

# Effects of Type 2 Diabetes upon Cardiovascular Diseases

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**Abstract:** Nowadays Type 2 diabetes is becoming a major health problem in the world. It has identified that Type 2 Diabetes Mellitus will lead to serious cardiovascular outcomes, which can cause several damages to the organs of the body and even death. This paper will emphasize the risk factors, which cause both Type 2 Diabetes Mellitus and Cardiovascular diseases and main microvascular and Macrovascular outcomes, which can conceivable in type 2 diabetic patients. A research has done in England with the information of CALIBER program, to investigate the association between T2DM and initial manifestations of CVD. [17] University of occupational and environmental health in japan has done a cross sectional study about, how does fluctuating of glucose level affect to vascular endothelial function.[8] Study design and participant ADVANCE was a factorial randomized controlled trial evaluates the effects of blood pressure-lowering and intensive blood glucose on vascular outcome, which was done by ADVANCE collaborative group. They have consisted 11149 participants from 215 centers in 20 countries. Swedish national diabetes register has done a research about additive effects of glycaemia and dyslipidemia on risk of cardiovascular diseases in type 2 diabetes mellitus. This study is consisted 22135 participants according to age (30–75 years), HbA1c  $\geq 5\%$  ( $\geq 31$  mmol/mol), BMI  $\geq 18$  kg/m<sup>2</sup> and plasma creatinine  $< 150$   $\mu$ mol/l. A history of CVD was present in 15%, a history of heart failure in 4% and atrial fibrillation in 3% of participants.[13]. People with type 2 diabetes have higher risk of cardiovascular morbidity. [19] Risk of myocardial infarction, stroke and even death is strongly associated with type 2 diabetes [3]. Diabetes and ischemic stroke are common that frequently occurring together [9]. Coronary heart disease is one of long-term complication in people with diabetes. [26] Diabetic retinopathy, diabetic neuropathy and diabetic nephropathy are microvascular complications that occurred due to diabetes. The risks of these microvascular complications are proportional to duration and magnitude of hyperglycemia. [18] There are common risk factors for both DM and CVD. High blood pressure, glycated HbA1c, total cholesterol are described in this article. Ultimately, it can be concluded as, there is a considerable relation between type 2 diabetes and cardiovascular diseases. However managing the appropriate threshold levels can reduce the risk of any kind of cardiovascular diseases.

**Keywords:** DM-diabetes mellitus, CVD-cardiovascular disease, UKPDS-United Kingdom prospective diabetes study

## 1. Introduction

Diabetes mellitus is defined as a heterogeneous metabolic disorder characterized by common feature of chronic hyperglycemia and glycosuria (presence of glucose in urine), with disturbance of carbohydrate, fat, and protein metabolism. Type 2 diabetes is known as maturity onset diabetes or non-insulin dependent diabetes mellitus. Mainly it affects older individuals and obese adolescent children. Type 2 diabetes can be occurred due to genetic predisposition and environmental and behavioral risk factors.[10]

Type 2 diabetes is the most prevalent form of diabetes. It is appeared later in life. It is a combination of insulin resistance (impairment in insulin-mediated glucose disposal) and defective secretion of insulin by beta cells. Moreover, all the cells will undergo atrophy gradually when we are aging, therefore, production and secretion of insulin decline in advancing age.[5]

About 60% of patients are affected with both CVD and DM. There is the risk of development of acute myocardial infarction in patients with type 2 DM is 6–10 times higher than in a general population. Combination of CVD and DM increase significant rate of mortality. Usually 50% of people in the world who are at age 40-59 have type 2 diabetes. Those people have significant serious complications, such as hypertension, angina, myocardial infarction and stroke, which depend on their age. MI is the most adverse outcome in elderly people (above 60), unless DM did not control properly.[2]

Type 2 Diabetes is a bulk of chronic diseases. One of the main complication arising from hyperglycemia is either injury to vasculature classify as microvascular or injury to the large body vessels also known as macro vascular.[18]

Neuropathy is microvascular which, developing in patients with diabetes. Neuropathy is known to be heterogeneous by their symptoms, patterns of neurologic involvement, course, risk covariates and pathologic alterations.[7]. Peripheral neuropathy is one of the most common microvascular complications in type 2 diabetes.

