The Burden of Hypoglycemia in Type 2 Diabetes: A Systematic Review of Patient and Economic Perspectives

Younan Zhang, MSci, Heather Wieffer, PhD, Rakhee Modha, PhD, Bharvi Balar, MPH, Michael Pollack, MS, and Girishanthy Krishnarajah, MPH, MBA/MS

Abstract

- **Objective**: To identify the magnitude of the burden of hypoglycemia in type 2 diabetes.
- **Methods**: Studies that reported data on the economic burden, impact on quality of life (QOL), or treatment satisfaction related to hypoglycemia in a type 2 diabetes population were identified from searches of literature databases and conference proceedings and reviewed.
- **Results**: Studies showed that hypoglycemia had a detrimental effect on QOL as measured by generic QOL instruments (EQ-5D, SF-36) and diminished treatment satisfaction levels among patients treated with oral antidiabetic agents (OADs), although the latter was not observed in insulin-treated patients. Previous hypoglycemia also increased fear of the condition among OAD-treated patients as measured by the Hypoglycemia Fear Scale. Hypoglycemia in OAD-treated patients was associated with decreased work productivity. Detailed evidence of the medical cost burden of hypoglycemic events was identified in 5 US studies of insulin-treated patients. Individual episodes requiring hospital admission were identified as particularly costly from the perspective of medical payers in both US and international studies. The higher frequency of less severe events together with their potential to significantly affect work productivity point to their importance from a payer and societal perspective.
- **Conclusion**: In light of the impact on the patient and wider society in economic as well as clinical terms, consideration of hypoglycemia should be an important part of clinical decision making.

Anti-hyperglycemic therapy used for the management of diabetes can be associated with hypoglycemia [1], a condition in which blood glucose concentration is below the level required for normal brain function [2]. Hypoglycemia has a substantial clinical impact, causing distress to affected individuals and impairing their ability to perform everyday activities [3]. The frequency of hypoglycemia in the general type 2 diabetes population is difficult to gauge because of the limited number of large-scale studies examining incidence and the lack of standardization in hypoglycemia diagnosis/reporting. In the UKPDS 73 study, 11% of type 2 diabetes patients on a variety of treatment regimens reported 1 or more hypoglycemic episodes of any severity per year [4]. In contrast, 24.5% of patients reported at least 1 hypoglycemic episode in a 3-month period in a U.S. study of predominantly female, African-American patients [5].

Hypoglycemia is particularly regarded as an issue in type 1 diabetes. However, the increasing number of patients who have type 2 diabetes points to a need to understand the impact of hypoglycemia in this population. In this paper, we examine the impact of hypoglycemic episodes in type 2 diabetes patients in terms of quality of life (QOL), treatment satisfaction, and economic burden.

Methods

**Literature Search**

Two reviews were conducted: 1 examining humanistic burden and 1 examining economic burden. For the humanistic burden review, MEDLINE and EMBASE were searched on 21 September 2009 with no date limits applied using search terms for type 2 diabetes, hypoglycemia, and relevant study designs and outcomes. For the economic review, in addition to MEDLINE and EMBASE, the Cochrane Economic Evaluations Database was searched with no date limits.

Three well-established conferences were selected as potential sources of data: the International Society for...
Pharmacoeconomics and Outcomes Research (ISPOR) Annual International Meetings, the ISPOR Annual European Congresses, and the American Diabetes Association (ADA) Annual Scientific Sessions. Abstracts from these meetings 2007–2009 were handsearched to further identify relevant studies. Abstracts from the European Association for the Study of Diabetes (EASD) Annual Meetings 2007–2009 were also handsearched for further studies relating to QOL.

