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The Impact of Diabetes Mellitus II on Longevity and Morbidity Risk

Literature Review

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PhD Research funded by the Actuarial Research Centre, Institute and Faculty of Actuaries

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Abstract

Life expectancy is a basic indicator of the heatlh conditions and social developments of a country among other factors (UN, 2018). Thus improved health conditions and socio-economic developments can imply an increased life expectancy resulting in people living longer than expected, better known as longevity risk in insurance business. However, poor life styles may lead to a reduced life expectancy growth rate due to life style diseases such as DM-II. The higher the morbidity rates the more is the decrease in life expectancy. Both longevity and morbidity risks have optimum levels that maximises insurance and business returns. Deviance from these levels can possibly lead to unwanted negative returns. Of interest is the increase in the number of non-communicable diseases in the top ten cause-of-death list from 4 in 2000 to 7 in 2015 (WHO, 2017a). In particular DM-II was reported by the WHO as being among the top six cause-of-death in 2015 and most of highest cause-of-death from the list are among its complications. This study investigates and presents the impact of DM-II on longevity and morbidity through the use of the The Health Improvement Network (THIN) database, Kaplan-Meier plots and Cox Proportional Harzard functions. The resulting models are then translated into actuarial models and application. Finally, an R-package is developed to compute impacts of several chronic disease on longevity and morbidity for actuarial and statistical use. This report is on the literature review that will be used for the study.

Chapter 1

Overview of Longevity and Diabetes Mellitus

1.1 Life Expectancy Historical Experience

Life expectancy has been on the increase for the past years in both developed and developing countries. This has drawn the attention of stakeholders including actuaries, statisticians, insurers and governments and has led to various studies on longevity risk especially in the actuarial and insurance fields in general and specifically, retirement pension systems.

However, in recent years there has been some significant decline in the growth of life expectancy in some countries, including UK (IFoA, 2011). This may be attributed to health challenges that includes antibiotic resistance (IFoA, 2016).

Recent levelling of death rates in older ages imply that important decisions have to be made in longevity forecasts used in pension funds and annuities. This slow-down or levelling off in the reduction of mortality rates, particularly for the old age population, has led to a decline in the average annual rise in life expectancy at age 65 in the UK, United States (US) and Canada since 2011. The UK's average annual rise in life expectancy at age 65 was 2.1 months over 2000 - 2011, falling to 0.4 months after

2011. To establish reasons behind the reduction requires more research. In the US, mortality rates have risen for the white working age population from 2011. Life and health insurers should monitor this trend of rising death rates as it could result in rising claims (Lu, 2017)

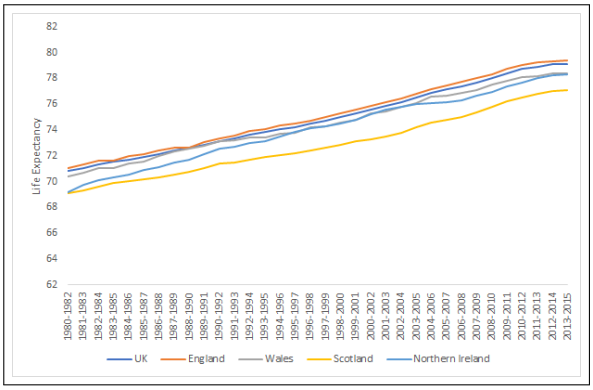
According to the Office of National Statistics (ONS) using the National Life Tables (UK:2013-2015) and assuming that the mortality rates remain the same, males life expectancy is 79.4 years and females 83.1 years. The life expectancy at 65 years ($\mathring{e}_{65}$) is 18.5 years for males while for females it is 20.9 years.The most common age of death in the UK is 85 for males and 89 for females.

ONS (2016) reported an increase in the number of deaths in 2015 which has slowed down the increase in life expectancy at birth ($\mathring{e}_0$). In the period 2013-2015, the highest number of deaths was recorded in those aged 85+ years constituting 57.4% for males and 68.8% for females. It is clear from the ONS report that despite the improvements in the life expectancy over the last 33 years (between 1980-1982 and 2013-2015), there has been some dips in the life expectancy between 2012-2014 and 2013-2015 at older ages as depicted in Figure 1.1 (ONS, 2016).

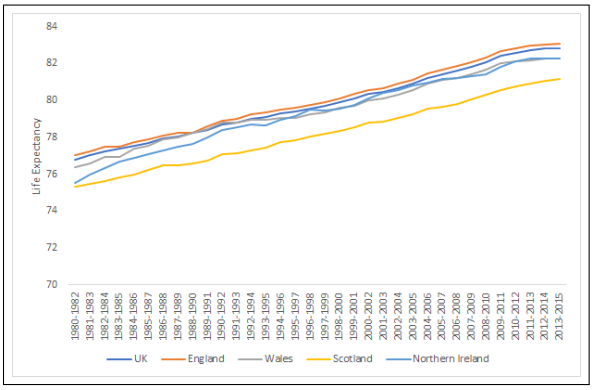
The total mortality rates increased by 4.2% between 2014 and 2015. For females it is was 5% and males 3.1%. However, the Age-Standardised Mortality Rate (ASMR) [1] was significantly higher in males than females (1 156 and 863 per 100 000 population respectively). Two-thirds of deaths occurred in the 75+ years age group, (ONS, 2016).

Hiam et. al. (2017), states four possible causes of significant spikes in population mortality: 1. Data artefact; 2. Environmental shock; 3. Major epidemic and; 4. Widespread failure of health and social care. They did not find that (1) and (2) could be reasons for the increase in the UK deaths in January 2015.

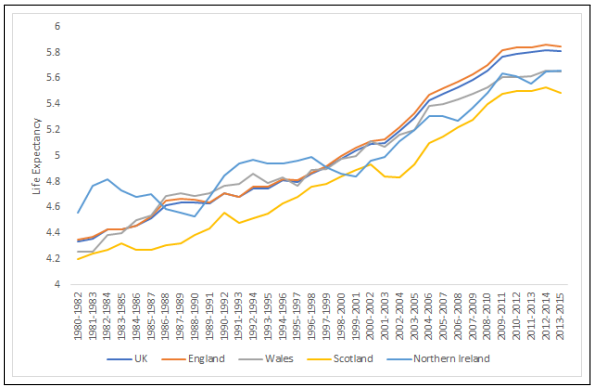
[1] ASMR is the weighted average of age - specific mortality rates per 100 000



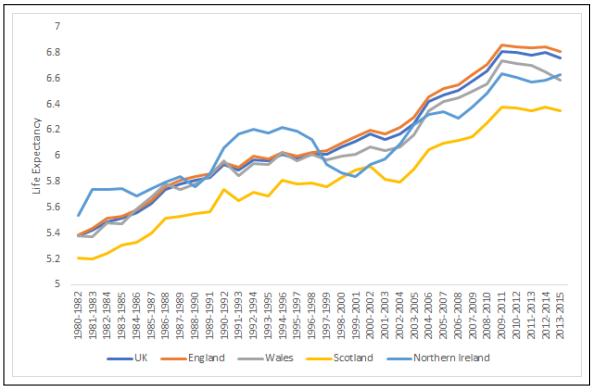
(a) Males ($\mathring{e}_0$)



(b) Females ($\mathring{e}_0$)



(c) Males ($\mathring{e}_{85}$)



(d) Females ($\mathring{e}_{85}$)

Figure 1.1: Life Expectancies: 1980-1982 to 2013-2015.
(a) and (b) at Birth; (c) and (d) at 85 years
Source: ONS (2016)

Infectious diseases are a causative factor, as in the recent winters higher than expected deaths have occurred compared to recent trends, especially among the elderly; in seasons dominated by the H3N2 flu virus. However, seasonal flu in the UK is a contributory factor and only accounted for less than 15% of all deaths in England and Wales in 2015. Flu cannot be the main causative reason because the higher numbers of deaths in the UK during the winter of 2014/2015 occurred when mean monthly temperatures were above average (Falkous, 2017). The question becomes, "What could be causing this, and also causing broadly similar slowdown in life expectancy trends over the same time period in some other European countries?", (Falkous, 2017).

There was the same decline in $\mathring{e}_0$ among European Union (EU) - 28 (EU-28) coun-

tries in 2015 (Eurostat, 2017). In 2015 alone a total of 5.2 million deaths were recorded in the EU-28, the highest number observed over the past five decade. The crude death rate, that is the number of deaths divided by the total population multiplied by 1000, reported reached a peak value of 10.2 in the EU-28 in 2015.

The $\mathring{e}_0$ in the EU-28 increased by 2.9 years over the last 15 years from 77.7 years to 80.6 years. It then declined in 2015 by 0.3 years compared to 2014 as depicted in Figure 1.3. This is the first decline since 2002. Hence, we agree with Eurostat that it is not possible to conclude whether the decline in $\mathring{e}_0$ is temporary or will continue. But at the same time it is a cause for concern.

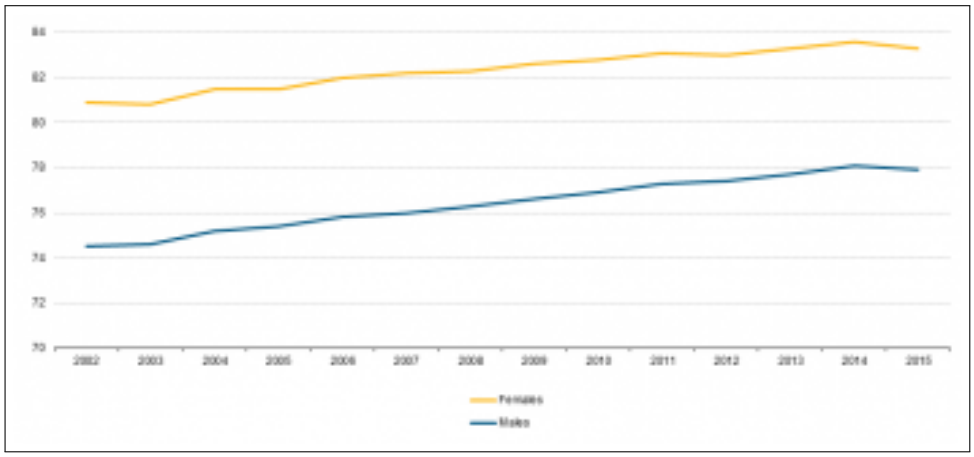


Figure 1.3: Life Expectancy at Birth, EU-28, 2002-2015

Source: Eurostat (2017)

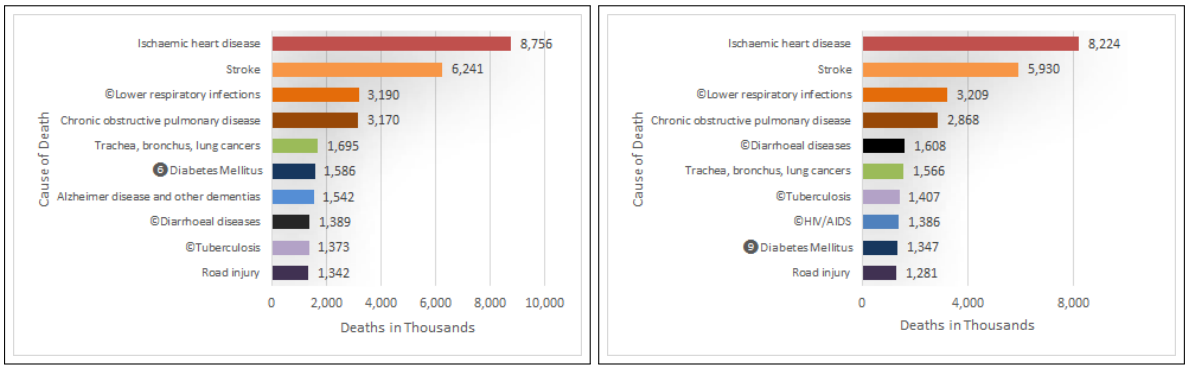
According to Eurostat (2017), nineteen of the EU-28 member states experienced a decline in the $\mathring{e}_0$ in 2015 compared to 2014, from a maximum of 1 year in Cyprus to a minimum of 0.1 years for Sweden. Eurostat also reported the same declining trend in the $\mathring{e}_{85}$. The trend was also noticeable at age 65. The $\mathring{e}_{65}$ in 2015 declined by 0.3 years compared to 2014; from a maximum of 0.6 years in both Cyprus and Italy to a minimum of 0.1 years in Denmark and Sweden. The same trends were experienced by Candidates, a country waiting to be fully accepted as a member of the EU after fulfilling economic and political requirements, and European Free Trade Association (EFTA) countries.

1.2 Overview of Major Causes of Death

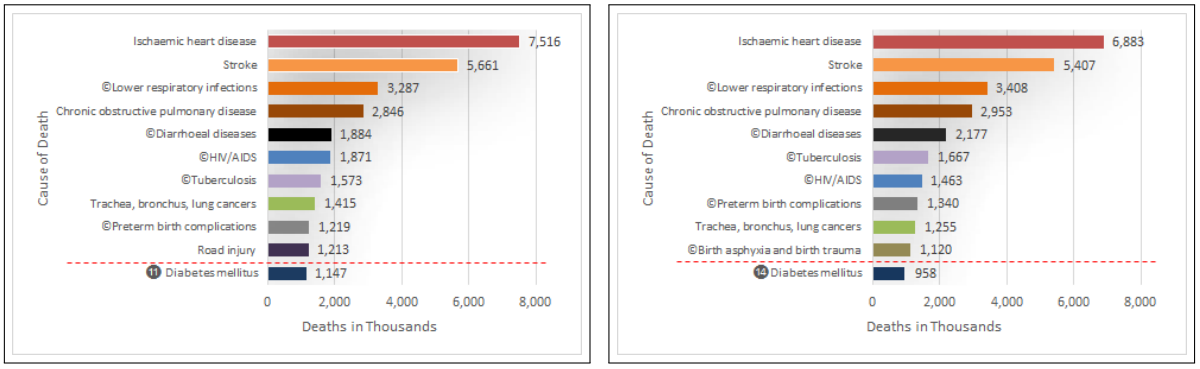
According to the World Health Organisation (WHO) Fact Sheets, 56.4 million died worldwide in 2015, of which 54% of the deaths were due to the top ten causes. Ischaemic Heart Disease (IHD) and Stroke are the world's biggest killers accounting for 15 million deaths worldwide. These have remained the biggest killers for the past 15 years (WHO, 2017a).

Chronic Obstructive Pulmonary Disease (COPD) constituted 6% of the deaths in 2015, while lung cancer together with trachea and bronchus cancers killed 3% of the global population. Diabetes Mellitus (DM) killed 3% in the same year. There was a significant increase in the number of those who died due to DM compared to 2000. Figure 1.4 shows a comparative change in the top ten causes of death between 2000 and 2015. It can be noted that Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS), Preterm Birth Complications and Birth Asphyxia and Birth Trauma are no longer part of the top ten causes of death worldwide. This could be due to improvements in health services. However, it is very interesting to note the advent of DM and Road Injury among the top ten causes of death. DM is now the sixth cause of death worldwide and is a risk factor for most of the top five causes of death. The number of non-communicable diseases among the top ten cause of death increased from 4 in 2000 to 7 in 2015.

