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Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes

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Abstract

Purpose of Review The aims of this review are to summarize recent data on mortality and cardiovascular disease (CVD) in type 1 and type 2 diabetes and to determine the interventions that could have contributed to a reduction in mortality.

Recent Findings Recent studies found a downward trend in mortality and CVD among both diabetics and non-diabetics worldwide over the last few decades. The decline among diabetics is steeper than that among non-diabetics. Despite a parallel trend of decline, an approximately twofold difference in mortality and CVD between the two populations remains.

Summary A greater emphasis on glycemic control, management of cardiovascular risk factors, quality improvement programs, and advances in treatment of conditions associated diabetes are the factors that potentially contributed to the improvement. Although the trend is encouraging, a rising prevalence of diabetes will continue the absolute disease burden to the society. Future interventions should focus on prevention of diabetes.

Keywords Diabetes mellitus, type 1 · Diabetes mellitus, type 2 · Mortality · Cardiovascular mortality · Cardiovascular disease · Cardiovascular risk · Trend

Introduction

Diabetes has reached epidemic proportions. In the 1990s, the worldwide prevalence of diabetes was 135 million, yet by the year 2025, this number is projected to rise to 300 million around the globe [1]. This rise in diabetes prevalence is significant because it is the seventh leading cause of death in the USA [2••]. Cardiovascular disease (CVD) is the leading cause of death in both type 1 diabetics (44%) and type 2 diabetics (52%) [3]. The World Health Organization's study on diabetes-related death certificates among adults older than 64 years of age showed that more than two-third of them died from heart disease [4]. Diabetes carries a tremendous healthcare and financial burden worldwide. For instance, in the USA, the cost of treating cardiovascular complications in type 2 diabetics is 58% higher than that of treating type 2 diabetes alone. This increase included a direct medical cost of approximately $9000 per person per year for the treatment of myocardial infarction, stroke, heart failure, and hypertension [5]. In addition to costs, the association between diabetes and CVD, together with the projected rise in prevalence of diabetes, will result in an increased utilization of healthcare services. This economic burden will force policymakers to implement solutions to mitigate this worldwide surge of diabetes [6]. In recent decades, there have been more intensive management strategies and more integrated chronic disease care models with improved patient education and self-management which could have a positive impact on diabetes control and diabetes-related cardiovascular complications. The Steno-2 study comparing the effects of intensified, target-driven therapy involving a combination of medications

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and focused behavior modification with conventional multifactorial management for risk factor modification (glycemic control, treatment of dyslipidemia, blood pressure control, and treatment of microalbuminuria) in type 2 diabetics showed that aggressive interventions reduced cardiovascular mortality and cardiovascular events by more than half [7]. Furthermore, many trials of quality improvement interventions such as disease monitoring with an electronic patient registry, physician reminders, and promotion of patient education and self-management strategies showed significant improvements in diabetes management by reducing the HbA1c, LDL cholesterol, and hypertension [8].

Despite this huge burden of diabetes, recent reports have shown a significant reduction in all-cause mortality and cardiovascular mortality in diabetics within the last two decades. A recent study from Sweden also revealed that the incidence of cardiovascular morbidity and mortality has decreased considerably in patients with both type 1 and 2 diabetes [9••]. Similarly, the US National Health Interview Survey from 1988 to 2015 showed a decline in all-cause mortality and vascular disease-related mortality among diabetics than non-diabetics [10••]. Therefore, the aims of our review paper are to summarize recent data on mortality and CVD in type 1 and type 2 diabetes and to determine the interventions that could have contributed to a reduction in mortality.

Mortality in Diabetes

Mortality in Type 1 Diabetes Mortality in type 1 diabetes has dramatically improved after the discovery of insulin in the early twentieth century. The discovery of antibiotics in the mid-twentieth century led to another dramatic fall in mortality among type 1 diabetics. When acute complications such as diabetic ketoacidosis and infection were no longer major causes of death in type 1 diabetes in the mid-century, the mortality pattern in type 1 diabetes shifted to chronic diabetes complications. Although the incidence of type 1 diabetes is increasing in the USA [11], there has been a remarkable downward trend in type 1 diabetes mortality since the mid-century, which appears to have leveled off in the last decade of the twentieth century [12••]. During the forty years preceding 2008–2009, the mortality from diabetes among youths aged 19 years and younger, presumably type 1 diabetes, decreased 61%, from 2.69 to 1.05 per million, calculated from the National Vital Statistics System data for 2-year or 3-year periods from 1968 to 2009 [13].

