



## Cardiovascular Disease in Adults with Type 2 Diabetes Mellitus

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“Singapore has the second-highest proportion of diabetics among developed nations”— so reads a headline of an article which appeared on the 2nd December 2015 edition of The Straits Times.

The finding is based on a news report by the International Diabetes Federation (IDF). It said 10.53% of people in Singapore aged between 20 and 79 are estimated to have the chronic disease, after correcting for age differences between the countries. Only the United States fared worse, with a percentage of 10.75. In fact, over the years, diabetes rates have risen from 8.6% of the adult population in 1992, to 11.3% in 2010. It was estimated that the rate would be 12.9% by 2015.

While it is good for Singapore to have the best airport, or the second most competitive economy in the world, to have the dubious honour of having the second highest proportion of diabetics among developed nations is not something we should be proud of. Rather, it is most alarming!

## Why is diabetes of concern to practising cardiologists?

This is because there is a strong correlation between cardiovascular disease (CVD) and diabetes. While “cancer” has been touted as the number one cause of death in Singapore for years, the label is actually a mixed bag of worms, comprising all types of cancers. Pneumonia has also over taken Ischaemic Heart Diseases (IHD), as the second major cause of death in Singapore since 2012 (Table 1). However, if one looks as CVD, which includes IHD (patients with narrowing of heart arteries, and those with heart attacks), cerebrovascular diseases (stroke patients), hypertension and hypertension-related heart disease patients (Table 2), death by CVD is almost identical to cancer, and they each are responsible for about one in three deaths in Singapore from 2012 to 2014!

According to data published by the American Heart Association (AHA), adults with diabetes are two to four times more likely to have heart disease or stroke than those without. Among patients with diabetes mellitus, it is estimated that at least two-thirds of patients aged 65 or older die from some form of heart disease; and 16% die of stroke. Hence, while CVD may account for one-third of total deaths per year, it could account for almost 80% of deaths in adult diabetics.

Table 1 **Principal Causes of Death**

	2012	2013	2014
Total No. of Deaths	18,481	18,938	19,393
% of Total Deaths			
1. Cancer	30.1	30.5	29.4
2. Pneumonia	16.8	18.5	19.0
3. Ischaemic heart diseases	16.1	15.5	16.0
4. Cerebrovascular diseases (including stroke)	9.3	8.9	8.4
5. External causes of morbidity & mortality	5.6	4.9	4.7
6. Hypertensive diseases (including hypertensive heart disease)	2.8	3.1	3.6
7. Urinary tract infection	2.4	2.6	2.6
8. Nephritis, nephrotic syndrome & nephrosis	2.4	2.4	2.0
9. Other heart diseases	1.9	2.0	1.9
10. Chronic obstructive lung disease	2.1	1.6	1.8

Source: Ministry Of Health Website (2016)

## What is new in CVD in type 2 diabetes?

### I. Diabetes Mellitus being Coronary Heart Disease Equivalent.

In addition to being a risk factor for CVD, diabetic patients tend to have a greater burden of atherosclerosis (plaques which formed on the wall of arteries, causing narrowing), and also more atherogenic risk factors than non-diabetics. The latter include hypertension, obesity, increased total-to-HDL-cholesterol ratio, and hypertriglyceridemia.

While it is a known fact that patients with diabetes are associated with increased risk of CVD, the concept that patients with diabetes mellitus should be treated as Coronary Heart Disease (CHD) equivalent—i.e., patients already suffering from CHD actually was derived largely in part by the paper published by Haffner and colleagues in the New England Journal of Medicine in 1998.

Their study showed that over a seven-year follow-up period of 1059 subjects with type 2 diabetes and 1,378 patients without diabetes, those with diabetes, with or without a prior myocardial infarction (heart attack), had a greater mortality from CHD compared to the non-diabetic group. Death from CHD being 42

Table 2 *Principal Causes of Death*

	2012	2013	2014
Total No. of Deaths	18,481	18,938	19,393
% of Total Deaths			
Ischaemic Heart Disease	16.1%	15.5%	16.0%
Cerebrovascular Disease (including stroke)	9.3%	8.9%	8.4%
Hypertensive Diseases (including hypertensive heart disease)	2.8%	3.1%	3.6%
Other Heart Diseases	1.9%	2.0%	1.9%
<b>Total % of Deaths from Cardiovascular Disease</b>	<b>30.1%</b>	<b>29.5%</b>	<b>29.9%</b>
<b>Total No. of Deaths from Cardiovascular Disease</b>	<b>5,563</b>	<b>5,587</b>	<b>5,799</b>

Source: Ministry Of Health Website / Singapore Heart Association Website (2016)

versus 16% for those with a prior heart attack, and 15 versus 2% for those without prior heart attack. Putting this in another way, the rate of the cardiovascular event risk in patients with diabetes but without previous heart attack (15%) is as high as the cardiovascular event risk in patients who have already suffered a heart attack but without diabetes (16%).

Both The National Cholesterol Education Program report from the United States and guidelines from Europe consider type 2 diabetes to be a CHD equivalent, and place patients with diabetes mellitus along with those who already developed CHD in the same "highest risk category".

However, the concept of all diabetes as considered CHD risk equivalent may be overly simplistic, because not all patients with diabetes are at the same cardiovascular risk. In fact, following the original study by Haffner et al., multiple studies from different cohorts provided varying conclusions on the validity of the concept of coronary risk equivalency in patients with diabetes.

New guidelines have started to acknowledge the heterogeneity in risk among diabetic patients, especially those without other risk factors (they considered this group of patients to be at lower risk).

They further suggested an individualised approach to cardiovascular risk estimation and stratification in patients with diabetes, before applying the universal label "Coronary Heart Disease equivalent", and the prescribed treatment associated with the label.

