensin-aldosterone system blockers to target multiple therapeutic pathways may optimally improve the cardiometabolic risk profile through both distinct and interrelated mechanisms. In the present article, we will discuss updated novel approaches, including potential multi-targeted intervention strategies, based on underlying pathophysiological processes. PMID: 21441697 [PubMed - indexed for MEDLINE]

READING 3 – Is high fructose consumption harmful?

Wiernsperger N, Geloen A, Rapin JR. Fructose and cardiometabolic disorders: the controversy will, and must, continue. Clinics (Sao Paulo). 2010 Jul;65(7):729-38. Review. PubMed PMID: 20668632; PubMed Central PMCID:PMC2910863.

URL: http://www.scielo.br/pdf/clin/v65n7/a13v65n7.pdf (free full-text)

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ABSTRACT

The present review updates the current knowledge on the question of whether high fructose consumption is harmful or not and details new findings which further pushes this old debate. Due to large differences in its metabolic handling when compared to glucose, fructose was indeed suggested to be beneficial for the diet of diabetic patients. However its growing industrial use as a sweetener, especially in soft drinks, has focused attention on its potential harmfulness, possibly leading to dyslipidemia, obesity, insulin resistance/metabolic syndrome and even diabetes. Many new data have been generated over the last years, confirming the lipogenic effect of fructose as well as risks of vascular dysfunction and hypertension. Fructose exerts various direct effects in the liver, affecting both hepatocytes and Kupffer cells and resulting in non-alcoholic steatotic hepatitis, a well known precursor of the metabolic syndrome. Hepatic metabolic abnormalities underlie indirect peripheral metabolic and vascular disturbances, for which uric acid is possibly the culprit. Nevertheless major caveats exist (species, gender, source of fructose, study protocols) which are detailed in this review and presently prevent any firm conclusion. New studies taking into account these confounding factors should be undertaken in order to ascertain whether or not high fructose diet is harmful. PMCID: PMC2910863 PMID: 20668632 [PubMed - indexed for MEDLINE]

READING 4 – Polycystic ovary syndrome impacts on health across the lifespan

Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med. 2010 Jun 30;8:41. Review. PubMed PMID: 20591140; PubMed Central PMCID: PMC2909929.

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2909929/pdf/1741-7015-8-41.pdf (free full-text)

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ABSTRACT

Polycystic ovary syndrome (PCOS) is of clinical and public health importance as it is very common, affecting up to one in five women of reproductive age. It has significant and diverse clinical implications including reproductive (infertility, hyperandrogenism, hirsutism), metabolic (insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, adverse cardiovascular risk profiles) and psychological features (increased anxiety, depression and worsened quality of life). Polycystic ovary syndrome is a heterogeneous condition and, as such, clinical and research agendas are broad and involve many disciplines. The phenotype varies widely depending on life stage, genotype, ethnicity and environmental factors including

lifestyle and bodyweight. Importantly, PCOS has unique interactions with the ever increasing obesity prevalence worldwide as obesity-induced insulin resistance significantly exacerbates all the features of PCOS. Furthermore, it has clinical implications across the lifespan and is relevant to related family members with an increased risk for metabolic conditions reported in first-degree relatives. Therapy should focus on both the short and long-term reproductive, metabolic and psychological features. Given the aetiological role of insulin resistance and the impact of obesity on both hyperinsulinaemia and hyperandrogenism, multidisciplinary lifestyle improvement aimed at normalising insulin resistance, improving androgen status and aiding weight management is recognised as a crucial initial treatment strategy. Modest weight loss of 5% to 10% of initial body weight has been demonstrated to improve many of the features of PCOS. Management should focus on support, education, addressing psychological factors and strongly emphasising healthy lifestyle with targeted medical therapy as required. Monitoring and management of long-term metabolic complications is also an important part of routine clinical care. Comprehensive evidence-based guidelines are needed to aid early diagnosis, appropriate investigation, regular screening and treatment of this common condition. Whilst reproductive features of PCOS are well recognised and are covered here, this review focuses primarily on the less appreciated cardiometabolic and psychological features of PCOS. PMCID: PMC2909929 PMID: 20591140 [PubMed - indexed for MEDLINE]

READING 5 – Maternal incronutrient deficiency and chronic disease

Christian P, Stewart CP. Maternal micronutrient deficiency, fetal development, and the risk of chronic disease. J Nutr. 2010 Mar;140(3):437-45. Epub 2010 Jan 13. Review. PubMed PMID: 20071652.