For inclusion, studies were required to examine cost, resource use, or QOL for adults diagnosed with type 2 diabetes in a routine treatment setting, and to report data describing the impact of hypoglycemia on QOL, treatment satisfaction, or fear of hypoglycemia, and/or costs attributable to hypoglycemia. Only studies published in the English language were included. Although the US market was of primary interest, studies in non-US settings in patients treated with oral antidiabetic agents (OADs) were also included to expand the information available for this patient population. Given that patient-reported outcomes were considered less country-specific than economic outcomes, studies from all countries were included in the humanistic burden review.

**Literature Review**

Abstracts were initially screened, and studies of potential interest meeting inclusion criteria were obtained for full text review. Two independent reviewers reviewed each publication; a third reviewer resolved any discrepancies. Where a single study reported data in more than 1 publication, all linked publications of a single study were compiled into a single entry in the data extraction grid to prevent double counting. The flow diagrams are shown in Figure 1 and Figure 2. Qualitative assessment was used to compare the studies. Quantitative analyses were not undertaken due to large variation in design, population, and the measurement and classification of hypoglycemia among studies.

**Results**

**Effect of Hypoglycemia on QOL**

Seventeen studies were identified as providing information...
regarding humanistic burden (QOL, treatment satisfaction, fear of hypoglycemia) in type 2 diabetes [6–29] (Table 1).

The majority of studies were carried out in Europe and North America; one study in insulin-treated patients was conducted in Japan. The included studies covered both insulin- and OAD-treated populations.

A number of studies examined QOL in patients controlled by OADs using the EQ-5D [30], a widely used generic instrument for evaluating QOL. The EQ-5D asks participants to report their QOL in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which can take 1 of 3 responses associated with 3 levels of severity (no problems/some or moderate problems/extreme problems), and yields a summary score. The EQ-5D also yields a single index value for health status based on a visual analogue scale (similar to a thermometer) for recording an individual's rating for their current health-related quality of life state (VAS score).

In the 4 studies using EQ-5D in patients treated solely with OADs [11,12,16,17], an association between experience of hypoglycemic symptoms and lower QOL was seen. A similar association was seen in a study of type 2 diabetes patients unsel ected by therapy [28] and patients treated with diet, OADs, and/or insulin [24,25].

The results of 4 studies in which EQ-5D QOL summary scores were reported for patients with and without hypoglycemic events are shown in Figure 3. For those reporting hypoglycemia, mean scores were lower for EQ-5D. In a study that included patients who had experienced severe hypoglycemic episodes (where outside assistance was required) [17], mean EQ-5D scores for those with no, mild, moderate, and severe/very severe hypoglycemic symptoms were 0.801, 0.733, 0.698 and 0.544, respectively. Previous studies have suggested that differences of this magnitude in EQ-5D score exceed the minimal important difference (a change which patients would perceive as beneficial and would mandate change in management) [31].

In studies that reported a VAS score [16,22,24], significantly lower scores were reported for patients reporting hypoglycemic symptoms versus those who did not (68.7
hypoglycemia vs. 73.5, \( P < 0.001 \) [16]; 64.8 vs. 69.0, \( P = 0.003 \) [24]; 71.3 vs. 76.3, \( P = 0.025 \) [22]). Matza et al observed significantly lower VAS scores in patients who experienced daytime hypoglycemia, but the difference in scores was not significantly different for nighttime hypoglycemia in this mixed therapy population (diet, insulin and/or OAD) [25]. Further, Jermendy et al [11] identified a negative association (\( P = 0.017 \)) between hypoglycemic episodes and VAS scores in a linear regression model, while Vexiu et al [17] identified a significant negative association between hypoglycemia experience as a dichotomous variable (yes/no) for the EQ-5D summary score in multivariate analysis (\( P \leq 0.001 \)).

Among the studies of patients on insulin, Mehta et al was the only study to measure QOL using the EQ-5D (as opposed to insulin-specific questionnaires) [6]. No significant association was observed between frequency of hypoglycemic events and QOL. However, patients in this study who completed different specific questionnaires reported more mood disturbance and less work satisfaction [6].