According to Eurostat (2017) diseases of the circulatory system, including those related to hypertension, cholesterol, DM and smoking, IHD and Cerebrovascular Diseases (CeVD) were the most common causes of death with IHD having a standardised death rate of 126 in 2014. Similarly, two of UK's constituencies, England and Wales, showed an exponential increase in the total number of deaths caused by DM from 2012 to 2014, see Figure 1.6 (ONS, 2017). It is therefore important to investigate DM mortality rates through analytical techniques and recommend mitigative solutions.



(a) 2015 (b) 2010



(c) 2005 (d) 2000

Figure 1.4: Top Ten Causes of Death in the World 2000,2005,2010,2015.
©- Communicable Diseases.
Source: (WHO, 2017a)

1.3 Diabetes Mellitus

1.3.1 General Overview of Diabetes Mellitus

DM is a chronic disease that arises when either one's pancreas does not produce insulin or the body fails to effectively make use of the insulin it produces (WHO, 2017b). When it is not controlled, hyperglycaemia or raised blood sugar develops. This leads to the serious damage for many of the body's systems, especially the nerves and the blood vessels. WHO estimated that 8.5% of those aged 18+ years have DM. In 2015 alone, DM directly caused 1.6 million deaths worldwide (Mathers and Loncar, 2006)

Types of Diabetes Mellitus

The five main types of DM are Diabetes Mellitus I (DM-I), DM-II, Gestational Diabetes Mellitus (GDM), Impaired Glucose Tolerance (IGT) and Impaired Fasting Glycaemia

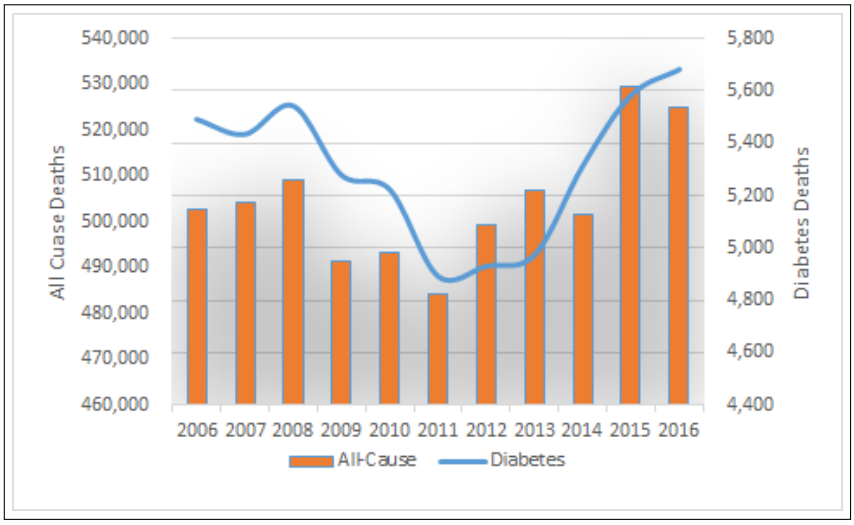


Figure 1.6: Number of deaths in England and Wales: All Cause and DM, 2006-2016. Source: ONS (2017)

(IFG). GDM is hyperglycaemia with blood sugar level higher than normal but below diagnostic level occurring during pregnancy. Women with GDM are at higher risk of having pregnancy complications and of developing DM-II. IFG and IGT, *pre-diabetes* are intermediate conditions usually preceding DM-II.

Pre - diabetes is a generic term that includes IFG, IGT and Glycated Haemoglobin (HbA_{1c}) in the 'at risk' range, those with HbA_{1c} between 6.0% and 6.4% inclusive. It is possible for an individual to have any or all of the pre-diabetic conditions (**?**NICE, 2012b). IGT individuals have 60% risk of having DM and at 50% risk of having Coronary Heart Disease (CHD) within 10 years (Yudkin and Montori, 2014; WHO, 2011). Individuals with pre-diabetes have annual DM-II incidence rates ranging from 3.6% to 7% depending on the pre-diabetes condition (**?**). Table 1.1 briefly describes and compares DM-I and DM-II. DM-II patients are often obese or overweight. DM-II is strongly genetic and related to life-style factors.

Diagnosis of DM-II may be missed for many months and during this quiet period, vulnerable body organs such as eyes, heart, kidney and feet may be damaged (Matthews et al., 2008; Fox and Kilvert, 2007).

Incidence rates for DM-I are increasing in many countries, while DM-II incidence rates are currently near-epidemic proportions. DM-II is now sadly found in children, especially in some ethnic groups (Scobie and Katherine, 2014).

Three main factors affecting blood glucose levels are: (1) diet, (2) insulin production and (3) exercise. Also in diabetic patients any form of stress, such as flu can raise the blood glucose levels (Scobie and Katherine, 2014).

DM is the most common cause of blindness in the working age population, the most common single cause of end-stage renal failure worldwide, and the main cause of non-traumatic lower limb amputation. Mortality due to DM related IHD and stroke is 2 to 4 times higher than in the age and sex matched non - diabetic population (Bilous and Donnely, 2010). Though incidence of DM-II increases with Body Mass Index (BMI), BMI does not reliably predict the risk of DM-II: only 50% of patients with BMI$> 40kg/m^2$ develop DM (Bilous and Donnely, 2010). DM is also known to develop in people who are lean (Bilous and Donnely, 2010).

DM-II cases constituting between 70% and 90+% of diabetic patients worldwide (Barnett, 2006; **?**). The Public Health England (PHE) estimated 3.8 million people diagnosed with DM in 2015 in England, of whom 90% were DM-II patients (PHE, 2016c). Also as will be noted in Section 1.5, diabetic cases in England constitute 84% of all diabetes cases in the UK. Due to its high prevalence rate we will restrict our study to DM-II patients.

Table 1.1: Causes, Prevention and Symptoms of DM-I and DM-II

Charactristics	***Causes***	***Prevention***	***Symptoms***
		DM-I	
Previously known as insulin-dependant, juvenile or childhood-onset. Characterised by deficiency in insulin production and requires daily administration of insulin.	Not Known	NOT preventable with current knowledge	Polyuria - excessive excretion of urine Polydipsia - excessive thirst Constant hunger Weight loss Vision changes, Fatigue
		DM-II	
Previously known as non-insulin-dependant or adult-onset. Comprises the majority of people with diabetes around the world. Arises due to the body's ineffective use of insulin. Until recently, it was a disease of the adults, but is now occuring increasingly frequently in children.	Largely a result of excessive body weight and physical inactivity.	Proper healthy diet Not smoking Avoiding alcohol Exercising	Similar to those of DM-I but are often less marked.

1.3.2 The Etiology of DM-II

DM-II is a medical condition caused mainly by life style choices. The following are factors that can trigger DM-II (Fox and Kilvert, 2007; Barnett, 2006):

1. *Poor Diet*

2. *Lack of Physical Activities* - lack of exercise reduces insulin sensitivity which may lead to Insulin Resistant (IR), which is a precursor of DM.

3. *Weight and Obesity* - majority of DM-II patients have a polygenic disorder that is closely related to obesity. Weight gain during adult life increases the risk of DM-II. An unmanaged weight gain of 13.5kg increases the risk of DM 4-5 times compared to those whose weight remains the same regardless of their initial weight.

4. *Genetics* - DM-II is a heterogeneous condition resulting from a complex interplay of genetics and environmental factors. On one end there are people who are genetically susceptible and heavily influenced by the environment while on the other hand there are people who have strong associations with specific genetic syndromes.

5. *IR* - usually leads to compensating hyperinsulinaemia which continues for years until islet β-cells no longer cope with the increased demand and start to fail. Hyperglycaemia then follows together with other symptoms and complications. IR is known to be present in DM-II and also that hepatic fat storage is associated with IR.

6. *Life Shocking Events* - events like heart attack or injuries from traffic accidents can lead to DM. This is because hormones produced in response to stress tend to oppose the effect of insulin and cause the blood glucose levels to rise.

7. *Medication* - may either precipitate DM as an unwanted side effect or make existing DM worse. The most important group of such medicines are hormones. Steroids such as *prednisolone* oppose insulin and hence cause an increase in the blood

glucose levels. The contraceptive pill is another culprit along with diuretics that have an anti-insulin effect.

8. *Abnormal Hormone Production* - may lead to DM, for example in the case of hyperthyroidism and acromegaly.

9. *Some Diseases and Medical Procedures* - glandular disorders, fatty liver disease, pancreatic disease, cystic fibrosis and medical procedures such as surgical removal of the pancreas may cause the development of DM.

1.3.3 Diagnosis and Treatment of DM-II

Diagnosis

The diagnosis of DM-II requires the identification of glycaemic cut-off that discriminates normal from diabetic individuals. The current cut-off is based on the blood glucose level above which microvascular complications have been shown to increase. Table 1.2 shows different diagnosis cut-off points recommended by the American Diabetes Association (ADA), International Expert Committee (IEC), WHO and National Institute for Health and Care Excellence (NICE) (Barnett, 2006; NICE, 2017c; IEC, 2009; WHO, 2006; Roberts et al., 2017). It is highly recommended for all asymptomatic adults above 45 years of age to participate in DM screening.

Treatment

Treatment of DM-II includes insulin or no-insulin medical treatments. Initially *change of life-style*, which includes diet and exercise, followed by *non-insulin medication* when *change of life style* alone fails to control the blood glucose levels. There are 7 main types of DM-II oral drugs, see Table 1.3. Apart from these, there are injectable incretin mimetics which mimic the action of Glucose-Like-Peptide 1 (GLP-1) hormone and have been used since 2005. Dipetidyl Peptidease - 4 (DPP-4) inhibitors is another group of oral medication that work in the same way as incretin mimetics. These work by inhibiting the action of DPP-4, an enzyme which destroys the hormone incretin. Incretins help

Table 1.2: Diabetes Diagnosis Cut-Off Markers

DM Type	**Test Used**	**Criteria for Diagnosis** WHO	ADA	IEC	NICE	**DM-II Incidence**
IGT	FPG 2HrPG OGT	<7 7.8-11.1 7-11.1	NR 7.8-11.1 7-11.1		<7 7.8-11.1 7-11.1	0.045
IFG	FPG	6.1-6.9	5.6-6.9	5.6-6.9	6.1-6.9	WHO: 0.047 ADA: 0.036
HbA_{1c} 'at risk' range	HbA_{1c} (%)	6.0-6.4	5.7-6.4	6.0-6.4	6.0-6.4	WHO: 0.036
DM-II	FPG 2HrPG* HbA_{1c} (%)	≥ 7 ≥ 11.1 ≥ 6.5	≥ 7 ≥ 11.1 ≥ 6.5	≥ 11.1 ≥ 6.5	≥ 7 ≥ 8.5 ≥ 6.5	NA

NR: Not Required; FPG: Fasting Plasma Glucose Test; OGT: Oral Glucose Tolerance Test; 2HrPG: 2Hr Plasma Glucose Test. Diagnosis units are in mmol/L. Incidence rates are per person-year. * NICE recommends testing after 90 minutes instead of 2Hrs

in the production of more insulin only when it is needed and at the same time reducing the amount of glucose produced by the liver when it is not needed. In the event that non-insulin therapy fails, insulin with or without non-insulin therapy is used. About a quarter of DM patients receive insulin medication and almost every child diagnosed with DM is treated using insulin (Fox and Kilvert, 2007). Table 1.4 briefly describes different types of insulin drugs (Diabetes UK, 2017).

1.4 Management of DM-II

The management of DM-II includes all facets of life of a diabetic individual: social, mental, spiritual and physical. Pateints also need to be well informed about DM-II, how to self - manage it and possible complications and their causes (NICE Guideline NG28) (Fox and Kilvert, 2007). Patients are advised to keep a healthy life-style which includes a healthy diet, regular exercise, stopping smoking, reducing or stopping alcohol intake, weight management, adherence to medication and regurlar medical reviews. In medical reviews, DM-II markers which include Blood Pressure (BP), total, non-high and High Density Lipoprotein (HDL) cholesterol concentration and HbA_{1c} are moni-

Table 1.3: Main Types of Oral and Non-Insulin Drugs used in DM-II Therapy

Group	**Description**	**Examples**
Sulphonylureas	increasses the amount of natural insulin produced by the pancreas	Gliclazide, Glibenclamide, Glipizide, Glimepiride, Tolbutamide
Biguanides	reduces the release of glucose from the liver and inceasing the uptake of glucose into the muscles	Metformin (Glucophage)
Thiazolidinediones	target IR and are used by people who have been unable to control their blood glucose levels with metformin or sulphonylurea. Also avalaible in combinations with metformin as Avandamet and Actophus Met	*Rosiglitazone (Avandin), Pioglitazone (Actos)
Alpha Glucosidase Inhibitor	slows digestion of carbohydrate in the intestines and suppresses the rise of blood glucose after meals	Acarbose, Glucobay
Prandial (mealtime) Glucose Regulators, Meglitinide Analogues	stimulate the release of insulin from the pancreas and are taken with meals. Can be used with or without metformin	Prandin/ Repaglinide, Nateglinide
Sodium-glucose contransporter 2 (SGLT-2)	reduces glucose reabsorption and increases urinary glucose excretion by reversibly inhibiting SGLT-2 in the renal proximal convoluted tubule.	Dapagliflozin, Canagliflozin, Empagliflozin
Dipetidyl peptidease - 4 (DPP-4) inhibitors	increases insulin secretion and reduces glucagon secretion by inhibiting DPP-4	Alogliptin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin
Glucagon-Like peptide - 1 (GLP-1) receptor	attaches to, and activates, the GLP-1 receptor to increase insulin secretion, suppresses secretion of glucagon, and slows down gastric emptying. Its an injectable drug.	Albiglutide, Dulaglutide, Exenatide, Liraglutide, Lixisenatide, Semaglutide

* Restricted by the USA Food and Drug Administration due to its effect of increasing myocardial infarction (MI) risk (Lim et al., 2018).

Table 1.4: The Four Types of Insulin

Type	**On-set**	**Peak Time**	**Duration**
Rapid-acting (Lispro)	Reaches blood within 15 mins	30 to 90 mins later	5hrs
Short-acting(Regular)	Reaches blood within 30 mins	2 - 4 hrs later	4 - 8hrs
Intermediate-acting (NPH and Lente)	Reaches blood within 2 to 6hrs	4 - 14hrs later	14 - 20hrs
Long-acting (Ultra-lente)	Reaches blood within 6 to 14hrs	Has no peak or very small peak 10 - 16hrs	20-24hrs

tored and screened for complications such as Cardiovascular Diseases (CVD)s (Fox and Kilvert, 2007; Matthews et al., 2008) and (NICE Guideline NG28).

Metformin is currently the first line drug therapy. At first, its dosage is increased over several weeks to minimise the risk of gastrointestinal side effects. Patients are prescribed a modified - release metformin if they experience gastrointestinal side effects. If their Estimated Glomerular Filtration Rate (eGFR) is less than 45ml/minute/1.73m^2, metformin dose is reviewed. If eGFR is less than 30ml/minute/1.73m^2, metformin is either stopped or prescribed with caution of the risk of a sudden deterioration in kidney function.