URL: http://jn.nutrition.org/content/140/3/437.full.pdf+html (free full-text)

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ABSTRACT

Early life nutritional exposures, combined with changes in lifestyle in adult life, can result in increased risk of chronic diseases. Although much of the focus on the developmental origins of disease has been on birth size and growth in postnatal life and the availability of energy and protein during these critical developmental periods, micronutrient deficiencies may also play an important role in fetal growth and development. Micronutrient status in fetal and early life may alter metabolism, vasculature, and organ growth and function, leading to increased risk of cardiometabolic disorders, adiposity, altered kidney function, and, ultimately, to type 2 diabetes and cardiovascular diseases. This review elucidates pathways through which micronutrient deficiencies lead to developmental impairment and describes the research to date on the evidence that micronutrient deficiencies in utero influence the development of chronic disease risk. Animal studies, observational human studies examining maternal diet or micronutrient status, and limited data from intervention studies are reviewed. Where data are lacking, plausible mechanisms and pathways of action have been derived from the existing animal and in vitro models. This review fills a critical gap in the literature related to the seminal role of micronutrients in early life and extends the discussion on the developmental origins of health and disease beyond birth size and energy and protein deficiency. PMID: 20071652 [PubMed - indexed for MEDLINE]

READING 6 – Maternal obesity on offspring obesity and cardiometabolic disease risk

Drake AJ, Reynolds RM. Impact of maternal obesity on offspring obesity and cardiometabolic disease risk. Reproduction. 2010 Sep;140(3):387-98. Epub 2010 Jun 18. Review. PubMed PMID: 20562299.

URL: http://www.reproduction-online.org/content/140/3/387.full.pdf+html (free full-text)

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ABSTRACT

The prevalence of obesity among pregnant women is increasing. In addition to the short-term complications of obesity during pregnancy in both mother and child, it is now recognised that maternal obesity has long-term adverse outcomes for the health of her offspring in later life. Evidence from both animal and human studies indicates that maternal obesity increases the risk for the offspring in developing obesity and altering body composition in child- and adulthood and, additionally, it also has an impact on the offspring's cardiometabolic health with dysregulation of metabolism including glucose/insulin homoeostasis, and development of hypertension and vascular dysfunction. Potential mechanisms include effects on the development and function of adipose tissue, pancreas, muscle, liver, the vasculature and the brain. Further studies are required to elucidate the mechanisms underpinning the programming of disease risk in the offspring as a consequence of maternal obesity. The ultimate aim is to identify potential targets, which may be amenable to prevention or early intervention in order to improve the health of this and future generations. PMID: 20562299 [PubMed - indexed for MEDLINE]

READING 7 – Managing mixed dyslipidemia in special populations

Miller M. Managing mixed dyslipidemia in special populations. Prev Cardiol. 2010 Spring;13(2):78-83. Review. PubMed PMID: 20377810; PubMed Central PMCID: PMC2923824.

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2923824/pdf/nihms-224667.pdf (free full-text)

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ABSTRACT

Controlling low-density lipoprotein cholesterol is one of the major focuses of cardiovascular care. However, the twin global pandemics of obesity and diabetes are promoting an increased prevalence of associated cardiometabolic risk factors. These factors include mixed dyslipidemia, which is prevalent among several important subgroups of the overall population. Cardiovascular risk increases as women reach and extend beyond menopause, partly reflective of dyslipidemia. In addition, women with polycystic ovary syndrome display a cluster of risk factors reminiscent of the metabolic syndrome. Certain ethnic groups are also at increased risk for type 2 diabetes or the metabolic syndrome. Dyslipidemia contributes significantly to overall cardiovascular risk in the elderly, and the frequency of children and adolescents presenting with type 2 diabetes or metabolic syndrome is increasing worldwide. Physicians should be aware of the possibility of mixed dyslipidemia in patients at elevated cardiometabolic risk. However, while combination therapy may successfully correct the associated dyslipidemia, it remains to be established whether the addition of a second agent improves coronary risk beyond statin monotherapy. PMCID: PMC2923824 PMID: 20377810 [PubMed - indexed for MEDLINE]

READING 8 – Recent advances in the management of chronic stable angina (I)

Kones R. Recent advances in the management of chronic stable angina I: approach to the patient, diagnosis, pathophysiology, risk stratification, and gender disparities. Vasc Health Risk Manag. 2010 Aug 9;6:635-56. Review. PubMed PMID: 20730020; PubMed Central PMCID: PMC2922325.

