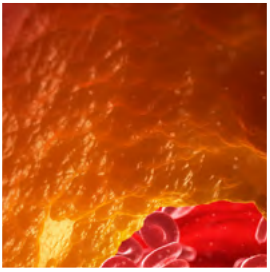
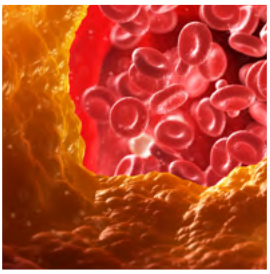
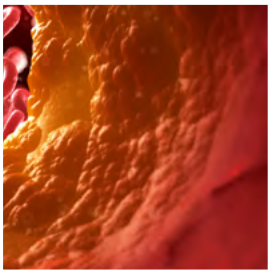
Scientific Highlights of the 2019 APAC Cardiometabolic Live Webinar







Saturday,
14 December 2019

9.30 - 10.30 CET

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

CONTENTS

INTRODUCTION

The heart is at the centre of this Live Webinar, with presentations on the effect of diabetes on the heart, the effect of subclinical thyroid dysfunction on the heart and the effect of hypertension on the heart. In each presentation, the interconnection between the cardiometabolic elements is apparent. For diabetes, the impact of different drugs for lowering glucose and improving cardiovascular outcomes as reported in randomised, clinical trials and in published Guidelines will be discussed by Professor Paolo Pozzilli. There is a complex relationship between the thyroid and the cardiovascular system, which is explained by Professor Nemencio A Nicodemus. Small changes in thyroid hormone concentrations can have a negative impact on the cardiovascular system, but there is the question of whether this hormone imbalance should be treated or not. Professor Brian Tomlinson explores the relationship between hypertension and coronary heart disease and the treatment options recommended from current Guidelines for particular subgroups of patients.

L1

Lowering cardiovascular risk in type 2 diabetes: Yes, we can

Paolo Pozzilli

Endocrinology and Metabolic Diseases Department
University Campus Bio-Medico of Rome (UCBM)
Rome, Italy

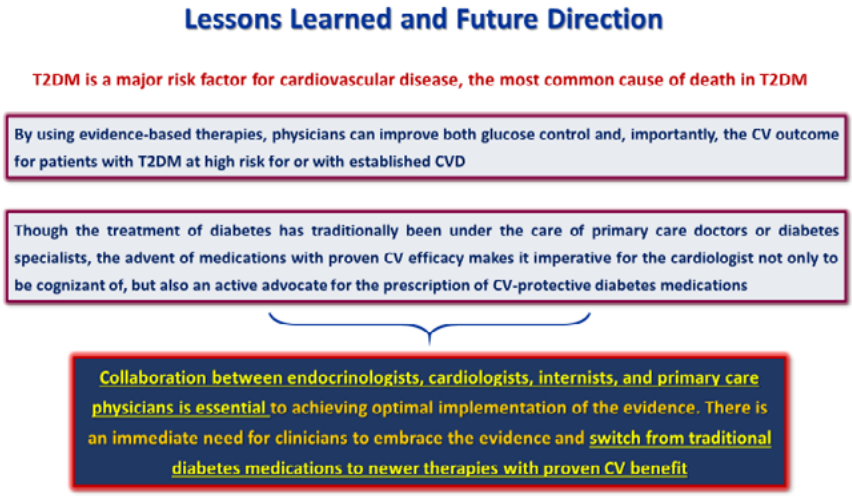
Cardiovascular disease (CVD) is a major challenge in the management of type 2 diabetes mellitus (T2DM), stated Professor Pozzilli, and reducing vascular complications is a major goal of diabetes therapy.