Neuropathic ulcer is the most common type of neuropathy. Neuropathy may be asymptomatic or symptomatic; when symptoms are present, it might be negative or positive. Negative symptoms are loss of sensation, loss of strength. Positive symptoms include pricking or pain.[4]

Diabetic nephropathy develops in approximately 40% of all patients with type 2 DM. hypertension, which cause CVD and main risk factor for diabetes, is a risk factor for diabetic nephropathy as well. Microalbuminuria is also a risk factor.[6]

Diabetic retinopathy is the most common microvascular complication. It depends on the severity, duration of diabetes and due to hypertension. These criteria were found by UKPDS. Before the diagnosis of diabetes, retinopathy symptoms might be occurred.[18]

Vascular endothelial dysfunction, which is influenced by fluctuation of blood glucose, occurs in early stage of

atherosclerosis, then it will prognosis to atherosclerosis and it will lead to diffuse and multi vascular damages in coronary arteries. [8] Reykjavik study has reported the relative risk was 2 (HR) in both sexes for total mortality and coronary heart disease mortality. Myocardial infarction or strokes were the first complications that they have.

Type 2-diabetes can lead to cardiovascular disease, if it is not under control. Particularly type 2 diabetes may have the following condition that contributes to their risk of developing cardiovascular disease. They are high blood pressure, high glucose level and cholesterol level. [3]

## 2. Materials and Methods

A research, which is done by England in 2015, by taking information such as linked primary care, hospital admission, disease registry and death certificate records from CALIBER program. It links data for people in England recorded in four electronic health data sources. Selected participant were 30 years or older between January 1, 1998 to march 25, 2010 and excluded with a history of CVD, and record of pregnancy within 6 months of entry.

Their cohort consisted of 1921260 individuals without CVD at baseline according to sex and type 2 DM status. In this study, they were aimed association between T2DM and 12 initial manifestations of CVD.[17]

Reactive hyperemia incidence and index of vascular endothelial function were measured using peripheral arterial tonometry on University of occupational and environmental health in Japan was done a cross sectional study about type 2 DM patients who admitted to it in April to November for glycemic control. Criteria were age (>20), blood glucose level at admission of <300mg/dl, no diabetic ketosis or non-ketotic hyperosmolar coma and absence of cardiac arrhythmia. Infectious diseases and coronary syndrome also were excluded. They were measured over 24 hours by continuous glucose monitoring on admission day 2 in 57 patients with type 2 DM. the admission day 3.[8]

11,140 patients were randomized to intensive or standard glucose control in the Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Glycemic exposure was assessed as the mean HbA1c measurements during follow-up and proper to the first event. 54 participants were excluded whole levels of HbA1c at baseline not available. There were 4112 participants from Asia (China, India, Philippines, and Malaysia) and 6974 from Europe, Australia, New Zealand and North America. [11] Swedish national diabetes register has done a research about additive effects of glycaemia and dyslipidemia on risk of cardiovascular disease. This study consisted 22,135 participants. Age 30–75 years, HbA1c  $\geq 5\%$  ( $\geq 31$  mmol/mol), BMI  $\geq 18$  kg/m<sup>2</sup> and plasma creatinine <150  $\mu$ mol/l. A history of CVD was present in 15%, a history of heart failure in 4% and atrial fibrillation in 3% of participants.[13]

## 3. Results

Lowering the blood pressure to a treatment goal of below 130/80 mmHg in high-risk patients, including people with diabetes, cerebrovascular and coronary arterial disease, or kidney disease. There is a conclusion that reduction of 10mmHg of blood pressure had a greater effect on reducing the risk of heart disease. It has estimated there will be 12% of reduction in the risk of any end related to diabetes and 15% reduction in risk of death related to diabetes. Myocardial infarction is the most common side effect in diabetes than microvascular complications such as retinopathy, nephropathy, and neuropathy. Moreover, 10mmHg reduction of systolic blood pressure will be affected to the diminution of Macrovascular and microvascular diseases at 11% and 13% respectively. According to retrospective cohort study, this was done with UK general practice database, 1990–2005. Systolic blood pressure below 110mm Hg and diastolic blood pressure below 75mmHg were associate with significantly increased risk of death in patients with DM and CVD. In patients with diabetes without established cardiovascular disease, systolic blood pressure below 120mmHg and diastolic blood pressure below 75mmHg were associated with a significant increased risk of mortality.[22]