URL: http://www.dovepress.com/articles.php?article_id=4852 (free full-text)

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ABSTRACT

The potential importance of both prevention and personal responsibility in controlling heart disease, the leading cause of death in the USA and elsewhere, has attracted renewed attention. Coronary artery disease is preventable, using relatively simple and inexpensive lifestyle changes. The inexorable rise in the prevalence of obesity, diabetes, dyslipidemia, and hypertension, often in the risk cluster known as the metabolic syndrome, drives the ever-increasing incidence of heart disease. Population-wide improvements in personal health habits appear to be a fundamental, evidence based public health measure, yet numerous barriers prevent implementation. A common symptom in patients with coronary artery disease, classical angina refers to the typical chest pressure or discomfort that results when myocardial oxygen demand rises and coronary blood flow is reduced by fixed, atherosclerotic, obstructive lesions. Different forms of angina and diagnosis, with a short description of the significance of pain and silent ischemia, are discussed in this review. The well accepted concept of myocardial oxygen imbalance in the genesis of angina is presented with new data about clinical pathology of stable angina and acute coronary syndromes. The roles of stress electrocardiography and stress myocardial perfusion scintigraphic imaging are reviewed, along with the information these tests provide about risk and prognosis. Finally, the current status of gender disparities in heart disease is summarised. Enhanced risk stratification and identification of patients in whom procedures will meaningfully change management is an ongoing quest. Current guidelines emphasise efficient triage of patients with suspected coronary artery disease. Many experts believe the predictive value of current decision protocols for coronary artery disease still needs improvement in order to optimise outcomes, yet avoid unnecessary coronary angiograms and radiation exposure. Coronary angiography remains the gold standard in the diagnosis of coronary artery obstructive disease. Part II of this two part series will address anti-ischemic therapies, new agents, cardiovascular risk reduction, options to treat refractory angina, and revascularisation. PMCID: PMC2922325 PMID: 20730020 [PubMed - indexed for MEDLINE]

READING 9 – Recent advances in the management of chronic stable angina (II)

Kones R. Recent advances in the management of chronic stable angina II. Anti-ischemic therapy, options for refractory angina, risk factor reduction, and revascularisation. Vasc Health Risk Manag. 2010 Sep 7;6:749-74. Review. PubMed PMID: 20859545; PubMed Central PMCID: PMC2941787.

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2941787/pdf/vhrm-6-749.pdf (free full-text)

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ABSTRACT

The objectives in treating angina are relief of pain and prevention of disease progression through risk reduction. Mechanisms, indications, clinical forms, doses, and side effects of the traditional antianginal agents - nitrates, ß-blockers, and calcium channel blockers - are reviewed. A number of patients have contraindications or remain unrelieved from anginal discomfort with these drugs. Among newer alternatives, ranolazine, recently approved in the United States, indirectly prevents the intracellular calcium overload involved in cardiac ischemia and is a welcome addition to available treatments. None, however, are disease-modifying agents. Two options for refractory angina, enhanced external counterpulsation and spinal cord stimulation (SCS), are presented in detail. They are both well-studied and are effective means of treating at least some patients with this perplexing form of angina. Traditional modifiable risk factors for coronary artery disease (CAD) - smoking, hypertension, dyslipidemia, diabetes, and obesity - account for most of the population-attributable risk. Individual therapy of

high-risk patients differs from population-wide efforts to prevent risk factors from appearing or reducing their severity, in order to lower the national burden of disease. Current American College of Cardiology/American Heart Association guidelines to lower risk in patients with chronic angina are reviewed. The Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation (COURAGE) trial showed that in patients with stable angina, optimal medical therapy alone and percutaneous coronary intervention (PCI) with medical therapy were equal in preventing myocardial infarction and death. The integration of COURAGE results into current practice is discussed. For patients who are unstable, with very high risk, with left main coronary artery lesions, in whom medical therapy fails, and in those with acute coronary syndromes, PCI is indicated. Asymptomatic patients with CAD and those with stable angina may defer intervention without additional risk to see if they will improve on optimum medical therapy. For many patients, coronary artery bypass surgery offers the best opportunity for relieving angina, reducing the need for additional revascularisation procedures and improving survival. Optimal medical therapy, percutaneous coronary intervention, and surgery are not competing therapies, but are complementary and form a continuum, each filling an important evidence-based need in modern comprehensive management. PMCID: PMC2941787 PMID: 20859545 [PubMed - indexed for MEDLINE]

READING 10
- Effectiveness of medications used to attenuate antipsychotic-related weight gain

Maayan L, Vakhrusheva J, Correll CU. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. Neuropsychopharmacology. 2010 Jun;35(7):1520-30. Epub 2010 Mar 24. Review. PubMed PMID: 20336059; PubMed Central PMCID: PMC3055458.