A review by Deedwania and Acharya (2019) of the CV protective effects of the newer classes of anti-hyperglycemic agents concluded that while the effects of sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) analogs were largely positive, dipeptidyl peptidase-4 (DPP-4) inhibitors were found to increase rates of heart failure hospitalization.[1] Work by Ali and colleagues reported reduced risk of all-cause mortality, CV death, or hospitalization for heart failure in patients with T2DM on a SGLT2 inhibitor compared with those taking placebo. The reduced risk of adverse CVD outcomes in people with T2DM held whether they had established CVD or were at risk of developing CVD.[2] For GLP-1 analogues, liraglutide in the LEADER clinical trial was found to lower the rate of first occurrence of death from CV causes, nonfatal myocardial infarction (MI) or nonfatal stroke compared with placebo,[3] and semaglutide in the SUSTAIN-6 clinical trial was responsible for a significantly lower rate of CV death, nonfatal MI, and nonfatal stroke compared with placebo in patients with T2DM at high CV risk.[4]

Although both SGLT2 inhibitors and GLP1-RA confer CV benefits, their mechanism of CVD prevention is different. Both drug classes protect the CV system through extraglycemic effects (beyond their benefit in reducing HbA1c), with GLP1-RA especially beneficial to those with atherosclerotic CV disease and SGLT2 inhibitors of special benefit to those with heart failure and compromised kidneys. These differences have been acknowledged by current American and European diabetes guidelines.[5,6]

Patients with CVD but no known T2DM should be screened for T2DM; patients with established CVD and T2DM should receive diabetes medication that also positively impacts their CVD.

Figure 1: Conclusion from Professor Pozzilli



L2

Thyroid and the heart: The odd couple

Nemencio Nicodemus Jr.

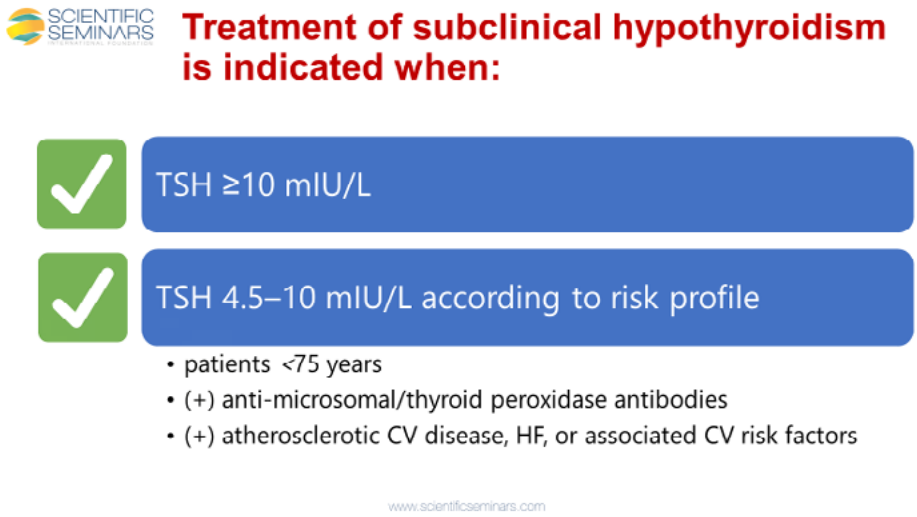
College of Medicine
University of the Philippines
Manila, Philippines

Professor Nicodemus opened his presentation by discussing the complex relationship that thyroid hormones have with the CV system. The main effects of thyroid hormones are on the heart (by influencing rate, rhythm, myocardial contraction, and risk of coronary artery disease), the vascular tree (through regulating blood pressure [BP] via smooth muscle tone and endothelial function), and by direct effects on CV risk factors (via lipid metabolism and modulation of inflammatory pathways).