The graph below, Figure 1.7, shows a typical management of DM-II. After diagnosis and life style changes have failed to control the blood glucose level, usually metformin is given as the first line drug. In the case of it being intolerant, DPP-4, pioglitazone, sulfonylurea can be used as monotherapy. Caution is exercised as pioglitazone is associated with risk of heart attack, bladder cancer and bone fracture especially for the aged. It should not be offered to DM-II patients who have a heart failure or history of heart failure, hepatic impairment, diabatic ketoacidosis, current or history of bladder cancer and uninvestigated macroscopic haematuria. Sodium-Glucose Contransporter 2 (SGLT-2) can also be used only if DPP-4 can be prescribed when sulfonylurea or pioglitazone can not be prescribed. If monotherapy fails, a dual therapy is prescribed

using the monotherapy drug and one of the others. In the case of metformin being the monotherapy drug, empagliflozin, canagliflozine, dapagliflozine and alogliptin can be used in dual therapy when sulfonylurea is contraindicated or the person is at a significant risk of hypoglycaemia or its consequences. Triple therapy is then administered when the dual therapy fails by adding another drug, in the case of metformin being tolerant. If the triple therapy fails, insulin therapy with or without non-insulin drugs is then prescribed. In case of metforming being intolerant insulin therapy is administered after the dual therapy fails.

GLP-1 mimetic can be used along metformin and sulfonylurea, in triple therapy, in cases where the DM-II patient has : *(i)* BMI greater than 35kg/m^2 (adjusted according to ethniciy) or (ii) BMI less than 35kg/m^2 and insulin therapy would have significant occupational implications or weight loss would benefit after significant obesity-related comorbities.

1.4.1 Complications of DM and their Management

DM-II is associated with serious complications including stroke, heart disease, blindness, kidney disease and amputations leading to disability and early death. Generally, half of the DM-II individuals showed signs of complications when diagnosed (Diabetes UK, 2016b). Complications can develop 5 to 6 years before diagnoses and the actual onset of DM-II can be 10 years earlier. Proper DM-II management reduces complication risks.

Eye Disease

Globally, 2.6% of blindness is attributed to DM (Bourne et al., 2013). Retinopathy affects the blood vessels connected to the retina and accounts for about 7% of the people registered blind in England and Wales and about 60% of DM-II individuals have some degree of retinopathy within 20 years of diagnosis (Diabetes UK, 2016b). DM-II patients have nearly 50% increased risk of developing glaucoma especially if they have high

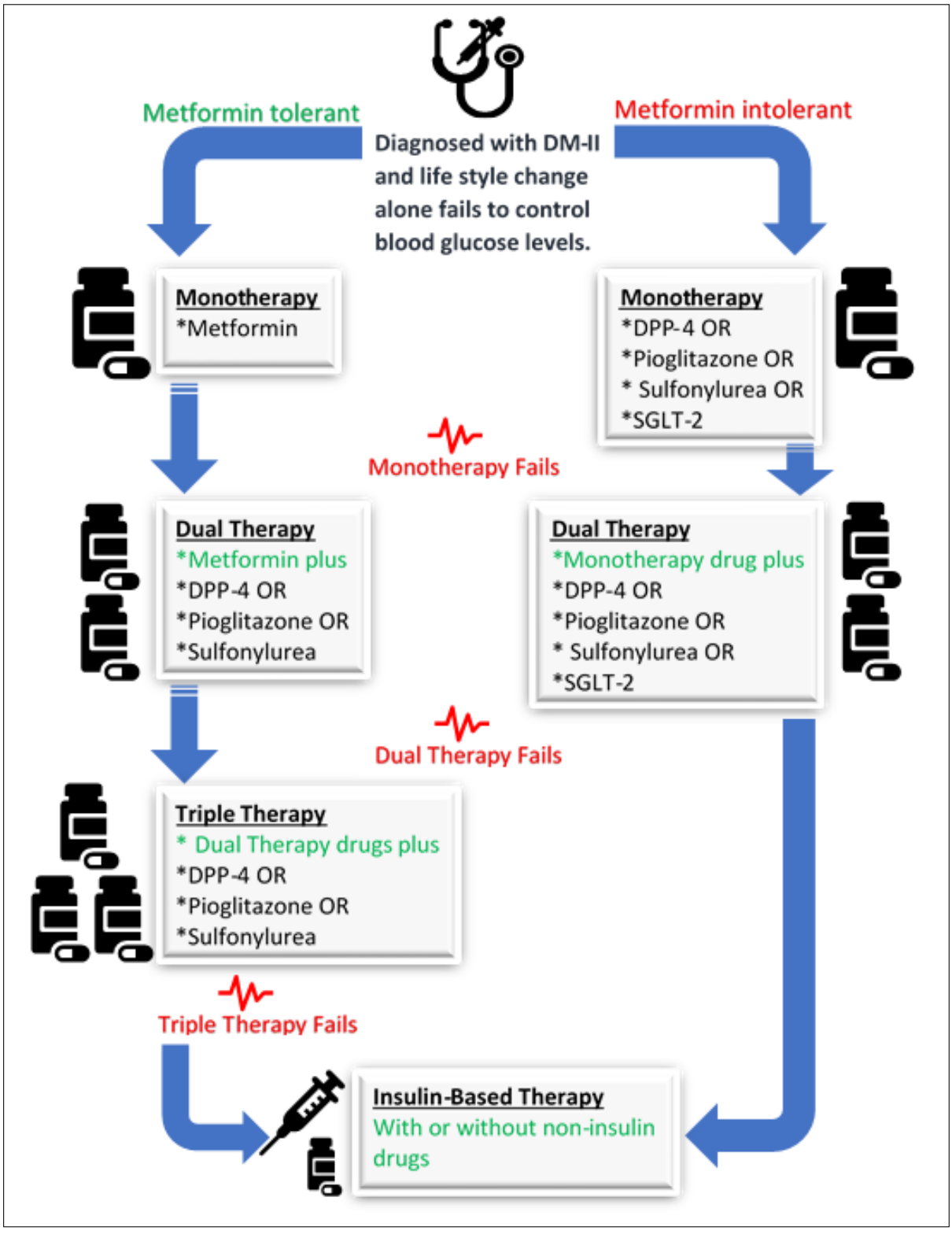


Figure 1.7: DM-II Therapy Management.

Source: (NICE, 2017b; Fox and Kilvert, 2007; Matthews et al., 2008)

blood pressure and up to 3 times increased risk of developing cataracts both of which can lead to blindness (Diabetes UK, 2016b). Drugs that can be administered include

Aflibercept solution for injection, Ranibizumab, Dexamethazone Intravitral Implant and Fluocinolone Acetonide Intravitreal Implant. However NICE does not recommend the use of Aflibercept solution for injection and dexamethazone intravitreal implant.

Erectile Dsyfunction (ED)

ED or impotence is one of the most common sexual problems experienced by men. About 35 to 90% of men with DM have ED according to a world literature review done in 2009 (Malavige and Levy, 2009). Statistics with respect to sexual dysfunction in women living with DM-II are not much available as this area is under-researched (Diabetes UK, 2016b).

Gastroparesis

It is a disorder that slows or stops the movement of food from the stomach to the small intestines. It can be treated alternating the use of Erythomycin and Metoclopramide or Domperidone. Metoclopramide can cause neurological effects such as short-term extrapyramidal disorders. Medical and Healthcare Products Regulatory Authority (MHRA) notes that Domperidone is associated with small risk of serious cardiac side effects.

Neuropathy

It damages the nerves that transmit impulses to and from the brain and spinal cord, to the muscles, skin, blood vessels and other organs. Chronic painful neuropathy is the most common and estimated to affect 26% of DM patients. Cardiovascular autonomic neuropathy (CAN) affects the nerves that control the heart and the blood vessels and DM-II patients who develop it have a higher mortality risk than those without (Diabetes UK, 2016b). Medication prescribed include amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment except in trigeminal nevralgia cases. There are also drugs that can be offered but in a specialist settings which include, morphine, cannabis sativa extract, lacosamide, oxacarbazine and topiramate (NICE Guideline CG173). Neuropa-

thy affects up to 50% of DM patients.

Chronic Kidney Disease (CKD)

Kidney disease accounts for 11% of deaths in DM-II individuals (Diabetes UK, 2016b). CKD can be screened through testing for proteinuria, haematuria or renal utrasound. Proteinuria is the presence of abnormal quantities of protein in the urine due to a glomeruli diseases and urine infection among others. Haematuria is the presence of blood in the urine caused by urinary tract infection, kidney stones and bladder cancer among others. Albumin to Creatinine Ratio (ACR) or Protein to Creatinine Ratio (PCR)) can be used for testing for proteinuria, but ACR is recommended to be used especially for DM patients . An ACR greater than 3mg/mmol indicates the presence of CKD, see Figure A.1 in Appendix C (NICE, 2015a). This is done by mesuaring the amount of albumin or protein loss in the urine of patients with a GFR of less than 60ml/min/1.73m^2. Reagent strips are mostly recommended when testing for haematuria. Risk is detected if the reagent strip result is 1+ or more. CKD is not progressive in many people.

Diabetic Foot Problems

Diabetic patients should be advised of the importance of basic foot care and footwear for the prevention of diabetes foot problems. Adult DM-II patients should be assessed for the diabetes foot problems at least annually (NICE, 2016a). Table B.1 in Appendix D gives the risk factors assertained in assessing DM-II patients for diabetes foot problems.

DM is the most common cause of lower limb amputations. About 7,400 leg, toe or foot amputations happen in England per year, translating to 140 amputations per week or 20 per day (PHE, 2016a). DM individuals are 30 times more likely to have an amputation than the general population (Khanolkar et al., 2008).

Lower Limb Peripheral Arterial Disease (LL PAD)

LL PAD is another DM-II complication. Peripheral Arterial Disease (PAD) is tested by the examination of legs and feet for ulcerations, femoral, popliteal and foot pulses; and measuring Ankle Branchial Pressure Index (ABI). The latter is done manually using a Doppler probe of suitable frequency in preference to an automated system. The index is calculated for each leg by dividing the highest ankle blood pressure by the highest arm blood pressure (NICE, 2012a). If the index is not within the nornal range 0.9-1.4, the DM-II individual is at risk of LL PAD (Stanford Medicine, 2018). PAD patients have an increased risk of mortality from CVD, mainly due to the increased risk of heart attack and stroke.

Non-Alcoholic Fatty Liver Disease (NAFLD)

NAFLD is another possible complication of DM-II. Alcohol history should be taken to rule out possibilities of alcohol-related liver disease. NICE discourages use of routine liver blood tests to rule out NAFLD. In assessing the risk, liver ultrasound should be done to test for NAFLD in children and young people (aged between 1 and 18) with DM-II (NICE, 2016b). Patients taking statins are adviced by NICE to continue taking medication except when liver enzymes double within 3 months of starting statins. For assessing advanced liver fibrosis in adults, Enhanced Liver Fibrosis Test (ELFT) is used. Adults are diagnosed to have advanced liver fibrosis if their ELFT score is equal to or greater than 10.51 and have NAFLD. Cirrhosis should be monitored in adults diagnosed with NAFLD and advanced liver fibrosis (NICE, 2016b). Diagnosis of cirrhosis can be established through blood tests, utrasound scan, Computerised Tomography (CT) scan or Magnetic Resonance Imaging (MRI) scan, liver biopsy and endoscopy (NHS, 2017). *Pioglitazone* or *vitamin E* are given to adults with advanced liver fibrosis but only in secondary or tertiary care settings (NICE Guideline NG49).

Cardiovascular Disease (CVD)

CVD includes heart disease, stroke, and all other diseases of the heart and circulation, such as hardening and narrowing of the arteries supplying blood to the legs, which is known as Peripheral Vascular Disease (PVD). DM individuals are twice at risk of developing CVD compared with non DM individuals (Diabetes UK, 2016b). CVD is the major cause of death among DM individuals accounting for 52% in people with DM-II (Diabetes UK, 2016b). DM-II patients have higher risk of developing stroke than the general population (Diabetes UK, 2016b).

Adults aged 85 years and above are at high risk of CVD because of age alone, especially those who smoke or have raised BP (NICE, 2017a). One of the tools that can be used for the assessment of a 10 year risk of CVD is the QRISK2. It is used for the primary prevention of CVD in all people aged less than or equal to 84 years. The tool can not be used for people with DM-I and those with eGFR less than $60/\text{ml}/\text{min}/1.73m^2$ and/ or albuminuria. People above the age of 40 are encouraged to have their CVD risk estimate reviewed on an ongoing basis (NICE, 2017a).

Threat to oral health is another complication as DM-II patients have an increased risk of inflammation of the tissues surrounding the teeth (periodontitis) which is a major cause of teeth loss and is associated with an increased risk of CVD in people with poor blood glucose control (IDF, 2015).

1.5 Epidemiology of DM-II

WHO estimated the global prevalence of DM to have increased from 4.7% in 1980 to 8.5% in 2014. The prevalence rates have been rising in the low- and middle-income countries.

In 2015 alone, an estimated 1.6 million deaths were attributed to DM. About 415 mil-

lion people worldwide are living with DM. This disease is now among the top 7 leading causes of death in the world. With the prevalence rates rising in low- and middle - income countries, the majority of deaths from DM occur in these countries due to limited access to basic technologies needed by diabetic patients in primary health care settings. The International Diabetes Federation (IDF) in 2015 estimated 193 million undiagnosed adults, aged 20-79 years, are living with DM. About 318 million were estimated to have IGT. IDF (2015) also estimated a total expenditure between US$673 billion and US$1.2 trillion in health care in 2015.

IDF projected a total of 642 million diabetic cases in 2040 if control measures are not taken and people continue with unhealthy life styles. The substantive increase in the prevalence is expected to be driven by the ageing population (**?**). Bagust et al. (2002) estimated not more than 3% increase in the total UK population between 2000 and 2060 but a maximum increase of 11% in the population aged 35 years and above by 2030. The global prevalence of DM-II cases would increase by approximately 20% in 2036 and DM related complications would rise by 20-30% between 2035 and 2045 (Bagust et al., 2002). The cost of health care related to treatment and complications is estimated to increase by 12% of the global DM health expenditure. Figure 1.8 shows an estimated increase of 55% of DM cases in 2040 worldwide. In the UK the cost of DM-II will present a serious clinical and financial challenge in the near future (Bagust et al., 2002).

In 2015, the global prevalence of DM was 1 in 11 adults and in 2040 it is estimated to be 1 in 10 adults. Globally, 269.7 million in the urban and 145.1 million in the rutral were diabetic. The numbers are estimated to increase to 477.9 million and 163.9 million, respectively (IDF, 2015).

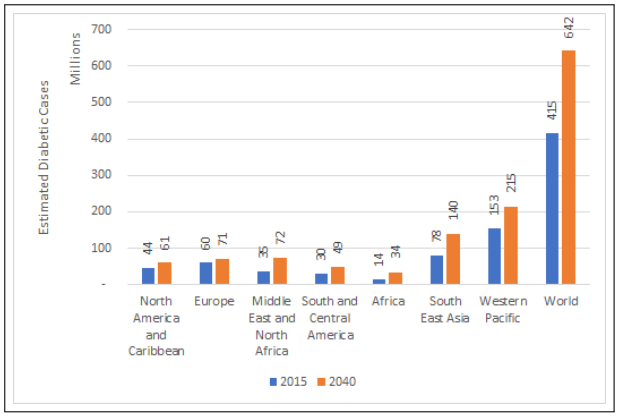


Figure 1.8: Number of DM Cases by cause in by IDF Region

Source: IDF (2015)

Top Ten Countries with the Highest Numbers of DM Patients and Highest Expenditure

China had the highest estimated number of diabetic patients in 2015, 109.6 million followed by India with 69.2 million patients. Countries with the highest costs were US, US$320 billion followed by China, US$51 billion, as shown in Table 1.5, (IDF, 2015) .