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3055458/pdf/npp201021a.pdf (free full-text)

Child Study Center, New York University School of Medicine, New York, NY, USA.

ABSTRACT

Antipsychotic-related weight gain and metabolic effects are a critical outcome for patients requiring these medications. A literature search using MEDLINE, Web of Science, PsycNET, and EMBASE for randomised, open and double-blind, placebo-controlled trials of medications targeting antipsychotic-induced weight gain was performed. Primary outcome measures were change and endpoint values in body weight and body mass index (BMI). Secondary outcomes included >or=7% weight gain, all-cause discontinuation, change in waist circumference, glucose and lipid metabolism parameters, and psychiatric symptoms. Sensitivity analyses were conducted to explain heterogeneity of the results. Across 32 studies including 1482 subjects, 15 different medications were tested: amantadine, dextroamphetamine, d-fenfluramine, famotidine, fluoxetine, fluvoxamine, metformin, nizatidine, orlistat, phenylpropanolamine, reboxetine, rosiglitazone, sibutramine, topiramate, and metformin+sibutramine. Compared with placebo, metformin had the greatest weight loss (N=7, n=334, -2.94 kg (confidence interval (CI:-4.89,-0.99)), followed by d-fenfluramine (N=1, n=16, -2.60 kg (CI:-5.14,-0.06)), sibutramine (N=2, n=55, -2.56 kg (CI:-3.91,-1.22)), topiramate (N=2, n=133, -2.52 kg (CI:-4.87,-0.16)), and reboxetine (N=2, n=79, -1.90 kg (CI:-3.07,-0.72)). Weight loss remained significant with metformin initiation after weight gain had occurred, but not when started concomitantly with antipsychotics. Nausea rates were not higher with any treatment compared with placebo. In all, 5 of 15 psychopharmacologic interventions aimed at ameliorating antipsychotic-induced weight gain outperformed placebo. Results were most robust for metformin, although these were modest and heterogeneous. Only one (negative) combination treatment study was available and head-to-head studies are absent. None of the agents were able to entirely reverse weight gain because of antipsychotics. At present, no treatment has sufficient evidence to recommend broad clinical usage. Antipsychotics with no or minimal cardiometabolic liability, as well as interventions that prevent or normalise adverse antipsychotic cardiometabolic effects are needed. PMCID: PMC3055458 PMID: 20336059 [PubMed - indexed for MEDLINE]

ORIGINAL PAPER

- Disseminated Cutaneous Zoster Can Occur in Healthy Individuals: A Case Series

DISSEMINATED CUTANEOUS ZOSTER CAN OCCUR IN HEALTHY INDIVIDUALS: A CASE SERIES

Dr Lee Hwee Chyen, Dr Chia Min Wee

ABSTRACT

Disseminated cutaneous zoster is a severe complication of varicella-zoster-virus infection. Zoster is known to occur in healthy individuals, while its disseminated cutaneous form usually occurs in severely immunocompromised hosts. Though uncommon, disseminated cutaneous zoster has been reported in healthy individuals, where age-related decline in cellular immunity is a single risk factor. We report three cases of disseminated cutaneous zoster in elderly patients aged from 71 to 80 years, discussing their clinical background, progression and outcome.

Keywords: Disseminated Zoster; Herpes Zoster; Immunocompetent; Elderly; Immunocompromised; Healthy; Post-herpetic neuralgia; Shingles

INTRODUCTION

Varicella-zoster-virus (VZV) is a neurotropic virus that causes primary varicella and subsequently remains dormant in the dorsal root and cranial nerve ganglia. Upon reactivation, it spreads from a single ganglion to the corresponding dermatome and neural tissue of the same segment, manifesting as herpes zoster.[1] The main risk factor for the development of zoster is age, and zoster is thought to occur as a consequence of declining VZV-specific cell mediated immunity occurring physiologically with age, or by any other forms of immunosuppression. Disseminated cutaneous zoster is one of the many debilitating complications of herpes zoster and typically occurs in an immunocompromised state. Most cases have been described to have a background history of malignancy, lymphoproliferative disorders, Human Immuno-deficiency Virus (HIV), or chemotherapy. Rare in immunocompetent individuals, cutaneous dissemination may also be followed by visceral involvement. We shall discuss three cases of disseminated cutaneous zoster, including that of a previously healthy individual.