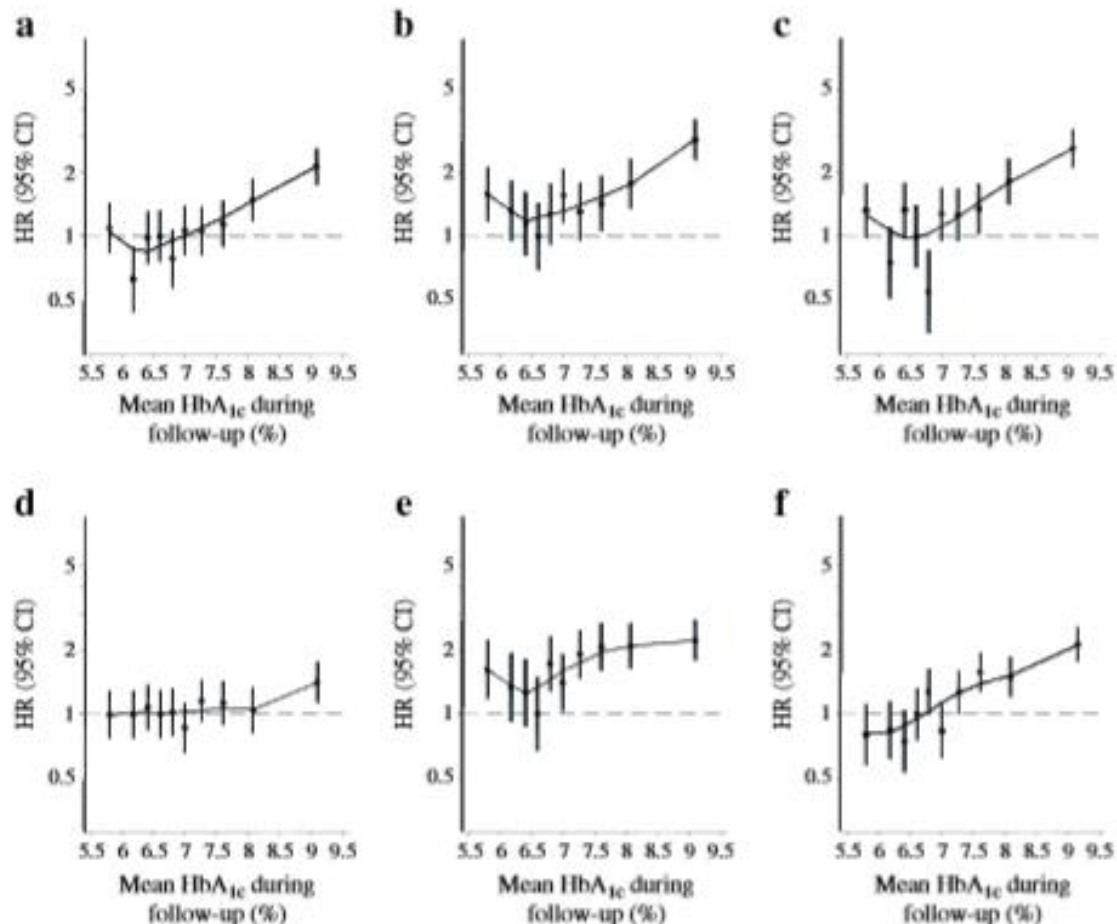
Prevention of hypertension in diabetic patient is higher than general population. Especially 40% patients with type 2 diabetes are hypertensive who is around age 40. When age comes to 75 the percentage getting increase up to 60%. Therefore, treatment for hypertension is more useful and common. Lower BP will reduce the incidence of stroke and myocardial infarction and microvascular complications as well. If we will able to control the blood pressure tightly, we will obtain 34% of reduction in myocardial infarction, sudden death, stroke and peripheral vascular disease. Microvascular disease such as nephropathy, neuropathy and retinopathy can be reduced in 37% by controlling tight blood pressure.

Joint national committee on prevention, detection, evaluation and treatment of high BP has recommended, target treatment goal of systolic BP is 130mmHg.[15, 16]. In 2002, American diabetes association also recommended that 130/80mmHg is the BP treatment goal for diabetic patients.[15]

Hyperglycemia is strongly associated with risk of Macrovascular and microvascular complications. Updated mean HbA1c can measure that. Nevertheless, these complications are adjusted for age, sex, and ethnic group, duration of diabetes, lipid concentration, blood pressure and smoking. Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study has analysis 11086 participants to identify HbA1c level and how does HbA1c level affect to CVD and if we were able to reduce 1% of HbA1c how will it affect to the CVD. In patients with type 2 diabetes, their HbA1c levels were associated with lower risks of Macrovascular Events and death down to threshold of 7% and microvascular events down to threshold of 6.5%.