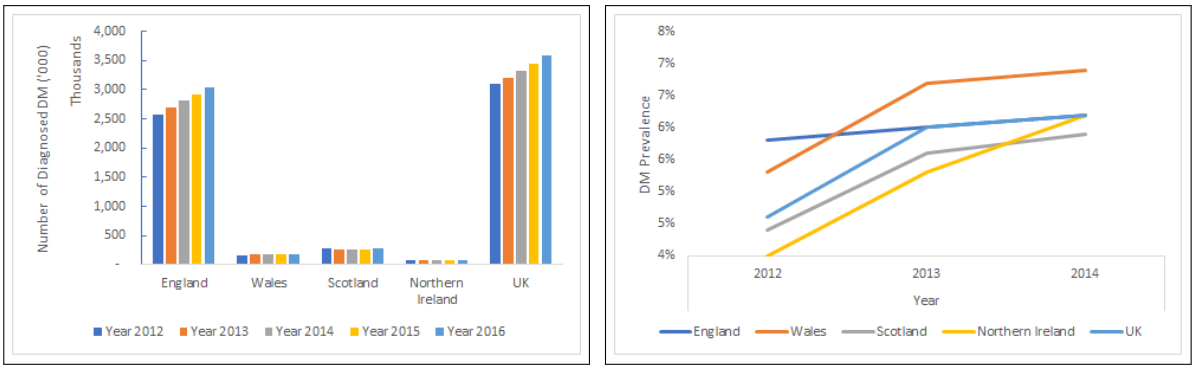
Table 1.5: Top Ten Countries with the Highest Numbers of DM Patients and Highest Expenditure

Country	**DM Prevelence x** 10^6		**Expenditure x** 10^9	
	Number	*Rank*	*US$*	*Rank*
China	109.6	1	51	2
India	69.2	2		
USA	29.3	3	320	1
Brazil	14.3	4	22	5
Russian Federation	12.1	5	14	8
Mexico	11.5	6		
Indonesia	10	7		
Egypt	7.8	8		
Japan	7.2	9	29	4
Bangladesh	7.1	10		
Germany			35	3
France			19	6
Canada			17	7
UK			13	9
Italy			12	10

Source: IDF (2015)

1.5.1 DM Statistics in the UK

Between 2012 and 2014 the prevalence rate of DM in the UK has increased from 4.6% to 6.2%. The total number of DM patients increased by more than 16%, from 3 094 681 in 2012 to 3 590 501 in 2016. England has the highest number of DM cases throughout the period but its prevalence rate is not far from the other three states. Its numbers constitute 84% of UK's cases. The DM prevalence rates for England and the UK at large in 2013 and 2014 were equal, 6% and 6.2%, respectively. Wales' prevalence rates in 2012 to 2014 were higher than UK's global prevalence rates. Scotland and Northern Ireland prevalence has been on the increase since 2012, see Figure 1.9. Of the four states, Wales is highly affected and Northen Ireland has the highest increase in prevalence rate (Diabetes UK, 2013, 2014, 2015a,b, 2016a). Overall, there has been an increase in the number of diagnosed DM cases throughout the four states. In England alone about 1 in 4 undiagnosed adults is believed to be diabetic translating to 940 000 people living with diabetes unknowingly. The prevalence is higher in males (9.6%) than in females (7.6%) in England (PHE, 2016b). PHE also estimated higher prevalence rates in people of South Asian and black ethnic groups (15.2%) compared to those from white, mixed or other ethnic groups (8.0%); and it estimated about £10 billion medical costs per year related to diabetes of which £8.8 billion per year was due to DM-II in England alone.



(a) Number of DM Cases (b) DM Prevalence Rates

Figure 1.9: DM and it Prevalence Rates in UK.

Source: (Diabetes UK, 2013, 2014, 2015a,b, 2016a)

Table 1.6: One year prevalence of CVD complications of DM-II.

Complication		**Type 2 and Other***	
		Complication Prevalence	*Prevalence (%)*
CVD	Angina	56,046	*3.1*
	Myocardial Infarction	14,762	*0.8*
	Heart Failure	56,817	*3.2*
	Stroke	19,350	*1.1*
Diabetes Specific Complications	Major Amputation	1,322	*0.1*
	Minor Amputation	2,918	*0.2*
	Renal Replacement Therapy (ESKD)	11,006	*0.6*

Note: * Other types of diabetes except for DM-I.

Source: NHS (2017): England and Wales

DM-II Complications Statistics in UK

Table 1.6 shows the number of complications and prevalence rates for DM-II patients in England and Wales (NHS, 2017). It reports that DM-II patients are 2 to 2.5 times more at risk of developing CVD. The complications with the highest rates were Angina and Heart Failure with 3.1% and 3.2% prevalence rates, respectively. Zeroing in on CVD, the percentage of DM-II patients admitted into the hospital show an exponentially increasing risk of CVD by age, starting from the 35-39 age group, *see* Figure 1.10. It can be seen that non-DM CVD patients' had higher admission percentages than DM-II and other Diabetes patients with CVD, in the 0-54 years and 85+ years age groups and DM-II and other Diabetes patients had high admission percentage for CVD in the 55-84 years age group compared to non-DM patients.

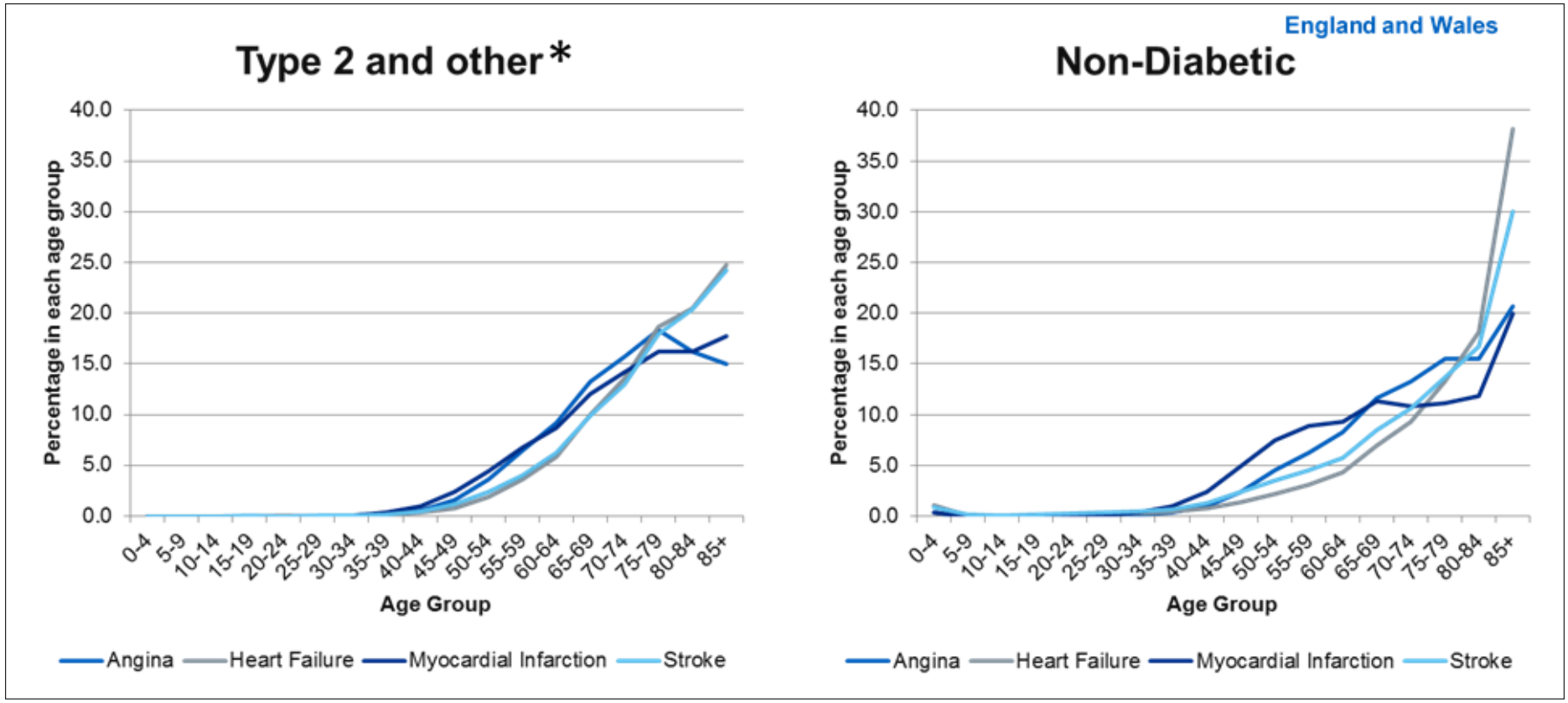


Figure 1.10: DM-II people admitted into hospital with CVD complications.

Note: *Other types of diabetes except for DM-I.

Source: NHS (2017)

1.6 Summary

The incidence of DM-II is increasing worldwide. Less than two decades ago the total number of deaths caused by DM was far less than a million that increased to 1.6 million in 2015. DM was not among the top ten causes-of-death until 2015. Today it is among the top six causes-of-deaths. The complications of DM-II include the top four causes-of-death, such as Stroke. Hence, it is of paramount importance to quantify the impact of DM-II on longevity as it constitute 70-90% of all DM cases (Hiam et al., 2017). DM-II is associated with poor life style and its prevalence is on the rise. It is therefore, important to show its negative impact on longevity and morbidity through survival techiniques and translating the results into statistical and actuarial use.

Chapter 2

Review of the Life Expectancy in DM-II Individuals

2.1 All-Cause Mortality and Life Expectancy in DM-II Individuals

Arora (2017) shows that life expectancy at birth is positively correlated with spending on health care per person, up to a limit, after which the benefit in life expectancy diminishes. Thus, medical therapies have limitations once a certain level of spending is exceeded. Extra spending on hospitals and specific surgery may not have any added benefits on life expectancy but may provide better quality of life. Life expectancy reflects not just health spending but the life style, such as alcohol consumption, smoking, education, socio-economic factors and so on.

DM-II has been responsible for significant mortality. Even though there has been a significant advancement in treatment, DM-II mortality rates are still considerably higher than those of the general population (Barr et al., 2008). The life expectancy of men and women aged 50 years and above with DM in the US, living in Framingham, Mass, between 1948 and 1951, was 7.5 years (95% CI: 5.5-9.5) and 8.2 years (95% CI: 6.7-10.4) less than non-diabetic counterparts (Franco et al., 2007). Franco et al. (2007) through

the use of the Poisson regression ("Gompterz" distribution) calculated the Hazard Ratios (HRs). They then used the Hazard Ratio (HR)s to calculate the life tables stratified by sex and presence of DM that were used for the computations of the differences in life expectancy. In a later study, between 1998 and 2015, UK men and women with DM-II, age 40 years in 1998, lost 5.4 and 6.3 years of life compared to non DM-II persons, respectively (Wright et al., 2016). Wright et al. (2016) adjusted their model for age, sex, ethnicity, deprivation and calender year. Though there are a number of papers on diabetes, there is still limited information on the potential association of diabetes with total life expectancy and cause-specific mortality (Franco et al., 2007; Wright et al., 2016). This association is not easily established since the associations of different risk factors with life expectancy can follow unexpected directions (Franco et al., 2007).

Franco et al. (2007) reported that variables such as total cholesterol and the presence of left ventricular hypertrophy, arthritis, ankle edema, or pulmonary disease did not have effect on the HR for CVD and all-cause mortality in diabetic men and women aged 50 years and above in the US. However, Franco et al. (2007) noted the limitations of their data, that was based on the period 1950s-1980s. They may have underestimated the true association of DM with $\mathring{e}_{50}$ because the incidence of DM-II has been on the increase owing to harmful life style changes.

Taylor et al. (2013), using data from the General Practice Research Database (GPRD) (2004-2010), found that DM-II patients have a two-fold increased risk of all-cause mortality (HR: 2.12 95% CI: 2.0-2.25), adjusted for smoking. Women were found to have a higher HR than men, and patients younger than 55 years of age were reported to have a higher HR than those aged 56 years and above when compared to those without DM.

Lind et al. (2013) studied the mortality trends of diabetic patients aged 20 years and above in Canada and the UK using the Ontario and THIN databases, respectively. The total number of subjects under study was 8 757 772 in 1996 and increased to 12 696 305

in 2009. The study showed the same mortality trends per 1000 person-years for both DM and non-DM patients. They reported a decline in the mortality rates. They also reported high mortality rate ratios for the young patients compared to the old patients for both countries.

Mulnier et al. (2006) reported a similar mortality risk pattern among the young DM-II patients (HR: 3.35 [95% CI: 2.86-3.93] for men aged 35-54 years and 3.07 [95%CI: 2.37-3.97] for women of the same age) and for the old patients aged 85-89 years (HR: 1.44 [1.3-1.6] for men and 1.65 [1.52-1.78] for women) when compared to patients without DM-II. Thus the younger the age the higher is the mortality risk among DM-II patients when compared to their counterparts.

A study by Currie et al. (2010) on the survival effect of HbA_{1c} among DM-II patient taken from the GPRD data (1986-2008) stratified into 5 regimens reported that the lowest HbA_{1c} group with a median of 6.4% and the highest HbA_{1c} group with a median of 10.5% had higher risks of all-cause mortality among DM-II individuals. Patients with HbA_{1c} less than 6.25% or greater than 7.25% had higher all-cause mortality hazard risk compared with those whose HbA_{1c} levels ranged from 6.25 to 6.75.

According to Kontopantelis et al. (2015) in a study based on the GPRD (2006 to 2012) of 246 544 DM-II patients, about 61% were taking metformin and 32% were using sulfonylurea. The least used was acarbose (0.5%). Though their study did not show the mortality and morbidity risks associated with the drugs the distribution is of vital importance when analysing clinical outcomes.

In a 20 year follow-up prospective study by Almdal et al. (2004) based on 13 105 DM-II patients from the Copenhagen City Heart Study, from 1976 to 1997, the Relative Ratio (RR) of death for both men and women was 1.5 to 2 compared to non DM-II patients. In women, the age groups that were reported to have higher RR of 1.7 to 2.7, were the

under 55 years and the 55-64 years compared to non diabatic women. Men in the under 55 years age group were reported to have a 2.5 times higher total mortality rate compared to non-diabetic men. Almdal et al. (2004) reported that smoking, hypertesion, high triglyceride level, high alcohol intake and low ($\leq$20kg/m^2) and high ($\geq$30kg/m^2) BMI independently increased the risk of death in women while in the men the variables excluding high tryglycerides and high BMI ($\geq$30kg/m^2) had the same effect. High activity and high cholesterol levels were reported to decrease the mortality risk (Almdal et al., 2004).