Table 1. Studies Included in QOL Review

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>No. of Patients</th>
<th>Therapy</th>
<th>QOL Measure(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehta 1999 [6]</td>
<td>UK</td>
<td>311</td>
<td>Insulin therapy</td>
<td>EQ-5D</td>
</tr>
<tr>
<td>Brod 2007 [7]</td>
<td>US</td>
<td>233</td>
<td>Biphasic insulin aspart or insulin glargine</td>
<td>Insulin Treatment Satisfaction Questionnaire</td>
</tr>
<tr>
<td>Ishii 2007 [8]</td>
<td>Japan</td>
<td>476</td>
<td>Human insulin switched to insulin lispro</td>
<td>Insulin Therapy Related Quality of Life</td>
</tr>
<tr>
<td>Leiter 2005 [10]</td>
<td>Canada</td>
<td>133</td>
<td>Insulin</td>
<td>Study-specific questionnaire</td>
</tr>
<tr>
<td>Marrett 2009 [12–15]</td>
<td>US</td>
<td>1984</td>
<td>OADs only (MF, SU, TZD or other alone or in combination)</td>
<td>EQ-5D, Hypoglycemia Fear Survey, Treatment Satisfaction Questionnaire for Medication</td>
</tr>
<tr>
<td>Mavros 2007 [16]</td>
<td>France, Germany</td>
<td>792</td>
<td>PPARγ agonist or SU added to MF</td>
<td>EQ-5D</td>
</tr>
<tr>
<td>Stargardt 2009 [18–20]</td>
<td>Germany</td>
<td>392</td>
<td>SU or TZD added to MF</td>
<td>Hypoglycemia Fear Survey, Treatment Satisfaction Questionnaire for Medication</td>
</tr>
<tr>
<td>Alvarez-Guisasola 2008 [21–23]</td>
<td>Finland, France Germany, Norway, Poland, Spain, UK</td>
<td>1709</td>
<td>SU or TZD added to MF</td>
<td>Treatment Satisfaction Questionnaire for Medication</td>
</tr>
<tr>
<td>Matza 2007 [25]</td>
<td>UK</td>
<td>130</td>
<td>Mixed: diet or insulin and/or oral</td>
<td>Psychological General Well-being Index</td>
</tr>
<tr>
<td>Tabaei 2004 [26]</td>
<td>US</td>
<td>1522</td>
<td>Mixed: diet or insulin and/or oral</td>
<td>Quality of Well-being–Self-Administered</td>
</tr>
<tr>
<td>Menard 2007 [27]</td>
<td>Canada</td>
<td>68</td>
<td>Mixed: insulin and/or oral</td>
<td>Diabetes QOL</td>
</tr>
<tr>
<td>Davis 2005 [28]</td>
<td>UK</td>
<td>861</td>
<td>Not stated (unselected T2DM population)</td>
<td>EQ-5D, SF-36</td>
</tr>
<tr>
<td>Matza 2007 [29]</td>
<td>UK</td>
<td>129</td>
<td>Mixed: diet or insulin and/or oral</td>
<td>N/A</td>
</tr>
</tbody>
</table>

\( MF = \) metformin; OAD = oral antidiabetic; PPARγ = peroxisome proliferator-activated receptor gamma; SU = sulfonylurea; TZD = thiazolidinedione.

MF = metformin; OAD = oral antidiabetic; PPARγ = peroxisome proliferator-activated receptor gamma; SU = sulfonylurea; TZD = thiazolidinedione.
Effect of Hypoglycemia on Treatment Satisfaction

The Treatment Satisfaction Questionnaire for Medication (TSQM) measures treatment satisfaction in 4 domains: treatment effectiveness, side-effect profile, convenience, and global satisfaction [39]. This measure was used in 3 studies of OAD-treated patients [12,18,21] (Figure 4). All studies showed that the experience of hypoglycemia was associated with lower global satisfaction. Marrett et al [12] also found significantly lower scores for the side-effects domain in patients reporting hypoglycemia compared with those who did not ($P \leq 0.001$). Alvarez-Guisasola et al [21] observed that experience of hypoglycemia was associated with a negative effect on all domains ($P < 0.001$ for all comparisons).