Glycemic exposure to Glycemic levels over time were assessed as mean HbA<sub>1c</sub> of measurement taken at baseline 6 months, 12 months for each individual. That average HbA<sub>1c</sub> is measured by weighting each measurement for the individual by the time intervals between measurements during follow up and prior to the first event. 11086 patients were included in observational analysis after the exclusion of 54 participants for a whom levels of HbA<sub>1c</sub> at baseline were not available. The mean

HbA<sub>1c</sub> was 7.5%. After the staging, they have estimated three risk threshold levels of HbA<sub>1c</sub> for three major outcomes. They are 6.57 (5.19-7.26) for macro vascular disease, 6.54 (6.16-6.75) for death, 6.14 (4.33-6.51) for microvascular disease. Therefore, ultimately it can be concluded as the threshold levels in the range of 6.5%-7% for macro vascular disease and death, and 6%-6.5% for microvascular diseases.



**Figure 1:** Adjusted HR for (a) major coronary events, (b) major cerebrovascular events, (c) cardiovascular death, (d) peripheral vascular events, (e) new or worsening nephropathy and (f) new or worsening retinopathy by decile of mean HbA<sub>1c</sub> levels during follow-up with locally weighted scatter plot smoothing lines

If the HbA<sub>1c</sub> is above threshold level, it will be 38% higher risk of a macro vascular event, 40% higher risk of microvascular event and 38% higher risk of death.

UKPDS has proved, there will be a reduction of CVD, by decreasing HbA<sub>1c</sub> level in 1%. Each 1% of HbA<sub>1c</sub> was associated with 37% reduction in risk for microvascular disease and 21% reduction in the risk of any endpoint or death related to diabetes. Steep for stroke and heart failure is less than other CVD. In addition, the lowest category of updated mean HbA<sub>1c</sub> will be a reason for myocardial infarction the microvascular disease.

They have estimated the reduction percentage of each CVD according to reduction of 1% of HbA<sub>1c</sub>. There will be a 14% reduction in fatal and nonfatal myocardial infarction, 12% on fatal and nonfatal stork, 37% in

microvascular endpoints, 19% in cataract extraction, 43% in amputation or death from peripheral vascular disease and 16% in heart failure.[11]. United Kingdom Prospective Diabetes Study has clearly shown a direct relationship between glycosylated HbA<sub>1c</sub> levels incidence of CVD. They have proved intensive glucose control might lead to reduction of all CVD.[23]

Cholesterol level is a major risk factor for having cardiovascular and cerebrovascular disease in diabetes mellitus. There will be defects in synthesis and clearance of plasma lipoproteins, which is known as dyslipidemia. Presence of low level of high-density lipoprotein, cholesterol, hypertriglyceridemia and postprandial lipemia are most frequent characteristics in type 2 diabetes. These factors accelerate the macro vascular disease.[9] This LDL play an important role in Atherogenesis. Cardiovascular event rates were significantly greater in those with



dyslipidemia, they are LDL-C > 2.6mmol/l, HDL-C ≤ 0.88mmol/l and TG ≥ 2.3mmol/l. these threshold levels have given By Fenofibrate Intervention and Event Lowering In Diabetes (FIELD) study and in the Action to Control Cardiovascular Risk in Diabetes (ACCORD).

Swedish national diabetes register has done this research by 22135 participants, female and male with type 2 diabetes mellitus (age 30-75, 15% with previous CVD, HbA1c ≥ 55, BMI ≥ 18kg/m<sup>2</sup>, plasma creatine < 150µmol/l, history of heart failure 4%, atrial fibrillation 3%) followed for 5years. Total mortality are the outcome that they considered.