From 2002 to 2006 to 2007 to 2011, the life expectancy at age 20 of type 1 diabetics in Sweden increased by approximately 2 years from 47.7 to 49.7 years for men but minimally for women. This is attributable to reduced cardiovascular mortality [14••]. A large population-based cohort study of over 30,000 adults with type 1 diabetes registered in the Swedish National Diabetes Register, with a mean follow-up of 11 years, found that type 1 diabetics had about a 29% reduction in all-cause mortality (hazard ratio (HR) 0.71 (0.66–0.78)), and by 23% in age-, sex-, and county-matched non-diabetic controls (HR 0.77 (0.72–0.83)) during the follow-up period. The reduction in all-cause mortality among type 1 diabetics did not differ significantly from the reduction among controls (HR 1.08 (0.99–1.18); $p = 0.09$) [9••].

Mortality in Type 2 Diabetes US-based cohorts and national survey studies found a 1.4–3.4 × increased age-adjusted risk for all-cause mortality in type 2 diabetics compared with those without diabetes [15••]. Although a trend of reduction in overall risk was found overtime, excess risk remained high even in modern days. The decreasing trend of mortality in type 2 diabetics parallels with that of non-diabetics. The relative risk remained around 2 during the last three decades of the twentieth century [16]. A 55-year follow-up of the Framingham Heart Study participants from 1950 to 2005 revealed that the excess mortality in diabetics over non-diabetics has decreased over time from about two-and-a-half-fold excess to twofold excess [17]. A large database study from the UK also found a twofold increased risk of all-cause mortality in diabetics compared with non-diabetics [18]. A 7-year nationwide prospective study of over 500,000 adults aged 30–79 years from ten different regions in China revealed that diabetics had a an approximately twofold increased risk of all-cause mortality, compared with non-diabetics [19••].

A large population-based cohort study of over 40,000 adults with type 2 diabetes registered in the Swedish National Diabetes Register, with a mean follow-up of ~ 6 years, found that type 2 diabetics had about a 21% reduction in all-cause mortality (hazard ratio (HR) 0.79 (0.78–0.80)) and by 31% in age-, sex-, and county-matched non-diabetic controls (HR 0.69 (0.68–0.70)) during the follow-up period. Contrary to type 1 diabetics in the same register (vide supra), the reduction in the all-cause mortality rate was 13% greater among controls than among type 2 diabetics (HR 0.87 (0.85–0.89); $p < 0.001$) [9••].

Cardiovascular Disease and Cardiovascular Mortality in Diabetes

In diabetics, macrovascular complications contribute more to mortality than microvascular complications [3, 5, 15••]. A multicenter prospective observational study of diabetes care in managed care found that angina, myocardial infarction, coronary angioplasty, bypass, and congestive heart failure were among the predictors of all-cause mortality in diabetics [20]. Diabetes was also associated with a significantly higher long-term mortality in both men and women after acute myocardial infarction [21].

CVD currently contributes to about a quarter to one-half of all deaths in type 1 diabetics with a duration of disease 10–19 years whereas it accounts for more than half of all deaths in those with a duration of diabetes greater than 20 years [12••, 22]. A cohort study of over 23,000 participants found that acute complications of diabetes contributed about a third of all deaths in type 1 diabetics younger than 30 years of age and cardiovascular disease accounted for more than half of all deaths in type 1 diabetics over 30 years of age. [23]. Age of onset appears to be a crucial determinant of CVD in type 1 diabetics. A register-based cohort study of type 1 diabetics in the Swedish National Diabetes Register showed that type 1 diabetics with disease onset before 10 years of age had a 30 × increased risk of coronary heart disease and acute myocardial infarction compared with matched controls from the general population [24••].

In the cohort from the Swedish National Diabetes Register [9••], there was a relative reduction in cardiovascular mortality of 42% (HR 0.58 (0.50 to 0.68)) among type 1 diabetics and 38% (HR 0.62 (0.53 to 0.72)) among controls. The reduction in cardiovascular mortality among type 1 diabetics did not differ significantly from the reduction among controls (HR 1.06 (0.89–1.26); $p = 0.53$). The frequency of hospitalization for CVD was reduced by 36% among type 1 diabetics (HR 0.64 (0.56–0.72)), and the reduction was greater among diabetics than among controls.

In a study sampling diabetic adults, presumably type 2, from ten different health plans, mortality rates were 19% over an 8-year period, with 40% of deaths being attributed to CVD [19••]. Approximately 15–81% of type 2 diabetics have at least one cardiovascular complication, and the most prevalent cardiovascular complication is hypertension, followed by myocardial infarction and heart failure [5]. The cardiovascular complications were more prevalent in institutionalized than in non-institutionalized type 2 diabetics.