CASE 1

A 79-year-old man presented with a 5-day history of a painful, vesicular eruption over the left side of the chest. This was preceded by a week of sharp, left-sided chest pain for which he had self-medicated with paracetamol. Aside from a childhood history of chickenpox and an uneventful appendicectomy, he had no significant history of chronic medical illness, medication or preceding symptoms.

On examination, blisters were noted in a linear, band-like cluster, along the left T7, T8 dermatomal distribution, not crossing the midline (Figure 1a). Multiple, diffuse vesicles were seen over the anterior chest and back (Figure 1b). Oral mucosa and genitalia were unaffected. Examination of other systems was unremarkable.

Routine full blood count, renal, liver panels and chest x-ray were within satisfactory limits. Specimens from the vesicles returned positive for VZV polymerase chain reaction (PCR). Further evaluation for underlying causes of immunosuppression (tumor markers, myeloma panel, retroviral screen and hepatitis markers) was negative.

Intravenous acyclovir was administered with simple oral analgesia. There was no further progression, the vesicles eventually dried up and he was discharged well.

Upon regular follow-up, he reported persistent pain despite resolution of the skin lesions, and was eventually referred to and treated for post-herpetic neuralgia (PHN) by the pain team.

CASE 2

An 80-year-old man, with diabetes and hypertension, reported recent right-sided anterior chest pain for which he consumed traditional herbal medication. 2 days later, blisters appeared over his right shoulder and progressed to involve the whole trunk despite immediate cessation of the herbs.

At the emergency department, multiple annular and vesicular lesions were found over the back, chest and neck, with no mucous-membrane involvement (Figure 2). Due to the recent drug history, the initial impression was that of drug-induced erythema multiforme. He was eventually reviewed by the dermatology team when the vesicles rapidly evolved into multiple herpetiform bullae (Figure 3). Specimens of the vesicles were positive for VZV PCR, and a skin biopsy performed over the back revealed features of a viral-induced vesicle, consistent with that of VZV infection. The lesions soon resolved and he was discharged well after a course of intravenous acyclovir. Retroviral screen, hepatitis and tumor markers were negative.

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CASE 3

A 71-year-old man with ischemic heart disease, hypertension and dementia was admitted for infected sacral sores. He was a nursing home resident, bedbound and minimally communicative for the past 2 years. Intravenous antibiotics were administered to treat the sepsis. Unfortunately, he also developed multiple vesicles, first over the left T8 dermatome and then over the neck and trunk. Specimen of vesicular fluid returned positive for VZV culture and PCR.

A course of acyclovir was administered along with the antibiotics. After regular deblistering and wound care, he was discharged upon resolution of the vesicles and pyrexia.

DISCUSSION

Disseminated cutaneous zoster is defined as greater than 20 vesicular lesions outside the primary and immediately adjacent dermatomes.[2]

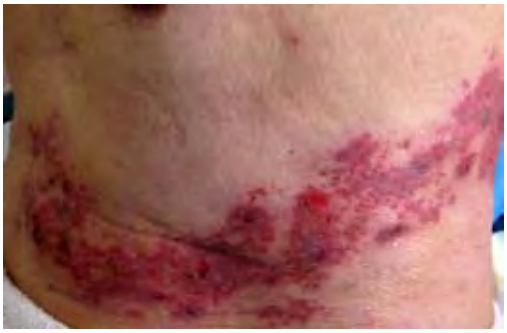

Figure 1a. Deblistered erosions in a linear, band-like cluster along the left T7, T8 dermatomal distribution, not crossing the midline