NDR study has examined patients according to baseline clinical characteristics such as age, sex, duration of diabetes, HbA1c level, total cholesterol, HDL cholesterol, TC/HDL, LDL cholesterol, triglycerol, weight, height,

smoking status, systolic blood pressure, cumulative Microalbuminuria, plasma creatine, type of hyperglycemic treatment, use of antihypertensive drugs and lipid lowering drugs (43%). They have done a cox regression analysis, to estimate 5 years event rates (1-survival rate) for the outcomes, and they have considered both TC/HDL and HbA1c. HR was higher with TC/HDL as predictor than with HbA1c as a predictor. HR with updated mean TC/HDL and HbA1c values were 1.31 and 1.13 for fatal/non-fatal CHD, 1.25 and 1.15 for fatal/non-fatal stroke, 1.29 and 1.13 for fatal/non-fatal CVD, 1.28 and 1.18 for fatal CVD. HR for total mortality were 1.18 and 1.07. The risk increase for fatal/non-fatal CHD was 31% per 1 SD increase of TC/HDL and 13% per 1 SD increase of HbA1c, with values of 25% and 15% for fatal/non-fatal stroke, and 29% and 13% for fatal/non-fatal CVD

**Table 2** HRs in 22,135 individuals with type 2 diabetes per 1 SD increase in baseline or updated mean values of TC/HDL or HbA<sub>1c</sub>

Outcome	Type of predictor	Endpoints (n)	TC/HDL		HbA <sub>1c</sub>		p for interaction
			HR (95% CI)	p value	HR (95% CI)	p value	
Fatal/non-fatal CHD	Baseline	1,607	1.19 (1.13, 1.25)	<0.001	1.10 (1.04, 1.16)	<0.001	0.02
	Updated mean	1,607	1.31 (1.25, 1.37)	<0.001	1.13 (1.07, 1.19)	<0.001	0.02
Fatal/non-fatal stroke	Baseline	742	1.16 (1.08, 1.25)	<0.001	1.09 (1.01, 1.18)	0.03	0.7
	Updated mean	742	1.25 (1.17, 1.34)	<0.001	1.15 (1.06, 1.24)	<0.001	0.6
Fatal/non-fatal CVD	Baseline	2,249	1.18 (1.13, 1.23)	<0.001	1.09 (1.04, 1.14)	<0.001	0.05
	Updated mean	2,249	1.29 (1.24, 1.34)	<0.001	1.13 (1.08, 1.18)	<0.001	0.1
Fatal CVD	Baseline	693	1.16 (1.08, 1.25)	<0.001	1.15 (1.06, 1.24)	<0.001	0.8
	Updated mean	693	1.28 (1.20, 1.38)	<0.001	1.18 (1.10, 1.28)	<0.001	0.5
Total mortality	Baseline	1,667	1.05 (1.01, 1.11)	0.03	1.07 (1.01, 1.12)	0.02	0.8
	Updated mean	1,667	1.18 (1.12, 1.24)	<0.001	1.07 (1.02, 1.13)	0.01	0.09

**Figure 2:** HRs were adjusted for age, diabetes duration, sex, systolic blood pressure, BMI, smoking, albuminuria >20 µg/min, antihypertensive drugs, lipid lowering drugs, type of hypoglycemic treatment, atrial fibrillation, history of CVD and history of heart fail.

UK prospective diabetes study has mentioned dyslipidemia is one of the major risk factors for CHD. Total cholesterol and LDL-cholesterol have been consistently associated with CHD.[13]

#### 4. Discussion

High blood pressure is most common risk factor that diabetic patients have. Therefore, pumping system get affected if someone has diabetes. Normal blood pressure of human body is 120/80mmHg. Diabetes will mainly affect to the systolic blood pressure. Systolic blood pressure is the highest pressure described as blood pushes through ventricles of heart to arteries. The type 2 diabetes, which can cause Macrovascular and microvascular disease, mostly affects systolic blood pressure. Systolic blood pressure will be affected to development of Macrovascular and microvascular disease. Even cardiovascular diseases are strongly associated with systolic blood pressure. Mortality related diabetes and all type of mortality were both strongly associated with blood pressure. Normally type 2 diabetic patients are having ≥140/90mmHg blood pressure. It can be increased up to 170mmHg (systolic blood pressure) according to age, sex,

ethnic group, smoking condition, lipid concentration. When systolic blood pressure reaches 170mmHg, it can cause myocardial infarction, stroke or any other microvascular complications.[1, 22]

Higher blood pressure is become most serious heart condition in type 2 diabetic patient because it is most common reason for heart disease as well. Therefore, it has been recommended to control the blood pressure to diabetic patients. Tight control of blood pressure aiming at a blood pressure of 150/85mmHg (with the angiotensin atenolol as main treatment) or with less tight control aiming at a blood pressure of 180/85mmHg. According to UK prospective diabetes studies has proved significant reductions in risk of diabetes related diseases by controlling blood pressure.[10, 12]

The main reason for diabetes is high level of glucose in the blood. Due to the dysfunction of β cells of pancreas, excess glucose will remain in the blood rather than storing in the liver or skeletal muscle. High glucose can reduce the levels of the powerful vasodilation nitric oxide in blood vessel, then that increases the risk of high blood pressure and gradually narrows down the vessels.