The Spanish study by Salinero-Fort et al. (2018) based on a period from 2007 to 2012 reported that male DM-II patients with a BMI less than 23kg/m^2 had the highest all-cause mortality (Adjusted Hazard Ratio (aHR): 2.78 [95% CI: 1.72-4.49]. The study showed a U-shaped mortality curve among men with DM-II with respect to BMI. Overall a BMI less than 23kg/m^2 was reported to have a higher significant effect on mortality when compared to a BMI in the range 23-26.8kg/m^2. They concluded that higher BMIs were not associated with a higher mortality risk among DM-II women patients, *See* Figure 2.1. Kontopantelis et al. (2015) and Soriano et al. (2015) have similar findings. They reported that there was less siginificant association between higher BMI and higher mortality among female DM-II patients than patients without DM-II. They adjusted for age, gender, diabetes duration, cardivascular diseases, complications of DM, smoking, blood pressure, HDL-cholesterol, Low Density Lipoprotein (LDL)-cholesterol, triglycerides, HbA_{1c}, albuminuria, treatment of hypertension, treatment of diabetes, statins and antiplatelet drugs.

A similar study based on the GPRD by Mulnier et al. (2006) of DM-II patients aged between 35 and 89 years in 1992, with a follow up period of less than 7 years, also reported a U shaped HR plot with respect to BMI showing that an increase from the normal BMI range was associated with an increased risk of mortality. They however, noted that different studies in the past had conficting conclusions on the effect of obesity or BMI on mortality.

Medication may increase mortality and complications risks among DM-II patients. Currie et al. (2010) noted that DM-II patients under insulin - based therapy had a higher risk of mortality compared to those on oral combination therapy such as metformin plus sulphonylurea therapy with an HR of 1.49 (95% CI: 1.39-1.59). Soriano et al. (2015) reported an increased risk of mortality with an increase in the number of prescribed drugs among DM-II patients. The study did not specify if they included study sujects using antidiabetic drugs only. We therefore assume that the numbers given include other non-diabetic drugs. This maybe due to more advanced DM-II in both studies. Toulis et al. (2017) retrospectively studied all-cause mortality and CVD incidence outcomes in a cohort of 22 124 DM-II patients from the THIN database, January 2013 to September 2015. The study has validated the results from an earlier study of empagliflozin clinical outcomes, using the dapagliflozin drug. Both drugs are SGLT-2 inhibitors. They found out that patients using dapagliflozin had a lower all-cause mortality risk compared to patients not using SGLT-2 inhibitors (Adjusted Incidence Relative Ratio (aIRR): 0.5[95% CI: 0.33-0.75]). The data were matched for age, sex, BMI, DM-II duration and smoking and adjusted for age, sex, BMI, smoking, HbA_{1c}, duration of diabetes, Systolic Blood Pressure (SBP), lipid-lowering medication, insulin use, eGFR, social deprivation index, presence of hypertension and Charlson comorbidity index.

Zimmerman et al. (2017) researched on 105 856 patients from the Cleveland Clinic in Ohio, US, between 2005 and 2014, and found out that DM-II patients with or without a history of CVD using GLP-1 receptor drugs, were overally at a lower risk of mortality and CVD risk. They adjusted for age, gender, race, income, BMI, LDL, cholesterol, eGFR, Diabetes Complications Severity Index (DCSI), Acute Myocardial Infarction (AMI) history, Cerebrovascular Accident (CVA) history, CHD history, hypertension, smoking status, use of statins and diabetic medications. Their study also reported that newly diagnosed DM-II patients using GLP-1 had an all-cause mortality HR of 0.80 [95% CI: 0.47-1.34]) compared to those using other drugs.

Several studies have shown that management of DM-II by intensifying treating increases the risk of mortality among DM-II patients (ADVANCE Collaborative Group, 2008; UKPDS Group and others, 1998; ACCORD Study Group, 2008). According to NICE (2015b) intensive treatment is presented as treating a DM-II patient with more than one drug in the case were monotherapy fails to reduce the HbA_{1c} level to a level below 6.5%. DM-II patients in an intensive treatment have their blood - glucose levels more frequently monitored than those on standard treatment. The treament dosage may also be increased. For example in the Action in Diabetes and Vascular Disease: Preterax and Diamocron Modified Release Controlled Evaluation (ADVANCE) study by ADVANCE Collaborative Group (2008) patients on intensive treatment were examined every 3 months while those on standard treatment were examined every 6 months.

In a meta-analysis by Boussageon et al. (2011) included 13 studies which were done between January 1950 and July 2010, intensive treatment was reported to increase the risk of mortality by 19% compared to patients under standard treatment. It included 34 533 DM-II patients aged 18 years and above, of whom 60% were men. DM-II patients were found to be at an increased risk of all-cause mortality (HR of 1.22% [95% CI: 1.01-1.46]) from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study due to intensive treatment. In their meta-analysis, 39% of patients already had a CVD at baseline which explained the high all-cause mortality risk.

Boussageon et al. (2011) reported that using intensive treatment increased the risk of CVD related deaths among DM-II patients compared to those using standard treatment (RR: 1.11 [95% CI: 0.86-1.43]). From their analysis they reported a 43% increase in CVD-caused deaths in intensive treatment cohort compared to the standard treatment cohort. They also reported that 50% of DM-II patients with Myocardial Infarction (MI) die before receiving medication.

In a study by Hayes et al. (2013) from the United Kingdom Prospective Diabetes Study

(UKPDS) Outcomes Model 2 project, based on 5 102 UKPDS patients aged 25-65 years, recruited between 1977 and 1991 and followed up for 20 years, several demographic, risk and event history factors were used to model a system that predicts the lifetime health outcomes of DM-II patients. For all-cause mortality, they used logistic models for patients with complication(s) and proportional hazards survival models (Gompetz distributed) in patients with no complications. Blindness and ulcers were found not to be associated with mortality. They also reported that smoking was an *independent significant* predictor of mortality but HbA_{1c} and SBP risk factors were not. Duration of DM was also found to be significantly associated with mortality. They reported that about 60% of DM-II patients would have died after 25 years.

Hayes et al. (2013) performed a sensitivity analysis on the risk factors by adding or subtracting 1 from the Standard Deviation (SD). Increasing/ decreasing the SD of SBP by 1 had a significant symmetric effect on the life expectancy of DM-II patients. Increasing the SD decreased the life expectancy by about 0.5 years and decreasing its SD increased the life expectancy by about 0.4 years. The other risk factors reported to have the same significant symmetric effect as SBP were LDL, HbA_{1c}, white blood cells and heart rate. A slight increase in SD of the BMI was reported to have a serious reduction in life expectancy compared to a slight decrease in SD whereas a slight change in haemoglobin and Atrial Fibrillation (AF) was reported not to have a significant association with life expectancy. Using the UKPDS Outcomes Model 2 (UKPDS-OM2) they predicted life expectancies of 25.1 years, 17.7 years and 11.7 years for DM-II patients aged 50-54 years, 60-64 years and 70-74 years, respectively. These rates were higher than those predicted in UKPDS-OM1 by 5.1 years, 3.8 years and 1.8 years, respectively (Hayes et al., 2013). When they compared their results with the UKPDS Outcomes Model 1 (UKPDS-OM1), they reported that UKPDS-OM1 had higher outcome incidences compared to Model 2. They included eGFR, micro- or - macroalbuminuria, heart rate and white blood cell counts which were not used in UKPDS-OM1. In addition they included the haemoglobin based on the results reported by Go et al. (2006)

that it is an independent predictor of mortality in Congestive Heart Disease (CHF) patients.

Jeong et al. (2017) suggested that depression was significantly associated with a higher mortality risk among 1 043 089 DM-II patients aged 30 years and above from a Korean database, with a study period between 2003 and 2013. The mortality HRs were high in all the age groups. The risk was higher among men or young age groups (Jeong et al., 2017). The reported total mortality HR accounted with depression was 1.43 [95% CI: 1.41-1.46] compared with those without depression. Depressed DM-II patients, aged between 30 and 39 years, had the highest mortality HR of 2.81 [95% CI:2.334-3.384] compared with non depressed patients. The HR decreased with an increase in age. The differences in the mortality of DM-II patients with and without depression was reported to be increasing thoughout the 21 years of follow-up.

2.2 Cause-Specific Mortality among DM-II Patients

2.2.1 CVD-Related Mortality among DM-II Patients

CVD accounts for about 70% of deaths among DM-II patients (Franco et al., 2007). The excess mortality between DM-II and non-DM-II patients is largely attributed to CVD (Leal et al., 2008). CVD increases the risk of dying among DM-II patients (HR: 2.2 [95% CI: 1.74-2.84] for women and 1.7 [95% CI: 1.38-2.07] for men) compared with non-DM-II patients with CVD. DM-II patients aged 50 years without CVD at baseline were reported to have lived 7.1 and 6.8 years more than those DM-II patients with CVD, in men and women respectively (Franco et al., 2007). Taylor et al. (2013) found that DM-II patients with CVD had a threefold increased risk of CVD mortality (HR: 3.28 95%CI: 2.91-3.70), adjusted for smoking, compared to those withouth DM-II.

The risk of CVD deaths increased with DM duration (Taylor et al., 2013). From a study of Spanish subjects (2007-2012), 51.9% deaths among DM-II individuals was at-

tributed to CVD (Salinero-Fort et al., 2018). A GPRD based study on 246 544 DM-II patients, from 2006 to 2012, by Kontopantelis et al. (2015) showed that those with macrovascular complications were at a higher risk of dying from CHD (HR: 2.14 [95% CI: 1.88-2.44]) and CeVD (HR: 1.6 [1.41-1.82]). From the same study men were found to be at a higher risk of dying from CHD with an HR of 1.5 [95% CI: 1.33-1.7] compared to women.

Smoking DM-II patients from the UKPDS with a SBP of 180, total: HDL cholesterol ranging from 4 to 8, aged 75 years and with an HbA_{1c} ranging between 6%-10% lived 1.2 years less, on average, than non-smokers (Leal et al., 2008). From their findings, the higher the HbA_{1c}, SBP and cholesterol (Total:HDL) the lower was the Expected Life Expectancy of an Individual aged x years ($\mathring{e}_x$). Improving modifiable risk factors like HbA_{1c} increases DM-II patients' longevity. Kontopantelis et al. (2015) also reported U shaped HRs when plotted against HbA_{1c}, SBP, Distolic Blood Pressure (DBP) and cholesterol. From their findings the category levels of HbA_{1c}, total cholesterol, SBP and DBP with the lowest mortality risks were 7.25-7.75%, 3.5-4.5mmol/L, 135-145mmHg and 82.5-87.5mmHg, respectively.

2.2.2 Kidney Diseases

As discussed in section 1.4.1 CKD accounts for 11% of deaths in DM-II individuals (Diabetes UK, 2016b). Wright et al. (2016) showed that renal failure had a mortality HR of 3.33 [95% CI: 3-3.69] in DM-II patients compared to those without DM-II. The eGFR can be used to measure the damage to the kidney and can be used as a predictor of mortality. In a study of DM-II patients, aged 20-89 years in 2000-2005, from the THIN database (UK), patients with an eGFR $\geq$ 60mL/min had the highest survival rates throughout the 11 years of follow up. The lower the eGFR the lower was the survival rate (Soriano et al., 2015). However, due to the bad recordings of ethinicity in

the THIN database, the study's eGFR calculated using the Cockcroft-Gault formula, may have underestimated eGFR particularly for the blacks (Soriano et al., 2015).

2.2.3 Dementia

Dementia is a condition in which there is a decline in memory, thinking, behaviour and ability to carry out day-to-day activities. Dementia can be classified as, Alzheimer, Vascular Dementia (VD), Dementia with Lewy Bodies (DLB), and diseases that contribute to frontotemporal dementia (WHO, 2017). Kim et al. (2017)'s study of 749 161 patients with DM-II only, 388 636 with Chronic Liver Disease (CLD) only, 122 590 with both DM-II and CLD and 5 080 631 controls with neither DM-II nor CLD, all aged 60 years and above at 2003 to 2005 and followed up to 2013, reported that DM-II alone highetened all-cause mortality among dementia patients (aHR: 1.46[95% CI: 1.45-1.47]). The presence of both diseases increased the mortality risk compared with the control group (aHR: 1.67[95% CI: 1.65-1.69]). They used data from the National Health Insurance Service of Korea and adjusted for age, sex, classes of national health insurance system, place of residence, hypertension, dyslipidemia, IHD, CVD, Heart Failure (HF), PAD, COPD, CKD and depression.

2.2.4 Other Cause-Specific Mortality among DM-II Patients

Wright et al. (2016) reported that DM-II persons had an aHR of cancer-specific mortality of 1.63 [95% CI: 1.60-1.67], Respiratory diseases (1.84 [95% CI: 1.79-1.89]), diseases of the nervous system (1.48 [95% CI: 1.39-1.58]) and diseases of digestive system (2.16 [95% CI: 2.06-2.27]) compared to non-DM-II patients.

2.2.5 Effect of Lifestyle on Mortality among DM-II Patients

Leal et al. (2008) using the UKPDS Outcomes model, reported that the Expected Life Expectancy of an Individual aged 55 years ($\mathring{e}_{55}$) of non-smoking DM-II male patients was between 3.6 and 9.4 years less than UK male general population's $\mathring{e}_{55}$, while those who smoked lived between 5.5 and 11.5 years less. This means that with controlled

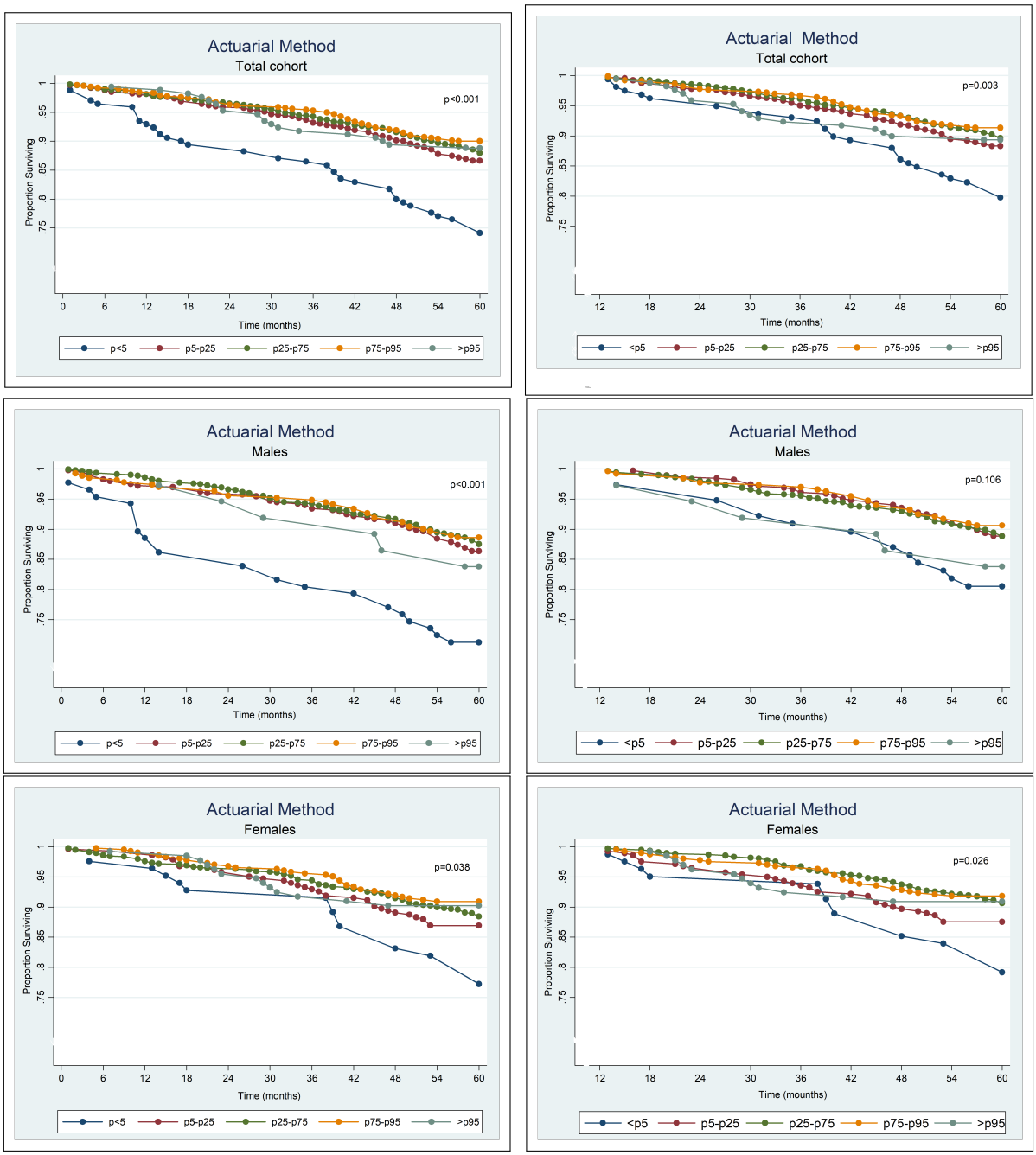


Figure 2.1: Five - year cumulative survival rates of the BMI categories calculated by actuarial method.