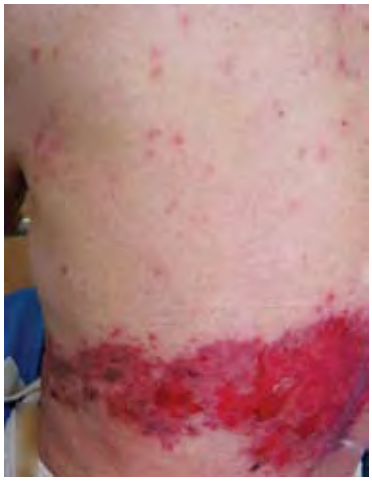

Figure 1b. Adjacent to the primary dermatomal lesion, there are also multiple vesicles distributed diffusely across the chest and back in a non-dermatomal fashion

Each of the cases in this series presented with dermatological features that were consistent with this criteria. These clinical findings were also accompanied by positive laboratory results which included that of VZV PCR and VZV viral cell cultures, thus supporting the diagnosis of disseminated cutaneous zoster.

Disseminated cutaneous zoster is relatively uncommon, and typically occurs in the setting of immunosuppression. Its incidence is as high as 10–40% in immunocompromised hosts, some of whom may develop visceral involvement.[2-7] Most cases have been described in patients with depressed cell-mediated immunity such as Human Immuno-deficiency Virus (HIV) infected patients, patients with malignancy, lymphoproliferative disorders, and recipients of chemotherapy or immunosuppressants.[2-7]

Cases of disseminated zoster should be diagnosed early and promptly treated with a 5-7 day course of intravenous acyclovir at 10mg/kg every 8 hours.[5,7]

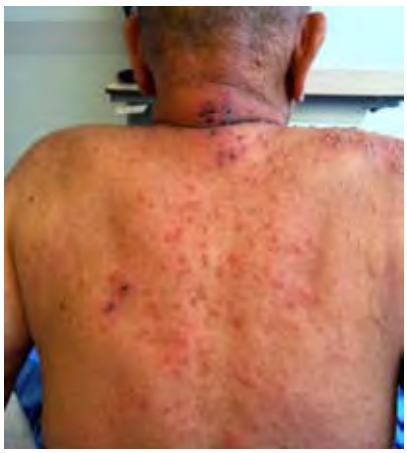

Figure 2. Multiple vesicles in a generalised distribution over the trunk, neck and the back of the scalp

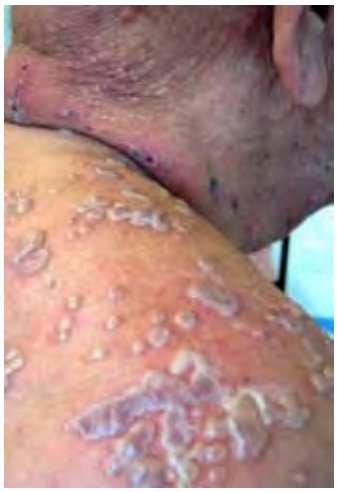

Figure 3. The vesicles evolved into large herpetiform bullae over the right shoulder. The other accompanying vesicles continued to spread across the entire trunk

Unlike Patient 3 who had multiple co-morbidities, Patient 1 was premorbidly well and showed no clinical or laboratory evidence suggestive of immunocompromise. The one possible predisposing factor in Case 1 is that of age-related decline in cellular immunity against VZV. To date, one rare case of disseminated zoster in an immunocompetent 39-year-old has been reported.[8] Otherwise, the average age for disseminated herpes in immunocompetent patients is 65.4 years.[8] Incidentally, patients in this series, immunocompetent or not, were above 70 years old. It would therefore be prudent to identify age as a significant risk factor for more severe forms of zoster.

Furthermore, reports have shown that developing disseminated zoster predisposes one to more debilitating complications such as PHN and visceral involvement.[2] Visceral zoster has been reported to occur in 10% of patients with disseminated cutaneous zoster, but to the best of our knowledge, has not been described in immunocompetent individuals.[8]

Patient 2 was warned of potential complications, but has since remained asymptomatic during outpatient follow-up. While patient 1 required treatment for PHN, he fortunately did not reveal any evidence suggestive of visceral involvement. Stratman et al reported an unusual case of a 77-year-old male who developed disseminated visceral zoster in the stomach that was confirmed histologically with a gastric biopsy.[8] In this case, the patient was significantly immunocompromised, with a background of non-Hodgkin's lymphoma, for which he had undergone 8 years of aggressive chemotherapy.