Brod et al [7] used the Insulin Treatment Satisfaction Questionnaire (ITSQ) [40] in an insulin-treated population and found no significant relationship between the number of minor hypoglycemic events (symptomatic or asymptomatic, minor was undefined) and overall treatment satisfaction. Diurnal hypoglycemic events, however, did have a significant negative impact on overall treatment satisfaction ($P < 0.01$); the authors suggested these may be more easily identified compared with nocturnal events and are more bothersome to daily functioning.

Fear of Hypoglycemia

The unpleasant symptoms and concerning consequences of hypoglycemia may result in fear of hypoglycemia. Fear of future hypoglycemic events may lead to corrective or counteractive action to prevent hypoglycemia at the expense of undesirably high glucose levels [41]. Three studies in OAD-treated patients examined fear of hypoglycemia with the Hypoglycemia Fear Survey [42].

The Hypoglycemia Fear Survey comprises 2 subscales, 1 that assesses hypoglycemia avoidance behavior and 1 measuring the degree of worry about hypoglycemia. Experience of hypoglycemia was associated with increased fear of hypoglycemia in 3 studies in OAD-treated patients (Figure 5) [12,17,18], with significant correlations between hypoglycemia and fear score in the regression models of Vexiau [17] and Marrett [12] ($P \leq 0.001$). Vexiau et al also showed a positive correlation ($P \leq 0.001$) with increasing severity of reported symptoms. Similarly, Stargardt et al [18] reported differences according to whether assistance was needed during episodes (worry score of 21.6 for those who needed assistance versus 12.1 for those who did not). In a mixed therapy population, Lundkvist et al [24] reported that patients with hypoglycemic symptoms had more worry and...
avoidance behavior compared with patients without symp-
toms ($P < 0.001$) [24].

**Economic Burden**

Eleven studies provided information on costs related to
hypoglycemia in type 2 diabetes [24,43–54] (Table 2). Eight
studies assessed only medical costs and/or resource use,
1 study measured nonmedical costs, and 2 studies exam-
ined both. Five of the medical cost studies examined the cost
burden to US insurers of hypoglycemia in patients treated
with different insulin therapies. No similarly detailed data
were available for the OAD-treated population.

Direct costs. The 5 studies in insulin-treated patients com-
pared hypoglycemia-associated costs incurred by patients
taking different insulin-based or analog (eg, glargine) prod-
ucts [48,49,51,53,54], with the aim of establishing the economic
consequences of the differences in hypoglycemia rates. These
studies identified the sum reimbursed for each claim by the
insurance provider. Events were identified through ICM-9
CM codes (250.8, 251.0, 251.1 and 251.2 with the additional
use of 250.3x by Fabunmi et al [51]). Claims were classified
by type of care utilized (eg, inpatient, outpatient).

The proportion of insurance claims stratified by resources
utilized for 3 studies is shown in Figure 6. Medical resource
use attributable to hypoglycemia was distributed between
primary and secondary care providers. Inpatient admis-
sions constituted approximately 20% of claims. Claims for
inpatient treatment imposed the greatest cost burden—
approximately 50% of the total mean cost [49,53] and 87%
of the total cost as modeled by Fabunmi et al [51]. The total
cost of hypoglycemia-associated claims as reported in 3
studies is shown in Table 3: mean cost of claims for hypo-
glycemia in patients treated with insulin (vial and syringe)
was around $1500 per year (2005), less in those treated with
insulin analogues (around $620 per year) [49,53].

