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Systematic Review

The Economic Burden of Cardiovascular Disease in Type 2 Diabetes: A Systematic Review

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ABSTRACT

Background: Cardiovascular diseases (CVDs) constitute major comorbidities in type 2 diabetes mellitus (T2DM), contributing substantially to treatment costs for T2DM. An updated overview of the economic burden of CVD in T2DM has not been presented to date. **Objective:** To systematically review published articles describing the costs associated with treating CVD in people with T2DM. **Methods:** Two reviewers searched MEDLINE, Embase, and abstracts from scientific meetings to identify original research published between 2007 and 2017, with no restrictions on language. Studies reporting direct costs at either a macro level (e.g., burden of illness for a country) or a micro level (e.g., cost incurred by one patient) were included. Extracted costs were inflated to 2016 values using local consumer price indexes, converted into US dollars, and presented as cost per patient per year. **Results:** Of 81 identified articles, 24 were accepted for analysis, of which 14 were full articles and 10 abstracts. Cardiovascular comorbidities in patients with T2DM incurred a significant burden at both the population and patient levels. From a population level, CVD costs contributed between 20% and 49% of the total direct costs of treating T2DM. The median annual costs per patient for CVD, coronary artery disease, heart failure, and stroke were, respectively, 112%, 107%, 59%, and 322% higher compared with those for T2DM patients without CVD. On average, treating patients with CVD and T2DM resulted in a cost increase ranging from $3418 to $9705 compared with treating patients with T2DM alone. **Conclusions:** Globally, CVD has a substantial impact on direct medical costs of T2DM at both the patient and population levels.

Keywords: cardiovascular disease, coronary artery disease, cost, ischemic heart disease, stroke.

Introduction

According to the International Diabetes Federation (IDF), the estimated number of people with diabetes in 2015 was 415 million, which is projected to rise to 642 million by the year 2040 [1]. The IDF estimates that the global cost of diabetes was US $673 billion in 2015, which is projected to rise to US $802 billion in 2040 [1]. More recently, Bommer et al. [2] estimated the global cost burden of treating diabetes to be US $1.31 trillion/y, an estimate that takes into account both direct costs and production losses due to morbidity or premature mortality.

A major comorbidity of diabetes is cardiovascular disease (CVD), which is estimated to affect about one-third (32.2%) of all people with diabetes [3]. In large prospective trials, type 2 diabetes mellitus (T2DM) has been identified as a significant risk factor for CVD, including stroke [4–6], angina [5], heart failure [6], myocardial infarction (MI) [6], and atherosclerosis [6]. Furthermore, adults with diabetes have a two- to threefold increased risk of heart attack and stroke [4]. CVD is also a major cause of death and disability among people with diabetes [7,8]. According to the Nurses Health Study, CVD was responsible for 20.1% of all deaths in people without diabetes as opposed to 47.2% in people with diabetes [9].

The high cost of managing diabetes presents a growing challenge for health care systems, and cardiovascular complications contribute substantially to these costs. According to Hex et al. [10], costs for treating CVD comprised 44.2% of the cost of complications and 35.3% of the overall cost of T2DM in the United Kingdom. In addition, the

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American Diabetes Association reported that cardiovascular complications, for people with both type 1 diabetes mellitus (T1DM) and T2DM, were responsible for 27% of the total cost of treating diabetes in the United States [11]. Costs for these complications were categorized as 84% inpatient, 10% physicians' offices, 3% emergency room, and 3% outpatient clinics [11].

Given the substantial clinical and economic burden of CVD among patients with T2DM, there has been increased focus on the joint management of CVD and T2DM. Current management approaches involve setting targets for glycated hemoglobin (HbA_{1c}), lipids, and blood pressure. Nevertheless, because the risk of CVD-related death increases both with tighter glycemic control (lower HbA_{1c}) and with higher HbA_{1c} [12,13], physicians must individualize HbA_{1c} targets according to several parameters including a patient's age and risk of CVD [14]. Furthermore, certain antidiabetic drugs belonging to the class of sulfonylureas are associated with an elevated risk of CVD among patients with diabetes [15]. There has therefore been increasing pressure from regulatory agencies that antidiabetic treatments demonstrate cardiovascular safety and benefits, especially for major cardiovascular events such as cardiovascular mortality, nonfatal MI, and stroke [16,17]. Following these regulatory requirements, several cardiovascular outcome trials (CVOTs) have been conducted. The results from these placebo-controlled CVOTs have demonstrated that certain antidiabetic treatments are associated with a significantly lower risk for cardiovascular events [18–21].