Notes: (a). Left graphs are results of sensitivity analysis on the right graphs' data. (b). BMI: p5=(<23kg/m^2); p5-p25=(23-26.8kg/m^2);p25-p75=(26.9-33.1kg/m^2);p75-p95=(33.2-39.4kg/m^2) and p95=(>39kg/m^2).

Source: Salinero-Fort et al. (2018)

modifiable risk factors the difference was smaller. DM-II patients who smoked and had an SBP of 120, total: HDL cholesterol ranging from 4 to 8, aged 55 years and with HbA_{1c} ranging from 6%-10% were found to live 2 years less, on average, than

non-smoking DM-II patients (Leal et al., 2008).

2.2.6 Effect of Ethnicity on Mortality among DM-II Patients

In the study by Wright et al. (2016) those of Asian origin had a lower adjusted cancer mortality, aHR of 0.43[95% CI: 0.36-0.51] and respiratory disease mortality, aHR of 0.60[0.48-0.76] compared with diabetic whites. The study showed that white patients lost more years of life due to DM-II than DM-II patients of Asian origin and black persons as depicted by Figure 2.3. Wright et al. (2016) also found that DM-II patients of Asian origin in the UK had a lower mortality HR followed by black and then white patients. Interestingly, those of Asian origin aged 65 years and above, with DM-II had up to 1.1 years more of life expectancy than their counterparts without DM-II. At the age of 40, it was reported that white men and women with DM-II loose 5 and 6 years of life expectancy compared to those without DM-II, respectively (Wright et al., 2016). Wright et al. (2016) reported a lower adjusted CVD mortality among DM-II patients of Asian origin (aHR 0.82[0.75-0.89]) compared with white DM-II patients. Wright et al. (2016) used abridged period life tables based on Chiang II method to estimate the life expectancy of DM-II and non-DM-II patients.

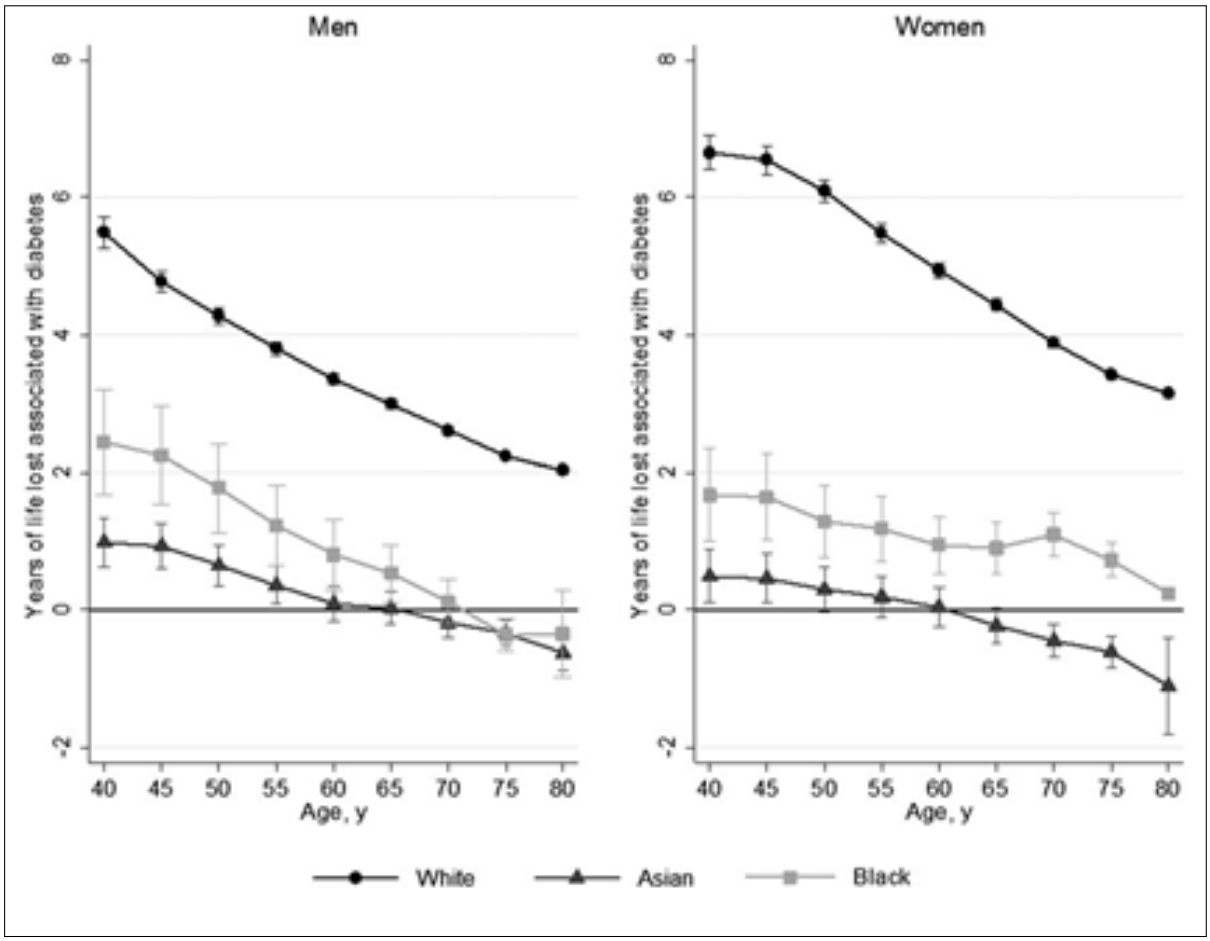


Figure 2.3: Differences in life expectancy between DM-II and non DM-II patients by age, sex and ethnicity

Source: Wright et al. (2016)

Chapter 3

Review of Morbidity among DM-II Patients

3.1 All-Cause Morbidity among DM-II Patients

DM-II significantly increases the risk of developing CVD. Between 2006 and 2012, macrovascular and microvascular diseases among DM-II patients had average incidence rates of 1.1% and 4.7%, respectively, (Kontopantelis et al., 2015). According to Franco et al. (2007), the hazard ratio (HR) of developing CVD is 2.5 for women aged 50 years and more and 2.4 for men of the same age compared with non-DM-II patients. Currie et al. (2010) reported a large vessel disease incidence of 1 707 among 20 817 (8.2%) DM-II patients with no previous history of the complications in the metformin plus sulfonylurea regimen compared to 1 608 among 13 475 (11.9%) patients on insulin-based therapies. They also found that good glycaemic control was linked to reduced frequency of microvascular but not macrovascular events after a follow-up median of 5 years.

Higher values of risk factors such as SBP puts DM-II individuals at high risk of complications. The risk of many types of secondary conditions increases with the duration of diabetes (Leal et al., 2008). Almdal et al. (2004) reported an increased adjusted RR for ischemic heart disease (IHD) in men aged 55 years and above and in women aged 55-64. The incidence for MI was reported to be higher in the less than 55 years and 55-64

years age groups in men (≥2 times higher) and women (≥4 times higher) when compared to their non-diabetic counterparts, respectively. Stroke incidence was reported to be increased (≥2 times higher) in the less than 55 years and greater than 64 years age groups in men while in women it was increased in the less than 55 years age group (≥2 times higher) and highly increased in the 55-64 years age group (≥6.5 times higher).

In a study of DM-II patients aged 30 years and above from a Korean database, with a period fron 2003 to 2013, the annual prevalence of depression was found to be consistantly higher in DM-II persons (Jeong et al., 2017). They reported that depression prevalence was 28.2% in DM-II patients. The prevalence rate in women was 22.6% in DM patients. Annual depression prevalance rates were reported to be increasing in DM-II patients throughout the 21 years of follow-up. In their study, it was reported that depressive DM-II patients were at a higher risk of diabetic foot ulcers.

Hasan et al. (2017) reported a 30% prevalence rate of magnesium deficiency (magnesium levels ≤ 1.6 mg/dl) among DM-II and that it is positively correlated with age in a study based on DM-II patients aged 35-70 years enrolled at the Diabetic Clinic in the Department of Medicine in Karachi from May 2012 to November 2012. The 46-55 years age group being the most affected. The proportion was higher in patients on oral hypoglycemic agents. Abnormal magnesium levels are known to cause the onset and pregression of DM complications such as coronary artery diseases (CAD), retinopathy, nephropathy, neuropathy and foot ulcertions (Hasan et al., 2017).

Hayes et al. (2013) reported that about 30% of DM-II after 25 years had MI as their first complication. The other complications had the following cumulative incidences as first events, stroke (≤15%), CHF (above 10%), IHD (above 20%), amputations (≤5%), renal failure (close to 2%), blindness (≤10%) and ulcers(≤3%). MI, stroke and amputation had cumulative death rates of ≤60%, ≤50% and ≤90% as second event compications after 25 years, respectively.

Patients whose SBP was less than 115mmHg or greater than 145mmHg were reported to be at a higher risk of macrovascular and microvascular complications (Kontopantelis et al., 2015). Overall incidence rates were 1.1% and 4.7% for macrovascular and microvascular diseases, respectively. Smoking DM-II patients or ex-smokers have high risk of developing macro-and microvascular diseases. DM-II patients were reported to have suffered from at least two comorbidities on average per year (Kontopantelis et al., 2015). The prevalence of DM-II complications were, retinopathy (19.9%), myocardial infaction (MI) (8%), neuropathy (4.7%), peripheral vascular disease (PVD) (4.7%), stroke (4.3%), CKD stages 4-5 (1.3%) and nephropathy excluding CKD stages 4-5 (0.5%) among others. In total, the average prevalence rates for macrovascular and microvascular complications were 17.6% and 27.4%, respectively. Soriano et al. (2015) reported that about 25-30% of DM-II patients in the UK have CKD stages 3-5. They also reported overall incidence rates of 9.26 cases [95% CI: 8.96-9.58] and 10.39 cases[95% CI:10.07-10.73], per 1000 person-years for MI and IS/TIA over median follow-up time of 6.64 years and 6.56 years, respectively. Hippisley-Cox and Coupland (2010) reported that DM-II patients had an increased the adjusted 5-year HR of moderate-severe CKD by 4.50 [95% CI: 4.14-4.89] for women and 6.07 [95% CI: 5.61-6.57] for men when compared with non-DM-II patients. The study was based on 1 574 749 patients from QResearch and 1 581 745 patients from the THIN databases, all aged between 35 and 74 years.

A study by van Staa et al. (2012) on 206 940 patients, from the GPRD, reported an equal overall risk of cancer for both DM and non-DM patients, aged 40 years and above. The study reported that DM patients were at a higher risk of developing cancer within the first six months of using antidiabetic drugs. The study population excluded DM-I patients and those with a history of cancer and included those with a prescription of antidiabetic drugs started at least a year after DM-II diagnosis. However, there was an increased risk for pancreatic, liver, uterus and cervical cancer among DM patients compared to non-DM patients. However, the study did not specify the index date at

which they calculate the age at diagnosis of DM-II. In their study they fully adjusted for age, sex, calendar year and other risk factors which included small-area socioeconomic status, smoking status, alcohol use, BMI and several health related variables. The study has many weaknesses such as metformin having a confounding effect on the other drugs as it is mainly used as the first treatment drug in most cases. The study also did not specify whether the sulfonylureas and thiazolidinediones therapies were used as monotherapy in cases were metformin was contraindicated or they were used as part of a dual therapy with metformin. Hence it is very difficult to trust the RRs found in the study as the effect of these drugs are dependant on each other.

Johnson et al. (2012) reported that substantive evidence has significanlty associated DM-II with some type of cancers. In their reveiw paper they reported that the strength of the association highly depends on the cancer site. They also found out that the strongest relationships are in liver and panceatic cancers although they have a 'reversal causality'. They also noted that endomentrial cancer is doubled in women with DM and the risks of breast, colorectal, bladder, non-Hodgkin lymphoma (NHL) and kidney cancers are 20-40% higher in DM-II patients. Prostate cancer was reported to be 10-20% less likely in men with DM-II. Lung and ovarian cancers were reported not to be significantly associated with DM-II and that DM-I was not associated with cancers related to DM-II. Hence, Johnson et al. (2012) advises that studies should avoid overal cancer incidence as the single endpoint but focus on specific cancer sites.

DM-II was found to be associated with an increased incidence of dementia by Kim et al. (2017) with an overall full adjusted HR of 1.27 [95% CI:1.27-1.28] alone and 1.28 [95% CI: 1.26-1.30] when co-existing with CLD compared to patients with no CLD and DM-II. DM-II was reported to have higher HR of any dementia compared to the control group. Davis et al. (2017) in a study of 1 291 DM-II patients matched with 5 159 non-DM patients from the Fremantle Diabetes Study Phase I database in Australia, recruited between 1993 and 1996 and followed up for 5 years, found out that

dementia incidence occured in 13.9% of DM patients compared to 12.4% in non-DM patients. Davis et al. (2017) found that the young DM-II patients were significantly at a higher risk of dementia (incidence RR (IRR): 1.7 [95% CI: 0.6-2.9]) compared to non-DM patients. Adjusting for age, sex and comorbidities they reported a subdistribution HR (sdHR) of 1.18[95% CI: 1-1.39] and a cause-specific HR (csHR) of 1.51[95% CI: 1.27-1.78] for DM-II on all-cause dementia. They reported that after the age of 65 years incidence rates for dementia where higher in DM-II patients compared to non-DM patients.