Contraction of blood vessel get affected (make it more contract than normal) due to the hyperglycemia. Glucose will influence arterial myocytes (which made by atrium) and then the cells that compose arterial tissue and blood vessels. Therefore, that phenomenon will leads to get heart attacks (myocardial infarction) by blocking coronary arteries. Not only will heart attacks but also there be many cardiovascular complications.[24]Usually our red blood cells have combined with glucose, named as glycated hemoglobin (HbA1C) once they bind. However, there must be reference value of HbA1c. That reference value is 2-6% (<6%). HbA1c will indicate how much sugar is in the blood and how does it control over 2-3 months. (RBC life span is 3 months)[16]

Fluctuation in blood glucose level can cause vascular endothelial dysfunction and play a critical role in onset and/or progression of atherosclerosis in type 2 DM. there were 2-6 times greater risk of having myocardial infarction in type 2 diabetic people than normal population and for stroke it was 2 to 3 times greater. By controlling HbA1c below critical level, we can inhibit the microvascular complications. [8]

In diabetic patients, their LDL concentration is increased due to very poor glycemic control. Lipogenesis and an exacerbation substrate availability also increased and apolipoproteins B-100 degradation decreased as well. These changes lead lipid profile marked by low-high density lipoprotein cholesterol, high triglyceride, increased Apo B synthesis and small dense LDL particles. This lipid disorder, named as arterogenic dyslipidemia or diabetic dyslipidemia, which is associated with insulin resistance. This abnormality in lipid count also leads to CVD.[19]Cholesterol is very important to health, but when the cholesterol levels are too high, it can be harmful by contributing to blocked or narrowed arteries. Unfortunately, people with diabetes are more prone to having unhealthy high cholesterol levels, which contribute to CVD. Patients with type 2 diabetes are at higher risk of CVD. Among CVD, Myocardial infarction and stroke were chosen as primary outcomes of major type two DM. this study needed to investigate and compare the association between type 2 diabetes and future risk of the most common initial cardiovascular manifestations in men and women.

According to CALIBER study information (They used linked primary care, hospital admission, disease registry, and death certificate records from the CALIBER program), they have selected particular participants who