## 2. Which is the best test to screen for presence of CVD in asymptomatic adult diabetic patients?

Given the fact that two-thirds of deaths among patients with diabetes is related to CVD, and that symptomatic patients would have in one way or another declared that they have established heart diseases, detecting CVD in asymptomatic patients with diabetes is, hence, important.

There exists a myriad of tests to screen for CVD in asymptomatic diabetic adults. These include:

- Treadmill Exercise Test
- Carotid Intima-Media Thickness
- Coronary Calcium Score
- Computed Tomography Coronary Angiography
- Stress Radionuclide Cardiac Imaging
- Echocardiography (including stress combined echocardiography), and
- Cardiac Magnetic Resonance Imaging.

It is important to point out that each test has its strengths and weakness, and each assesses different aspects of the heart, and heart conditions.

Cardiologists will usually decide on the test to order based on history provided by patients (including previous tests carried out, if any), and physical examination, including baseline resting 12-lead Electrocardiogram (ECG) findings. It is important to point out that a normal resting ECG in no way rules out the presence of CHD in asymptomatic patients with diabetes. For patients with symptoms suggestive of angina, some form of exercise-related test, and at times invasive coronary angiography, would be the test of choice. For asymptomatic patients with diabetes, I favour Coronary Artery Calcium score assessment.

Coronary calcium score assessment is obtained by performing a Computed Tomographic (CT) scan study, without the use of contrast. The amount of radiation exposure is small, compared to a full CT coronary angiography study. X-ray pictures generated will show whether patients have specks of calcium deposited in their heart arteries. Normal heart arteries do not have calcium deposits in their wall, i.e., zero calcium score. Presence of calcium in heart arteries implies that they already have narrowing (or wall thickening—atherosclerotic plaques) in their heart arteries, hence, Coronary Artery Disease.

On Coronary Artery Calcium (CAC), studies have established that:

- The amount of CAC is closely associated with the amount and degree of heart artery narrowing. As a general rule, when one's calcium score is >400, the chance that that particular patient has a >50% narrowing in the heart artery is high;
- Adult patients with type 2 diabetes harbour larger amounts of CAC than non-diabetic patients of a similar age;
- In general adult population, non-diabetic women tend to develop CHD a decade older, compared to men of the same age without diabetes. However, adult women and men with type 2 diabetes have been shown to have a similar extent of CAC deposits, indicating that diabetes negates the well-known advantage of women over men in developing CAD;
- CAC is better than some traditional risk scores (e.g. Framingham risk score and the United Kingdom Prospective Diabetes Study or UKPDS score) in predicting the occurrence of cardiovascular events;
- Sequential CAC imaging has shown that rapid progression of CAC identifies patients at higher risk for future CHD events; and
- 40% of adult diabetic patients have a CAC score <10 and a very low mortality rate. This again suggests that not all diabetes patients are of the same risk, or that they are all CHD equivalent.

Taking the above into consideration, the overall evidence would support the use of CAC scanning for detection, risk stratification and to perhaps to guide management in the asymptomatic adult diabetes patient.

### 3. Any new oral medication for type II adult diabetes which might offer better CV outcome?

In spite of the strong link between hyperglycaemia and CVD risk, the evidence that intensive glycaemic control reduces this risk is limited, compared with the well-proven risk reduction in microvascular and neuropathic complications.

In the United Kingdom Prospective Diabetes Study (UKPDS study), new type 2 diabetes patients managed with intensive therapy (sulphonylureas or insulin) were compared to those managed with conventional therapy (dietary intervention only). The intensively treated group achieved a lower HbA1c of 0.9%, compared to the conventional group.

Despite this, it only produced a significant 25% risk reduction for microvascular outcomes, but not for heart attack, stroke or death from any cause (all-cause mortality).

However, long term follow-up of the UKPDS cohort showed that some 10 years after the study ended, other than significant reductions in earlier noted microvascular complications, there is significant reduction in death from any causes, heart attack and diabetes-related end points despite subsequent similar mean HbA1c levels (8%) in both groups. This is known as glucose "Legacy Effect"—that early interventions for glucose control may lead in the long term to a benefit in CVD risk reductions.

It is possible that the legacy effect may also occur in other risk factors like hypertension and hyperlipidemia. Hence, despite the relative paucity of macrovascular outcome data, good glucose control in type 2 asymptomatic patients with diabetes is still important in terms of CVD prevention.

A relatively new oral diabetic medicine has been shown to provide good CV outcome results in a well conducted study (EMPA-REG OUTCOME trial). Empagliflozin (Jardiance) is an oral hypoglycaemic agent, and a highly selective sodium glucose cotransporter 2 (SGLT2) inhibitor. It reduces renal glucose reabsorption, increases urinary glucose excretion, and is associated with osmotic diuresis, reductions in body weight and blood pressure.

In adult patients with type 2 diabetes and high CV risk, Empagliflozin, on top of standard of care, was shown to reduce the primary composite outcome of CV death, non-fatal myocardial infarction or non-fatal stroke, as well as hospitalisation rates for heart failure and overall mortality compared with placebo. This is exciting as this new medicine is the only diabetes medication to show a significant reduction in both CV risk and CV death in a dedicated outcome study.

### Summary

Increased cardiovascular morbidity and mortality in adult patients with type 2 diabetes is well established. Diabetes is associated with at least a two-fold increased risk of coronary heart disease; and approximately two-thirds of deaths among persons with diabetes are related to cardiovascular disease. However, recent advances in medicine enables us to detect CVD earlier in asymptomatic adults with type 2 diabetes, and offer more accurate risk assessment and stratification in them. In addition, a new oral diabetes mellitus drug has also been shown to improve CV outcomes. Future advances in the coming years will allow us to make greater strides in lowering clinical CVD in this high-risk patient population.