About 60% of DM-II patients were reported to have Diabetes Retionopathy (DR) (Diabetes UK, 2018). In a 10-year DR incidence study by Mathur et al. (2017), from 2004 to 2014, based on 338 390 DM-II patients from the GPRD, DR risk was found to vary significantly by region in the UK, age group and gender. The risk of developing severe DR was found to vary by ethnicity and an increase of DM-II duration by 5 years at baseline increased the DR risk by 17%, Mathur et al. (2017). Their study also showed that incidence rates were increasing from 2004 up to 2011 and then were decreasing. The age group that was reported to be at increased DR risk compared to the 55-64 years age group was 45-54 years age group (adjusted HR: 1.12[95% CI: 1.02-1.23]). They also found that the lower the age group, the higher the severe DR risk compared to the 55-64 years age group. The youngest age group 12-34 years was reported to have an adjusted HR of 1.46 [95% CI: 1.04-2.05]. In an earlier study by Younis et al. (2003) based on 20 570 DM-II patients without DR at baseline enrolled in the Liverpool Diabetic Eye Study, the incidence of sight-threatening DR was reported to be 0.3% [95% CI: 0.1-0.5] in the first year, increasing to 1.8%[95%CI: 1.2-2.5] in year 5.

3.2 Effects of Drugs on the Morbidity among DM-II Patients

Several studies have considered the effect of DM drugs on morbidity. van Staa et al. (2012) reported a high risk of cancer among DM-II patients under insulin therapy, with an adjusted relative rate (RR) of 1.79 [95% CI: 1.53,2.10], within the first 6 months of use when compared to those taking metformin. Sulfonylurias was reported to have an adjusted relative rate of 1.34 [95% CI: 1.19,1.51] when compared with metformin. DM-II patients under thiazolidinedones therapy had a lower relative rate of cancer of 0.83 [95% CI: 0.70,]. They also reported a decreasing trend in the adjusted relative rate after the 6 month of treatment for all the drugs. Currie et al. (2009) using the data from 64 809 patients aged 40 years and above from the THIN database reported the same trend. The data used was from 2001. They suggested that cancer should be considered as one of the complications of DM. However, Mamtani et al. (2014) challenged the fact that metformin has the lowest risk of cancer when compared to other DM-II drugs. They used the same database as Currie et al. (2009), with a period from July 2000 to August 2010. In their study they used the data of 87 600 new patients whose first therapy was either metformin or sulfonylureas. They discovered that metformin has no association with a reduced incidence of bladder cancer when compared to sulfonylureas. All the papers agreed that metformin patients are younger than those using other drug therapies. Therefore it is of paramount importance to compare the incidence rates by age as it is an independent factor in predicting morbidity rates. However, Johnson et al. (2012) reported that in as much as glucose-lowering therapies have been indicated to be associated with modulating the risk of cancer incidence in DM-II patients, there has been a considerable disagreement among the clinical community. They also reported that high endogenous insulin levels and/ or administration of exogenoues insulin could theoretically increase the risk of neoplastic diseases.

The meta-analysis by Boussageon et al. (2011) also reported a non-significant effect

of intensifying treatment towards the reduction of all MI (RR: 0.9 [95% CI: 0.81-1.01]). However, they reported a reduction in the risk of non-fatal MI (RR: 0.85 [95% CI: 0.74-0.96]) compared to standard treatment. When they analysed only the high quality studies, the reduction effect for non-fatal MI disappeared (RR: 0.83 [95% CI: 0.63-1.10]) and the risk of all MI increased (RR: 1.34[95% CI: 0.77-2.35]). Intensive treatment was also reported not to cause a significant reduction in non-fatal strokes risk (RR: 1 [95% CI: 0.83-1.21]), all strokes risk (RR: 0.96 [95% CI: 0.83-1.13]) or congestive heart failure (HF) with a RR of 1.17 [95% CI: 0.91-150]. When they restricted the study to high quality studies, congestive HF had an increased risk (RR: 1.47 [95% CI: 1.19-1.83]). In the same meta-analysis, the risk of severe hypoglycaemia was more than two-fold in the intensive treatment cohort compared to the standard treatment cohort (RR: 2.33 [95% CI: 1.62-3.36]). GLP-1 drugs were reported to have less significant effect on the reduction of acute myocardial infaction (AMI) in old DM-II patients, HR of 0.82 [95% CI: 0.66-1.03] (Zimmerman et al., 2017). Treating DM-II with dapagliflozin was reported not to have a statistical significant reduction in CVD incidence rate when compared to patients not using SGLT-2 inhibitors, aIRR: 0.89 [95% CI: 0.61-1.31], (Toulis et al., 2017).

Idris et al. (2012) in a retrospective cohort study of 103 368 patients with DM-II and no DME selected from the THIN database found that thiazolidinediones (TZD) have an increased risk of diabetes macular edema (DME). The study period was from January 2000 to November 2009. At 1 year follow up patients under TZD therapy had an incidence rate of 1.3%, 1.1 percent points higher than patients using other drugs. The odds ratio (OR) was 2.3 [95% CI: 1.5-3.6] at 1 year follow-up and they were reported to have a HR of 2.3 [95% CI: 1.7-3.0] at 10 years of follow up when compared to non-TZD users. DME is a major sight-threaning complication that affects up to 20% of DM-II patients (Idris et al., 2012). The incidence rate were reported to increase with the duration of the treatment using TZD. A combination of TZD and Insulin was reported to hightten the risk of DM-II patients developing DME, HR: 4.39 [2.46-7.84]) (Idris et al., 2012).

DM-II patients were reported to have a sight-threatening DR 5-year incidence rate of 23.3% [95% CI: 11.7-34.9] for patients under insulin therapy, 4.4% [95% CI:2.4-6.4] for those under oral hypoglycaemia and 1.4 [95% CI:0.4-2.4]% for those under dietary treament (Younis et al., 2003).

Hippisley-Cox and Coupland (2010) in a double barreled cohort study of 1 574 749 and 1 581 745 patients, aged 35 to 74 years within the period January 2002 and December 2008, from the QResearch and THIN databases, respectively, stated that the health burden due to CKD is expected to increase as a result of the ageing population and the global increase in DM-II prevalence. They used the QResearch patients as a derivation cohort and THIN patients as validation cohort for the development of the QKidney Score algorithm to estimate an individual's 5-year risk of moderate-severe CKD and 5-year risk of End Stage Kidney Failure in a primary care database. In both cohorts, the overal incidence rates for both risks increased with age. DM-II patients were more than at fourfold risk of developing moderate-severe CKD (adjusted HR: 4.5 [95% CI: 4.14-4.89] for women and 6.07 [95% CI: 5.61-6.57] for men) or End Stage Kidney Failure (adjusted HR: 4.68 [95% CI: 3.58-6.11] for women and 2.79 [95% CI: 2.17-3.58]) for men (Hippisley-Cox and Coupland, 2010).

The incidence rates of MI and IS/ TIA among DM-II patients with respect to eGFR both increased with time. The lower the eGFR, the higher was the incidence rate and also the higher the CKD stage, the higher were the incidence rates (Soriano et al., 2015).

3.2.1 Effect of Intensive Treatment on the Morbidity among DM-II Patients

The ADVANCE and UK Prospective Diabetes Study 33 (UKPDS 33) both reported the same results on the instensification of treatment with sulfonyureas as the drugs of interest regardless of a study gap of about 10 years in between them. Intensive treat-

ment was reported to be associated with a reduction in microvascular diseases (mainly after 2 years in ADVANCE) and not macrovascular diseases (ADVANCE Collaborative Group, 2008; UKPDS Group and others, 1998). ADVANCE Collaborative Group (2008) reported that intesive treatment reduced SBP with an average difference of 1.6 $mmHg$. Both studies reported more weight gain in patients under intensive treatment than those on standard treatment. ADVANCE Collaborative Group (2008) reported a mean weight difference of $0.7kg$ between the two study groups. This may explain why intensive treatment was reported not to be associated with macrovascular diseases among other reasons as weight gain or obesity is known to be risk factor for CVDs. However, in both studies intensive treatment reduced the levels of HbA_{1c} to the targetted level on average, 6.5% in the ADVANCE. Intensive treatment was also found to be associated with the occurrence of severe hypoglycemic events (0.7%per year) compared to standard treatment (0.4% per year) according to ADVANCE. Insulin was reported to have a greater association with weight gain and hypoglycemic events compared to other treatments with 3% and 40% each year for severe and minor hypoglycemic episodes, respectively (UKPDS Group and others, 1998).

In another intensive study known as ACCORD done by ACCORD Study Group (2008), DM-II patients assigned to recieve intensive therapy were reverted to a standard therapy after a mean of 3.5 years of follow up when it was found that intensive therapy was associated with higher mortality (HR: 1.22 [95%: 1.01-1.46]). The study also confirmed higher incidence of hypoglycemia and weight gain among DM-II patients receiving intensive therapy. The study also confirmed that intensive treatment was not associated with reduction in macrovascular events but with microvascular events. ACCORD Study Group (2008) also reported a higher reduction in HbA_{1c} and BP levels among patients assigned to intensive therapy.

Bibliography

ACCORD Study Group (2008). Effects of intensive glucose lowering in type 2 diabetes. *New England Journal of Medicine*, 358(24):2545–2559.

ADVANCE Collaborative Group (2008). Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *New England Journal of Medicine*, 358(24):2560–2572.

Almdal, T., Scharling, H., Jensen, J. S., and Vestergaard, H. (2004). The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13 000 men and women with 20 years of follow-up. *Archives of Internal Medicine*, 164(13):1422–1426.

Arora, S. (2017). The relationship between health spending and life expectancy. *Longevity Bulletin*, Issue(10):15–17.

Bagust, A., Hopkinson, P., Maslove, L., and Currie, C. (2002). The projected health care burden of Type 2 diabetes in the UK from 2000 to 2060. *PubMed*, 19(4):1–5.

Barnett, A. H. (2006). *Best Practice and Research Compendium*. Elsivier Limited.

Barr, E. L., Zimmet, P. Z., and Shaw, J. E. (2008). Mortality and life expectancy associated with diabetes. *The Epidemiology of Diabetes Mellitus, Second Edition*, pages 603–625.

Bilous, R. and Donnely, R. (2010). *Handbook of Diabetes 4th Edition*. Wiley-Blackwell.

Bourne, R. R., Stevens, G. A., White, R. A., Smith, J. L., Flaxman, S. R., Price, H., Jonas, J. B., Keeffe, J., Leasher, J., and Naidoo, K. (2013). Causes of vision loss worldwide, 1990–2010: a systematic analysis. *The Lancet Global Health*, 1(6):e339–e349.

Boussageon, R., Bejan-Angoulvant, T., Saadatian-Elahi, M., Lafont, S., Bergeonneau, C., Kassaï, B., Erpeldinger, S., Wright, J. M., Gueyffier, F., and Cornu, C. (2011). Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. *BMJ*, 343:d4169.

Currie, C., Poole, C., and Gale, E. (2009). The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia*, 52(9):1766–1777.

Currie, C. J., Peters, J. R., Tynan, A., Evans, M., Heine, R. J., Bracco, O. L., Zagar, T., and Poole, C. D. (2010). Survival as a function of hba1c in people with type 2 diabetes: a retrospective cohort study. *The Lancet*, 375(9713):481–489.

Davis, W. A., Zilkens, R. R., Starkstein, S. E., Davis, T. M., and Bruce, D. G. (2017). Dementia onset, incidence and risk in type 2 diabetes: a matched cohort study with the Fremantle Diabetes Study Phase I. *Diabetologia*, 60(1):89–97.

Diabetes UK (2013). Facts and figures: Diabetes prevalence 2012. diabetes.org.uk/professionals/position-statements-reports/statistics/diabetes-prevelence-2012. Accessed: 08/11/2017.

Diabetes UK (2014). Facts and figures: Diabetes prevalence 2013. diabetes.org.uk/professionals/position-statements-reports/statistics/diabetes-prevelence-2013. Accessed: 08/11/2017.

Diabetes UK (2015a). Facts and figures: Diabetes prevalence 2014. diabetes.org.uk/professionals/position-statements-reports/statistics/diabetes-prevelence-2014. Accessed: 08/11/2017.

Diabetes UK (2015b). Facts and figures: Diabetes prevalence 2015. diabetes.org.uk/professionals/position-statements-reports/statistics/diabetes-prevelence-2015. Accessed: 08/11/2017.

Diabetes UK (2016a). Facts and figures: Diabetes prevalence 2016. diabetes.org.uk/professionals/position-statements-reports/statistics/diabetes-prevelence-2016. Accessed: 08/11/2017.

Diabetes UK (2016b). Facts and stats. diabetes.org.uk/professionals/position-statements-reports/statistics. Accessed: 08/11/2017.

Diabetes UK (2017). About insulin. www.diabetes.co.uk/about-insulin.html. Accessed: 08/11/2017.

Diabetes UK (2018). Research spotlight-diabetic retinopathy. www.diabetes.org.uk/Research/Research-round-up/Research-spotlight/Research-spotlight-diabetic-retinopathy. Accessed on 23/04/2018.

Eurostat (2017). Mortality and life expectancy statistics. ec.europa.eu/eurostat/statistics-explained/index.php/Mortality-and-life-expectancy-statistics. Accessed: 12/11/2017.

Falkous, C. (2017). Current Changes in Life Expectancy in UK. *Longevity Bulletin*, Issue(10):6–9.

Fox, C. D. and Kilvert, A. D. (2007). *Type 2 Diabetes*. London.

Franco, O. H., Steyerberg, E. W., Hu, F. B., Mackenbach, J., and Nusselder, W. (2007). Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. *Archives of Internal Medicine*, 167(11):1145–1151.

Go, A. S., Yang, J., Ackerson, L. M., Lepper, K., Robbins, S., Massie, B. M., and Shlipak, M. G. (2006). Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: the Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study. *Circulation*, 113(23):2713–2723.

Hasan, M., Sultan, S., Ashfaq, S., and Irfan, S. M. (2017). Hypomagnesemia in Type II Diabetes Mellitus Patients; An Experience From a Tertiary Care Center. *Ann. Pak. Inst. Med. Sci*, 13(2):146–150.

Hayes, A., Leal, J., Gray, A., Holman, R., and Clarke, P. (2013). UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. *Diabetologia*, 56(9):1925–1933.

Hiam, L., Dorling, D., Harrison, D., and McKee, M. (2017). What caused the spike in mortality in england and wales in january 2015? *Journal of the Royal Society of Medicine*, 110(4):131–137.

Hippisley-Cox, J. and Coupland, C. (2010). Predicting the risk of Chronic Kidney Disease in Men and Women in England and Wales: prospective derivation and external validation of the QKidney® Scores. *BMC Family Practice*, 11(1):49.

IDF (2015). IDF Atlas 2015. https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/13-diabetes-atlas-seventh-edition.html. Accessed: 22/05/2018.

Idris, I., Warren, G., and Donnelly, R. (2012). Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. *Archives of Internal Medicine*, 172(13):1005–1011.

IEC (2009). Interbational Expert Committee Report on the Role of the HbA_{1c} Assay in the Diagnosis of Diabetes. *Diabetes Care*, 32(7):1327–1333.