Past studies have not definitively quantified the added costs due to treating and managing CVD in patients with T2DM. In 2016, the IDF issued a report on the prevalence of CVD in T2DM, but did not estimate costs attributable to CVD [7]. To date, there is no global review summarizing the economic burden of treating CVD among patients with T2DM. Although some reviews have evaluated the cost of CVD among patients with diabetes, these studies have been specific to a single country or have not separated T1DM and T2DM and rather treated them as a single group [22–24]. Therefore, we undertook this research to systematically review published literature on the economic impact of CVD in T2DM. The focus of this study was to describe the costs associated with treating T2DM patients for CVD at both the patient and population levels (i.e., a "partial" economic evaluation). The findings from this study can be used to inform estimates on the impact of cardiovascular complications on health care costs for T2DM. These can then inform "full" economic evaluations (i.e., in studies reporting both costs and consequences), such as studies evaluating the cost effectiveness of interventions aimed at controlling diabetes and its complications.

Methods

Study Design

A comprehensive search of published literature was carried out using MEDLINE and Embase. The search was restricted to publications from January 2007 to end 2016 for all languages. Furthermore, abstracts were reviewed from selected key scientific meetings, including the International Society for Pharmacoeconomic Outcomes and Research, the American Diabetes Association, the European Association for the Study of Diabetes, the American Association of Clinical Endocrinologists, and the European Society of Cardiology and the American Heart Association's scientific sessions. The review was done by two independent researchers and was completed on March 6, 2017. Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2017.12.019 displays the results from the MEDLINE search. The review followed the Preferred Reporting System for Systematic Reviews and Meta-Analysis (PRISMA) strategy, presented in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2017.12.019.

Eligibility Criteria

Our inclusion criteria were developed according to the PICOS model (Populations/People/Patient/Problem; Intervention(s); Comparison; Outcome; Study design) [25], which appears in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2017.12.019. Accepted articles were published in any language between January 2007 and the end of 2016. Included articles examined adult patients 18 years and older with T2DM as well as some form of CVD. For this review, CVD included MI/heart attack, angina, stroke, congestive heart failure, coronary artery disease (CAD), or atherosclerosis. Cardiovascular death and cardiac death were also included as outcomes of interest. Excluded were early manifestations of CVD and risk factors for CVD such as hypertension, metabolic syndrome, or measurements of carotid intima media thickness. Also excluded were articles that quantified resource utilization but did not apply a cost to those results.

Included studies reported the monetary burden associated with CVD in patients with T2DM. Both direct and indirect costs (i.e., health-related and broader societal costs such as lost productivity, respectively) were of interest. The focus could be either at the macro level (i.e., burden of illness for a country) or at the micro level (i.e., the cost to treat one patient over a specified time frame). Study designs of interest were observational, including longitudinal cohorts, cohort studies, or cross-sectional studies.

Study Selection and Data Extraction

After duplicates were removed, the first selection of articles was made on the basis of titles and abstracts. Articles selected for full-text review were screened according to the eligibility criteria. The final selection of articles was compared and adjudicated through a consensus discussion between two reviewers.

One reviewer extracted the data, which were checked independently by a second reviewer. In the case of discrepancy, a third reviewer adjudicated, whose decision was considered final. For each study included, the study characteristics including 1) publication year; 2) country of study; 3) level of analysis, that is, patient or population; 4) types of costs measured; 5) the data collection period; 6) the type of data collected; and 7) the type of analysis, if any, conducted to calculate total costs were extracted. For patient-level studies, cost data pertaining to CVD-related procedures, including 1) type of CVD comorbidity; 2) type of cost, that is, inpatient, outpatient, or total; 3) calculated cost per type of cost; and 4) comorbidity were extracted. For population-level studies, data pertaining to 1) total annual T2DM-related expenditures, 2) type of CVD comorbidity measured, and 3) total annual CVD-related expenditures were extracted.

Data Analysis

To facilitate comparison across studies, all costs were inflated to 2016 values using local inflation rates. These values were then converted to US dollar values based on end of 2016 exchange rates published by the US Federal Reserve [26]. Data were then tabulated and analyzed descriptively. We calculated means and SDs, medians, and, where data were combined, we used weighted means using sample sizes to weight. The final outputs of the analysis were total annual burden per country and average cost per patient per year for population- and patient-level studies, respectively.