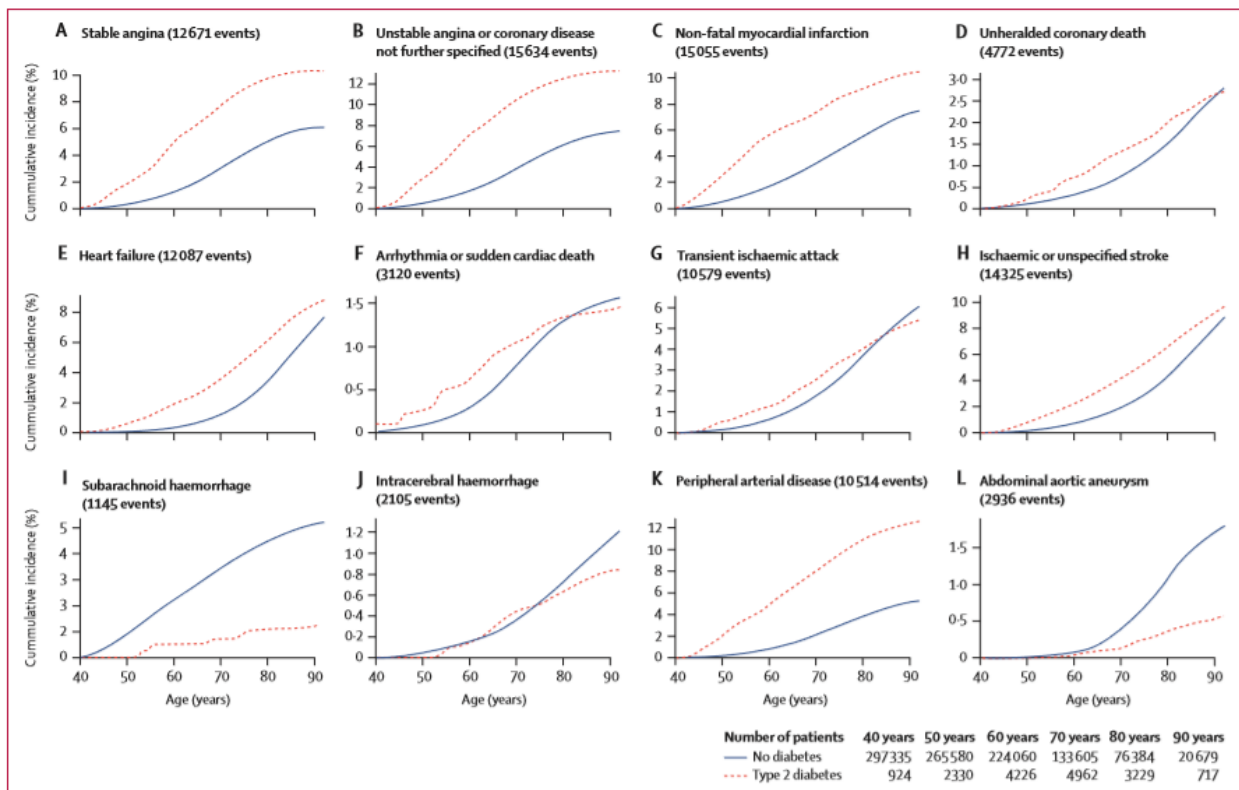
developed new-onset diabetes during follow-up were analyzed. According to their baseline status of no diabetes. They excluded people with type 1DM and uncertain type. Their criteria were mean HbA1c (3 years before study and ignoring values occurring after an endpoint), BMI, HDL Cholesterol, Cholesterol and systolic blood pressure. Study has presented 12 primary CVD such as stable angina, unstable angina, myocardial infarction, unheralded coronary death, heart failure, transient ischemic attack, ischemic stroke, subarachnoid hemorrhage, intracerebral hemorrhage, peripheral arterial disease, abdominal aortic aneurysm, and a composite outcome classified as arrhythmia or sudden cardiac death, which consisted of cardioversion, ventricular arrhythmia, implantable cardioverter defibrillator, cardiac arrest, or sudden cardiac death. Secondary outcomes were cardiovascular mortality.

HbA1c was the measurements, which use to estimate the hazard ratio. They grouped patients type 2DM into categories by the HbA1c concentration. These threshold levels were 6.5% (48mmol/mol, threshold for diagnosis of diabetes), 7.5% (58mmol/mol, threshold for imitation of insulin or thiazolidinedione) according to UK guidelines.