Less information was available on the economic burden
associated with hypoglycemia in non-insulin-treated pa-
tients. Leese [46] found a lower frequency of hypoglycemic
events in this population and a lower frequency of severe
hypoglycemic events requiring emergency treatment. A
study in Germany [45] found hypoglycemic events requir-
ing emergency medical attention in the general type 2
diabetes population (nonspecific treatment regimens) were
resource-intensive: 95% required hospital admission, with
an average length of stay of 9.5 days. The cost of hypogly-
cemic episodes in a type 2 diabetes population in Sweden
was estimated by Jonsson et al [43] based on incident rates
reported in the literature and unit costs for Sweden (€ 2005)
and is presented in Table 4.

---

**Figure 4.** TSQM global scores for patients experiencing/not experiencing hypoglycemia.

**Figure 5.** HFS-II scores for patients experiencing/not experiencing hypoglycemia.
Indirect costs. In assessing the impact of hypoglycemia, it is important to consider indirect as well as direct costs. The 3 studies examining nonmedical costs [24,43,44] showed hypoglycemic symptoms to be associated with a decrease in work productivity. Williams et al [44] used the Work Productivity and Activity Impairment (WP AI) Questionnaire [55] and Diabetes Productivity Measure (DPM) [56] to gauge the effect of hypoglycemic symptoms in an OAD-treated type 2 diabetes population. The WP AI assesses time missed from work and impairment of work and of other daily activities. The DPM assesses the effect of diabetes symptoms on work and life productivity. In employed respondents, experience of hypoglycemic symptoms was associated with 12.9% greater work impairment and 11.4% less work productivity [44]. This was equated to a loss of approximately 5 hours work time in a 40-hour week, at a cost of $70.44 to $79.63 per week ($3663–$4141 per year).

Patients experiencing hypoglycemic symptoms were found less likely to be employed. In a Swedish study, Lundkvist et al [24] found that 20% of patients who had experienced symptomatic hypoglycemia were in full- or part-time employment compared with 31% of patients who had not [24]. The proportion of patients retired due to illness or on sick leave was 25% in the symptomatic hypoglycemia group but only 12% in the asymptomatic group. Based on a very small sample (23 employed individuals experiencing hypoglycemic symptoms of which 3 reported reduced working capacity), the total indirect cost of reduction in working capacity due to hypoglycemia was estimated at $14.10 per month per patient with hypoglycemic symptoms.

The indirect costs per hypoglycemic episode by event severity in a Swedish population were calculated by Jonsson et al [43]. The calculated values were based on the costs associated with loss of work productivity of the patient suffering the hypoglycemic event and the loss of work productivity of the patient’s carer if the person was not a medical professional (Table 4). Based on the calculated direct