Both subclinical hypothyroidism and subclinical hyperthyroidism are associated with increased CV risk and mortality, with some differences in the mechanisms involved in each type of dysfunction. Subtle changes (both increases and decreases) in thyroid hormone concentrations adversely influence the CV system.[7]

Thyroid hormones regulate different pathways involved in CVD. For example, thyroid dysfunction is associated with dyslipidemia (increased total cholesterol and low-density lipoprotein). As a consequence, hypothyroidism (including subclinical hypothyroidism) is associated with increased carotid intima-media thickness, a precocious marker of atherosclerosis, and with CV mortality - as seen in a 2019 meta-analysis of >1500 patients from 23 studies.[8] indeed, the CV consequences of subclinical hypothyroidism, including hypertension, dyslipidemia, endothelial dysfunction, atherosclerosis/coronary artery disease, heart failure, arrythmias/atrial fibrillation, and increased risk of stroke are all apparent with thyroid stimulating hormone (TSH) levels between 4.5 and 10 mIU/L, but are more so once TSH levels >10 mIU/L.[7] However, there was no difference between either placebo or levothyroxine (LT4) treatment on carotid intima-media thickness in a meta-analysis of seven studies.[9] A clinical practice guideline published in 2019 recommended against use of thyroid hormones in adults with subclinical hypothyroidism (a recommendation that does not apply to women who are trying to become pregnant or patients with TSH >20 mIU/L and may not apply to patients with severe symptoms or young adults, such as those ≤30 years old).[10] Data suggest that the association between subclinical hypothyroidism and CV disease is limited to younger patients.

Figure 2: When to treat subclinical hypothyroidism



L3

Hypertension and coronary artery disease

Brian Tomlinson

Faculty of Medicine
Macau University of Science & Technology
Taipa, Macau, China

Hypertension is a major contributor to coronary atherosclerosis explained Professor Tomlinson, and in addition, hypertension causes structural or functional changes in arteries or end organs, including the heart, blood vessels, brain, eyes, and kidneys, which are markers of pre-clinical or asymptomatic CV disease. Further, the INTERHEART study[11], a standardised case-control study of acute MI in 52 countries (>15,000 cases and >14,800 controls) found that the major risk factors for MI worldwide in both sexes and at all ages in all regions were abnormal lipids, smoking, psychosocial status and hypertension.

To treat hypertension, the 2018 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) Hypertension Guidelines[12] indicate that beta-blockers are first-line drugs in patients with hypertension and coronary artery disease, heart failure, increased heart rate (HR) and atrial fibrillation. Guidelines further state that SBP targets for hypertensive patients with CV disease, should be <130 mmHg but not <120 mmHg in patients younger than 65 years. In patients older than 65 years SBP should be between 130 and 140 mmHg. Diastolic BP should be lowered to <80 mmHg but not <70 mmHg. In hypertensive patients with a history of MI, beta-blockers and renin-angiotensin system (RAS) blockers are recommended as part of treatment. In patients with symptomatic angina, beta-blockers and/or calcium channel blockers (CCBs) are recommended.

Beta-blockers were one of the main drugs used in the ISCHEMIA study, which compared an invasive strategy (INV) with a conservative strategy (CON) in stable patients with moderate or severe ischemia.[13] INV consisted of optimal medical therapy (OMT) plus catheterization plus optimal revascularization and CON of OMT only, with catheterization reserved for OMT failure. This trial found no evidence of lower risk of CV events (CV death, MI, hospitalization for unstable angina, heart failure or resuscitated cardiac arrest) with an invasive strategy compared with a conservative strategy.

The ESC 2019 Guidelines for the diagnosis and management of chronic coronary syndromes[14] recommend office SBP should be controlled to 120-130 mmHg in those ≤65 years, but to 130-140 mmHg in older patients (aged >65 years). Further,

these Guidelines recommend beta-blockers and RAS blockers for hypertensive patients with a recent MI, and for patients with symptomatic angina, beta-blockers and/or CCBs are recommended. The combination of ACE inhibitors and angiotensin receptor blockers (ARBs) is not recommended. Second-line drugs for chronic coronary syndrome treatment are ivabradine, nicorandil and ranolazine. In addition, short-acting nitrates are still crucial for angina.