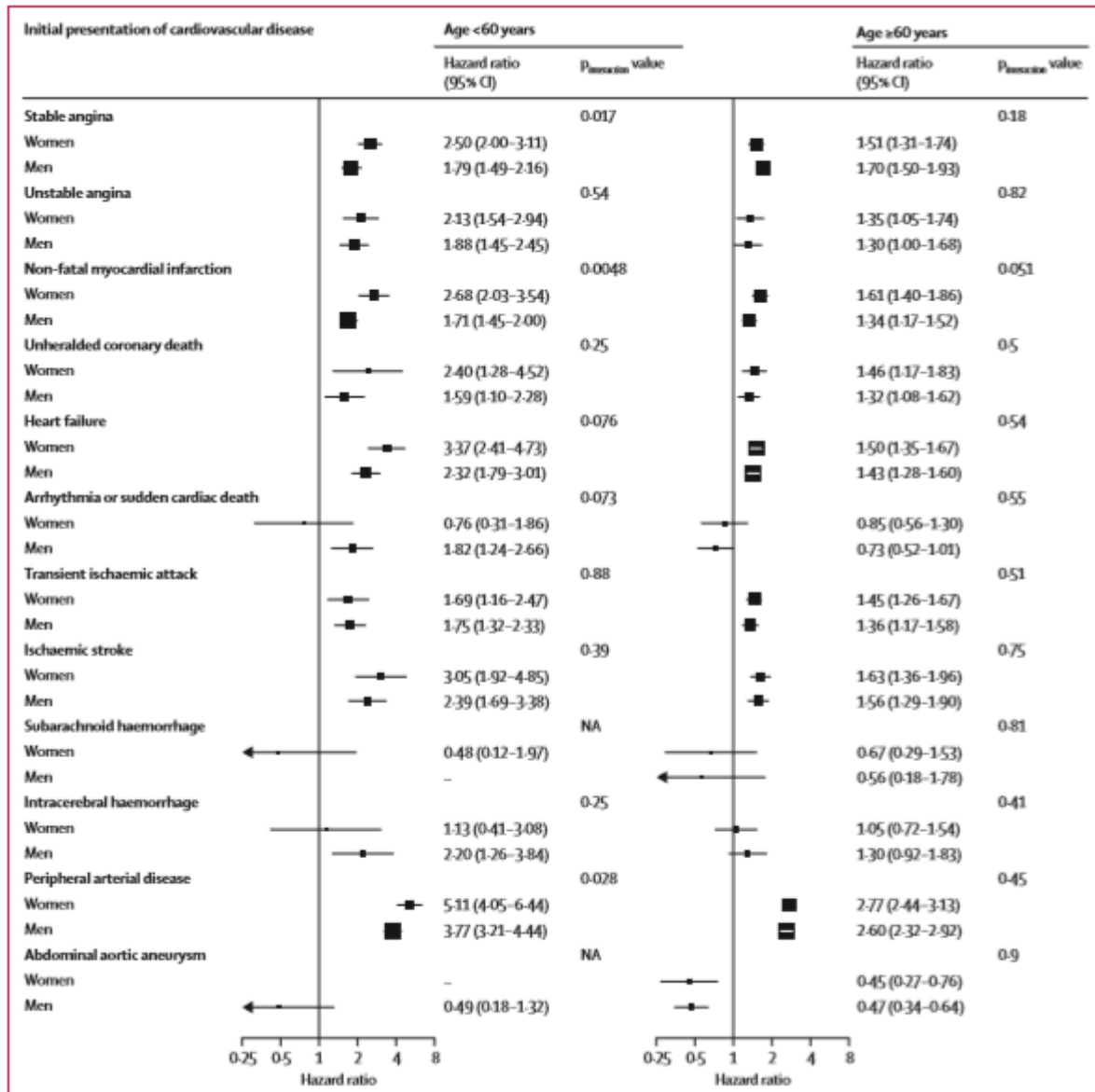
These CVD can be different according to age, sex and duration of diabetes. Although absolute risk of coronary heart disease: mortality and morbidity is lower in women than men are. Coronary heart disease HR was 2.63for women and 1.85 for men with diabetes. This is because of estrogen hormone, which is present in women and which can increase HDL, decrease LDL, relaxes, smooth and dilates blood vessels so blood flow increases. For other CVD sex, difference was not affected.

Peripheral arterial disease was the largest CVD among all the CVD. Though there was a difference between people with diabetes and without diabetes, women with type 2 diabetes at age 40 years has 9.7% risk, men at age 40 it was 11.7% of developing peripheral arterial disease as first presentation. At age 80 and without diabetes they were 3.3% and 4.5%. Moreover, they have observed, slightly greater risk of non-fatal myocardial infarction associated with type 2 DM in women younger than 60 years than in men younger than 60 years. Although there was not a significant statistically different between sex.

People with diabetes at age 40 are more prone to have coronary heart disease, transient ischemic attack, ischemic stroke and peripheral arterial disease.[17]



**Figure 3:** Cumulative incidence curves for the incidence of first presentation of 12 cardiovascular diseases in patients aged  $\geq 40$  years, by diabetes status the curves begin at age 40 years rather than 30 years because 40 years is a typical age for a patient to develop type 2 diabetes



**Figure 4:** Hazard ratios for association of type 2 diabetes with 12 cardiovascular diseases by sex and age Hazard ratios by sex and age group for the association of different initial presentations of cardiovascular disease with type 2 diabetes, adjusted for age, BMI, deprivation, HDL cholesterol, total cholesterol, systolic blood pressure, smoking status and statin and antihypertensive drug prescriptions. NA= not applicable.

### 5. Conclusion

According to the results, which is refer in this article, it can be conclude as; there is a greater association between type 2 diabetes and cardiovascular disease. However, if patents are able to manage the threshold levels of risk factors, there will be a significant reduction in any CVD, which caused by type 2 diabetes.

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