A 50% reduction in the rate of incident CVD events among diabetic adults was reported in a cohort study drawn from the Framingham Heart Study with a follow-up of up to 12 years [25]. In the same cohort, non-diabetics also had a smaller but statistically similar 35% reduction in CVD event rates. The absolute risk of CVD remained twofold greater than non-diabetics. Another retrospective cohort study with participants from Ontario, Canada, with an 8-year follow-up, found a greater reduction of hospital admission rates for myocardial infarction and stroke in the diabetic than the non-diabetic population [26]. A similar greater reduction in case fatality rates related to myocardial infarction and stroke among diabetics than non-diabetics was found in this cohort. Since the prevalence of diabetes also increased during the same period, a fall of CVD rates among diabetics did not necessarily translate into a reduction of total absolute CVD burden in the society.

A prospective cohort study using the data from the National Health and Nutrition Examination Survey (NHANES) of the USA found a substantially improved outcomes for total, cardiovascular, and cardiac deaths in people with diabetes during the 2005–2010 NHANES compared with the 1999–2004 NHANES [27••]. Analysis of the data from the National Health Interview Survey, the National Hospital Discharge Survey, the United States Renal Data System, and the US National Vital Statistics System found a substantial decline of incidence of myocardial infarction, stroke, and amputation by approximately half within the two decades between 1990 and 2010 among adults with diabetes [28]. Rate reductions were larger among diabetics than non-diabetics, resulting in a reduction in the relative risk of complications associated with diabetes. From 1998 to 2014, age-adjusted hospitalization rates declined significantly for acute coronary syndrome, cardiac dysrhythmia, heart failure, hemorrhagic stroke, and ischemic stroke among diabetics aged 35 and older, as estimated from the US National Inpatient Sample data [29••]. The corresponding rates for non-diabetics also declined during this period, with the exception of cardiac dysrhythmia. At the end of this period, rates among diabetics remained two- to fourfold higher than those among non-diabetics.

A retrospective population-based study of the data from the National Health Insurance Service (NHIS) database of South Korea revealed a substantial relative reduction in the incidence of CVD, with the exception of percutaneous coronary intervention, in the Korean population with type 2 diabetes between 2006 and 2013 [30••]. This finding could be attributable to significant risk factor modifications such as improved blood pressure control and decreased smoking rate in Korea over the past few decades [31]. A case-control study using the National Hospital Discharge Database in Spain showed that type 2 diabetics had a 15% higher mortality rate during admission for myocardial infarction, a 6% higher mortality for stroke, and a 6% higher mortality rate for all cardiovascular events combined, than non-diabetic matched controls [32••]. Aforementioned prospective study from China [19••] also revealed that diabetics had a higher mortality from ischemic heart disease and stroke.

In the type 2 diabetic cohort from the Swedish National Diabetes Register [9••], there was a relative reduction in cardiovascular mortality of 46% (HR 0.54 (0.52–0.55)) among type 2 diabetics and 50% (HR 0.50 (0.49–0.52)) among controls. The reduction in cardiovascular mortality among controls was 6% greater than the reduction among type 2 diabetics. (HR 0.94 (0.90–0.98); $p = 0.004$). The frequency of hospitalization for CVD was reduced by 44% among type 2 diabetics (HR 0.56 (0.54–0.57)), and the reduction was greater among diabetics than among controls.

The most recent trends on mortality data in diabetics and non-diabetics in the USA is reported by Gregg et al. [10••] in their analysis of data from the National Health Interview Survey, conducted by the Centers for Disease Control and

Prevention. Since the survey simply asked the respondents whether their doctors have told them having diabetes or "sugar diabetes," there was no distinction between type 1 and type 2 diabetes in the analysis. The sample population was defined as adults aged 18 and older at baseline. The analysis showed that the mean ages of participants at baseline were 60 and 43 for diabetics and non-diabetics respectively; hence, it can be inferred that majority of participants with diabetes were type 2 diabetics. The excess all-cause mortality in diabetics (vs. non-diabetics) has declined from 11.3% (8.5–14.1) in 1988–1994 to 5.9% (5.3–6.5) in 2010–2015. The relative risk of all-cause mortality in diabetics (vs. non-diabetics) has declined from 2.0 (1.7–2.2) to 1.6 (1.6–1.7) within the same period. The excess vascular disease-related mortality has also similarly declined from 5.8% (4·0–7·6) to 2.3% (1.9–2.7) with corresponding relative risk from 2.1 (1.8–2.5) to 1.8 (1.7–2.0).