Viral dissemination generally occurs 6 to 10 days from the initial onset of localised cutaneous lesions. As such, the prevention of disseminated zoster begins from the time a patient first presents to the clinician with early zoster. In uncomplicated herpes zoster, it is important to initiate antiviral therapy as soon as possible, preferably within 48 to 72 hours from the onset of the cutaneous symptoms.[9] Early commencement of therapy aims to relieve symptoms and prevent further complications such as PHN and secondary bacterial infections. Above all, in the context of our discussion, this reduces the risk of viral dissemination.

CONCLUSIONS

Disseminated zoster is a debilitating complication of herpes zoster, and generally occurs in severely immunodeficient hosts. While dissemination can present with visceral involvement, such visceral dissemination has not been described in immunocompetent patients.[8] Disseminated cutaneous zoster, however, may rarely occur in immunocompetent individuals.[5,7] Our case series illustrates that cutaneous dissemination of zoster can occur in healthy individuals, with a propensity towards elderly persons.[10] Increased age is a risk factor for developing more severe forms of herpes zoster, as a result of age-related decline in cell-mediated immunity. Immunocompetent but elderly individuals should therefore be identified as a group more susceptible to cutaneous dissemination compared to that of younger counterparts. Vigilant monitoring and regular follow-up of all patients is recommended.

KEY POINTS

- Disseminated cutaneous zoster can occur in healthy individuals, with a predilection for elderly persons, due to age-related physiological decline in cellular immunity.
- It can be a diagnostic challenge during initial presentation, hence the importance of clinical history and close monitoring. This includes a detailed drug history, particularly in Southeast-Asian populations where many consume traditional medication which may contain corticosteroids or other immunosuppressants.
- Disseminated cutaneous zoster in immunocompetent but elderly patients warrants prompt identification and commencement of therapy, to reduce risk of further complications such as encephalitis and other visceral involvement.
- Upon confirming the diagnosis, patients should be screened for other underlying causes of immunosuppression such as infections and malignancy.
- Close review of all patients is recommended, to monitor for debilitating complications, preventing further morbidity and mortality.

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Selected Safety Information

CONTRAINDICATIONS Hypersensitivity to the active substances or to any of the excipients. The combination of EZETROL with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases. **PRECAUTIONS Liver Enzymes:** In controlled co-administration trials in patients receiving EZETROL with a statin, consecutive transaminase elevations (≥3 X the upper limit of normal [ULN]) have been observed. When EZETROL is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin. **Skeletal Muscle:** In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with EZETROL compared with the relevant control arm (placebo or statin alone). However, myopathy and rhabdomyolysis are known adverse reactions to statins and other lipid-lowering drugs. In clinical trials, the incidence of CPK >10 X ULN was 0.2% for EZETROL vs 0.1% for placebo, and 0.1% for EZETROL co administered with a statin vs 0.4% for statins alone. All patients starting therapy with EZETROL should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. EZETROL and any statin that the patient is taking concomitantly should be immediately discontinued if myopathy is diagnosed or suspected. The presence of these symptoms and a creatine phosphokinase (CPK) level >10 times the ULN indicates myopathy. **Hepatic Insufficiency** Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, EZETROL is not recommended in these patients. **Fibrates** The co-administration of ezetimibe with fibrates other than fenofibrate has not been studied. Therefore, co-administration of EZETROL and fibrates (other than fenofibrate) is not recommended. If cholelithiasis is suspected in a patient receiving EZETROL and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered. **Cyclosporine** Caution should be exercised when initiating ezetimibe in the setting of cyclosporine. Cyclosporine concentrations should be monitored in patients receiving EZETROL and cyclosporine. The degree of increase in ezetimibe exposure may be greater in patients with severe renal insufficiency. **Anticoagulants** If EZETROL is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored. **SIDE EFFECTS** The most commonly reported adverse reactions (incidence ≥2% and greater than placebo) in the EZETROL monotherapy controlled clinical trial database of 2396 patients were: upper respiratory tract infection (4.3%), diarrhea (4.1%), arthralgia (3.0%), sinusitis (2.8%), and pain in extremity (2.7%). The most commonly reported adverse reactions (incidence ≥2% and greater than statin alone) in the EZETROL + statin controlled clinical trial database of 11,308 patients were: nasopharyngitis (3.7%), myalgia (3.2%), upper respiratory tract infection (2.9%), arthralgia (2.6%) and diarrhea (2.5%). ***Post-marketing Experience*** The following additional adverse reactions have been identified during post-approval use of EZETROL: Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria; erythema multiforme; arthralgia; myalgia; elevated creatine phosphokinase; myopathy/rhabdomyolysis (very rarely); elevations in liver transaminases; hepatitis; abdominal pain; thrombocytopenia; pancreatitis; nausea; dizziness; paresthesia; depression; headache; cholelithiasis; cholecystitis.