IFoA (2011). Longevity Bulletin: Is life ecpectancy the life span we should expect. https://www.actuaries.org.uk/search/site. Accessed: 22/05/2018.

IFoA (2016). Longevity Bulletin: Antimicrobial resistance. https://www.actuaries.org.uk/search/site/. Accessed: 22/05/2018.

Jeong, J., Um, Y. H., Ko, S., Park, J., Park, J., Han, K., Ko, K., et al. (2017). Depression and mortality in people with type 2 diabetes mellitus, 2003 to 2013: a nationwide population-based cohort study. *Diabetes & Metabolism Journal*, 41(4):296–302.

Johnson, J., Carstensen, B., Witte, D., Bowker, S., Lipscombe, L., Renehan, A., Diabetes, Consortium, C. R., et al. (2012). Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. *Diabetologia*, 55(6):1607–1618.

Khanolkar, M., Bain, S., and Stephens, J. (2008). The diabetic foot. *QJ Moed*, 101(9):685–695.

Kim, H. M., Lee, Y.-h., Han, K., Lee, B.-W., Kang, E. S., Kim, J., and Cha, B.-S. (2017). Impact of diabetes mellitus and chronic liver disease on the incidence of dementia and all-cause mortality among patients with dementia. *Medicine*, 96(47):e8753.

Kontopantelis, E., Springate, D. A., Reeves, D., Ashcroft, D. M., Rutter, M., Buchan, I., and Doran, T. (2015). Glucose, blood pressure and cholesterol levels and their relationships to clinical outcomes in type 2 diabetes: a retrospective cohort study. *Diabetologia*, 58(3):505–518.

Leal, J., Gray, A. M., and Clarke, P. M. (2008). Development of life-expectancy tables for people with type 2 diabetes. *European Heart Journal*, 30(7):834–839.

Lim, S., Eckel, R. H., and Koh, K. K. (2018). Clinical implications of current cardiovascular outcome trials with sodium glucose cotransporter-2 (SGLT2) inhibitors. *Atherosclerosis*, 272:33–40.

Lind, M., Garcia-Rodriguez, L., Booth, G., Cea-Soriano, L., Shah, B., Ekeroth, G., and Lipscombe, L. (2013). Mortality trends in patients with and without diabetes in Ontario, Canada and the UK from 1996 to 2009: a population-based study. *Diabetologia*, 56(12):2601–2608.

Lu, J. (2017). Summary on the Longevity Bulletin Issue 10. *Longevity Bulletin*, Issue(10):4–5.

Malavige, L. S. and Levy, J. C. (2009). Erectile dysfunction in diabetes mellitus. *The Journal of Sexual Medicine*, 6(5):1232–1247.

Mamtani, R., Pfanzelter, N., Haynes, K., Finkelman, B. S., Wang, X., Keefe, S. M., Haas, N. B., Vaughn, D. J., and Lewis, J. D. (2014). Incidence of bladder cancer in patients with type 2 diabetes treated with metformin or sulfonylureas. *Diabetes Care*, 37(7):1910–1917.

Mathers, C. D. and Loncar, D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine*, 3(11):e442.

Mathur, R., Bhaskaran, K., Edwards, E., Lee, H., Chaturvedi, N., Smeeth, L., and Douglas, I. (2017). Population trends in the 10-year incidence and prevalence of diabetic retinopathy in the UK: a cohort study in the Clinical Practice Research Datalink 2004–2014. *BMJ Open*, 7(2):e014444.

Matthews, D. et al. (2008). *Diabetes*. Oxford University Press.

Mulnier, H., Seaman, H., Raleigh, V., Soedamah-Muthu, S., Colhoun, H., and Lawrenson, R. (2006). Mortality in people with type 2 diabetes in the UK. *Diabetic Medicine*, 23(5):516–521.

NHS (2017). Cirrhosis. www.nhs.uk/conditions/cirrhosis. Accessed: 30/01/2018.

NICE (2012a). Peripheral arterial disease: diagnosis and management (2012): NICE Guideline CG147. pathways.nice.org.uk/pathways/lower-limb-peripheral-arterial-disease#content=view-node%3Anodes-assessment-and-diagnosis/. Accessed: 22/05/2018.

NICE (2012b). Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. https://www.nice.org.uk/guidance/ph38. Accessed: 22/05/2018.

NICE (2015a). Chronic disease in adults: assessment and management. www.nice.org.uk/guidance/cg182/chapter/. Accessed: 29/01/2018.

NICE (2015b). Type 2 diabetes in adults: management. https://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-pdf-1837338615493. Accessed: 21/05/2018.

NICE (2016a). Diabetes Foot Problems: Prevention and Management (2016): NICE Guideline NG19. pathways.nice.org.uk/pathways/foot-care-for-people-with-diabetes#content=view-node%3Anodes-principles-of-care/. Accessed: 22/05/2018.

NICE (2016b). Non-alcoholic fatty liver disease (NAFLD): assessment and management (2016): NICE Guideline NG49. pathways.nice.org.uk/pathways/non-alcoholic-fatty-liver-disease#path=view%3A/pathways/non-alcoholic-fatty-liver-disease/. Accessed: 22/05/2018.

NICE (2017a). Identification and assessment of cardiovascular disease risk. pathways.nice.org.uk/pathways/cardiovascular-disease-prevention#path=view%3A/pathways/cardiovascular-disease-prevention/. Accessed: 23/02/2018.

NICE (2017b). Managing blood glucose in adults with type 2 diabetes. pathways.nice.org.uk/pathways/type-2-diabetes-in-adults#path=view%3A/pathways/type-2-diabetes-in-adults/. Accessed: 24/02/2018.

NICE (2017c). Type 2 diabetes: prevention in people at high risk. www.nice.org.uk/guidance/PH38/chapter/Recommendations#risk-assessment. Accessed: 26/01/2018.

ONS (2016). National life tables UK:20132015. ons.gov.uk/peoplepopulationandcommunity/. Accessed: 02/11/2017.

ONS (2017). Deaths registered in England and Wales (series DR). ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/. Accessed: 22/02/2018.

PHE (2016a). Diabetes footcare activity profiles. Using the average annual number of amputations per year from 2012-2015.

PHE (2016b). Diabetes Prevalence Model. https://www.gov.uk/government/publications/diabetes-prevalence-estimates-for-local-populations. Accessed: 22/05/2018.

PHE (2016c). Technical document for the diabetes prevalence model for England 2016. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/612307/Diabetesprevalencemodeltechnicaldocument.pdf. Accessed: 22/05/2018.

Roberts, S., Barry, E., Craig, D., Airoldi, M., Bevan, G., and Greenhalgh, T. (2017). Preventing type 2 diabetes: systematic review of studies of cost-effectiveness of lifestyle programmes and metformin, with and without screening, for pre-diabetes. *BMJ Open*, 7(11):e017184.

Salinero-Fort, M. Á., San-Andrés-Rebollo, F. J., Jiménez-García, R., and de Miguel-Yanes, J. M. (2018). Body mass index and all-cause mortality among type 2 diabetes mellitus patients. *European Journal of Internal Medicine*, 47:e28.

Scobie, I. and Katherine, S. (2014). *Diabetes Mellitus*. Health Press Limited.

Soriano, L. C., Johansson, S., Stefansson, B., and Rodríguez, L. A. G. (2015). Cardiovascular events and all-cause mortality in a cohort of 57,946 patients with type 2 diabetes: associations with renal function and cardiovascular risk factors. *Cardiovascular Diabetology*, 14(1):38.

Stanford Medicine (2018). Measuring and Understanding the Ankle Brachial Index (ABI). www.stanfordmedicine25.stanford.edu/the25/ankle.html. Accessed: 30/01/2018.

Taylor, K. S., Heneghan, C. J., Farmer, A. J., Fuller, A. M., Adler, A. I., Aronson, J. K., and Stevens, R. J. (2013). All-cause and cardiovascular mortality in middle-aged people with type 2 diabetes compared with people without diabetes in a large UK primary care database. *Diabetes Care*, 36(8):2366–2371.

Toulis, K. A., Willis, B. H., Marshall, T., Kumarendran, B., Gokhale, K., Ghosh, S., Thomas, G. N., Cheng, K. K., Narendran, P., Hanif, W., et al. (2017). All-cause mortality in patients with diabetes under treatment with dapagliflozin: a population-based, open-cohort study in The Health Improvement Network Database. *The Journal of Clinical Endocrinology & Metabolism*, 102(5):1719–1725.

UKPDS Group and others (1998). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet*, 352(9131):837–853.

UN (2018). Life expectancy at birth. www.un.org/esa/sustdev/natlinfo/indicators/methodology_sheets/health/life_expectancy.pdf. Accessed: 25/04/2018.

van Staa, T., Patel, D., Gallagher, A., and De Bruin, M. (2012). Glucose-lowering agents and the patterns of risk for cancer: a study with the General Practice Research Database and secondary care data. *Diabetologia*, 55(3):654–665.

WHO (2006). Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/. Accessed:22/05/2018.

WHO (2011). Use of glyserated haemoglobin (hba_{1c}) in the diagnosis of diabetes mellitus. abbrevated report of a WHO consultation. http://www.who.int/diabetes/publications/report-hba1c_2011.pdf. Accessed: 22/05/2018.

WHO (2017). Dementia. http://www.who.int/mediacentre/factsheets/fs362/en/. Accessed: 11/04/2018.

WHO (2017a). Fact sheets 310. who.int/mediacentre/factsheets/fs310/en/. Accessed: 03/11/2017.

WHO (2017b). Fact Sheets 312. who.int/mediacentre/factsheets/fs312/en. Accessed: 02/11/2017.

Wright, A. K., Kontopantelis, E., Emsley, R., Buchan, I., Sattar, N., Rutter, M. K., and Ashcroft, D. M. (2016). Life expectancy and cause-specific mortality in type 2 diabetes: a population-based cohort study quantifying relationships in ethnic subgroups. *Diabetes Care*, page dc161616.

Younis, N., Broadbent, D. M., Vora, J. P., and Harding, S. P. (2003). Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye Study: a cohort study. *The Lancet*, 361(9353):195–200.

Yudkin, J. S. and Montori, V. M. (2014). The epidemic of pre-diabetes: the medicine and the politics. *The BMJ*, 349:e4485.

Zimmerman, R. S., Hobbs, T. M., Wells, B. J., Kong, S. X., Kattan, M. W., Bouchard, J., Chagin, K. M., Yu, C., Sakurada, B., Milinovich, A., et al. (2017). Association of glucagon-like peptide-1 receptor agonist use and rates of acute myocardial infarction, stroke and overall mortality in patients with type 2 diabetes mellitus in a large integrated health system. *Diabetes, Obesity and Metabolism*, 19(11):1555–1561.

Appendices

Appendix A

Additional Figures

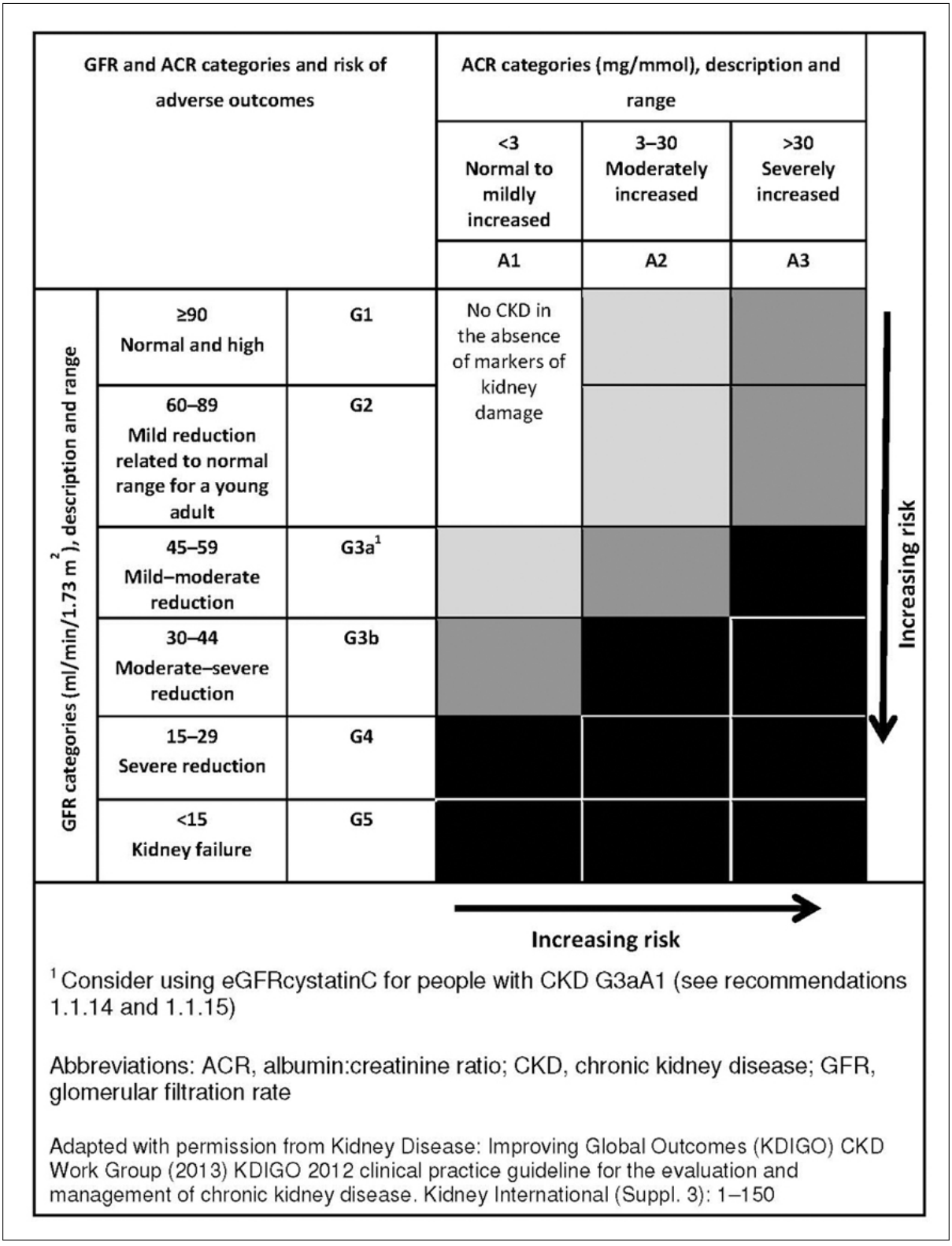


Figure A.1: Chronic Kidney Disease Classification

Source: NICE (2015)

Appendix B

Additional Tables

Table B.1: Risk Assessment of Diabetes Foot Problems

Diabetes Foot Problems Risk			
Low	**Moderate**	**High**	**Active**
No Risk Factors except callus alone	Deformity OR	Previous Ulceration OR	Ulceration OR
	Neuropathy OR	Previous Amputation OR	Spreading Infection OR
	Non-Critical Limb Ischaemia	On Renal Replacement Therapy OR	Critical Limb Ischaemia OR
		Neuropathy and Non-Critical Limb Ischaemia together OR	Gangrene OR
		Neuropathy in Combination with Callus and / or Deformity OR	Suspicion of Acute Charcot Arthropathy or unexplained hot, red, swollen foot with or without pain
		Non-Critical Limb Ischaemia in Combination with Callus and / or Deformity.	

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