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Perspective</th>
<th>Therapy</th>
<th>Method</th>
<th>Costs Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jonsson 2006 [43]</td>
<td>Sweden</td>
<td>Third party payer/society</td>
<td>Mixed: insulin or oral</td>
<td>Cost of illness based on published cost and incidence data</td>
<td>Medical and nonmedical</td>
</tr>
<tr>
<td>Lundkist 2005 [24]</td>
<td>Sweden</td>
<td>Third party payer/society</td>
<td>Mixed: insulin or oral</td>
<td>Medical record review and survey of hypoglycemic incidence combined with published cost estimates</td>
<td>Medical and nonmedical</td>
</tr>
<tr>
<td>Williams 2009 [44]</td>
<td>US</td>
<td>Patient/society</td>
<td>OADs</td>
<td>Patient-reported survey using questionnaires relating to work productivity</td>
<td>Nonmedical</td>
</tr>
<tr>
<td>Holstein 2002 [45]</td>
<td>Germany</td>
<td>Third party payer (public)</td>
<td>Mixed (unselected population)</td>
<td>Prospective surveillance of medical service use in regional population</td>
<td>Medical</td>
</tr>
<tr>
<td>Leese 2003 [46]</td>
<td>Scotland</td>
<td>Third party payer (public)</td>
<td>Mixed: insulin, sulphonyl-urea, metformin/diet</td>
<td>Retrospective analysis of medical records of validated register of diabetic patients in one area</td>
<td>Medical</td>
</tr>
<tr>
<td>Riewpaiboon 2007 [47]</td>
<td>Thailand</td>
<td>Provider</td>
<td>Unclear: notes some patients treated with insulin</td>
<td>Review of medical records combined with unit costs</td>
<td>Medical</td>
</tr>
<tr>
<td>Bullano 2006 [48]</td>
<td>US</td>
<td>Third party payer (private insurer)</td>
<td>Insulin glargine vs. premixed insulin combination</td>
<td>Retrospective claims databases analysis, comparison of therapies</td>
<td>Medical</td>
</tr>
<tr>
<td>Cobden 2007 [49,50]</td>
<td>US</td>
<td>Third party payer (private insurer)</td>
<td>Insulin analogue vial/syringe vs. biphasic insulin pen</td>
<td>Retrospective claims databases analysis, comparison of therapies</td>
<td>Medical</td>
</tr>
<tr>
<td>Fabunmi 2009 [51,52]</td>
<td>US</td>
<td>Third party payer (private insurer)</td>
<td>Exenatide vs. insulin glargine</td>
<td>Retrospective claims databases analysis, comparison of therapies</td>
<td>Medical</td>
</tr>
<tr>
<td>Lee 2006 [53]</td>
<td>US</td>
<td>Third party payer (private insurer)</td>
<td>Conventional human/analogue insulin injection converting to prefilled insulin analogue pen</td>
<td>Retrospective claims databases analysis, before and after comparison</td>
<td>Medical</td>
</tr>
<tr>
<td>Leahy 2007 [54]</td>
<td>US</td>
<td>Third party payer (private insurer)</td>
<td>Insulin glargine vs. NPH insulin</td>
<td>Retrospective claims databases analysis, comparison of therapies</td>
<td>Medical</td>
</tr>
</tbody>
</table>
and indirect costs, the annual cost of hypoglycemia for the type 2 diabetes population in Sweden was calculated as €4.25 million (2005). The greatest contributor to the total national burden was found to be moderate hypoglycemic events (€2.65 million). OAD-treated type 2 diabetes patients were responsible for 20% of this burden (€0.83 million).

**Discussion**

A significant body of evidence shows that hypoglycemic episodes have a detrimental effect on QOL and treatment satisfaction in patients with type 2 diabetes. Fewer studies were identified that examined the economic implications of hypoglycemia in type 2 diabetes, and most were limited to examination of medical costs.

Although hypoglycemic events are typically associated with insulin therapy for diabetes, examination of the available evidence has highlighted a burden also in OAD-treated patients. In 4 studies of patients treated with metformin-based combination therapy, there was a prevalence of hypoglycemic symptoms of about 30% in a 6-month period [11,16–18]. This prevalence is higher than that usually reported for OAD-treated patients. Further, 63% of patients in Marrett et al's study [12] reported 1 or more symptoms of hypoglycemia in the past 6 months [12]. These prevalence rates may reflect the different reporting methods and/or definitions used in these studies.

While the frequency of events in OAD-treated patients may be lower than that in insulin-treated patients, the size of this population suggests a substantial direct and indirect economic burden. OAD-treated patients constitute the majority of the type 2 diabetes population, so the total number of events and hence the attributable cost may not be small. Furthermore, the impact of hypoglycemia on work productivity, even in events not requiring medical care, imposes a further economic burden on patients and employers.

Using a robust multistring search strategy across several large literature databases, with no date limits, we sought to capture the studies of interest where the burden of hypoglycemia was a key focus. The authors recognize there may be additional published data relevant to the research question that was not identified through these searches; however this is unlikely to change the conclusions. Differences in the methodologies and classification of hypoglycemia between studies and the lack of evidence, particularly with respect to medical costs attributable to OAD-treated patients, also places limitations on our ability to draw conclusions. Identification and correct attribution of events and symptoms

---

**Figure 6.** Proportion of medical insurance claims per health care resource type.
to hypoglycemia is also a challenge, particularly in patient-reported outcome studies.