Discussion

The reduction in mortality and cardiovascular disease in diabetics observed during the recent decades is most likely multifactorial and could be attributed to different interventions. Factors include but not limited to early institution of interventional measures in patients at risk, better control of diabetes with improvement in fasting blood glucose levels, a decline in frequency of hypoglycemia events, and overall improvement of HbA1c. Furthermore, options of pharmacologic therapies to treat diabetes have recently expanded. Cardiovascular safety, reduction of cardiovascular events, and decrease of cardiovascular-related mortality are highly scrutinized clinical outcomes and driving factors of treatment selection (and drug development) in diabetes. For instance, in 2008, the US Food and Drug Administration issued guidelines requiring new diabetes mellitus therapies to demonstrate cardiovascular safety in emergent drugs [33].

A systematic review on effectiveness of quality improvement strategies on the management of diabetes found that the quality improvement strategies [8] reduced HbA1c, LDL cholesterol, and blood pressure compared with usual care, especially when baseline levels of these parameters were relatively higher, although improvements were modest. Such quality improvement strategies, integrated care of patients with chronic disease through disease management programs and advancements in clinical decision-making support could have contributed to a reduction in all-cause mortality, cardiovascular mortality, and cardiovascular disease in individuals with type 1 and type 2 diabetes.

Newer drugs with favorable cardiovascular effects, in addition to lowering blood glucose properties have been introduced within the last decade. Although the use of these medications cannot be attributed to the decline in mortality and cardiovascular disease among diabetics over the last few decades since they have not been in the market for that long, they may potentially contribute to a further decline in mortality and cardiovascular disease in recent years and the future. Among the emerging drugs with beneficial cardiovascular effects [34], glucagon-like peptide-1 receptor agonists (GLP1RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2I) have been comprehensively studied as discussed in detail below.

A randomized controlled trial of over 9000 participants with an approximately 4-year follow-up, adding liraglutide to standard care, improved survival and reduced cardiovascular outcomes. All-cause mortality was lower in the liraglutide group (8.2%) than in the placebo group (9.6%) (HR 0.85 (0.74–0.97); $p = 0.02$). The rate of composite of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) was also lower in the liraglutide group (13%) than that in the placebo group (15%) (HR 0.87 (0.78–0.97); $p < 0.001$ for non-inferiority; $p = 0.01$ for superiority). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than that in the placebo group. Deaths from cardiovascular causes were significantly reduced in the liraglutide group (4.7%) compared with the placebo group (6.0%) (HR 0.78 (0.66–0.93); $p = 0.007$) [35••]. Contrary to the above, a randomized controlled trial in type 2 diabetics and a recent acute coronary syndrome, the addition of another GLP1RA lixisenatide to locally determined standards of care, did not significantly change the rate of major cardiovascular events [36•].

In a randomized controlled trial of over 7000 participants with a median follow-up of 3 years, adding empaglifozin, an SGLT2I, to the standard care reduced the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke by 14% (absolute rate 10.5% in the empaglifozin group vs. 12.1% in the placebo group; HR 0.86 (0.74–0.99); $p = 0.04$ for superiority) and cardiovascular mortality by 38% (absolute rate 3.7% in the empaglifozin group vs. 5.9% in the placebo group; HR 0.62 (0.49–0.77); $p < 0.001$) [37•]. It is noteworthy that over 20% of these high-risk participants did not receive statin, raising the question that the attributable benefit of empaglifozin could potentially be lower than what it seems to be. A meta-analysis of 81 trials with a total of 37,195 participants reported that SGLT2 inhibitors appeared to reduce both all-cause and cardiovascular mortality, primarily due to a reduction in the risk of heart failure in diabetes [38••].

Findings in these two clinical trials with liraglutide and empaglifozin led to the American Diabetes Association to revise their clinical practice guidelines recently. Their guideline now recommends that in patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antidiabetic therapy should begin with lifestyle management and metformin, and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors [39••].

Conclusion

Over the recent decades, there is a marked downward trend in mortality and cardiovascular disease among both diabetics and non-diabetics, with the decline among diabetics being more profound that that among non-diabetics, in different regions across the globe. A greater emphasis for diabetic control and cardiovascular risk factors in management of individuals with diabetes and advances in treatment of diabetic complications (cardiovascular disease, infection) is most likely to be major factors responsible for this encouraging trend. Quality improvement efforts such as electronic patient registry, physician reminders, and promotion of patient-education and self-management strategies could also have contributed. In contrast, obesity epidemic has increased the prevalence of diabetes mellitus worldwide, resulting in potential blunting of absolute burden of diabetes in the society despite a decreasing trend in all-cause mortality, cardiovascular mortality, and CVD. A greater emphasis should be given to prevention and treatment of obesity in order to improve the adverse impact of diabetes on the society globally.

Compliance with Ethical Standards

Conflict of Interest Thwe Htay, Kyaw Soe, Arianna Lopez-Perez, Amy HoangAnh Doan, Michael A. Romagosa, and KoKo Aung declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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