A more individualized approach to patients, considering their comorbidities and underlying mechanisms of angina - the diamond approach - was published during 2019.[15] Apart from for bradycardia, in all other clinical conditions, beta-blockers were considered first-line treatment.

Several mechanisms account for the beneficial effect of beta-blockers in patients with coronary artery disease:

- Reduction in myocardial oxygen demand (via a **decrease in HR**, BP, rate-pressure product, in atrioventricular (AV) conduction, ventricular contractility)
- Slowing the HR prolongs the coronary diastolic filling period
- Redistribution of coronary blood flow to vulnerable subendocardial regions
- Increase in the threshold to ventricular fibrillation (reduction of ectopic activity)
- Reduction in infarct size and reduction in the risk of cardiac rupture
- Reduction in the rate of reinfarction
- Regression of the atheromatous process
- Atheromatous plaque stabilisation (rupture less likely)

It is important to underline that benefits are mediated by blockade of β1- receptors. Other important therapeutic options for the management of chronic coronary syndromes are antithrombotic therapy by antiplatelet or oral anticoagulants according to the clinical settings, and lipid-lowering treatment.

Figure 2: Hypertension and coronary artery disease - conclusions

SCIENTIFIC SEMINARS

Conclusions

- Hypertension is a major cause of angina through atheromatous coronary artery disease and this is worsened by left ventricular hypertrophy
- Beta-blockers and/or calcium channel blockers are indicated as first-line treatment for patients with hypertension and coronary artery disease and for relief of symptoms of chronic coronary syndromes (CCS)
- Beta-blockers are specifically indicated for heart rate control in CCS patients with high heart rate or atrial fibrillation and for reduction of CV events in those with left ventricular dysfunction, systolic heart failure or previous myocardial infarction
- Optimal medical therapy was as effective as an invasive strategy in stable patients with moderate or severe ischemia in the ISCHEMIA trial

REFERENCES

1. Deedwania P, Acharya T. Cardiovascular protection with anti-hyperglycemic agents. Am J Cardiovasc Drugs 2019;19(3):249-57.
2. Ali A, Bain S, Hicks D, et al, As part of The Improving Diabetes Steering Committee. SGLT2 Inhibitors: Cardiovascular benefits beyond HbA1c-translating evidence into practice. Diabetes Ther 2019;10(5):1595-622.
3. Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375(4):311-22.
4. Marso SP, Bain SC, Consoli A, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375(19):1834-44.
5. American Diabetes Association. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl 1):S90-102.
6. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018 Dec;41(12):2669-701.
7. Manolis AA, Manolis TA, Melita H, Manolis AS. Subclinical thyroid dysfunction and cardiovascular consequences: An alarming wake-up call? Trends Cardiovasc Med. 2019. pii: S1050-1738(19)30029-5.
8. Gong N, Gao C, Chen X, et al. Endothelial function in patients with subclinical hypothyroidism: A meta-analysis. Horm Metab Res 2019;51(11):691-702.
9. Swaid B, Kheiri B, Sundus S, et al. The effect of levothyroxine treatment in individuals with subclinical hypothyroidism on surrogate markers of atherosclerosis: a meta-analysis of randomized controlled trials. J Community Hosp Intern Med Perspect 2019;9(4):305-309.
10. Bekkering GE, Agoritsas T, Lytvyn L, et al. Thyroid hormones treatment for subclinical hypothyroidism: A clinical practice guideline. BMJ 2019;365:l2006.
11. Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364(9438):937-52.
12. Williams B, Mancia G, Spiering W, et al; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39(33):3021-104.
13. Hochman JS, AHA Scientific Sessions, 2019.
14. Knuuti J, Wijns W, Saraste A, et al; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41(3):407-77.
15. Ferrari R, Censi S, Squeri A. Treating angina. Eur Heart J Suppl 2019;21(Suppl G):G1-G3.

Scientific Seminars International Foundation
Via di Porta Pinciana, 6 - 00187 Roma
www.scientificseminars.com