The evidence suggests that the burden of hypoglycemia in type 2 diabetes should be a factor in choosing an antihyperglycemic intervention and making modifications to a treatment regimen. The emphasis on achieving tight glycemic control has been recently questioned in light of inconclusive evidence of benefit from large-scale clinical trials and the burden of adverse events and costs [57,58]. There is growing interest in selecting antihyperglycemic therapies, including classes of OADs, based on their profile of benefits and harms. Consideration of benefits includes the potential for short-term glycemic control together with long-term durability and prevention of complications. The propensity to cause side effects, such as weight gain, gastrointestinal symptoms and cardiovascular risk, also varies. Of the identified harms, hypoglycemia is an important factor to weigh against the clinical benefits when striving for glycemic control. Indeed, minimization of the risk and severity of hypoglycemia was identified as a priority in selection of antihyperglycemic medication in the recent American Association of Clinical Endocrinologists/American College of Endocrinology consensus statement [59]. In light of the impact on the patient and wider society in economic as well as clinical terms, consideration of hypoglycemia should be an important part of clinical decision making.

Corresponding author: Heather Wieffer, PhD, Heron Evidence Development Ltd, Butterfield Technology and Business Park, Stopsley, Luton LU2 8DL, UK, heather.wieffer@heronhealth.com.

Funding/support: This work was sponsored by Bristol Myers Squibb and AstraZeneca.

References


Table 3. Annual Total Costs Per Patient Attributable to Hypoglycemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Cost Year</th>
<th>Treatment Arm</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Expected Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobden 2007 [49,50]</td>
<td>2005</td>
<td>Insulin vial and syringe</td>
<td>$1528 ($2336)</td>
<td>$490</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biphasic insulin analog pen</td>
<td>$620 ($899)</td>
<td>$142</td>
<td></td>
</tr>
<tr>
<td>Lee 2006 [53]</td>
<td>2005</td>
<td>Insulin vial and syringe</td>
<td>$1415 ($2556)</td>
<td>$533</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insulin analog pen</td>
<td>$627 ($993)</td>
<td>$172</td>
<td></td>
</tr>
<tr>
<td>Fabunmi 2009* [51,52]</td>
<td>Data gathered 2005–2008</td>
<td>Exenatide</td>
<td></td>
<td></td>
<td>$78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insulin glargine</td>
<td></td>
<td></td>
<td>$196</td>
</tr>
</tbody>
</table>

*Estimate derived from model using event incidence rates (adjusted for patient characteristics) and estimated per event hypoglycemia costs based on mean and median costs per event pooled for both treatment groups. For ease of comparison in this table, reported cost per 100 patients has been converted to cost per patient.

Table 4. Costs Per Hypoglycemic Episode Calculated by Jonsson [43]

<table>
<thead>
<tr>
<th>Event Severity</th>
<th>Estimated Medical Cost/Event</th>
<th>Estimated Work Days Lost</th>
<th>Estimated Indirect Cost/Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild—patient experiences hypoglycemic symptoms requiring assistance from a second person but no medical attention is needed</td>
<td>€26.0</td>
<td>0.22</td>
<td>37.0</td>
</tr>
<tr>
<td>Moderate—patient seeks medical attention for hypoglycemia but is not admitted to hospital overnight</td>
<td>€334.7</td>
<td>0.27</td>
<td>45.3</td>
</tr>
<tr>
<td>Severe—patient is admitted to hospital because of hypoglycemia</td>
<td>€2806.8</td>
<td>6.60</td>
<td>1110.6</td>
</tr>
</tbody>
</table>
policies to improve blood glucose or blood pressure control (UKPDS 37). Diabetes Care 1999;22:1125–36.