MSD

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Before prescribing Ezetrol, please consult the full prescribing information.

Reference

1. Bays H. Ezetimibe. *Expert Opin. Investig. Drugs* (2002) 11(11):1587-1604.

31-Aug-2013 EZT-2011-SG-4998-J

For the Treatment of Primary Hypercholesterolemia or Mixed Hyperlipidemia

Powerful LDL-C Reduction through Dual Inhibition

03-Dec-2011 VYT-2007-SG-3530-0 (Reval 3)

Selected Safety Information

CONTRAINDICATIONS Hypersensitivity to the active substances or to any of the excipients. Active liver disease or unexplained persistent elevations of serum transaminases. Pregnancy and nursing. **PRECAUTIONS Myopathy/Rhabdomyolysis:** Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. Predisposing factors for myopathy include advanced age (≥65 years), female gender, uncontrolled hypothyroidism, and renal impairment. All patients on VYTORIN should be advised of the risk of myopathy and told to promptly report any unexplained muscle pain, tenderness, or weakness. Therapy with VYTORIN should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and a CK level >10 times the upper limit of normal indicates myopathy. In most cases, when patients were promptly discontinued from simvastatin treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with VYTORIN or whose dose is being increased. Therapy with VYTORIN should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes. **Myopathy Caused by Drug Interactions:** Simvastatin is metabolized by CYP3A4. Use of VYTORIN concomitantly with potent CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone or large quantities of grapefruit juice over 1 liter daily) should be avoided. The concomitant use of VYTORIN and fibrates (especially gemfibrozil) should be avoided. Although not recommended, the dose of VYTORIN should not exceed 10/10 mg if used with gemfibrozil. The dose of VYTORIN should not exceed 10/10 mg daily in patients receiving cyclosporine or danazol, 10/20 mg daily in patients receiving amiodarone or verapamil, 10/40 mg daily in patients receiving diltiazem, and 10/80 mg daily in patients receiving amlodipine, due to the increased risk of myopathy. The benefit of further alterations in lipid levels by the combined use of VYTORIN with niacin (≥1 g/day) should be carefully weighed against the potential risks of myopathy. Because the risk of myopathy is higher in Chinese than in non-Chinese patients, caution should be used when treating Chinese patients with VYTORIN (particularly doses of 10/40 mg or higher) coadministered with niacin (≥1 g/day). Chinese patients should not receive VYTORIN 10/80 mg daily with niacin (≥1 g/day). Patients on fusidic acid and VYTORIN should be closely monitored. Temporary suspension of VYTORIN treatment may be considered. **Liver Enzymes:** In controlled coadministration trials in patients receiving ezetimibe with simvastatin, consecutive transaminase elevations (≥3 X ULN) have been observed. It is recommended that LFTs be performed before treatment with VYTORIN begins and thereafter when clinically indicated. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If an increase in AST or ALT of ≥3 × ULN persists, discontinue the drug. VYTORIN should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. **Hepatic Insufficiency:** Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, VYTORIN is not recommended in these patients. **Anticoagulants:** If VYTORIN is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored. **SIDE EFFECTS** VYTORIN was generally well tolerated. In clinical trials, common adverse effects (≥1/100, <1/10) with VYTORIN were increased ALT and/or AST, increased blood CK and myalgia. **Post-marketing Experience** The following additional adverse reactions have been reported in post-marketing use with VYTORIN or during clinical studies or post-marketing use with one of the individual components : abnormal liver function test, thrombocytopaenia; anaemia, peripheral neuropathy; memory impairment, cough; interstitial lung disease, constipation; pancreatitis; gastritis, nausea, alopecia; hypersensitivity reactions, including rash, urticaria, anaphylaxis, angio-edema; erythema multiforme, muscle cramps; myopathy/ rhabdomyolysis, decreased appetite, hot flush; hypertension, pain, hepatitis/jaundice; hepatic failure; cholelithiasis; cholecystitis, erectile dysfunction and depression. An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnea and malaise.

Before prescribing, please consult the enclosed local physician circular.

MSD

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VYTORIN®
(ezetimibe/simvastatin)

One Product. Two Paths. Powerful Results!